JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

Nonsolvent Application of Ionic Liquids: Organo-Catalysis by 1-Alkyl-3-methylimidazolium Cation Based Room-Temperature Ionic Liquids for Chemoselective *N-tert*-Butyloxycarbonylation of Amines and the Influence of the C-2 Hydrogen on Catalytic Efficiency

Anirban Sarkar, Sudipta Raha Roy, Naisargee Parikh, and Asit K. Chakraborti*

Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S.A.S. Nagar 160 062, Punjab, India

Supporting Information

ABSTRACT: 1-Alkyl-3-methylimidazolium cation based ionic liquids efficiently catalyze *N-tert*-butyloxycarbonylation of amines with excellent chemoselectivity. The catalytic role of the ionic liquid is envisaged as "electrophilic activation" of di-*tert*-butyl dicarbonate (Boc_2O) through bifurcated hydrogen bond formation with the C-2 hydrogen of the 1-alkyl-3-methylimidazolium cation and has been supported by a downfield shift of the imidazolium C-2 hydrogen of 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][NTf_2]) from δ 8.39 to 8.66 in the presence of Boc_2O in the ^1H NMR and a drastic reduction of the catalytic efficiency with 1-butyl-2,3-dimethylimidazolium ionic liquids that are devoid of the C-2 hydrogen. The differential time required for reaction with aromatic and aliphatic amines has offered means for selective *N-t*-Boc formation during inter and intramolecular competitions. Preferential *N-t*-Boc formation with secondary aliphatic amine has been achieved in the presence of primary aliphatic amine. Comparison of the catalytic efficiency for *N-t*-Boc formation with a common substrate revealed that [bmim][NTf_2] is superior to the reported Lewis acid catalysts.

$$(R)ArNH_2 + (Boc)_2O \xrightarrow[\text{rt, 0.5 - 45 min}]{\text{IL (2.5 mol \%)}} \underset{(80\text{-}99\%)}{(R)ArNHBoc}$$

INTRODUCTION

Modulating the reactivity of amine functionality is a requisite exercise with 39% frequency in the preparation of drug molecules.[1] Protection of amine through acylation[2] is an easy approach but requires harsh reaction conditions,[3] which are not compatible with a multifunctional substrate, to regenerate the amine. An alternative and preferred strategy is *N-tert*-butoxycarbonylation[4] due to the stability of *tert*-butylcarbamates (*N-t*-Boc) toward a variety of routinely adopted experimental conditions and ease of regeneration of the parent amines under mild acidic conditions. Thus, the development of more effective methodologies for *N-t*-Boc formation has a long-standing interest in organic synthesis.[5]

The increasing influence of green chemistry on chemical research[6] urges for greener reaction conditions. The prime attention toward this direction is on the use of an alternative reaction medium, and ionic liquids (ILs) are hailed as green solvents of the future.[7] However, ILs do not always exhibit innocuous behavior,[8] which puts their green image under scrutiny[9] on several issues such as combustibility,[10] toxicity,[11] and biodegradability.[12] These are deterrents for the enthusiasm for the use of ILs as reaction media. Therefore, to benefit from the spectacular ability of ILs to accelerate organic reactions and modulate selectivity, the "non-solvent" application of ILs is gaining momentum.[13]

In the pursuit of exploring catalytic uses of ILs,[14] we report herein that the 1-alkyl-3-methylimidazolium (bmim: alkyl = *n*-butyl; emim: alkyl = ethyl) cation based room-temperature ionic liquids (RTILs) are efficient organo-catalysts for chemoselective *N-tert*-butyloxycarbonylation of amines and that the catalytic efficiency of the bmim cation-based ILs is influenced by the C-2 hydrogen of the bmim cation.

RESULTS AND DISCUSSION

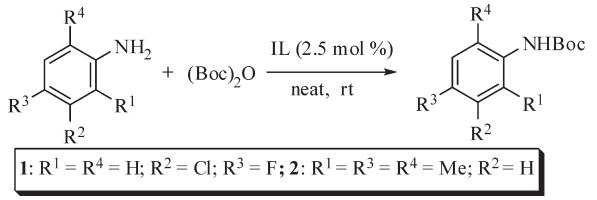
For catalyst selection 3-chloro-4-fluoroaniline (**1**) and 2,4,6-trimethylaniline (**2**) were chosen as model substrates as representatives of electron-deficient and sterically hindered aromatic amines, respectively, for *N-t*-Boc formation by reaction with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of various 1-alkyl-3-methylimidazolium RTILs (Scheme 1), and the results are summarized in Table 1.

The 1-alkyl-3-methylimidazolium-derived RTILs exhibited very good to excellent catalytic activity (entries 1−14, Table 1). However, the catalytic efficiency of the protic IL [Hmim][BF_4] was found to be significantly inferior to that of the bmim cation containing ILs (entry 15, Table 1). Poor yields were obtained in carrying out the reactions in the absence of any IL (entries 16−18, Table 1) and highlighted the necessity of the catalytic assistance of the ILs for *N-t*-Boc formation. For reactions that afforded lesser/poor yields of the *N-t*-Boc derivatives, the corresponding unreacted starting amine remained unchanged and could be recovered.

To demonstrate the general usability of the ILs as organo-catalysts for *N-t*-Boc formation, we chose 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide [bmim][NTf_2] because of its advantageous physicochemical properties such as

Received: May 28, 2011
Published: July 21, 2011

Scheme 1. Ionic Liquid Catalyzed Reaction of 1 and 2 with Boc_2O



1: $R^1 = R^4 = H$; $R^2 = Cl$; $R^3 = F$; **2**: $R^1 = R^3 = R^4 = Me$; $R^2 = H$

Table 1. *N-t*-Boc Formation from 1 and 2 Catalyzed by RTILs[a]

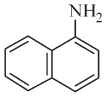
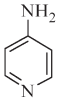
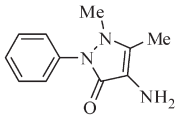
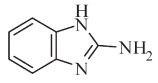
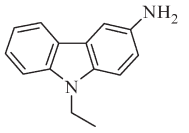
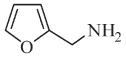
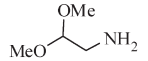
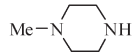
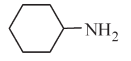
entry	IL	yield (%)[b] from **1**	yield (%)[c] from **2**
1	[emim][Cl]	93	85
2	[emim][PF_6]	93	86
3	[bmim][Br]	93	82
4	[bmim][BF_4]	92	82
5	[bmim][PF_6]	91	75
6	[bmim][NTf_2]	95[d,e]	86
7	[bmim][$MeSO_3$]	93	82
8	[bmim][$MeSO_4$]	92	75
9	[bmim][HSO_4]	89	75
10	[bmim][$N(CN)_2$]	91	82
11	[bmim][OAc]	86	74
12	[bmim][ClO_4]	84	76
13	[bmim][N_3]	84	75
14	[bmim][HCO_2]	85	80
15	[Hmim][BF_4][f]	20	50
16	none	20[g]	35[g]
17	none	nil[h]	15[h]
18	none	15[i]	17[i]

[a] The amine (2.5 mmol) was treated with $(Boc)_2O$ (2.5 mmol, 1 equiv) in the presence of the IL (2.5 mol %) under neat conditions at rt. [b] Yield of the purified *N-t*-Boc derivative of **1** obtained after 15 min reaction. [c] Yield of the purified *N-t*-Boc derivative of **2** obtained after 45 min reaction. [d] The use of 1 mol % of the IL afforded 70% yield of the *N-t*-Boc amine after 15 min. [e] The use of 5 mol % of the IL afforded the *N-t*-Boc amine in 82 and 96% yields after 10 and 15 min, respectively. [f] Hmim = *N*-methylimidazolium. [g] The reaction was performed under neat condition in the absence of any IL. [h] The reaction was performed in dioxane (2.5 mL) in the absence of any IL. [i] The reaction was performed in dioxane−water (1:1) (2.5 mL) in the absence of any IL.

lower melting point, lower viscosity, and increased hydrophobicity that would be beneficial in the ease of handling and recovery of the IL for reuse.[15] The optimal catalyst amount was found to be 2.5 mol %. The use of lesser amounts (e.g., 1 mol %) of the IL afforded inferior product yield (Table 1, entry 6, footnote d). On the other hand, the use of higher quantities (e.g., 5 mol %) of the IL did not provide any significant advantage in terms of reducing the reaction time (Table 1, entry 6, footnote e).

Therefore, various aromatic, heteroaromatic, aryl alkyl, heteroaryl alkyl, and alkyl amines were treated with Boc_2O under the catalytic influence of [bmim][NTf_2] (Table 2). The corresponding *N-t*-Boc derivatives were formed in excellent yields in a short time (1−45 min) without competitive formation of isocyanate,[16] urea,[16c] and *N,N*-di-Boc[16c,17] (IR, GCMS). No *O*/*S*-*t*-Boc formation (IR) took place with substrates having an OH/SH group

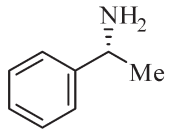
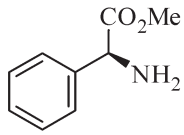
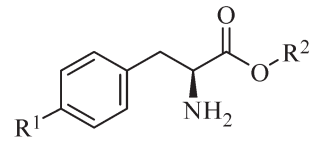
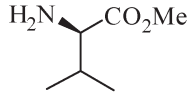
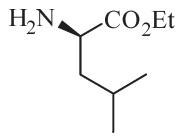
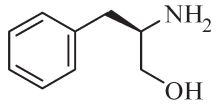
Table 2. [bmim][NTf_2]-Catalyzed *N-t*-Boc Formation of Amines[a]

Entry	Substrate	Time (min)	Yield (%)[b,c]
1	$R^1 = R^5 = R^2 = R^3 = R^4 = H$	2	95
2	$R^1 = R^5 = H$; $R^2 = R^3 = R^4 = OMe$	15	86
3	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OMe$	10	92
4	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Me$	10	96
5	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OCH_2Ph$	2	92
6	$R^2 = R^4 = H$; $R^1 = R^3 = R^5 = Me$	45	86[d]
7	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = F$	10	95
8	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Cl$	10	98
9	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Br$	12	95
10	$R^1 = Me$; $R^2 = R^4 = R^5 = H$; $R^3 = Br$	15	99
11	$R^1 = R^4 = R^5 = H$; $R^2 = Cl$; $R^3 = F$	15	95[e]
12	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OH$	10	80[f]
13	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = SH$	15	92[g]
14	$R^1 = OH$; $R^2 = R^3 = R^4 = R^5 = H$	15	88[f]
15	$R^1 = OH$; $R^2 = R^4 = R^5 = H$; $R^3 = Me$	15	95[f]
16	$R^1 = OH$; $R^2 = R^3 = R^5 = H$; $R^4 = Me$	15	94[f]
17	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = NHCOCH_3$	45	80
18		45	85
19		5	98
20		30	83
21		2	80
22		5	98
23		2	98[h]
24		2	96[i]
25		1	95[j]
26		5	98[k]

[a] The amine (2.5 mmol) was treated with Boc_2O (2.5 mmol, 1 equiv) in the presence of [bmim][NTf_2] (2.5 mol %) at rt (~30−35 °C). [b] Yield of the *N-t*-Boc compound. [c] The products were characterized by IR, NMR, and MS. [d] The *N-t*-Boc product was formed in 55 and 28% yields after 2 h in dioxane and dioxane−water (1:1), respectively, in the absence of the IL. [e] The product was formed in 65 and 35% yields after 6 h in dioxane and dioxane−water (1:1), respectively, in the absence of the IL. [f] No *O-t*-Boc product was formed. [g] No *S-t*-Boc product was formed. [h] The *N-t*-Boc product was formed in 18 and 15% yields in dioxane and dioxane−water (1:1), respectively, in the absence of the IL. [i] The *N-t*-Boc product was formed in 32 and 25% yields in dioxane and dioxane−water (1:1), respectively, in the absence of the IL. [j] The *N-t*-Boc product was formed in 12 and 10% yields in dioxane and dioxane−water (1:1), respectively, in the absence of the IL. [k] The *N-t*-Boc product was formed in 45 and 36% yields in dioxane and dioxane−water (1:1), respectively, in the absence of the IL.

dx.doi.org/10.1021/jo201102q |*J. Org. Chem.* 2011, 76, 7132–7140

Table 3. [bmim][NTf_2]-Catalyzed *N-t*-Boc Formation of Chiral Amines, Esters of α-Amino Acids, and Amino Alcohol[a]

Entry	Substrate	Time (min)	Yield (%)[b,c]
1		0.5	98[d]
2		2	98[e]
3	 R^1 = H, R^2 = Me	2	96
4	R^1 = OH, R^2 = Me	10	95[f,g]
5	R^1 = OH, R^2 = Et	10	94[f]
6		5	91
7		2	92
8		2	97[h,i]

[a] The substrate (2.5 mmol) was treated with Boc_2O (2.5 mmol, 1 equiv) in the presence of [bmim][NTf_2] (2.5 mol %) at rt (~30−35 °C). [b] Yield of the *N-t*-Boc compound. [c] The products were characterized by IR, NMR and MS. [d] The enantiomeric amine afforded 95% yield. [e] The *N-t*-Boc was formed in 18, 25, and 12% yields in dioxane, water, and dioxane−water (1:1), respectively, for 20 min in the absence of the IL. [f] No *O-t*-Boc product was formed. [g] The *N-t*-Boc was formed in 43 and 39% yields after 20 min in dioxane and dioxane−water (1:1), respectively, in the absence of the IL. [h] No *O-t*-Boc or oxazolidinone formation was observed. [i] The *N-t*-Boc was formed in 49 and 43% yields after 10 min in dioxane and dioxane−water (1:1), respectively, in the absence of the IL.

(entries 12−16).[14b,18] In case of 2-aminophenols (entries 14−16) oxazolidinone,[16c,19] formation was not observed. Aminoacetaldehyde dimethyl acetal, an acid-sensitive substrate, underwent clean conversion to the *N-t*-Boc derivative (entry 24).

The mildness of the procedure was next demonstrated (Table 3) with chiral amines (entry 1), esters of α-amino acids (entries 2−7), and amino alcohol that gave optically pure *N-t*-Boc derivatives (determined by optical rotation).[20] The amino alcohol (entry 8) did not produce any side product due to competitive *O-t*-Boc or oxazolidinone formation.

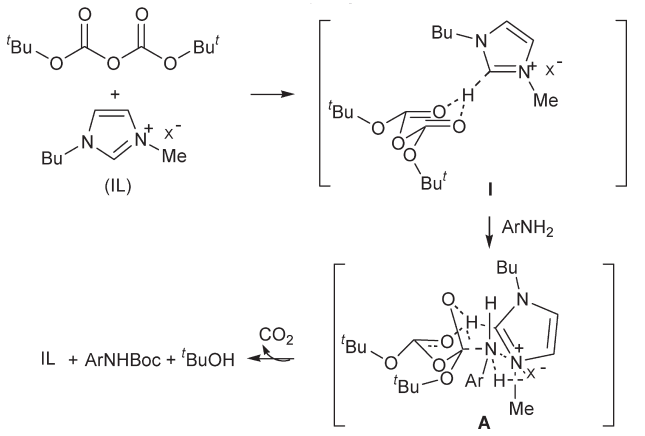
As aliphatic amines are more nucleophilic than aromatic amines it was anticipated that with such substrates the use of the IL may not offer any distinct advantage. Therefore, a few representative amines (Table 2, entries 23−26; Table 3, entries 2, 4, and 8) were treated with Boc_2O in dioxane and dioxane−water (1:1) in the absence of the IL, and in each case, poor yields of the *N-t*-Boc derivatives were obtained compared to the IL-catalyzed reactions highlighting the catalytic assistance provided by the IL.

Table 4. Reusability of [bmim][NTf_2] during the *N-t*-Boc Formation of 1[a]

use[b]	scale[c] (mmol)	amt used[d] (g)	amt rec[e] (g)	rec[f] (%)	yield[g] (%)
first (fresh)	25	0.261	0.251	96	95
first recycle	25	0.251	0.238	95	95
second recycle	25	0.238	0.222	93	92
third recycle	25	0.222	0.200	90	90
fourth recycle	25	0.200	0.172	86	87
fifth recycle	25	0.172	0.143	83	85

[a] The amine **1** (3.63 g, 25 mmol) and $(Boc)_2O$ (5.74 mL, 25 mmol, 1 equiv) in a 25 mL round bottomed flask, [bmim] [NTf_2] (0.26 g, 2.5 mol %) at rt (30−35 °C) for 15 min. [b] Refers to the status of the IL use. [c] Amount of **1** used for the reaction. [d] Amount of the IL used. [e] Amount of the IL recovered. [f] Refers to the recovered IL. [g] Refers to the yield of the *N-t*-Boc derivative of **1** after purification.

Scheme 2. Role of the IL in Catalyzing *N-t*-Boc Formation



We next planned to assess the feasibility of recovery and reuse of the IL and observed that based on the solubility of the *N-t*-Boc product and the IL [bmim][NTf_2] an appropriate solvent could be chosen to separate the IL from the product. In case of the reaction with **1** we observed that the *N-t*-Boc product is soluble in Et_2O but [bmim][NTf_2] is insoluble in Et_2O. The differential solubility of the product and the catalyst/IL enable us to extract the product by extraction of the reaction mixture with a minimal amount of Et_2O whereupon the catalyst was retained in the reaction flask and could be reused after activation under vacuum at 80 °C for 0.5 h. Thus, the IL was recovered and reused for five subsequent fresh batches of reaction without significant decrease in the catalytic activity. The recovery efficiency was 96−83% with 95−85% yields of the *N-t*-Boc compound (Table 4). The large-scale (25 mmol) preparation of the *N-t*-Boc compound demonstrated the potential for scale-up operation.

The role of the ILs is depicted in Scheme 2. The C-2 hydrogen of imidazolium ion exhibits acidic character[21] and possesses hydrogen bond donor (HBD) ability.[22] The hydrogen bond (H−B) formation ability of the C-2 H in 1-butyl-3-methylimidazlium (bmim) based ionic liquids (ILs) plays a crucial role in

dx.doi.org/10.1021/jo201102q |J. Org. Chem. 2011, 76, 7132–7140

Table 5. Influence of the C-2 Hydrogen on the Catalytic Efficiency of ILs for *N*-*t*-Boc Formation of 1 and 2[a]

entry	IL	yield[b] (%) from **1**	yield[c] (%) from **2**
1	none	20	35
2	[bdmim][BF_4]	21	41
3	[bdmim][PF_6]	25	40
4	[bdmim][NTf_2]	20	40
5	[bdmim][$MeSO_4$]	20	39
6	[bdmim][$N(CN)_2$]	21	45
7	[bdmim][OAc]	24	37
8	[bdmim][ClO_4]	27	37
9	[bdmim][N_3]	20	35
10	[bdmim][HCO_2]	24	38

[a] The amine (2.5 mmol) was treated with $(Boc)_2O$ (2.5 mmol, 1 equiv) in the presence of the IL (2.5 mol %) under neat conditions at room temperature. [b] Yield of the purified *N*-Boc derivative of **1** obtained after 15 min reaction. [c] Yield of the purified *N*-Boc derivative of **2** obtained after 45 min reaction.

their catalytic activity.[14] The IL acts as an inducer of "electrophilic activation" of Boc_2O through bifurcated hydrogen bond[23] formation between the C-2 hydrogen of the bmim moiety and the carbonyl oxygen atoms of $(Boc)_2O$ (TS I). The anions of bmim-based ILs are hydrogen bond acceptors.[24] The counteranion (X^-) of the IL may also play an important role in modulating the reactivity/selectivity of the amine through the intermediate **A** wherein the anion forms H−B with one of the NH_2 hydrogens and exerts nucleophilic activation effect.[25] The H−B formation between the anion and the hydrogen of the NH_2 group brings the amino nitrogen in close proximity to the electrophilically activated carbonyl group of Boc_2O to facilitate the nucleophilic attack and ease of formation of the *N*-*t*-Boc product. Therefore, the overall catalytic influence of the IL may be realized as "electrophile−nucleophile dual activation"[26] through a cooperative hydrogen-bonded network.[5g,14,27] An alternative pathway involving 2-carbo-*tert*-butoxyimidazolininium intermediate, presumed to be formed by the reaction of a nucleophilic heterocyclic carbene (NHC) with Boc_2O, does not seem to be operative on the following grounds: (i) the formation of NHCs normally requires the use of a strong base[28] and (ii) the IL is recovered and found to be identical (spectral data) with the unused IL.[29,30]

To demonstrate the influence of the C-2 hydrogen on the overall catalytic efficiency of the ILs, the reactions of **1** and **2** with Boc_2O were performed in the presence of several 1-butyl-2,3-dimethylimidazolium (bdmim)-based ILs that are devoid of the C-2 hydrogen (Table 5). A drastic decrease in the catalytic power was observed in these bdmim-derived ILs compared to that of the corresponding bmim-based ILs (compare the results of entries 2−10 in Table 5 with those of entries 4−6, 8, and 10−14 of Table 1). These signified the important role of the C-2 hydrogen of the bmim cation in imparting catalytic activity to the ILs. However, the lack of appreciable catalytic activity of [Hmim]-[BF_4] can be rationalized by the inferior ability of the C-2 hydrogen of Hmim cation to form H−B as compared to that of the 1,3-dialkylimidazolium cation because of its lower acidic property.[31]

To further demonstrate the importance/role of the imidazolium C-2 hydrogen in electrophilc activation of Boc_2O through its involvement in the H−B formation with the carbonyl oxygen atoms of Boc_2O in the intermediate **I** (Scheme 2) we designed/performed ^1H NMR experiments.[29] The ^1H NMR spectra of samples containing equimolar mixture of [bmim][NTf_2] and

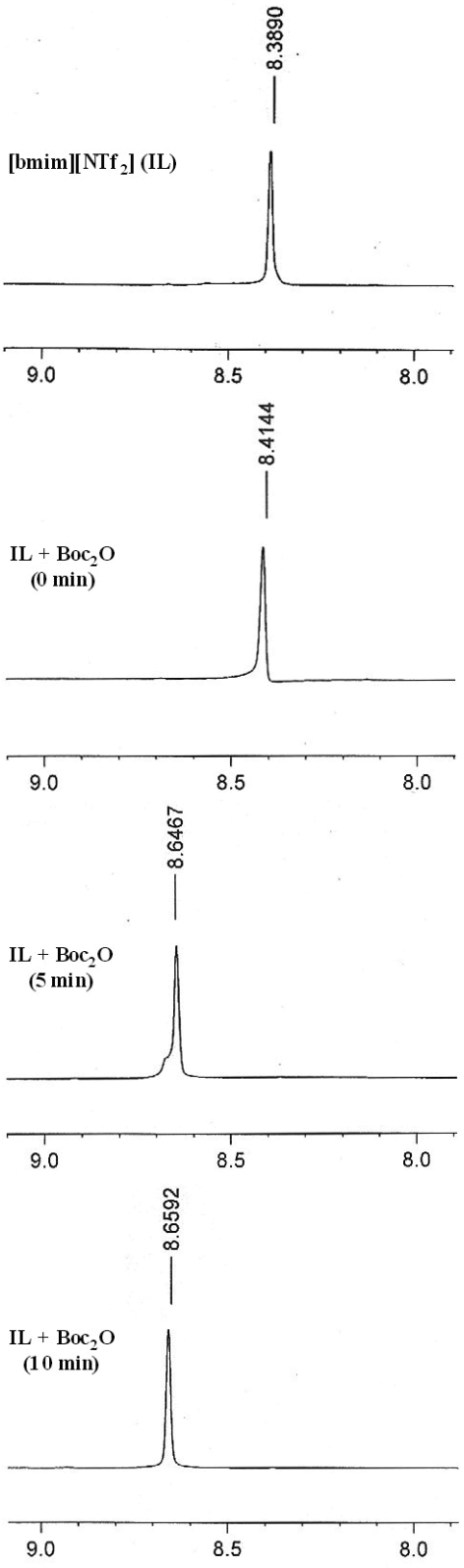
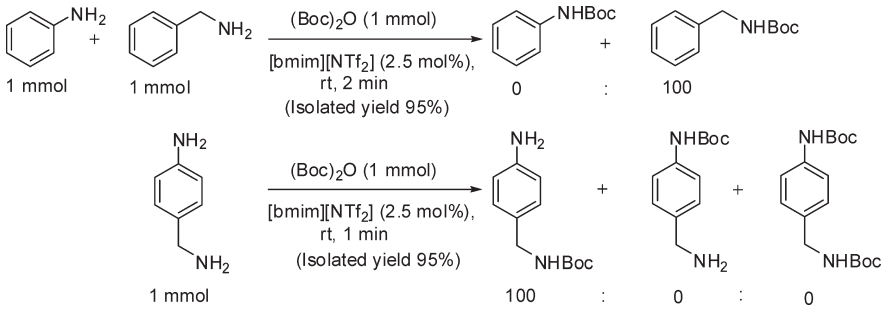


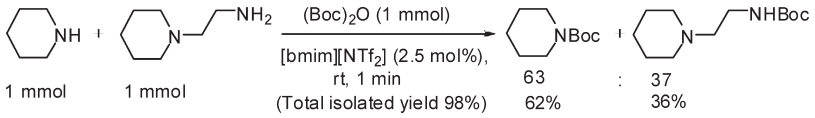
Figure 1. Shift of the C-2 H of the bmim moiety of [bmim][NTf_2] in the presence of Boc_2O in the NMR reflecting H−B formation between the C-2 H and Boc_2O.

dx.doi.org/10.1021/jo201102q |*J. Org. Chem.* 2011, 76, 7132–7140

Scheme 3. [bmim][NTf_2]-Catalyzed Selective *N*-*t*-Boc Formation during Competition of Aromatic and Aliphatic Amines



Scheme 4. [bmim][NTf_2]-Catalyzed Selective *N*-*t*-Boc Formation during Competition of Primary and Secondary Aliphatic Amines



$(Boc)_2O$ were recorded (using D_2O as an external lock) at different time intervals (0, 5, 10 min) to observe any shift of C-2 the proton of the bmim moiety of the IL (catalyst). In the ^1H NMR the sample of the catalyst/IL [bmim][NTf_2] alone, the bmim C-2 proton signal appears at δ 8.38. However, the signal shifted to δ 8.41 when the spectra of the equimolar mixture of the IL and $(Boc)_2O$ were recorded immediately after mixing (0 min). The absorption of the C-2 proton further shifted to δ 8.65 when the spectra of equimolar mixture of the IL and $(Boc)_2O$ were recorded after 5 and 15 min after mixing. The downfield shift of the C-2 proton signal from δ 8.38 to 8.65 (Figure 1) is indicative of the fact that the C-2 hydrogen of the IL is involved in hydrogen bond formation with Boc_2O to form **I** (Scheme 2).

The selective formation of *N*-*t*-Boc over *O*-*t*-Boc with substrates bearing NH_2 and OH groups is due to the better nucleophilicity of the NH_2 group. Because of the better nucleophilicity of aliphatic amines compared to aromatic amines, the *N*-*t*-Boc formation takes place over shorter time periods in the case of aliphatic amines. On a similar note, the reaction of the secondary aliphatic amine occurs at a faster rate than that of the aliphatic primary amine. The rate of *N*-*t*-Boc formation is also sensitive to the steric factors surrounding the amine moiety (compare entry 1 with entries 6, 10, 18, and 20; Table 2). However, the overall course/progress of the reaction may not be solely governed by the substrate nucleophilicity. The anion (X^-) is likely to undergo H−B formation with the *N*-H hydrogen to induce nucleophilic activation as well as to bring the amino nitrogen atom in close proximity to the carbonyl carbon of Boc_2O and facilitate *N*-*t*-Boc formation. The weak H−B formation ability of the S−H hydrogen in intermediate **A** (Scheme 1) may account for the lack of *S*-*t*-Boc formation with amino thiol (entry 13, Table 2). The influence of such an H−B effect of the anion may account for the longer reaction time with more nucleophilic anilines (entries 2−4, 6, 12−16; Table 2) compared to aniline (entry 1, Table 2), as the amino hydrogen atoms of these aniline derivatives are inferior HBDs compared to those of aniline.[32]

The varying electronic environment between aromatic and aliphatic amines encouraged us to study the selective *N*-*t*-Boc formation during inter- and intramolecular competition of an aromatic amine with an aliphatic amine (Scheme 3). The reaction of aniline (1 mmol) and benzylamine (1 mmol) with $(Boc)_2O$ (1 mmol) afforded exclusive formation of the *N*-*t*-Boc derivative of benzyl amine. For intramolecular competition between an aromatic and an aliphatic amino group we considered 4-aminobenzylamine as the model substrate. However, we realized that the treatment of 4-aminobenzylamine with $(Boc)_2O$ may lead to the formation of three products: the (4-aminobenzyl)carbamic acid *tert*-butyl ester and the (4-aminomethylphenyl)carbamic acid *tert*-butyl ester as the mono-*N*-*t*-Boc compounds and the di-*N*,*N*′-*t*-Boc of 4-aminobenzylamine. The treatment of 4-aminomethylaniline (1 mmol) with $(Boc)_2O$ (1 mmol) under the catalytic influence of [bmim][NTf_2] resulted in selective *N*-*t*-Boc formation at the alkyl amino group affording (4-aminobenzyl)-carbamic acid *tert*-butyl ester as the sole product. The corresponding product has been reported to be formed in 69−75% yields by treatment of the diamine with 1 equiv of $(Boc)_2O$ in the presence of stoichiometric quantities of *N*,*N*-diisopropylethylamine at 0 °C for 4 h followed by 12 h at rt.[33] However, when the reaction of 4-aminomethylaniline (1 mmol) with $(Boc)_2O$ (1 mmol) following this reported procedure was performed, the product mixture obtained after the usual work-up on subjection to ^1H NMR analysis was found to be a 85:15 mixture of the mono- and the di-Boc derivatives[29] on comparison with the ^1H NMR of an authentic sample of the di-*N*,*N*′-*t*-Boc of 4-aminobenzylamine prepared following an unambiguous route [the [bmim][NTf_2]-catalyzed reaction of 4-aminobenzylamine with 2 molar equiv of $(Boc)_2O$] different from that of the reported procedure.[34] These results clearly highlight the advantage of the catalytic use of [bmim][NTf_2] in terms of selectivity, shortening of the reaction time, and increasing the product yield.

We next performed intermolecular competitive study to observe any selectivity in *N*-*t*-Boc formation between a secondary and a primary aliphatic amine (Scheme 4) as secondary amines generally take lesser reaction time due to better nucleophilicity. The treatment of piperidine (1 mmol) and 2-piperidinoethylamine (1 mmol) with $(Boc)_2O$ (1 mmol) afforded 63:37 selectivity in favor of the secondary amine.

dx.doi.org/10.1021/jo201102q |*J. Org. Chem.* 2011, 76, 7132–7140

Table 6. Comparison of the Catalytic Efficiency of [bmim][NTf_2] with That of Reported Lewis Acid Catalysts for *N*-*t*-Boc Formation from 1[a]

entry	catalyst	mol %[b]	solvent	yield[c,d] (%)	lit ref[e]
1	$Zn(ClO_4)_2 \cdot 6H_2O$	5	neat	25	5a
2	$Zn(ClO_4)_2 \cdot 6H_2O$	5	DCM	10	5a
3	$ZrCl_4$	10	neat	30	5b
4	$ZrCl_4$	10	MeCN	22	5b
1	$LiClO_4$	20	neat	28	5c
2	$LiClO_4$	20	DCM	15	5c
5	$Cu(BF_4)_2 \bullet XH_2O$	1	neat	56	5d
8	$InBr_3$	1	neat	15	5e
9	$InCl_3$	1	neat	17	5e
10	$HClO_4-SiO_2$	1	neat	25	5f
11	Montmorillonite K 10	10	neat	40	5h
12	[bmim][NTf_2]	2.5	neat	95	this work
13	[bmim][NTf_2]	2.5	DCM	82	this work
14	[bmim][NTf_2]	2.5	MeCN	75	this work
15	none		neat	20	this work
16	none		DCM	10	this work
17	none		MeCN	10	this work

[a] The amine 1 (2.5 mmol) was treated with $(Boc)_2O$ (2.5 mmol, 1 equiv) in the presence of the catalyst (2.5 mol %) under neat conditions (except for entries) at room temperature for 15 min. [b] Amount of the catalyst used with respect to **1**. [c] Yield of the purified *N*-Boc derivative of **1**. [d] The unreacted starting amine remained unchanged wherever the yield of the *N*-*t*-Boc derivative was poor. [e] The corresponding literature wherein this catalyst has been reported for the use in *N*-*t*-Boc formation.

Finally, to demonstrate the superior catalytic activity of [bmim][NTf_2] for *N*-*t*-Boc formation compared to the Lewis acid catalysts we performed the reaction of **1** with Boc_2O in the presence of a few selective reported Lewis acid catalysts and compared the results with those obtained during the [bmim][NTf_2]-catalyzed reactions. The results (Table 6) clearly established that [bmim][NTf_2] is more efficient in *N*-*t*-Boc formation from amines than these Lewis acid catalysts.

CONCLUSIONS

In conclusion, we have described herein nonsolvent application of 1-alkyl-3-methylimidazolium cation based RTILs for chemoselective *N*-*tert*-butyloxycarbonylation of amines. The IL [bmim][NTf_2] has been used in catalytic quantities (2.5 mol %) for chemoselective *N*-*t*-Boc formation of various functionalized amines. Chiral amines, amino alcohol, and esters of α-amino acids afforded the corresponding optically pure *N*-*t*-Boc compounds. The IL can be recovered and reused for consecutive batches of reactions without significant loss of the catalytic property. The IL acts as an "electrophilic activation" agent through H−B formation of the C-2 hydrogen of the bmim cation with Boc_2O as evidenced by the lack of appreciable catalytic efficiency of bmim-based ILs that are devoid of the C-2 hydrogen in the imidazolium moiety and a dwonfield shift of the C-2 hydrogen in [bmim][NTf_2] in the presence of Boc_2O in the ^1H NMR. The counteranion also plays significant role in "nucleophilic activation" by H−B formation with the amine hydrogen and may account for the longer reaction times for substitued anilines with higher pK_a values of the NH_2 hydrogens compared to that of aniline although these aniline derivatives are more nucleophilic than aniline. The IL [bmim][NTf_2] proved to be superior in its catalytic action for *N*-*t*-Boc formation from a reference/common amine substrates than some of the reported Lewis acid catalysts. The organo-catalytic procedure for the *N*-*t*-Boc formation described in the present work has distinct advantages such as the (i) catalyst reuse and nonhazardous reaction conditions, (ii) operation at rt, (ii) short reaction time, (iii) high yields, and (iv) excellent chemoselectivity that fulfill the triple bottom line philosophy of green chemistry.[35]

EXPERIMENTAL SECTION

General Methods. The ^1H and ^{13}C NMR spectra were recorded on a 300 MHz or a 400 MHz NMR spectrometer in $CDCl_3$ with residual undeuterated solvent ($CDCl_3$: 7.26/77.0) using Me_4Si as an internal standard. The chemical shifts (δ) values are given in ppm and *J* values in Hz. The IR spectra were recorded either as KBr pellets (for solids) or neat or in CCl_4 (for liquids) on a FTIR spectrometer. The mass spectra were recorded under EI. Melting points were measured using a melting point apparatus and were uncorrected. Open column chromatography and thin-layer chromatography (TLC) were performed on silica gel [60−120 mesh, F254 and commercially available silica gel, respectively]. Evaporation of solvents was performed at reduced pressure using a rotary vacuum evaporator. All chemicals were purchased and used as received.

Typical Procedure for *N*-*t*-Boc Formation Catalyzed by [bmim][NTf_2]. To the mixture of **2** (0.33 g, 2.5 mmol) and Boc_2O (0.54 g, 2.5 mmol, 1 equiv) was added [bmim][NTf_2] (0.03 g, 2.5 mol %), and the reaction mixture was stirred magnetically at rt (30−35 °C). After complete consumption of **2** (TLC, 45 min), the reaction mixture was extracted with Et_2O (3 × 5 mL), and the combined Et_2O extracts were concentrated under vacuum rotary evaporation. The residue was passed through a bed of silica gel (10 g; 60−120 mesh) and eluted with 10% EtOAc in hexane (300 mL) to afford the (2,4,6-trimethylphenyl)carbamic acid *tert*-butyl ester as a white or off-white solid (0.50 g, 86%), identical (spectral data) with an authentic sample.[5d]

Typical Large-Scale Procedure for *N*-*t*-Boc Formation and Catalyst Recovery. To a magnetically stirred mixture of **1** (3.63 g, 25 mmol) and $(Boc)_2O$ (5.74 mL, 25 mmol, 1 equiv) in a 25 mL round-bottom flask was added [bmim] [NTf_2] (0.26 g, 2.5 mol %), and the mixture was stirred at rt (30−35 °C) until completion of the reaction (15 min, TLC). The reaction mixture was extracted with Et_2O (3 × 5 mL). The combined ethereal extracts were concentrated to crystallize out the *tert*-butyl carbamate of 3-chloro-4-fluoroaniline as a solid (5.8 g, 95%), identical (mp and spectral data) with an authentic sample.[5d] The IL (catalyst) that remained in the reaction flask ([bmim] [NTf_2] is insoluble in Et_2O) was activated under vacuum at 80 °C for 0.5 h and reused for further reactions.

Reusability of [bmim][NTf_2] Recovered from the Reaction of 1 with Boc_2O. After complete consumption of **1** during the *N*-*t*-Boc formation catalyzed by [bmim][NTf_2], the catalyst (IL) was recovered and reused in the following way:

(i) The *N*-*t*-Boc product was isolated by extracting the reaction mixture with ether (3 × 5 mL) followed by concentrating the combined ethereal extracts to crystallize out the product.

(ii) The IL ([bmim][NTf_2]) remained in the reaction flask ([bmim][NTf_2] is insoluble in Et_2O) and was activated under vacuum at 80 °C for 30 min. The amount of the recovered catalyst was estimated by subtracting the weight of the empty reaction flask from the combined weight of the flask and the recovered IL (0.25 g; 96% recovery).

(iii) The reaction flask containing the activated catalyst/IL was charged with a fresh batch of **1** (3.63 g, 25 mmol) and

dx.doi.org/10.1021/jo201102q |*J. Org. Chem.* 2011, 76, 7132–7140

$(Boc)_2O$ (5.74 mL, 25 mmol, 1 equiv) to afford the *N*-*t*-Boc derivative (5.8 g, 95%).

(iv) Following the above sequence of procedures the catalyst was recovered and reused five consecutive times without any significant loss of catalytic activity

Synthesis of an Authentic Sample of (4-Aminobenzyl)-carbamic Acid *tert*-Butyl Ester Following the Reported Procedure[33a]. To a solution of 4-aminobenzylamine (0.244 g; 2 mmol) in THF (4 mL) were added $(Boc)_2O$ (0.436 g, 2 mmol) and *N*,*N*-diisopropylethylamine (0.28 g, 2.24 mmol, 0.39 mL). The reaction mixture was stirred for 4 h at 0 °C and then warmed to rt, and the stirring was continued for 12 h. The resultant reaction mixture was filtered, and the filtrate was concentrated under rotary vacuum evaporation. The residue was dissolved in toluene (15 mL), washed successively with brine (3 × 5 mL), 0.1 N KOH (3 × 5 mL), and brine again (5 mL), dried (anhyd $MgSO_4$), and concentrated under reduced pressure to afford the crude product (0.4 g) which was subjected to ^{1}H NMR and was found to be an 85:15 mixture of the mono-*N*-*t*-Boc (with respect to the aliphatic amine) and di-*N*-*t*-Boc on the basis of the integration of the benzylic protons. Recrystallization ($CHCl_3$−hexane) of the crude product afforded the mono-*N*-*t*-Boc (4-aminobenzyl)carbamic acid *tert*-butyl ester (0.32 g, 71%). IR (KBr) ν: 1689 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.45 (bs, 9 H), 3.64 (bs, 2 H), 4.18 (d, J = 5.4, 2 H), 4.70 (bs, 1 H), 6.62−6.65 (m, 2 H), 7.07 (d, J = 8.20 Hz, 2 H). MS (EI): m/z 222 (M^+).

Synthesis of an Authentic Sample of Di-*N*,*N*′-*t*-Boc of 4-Aminobenzylamine. The di-*N*,*N*′-*t*-Boc of 4-aminobenzylamine was prepared following an unambiguous route different from that of the reported[34] procedure. To the mixture of 4-aminobenzylamine (0.122 g, 1 mmol) and $(Boc)_2O$ (0.218 g, 2 mmol, 2.0 equiv) was added [bmim]-[NTf_2] (0.010 g, 2.5 mol %), and the reaction mixture was stirred magnetically at rt (∼30−35 °C). After 50 min, the mixture was diluted with EtOAc (5 mL), washed with water (2 × 5 mL), dried (anh $MgSO_4$), and concentrated under reduced pressure to afford the di-*N*,*N*′-*t*-Boc of 4-aminobenzylamine as a white solid (293 mg, 91%). IR (KBr) ν: 1630, 1685 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.45 (s, 9 H), 1.51 (s, 9H), 4.25 (d, J = 5.4 Hz, 2 H), 4.77 (bs, 1 H), 6.45 (bs, 1 H), 7.20 (d, J = 8.40 Hz, 2 H), 7.31 (d, J = 8.36 Hz, 2 H). MS (EI): m/z 322(M^+).

Characterization of the Compounds. *Phenylcarbamic Acid tert-Butyl Ester (Table 2, Entry 1).* IR (KBr) ν: 1689 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.51 (s, 9 H), 6.48 (bs, 1 H), 7.02−7.05 (m,1 H), 7.25−7.36 (m, 4 H). MS (EI): m/z 193 (M^+).[5g]

(3,4,5-Trimethoxyphenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 2). IR (KBr) ν: 1694 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.51 (s, 9 H), 3.79 (s, 3 H), 3.83 (s, 6 H), 6.47 (bs, 1 H), 6.65 (s, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.3, 56.1, 60.7, 80.5, 96.1, 133.7, 134.5, 152.7, 153.4; MS (EI): m/z 283 (M^+). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.36; H, 7.42; N, 4.94. Found: C, 59.30; H, 7.38; N, 4.96.

(4-Methoxyphenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 3). IR (KBr) ν: 1689 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (s, 9 H), 3.77 (s, 3 H), 6.35 (bs, 1 H), 6.80−6.85 (m, 2 H), 7.24−7.27(m, 2 H). MS (EI): m/z 223 (M^+).[5d]

(4-Methylphenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 4). IR (KBr) ν: 1701 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (s, 9 H), 2.28 (s, 3 H), 6.41 (bs, 1 H), 7.07 (d, J = 8.2 Hz, 2 H), 7.23 (d, J = 8.2 Hz, 2 H). MS (EI): m/z 207 (M^+).[5d]

(4-Benzoyloxyphenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 5). IR (KBr) ν: 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (s, 9 H), 5.02 (s, 2 H), 6.36 (bs, 1 H), 6.87−6.92 (m, 2 H), 7.23−7.30 (m, 2 H), 7.31−7.42 (m, 5 H). MS (EI): m/z 299 (M^+).[5d]

(2,4,6-Trimethylphenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 6). IR (KBr) ν: 1711 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.49 (bs, 9 H), 2.21 (s, 6 H), 2.25 (s, 3 H), 5.80 (bs, 1 H), 6.86 (s, 2 H). MS (EI): m/z 235 (M^+).[5d]

(4-Fluorophenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 7). IR (KBr) ν: 1694 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.51 (s, 9 H), 6.44 (bs, 1 H), 6.93−7.01 (m, 2 H), 7.26−7.32 (m, 2 H). MS (EI): m/z 211 (M^+).[5d]

(4-Chlorophenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 8). IR (KBr) ν: 1689 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.51 (s, 9 H), 6.50 (bs, 1 H), 7.22−7.32 (m, 4 H). MS (EI): m/z 227 (M^+).[5q]

(4-Bromophenyl)carbamic acid tert-Butyl Ester (Table 2, Entry 9). IR (KBr) ν: 1694 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.51 (s, 9 H), 6.49 (bs, 1 H), 7.25 (d, J = 8.5 Hz, 2 H), 7.38 (d, J = 8.6 Hz, 2 H). MS (EI): m/z 272 (M^+).[5d]

(4-Bromo-2-methylphenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 10). IR (KBr) ν: 1698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (s, 9 H), 2.21 (s, 3 H),6.23 (bs, 1 H), 7.27−7.30 (m, 2 H), 7.70−7.73 (m, 1 H). MS (EI): m/z 286 (M^+).[5d]

(3-Chloro-4-fluorophenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 11). IR (KBr) ν: 1689 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.51 (s, 9 H), 6.49 (bs, 1 H), 7.03−7.10 (m, 2 H), 7.56−7.57 (m, 1 H). MS (EI): m/z 245 (M^+).[5d]

(4-Hydroxyphenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 12). IR (KBr) ν: 1697 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (s, 9 H), 5.48 (bs, 1 H), 6.35 (bs, 1 H), 6.71−6.74 (m, 2 H), 7.15 (d, J = 8.654, 2 H). MS (EI): m/z 109 (M^+).[5d]

(4-Mercaptophenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 13). IR (KBr) ν: 1698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.50 (s, 9 H), 3.38 (s, 1 H), 6.46 (bs, 1 H), 7.24 (m, 4 H). MS (EI): m/z 109 (M^+). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 28.9, 81.2, 119.9, 123.9, 131.6, 137.3, 153.2. MS (EI): m/z 225 (M^+).[5d]

(2-Hydroxyphenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 14). IR (KBr) ν: 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.51 (s, 9 H), 6.68 (bs, 1 H), 6.82−6.88 (m, 1 H), 6.94−7.10 (m, 3 H), 8.16 (bs, 1 H). MS (EI): m/z 109 (M^+).[5d]

(2-Hydroxy-4-methylphenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 15). Dark yellow solid. Mp: 88−89 °C. IR (KBr) ν: 3432, 3286, 1688, 1154 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.52 (bs, 9 H), 2.26 (s, 3 H), 6.56 (bs, 1 H), 6.65 (d, J = 7.9 Hz, 2 H), 6.79 (s, 1 H), 6.88 (d, J = 8.2 Hz, 2 H), 8.17 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.3, 28.8, 82.5, 119.9, 121.9, 123.4, 136.3, 147.9, 155.7. MS (EI): m/z 166 (M^+− 57). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found C, 64.50; H, 7.70; N, 6.26.

(2-Hydroxy-5-methylphenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 16). White solid. Mp: 98−99 °C. IR (KBr) ν: 3427, 3308, 1689, 1153 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.51 (bs, 9 H), 2.23 (s, 3 H), 6.65 (bs, 1 H), 6.79−6.85 (m, 2 H), 6.95 (s, 1 H), 7.78 (bs, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.1, 28.8, 82.4, 118.7, 122.1, 126.3, 130.8, 145.3, 155.4. MS (EI): m/z 166 (M^+− 57). Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.49; H, 7.72; N, 6.28.

(4-Acetylaminophenyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 17). IR (KBr) ν: 1693 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.51 (s, 9 H), 2.15 (s, 3 H), 6.45 (bs, 1 H), 7.16 (bs, 1 H), 7.29 (d, J = 9 Hz, 2 H), 7.40 (d, J = 9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 24.9, 28.9, 30.2, 81.1, 119.9, 121.5, 133.8, 135.22, 153.5, 169.0. MS (EI): m/z 250 (M^+).[36]

Naphthalen-1-yl-carbamic Acid tert-Butyl Ester (Table 2, Entry 18). IR (KBr) ν: 1697 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.55 (s, 9 H), 6.85 (bs, 1 H), 7.74 (m, 3 H), 7.62 (d, J = 6 Hz, 2 H), 7.87 (m, 3 H). MS (EI): m/z 243 (M^+).[5i]

Pyridin-4-yl-carbamic Acid tert-Butyl Ester (Table 2, Entry 19). IR (KBr) ν: 1728, 1606 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.52 (s, 9 H), 7.32 (t, J = 3 Hz, 2 H), 8.43 (t, J = 3 Hz, 2 H). MS (EI): m/z 194 (M^+).[5g]

(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)carbamic Acid tert-Butyl Ester (Table 2, Entry 20). IR (KBr) ν: 1715 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.48 (s, 9 H), 2.26 (s, 3 H), 3.03 (s, 3 H), 5.98 (bs, 1 H), 7.26−7.31 (m, 1 H), 7.38−7.51 (m, 4 H). MS (EI): m/z 303 (M^+).[5d]

(1H-Benzoimidazol-2-yl)carbamic Acid tert-Butyl Ester (Table 2, Entry 21). IR (KBr) ν: 1734, 1633 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.71 (m, 9 H), 7.02−7.07 (bs, 2 H), 7.19 (t, J = 6 Hz, 1 H), 7.33 (d, J = 6 Hz, 1 H), 7.61 (d, J = 6 Hz, 1 H). MS (EI): m/z 233 (M^+).[5g]

(9-Ethyl-9H-carbazol-3-yl)carbamic Acid tert-Butyl Ester (Table 2, Entry 22). IR (KBr) ν: 1692 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.25 (t, J = 9 Hz, 3 H), 1.58 (s, 9 H), 4.20−4.36 (m, 2 H), 6.55 (bs, 1 H), 7.16−7.46 (m, 5 H), 8.04−8.07 (m, 1 H), 8.18 (s, 1 H). MS (EI): m/z 310 (M^+).[5g]

Furan-2-ylmethylcarbamic Acid tert-Butyl Ester (Table 2, Entry 23). IR (KBr) ν: 1701 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.45 (m, 9 H), 4.28 (d, J = 6 Hz, 2 H) 4.80 (bs, 1 H), 6.19 (s, 1 H), 6.28−6.30 (m, 1 H), 7.32−7.33 (m, 1 H). MS (EI): m/z 197 (M^+).[5g]

(2,2-Dimethoxyethyl)carbamic Acid tert-Butyl Ester (Table 2, Entry 24). IR (CCl_4) ν: 1686 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44 (s, 9 H), 3.25−3.38 (m, 8 H) 4.37 (t, J = 6 Hz, 1 H), 4.86 (bs, 1 H). MS (EI): m/z 205 (M^+).[5g]

4-Methyl-piperazine-1-carboxylic Acid tert-Butyl Ester (Table 2, Entry 25). IR (CCl_4) ν: 1696 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.45 (s, 9 H), 2.29 (s, 3 H), 2.29−2.35 (m, 4 H), 3.42−3.45 (m, 4 H). MS (EI): m/z 200 (M^+).[5g]

Cyclohexylcarbamic Acid tert-Butyl Ester (Table 2, Entry 26). IR (KBr) ν: 1681 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.03−1.15 (m, 3 H), 1.26−1.34 (m, 2 H) 1.43 (s, 9 H), 1.57−1.71 (m, 3 H), 1.90−1.93 (m, 2 H), 3.43 (bs, 1 H), 4.44 (bs, 1 H). MS (EI): m/z 199 (M^+).[5g]

(R)-(1-Phenylethyl)carbamic Acid tert-Butyl Ester (Table 3, Entry 1). IR (KBr) ν: 1687 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.42 (bs, 12 H), 4.8 (bs, 2 H), 7.24−7.35 (m, 5 H). MS (EI): m/z 164 (M^+− 57).[5d]

(S)-2-tert-Butoxycarbonylaminophenylacetic Acid Methyl Ester (Table 3, Entry 2). IR (KBr) ν: 1684 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.43 (s, 9 H), 3.71 (s, 3 H), 5.32 (d, J = 7.17 Hz, 1 H), 5.54 (bs, 1 H), 7.34 (m, 5 H). Optical rotation: reported $[\alpha]^{20}_D$ +135.7 (c = 0.08, $CHCl_3$), found $[\alpha]^{20}_D$ −135.2 (c = 0.08, $CHCl_3$).[36]

(S)-2-tert-Butoxycarbonylamino-3-phenylpropionic Acid Methyl Ester (Table 3, Entry 3). IR (KBr) ν: 1683 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.41 (bs, 9 H), 3.08−3.10 (m, 2H), 3.7 (s, 3 H), 4.59 (s, 1 H), 5.02 (s, 1 H), 7.12 (m, 2 H), 7.26 (m, 3 H). Optical rotation: reported $[\alpha]^{20}_D$ −4.0 (c = 2.0, MeOH), found $[\alpha]^{20}_D$ −4.2 (c = 2.0, MeOH).[5d]

(S)-2-tert-Butoxycarbonylamino-3-(4-hydroxyphenyl)propionic Acid Methyl Ester (Table 3, Entry 4). IR (KBr) ν: 1687 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.42 (bs, 9 H), 3.00 (t, J = 6 Hz, 2 H), 3.71 (s, 1 H), 4.54 (d, J = 6 Hz, 1 H), 4.98 (d, J = 6 Hz, 1 H), 5.25 (bs, 1 H), 6.73 (d, J = 9 Hz, 2 H), 6.97 (d, J = 9 Hz, 2 H). Optical rotation: reported $[\alpha]^{22}_D$ +51.0 (c = 1.0, $CHCl_3$), found $[\alpha]^{25}_D$ 51.4 (c = 1.0, $CHCl_3$).[5g]

(S)-2-tert-Butoxycarbonylamino-3-(4-hydroxyphenyl)propionic Acid Ethyl Ester (Table 3, Entry 5). IR (KBr) ν: 1685 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.24 (t, J = 6 Hz, 3 H), 1.42 (bs, 9 H), 2.99 (t, J = 6 Hz, 2 H), 4.16 (q, J = 6.9 Hz, 2 H), 4.51 (d, J = 6 Hz, 1 H), 5.00 (d, J = 9 Hz, 1 H), 5.50 (bs, 1 H), 6.72 (d, J = 9 Hz, 2 H), 6.97 (d, J = 9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 28.3, 37.6, 54.7, 61.5, 80.2, 115.5, 127.6, 130.4, 155.1, 155.3, 172.2. Optical rotation: $[\alpha]^{20}_D$ +1.05 (c = 0.5, MeOH). Anal. Calcd for $C_{16}H_{23}NO_5$ C, 62.12; H, 7.49; N, 4.53. Found: C, 62.10; H, 7.51; N, 4.52.

(S)-2-tert-Butoxycarbonylamino-3-methylbutyric Acid Methyl Ester (Table 3, Entry 6). IR (KBr) ν: 1684 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.92 (dd, J = 6 Hz, 18 Hz, 6 H), 1.44 (s, 1 H), 2.10 (m, 1 H), 3.73 (s, 3 H), 4.15 (m, 1 H), 5.00 (bs, 1 H). Optical rotation reported: $[\alpha]^{20}_D$ − 22.0 (c = 1, MeOH), found $[\alpha]^{20}_D$ −22.2 (c = 1, MeOH).[37]

(S)-2-tert-Butoxycarbonylamino-4-methylpentanoic Acid Ethyl Ester (Table 3, Entry 7). IR (KBr) ν: 1687 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.94 (d, J = 6 Hz, 6 H), 1.27 (t, J = 6 Hz, 3 H), 1.44 (m, 12 H), 4.21 (m, 3 H), 4.97 (d, J = 6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 21.9, 22.8, 24.8, 28.3, 29.7, 41.9, 52.1, 61.1, 79.8, 155.4, 173.6. Optical rotation: $[\alpha]^{20}_D$ −25.7 (c = 0.95, MeOH). Anal. Calcd for $C_{13}H_{25}NO_4$: C, 60.12; H, 9.71; N, 5.40. Found: C, 60.10; H, 9.73; N, 5.39.

(S)-1-Hydroxymethyl-2-phenylethyl)carbamic Acid tert-Butyl Ester (Table 3, Entry 8). IR (KBr) ν: 1685 cm$^{-1.}$ ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.41 (bs, 9 H), 2.45 (bs, 1 H), 2.84 (d, J = 7.01 Hz, 2 H), 3.55−3.56 (m, 1 H), 3.66−3.68 (m, 1 H), 3.87 (bs, 1 H), 4.76 (d, J = 6.77 Hz, 1 H), 7.20−7.32 (m, 5 H). Optical rotation reported: $[\alpha]^{25}_D$ −27.0 (c = 1, $CHCl_3$), found $[\alpha]^{20}_D$ −26.7.0 (c = 1, $CHCl_3$).[5d]

(4-Aminobenzyl)carbamic Acid tert-Butyl Ester (Scheme 3). IR (KBr) ν: 1689 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.45 (bs, 9 H), 3.65 (bs, 2 H), 4.17 (d, J = 5.25, 2 H), 4.75 (bs, 1 H), 6.63 (d, J = 8.22 Hz, 2 H), 7.06 (d, J = 8.00 Hz, 2 H). MS (EI): m/z 222 (M^+).[33a]

■ ASSOCIATED CONTENT

Supporting Information. Experimental design of NMR study and scanned spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: 91-(0)-172 2214683. Fax: 91-(0)-172 2214692. E-mail: akchakraborti@niper.ac.in.

■ ACKNOWLEDGMENT

Financial support received from CSIR (SRF to A.S. and S.R.R.) and DST (SR/S1/OC-33/2008), New Delhi, India.

■ REFERENCES

(1) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.

(2) (a) Chakraborti, A. K.; Gulhane, R. *Tetrahedron Lett.* **2003**, *44*, 3521. (b) Chakraborti, A. K.; Gulhane, R. *J. Chem. Soc., Chem. Commun.* **2003**, *44*, 1896. (c) Chakraborti, A. K.; Gulhane, R. *Tetrahedron Lett.* **2003**, *44*, 6749. (d) Chakraborti, A. K.; Sharma, L.; Gulhane, R.; Shivani *Tetrahedron* **2003**, *59*, 7661. (e) Chakraborti, A. K.; Gulhane, R.; Shivani *Synlett* **2003**, 1805. (f) Chakraborti, A. K.; Gulhane, R.; Shivani *Synthesis* **2004**, 111. (g) Chakraborti, A. K.; Gulhane, R. *Synlett* **2004**, 627. (h) Shivani; Gulhane, R.; Chakraborti, A. K. *J. Mol. Catal. A: Chem.* **2007**, *264*, 208–213.

(3) Dilbeck, G. A.; Field, L.; Gallo, A. A.; Gargiulo, R. J. *J. Org. Chem.* **1978**, *43*, 4593.

(4) (a) Lutz, C.; Lutz, V.; Knochel, P. *Tetrahedron* **1998**, *54*, 6385. (b) Greene, T. W.; Wuts, P. G. M. *Protecting Group in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999. (c) Theodoridis, G. *Tetrahedron* **2000**, *56*, 2339. (d) Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701. (e) Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. *Chem. Rev.* **2004**, *104*, 199.

(5) Recent examples: (a) Bartoli, G.; Bosco, M.; Locatelli, M.; Marcantoni, E.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Synlett* **2004**, 1794. (b) Sharma, G. V. M.; Reddy, J. J.; Lakshmi, P. S.; Radha Krishna, P. *Tetrahedron Lett.* **2004**, *45*, 6963. (c) Heydari, A.; Hosseini, S. E. *Adv. Synth. Catal.* **2005**, *347*, 1929. (d) Chankeshwara, S. V.; Chakraborti, A. K. *Tetrahedron Lett.* **2006**, *47*, 1087. (e) Chankeshwara, S. V.; Chakraborti, A. K. *Synthesis* **2006**, 2784. (f) Chankeshwara, S. V.; Chakraborti, A. K. *Org. Biomol. Chem.* **2006**, *4*, 2769. (g) Chankeshwara, S. V.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 3259. (h) Chankeshwara, S. V.; Chakraborti, A. K. *J. Mol. Catal. A: Chem.* **2006**, *253*, 198. (i) Jia, X.; Huang, Q.; Li, J.; Li, S.; Yang, Q. *Synlett* **2007**, 806. (j) Upadhyay, D. J.;

Barge, A.; Stefania, R; Cravotto, G. *Tetrahedron Lett.* **2007**, *48*, 8318. (k) Heydari, A.; Shiroodi, R. K.; Hamadi, H.; Esfandyari, M.; Pourayoubi, M. *Tetrahedron Lett.* **2007**, *48*, 5865. (l) Sunitha, S.; Kanjilal, S.; Reddy, P. S.; Prasad, R. B. N. *Tetrahedron Lett.* **2008**, *49*, 2527. (m) Khaskar, S.; Heydari, A.; Tajbaksh, M.; Vahdat, S. M. *Tetrahedron Lett.* **2008**, *49*, 3527. (n) Heydari, A.; Khaskar, S.; Tajbaksh, M. *Synthesis* **2008**, 3126. (o) Shiva Kumar, K.; Iqbal, J.; Pal, M. *Tetrahedron Lett.* **2009**, *50*, 6244. (p) Akbari, J.; Heydari, A.; Mamani, L.; Hosseini, S. H. C. R. *Chimie* **2010**, *13*, 544.

(6) Alfonsi, K.; Colberg, J.; Dunn, P. J.; Fevig, T.; Jennings, S.; Johnson, T. A.; Kleine, H. P.; Knight, C.; Nagy, M. A.; Perry, D. A.; Stefaniak, M. *Green Chem.* **2008**, *10*, 31.

(7) Earle, M. J.; Sheldon, R. A. *Pure. Appl. Chem.* **2000**, *72*, 1391.

(8) Dupont, J.; Spencer, J. *Angew. Chem.* **2004**, *43*, 5296.

(9) Ranke, J.; Stolte, S.; Störmann, R.; Arning, J.; Jastorff, B. *Chem. Rev.* **2007**, *107*, 2183.

(10) Smiglak, M.; Reichert, W. M.; Holbrey, J. D.; Wilkes, J. S.; Sun, L.; Thrasher, J. S.; Kirichenko, K.; Singh, S.; Katritzky, A. R.; Rogers, R. D. *Chem. Commun.* **2006**, 2554.

(11) Costello, D. M.; Brown, L. M.; Lamberti, G. A. *Green Chem.* **2009**, *11*, 548.

(12) Coleman, D.; Gathergood, N. *Chem. Soc. Rev.* **2010**, *39*, 600.

(13) Dominguez de Maria, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6960.

(14) (a) Chakraborti, A. K.; Raha Roy, S.; Kumar, D.; Chopra, P. *Green Chem.* **2008**, *10*, 1111. (b) Chakraborti, A. K.; Raha Roy, S. *J. Am. Chem. Soc.* **2009**, *131*, 6902. (c) Raha Roy, S.; Chakraborti, A. K. *Org. Lett.* **2010**, *12*, 3866. (d) Sarkar, A.; Raha Roy, S.; Chakraborti, A. K. *Chem. Commun.* **2011**, *47*, 4538. (e) Raha Roy, S.; Jadhavar, P. S.; Seth, K.; Sharma, K. K.; Chakraborti, A. K. *Synthesis* **2011**, 2261.

(15) Chiappe, C.; Pieraccini, D. *J. Phys. Org. Chem.* **2005**, *18*, 275.

(16) (a) Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem., Int. Ed.* **1995**, *34*, 2497. (b) Knölker, H.-J.; Braxmeier, T. *Tetrahedron Lett.* **1996**, *37*, 5861. (c) Basel, Y.; Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368.

(17) Darnbrough, S.; Mervic, M.; Condon, S. M.; Burns, C. J. *Synth. Commun.* **2001**, *31*, 3273.

(18) (a) Chankeshwara, S. V.; Chebolu, R.; Chakraborti, A. K. *J. Org. Chem.* **2008**, *73*, 8615. (b) Chebolu, R.; Chankeshwara, S. V.; Chakraborti, A. K. *Synthesis* **2008**, 1448.

(19) (a) Lago, M. A.; Samanen, J.; Elliot, J. D. *J. Org. Chem.* **1992**, *57*, 3493. (b) Curran, T. P.; Pollastri, M. P.; Abelleira, S. M.; Messier, R. J.; McCollum, T. A.; Rowe, C. G. *Tetrahedron Lett.* **1994**, *35*, 5409. (c) Bach, T.; Schröder, J. *Tetrahedron Lett.* **1997**, *38*, 3707. (d) Ghosh, A. K.; Shin, D.; Mathivanan, P. *J. Chem. Soc., Chem. Commun.* **1999**, 1025. (e) Okumoto, H.; Nishihara, S.; Yamamoto, S.; Hino, H.; Nozawa, A.; Suzuki, A. *Synlett* **2000**, 991. (f) Benedetti, F.; Norbedo, S. *Tetrahedron Lett.* **2000**, *41*, 10071.

(20) (a) Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, 181. (b) Green, R.; Taylor, P. J. M.; Bull, S. D.; James, T. D.; Mahon, M. F.; Merritt, A. T. *Tetrahedron: Asymmetry* **2003**, *14*, 2619.(c) Aldrich Handbook of Fine Chemicals and Laboratory Equipments, India 2003−2004, p 336. (d) Aldrich Advancing Science, India 2005−2006, pp. 514. (e) Donboo Amino Acid Co. Ltd., http://www.donboo.com/english/detail.asp?id=221.

(21) Choi, D. S.; Kim, D. H.; Shin, U. S.; Deshmukh, R. R.; Lee, S.; Song, C. E. *Chem. Commun.* **2007**, 3467.

(22) (a) Aggarwal, A.; Kancaster, N. L.; Seth, A. R.; Welton, T. *Green Chem.* **2002**, *4*, 517. (b) Lungwitz, R.; Friedrich, M.; Linert, W.; Spange, S. *New J. Chem.* **2008**, *32*, 1493.

(23) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48.

(24) Lungwitz, R.; Spange, S. *New J. Chem.* **2008**, *32*, 392.

(25) H−B-induced nucleophilic activation has been reported during "demand based" thiolate anion generation protocol: (a) Nayak, M. K.; Chakraborti, A. K. *Chem. Lett.* **1998**, 297. (b) Chakraborti, A. K.; Sharma, L.; Nayak, M. K. *J. Org. Chem.* **2002**, *67*, 2541.

(26) Electrophile−nucleophile dual activation by coordinating alkali metal cation: (a) Basak (née Nandi), A.; Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett.* **1998**, *39*, 4883. (b) Chakraborti, A. K.; Basak (née Nandi), A.; Grover, V. *J. Org. Chem.* **1999**, *64*, 8014. (c) Bhagat, S.; Sharma, R.; Sawant, D. M.; Sharma, L.; Chakraborti, A. K. *J. Mol. Catal. A: Chem.* **2006**, *244*, 20. (d) Bhagat, S.; Sharma, R.; Chakraborti, A. K. *J. Mol. Catal. A: Chem.* **2006**, *260*, 235.

(27) (a) Khatik, G. L.; Kumar, R.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 2433. (b) Chakraborti, A. K.; Rudrawar, S.; Jadhav, K. B.; Kaur, G.; Chankeshwara, S. V. *Green Chem.* **2007**, *9*, 1335. (c) Parikh, N.; Kumar, D.; Raha Roy, S.; Chakraborti, A. K. *Chem. Commun.* **2011**, *47*, 1797.

(28) Typically deprotonation of the imidazolium cation requires an alkoxide base as the pK_a values of imidazolium ions are in the range 16−20: Alder, R. W.; Allen, P. R.; Williams, S. J. *J. Chem. Soc. Chem. Commun.* **1995**, 1267.

(29) Supporting Information.

(30) NHCs are generally associated with a transition-metal species for exhibiting catalytic property (and are the likely intermediates in various transition-metal-catalyzed reactions performed in RTILs as solvent) but normally undergo dimerisation (particularly the ones that is not associated with some transition metal ion) and under such cases the precursor ILs are not recoverable/recyclable.

(31) Amyes, T. L.; Diver, S. T.; Richard, J. P.; Rivas, F. M.; Toth, K. *J. Am. Chem. Soc.* **2004**, *126*, 4366.

(32) The pK_a values of aniline, 4-methylaniline, 2-hydroxyaniline, 4-methylaniline, 4-fluoroaniline, and 4-hydroxyaniline are 4.52, 4.65, 4.72, 5.12, 5.29, and 5.50, respectively. Brown, H. C. et al. In Braude, E. A.; Nachod, F. C. *Determination of Organic Structures by Physical Methods*; Academic Press: New York, 1955. Gross, K. C.; Seybold, P. G.; Inga, Z. P.; Murray, J. S.; Politzer, P. *J. Org. Chem.* **2001**, *66*, 6919.

(33) (a) Zhang, W.; Simanek, E. E. *Org. Lett.* **2000**, *2*, 843. (b) Chakrabarti, S.; Isaacs, L. *Supramol. Chem.* **2008**, *20*, 191.

(34) Strazzoline, P.; Melloni, T.; Giumanini, A. G. *Tetrahedron* **2001**, *57*, 9033.

(35) (a) Sheldon., R. A. *Chem. Ind.* **1997**, *1*, 12. (b) Clark, J. H. *Green Chem.* **1999**, *1*, 1.

(36) Vilaivan, T. *Tetrahedron Lett.* **2006**, *47*, 6739.

(37) Aldrich Catalogue, India, 2009−2010