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An efficient and chemoselective Brønsted acidic ionic liquid-catalyzed *N*-Boc protection of amines

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Abstract

The first report of a Brønsted acidic ionic liquid, 1-methylimidazolium tetrafluoroborate [(HMIm)BF_4], catalyzed efficient and chemoselective *N*-Boc protection of various amines using $(Boc)_2O$ is presented. Optically pure amino alcohols and amino acid esters were converted efficiently to their corresponding optically pure *N*-Boc derivatives. The reported method is mild, solvent-free and has the advantages of both homogeneous and heterogeneous catalysis with high product yields, selectivity and ease of product separation.

Keywords: Amines; Brønsted acidic ionic liquid; Chiral aminols; Chiral amino acid esters; Di-*tert*-butyl pyrocarbonate; *N*-Boc protection

Sequential protection and deprotection of any polyfunctional molecule often needs a selective and efficient protecting reagent together with mild reaction conditions. The protection of an amine is an important step in synthetic organic chemistry. Even though a variety of amine protecting groups are available in the literature, the *tert*-butyl carbonyl group (abbreviated as Boc or *t*-Boc) is one of the most widely studied.[1–5] Commercially available di-*tert*-butyl pyrocarbonate, $(Boc)_2O$, is an efficient reagent for *N*-Boc protection. There are a variety of *N*-Boc protection strategies available in the literature.[6,7] However, these methods have several drawbacks such as long reaction times, formation of side-products during base-catalyzed reaction,[6] excess reagents in the case of Lewis acid-catalyzed reactions,[8] and difficulty in the preparation of solid acid catalysts in some cases during solid acid-catalyzed reactions.

The challenge of designing a protocol for efficient Boc protection of amines, which is mild as well as environment-friendly and which has the advantages of solid catalysts, continues to draw attention. Though various catalysts have been employed for the preparation of *N*-Boc derivatives, reports of using a Brønsted acid catalyst are scanty in the literature.[9] A Brønsted acidic ionic liquid (IL) could be an ideal alternate system, which has all the characteristics of solid catalysts and a greener outlook at the same time.

In recent years, ILs have attracted significant attention as green solvents for many chemical and biochemical transformations.[10,11] 1-Methylimidazolium tetrafluoroborate, [(HMIm)BF_4], has been exploited as an efficient Brønsted acid IL in various organic transformations.[12–14] This IL is much simple to prepare without the use of organic solvents as compared to other imidazolium based ILs, which thus makes it an ideal IL for exploration. In the present work, we report a Brønsted acidic ionic liquid, [(HMIm)-BF_4], catalyzed synthetic protocol for the efficient and selective *tert*-butoxy carbonylation of amines. The protection protocol is conducted at room temperature under solvent-free conditions.

Various aromatic, heteroaromatic, aliphatic (cyclic and acyclic) and heterocyclic amines were treated with $(Boc)_2O$ (1:1 mol/mol) under solvent-free conditions at ambient temperature (~30–35 °C) in [(HMIm)BF_4] (10 mol %) and the results are summarized in Table 1. Nearly all the

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Table 1
[(HMIm)BF_4]-catalyzed Boc protection of various amines

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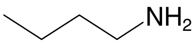
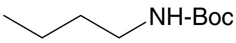
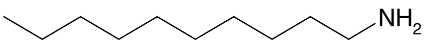
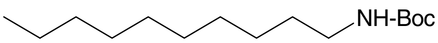
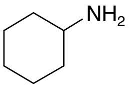
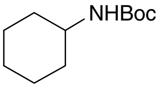
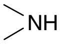
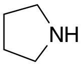
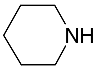
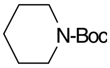
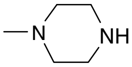
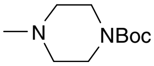
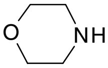
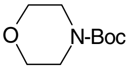
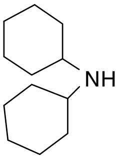
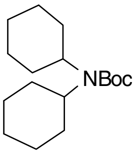
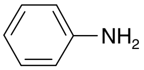
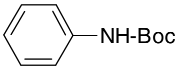
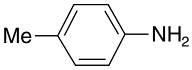
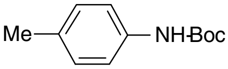
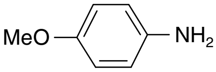
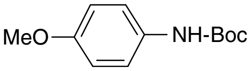
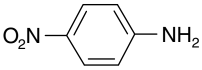
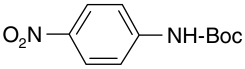
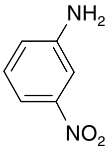
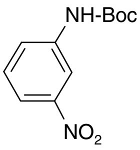
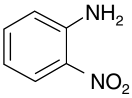
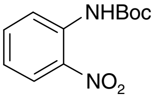
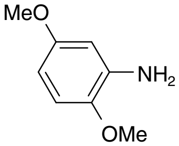
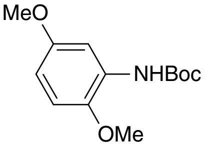
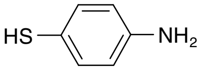
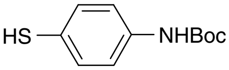
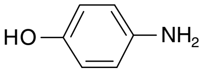
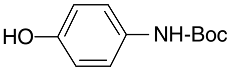
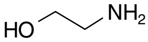
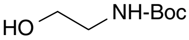
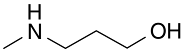
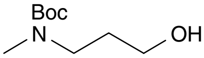
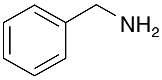
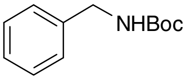
1			5	100
2			20	100
3			10	100
4			2	100
5			5	100
6			2	100
7			2	100
8			5	100
9			30	92
10			15	100
11			10	98
12			5	100
13			60	68
14			60	78
15			90	25

Table 1 (*continued*)

Entry	Substrate	Product	Time (min)	Isolated yield (%)
16			60	55
17			20	82
18			30	88
19			2	100
20			5	100
21			5	100
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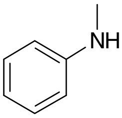
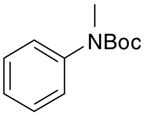
23			30	55
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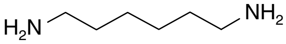
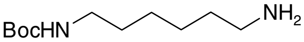
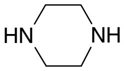
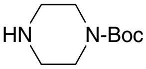
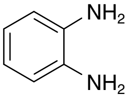
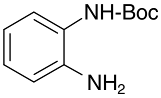
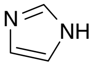
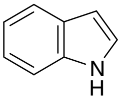
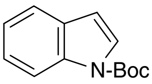
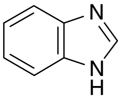
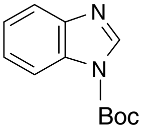
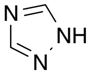
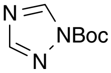
25			2	96
26			2	98
27			5	90
28			5	100
29			120	75
30			30	96
31			60	78

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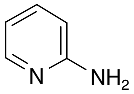
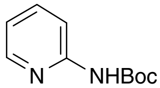
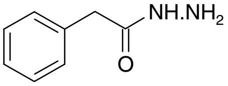
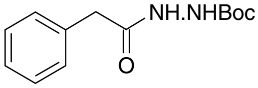
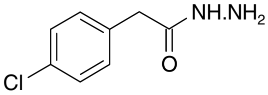
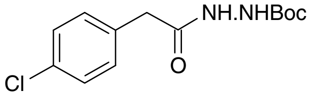
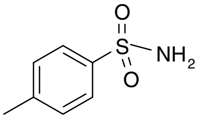
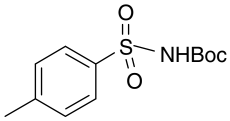
Table 1 (*continued*)

Entry	Substrate	Product	Time (min)	Isolated yield (%)
32			15	95
33			90	86
34			120	72
35			90	85

amines reacted efficiently affording the corresponding Boc protected amines in good to excellent yields in 2–120 min. In most cases, the products were obtained in quantitative conversion. All the products were characterized by using IR, NMR and mass spectroscopy and by elemental analysis.

Aliphatic (cyclic and acyclic) primary and secondary amines (Table 1; entries 1–9) gave the corresponding *N*-Boc products in 92–100% yields in 2–30 min. Aniline undergoes quantitative Boc protection at a much faster rate (15 min) in [(HMIm)BF_4] (Table 1; entry 10) compared to those methods using other Lewis acid/solid acid-catalyzed protection strategies.[6,7,9,15] *N*-Boc protection of indole (Table 1; entry 29) was moderate.[16] Moreover, the reported protection strategy yields mono-protected amines exclusively in 2–5 min when diamines were subjected to Boc protection (Table 1; entries 25–27). Even aromatic amines containing an electron-withdrawing group and a sulfonamide undergo *N*-Boc protection at a faster rate and in good yields compared to other catalysts reported in the literature.[6,7,9,15] From these results, it is evident that the studied IL, [(HMIm)BF_4], is a mild, highly efficient and a green catalyst for *N*-Boc protection of amines. The chemoselectivity of the IL was also assessed by performing *N*-Boc protection of amines in bifunctional compounds (Table 1; entries 17–20). Excellent chemoselectivity was observed for substrates with OH and SH functionalities providing *N*-Boc derivatives as the major products, and no significant *O*/*S*-*tert* butoxy carbonylation took place.

The results obtained highlight the influence of electronic environment on controlling the rate of the protection of the amine group.[7] This encouraged us to study the competitive *N*-Boc protection of an aromatic amines in the presence of an aliphatic amine and a primary aromatic amine in the presence of a secondary aromatic amine. The reaction of an equimolar amount of aniline, benzyl amine and $(Boc)_2O$ in [(HMIm)BF_4] afforded the corresponding *N*-Boc-benzyl amine in 90% conversion and *N*-Boc-aniline only in 10% conversion after 15 min according to GC. A competitive reaction was also conducted taking an equimolar amount of aniline, *N*-methyl aniline and $(Boc)_2O$ in [(HMIm)BF_4]. The GC results obtained after 40 min showed exclusive formation of *N*-Boc-aniline.

The IL-catalyzed *N*-Boc protection strategy was also studied for the protection of some selected chiral amino acid alcohols and esters and the results are summarized in Table 2. Chiral aminols and amino acid esters were converted efficiently to their corresponding optically active products as determined by optical rotation measurements and by comparison with literature values under similar conditions.[6,7,17]

The feasibility of any catalytic process depends on the reusability of the catalyst. In the present work, the reusability of [(HMIm)BF_4] was assessed by conducting *N*-*tert*-butoxy carbonylation of aniline over four successive cycles without any pre-treatment of the IL. The results shown in Table 3 indicate no significant loss of activity of the Brønsted acidic IL.

The Brønsted acidic promoting nature of [(HMIm)BF_4] is quite apparent from the IR and NMR study to understand the mechanistic aspects (See Supplementary data). In the IR spectrum of an equimolar mixture of [(HMIm)BF_4] and $(Boc)_2O$, the doublet frequency bands of the C=O stretching vibration of free $(Boc)_2O$ appearing at 1808 and 1761 cm^{-1} shifted to 1786 cm^{-1} on complexation with [(HMIm)BF_4]. This indicates that the β-diketone moiety of $(Boc)_2O$ disappeared in TS-1. Moreover, the appearance of a new band at 1326 cm^{-1} could be due to the C–O–H *in plane* bending vibrations of TS-1 (Scheme 1).

Table 2
[(HMIm)BF_4]-catalyzed Boc protection of amino acid derivatives

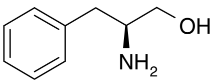
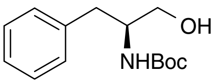
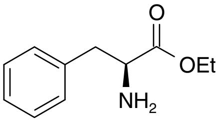
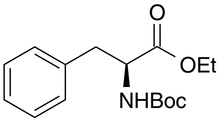
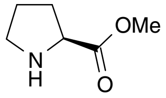
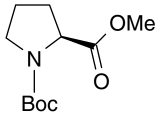
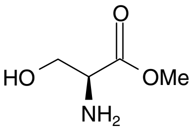
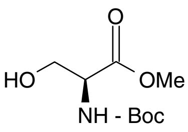
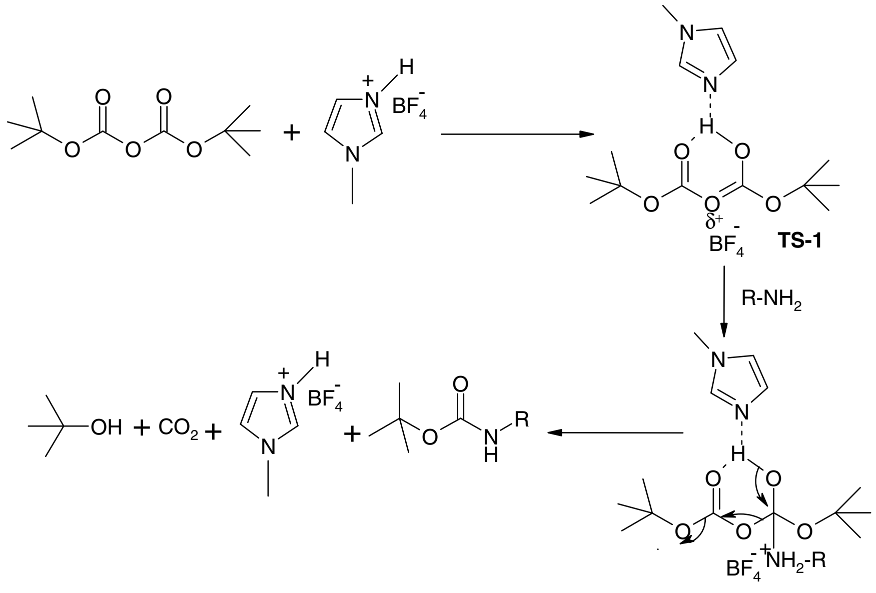
Entry	Amine	Product	Time (min)	Isolated yield (%)	$[\alpha]_D^{25}$
1			15	90	−26.5 (*c* 1, $CHCl_3$)
2			45	88	−4.4 (*c* 1, CH_3OH)
3			10	96	−54.7 (*c* 1, $CHCl_3$)
4			30	82	−17.4 (*c* 1, CH_3OH)

Table 3
Recycling of [(HMIm)BF_4] in the synthesis of *N*-Boc-aniline[a]

Cycle	Isolated yield (%)
1	98
2	98
3	95
4	90

[a] Reaction time: 15 min.

The proposed mechanistic pathway was further confirmed by recording the ^1H NMR spectrum of an equimolar mixture of [(HMIm)BF_4] and $(Boc)_2O$ in DMSO. The spectrum of the mixture showed a new broad peak at δ 3.9–4.2 indicating the presence of an OH functionality in TS-1 (confirmed by D_2O exchange). The NH peak of free [(HMIm)BF_4] appearing at δ 6.9–7.1 disappeared on complexation with $(Boc)_2O$ supporting TS-1 formation. Furthermore, three types of methyl protons of the *tert*-butyl group were observed: one peak at δ 1.55 being the same as in free $(Boc)_2O$ and the other two appearing at δ 1.08 and δ 1.58 are due to two different *tert*-butyl protons in TS-1. Thus, the mechanistic pathway involved the initial activation of the carbonyl oxygen atoms of $(Boc)_2O$ by [(HMIm)BF_4] followed by the nucleophilic attack at the carbonyl group by the amine in one-pot resulting in the



Scheme 1. Proposed mechanism for the [(HMIm)BF_4]-catalyzed *N*-Boc protection of amines.

formation of the *N*-Boc protected amine. This is accompanied by the generation of *tert*-butanol and carbon dioxide (Scheme 1).

In conclusion, we have described here the first example of a Brønsted acidic ionic liquid-catalyzed *N*-*tert*-butoxy carbonylation of amines. The reported protocol is efficient, inexpensive, chemoselective and the IL is reusable. The advantages of the present method are (i) the use of a green and easy to handle catalyst; (ii) the ease of preparation of [(HMIm)BF_4]; (iii) mild and solvent-free reaction conditions; (iv) the ease of extraction of the product/substrate from ionic liquid; (v) [(HMIm)BF_4] could be directly reused after drying without any significant loss of activity and (vii) excellent chemoselectivity.

The Brønsted acidic ionic liquid, 1-methylimidazolium tetrafluoroborate [(HMIm)BF_4], was prepared according to the reported procedure.[11]

General procedure for the Boc protection of amines: To a magnetically stirred mixture of $(Boc)_2O$ (1.5 mmol) and [(HMIm)BF_4] (0.015 mmol), amine (1.5 mmol) was added and the mixture was stirred at ambient temperature (~30–35 °C) for the specified period of time. The progress of the reaction was monitored by TLC and GC–MS. The mixture was diluted with Et_2O and the IL settled at the bottom. The supernatant was decanted off and the IL was washed with Et_2O (2 mL) and the combined ethereal solution concentrated under vacuum. In some cases, the Boc protected product was found to be sufficiently pure (GC–MS and NMR) and did not require any further purification. In most cases, the product was purified by silica gel column chromatography (5–15% EtOAc in hexane). The ionic liquid was recovered, dried under vacuum for 10 min at 80 °C and reused.

All products were characterized by IR, NMR, mass spectrometry and elemental analysis and by comparison with those reported in the literature.[6,7,15,16,18]

Supplementary data

Spectra based on IR and NMR of an equimolar mixture of [(HMIm)BF_4] and $(Boc)_2O$ for establishing the mechanistic pathway of the [(HMIm)BF_4]-catalyzed Boc protection of amines are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.126.

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