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Short Communication

Sulfonic acid-functionalized ordered nanoporous Na^+-montmorillonite (SANM): A novel, efficient and recyclable catalyst for the chemoselective *N*-Boc protection of amines in solventless media

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ABSTRACT

Sulfonic acid-functionalized ordered nanoporous Na^+-montmorillonite (SANM) was used as an efficient catalyst for *N*-*tert*-butoxycarbonylation of amines with di-*tert*-butyl dicarbonate under solvent-free conditions at room temperature. Various aliphatic, aromatic, heterocyclic amines and aminols were protected as their corresponding mono-carbamates in excellent yields and short reaction times. No competitive side reactions such as isocyanate, urea, and *N*,*N*-di-Boc formation were observed. The reported method is mild, chemoselective and has the advantages such as heterogeneous catalysis, low cost and the recyclability of the catalyst.

1. Introduction

Protection and deprotection of organic functional groups play an essential role in the multistep organic synthesis [1,2]. The presence of an amino group in various biologically active compounds makes its protection a necessity during their synthesis. The *tert*-butoxycarbonyl (Boc) group is one of the most useful functionalities for the protection of amines and amine derivatives, owing to its stability towards nucleophiles in strong basic conditions and because of its easy removal [1,2].

Various reagents and procedures have been employed over the years to introduce this group using Boc_2O, and the examples of them are nucleophilic basic catalysts such as DMAP [3,4], NH_2OH [5] or K_2CO_3[1] and, Lewis acid catalysts like iodine [6], yttria–zirconia [7], $ZrCl_4$[8], $Zn(ClO_4)_2 \cdot 6H_2O$ [9], $LiClO_4$[10], montmorillonite K10 or KSF [11] and $La(NO_3)_3$[12]. These procedures, although effective, have various drawbacks such as requirement of long reaction times, use of solvent, potential hazards (e.g., perchlorates are strong oxidizers and explosive in nature [13,14] and $ZrCl_4$ is highly moisture sensitive, decomposes on storing and liberates corrosive HCl fumes), difficulty in preparation of catalyst (e.g., preparation of yttria–zirconia involves use of sulfuric acid at 500 °C) and formation of side-products such as isocyanates [15,16], poly-acylated products [17], urea [18] and *N*,*N*-di-Boc derivatives [18,19].

In recent years, there has been considerable growth of interest in the catalysis of organic reactions by solid acid catalysts. Solid catalysts provide numerous opportunities for recovering and recycling catalysts from reaction environments. These features can lead to improved processing steps, better process economics, and environmentally friendly industrial manufacturing. Silica materials with ordered structure are the best candidate to be used as solid acid catalysts. Clays and zeolites as silica nanostructure materials have been widely used in organic transformations as solid acid catalysts, because they have many advantages such as ease of handling, non-corrosiveness, low cost and ease of regeneration. One of the best-known examples of zeolites is MCM-41, which is a structurally well-ordered mesoporous material with a narrow pore size distribution between 1.5 and 10 nm, depending on the surfactant cation and a very high surface area up to 1500 $m^2 g^{-1}$. It has been proven that Si-MCM-41 lacks Brönsted acid sites and exhibits only weak hydrogen-bonded type sites. An additional possibility to develop acidic solids is the modification of the surface of suitable support materials, as the chemical functionalities of these materials can be uniformly modified by covalent anchoring of different organic moieties [20]. Also owing to their Brönsted and Lewis acidities, clays, both in their natural and ion exchanged forms are used as efficient catalysts for various organic transformations. However traditional heterogeneous catalysts are rather limited in the nature of their active sites and thus the scope of reactions that they can accomplish [21], for example montmorillonite K-10 only have H^+ sites in its galleries and reactants must be entered into galleries for the reaction [22] and other clays should change their gallery's cations with active cations, that required hard procedure for preparation and long time [23]. These require the simple surface

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modification of these solids to increase their active sites for better interaction with reactants.

2. Experimental

2.1. Materials

Chemicals were purchased from Southern Clay Products, Fluka, Merck, and Aldrich chemical companies. All yields refer to the isolated products. Products were characterized by their physical constants and comparison with authentic samples. The purity determination of the substrate and reaction monitoring were accompanied by TLC on silica-gel polygram SILG/UV 254 plates.

2.2. Instrumention

Thermogravimetric analyses (TGA) were conducted by using a TGA PYRIS 1 thermoanalyzer instrument. Samples were heated from 25 to 600 °C at ramp 10 °C/min under N_2 atmosphere. Wide-angle X-ray diffraction (XRD) measurements were performed at room temperature on a Siemens D-500 X-ray diffractometer (Germany), using Ni-filtered Co-Kα radiation ($\lambda = 0.15418$ nm). Elemental analyses of the samples were performed on Elemental Vario EL III instrument. The IR (KBr) spectra were recorded on Shimadzu Corporation 200-91-527 instrument. The pristine clay and its sulfonated derivative dried at 100 °C in oven before recording the spectrum. N_2 physisorption at liquid nitrogen temperature using a SHIBATA APP.SA-1100 surface area analyzer and standard multipoint BET analysis methods were carried out. Samples were degassed in flowing N_2 for 2 h at 250 °C before N_2 physisorption measurements were obtained.

2.3. Catalyst preparation

A 500 mL suction flask charged with 2.5 g Na^+-montmorillonite (Southern Clay Products) and 10 mL $CHCl_3$, was equipped with a constant pressure dropping funnel containing chlorosulfonic acid (0.50 g, 9 mmol) and a gas inlet tube for conducting HCl gas into water as adsorbing solution. Chlorosulfonic acid was added drop wise over a period of 30 min while the reaction mixture was stirred slowly in an ice bath (0 °C). After addition was completed, the mixture was stirred for additional 30 min to remove all HCl. Then, the mixture was filtered and the solid residue washed with methanol (20 mL) and dried at room temperature to obtain SANM as white powder (2.58 g).

2.4. Catalyst characterizations

2.4.1. Thermal analysis

Thermogravimetric analysis (TGA) was performed for characterization of SANM in comparison with sodium montmorillonite. Fig. 1 provides the TGA curve of pristine clay (Na^+–MMT) and catalyst. The TGA curve of Na^+–MMT displays a weight loss below 100 °C which is corresponding to the loss of the physically adsorbed water, also there is a slight weight loss (ca. 8 wt.%) in the range of 100–600 °C, possibly corresponding to dehydroxylation of montmorillonite.

For SANM there is a small mass loss (ca. 1 wt.%) in the range of 25–240 °C, attributed to the loss of the bonded H_2O within the gallery similar to Na^+–MMT. However a greater mass loss which started from 240 °C can be attributed to the decomposition of $-SO_3H$ group anchored to the clay surface. These show that Na^+–MMT–SO_3H has a greater thermal stability (until 240 °C) than Na^+–MMT [24].

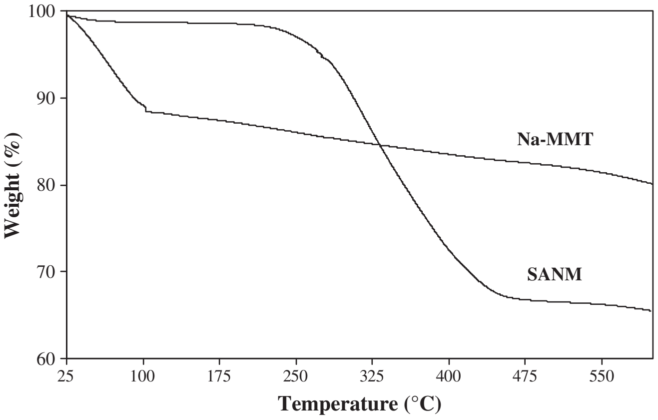


Fig. 1. TGA curves of Na^+–MMT and SANM.

2.4.2. Powder X-ray diffraction

In the reaction between sodium montmorillonite and chlorosulfonic acid, the expansion of the montmorillonite layers was demonstrated by X-ray diffraction. The XRD patterns of the montmorillonite before and after sulfonation are shown in Fig. 2. It should be noted that sodium montmorillonite and sulfonated sodium montmorillonite were dried at 100 °C before analyses. The basal spacing for the Na^+–MMT is 9.8°A with $2\theta = 9°$. As shown by the XRD patterns, the basal spacing of the sulfonic anchored sodium montmorillonite is obviously bigger than that of Na^+–MMT (12.9°A), indicating that the sulfonic acid moiety has been intercalated into montmorillonite interlayer spaces. This increase in the basal spacing can lead to the better interaction between the reactants in the acid catalysis reactions, comparing to the montmorillonites K-10 and KSF [22].

2.4.3. IR analysis

The infrared spectra of Na^+–MMT and Na–MMT–SO_3H are presented in Fig. 3. In the case of Na^+–MMT, the peak at 3623 cm^{-1} attributed to the OH units bonded to the aluminum and/or magnesium in Na^+–MMT. The peaks at ca. 3433 and 1640 cm^{-1} correspond to the $-OH$ stretching vibration of the adsorbed water and the bands at 1040 and 914 cm^{-1} can be collectively attributed to Si–O stretching vibrations [25].

The spectrum of sulfonated clay displays almost the same pattern as that of pristine clay, but the intensity of free $-OH$ peak at 3623 cm^{-1} is reduced in modified clay, that it is due to free —OH sulfonation. Also the band between 900 and 1300 cm^{-1} that centered in 1040 cm^{-1} is flattened in sulfonated clay which can be attributed to the integration of the additional S–O bands with Si–O stretching bonds.

2.4.4. Elemental analysis

Because the pristine clay (sodium montmorillonite) doesn't have any sulfur content, the elemental analysis was used for the determination of the amount of sulfur content of SANM. The results

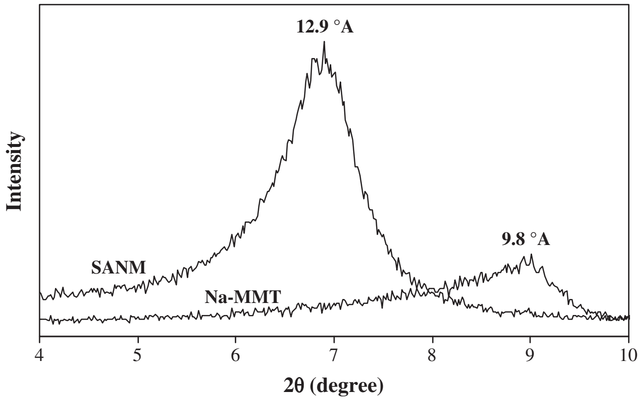


Fig. 2. XRD patterns of Na^+–MMT and SANM.

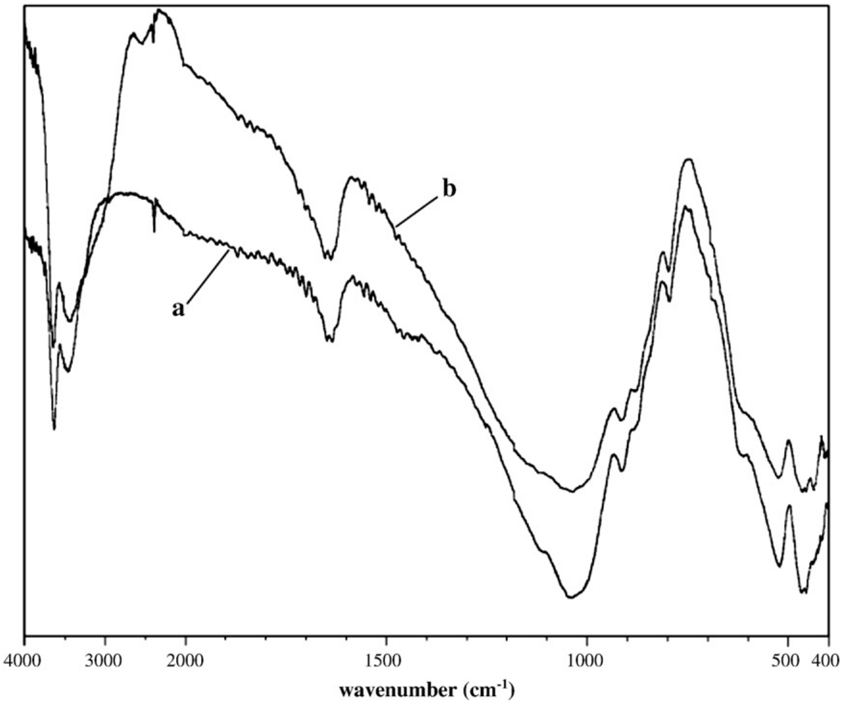
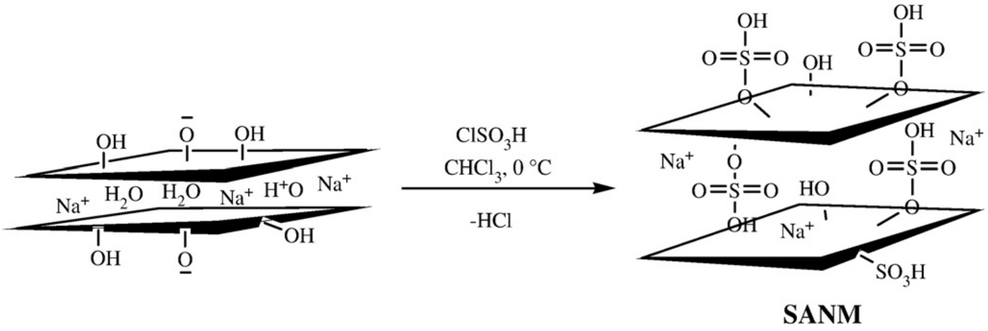


Fig. 3. IR spectra of Na^+–MMT (a) and sulfonated Na^+–MMT (b).



Scheme 1. Preparation of SANM.

obtained showed that 1 mg of sulfonated sodium montmorillonite consists 0.32% of sulfur. On the basis of the sulfur moiety it can be concluded that the amount of H^+ sites is 0.42 mol g^{-1} of SANM.

2.4.5. Surface area and pore distribution measurements

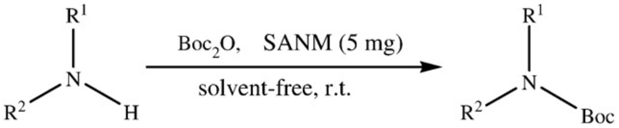
N_2 adsorption measurements, which have been a powerful tool for nano- or mesoporous material characterization, were performed to obtain more insights into the modified porous nano-silica materials. The textural properties of Na-montmorillonite were substantially maintained over sulfonic acid functionalization. A slight decrease in surface area was observed for Na-montmorillonite and SANM from 53 to 40 m^2/g, respectively. This suggests that sulfonic acid may be well confined in the pores of the mesoporous clay, Na-montmorillonite, and indicates an ordered mesoporosity of the support even after the intercalation of sulfonic acid moieties [26].

2.5. General procedure for synthesis of N-tert-butylcarbamates

An amine (1 mmol) was added to a magnetically stirred mixture of SANM (5 mg) and di-*tert*-butyl dicarbonate (0.24 g, 1.1 mmol) at room temperature. The mixture was stirred until completion of reaction (TLC or GC), then diluted with EtOAc (10 mL) and filtered. The residue contained only the catalyst and was kept for recovery. The filtrate was washed with water (3 × 20 mL) and brine (2 × 20 mL) and dried over anhydrous $MgSO_4$, then solvent was distilled off under vacuum to yield the highly pure *N*-Boc derivative. ^1H NMR, ^{13}C NMR and IR spectra were consistent with the assigned structures and by comparison with those reported in the literature [6–12].

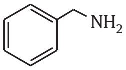
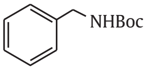
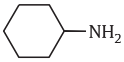
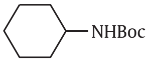
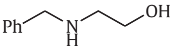
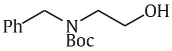
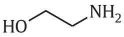
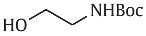
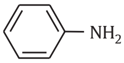
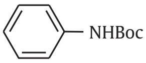
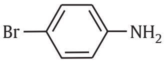
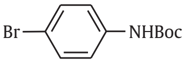
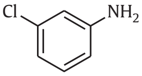
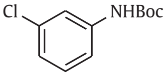
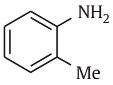
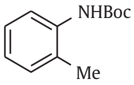
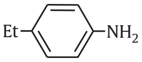
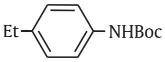
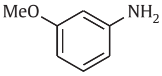
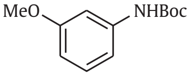
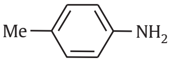
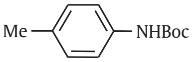
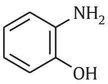
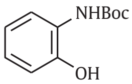
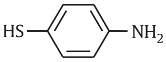
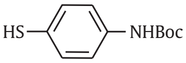
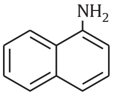
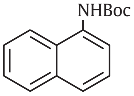
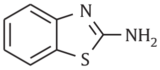
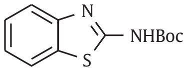
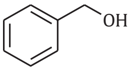
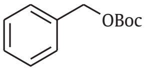
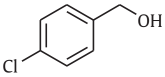
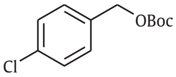
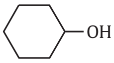
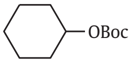
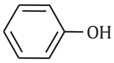
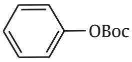
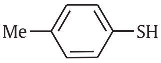
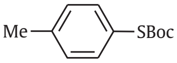
3. Results and discussion

Protection of amines with di-*tert*-butyl dicarbonate under base-catalyzed condensation leads to the formation of *N*-*tert*-Boc protected amines, CO_2 and *t*-BuO^-. The liberated *t*-BuO^-undergoes proton exchange with the *N*-*tert*-Boc products to form isocyanates, which can further react with the starting amine to form urea derivatives. In the



Scheme 2. *N*-Boc protection of amines.

Table 1
Boc protection of amines in the presence of SANM under solvent-free conditions.[a]

Entry	Substrate	Product	Time (min)	Conv. (%)	Yield[a] (%)
1			1	100	96
2			1	100	91
3			5	100	93
4			1	100	88
5			5	100	95
6			20	100	95
7			63	100	94
8			15	100	97
9			7	100	90
10			22	100	96
11			20	100	94
12			180	100	95
13			3 h	100	94
14			8.1 h	100	97[b]
15			10	100	98
16			6 h	0	Nr[c]
17			6 h	0	Nr[c]
18			6 h	0	Nr[c]
19			6 h	0	Nr[c]
20			6 h	0	Nr[c]

Products were characterized by their physical constants, comparison with authentic samples and IR and NMR spectroscopy.

[a] Isolated yield.

[b] 1 mL of CH_3CN is added to reaction mixture.

[c] The starting material remained unchanged.

parallel pathway, in the presence of *t*-BuO$^-$, *N*-*tert*-Boc protected amines react with $(Boc)_2O$ to form *N*,*N*-di-Boc derivatives [11]. These side reactions may be eliminated if the *in situ* generation of *t*-BuO$^-$ can be avoided. In some examples of Lewis acid-catalyzed reactions [7–10], the side products such as isocyanates, *N*,*N*-di-Boc and urea derivatives were not formed. These observations are attributed to the coordination of the catalyst with the carbonyl groups of $(Boc)_2O$ which activates them for the nucleophilic attack of amine producing the desired products and *t*-BuOH instead of *t*-BuO$^-$. Hence, electrophilic strategy provided a better method for *N*-*tert*-butoxycarbonylation of amines.

Recently, preparation of new catalysts for the organic reactions, by modification of the hydroxyl groups of various hetero and homogenous compounds by sulfonic moiety, became an important part of our research program [27–30].

In continuation of these studies, herein, we wish to report the preparation of sulfonic acid-functionalized ordered nanoporous Na^+-montmorillonite (SANM) and its application, as a new, efficient and recyclable catalyst, in the Boc protection of amines (Schemes 1 and 2).

SANM can be easily prepared by the drop wise addition of chlorosulfonic acid to a mixture of Na–MMT in $CHCl_3$ at 0 °C. It is important to note that, this reaction is easy and clean without any extra work-up procedure due to immediate emission of HCl gas from the reaction vessel. This white heterogeneous, nonhygroscopic solid acid is very stable under reaction conditions.

In order to optimize the reaction conditions, we conducted the *N*-Boc protection of benzyl amine (1 mmol) with Boc_2O (1.1 mmol) in the presence of SANM (10 mg) with stirring at ambient temperature without solvent, which is completed immediately. Reduction of the amount of SANM to 5 mg/mmol of amine did not affect the result of the reaction. To illustrate the efficiency of SANM in these reactions, protection of benzyl amine, was also carried out in the presence of Na^+ montmorillonite. The reaction was not completed after 1 h. Obviously, the sulfonation of Na–MMT is important for the reaction.

After optimization of the reaction condition various aliphatic, aromatic and heterocyclic amines and aminols were subjected to *N*-Boc protection with $(Boc)_2O$ under the selected conditions. The results are summarized in Table 1.

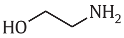
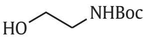
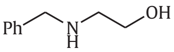
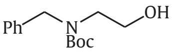
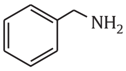
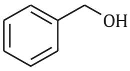
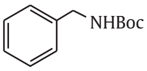
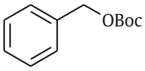
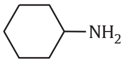
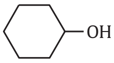
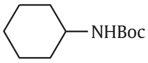
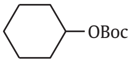
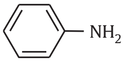
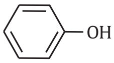
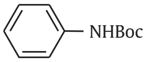
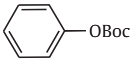
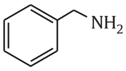
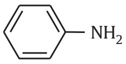
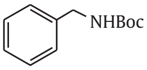
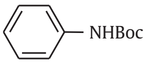
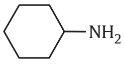
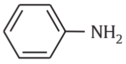
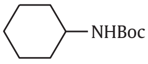
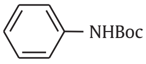
Aliphatic amines (Table 1; entries 1 and 4) gave the corresponding *N*-Boc products in 88–96% yields in 1–5 min. Aromatic amines having various substituents such as Br, Cl, Me, Et, OMe, OH and SH groups were converted to their *N*-*tert*-Boc derivatives efficiently (entries 5–13). Amino groups attached to naphtalene (entry 14) and aromatic heterocycle (entry 15) afforded the desired products in quantitative yields. No isocyanate or urea formation was observed at all (IR). Under the selected conditions *N*-Boc protection of alcohols, phenols and thiols was not successful and the starting material was recovered unchanged after 6 h (Table 1, entries 16–20).

The selectivity of a method determines the importance of its application in organic reactions. Therefore, the chemoselectivity of this method was also investigated and the results are reported in Table 2.

After performing one reaction under the conditions described in Table 1, the catalyst was recovered by filtration, washed with acetone (10 mL), and dried at 100 °C then reused for a consecutive run under the same reaction conditions. Thus, after the first run, which gave the corresponding carbamate from benzyl amine in 100% conversion, and after recovery, the catalyst was subjected to a second Boc protection reaction from which it also gave the benzyl carbamate in 100% conversion; the average time for 25 consecutive runs was 1.88 min and 100% conversion for all, which clearly demonstrates the practical recyclability of this catalyst (Fig. 4). This reusability demonstrates the high stability and turnover of solid silica based sulfonic acid (SANM) under the conditions employed. It should be noted that, the recyclability test was stopped after 25 runs.

The possible mechanism for the *N*-Boc protection of various amines in the presence of SANM as a promoter is shown in Scheme 3. On the basis of this mechanism, SANM catalyzes the reaction by the electrophilic activation of $(Boc)_2O$ to form a zwitterionic species, making the carbonyl group susceptible to nucleophilic attack by the amine. Successive elimination of CO_2 and *tert*-BuOH results in the formation of *N*-Boc derivatives and regenerates SANM in the reaction mixture [31].

Table 2
Chemoselective *N*-Boc protection.

Entry	Substrate (s)	Product (GC yield)	Time (min)
1		 100	1
2		 100	5
3	 + 	 +  100 0	1
4	 + 	 +  100 0	1
5	 + 	 +  100 0	18
6	 + 	 +  100 0	1
7	 + 	 +  100 0	2

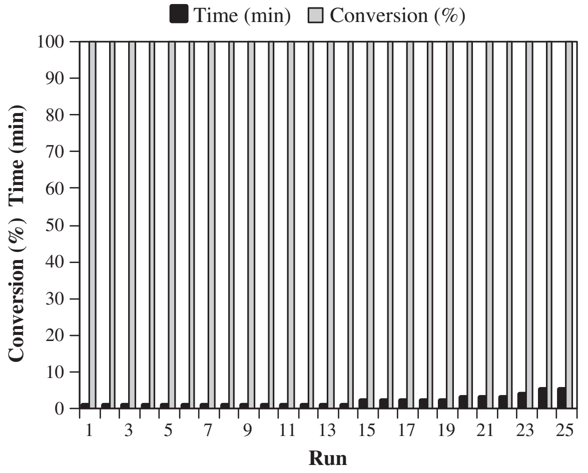


Fig. 4. Recyclability of SANM for the *N*-Boc protection of benzyl amine.

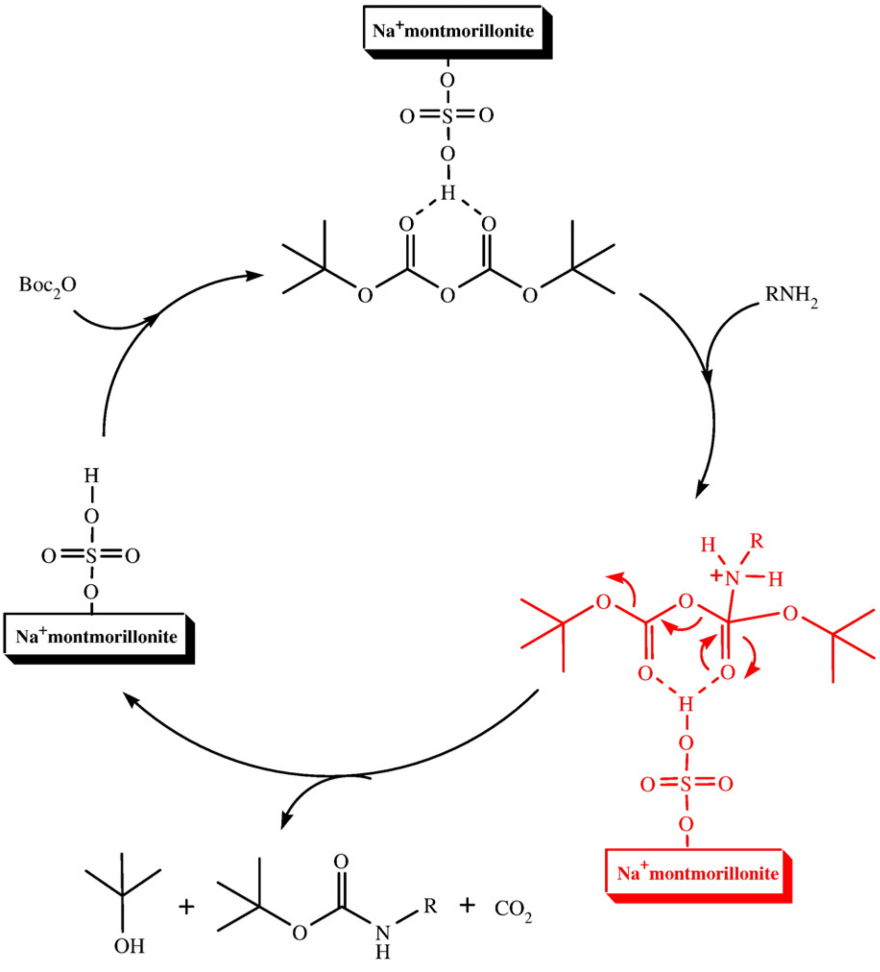
Table 3
Compared performance of various catalysts in the *N*-Boc protection of aniline.

Entry	Catalyst	Catalyst load	Time (min)	Solvent	Yield (%)
1	SANM [this work]	5 mg	5	Neat	96
2	Yttria–zirconia [7]	18.6 g	14 h	CH_3CN	90
3	$Zn(ClO_4)_2.6H_2O$ [9]	28 mg	12 h	CH_2Cl_2	92
4	[TMG][Ac] [31]	18 mg	5	Neat	98
5	Sulfonic acid functionalized silica [32]	20 mg	45	CH_2Cl_2	83
6	Iodine [33]	10 mol%	30	Neat	95
7	$Yb(OTf)_3$[33]	10 mol%	30	Neat	89
8	$FeCl_3$[33]	10 mol%	30	H_2O	95
9	Uncatalyzed [33]	–	48 h	Neat	60
10	Silica gel [33]	50 mg	18 h	Neat	69
11	$H_3PW_{12}O_{40}$[34]	15 mg	8	CH_2Cl_2	85
12	Thioglycoluril [35]	10 mol%	8	EtOH	95
13	Thiourea [36]	7.6 mg	40	Toluene	95
14	Sulfamic acid [37]	5 mol%	5	H_2O	99
15	Sulfamic acid [37]	5 mol%	5	Neat	98
16	$HClO_4$–SiO_2[38]	50 mg	5	Neat	100

To illustrate the efficiency of the present method, Table 3 compares our result in *N*-Boc protection of aniline with the same result reported by the relevant reagents in the literature.

4. Conclusion

In conclusion, we have developed a simple, efficient and chemoselective protocol for the *N*-*tert*-butoxycarbonylation of various amines using SANM as a novel heterogeneous catalyst. The protocol is highly chemoselective offering potential in different applications. The methodology also has several other advantages such as: (i) high reaction rates and excellent yields (ii) no side reactions (iii) ease of preparation and handling of the catalyst (iv) cost efficiency and effective reusability of the catalyst (v) use of inexpensive catalyst with lower loading; and (vi) simple experimental procedure and solvent-free conditions. Further work to explore this novel catalyst in other organic transformations is in progress.



Scheme 3. Proposed mechanism.

Acknowledgment

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