

# Nano- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>: Efficient, Reusable and Green Catalyst for *N*-*tert*-Butoxycarbonylation of Amines in Water

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## Abstract

An efficient and versatile practical protocol for the chemoselective *N*-*tert*-butoxycarbonylation of amines using Nano- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> and (BOC)<sub>2</sub>O. Nano- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> was applied as an efficient, green, heterogeneous and reusable catalyst at ambient temperature; the method is general for the preparation of *N*-Boc derivatives of aliphatic, heterocyclic, aromatic as well as amino acid derivatives.

## Keywords

Nano- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>, *N*-Boc Protection, Amine, Heterogeneous Catalyst, Water

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## 1. Introduction

The protection and deportation of amines have become a very important and widely used method for many multi-step organic syntheses. Among the various groups reported for the protection of amines, the use of *N*-*tert*-butoxycarbonyl (*N*-Boc) group has become very popular [1]-[3]. Different groups are available for *N*-*tert*-butylcarbamate such as (Boc)<sub>2</sub>O, BocONH<sub>2</sub>, BocN<sub>3</sub> and 1-(*tert*-butoxycarbonyl) benzotriazole [4]-[8].

*N*-*tert*-Butoxycarbonylation of amines has received considerable attention in synthesis due to the stability of the *N*-*tert*-butoxycarbonyl group toward basic and nucleophilic attack and its labile nature in the presence of acid, commercial availability, low cost and efficiency. Various reagents and methods have been developed in the past years for the *N*-*tert*-butyloxycarbonylation of amines.

The conventional procedure employs di-*tert*-butyldicarbonate (Boc)<sub>2</sub>O and base catalysts such as 4-(*N*,

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*N*-dimethylamino) pyridine DMAP, [9] [10], NaHMDS, [11], K<sub>2</sub>CO<sub>3</sub>, [12] and Et<sub>3</sub>N, [13], the last one being most commonly used.

Further, modified methods have been reported with amines and (Boc)<sub>2</sub>O in the presence of Lewis acids. Many of these procedures involve the use of corrosive and moisture-sensitive reagents like ZrCl<sub>4</sub>, [14], LiClO<sub>4</sub>, [15], Cu(BF<sub>4</sub>)<sub>2</sub>, HClO<sub>4</sub>, [16] and La(NO<sub>3</sub>)<sub>3</sub> [17].

In recent years, several new and efficient methods have been developed including the use of Montmorillonite K10, [18], thiourea [19], HFIP, sulfamic acid, Amberlyst 15.

However, most of these methods still have several drawbacks, such as the air-sensitive nature of the catalysts unpleasant smell, high toxicity, corrosiveness, and non-recyclability of these catalysts make the method objectionable, especially from the point of view of green chemistry.

Recently several methods for *N*-protection of amino groups have been reported with the “green chemistry” concept. Water and ionic liquids were used as solvents.

## 2. Results and Discussion

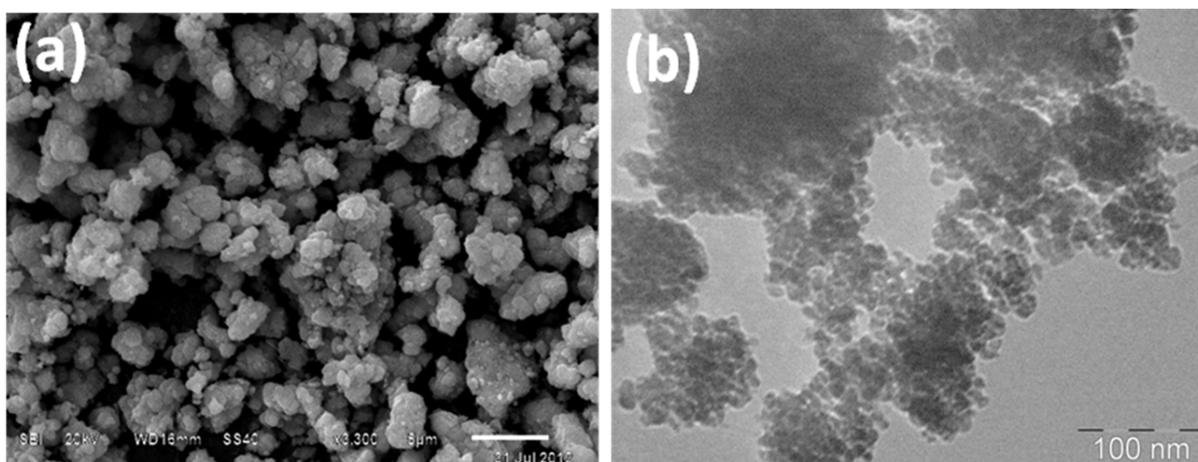
In our continuous research for green and eco friendly chemical methods, water is the key solvent, and there is increasing interest in using it as green solvent for organic conversions. However, reports about using water as a catalyst to promote organic reactions are very limited. Compared to conventional solvents water is preferred for organic reaction. Because of cheap, nontoxic, no explosive, and environmentally acceptable [20]. Thus, the use of water instead of organic solvents has gained much importance in the development of sustainable protection in generally chemistry.

In this paper, we report efficient and eco-friendly protocol for chemoselective *N*-*tert*-butyloxycarbonylation of various structurally amines in water-related system under room temperature conditions in the absence of any acid/base-catalyst.

Nano- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> particles are considered to be attractive as catalysts for their greater reactivity, due to high surface area, recovered easily from the reaction mixture and reusable for further reaction, therefore the method being more Efficient [21].

The morphology and size of the Nano- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> particles were analyzed by X-ray diffraction (XRD), scanning electron microscopy (SEM) and transmission electron microscopy (TEM) as shown in **Figure 1** and **Figure 2**. The average grain size of zinc oxide nano particles was calculated using the Scherrer formula and was found to be about 15 nm indicating nano crystalline nature. No other metal phases were detected by XRD (**Figure 2**). The low magnification SEM and TEM images (**Figure 1(a)** and **Figure 1(b)**) shows small nano sized grains having spherical and hexagonal morphology nano particles. The presence of some larger particles attributes aggregating or overlapping of smaller particles.

In continuation of our search in organic synthesis by different methods with the use of nano catalyst, we report an easy and efficient method for the *N*-*tert*-butoxycarbonyl of various amines using Fe<sub>2</sub>O<sub>3</sub> nanoparticle in water media (**Scheme 1**).



**Figure 1.** (a) SEM; (b) TEM images of Nano-Fe<sub>2</sub>O<sub>3</sub> particles.

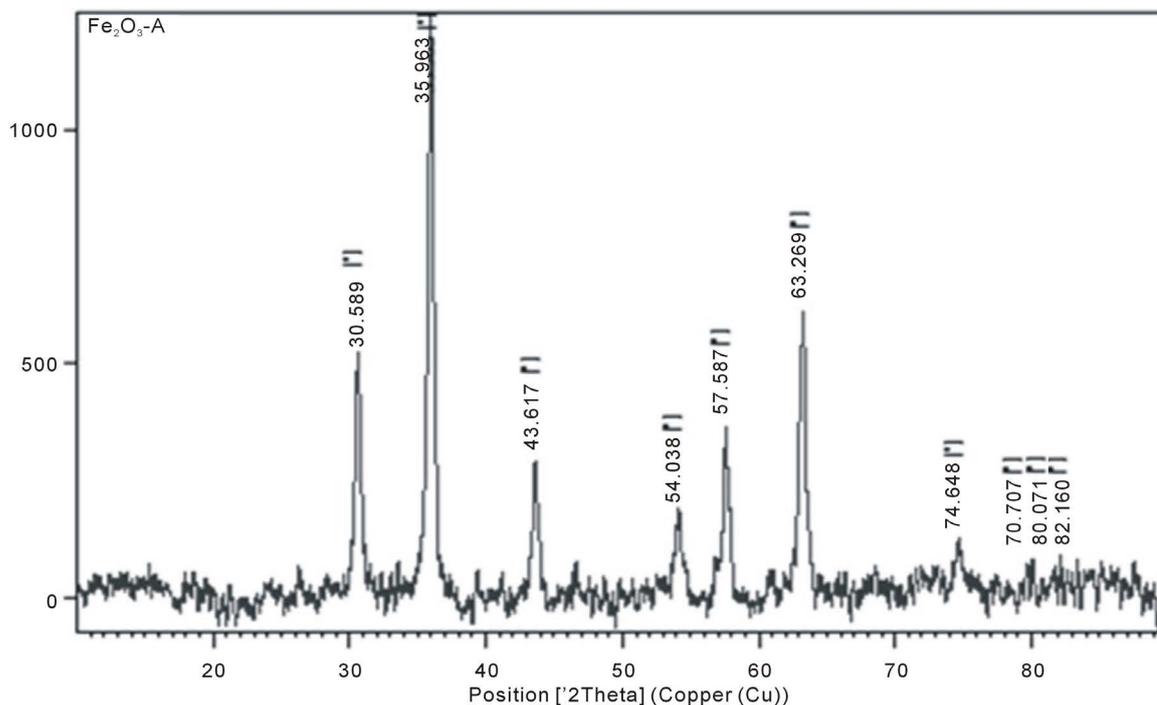
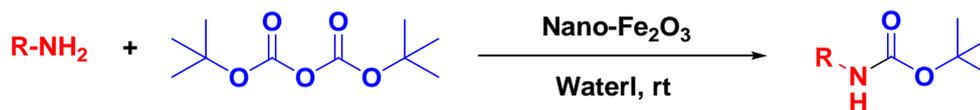


Figure 2. XRD Pattern for Nano-Fe<sub>2</sub>O<sub>3</sub> particles.



Scheme 1. Fe<sub>2</sub>O<sub>3</sub> Mediated *N-tert* butoxycarbonylation.

To the best of our knowledge, the use of Nano- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> for the *N-tert*-butoxycarbonylation of amine in water has not been reported.

In our initial study (Scheme 1), aniline was reacted with di-*tert*-butyldicarbonate in the presence of Nano- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> in water at room temperature for 60 mins when the expected product was obtained in 95%. (Table 1, entry 1), While the same reaction was performed in presence of Nano- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> without solvent at room temperature afforded the *N-tert*-butoxycarbonylated compound in low yield with starting aniline remaining unreacted.

In presence of electron withdrawing or donating substituents on different aromatic amines the reactions proceeded efficiently to provide the desired products in good yields (Table 1, entries 2 - 7) Also, the method provides chemoselective process for the substrates with OH or SH group (Table 1, entries 10 and 11) giving *N*-Boc derivatives with good yields.

The diamine gave selective *N*-Boc protected compound with 1.0 equivalent of (Boc)<sub>2</sub>O in the presence another amino group, however, with 2.0 equivalent of (Boc)<sub>2</sub>O both the amino group were reacted giving excellent yield of the product (Table 1, entries 8 and 9).

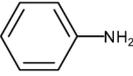
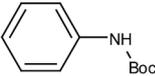
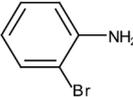
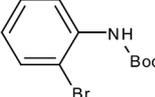
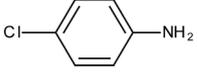
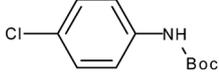
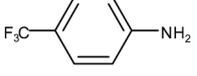
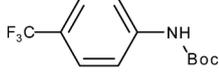
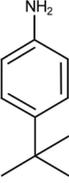
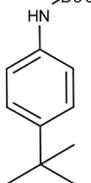
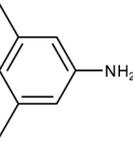
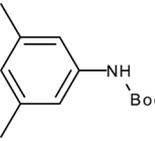
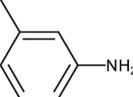
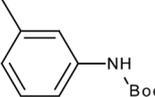
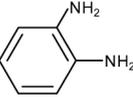
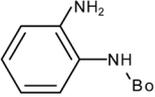
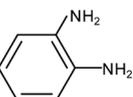
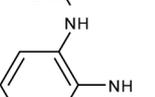
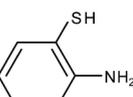
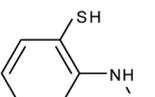
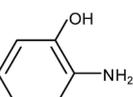
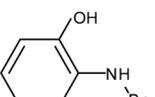
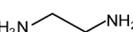
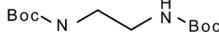
In all cases, the expected *N*-Boc protected amines were obtained in excellent yield as summarized in Table 1 The *N*-Boc protected amines were fully characterized by recording their <sup>1</sup>H, <sup>13</sup>C NMR, IR spectroscopy and elemental analysis.

From these studies, Nano- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> has been proved as efficient reusable catalyst for *N-tert*-butoxycarbonylation of amines in water.

### 3. Experimental Section

General procedure for *N-tert*-butoxycarbonylation of amines:—To a stirred solution of amine (2 mmol) and (Boc)<sub>2</sub>O (2.1 mmol) in water was added Nano- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> (10 mol%) catalyst. The reaction mixture was stirred at

**Table 1.** *N*-*tert*-butoxycarbonylation of aromatic and aliphatic amines in presence of Nano- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> (Scheme 1).

Entry	Amines	Product	Yield (%)	Time (min)
1			95	60
2			92	70
3			90	90
4			78	120
5			89	90
6			91	60
7			93	60
8			80	30
9			92	120
10			91	80
11			93	60
12			88	120

Continued

13			90	90
14			94	120
15			93	120
16			96	180
17			92	80
18			86	90
19			93	90

room temperature (30°C - 35°C). On completion (indicated by thin layer chromatography), the reaction was filtered through a sintered funnel and washed thoroughly with water. The combined filtrate was extracted with ethyl acetate dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, then concentrated the solvent under reduced pressure to get the crude product. The pure products were obtained by column chromatography using Ethyl acetate and hexane as an eluents.

All commercial chemicals and solvents were without further purification. All reactions were carried out under inert argon atmosphere. Melting points were determined on a capillary melting point apparatus and are uncorrected. The <sup>1</sup>H NMR was recorded in the indicated solvent on a Varian 300 MHz spectrometer with TMS as internal standard. All chemical shifts (δ) were reported in ppm from internal TMS. Mass spectra were measured on a Jeol JMS D-300 spectrometer. Infrared spectra were recorded in KBr on Bruker-IFS-66 FTIR spectrophotometer. The homogeneity of the compounds was checked using precoated TLC plates (E.Merk Kieselgel 60 F<sub>254</sub>).

#### 4. Conclusions

In summary, we have developed a green, inexpensive and efficient method for water-mediated *N*-*tert*-butoxycarbonylation of amines at room temperature using Nano-Fe<sub>2</sub>O<sub>3</sub>. The absence of acid/base and the use of water make this procedure environmentally friendly.

**Tert-butyl phenylcarbamate (01):** <sup>1</sup>H NMR (300 MHz, DMSO d<sub>6</sub>) δ = 1.50 (s, 9H), 7.68 - 7.37 (m, 5H), 8.30 (brs, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 28.07, 80.7, 121.6, 124.4, 129.0, 134.07, 154.12.

**Tert-butyl 2-bromophenylcarbamate (02):** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.45 (s, 9H), 7.61 (m, 2H), 7.12 (d, 1H), 7.35 (s, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 28.07, 80.7, 112.18, 119.19, 123.62, 128.06, 132.01, 136.08, 146.57, 152.12, IR (KBr): 3415, 2979, 1735, 1517, 1433, 1158, 1119, 749.

**Tert-butyl 4-chlorophenylcarbamate (03):** <sup>1</sup>H NMR (300 MHz, DMSO d<sub>6</sub>): δ = 1.48 (s, 9H), 7.36 (d, 2H J = 8.2 Hz), 7.71 (d, 2H J = 8.2 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): d = 28.34, 80.19, 121.40, 128.66, 130.64, 136.69, 153.91.

**Tert-butyl 4-(trifluoromethyl)phenylcarbamate (04):** <sup>1</sup>H NMR (300 MHz, DMSO d<sub>6</sub>): δ = 1.47 (s, 9H), 7.63 (d, 2H, j = 8Hz), 7.80 (d, 2H, J = 8 Hz), 8.10 (brs, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): d = 28.34, 80.19,

120.90, 124.86, 125.66, 126.7, 138.91, 152.91.

**Tert-butyl 4-tert-butylphenylcarbamate (05):**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.35 (s, 9H), 1.60 (m, 12H), 6.43 (s, 1H), 7.30 (m, 4H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 27.34, 28.29, 31.33, 34.14, 80.19, 118.40, 125.66, 135.64, 146.69, 152.91. IR (KBr): 3443, 2963, 1703, 1526, 1396, 1235, 1075, 769.

**Tert-butyl 3,5-dimethylphenylcarbamate (06):**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.50 (s, 9H), 2.27 (s, 6H), 6.43 (s, 1H), 6.67 (s, 1H), 6.98 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 21.23, 28.31, 80.24, 116.23, 124.73, 138.13, 138.60, 152.78; IR (KBr): 3359, 3010, 2987, 2917, 1694, 1523, 1435, 1278, 1159, 1075, 843, 617  $\text{cm}^{-1}$ .

**Tert-butyl m-tolylcarbamate (07):**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.57 (s, 9H), 2.129 (s, 3H), 6.38 (brs, 1H), 6.58 (d, 1H), 7.00 (d, 1H), 7.11 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 24.51, 28.54, 80.10, 118.92, 121.72, 124.86, 128.96, 136.7, 139.87, 153.81.

**Tert-butyl 2-aminophenylcarbamate (08):**  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 1.49 (s, 9H), 4.30 (brs, 1H), 7.50 (d, 2H), 7.64 (d, 2H), 8.01 (brs, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 28.56, 79.66, 116.45, 119.25, 122.65, 123.51, 126.35, 146.32, 154.23.

**Tert-butyl 2-mercaptophenylcarbamate (10):**  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 1.47 (s, 9H), 6.69 (t, 1H), 6.83 (m, 2H), 7.60 (d, 1H), 7.81 (brs, 1H), 9.78 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 28.44, 81.10, 124.70, 124.86, 125.76, 129.7, 153.91.

**Tert-butyl 2-hydroxyphenylcarbamate (11):**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.45 (s, 9H), 6.72 (d, 1H), 6.82 (m, 2H), 7.59 (d, 1H), 7.75 (s, 1H), 9.70 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 28.27, 82.08, 118.72, 120.78, 121.33, 125.53, 125.62, 147.33, 155.03; IR (KBr): 3426, 3293, 2979, 2933, 2561, 1692, 1526, 1454, 1153, 1051, 744, 614  $\text{cm}^{-1}$ .

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