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## **Synopsis**

Nanocrystalline titania based sulfonic acid  $(TiO_2$ -Pr-SO<sub>3</sub>H) as a new, highly efficient and recyclable solid acid catalyst for the *N*-Boc protection of amines at room temperature

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Sulfonic acid-functionalized nanoporous titania (TiO<sub>2</sub>-Pr-SO<sub>3</sub>H) was prepared from the reaction of (3-mercaptopropyl) trimethoxysilane and TiO<sub>2</sub>. The morphology and acidity of synthesized catalyst was characterized by various techniques and the catalytic performance of TiO<sub>2</sub>-Pr-SO<sub>3</sub>H was investigated in the *N-tert*-butoxycarbonylation of amines under solvent-free conditions.



Nanocrystalline titania-based sulfonic acid (TiO<sub>2</sub>-Pr-SO<sub>3</sub>H) as a new, highly efficient and recyclable solid acid catalyst for the N-Boc protection of amines at room temperature

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## Abstract

Sulfonic acid-functionalized nanoporous titania (TiO<sub>2</sub>-Pr-SO<sub>3</sub>H) was prepared from the reaction of (3mercaptopropyl) trimethoxysilane and TiO<sub>2</sub>, then by oxidation of thiols group with hydrogen peroxide. The morphology and acidity of synthesized catalyst was characterized by FT-IR, SEM, TEM, TGA and XRD techniques and Hammett acidity test. The catalytic performance of TiO<sub>2</sub>-Pr-SO<sub>3</sub>H was investigated in the *Ntert*-butoxycarbonylation of amines under solvent-free conditions at room temperature. Our novel method is mild, chemoselective and has the advantages such as heterogeneous catalysis, low cost and the recyclability of the catalyst.

Keywords: Heterogeneous catalysis; solid acid, di-tert-butyl dicarbonate (Boc<sub>2</sub>O); N-Boc protection; TiO<sub>2</sub>.

#### 1. Introduction

The development of mild and selective methods for the protection and deprotection of functional groups continues to be an important tool in the synthetic chemistry of polyfunctional molecules [1]. The presence of an amino group in various biologically active compounds makes its protection as a necessity during their synthesis. Among the various amine protecting groups, the *tert*-butoxycarbonyl (Boc) is one of the most used, owing to its stability towards nucleophiles and strong basic conditions and because of its easy removal [1]. Various reagents and procedures have been employed over the years to introduce this group using *ditert*-butyl dicarbonate (Boc<sub>2</sub>O). The conventional procedure employs (Boc)<sub>2</sub>O and base catalysts such as DMAP [2, 3], NaHMDS [4], K<sub>2</sub>CO<sub>3</sub> [5], and Et<sub>3</sub>N [6], the last one being most commonly used. However the unpleasant smell, high toxicity, requirement in large excess, and non-recyclability of these catalysts makes the method objectionable, especially from the standpoint of green chemistry.

Lately acid-catalyzed *N*-Boc protection of amines has been widely studied with many homogeneous as well as heterogeneous catalysts. Many of these procedures involve I<sub>2</sub> [7], yttria-zirconia [8], ZrCl<sub>4</sub> [9], Zn(ClO<sub>4</sub>)<sub>2</sub>.6H<sub>2</sub>O [10], LiClO<sub>4</sub> [11], Cu(BF<sub>4</sub>)<sub>2</sub> [12], La(NO<sub>3</sub>)<sub>3</sub> [13], montmorillonite clays [14, 15], sulfonic acid functionalized silica [16], H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> [17], thioglycoluril [18], thiourea [19], sulfamic acid [20], HClO<sub>4</sub>-SiO<sub>2</sub> [21], saccharin sulfonic acid [22], ionic liquids [23, 24] and catalyst free conditions [25]. 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 [26, 27] and ZrCl<sub>4</sub> 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 [28, 29], poly-acylated products [30], urea [31] and *N*,*N*-di-Boc derivatives [31, 32].

In recent years, there has been considerable growth of interest in the catalysis of organic reactions by solid acid catalysts. Solid acid catalysts provide numerous opportunities for recovering and recycling

catalysts from reaction environments [33]. These features can lead to improved processing steps, better process economics, and environmentally friendly industrial manufacturing. In general, metal oxides have been used extensively either as such or as supports in conjunction with other active components for many industrial oxidation, reduction and acid–base catalyzed reaction. Among the semiconductor oxides  $TiO_2$  due to its low cost and long term stability has been widely used as solid acid catalyst in organic transformations; such as chemoselective trimethylsilylation of alcohols and phenols [34], Friedel–Crafts alkylation of indoles [35], synthesis of bis(indolyl) methanes [36], Mannich synthesis of  $\beta$ -aminocarbonyls [37] and esterification of free fatty acids [38].

However traditional heterogeneous catalysts have many limitations in the nature of their active sites. For example nanoparticles of  $TiO_2$  only can catalyze the reactions with their low Lewis acidic properties therefore modification of these nanoparticles very attended by chemists [39-42].

With this in mind, in the present study, the synthesis of chemically adsorbed sulfonic acid on  $TiO_2$  ( $TiO_2$ -Pr-SO\_3H) by the reaction of (3-mercaptopropyl) trimethoxysilane and  $TiO_2$ , and oxidation of thiols group with  $H_2O_2$  is reported. The characterization of  $TiO_2$ -Pr-SO<sub>3</sub>H was performed by means of various techniques such as Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD), scanning electron microscopy (SEM), transmition electron microscopy (TEM) and thermogravimetric analysis (TGA). The acidic property of the synthesized catalyst was evaluated by the calculation of Hammett acidity function [43]. The assessment of the catalyst was carried out in the *N-tert*-butoxycarbonylation of amines under solvent-free conditions at room temperature (Scheme 1).

## 2. Experimental

## 2.1. Materials

Chemicals were purchased from 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 thin-layer chromatography (TLC) on silica-gel polygram SILG-UV 254 plates.

#### 2.2. Instrumention

Thermogravimetric analyses were conducted using a TGA PYRIS 1 thermoanalyzer instrument (PerkinElmer Instruments, Waltham, MA, USA). Samples were heated from 25 °C to 600 °C at ramp 10°C/min under N<sub>2</sub> atmosphere. Wide-angle XRD measurements were performed at room temperature on a Siemens D-500 X-ray diffractometer (Munich, Germany), using Ni-filtered Cu-K $\alpha$  radiation ( $\lambda$ =0.15418 nm). IR and FT-IR spectra were obtained in KBr wafers on Shimadzu IR-470 (Kyoto, Japan) and Perkin Elmer RX1 (Waltham, MA, USA) spectrophotometers respectively. TEM analysis was performed on a Philips model CM 10 (FEI Co., Hillsboro, OR, USA) instrument. Sample was prepared by sonicating a small amount of powder in methanol, and then placing a drop of the mixture on a 3-mm TEM Cu grid having a lacey carbon support film. Scanning election microphotographs were obtained on a LEO 1430VP instrument. The absorption spectra in the UV-visible regions were recorded by a Perkin Elmer LAMBDA 25 recording spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured in CDCl<sub>3</sub> with a Brucker DRX-400AVANCE (Karlsruhe, Germany) spectrometer at 400 and 100 MHz, respectively.

## 2.3. Catalyst preparation

## 2.3.1. Synthesis of 3-mercaptopropyltitania

To 20 g of  $TiO_2$  (anatase, from Sigma-Aldrich) in dry toluene, 25 mL of (3-mercaptopropyl) trimethoxysilane was added, and the reaction mixture was refluxed for 24 h. After this period, the mixture was filtered to obtain 3-mercaptopropyltitania (MPT), which was washed with acetone and dried.

#### 2.3.2. Oxidation of 3-mercaptopropyltitania (MPT)

MPT was oxidized with 10 wt. %  $H_2O_2$  in methanol (20 mL) for 24 h at room temperature. The prepared sample was then treated with 1 N  $H_2SO_4$  at ambient temperature for complete protonation, and then the mixture was filtered and washed with  $H_2O_2$ , and acetone to obtain TiO<sub>2</sub>-Pr-SO<sub>3</sub>H catalyst (Scheme 2).

#### 2.4. Catalyst characterizations

#### 2.4.1. FT-IR analysis

FT-IR spectra for the pure TiO<sub>2</sub> and TiO<sub>2</sub>-Pr-SO<sub>3</sub>H samples are shown in Fig. 1. In the case of TiO<sub>2</sub>, the peaks at 3446 and 1773 cm<sup>-1</sup> correspond to the –OH stretching and bending vibrations of the adsorbed water respectively. The spectrum of functionalized TiO<sub>2</sub> by sulfonic acid displays almost the same pattern as that of pristine TiO<sub>2</sub>, but the band at 3000 to 3600 cm<sup>-1</sup> that centered in 3444 cm<sup>-1</sup> is flattened in sulfonated TiO<sub>2</sub> which can be attributed to the modification of TiO<sub>2</sub>. CH stretching vibrations of silylating agent was observed at 2963 and 2908 cm<sup>-1</sup>, and the bands at 1040 and 914 cm<sup>-1</sup> can be collectively attributed to Si–O stretching vibrations. Furthermore the peak corresponding to 1375 cm<sup>-1</sup> is the stretching frequency of S=O in SO<sub>3</sub>H. Also, the band around 2357 cm<sup>-1</sup> in TiO<sub>2</sub> is attributed to ambient CO<sub>2</sub>, which probably aggregation of TiO<sub>2</sub> nanoparticles in TiO<sub>2</sub>-Pr-SO<sub>3</sub>H is leaded to eliminate of this peak (see SEM images).

### 2.4.2. Wide-angle X-ray diffraction

XRD patterns of TiO<sub>2</sub> and TiO<sub>2</sub>–Pr–SO<sub>3</sub>H are given in Fig. 2. XRD patterns clearly show anatase lines. It seems the peak intensities of TiO<sub>2</sub> and TiO<sub>2</sub>–Pr–SO<sub>3</sub>H are almost same as those of TiO<sub>2</sub>, and the sulfate modification does not change the phase of TiO<sub>2</sub>. The average crystallite sizes of TiO<sub>2</sub> and TiO<sub>2</sub>–Pr–SO<sub>3</sub>H, determined using Debye–Scherrer equation, are 15.3 and 20 nm, respectively, which demonstrated that sulfate modification increases the size of TiO<sub>2</sub>.

#### 2.4.3. SEM analysis

The representative SEM images of  $TiO_2$  and  $TiO_2$ –Pr–SO<sub>3</sub>H are shown in Fig. 3a,b,c,d with ×30000 and 50000 magnifications. All of the SEM images exhibit a cloud-like structure and small spherical-shaped particles. In  $TiO_2$ –Pr–SO<sub>3</sub>H, aggregation of  $TiO_2$  nanoparticles was clearly seen. However, the SEM micrographs of the catalyst show some modifications with respect to  $TiO_2$  such that the primary surface structure of  $TiO_2$  has changed.

#### 2.4.4. TEM analysis

TEM images of  $TiO_2$ -Pr-SO<sub>3</sub>H are shown in Fig. 4.  $TiO_2$ -Pr-SO<sub>3</sub>H particles are seen in different sizes ranging from 20 to 100 nm, and the average crystallite sizes of  $TiO_2$ -Pr-SO<sub>3</sub>H, determined using XRD, was 20 nm. As can be seen in Fig. 4, the particles are slightly corroded in the modification path. This is indicated in the figure by the arrow.

#### 2.4.5. Thermal analysis

TGA was performed for the characterization of  $TiO_2$ -Pr-SO<sub>3</sub>H in comparable with  $TiO_2$  (Fig. 5). The TGA curve of  $TiO_2$  display a weight loss (4 wt.%) below 100 °C which corresponds to the loss of the physically adsorbed water. Also, there is a slight weight loss (3 wt.%) in the range of 100 °C to 600 °C, which possibly corresponds the to dehydroxylation of  $TiO_2$ .

TGA of catalyst shows an initial weight loss (4 wt.%) due to the desorption of water below 100 °C. This is followed by a second weight loss that started at 245 °C, corresponding to the loss of the covalently bound organic group. From this weight loss, it is calculated that the loading of the organic group bound to the titania surface was 2.52 mmol  $g^{-1}$ . Also from the TGA, we understood that TiO<sub>2</sub>-Pr-SO<sub>3</sub>H has a greater thermal stability (until 245 °C) relative to TiO<sub>2</sub> [44].

#### 2.4.6 Surface Acidity studies

The Hammett acidity function  $(H_0)$  can effectively express the acidity strength of an acid in organic solvents, [45-47]. It can be calculated using the following equation:

$$H_0 = pK(I)_{aq} + log([I]_s / [IH^+]_s)$$

Here, 'I' represents the indicator base (mainly substituted dinitroanilines), and  $[IH^+]s$  and  $[I]_s$  are respectively the molar concentrations of the protonated and unprotonated forms of the indicator. The pK(I)<sub>aq</sub> values are already known (for example the pK(I)<sub>aq</sub> value of 4-nitroaniline is 0.99) and can be obtained from many references. According to the Lambert–Beer's Law, the value of  $[I]_s/[IH^+]_s$  can be determined and calculated using the UV–visible spectrum.

In our experiment, 4-nitroaniline was chosen as the basic indicator and  $CCl_4$  was chosen as the solvent because it is aprotic. The maximal absorbance of the unprotonated form of 4-nitroaniline was observed at 329 nm in  $CCl_4$ . As Fig. 6 shows, the absorbance of the unprotonated form of the indicator in  $TiO_2$ -Pr-SO<sub>3</sub>H was weak as compared to the sample of the indicator in  $CCl_4$ , which indicated that the indicator was partially in the form as [IH<sup>+</sup>]. The results obtained are listed in Table 1, which shows the acidity strength of  $TiO_2$ -Pr-SO<sub>3</sub>H.

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

An amine (1 mmol) was added to a magnetically stirred mixture of  $TiO_2$ -Pr-SO<sub>3</sub>H (10 mg) and di-*tert*butyl dicarbonate (240 mg, 1.1 mmol) at room temperature. The mixture was stirred until completion of the reaction (TLC), then diluted with EtOAc (10 mL) and filtered. The residue contains only the catalyst and kept for recovery. The filtrate was washed with water (3×20 mL) and brine (2×20 mL) and dried over anhydrous MgSO<sub>4</sub>, then solvent was distillated off under vacuum to yield the highly pure *N*-Boc derivative.

#### 2.6. Selected spectral data

2.6.1. tert-Butyl 3-phenylpropylcarbamate: Colorless oil; IR (KBr): v = 3390, 2988, 2930, 1686, 1610, 1508, 1358, 1317, 1289, 1258, 1170, 998, 855 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 1.50 (s, 9H), 1.83 (qin, *J* = 7.2, 7.6 Hz, 2H), 2.67 (dd, *J*= 7.6 and 8.0, 2H), 3.18 (d, *J*= 6.0 Hz, 2H), 4.74 (s, 1H, N-H), 7.22 (dd, *J*= 5.6 and 7.6 Hz, 3H), 7.32 (d, *J*= 8.0 Hz, 2H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  = 28.5, 31.8, 33.2, 40.3, 125.9, 128.40, 128.44, 141.6, 156.1 ppm.

2.6.2. *tert-butyl* 4-*methylbenzylcarbamate:* Off-White solid; m.p. 72-73 °C; IR (KBr): v = 3395, 2980, 2920, 1680, 1600, 1508, 1360, 1320, 1295, 1260, 1172, 1000, 858, 761, 694 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ = 1.50 (s, 9H), 2.36 (s, 3H), 4.30 (d, *J*= 5.2, 2H), 4.88 (br s, 1H), 7.16 (d, *J*= 7.6 Hz, 2H), 7.20 (d, *J*= 8.0 Hz, 2H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ = 21.1, 28.4, 44.5, 79.4, 127.5, 129.3, 135.9, 137.0, 155.9 ppm.

2.6.3. *tert-butyl cyclohexylcarbamate:* Colorless solid; m.p. 65-67°C; IR (CCl<sub>4</sub>) v = 3364, 2973, 2934, 2854, 1681, 1520 1448, 1366, 1315, 1251, 1233, 1168 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 1.04-1.15 (m, 3H), 1.26-1.34 (m, 2H), 1.44 (s, 9H), 1.57- 1.71 (m, 3H), 1.90-1.93 (m, 2H), 3.43 (bs, 1H), 4.43 (bs, 1H) ppm.

2.6.4. *tert-butyl 3-methoxyphenylcarbamate*: Brown solid, m.p. 52-54 °C; IR (KBr): v = 3320, 2990, 2920, 1690, 1600, 1530, 1450, 1420, 1362, 1285, 1240, 1160, 1045, 1032, 960, 870, 842 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 1.55 (s, 9H), 3.82 (s, 3H), 6.61 (dd, *J*=8.0 and 8.4 Hz, 1H), 6.64 (br s, 1H), 6.87 (d, *J*= 8.0 Hz, 1H), 7.14 (s, 1H), 9.19 (dd, *J*= 8.0 and 8.4 Hz, 1H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz): δ 28.4, 55.3, 80.5, 104.1, 108.9, 110.7, 129.7, 139.7, 152.7, 160.3 ppm.

2.6.5. *tert-butyl-* 2-(*phenylamino*)*ethylcarbamate:* White solid; m.p. 80-82 °C; IR (KBr): v = 3414, 3395, 2980, 2920, 1680, 1600, 1508, 1360, 1320, 1295, 1260, 1172, 1000, 858, 761, 694 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>,

400 MHz):  $\delta = 1.50$  (s, 9H), 3.28 (t, J = 5.6 Hz, 2H), 3.39 (m, 2H), 4.02 (br s, 1H), 4.90 (br s, 1H), 6.64 (d, J = 8.0 Hz, 2H), 6.74 (dd, J = 7.2 and 7.6 Hz, 1H), 7.21 (dd, J = 7.6 and 8.0 Hz, 2H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta = 28.4$ , 40.11, 44.37, 79.58, 112.76, 117.54, 129.34, 148.06, 156.47 ppm.

#### **3. Results and discussion**

In order to optimize the reaction conditions, we conducted the *N*-Boc protection of benzyl amine with  $Boc_2O$  in the presence of various amount of  $TiO_2$ -Pr-SO<sub>3</sub>H with stirring at ambient temperature without solvent, and the results are summarized in Table 2. It is clear that, the reaction can be carried out in the presence of catalytic amount of  $TiO_2$ -Pr-SO<sub>3</sub>H and the yields are excellent, it was found that the reaction is not accomplish without the catalyst. It is notable that, this reaction carried out in the presence of bare  $TiO_2$  too, and *tert*-butyl benzylcarbamate obtained after 60 min with 45% yield. This demonstrated that the modification of  $TiO_2$  for promotion of this reaction is necessary.

After these preliminary experiments, catalytic amount of  $TiO_2$ -Pr-SO<sub>3</sub>H (10 mg) was used for *N-tert*butoxycarbonylation of various aliphatic, aromatic and heterocyclic amines and aminols. The results are summarized in Table 3.

Aliphatic amines (Table 3; entries 1- 11) gave the corresponding *N*-Boc products in 89–98% yields. It is notable that, 2-cyclohexenylethanamine (Table 3, entry 6), was protected rapidly without the isomerization of double bond. Aromatic amines having various substituents such as Br, Me, Et and OMe groups were converted to their *N-tert*-Boc derivatives efficiently (entries 12–21). Amino groups attached aromatic heterocycle (entry 21) afforded the desired products in quantitative yields. The reaction conditions were mild enough so that the acid sensitive moieties such methoxy group maintained intact under the reaction conditions (entries 2, 3 and 16). Also amines with two adjacent amino groups successfully protected (entries 11, 18). No isocyanate or urea formation was observed at all (IR and NMR). Under the selected conditions

*N*-Boc protection of alcohols, phenols and thiols was not successful and the starting material was recovered unchanged after 2 h (Table 3, entries 22-27).

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 4.

After performing one reaction under the conditions described in Table 3, the catalyst was recovered by filtration, washed with acetone and dried at 100 °C for 1 h and then reused for more 14 consecutive run under the same reaction conditions (Fig. 7). This reusability demonstrates the high stability and turnover of titania-based sulfonic acid (TiO<sub>2</sub>-Pr-SO<sub>3</sub>H) under the conditions employed. It should be noted that, the recyclability test was stopped after 15 runs.

The possible mechanism for the *N*-Boc protection of various amines in the presence of  $TiO_2$ -Pr-SO<sub>3</sub>H as a promoter is shown in Scheme 3. On the basis of this mechanism,  $TiO_2$ -Pr-SO<sub>3</sub>H catalyzes the reaction by the electrophilic activation of (Boc)<sub>2</sub>O to form a zwitterionic species, making the carbonyl group susceptible to nucleophilic attack by the amine. Successive elimination of CO<sub>2</sub> and *tert*-BuOH results in the formation of *N*-Boc derivatives and regenerates TiO<sub>2</sub>-Pr-SO<sub>3</sub>H in the reaction mixture.

To illustrate the efficiency of the present method, Table 5 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  $TiO_2$ -Pr-SO<sub>3</sub>H as a novel heterogeneous catalyst. The protocol is a 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)

simple experimental procedure and solvent-free conditions. Further work to explore this novel catalyst in other organic transformations is in progress.

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## Scheme, figure and table captions

Scheme 1. N-Boc protection of amines.

Scheme 2. Preparation of nanoporous titania-based sulfonic acid (TiO<sub>2</sub>-Pr-SO<sub>3</sub>H).

Scheme 3. Proposed mechanism.

Fig. 1. FT-IR spectra of TiO<sub>2</sub> and TiO<sub>2</sub>–Pr–SO<sub>3</sub>H.

Fig. 2. XRD patterns of TiO<sub>2</sub> and TiO<sub>2</sub>–Pr–SO<sub>3</sub>H.

Fig. 3. SEM images of TiO<sub>2</sub> and TiO<sub>2</sub>-Pr-SO<sub>3</sub>H. TiO<sub>2</sub> (a) ×30000 and (b) ×50000 magnifications and TiO<sub>2</sub>-

 $Pr-SO_3H(c) \times 30000$  and (d)  $\times 50000$  magnifications.

**Fig. 4.** TEM images of  $TiO_2$ –Pr–SO<sub>3</sub>H ( $\rightarrow$  = corroded).

**Fig. 5.** TGA curves of TiO<sub>2</sub> and TiO<sub>2</sub>-Pr-SO<sub>3</sub>H.

Fig. 6. Absorption spectra of 4-nitroaniline (indicator; curve A) and TiO<sub>2</sub>-Pr-SO<sub>3</sub>H (catalyst; curve B) in

CCl<sub>4</sub>.

Fig. 7. Reusability of the catalyst.

**Table 1.** Calculation of Hammett acidity function (H<sub>0</sub>) of TiO<sub>2</sub>-Pr-SO<sub>3</sub>H.

**Table 2.** Reaction of benzyl amine and  $Boc_2O$  in the presence of different amount of  $TiO_2$ -Pr-SO<sub>3</sub>H at room temperature under solvent-free conditions.<sup>a</sup>

Table 3. *N*-Boc protection of amines in the presence of TiO<sub>2</sub>-Pr-SO<sub>3</sub>H under solvent-free conditions.

 Table 4. Chemoselective N-Boc protection.

**Table 5.** Compared catalytic performance of  $TiO_2$ -Pr-SO<sub>3</sub>H with some of the various catalysts in the *N*-Bocprotection of aniline.



 $R^1$  and  $R^2$ = Alkyl or Aryl

Scheme 1.

-



Scheme 2.







Fig. 2.





1.00

(C)











Fig. 4.







Entry	Catalyst	A <sub>max</sub>	<b>[I]</b> <sub>s</sub> (%)	[ <b>IH</b> <sup>+</sup> ] <sub>s</sub> (%)	H <sub>0</sub>
1		2.4113	100	0	
2	TiO <sub>2</sub> -Pr-SO <sub>3</sub> H	1.1862	49.19	50.80	0.98

Table 1.

Condition for UV–visible spectrum measurement: solvent, CCl<sub>4</sub>; indicator, 4-nitroaniline (pK(I)<sub>aq</sub> = 0.99),  $1.44 \times 10^{-4}$  mol/L; catalyst, TiO<sub>2</sub>-HClO<sub>4</sub>, 20 mg, 25 °C.

25

Entry	Amount of catalyst (mg)	Time (min)	Yield (%) <sup>b</sup>
1		1h	75
2	5	35	87
3	10	20	95
4	15	20	94
5	20	20	96

# Table 2.

<sup>a</sup> Reaction conditions: benzyl alcohol, 1 mmol; Boc<sub>2</sub>O, 1.1 mmol.

<sup>b</sup> Isolated yield.

26

Entry	Substrate	Product	Time (min)	Yield <sup>a,b</sup> (%)
1	NH <sub>2</sub>	NHBoc	18	91
2	H <sub>3</sub> CO OCH <sub>3</sub> NH <sub>2</sub>	H <sub>3</sub> CO VHBoc OCH <sub>3</sub>	15	98
3	H <sub>3</sub> CO NH <sub>2</sub>	H <sub>3</sub> CO NHBoc	16	96
4	NH <sub>2</sub>	NHBoc	20	95
5	H <sub>3</sub> C NH <sub>2</sub>	H <sub>3</sub> C NHBoc	22	90
6	NH <sub>2</sub>	NHBoc	10	93
7	$\longrightarrow$ -NH <sub>2</sub>	-NHBoc	8	94
8	HO NH <sub>2</sub>	HO	12	89
9			30	91
11	NH <sub>2</sub> NH <sub>2</sub>	NHBoc NHBoc	18	91 <sup>c</sup>
12		NHBoc	25	98
13	Br-NH2	Br	35	89
14		NHBoc Me	45	91
15	Et—NH2	Et—	30	94

# Table 3.

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16	MeO NH <sub>2</sub>	MeO	24	91
17	Me NH <sub>2</sub>	Me-NHBoc	40	86
18	NH <sub>2</sub> NH <sub>2</sub>	NHBoc NHBoc	38	95°
19		H N NHBoc	9	87
21	N-NH <sub>2</sub>	NHBoc	18	89
22	ОН	OBoc	2 h	N.R <sup>d</sup>
23	—он	OBoc -OBoc	2 h	N.R <sup>d</sup>
24	<b>ОН</b>	OBoc	2 h	N.R <sup>d</sup>
25	SH	SBoc	2 h	N.R <sup>d</sup>
26	<b>──</b> SH	SBoc	2 h	N.R <sup>d</sup>
27	⟨ <b>→</b> −sh	SBoc	2 h	N.R <sup>d</sup>

<sup>a)</sup> Products were characterized by their physical constants, comparison with authentic samples and IR and NMR spectroscopy. <sup>b)</sup> Isolated yield.

<sup>c)</sup> 2 eq of (Boc)<sub>2</sub>O was used.

<sup>d)</sup> The starting material remained unchanged.

Entry	Substrate(s)	Product (GC Yield)	Time (min)
1	HO NH <sub>2</sub>	HO NHBoc 100	15
2	H NH2	H NHBoc 100	10
3	₩ <sup>1</sup> + <sup>OH</sup>	Г NHBoc + 100 0 0	25
4	────№Н2 +	—-NHBoc 100 + ОВос 0	7
5	√−№12 + √√−ОН	С-NHBoc + + 100 0	35

Table 5.

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Entry	Catalyst	Catalyst load	Time (min)	Solvent	Yield (%)
1	TiO <sub>2</sub> -Pr-SO <sub>3</sub> H [This work]	10 mg	25	neat	98
2	Iodine [7]	10 mol %	30	neat	95
3	Yttria-zirconia [8]	18.6 g	840	CH <sub>3</sub> CN	90
4	Zn(ClO <sub>4</sub> ) <sub>2</sub> .6H <sub>2</sub> O [9]	28 mg	720	CH <sub>2</sub> Cl <sub>2</sub>	92
_	Sulfonic acid functionalized	20 m a	45	CH <sub>2</sub> Cl <sub>2</sub>	83
5	silica [16]	20 mg			
6	$H_{3}PW_{12}O_{40}[17]$	15 mg	8	$CH_2Cl_2$	85
7	Thioglycoluril [18]	10 mol %	8	EtOH	95
8	Thiourea [19]	7.6 mg	40	Toluene	95
9	Sulfamic acid [20]	5 mol %	5	H <sub>2</sub> O	99
10	[TMG][Ac] [23]	18 mg	5	neat	98

- Introducing new solid phase catalyst for organic transformations
- Characterization and application of TiO<sub>2</sub>-Pr-SO<sub>3</sub>H for *N-tert*-butoxycarbonylation of amines
- Catalysis under solvent-free conditions at room temperature
- Generality of method , high yields, short reaction times and recyclability of the catalyst

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