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Highly Efficient and Selective *N*-alkylation of Amines with Alcohols Catalyzed by *in-situ* Rehydrated Titanium Hydroxide

Feng Niu^{a,b}, Qiyan Wang^{a,b}, Zhen Yan^b, Bright Kusema^b, Andrei Y. Khodakov^{a*} and
Vitaly V. Ordonsky^{b*}

^a *Univ. Lille, CNRS, Centrale Lille, ENSCL, Univ. Artois, UMR 8181 - UCCS - Unité
de Catalyse et Chimie du Solide, F-59000 Lille, France.*

^b *E2P2L, UMI 3464 CNRS-Solvay, 3966 Jin Du Rd., 201108 Shanghai, China*

⁵⁴ **Corresponding authors: Andrei Khodakov E-mail:andrei.khodakov@univ-lille.fr;*
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⁵⁶ *Vitaly Ordormsky E-mail:vitaly.ordonsky-ext@solvay.com*
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Abstract

Catalytic *N*-alkylation of amines by alcohols to produce desired amines is an important catalytic reaction in industry. Various noble metal-based homogeneous and heterogeneous catalysts have been reported for this process. Development of cheap non-noble metal heterogeneous catalysts for *N*-alkylation reaction would be highly desirable. Hereby, we propose the *N*-alkylation of amines by alcohols over a cheap and efficient heterogeneous catalyst - titanium hydroxide. The catalyst provides the selectivity higher than 90% to secondary amines for functionalized aromatic, aliphatic alcohols and amines at high catalytic activity and stability. Mild Brønsted acidity formed by continuous rehydration of Lewis acidity excludes side reactions and deactivation by adsorbed species. The mechanism of the reaction involves dehydration of alcohols to ethers with subsequent C-O bond cleavage by amine with formation of secondary amine and recovery of alcohol.

Keywords: *N*-alkylation; Amines; Alcohols; Heterogeneous; Titanium hydroxide; Alkoxides

Introduction

Complex amines are very important intermediates in chemical industry and life science. They are widely used in the production of agrochemicals, pharmaceuticals, organic dyes, detergents, fabric softeners, surfactants, corrosion inhibitors, lubricants, polymers and so on [1,2,3]. Due to the widespread use of these products, a number of synthesis routes have been developed based on classic nucleophilic substitution, like Buchwald-Hartwig [4], Ullmann reactions [5], and hydroamination [6,7,8]. Conventionally, *N*-alkyl amines are synthesized using alkylating agents, such as alkyl halides, which is environmentally unfriendly due to the toxic nature of halides and production of large amount of inorganic salts as waste. The selectivity to desired amines is generally low due to further over-alkylation [9,10,11].

In the last few decades, three main strategies have been applied for amination of alcohols: (i) "Borrowing Hydrogen" methodology using either noble metal based Ru- [12], Pd- [13], Ir- [14], Rh- [15], and Pt- [16] complexes, and more recently non-noble metal Mn- [17,18], Co- [19,20,21], Ni- [22,23,24,25] and Fe- [26] complexes. Also various of heterogeneous catalysts [27,28,29,30,31,32,33,34] have been used. (ii) Tsuji-Trost type reactions for allylic alcohols using Pd [35] or Ni [36] complexes. (iii) Lewis-acid catalyzed reactions using a variety of salts and ligands [37,38]. Among the best performing catalysts, different metal triflates and triflimides, including the parent triflic acid (HOTf) were found active for synthesis of secondary amines through *N*-alkylation of amines with alcohols based on S_N1 or S_N2 mechanisms [39]. However, these processes have several disadvantages due to use of expensive non-recoverable catalysts, difficulties in catalyst-product separation and indispensable use of additives or co-catalysts such as inorganic or organic bases and stabilizing ligands [40]. Thus, development of easily recoverable and recyclable

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3 non-noble metal based heterogeneous catalysts for *N*-alkylation system is still a
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5 challenging topic.
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8 Herein, we firstly report the selective *N*-alkylation of amines by alcohols in the
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10 absence of hydrogen, bases and organic ligands under ambient pressure of N₂ by an
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12 easily prepared transition metal- and solid acid-based heterogeneous catalyst such as
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14 titanium hydroxide. For comparison, a number of metal oxides and hydroxides have
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16 been tested in the *N*-alkylation process. Interestingly, titanium hydroxide exhibits the
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18 highest activity and selectivity towards the desired amine. In addition, the titanium
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20 hydroxide catalyst provides high catalyst stability and good substrate tolerance for
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22 amination of different alcohols and substituted amines under optimized conditions. To
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24 the best of our knowledge, this new efficient heterogeneous catalyst provides a green
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26 route for selective synthesis of amines.
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31 In terms of catalytic mechanism, it is generally accepted that substitution of
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33 OH-groups with N nucleophiles proceeds via a S_N1 or S_N2 type mechanism, in the
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35 presence of hard Lewis or Brønsted acids [41]. In this work, we show that
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37 *N*-alkylation process of alcohols involves intermediate formation of ethers, which
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39 could be a kinetic relevant step of the whole reaction. The high yield of secondary
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41 amine can be attributed to the easier C-O bond cleavage in the ether by amines based
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43 on effect of mild Brønsted acidity formed by adsorbed water over Lewis acid sites.
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48 **Experimental Section**

49 **Catalyst preparation**

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51 Titanium hydroxide was prepared through the hydrolysis of titanium isopropoxide
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53 (99%, supplied by J&K) under neutral condition. 200 ml of distilled water was heated
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55 up to 60 °C and 10 mL titanium isopropoxide was added dropwise using a peristaltic
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57 pump (0.05 mL/min) under continuous stirring (500 rpm) for almost 10 h. Then the
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3 obtained white suspension was centrifuged and washed with ethanol and distilled
4 water for several times followed by drying in vacuum at 80 °C overnight. The
5 obtained sample was denoted as TiOH. The hydrolysis of isopropoxide in hot water is
6 an easy and efficient method to produce amorphous titanium hydroxide with high
7 purity (no NH₃ or Cl⁻) and surface area. This sample has been further calcined at 180
8 °C and 400 °C for 2 h to produce dehydrated samples denoted as TiOH-180 and
9 TiOH-400, respectively.

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19 The hydroxides of Al (Al-OH) and Zr (Zr-OH) have been prepared in the similar
20 way using alkoxides of aluminium t-butoxide, aluminium isopropoxide, zirconium
21 butoxide and zirconium ethoxide. For comparison, different metal oxides and
22 commercial zeolite ZSM-5 were also used for this reaction as references. The
23 hydrolyzed AlOH sample was calcined under 180 °C, which was denoted as
24 AlOH-180.

35 **Catalytic test**

36
37 Typical procedure for *N*-alkylation of amines with alcohols was carried out in a
38 30 mL stainless steel autoclave geared with a pressure gauge and a safety rupture disk.
39 In a typical experiment, the reactor was charged with 4.62 mmol benzyl alcohol, 21.5
40 mmol aniline and 100 mg of catalyst. 2 g xylene, THF or water was used as a solvent.
41 Then, the reactor was purged with N₂ several times to remove the air. Finally, the
42 reactor was placed on a hot plate equipped with a magnetic stirrer (500 rpm) at 50
43 °C-180 °C for 0.5-48 h. After the reaction, the reactor was cooled down to room
44 temperature, and the mixture was filtrated and analyzed using an Agilent 7890 GC
45 equipped with a HP-5 capillary column using biphenyl as the internal standard for
46 calculation of alcohol conversion and product yields. After each amination test, the
47 catalyst was washed with ethanol and separated by centrifugation several times and
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3 dried at 80 °C for 10 h for further test of the recyclability. The used catalyst after
4 reaction was denoted as TiOH-80-AR. For the rehydration of the dehydrated catalysts
5 TiOH-180, water was added into the reactor before catalytic test. For characterization,
6 the catalyst was suspended in distilled water overnight followed by drying under
7 vacuum at 80 °C before test. The corresponding rehydrated samples were denoted as
8 TiOH-180-Re, TiOH-400-Re, TiO₂-Re and AlOH-180-Re.
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18 **Characterization methods**

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20 The powder X-ray diffraction (XRD) patterns were obtained using an X-ray
21 diffractometer (D5000, Siemens) using Cu K α radiation ($\lambda = 0.15418$ nm). Scans
22 were recorded in the 2θ range of 10-80° using a step size of 0.02° and a step time of 5
23 s.
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29 The BET specific surface areas and pore size were measured from the N₂
30 adsorption-desorption isotherms at 77 K on an automated gas sorption analyzer
31 Micromeritics ASAP 2010.
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36 Thermogravimetric analysis (TGA) was carried out in air flow at the temperature
37 range of 20-900 °C with a heating rate of 5 °C·min⁻¹ on a Mettler Toledo
38 SMP/PF7458/MET/600W instrument.
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43 The FTIR (Perkin-Elmer 1720) spectra of the titanium hydroxide catalysts were
44 measured in the range from 4000 to 1200 cm⁻¹ to trace the variation of surface
45 hydroxyl group of the catalysts. To investigate the nature of acid sites in the catalyst,
46 the pyridine adsorption FTIR technique was employed and spectra were recorded in
47 the range of 1700-1400 cm⁻¹. The self-supported wafers of all the catalysts were
48 prepared by a pellet press instrument and the samples were degassed at 100 °C for 30
49 minutes followed by saturation with pyridine as reported elsewhere [42]. To explain
50 the mechanism of alcohol dehydration over titanium hydroxide, *in-situ* FTIR was
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3 performed through heating the pellet from 25 to 180 °C (step 25 °C) in benzyl alcohol
4 vapors (20 Torr).
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8 The NH₃ temperature programmed desorption (NH₃-TPD) was carried out on a
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10 Micromeritics AutoChem 2920 with a thermal conductivity detector (TCD). In all the
11 experiments, ~50 mg of sample was calcined at 100 °C for 1 h in helium gas flow (20
12 mL (STP)/min) and then cooled down to 40 °C followed by saturation with 10%
13 ammonia-helium for 1 h. Then the sample was flushed with helium for 1 h to remove
14 the surface physisorbed ammonia. Finally, the desorption profiles were recorded in
15 the temperature range of 40 °C-800 °C with a heating rate of 5 °C min⁻¹.
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25 **Results and Discussion**

26 **Catalysis over oxides and hydroxides**

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30 The additive-free *N*-alkylation reaction of benzyl alcohol (**1**) with aniline (**2**) to
31 give corresponding secondary amine *N*-phenylbenzylamine (**3**) has been used as a
32 model reaction over different non-noble metal hydroxide, oxide and zeolite catalysts
33 (**Table 1**). The product has been identified by GC-MS, ¹H-NMR and ¹³C-NMR
34 analysis (**Figure S1, S2, S3, SI**). The blank test without catalyst did not show
35 formation of desired amine (entry 1). The titanium hydroxide obtained by hydrolysis
36 of titanium isopropoxide showed the highest catalytic activity and gave the desired
37 secondary amine *N*-phenylbenzylamine (**3**) with the 99.6% yield (entry 2) without
38 formation of secondary imine. Only traces of dibenzyl ether have been detected as
39 byproduct. The product yield was slightly lower for the reaction performed without
40 solvent due to easier formation of tertiary amine through condensation reaction (entry
41 3). It is interesting to note that the reaction can be performed in aqueous phase (entry
42 5), however, organic solvents provide the highest yield of the product (entry 4). The
43 reaction in air atmosphere provides a bit lower yield than that under N₂ mainly due to
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3 the partial oxidation of benzyl alcohol to benzoic acid (entry 6). Hydroxides of Al and
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5 Zr prepared by hydrolysis of different types of alkoxides could afford the maximum
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7 yield of *N*-phenylbenzylamine of only 16.9% (entry 7-10). Additionally, different
8
9 metal oxides were also tested for *N*-alkylation reaction. The yield was lower than 2%
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11 for TiO₂, CeO₂, ZrO₂, MgO, SiO₂ and Al₂O₃ (entry 11-16). The alkylation yield for
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13 commercial zeolite ZSM-5 was only 25% (entry 17).
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17 Titanium hydroxide (TiOH-80) was the most active catalyst. The reaction
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19 temperature dependence of the secondary amine yield in the *N*-alkylation of benzyl
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21 alcohol with aniline on this catalyst was further investigated (**Figure S4, SI**). Below
22
23 100 °C, there was nearly no activity in this reaction. The conversion gradually
24
25 increases as the temperature increases from 100 to 180 °C reaching full conversion.
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27 The apparent activation energy of the reaction corresponds to 66.4 kJ/mol (**Figure 1a**).
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29 The time course of the secondary amine synthesis over titanium hydroxide (TiOH-80)
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31 at 180 °C was investigated (**Figure 2**). The reaction proceeded smoothly to afford the
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33 corresponding secondary amine with 99% yield in 15 h. Dibenzyl ether was observed
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35 at the initial stage and its yield slowly decreased with time, suggesting the dibenzyl
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37 ether could be an intermediate. The reaction seems to proceed in two consecutive
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39 steps: 1) transformation of benzyl alcohol to dibenzyl ether and 2) secondary amine
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41 formation from dibenzyl ether with aniline.
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48 **Characterization**

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50 To identify, whether the high performance of secondary amine synthesis comes
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52 from the suitable acidic sites formed from surface hydroxyl group of the catalyst,
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54 titanium hydroxide obtained by hydrolysis was calcined at different temperatures. The
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56 TGA analysis (**Figure 3a**) shows that titanium hydroxide exhibited weight loss in two
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58 main steps. The initial weight loss below 250 °C can be assigned to desorption of
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3 surface water. The weight loss between 250 °C and 450 °C could be due to the
4 removal of surface hydroxyl groups through dehydroxylation process [43]. No
5 obvious weight loss was detected for TiOH-400 sample. This indicates that high
6 crystalline TiO₂ phase was formed after calcination at 400 °C. The catalyst
7 TiOH-80-AR after reaction showed similar weight loss compared to the fresh catalyst.
8 This indicates similar content of hydroxyl groups and rehydration of the catalyst
9 during reaction. The state of the material during calcination at different temperatures
10 has been studied by XRD. The parent sample and sample after calcination at 180 °C
11 are amorphous, the presence of anatase was detected after calcination at 400 °C [44].
12 XRD showed that the catalyst was still amorphous after reaction (**Figure 3b**).

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26 FTIR has provided further information about the concentration and acidity of
27 surface hydroxyl groups in titanium hydroxide. As shown in **Figure 4a**, the titanium
28 hydroxide without calcination exhibited a broad peak at 3600 cm⁻¹ and a peak at 1626
29 cm⁻¹ due to the stretching vibration of hydroxyl groups interacting with adsorbed
30 water and bending vibration of hydroxyl groups of adsorbed water, respectively [45].
31 As the calcination temperature increased, the intensity of the peak at 1626 cm⁻¹
32 decreased and finally disappeared at 400 °C with significant narrowing of the peak at
33 3600 cm⁻¹. It indicates desorption of water and significant decrease in the amount of
34 hydroxyl groups during dehydration of hydroxide and its transformation to anatase
35 phase.
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49 To identify the acidic properties of the surface hydroxyl groups of the catalyst,
50 FTIR spectra of pyridine adsorbed on titanium hydroxide calcined at different
51 temperatures were recorded (**Figure 4b**). The interaction of pyridine with Lewis acid
52 sites gives rise to the specific bending vibration bands of pyridine ring at 1448 cm⁻¹,
53 1575 cm⁻¹ and 1605 cm⁻¹ [42]. The peak located at 1540 cm⁻¹ can be assigned to the
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3 interaction of pyridine with Brønsted acid sites. It can be observed that an increase in
4 the calcination temperature of titanium hydroxide to 180 °C leads to decrease in the
5 intensity of all the peaks related to Lewis acid sites and nearly disappearance of
6 Brønsted acid sites [43]. Further increase in the calcination temperature to 400 °C
7 results in disappearance of all adsorbed pyridine species over the catalyst, which
8 means nearly no acidic sites left on the catalyst. It is interesting to note that the
9 process of dehydration is reversible and treatment of TiOH-180 in water leads to
10 recovery of adsorbed pyridine species corresponding to Brønsted and Lewis acid sites
11 (**Figure 4b**). However, rehydration process did not lead to acidity generation over the
12 crystalline sample TiOH-400, which could be explained by high stability of anatase
13 structure. Thus, defected labile nature of titanium hydroxide provides both Brønsted
14 and Lewis acid sites, which disappear during dehydration procedure due to the
15 process of healing of defected sites (**Figure 5**). Indeed, the formation of Brønsted and
16 Lewis acid sites can be proposed as reaction of protonation of hydroxyl groups with
17 subsequent dehydration. The easy rehydration process provide constant presence of
18 both types of acid sites in the catalyst during reaction (**Figure 5**).

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40 To further identify the amount and strength of the acid sites, temperature
41 programmed desorption of ammonia (NH₃-TPD) has been measured as shown in
42 **Figure 6**. The highest amount of acid sites is observed over pristine titanium
43 hydroxide TiOH-80 with the broad desorption peak at 168 °C and narrow intensive
44 peak at 312 °C corresponding to weak and intermediate acid sites, respectively [46].
45 Calcination of titanium hydroxide at 180 °C leads to nearly disappearance of
46 intermediate acidity with the weak acidity peak shift to lower temperatures (100 °C).
47 Combined with the results of Py-FTIR, it indicates that high temperature peak
48 (intermediate acidity) can be assigned to desorption of pyridine from Brønsted acidic
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3 sites and low temperature peak (weak acidity) to desorption of pyridine from Lewis
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5 acidic sites. The sample further calcined at 400 °C did not show any obvious NH₃
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7 desorption.
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10 The NH₃-TPD results for titanium hydroxide were compared with those obtained
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12 for aluminum hydroxide and zeolites. Aluminum hydroxide also shows the presence
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14 of weak and intermediate acid sites. The broad desorption peaks at 220 °C and 420 °C
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16 for ZSM-5 can be respectively assigned to intermediate and strong acidities. The
17
18 amount of acid sites for all the samples calculated through integration and calibration
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20 is listed in [Table S1, SI](#).
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24 The samples pre-treated at different temperatures have been additionally tested in
25
26 the *N*-alkylation reaction. The initial reaction rate for different samples is shown in
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28 [Figure 7](#). The initial reaction rate for the sample TiOH-80 ([Figure 1b](#), [Figure 7](#)) was
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30 12.8 mmol/g·h, which was nearly twice higher than that of dehydrated sample
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32 TiOH-180 (6.84 mmol/g·h). Calcination at 400 °C almost totally deactivates the TiOH
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34 catalyst in *N*-alkylation reaction. It means that anatase structure of TiO₂ without any
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36 significant amount of acid sites is not active in *N*-alkylation of benzyl alcohol with
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38 aniline. The catalytic test over commercial TiO₂ catalyst further confirms this
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40 conclusion ([Table 1](#)). It is interesting to note that the sample calcined at 180 °C with
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42 low content of acid sites ([Table S1, SI](#)) still provides significant activity in amination
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44 reaction. This result can be explained by rehydration of amorphous titanium oxide by
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46 water, which produces new acid sites for the reaction. Indeed, the structure of
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48 amorphous oxide is very labile and interaction of Lewis acid sites with water formed
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50 during reaction should result in regeneration of Brønsted acidity
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56 Crystalline anatase TiO₂ cannot be rehydrated to form acidity during reaction.
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58 This suggestion has been further proven by addition of extra water before amination
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3 test with the dehydrated catalysts (**Figure 7**). The reaction rate (12.55 mmol/g·h) for
4 amorphous titanium hydroxide (TiOH-180) was almost recovered to the initial state
5 after addition of water. We could propose reversible process of dehydration and
6 rehydration for titanium hydroxide during reaction, which provides permanent acidity
7 for amination reaction [47,48] (**Figure 5**).
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10 To investigate the structure-performance correlation, BET analysis of all catalysts
11 has been performed. There is no obvious relationship between reaction activity and
12 surface area or pore structure of the catalysts (**Table S2, SI**). Indeed, high surface area
13 of hydroxides AlOH and ZrOH or oxides Al₂O₃ and SiO₂ does not provide high
14 activity of these catalysts in amination.
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17 Analysis of the structure-catalytic performance relationship shows good
18 correlation between intermediate acidity measured by NH₃ desorption in the range
19 200-400 °C and reaction rate in amination over different catalysts (**Figure S5, SI**). It
20 is obvious that the reaction rate increases with increase in the intermediate acidity.
21 However, high content of intermediate acid sites over Al-OH does not lead to high
22 activity in amination. The possible explanation of this effect could be low rehydration
23 of Al-OH at the reaction conditions. Dehydration of Al-OH at 180 °C leads to
24 significantly lower activity in comparison with the parent catalyst Al-OH (**Figure S6,**
25 **SI**). Rehydration of AlOH-180 does not show significant increase of the activity in
26 comparison with the rehydration of TiOH-180. This fact could be explained by less
27 labile structure of Al hydroxide in terms of reversible hydration-dehydration process.
28 The activity recovery for the rehydrated sample TiOH-180 was mainly attributed to
29 the continuous regeneration of intermediate Brønsted and Lewis acidic sites, (**Figure**
30 **5**). The lower activity for ZSM-5 was partially because of quasi-irreversible
31 adsorption of aniline on the zeolite strong acid sites under the reaction conditions.
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3 Consequently, we could assume that weak and strong acidities would not play a
4 determining role in amination reaction. Titanium hydroxide with optimum
5 intermediate acidity and able to be rehydrated shows an exceptional catalytic
6 performance for the *N*-alkylation reactions.
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12 13 **Mechanism**

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15 Among various strategies for amines synthesis, amination of alcohols using a
16 borrowing hydrogen methodology (or hydrogen auto-transfer process) has been
17 regarded as a highly atom-efficiency choice [49,50,51]. In this approach (**Figure 8 (a)**)
18 alcohol was first dehydrogenated to the corresponding aldehyde with assistance of
19 noble metals like Ru, Pt, Pd, Ir [52,53,54,55]. Then the aldehyde was nucleophilically
20 attacked by an amine to form secondary imine with the eliminating of water as the
21 only byproduct. Finally, imine was hydrogenated to the desired secondary amine.
22 During the whole process, additional hydrogen is usually added for inhibition of the
23 catalyst deactivation and fast hydrogenation step to suppress secondary processes.
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36 In our case, the non-metallic acidic heterogeneous catalyst such as titanium
37 hydroxide without dehydrogenation/ hydrogenation functions was found to be very
38 efficient for the direct *N*-alkylation of benzyl alcohol with aniline to give desired
39 secondary amine. A possible reaction mechanism in this case can be based on S_N2
40 mechanism of direct nucleophilic attack of α -carbon atom by N of aniline [56,57]. The
41 effect of the ratio of aniline to benzyl alcohol from 0 to 10 on the reaction selectivity
42 is displayed in **Figure 9a**. It is interesting and obvious to note the presence of
43 dibenzyl ether, which might be produced by dehydration of benzyl alcohol. The
44 intermolecular dehydration of benzyl alcohol catalyzed by acid sites of metal oxides
45 like alumina has been observed earlier [58,59,60]. Surprisingly, in the presence of
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3 larger amounts of aniline (amine to alcohol ratio >1), the dehydration of benzyl
4 alcohol is completely suppressed. There are two possible explanations of this effect:
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8 1) acid sites of titanium hydroxide are responsible for dehydration of alcohol and
9 amination of alcohol. The presence of excess of aniline suppresses the first
10 reaction;
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- 13 2) ether is the primary product of the reaction. The ammonolysis of the ether by
14 aniline proceeds much faster than that of the relevant alcohol.
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19 To provide experimental evidence for the second hypothesis, the catalytic
20 reaction of dibenzyl ether with aniline over titanium hydroxide was investigated
21 (Figure 9 (b)). No product was formed without catalyst. TiOH-80 clearly catalyzed
22 the ammonolysis reaction of dibenzyl ether with high initial reaction rate (80
23 mmol/g·h), which was about 6 times higher than that of the whole *N*-alkylation
24 reaction (12.8 mmol/g·h) (Figure 1b, Figure 6). It demonstrates that the
25 ammonolysis of dibenzyl ether through C-O bond cleavage [61,62,63,64] to the
26 desired secondary amine proceeds much faster than the relevant reaction of benzyl
27 alcohol. This indicates that dehydration of alcohol could be the limiting step of the
28 whole *N*-alkylation reaction (Figure 8b). Water was the only byproduct during the
29 whole reaction process. The product yield for the ammonolysis reaction dramatically
30 decreased from 86 % to nearly 0 as the pretreatment temperature increased from 180
31 to 400 °C (inset of Figure 9b). It indicates that the ammonolysis of dibenzyl ether
32 requires acid sites as well, which is consistent with the previous report [65]. However,
33 the reaction is less sensitive to amount of acid sites in comparison with dehydration of
34 alcohol to ether.
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55 To investigate the alcohol dehydration process on the acid sites of titanium
56 hydroxide, in-situ FTIR experiments were performed (Figure 10, Figure S7, SI).
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3 Adsorption of benzyl alcohol leads to appearance of the bands at 1230, 1380, 1360,
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5 1447, 1470 and 1494 cm^{-1} . The bands at 1447 and 1494 cm^{-1} can be assigned to the
6
7 in-plane C-O-H bending modes [66]. The bands at 1230 and 1470 cm^{-1} are associated
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9 usually with methylene group [67]. The bands at 1360 and 1380 cm^{-1} can be assigned
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11 to aromatic skeletal vibrations [68].
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15 As the temperature increased from room temperature to N-alkylation temperature,
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17 the additional bands appears at 1600 cm^{-1} and 1575 cm^{-1} (**Figure 10, Figure S7, SI**)
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19 These bands can be assigned to bending vibrations of strongly adsorbed water over
20
21 Lewis acid sites and C=C stretching vibrations in benzyl ether [69]. Additionally the
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23 band at 3510 cm^{-1} of OH stretching vibration increases at higher temperature (**Figure**
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25 **S7, SI**). This indicates dehydration of alcohol with formation of water and ether.
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29 The FTIR spectrum of the catalyst after reaction and intensive washing in
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31 xylene shows the peaks at 1380 and 1360 cm^{-1} similar to FTIR spectra after benzyl
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33 alcohol adsorption (**Figure 11**). In order to verify if these species could be
34
35 intermediates during catalytic reaction, the catalyst after reaction has been treated at
36
37 the reaction conditions in pure xylene. The liquid phase after reaction contained 0.33
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39 mmol (3.3 mmol ether/ g_p) of dibenzyl ether which was the only product of the
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41 reaction (**Figure S8, SI**). The amount of the product corresponds well to the amount
42
43 of acidic active sites determined by TPD of NH_3 (**Table S1, SI**). FTIR analysis shows
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45 that surface species have disappeared after reaction (**Figure 11**). In order to identify
46
47 the localization of these species, Py has been adsorbed over the catalyst before and
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49 after treatment in solvent (**Figure 11**). It is interesting to note that the peak attributed
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51 to adsorption of Py over Lewis acid sites decreased significantly after reaction but has
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53 been totally recovered after treatment in xylene. The possible explanation of this
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55 effect could be formation of surface alkoxide species by interaction of alcohol with
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3 Lewis acid sites (**Figure 11**). The presence of intermediate surface alkoxides have
4 been observed earlier over alumina [70]. FTIR analysis of low wavenumber region
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6 (**Figure 11**) of the catalyst after reaction (TiOH-80-AR) shows intensive bands at
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8 1126, 1070 and 1041 cm^{-1} , which has been earlier assigned to vibration modes of
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10 Ti-O-C species in alkoxides [71].
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15 The kinetic analysis of the reaction of benzyl alcohol dehydration to benzyl ether
16 shows that it corresponds to the second order similar to the whole N-alkylation
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18 reaction (**Figure S9, SI**).
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22 Based on the catalytic and characterization results discussed above, a possible
23
24 reaction mechanism of ether formation on acidic titanium hydroxide as key
25
26 intermediate for further ammonolysis to *N*-alkylation product was proposed in **Figure**
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28 **12**. The alcohol reacts with Lewis acid sites over the TiOH catalyst with formation of
29
30 surface alkoxides. Protonation of oxygen of alkoxide species by hydroxyl group with
31
32 $\text{S}_{\text{N}}2$ attack of α -carbon by oxygen of another alkoxide results in formation of ether
33
34 and partial hydration of the catalyst. Subsequent dehydration leads to regeneration of
35
36 the active sites. Thus, synergetic effect of mild Brønsted and Lewis acid sites over
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38 titanium hydroxide for activation of alcohol able to transform it to ether by
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40 dehydration is necessary. These properties make titanium hydroxide unique for this
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Adsorption of pyridine over other catalysts confirms this assumption. Oxides containing mainly Lewis acid sites and zeolite with Brønsted acidity provide low activity in *N*-alkylation reaction (**Table S3, SI**). Presence of both Brønsted and Lewis acid sites can be observed also over other hydroxides like Al-OH, however, catalyst cannot be rehydrated in-situ during reaction losing activity in time (**Figure S6, SI**).

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3 Thus, amount, nature and regenerability of acid sites are the key factors affecting
4 activity of the catalyst in N-alkylation reaction.
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8 To investigate the stability and reusability of titanium hydroxide, the used
9 catalyst was washed with ethanol and separated from the liquid phase by
10 centrifugation for several cycles and dried at 80 °C for 10 h. As shown in **Figure 13**,
11 the titanium hydroxide could be used for at least three catalytic cycles without
12 obvious change in reaction rate and amine yield, indicating good stability and
13 recyclability for titanium hydroxide.
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22 **Substrate scope**

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24 The scope of the present titanium hydroxide system with regard to alkylation of
25 various amines and alcohols was also examined. **Table 2** shows that the catalyst can
26 be used for selective conversion with aniline of structurally diverse aromatic and
27 biomass based alcohols to the secondary amines (entry 1-5). The *o*-methyl benzyl
28 alcohol (entry 4) was less reactive, which could be due to the steric hindrance effect
29 of the methyl group at the *o*-position [34]. Aniline derivatives bearing an
30 electron-donating or electron-withdrawing group also reacted with benzyl alcohol to
31 afford the corresponding secondary amines with the yields higher than 90 % (entry
32 6-9).
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45 Aliphatic amines (butylamine and dibutylamine) can be also used for the
46 synthesis of secondary and tertiary amines by reaction with benzyl alcohol,
47 respectively (entry 10 and 11). However, the yield of the product in this case is lower
48 than in the case of aromatic amines (<50 %) with significant contribution of ethers in
49 the products due to the lower reactivity of aliphatic amine. The reaction conditions
50 have been modified: the time of the test, amount of the catalyst were increased, while
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3 the loading of reagents were decreased (entry 12 and 13). Higher yield of the products
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5 comparable to the aromatic amines ($\approx 90\%$) was obtained.
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9 Titanium hydroxide provides high selectivity at reasonable conversions for the
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11 reaction of octanol, tetrahydrofurfuryl alcohol and isopropanol with aniline (entry
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13 14-16). There is still a significant contribution of ether but the yield of the target
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15 product can be easily improved by increase of the contact time as it has been
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17 demonstrated earlier (entry 12 and 13).
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21 Titanium hydroxide also provides reasonable yield of secondary aliphatic amine
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23 through *N*-alkylation of aliphatic alcohols (primary and secondary) with aliphatic
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25 amines (entry 17-20). The main difference in comparison with aromatic alcohols and
26
27 amines is higher contribution of ether in the case of aliphatic amines and alcohols
28
29 (**Table 2**). Note that variation of the product yields with time of aliphatic amine
30
31 remains consistent with the hypothesis about the role of ether as an intermediate of
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33 alcohol ammonolysis. Indeed, *N*-alkylation of isopropanol with aniline demonstrate
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35 continuous increase of the yield of the product and a volcano curve for the
36
37 di-isopropyl ether as a function of time (**Figure S10, SI**). Thus, unique structure of
38
39 titanium hydroxide provides efficient amination of aromatic and aliphatic alcohols by
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41 aromatic and aliphatic amines toward secondary and tertiary amines.
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46 47 **Conclusions**

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49 In summary, we have demonstrate that a non-noble metal solid titanium hydroxide
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51 acts as a stable, reusable and efficient heterogeneous catalyst for *N*-alkylation of
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53 amines with alcohols to secondary amines without hydrogen, bases or organic ligands
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55 promotion. The conversion and selectivity of titanium hydroxide were much higher
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57 than other hydroxides, metal oxides and zeolite due to the availability of mild
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3 intermediate Brønsted and Lewis acidities formed by rehydration-dehydration
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5 processes. The high yield for direct secondary amine synthesis can be attributed to the
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7 acidic catalytic intermolecular dehydration of alcohol to form corresponding ether
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9 followed by easier ether ammonolysis.
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13 **Supporting Information**

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16 GC-MS, ^1H NMR, ^{13}C NMR, FTIR, reaction activity, catalytic reaction rate, kinetic
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18 analysis, ether formation, acidity of the catalysts and BET analysis.
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20 This information is available free of charge on the ACS Publications website.
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23 **Data availability**

24
25 All data are available from the authors upon reasonable request.
26
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28

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31
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Table 1. Amine synthesis from benzyl alcohol and aniline over various non-noble metal oxides and hydroxides (benzyl alcohol (4.62 mmol), aniline (21.5 mmol), xylene 2 g, catalyst 0.1 g, reaction temperature 180 °C, 15 h, atmospheric N₂)

c1ccc(cc1)CO + Nc1ccccc1
 $\xrightarrow[\text{xylene (2 g)}]{180\text{ }^\circ\text{C, 15 h, cat}}$
Nc1ccc(cc1)Cc2ccccc2 + H₂O

1 **2** **3**

Entry	Catalyst	Yield of 3 (%)		Entry	Catalyst	Yield of 3 (%)	
	<i>Hydroxides</i>				<i>Oxides</i>		
1	—	0		11	TiO ₂	1.4	
2	Ti-OH	99.6		12	MgO	<1	
3	^a Ti-OH	92.4		13	SiO ₂	<1	
4	^b Ti-OH	99.2		14	Al ₂ O ₃	<1	
5	^c Ti-OH	97		15	CeO ₂	0	
6	^d Ti-OH	89.8		16	ZrO ₂	<1	
7	^e Al-OH	16.9			<i>Zeolites</i>		
8	^f Al-OH	10		17	ZSM-5	25	
9	^g Zr-OH	8.1					
10	^h Zr-OH	12					

^aNo solvent used; ^bunder solvent THF; ^cunder water; ^dunder air; ^ehydrolysis from aluminium t-butoxide; ^fhydrolysis from aluminium isopropoxide; ^ghydrolysis from zirconium butoxide; ^hhydrolysis from zirconium ethoxide.

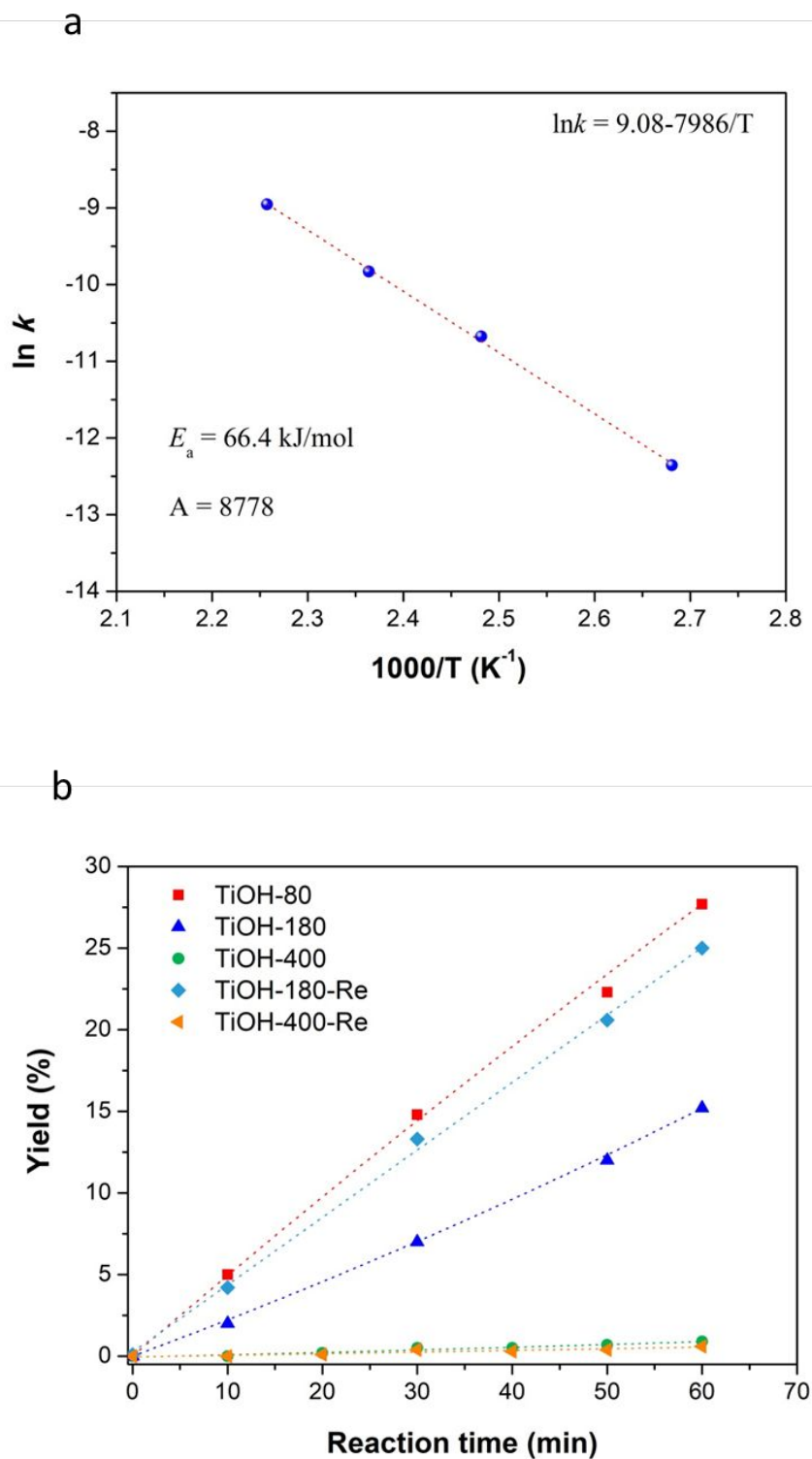


Figure 1 The Arrhenius plot of secondary amine yield for *N*-alkylation from benzyl alcohol and aniline over titanium hydroxide TiOH-80 (a) and time dependence for *N*-alkylation with catalysts before and after dehydration (b)

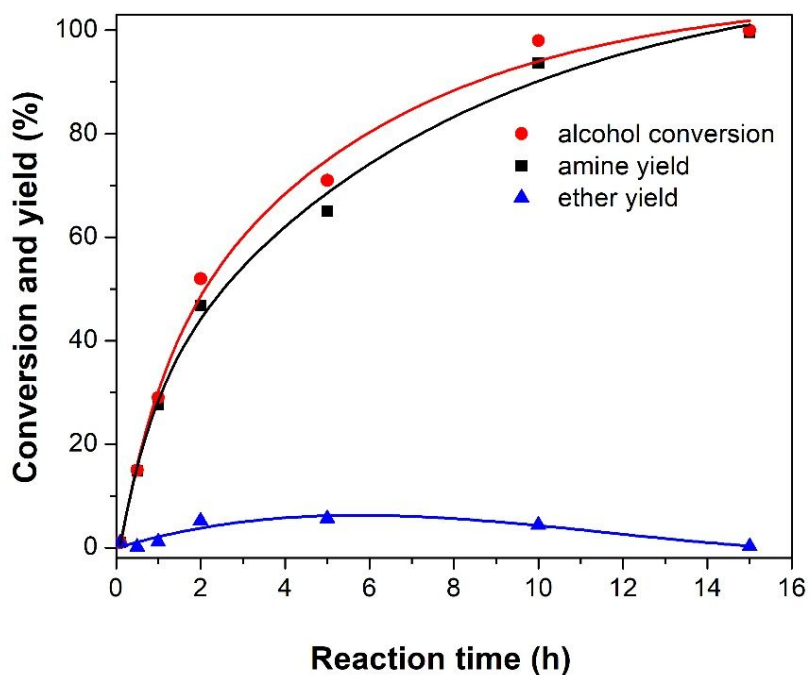


Figure 2 Time dependence on amine yield for *N*-alkylation from benzyl alcohol and aniline over titanium hydroxide. (Benzyl alcohol 4.62 mmol, aniline 21.5 mmol, xylene 2 g, catalyst 100 mg, 180 °C, atmospheric N₂.)

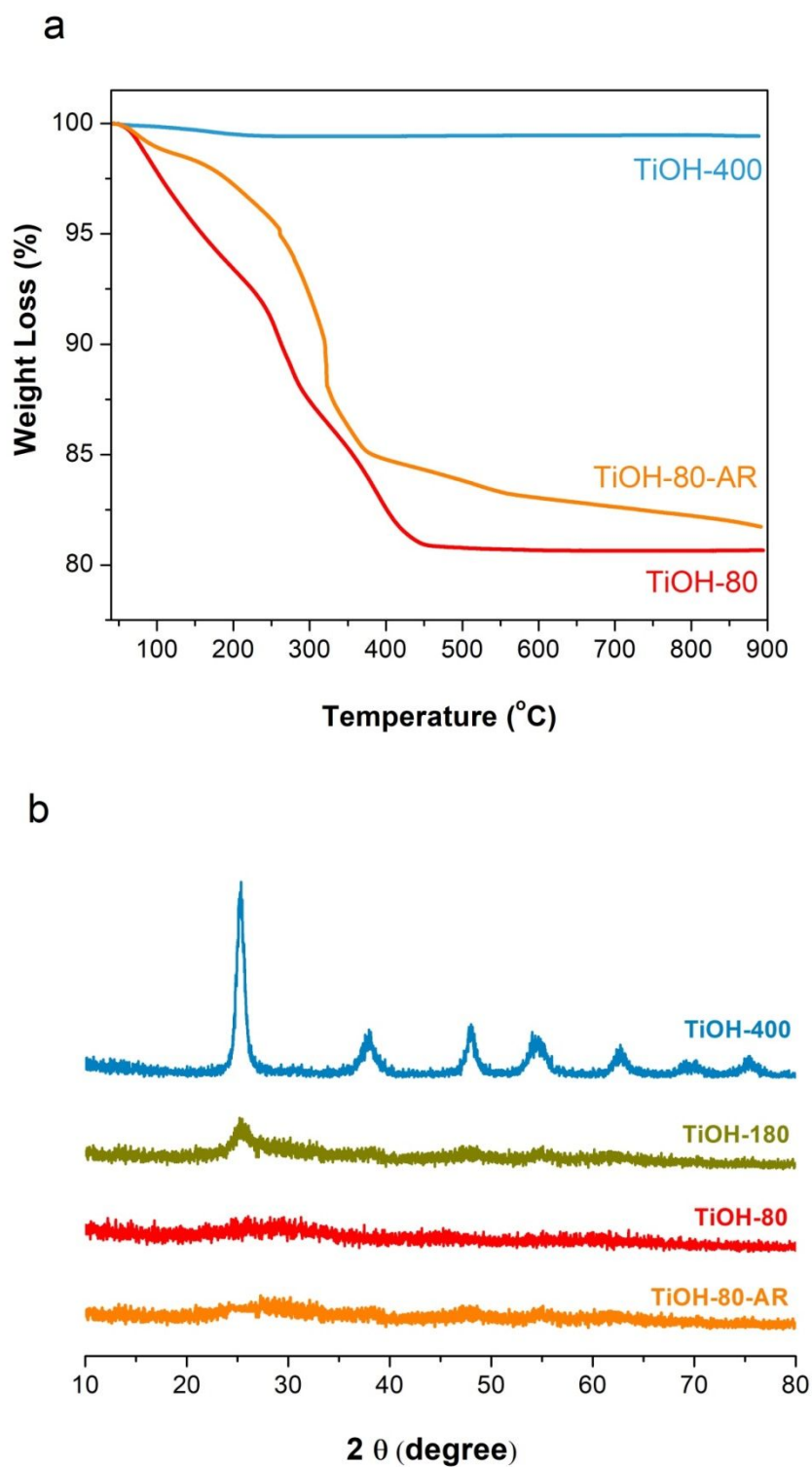


Figure 3 Characterization of titanium hydroxide catalysts using TG analysis (a) and XRD (b)

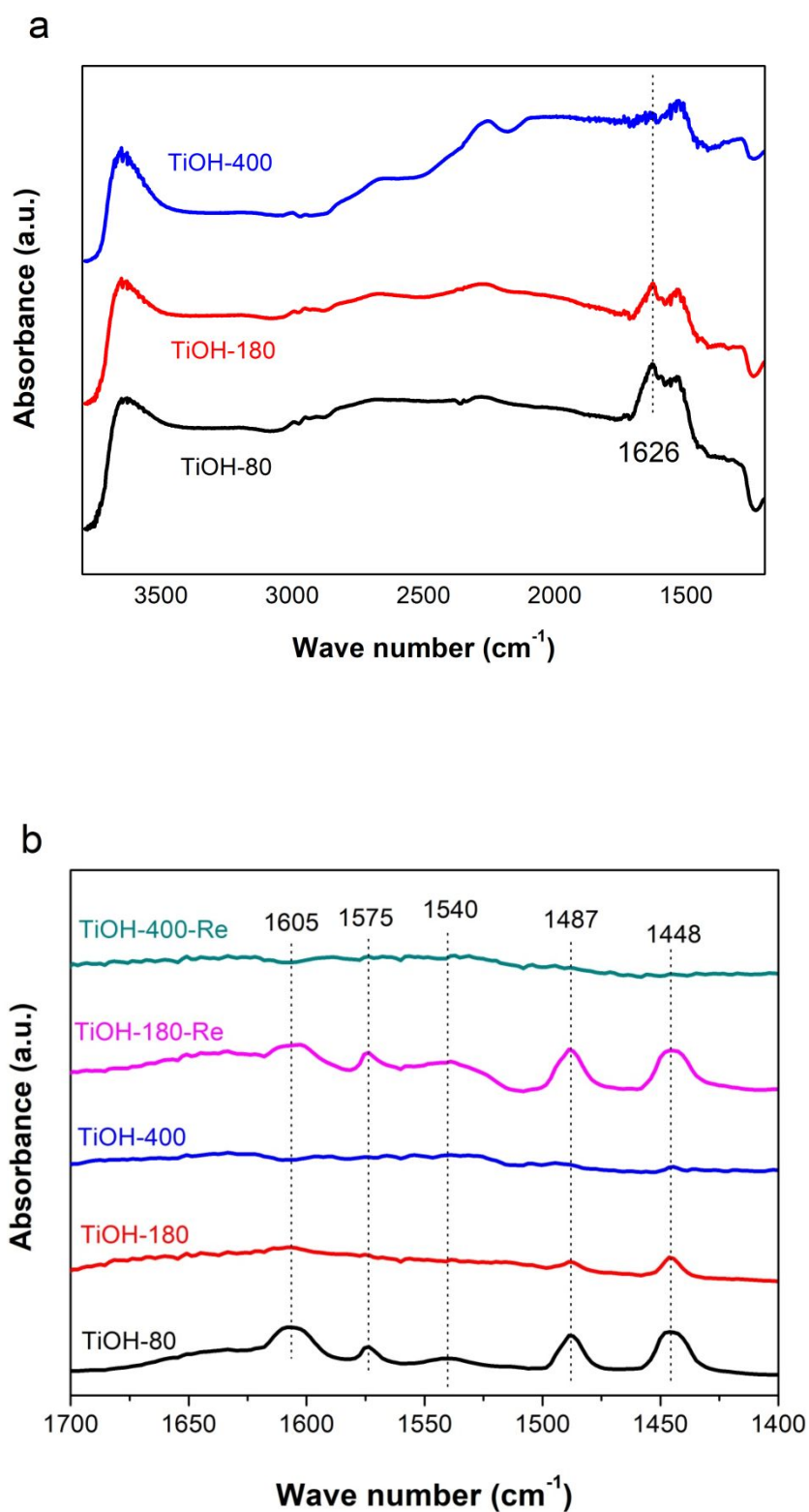
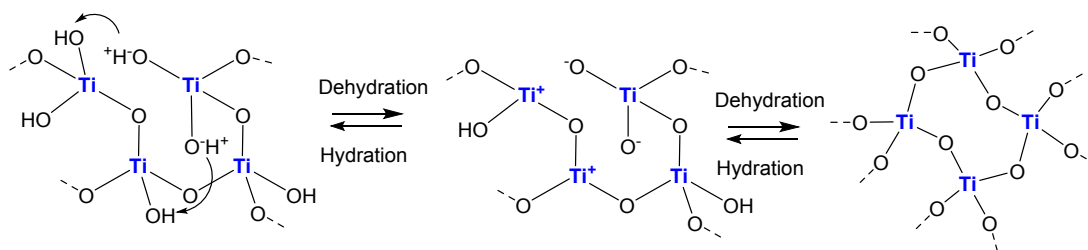


Figure 4 FTIR spectra of titanium hydroxide catalysts (a) and Py adsorption over titanium hydroxide catalysts (b)



13 **Figure 5** Proposed process of dehydration and rehydration for titanium hydroxide
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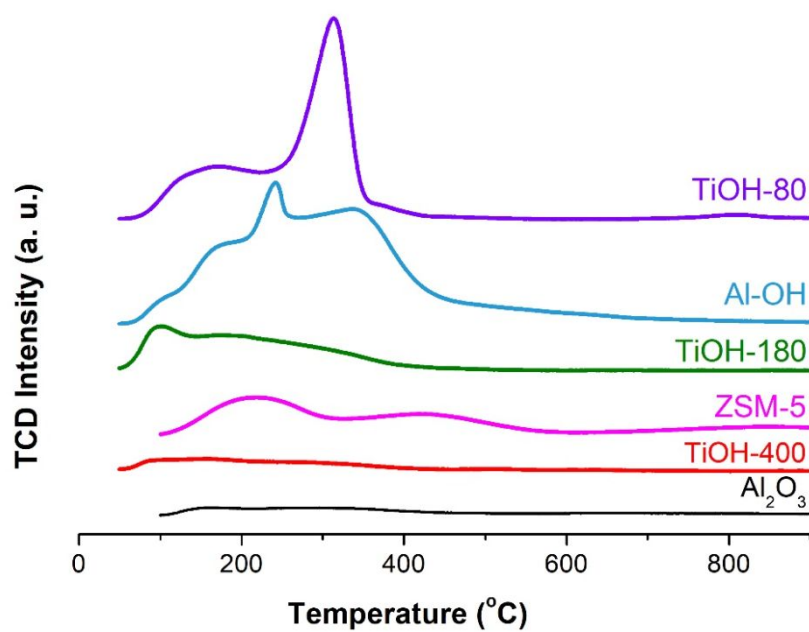


Figure 6 NH₃-TPD profiles of different samples

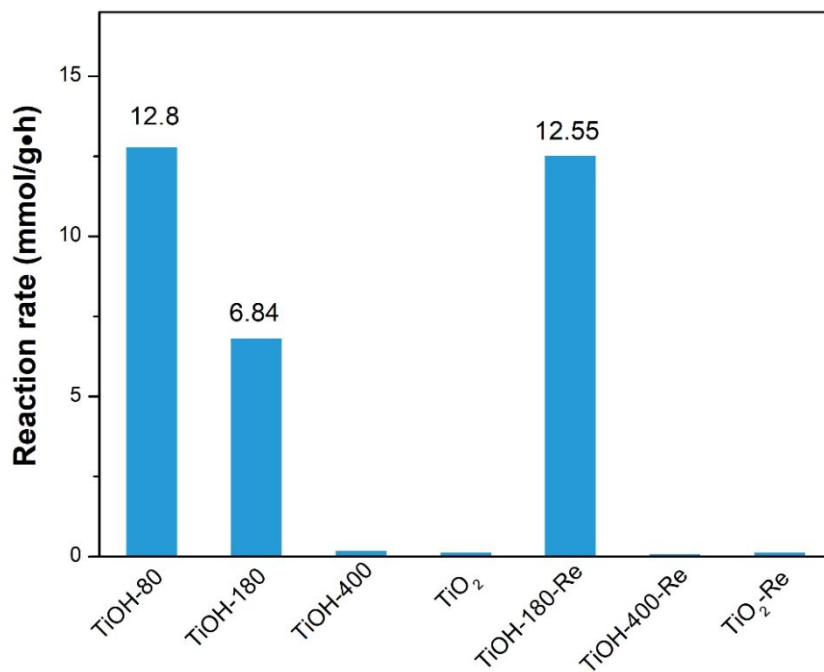


Figure 7 Comparison of the initial reaction rate for titanium hydroxide and calcined samples at different temperature (Benzyl alcohol 4.62 mmol, aniline 21.5 mmol, xylene 2 g, catalyst 100 mg, 15 h, atmospheric N₂).

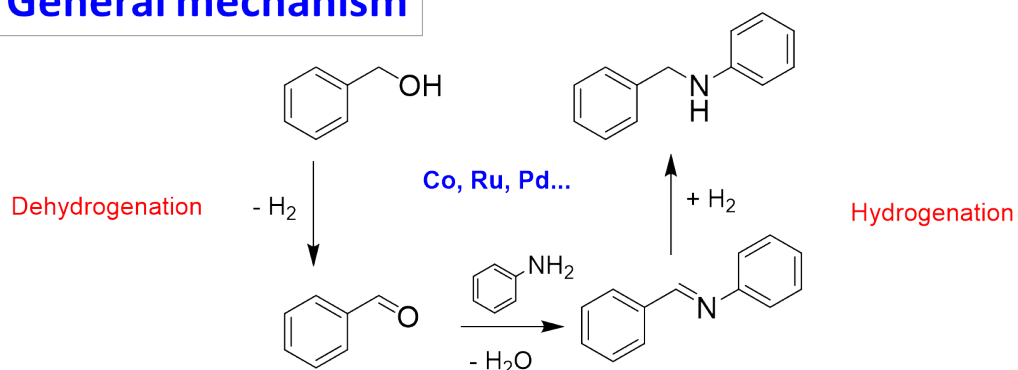
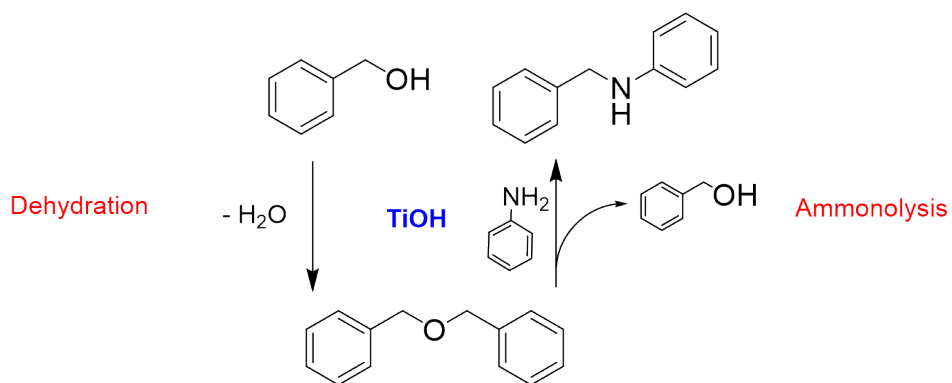
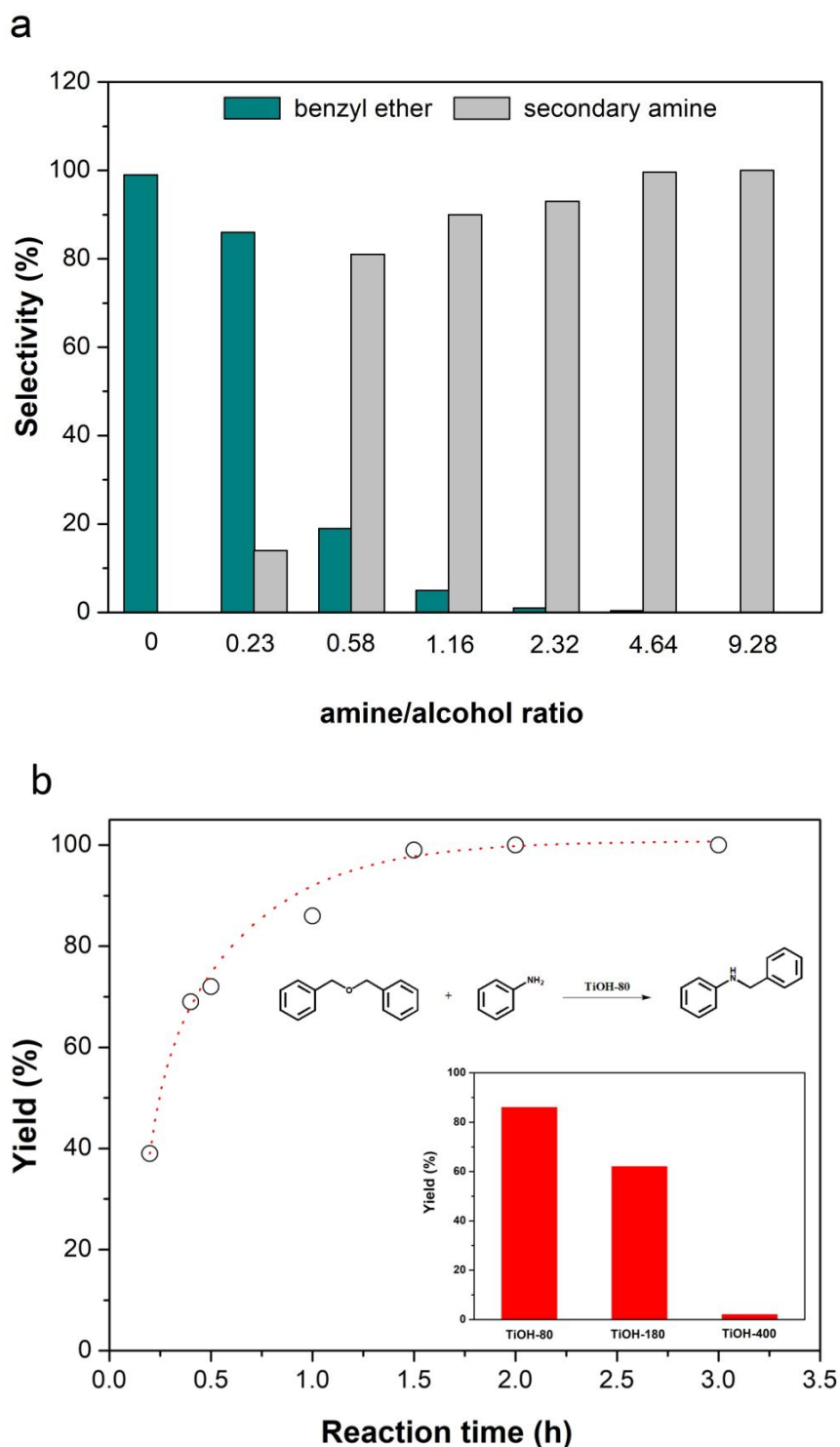
(a) General mechanism**(b) Our case**

Figure 8 (a) General hydrogen borrowing mechanism and (b) proposed non metallic mechanism through ether formation.



53 **Figure 9** (a) Products distribution under different amine/alcohol molar ratio. Condition: benzyl
54 alcohol 4.62 mmol, aniline/benzyl alcohol molar ratio 0-9.28, xylene 2 g, catalyst 100 mg, 15
55 h, atmospheric N₂. (b) Time dependence for amine formation directly from dibenzyl ether.
56 Condition: dibenzyl ether 5 mmol, aniline 20 mmol, xylene 2 g, catalyst 100 mg, atmospheric
57 N₂ (inset: reaction performed with different catalysts for 1 h).
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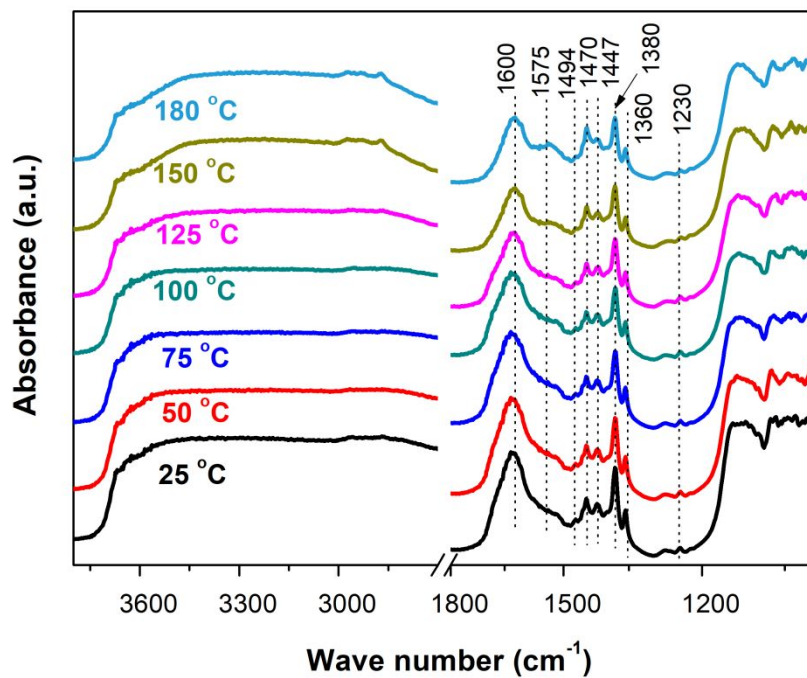


Figure 10 In-situ FTIR spectra of titanium hydroxide exposed to benzyl alcohol vapor calcined under different temperature.

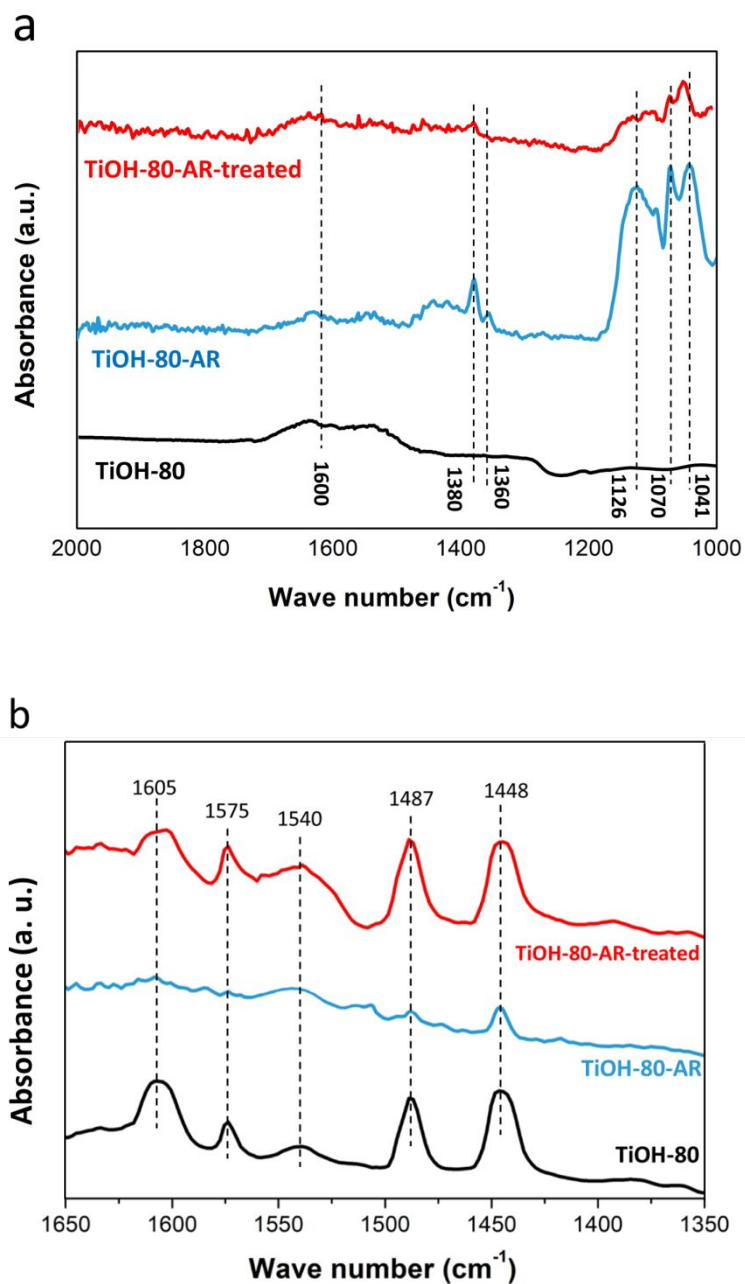


Figure 11 FTIR spectra of titanium hydroxide (a) and Py adsorption (b) before reaction (TiOH-80), after reaction (TiOH-80-AR) and treatment in xylene (TiOH-80-AR-treated)

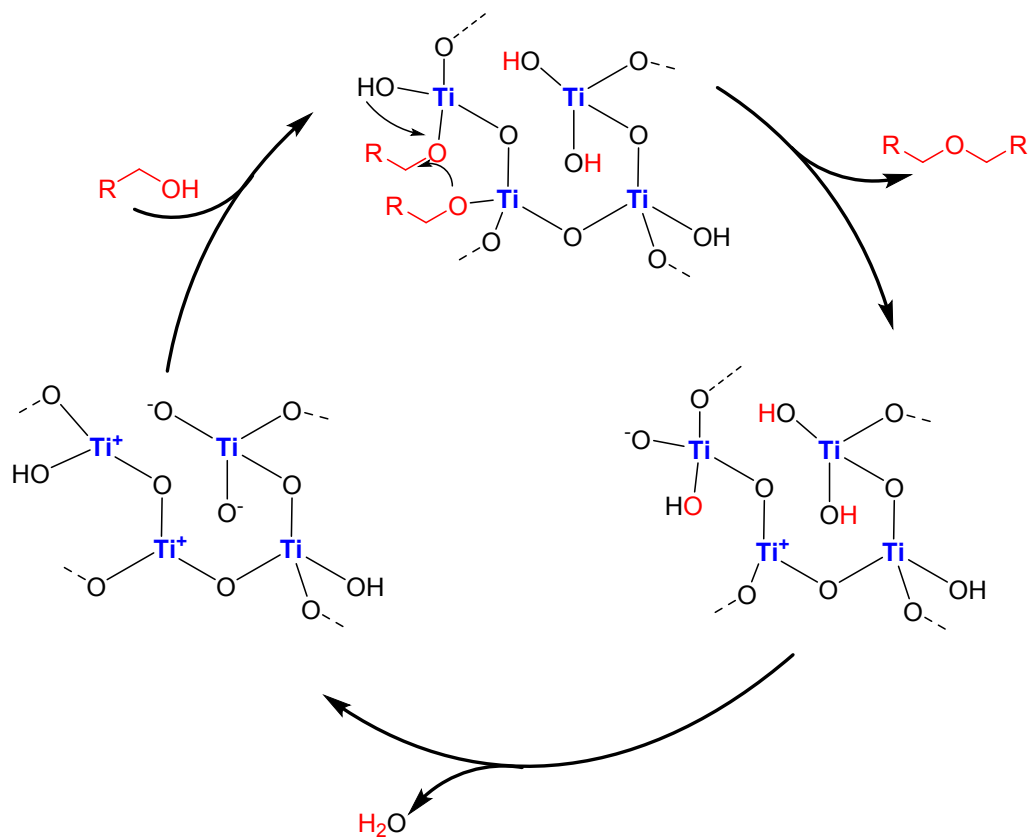


Figure 12 Scheme of the reaction mechanism of alcohol dehydration over TiOH.

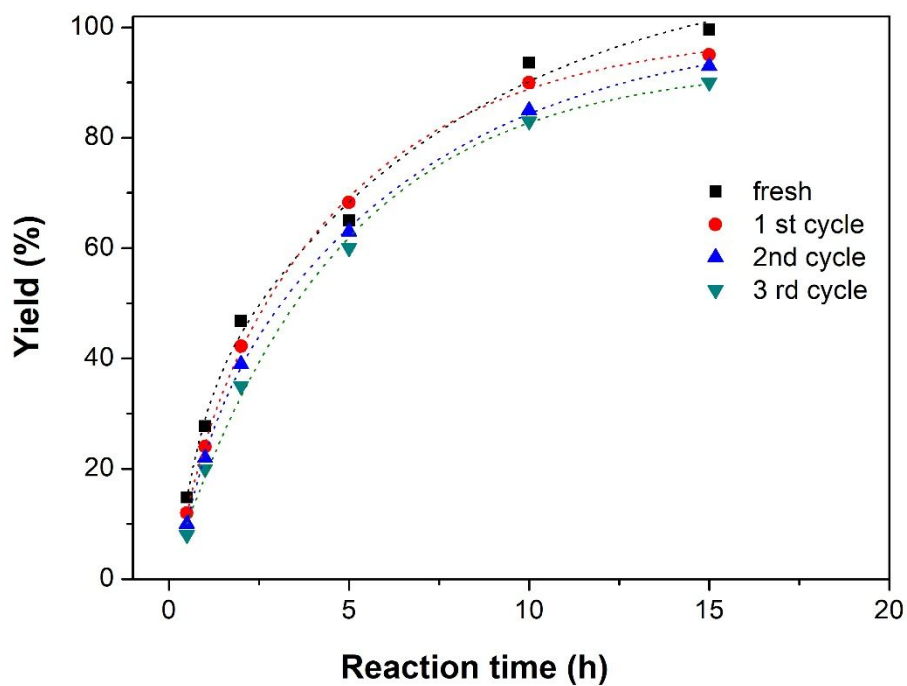
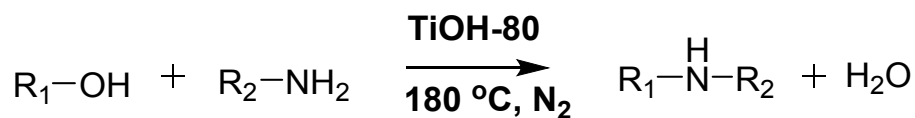
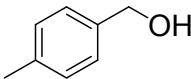
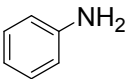
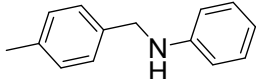
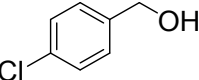
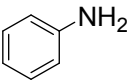
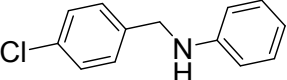
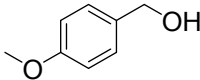
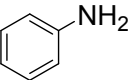
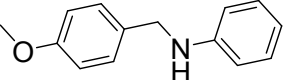
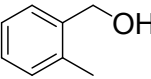
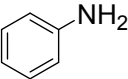
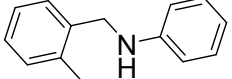
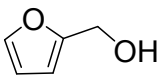
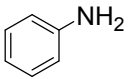
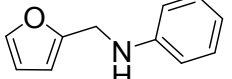
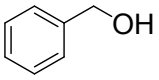
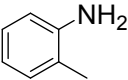
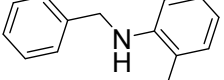
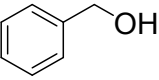
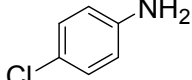
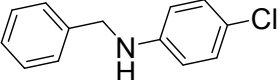
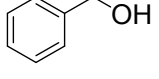
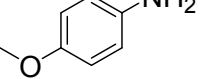
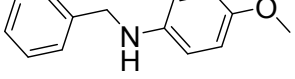
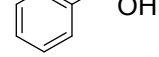
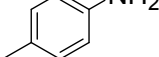
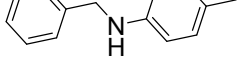
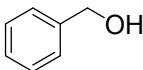
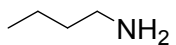
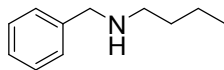
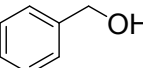
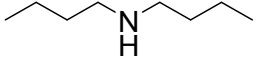
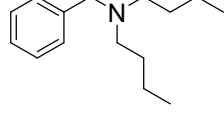
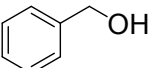
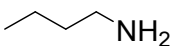
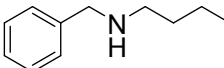
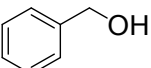
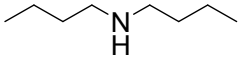
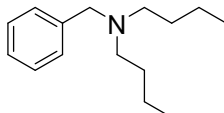
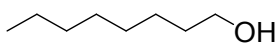
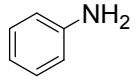
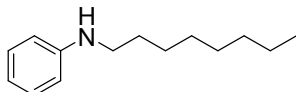
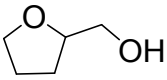
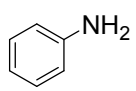
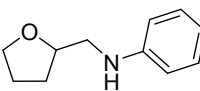

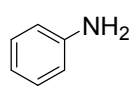
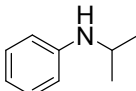
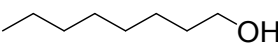
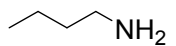
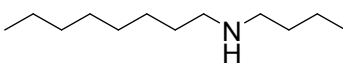

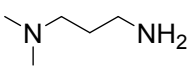
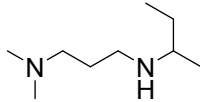
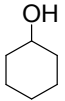
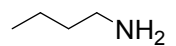
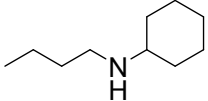
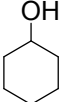
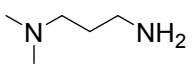
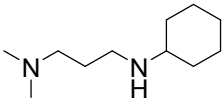


Figure 13 Reusability test of *N*-alkylation of benzyl alcohol with aniline using titanium hydroxide. Reaction conditions: alcohols (4.62 mmol), amines (21.5 mmol), xylene 2 g, catalyst 100 mg, reaction temperature 180 °C, 15 h, atmospheric N₂.

Table 2 Scope of alcohols and amines for amine synthesis^a

Entry	Alcohols	Amines	Products	Conv. %	Sele. %	Ethers (%)
1				99.4	100	0
2				99	100	0
3				97	98	0
4				90	91	2
5				100	98	0
6				99	95	0
7				99	97	0
8				100	99	0
9				100	99	0

1							
2							
3							
4							
5							
6	e10				78	62	30
7							
8							
9							
10	e11				69	40	54
11							
12							
13							
14							
15	d12				93	96	3
16							
17							
18							
19	d13				91	92	4
20							
21							
22							
23							
24							
25	e14				65	76	21
26							
27							
28							
29							
30	e15				62	68	24
31							
32							
33							
34							
35	e16				74	70	25
36							
37							
38							
39	f17				55	64	31
40							
41							
42							
43							
44	f18				60	61	34
45							
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48	f19				67	66	29
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53	f20				64	71	26
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60

^aReaction conditions: alcohols (4.62 mmol), amines (21.5 mmol), xylene 2 g, catalyst 100 mg, reaction temperature 180 °C, 15 h, atmospheric N₂; ^b24 h; ^c48 h; ^d48 h (alcohols 0.5 mmol, amines 2.3 mmol, xylene 2 g, catalyst 200 mg); ^e72 h; ^f96 h.

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