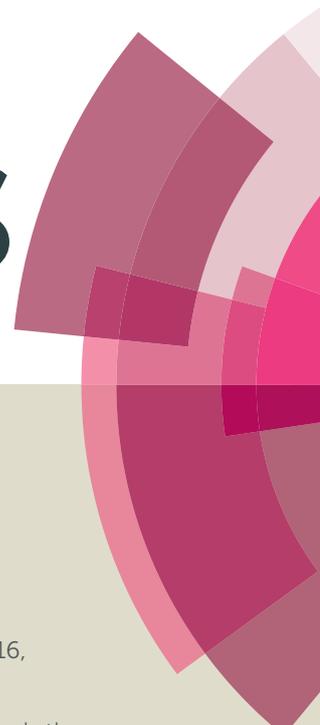


# RSC Advances



This article can be cited before page numbers have been issued, to do this please use: V. G. R. Peddiahgari, R. P. R. Bhoomireddy, D. Praveen Kumar, N. R. Bijivemula and M. V. Shankar, *RSC Adv.*, 2016, DOI: 10.1039/C5RA25064A.



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

*Accepted Manuscripts* are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



## Rapid synthesis of alkylaminophenols *via* Petasis Borono-Mannich reaction using protonated trititanate nanotubes as robust solid-acid catalyst

Received 00th January 20xx,  
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Bhoomireddy Rajendra Prasad Reddy,<sup>a</sup> Peddiahgari Vasu Govardhana Reddy,<sup>\*\*a</sup> Dharani Praveen Kumar,<sup>b</sup> Bijivemula N. Reddy<sup>c</sup> and Muthukonda V. Shankar<sup>\*b</sup>

An effective and rapid synthesis of alkylaminophenols using one-pot three-component Petasis Borono-Mannich (PBM) reaction was carried out using protonated trititanate (H<sub>2</sub>Ti<sub>3</sub>O<sub>7</sub>) nanotubes as a heterogeneous solid-acid catalyst. Complimentary to earlier reports, Ti-O based materials with various morphologies, such as fine particles, nanospheres, nanorods, and tubes were explored for their catalytic activity in PBM reaction. XRD pattern revealed the layered trititanate structure of nanotubes and nanorods; anatase and biphasic anatase-rutile structure for fine particles and nanospheres, respectively. Surface area analysis and NH<sub>3</sub>-TPD adsorption results confirmed the larger surface area and high concentration of Brønsted and Lewis acid sites present in H<sub>2</sub>Ti<sub>3</sub>O<sub>7</sub> nanotubes. The catalytic efficiency for PBM reaction is observed in the following order: H<sub>2</sub>Ti<sub>3</sub>O<sub>7</sub> nanotubes > H<sub>2</sub>Ti<sub>3</sub>O<sub>7</sub> nanorods > TiO<sub>2</sub> nanospheres > TiO<sub>2</sub> fine particles. The remarkable catalytic performance of H<sub>2</sub>Ti<sub>3</sub>O<sub>7</sub> nanotubes was ascribed to the plenty of hydroxy groups and high concentration of Brønsted and Lewis acid sites on the tubular surface, which is essential for adsorption and catalytic reaction. The recyclability of H<sub>2</sub>Ti<sub>3</sub>O<sub>7</sub> catalyst is another emphasis for the proposed methodology. For the first time, we reported novel alkylaminophenols bearing 2-(pyrimidin-2-yl)-2,5-diazabicyclo[2.2.1]heptane.

### 1. Introduction

The Petasis Borono-Mannich (PBM) reaction is a convenient one-pot three component reaction due to broad substrate scope, easy access to building blocks and amenability to combinatorial synthesis strategies, besides structurally diverse molecular libraries.<sup>1</sup> This PBM reaction can be useful for the synthesis of Conduramines,<sup>2a,b</sup> tetrahydroisoquinoline-1-carboxylic acids,<sup>2c</sup> 1, 4-benzodiazepine-3,5-diones,<sup>2d</sup> quinoxalines,<sup>2e</sup> α-amino acids,<sup>2f-k</sup> allylamines,<sup>2l</sup> 2H-chromenes,<sup>2m-o</sup> tertiary amines,<sup>2p,q</sup> 2-hydroxy-1,4-dihydrobenzoxazines,<sup>2r</sup> 1,2,3,4-tetrahydrocarbazoles,<sup>2s</sup> allenes,<sup>2t</sup> N-benzylpropargylamines,<sup>2u</sup> oxadiazolones & oxazolidinones,<sup>2v</sup> 2,5-dihydrofurans,<sup>2w</sup> α-amino alcohols,<sup>2x,y</sup> 2-amino morpholines,<sup>2z</sup> 2-hydroxymorpholines & amino diols,<sup>2aa</sup> α-hydrazinocarboxylic acids<sup>2ab</sup> and α-aryl glycines.<sup>2ac-ae</sup> In

general, the reaction tends to proceed exceptionally well when there is a free hydroxyl group on the aldehyde fragment, allowing the formation of an activated boronate complex. For the first time, Petasis and co-workers reported that organoboronic acids react with amines and salicylaldehydes to give alkylaminophenols.<sup>3</sup> Many improved procedures with new catalysts such as CuBr + bpy,<sup>4a,b</sup> BF<sub>3</sub>·OEt<sub>2</sub>,<sup>4c</sup> InBr<sub>3</sub>,<sup>2i</sup> Yb(OTf)<sub>3</sub>+ Pd(TFA)<sub>2</sub>,<sup>4d</sup> 4 Å MS<sup>4e</sup> and CoFe<sub>2</sub>O<sub>4</sub> nanoparticles<sup>4f</sup> for PBM reaction have been reported. On the other hand for green approach, chitosan,<sup>5a</sup> glycerol,<sup>5b</sup> ionic liquids ([bmim]BF<sub>4</sub>)<sup>5c</sup> and microwave irradiation<sup>5d</sup> were employed to accelerate the PBM reaction. The PBM reaction has also been developed in water,<sup>6a,b</sup> solvent free conditions<sup>6c</sup> and in solid-phase approach.<sup>6d</sup>

Nowadays, catalytic applications of metal and metal oxide nanoparticles in various organic transformations have gained much attention due to their stability under reaction conditions, dual acid/base properties, reusability, low toxicity, and non-hygroscopic properties.<sup>7</sup> Owing to these attractive features of nano-size metal oxide catalysts; we have focused on titanium oxide (TiO<sub>2</sub>) based nanostructures, which efficiently catalyze diverse synthetically important reactions.<sup>8</sup> Among TiO<sub>2</sub> nanomaterials, one-dimensional (1-D) nanostructures such as tubes, rods, and wires attracted much attention due to their unique properties *viz.*, large surface-to-volume-ratio, better dispersibility, decreased inter-crystalline contacts and increased accessibility of acid sites.<sup>8a-c, 9</sup> 1-D TiO<sub>2</sub> nanostructures have been extensively investigated in areas

<sup>a</sup> Department of Chemistry, Yogi Vemana University, Kadapa - 516 003, Andhra Pradesh, INDIA. Tel.: +91-9985200965; fax: +91-8562-225419; e-mail: [pvqr@yogivemanauniversity.ac.in](mailto:pvqr@yogivemanauniversity.ac.in)

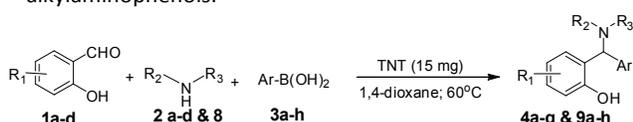
<sup>b</sup> Nano Catalysis and Solar Fuels Research Laboratory, Department of Materials Science & Nanotechnology, Yogi Vemana University, Kadapa - 516 003, Andhra Pradesh, INDIA. Tel.: +91-9966845899; fax: +91-8562-225419; e-mail: [shankar@yogivemanauniversity.ac.in](mailto:shankar@yogivemanauniversity.ac.in)

<sup>c</sup> Department of Chemistry, Vellore Institute of Technology, Vellore, Tamil Nadu, INDIA

† Electronic Supplementary Information (ESI) available: General experimental details, catalysts characterization, characterization data and copies of the NMR (<sup>1</sup>H & <sup>13</sup>C) spectra of all synthesized compounds, HRMS spectra of **4e**, **4p**, **9a** and **9d**; and EI-Mass Spectra of **4a** and **4b**. See DOI: 10.1039/x0xx00000x

such as organocatalysis, photocatalysis, electrocatalysis, sensors, lithium batteries and treatment of autoimmune diseases.<sup>10</sup> In the field of catalysis, most of the studies for the material are directed towards the utilization of the material as a support with a large surface area.

In our recent studies,  $H_2Ti_3O_7$  nanotubes (TNT) and nanorods (TNR) were used as efficient solid-acid catalysts for the synthesis of tertiary  $\alpha$ -aminophosphonates.<sup>11</sup> In continuation of our research interest on the introduction of nano-size  $TiO_2$  catalysts in organic synthesis, for the first time we report our investigations towards the synthesis of alkylaminophenols by one-pot three-component PBM reaction of *o*-hydroxybenzaldehydes, secondary amines, and boronic acids in the presence of three different Ti-O based nanostructures. Further, we also extended this reaction for the synthesis of 2-(pyrimidin-2-yl)-2,5-diazabicyclo[2.2.1]heptane derived alkylaminophenols.



Scheme 1. TNT catalyzed PBM reaction

## 2. Experimental

### 2.1. Hydrothermal synthesis of $H_2Ti_3O_7$ nanotubes and nanorods

High purity chemicals were used for the synthesis of catalysts. Photocatalyst grade titanium dioxide ( $TiO_2$  P-25) composed of anatase 80% and rutile 20% was procured from Degussa Corporation, Germany. Titanium dioxide (anatase 99%,  $TiO_2$ , LAB) was purchased from Merck, India. Analytical reagent (A.R) grade chemicals of sodium hydroxide pellets (97%), hydrochloric acid (37%), and ethanol (99.9) were supplied by Merck, India and used without any further purification. De-ionized water used for synthesis and washing process. In a typical synthesis process,  $TiO_2$  fine particles (2.5 g) dispersed in 10 M NaOH aqueous solution (200 mL) and heated either at 130 °C/20 h (for nanotubes) or 180 °C/20 h (for nanorods) in Teflon-lined autoclave (capacity 250 mL). The white precipitate obtained was subjected to washing twice with distilled water (800 mL) followed by dil. HCl (0.1 N, 200 mL), finally with ethanol (200 mL) and dried at 80 °C for 12 h.<sup>10c-g</sup> Thus obtained catalysts were denoted as TNT and TNR respectively. A portion of TNT was placed in a ceramic boat and calcined at 350 °C for 5 h at a heating rate of 2 °C  $min^{-1}$ . The resulting catalyst is denoted as calcined  $TiO_2$  nanotubes (cTNT).

### 2.2. General procedure for TNT catalyzed PBM reaction

To a magnetically stirred mixture of *o*-hydroxybenzaldehyde (1.0 mmol), secondary amine (1.3 mmol) and boronic acid (1.2 mmol) in 1,4-dioxane was added TNT (15 mg) and the mixture was stirred at 60 °C for respective times (Table 2 and Table 3). After completion of the reaction (TLC monitoring), the catalyst was separated by centrifugation and subsequent washing with EtOAc. The recovered catalyst was reused for next cycle. The

combined filtrates were washed with 0.15 N HCl (5 mL, to remove the excess secondary amine), 0.1 N NaOH (3 mL, to remove the excess boronic acid) and brine, then dried over anhydrous  $Na_2SO_4$ , filtered, and concentrated on a rotary evaporator to give pure product (not required column purification) as an oil, which slowly turned into colourless solid. The products were structurally assigned by their IR, NMR ( $^1H$  &  $^{13}C$ ) and mass spectral (HRMS) analysis.

## 3. Results and discussion

### 3.1. Morphology, Crystal structure and Surface properties of Ti-O based catalysts

HR-TEM image of TNT catalyst (Fig. 1a) showed a bundle of random aligned open ended nanotubes having length between 200 to 500 nm. The TEM image of single nanotube displays (Fig.1b) cylindrical in shape hollow inside, have four layers on the wall, the inner and outer diameters of the tubes have 3-5 nm and 8-12 nm, respectively. Fig. S1 (ESI<sup>†</sup>) shows the HR-TEM images of  $TiO_2$  fine particles (TFP),  $TiO_2$  nanospheres (TNP), TNR, and cTNT. The catalysts TFP and TNP displayed spherical particles with irregular shapes and dark spots observed due to overlapping of particles with each other. The particle size of TFP and TNP measures in the range of 60-160 nm and 23-28 nm, respectively. TNR catalyst showed the random alignment of rods and varied in length of rod > 1  $\mu m$ . The image of single nanorod confirms the clean surface completely filled inside. The calcined material cTNT displayed fragmented tubes, rods and particles at nanoscale which are laying one over another.

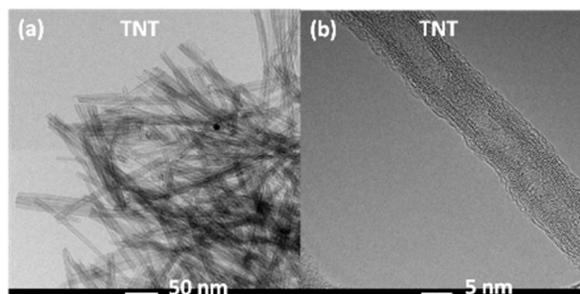


Fig. 1 HR-TEM images of TNT catalyst

The XRD pattern of TNT and TNR catalysts (Fig. 2) showed four characteristic peaks at  $2\theta = 10.2^\circ$  (200),  $24.1^\circ$  (202),  $28.3^\circ$  (112) and  $48.2^\circ$  (303), which can be well indexed as the monoclinic structure of layered  $H_2Ti_3O_7$  (JCPDS No. 47-0561). A characteristic diffraction peak exhibited at  $10.2^\circ$  illustrated the presence of typical layered crystal structure. The broad diffraction pattern of TNT and TNR suggests the moderate crystallinity of the catalysts. The XRD pattern of TFP, TNP and cTNT catalysts (Fig. S2, ESI<sup>†</sup>) showed characteristic diffraction peaks centred at  $2\theta = 25.4^\circ$  (101),  $37.5^\circ$  (004),  $48.3^\circ$  (200),  $53.9^\circ$  (105) and  $55.1^\circ$  (211) can be well indexed as anatase phase with tetragonal structure (JCPDS No. 21-1272). In the case of TNP and cTNT catalysts a minor peak at  $2\theta = 27.5^\circ$  (110) appeared which confirms the presence of rutile-

## RSC Advances

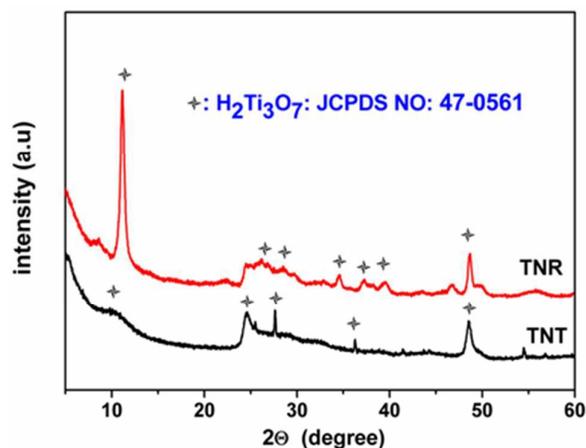
## PAPER

**Table 1.** Physical properties of various Ti-O based catalysts

Catalyst	Morphology	Crystal Phase	$S_{\text{BET}}^a$ ( $\text{m}^2 \cdot \text{g}^{-1}$ )	Acid concentration <sup>b</sup> ( $\text{mmol} \cdot \text{g}^{-1}$ )	
				BAS <sup>c</sup>	LAS <sup>d</sup>
TFP	Spherical	Anatase	5.1	n.d.	0.006
TNP	Spherical	Anatase/Rutile	51	n.d.	0.445
TNR	Rods	Trititanate	24	0.046	1.510
TNT	Tubes	Trititanate	286	1.613	2.162
cTNT	Rods, tubes and particles	Anatase/Rutile	57	n.d.	n.d.

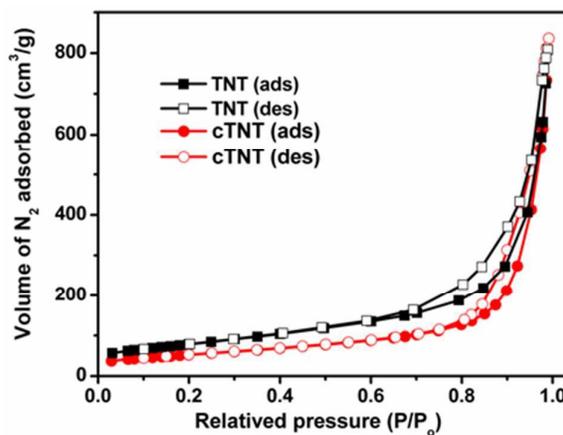
<sup>a</sup> surface area of titania nanostructures, <sup>b</sup> acid sites concentrations of the titania nanostructures were estimated from the  $\text{NH}_3$ -TPD, <sup>c</sup> Brønsted acid sites, <sup>d</sup> Lewis acid sites and n.d. = not detected.

phase with tetragonal structure (JCPDS No. 21-1276) in addition to anatase phase.

**Fig. 2** XRD patterns of TNT and TNR catalysts

The  $\text{N}_2$ -adsorption-desorption isotherms of TNT and cTNT (Fig. 3) showed typical type IV isotherms with a hysteresis loop at relative low-pressure  $P/P_0 \geq 0.8$ . According to the IUPAC classification, it confirms the mesoporous nature of TNT and cTNT.<sup>12</sup> Surface area of the catalysts were found to decrease in the following order  $\text{TNT} > \text{cTNT} > \text{TNP} > \text{TNR} > \text{TFP}$ . The standard  $\text{TiO}_2$  nanospheres showed surface area  $51 \text{ m}^2 \cdot \text{g}^{-1}$  is consistent with literature report.<sup>13</sup> The surface area of TFP is  $5.1 \text{ m}^2 \cdot \text{g}^{-1}$  which can be used as a precursor for the preparation of TNT and TNR. The BET surface area of as-synthesized TNT and TNR is 286 and  $24 \text{ m}^2 \cdot \text{g}^{-1}$  respectively, which is  $\sim 56$  and 4 folds higher than that of TFP. The surface area of cTNT catalyst was declined to  $57 \text{ m}^2 \cdot \text{g}^{-1}$ . The above results indicate that TNT has porous and nanotubular morphology resulting in a high

surface area that leads to a large volume of nitrogen adsorption both on the interior and exterior of the tubes. Fig. S3 (ESI<sup>+</sup>) shows the  $\text{N}_2$  adsorption-desorption isotherms TNP and TNR.

**Fig. 3**  $\text{N}_2$ -Adsorption-desorption Isotherms of TNT and cTNT catalysts

The pore size distribution curve of TNT by (Fig. 4) the BJH method consists of two portions with peak values of ca. 2.1-4.2 nm and 4.2-23 nm. Taking into account of the morphology of TNT, the smaller pores relates to the inner hollow spaces of the nanotubes; while, the larger pores refers to the pores between the nanotubes.<sup>14</sup> The cTNT exhibits pore with a larger size than TNT due to space between the deformed tubes, rods, and particles (Fig. 4). The pore size distribution curves of TNP and TNR (Fig. S4, ESI<sup>+</sup>) represents that there were no significant distribution peaks were observed for pores hence these catalysts are non-porous materials.

The Brønsted and Lewis acid sites on the catalysts were examined by probing desorption spectra of adsorbed ammonia using temperature programmed desorption analysis (TPD) (Fig. 5). The peak at high temperature region of TNT and TNR (302 °C for TNT, 326.1 °C for TNR)<sup>15</sup> and peak at 276.8 °C for TNP and 288 °C for TFP were observed (except cTNT), it is ascribed to Lewis acid sites of coordinatively unsaturated Ti<sup>4+</sup> sites present on the surface of the catalysts. Another peak noticed at the low-temperature region of TNT and TNR (160.9 °C for TNT and 148.8 °C for TNR)<sup>16</sup> which is assigned to Brønsted acid sites on TNT and TNR catalysts. This is attributed to linear Ti-OH and bridged Ti-OH-Ti sites present in TNT and TNR. In the case of cTNT, calcination at 400 °C for 5 h induced the dehydration (loss of surface -OH groups) accompanied by phase transformation to anatase-rutile biphasic material besides partial collapse of nanotubes to particles leading to a poor concentration of acid sites. The concentration of acid sites of catalysts are depicted in Table 1.

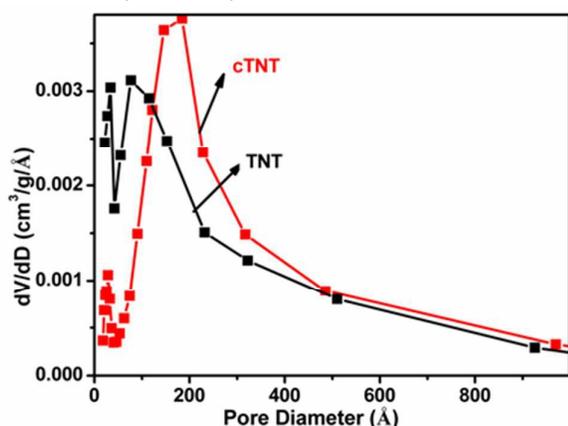


Fig. 4 BJH pore size distributions of TNT and cTNT catalysts

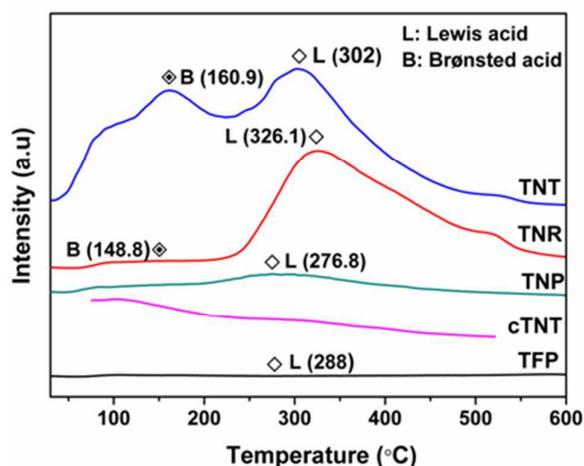


Fig. 5 NH<sub>3</sub>-TPD of TFP, TNP, TNR, TNT and cTNT catalysts

### 3.2. Catalytic activity

To develop an optimal catalyst for PBM reaction from Ti-O based catalysts, the synthesis of 2-(morpholino(phenyl)methyl) phenol (**4a**) via a three-component reaction of salicylaldehyde (**1a**), morpholine (**2a**) and phenylboronic acid (**3a**) and the

reaction was conducted in toluene at 60 °C. From Fig. 6 it is clearly evidenced that, the TFP and cTNT catalysts were displayed negligible catalytic activity whereas the catalytic activities of TNP and TNR were found to be moderate. In contrast to the catalytic activity of TFP, TNP, TNR and cTNT; the TNT exhibited significant catalytic performance with 75% of yield in 60 min and with an increase in reaction time, no improvement in the product yield was observed. However, the reaction did not occur in the absence of the catalyst.

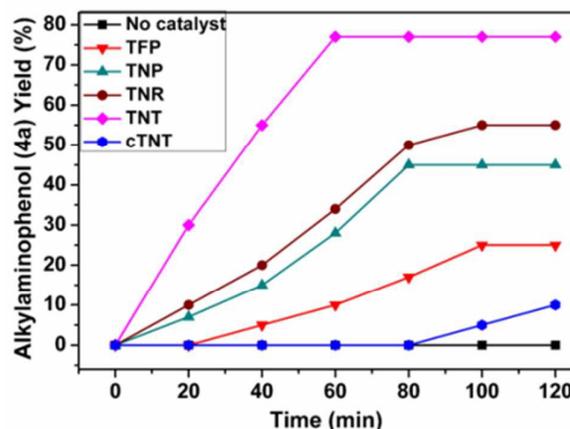
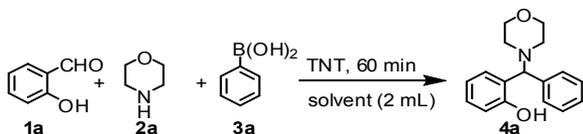


Fig. 6 Time courses of the alkylaminophenol (**4a**) formation using various Ti-O based catalysts.

Reaction conditions: Catalyst (20 mg), salicylaldehyde (1 mmol), morpholine (1 mmol), phenylboronic acid (1 mmol), toluene (2 mL) and at 60 °C.

Catalytic performance of Ti-O based catalysts is explained in terms of the concentration of acid sites, surface area and density of -OH groups present in catalyst systems (Table 1). Both TFP and TNP mainly composed of anatase phase, the larger surface area and a higher concentration of acid sites of TNP beneficial for obtaining a higher yield than TFP. The higher catalytic activity of TNR than TNP is ascribed to the presence of -OH groups on 1-D morphology, less agglomeration and more acid sites even though the surface area of TNR is nearly 50% lower. Although, TNT catalyst has similar crystalline structure and morphology however due to the presence of hollow inner space in TNT possess higher surface area than TNR itself. Surface area, Brønsted and Lewis acid sites concentration of TNT is about 11, 35 and 2 folds, respectively higher than TNR and the presence of large amount of -OH groups in TNT enhances the catalytic activity of TNT. The cTNT catalyst showed lowest reaction yield due to the absence of acid sites and surface -OH groups. It is explained that concentration of acid sites and amount of -OH groups is extremely important than the surface area of the same type of catalyst. Literature reports also illustrate that acid catalysts promote the PBM reaction effectively.<sup>2i, 4c,d & 5a</sup>

On the basis of this encouraging results, efforts were made to optimize the conditions (like the ratio of the substrates, solvents, catalyst loading and temperatures) to attain the best possible yield. Investigation on the ratio of reactants indicates-

**Table 2.** Optimization of reaction parameters

Entry	1a/2a/3a (ratio)	solvent	Catalyst loading (mg)	T (°C)	Yield <sup>a</sup> (%)
1	1.0/1.0/1.0	Toluene	20	60	75
2	1.0/1.1/1.1	Toluene	20	60	78
3	1.0/1.2/1.2	Toluene	20	60	81
4	1.0/1.3/1.2	Toluene	20	60	89
5	1.0/1.2/1.3	Toluene	20	60	83
6	1.0/1.3/1.3	Toluene	20	60	89
7	1.0/1.4/1.2	Toluene	20	60	89
8	1.0/1.3/1.2	Water	20	60	<10
9	1.0/1.3/1.2	Ethanol	20	60	<10
10	1.0/1.3/1.2	DMF	20	60	n.d.
11	1.0/1.3/1.2	DMSO	20	60	n.d.
12	1.0/1.3/1.2	MeCN	20	60	63
13	1.0/1.3/1.2	THF	20	60	52
14	1.0/1.3/1.2	---	20	60	<10
15	1.0/1.3/1.2	1,4-dioxane	20	60	96
<b>16</b>	<b>1.0/1.3/1.2</b>	<b>1,4-dioxane</b>	<b>15</b>	<b>60</b>	<b>96</b>
17	1.0/1.3/1.2	1,4-dioxane	12.5	60	89
18	1.0/1.3/1.2	1,4-dioxane	10	60	76
19	1.0/1.3/1.2	1,4-dioxane	15	40	83
20	1.0/1.3/1.2	1,4-dioxane	15	RT	51
21	1.0/1.3/1.2	1,4-dioxane	15	>80	79

The bold values are the most effective conditions for the model reaction. Reaction conditions: All reactions were performed on a 1 mmol scale with 2 mL solvent for 60 min. n.d. = not detected. <sup>a</sup> Isolated yield.

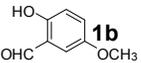
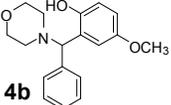
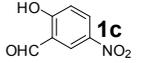
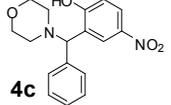
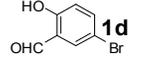
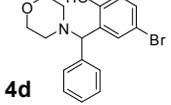
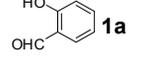
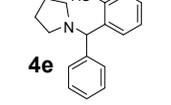
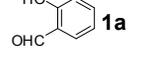
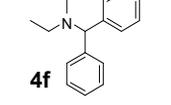
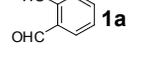
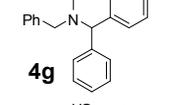
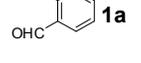
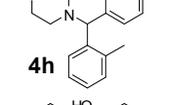
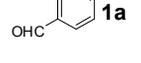
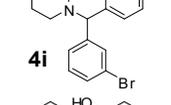
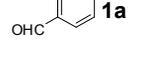
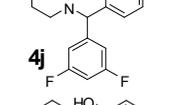
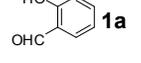
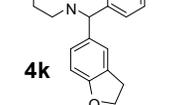
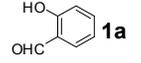
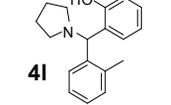
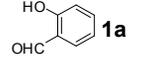
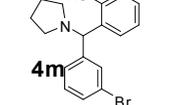
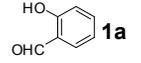
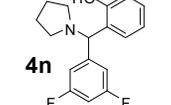
that a 1.0:1.3:1.2 ratio of **1a/2a/3a** gave the best result with an isolated yield 89% (Table 2, Entry 4). In the present study, use of 1.3 eq of amines and 1.2 eq boronic acids has specific advantage i.e. *o*-hydroxy aldehyde conversion was increased. These excess amines and boronic acids were conveniently removed by simple acid-base work up to avoid the usage of column separation.<sup>4f</sup> Subsequently, solvent screening showed that 1,4-dioxane provided an improved yield of 96% (Table 2, Entry 15), while MeCN, THF were less effective and afforded the product in 63% and 59% yields, respectively (Table 2, Entries 12 and 13). Replacement of toluene with other solvents, such as water, ethanol, DMF, DMSO and solvent free

**Table 3.** Coupling of *o*-hydroxybenzaldehydes, secondary amines and aryl/heteroaryl boronic acid catalyzed by TNT (15 mg) in 1, 4-dioxane.

Entry	Aldehyde (1a-d)	Amine (2a-e)	Boronic acid (3a-d)	Product (4a-r)	Time (min)	Yield <sup>a</sup> (%)
1					60	96

conditions, either delivered quite low yields (Table 2, Entries 8, 9 and 14) or gave no products (Table 2, Entries 10 and 11). Further, reducing the amount of catalyst to 10 mg (Table 2, Entry 18) down from 20 mg (Table 2, Entry 14), had a negative effect on the yield of the reaction. A compromise of 15 mg (Table 2, Entry 15), however, seemed to be sufficient. Likewise, reduction in temperature of the reaction also seemed to have a deleterious effect on the yield (Table 2, Entries 19-20). Further elevating the reaction temperature to 80 °C led to decrease in yield (Table 2, Entry 21) (possibly because of the volatility of the amine employed). As can be seen, from **Table 2** the best conditions for the synthesis of **4a** catalyzed by TNT is **Entry 16**.

Using the optimized reaction conditions, a variety of structurally different salicylaldehydes, secondary amines, and boronic acids were employed as reaction substrates, to explore the scope and generality of the TNT promoted PBM reaction. The results are outlined in **Table 3**. At the beginning of the investigation to the salicylaldehydes substrate scope, morpholine, and phenylboronic acid were used as model substrates and salicylaldehyde; 5-OCH<sub>3</sub>/5-NO<sub>2</sub>/5-Br substituted salicylaldehydes were examined for the PBM reaction (Table 3, entries 1-4). The results indicate that no significant changes in the yields were observed with different substituents on salicylaldehyde. In contrast, the reaction with benzaldehyde; 3-OH/2-OCH<sub>3</sub>/2-Cl substituted benzaldehydes were failed to participate in this reaction it indicates the importance of *ortho* hydroxy group on the aldehyde fragment. To expand the scope of secondary amine substrates, a combination of salicylaldehyde-phenylboronic acid-secondary amine was chosen and various amines were examined (Table 3, entries 1 & 5-7). The results indicate that cyclic (pyrrolidine/morpholine) and acyclic (diethyl/*N*-benzylmethyl) secondary amines gave excellent yields of products under the standard reaction conditions (Table 3, entries 1 and 5-7). However, no product was observed when diphenyl/benzyl amine as substrates and trace amount of product was obtained with a diisopropyl amine. Subsequently, a variety of boronic acids were also examined for the PBM reaction using salicylaldehyde and morpholine as model substrates (Table 3, entries 1 & 8-11). The reaction proceeded smoothly with phenylboronic acid and 2-Me/3-Br/3, 5-di-F substituted phenyl boronic acids and gave the corresponding alkylamino phenol in good yield (Table 3, entries 1 & 8-10). In the case of 2, 3-dihydrobenzofuran-5-ylboronic acid (Table 1, entry 11), 93% product yield was obtained. No desired product was observed when employed furan-3-ylboronic acid and pyridin-3-ylboronic acid.<sup>17</sup>

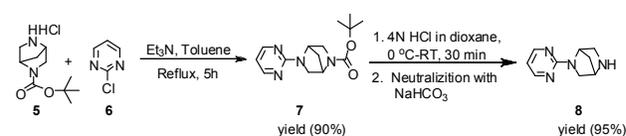
2					50	93
3					65	88
4					60	90
5					45	98
6					50	97
7					60	90
8					55	87
9					60	96
10					50	85
11					50	93
12					60	89
13					60	97
14					65	89

15					90	87
16					55	94
17					60	87

Reaction conditions: *o*-hydroxybenzaldehyde (1 mmol), secondary amine (1.3 mmol), boronic acid (1.2 mmol), TNT (15 mg), 1,4-dioxane (2 mL) and at 60 °C. <sup>a</sup> Isolated yield.

The applicability of optimized reaction conditions was further extended to the synthesis of novel 2-(pyrimidin-2-yl)-2,5-diazabicyclo[2.2.1]heptane bearing alkylaminophenols (**9a-h**) using as synthesized 2-(pyrimidin-2-yl)-2,5-diazabicyclo[2.2.1]heptane (**8**), *o*-hydroxybenzaldehydes and boronic acids. 2-(Pyrimidin-2-yl)-2,5-diazabicyclo[2.2.1]heptane (**8**) can be synthesized from *tert*-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate hydrochloride (**5**) and 2-chloropyrimidine (**6**) in the presence of triethylamine in toluene at reflux temperatures for five hours to form *tert*-butyl-5-(pyrimidin-2-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**7**) and subsequently

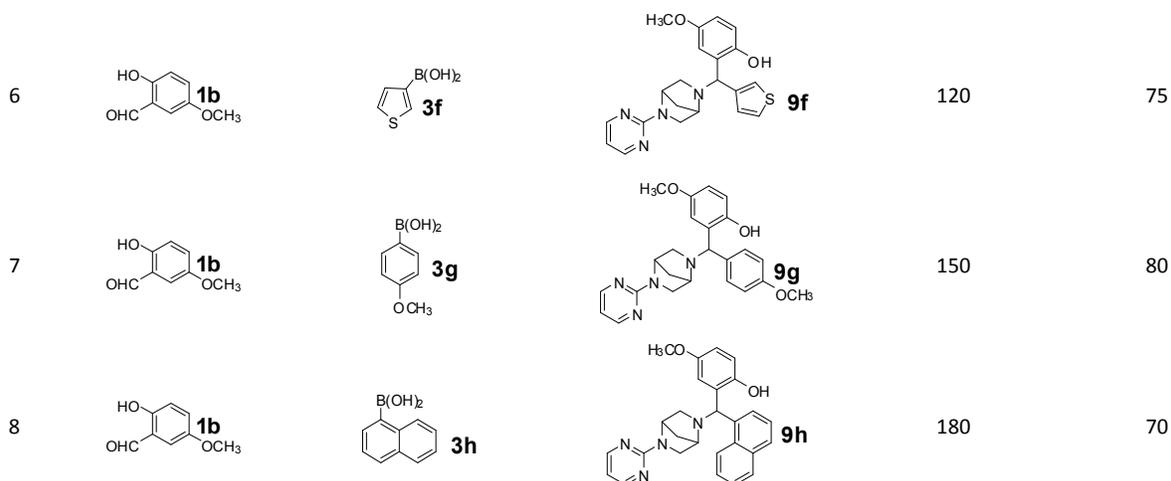
deprotection of *tert*-butyl carboxylate group of **7** with dioxane-HCl in dichloromethane (**Scheme 2**).



**Scheme 2.** Synthesis of 2-(pyrimidin-2-yl)-2,5-diazabicyclo[2.2.1]heptane

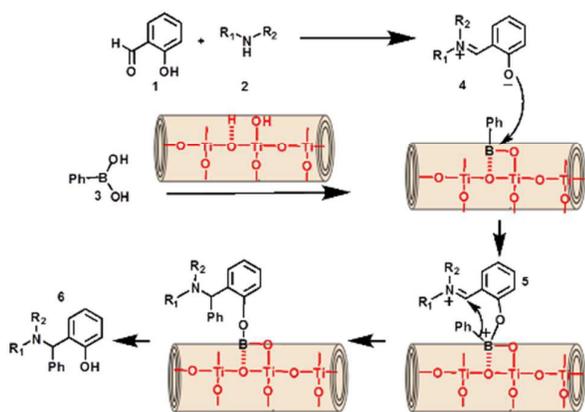
**Table 4.** Coupling of *o*-hydroxybenzaldehydes, 2-(pyrimidin-2-yl)-2,5-diazabicyclo[2.2.1]heptane and aryl/heteroaryl boronic acid catalyzed by TNT (15 mg) in 1,4-dioxane.

Entry	Aldehyde ( <b>1a, b</b> )	Boronic acid ( <b>3a, b &amp; 3f-h</b> )	Product ( <b>9a-h</b> )	Time (min)	Yield <sup>a</sup> (%)
1				90	81
2				120	79
3				90	82
4				120	79
5				180	75



Reaction conditions: *O*-hydroxybenzaldehyde (1 mmol), 2-(pyrimidin-2-yl)-2,5-diazabicyclo [2.2.1] heptane (1.3 mmol), boronic acid (1.2 mmol), TNT (15 mg), 1,4-dioxane (2 mL) and at 60 °C. <sup>a</sup> Isolated yield.

From these results, a plausible mechanism is proposed for the process of TNT catalyzed PBM reaction. Initially, a nucleophilic addition of the amine to *o*-hydroxy aldehyde produced the key iminium intermediate (**4**). Co-ordination between the oxygen anion of phenolate and the boron atom of boronic acid lead to the formation of a tetracoordinate borate (**5**) intermediate. Subsequently, the aryl carbanion moiety of boronic acid favorably attacked the iminium ion. Finally, hydrolysis took place to form the desired product (**6**) by the loss of a boric acid (**Fig.7**).



**Fig. 7** Plausible mechanism for TNT catalyzed PBM reaction

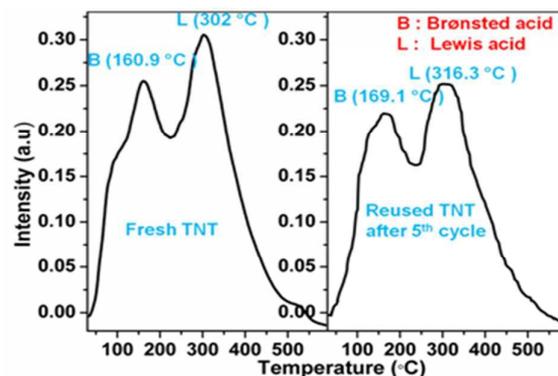
For practical applications of heterogeneous catalysts, the level of reusability is a very important factor. The recyclability of TNT catalyst was investigated in the coupling reaction of salicylaldehyde, morpholine, and phenylboronic acid. After each run, the TNT catalyst was separated by centrifugation, washed twice with EtOAc and dried in an oven at 100 °C for 6 h. The recovered TNT catalyst was reused for five times in this PBM reaction and smooth loss of activity was observed from the 4<sup>th</sup> cycle (**Table 5**). It may be due to the decrease in

concentration of acid sites on the catalyst surface. Which is confirmed by NH<sub>3</sub>-TPD experiment, the concentration of Brønsted and Lewis acid sites of TNT after the 5<sup>th</sup> cycle was found to be 0.826 and 1.721 mmol g<sup>-1</sup>, respectively (**Fig. 8**).

**Table 5.** TNT Catalyst recycling studies in the coupling of salicylaldehyde, morpholine, and phenylboronic acid.

Run	1	2	3	4	5
Yield <sup>a</sup> (%)	96	96	96	93	86

Reaction conditions: Salicylaldehyde (1 mmol), morpholine (1.3 mmol), phenylboronic acid (1.2 mmol), TNT (15 mg), 1,4-dioxane (2 mL), at 60 °C and for 60 min. <sup>a</sup> Isolated yield.



**Fig. 8** NH<sub>3</sub>-TPD profile of (a) Fresh TNT and (b) Reused TNT after the fifth cycle.

### 3. Conclusion

We demonstrated here that PBM reaction can run in the presence of Ti-O based solid-acid catalysts. Among them, H<sub>2</sub>Ti<sub>3</sub>O<sub>7</sub> nanotubes showed the remarkable catalytic performance due to the presence of sufficient Brønsted and Lewis acid sites and -OH groups on the large surface area of nanotubes. This method offers several advantages including: 1) good to excellent yields for a variety of substrates in short

reaction times, 2) simple work-up procedure (not required column purification), 3) catalyst is readily prepared from available low cost starting materials, 4) catalyst has very good stability in air, moisture and elevated temperatures and 5) high recoverability and the reusability of the catalyst. Further, it is worthy to mention that first time we have shown the synthesis of alkylaminophenols from 2-(pyrimidin-2-yl)-2,5-diazabicyclo-[2.2.1]heptane.

## Acknowledgements

Financial support from Department of Atomic Energy, Board of Research in Nuclear Sciences (2012/37C/33/BRNS), Mumbai, India and Department of science and technology (SR/FT/CS-013/2010/DST), New Delhi, India is gratefully acknowledged. B.R.P Reddy thanks to the CSIR-UGC, New Delhi, India for the award of Junior Research Fellowship. Authors thankful to coordinator, DST-FIST, Department of Physics, YV University for providing XRD facility. Authors are thankful to Dr. M. Karthik and Dr. V. Roddatis of CIC ENERGIGUNE, Spain for their support in the characterization of catalysts.

## References

- (a) N. Kumagai, G. Muncipinto and S. L. Schreiber, *Angew. Chem. Int. Ed.* 2006, **45**, 3635-3638; (b) G. Muncipinto, T. Kaya, J. A. Wilson, N. Kumagai, P. A. Clemons and S. L. Schreiber, *Org. Lett.* 2010, **12**, 5230-5233; (c) T. E. Nielsen and S. L. Schreiber, *Angew. Chem. Int. Ed.* 2008, **47**, 48-56.
- (a) P. Ghosal and A. K. Shaw, *J. Org. Chem.* 2012, **77**, 7627-7632; (b) A. Rajender and B. V. Rao, *Tetrahedron Lett.* 2013, **54**, 2329-2331; (c) M. Chrzanowska, A. Grajewska, Z. Meissner, M. Rozwadowska and I. Wiatrowska, *Tetrahedron* 2012, **68**, 3092-3097; (d) S. Noushini, M. Mahdavi, L. Firoozpour, S. Moghimi, A. Shafiee and A. Foroumadi, *Tetrahedron*, 2015, **71**, 6272-6275; (e) M. Ayaz, J. Dietrich and C. Hulme, *Tetrahedron Lett.* 2011, **52**, 4821-4823; (f) P. G. Cornier, C. M. L. Delpiccolo, D. B. Boggian and E. G. Mata, *Tetrahedron Lett.* 2013, **54**, 4742-4745; (g) P. F. Kaiser, Q. I. Churches and C. A. Hutton, *Aust. J. Chem.* 2007, **60**, 799-810; (h) N. A. Petasis and I. A. Zavialov, *J. Am. Chem. Soc.* 1997, **119**, 445-446; (i) Y. Li and M. H. Xu, *Org. Lett.* 2012, **14**, 2062-2065; (j) T. Koolmeister, M. Sodergren and M. Scobie, *Tetrahedron Lett.* 2002, **43**, 5965-5968; (k) H. Jourdan, G. Gouhier, L. V. Hijfte, P. Angibaud and S. R. Piettre, *Tetrahedron Lett.* 2005, **46**, 8027-8031; (l) N. A. Petasis and I. Akritopoulou, *Tetrahedron Lett.* 1993, **34**, 583-586 (m) Q. Wang and M. G. Finn, *Org. Lett.* 2000, **2**, 4063-4065; (n) G. W. Kabalka, B. Venkataiah and B. C. Das, *Synlett*, 2004, 2194-2196; (o) N. A. Petasis and A. N. Butkevich, *J. Organomet. Chem.* 2009, **694**, 1747-1753; (p) J. Wang, P. Li, Q. Shen and G. Song, *Tetrahedron Lett.* 2014, **55**, 3888-3891; (q) K. J. Koroluk, D. A. Jackson, and A. P. Dicks, *J. Chem. Educ.* 2012, **89**, 796-798; (r) L. Chouguat, R. Boulcina, B. Carboni, A. Demonceau and A. Debache, *Tetrahedron Lett.* 2014, **55**, 5124-5128; (s) S. Neogi, A. Roy and D. Naskar, *J. Comb. Chem.* 2010, **12**, 617-629; (t) D. A. Mundal, K. E. Lutz and R. J. Thomson, *J. Am. Chem. Soc.* 2012, **134**, 5782-5785; (u) H. Feng, H. Jia, and Z. Sun, *J. Org. Chem.* 2014, **79**, 11812-11818; (v) S. T. L. Quement, T. Flagstad, R. J. T. Mikkelsen, M. R. Hansen, M. C. Givskov and T. E. Nielsen, *Org. Lett.* 2012, **14**, 640-643; (w) C. X. Cui, H. Li, X. J. Yang, J. Yang and X. Q. Li, *Org. Lett.* 2013, **15**, 5944-5947; (x) N. A. Petasis and I. A. Zavialov, *J. Am. Chem. Soc.* 1998, **120**, 11798-11799; (y) G. K. S. Prakash, M. Mandal, S. Schweizer, N. A. Petasis and G. A. Olah, *Org. Lett.* 2000, **2**, 3173-3176; (z) T. Regnier, F. Berree, O. Lavastre and B. Carboni, *Green Chem.* 2007, **9**, 125-126; (aa) F. Berree, A. Debache, Y. Marsac, B. Collet, P. G. L. Bleiz and B. Carboni, *Tetrahedron*, 2006, **62**, 4027-4037; (ab) D. E. Portlock, D. Naskar, L. West and M. Li, *Tetrahedron Lett.* 2002, **43**, 6845-6847; (ac) N. A. Petasis, A. Goodman and I. A. Zavialov, *Tetrahedron*, 1997, **53**, 16463-16470; (ad) D. Font, M. Heras and J. M. Villalgorido, *Tetrahedron*, 2008, **64**, 5226-5235; (ae) N. J. McLean, H. Tye and M. Whittaker, *Tetrahedron Lett.* 2004, **45**, 993-995.
- N. A. Petasis and S. Boral, *Tetrahedron Lett.* 2001, **42**, 539-542.
- (a) R. Frauenlob, C. Garcia, G. A. Bradshaw, H. M. Burke and E. Bergin, *J. Org. Chem.* 2012, **77**, 4445-4449; (b) R. Frauenlob, C. Garcia, S. Butler and E. Bergin, *Appl. Organometal. Chem.* 2014, **28**, 432-435; (c) S. Stas and K. A. Tehrani, *Tetrahedron*. 2007, **63**, 8921-8931; (d) T. Beisel and G. Manolikakes, *Org. Lett.* 2013, **15**, 6046-6049; (e) X. Shi, D. Hebrult, M. Humora, W. F. Kiesman, H. Peng, T. Talreja, Z. Wang and Z. Xin, *J. Org. Chem.* 2012, **77**, 1154-1160; (f) A. M. Kulkarni, K. S. Pandit, P. V. Chavan, U. V. Desai and P. P. Wadgaonkar, *RSC. Adv.* 2015, **5**, 70586-70594.
- (a) S. S. Reddy, B. R. P. Reddy and P. V. G. Reddy, *Tetrahedron Lett.* 2015, **56**, 4984-4989; (b) T. Rosholm, P. M. P. Gois, R. Franzen and N. R. Candeias, *Chemistry Open*, 2015, **4**, 39-46; (c) J. S. Yadav, B. V. Subba Reddy and P. N. Lakshmi, *J. Mol. Catal. A: Chem.* 2007, **274**, 101-104; (d) M. Follmann, F. Gaul, T. Schafer, S. Kopec and P. Hamley, *Synlett.* 2005, 1009-1011.
- (a) N. R. Candeias, L. F. Veiros, C. A. M. Afonso and P. M. P. Gois, *Eur. J. Org. Chem.* 2009, 1859-1863; (b) N. R. Candeias, P. M. S. D. Cal, V. Andre, M. T. Duarte, L. F. Veiros, P. M. P. Gois, *Tetrahedron*, 2010, **66**, 2736-2745; (c) L. Ying, W. Limin, S. Yuanyuan and Y. Jianjun, *Chin. J. Chem.* 2010, **28**, 2039-2044; (d) S. R. Klopfenstein, J. J. Chen, A. Golebiowski, M. Li, S. X. Peng and X. Shao, *Tetrahedron Lett.* 2000, **41**, 4835-4839; (e) A. Golbiowski, S. R. Klopfenstein, J. J. Chen and X. Shao, *Tetrahedron Lett.* 2000, **41**, 4841-4844.
- (a) A. Dandia, V. Parewa, S. L. Gupta, A. Sharma, K. S. Rathore, A. Sharma and A. Jain, *Catal. Commun.* 2015, **61**, 88-91; (b) S. Bajpai, S. Singh and V. Srivastava, *RSC Adv.* 2015, **5**, 28163-28170; (c) F. Nemati, A. Elhampour, H. Farrokhi and M. B. Natanzi, *Catal. Commun.* 2015, **66**, 15-20; (d) E. Mosaddegh and A. Hassankhani, *Catal. Commun.* 2015, **71**, 65-69; (e) A. Farrokhi, K. Ghodrati and I. Yavari, *Catal. Commun.* 2015, **63**, 41-46; (f) R. Yang, T. Tao, Y. Dai,

## PAPER

## RSC Advances

- Z. Chen, X. Zhang and Q. Song, *Catal. Commun.* 2015, **60**, 96-99.
- 8 (a) M. Kitano, K. Nakajima, J. N. Kondo, S. Hayashi and M. Hara, *J. Am. Chem. Soc.* 2010, **132**, 6622-6623; (b) M. Kitano, E. Wada, K. Nakajima, S. Hayashi, S. Miyazaki, H. Kobayashi and M. Hara, *Chem. Mater.* 2013, **25**, 385-393; (c) E. Wada, M. Kitano, K. Nakajima and M. Hara, *J. Mater. Chem. A* 2013, **1**, 12768-12774; (d) M. L. Kantam, S. Laha, J. Yadav and B. Sreedhar, *Tetrahedron Lett.* 2006, **47**, 6213-6216; (e) M. L. Kantam, S. Laha, J. Yadav, B. M. Choudary and B. Sreedhar, *Adv. Synth. Catal.* 2006, **348**, 867-872; (f) S. M. Baghbanian, M. Farhang and R. Baharfar, *Chin. Chem. Lett.* 2011, **22**, 555-558; (g) M. H. Sarvari, *Tetrahedron*, 2008, **64**, 5459-5466; (h) M. Z. Kassaee, H. Masrouri, F. Movahedi and R. Mohammadi, *Helv. Chim. Acta.* 2010, **93**, 261-264; (i) S. De, S. Dutta, A. K. Patra, A. Bhaumik and B. Saha, *J. Mater. Chem.* 2011, **21**, 17505-17510; (j) S. S. Prasad, S. H. Jayaprakash, K. U. Rao, N. B. Reddy, P. C. R. Kumar and C. S. Reddy, *Org. Commun.* 2014, **7**, 98-105; (k) R. Saladino, U. Ciambecchini, C. Crestini, G. Costanzo, R. Negri and E. D. Mauro, *Chem. Bio. Chem.* 2003, **4**, 514-521; (l) S. Rana, M. Brown, A. Dutta, A. Bhaumik and C. Mukhopadhyay, *Tetrahedron Lett.* 2013, **54**, 1371-1379; (m) R. Sarkar and C. Mukhopadhyay, *Tetrahedron Lett.* 2013, **54**, 3706-3711; (n) A. Amoozaadeh, S. Golian and S. Rahmani, *RSC Adv.* 2015, **5**, 45974-45982.
- 9 (a) T. Kasuga, M. Hiramatsu, A. Hoson, T. Sekino and K. Niihara, *Langmuir*. 1998, **14**, 3160-3163; (b) X. Chen and S. S. Mao, *Chem. Rev.* 2007, **107**, 2891-2959; (c) C. N. R. Rao, A. Govindaraj, F. L. Deepak, N. A. Gunari and M. Nath, *Appl. Phys. Lett.* 2001, **78**, 13-26.
- 10 (a) S. H. Kang, S. H. Choi, M. Kang, J. Y. Kim, H. S. Kim, T. Hyeon and Y. E. Sung, *Adv. Mater.* 2008, **20**, 54-58; (b) H. Zhu and Q. Li, *Nanoscale Res. Lett.* 2013, **8**, 230-235; (c) D. P. Kumar, M. V. Shankar, M. M. Kumari, G. Sadanandan, B. Srinivas and V. D. Kumari, *Chem. Commun.* 2013, **49**, 9443-9446; (d) D. P. Kumar, N. L. Reddy, M. V. Shankar, M. M. Kumari, B. Srinivas and V. D. Kumari, *Journal of Catalyst & Catalysis*, 2014, **1**, 13-20; (e) D. P. Kumar, N. L. Reddy, M. M. Kumari, B. Srinivas, V. D. Kumari, V. Roddatis, O. Bondarchunk, M. Karthik, B. Nepplian and M. V. Shankar. *Sol. Ener. Mat. Sol. Cells*, 2015, **136**, 157-165; (f) M. M. Kumari, D. P. Kumar, P. Haridoss, V. D. Kumari and M. V. Shankar, *Intl. J. Hyd. Ener.* 2015, **40**, 1665-1674; (g) D. P. Kumar, N. L. Reddy, B. Srinivas, V. D. Kumari, V. Roddatis, O. Bondarchunk, M. Karthik, Y. Ikuma and M. V. Shankar. *Sol. Ener. Mat. Sol. Cells*, 2016, **146**, 63-71; (h) T. Sree Latha, L. Dakshayani, D. Praveen Kumar, M.V. Shankar and C. Madhava Reddy. *RSC Advances*, 2016, Accepted.
- 11 (a) B. R. P. Reddy, P. V. G. Reddy and B. N. Reddy, *New J. Chem.* 2015, **39**, 9605-9610; (b) B. R. P. Reddy, M. V. K. Reddy, P. V. G. Reddy, D. P. Kumar and M. V. Shankar, *Tetrahedron Lett.* 2015, DOI:10.1016/j.tetlet.2016.01.001
- 12 (a) C. Liao, H. P. Wang and H. P. Lin, *Int. J. Photoenergy*. 2013, **2013**, 1-7; (b) R. Doong, S. Chang and C. Tsai, *Appl. Catal. B* 2013, **129**, 48-55.
- 13 O. Rosseler, M. V. Shankar, M. Du, L. Schmidlin, N. Keller and V. Keller, *J. Catal.* 2010, **269**, 179-190.
- 14 (a) D. V. Bavykin, V. N. Parmon, A. A. Laokin and F. C. Walsh, *J. Mater. Chem.* 2004, **14**, 3370-3377; (b) S. Zu, A. Du, J. Liu, J. Ng and D. D. Sun, *Int. J. Hydrogen Energy*. 2011, **36**, 6560-6568.
- 15 (a) L. Chmielarz, P. Kustrowski, M. Zbroja, W. Lasocha and R. Dziembaj, *Catal. Today*, 2004, **90**, 43-49; (b) T. Matsuda, M. Asanuma and E. Kikuchi, *Appl. Catal.* 1988, **38**, 289-299; (c) C. Gannoun, R. Delaigle, P. Eloy, D. P. Debecker, A. Ghorbel and A. E. Gaigneaux, *Catal. Commun.* 2011, **15**, 1-5; (d) C. Gannouna, A. Turkia, H. Kochkara, R. Delaiglec, P. Eloyc, A. Ghorbela and E. M. Gaigneauxca, *Appl. Catal. B*, 2014, **147**, 58-64.
- 16 (a) M. E. Manriquez, T. Lopez, R. Gomez and T. Navarrete, *J. Mol. Catal. A: Chem.* 2004, **220**, 229-237; (b) A. V. Grigorieva, V. V. Yuschenko, I. I. Ivanova, E. A. Goodilin and Y. D. Tretyakov, *J. Nanomater.* 2012, **2012**, 7.
- 17 S. Voisin, A. Bouillon, J. C. Lancelot, A. Lesnard, H. Oulyadi and S. Rault, *Tetrahedron Lett.* 2006, **47**, 2165-2169

## Graphical Abstract

**Rapid synthesis of alkylaminophenols *via* Petasis Borono-Mannich reaction using protonated trititanate nanotubes as robust solid-acid catalyst**

Bhoomireddy Rajendra Prasad Reddy<sup>a</sup>, Peddiahgari Vasu Govardhana Reddy <sup>\*\*a</sup>, Dharani Praveen Kumar<sup>b</sup>, Bijivemula N. Reddy<sup>c</sup> and Muthukonda V. Shankar<sup>\*b</sup>

Petasis Borono-Mannich reaction was applied to synthesis of alkylaminophenols from *o*-hydroxybenzaldehydes, secondary amines and boronic acids in presence of H<sub>2</sub>Ti<sub>3</sub>O<sub>7</sub> nanotubes as reusable solid-acid catalyst.

