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# Scalable preparation of stable and reusable silica supported palladium nanoparticles as catalysts for N-alkylation of amines with alcohols



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# ABSTRACT

The development of nanoparticles-based heterogeneous catalysts continues to be of scientific and industrial interest for the advancement of sustainable chemical processes. Notably, up-scaling the production of catalysts to sustain unique structural features, activities and selectivities is highly important and remains challenging. Herein, we report the expedient synthesis of Pd-nanoparticles as amination catalysts by the reduction of simple palladium salt on commercial silica using molecular hydrogen. The resulting Pd-nanoparticles constitute stable and reusable catalysts for the synthesis of various N-alkyl amines using borrowing hydrogen technology without the use of any base or additive. By applying this Pd-based catalyst, functionalized and structurally diverse N-alkylated amines as well as some selected drug molecules were synthesized in good to excellent yields. Practical and synthetic utility of this Pdbased amination protocol has been demonstrated by upscaling catalyst preparation and amination reactions to several grams-scales as well as recycling of catalyst. Noteworthy, this Pd-catalyst preparation has been up-scaled to kilogram scale and catalysts prepared in both small (1 g) and large-scale (kg) exhibited similar structural features and activity.

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# 1. Introduction

The development of simple and efficient catalysts for sustainable organic synthesis is of central importance in both academic research and industry [1–16]. In particular, heterogeneous catalysts are more promising due to their high stability and reusability [4-18]. Among these, supported metal nanoparticles-based catalysts are highly preferable in ordered to achieve sufficient activity and selectivity [8-18]. Due to their low energy consumption and tunable properties, these nanomaterials have emerged as important class of catalysts for various chemical processes [8-18]. Moreover, the activity and selectivity of supported nano-catalysts can be controlled by the size and shape of the nanoparticles as well as the kind of support used [8–18]. Hence, for the preparation of highly efficient nanoparticles-based catalysts, the use of simple precursors, the choice of heterogeneous support and the preparation method play crucial roles [8–16]. In addition to these factors, it is imperative to use convenient, abundant and greener reducing

\* Corresponding author. *E-mail address:* jagadeesh.rajenahally@catalysis.de (R.V. Jagadeesh). agents [19-23]. Compared to frequently used traditional stoichiometric reducing agents such as N<sub>2</sub>H<sub>4</sub> (carcinogen), metal borohydrides (more sensitive and produce waste) and inorganic bases (produce waste), molecular hydrogen represents more economical. greener reductant for the preparation of nanoparticles [19–24]. Especially for the large-scale productions, molecular hydrogen is more suitable, which does not produce any waste in contrast to stoichiometric reducing agents [19–24]. One major challenge in nanomaterials is their upscaling to the scale of kilograms in research laboratories [25-27]. Majority of the nanomaterials, prepared until today, are suffered from their upscaling procedures while maintaining their unique structure activity and homogeneity [25–27]. Herein, we report expedient procedure for the preparation of silica supported Pd-nanoparticles in gram- and kilogramscale by simple impregnation and reduction method by using molecular hydrogen as reductant at moderately low temperature. The resulting Pd-catalysts were stable and reusable for selective base and additive-free synthesis of N-alkyl amines as well as selected drug molecules ranging from easily accessible, abundant primary to complex secondary amines and alcohols.

Amines are highly useful chemicals due to their extensive applications in different disciplines such as chemistry, biology,



medicine, energy, and so on [28–35]. These valuable compounds represent fine and bulk chemicals and serve as essential precursors and key feedstock for advanced chemicals, pharmaceuticals, agrochemicals and materials [28-35]. The amine functionality constitutes an integral part of many life science molecules, natural products, and biomolecules [28-35]. It is also known that more than 170 out of 200 drugs prescribed, in the year of 2016, contain amine moieties, which clearly demonstrates the extreme importance of amines in the discovery of new drugs [30]. Regarding the synthesis of higher value of amines as well as their functionalization, N-alkylation of amines using alcohols, the so called 'borrowing hydrogen technology' represents more sustainable and waste-free methodology that produces water as the only byproduct [36–63]. With respect to the potential catalysts for this reaction, homogeneous metal-complexes have been efficiently used [36-57]. Despite their elegant activity and selectivity, majority of these homogeneous complexes are rather sensitive (to air. moisture, or both) and/or incorporate sophisticated (synthetically demanding) ligand systems [38-57]. In contrast, heterogeneous catalysts are extremely stable, easily recyclable, and hence, they are certainly vital for the advancement of cost-effective, sustainable industrial processes [58–66]. In this respect, heterogeneous catalysts based on Ru [58], Ni [59], Cu-Fe [60], Ag [61] and Pd [62–66], have been applied for N-alkylation of amines. Despite these, still the development of stable and reusable catalysts, especially based on nanoparticles is highly desired and continues to attract scientific interest for the base- or additive-free synthesis of N-alkyl amines.

#### 2. Experimental section

#### 2.1. Materials and methods

Palladium(II) acetylacetonate (Aldrich), tetraethyl orthosilicate (TEOS; Aldrich), cetyltrimethylammonium bromide (CTAB; Alfa Aesar), concentrated ammonia (28–30%; Aldrich), silicon dioxide (LOBA; **Cat-1**), silicon dioxide (lab prepared; **Cat-2**), silicon dioxide (Silica for hydrodesulfurization, in the shape of pellets provided by Dr. Tiancun Xiao, Senior Research Fellow, Inorganic Chemistry Laboratory, University of Oxford; **Cat-3**), titanium dioxide (Fluka, Cat-4), and acetone (Sigma-Aldrich) were commercially accessible (except Cat-3) and were used as received. Deionized water (18.2 MΩ.cm) was supplied by using Milli-Q water purification system (Millipore). Commercial catalysts (Cat 5 and 6) were purchased from sigma aldrich. GC and GC–MS were recorded on Agilent 6890 N instrument. GC conversion and yields were determined by GC- <sup>13</sup>C NMR data were recorded on a Bruker ARX 300 and Bruker ARX 400 spectrometers using CDCl<sub>3</sub>, solvents.

#### 2.2. Catalysts preparation

Palladium nanoparticles (PdNPs) supported on commercial silicon dioxide was obtained in two-step synthesis procedure. First, 1.0 wt% Pd/SiO<sub>2</sub> by wet impregnation using acetone as a solvent to mix the appropriate amounts of both of support (0.97 g) and Pd(acac)<sub>2</sub> (0.03 g). The resultant mixture was ultrasonicated at room temperature for an hour by using an ultrasonic bath to disperse the SiO<sub>2</sub> support. In the second step, after solvent evaporation, the obtained solid sample was oven-dried at 80 °C for two hours, followed by H<sub>2</sub> reduction at 150 °C for two hours to come up with 1.0 wt/wt% PdNPs supported on SiO<sub>2</sub> (**Cat-1**). For catalyst scale up, similar procedure was followed to prepare two-kilogram (2 Kg) catalyst using relative amount of starting materials. In order to explore the influence of the nature of support on the catalytic activity of PdNPs toward amination reactions, different Pd basedcatalysts were synthesized using above similar procedure. The other catalysts were denoted as follows: PdNPs supported on lab prepared meso-SiO<sub>2</sub> (**Cat-2**), PdNPs on other commercial SiO<sub>2</sub> (**Cat-3**), and PdNPs on TiO<sub>2</sub> (Cat-4). In addition, two commercial catalysts were also used for comparison, namely Pd/C (**Cat-5**) and Pd/Al<sub>2</sub>O<sub>3</sub> (Cat-6). Meso-SiO<sub>2</sub> was prepared by the hydrolysis of TEOS (~50.38 mmol) in aqueous solution containing ammonia (35.0 mL), CTAB (~10.0 mmol), and water (720 g) and stirred overnight, followed by filtration of the precipitated white solid, washing with copious amount of water, drying at room temperature, and finally calcination at 600 °C for three hours.

#### 2.3. Catalyst characterization

Pd metal content in each catalyst was determined by using a Varian Vista-MPX ICP-OES instrument. The specific surface area, based on Brunauer-Emmett-Teller method (S<sub>BET</sub>) was measured by N<sub>2</sub> physisorption at -196 °C by using a Micromeritics ASAP 2010 adsorption analyzer. X-ray powder diffraction (XRPD) patterns were obtained by using a D8 advance Bruker instrument. operated at 40 mA and 40 kV by using CuK $\alpha$  radiation and a Ni filter, in the 2-theta range between 10° and 80°. To investigate the morphology and particle sizes of our catalysts, a JEM-2100F JEOL TEM was used. The X-ray photoelectron spectroscopy (XPS) analyses were carried out on a PHI 5000 VersaProbe-Scanning ESCA microprobe (ULVAC-PHI, Japan/USA) instrument at a base pressure of  $5.5 \times 10^{-7}$  Pa, where the X-ray source of Al-K<sub>2</sub> (hv = 1486.6 eV) with spot size of 200 µm was used. Temperature programmed reduction (TPR), H<sub>2</sub> chemisorption, CO<sub>2</sub>-TPD studies were recorded by using a Micromeritics AutoChem II 2920. Reduction profiles were achieved by passing a mixture of 10% H<sub>2</sub>/He at a rate of 50 mL/min (STP) over an amount of 0.1 g of catalyst. The temperature was gradually ramped from room temperature to 500 °C at a heating rate of 10 °C/min. The total consumption of H<sub>2</sub> was calculated by a thermal conductivity detector (TCD) as a function of temperature.

#### 2.4. Catalytic amination reactions

Dried pressure tube was charged with magnetic stir bar and 50 mg of Pd@SiO<sub>2</sub> catalysts (1 mol% with respect to amine). Then, 1.0 mL o-xylene was added, followed by the addition of 0.5 mmol of amine and 1 mmol of benzyl alcohol. The pressure tube was flushed with argon was closed with screw cap. Then it was placed in the preheated aluminum block and reaction was allowed to progress for 30 h at 150 <sup>o</sup>C. After completion of the reaction, pressure tube was removed from aluminum block and cooled down to room temperature. The catalyst was filtered out by ciliate and reaction products were analyzed by GC-MS and the corresponding amines were purified by column chromatography. The yields of selected amines were determined by GC analysis using n-hexadecane as standard. For this purpose, after completion of the reaction, nhexadecane (100 µL) as standard was added to the reaction pressure tube and the reaction products were diluted with ethyl acetate followed by filtration using plug of silica and then subjected GC analysis.

# 3. Results and discussion

We started our investigations to develop simple Pd-based nanocatalysts in one-gram scale. For this purpose, we used palladium (II) acetylacetonate as precursor and silicon dioxide  $(SiO_2)$  as support to prepare 1 wt% Pd@SiO<sub>2</sub> (**Cat-1**) (Fig. 1). First, we immobilized Pd salt on silica support and then reduce Pd(II) to Pd(0) under flow of molecular hydrogen at certain temperature



Fig. 1. Preparation of silica supported Pd-nanoparticles.

(Fig. 1). In addition, other supported Pd-catalysts have also been prepared using similar procedure (Table 1).

All the prepared Pd-materials were tested for their activities in the reaction of aniline with benzyl alcohol for the synthesis of *N*-benzylaniline, an industrially important product, as model reaction. The effect of nature of support on the yield of N-benzylaniline is presented in Table 1.

Among the different supports, silica supported ones exhibited well to excellent activity (Table 1; entries 1–3; **Cats 1–3**). Among these three, Pd supported on silica obtained from commercially available SiO<sub>2</sub>·xH<sub>2</sub>O (**Cat-1**) showed the best activity and selectivity for the *N*-benzylation of aniline and produced desired secondary amine in 97% yield (Table 1; entry 1). In addition to SiO<sub>2</sub>, PdNPs supported on TiO<sub>2</sub> (**Cat-4**) was also prepared and tested in the benchmark reaction. This catalyst displayed less activity compared to silica supported materials (Table 1, entry 4). In order to compare the activity of **Cat-1**, the commercially available Pd-based catalysts such as Pd@C (**Cat-5**) and Pd@Al<sub>2</sub>O<sub>3</sub> (**Cat-6**) were also tested and were found much less active than **Cat-1** (Table 1; entries 5–6). Furthermore, the catalytic performance of pure support (i.e. SiO<sub>2</sub>·xH<sub>2</sub>O) was also tested and found totally inactive, as expected (Table 1, entry 7).

In order to know the structural features and better understanding of catalytic properties and activities, the silica supported Pdcatalysts (**Cat 1–3**), were characterized by different techniques such as ICP-OES (inductively-coupled plasma optical emission spectroscopy), BET surface area (Brunauer–Emmett–Teller), XRD (X-ray powder diffraction), TEM (transmission electron microscopy), XPS (X-ray photoelectron spectroscopy) and H<sub>2</sub>-TPR (H<sub>2</sub> temperature programmed reduction) and chemisorption. ICP-OES analysis confirmed that the content of Pd on various SiO<sub>2</sub> supports is very close to the nominal content of Pd (1.0 wt/wt %: Table 2: entries 1). The BET surface areas and total pore volumes (PV) of the SiO<sub>2</sub> supported PdNPs were found to be dependent on the nature of support applied and were varied in the range from 462 to 980 m<sup>2</sup>/g and 0.4 and 1.1 cm<sup>3</sup>/g, respectively. Among all the catalysts, the active catalysts, (i.e. Cat-1 and Cat-2) exhibited relatively high surface areas (477 and 980  $m^2/g$ ). (Table 2, entries 2–4). The BET surface areas of pure supports were notably decreased after the impregnation of PdNPs due to pore blockage. Furthermore, the nature of support has also shown considerable role on the size of Pd particles and size distribution (Table 2; entry 5). In addition, the H<sub>2</sub> chemisorption analysis showed that Cat-1 had the highest metal dispersion among the others (Table 2, entry 6). These results clearly showed that the differences in the metal dispersion depended on the type of SiO<sub>2</sub> used as a support. Among all, Cat-1 represented the highest metal dispersion. The size and nature of the interaction between the metal particle and support plays an important role to determinate the catalytic performance. Therefore, the surface interaction between PdNPs and SiO<sub>2</sub> support of different catalysts (Cat-1-3) was studied by H<sub>2</sub>-TPR (Fig. 2). All catalvsts showed mainly two peaks with different intensities in the reduction regions between 60 and 100 °C. The TPR curves of Cat-**1–3** were dominated by intense peaks in the range between 60 and 70 °C, which could be attributed to the reduction of Pd<sup>2+</sup> located in hydrophobic and hydrophilic regions. This result is in agreement with those reported by Guo et al. [67]. However, the second peak between 70 °C and 100 °C was broad with much lower

# Table 1

Pd-catalyzed N-benzylation of aniline: activity of catalysts.



| Entry | Catalyst   | Yield of N-benzylaniline (%) |
|-------|--|------------------------------|
| 1     | <b>Cat-1</b> (Pd@SiO <sub>2</sub> ) (commercial SiO <sub>2</sub> ·xH <sub>2</sub> O) | 97 (96%)                     |
| 2     | <b>Cat-2</b> (Pd@SiO <sub>2</sub> ) (lab prepared meso-SiO <sub>2</sub> )            | 90                           |
| 3     | <b>Cat-3</b> (Pd@SiO <sub>2</sub> ) (other commercial SiO <sub>2</sub> )             | 50                           |
| 4     | <b>Cat-4</b> (Pd@TiO <sub>2</sub> ) (commercial TiO <sub>2</sub> )                   | 26                           |
| 5     | <b>Cat-5</b> (Pd@C) (commercial catalyst; 5 wt% Pd)                                  | 20                           |
| 6     | <b>Cat-6</b> (Pd@Al <sub>2</sub> O <sub>3</sub> ) (commercial catalyst; 5 wt% Pd)    | 15                           |
| 7     | SiO <sub>2</sub> ·xH <sub>2</sub> O  | < 1                          |

**Reaction conditions:** 0.5 mmol aniline, 1 mmol benzyl alcohol, weight of catalyst corresponds to 1 mol% Pd, 1 mL o-xylene, 150 °C, 30 hrs. Yields were determined by GC using hexadecane as standard. Yield given in the parenthesis refer to the catalyst prepared in kg scale.

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| Metal content (%), BET surface area ( $S_{BET}$ ), and pore volume (PV), particle size and metal dispersion analysis of Pd@SiO <sub>2</sub> catalysts. |   |       |       |       |  |  |
|--|---|-------|-------|-------|--|--|
| Entry  | Analysis                                      | Cat-1 | Cat-2 | Cat-3 |  |  |
| 1  | Pd-content (wt %)                             | 0.98  | 0.98  | 1.02  |  |  |
| 2  | Support $S_{BET}$ (m <sup>2</sup> /g)         | 527   | 1109  | 500   |  |  |
| 3  | Catalyst S <sub>BET</sub> (m <sup>2</sup> /g) | 477   | 980   | 462   |  |  |
| 4  | Catalyst pv $(cm^3/g)$                        | 0.54  | 1.1   | 0.4   |  |  |
| 5  | Pd Particle size (nm)                         | 4-12  | 6-14  | 6-14  |  |  |

12

| Motal  | contont ( | <i>(</i> %)           | DET | curfaco | 2502 | (S)  | and   | noro | volumo  | $(\mathbf{D}V)$ | particlo | cizo | and motal | dicr | orcion  | analı  | rcic o | f DA@C | in.    | catal | vete  |
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| vietai | content ( | <i>/</i> 0 <b>)</b> , | DLI | Suilace | died | SBET | , anu | pore | voluine | (PV),           | particle | SIZE | and metal | uist | Jeision | diidiy | 1515 0 | i ruws | $10_2$ | Caldi | ysts. |

Catalyst prepared in 2 kg scale.



Metal dispersion (%)

Fig. 2. H<sub>2</sub>-TPR profiles of PdNPs supported on different SiO<sub>2</sub> (Cats 1-3).

intensity. Such results might be attributed to the reduction of Pd<sup>2+</sup> to Pd<sup>0</sup>. The most active catalyst (**Cat-1**) displayed the maximum intense second peak in comparison to the other two catalysts, indicating stronger metal-support-interaction (SMSI) between Pd and SiO<sub>2</sub>, and hence displayed better activity.

The identification of crystallinity and phase composition in the SiO<sub>2</sub> supported Pd nanoparticles were executed by XRD. The XRD patterns of Cat-1-3 are presented in Fig. 3. The XRD patterns of all these showed mainly the characteristic peaks of amorphous silica. No peaks related to Pd-particles were detected, indicating that very fine palladium metal nanoparticles were magnificently dis-



Fig. 3. XRD patterns of PdNPs supported on different SiO<sub>2</sub> (Cat 1-3).

persed in the silica matrix for the material with low-Pd loadings. In addition, the XRD analysis also confirmed that there is no mixed oxide phase appeared between Pd and SiO<sub>2</sub>.

5

Cat-1\* 09 527 450 0.52

2 - 7

10

The size and morphology of PdNPs supported on different SiO<sub>2</sub> were studied by TEM. Representative TEM images of the Pd catalysts are presented in Fig. 4, along with their corresponding histograms of the particle size distributions, the high resolution (HR)-TEM, and the selected area electron diffraction (SAED) patterns. Fig. 4 (ia-ic) shows well-dispersed Pd particles with spherical morphology, but with varying Pd particle size distribution, depending on the identity of silica support. Among all catalysts, **Cat-1** resulted in a narrow particle size distribution in the range of 4–12 nm, but the major contribution arising from the particles in the range of 5-10 nm. The particle size distribution of Cat-1 (insert in Fig. 4a-i) was the narrowest for PdNPs in comparison to the other two catalysts (Cat-2 and Cat-3). Bigger PdNPs could be observed for Cat-2 and Cat-3 (Fig. 4b-i and c-i), where their size varied in the range from 4 to 16 nm (inset Fig. 4b-i and c-i). Furthermore, HRTEM images (Fig. 4-(aii-cii) of all catalysts obviously confirmed that the PdNPs were spherical and dispersed over the surface of the supports. Fig. 4a-ii shows that the lattice fringe with d-spacing value of 0.14 nm, which corresponding well to the Pd (111) crystal planes, respectively. The corresponding SAED patterns of the PdNPs image are presented in Fig. 4a-iii. Its characteristic diffraction patterns revealed the presence of Pd (111) and (220) crystal facets. On the other hand, the value of d-spacing of Cat-2 (Fig. 4b-ii) was estimated to be 0.220 nm, corresponding well to Pd (111) crystal plane. In case of Cat-3, d-spacing was estimated to be 0.225 nm, corresponding to Pd (111). SAED patterns of Cat-2 and Cat-3 are shown in Fig. 4(biii-ciii) and their characteristic diffraction patterns revealed the presence of crystal facet of Pd (111).

The XPS technique is powerful to estimate the chemical state of Pd species and surface composition of Pd/SiO<sub>2</sub> catalyst. The XP spectra of tested catalysts are illustrated in Fig. 5 (Cat 1-3). In addition, the summary of XPS results such as B.E. and atomic ratios for supported Pd catalysts are given in Table 3. The appearance of Pd3d<sub>5/2</sub> peaks at 336.0, 335.1, and 335.2 eV for Cat-1, Cat-2, Cat-**3**, respectively, indicate the presence of metallic Pd species in all the catalysts, irrespective of the source of  $SiO_2$  used. The Pd3d<sub>3/2</sub> peaks appeared at 341.2, 340.3, and 340.3 eV, respectively, for Cat-1, Cat-2, Cat-3. Energy separation between the Pd 3d<sub>5/2</sub> and 3d<sub>3/2</sub> photoelectric lines for all samples ranged from 5.1 to 5.2 eV. These peak positions and peak separations are in good agreement with those reported in the literature for the presence of Pd(0) [68,69]. As shown in Fig. 5, the slight deviations in the binding energy of Pd(0) peaks, in all the three samples, could be due to different binding of Pd particles with the different types of SiO<sub>2</sub> supports used.

The highest surface enrichment in Pd was detected for Cat-1, as it was indicated by the highest metal to support (M/S) surface ratios (Table 3). This enrichment in Pd in the near-surface-region could be crucial for enhancing the catalytic performance of our Pd/SiO<sub>2</sub> catalysts. Such results are in line with the chemisorption

Table 2

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Fig. 4. TEM images (ai-ci), histogram of Pd particle size distribution (inset a-c), HRTEM images (aii-cii), and SAED patterns (aiii-ciii) of Cat 1-3, respectively.



Fig. 5. XPS Pd3d spectra of Cat-1 (a), Cat-2 (b), and Cat-3 (c).

analysis for the catalysts with relatively low-metal loadings, where the metal surface may be covered by Si–O groups due to simultaneous crystallization of Pd and SiO<sub>2</sub>. It is also possible that some of the Pd metal surfaces was partially oxidized, while the core of the Pd particles is metallic. Moreover, Si 2p peaks in all samples were dominated by a peak of Si<sup>4+</sup> at 103.6 eV [70].

# Table 3 XPS results of Pd 3d5/2 and Pd3d3/2 for different silica supported Pd-catalysts.

| Catalyst | Pd3d <sub>5/2</sub> | Pd3d <sub>3/2</sub> | ΔΕ  | M/S ratio |
|----------|---------------------|---------------------|-----|-----------|
| Cat-1    | 336.0               | 341.2               | 5.2 | 0.010     |
| Cat-2    | 335.1               | 340.3               | 5.2 | 0.008     |
| Cat-3    | 335.2               | 340.3               | 5.1 | 0.006     |



Fig. 6. CO<sub>2</sub>-TPD profiles of Cat-1, Cat-2, and Cat-3.

The basic properties of our catalysts were evaluated by CO<sub>2</sub>-TPD because basicity is a key for the alkylation of amines by alcohols. Fig. 6 shows the pattern of  $CO_2$ -TPD, where the various types of basic sites are distinguished depending on temperature. All of the three catalysts, Cat-1, Cat-2, and Cat-3, exhibited desorption peaks in the weak, intermediate, strong, and very strong regions, where the highest intensity of the peaks was observed for **Cat-1** and the lowest was for **Cat-3**. The first desorption peak in the range of 50-150 °C corresponded to the weak basic sites, whose peak maxima shifted towards higher temperature range moving from  $\sim$ 73 °C for **Cat-3** to  $\sim$ 76 °C for **Cat-2** to  $\sim$ 88 °C for **Cat-1**, indicating that **Cat-1** had the strongest CO<sub>2</sub> adsorption in the weak basic site region. The regions of intermediate, strong, and very strong basic sites overlapped among them. However, distinguished peak in each region could be recognized. For the intermediate basic site region, each of **Cat-1** and **Cat-3** displayed a shoulder, rather than a peak, centered at ~305 °C and ~266 °C. On the other hand, Cat-2 showed a more characteristic peak, centered at ~267 °C. The intensity of intermediate basic site region reduced in the following order: Cat-1 > Cat-2 > Cat-3, indicating that Cat-1 had the strongest adsorption for CO<sub>2</sub>. In the strong basic site region in the temperature range of 300-450 °C, Cat-3 exhibited two peaks connected by a small valley, where the first one centered at  ${\sim}307~^{\circ}\text{C}$  and the second one centered at  $\sim$ 420 °C. On the other hand, Cat-2 showed a peak centered at ~418 °C, while Cat-3 had its broad peak centered at  $\sim$ 397 °C in the strong basic site region. Once again, the intensity of the peaks in this region reduced from Cat-1 to Cat-2 to Cat-3.

In the very strong basic site region, each catalyst showed a broad peak, but with one hump centered at ~650 °C for Cat-3 and two humps for both of **Cat-1** and Cat-2. The two humps for **Cat-1** were centered at ~570 °C and 723 °C, while they were centered at ~530 °C and 703 °C for Cat-2. The intensity of the peaks was also highest for **Cat-1** and then declined for **Cat-2** and **Cat-3**. The CO<sub>2</sub>-TPD profile revealed that the most intense peaks for all of the catalysts were found in the strong basic site region, followed

by the very strong and the intermediate sites, and finally the weak sites. This probing of basicity of the catalyst by the acidic molecule of  $CO_2$  could be linked to the observed catalytic performance of the catalysts and to needless of adding a base to the reaction medium.

Studying the effect of upscaling of catalyst is of great interest for industry. Obviously, the scale-up of catalyst has been intensely studied to ensure that both physico-chemical and catalytic properties are comparable to the one-gram scale. Therefore, the most active catalyst in the present study (i.e. Cat-1) was produced on two-kilogram (2 kg) scale and its properties and activities were compared with those obtained at one-gram scale. The effect of upscaling on physico-chemical features was studied using different methods. For instance, ICP analysis confirmed that the metal loading was in agreement with the nominal content of Pd (1 wt%). The BET surface area of the up-scaled catalyst was slightly decreased to 450  $m^2/g$ . However, the amorphous nature did not change during the upscaling procedure. In addition, TEM images in Fig. 7 confirms that the observed Pd particle size is identical and is similar to the 1 g scale results with particle size ranging between 6 and 14 nm. Such result clearly indicates that the preparation method is easy and is suitable for the synthesis of SiO<sub>2</sub> supported PdNPs on a large scale. Notably, this up-scaled catalyst exhibited similar activity and selectivity to one-gram scale catalyst (Table 1, entry 1).

After having developed the active catalyst (**Cat-1**), we demonstrated its general applicability for the alkylation of different amines using alcohols. At first, we investigated the reaction of different primary amines and benzyl alcohol. As shown in Scheme 1, various simple and substituted aromatic, heterocyclic and aliphatic amines were reacted with benzyl alcohol to produce their corresponding *N*-benzylated amines in good to excellent yields. Simple and halogenated *N*-benzylanilines were obtained in up to 97% yield (Scheme 1, products 3–8).

In organic synthesis and drug discovery, synthesis of functionalized amines is of huge importance because they serve as intermediates and starting materials for the preparation of advanced and biologically relevant molecules. Hence, demonstrating a chemoselectivity in organic synthesis is a noteworthy task. To present this application, aniline containing different functional groups such as hydroxyl, thiol, nitroether, thioether, ketone, nitrile, and ester were selectively reacted with benzyl alcohol to produce their corresponding *N*-benzylated amines without affecting these functional groups (Scheme 1; products 9–16). In addition to aromatic and heterocyclic amines, benzylic and aliphatic amines were also underwent *N*-alkylation to produce corresponding secondary amines in up to 88% yields (Scheme 1, products 20–22).



Fig. 7. HRTEM for Pd/SiO2 (Cat-1) prepared in 2 Kg scale.



**Scheme 1.** Pd@SiO<sub>2</sub> catalyzed synthesis of *N*-alkyl amines using different primary amines and benzyl alcohol. Reaction conditions: 0.5 mmol amine, 1 mmol benzyl alcohol, 50 mg Cat-1 (1 mol% Pd), 1 mL o-xylene, 150 °C, 30 h, isolated yields.

In subsequent experiments, we performed the synthesis of biologically and pharmaceutically relevant amines (Scheme 2). Different cyclic amines such as piperidine, tetrahydroquinoline, piperazine and pyrrolidine were selectively benzylated to produce tertiary amines of biological relevance. For instance, existing drugs such as 4-benzylpiperidine (monoamine oxidase inhibitor), benzylpiperazine (BZP; recreational drug with euphoriant and stimu-



**Scheme 2.** *N*-benzylation of piperidine, piperazine and urea derivative using **Cat-1** catalyst. Reaction conditions: 0.5 mmol amine, 1 mmol benzyl alcohol, weight of catalyst corresponds to 1 mol% Pd, 1 mL *o*-xylene, 150 °C, 30, isolated yields.

lant properties) and methylbenzylpiperazine (MBZP; stimulant drug) (Scheme 2; products: 23, 25 and 26) have been prepared in up to 91% yield. In addition, we also showcased the possibility for the amination of maleimide, an important building block in organic synthesis (Scheme 2, product 28).

After performing the benzylation of different amines, we carried out the synthesis of *N*-alkylated amines using different alcohols (Scheme 3). Substituted, benzylic alcohols, piperonyl alcohol, anthracenemethanol, and tetrahydronaphthalene methanol as well as secondary alcohols such as 1-phenylethanol were successfully reacted with different primary and secondary amines (products 21–33). In addition to aromatic alcohols, our Cat-1 was also active for the reaction of aliphatic alcohols with amines. Different aliphatic alcohols such as cyclohexanol, N-hexanol, and ethylene glycol as well as allylic alcohols such as cinnamyl and allyl alcohols were also underwent alkylation with primary and secondary amines. The synthesis of methylenedioxybenzyl-piperazine (designer drug), piribedil (antiparkinsonian agent), and cinnarizine (antihistamine and calcium channel blocker) were also synthesized (Scheme 3, products 31, 32 and 37).

To present synthetic and practical utility of this Pd-catalyzed amination protocol, we carried out upscaling of reaction to several grams. As shown in Scheme 4, four different *N*-benzylated amines were prepared in up to 10 g under similar reaction conditions. The yields of the desired amines, from these up-scaled reactions, were very much comparable and were quite consistent with those obtained from mg (small) scale.

Catalyst stability, recycling, and reusability are very important features for the advancement of cost-effective, industrial processes. Our **Cat-1** was highly stable, conveniently recycled, and reused up to six times without any significant loss of its catalytic activity (Fig. 8). The recycled catalyst was subjected to ICP analysis and it was found that there was no leaching of Pd in the recycled catalyst.

The performance of our  $Pd@SiO_2$  catalyst has been compared with the previously known Pd-based heterogeneous catalysts for N-alkylation of amines using alcohols. The Pd/AlO(OH) catalyst



**Scheme 3.** Cat-1 for catalyzing *N*-alkylation by using different alcohols. Reaction conditions: 0.5 mmol amine, 1 mmol alcohol, 50 mg **Cat-1** (1 mol% Pd), 1 mL *o*-xylene, 150 °C, 30 hrs.



**Scheme 4.** Upscaling of Cat-1 for N-alkylation reaction. Reaction conditions: 1–10 g aromatic amine, 2 equivalent benzyl alcohol, 1 mol% of catalyst, 10–50 mL *o*-xylene, 30 h, 150 °C, isolated yields.



**Fig. 8.** Recycling **Cat-1.** Reaction conditions: 5 mmol aniline, 10 mmol benzyl alcohol, weight of catalyst corresponds to 1 mol%, 10 mL *o*-xylene, 150 °C, 30 hrs. Yields were determined by GC.

reported by Park and coworkers [63] required molecular hydrogen as the external reducing agent. Next, Astruc et al. [64] have reported commercial Pd/C catalyst, which required 3 equivalent of sodium formate as additive. Further, Li and co-workers [65] have developed Pd@MIL-100 based photocatalyst, which produced 8-86% of N-alkylated amines. By applying our Pd@SiO<sub>2</sub> catalyst we obtained 44–97% of N-alkylated amines without the use of any additive or external molecular hydrogen. In addition, to the synthesis of simple and structurally diverse N-alkyl amines, the preparation of bio-active molecules has also been demonstrated using Pd@SiO<sub>2</sub> catalyst.

This Pd-catalyzed N-alkylation reaction proceeds *via* the 'borrowing hydrogen technology' (Scheme 5). First, the activation and dehydrogenation of alcohol on Pd@SiO<sub>2</sub> takes place to generate corresponding aldehyde with the liberation of hydrogen (*in situ* hydrogen). Next aldehyde condenses with primary amine and forms corresponding imine (in case of secondary amine the formation of enamine or iminium ion takes place). The acidic nature of SiO<sub>2</sub> accelerates the formation of imine. Finally, the activation of imine (iminium ion in case of secondary amine) on Pd@SiO<sub>2</sub> catalyst, followed by the reduction with *in situ* generated hydrogen produces corresponding secondary or tertiary amine as the desired product (Scheme 5).

# 4. Conclusions

In conclusion, we developed simple Pd-nanoparticles (Pd@SiO2; Cat-1) as amination catalysts by the reduction of Pd-salt on silica using hydrogen. Notably, we demonstrated a convenient and practical protocol for upscaling this Pd-based catalyst production up to 2 kg with retaining structural reliability, activity and selectivity to that of small preparations (1 g-scale). Applying this Pd-based amination protocol, various structurally diverse and functionalized Nalkylated amines including selected drug molecules have been prepared *via* borrowing hydrogen technology starting from various amines and alcohols. Further, gram-scale synthesis of selected amines has been showcased. The superior catalytic performance of Cat-1 compared to other catalysts of this study can be attributed to the formation of small Pd nanoparticles, clear enrichment of metallic Pd in the near-surface region and high dispersion of active Pd species. Remarkably, this catalyst system can be recycled up to 6 times without any loss of catalytic activity or selectivity.



Scheme 5. Plausible reaction mechanism for the Pd@SiO2-catalyzed N-alkylation of amines with alcohols.

## **Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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# Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcat.2019.12.012.

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