## **RSC Advances**

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Cite this: RSC Adv., 2014, 4, 2601

Synthesis of imines from amines in aliphatic alcohols on Pd/ZrO<sub>2</sub> catalyst under ambient conditions<sup>†</sup>

Received 23rd August 2013 Accepted 28th October 2013 Wenjing Cui,<sup>ab</sup> Bao Zhaorigetu,<sup>\*a</sup> Meilin Jia,<sup>a</sup> Wulan Ao<sup>a</sup> and Huaiyong Zhu<sup>c</sup>

DOI: 10.1039/c3ra44625e

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Synthesis of imines from amines and aliphatic alcohols  $(C_1-C_6)$  in the presence of base on supported palladium nanoparticles has been achieved for the first time. The catalytic system shows high activity and selectivity in open air at room temperature.

Imines, a kind of nitrogenated compounds, are used as lipoxygenase inhibitors, anti-inflammatory agents and anti-cancer agents in therapeutic applications as well as nucleophilic addition reagents in organic reactions.1 Synthesis and application of imines play a pivotal role in modern organic synthesis.<sup>2</sup> Generally, condensation of amine and carbonyl compound (aldehyde or ketone) is used for the synthesis of imines.<sup>3</sup> However, owing to the unstable and reactive nature of the electrophilic carbonyl compound, it is desirable to obtain imines from more stable compounds.4 Oxidation of secondary amines,1,5 self-coupling of amines6 and coupling of alcohols and amines7 are alternative methods for imines synthesis. It commonly requires higher temperature (around 100 °C), O<sub>2</sub> atmosphere as well as longer reaction time (>24 h) to produce imines through oxidation of secondary amines.5a,8 The products of self-coupling of amines are always limited to symmetric imines.9 Coupling of alcohols and amines is the superior choice as alcohols are much greener, more stable and readily available starting materials. The possible reaction mechanism involves: an alcohol is oxidized to the reactive carbonyl compound (key step), which afterwards condenses with an amine to form an unstable intermediate, hemiaminal, which finally transforms to the imine by elimination of one molecule of water (Scheme 1).

"Inner Mongolia Key Laboratory of Green Catalysis, Inner Mongolia Normal University, Hohhot, China. E-mail: wenjing\_cui@126.com; zrgt@imnu.edu.cn; Fax: +86 0471-4392036; Tel: +86 0471-4393099 Ru-catalyzed,<sup>10</sup> Ir-catalyzed,<sup>11</sup> Pd-catalyzed,<sup>12</sup> Au-catalyzed,<sup>13</sup> Cucatalyzed9,14 and base-catalyzed15 imines synthesis from amines and alcohols were reported. However, these reactions are always limited to aromatic (benzylic) alcohols and unsaturated (cinnamyl, allylic and propargyl) alcohols, which can be oxidized readily to corresponding aldehydes.<sup>12-14,15b,16</sup> Aliphatic alcohols are more difficult to activate than aromatic alcohols and unsaturated alcohols. Several methods are available to synthesize imines from amines and aliphatic alcohols, but severe drawbacks still remain. For example, Ru catalysts required high temperature (reflux), prolonged reaction periods (24-56 h) to form desired imines with moderate selectivity and yield.10b,17 A recent Au/Pd alloy catalyst was employed to synthesize imines under 60 °C, however, only 58% yield of imine was obtained after 12 h. In this catalytic system, benzylamine and octanol were used as substrates and dioxygen was necessary for the oxidation.18 The coupling reactions of amines with aliphatic alcohols were great challenges,<sup>10b,14,15,19</sup> and to the best of our knowledge, imines are synthesized from amines with smaller and less reactive aliphatic alcohols  $(C_1-C_6)$  was not known yet.

We herein report an original and efficient method for synthesis of imine by adding amine in aliphatic alcohol ( $C_1$ – $C_6$ ) which acting as both reagent and solvent.

Initially, 1 wt% Pd/ZrO<sub>2</sub> catalyst was prepared according to the literiture.<sup>20</sup> TEM image (Fig. S1a<sup>†</sup>) shows that palladium nanoparticles (Pd NPs) are spheroidal in shape and welldispersed on ZrO<sub>2</sub> support. The particle size distribution is within the region of *ca.* 2–8 nm with average size of 5 nm (Fig. S1b<sup>†</sup>). The diffraction peaks of XRD characterization are assigned to the baddeleyite ZrO<sub>2</sub> phase. No crystal Pd can be



Scheme 1 Likely mechanism for synthesis of imines from amines and alcohols.



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<sup>&</sup>lt;sup>b</sup>College of Chemical Engineering, Inner Mongolia University of Technology, Hohhot, 010051, China

<sup>&</sup>lt;sup>c</sup>School of Chemistry, Physics and Mechanical Engineering, Queensland University of Technology, Queensland, 4001, Australia

<sup>†</sup> Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra44625e

**RSC** Advances

detected, which confirmed Pd NPs are highly dispersed (Fig. S2<sup> $\dagger$ </sup>). XPS information of the catalyst suggests that the Pd<sup>0</sup> presented on the surface of the catalyst (Fig. S3<sup>†</sup>).

Subsequently, benzylamine (1a) and ethanol (2a) were used as model compounds to investigate synthesis of N-ethylidenebenzylamine (3aa) on 1 wt% Pd/ZrO2 under various conditions and the results are summarized in Table 1. When the reaction of 1a with 2a was carried out at 20 °C, the yield of 3aa was much lower (entry 1). Further increasing the temperature, the yield was improved. The most efficient temperature was 30 °C as the yield of desired imine was not further improved at 40 °C (entries 2 and 3). The selectivity of 3aa was almost full, and no other byproduct was detected in the reaction.

The effect of the base was also examined (entries 4-7). The base was considered to be essential for the first hydrogen abstraction in the oxidation of alcohols21 and no product was detected in the reaction without base. KOH and NaOH are the most efficient bases for synthesis of imines. Other base, K<sub>2</sub>CO<sub>3</sub> and Na<sub>2</sub>CO<sub>3</sub>, furnished the imine in lower yield. It appears that the alkalinity of the base has significant influence on the conversion of the benzylamine, while the excellent selectivity of imine was always observed for each of bases. Furthermore, the high reaction efficiency still remained when the amount of KOH was reduced, so it was more cost effective to fix the amount of KOH to 0.1 mmol rather than any others (entries 8-10).

With the optimized reaction conditions, a series of aliphatic alcohols and amines were tested to explore the scope and limitation of the catalytic system (Table 2). The selectivity to desired imine was incredible and no other reported products, such as secondary amine and amide, were detected. The reaction of benzylamine with primary aliphatic alcohols afforded the products (3aa-ah) in good to excellent yields and the yields of imines from benzylamine with linear primary aliphatic alcohols (entries 1-6) are higher than that with branched primary aliphatic alcohols (entries 7 and 8). However, the

Table 1         Optimization of the reaction conditions <sup>a</sup>								
$NH_2 + OH \xrightarrow{1wt\%Pd/ZrO_2} N \xrightarrow{N}$ 1a 2a 3aa								
Entry	Base, <i>x</i> (mmol)	Temp. (°C)	$\operatorname{Yield}^{b}(\%)$	TON	TOF $(h^{-1})$			
1	KOH, 0.5	20	57	606	165			
2	KOH, 0.5	30	94	1000	238			
3	КОН, 0.5	40	94	1000	270			
4	NaOH, 0.5	30	93	989	220			
5	$Na_2CO_3, 0.5$	30	23	245	63			
6	$K_2CO_3, 0.5$	30	75	798	167			
7	КОН, 0	30	0	0	0			
8	KOH, 0.3	30	94	1000	239			
9	КОН, 0.1	30	92	979	221			
10	KOH, 0.05	30	87	926	207			

<sup>a</sup> Reaction conditions: 1a (1 mmol), 2a (10 mL), 1 wt% Pd/ZrO<sub>2</sub> (10 mg), base, air atmosphere, 30 °C, 6 h. TON = n (converted benzylamine)/n(Pd); TOF  $(h^{-1}) =$  TON at the first hour. <sup>b</sup> Yield was determined by GC analysis.

 Table 2
 The reaction of different alcohols with benzvlamine<sup>a</sup>

1

	Ar NH <sub>2</sub> + R OH	1wt%Pd/ZrO <sub>2</sub> KOH, 30℃ Ar	`N <sup>^^</sup> R 3
Entry	1	2	Yield <sup>b</sup> (%)
1 2	1a 1a	СН <sub>3</sub> -ОН (2 <b>b</b> ) 2 <b>a</b>	85 94
3	1a	OH (2c)	84
4	1a	OH (2d)	83
5	1a	OH (2e)	96
6	1a	OH (2f)	82
7	1a	└OH (2g)	77 $(86)^d$
8	1a	Он (2h)	$70 (83)^d$
9	1a	OH └── (2i)	$10 (76)^{c,d}$
10	1a	OH └── (2j)	12 (97) <sup>c</sup>
11	1a	OH └── (2k)	2 (97) <sup>c</sup>
12	1a	-C-OH (21)	0
13	$CI$ $NH_2$ $(1b)$	2a	99 <sup>e</sup>
14	$H_3C$ $NH_2$ $(1c)$	2a	99 <sup>e</sup>
15	$H_3CO$ $NH_2$ $(1d)$	2a	99 <sup>e</sup>
16	$OCH_3$ (1e)	2a	99 <sup>e</sup>
17	$\bigcup_{\text{OCH}_3}^{\text{NH}_2} (1f)$	2a	99 <sup>e</sup>
18	NH <sub>2</sub> (1g)	2a	99 <sup>e</sup>
19	$\operatorname{NH}_{2}(1\mathbf{h})$	2a	99 <sup>e</sup>
20	NH <sub>2</sub> (1i)	2a	99 <sup>e</sup>
21	◯ <sup>−</sup> NH <sub>2</sub> (1j)	2a	99 <sup>e</sup>
22	$\sim NH_2$ (1k)	2a	99 <sup>e</sup>
23	√−NH₂ (11)	2a	$31(43)^d$

 $^a$  Reaction conditions: 1 (1 mmol), 2 (10 mL), 1 wt% Pd/ZrO<sub>2</sub> (10 mg), KOH (0.1 mmol), air atmosphere, 30 °C, 6 h.  $^b$  Yield was determined by GC analysis.  $^c$  10 mg Au-Pd/ZrO<sub>2</sub>.  $^d$  Reaction time 12 h.  $^e$  Reaction time 3 h.

reaction of benzylamine with secondary aliphatic alcohols only gave the corresponding imines (**3ai–ak**) in lower yields under the same conditions (entries 9–11). Firstly, this is attributed to the steric hindrance of secondary alcohols, so it makes difficult to oxidize secondary alcohols into ketones. In addition, ketones react with amines more slowly to form ketimines than aldehydes do.<sup>7b</sup> The reaction using tertiary alcohol (*tert*-butyl alcohol) was also examined, however, it resulted in no reaction (entry 12). It was obviously because tertiary alcohol had no  $\alpha$ -H and can not be oxidized.

Apart from Pd/ZrO<sub>2</sub> catalyst, Au/ZrO<sub>2</sub> and Au–Pd/ZrO<sub>2</sub> alloy catalysts were also used in above reactions (Table S1<sup>†</sup>). To our delight, Au–Pd/ZrO<sub>2</sub> catalyst was much more active than Pd/ ZrO<sub>2</sub> in the reactions of benzylamine and secondary aliphatic alcohols, and the yields of ketimines were largely improved (Table 2, entries 9–11). The significant enhancement of the catalytic activity can be explained by the electronic heterogeneity (Pd in the alloy NPs expresses more electropositive properties and Au expresses more electronegative properties<sup>18</sup>), which can lead to enhancement the interaction between the alloy NPs and the reactant molecules.<sup>22</sup>

Next, the reactions of various amines with ethanol were also investigated (Table 2, entries 13–23). Substituted benzylamine with 4-chloro (**1b**), 4-methyl (**1c**), 4-methoxy (**1d**), 3-methoxy (**1e**) and 2-methoxy (**1f**) groups reacted well with ethanol to afford the products (**3ba-3fa**) in 99% yields after 3 h (entries 13–17). It seems that both the electron donating and electron withdrawing substituents on benzylamine can facilitate the reaction. Similarly, treatment ethanol with 2-phenylethylamine (**1g**),  $\alpha$ -methylbenzylamine (**1h**), aminodiphenylmethane (**1i**) or cyclohexylamine (**1j**) also led to form the desired imines in 99% yields. Moreover, aliphatic amine (**1k**) also reacted efficiently with ethanol to give excellent yield of the imine (**3ka**). The reaction of low nucleophilic aniline (**1l**) with ethanol, nevertheless, yielded the *N*-benzylideneaniline (**3la**) in 43% only, even though the reaction was last for 12 h.<sup>23</sup>

After the reaction, the catalyst was easily separated by filtration and its recyclability was investigated in the reaction of benzylamine and ethanol to synthesize the corresponding imine. To our delight, the catalytic activity of Pd/ZrO<sub>2</sub> remained almost unchanged after 5 runs.

According to the references, the Pd-catalyzed synthesis of imine may proceed *via* the sequence of aerobic alcohol oxidation and dehydrating condensation of the generated carbonyls with the amines.<sup>12b,17</sup> (Scheme 1) Note that carbonyl intermediate was not detected by GC-MS under our experimental conditions. We believe that alcohol oxidation is the rate-determining step and carbonyl intermediate is produced in low concentration and consumed readily by condensation with amine.

We further investigated the condensation step, *n*-butyraldehyde (1 mmol) was used as initial reagent which coupled with benzylamine (1 mmol) to synthesize corresponding imine. Neither the catalyst nor the base was required for the aldimine formation even at lower temperature (20 °C). In contrast, both catalyst and base are essential to form ketimine when using acetone and benzylamine as reactants. Moreover, it resulted in decreasing the selectivity of imines which were synthesized from carbonyls and amines. Therefore, we further inferred the high imine selectivity in our reaction system depended on the low concentration of carbonyls which were generated by alcohols and consumed readily *in situ* with amine.

In conclusion, we developed a one-pot method for the direct synthesis of imines catalyzed by 1 wt% Pd/ZrO<sub>2</sub> at 30 °C under air atmosphere. This is a general, efficient and versatile access to formation of imines from amines with short-chain aliphatic alcohols  $(C_1-C_6)$ . For one advantage, the environmentally benign method occurs under ambient conditions (30 °C and using air as the economic oxidant) and achieves high yield to imine. In order to achieve high yield of ketimines from amines with secondary alcohols which are relatively restricted, Au-Pd alloy catalyst was introduced and better results were obtained. For another, the selectivity to desired imine was excellent and no other reported products were detected. The full selectivity can be explained that oxidation of alcohols to the corresponding aldehydes which were only present in small amounts and consumed in situ, consequently, such side reactions can be diminished. Deeper mechanistic study of this method is underway.

We gratefully acknowledge the financial supports from the National Natural Science Foundation of China (no. 20966008) and Opening Project of Natural Science Foundation of Inner Mongolia (no. 2010KF02).

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