Catal Lett (2012) 142:389–396
DOI 10.1007/s10562-012-0778-4

Reductive Amination of Carbonyl Compounds over Silica Supported Palladium Exchanged Molybdophosphoric Acid Catalysts

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Received: 12 July 2011 / Accepted: 28 January 2012 / Published online: 17 February 2012

Abstract Palladium exchanged molybdophosphoric acid supported on silica is reported as a highly effective catalyst for direct reductive amination of carbonyl compounds. The catalysts are characterized by X-ray diffraction and FT-infrared spectroscopy. The characterization results support the existence of Keggin ion of heteropoly molybdate on silica. The catalyst is facile, water tolerable and environmentally benign for reductive amination. A variety of secondary and tertiary amines can be synthesized over this catalyst in excellent yields under mild reaction conditions. A plausible reaction mechanism is proposed for the reductive amination of carbonyl compounds over this catalyst.

Keywords Carbonyl compounds · Amines · Reductive amination · Palladium · Molybdophosphoric acid

1 Introduction

Reductive amination of carbonyl compounds, or reductive alkylation of amines, where the reaction of amines with aldehydes and ketones in the presence of a reducing agent is one of the widely used and fundamental reaction in organic synthesis [1–3]. In this reductive amination the overall process involves the formation of an imine or iminium intermediate followed by reduction to alkylated amines. Reductive amination of carbonyl compound is a very important and powerful tool for chemists to target the synthesis of structurally diverse primary, secondary and tertiary amines [4, 5]. Amines and their derivatives are highly versatile building blocks for various organic substrates and are essential starting materials for variety of biological active compounds. Amines and their derivatives are widespread among natural products such as alkaloids, amino acids, nucleic acids [6–12].

Two synthetic methods are commonly used for reductive amination. One is the direct reductive amination, in which a mixture of carbonyl compound and amine are treated directly with suitable reducing agents in a single operation without formation of an intermediate imine or iminium salt. The other one is a stepwise or indirect reaction, in which the first step is the conversion of amine into imine and further reduction of imine reduced into higher alkylated amine. In indirect reductive amination method the imine derivative can be isolated from the reaction mixture [2, 8, 13].

The direct reductive amination of aldehydes and ketones is used extensively compared to indirect method to prepare primary, secondary, and tertiary amines. Direct reductive amination is performed under anhydrous conditions in order to avoid decomposition of the reducing agents or catalysts, and at the same time to enhance the generation of the intermediate imines or iminiun salts.

There are several reagents and catalysts reported in the literature for reductive amination, following direct as well as indirect approaches [14–17]. In most of these methods are used acid catalyst/reagent along with a reducing agent like $NaBH_4$. Pd and In based homogeneous catalysts are reported for the direct reductive amination [6, 11, 18, 19]. Most of these methods have some drawbacks in one way or another such as excess amount of reagents, acidic conditions, higher reaction temperature, prolonged reaction time, inert conditions and toxic by-products. Recently

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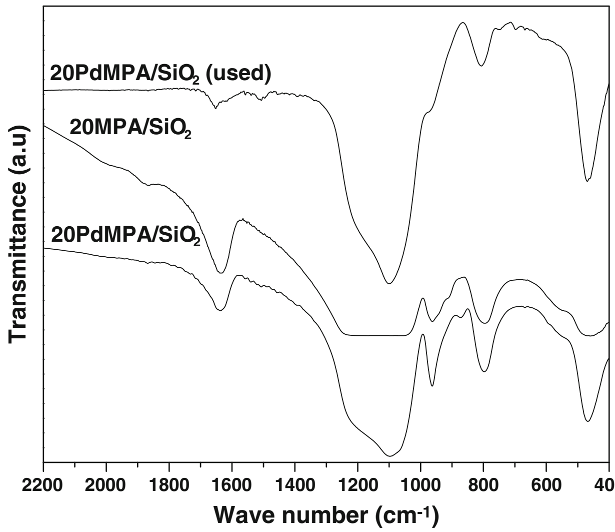


Fig. 1 FT-IR Spectra of silica supported palladium exchanged molybdophosphoric acid and silica supported molybdophosphoric acid catalysts

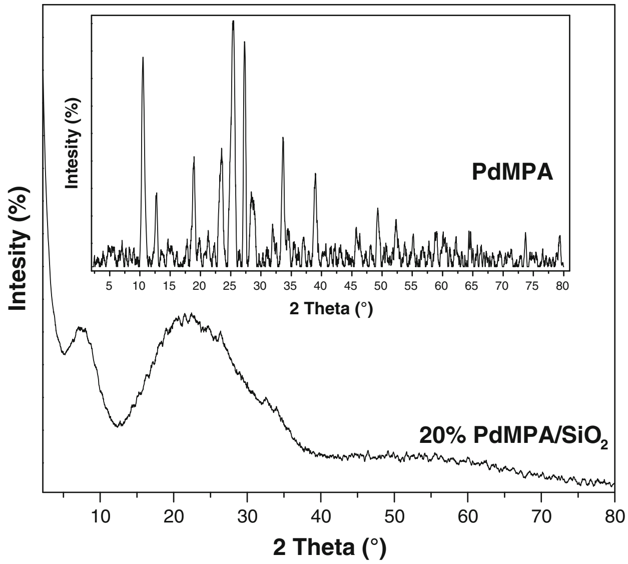


Fig. 2 XRD patterns of silica supported palladium exchanged molybdophosphoric acid and bulk palladium exchanged molybdophosphoric acid catalysts

Table 1 Comparison of catalysts for reductive amination of benzaldehyde with aniline

Catalyst	Imine yield[a] (%)	Amine yield[a] (%)	Alcohol yield[a] (%)
20% PdMPA/SiO_2	0.8	93	1.2
20% CuMPA/SiO_2	86.5	0.5	–
20% MPA/SiO_2	79.4	–	–
20% CuMPA/SiO_2 (reduced)	54.5	–	–
PdMPA	7.0	63	12
2% Pd/SiO_2	6.3	73	20
Blank	38	–	–

Reaction conditions: benzaldehyde (1 mmol); aniline (1 mmol); catalyst weight (50 mg); solvent 3 ml; reaction temperature: 60 °C, reaction time: 30 min H_2 atmosphere

[a] Yields were determined by GC–MS analysis

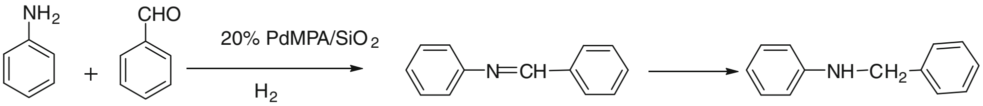
heterogeneous gold (I), Pt, Pd catalysts supported on different acid and base supports are used for reductive amination reaction [20]. These catalysts have advantages over homogenous catalysts. However, reported conversions are low and require long reaction time and high temperature. Though many of the reported protocols for reductive amination reaction work well for the preparation of tertiary amines and synthesis of secondary amines is compromised by over alkylation in many cases [7, 14–17]. Thus, it is necessary to develop an alternative method that employs simple and environmentally benign conditions for all three types of amines.

Heteropoly acids (HPAs) particularly Keggin types are known as better acid and oxidation catalysts. HPAs are noncorrosive and environmentally benign catalysts used for different organic transformations both in homogenous and heterogeneous conditions [21]. HPA has been attained much attention due to their unique properties such as well-defined structure, Bronsted acidity and possibility to modify their acid–base properties. These catalysts have the ability to accept and release electrons and possess high proton mobility [22]. In continuation of our interest for the application of heteropolyacids as environmentally benign catalysts for various organic transformations [23, 24], we report a heterogeneous palladium exchanged molybdophosphoric acid (MPA) supported on silica catalyst for the reductive amination of aldehydes and ketones. Most of the reductive amination catalysts are water sensitive and non selective [16]. The advantage of the present catalyst is that it is not water sensitive and also selective for monoalkylation.

2 Experimental

2.1 Catalyst Preparation

The palladium containing MPA catalyst was prepared by exchanging the protons of 12-MPA in stepwise. Initially 0.281 g of barium hydroxide was added to the aqueous solution containing 2.0 g of MPA to exchange its protons with Ba. Later aqueous solution containing 0.20 g of $PdSO_4$ was added slowly while stirring to replace Ba with Pd by eliminating Ba as $BaSO_4$. Thus the Pd exchanged MPA (PdMPA) was recovered from the solution by recrystallization [25]. The Pd containing MPA on silica was prepared by wet impregnation method. The required



Scheme 1 Reaction pathway for the reductive amination of carbonyl compounds

Table 2 Reductive amination in presence of different solvents

Solvent	Yield[a] (%)		
	Imine	Amine	Benzyl alcohol
H_2O	34.7	55.7	2.7
EtOH	3.0	74.6	1.8
MeOH	2.1	53.0	2.1
Isopropanol	13.5	64.0	2.5
1,4-dioxane	31.5	46.2	1.0
DMF	0.8	93.0	1.2
Toluene	8.0	67.0	3.0

Reaction conditions: benzaldehyde (1 mmol); aniline (1 mmol); catalyst weight (50 mg); reaction temperature: 60 °C, reaction time: 30 min H_2 atmosphere

[a] Yields were determined by GC–MS analysis

amount of PdMPA (0.8 g) dissolved in distilled water (10 ml) and added to silica (4 g). The catalyst mass was dried on water bath and further dried at 120 °C for 12 h in oven. Finally the catalyst was calcined at 300 °C for 2 h. The amount of PdMPA on silica was 20 wt%. Similarly 20 wt% MPA supported on silica was also prepared in the same procedure where MPA was taken instead of PdMPA. The amount of Pd exchanged with the proton of MPA is calculated by atomic absorption spectroscopy (AAS) analysis. The protons present in MPA are partially exchanged with Pd ion. Based on these results the PdMPA is in the form of $Pd_{2.8}H_{0.2}$MPA. The Cu exchanged MPA supported on silica was prepared with similar procedure as described above by taking calculated amount of Cu $(NO_3)_2$ instead of $PdSO_4$.

2.2 Characterization of Catalysts

X-ray powder diffraction patterns were recorded on of Rigaku Miniflex diffractometer using Cu Kα radiation (1.5406 Å) at 40 kV and 30 mA and secondary graphite monochromatic. The measurements were obtained in steps of 0.045° with account time of 0.5 s and in the 2θ range of 10–80°. The FT-IR spectrum was recorded on a Bio-rod Excalibur series spectrometer using the KBr disc method.

2.3 General Reaction Procedure

In a typical reaction procedure a mixture of aldehyde (1 mmol), aniline (1 mmol) and DMF (3 ml) were taken in 25 ml two-necked round bottom flask. About 50 mg of catalyst was added to the reaction mixture and stirred at 60 °C on oil bath under hydrogen at atmospheric atmosphere. The progress of the reaction was monitored by using thin layer chromatography. The products were identified by GC–MS (SHIMADZU-2010) analysis by separating the products on a DB-5 column.

3 Results and Discussion

The FTIR spectra of the catalysts are presented in Fig. 1. The 20% PdMPA/SiO_2 and 20% MPA/SiO_2 catalysts showed similar IR patterns. The IR bands were observed at 1,093, 961, 861 and 789 cm^{-1}, attributed to characteristic Keggin ion stretching vibrations of P–O_d, Mo=O_t, Mo–O_b–Mo and Mo–O_c–Mo respectively [26]. This indicates that during the exchange of Pd with protons of MPA the Keggin ion structure is intact and the Keggin structure is present on the support.

X-ray diffractogram of 20% PdMPA/SiO_2 catalyst is shown in Fig. 2 and the diffractogram of bulk PdMPA also shown in the insert of the figure. The XRD patterns related to Keggin ion structure are clearly seen for the bulk PdMPA. The characteristic peaks at 2θ values of 10.5°, 23.7°, 26.1°, 30.2° and 35.6° are assigned to Keggin structure of MPA. When PdMPA is supported on silica the catalyst showed broad XRD patterns. This suggests that the Keggin ion of PdMPA was highly dispersed on silica. Even though the Keggin patterns are not seen in XRD for the supported catalysts, the existence of the Keggin structure can be conformed from FT-IR and XRD of bulk PdMPA analysis.

Initially the reaction of benzaldehyde with aniline using a series of silica supported heteropoly molybdate catalysts was studied and the results are shown in Table 1. The catalysts 20% MPA/SiO_2 and 20% CuMPA/SiO_2 yielded mainly imine. The reduction of imine to amine is relatively low over these catalysts. The 20% PdMPA/SiO_2 catalyst afforded about 93% yield to amine. This result indicates that MPA and Cu containing MPA are able to catalyse the formation of imine and further reduction to amine is very low. Silica supported copper exchanged MPA catalyst after was subjected to reduction to reduce Cu and studied for this reaction. This catalyst also yielded only imine. This result suggests that no further reduction took place with copper ions and copper metal. The pre-reduced 2% Pd/SiO_2

Table 3 Synthesis of substituted reductive amination products over 20% PdMPA/SiO_2 catalyst

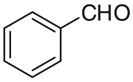
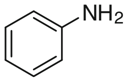
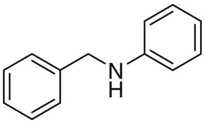
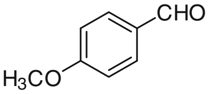
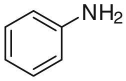
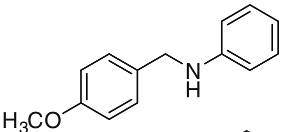
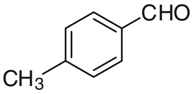
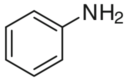
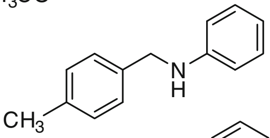
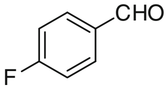
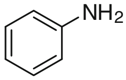
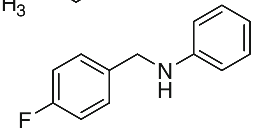
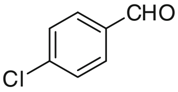
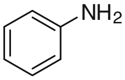
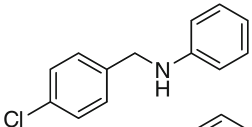
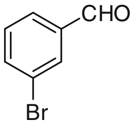
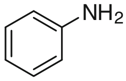
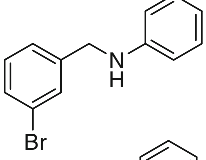
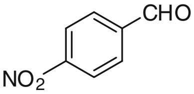
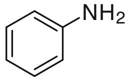
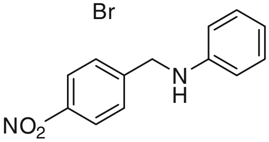
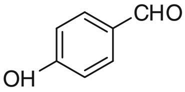
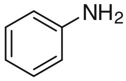
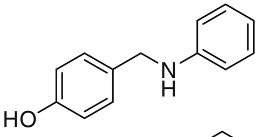
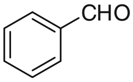
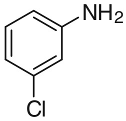
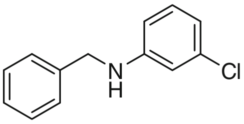
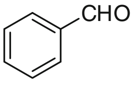
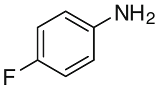
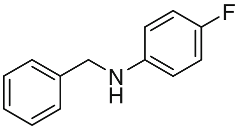
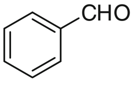
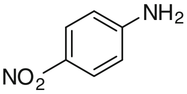
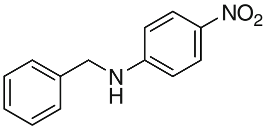
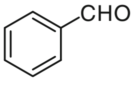
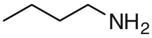
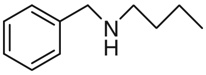
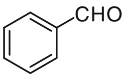
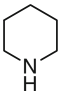
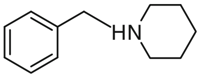
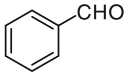
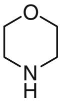
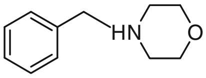
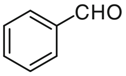
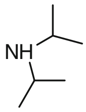
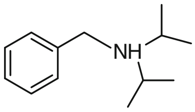
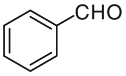
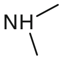
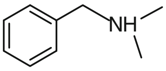
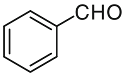
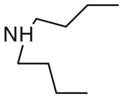
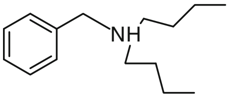
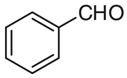
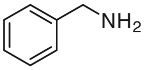
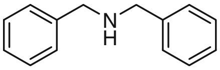
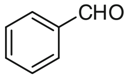
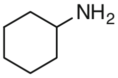
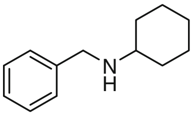
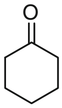
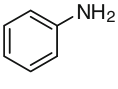
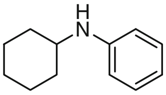
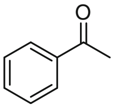
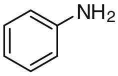
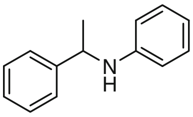
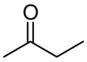
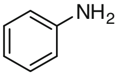
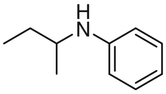
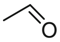
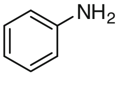
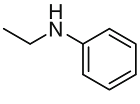
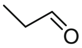
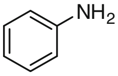
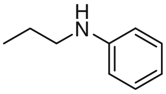
S.No	Aldehyde	Amine	Amine	Imine yields ^{a}	Amine yields ^{a}
1				2.2	93.0
2				1.8	75.7
3				2.8	81.5
4				3.7	91.8
5				11.9	78.6
6				18.3	66.9
7				17.0	44.8
8				7.5	55.3
9				10.1	63.0
10				22.7	54.0
11				10.5	40.5
12				88.5	0.35

Table 3 continued

S.No	Cabonyl compound	Amine	Amine	Imine yields[a]	Amine yields[a]
13				-	82.0
14				-	92.0
15				-	80.0
16				-	15.4
17				-	66.2
18				4.8	91.0
19				4.4	54.0
20				2.0	30.8
21				-	trace
22				-	10.5
23				-	18.2
24				-	27.5

Reaction conditions: benzaldehyde (1 mmol); aniline (1 mmol); catalyst weight (50 mg); solvent 3 ml; reaction temperature: 60 °C, reaction time: 30 min H_2 atmosphere

[a] Yields were determined by GC–MS analysis

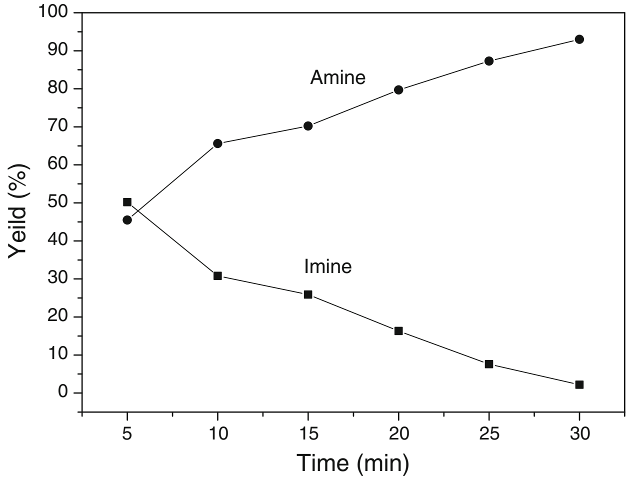


Fig. 3 Time on stream analysis for the synthesis of amine over 20% PdMPA/SiO_2. Reaction conditions: benzaldehyde (1 mmol); aniline (1 mmol); catalyst weight (50 mg); solvent 3 ml; reaction temperature: 60 °C

catalyst also yielded reasonably high amount of amine. Based on the above results the reaction path way over the catalyst can be illustrated as shown in Scheme 1. Suitable solvent system for reductive amination of aniline and benzaldehyde as a test reaction was checked by carrying the reaction with different solvents and the results are shown in Table 2. It is found that DMF was best solvent as it gave high yield compared to other solvents. The high activity with DMF solvent might be related to stabilization of the imine–pd complex formed initially stabilized by DMF compared to other solvents. Such stabilization of imine–Pd complex by DMF was reported [27]. The stabilized imine–Pd complex undergoes easy reduction to yield amine. It is noteworthy to mention that the present catalyst is active in many solvents including water.

Various aldehydes and amines were subjected to reductive amination over 20% PdMPA/SiO_2 catalyst and the results are presented in Table 3. The reductive amination of aldehydes are more facile than ketones. At the same time aromatic aldehydes are more active than aliphatic aldehydes. Aromatic aldehydes with electron donating groups smoothly underwent reductive amination to give their corresponding N-phenyl amines in good yield without affecting the functional groups. Aromatic aldehydes with halo group gave desired amine in good yields and the reactivity of fluorine and chlorine containing aldehydes are more active than bromo aldehydes. Aromatic aldehydes and amines with electron withdrawing group such as $–NO_2$ gave low yield. This might be because of the reduction of NO_2 group during the reaction. In the case of acetophenone, the formation of 1-phenylethanol was more than actual amine product. The formation of 1-phenylethanol by the reduction of ketone was found to be the major pathway

Scheme 2 Plausible reaction mechanism for reductive amination over silica supported palladium exchanged molybdophosphoric acid catalyst

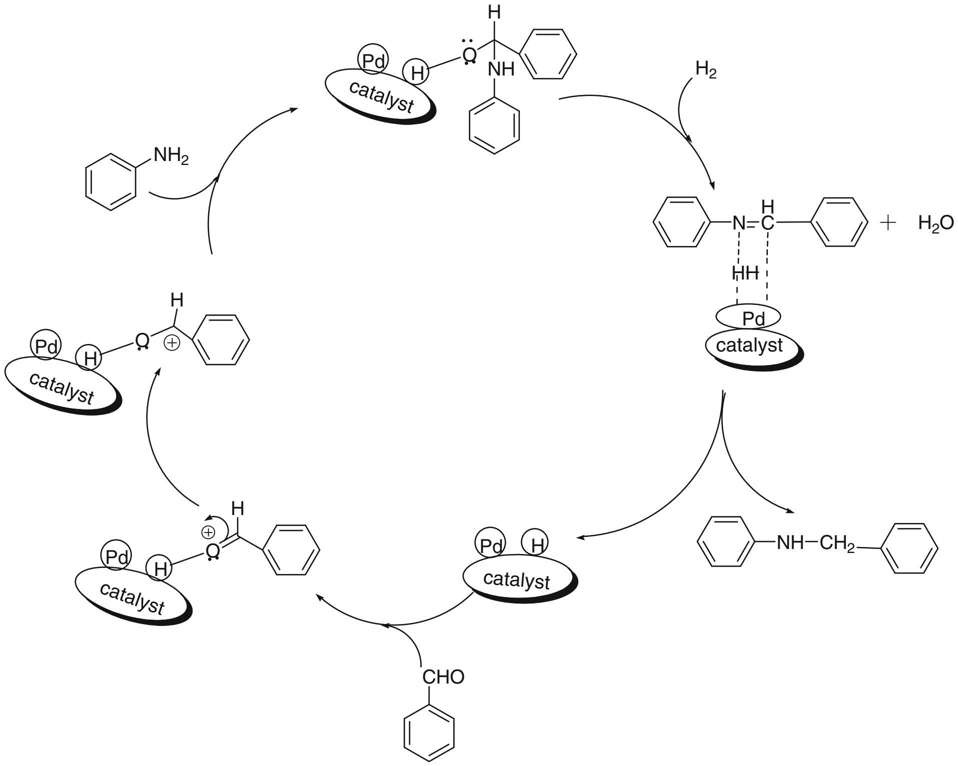


Table 4 Recycling results of 20% PdMPA/SiO_2 catalyst

S. no.	No. of recycles	Imine yield (%)	Amine yield (%)	Alcohol yield (%)	Catalyst recovery (%)
1	0	0.8	93	1.2	–
2	1	0.6	90	0.9	95
3	2	1.3	87	0.6	92
4	3	1.7	84	0.5	90

in this case. Hetero atom containing amines undergo reductive amination smoothly with high yield. This catalyst is also effective when secondary amines with or without branching is used for the reductive amination with aldehydes (Table 3, s.·no. 15–17).

The time on stream analysis for the reductive amination over 20% PdMPA/SiO_2 catalyst was studied and the results are shown in Fig. 3. This study was undertaken to know about the formation of both intermediate imine and product amine as shown in Scheme 1. Initially at the start of the reaction the formation of imine is more and as the reaction progresses the formation of amine is gradually increased. These results suggest that the reaction undergoes via the formation of imine which easily undergoes reduction on Pd sites to yield amine.

The plausible reaction mechanism over this catalyst is schematically shown in Scheme 2. In this reaction the first step is the formation of the imine intermediate by the reaction of condensation between carbonyl compound and amine on the catalyst surface utilizing the acidic sites present on the catalyst surface. This imine was coordinated with the hydrogen atoms activated by Pd sites of the catalyst and undergoes subsequent reduction to yield amine derivative. The time on stream analysis supports the proposed mechanism as the formation of imine is observed. The catalyst without palladium (20% MPA/SiO_2) yielded only the imine as a main product suggesting the requirement of Pd for the reduction imine. The formation of imine mainly over silica supported CuMPA and MPA reiterate the importance of Pd in reducing the imine that formed on the acidic sites of the catalyst. The present catalyst overcomes the requirement of both acid catalyst/reagent along with a reducing agent generally required for reductive amination.

3.1 Recyclability of the Catalysts

After completion of the reaction, the catalyst was separated by simple filtration and washed 2–3 times with DMF and dried in hot air oven at 120 °C for 1 h. The dried catalyst was reused. The recovery of the catalyst is varied with in 95–90%. The results obtained by recycling of the catalyst are shown in Table 4. The amination product after three cycles was almost constant and the results suggest the reusability of the catalyst. The Pd content of the fresh and used (after 4th cycle) catalysts were estimated. The Pd content in these catalysts was 3.067 and 3.052 mmol for fresh and used catalysts respectively. The consistent activity upon reuse and the similar content of Pd before and after reaction reiterates the heterogeneity of the catalyst.

4 Conclusions

Silica supported palladium exchanged MPA catalyst was prepared with intact Keggin structure. 20% PdMPA/SiO_2 was an efficient catalyst for reductive amination of various aldehydes and ketones. This catalyst is active even when various secondary, cyclic and acyclic amines are used and afforded the corresponding secondary and tertiary amines in high yields. This method is very advantageous in terms of its mild reaction conditions, mono alkylation than conventional catalytic/reagents and heterogeneity environmentally benign nature of the catalyst.

Acknowledgments A. Srivani thanks Council of Scientific and Industrial Research (CSIR), India for financial support in the form of a Junior Research Fellowship.

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