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COMMUNICATION

Poly(vinyl)chloride supported palladium nanoparticles: catalyst for rapid hydrogenation reactions†

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Palladium nanoparticles supported over poly(vinyl)chloride matrix (PVC-Pd^0) are prepared through an efficient and inexpensive protocol. The catalyst has been characterized by XRD, SEM and TEM and its utility for the reduction of a range of functional groups as well as for the removal of some common protecting groups employed in peptide chemistry is demonstrated.

Reduction of organic substrates such as nitro, azido, carbonyls and C–C multiple bonds is of paramount interest in organic synthesis.[1] This is a key operation with a wide spectrum of applications in pharmaceutical industries and in the synthesis of biologically significant compounds.[2] Some of the well known protocols developed for such conversions include electron transfer reduction, metal acid reduction, hydride transfer reduction and hydrogenation reaction.[3,4] In particular, reductions involving heterogeneous catalytic systems which employ molecular hydrogen over metal supports such as Pd, Fe, Zn, Mg, Pt, *etc*., have been much sought-after protocols owing to their reaction efficiency, yield, selectivity and minimum side reactions. Among them, catalytic hydrogenation has acquired much significance and the reductions employing commercially available palladium dispersed in activated charcoal (Pd/C) in the presence of hydrogen continues to be a major choice[5] due to the several advantages in-spite of safety concerns, which warn against the use of hydrogen gas. In peptide chemistry, catalytic hydrogenation is a valuable tool especially for the removal of commonly employed protectors such as benzyloxycarbonyl (Z), benzyl ester (OBz), benzyl ether (for Ser, Thr, Tyr, Trp), His-Bzl, NO_2 group (used for guanidine protection of Arg) *etc*. However in general, catalytic hydrogenation is a time consuming process often requiring pressure vessels and special equipment such as Parr equipment. Owing to the exhaustive application of Pd mediated catalytic hydrogenation, we became interested to explore new possibilities in catalyst design.

Metal nanoparticles have gained substantial attention in recent years in both chemistry and biology.[6,7] Smaller size of the metal nanoparticles leads to high surface/volume ratio and consequently, large number of potential active sites would be available to the substrates, as a result, enhancement in their catalytic activity. However, metal nanoparticles, due to high surface energy, are not stable as such. For instance, palladium nanoparticles aggregate into Pd black, which possesses lesser catalytic activity.[8] Hence immobilization of metal nanoparticles into a suitable rigid matrix has come into practice. In particular, Pd nanoparticles are stabilized by dispersing them in porous materials, ionic liquids, surfactants, dendrimers, functionalized polymers, biopolymers, various ligands, silica in supercritical CO_2, *etc*.[9–11] The stabilizing medium serves as a supporting material for protecting the nanoparticles from aggregation, provides the desired chemical interface between the nanoparticles and substrate, prevents the metal from being leached out of the matrix during the reaction and thus facilitates the overall reaction. Though several reports are available on palladium nanoparticles,[12] most of their applications have been devoted to catalyze/mediate C–C bond forming reactions such as Suzuki–Miyaura, Heck and Stille couplings.[13–16] However, reduction of a few nitro and alkene compounds using Pd(0) nanoparticles stabilized through bayberry tannin-grafted SiO_2 beads has been reported.[17] Uozumi *et al.*, developed an amphiphilic-PS-PEG resin supported Pd(0) nanoparticles for dehalogenation and hydrogenation in water medium.[18a]

The majority of the protocols developed for the preparation of Pd(0) nanoparticles demand special supports, multi-steps, laborious and time consuming techniques and, are in general, expensive.[18b–d] Keeping in mind the advantages of nanoparticles and the need for efficient catalysts for reduction as well as catalytic hydrogenation reactions, the development of a simple protocol for the preparation of supported Pd nanoparticles would be highly useful. The limitation of some of the existing techniques and the success of many of the so far developed ones stimulated this study. We have explored the preparation of poly(vinyl) chloride (PVC) supported Pd nanoparticles and have demonstrated the utility for rapid reduction of a range of functional groups as well as deprotection of some commonly employed protectors in peptide chemistry.

Poly(vinyl)chloride is a widely used and commercially available inexpensive polymer. It can be functionalized easily and hence, is a support of choice during heterogeneous catalyst preparation. Pd nanoparticles supported over PVC-amino ethanol matrix[19] and PVC-Schiff's base[20] have been prepared and employed as

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† Electronic supplementary information (ESI) available: SEM and TEM images of PVC-Pd^0 catalyst recovered after 3 reaction cycles, characterization data for selected compounds along with copies of spectra. See DOI: 10.1039/c0ob00962h

efficient catalysts in Suzuki and Heck reactions. In these studies, the polymer was designed so as to carry out *in situ* reduction of $PdCl_2$ into Pd(0) particles without the assistance of a foreign reducer. However, the prior functionalization of the polymer requires an extra step. We envisaged a straightforward protocol for dispersing Pd nanoparticles into the unmodified commercially available PVC matrix. An external reducing agent $NaBH_4$ is used to reduce $PdCl_2$ to Pd(0) in the PVC matrix. Accordingly, a previously stirred suspension of PVC and $PdCl_2$ (4 : 1: wt/wt) in ethanol was heated to reflux and then treated with a solution of $NaBH_4$ in ethanol for a few minutes. Initial brownish suspension due to the presence of $PdCl_2$ turned colorless upon addition of reducing agent indicating the complete conversion of Pd(II) to Pd(0). Overall, the preparation of catalyst was complete in about two hours. Our attempts to carry out the reduction with citric acid and sodium hydroxide in separate experiments turned out to be futile. The preparation of PVC supported Pd nanoparticles (PVC-Pd^0) in the present method was repeated several times to check the reproducibility of the protocol and up to 5 grams of catalyst was prepared successfully per batch. The palladium nanoparticles were filtered, washed and dried *in vacuo* and characterized *via* X-ray powder diffraction (XRD), scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

Pd(0) loading to the polymer matrix was determined to be 12.8% by ICP-OES. Three peaks were observed in the XRD pattern at 2θ values of 40°, 46° and 68° that could respectively be attributed to the 111, 200 and 220 facets of Pd(0).[21] (Fig. 1). The TEM image shows that the Pd nanoparticles are formed within a size range of 20 nm (Fig. 2).

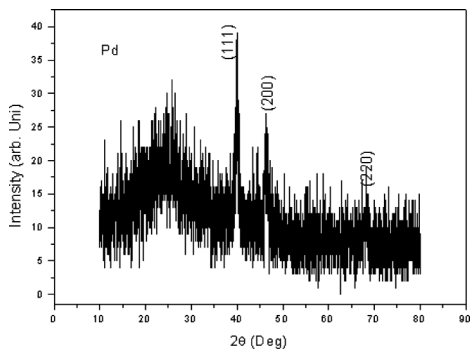


Fig. 1 XRD image of PVC-Pd^0.

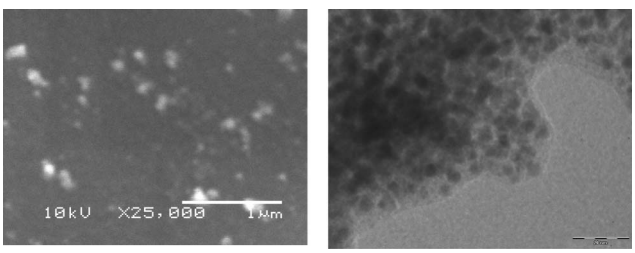
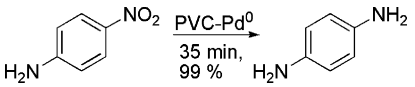


Fig. 2 **A**. SEM image of PVC-Pd^0. **B**. TEM image of PVC-Pd^0.

In the next stage, the utility of the PVC-Pd^0 for catalytic hydrogenation reactions was demonstrated. Initially, hydrogenation of nitro compounds was examined keeping in view the significance of nitro reduction in the pharmaceutical industry. Accordingly, a solution of *p*-nitroaniline (200 mg, Table 1, entry 1) in ethanol was treated with PVC-Pd^0 (20 mg) and the reaction mixture was stirred at rt in hydrogen atmosphere. The starting material consumed completely in 35 min (TLC analysis) and the resulting *p*-phenylenediamine was isolated through filtration followed by *in vacuo* evaporation of the filtrate (Scheme 1). The same conversion was reported to take 3–4 h for completion under conventional conditions (Pd/C–H_2),[22] which illustrates the advantage of the catalyst developed in the present study (see ESI). On increasing the catalyst amount to 20% by wt (with respect to substrate), a slight improvement in the reaction rate (25 min) was observed and when it was 5%, the reaction took over an hour for completion. After this optimization, a few more nitro compounds (entries 2–6, Table 1) were reduced satisfactorily.



Scheme 1 Reduction of nitro group.

Compounds bearing azide functionality were also reduced with PVC-Pd^0 and a smooth conversion into the corresponding amines was observed. An aliphatic azide and a benzyl azide (entries 7 and 8) were reduced in about 35–40 min in excellent yields. The same was true with 2,3,4,6-tetra-*O*-acetyl-(α)-D-glucopyranosyl-1-azide as well (entry 9).

In the next set of experiments, the reduction of aldehydes into hydroxy compounds was undertaken. The conversion of benzaldehyde into benzyl alcohol (entry 10) and salicylaldehyde into salicylal (entry 11) was satisfactory both in terms of yield and reaction duration. Reduction of isovaleraldehyde (entry 12) was monitored through IR (disappearance of carbonyl stretching frequency at 1730 cm^{-1}) and was complete in 20 min. However, the reduction of a ketone (benzophenone) took a longer time and after 90 min the corresponding hydroxy compound was isolated in 51% (entry 13). At this point, the recycling efficacy of PVC-Pd^0 was examined taking benzaldehyde as a specimen example. In a typical set of experiments, benzaldehyde (0.2 mL, 1.8 mmol) was subjected to reduction in the presence of PVC-Pd^0 (20 mg). After the completion of reaction, the catalyst was recovered (94% by weight) and was again used for the reduction of benzaldehyde. Reactivity of recovered PVC-Pd^0 was scrutinized up to three cycles and consistency in the yield and the reduction time was recorded in all the trials. The SEM and TEM images of the catalyst analyzed at the end of the third cycle showed no deterioration compared to that of the fresh catalyst (see ESI). The recycling efficacy of the catalyst was witnessed considering the example of reduction of *O*-nitrophenol as well. The palladium content of the PVC-Pd^0 recovered after three reaction cycles as analysed by ICP-OES was 11.6%.

The reduction of C–C double bond in the methyl cinnamate took about 50 min for completion (entry 14). The reduction of the alkyne functionality of propargyl alcohol and *N*-phenylpropiolamide (entries 15 and 16) was observed in 55–60 min. The quantitative conversion of the former into n-propanol was confirmed through IR analysis. In the subsequent experiments, the PVC-Pd^0 catalyst system was employed to reduce a couple of imines to the respective class of substituted amines.

Table 1 List of substrates employed for PVC-Pd^0 mediated catalytic hydrogenation

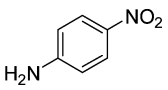
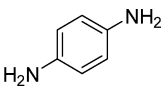
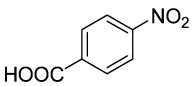
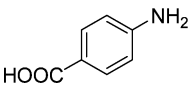
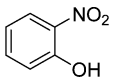
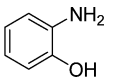
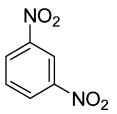
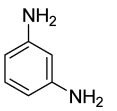
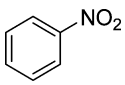
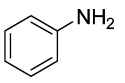
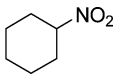
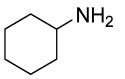
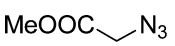
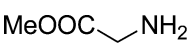
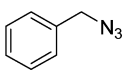
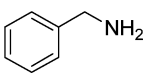
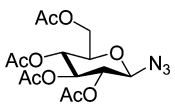
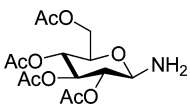
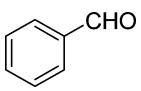
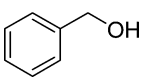
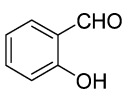
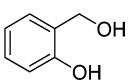
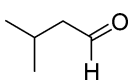
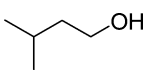
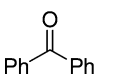
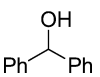
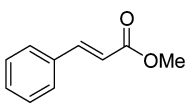
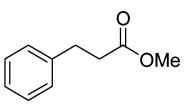
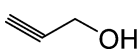
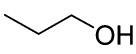
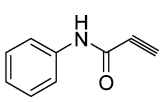
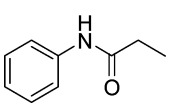
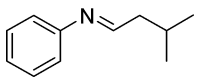
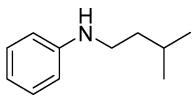
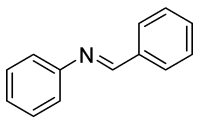
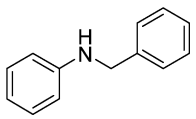
Entry	Substrate	Product	Time (min)	Yield[a] (%)
1			35	99
2			40	92
3			35	95
4			45	97
5			25	100
6			25	98[b]
7			35	98
8			35	96
9			40	94
10			30	100
11			35	98
12			20	100[b]
13			90	51
14			45	91
15			55	96[b]
16			60	94

Table 1 *(Contd.)*

Entry	Substrate	Product	Time (min)	Yield[a] (%)
17			35	87
18			40	94

[a] Isolated yield. [b] % conversion as determined by TLC.

For this, in a case study, aniline was treated with an equimolar quantity of isovaleraldehyde in MeOH and the reaction was followed through TLC analysis. After complete consumption of aldehyde, the *in situ* formed imine (entry 17, Table 1) was subjected to catalytic hydrogenation. It was complete (TLC and IR monitoring) in about 35 min and the product was isolated through usual work-up. One more example for this category of reaction was added by reducing the imine obtained from benzaldehyde and benzyl amine (entry 18, Table 1).

As a second objective of the present study, we focused towards the demonstration of the application of PVC-Pd^0 for the rapid removal of several protecting groups commonly employed in peptide chemistry. Notably, catalytic transfer hydrogenation (CTH) has gained much focus in this area which offers the advantage of circumventing the use of hydrogen gas that warrants potential safety concerns.[23,24] In CTH, hydrogen transfer agents such as formic acid, cyclohexene, hydrazine, ammonium formate, *etc*., are employed in place of hydrogen gas.[25–27] However, catalytic hydrogenation has an edge over CTH, of being carried out under neutral conditions, hence compatible to both acid and base labile functionalities and also minimum side reactions. This stimulated us to check the applicability of polymer bound palladium nanoparticles for a quick and convenient hydrogenation for the removal of Z, benzyl ester and benzyl ether protectors used for amino acids.

In a typical experiment, Z-Phe-OH was subjected to hydrogenation in the presence of PVC-Pd^0 as described above. To our delight, the deprotection was complete in 30 min and H-Phe-OH (entry 1, Table 2) was isolated quantitatively through filtration followed by evaporation of the solvent. The product was initially

Table 2 Deprotection reactions *via* PVC-Pd^0 catalyst

Entry	Substrate	Product	Time (min)	Yield[a] (%)
1	Z-Phe-OH	H-Phe-OH	30	100
2	Z-Lys(Boc)OH	H-Lys(Boc)OH	40	90
3	Fmoc-Pro-OBzl	Fmoc-Pro-OH	50	95
4	Fmoc-Leu-OBzl	Fmoc-Leu-OH	45	100
5	Boc-Asp(OBzl)OH	Boc-Asp-OH	60	80
6	Boc-His(Bzl)-OH	Boc-His-OH	60	85
7	Boc-Tyr-(OBzl)-OH	Boc-Tyr-OH	45	93
8	Boc-Thr(Bzl)OMe	Boc-Thr-OMe	50	100
9	Z-Glu(OBzl)OH	H-Glu-OH	80	98
10	Z-Ala(Oxa)	Ala(Oxa)	25	100

[a] Isolated yield.

Table 3 Catalytic hydrogenation of protected peptides using PVC-Pd^0

Entry	Protected peptide	Product	Time (min)	Yield[a] (%)	mp (°C)
1	Fmoc-MeLeu-MeLeu-OBzl	Fmoc-MeLeu-MeLeu-OH	50	95	116–119
2	Fmoc-MeLeu-Val-MeLeu-Ala-OBzl	Fmoc-MeLeu-Val-MeLeu-Ala-OH	70	68	gum
3	Z-Phe-Phe-OEt	Phe-Phe-OEt	40	100	246–248[25]
4	Z-Pro-Val-Gly-OEt	Pro-Val-Gly-OEt	65	92	128–130[26a]
5	Z-Ala-Asp(OBzl)-Ser-Gly-OH	Ala-Asp-Ser-Gly	110	78	191–193[26a]
6	Z-Leu-Phe-Gly-Gly-Arg(NO_2)-OMe	Leu-Phe-Gly-Gly-Arg-OMe	95	83	127–130[29]

[a] Isolated yield.

confirmed by comparing the physical constant with the reported value [mp: 270–272 °C (dec); reported value: 270-275 °C][28] and then using analytical methods. The catalyst worked well for the deprotection of benzyl esters also (entry 3, 4, Table 2). Boc-His(Bzl)OH was converted to Boc-His-OH in 85% yield in about 60 min (entry 6). Benzyl ethers of Boc-Tyr(Bzl)OH and Boc-Thr(Bzl)OMe were deprotected in a short duration in excellent yields (entries 7, 8). Boc-Asp(OBzl)OH and Z-Glu(OBzl)OBzl were hydrogenated into Boc-Asp-OH and Glu respectively in 80 and 98% yields. Oxazolidinone derived from Z-Ala-OH was subjected to hydrogenation in the present approach and amino free-alanyl 5-oxazolidinone (entry 10) was isolated quantitatively in 25 min.

A hindered dipeptide Fmoc-(NMe)Leu-(NMe)Leu-OBzl was hydrogenated in 50 min and the corresponding free carboxy peptide was isolated in 95% yield (Table 3, entry 1). Fmoc group removal was not noticed in these experiments. A tetrapeptide fragment of cyclosporine-*O*, Fmoc-MeLeu-Val-MeLeu-Ala-OBzl (Table 3, entry 2) was successfully debenzylated and the product was isolated in a good yield. Z-protected di-, tri- and tetrapeptides were also hydrogenated in reasonably short duration (Table 3, entries 3, 4, 5). Finally, the Z and the Bzl groups present in the pentapeptide fragment related to Fibrinopeptide B of green monkey were completely removed in one and a half hours (Table 3, entry 6).[29] The melting points of the free peptides were in agreement with the reported data. In all the above experiments, the PVC-Pd^0 worked exceptionally well and drove the reactions in a short duration (See ESI).‡

In summary, a rapid and economic protocol has been developed to prepare PVC supported Pd(0) nanoparticles and the catalyst has been characterized through ICP-OES, TEM, SEM and XRD studies. The catalyst preparation is very simple and is reproducible even in an unsophisticated laboratory. The utility of PVC-Pd^0 as an efficient catalyst for the hydrogenation of a range of substrates such as nitro, azido, carbonyl, alkene, alkyne and imino compounds has been investigated. In all the cases, the reduction was rapid and the yields were satisfactory. The activity of the recycled catalyst was studied up to three reaction cycles successfully. Further, the catalyst was employed for the deprotection of common protectors employed in peptide chemistry such as Z, benzyl ester and benzyl ether. In all the cases, the hydrogenation was complete in a short duration compared to the conventionally used Pd/C. Thus palladium nanoparticles supported over unmodified PVC developed in the present work represent a class of economic and recyclable catalysts for rapid hydrogenation reactions.

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Notes and references

‡ **Experimental section**

General remarks. TEM analyses were performed on a PHILIPS CM 200 instrument operating at 20–200 kV with a resolution of 2.4 Å. XRD studies were carried out on a Bruker D8 Advance diffractometer (Cu-Kα source, $\lambda = 1.5405$ Å). SEM measurements were made on a JEOL JSM 5600LV electron microscope. PVC was purchased from Sigma–Aldrich as granules and used as such. ICP-OES measurements were made on Perkin Elmer OPTIMA 5300DV.

Typical procedure for the preparation of PVC-Pd^0. A suspension of PVC (600 mg) in ethanol (110 mL) was stirred for 2 h along with $PdCl_2$ (150 mg, 0.847 mmol). It was then heated to reflux for 5 min during which a solution of $NaBH_4$ (37 mg, 1 mmol) in ethanol (2 mL) was added slowly. The brownish solution immediately turned colorless indicating the reduction of Pd(II) salt to Pd(0). It was then allowed to cool, and the black precipitate was filtered, excess $NaBH_4$ was quenched with water and the black powder of PVC-Pd^0 was washed with methanol and water. It was dried under vacuum and characterized.

Reduction of *p*-nitroaniline to *p*-phenylenediamine. A solution of *p*-nitroaniline (200 mg, 1.44 mmol) in ethanol (5 mL) was stirred under hydrogen atmosphere (balloon pressure) in the presence of PVC-Pd^0 (20 mg) till completion of the reduction (TLC analysis). It was filtered and the filtrate was evaporated to afford the product.

Typical experimental for the removal of Z group. To a solution of Z-Phe-OH (200 mg, 0.66 mmol) in ethanol (7 mL), PVC-Pd^0 (20 mg) was added and the mixture was stirred under hydrogen atmosphere for 30 min. It was filtered and the filtrate was concentrated *in vacuo* to afford H-Phe-OH.

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