

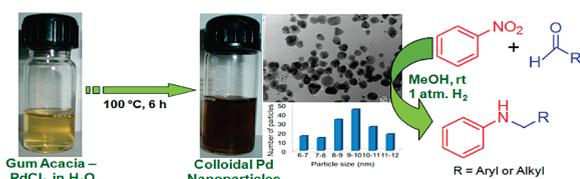
Direct One-Pot Reductive Amination of Aldehydes with Nitroarenes in a Domino Fashion: Catalysis by Gum-Acacia-Stabilized Palladium Nanoparticles

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This note describes the direct reductive amination of carbonyl compounds with nitroarenes using gum acacia-palladium nanoparticles, employing molecular hydrogen as the reductant. This methodology is found to be applicable to both aliphatic and aromatic aldehydes and a wide range of nitroarenes. The operational simplicity and the mild reaction conditions add to the value of this method as a practical alternative to the reductive amination of carbonyl compounds.

Metal nanoparticles are attractive for catalysis because of their large surface area-to-volume ratio, which allows the effective utilization of expensive metals.¹ Palladium nanoparticles, particularly with dimension less than 10 nm, exhibit unexpectedly high catalytic activities toward different types of reactions, a property not revealed in bulk palladium.² Unfortunately, however, aggregation of naked nanoparticles often prohibits tailoring of particle size.³ To overcome this problem, palladium nanoparticles are generally dispersed on support materials, among which polymers are commonly used.⁴ There is considerable interest in exploiting natural polymer macrostructures, and in particular

those of polysaccharides, to create high-performance and environmentally friendly catalysts that are chemically stable but biodegradable. Gum acacia (GA) is a highly branched, neutral or slightly acidic arabinogalactan polysaccharide, obtained naturally from the stems and branches of the *Acacia Senegal* tree. Nontoxic and biocompatible properties of GA made it widely used in food and pharmaceutical industry as an additive or emulsifying agent. Moreover, it is also being increasingly used as a stabilizer for various novel nanomaterials.⁵

Recently, we have reported the reduction and stabilization of silver nanoparticles at room temperature using naturally occurring GA.⁶ Continuing pursuit in the synthesis of nanoparticles, we have developed an efficient straightforward approach for the aqueous-phase synthesis of Pd nanoparticles (9 ± 1 nm) using gum acacia as both a reducing and stabilizing agent.

Sequential transition metal catalysis is a conceptually challenging field of research and has recently aroused considerable interest.⁷ Most remarkably, without further catalyst addition a particular metal readily shifts gears to catalyze further transformations either in a parallel or in a sequential fashion.⁸ Additionally, one-pot transformations are economically and ecologically highly intriguing for developing efficient new synthetic processes in a domino fashion, generating a suitable reactive functionality en route.⁹ The reductive amination reaction remains one of the most powerful and widely utilized transformations that allow the direct conversion of carbonyl compounds into amines using simple operations.¹⁰ The reaction offers compelling advantages over other amine syntheses, including brevity, wide commercial availability of substrates, generally mild reaction conditions, and no need to isolate the imine intermediate. The resulting amines and their derivatives are highly versatile building blocks for various organic substrates and are essential precursors to a variety of biologically active compounds, such as pharmaceuticals and agrochemicals.¹¹

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Several reagents that effect reductive amination have been recently developed, including the following: catalytic hydrogenation,¹² Zn–AcOH,¹³ Et₃SiH–CF₃CO₂H,¹⁴ Bu₃SnH–DMF,¹⁵ InCl₃–Et₃SiH,¹⁶ triazole-derived iridium(I) carbene complexes,¹⁷ [Ir(cod)₂]BF₄,¹⁸ Rh(I) catalysts,¹⁹ and various modified borohydride derivatives.²⁰ However, in terms of functional group tolerance, side reactions, and reaction conditions, most of these reagents may have one or more drawbacks. Moreover, since carbonyl compounds themselves are also reduced under the conditions used, many of these reactions require an excess amount of the amines to obtain good yields of products. As a result, the choice of reducing agent is very critical to the success of the reaction, since the reducing agent must reduce imines selectively over aldehydes.

Recently, attempts have been made to carry out reductive amination of carbonyl compounds directly with nitrobenzene for the preparation of N-alkylated aromatics. Yoon et al. reported reduction of nitroaromatics using a decaborane–Pd/C system followed by reductive amination with carbonyls using decaborane.²¹ Rhee et al. reported on reductive N-alkylation of anilines and nitroarenes with aldehydes using HCOO[−]NH₄⁺/Pd/C.²² Although these methods are encouraging, there is a considerable scope for improvement. For example, Yoon's method requires acetic acid to prevent reductive etherification and high temperature, and Rhee's method is not applicable to aromatic aldehydes. Clearly, the development of improved procedures in which more sustainable catalysts and wide applications are used has remained an elusive goal. More recently, Syndes et al. reported reductive monoalkylation of nitroaryls in the absence of any additives.²³ To the best of our knowledge, however, no palladium nanoparticles promoted reductive N-alkylation of nitroarenes using molecular hydrogen as reducing agent and in the absence of any additives has been reported to date. In the present work, we report our investigations on the application of GA-Pd nanoparticles for the practical and atom economic synthesis of mono N-alkyl amines through reductive amination of aldehydes with nitroarenes under the atmospheric pressure of hydrogen. The overall process involves the reduction of nitro compound to amine and the formation of an imine or iminium

ion intermediately upon reaction of a carbonyl compound with amine, followed by in situ reduction to an alkylated amine of higher order in a single operation.

The palladium nanoparticles immobilized in GA were prepared by the reaction of PdCl₂ with GA in water at 100 °C for 6 h, without using any reducing or stabilizing agent. The palladium nanoparticles stabilized with GA were separated by adding acetone to the reaction mixture. Since GA around the nanoparticles is not soluble in most organic solvents, it passivates the surface of the Pd nanoparticles and suppresses the growth and agglomeration of the particles. It also protects from oxidation, although hydrogen can penetrate through, similar to PVP-coated Pd nanoparticles.²⁴ The prepared catalyst was well characterized with XRD, TEM, XPS, IR, UV–vis, and AAS.²⁵ Figure 1 shows the TEM images of Pd nanoparticles synthesized using gum acacia as both reducing and stabilizing agent at 100 °C for 6 h. As can be seen in the TEM images both in the fresh and used catalysts the particle size is in the range of 9 ± 1 nm and also clearly confirms no change in the morphology even after five cycles.

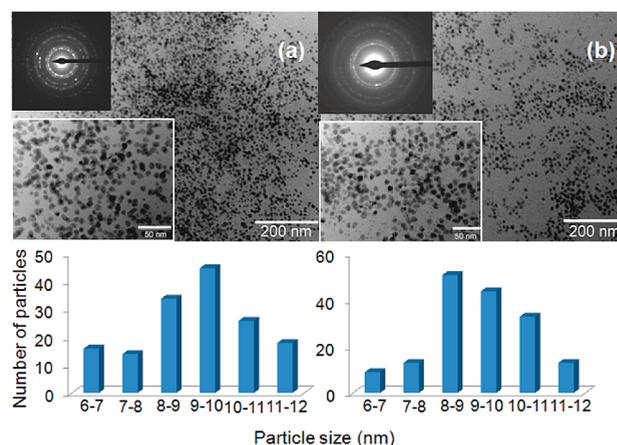
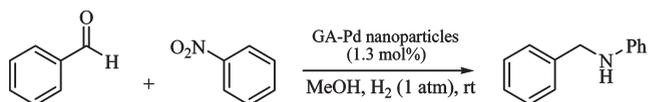


FIGURE 1. TEM images and histograms showing the particle size distribution of GA-Pd nanoparticles before (a) and after (b) catalysis observed at 120 kV. Inset shows the selected area diffraction patterns and images in enlarged scale.

SCHEME 1



An initial evaluation of the proposed reductive amination was performed with benzaldehyde and nitrobenzene, under an atmospheric pressure of hydrogen at room temperature in methanol using different palladium catalysts (Table 1). Optimum yield of the product (88%) was obtained by using GA-Pd(0) (entry 1). No product was formed when the reaction was run in absence of the catalyst. When the reaction was performed in the presence of Pd-SiO₂ and Pd-TiO₂, the nitrobenzene was reduced to the corresponding amine moderately, but the hydrogenation of in situ

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(25) Catalyst characterization data given in Supporting Information.

TABLE 1. Comparative Study of Different Supported Palladium Catalyst for Reductive Amination^a

entry	catalyst	time (h)	yield (%) ^b
1	GA-Pd	6	88
2	Pd-TiO ₂	24	0
3	Pd-SiO ₂	24	0
4	Pd-C	6	20

^aReaction conditions: benzaldehyde (1 mmol) nitrobenzene (1.2 mmol), catalyst (1.3 mol %), and methanol (5 mL) at room temperature under H₂ atmosphere for 6 h.

generated imine did not proceed even at elevated temperatures (entries 2 and 3). Commercially available 10% Pd/C also failed to form any perceptible amount of the product in the hydrogenation of imine intermediate, although a good amount of amine was formed from the nitrobenzene under our reactions conditions (entry 4). The enhanced activity of GA-Pd catalyst over other supported palladium catalysts screened results from the high surface area and strong hydrogen-trapping property of palladium nanoparticles compared to bulk palladium.^{2a}

The heterogeneity of the catalyst is also evaluated to study whether the reaction using solid Pd catalysts occurred on the solid surface or was catalyzed by Pd species in the liquid phase. To address this issue, we conducted two separate experiments with benzaldehyde and nitrobenzene. In the first experiment, the reaction was terminated after 1 h, and the conversion of nitrobenzene was found to be 31%. At this juncture, the catalyst was separated from the reaction mixture and the reaction was continued with the filtrate for an additional 5 h. In the second experiment, the reaction was terminated after 2 h at 55% conversion, and the catalyst was removed. The reaction was continued with the filtrate for an additional 5 h. In both the cases, the conversion remained almost unchanged. Pd was not detected in the filtrate in either experiment by ICP-AES. These studies demonstrate that only the Pd bound to acacia during the reaction is active and the reaction proceeds on the heterogeneous surface.

As can be seen from Table 2, for both aliphatic and aromatic aldehydes, GA-Pd catalyst is recyclable and can be recovered by simple filtration in air and reused without significant loss of catalytic activity (Table 2).

TABLE 2. Reductive Amination of Aldehydes with Nitrobenzene over Five Cycles^a

entry	aldehyde	cycle (% yield)					average % yield
		first	second	third	fourth	fifth	
1	C ₃ H ₇ -CHO	92	90	89	90	87	90
2	C ₆ H ₆ -CHO	88	87	84	84	81	85

^aReaction conditions: aldehyde (1 mmol), nitrobenzene (1.2 mmol), and Pd catalyst (1.3 mol %) at room temperature for 6 h under 1 atm of hydrogen.

Under the optimized reaction conditions, the scope of the reaction was explored with structurally and electronically diverse aldehydes with a wide range of nitroarenes. As revealed in Table 3, various aldehydes were reductively aminated with nitrobenzene under ambient pressure of molecular hydrogen. The aldehydes used for this study included aromatic and aliphatic examples. Irrespective of the electronic nature of the substituent, aromatic aldehydes reacted smoothly to give the corresponding products in good yields (Table 3, entries 1–6). On the other hand, aliphatic

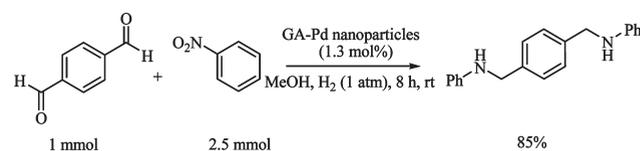
TABLE 3. GA-Pd Nanoparticles Catalyzed Reductive Amination of Different Aldehydes with Nitrobenzene under H₂ Atmosphere^a

entry	aldehyde	product	time (h)	yield (%)
1			6	88
2			6	85
3			5	94
4			5	92
5			5	87
6			5	90
7			4	95
8			4	92
9			4	96
10			5	94

^aReaction conditions: aldehyde (1 mmol), nitrobenzene (1.2 mmol), methanol (5 mL), and Pd catalyst (1.3 mol %) at room temperature.

aldehydes regardless of whether they are linear or α -branched underwent the reductive amination rapidly and gave the products in excellent yield without any byproducts (Table 3, entries 7–10).

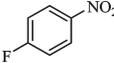
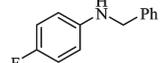
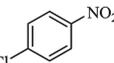
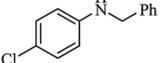
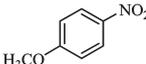
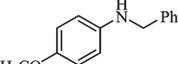
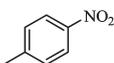
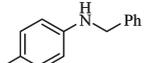
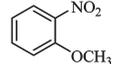
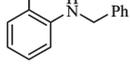
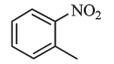
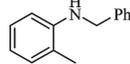
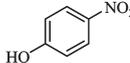
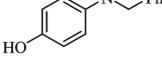
Similarly, terephthalaldehyde also underwent reductive amination smoothly to give the corresponding product in good yield (Scheme 2).

SCHEME 2

Aliphatic aldehydes gave excellent yield of the desired products because the imine intermediate formed is unstable and is readily converted to the product by hydrogenation. On the other hand, in case of aromatic aldehydes, though the imine intermediate formed is stable, it undergoes backward reaction to form aldehyde and amine, resulting in a competition between hydrogenation and backward reaction that leads to a decrease in yield.

In light of these excellent results various nitroarenes were subjected to the reductive amination with benzaldehyde to explore the scope of nitro substrates (Table 4). Unsubstituted (Table 3) as well as substituted 4-methyl, 4-fluoro, 4-methoxy, 2-methoxy, 2-methyl, 4-hydroxy nitrobenzenes

TABLE 4. GA-Pd Nanoparticles Catalyzed Reductive Amination of Benzaldehyde with Different Nitroarenes under H₂ Atmosphere^a

entry	nitrobenzene	product	time (h)	yield (%)
1			6	85
2			6	82
3			6	91
4			6	90
5			6	92
6			6	88
7			6	76

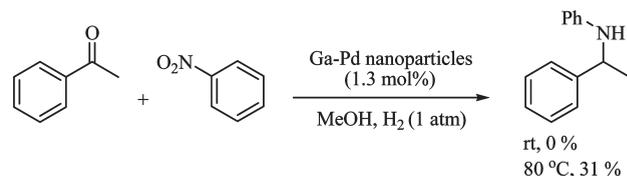
^aReaction conditions: benzaldehyde (1 mmol), nitroarene (1.2 mmol), methanol (5 mL), and Pd catalyst (1.3 mol %) at room temperature.

gave the desired product in comparable yields. However, for 4-hydroxy nitrobenzene though TLC showed complete conversion, isolation of the final product by column chromatography gave the product in only 76% yield. It was observed that in all of these reactions there was no formation of any side products.

Apart from the reductive amination of aldehydes with nitrobenzene, we are also interested in similar reactions of other carbonyl compounds. Some preliminary experiments demonstrate the feasibility of our method for the reductive amination of acetophenone with nitrobenzene at 80 °C temperature as shown in Scheme 3. The result is, however, interesting because acetophenone has shown to be an inert or a difficult substrate in some reported reductive amination reactions.²⁶

In conclusion, we have developed a simple and efficient method for the synthesis of *N*-alkyl amines via reductive amination using a new readily recoverable hybrid catalyst

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SCHEME 3

that combines the catalytic power of transition-metal complexes with the architecture of polysaccharides under ambient pressure of hydrogen. This protocol can be used to generate a diverse range of *N*-alkyl amines in good to excellent yields. The simple procedure for catalyst preparation, easy recovery, and reusability of the catalyst is expected to contribute to its utilization for the development of benign chemical processes and products.

Experimental Section

Typical Experimental Procedure for the Reductive Amination of Aldehydes with Nitroarenes. The catalyst GA-Pd (100 mg, 1.3 mol %) was suspended in methanol (3 mL), and a hydrogen balloon was fitted to the flask. The suspended catalyst was stirred under hydrogen atmosphere for 20 min at room temperature, and then a solution of the nitroarene (1.2 mmol) and aldehyde (1 mmol) dissolved in methanol (2 mL) was added to it. The resultant solution was stirred under hydrogen atmosphere at room temperature for the specified period. The progress of the reaction was monitored by TLC. The reaction mixture was filtered, and the solvent was removed under reduced pressure to give the crude product. It was purified by column chromatography on silica gel using hexane–ethyl acetate mixture as eluent.

Benzyl-phenyl-amine (Table 3, entry 1). IR (neat): 3418, 2923, 1735, 1601, 1505, 1252, 1069, 749 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 3.93 (brs, 1H), 4.31 (brs, 2H), 6.56 (d, 2H, *J* = 7.8 Hz), 6.65 (t, 1H, *J* = 7.2 Hz), 7.11 (d, 2H, *J* = 7.5 Hz), 7.21–7.35 (m, 5H). ¹³C NMR (75 MHz, CDCl₃): δ 48.26, 112.70, 117.5, 127.2, 127.4, 128.6, 129.2, 139.4, 148. ESI MS (*m/z*): 184 (*M* + *H*).

Reuse of Catalyst. After completion of the reaction the catalyst was recovered by filtration and washed several times with ethyl acetate and then ether and dried for further reuse. The catalyst showed consistent activity for five cycles.

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Supporting Information Available: General experimental procedures, catalyst preparation and characterization data of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.