REDUCTIVE AMINATION OF ALDEHYDES AND AMINES WITH AN EFFICIENT PD/NIO CATALYST

Huimin Yang,1,2 Xinjiang Cui, Youquan Deng, and Feng Shi

1Center for Green Chemistry and Catalysis, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, China
2University of the Chinese Academy of Sciences, Beijing, China

GRAPHICAL ABSTRACT

Abstract By applying a simple Pd/NiO catalyst, the reductive amination of amines and aldehydes can progress efficiently under mild reaction conditions, and 24 substituted amines with different structures were synthesized with up to 98% isolated yields.

Keywords Aldehydes; amination; amines; palladium

INTRODUCTION

The formation of N-alkyl amines is one of the most important transformations in organic chemistry.[1–2] In particular, N-alkyl amines are important building blocks for natural products, pharmaceuticals, and agrochemicals. The reaction of amines and alkyl halides with the addition of stoichiometric amounts of inorganic bases is the most effective and universal method.[3–5] However, this method often suffers from drawbacks such as use of toxic substrates and generation of inorganic salt waste. Moreover, various methods have been developed for the synthesis of N-alkyl amines such as amination of alcohols,[6–9] the reaction of amines with amines, hydroamination,[10–16] and hydroaminomethylation[17–21].

Reductive amination is a general and attractive reaction for the synthesis of N-alkyl amines that includes two synthetic steps: C=N double-bond formation and hydrogenation of the imine derivatives. The traditional protocol for reductive amination

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Address correspondence to Feng Shi, Center for Green Chemistry and Catalysis, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, No. 18, Tianshui Middle Road, Lanzhou 730000, China. E-mail: fshi@licp.cas.cn

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is based on the use of a stoichiometric amount of boron hydrides.[22–27] To develop a clean and economic way for the reductive amination reaction, the application of molecular hydrogen as reducing agent in the presence of homogeneous Pd or Ru catalysts was developed successfully.[28–30] However, the use of a homogeneous catalyst system faces problem in catalyst–product separation and catalyst recycling. Heterogeneous catalysts are ligand-free, easy to isolate, and can be reused.[31–34] Taking these advantages into account, the exploration of reductive amination reaction with heterogeneous catalyst is highly desirable.[35–40]

Although good results were obtained, the known heterogeneous catalyst system is limited by the relatively poor generality or rigorous reaction conditions. Here, we report Pd/NiO, which was an active catalyst for nitrobenzene hydrogenation,[41] for the reductive amination reaction under a hydrogen atmosphere and at room temperature.

RESULTS AND DISCUSSION

The structure of the catalysts were characterized by transmission electron microscopy (TEM) and high-resolution (HR) TEM (Fig. 1), which suggested that the palladium particles were well dispersed and the average size of the palladium particles in Pd/NiO was about 5 nm (Fig. 1a). The Pd(111) crystal lattice can be clearly observed from the HR-TEM picture (Fig. 1b). The x-ray diffraction (XRD) diffraction patterns of NiO suggested that it was a better crystallized structure and obvious Ni (111), (200), and (220) peaks were observed (PDF-87-0712). The introduction of palladium did not change the crystal structure of NiO. Moreover, there was no observable diffraction peak of palladium, which suggested that the palladium species were highly dispersed over the NiO support. X-ray photoelectron spectroscopy (XPS) analysis showed typical binding energies of NiO (854.3 eV) and Pd (335.4 eV). According to inductively coupled plasma–atomic emission spectroscopy (ICP-AES) analysis, the palladium loading is 1.1 wt%.

Initially, the reductive amination of benzaldehyde and aniline was used as the model reaction for reaction conditions optimization under 1 atm hydrogen using Pd/NiO as catalyst. The solvents were optimized first (Table 1). Clearly, benzotrifluoride, acetonitrile, and dichloromethane are suitable solvents for the reaction (entries 1–3). The yields to N-benzyl aniline were 33–69% with >90% aniline conversions. The major by-product is the imine, which is not hydrogenated. Possibly, these solvents are

Figure 1. TEM and HR-TEM pictures of Pd/NiO (scale bar: a, 20 nm; b, 5 nm).
Table 1. Optimization of reaction conditions

| Entry | Solvent        | Temp. (°C) | Cat. (mg) | Time (h) | Conv. (%)<sup>b</sup> | Sel. (%)<sup>b</sup> | Yield (%)<sup>c</sup> |
|-------|----------------|------------|-----------|----------|------------------------|----------------------|----------------------|
| 1     | Benzotrifluoride | 25         | 20        | 10       | 94                     | 73                   | 69                   |
| 2     | Acetonitrile    | 25         | 20        | 10       | 90                     | 64                   | 58                   |
| 3     | Dichloromethane | 25         | 20        | 10       | 95                     | 35                   | 33                   |
| 4     | Acetone         | 25         | 20        | 10       | 89                     | 96                   | 85                   |
| 5     | THF             | 25         | 20        | 10       | 80                     | 96                   | 77                   |
| 6     | MeOH            | 25         | 20        | 10       | 41                     | 92                   | 38                   |
| 7     | Toluene         | 25         | 20        | 10       | 94                     | 95                   | 89                   |
| 8     | Xylene          | 25         | 20        | 10       | 93                     | 96                   | 89                   |
| 9     | Isopropanol     | 25         | 20        | 10       | 95                     | 96                   | 91                   |
| 10    | EtOH            | 25         | 20        | 10       | 95                     | 95                   | 90                   |
| 11    | EtOH            | 25         | 20        | 12       | 91                     | 95                   | 86                   |
| 12    | EtOH            | 25         | 20        | 12       | 77                     | 95                   | 71                   |
| 13    | EtOH            | 75         | 20        | 12       | 65                     | 94                   | 61                   |
| 14    | EtOH            | 25         | 5         | 12       | 91                     | 96                   | 87                   |
| 15    | EtOH            | 25         | 10        | 12       | 97                     | 96                   | 93                   |
| 16    | EtOH            | 25         | 30        | 12       | 80                     | 95                   | 76                   |

<sup>a</sup>Reaction conditions: benzaldehyde (1.0 mmol), aniline (1.0 mmol), Pd/NiO (20 mg, 0.2 mol% Pd to aniline), under hydrogen atmosphere, solvent (2 mL).

<sup>b</sup>Conversion of aniline. Selectivity to N-benzyl aniline.

<sup>c</sup>GC yield determined by GC-FID using biphenyl as external standard material.

unfavorable for the imine hydrogenation. In reverse, lower conversions were obtained with high N-benzyl aniline selectivities if acetone, tetrahydrofuran (THF), and methanol were used as the solvents (entries 4–6). The selectivities in these reactions were >90% but the aniline conversions were 41–89%. According to gas chromatography–mass spectrometry (GC-MS) analysis, it was found that a large amount of toluene was generated via benzaldehyde hydrogenation, which resulted in the lower conversion of aniline. Better results were obtained if toluene, xylene, isopropanol, and ethanol were used as the solvents (entries 7–10). Although trace amounts of imine and toluene are detectable in these cases, the yields of N-benzyl aniline reached 89–91%. If the reaction time was prolonged, relatively lower yield was obtained, which suggested that the reaction was reversible and a small amount of N-benzyl aniline was dehydrogenated (entry 11). Similarly, higher reaction temperature or catalyst loadings resulted in lower yields, also due to the hydrogenation of benzaldehyde to toluene (entries 12–14). Although a good result was also gained with lower catalyst loadings in the reductive amination of aniline and benzaldehyde, (entries 15 and 16), the application of lower catalyst loadings caused poor generality in the reductive amination of other compounds. Therefore, 20 mg catalyst was used for the next exploration.
Table 2. Reductive amination of benzaldehyde with various amines

| Entry | R₁-NH₂ | R₁-NH₂ | Yield (%)<sup>b</sup> |
|-------|--------|--------|------------------------|
| 1     |        |        | 88<sup>c</sup>         |
| 2     |        |        | 84                     |
| 3     |        |        | 97                     |
| 4     |        |        | 92                     |
| 5     |        |        | 90                     |
| 6     |        |        | 84                     |
| 7     |        |        | 92                     |
| 8     |        |        | 98                     |
| 9     |        |        | 98<sup>c</sup>         |
| 10    |        |        | 98                     |
| 11    |        |        | 96                     |
| 12    |        |        | 98                     |
| 13    |        |        | 98                     |

<sup>a</sup>Reaction conditions: benzaldehyde (1.0 mmol), amine (1.0 mmol), Pd/NiO (20 mg), under hydrogen atmosphere, EtOH (2 mL), 25 °C, 12 h.
<sup>b</sup>Isolated yield.
<sup>c</sup>GC yield determined by GC-FID using biphenyl as external standard material.
Table 3. Reductive amination of aniline with various aldehydes

| Entry | R₂-CHO | R₃-CHO | Yield (%)ᵇ |
|-------|--------|--------|------------|
| 1     | ![Image](image1.png) | ![Image](image2.png) | 96         |
| 2     | ![Image](image3.png) | ![Image](image4.png) | 98         |
| 3     | ![Image](image5.png) | ![Image](image6.png) | 96         |
| 4     | ![Image](image7.png) | ![Image](image8.png) | 93         |
| 5     | ![Image](image9.png) | ![Image](image10.png) | 97         |
| 6     | ![Image](image11.png) | ![Image](image12.png) | 93         |
| 7     | ![Image](image13.png) | ![Image](image14.png) | 97         |
| 8     | ![Image](image15.png) | ![Image](image16.png) | 87         |
| 9     | ![Image](image17.png) | ![Image](image18.png) | 94         |
| 10    | ![Image](image19.png) | ![Image](image20.png) | 95         |
| 11    | ![Image](image21.png) | ![Image](image22.png) | 98         |

ᵃReaction conditions: benzaldehyde (1 mmol), amine (1 mmol), Pd/NiO (20 mg), under hydrogen atmosphere, EtOH (2 mL) at 25 °C for 12 h.
ᵇIsolated yield.
The optimized reaction conditions (i.e., 1 mmol amine, 1 mmol aldehyde, 20 mg catalyst, 2 mL ethanol, rt, and 12 h) were used in the generality testing. As shown in Table 2, the reductive amination of benzaldehyde with aniline and 1-naphthylamine can obtain the desired products in good yield of 84% and 88% (entries 1 and 2). Benzylamines with electron-withdrawing and electron-donating groups can also be converted into the desired products in good to excellent yields (entries 3–6). Interestingly, the reductive amination reactions of benzaldehyde with primary amines containing different heterocyclic ring structures (i.e., pyridin-2-amine, furan-2-ylmethylamine, and 2-(piperazin-1-yl)ethanamine) can progress well with up to 98% isolated yields (entries 6–8). Excellent results were also obtained if aliphatic amines such as butan-1-amine, heptan-1-amine, and dodecan-1-amine were used as the starting materials (entries 9–11). The yields of products all reached 98% in the reactions of benzaldehyde with typical secondary amines 1-phenylethanamine and cyclohexanamine (entries 12 and 13).

Next, aldehydes with different structures can react with aniline to give the desired products, too (Table 3). Irrespective of the structure and position of the substituting groups, good to excellent yields (i.e., 87–98%) of the corresponding products were obtained (entries 1–9). Thus there were no remarkable steric and electronic effects on the reactivity of the aromatic aldehydes. It is noteworthy that 95% of the corresponding product was obtained when furan-2-carbaldehyde was used (entry 10). Typical aliphatic aldehyde (i.e., butaldehyde) can also be converted into the desired N-benzyl butyl amine successfully with 98% yield under these reaction conditions (entry 11).

Moreover, to see if the dissolved catalytic species from Pd/NiO catalyzed the reaction, after the first run, 1.0 mmol aniline and 1.0 mmol benzaldehyde were added into the reaction solution again after removing the catalyst. However, there is not any observable N-benzyl aniline formation by GC–flame ionization detection (FID) after it was reacted for another 12 h. These results excluded the possible contribution of homogeneous catalytic species leached from Pd/NiO catalyst. Finally, the reusability of the Pd/NiO catalyst was tested. The catalyst can be easily separated from the mixture solution by centrifugation. Then the catalyst was washed by ethanol two times and reused directly without other treatment. Clearly, the catalyst showed high catalytic activity on the reductive amination of benzaldehyde and aniline even if the catalyst was reused in the fifth run (Table 4). It suggests that the catalyst is potentially reusable.

**Table 4.** Recycling exploration of Pd/NiO

| Run | Yield (%) |
|-----|-----------|
| 1   | 88        |
| 2   | 90        |
| 3   | 89        |
| 4   | 87        |
| 5   | 91        |

*Reaction conditions: benzaldehyde (1.0 mmol), aniline (1.0 mmol), Pd/NiO (20 mg), and solvent (2 mL), under hydrogen atmosphere, 12 h, 25 °C.

*GC yield.
EXPERIMENTAL

Representative Procedure for the Reductive Amination Reactions of Aldehydes and Amines

Here, 1.0 mmol amine, 1.0 mmol aldehyde, 2 mL solvent, and 20 mg catalyst were added into a 40-mL reaction tube. The mixture was reacted at 25 °C and under hydrogen atmosphere for 12 h. Then, the reaction mixture was filtrated to remove the catalyst. Pure products can be obtained simply after removing the solvent and other impurities using rotary evaporation and vacuum drying. All the products were analyzed by GC-MS and 1H NMR.

Preparation of the NiO Nanoparticles

The catalyst samples were prepared starting from sol-gel polymerization of resorcinol and formaldehyde with Na2CO3 as a catalyst with 50% Ni-doped monolithic carbon aerogels. Typically, resorcinol (2.20 g, 20 mmol), formaldehyde (3.25 g, 40 mmol, 36.5% in water, methanol stabilized), and 6 mL distilled water were added into a 100-mL PTFE autoclave and the mixture was stirred for 0.5 h. Subsequently, an aqueous solution of 5.8 g Ni(NO3)2·6H2O and a 0.9 M solution of Na2CO3 (4 mL) were added into the mixture. After vigorous stirring for 1 h, the autoclave was sealed and kept at 80 °C for 1 day. Then the autoclave was cooled to room temperature. The wet gels were placed into a round-bottomed flask and vacuum dried at 130 °C for 3 h. After being pyrolyzed at 800 °C for 5 h in nitrogen flow (20 mL/min), about 7 g black solid was obtained. Then the black solid was treated at 500 °C for 5 h in a flow of oxygen (20 mL/min) to afford the NiO nanoparticles (about 4.1 g).

Preparation of Pd/NiO Catalysts

The Pd that was supported on NiO was prepared according to a sol-immobilization method. For the 1.1 wt% Pd/NiO catalyst, the detailed preparation procedure employed is described: an aqueous solution of H2PdCl4 (0.067 mL, 35 mg mL⁻¹) was added to distilled water (5 mL). Then, an aqueous solution of PVA (1.2 mL, 5 mg mL⁻¹) was added. After 30 min, a freshly prepared 0.1 M solution of NaBH4 (NaBH4/Pd, 4:1 mol/mol) was then added to form a dark-brown sol. After 30 min of sol generation, the colloid was immobilized by adding NiO powder (100 mg). The solution was acidified to pH 1 by sulfuric acid under string conditions and was stirred for another 2 h. The resulting solid was washed with distilled water (3 × 40 mL) and dried in air at 80 °C for 2 h to afford the Pd/NiO catalyst.

Reductive Reaction of Aldehydes and Amines

In this procedure, 1.0 mmol amine, 1.0 mmol aldehyde, 2 mL solvent, and 20 mg catalyst were added in a 40-mL reaction tube. The mixture was reacted at 25 °C and under hydrogen atmosphere for 12 h. After the reaction, the reaction mixture was detected by GC-MS. The product was obtained by thin-layer chromatography and analysis by NMR.
CONCLUSION

In conclusion, we have developed a simple Pd/NiO catalyst system for the reductive amination reaction under mild reaction conditions. The Pd/NiO catalyst exhibited excellent activity and selectivity in the reductive amination reaction using various amines and aldehydes as the substrates. In addition, the Pd/NiO catalyst can be easily recycled for several runs without deactivation.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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