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Highly chemoselective hydrogenation of active benzaldehydes to benzyl alcohols catalyzed by bimetallic nanoparticles

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ABSTRACT

By using novel Pd/Ni bimetallic nanoparticles as a catalyst, the active benzaldehydes were hydrogenated to the corresponding benzyl alcohols as unique products in practical quantitative yields. The undesired catalytic hydrogenolysis of the benzyl alcohol was inhibited completely. By using this hydrogenation as a key step, the total synthesis of the natural product gastrodin was achieved with less total steps and a higher total yield.

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EDG (electron donating group)-substituted benzaldehydes 1 are also called active benzaldehydes, which can be prepared easily by Vilsmeier reaction.¹ Reduction of **1** to the corresponding benzyl alcohols **2** is a fundamental transformation in organic synthesis² and numerous important compounds have been synthesized by this transformation. As shown in Figure 1, the natural product gastrodin is an OTC medicine that can be utilized for sedation, anticonvulsion and anti-epilepsy.³ 4-Methoxy-3-(3-methoxypropoxy) benzyl alcohol is a key precursor for the synthesis of aliskiren, a clinical medicine used as an rennin inhibitor that can be taken orally.4

Investigation showed that the transformation of 1 to 2 is achieved normally by using hydride reagent reduction⁵ rather than metal-catalyzed hydrogenation in the literature. For example, Pd-catalyzed hydrogenation is characterized by its extremely clean hydrogen resource and convenient work-up procedure, but it is rarely used for this purpose. As shown in Scheme 1, this must have resulted from the fact that the catalytic hydrogenolysis of benzyl alcohol 2 also proceeds smoothly under the catalytic hydrogenation conditions to give the byproduct toluene **3**.⁶ In many cases, the byproduct **3** was even a major or a unique product.⁷

In recent years, several novel catalytic systems⁸ were reported for highly chemoselective hydrogenation of 1 to 2. The fact that they were not used in practice may be caused by the difficult preparation of the catalyst and the use of additives. Herein, we would like to report a novel Pd/Ni bimetallic nanoparticles-

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catalyzed hydrogenation, by which highly efficient and chemoselective transformation of 1 to 2 was achieved in practical quantitative

Scheme 1. Pd-catalyzed hydrogenation and hydrogenolysis.

yields. The method meets the needs of the laboratory scale transformation of **1** to **2** with three advantages: (a) easy preparation of the Pd/Ni bimetallic nanoparticles; (b) no need for any additives; (c) convenient work-up by magnetic separation.

In our recent work,⁹ novel Pd/Ni bimetallic nanoparticles were prepared by simply boiling the mixture of Raney-Ni and Na₂PdCl₄ in H₂O for 6 h. When they were used as a catalyst, nitrobenzylamines



CH₂OH







etrahedror





Pd-Catalved

Hvdrogenolvsi



CHO

FD

Pd-Catalyed

Hydrogention



were chemoselectively hydrogenated into aminobenzylamines. Since the Pd/Ni ratio was about 1:99 (by wt %), we hypothesized that most or all of the Pd-atoms on the surface of this catalyst were surround by Ni-atoms to form the heterometallic Pd–Ni bonds. Unlike the Pd–Pd and Ni–Ni bonds, Pd–Ni bond is a polarized bond that may be described as $^{\delta}$ -Pd–Ni $^{\delta+}$ (electronic effect or ligand effect), by which the Pd/Ni bimetallic catalyst demonstrated novel catalytic ability and chemoselectivity that differ from their parent metals.¹⁰ As shown in Scheme 2, the polarized Pd/Ni bimetallic catalyst may have stronger adsorptivity for the heteroatom double bond than for the heteroatom single bond. This hypothesis also strongly implied that the EDG-substituted benzaldehydes 1 (with heteroatom double bond) may be chemoselectively hydrogenated into the corresponding benzyl alcohols 2 (with heteroatom single bond) by using the same catalyst.

To prove our hypothesis, 3,4,5-trimethoxybenzylaldehyde (1a) was used as a model substrate because its hydrogenation product 3,4,5-trimethoxybenzyl alcohol (2a) is highly sensitive to further catalytic hydrogenolysis. As shown in Scheme 3, five commercial Pd-catalysts **A**–**E** were initially tested on the hydrogenated of 1a and three products 2a, 3a and 4a were detected with variable ratios. But, none of them gave an acceptable hydrogenation chemoselectivity.

As was expected, the hydrogenation of **1a** gave **2a** as a unique product over the Pd/Ni bimetallic catalyst. As shown in Table 1, **2a** was obtained in 94% yield and 100% chemoselectivity under the conditions listed in entry 1. Since the net weight of palladium metal used in this entry was much more than that used in Scheme 3, the chemoselectivity must arise from the synergistic effects of the Pd/Ni bimetallic catalyst. The quantitative yield and chemoselectivity of **2a** were obtained when 30 wt % Pd/Ni bimetallic catalysts were used (entry 3). Although **2a** was obtained in lower yield (91%) by use of 20 wt % Pd/Ni bimetallic catalysts, its



Scheme 2. Proposed chemoselective hydrogenation.



Scheme 3. Hydrogenations over five commercial Pd-catalysts. Cat-A: Acros-199620100, palladium hydroxide on carbon powder, 20% Pd. Cat-B: Aldrich-330108, palladium, 10 wt % on activated carbon. Cat-C: Alfa Acesar-A26D10, palladium, 5 wt % on activated carbon powder, unreduced. Cat-D: Alfa Acesar-K08P30, palladium, 5 wt % on activated carbon powder, reduced, acidic catalyst. Cat-E: Shanxi Kaida product, palladium, 10 wt % on activated carbon powder.

Table 1

The hydrogenations of **1a** catalyzed by the Pd/Ni bimetallic catalyst^a



Entry	1% Pd/Ni (wt %)	Time ^b (h)	Pressure (psi)	Yield of 2a^c (%)
1	100	1.5	_	94
2	50	2.5	_	97
3	30	3.5	_	98
4	20	6.5	_	91 ^d
5 ^e	20	6.0	30	98
6 ^e	10	6.0	30	71 ^d
7 ^e	10	6.0	60	96
3 4 5 ^e 6 ^e 7 ^e	30 20 20 10 10	3.5 6.5 6.0 6.0 6.0	 30 30 60	98 91 ^d 98 71 ^d 96

^a A mixture of **1a** (196 mg, 1 mmol) and the Pd/Ni bimetallic catalyst in MeOH (10 mL) was stirred under H_2 at room temperature (on an atmospheric pressure hydrogenation apparatus).

The time was when the absorption of hydrogen ceased.

Separated yield was obtained.

^d Only the unreacted substrate **1a** was recovered.

^e The experiments proceeded on a Parr-hydrogenator.

chemoselectivity was not affected (entry 4). When the hydrogenation was operated on a Parr-hydrogenator by slightly increasing the hydrogen pressure, 10 wt % Pd/Ni bimetallic catalysts were good enough to produce excellent results (entries 5–7).

The conditional experiments for reaction solvents and recycling studies of the Pd/Ni bimetallic catalyst gave very similar results to those reported in our previous work.⁹ For example, MeOH was the best solvent for this hydrogenation and the catalytic activity of the catalyst decreased sharply after four recycles. Thus, the standard



Scheme 4. The scope of the hydrogenation.



Scheme 5. *Reported method:* (i) 4-hydroxy-benzyldehyde, aq NaOH, acetone, rt, 12 h, 35%; (ii) KBH₄, *i*-PrOH, rt, 0.5 h, 87%; (iii) Ac₂O, pyridine, 100 °C, 6 h, 100%; (iv) MeONa, MeOH, rt, 12 h, 90%. Total 27.4% yield for four steps. *Our method:* (v) 1% Pd/ Ni bimetallic catalyst (30 wt %), H₂ (atm), MeOH, rt, 2 h, 100%. Total 31.5% yield for three steps.

conditions¹² for the chemoselective hydrogenation of **1** to **2** over the Pd/Ni bimetallic catalyst were assigned as shown in Scheme 4 and its scope was studied. As was expected, the quantitative chemoselectivity was obtained for all tested substrates. Since the products **2f–2i** contain strong coordination groups, they are usually difficult to be synthesized in excellent yields by using hydride reagent reduction. However, they were obtained in excellent yields under our standard conditions. In the preparation of **2n**, the aldehyde group was hydrogenated into the alcohol group smoothly, while the benzyl ether group stayed intact throughout. This result gave new evidence to support our hypothesis that the polarized Pd/Ni bimetallic catalyst may have much weaker adsorptivity for the heteroatom single bond.

In literature, the most practical route for the total synthesis of gastrodin¹¹ is shown in Scheme 5. Although the reduction of **5** by KBH_4 (step ii) proceeded smoothly, the desired product **6** usually was obtained as a mixture with some partial deacylated products. When the mixture of **6** was saponified directly, the final product gastrodin must be purified by an ion-exchange resin chromatography since the deacylated products strongly coordinated with boron and sodium ions. Therefore, a reacylation for the mixture of 6 (step iii) was an essential step because the reacylated product 7 can be purified conveniently by recrystallization or by a normal flash chromatography. However, when 5 was hydrogenated over the Pd/Ni bimetallic catalyst (step v), the desired 6 was obtained in almost quantitative yield. Since the Pd/Ni bimetallic catalyst was used barely without any additives and was recovered by a magnetic separation, the product 6 was pure enough for the direct saponification (step iv) without further purification. Thus, our method has less total steps and a higher total yield for the total synthesis of gastrodin.

In conclusion, the catalytic hydrogenation of the active benzaldehydes to the corresponding benzyl alcohols is a challenging task in organic synthesis because the further catalytic hydrogenolysis of the benzyl alcohols into the corresponding methylbenzenes proceeds under the same conditions. However, this problem can be solved completely by simply using Pd/Ni bimetallic nanoparticles as a catalyst. The highly chemoselective hydrogenation may have resulted from the fact that the polarized Pd/Ni bimetallic catalyst has weak adsorptivity for the heteroatom single bonds. When this hydrogenation was used as the key step in the total synthesis of the natural product gastrodin, less total steps and a higher total yield were achieved.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09. 154.

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- 12. Typical procedure for hydrogenation of 3,4,5-trimethoxybenzyl-aldehyde (1a) to 3,4,5-trimethoxybenzyl alcohol (**2a**). A mixture of **1a** (196 mg, 1 mmol) and 1% Pd/Ni bimetallic catalyst⁰ (60 mg, 30 wt %) in MeOH (10 mL) was stirred under H₂ at room temperature and atmospheric pressure (on an atmospheric pressure hydrogenation apparatus) until the absorption of hydrogen ceased (3.5 h). After the catalyst was removed off by a magnetic stirring bar, the solution was evaporated in a vaporator to give the product **2a** as a colorless oil (195 mg, 98%), which is pure enough for ¹H and ¹³C NMR determinations. ¹H NMR (300 MHz, CDCl₃) δ 6.59 (s, 2H), 4.61 (d, 2H, *J* = 5.49 Hz), 3.86 (s, 6H), 3.83 (s, 3H), 1.92 (t, 3H, *J* = 5.49 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 153.3, 137.2 (2C), 136.6 (2C), 103.7, 65.4 (2C), 60.8, 56.0.

The same procedure was used to chemoselectively hydrogenate the substrates **1b–1t** to **2b–2t**. In some cases, the flash chromatography was required for the purification of the products.