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| Title            | Efficient chemoselective hydrogenation of organic azides catalyzed by palladium nanoparticles with alkyne-derived homogeneous supports   |
| Author(s)        | Arai, Noriyoshi; Onodera, Nozomi; Ohkuma, Takeshi  |
| Citation         | Tetrahedron Letters, 57(37), 4183-4186<br><a href="https://doi.org/10.1016/j.tetlet.2016.08.002">https://doi.org/10.1016/j.tetlet.2016.08.002</a>  |
| Issue Date       | 2016-09-14   |
| Doc URL          | <a href="https://hdl.handle.net/2115/71461">https://hdl.handle.net/2115/71461</a>  |
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| Type             | journal article  |
| File Information | Ohkuma-TL57(37).pdf  |

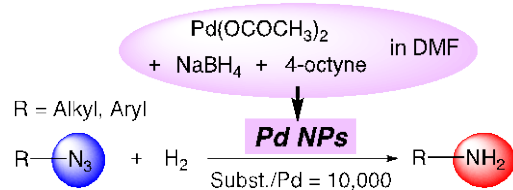


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### Efficient chemoselective hydrogenation of organic azides catalyzed by palladium nanoparticles with alkyne-derived homogeneous supports

Noriyoshi Arai, Nozomi Onodera, and Takeshi Ohkuma\*



Aromatic ketone, aldehyde, halides, benzylic OH,  
and aliphatic  $\text{NO}_2$  can tolerate under the conditions.

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## Efficient chemoselective hydrogenation of organic azides catalyzed by palladium nanoparticles with alkyne-derived homogeneous supports

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### ARTICLE INFO

#### Article history:

Received

Received in revised form

Accepted

Available online

#### Keywords:

Palladium

Nanoparticles

Hydrogenation

Organic azide

Chemoselective

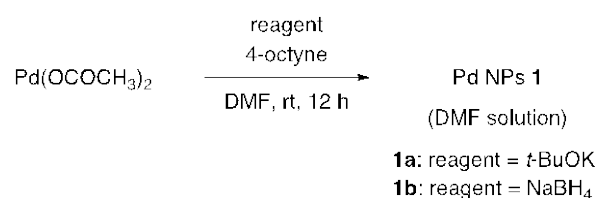
### ABSTRACT

Catalytic chemoselective hydrogenation of organic azides using palladium nanoparticles stabilized by alkyne derivatives was studied. A broad range of aromatic and aliphatic azides were smoothly reduced to the corresponding amines in excellent yields with a quite small amount of the catalyst. Hydrogenation of 3-phenylpropylazide gave 3-phenylpropylamine almost quantitatively with a substrate-to-palladium molar ratio (S/Pd) of 12,900 under 8 atm of H<sub>2</sub>. The reaction under 1 atm of H<sub>2</sub> also proceeded smoothly with an S/Pd of 1,000. Several reduction-sensitive functional groups, such as carbonyl, halide, benzylic OH, and aliphatic nitro were well tolerated under the reaction conditions.

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Amines are quite important compounds in various research fields, including pharmaceuticals, dyes, agrochemicals, and so on.<sup>1</sup> Reduction of azides is one of the simplest and most reliable methods for the preparation of amines.<sup>2</sup> Although a number of reactions have been reported for this important transformation,<sup>3–5</sup> catalytic hydrogenation is superior to the others both from an economical and ecological point of view, especially in a large scale preparation.<sup>6</sup> Palladium(0) supported on charcoal is widely used as a catalyst in this reaction.<sup>7</sup> However, problems in chemoselectivity are occasionally encountered when the substrate contains functional groups sensitive under the reaction conditions of hydrogenation.<sup>8,9</sup> To address this issue, deliberately designed catalysts have been developed for the chemoselective hydrogenation.<sup>10,11</sup>

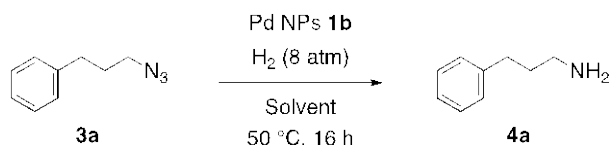
We recently reported novel palladium nanoparticles (Pd NPs **1**) prepared from Pd(OCOCH<sub>3</sub>)<sub>2</sub> and 2 equiv of *t*-C<sub>4</sub>H<sub>9</sub>OK (**1a**) or NaBH<sub>4</sub> (**1b**) with 10 equiv of 4-octyne in DMF at ambient temperature for 12 h (Scheme 1).<sup>12</sup> Pd NPs **1** in DMF (10 mM) are homogeneously dispersed and have a shelf-life of more than a year at ambient temperature without aggregation. These Pd NPs exhibited excellent catalytic activity in selective partial hydrogenation of alkynes and chemoselective hydrogenation of nitroarenes.<sup>12,13</sup> In the course of our study, we found that the Pd NPs **1b** efficiently catalyze chemoselective hydrogenation of aryl and alkyl azides. Here, we would like to describe the features of the convenient functional group transformation.



**Scheme 1.** Preparation of Pd NPs **1**.

We chose 3-phenylpropylazide (**3a**) as a standard substrate to optimize the reaction conditions (Table 1). When the azide **3a** was hydrogenated in THF at 50 °C under 8 atm of hydrogen in the presence of a catalytic amount of Pd NPs **1b** (substrate-to-palladium molar ratio (S/Pd) = 1.3×10<sup>4</sup>, loaded as a 5.0 mM DMF solution), the reaction was completed within 16 h to give 3-phenylpropylamine (**4a**) in nearly quantitative yield (Table 1, Entry 1). The S/Pd per time-to-full conversion (TOF<sub>av</sub>) was 7.9×10<sup>2</sup> h<sup>-1</sup>. The reaction also proceeded under atmospheric pressure of hydrogen (Entry 2). The starting material **3a** was completely consumed, but the yield of **4a** was 79%. <sup>1</sup>H NMR analysis of the crude reaction mixture showed that remaining **3a** was converted to dimeric imine, though the reaction pathway was not clear. THF was a solvent of choice, but methanol, ether, and hexane were also useful solvents (Entries 3–5). On the other hand, the reactions in toluene, dichloromethane, and ethyl acetate were much slower than those in the solvents described above, resulting in unsatisfactory product yields (Entries 6–8).

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**Table 1.** Hydrogenation of Azide **3a** Catalyzed by Pd NPs **1b**

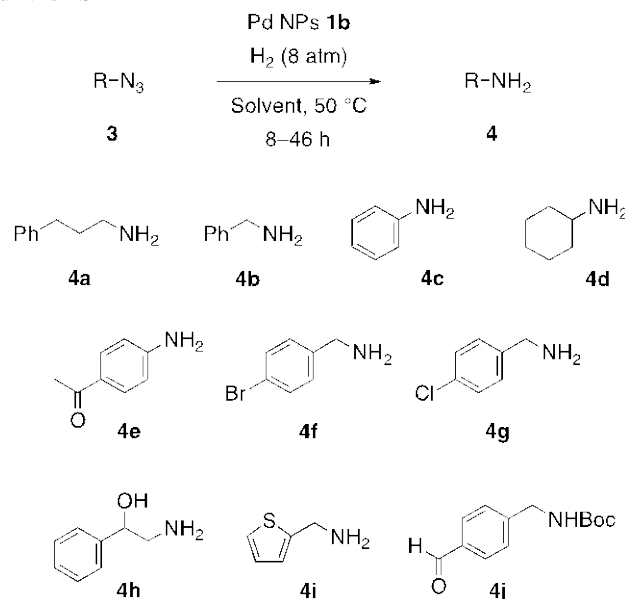
| Entry          | S/Pd  | Solvent                         | Conv. (%) | Yield <sup>a</sup> (%) |
|----------------|-------|---------------------------------|-----------|------------------------|
| 1              | 12700 | THF                             | 100       | >99                    |
| 2 <sup>b</sup> | 1000  | THF                             | 100       | 79                     |
| 3              | 12700 | CH <sub>3</sub> OH              | 100       | 95                     |
| 4              | 13000 | Et <sub>2</sub> O               | 100       | 95                     |
| 5              | 12900 | Hexane                          | 100       | 97                     |
| 6              | 12600 | Toluene                         | 56        | 54                     |
| 7              | 12800 | CH <sub>2</sub> Cl <sub>2</sub> | 25        | 23                     |
| 8              | 12500 | AcOEt                           | 6         | 3                      |

<sup>a</sup> Estimated by <sup>1</sup>H NMR by using 1,3,5-trimethoxybenzene as an internal standard.

<sup>b</sup> Under 1 atm of H<sub>2</sub>.

The stage was set for investigating the scope of this transformation. Hydrogenation of a range of aromatic and aliphatic azides was carried out, and the results are summarized in Table 2. Hydrogenation of azide **3a** proceeded smoothly to give the corresponding amine **4a**, which was isolated as Boc carbamate with a slight loss of the product (Entry 1). Benzyl, phenyl, and cyclohexyl azides (**3b–d**) were also successfully converted to the amines in high yields (Entries 2–5). Methanol could be employed as well as THF in some cases. In the hydrogenation of 4'-azidoacetophenone (**3e**), the azide moiety was selectively reduced to amine without loss of the carbonyl group to afford 4'-aminoacetophenone (**4e**) in excellent yield (Entry 6).<sup>14</sup> We generally performed the reactions under gentle warming in a water bath in order to secure the catalyst activity and to keep the temperature constant throughout the reaction; however, the reaction could also be carried out at ambient temperature (Entry 7). It should be noted that the hydrogenation of 4-halobenzyl azides (**3f** and **3g**) gave the amines **4f** and **4g** without hydrogenolysis of the halide moieties (Entry 8 and 9).<sup>15</sup> The hydroxy group at the benzylic position remained intact throughout the hydrogenation of **3h** to give the amine **4h** in nearly quantitative yield (Entry 10).<sup>16</sup> Unfortunately, the hydrogenation of thienyl azide **3i** hardly proceeded, even with a relatively large amount of the catalyst, probably due to poisoning by sulfur (Entry 11). In the hydrogenation of 4-formylbenzyl azide, azide group was hydrogenated faster than formyl group. The reaction must be carried out in the presence of Boc<sub>2</sub>O to avoid self-condensation, although the addition of Boc<sub>2</sub>O caused retardation of the reaction. The starting material **3j** was consumed in 46 h to give **4i** in 53% yield, accompanied by the formation of *p*-phthalaldehyde, 4-cyanobenzaldehyde (apprx. 5% each), and a mixture of unidentified compounds (Entry 12). Selective hydrogenation in the presence of alkene moiety turned out to be difficult.

Chemoselective hydrogenation of azides catalyzed by palladium on boron nitride was reported.<sup>11a</sup> The amine products were obtained with keeping functionalities, such as ketone, nitro, alkene, and benzylic ester intact. The catalyst turnover number reached to 990. Though our catalytic system has room for improvement in the chemoselectivity, it has an advantage over the preceding method from a standpoint of catalyst turnover.

**Table 2.** Substrate Scope in the Hydrogenation of Azides **3** with Pd NPs **1b**

| Entry           | <b>3</b>  | S/Pd  | Solvent            | Time (h) | Yield of <b>4</b> <sup>a</sup> (%) |
|-----------------|-----------|-------|--------------------|----------|------------------------------------|
| 1               | <b>3a</b> | 12900 | THF                | 16       | >99 (87) <sup>b,c</sup>            |
| 2               | <b>3b</b> | 10800 | THF                | 21.5     | 99 (88) <sup>b,c</sup>             |
| 3               | <b>3b</b> | 11000 | CH <sub>3</sub> OH | 24       | 83                                 |
| 4               | <b>3c</b> | 1100  | CH <sub>3</sub> OH | 24       | 94                                 |
| 5               | <b>3d</b> | 5100  | THF                | 24       | 94 (84) <sup>b,d</sup>             |
| 6               | <b>3e</b> | 10000 | THF                | 18       | 99 (93) <sup>b</sup>               |
| 7 <sup>e</sup>  | <b>3e</b> | 5000  | CH <sub>3</sub> OH | 8        | >99 (99) <sup>b</sup>              |
| 8               | <b>3f</b> | 4900  | THF                | 24       | 89 (78) <sup>b,c</sup>             |
| 9               | <b>3g</b> | 5600  | THF                | 22       | 86 (94) <sup>b,c,f</sup>           |
| 10              | <b>3h</b> | 9900  | THF                | 24       | >99 (99) <sup>b,c</sup>            |
| 11              | <b>3i</b> | 2000  | THF                | 24       | 53                                 |
| 12 <sup>g</sup> | <b>3j</b> | 5000  | THF                | 46       | 52 (53) <sup>b</sup>               |

<sup>a</sup> Estimated by <sup>1</sup>H NMR by using 1,3,5-trimethoxybenzene (Entries 2–4, 6–8), triphenylmethane (Entry 5, 9, and 12), or 1,1,2,2-tetrachloroethane (Entries 1, 10, and 11) as an internal standard.

<sup>b</sup> The isolated yield is given in parentheses.

<sup>c</sup> Isolation was carried out after Boc protection.

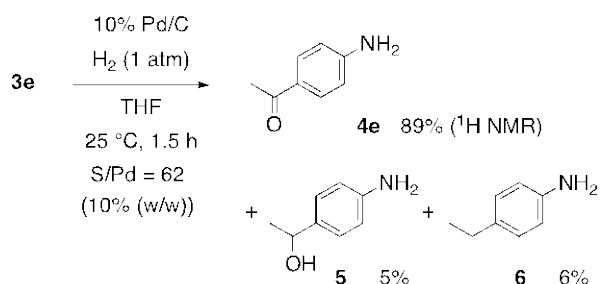
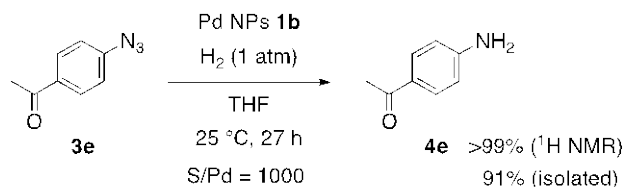
<sup>d</sup> Isolation was carried out after benzoylation.

<sup>e</sup> Carried out at ambient temperature.

<sup>f</sup> Small amounts (apprx. 10%) of homodimeric imine were detected in the crude mixture (see ref. 18). The isolated yield higher than NMR yield was attributed to reproduction of amine **4g** by the hydrolysis of the imine during Boc protection.

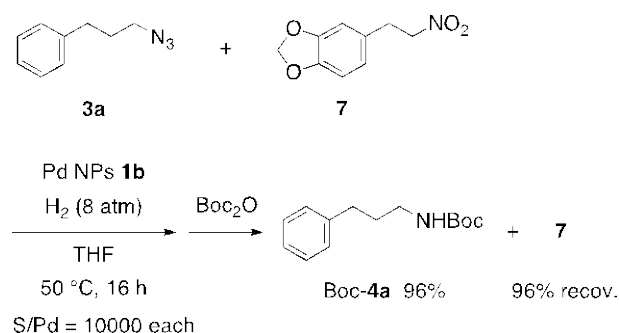
<sup>g</sup> The hydrogenation was carried out in the presence of Boc<sub>2</sub>O in order to avoid self-condensation.

To demonstrate the chemoselective feature of this catalyst, we compared the hydrogenation of **3e** by using conventional hydrogenation conditions with commercially available Pd/C (Scheme 2).<sup>17</sup> When the azide **3e** was hydrogenated at 25 °C under 1 atm of hydrogen in the presence of Pd NPs **1b** (**3e**/Pd molar ratio was 1000), 4'-aminoacetophenone (**4e**) was produced quantitatively, with complete retention of the carbonyl moiety without any control of the reaction. In marked contrast, hydrogenation of **3e** under typical reaction conditions with commercial Pd/C (10%) gave about 10% of over-reduced compounds **5** and **6** as byproducts. Although, we can not rule out the possibility that **4e** would be selectively obtained by stopping the reaction at an earlier stage, much care must be taken to avoid over reduction.



Scheme 2. Comparison with commercial Pd/C.

Since we already found that the Pd NPs **1b** shows excellent catalytic activity in the hydrogenation of aromatic nitro compounds,<sup>13</sup> chemoselective reduction of azide over aromatic nitro group seems difficult. However, an aliphatic azide **3a** was hydrogenated prior to an aliphatic nitro compound **7** as demonstrated in Scheme 3. The competitive reaction was conducted under the typical conditions. The Boc-protected amine **4a** was obtained in high yield after treatment with  $\text{Boc}_2\text{O}$ , while nitro compound **7** was recovered quantitatively.



Scheme 3. Competitive reaction between azide **3a** and nitro compound **7**.

It may be worth noting that the Pd NPs **1b** can be handled as dilute stock solution with a shelf-life of longer than one year under the air and easily added to a reaction mixture in very small amounts, whereas the solid Pd/C is occasionally susceptible to poisoning by impurities in its use of very small quantity.

In summary, the Pd NPs stabilized by alkyne derivatives exhibit excellent catalytic activity in hydrogenation of organic azide compounds. The substrate-to-palladium molar ratio reaches over  $10^4$ . The reaction under atmospheric pressure of hydrogen is also available. A range of aromatic and aliphatic azides that have a sensitive functional group under reductive conditions are hydrogenated to the corresponding amines in high yields, while retaining their sensitive functionality.

## Acknowledgments

This work was supported by Grants-in-Aid from the Japan Society for the Promotion of Science (JSPS) (No. 15H03802) and the MEXT (Japan) program "Strategic Molecular and Materials Chemistry through Innovative Coupling Reactions" of Hokkaido University.

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### Supplementary Material

Supplementary data (preparative method of Pd NPs **1b** and NMR spectra of compounds **4a–j**) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.###>.

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