

# The Formation of a Novel Pd/C–Ethylenediamine Complex Catalyst: Chemoselective Hydrogenation without Deprotection of the *O*-Benzyl and *N*-Cbz Groups

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A Pd/C catalyst formed an isolable complex with ethylenediamine employed as the catalytic poison via one-to-one interaction between Pd metal and ethylenediamine, and this complex catalyst [Pd/C(en)] chemoselectively hydrogenated a variety of reducible functionalities such as olefin, acetylene, nitro, benzyl ester, and azido in the presence of an *O*-benzyl or *N*-Cbz protective group. These findings reinforce the versatility potential of *O*-benzyl and *N*-Cbz as protective groups in organic synthesis, and the Pd/C(en) catalyst has been identified as a novel and chemoselective catalyst for the hydrogenation.

The development of modified Pd catalysts for chemoselective hydrogenation has been a long-standing goal in synthetic chemistry.<sup>1</sup> Many applications of catalyst poisons have been studied, but those methods are usually lacking in generality except for only a few examples such as the Lindlar catalyst.<sup>2</sup> Recently, we documented that addition of ammonia, pyridine, or ammonium acetate to a Pd/C-catalyzed reduction system selectively inhibited the hydrogenolysis of an aliphatic benzyl ether with smooth hydrogenation of other reducible functionalities such as olefin, Cbz, benzyl ester, and azido.<sup>3</sup> However, the benzyl group of a phenolic ether is easily deprotected under the same conditions.<sup>3,4</sup> During our efforts to overcome this problem, we found that a Pd/C catalyst formed an isolable complex with ethylenediamine employed as the catalytic poison and it selectively catalyzed hydrogenation of various functional groups without the hydrogenolysis of the *O*-benzyl protective group (even in phenolic benzyl ethers) or the *N*-Cbz protective group of aliphatic amines. This paper describes the creation and application of a novel Pd/C–ethylenediamine complex catalyst [Pd/C(en)].

## Result and Discussion

Upon addition of ethylenediamine instead of ammonia<sup>3</sup> to the 5% Pd/C-catalyzed system, the hydrogenolysis of the phenolic benzyl ether, for example, *N*-Boc-*O*-benzyl-tyrosine (**1**), was not suppressed similar to the case of addition of ammonia to give the debenzylated product (**2**) in 81% yield (Figure 1 and Table 1, entry 9). However, we noticed that the catalyst activity was gradually suppressed depending on the time taken for the preliminary processing with ethylenediamine. The hydrogenolysis activity of 5% Pd/C toward the benzyl protective group of **1** was analyzed in relation to the time elapsed in pretreatment with ethylenediamine as indicated in Figure 1. After processing with ethylenediamine for 30 h, the 5% Pd/C was no longer active catalytically in the hydrogenolysis of even the phenolic benzyl ether (see Figure 1).<sup>5</sup> From these results, isolation of the pretreated 5% Pd/C catalyst with ethylenediamine was attempted.

Thus, a suspension of 10 g of commercial Pd/C<sup>6</sup> and large excess (ca. 70 equiv vs Pd metal of Pd/C) of ethylenediamine in methanol was stirred for 48 h<sup>7</sup> at ambient temperature under an argon atmosphere to prevent ignition (Pd/C is highly pyrophoric), and then the solid phase was filtered, washed vigorously with methanol and ether, and finally dried under a vacuum pump for 48 h at ambient temperature. The nitrogen analysis of the isolated catalysts indicated that ethylenediamine and Pd metal are approximately in the molar ratio 1:1.<sup>8</sup> The isolated catalysts [Pd/C(en)] also completely lost the catalytic activity toward the hydrogenolysis of **1**. Since the treatment of ethylenediamine with Pd black or 5% Pd on alumina powder instead of Pd/C did not form such

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(1) (a) Freifelder, M. In *Practical Catalytic Hydrogenation Techniques and Applications*; Wiley-Interscience: New York, 1971; p 398. (b) Rylander, P. N. In *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, 1979; p 271. (c) *Idem*. In *Hydrogenation Methods*; Academic Press: New York, 1985; p 157. (d) Siegel, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 8, p 417. (e) Hudlicky, M. In *Reductions in Organic Chemistry*; American Chemical Society: Washington, DC, 1996.

(2) An ingenious Pd-based catalyst using catalyst poisons for the improvement of the desired selectivity is represented by the Lindlar catalyst: (a) Lindlar, H. *Helv. Chim. Acta* **1953**, *35*, 446. (b) Ulan, J. G.; Kuo, E.; Maier, F.; Rai, R. S.; Thomas, G. *J. Org. Chem.* **1987**, *52*, 3126. (c) Ulan, J. G.; Maier, W. F.; Smith, D. A. *J. Org. Chem.* **1987**, *52*, 3132 and references therein.

(3) (a) Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465. (b) Czech and Bartsh have reported a single example of the inhibition of the benzyl ether hydrogenolysis of 11-(benzyloxy)-1-undecene with *n*-BuNH<sub>2</sub> to form benzyl undecyl ether: Czech, B. P.; Bartsh, R. A. *J. Org. Chem.* **1984**, *49*, 4077.

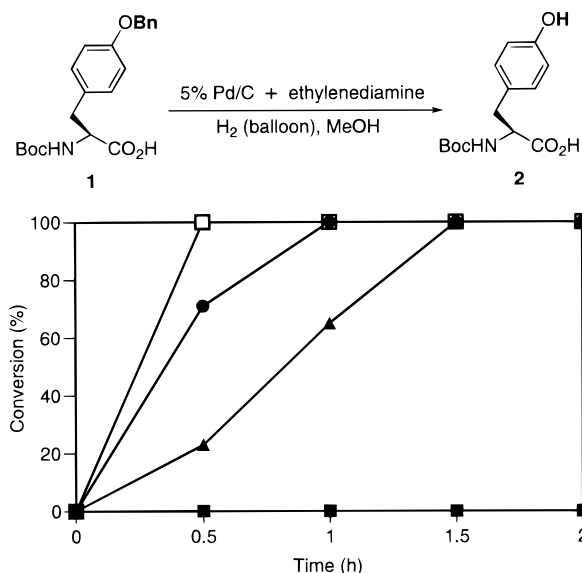
(4) Sajiki, H.; Kuno, H.; Hirota, K. *Tetrahedron Lett.* **1997**, *38*, 399.

(5) Control experiment was run with no ethylenediamine in the presence of the commercial 5% Pd/C for the hydrogenation of **1** in MeOH. The hydrogenation does not tolerate the *O*-benzyl protective group of **1** even after 30 h prestirring.

(6) The catalysts used were 5% Pd/C (Aldrich, Nakarai or Kishida), and no difference in the quality among 5% Pd/C(en) catalysts was detected depending upon their supplier.

(7) The mixture was stirred for appropriate time (48 h) just to make sure.

(8) 5% Pd/C(en) catalyst contains 1.35–1.75% nitrogen.



**Figure 1.** The time course of the hydrogenolysis of *N*-Boc-*O*-benzyltyrosine (**1**) was investigated as described below: 5% Pd/C (2 mg, 1  $\mu$ mol of Pd) was stirred with ethylenediamine (0.7 mL of 0.1 M solution in methanol, 70  $\mu$ mol) at ambient temperature. After being stirred for appropriate time ( $\square$ , 0–12 h;  $\bullet$ , 16 h;  $\blacktriangle$ , 22h;  $\blacksquare$ , 30 h), the substrate **1** (19 mg, 50  $\mu$ mol) was added to the stirred suspension. The mixture was hydrogenated (balloon), and the reaction was followed by TLC scanner (Shimadzu CS-9000).

a selective catalyst (no nitrogen was detected in the elemental analysis), the carbon support of Pd/C(en) seems to play an important role as an electron-accepting species<sup>9a–d</sup> or polymer support<sup>9e–h</sup> of the complex.

The XPS (X-ray Photoelectron Spectroscopy) of Pd/C(en) was measured to gain insight into the surface interaction step of Pd metal. Although the core binding energy of a commercial Pd/C catalyst (Aldrich) is 335.4 and 337.1 eV and corresponds to that of Pd zero on a carbon support,<sup>10</sup> the observed Pd 3d<sub>5</sub> peaks in the Pd/C(en) catalyst shifted to significantly higher energies with 335.8 and 338.4 eV. Further, N 1s (399.80 eV) was observed in the Pd/C(en), while no significant N 1s peak was found in the Pd/C.

To explore the scope of the 5% Pd/C(en) catalyst, the hydrogenation of a number of substrates was investigated. The results shown in Table 1 demonstrate that the hydrogenation activity toward a wide variety of functionalities (olefin,<sup>11</sup> acetylene, azido, benzyl ester, and

**Table 1.** Chemoselective Hydrogenation in the Presence of *O*-Benzyl or *N*-Cbz Protective Group Using Pd/C(en) Catalyst<sup>a</sup>

Entry	Substrate	Time (h)	Product	Yield (%) <sup>b</sup>
1	PhCH=CHCH <sub>2</sub> OBn	0.25 <sup>c</sup>	Ph(CH <sub>2</sub> ) <sub>3</sub> OBn <sup>16,17</sup>	95
2		24		91
3	N <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> OBn <sup>18</sup>	6 <sup>c</sup>	NH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> OBn <sup>19</sup>	93
4	Boc-Ser(Bn)-OBn	0.33 <sup>c</sup>	Boc-Ser(Bn)-OH	91
5		2 <sup>c</sup>		98
6 <sup>d</sup>	MPMO-	2 <sup>c</sup>	MPMO-	97
7 <sup>d</sup>		2 <sup>c</sup>		96
8	Boc-Tyr(Bn)-OMe	24	recovery	92
9 <sup>c</sup>	Boc-Tyr(Bn)-OH	24	recovery	81
10 <sup>c</sup>		2 <sup>c</sup>		94
11	Cbz-Tyr(Bn)-OMe	24	recovery	92
12 <sup>f</sup>		24		77
13 <sup>f</sup>		17		92
14 <sup>f</sup>		7		77
15 <sup>e</sup>		3		75

<sup>a</sup>Unless otherwise specified, the reaction was carried out using 0.2 mmol of the substrate in methanol (1 mL) with Pd/C(en) (10% of the weight of the substrate) under hydrogen atmosphere (balloon) for the given reaction time. <sup>b</sup>Isolated yield. <sup>c</sup>Although the hydrogenation was completed within the indicated period, the benzyl group remained intact even after 24 h. <sup>d</sup>Reaction performed with dioxane as a solvent for the solubility of the substrate. <sup>e</sup>Reaction was performed in the presence of DMAP (1.4 equiv. vs. substrate). <sup>f</sup>Reaction performed with THF as a solvent.

nitro) is retained. No hydrogenolysis of the benzyl or *p*-methoxybenzyl (MPM) protective group of the phenolic ether<sup>4</sup> was observed (entries 6–11), not to mention the benzyl group of the aliphatic ether (entries 1–5).<sup>3,4,11</sup> Rather unexpectedly, the hydrogenation conditions are also compatible with the presence of an *N*-Cbz protective group of aliphatic amine (entries 11–15).<sup>12</sup> There is no report in the literature where an *N*-Cbz protective group<sup>13</sup> was not selectively hydrogenolyzed under the catalytic hydrogenation condition, to the best of our knowledge.<sup>11</sup> Although the hydrogenetic debenzoylation of aromatic

(9) The zerovalent Pd complexes that consist of an electron-rich d<sup>10</sup> metal center with an electron-donating nitrogen ligand should (A) be stabilized with an electron-accepting species or (B) be supported by a polymer-backbone. (A) For examples: (a) Cavell, K. J.; Stufkens, D. J.; Vrieze, K. *Inorg. Chim. Acta* **1980**, *47*, 67. (b) Sustmann, R.; Lau, J.; Zipp, M. *Tetrahedron Lett.* **1986**, *105*, 356. (c) *Idem. Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 356. (d) van Asselt, R.; Elsevier: C. J.; Smeets, W. J. J.; Spek, A. L. *Inorg. Chem.* **1994**, *33*, 1521. (e) Klein, R. A.; Witte, P.; van Belzen, R.; Fraanje, J.; Goubitz, K.; Numan, M.; Schenk, H.; Ernsting, J. M.; Elsevier: C. J. *Eur. J. Inorg. Chem.* **1998**, *319*, 9 and references therein. (B) For examples: (f) Card, R. J.; Neckers, D. C. *J. Am. Chem. Soc.* **1977**, *99*, 9, 7733. (g) *Idem. Inorg. Chem.* **1978**, *17*, 2345. (h) *Idem. Isr. J. Chem.* **1978**, *17*, 269. (i) Card, R. J.; Liesner, C. E.; Neckers, D. C. *J. Org. Chem.* **1979**, *44*, 1095.

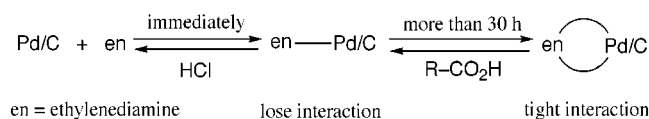
(10) Maier, W. F.; Chettle, S. J.; Rai, R. S.; Thomas, G. *J. Am. Chem. Soc.* **1986**, *108*, 2608.

(11) Ghosh and Krishnan have recently reported a chemoselective catalytic hydrogenation of alkenes using the Lindlar catalyst. In their report, they mentioned that the *N*-Cbz protective group does not survive even using the Lindlar catalyst: Ghosh, A. K.; Krishnan, K. *Tetrahedron Lett.* **1998**, *39*, 947.

(12) A feature of the hydrogenation of an *N*-Cbz derivatives is that the catalyst activity of Pd/C(en) toward the *N*-Cbz protective group is strongly influenced by the solvent. The *N*-Cbz group of *N*-Cbz-diallylamine and *N*-Cbz-propargylamine were completely deprotected in MeOH as a solvent within only 3 and 0.5 h, respectively. However, no deprotection of the *N*-Cbz group was observed in THF as a solvent as can be seen from entries 13 and 14. Further, limitations of this methodology are that complete deprotection of the *N*-Cbz protective group of aromatic amine would be observed even in THF.

(13) Green, T. W.; Wuts, P. G. In *Protective Groups in Organic Synthesis*; 2nd ed.; John Wiley & Sons: New York, 1991; p 335 and references therein.

Scheme 1



benzyl ethers possessing a carboxylic acid or a benzyl ester moiety which was smoothly hydrogenolyzed to the carboxylic acid was observed, an addition of DMAP (1.4 equiv vs substrate, entries 9 and 10) to quench the acid moiety caused the suppression of the debenzylation of the phenolic *O*-benzyl protective group. A similar result was observed in the hydrogenation of an *N*-Cbz protective substrate (entry 15). These facts were supported by an acetic acid addition experiment.<sup>14</sup> On the other hand, the aliphatic benzyl ether of Boc-Ser(Bn)-OBn was not hydrogenolyzed even in the presence of a carboxylic acid moiety within the product (entry 4).<sup>15</sup> The Pd/C(en) is nonpyrophoric compared with commercial Pd/C and stored for more than one year retained the same activity.

A drastic change in the catalytic activity of 5% Pd/C in the processing with ethylenediamine for a relatively long period (30 h, see Figure 1) indicates the two-stage interaction between Pd and ethylenediamine. An immediate interaction (loose interaction) with ethylenediamine eliminates the hydrogenolysis ability for only an aliphatic benzyl ether,<sup>3</sup> and then an advanced interaction (tight interaction), which is slowly formed, strips the ability even for a phenolic benzyl ether and an *N*-Cbz protective group of aliphatic amine from 5% Pd/C. These processes may result in the formation of the Pd/C(en) catalyst (Scheme 1). The presence of the carboxylic acid moiety within the molecule inhibited the tight interaction to allow a change to the loose interaction (see entries 4, 9, 10, and 15 in Table 1). A similar finding was observed by the addition of acetic acid to the Pd/C(en)-catalyzed reaction system.<sup>14</sup> On the other hand, by the treatment with concd HCl in MeOH for 10 min, the 5% Pd/C(en) catalyst reverted to 5% Pd/C which possesses nearly equal catalytic activity with fresh 5% Pd/C.<sup>20</sup> Although the mechanism for the suppression process is unclear at the present time, the chemoselectivity of the Pd/C(en)-

catalyzed hydrogenation may arise from the formation of a rigid five-membered chelate ring comprised of ethylenediamine and Pd.

In summary, the present study provides indication that the strong one-to-one interaction of ethylenediamine with Pd metal of Pd/C is formed in two steps. The Pd/C(en) catalyst displays good selectivity in the reduction of reducible functionalities such as olefin, acetylene, nitro, benzyl ester, and azido in the presence of an *O*-benzyl or *N*-Cbz protective group. These findings reinforce the versatility of *O*-benzyl and *N*-Cbz as protective groups in organic synthesis, and the Pd/C(en) catalyst has been identified as a novel and chemoselective catalyst for hydrogenation.

## Experimental Section

**General Procedure for the Chemoselective Hydrogenation of *O*-Benzyl Ether and *N*-Cbz Derivatives.** After two vacuum/H<sub>2</sub> cycles to remove air from the reaction tube, the stirred mixture of the substrate (0.2 mmol), 5% Pd/C(en) (10% of the weight of the substrate) in MeOH, and 1,4-dioxane or THF (1 mL) was hydrogenated at ordinary pressure (balloon) and temperature (ca. 20 °C) for the appropriate time (see Table 1). The reaction mixture was filtered using a membrane filter (Millipore Dimex-13, 0.22 μm), and the filtrate was concentrated in vacuo. The resulting product was purified by flash silica gel column chromatography, if necessary. All substrates and compounds were identified by comparison of spectral data with literature results and/or with authentic (commercial) samples or characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, MS, and elemental analysis or HRMS.

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**Supporting Information Available:** General experimental procedures, spectral data for all new substrates and products listed in Table 1, and XPS data for commercial Pd/C and Pd/C(en) (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) Although the hydrogenation of Boc-Tyr(Bn)-OMe, which does not possess a carboxylic acid moiety, gave only recovery (Table 1, entry 8), the addition of AcOH to the reaction mixture resulted in a hydrogenolysis of the benzyl group to give Boc-Tyr-OMe in 95% yield.

(15) The hydrogenation of Ph(CH<sub>2</sub>)<sub>3</sub>OBn<sup>16</sup> using 5% Pd/C(en) catalyst in AcOH as a solvent for 50 h also gave only recovery.

(16) (a) Torii, S.; Takagishi, S.; Inokuchi, T.; Okumoto, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 775. (b) Akiyama, T.; Hirofuji, H.; Ozaki, S. *Ibid.* **1992**, *65*, 1932.

(17) The hydrogenolysis of the benzyl group of Ph(CH<sub>2</sub>)<sub>3</sub>OBn was not observed no matter how great a pressure (42 atm, 24 h) of hydrogen was applied.

(18) Balderman, D.; Kalir, A. *Synthesis* **1978**, 24.

(19) (a) Lappas, L. C.; Jenkins, G. L. *J. Am. Pharm. Assoc. Sci. Ed.* **1952**, *41*, 257. (b) Armarego, W. L. F.; Milloy, B. A.; Pendergast, W. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2229. (c) Bernotas, R. C.; Cube, R. V. *Synth. Commun.* **1990**, *20*, 1209.

(20) A suspension of 50 mg of 5% Pd/C(en) and 2 mL of concd HCl in methanol (10 mL) was stirred for 10 min at ambient temperature, and then the solid phase was filtered, washed vigorously with methanol and ether, and dried under a vacuum pump for 48 h at ambient temperature. Hydrogenation of Ph(CH<sub>2</sub>)<sub>3</sub>OBn<sup>16,17</sup> with the above prepared catalyst resulted in a cleavage of the benzyl group to give Ph(CH<sub>2</sub>)<sub>3</sub>OH in 96% yield. Additionally, Ph(CH<sub>2</sub>)<sub>3</sub>OBn was smoothly hydrogenolyzed with 5% Pd/C(en) in the presence of concd HCl in MeOH.