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# Efficient deprotection of *N*-benzyloxycarbonyl group from amino acids by hydroxyapatite-bound Pd catalyst in the presence of molecular hydrogen

Makoto Murata, Takayoshi Hara, Kohsuke Mori, Masahiko Ooe, Tomoo Mizugaki, Kohki Ebitani and Kiyotomi Kaneda\*

*Department of Chemical Science and Engineering, Graduate School of Engineering Science, Osaka University, 1–3 Machikaneyama, Toyonaka, Osaka 560-8531, Japan*

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**Abstract**—Hydroxyapatite-bound Pd catalyst was found to be highly effective for the deprotection of *N*-benzyloxycarbonyl group from amino acids in the presence of molecular hydrogen. The catalyst was also applicable to the hydrogenolysis of a sterically encumbered core-*Z*-protected poly(amido amine) dendrimer, affording the dendritic amino compound in 99% yield. © 2003 Elsevier Science Ltd. All rights reserved.

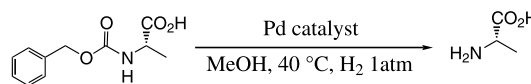
Benzyloxycarbonyl (*Z*) group is a widely utilized amine protecting group in peptide chemistry,<sup>1</sup> in which its removal is achieved with molecular hydrogen in the presence of Pd/C catalyst.<sup>2</sup> However, a large amount of the Pd/C is often used for the deprotection from sterically hindered compounds.<sup>3</sup> An alternate method for the removal of the *Z* group involves the use of homogeneous acids,<sup>4</sup> such as trifluoroacetic acid/thioanisole; however, this method can potentially damage other acid-labile groups, and moreover, often shows low selectivity for multifunctional molecules. In view of the current interest in environmentally benign organic synthetic methodologies, much attention has been paid to the development of highly efficient heterogeneous catalysts for removal of the *Z* group with functional group tolerance.

We have previously reported that a hydroxyapatite-bound Pd complex (PdHAP) can act as an efficient heterogeneous catalyst for the oxidation of alcohols in the presence of molecular oxygen.<sup>5</sup> Subsequently, our ongoing studies of the PdHAP and its applications in practical organic synthesis have revealed the enhanced deprotection of *Z* groups in the presence of molecular hydrogen. Herein, we describe the use of this PdHAP

catalyst system as a simple and strong protocol for the removal of the *Z* group from bulky compounds.

Calcium hydroxyapatite (HAP),  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ , was synthesized according to procedures described in literature.<sup>6</sup> HAP (2.0 g) was stirred in a  $\text{PdCl}_2(\text{PhCN})_2$  ( $2.67 \times 10^{-4}$  M) solution in acetone (150 mL) at 25°C for 3 h. The obtained slurry was filtered, washed with acetone, and dried under vacuum to yield the PdHAP as a pale yellow powder (2.01 g; Pd content: 0.02 mmol  $\text{g}^{-1}$ ). Using elemental analysis, XPS, EDAX, IR, and Pd-K edge XAFS, the local structure of Pd in the powder was characterized as monomeric  $\text{PdCl}_2$  species that are grafted on the surface of HAP by chemisorp-

**Table 1.** Hydrogenolysis of *Z*-L-alanine by various heterogeneous Pd catalysts<sup>a</sup>



Entry	Pd catalyst	Isolated yield (%)
1	PdHAP (0.2 wt% Pd)	92
2	5% Pd/C	68
3	0.5% Pd/C	67
4	0.5% Pd/SiO <sub>2</sub>	64
5	0.5% Pd/Al <sub>2</sub> O <sub>3</sub>	60

<sup>a</sup> Reaction conditions: *Z*-L-alanine 1 mmol, catalyst 0.004 mmol of Pd, MeOH 5 mL, 40°C, 1.5 h, H<sub>2</sub> atmosphere.

**Keywords:** hydrogenolysis; benzyloxycarbonyl; heterogeneous palladium catalyst; hydroxyapatite; dendrimer.

\* Corresponding author. Tel./fax: +81-6-6850-6260; e-mail: [kaneda@cheng.es.osaka-u.ac.jp](mailto:kaneda@cheng.es.osaka-u.ac.jp)

tion.<sup>5</sup> Under the deprotection conditions, the PdCl<sub>2</sub> species were readily transformed into Pd nanoclusters with a mean diameter of 30 Å having a narrow size distribution, as confirmed by TEM analysis.

A general procedure for the deprotection of Z-protected amino acids catalyzed by the PdHAP in the presence of molecular hydrogen is described as follow. The PdHAP (0.2 g, 0.004 mmol Pd) in methanol (1 mL) was stirred at 40°C for 0.5 h under hydrogen atmosphere. To this heterogeneous mixture was added a

methanol solution (4 mL) of Z-protected compound (1 mmol), and the combined reaction mixture was vigorously stirred at 40°C. Upon completion of the reaction, the spent catalyst and solid product were filtered, then washed with water to dissolve the product. The aqueous filtrate was evaporated under reduced pressure to afford an analytically pure amino acid, as confirmed by <sup>1</sup>H NMR.

Catalytic activities of heterogeneous Pd catalysts for the deprotection of Z-L-alanine with molecular hydrogen in

**Table 2.** Hydrogenolysis of various Z-protected amino acids catalyzed by PdHAP<sup>a</sup>

Entry	Substrate	Product	Solvent	Time (h)	Isolated yield (%)
1			MeOH	1	99
2 <sup>b</sup>			MeOH	1	99
3			DMF	1	84
4			THF	1	45
5			EtOH	1	40
6			toluene	1	23
7			DMA	1	22
8			MeOH	2	94
9			MeOH	3	92
10			MeOH	3	93
11 <sup>c</sup>			MeOH	3	84
12			MeOH	1	99
13 <sup>d</sup>			MeOH	3	96
14 <sup>d</sup>			MeOH	12	88
15 <sup>d</sup>			MeOH	12	96

<sup>a</sup>Reaction conditions: substrate 1.0 mmol, PdHAP 0.2 g (0.004 mmol of Pd), MeOH 5 mL, 40 °C, H<sub>2</sub> atmosphere.

<sup>b</sup>PdHAP was reused. <sup>c</sup>PdHAP 0.3 g (0.006 mmol of Pd) was used. <sup>d</sup>MeOH 10 mL was used.

methanol were initially studied. As summarized in Table 1, the PdHAP exhibited the highest activity among the conventional Pd catalysts such as Pd/C, Pd/SiO<sub>2</sub>, and Pd/Al<sub>2</sub>O<sub>3</sub>, affording deprotected alanine in 92% yield (entries 1–5). In the case of the PdHAP, the optical rotation of the product was comparable to that of authentic L-alanine [ $\alpha$ ]<sub>D</sub><sup>14</sup> = +2.3 (*c* 6, water).

As shown in Table 2, excellent yields of the corresponding amino acids were obtained from the hydrogenolysis of various Z-protected compounds. For example, deprotection of Z-proline using the PdHAP in methanol readily afforded proline in 99% yield within 1 h. Among the solvents tested, DMF was also shown to be a favorable solvent for the deprotection of Z-proline, whereas the use of DMA, THF, ethanol, and toluene solvents resulted in poor yields of proline (entries 3–7).

Next, our studies involved the hydrogenolysis of Z groups in the presence of *tert*-butyl groups, which were potentially decomposed at elevated temperature.<sup>7</sup> Notably, the PdHAP showed high catalytic activity under mild conditions to afford the corresponding *tert*-butyl-protected products in high yields (entries 12 and 13). The PdHAP catalyst was also applied to the removal of benzyl group from Z-glu(OBnz)-OH to give glutamic acid in a high yield (entry 15).

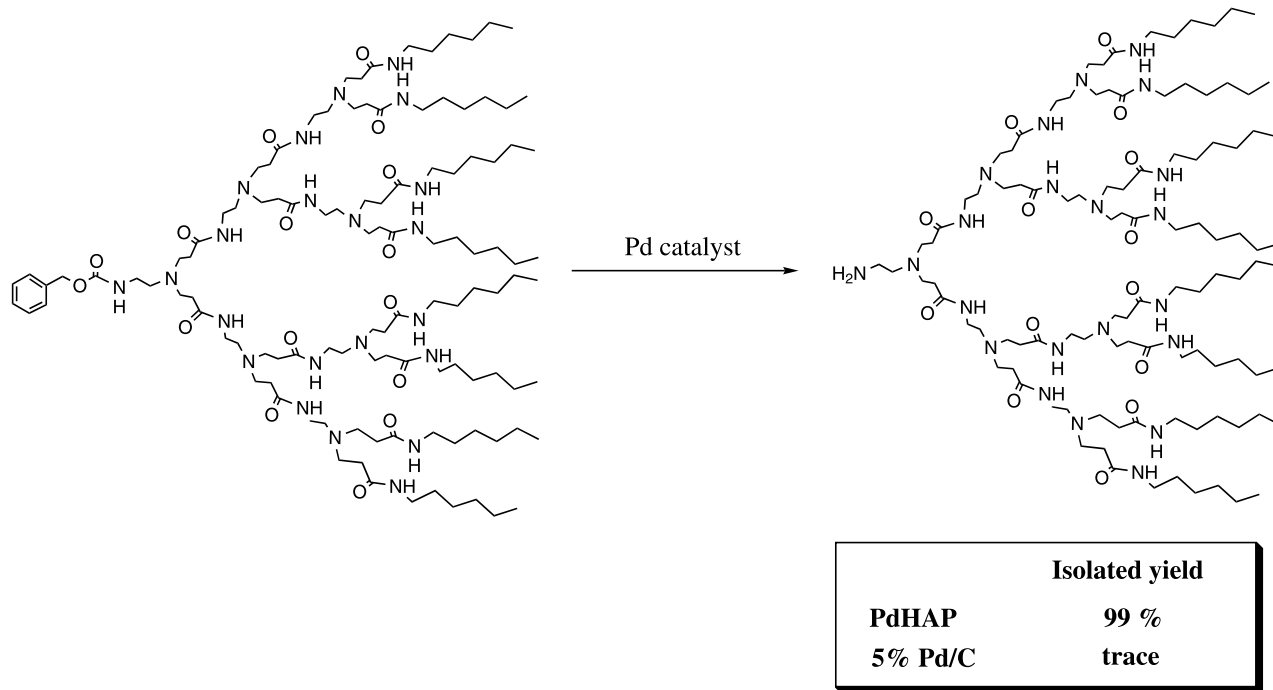
Upon completion of the reaction, the spent PdHAP was separated from the reaction mixture by simple filtration and reused without any loss of its activity; for example, proline was afforded in 99% yield in an experiment using recycled catalyst (entry 2).

The PdHAP catalyst system was also shown to be effective in the removal of Z group from sterically hindered compounds. For the deprotection of a core-Z-protected poly(amido amine) dendrimer functionalized with *n*-hexyl groups,<sup>8,9</sup> the PdHAP afforded the dendritic amino compound in 99% yield (Scheme 1). In contrast, 5% Pd/C catalyst did not exhibit any measurable activities. The prominent catalysis of the PdHAP might be due to the highly dispersed Pd nanoclusters with a narrow particle size distribution on the non-porous hydroxyapatite surfaces.<sup>5</sup>

In summary, the PdHAP was found to be an effective catalyst for the deprotection of *N*-benzyloxycarbonyl compounds with molecular hydrogen. This heterogeneous PdHAP catalyst system has the following advantages: (1) high catalytic activity and substrate tolerance, (2) simple work-up procedures and reusable catalyst, and (3) applicability to sterically hindered substrate. We expect that the PdHAP catalyst can be widely utilized for organic functional group transformations, including oligo- and macromolecular syntheses.

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**Scheme 1.** Reaction conditions: Z-protected dendrimer 0.6 mmol, Pd catalyst 0.002 mmol of Pd, MeOH 5 mL, 40°C, 24 h, H<sub>2</sub> atmosphere.

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- Core-Z-protected poly(amido amine) dendrimer **1** was synthesized by the divergent method according to literature.<sup>8</sup> Characterizations of **1** and the amino product **2** were as follows. **1**: IR (KBr) 3080 ( $\nu_{\text{N-H}}$ ), 2958, 2928, 2856 ( $\nu_{\text{C-H}}$ ), 1654 ( $\nu_{\text{C=O}}$ , amide), 1560 ( $\delta_{\text{N-H}}$ , amide). <sup>1</sup>H NMR (400 MHz, DMSO, TMS, 40°C)  $\delta$  7.42 (br, NH), 7.34 (br, NH), 7.08–6.92 (m, aromatic CH of Z), 5.08 (s, CH<sub>2</sub> of Z), 3.20 (br, NHCH<sub>2</sub>CH<sub>2</sub>N), 3.17 (m, CH<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>), 2.68 (br, NCH<sub>2</sub>CH<sub>2</sub>CONH), 2.55 (m, NHCH<sub>2</sub>CH<sub>2</sub>N), 2.31 (br, NCH<sub>2</sub>CH<sub>2</sub>CONH), 1.48 (m, CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 1.28 (m, (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 0.88 (m, (CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (400 MHz, DMSO, TMS, 40°C)  $\delta$  172.3 (CONH), 156.6 (CONH of Z), 136.7 (quaternary aromatic carbon of Z), 128.3–127.8 (aromatic carbon), 66.4 (CH<sub>2</sub> of Z), 52.6 (NHCH<sub>2</sub>CH<sub>2</sub>N), 51.3 (NCH<sub>2</sub>CH<sub>2</sub>CONH), 39.5 (CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 37.7 (NHCH<sub>2</sub>CH<sub>2</sub>N), 34.4 (NCH<sub>2</sub>CH<sub>2</sub>CONH), 31.7 (CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 29.6 (CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>), 26.7 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 22.6 (CH<sub>2</sub>CH<sub>3</sub>), 14.0 ((CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>). **2**: IR (KBr) 3080 ( $\nu_{\text{N-H}}$ ), 2929, 2857 ( $\nu_{\text{C-H}}$ ), 1647 ( $\nu_{\text{C=O}}$ , amide), 1559 ( $\delta_{\text{N-H}}$ , amide). <sup>1</sup>H NMR (400 MHz, DMSO, TMS, 40°C)  $\delta$  7.81–7.73 (br, NH), 3.16 (br, NHCH<sub>2</sub>CH<sub>2</sub>N), 3.01 (m, CH<sub>2</sub>(CH<sub>2</sub>)<sub>4</sub>CH<sub>3</sub>), 2.65 (br, NCH<sub>2</sub>CH<sub>2</sub>CONH), 2.44 (m, NHCH<sub>2</sub>CH<sub>2</sub>N), 2.18 (br, NCH<sub>2</sub>CH<sub>2</sub>CONH), 1.38 (m, CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 1.24 (m, (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 0.86 (m, (CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (400 MHz, DMSO, TMS, 40°C)  $\delta$  170.9 (CONH), 52.0 (NHCH<sub>2</sub>CH<sub>2</sub>N), 49.6 (NCH<sub>2</sub>CH<sub>2</sub>CONH), 39.3 (CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 36.8 (NHCH<sub>2</sub>CH<sub>2</sub>N), 33.2 (NCH<sub>2</sub>CH<sub>2</sub>CONH), 30.8 (CH<sub>2</sub>(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>), 29.0 (CH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>), 26.0 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 21.9 (CH<sub>2</sub>CH<sub>3</sub>), 13.7 ((CH<sub>2</sub>)<sub>5</sub>CH<sub>3</sub>).