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Suppression Effect of the Pd/C–Catalyzed Hydrogenolysis of a Phenolic Benzyl Protective Group by the Addition of Nitrogen–Containing Bases‡

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Abstract: A mild and chemoselective hydrogenation method using 5% Pd/C for olefin, *N*-Cbz, benzyl ester and nitro functionalities distinguishing from the benzyl protective group for the phenolic hydroxyl group has been developed by the employment of 2,2'-dipyridyl as an additive. The suppressive effect on the benzyl ether hydrogenolysis was strongly influenced by the sorts of nitrogen-containing bases employed as an additive. © 1998 Elsevier Science Ltd. All rights reserved.

An *O*-benzyl protective group has been very useful in contemporary organic synthesis[1] and is one of the most used protective groups as it is stable under a variety of reaction conditions but removed by mild catalytic hydrogenolysis.[2] There is currently extensive interest in controlling the Pd/C-catalyzed hydrogenolysis of the *O*-benzyl protective group in an organic compound containing other reducible functional groups.

While amines and nitrogen–containing bases have been well known as catalyst poisons of the palladium (0) catalyst for hydrogenation, only few general methods using the catalyst poisons to gain the chemoselectivity have appeared.[3] Recently, we have reported the addition of a catalytic amount of ammonia, pyridine or ammonium acetate to the hydrogenation system remarkably suppressed the Pd/C–catalyzed hydrogenolysis of only the aliphatic *O*-benzyl protective group in coexistence with other reducible functionalities, *e.g.*, olefin, *N*-Cbz, benzyl ester or azide.[4,5] However, the selective suppression of hydrogenolysis was not applicable to the benzyl protective group for phenolic hydroxyl functions.[4–6] The problem has been temporarily solved by the employment of a 4-methoxybenzyl (MPM) protective group instead of the more reducible benzyl group for phenolic hydroxyl functions.[7] During the course of our further study on the Pd/C–catalyzed chemoselective hydrogenolysis, we found large difference in the suppressive effect on the hydrogenolysis of *O*-benzyl protective groups depending upon the nitrogen–containing bases employed as an additive. Herein, we describe a general procedure for the selective suppression of the Pd/C catalyzed hydrogenolysis of the phenolic benzyl group and the structural factors of the additives that affect the suppression of the hydrogenolysis.

At the beginning, we attempted a Pd/C-catalyzed hydrogenolysis of *N*-Boc-*O*-benzyl-L-tyrosine methyl ester (**1**) to *N*-Boc-L-tyrosine methyl ester (**2**) in the presence of various sorts of amines in MeOH at ordinary pressure and temperature. When ammonia, methylamine, triethylamine and pyridine were used the reactions led to the smooth loss of the *O*-benzyl protective group (Scheme 1 and Table 1).[8] Upon employment of a 1,2-

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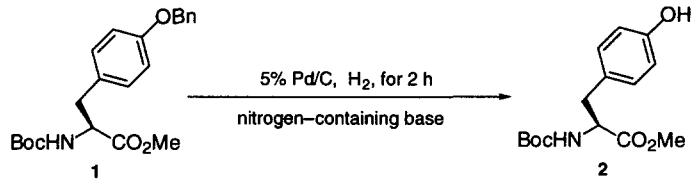
ambident amine, ethylenediamine, the hydrogenolysis of the benzyl group of **1** was dramatically suppressed. To explore this suppressive effect, some alkylenediamines were examined as the additive (Table 1). 1,4-Butanediamine and 1,10-decanediamine did not indicate any significant suppressive effect on the hydrogenolysis to afford a large amount of deprotected product (**2**) after 2 h. The length of the C-C chain between two nitrogen atoms plays a crucial role in these inhibitions and the addition of ethylenediamine (C–2) as the ambident amine gave the best suppressive effect among the alkylenediamines. An analogous experiment with diethylenetriamine which possesses three nitrogen atoms gave much better results. On the basis of these observations, *o*-phenylenediamine, 8-aminoquinoline, 2,2'-dipyridyl and 1,10-phenanthroline were investigated (Table 1).[9] It is noteworthy that the debenzylation of **1** was completely blocked by utilizing Pd/C-2,2'-dipyridyl or 1,10-phenanthroline combinations.

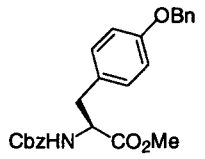
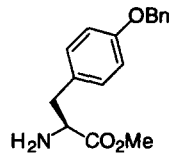
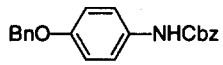
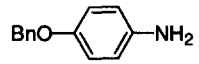
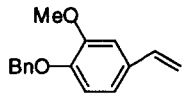
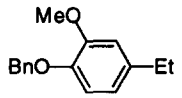
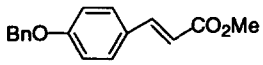
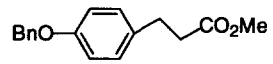
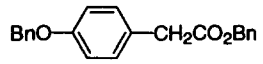
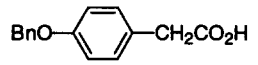
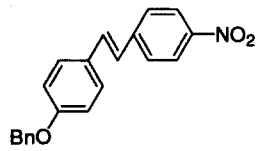
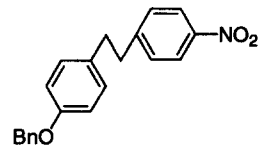
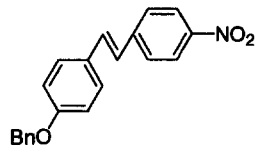
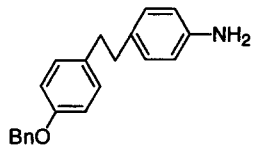
Table 1. Recovery (%) of **1** after hydrogenolysis for 2 h at ordinary pressure and temperature with 5% Pd/C in the presence of amine or nitrogen-containing base.[8]



Amine or base	Recovery (%)	Amine or base	Recovery (%)
None	0	1,4-Butanediamine	5
Ammonia	0	1,10-Decanediamine	2
Methylamine	0	Diethylenetriamine	93
Triethylamine	0	*o*-Phenylenediamine	81
Pyridine	0	8-Aminoquinoline	89
Ethylenediamine	72	2,2'-Dipyridyl	100
1,3-Propanediamne	59	1,10-Phenanthroline	100

The present inhibition procedure for the deprotection of the phenolic benzyl group can be applied to the selective hydrogenation of some substrates which possess other reducible functionalities (*N*-Cbz, olefin or nitro functions) within the molecule. 2,2'-Dipyridyl was chosen as an additive for its high performance and the stability under the reaction conditions.[9] As shown in Table 2,[10] the hydrogenation of *N*-Cbz (entries 1 and 2), olefin (entries 3, 4 and 6), benzyl ester (entry 5) and nitro (entry 7) functions proceeded chemoselectively, retaining the phenolic benzyl group. Careful hydrogenation (2 h) of 4-benzyloxy-4'-nitrostilbene selectively hydrogenated only the olefinic moiety (84%, entry 6). Long period hydrogenation (24 h) reduced both olefin and nitro functionalities to provide 4-amino-4'-benzyloxybibenzyl in 86% yield (entry 7). No debenzylation of the *O*-benzyl ethers was observed in all cases.

Table 2. Chemoselective hydrogenation of phenolic benzyl ether derivatives.[10]

Entry	Substrate	Product	Time (h)	Yield (%)[a]
1			24[b]	91
2			22[b]	82
3			3	89
4			15[b]	95
5			24[b]	92
6			2	84
7			24	86

[a]Yields refer to products isolated. All compounds were characterized by ^{1}H NMR, MS and elemental analysis or HRMS. [b]Although the reaction was completed within 2–5 h, the benzyl protective group remained intact even after the shown time.

At present, detailed mechanistic studies have not been undertaken and the exact process of the occurrence of the inhibitory effect is unclear. The structural parameter of the additive for the perfect suppression of the debenzylation seems to be the π-electron of the aromatic ring systems and the 1,2-ambident base moiety. The latter possesses a possibility to form the five-membered cyclic Pd-complex as a bidentate ligand. To the best of our knowledge, it is unprecedented that a bidentate nitrogen-containing base was employed as a catalyst poison to control the Pd catalyzed hydrogenation.

In conclusion, we have developed a mild and chemoselective hydrogenation method for olefin, *N*-Cbz, benzyl ester and nitro functionalities distinguishing from the benzyl protective group for the phenolic hydroxyl group by the employment of 2,2'-dipyridyl as an additive. This finding would increase the utility of the *O*-benzyl protective group in organic synthesis. We shall use 5% Pd/C as a catalyst for the hydrogenation with

removal of all the *O*-benzyl protective groups.[1] Moreover, the use of 5% Pd/C and ammonia combination as a catalyst suppresses the hydrogenolysis of only an aliphatic *O*-benzyl protective group[4] and by use of 5% Pd/C and 2,2'-dipyridyl combination, the aliphatic and the phenolic *O*-benzyl protective groups can be retained.

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REFERENCES AND NOTES

‡Dedicated to Professor Satoru Masamune on the occasion of his 70th birthday.

[1] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., New York, 2nd ed., **1991**, pp. 47-53 and 156-158.

[2] For reviews, see: a) Rylander, P. N. *Hydrogenation Methods*, Academic Press, New York, **1985**, pp. 157-163; b) *Idem.*, *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, New York, **1979**, pp. 271-279; c) Freifelder, M. *Practical Catalytic Hydrogenation Techniques and Applications*, Wiley-Interscience, New York, **1971**, pp. 398-413 and 428-440.

[3] The best known of the chemoselective catalysts is the Lindlar catalyst, Pd-Pb-on-calcium carbonate, which has been used successfully for the selective hydrogenation of acetylenes to olefins, and the hydrogenation of acid chlorides to aldehydes, see: ref. [2]-a) pp. 53-65 and 153-156.

[4] Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465–3468.

[5] Czech and Bartsch also reported the inhibition of Pd/C–catalyzed hydrogenolysis of 11-(benzyloxy)-1-undecene using *n*-butylamine as an additive, see: Czech, B. P.; Bartsch, R. A. *J. Org. Chem.* **1984**, *49*, 4076–4078.

[6] Several suppressions of aliphatic *O*–benzyl ether hydrogenolysis in the presence of intramolecular amine have appeared in literature.[5,11] However, phenolic *O*–benzyl ether in spite of the presence of intramolecular amine was debenzylated, see: a) Forbes, E. J. *J. Chem. Soc.* **1955**, 3926–3932. b) Kirby, G. W.; Tiwari, H. P. *J. Chem. Soc. (C)* **1966**, 676–682.

[7] Sajiki, H; Kuno, H.; Hirota, K. *Tetrahedron Lett.* **1997**, *38*, 399-402.

[8] These reactions were followed by a TLC scanner (Shimadzu CS-9000). All reactions were carried out at ordinary pressure (balloon) and temperature (*ca.* 20 ℃) with 5% Pd/C (10 weight%) in MeOH in the presence of 0.5 equiv. of amine or nitrogen–containing base .

[9] 1,10-Phenanthroline could also be partially hydrogenated under the reaction conditions.

[10] Needless to say, no competitive reduction of an aliphatic benzyl ether was observed. *General procedure*: After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of the substrate (0.2 mmol), 5% Pd/C (10 weight %) and 2,2'-dipyridyl (0.1 mmol) in MeOH or 1,4-dioxane (1 ml) was hydrogenated at ordinary pressure (balloon) and temperature (*ca.* 20 ℃) for the appropriate time. The reaction mixture was filtered (Celite® cake), the filtrate was concentrated and the residue was partitioned between $CHCl_3$ or AcOEt and water. The organic layer was washed with dilute $NaHSO_4$ solution and brine (see ref. [12]), dried ($MgSO_4$) and concentrated to provide the product without any by-product. The resulting product was purified by flash silica gel column chromatography, if necessary.

[11] For examples, a) Pennings, M. L. M.; Reinhoudt, D. N. *J. Org. Chem.* **1983**, *48*, 4043–4048. b) Fleet, G. W.; Smith, P. W. *Tetrahedron Lett.* **1985**, *26*, 1469–1472.

[12] If the product possesses an amino moiety (Table 2, entries 1, 2 and 7), the organic layer was washed with only brine. After concentration, the residue was purified by flash silica gel column chromatography to remove 2,2'-dipyridyl.