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Markedly chemoselective hydrogenation with retention of benzyl ester and *N*-Cbz functions using a heterogeneous Pd-fibroin catalyst

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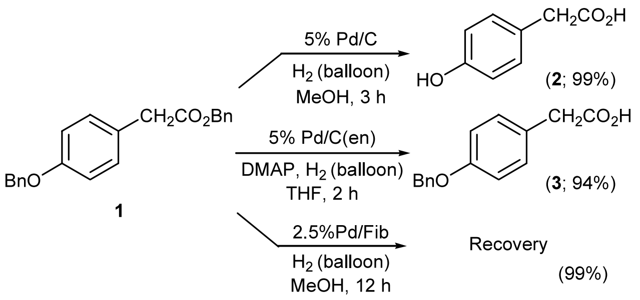
Abstract—The chemoselective catalytic hydrogenation of acetylene, olefin and azido derivatives bearing benzyl ester and *N*-Cbz functionalities using a Pd-fibroin (Pd/Fib) catalyst was investigated. Perfect selectivity was accomplished, and the benzyl ester and *N*-Cbz functionalities are tolerated under the reaction conditions.

Despite numerous literature precedents, chemoselective reduction of reducible functionalities such as alkynes alkenes and azides remains a challenge in organic synthesis.[1] Especially, while benzyl ester or *N*-Cbz protective groups are widely used in organic synthesis, they are labile under hydrogenation conditions, and it is extremely difficult to keep such groups intact during a synthetic process involving hydrogenation steps.[2] In order to solve this problem, Misiti et al. have reported 3% Pd/C-catalyzed selective hydrogenation of a di-substituted olefin of γ-amino-α,β-unsaturated (conjugate) esters in the presence of a benzyl ester or *N*-Cbz protective group.[3] However, the method has limitation with regard to generality, and the stability of the benzyl esters and *N*-Cbz groups under the conditions was time-dependent.[3,4] Recently, we reported the Pd/C-ethylenediamine [Pd/C(en)] catalyzed chemoselective hydrogenation with retention of the *N*-Cbz protective group of aliphatic amines although the chemoselective hydrogenation with retention of the aromatic *N*-Cbz groups or benzyl esters could not be accomplished.[5,6]



Scheme 1. Influence of catalysts on the hydrogenolysis of **1**.

We have also recently established that $Pd(OAc)_2$ formed an isolable Pd(0) complex with silk fibroin as a stationary phase using methanol as a solvent and a reductant, and the resulting fibroin-supported catalyst (Pd/Fib) selectively catalyzed the hydrogenation of olefins and azides without hydrogenolysis of the aromatic carbonyl, aromatic halogen and benzyl ether functionalities.[7,8]

During our efforts to extend the applicability of the Pd/Fib catalyst, we found that Pd/Fib indicates almost no catalytic activity towards the hydrogenolysis of benzyl ether, benzyl ester and *N*-Cbz functionalities, compared with Pd/C and Pd/C(en).[5] The hydrogenolysis of 4-benzyloxyphenylacetic acid benzyl ester (**1**) catalyzed by 2.5% Pd/Fib resulted in no reaction even after 24 h at ordinary hydrogen pressure (Scheme 1).

On the other hand, the use of 5% Pd/C (Aldrich) as a catalyst resulted in the hydrogenolysis of both the benzyl ether and the benzyl ester of **1** to give the corresponding 4-hydroxyphenylacetic acid (**2**) in 99% isolated yield. 5% Pd/C(en) catalyzed chemoselective hydrogenation of only the benzyl ester of **1** with retention of the benzyl ether to give the corresponding 4-benzyloxyphenylacetic acid (**3**) in 94% isolated yield.[5a] Judging from these results so far obtained, we are now in a position to disclose that the Pd/Fib catalyst is very efficient for chemoselective hydrogenation with retention of the benzyl ester within a molecule.

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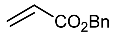
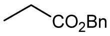
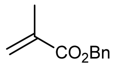
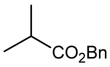
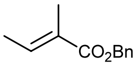
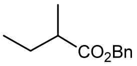
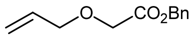
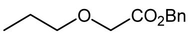
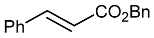
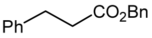
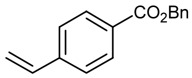
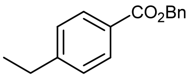
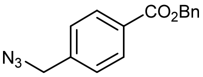
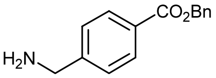
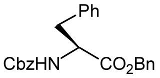
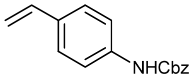
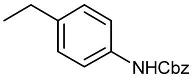
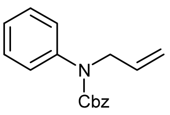
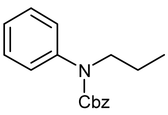
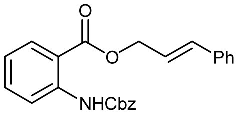
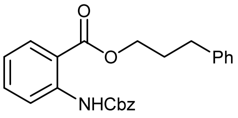
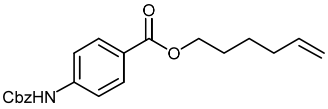
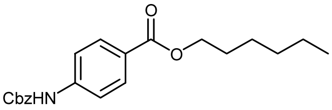
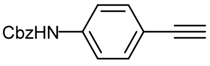
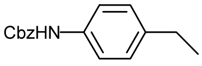
Table 1. Chemoselective hydrogenation of the olefin or azido functionality with retention of the benzyl ester or aromatic *N*-Cbz protective group using 2.5% Pd/Fib catalyst[a]

Entry	Substrate	Solvent[b]	Time (h)	Product	Yield (%)[c]
1		THF-d_6	7		91[d]
2		THF-d_6	7		93[d]
3[e]		MeOH	18		77
4		MeOH	8		99
5		THF	24		98
6		MeOH	6		97
7		MeOH	17		100
8		THF	26	recovery	91
9		THF	5		92
10		MeOH	48		97
11[f]		THF	34		99
12		MeOH	22		100
13[g]		MeOH	32		92

[a] Unless otherwise specified, the reaction was carried out using 1.0 mmol of the substrate in solvent (5 mL) with 2.5% Pd/Fib (10% of the weight of the substrate) under hydrogen atmosphere (balloon) for the given reaction time.

[b] The reaction performed with THF as a solvent when the formation of a certain amount of the over-reduced product was observed in MeOH.

[c] Isolated yield unless otherwise noted.

[d] Determined by ^1H NMR.

[e] Under 5 atm pressure of H_2.

[f] Under 10 atm pressure of H_2.

[g] Under 3 atm pressure of H_2.

To explore the scope of the 2.5% Pd/Fib catalyst, the hydrogenation of a number of substrates containing a benzyl ester was investigated (Table 1, entries 1–8). The results shown in entries 1–7 demonstrated that the chemoselective hydrogenation could be accomplished by employing benzyl ester derivatives including α,β-unsaturated benzyl esters with terminal and internal olefin and azido functionalities. On occasions when the partial hydrogenolysis of the benzyl ester of the substrate occurred in MeOH, the use of THF as a solvent gave satisfactory results (entries 1, 2, 5 and 8).[5,9,10] A similar tolerance was observed in the 2.5% Pd/Fib-catalyzed hydrogenolysis of an aliphatic *N*-Cbz protected phenylalanine (entry 8). There is no report in the literature where an *N*-Cbz protective group[2] of aromatic amines was not hydrogenolyzed under the palladium-catalyzed hydrogenation conditions although we have recently reported the *N*-Cbz group of aliphatic amines is inert toward the Pd/C(en)-catalyzed hydrogenolysis.[5] Accordingly, this background encouraged us to examine the chemoselective hydrogenation of various aromatic *N*-Cbz compounds possessing other reducible functionalities within a molecule. The chemoselective hydrogenation of olefin (entries 9–12) and acetylene (entry 13) functionalities was completely achieved and the desired products were obtained in excellent isolated yields. It is noteworthy that the hydrogenolysis of the benzyl ester and aromatic *N*-Cbz functionalities is also entirely depressed under 3-10 atm pressure of hydrogen conditions (entries 3, 11 and 13).

The chemoselectivity of the hydrogenation could be attributable to the catalyst poison effect of the coordinated silk fibroin support toward the zero valent palladium metal. In the Pd/Fib catalyst, the original affinity of palladium for benzyl esters and *N*-Cbz protective groups[1b,d] was drastically reduced by fibroin.[11]

In summary, we have developed a mild and chemoselective hydrogenation method using 2.5% Pd/Fib as a catalyst, which is widely applicable to the selective hydrogenation of a variety of olefin, azido and acetylene functionalities leaving intact the benzyl esters and aromatic *N*-Cbz protective groups. The hydrogenolysis of the extremely reducible benzyl ester and aromatic *N*-Cbz protective groups could be completely suppressed. We believe that the present method should find broad application in organic synthesis.

Acknowledgements

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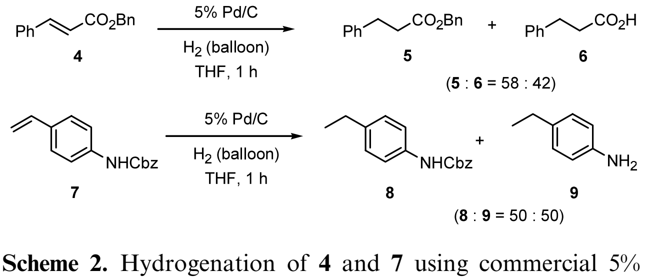
References

1. For selected reviews on reductions, see: (a) Larock, R. C. *Comprehensive Organic Transformations*; 2nd ed.; Wiley-VCH: New York, 1999; (b) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley-Interscience: New York, 2001; (c) Hudlicky, M. *Reductions in Organic Chemistry*; 2nd ed.; ACS: Washington, DC, 1996; (d) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985.
2. Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed; John Wiley & Sons: New York, 1999.
3. Misiti, D.; Zappia, G.; Monach, G. D. *Synthesis* **1999**, 873–877.
4. Kuzuhara et al. have reported the chemoselective hydrogenation of an azido group in the presence of an aliphatic *N*-Cbz protective group using Raney Ni, which must be added into the reaction mixture in small portions with careful monitoring to avoid cleavage of the *N*-Cbz group: Kuzuhara, H.; Mori, O.; Emoto, S. *Tetrahedron Lett.* **1976**, 379–382.
5. (a) Sajiki, H.; Hattori, K.; Hirota, K. *J. Org. Chem.* **1998**, *63*, 7990–7992; (b) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2000**, *56*, 8433–8441.
6. Quit a few methods to maintain the benzyl ester intact during a synthetic process involving conjugate reduction (non-hydrogenation) steps have been reported. (a) Mathoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291–293; (b) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 5678–5680; (c) Kelly, T. R.; Xu, W.; Ma, Z.; Li, Q.; Bhushan, V. *J. Am. Chem. Soc.* **1993**, *115*, 5843–5844.
7. Sajiki, H.; Ikawa, T.; Yamada, H.; Tsubouchi, K.; Hirota, K. *Tetrahedron Lett.* **2003**, *44*, 171–174.
8. Akabori and Izumi et al. reported the pioneering preparation of the silk-supported palladium catalyst in a fundamentally different way although their catalyst indicates totally different catalyst activity from our Pd/Fib catalyst. (a) Akabori, S.; Sakurai, S.; Izumi, Y.; Fujii, Y. *Nature* **1956**, *178*, 323–324; (b) Izumi, Y. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 932–936, 936–942 and 942–945; (c) Akamatsu, A.; Izumi, Y.; Akabori, S. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 1067–1072; (d) Akamatsu, A.; Izumi Y.; Akabori, S. *Bull. Chem. Soc. Jpn.* **1961**, *35*, 1706–1711.
9. Sajiki, H.; Hattori, K.; Hirota, K. *Chem. Eur. J.* **2000**, *6*, 2200–2204.
10. We have quite recently reported the frequent and unexpected cleavage of *tert*-butyldimethylsilyl (TBDMS) ethers to form the parent alcohols under mild hydrogenation conditions using 10% Pd/C in MeOH although TBDMS ethers have been believed to be stable under hydrogenation conditions. Furthermore, we have reported a remarkable solvent effect toward the Pd/C-catalyzed cleavage of TBDMS and triethylsilyl (TES) ethers and it was applied to the development of a chemoselective hydrogenation method for olefin, benzyl ether and acetylene functionalities distinguishing from the TBDMS and TES protective groups of a hydroxy group by the employment of EtOAc or MeCN as a solvent. See: Sajiki, H.; Ikawa, T.; Hattori, K.; Hirota, K. *Chem. Commun.* **2003**, 654–655 and references cited therein.
11. The catalyst activity of commercial 5% Pd/C (Aldrich) toward reducible functionalities is much higher than the catalyst activity of 2.5% Pd/Fib. The olefins of **4** and **7** were completely hydrogenated within 1 h (Scheme 2) while the complete hydrogenation of the olefins required much longer time (24 h and 5 h, respectively; Table 1, entries 5 and 9).



Scheme 2. Hydrogenation of **4** and **7** using commercial 5% Pd/C catalyst in THF.