DOI: 10.1002/adsc.200900316

Development of Molecular Sieves-Supported Palladium Catalyst and Chemoselective Hydrogenation of Unsaturated Bonds in the Presence of Nitro Groups

Tomohiro Maegawa,[a,b] Tohru Takahashi,[a] Masatoshi Yoshimura,[c] Hiroyasu Suzuka,[c] Yasunari Monguchi,[a] and Hironao Sajiki[a,*]

[a] Laboratory of Organic Chemistry, Department of Organic and Medicinal Chemistry, School of Pharmaceutical Sciences, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502-8585, Japan
Fax: (+81) 58-237-5979; e-mail: sajiki@gifu-pu.ac.jp
[b] Current address: Graduate School of Pharmaceutical Sciences, Osaka University, 1–6 Yamada-oka, Suita, Osaka 565-0871, Japan
[c] N.E. Chemcat Corporation, Numazu Plant, 678 Ipponmatsu, Numazu, Shizuoka 410-0314, Japan

Received: May 7, 2009; Revised: June 26, 2009; Published online: September 10, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900316.

Abstract: The chemoselective hydrogenation of unsaturated bonds and azide functionalities is achieved in the presence of nitro groups by a heterogeneous palladium catalyst supported on molecular sieves (MS3A). The present method shows a wide-range of applicability with regard to substrates and the catalyst can be easily prepared and reused at least three times without any loss of activity.

Keywords: chemoselective hydrogenation; heterogeneous catalysis; molecular sieves; nitro compounds; palladium

Chemoselective hydrogenation is one of the most desirable reactions in organic synthesis, such as the total synthesis of complex molecules bearing many reducible functional groups.[1] The nitro group is a useful functional group as precursor of amine and oxime functionalities and can be easily introduced on an aromatic ring by an electrophilic substitution reaction. Since aromatic nitro groups are very susceptible to transition metal-catalyzed hydrogenation,[1b] it is unfortunately difficult to achieve the selective hydrogenation of unsaturated bonds while maintaining the nitro functions intact, the only exception being a sole hydrogenation method using homogeneous Wilkinson's catalyst.[2] Furthermore, such a chemoselective transformation is also extremely difficult using other reductive methods and very few potential methods using baker's yeast,[3] a metal hydride,[4] and siloxane[5] are available. In terms of industrial applications, heterogeneous catalytic hydrogenations are more favorable but no method exists to date.

During the course of investigations on a chemoselective hydrogenation, we found that the addition of amines and sulfides, such as Et_3N, pyridine and diphenyl sulfide, effectively works as a partial catalyst poison to control the catalytic activity of Pd/C. As a result, we developed Pd/C-catalyzed chemoselective hydrogenation methods between various reducible functions using the appropriate catalyst poison.[6] As an extension of these methods, we prepared the isolable amine- and sulfur-poisoned catalysts; i.e., the Pd/C-ethylenediamine complex [Pd/C(en)],[7] Pd-polyethyleneimine complex (Pd/PEI).[8] and Pd/C-diphenyl sulfide complex [Pd/C(Ph_2S)],[9] for the chemoselective hydrogenations (Figure 1).

Furthermore, we also developed a silk fibroin, a protein produced by silkworms possessing very few residues of sulfur-containing amino acids, a supported

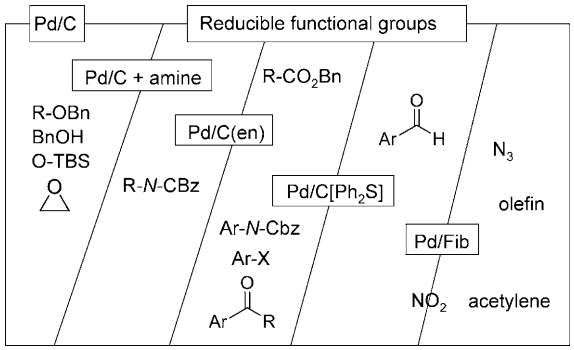


Figure 1. Pd-catalyzed chemoselective hydrogenation with combination of various catalytic poisons.

Pd-catalyst, and a Pd-fibroin complex (Pd/Fib),[10] as the selective hydrogenation catalyst of C-C or N-C multiple bonds in the presence of many other reducible functionalities as summarized in Figure 1. Based on these results, we noticed the significance of the catalyst support for an excellent chemoselectivity.

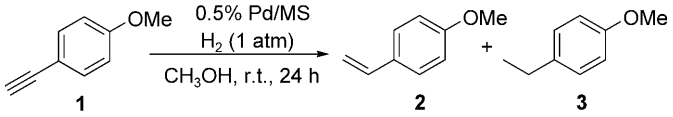
Many types of zeolite possessing wide varieties of surface area, pore size, polarity of the inside cavity, and so on were reported in the literature, depending on the preparation methods.[11] Molecular sieves (MS) are well known as a representative zeolite and they are widely utilized in many chemical fields. MS possessing different pore sizes are commercially available and we expected that such characteristics may affect the reactivity of the Pd catalysts. Therefore, we chose an MS as the catalyst support for the chemoselective hydrogenation. Herein, we report the preparation of novel MS-supported Pd catalysts (Pd/MS) and the chemoselective hydrogenation of olefin, acetylene and azide functionalities in the presence of a nitro group using a Pd/MS catalyst.

Initially, we prepared the 0.5% Pd-MS (0.5% Pd metal *vs.* MS) complex (Scheme 1).[10] Different types of molecular sieves (MS3A, 4A, 5A and 13X) were soaked in a CH_3OH solution of $Pd(OAc)_2$ and stirred for 6 days until the rust-colored supernatant solution turned clear. The suspension was then collected by filtration and washed with CH_3OH and H_2O to give the Pd/MS catalyst as a gray powder. Pd metal absorbed on the MS was nearly 0.5 wt% of the catalyst based on XRF analysis, and the XANES analysis of the Pd/MS catalyst showed that most of (>90%) the absorbed Pd species existed as Pd(0).

We then examined the catalyst activities against the hydrogenation of each catalyst using 4-ethynylanisole as the substrate (Table 1). Interestingly, each catalyst showed a different catalyst activity. Since 0.5% Pd/MS3A indicated an appropriate and mild reactivity toward the hydrogenation of the unsaturated bond, therefore, we expect that the Pd/MS3A would exhibit a novel chemoselectivity for the hydrogenation among the various reducible functionalities.

We attempted the hydrogenation of a variety of substrates possessing different types of reducible functionalities within the molecule (Table 2). Consequently, unsaturated bonds including the azide were completely hydrogenated to the corresponding saturated bonds (entries 1–8, 10 and 11). No hydrogenolysis of benzyl esters (entries 2–4), benzyl ethers (entries 5 and 6), aromatic bromide (entry 7) and *N*-Cbz (entry 11) were observed. Furthermore, nitriles (entries 8 and 9) and aromatic ketones (entries 9 and 10) were tolerated under the Pd/MS3A-catalyzed hydrogenation conditions even after 24 h.

Table 1. Catalytic activity for the hydrogenation of 4-ethynylanisole.[a]



Entry	Catalyst	**1**:**2**:**3**[b]
1	Pd/MS3A	0:10:90
2	Pd/MS4A	0:84:16
3	Pd/MS5A	31:69:0
4	Pd/MS13X	63:37:0

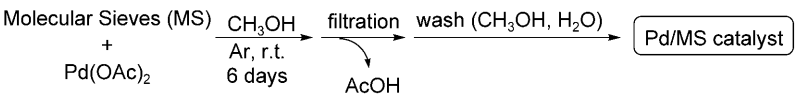
[a] The reaction was carried out using 0.25 mmol of 4-ethynylanisole and 10 wt% of the catalyst in CH_3OH at room temperature for 24 h under an ordinary H_2 atmosphere.

[b] The ratio was determined by ^1H NMR.

During the investigation, we surprisingly found that Pd/MS3A-catalyzed hydrogenation conditions never affected an aromatic nitro group (Scheme 2). The aromatic nitro groups are very susceptible to hydrogenation and easily reduced to the corresponding amines *via* nitroso intermediates. Therefore, it is extremely hard to logically achieve the chemoselective hydrogenation of unsaturated multiple bonds in the presence of nitro groups.[1]

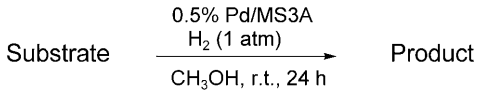
Such a background led us to explore the applicability of Pd/MS3A for the chemoselective hydrogenation of unsaturated multiple bonds of diverse nitro-containing compounds (Table 3). Nitro functionalities as well as the aliphatic nitro function remained intact during the 24 h hydrogenation. The chemoselective hydrogenation between the nitro groups and multiple bonds as well as azide groups (entries 1–5) was completely achieved. Other reducible functionalities such as the aryl bromide, *N*-Cbz and benzyl ester were also tolerated under these conditions (entries 6–8).

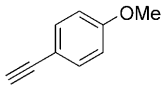
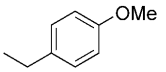
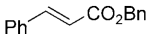
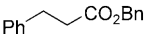
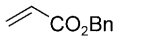
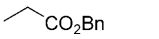
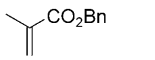
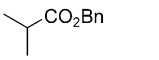
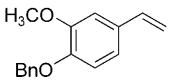
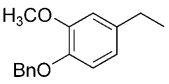
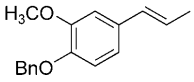
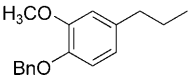
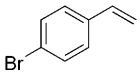
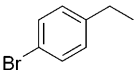
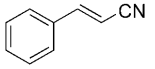
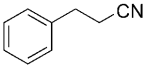
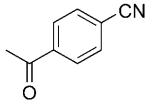
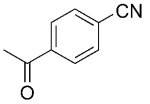
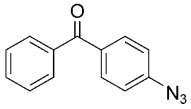
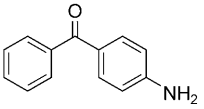
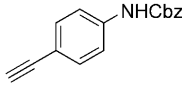
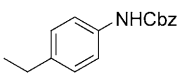
The STEM analysis showed that Pd on the Pd/MS3A catalyst existed as a nanoparticle [<10 nm (<100 Å)] and most of the Pd cluster may exist on the surface of the MS, not inside the cavity (Figure 2). This is also supported by the EXAFS analysis (Figure 3) because of few correlations between Pd and Si or Al atoms in MS. Surprisingly, the surface area of the Pd metal of Pd/MS3A ($22\ m^2\,g^{-1}$ Pd) was only one-tenth of that of Pd/Al_2O_3 by a surface area analysis using the CO adsorption method. The postu-



Scheme 1. Preparation of the Pd/MS catalyst.

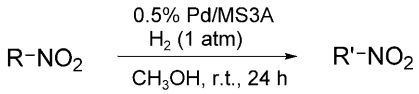
Table 2. Chemoselective hydrogenation using heterogeneous Pd/MS3A.[a]

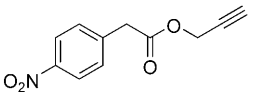
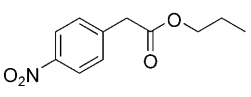
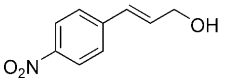
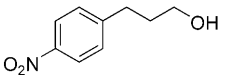
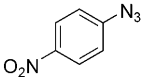
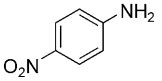
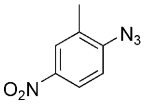
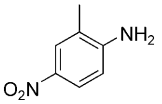
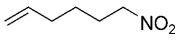
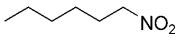
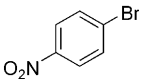
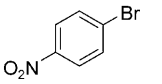
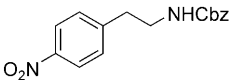
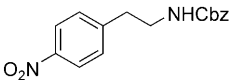
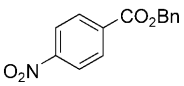
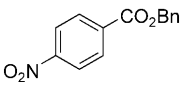


Entry	Substrate	Product	Yield [%]
1[b]			83
2			94
3			91
4			56[c]
5			98
6			100
7			72
8			92[d]
9			95
10			94
11			95

[a] The reaction was carried out using 0.25 mmol of substrate and 10 wt% of 0.5% Pd/MS3A in CH_3OH at room temperature for 24 h under an ordinary H_2 atmosphere.
[b] The reaction was performed for 36 h.
[c] The low yield of product was due to its volatile nature.
[d] 6% of starting material unchanged after 24 h.

Table 3. Chemoselective hydrogenation in the presence of a nitro group using heterogeneous Pd/MS3A.[a]



Entry	Substrate	Product	Yield [%]
1			95
2			90
3			98[b]
4			90[b]
5			68[c]
6			96
7			94
8			98

[a] The reaction was carried out using 0.25 mmol of substrate and 10 wt% of 0.5% Pd/MS3A in CH_3OH at room temperature for 24 h under an ordinary H_2 atmosphere.
[b] A trace amount of a diamino compound was detected (<1%).
[c] The low yield is due to its volatile nature.

lated expression mechanism of the chemoselectivity of the Pd/MS3A-catalyzed hydrogenation could be correlated with the reduction of the active surface area of Pd metal although it is not clear why the Pd nanoparticle on MS3A showed such a small surface area. The differences of catalyst activity between each Pd/MS catalyst with different pores size may be due to the adsorption affinity of substrate into the cavity (Table 1).

Finally, we examined the reusability of the Pd/MS3A. As a result, the catalyst could be reused at least three times without any significant loss of activity and without a reactivation process (Table 4).

In conclusion, we have developed a novel heterogeneous and chemoselective hydrogenation catalyst, Pd/MS3A. Only unsaturated multiple bonds including azide functions were reduced without reduction of other reducible functionalities including nitro groups

Scheme 2. Chemoselective hydrogenation in the presence of a nitro group.

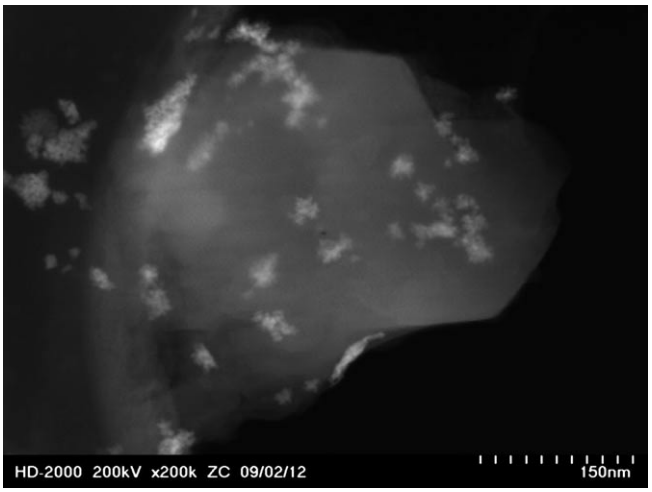
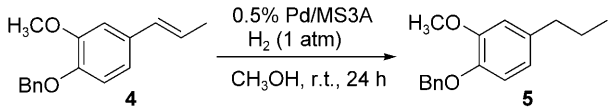


Figure 2. STEM of 0.5% Pd/MS3A.

Table 4. Reuse of the Pd/MS3A catalyst.[a]



Recycle	Selectivity (**1**:**2**)	Yield [%]
1	0:100	100
2	0:100	100
3	0:100	100

[a] The substrate (0.25 mmol), Pd/MS3A (10 wt%) and CH_3OH (1.0 mL) was used.

under the given conditions. This is the first report of the chemoselective heterogeneous hydrogenation in the presence of nitro functionalities and the size of the Pd cluster and pore size of the MS may affect the chemoselective hydrogenation. The present method indicates a wide applicability of substrates and has advantages of easy preparation, handling and reusability of the catalyst.

Experimental Section

Preparation of Pd/MS catalyst

To the solution of $Pd(OAc)_2$ (52.7 mg, 0.23 mmol, 0.5 wt% *vs.* MS) in CH_3OH (50 mL) were added molecular sieves (powder) (5.0 g) and stirred for 6 days until the color of the supernatant of the suspension turned clear. The suspension was then filtered and the obtained solid was washed with CH_3OH and H_2O and dried under vacuum to give the 0.5% Pd/MS catalyst as a grey powder.

Chemoselective Hydrogenation

The mixture of the substrate (0.25 mmol), 0.5% Pd/MS3A (10 wt% of substrate) and CH_3OH (1.0 mL) was exposed to H_2 gas using an H_2-filled balloon, and then stirred at room temperature for 24 h. The reaction mixture was filtered through a membrane filter (Millipore, Millex®-LH, 0.45 μm) and the filtrate was concentrated under reduced pressure to produce the product.

XANES experiments were performed at the BL14B2 in the SPring-8 with the approval of the Japan Synchrotron Radiation Research Institute (JASRI) (proposal no. 2008 A1896).

References

[1] a) R. C. Larock, *Comprehensive Organic Transformations*, 2nd edn., Wiley-VCH, New York, **1999**; b) S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, Wiley-Interscience, New York, **2001**; c) M. Hudlicky, *Reductions in Organic*

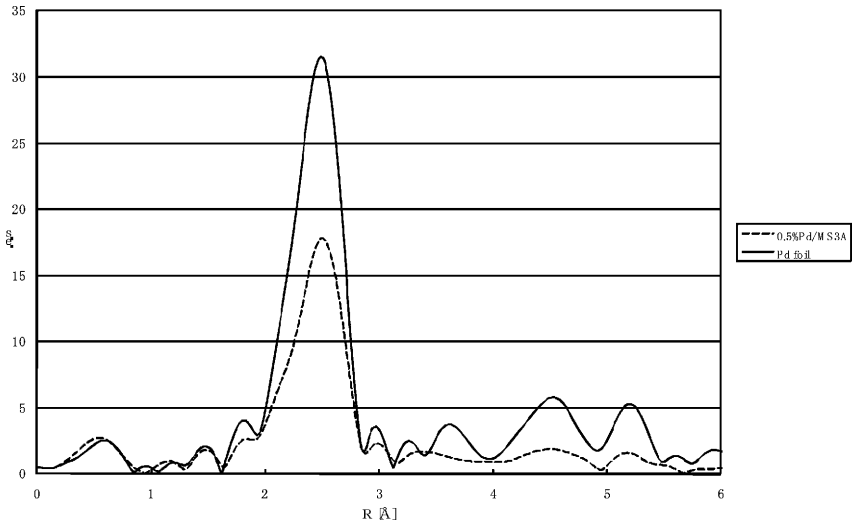


Figure 3. Pd K-edge $K^3\chi(k)$ EXAFS Fourier transforms of 0.5% Pd/MS3A and Pd foil.

Chemistry, 2nd edn., ACS, Washington, DC, **1996**; d) P. N. Rylander, *Hydrogenation Methods*, Academic Press, New York, **1985**.

[2] M. Takeshita, S. Yoshida, Y. Kohno, *Heterocycles* **1994**, *37*, 553–562.

[3] a) J. M. Aizpurua, M. Oiarbide, C. Palomo, *Tetrahedron Lett.* **1987**, *28*, 5363–5366; b) A. Gupta, A. Haque, Y. D. Vankar, *Chem. Commun.* **1996**, 1653–1654.

[4] S. Chandrasekhar, G. Chandrashekar, M. S. Reddy, P. Srihari, *Org. Biomol. Chem.* **2006**, *4*, 1650–1652.

[5] a) R. E. Harmon, J. L. Parsons, D. W. Cooke, S. K. Gupta, J. Schoolenberg, *J. Org. Chem.* **1969**, *34*, 3684–3685; b) A. Jourdant, E. González-Zamora, J. Zhu, *J. Org. Chem.* **2002**, *67*, 3163–3164.

[6] a) Amine-poisoned chemoselective hydrogenation: H. Sajiki, *Tetrahedron Lett.* **1995**, *36*, 3465–3468; b) H. Sajiki, K. Hirota, *Tetrahedron* **1998**, *54*, 13981–13996; c) H. Sajiki, H. Kuno, K. Hirota, *Tetrahedron Lett.* **1997**, *38*, 399–402; d) H. Sajiki, H. Kuno, K. Hirota, *Tetrahedron Lett.* **1998**, *39*, 7127–7130; e) sulfur-poisoned chemoselective hydrogenation: A. Mori, Y. Miyakawa, E. Ohashi, T. Haga, T. Maegawa, H. Sajiki, *Org. Lett.* **2006**, *8*, 3279–3281; f) A. Mori, T. Mizusaki, Y. Miyakawa, E. Ohashi, T. Haga, T. Maegawa, Y. Monguchi, H. Sajiki, *Tetrahedron* **2006**, *62*, 11925–11932.

[7] a) H. Sajiki, K. Hattori, K. Hirota, *J. Org. Chem.* **1998**, *63*, 7990–7992; b) K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron* **2000**, *56*, 8433–8441; c) H. Sajiki, K. Hattori, K. Hirota, *J. Chem. Soc. Perkin Trans. 1* **1998**, 4043–4044; d) K. Hattori, H. Sajiki, K. Hirota, *Chem. Commun.* **1998**, 1041–1042; e) K. Hattori, H. Sajiki, K. Hirota, *Chem. Eur. J.* **2000**, *6*, 2200–2204; f) K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron Lett.* **2000**, *41*, 5711–5714; g) T. Maegawa, Y. Fujita, A. Sakurai, A. Akashi, M. Sato, K. Oono, H. Sajiki, *Chem. Pharm. Bull.* **2007**, *55*, 837–839; h) K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron* **2001**, *57*, 2109–2114.

[8] H. Sajiki, S. Mori, T. Ohkubo, T. Ikawa, A. Kume, T. Maegawa, Y. Monguchi, *Chem. Eur. J.* **2008**, *14*, 5109–5111.

[9] A. Mori, T. Mizusaki, M. Kawase, T. Maegawa, Y. Monguchi, S. Takao, Y. Takagi, H. Sajiki, *Adv. Synth. Catal.* **2008**, *350*, 406–410.

[10] a) H. Sajiki, T. Ikawa, K. Hirota, *Tetrahedron Lett.* **2003**, *44*, 171–174; b) H. Sajiki, T. Ikawa, K. Hirota, *Tetrahedron Lett.* **2003**, *44*, 8437–8439; c) T. Ikawa, H. Sajiki, K. Hirota, *Tetrahedron* **2005**, *61*, 2217–2231; d) Y. Kitamura, A. Tanaka, M. Sato, K. Oono, K. , T. Ikawa, T. Maegawa, Y. Monguchi, H. Sajiki, *Synth. Commun.* **2007**, *37*, 4381–4388.

[11] For the review, see: S. E. Sen, S. M. Smith, K. A. Sullivan, *Tetrahedron* **1999**, *55*, 12657–12698, and references cited therein.

