

Novel Palladium-on-Carbon/Diphenyl Sulfide Complex for Chemoselective Hydrogenation: Preparation, Characterization, and Application

Akinori Mori,^a Tomoteru Mizusaki,^{a,b} Masami Kawase,^a Tomohiro Maegawa,^a Yasunari Monguchi,^a Shinobu Takao,^b Yukio Takagi,^b and Hironao Sajiki^{a,*}

^a Laboratory of Medicinal Chemistry, 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 N. E. Chemcat Corporation, 678 Ipponmatsu, Numazu, Shizuoka 410-0314, Japan

Received: December 7, 2007; Revised: December 28, 2007; Published online: February 5, 2008



Supporting information for this article is available on the WWW under <http://asc.wiley-vch.de/home/>.

Abstract: A diphenyl sulfide immobilized on palladium-on-carbon system, Pd/C[Ph₂S], was developed to achieve the highly chemoselective hydrogenation of alkenes, acetylenes, azides, and nitro groups in the presence of aromatic ketones, halides, benzyl esters, and N-Cbz protective groups. Instrumental analyses of the heterogeneous catalyst demonstrated that diphenyl sulfide was embedded on Pd/C *via* coordination of its sulfur atom to palladium metal or physical interaction with graphite layers of the activated carbon. The catalyst could be recovered and reused at least five times without any significant loss of the reactivity.

Keywords: chemoselectivity; diphenyl sulfide; heterogeneous catalysis; hydrogenation; palladium

The development of chemoselective transformations of functional groups has been of great importance in synthetic organic chemistry.^[1] Chemoselective hydrogenation, in particular, contributes to the synthesis of complicated natural products, pharmaceuticals, and functional materials.^[2] A number of selective hydrogenation methods has been reported that minimize undesired reductions, e.g., platinum metal sulfides^[3] and the ZnX₂-Pd/C or Pt/C systems^[4] have been applied to the selective hydrogenation of nitro groups in the presence of aromatic halides to obtain haloaniline derivatives. A recent study reported that a polymer-incarcerated platinum species worked for the selective reduction of olefins, acetylenes, and aromatic nitro groups while leaving benzyl ethers and aromatic halides untouched.^[5] Other methods for the chemoselective hydrogenation of aromatic nitro groups using va-

nadium-promoted Raney nickel,^[6] Ir/C-MgO,^[7] and Pt/Al₂O₃-P(OPh)₃^[7] were also reported to give aniline derivatives which bear aromatic chlorides and aromatic carbonyl groups. Semihydrogenations of acetylenes to olefins was also achieved by use of nickel^[8] or gold^[9] nanoparticles. However, only a few catalyst systems such as the Lindler and Rosenmund methods are practically useful.^[10] During the course of our study on the heterogeneous transition metal-catalyzed chemoselective hydrogenation during the past decade, we have established a chemoselective hydrogenation method using a nitrogen-containing base and Pd/C,^[11] which hydrogenates olefins, acetylenes, nitro groups and so on, while leaving benzyl ethers untouched. Recently, we reported that the addition of diphenyl sulfide (Ph₂S) to the Pd/C-catalyzed hydrogenation system achieved the chemoselective hydrogenation of olefin, acetylene and azide functionalities in the presence of other functional groups, such as aromatic carbonyls, and halides, benzyl esters, N-Cbz (benzyloxy-carbonyl) protecting groups and cyano groups.^[12] In spite of such unique chemoselectivities, this method requires the removal of Ph₂S from the reaction mixture using silica gel column chromatography. Therefore, the development of a Pd/C-Ph₂S complex, Pd/C[Ph₂S], by immobilization of Ph₂S onto Pd/C^[13] as a heterogeneous and chemoselective hydrogenation catalyst possessing a chemoselectivity similar to the addition of Ph₂S to the Pd/C-catalyzed hydrogenation system was strongly desired.

Detailed investigations of Ph₂S on Pd/C led us to establish the preparation method of the Pd/C-Ph₂S complex (Pd/C[Ph₂S]). A suspension of 10% Pd/C and Ph₂S (2.0 equiv. *vs.* Pd metal of Pd/C) in methanol was stirred for 5 days at room temperature under an argon atmosphere, and then the resulting black powder was collected by filtration, washed successive-

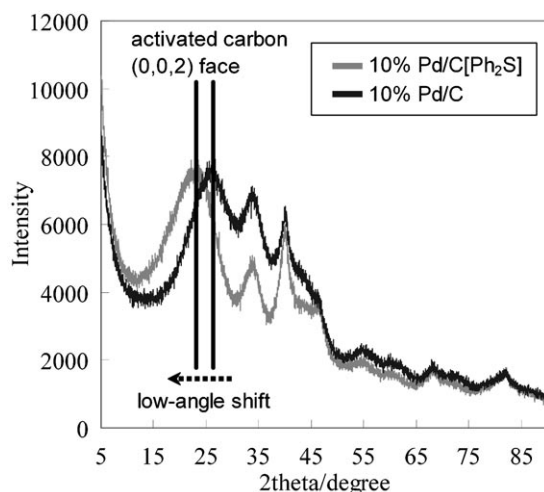


Figure 1. XRD analysis of Pd/C[Ph₂S].

ly with methanol and ether, and finally dried under reduced pressure to give a complex which consists of Pd/C and Ph₂S. The elemental analysis of the complex indicated that the ratio of Pd metal and Ph₂S was 1:1.27. As the result of the XRD (X-ray diffraction) analysis,^[14] it was observed that the (0,0,2) face of the activated carbon of this complex was shifted to a lower angle compared to that of commercial Pd/C (Figure 1). This result means that a certain amount of Ph₂S penetrates into the graphite layers of the activated carbon.^[15] Furthermore, EPMA (electron probe micro analyzer^[16]) data (Figure 2) showed that Ph₂S and the Pd metal are not necessarily evenly distributed on the carbon support.

The XPS (X-ray photoelectron spectroscopy) spectrum of Pd 3d of Pd/C[Ph₂S] indicates a certain and partial interaction of Ph₂S with the Pd metal. One of the binding energy peaks of the Pd metal of Pd/C[Ph₂S] was observed at 337.7 eV which is obviously higher than that of the Pd(0) standard (335.1–335.5 eV) (Figure 3),^[17] suggesting that the peak should be derived from the Pd–S complex, and a portion of the Pd metal is strongly bound to Ph₂S. Furthermore, a comparison of the effective Pd metal surface area,^[18] determined by measurement of the CO absorbability, between Pd/C and Pd/C[Ph₂S] indicated that 47% of the active sites on the Pd surface of Pd/C[Ph₂S] were covered by Ph₂S. These results indicated that about one-half of the fresh Pd(0) surface (active sites) of the original Pd/C still remained intact and the other half had interacted with Ph₂S by the Pd–S bond based upon the moderately-occluded sulfur lone pair. Therefore, Pd/C[Ph₂S] should possess a very weak catalyst activity and was expected to produce chemoselective hydrogenation among some reducible functionalities.

To explore the catalyst activity of Pd/C[Ph₂S], the hydrogenation of various substrates was carried out

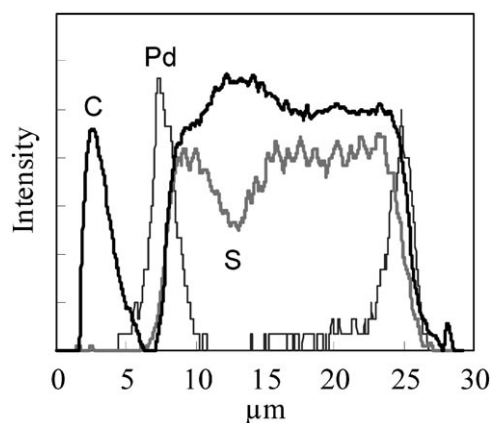


Figure 2. EPMA analysis of Pd/C[Ph₂S].

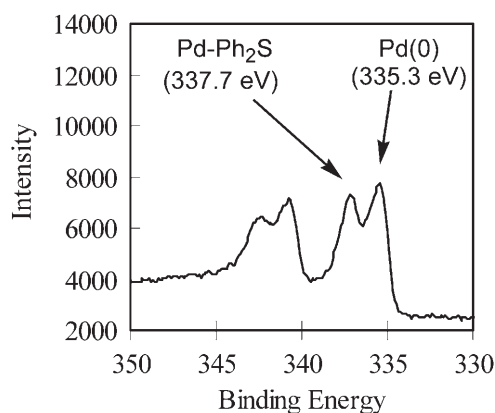


Figure 3. XPS analysis of Pd/C[Ph₂S].

(Table 1). Both olefin and acetylene functionalities were selectively hydrogenated without any reduction of the aromatic ketones by Pd/C[Ph₂S] (entries 1, 3–5), although aromatic ketones are very smoothly hydrogenolyzed to methylene compounds *via* the formation of the intermediary benzyl alcohols using commercial Pd/C as a catalyst (entry 2).^[13b,h] It is well known that aromatic chlorides are partially hydrogenated under the Pd/C-catalyzed hydrogenation conditions.^[2a] In contrast, Pd/C[Ph₂S] did not catalyze the hydrogenolysis of aromatic chlorides at all (entry 6), and the selective hydrogenation of olefins with retention of the aromatic chlorides was available (entries 7–9). Benzyl esters and N-Cbz protecting groups are widely used in organic synthesis as protecting groups,^[19] because of their easy introduction to carboxylic acids and amines, respectively, as well as easy deprotection using the Pd/C-catalyzed hydrogenation, therefore, it is extremely difficult to keep such groups intact during a synthetic process including the hydrogenation steps. If these protecting groups survive under the hydrogenation conditions, Pd/C[Ph₂S] would provide new applications. We then examined

Table 1. Chemoselective hydrogenation of olefin or acetylene in the presence of aromatic ketone using Pd/C[Ph₂S].^[a]

Substrate $\xrightarrow[\text{MeOH, 24 h}]{10\% \text{ Pd/C[Ph}_2\text{S] H}_2 \text{ (balloon)}}$ Product							
Entry	Substrate	Product	Yield [%] ^[b]	Entry	Substrate	Product	Yield [%] ^[b]
1			98	14			98
2 ^[c]			100	15			94
3			88	16			80
4			97	17			91
5			94	18			97
6		Recovery	99	19			91
7			100 ^[d]	20			97
8			100	21			91
9			99	22			91
10			100 ^[d]	23			91
11			100 ^[d]	24			99
12			99	25			95
13			99				

^[a] Unless otherwise noted, the reaction was carried out using 500 μmol of the substrate in MeOH (1.0 mL) with 10% Pd/C[Ph₂S] (10 wt% of the substrate) with vigorous stirring at room temperature (*ca.* 20°C) under ordinary hydrogen pressure (balloon) for 24 h.

^[b] Isolated yield.

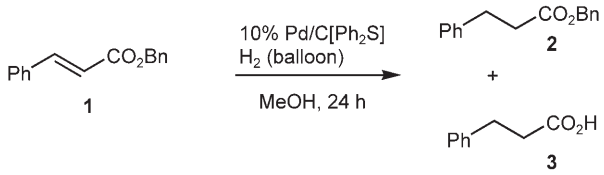
^[c] The reaction was carried out using 10% Pd/C (10 wt% of the substrate) instead of Pd/C[Ph₂S].

^[d] The reaction was carried out in CD₃OD (1.0 mL) and the yield was determined by ¹H NMR because of the low-boiling point property of the product.

the application of Pd/C[Ph₂S] to the chemoselective hydrogenation of olefin and acetylene functionalities in the presence of benzyl ester and N-Cbz protecting groups (entries 10–17). No hydrogenolysis of either the benzyl ester or N-Cbz protecting groups was observed during the smooth hydrogenation of olefin or acetylene moieties.^[20]

While nitro groups are easily reduced to amines under the Pd/C-catalyzed hydrogenation conditions,^[2a]

the addition of Ph₂S to the reaction led to an incomplete hydrogenation and produced a complex mixture,^[12] because hydroxylamine-accumulation followed by dimerization probably took place.^[6,7,21] On the other hand, Pd/C[Ph₂S] was able to be applied to the hydrogenation of the nitro groups without any side reaction. The desired amine was obtained in a nearly quantitative yield as the sole product (entries 18–21) with the coexisting aromatic carbonyl (en-

Table 2. Reuse test of Pd/C[Ph₂S].


Run	Ratio of 1:2:3	Yield of 2 ^[a]	Yield of Recovered Pd/C-[Ph ₂ S]
1	0:100:0	100	99
2	0:100:0	92	98
3	0:100:0	97	97
4	0:100:0	99	100
5	0:100:0	99	100

^[a] Isolated yield.

tries 18 and 21), aromatic chloride (entry 19) and benzyl ester (entry 20) functionalities intact. The hydrogenation of the azide moiety using Pd/C[Ph₂S] was also investigated (entries 22–25) and they were efficiently hydrogenated to the corresponding amines regardless of the electronic circumstances of the aromatic ring.

We next investigated the reusability of Pd/C[Ph₂S] in the chemoselective hydrogenation of benzyl cinnamate. Pd/C[Ph₂S] could be reused at least until the fifth run without significant loss of the selectivity and yield (Table 2).^[22]

In summary, we have developed a novel and isolable diphenyl sulfide-supported Pd/C catalyst (Pd/C[Ph₂S]) possessing an excellent chemoselectivity toward hydrogenation; olefin, acetylene, nitro, and azide functionalities were smoothly hydrogenated, while aromatic carbonyl and halide, benzyl ester and N-Cbz functionalities were not. Such an efficient expression of the chemoselectivity has its roots in the catalyst properties based upon the reasonable and partial interaction with Ph₂S on the active sites of the Pd surface (Pd–S bonding). These findings reinforce the versatility of such reducible functionalities in synthetic chemistry, and the Pd/C[Ph₂S] catalyst has been recognized as a chemoselective and convenient catalyst for hydrogenation.

Experimental Section

Preparation of Pd/C[Ph₂S]

A suspension of 532 mg of 10% Pd/C and Ph₂S (166 μ L, 2.00 equiv. vs. Pd metal of Pd/C) in MeOH (5 mL) was stirred for 5 days at room temperature under an argon atmosphere, and then the resulting solid was collected on filter paper, washed successively with methanol (10 mL $\times$ 2) and ether (10 mL $\times$ 2), and then dried under reduced pressure for 24 h to give Pd/C[Ph₂S]. The Pd/C[Ph₂S] could be

stored in a regular reagent bottle at room temperature without any special handling and alternation of the catalyst activity.

General Procedure for the Chemoselective Hydrogenation using Pd/C[Ph₂S]

A substrate (0.50 mmol), Pd/C[Ph₂S] (10 wt% of the substrate), and MeOH (1 mL) were added to a test tube containing a stir bar and sealed with a septum. After two vacuum/H₂ cycles to replace the air inside with hydrogen, the mixture was vigorously stirred at room temperature under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex[®]-LH, 0.45 μ m) and the filtrate was concentrated under vacuum to provide the pure product without further purification.

References

- [1] R. C. Larock, *Comprehensive Organic Transformations*, 2nd edn., Wiley VCH: New York, **1999**.
- [2] a) S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, Wiley-Interscience: New York, **2001**; b) M. Hudlicky, *Reductions in Organic Chemistry*, 2nd edn., ACS, Washington, DC, **1996**; c) P. N. Rylander, *Hydrogenation Methods*, Academic Press, New York, **1985**.
- [3] S. F. Dovell, H. Greenfield, *J. Am. Chem. Soc.* **1965**, *87*, 2767–2768.
- [4] G. Wu, M. Huang, M. Richards, M. Poirier, X. Wen, R. W. Draper, *Synthesis* **2003**, 1657–1660.
- [5] Y. Miyazaki, H. Hagio, S. Kobayashi, *Org. Biomol. Chem.* **2006**, *4*, 2529–2531.
- [6] M. Studer, S. Neto, H.-U. Blaser, *Topics in Catalysis* **2000**, *13*, 205–212.
- [7] M. Hoogenraad, J. B. van der Linden, A. A. Smith, *Org. Process Res. Dev.* **2004**, *8*, 469–476.
- [8] Benzyl ether could survive in the semihydrogenation conditions using nickel nanoparticles, see F. Alonso, I. Osante, M. Yus, *Tetrahedron* **2007**, *63*, 93–102.
- [9] Y. Segura, N. López, J. Pérez-Ramírez, *J. Catal.* **2007**, *247*, 383–386.
- [10] a) H. Lindlar, *Helv. Chim. Acta* **1952**, *35*, 446–450; b) H. Lindlar, R. Dubuis, *Org. Synth. Coll. Vol.* **5**, **1973**, 880–882; c) K. W. Rosenmund, *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 585–594; d) K. Rosenmund, F. Zetsche, *Ber. Dtsch. Chem. Ges.* **1921**, *54B*, 425–437.
- [11] a) H. Sajiki, *Tetrahedron Lett.* **1995**, *36*, 3465–3468; b) H. Sajiki, H. Kuno, K. Hirota, *Tetrahedron Lett.* **1997**, *38*, 399–402; c) H. Sajiki, H. Kuno, K. Hirota, *Tetrahedron Lett.* **1998**, *39*, 7127–7130; d) H. Sajiki, K. Hirota, *Tetrahedron* **1998**, *54*, 13981–13996; e) H. Sajiki, *Yakugaku Zasshi* **2000**, *120*, 1091–1103; f) H. Sajiki, K. Hirota, *Chem. Pharm. Bull.* **2003**, *51*, 320–324.
- [12] a) A. Mori, Y. Miyakawa, E. Ohashi, T. Haga, T. Maegawa, H. Sajiki, *Org. Lett.* **2006**, *8*, 3279–3281; b) A. Mori, T. Mizusaki, Y. Miyakawa, E. Ohashi, T. Haga, T. Maegawa, Y. Monguchi, H. Sajiki, *Tetrahedron* **2006**, *62*, 11925–11932.

- [13] We have developed a Pd/C-ethylenediamine complex [Pd/C(en)] as a chemoselective hydrogenation catalyst by immobilization of ethylenediamine to Pd/C; a) H. Sajiki, K. Hattori, K. Hirota, *J. Org. Chem.* **1998**, *63*, 7990–7992; b) H. Sajiki, K. Hattori, K. Hirota, *J. Chem. Soc., Perkin Trans. 1* **1998**, 4043–4044; c) H. Sajiki, K. Hattori, K. Hirota, *Chem. Commun.* **1999**, 1041–1042; d) K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron Lett.* **2000**, *41*, 5711–5714; e) H. Sajiki, K. Hattori, K. Hirota, *Chem. Eur. J.* **2000**, *6*, 2200–2204; f) K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron* **2000**, *56*, 8433–8441; g) K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron* **2001**, *57*, 2109–2114; h) K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron* **2001**, *57*, 4817–4824; i) H. Sajiki, K. Hirota, *J. Org. Synth. Chem. Jpn.* **2001**, *59*, 109–120.
- [14] G. Fagherazzi, P. Canton, P. Riello, F. Pinna, N. Pernicone, *Catal. Lett.* **2000**, *64*, 119–124.
- [15] a) B. E. Warren, *Phys. Rev.* **1941**, *59*, 693–698; b) T. Suzuki, K. Kaneko, *Carbon* **1988**, *26*, 743–745; c) F. Rodriguez-Reinoso, J. M. Martin-Martinez, C. Prado-Burguete, B. McEnaney, *J. Phys. Chem.* **1987**, *91*, 515–516.
- [16] X. Z. Li, Y. Deng, Y. J. Yan, H. F. Huang, W. Z. Yu, C. X. Li, *J. New Energy* **2001**, *6*, 80–86.
- [17] W. F. Maier, S. J. Chettle, R. S. Rai, G. Thomas, *J. Am. Chem. Soc.* **1986**, *108*, 2608–2616.
- [18] The effective Pd metal surface area was measured by a CO pulse adsorption method using a thermal conductivity detector.
- [19] P. G. M. Wuts, T. W. Greene, *Greene's Protective Groups in Organic Synthesis* 4th edn., Wiley-Interscience: New Jersey, **2007**.
- [20] Recently, we reported the Pd-Fibroin complex (Pd/Fib) catalyzed chemoselective hydrogenation method of C–C and N–N multiple bonds in the presence of reducible functionalities, e.g., benzyl esters and N-Cbz protective groups, although the use of a suppressive solvent for the Pd/Fib-catalyzed hydrogenation, such as THF, AcOH, or CH₂Cl₂, is necessary to obtain a satisfactory selectivity, see: T. Ikawa, H. Sajiki, K. Hirota, *Tetrahedron* **2005**, *61*, 2217–2231.
- [21] For the vanadium-promoted hydrogenation of the nitro groups: P. Baumeister, H.-U. Blaser, M. Studer, *Catal. Lett.* **1997**, *49*, 219–222.
- [22] Leached palladium and sulfur were not detected (below measurable limits: <1 ppm for Pd and <20 ppm for sulfur) after the 2nd run of the reuse test. See the Supporting Information.