Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 62 (2006) 11925–11932
Tetrahedron

Chemoselective hydrogenation method catalyzed by Pd/C using diphenylsulfide as a reasonable catalyst poison

Akinori Mori, Tomoteru Mizusaki, Yumi Miyakawa, Eri Ohashi, Tomoko Haga, Tomohiro Maegawa, Yasunari Monguchi and Hironao Sajiki*

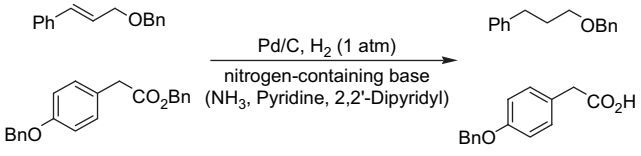
Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502-8585, Japan

Received 30 August 2006; accepted 21 September 2006
Available online 27 October 2006

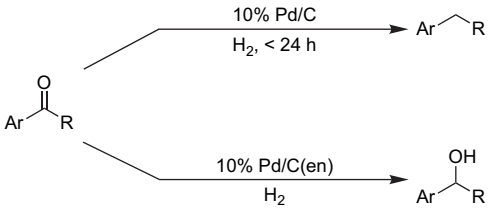
Abstract—While Pd/C is one of the most useful catalysts for hydrogenation, the high catalyst activity of Pd/C causes difficulty in its application to chemoselective hydrogenation between different types of reducible functionalities. In order to achieve chemoselective hydrogenation using Pd/C, we investigated catalyst poison as a controller of the catalyst activity. We found that the addition of Ph_2S (diphenylsulfide) to the Pd/C-catalyzed hydrogenation reaction mixture led to reasonable deactivation of Pd/C. By the use of the Pd/C–Ph_2S catalytic system, olefins, acetylenes, and azides can be selectively reduced in the coexistence of aromatic carbonyls, aromatic halides, cyano groups, benzyl esters, and *N*-Cbz (benzyloxycarbonyl) protecting groups. The present method is promising as a general and practical chemoselective hydrogenation process in synthetic organic chemistry.

1. Introduction

Palladium on activated carbon (Pd/C) is extensively used as a heterogeneous catalyst for hydrogenation in synthetic organic chemistry because of its high catalyst activity, cost-efficiency, easy separation from the reaction mixture, and reusability.[1] However, Pd/C is too active to catalyze selective hydrogenation among the different types of reducible functionalities. Deactivator of the catalyst is recognized as a catalyst poison and it is reported that the deactivation effect depends on the kind or/and amount of the catalyst poison.[1b] Therefore, an appropriate use of the catalyst poison in Pd/C-catalyzed hydrogenation could control the catalyst activity leading to chemoselective hydrogenation.[1] We have reported a method of chemoselective hydrogenation of olefin or benzyl ester functionalities without deprotection of the *O*-benzyl protecting groups by the addition of nitrogenous catalyst poisons such as NH_3, pyridine, or 2,2′-dipyridyl (Scheme 1).[2] We also developed a carbon-supported Pd-ethylenediamine complex [Pd/C(en)],[3] and in the hydrogenation of aromatic ketones using Pd/C(en), a selective partial reduction was achieved to afford the corresponding benzyl alcohol without hydrogenolysis, although Pd/C-catalyzed hydrogenation removed the carbonyl oxygen from the aromatic ketone derivatives (Scheme 2).[3]



Scheme 1.



Scheme 2.

In order to establish a catalytic hydrogenation system possessing a distinct chemoselectivity, we focused on sulfur-containing compounds with the expectation that they should work more effectively as catalyst poisons than nitrogenous compounds. Sulfur-containing catalyst poisons have been reported: quinoline-S is used for Rosenmund reduction in order to avoid the over-reduction of aldehydes to the corresponding alcohols;[4] thiophene or butylmercaptan is used for the selective reduction of olefin tolerating *O*-benzyl protecting groups;[5] platinum sulfide (PtS) catalyzes the conversion from halonitrobenzenes to haloanilines without dehalogenation.[6] During our effort to establish a chemoselective hydrogenation method using Pd/C by the addition of sulfur-containing compounds, we found that the addition

* Corresponding author. Tel.: +81 58 237 3931; fax: +81 58 237 5979; e-mail: sajiki@gifu-pu.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.09.094

of diphenylsulfide (Ph_2S) moderately depressed the catalyst activity of Pd/C to acquire distinguishing chemoselectivity on hydrogenation.[7] In this paper, we describe detailed results and discussion about the scope of the chemoselective hydrogenation using the Pd/C–Ph_2S system.

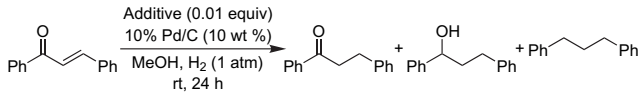
2. Results and discussion

We initially examined the suppressing effect of sulfuric catalyst poisons on the Pd/C-catalyzed hydrogenolysis of chalcone (**1a**) possessing an aromatic ketone and an olefin functionality within the molecule (Table 1). Both olefin and aromatic ketone of **1a** were readily reduced under the Pd/C-catalyzed hydrogenation conditions without any catalyst poison (entry 1); 0.01 equiv of diphenyldisulfide (Ph_2S_2) and thiophenol (PhSH) deactivated the Pd/C completely and no reaction took place (entries 2 and 3). Pd/C-catalyzed hydrogenation with 0.01 equiv of diphenylsulfide (Ph_2S) is the best combination for the chemoselective hydrogenation between olefin and aromatic ketone (entry 5): olefin was reduced to alkane without the reduction of the ketone. The olefin moiety was successfully reducing even with increased amount (to 0.1 equiv) of Ph_2S (entry 6). Unfavorable formation of **3a** was detected, when the amount of Ph_2S was reduced to 0.001 equiv (entry 4). In contrast, diphenylsulfone (Ph_2SO_2) and diphenylsulfoxide (Ph_2SO) were inadequate to inhibit the over-reduction of aromatic ketone to **3a** (entries 7 and 8). Next, we assessed the addition effect of aliphatic sulfur-containing compounds. While the addition of alkyl thiols to the reaction mixture brought about strong inhibition of the reaction of **1a** (entries 9–11), thioether, 2-(methylthio)ethanamine, exerted a milder effect to give **3a** exclusively (entry 12). Dimethylsulfide (Me_2S), dimethylsulfoxide (Me_2SO), and dimethylsulfone (Me_2SO_2) were not effective to achieve the chemoselectivity to **2a** (entries 13–15). Compared with the results in entries 5 and 13, the benzene ring is likely to play an important role as well as the sulfur atom to attain the desired chemoselectivity. The benzene rings of Ph_2S may be able to coordinate with Pd metal in a similar manner to that of a Pd-π-aryl complex or adsorb to the hydrophobic charcoal of Pd/C, leading to the stronger poisoning effect of Pd/C. Eventually, we chose the catalytic amount (0.01 equiv toward the substrate) of Ph_2S as the optimum additive for chemoselective hydrogenation because of its moderate strength as a catalyst poison, cost-efficiency, and odorless nature.

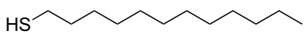
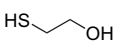
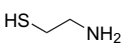
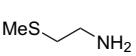
Next, we investigated the chemoselectivity in the hydrogenation of carbonyl compounds containing an alkene or alkyne moiety under our optimal conditions (Table 2). The carbonyl moiety was not reduced in all cases, while the alkene or alkyne moiety within the molecule was smoothly hydrogenated (entries 1–5).

We attempted to apply the reaction conditions to an alkene possessing an aromatic aldehyde in the molecule (Scheme 3). Contrary to our expectation, it was difficult to block the hydrogenation of the aromatic aldehyde to the corresponding benzyl alcohol under the same conditions due to the high reactivity of aromatic aldehyde toward the hydrogenation.

Table 1. Assessment of additives for chemoselective hydrogenation between olefin and aromatic ketone using chalcone (**1a**) as a substrate

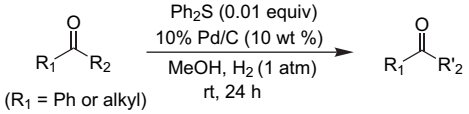


1a **2a** **3a** **4a**

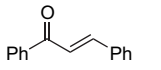
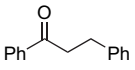
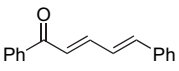
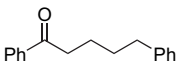
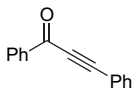
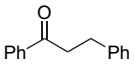
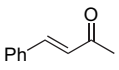
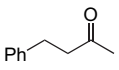
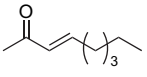
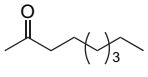
Entry	Additive	**1a**:**2a**:**3a**:**4a**[a]
1	None	0:0:0:100
2	Ph_2S_2	100:0:0:0
3	PhSH	100:0:0:0
4	Ph_2S (0.001 equiv)	0:94:6:0
5	*Ph_2S*	*0:100:0:0*
6	Ph_2S (0.1 equiv)	0:100:0:0
7	Ph_2SO	0:93:7:0
8	Ph_2SO_2	0:0:100:0
9		77:23:0:0
10		100:0:0:0
11		100:0:0:0
12		0:100:0:0
13	Me_2S	0:42:58:0
14	Me_2SO	0:0:100:0
15	Me_2SO_2	0:0:48:52

[a] The ratio was determined based on ^1H NMR analysis.

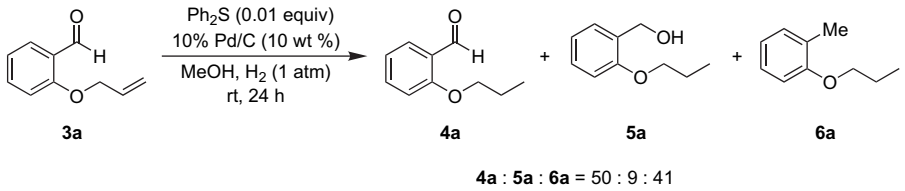
Table 2. Selective hydrogenation of olefin in the presence of aromatic or aliphatic ketone



(R_1 = Ph or alkyl)

Entry	Substrate	Product	Yield (%)
1	 **1a**	 **2a**	quant
2	 **1b**	 **2b**	99
3	 **1c**	 **2a**	quant
4	 **1d**	 **2d**	84[a]
5	 **1e**	 **2e**	68[b]

[a] The reaction was completed within 13 h.
[b] The reaction was completed within 1.5 h. The low isolated yield of **2e** was due to the volatile nature.



Scheme 3. First attempt for chemoselective hydrogenation of olefin in the presence of aromatic aldehyde.

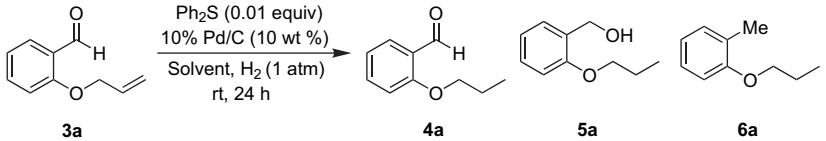
We have reported that the choice of solvent was an important factor to control the chemoselective suppression of epoxides[3c,e] or silyl ethers[8] under the hydrogenation conditions. In the former case, use of THF instead of MeOH as a solvent achieved the Pd/C(en)-catalyzed chemoselective hydrogenation of olefin, nitro, and azide moieties with retention of the epoxide functions. In the latter case, TBDMS (*tert*-butyldimethylsilyl) and TES (triethylsilyl) ethers were cleanly deprotected in MeOH under the Pd/C-catalyzed hydrogenation conditions, while neither TBDMS nor TES ether was cleaved in AcOEt (ethyl acetate) or MeCN (acetonitrile), respectively. With an expectation of complete suppression of the reduction of the aromatic aldehydes, hydrogenolysis of **3a** in a variety of solvents was investigated (Table 3). The hydrogenation of the aldehyde moiety of **3a** proceeded in MeOH (Scheme 3 and Table 3, entry 1), whereas the aldehyde moiety survived completely in THF, AcOEt, MeCN, or 1,4-dioxane (entries 2–5). These solvents made the chemoselective reduction of **3a** possible between the alkene moiety and the aldehyde moiety, because such solvent may be able to coordinate to Pd/C and further reduce the catalyst activity.

The results of the hydrogenation of a variety of aromatic aldehydes in AcOEt are summarized in Table 4. Aromatic aldehydes with an electron-donating group on the benzene ring never hydrogenate (entries 1–3) and a coexisting olefin in the molecule was selectively hydrogenated to the corresponding alkane (entries 2 and 3). Aryl aldehydes bearing an electron-withdrawing group on the benzene ring did also not undergo the reduction under these reaction conditions (entries 4–7).

We next investigated the selectivity of the hydrogenation between olefin and aromatic halide moieties (Table 5). A selective hydrogenation method without hydrogenolysis of aromatic halides could be useful for synthetic organic chemistry. Complete inhibition of the hydrogenolysis of aromatic chlorides using our chemoselective hydrogenation method was achieved (entry 1) and the olefin moiety was hydrogenated smoothly and selectively without dechlorination (entries 2–5). However, the addition of 0.01 equiv of Ph_2S was insufficient to prevent debromination and an increase in the amount of Ph_2S was required (entries 6 and 7). With use of 0.1 equiv of Ph_2S, the olefin moiety was selectively hydrogenated without debromination of the corresponding aromatic bromide (entry 8). In the case of the aromatic iodide as a substrate, no deiodination was also observed (entry 9). These results show that our hydrogenation conditions using Ph_2S are useful in the selective hydrogenation of olefins without the reduction of aromatic halides.

Benzyl ester and *N*-Cbz (benzyloxycarbonyl) protecting groups are widely used due to their easy deprotectable nature.[9] However, the selective hydrogenation of other reducible functionalities without deprotection of benzyl ester or *N*-Cbz protective group is very difficult to attain at a practically useful level. Only a few methods are known in the literature. Zappia et al. reported that use of 3% Pd/C in AcOEt led to the selective hydrogenation of olefin leaving the benzyl ester or *N*-Cbz protective group intact, but these protective groups were time-dependently taken off under their conditions.[10] We also reported that *aliphatic N*-Cbz protective groups were not cleaved by hydrogenolysis using Pd/C(en) as a catalyst, while *aromatic N*-Cbz protective groups could not survive under the same conditions;[3a,f,i] Pd/Fib could also hydrogenate the olefin moiety selectively without the deprotection of both benzyl ester and the *N*-Cbz protective group in THF.[11] We attempted to apply the present Pd/C–Ph_2S system to the selective hydrogenation of olefin in the presence of benzyl ester or the *N*-Cbz protective group (Table 6). The selective hydrogenation of olefin was achieved without hydrogenolysis of the coexisting benzyl ester (entries 1–5). Both aliphatic and aromatic *N*-Cbz

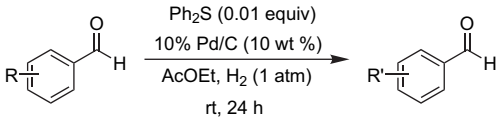
Table 3. Solvent effect on the hydrogenation of an aromatic aldehyde

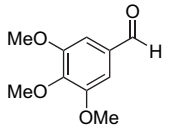
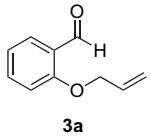
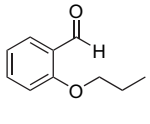
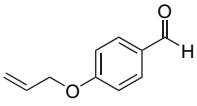
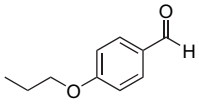
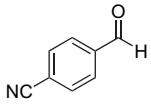
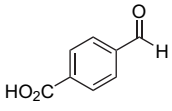
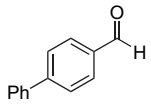
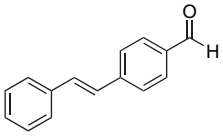
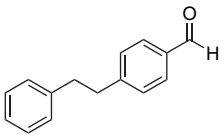


Entry	Solvent	**3a**:**4a**:**5a**:**6a**[a]
1	MeOH	0:50:9:41
2	THF	0:100:0:0
3	AcOEt	0:100:0:0
4	MeCN	0:100:0:0
5	1,4-Dioxane	0:100:0:0

[a] The ratio was determined based on ^{1}H NMR analysis.

Table 4. Suppression of the hydrogenation of aromatic aldehyde and selective hydrogenation of olefin in the presence of aromatic aldehyde



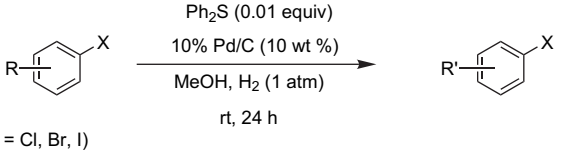
Entry	Substrate	Product	Yield (%)[a]
1	 **3c**	Recovery	99[b]
2	 **3a**	 **4a**	91
3	 **3d**	 **4d**	95
4	 **3e**	Recovery	92[b,c]
5	 **3f**	Recovery	96[b]
6	 **3g**	Recovery	94[b,c]
7	 **3h**	 **4h**	93[b,d]

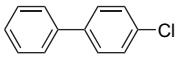
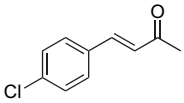
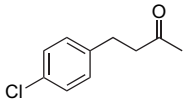
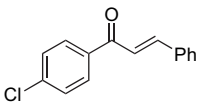
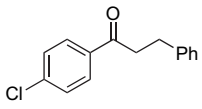
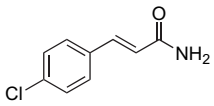
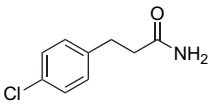
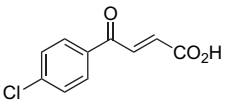
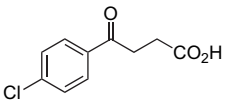
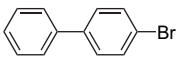
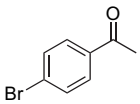
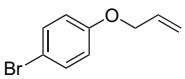
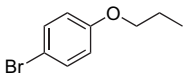
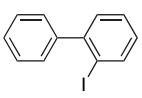
[a] Isolated yield.
[b] Isolated yield of the recovered substrate.
[c] MeCN was used as a solvent.
[d] Small amount of intractable material contained.

protective groups were stable under the hydrogenation conditions (entries 6–8). Our method is proved to be useful for the selective hydrogenation of the alkene moiety in the presence of benzyl ester or the *N*-Cbz protective group.

Aromatic cyano groups are also known as a reducible functionality under Pd/C-catalyzed hydrogenation conditions. We examined if a cyano group could undergo the reduction under our conditions (Table 7). The hydrogenation of an

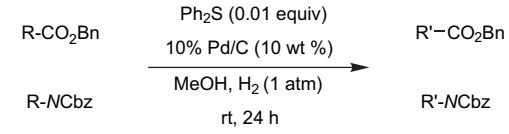
Table 5. Suppression of the hydrogenation of aromatic halide and selective hydrogenation of olefin in the presence of aromatic halide

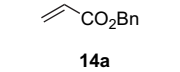
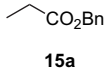
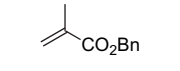
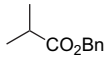
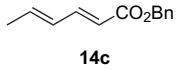
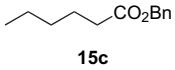
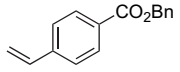
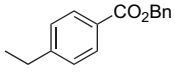
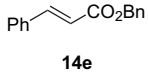
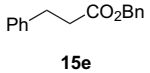
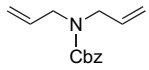
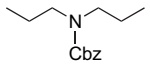
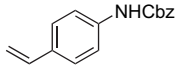
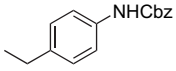
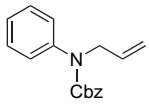
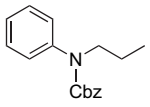


Entry	Substrate	Product	Yield (%)[a]
1	 **9a**	No reaction	75[b]
2	 **9b**	 **10b**	98
3	 **9c**	 **10c**	97
4	 **9d**	 **10d**	90[c]
5	 **9e**	 **10e**	99
6	 **11a**	No reaction	>99[d,e]
7	 **11b**	No reaction	82[b,d]
8	 **11c**	 **12c**	>99[e,f]
9	 **13a**	No reaction	96[b]

[a] Isolated yield.
[b] Isolated yield of the recovered substrate.
[c] The yield was determined based on ^{1}H NMR analysis.
[d] Ph_2S (0.5 equiv) was used.
[e] Determined by GC–MS analysis. A trace of debromination was detected.
[f] Ph_2S (0.1 equiv) was used.

Table 6. Selective hydrogenation of olefin in the presence of benzyl ester or *N*-Cbz protective group



Entry	Substrate	Product	Yield (%)[a]
1	 **14a**	 **15a**	100[b]
2	 **14b**	 **15b**	100[b]
3	 **14c**	 **15c**	quant
4	 **14d**	 **15d**	95
5	 **14e**	 **15e**	94
6	 **16a**	 **17a**	quant
7	 **16b**	 **17b**	98
8	 **16c**	 **17c**	99

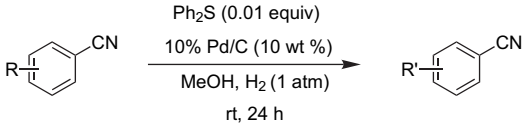
[a] Isolated yield.
[b] The yield was determined based on ^{1}H NMR analysis.

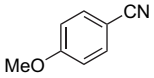
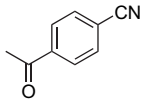
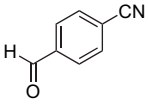
aromatic cyano group did not proceed, regardless of whether the benzene ring was substituted with an electron-donating group or an electron-withdrawing group (entries 1–3).

Next, we investigated the catalyst poison effect of Ph_2S toward an azide functionality (Table 8). The addition of Ph_2S to the reaction mixture did not affect the reduction of azide and the corresponding amine was obtained quantitatively (entries 1 and 2).

Several methods for the selective reduction of the nitro group in the presence of other functionalities such as aromatic carbonyls, aromatic halides, and nitriles have been also reported.[6,12] Application of the present method to nitro compounds was attempted (Table 9). The hydrogenation of **21a** was not complete, but led to the formation of a complex mixture (entry 1). As shown in entries 2 and 3, the hydrogenation of nitro compounds substituted with either an electron-donating (**21b**) or electron-withdrawing group (**21c**) on the benzene ring resulted in incompletion. Hence,

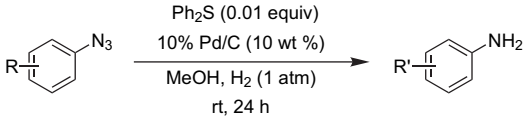
Table 7. Suppression on the hydrogenation of aromatic cyano group

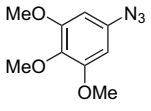
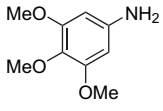
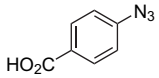
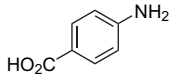


Entry	Substrate	Result
1	 **18a**	Recovery of substrate, 100%[a]
2	 **18b**	Recovery of substrate, 100%[a]
3	 **3e**	Recovery of substrate, 94%[b,c]

[a] Determined by ^{1}H NMR.
[b] Isolated yield of the recovered substrate.
[c] MeCN was used as a solvent.

Table 8. Pd/C–Ph_2S catalyzed hydrogenation of azide



Entry	Substrate	Product	Yield (%)[a]
1	 **19a**	 **20a**	quant
2	 **19b**	 **20b**	quant

[a] Isolated yield.

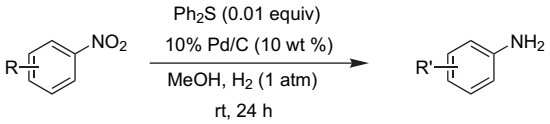
currently it seems difficult to achieve good selectivity in the hydrogenation of nitro groups.

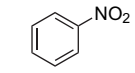
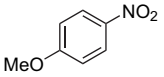
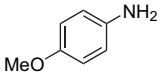
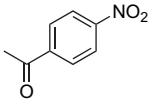
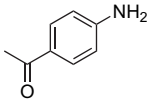
We investigated the reusability of the catalyst without further addition of Ph_2S using benzyl cinnamate (**14e**) as a substrate (Table 10). The hydrogenation using fresh Pd/C and Ph_2S proceeded selectively (Table 6, entry 5 and Table 10, entry 1). The activity of the recycled Pd/C was notably decreased and the reduction of the olefin moiety was even incomplete (entries 2 and 3). These results suggest that recycling the Pd/C used for the hydrogenation seems difficult.

3. Conclusion

During the investigation of the influence of sulfur-containing catalyst poison toward Pd/C in hydrogenation, we found that

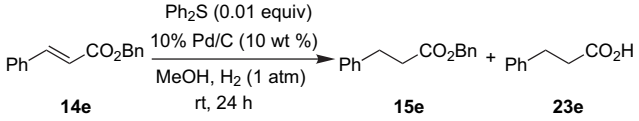
Table 9. Attempt on the Pd/C–Ph_2S catalyzed hydrogenation of nitro compound



Entry	Substrate	Result	Yield (%)[a]
1	 **21a**	Complex mixture[b]	—
2	 **21b**	 **22b**	67[c]
3	 **21c**	 **22c**	53[d]

[a] The yield was determined based on ^{1}H NMR analysis.
[b] Nitro, amine, and diazo compounds were observed by ^{1}H NMR.
[c] Thirty-three percent of the substrate remained intact.
[d] Forty-seven percent of the substrate remained intact.

Table 10. Reuse of Pd/C



Entry	Reuse	**14e**:**15e**:**23e**[a]
1	—	0:100:0
2	First	8:92:0
3	Second	80:20:0

[a] The ratio was determined based on ^{1}H NMR analysis.

Ph_2S was an appropriate catalyst poison to degrade the activity of Pd/C moderately and developed a chemoselective hydrogenation method using the combination of Pd/C and Ph_2S. The addition of only a catalytic amount (0.01–0.1 equiv) of Ph_2S to Pd/C-catalyzed hydrogenation mixtures led to the complete chemoselective hydrogenation of olefin and azide functionalities in the presence of other reducible functional groups, such as aromatic carbonyl, aromatic halide, aromatic cyano group, benzyl ester, and *N*-Cbz protective group. The other distinctive features of this method are the non-use of expensive reagents and the simple and virtually odorless operation. The present chemoselective hydrogenation method should be practically useful in synthetic organic, medicinal, and process chemistry fields.

4. Experimental

4.1. General

Pd/C (10%) was purchased from Aldrich (catalog no. 205699). MeOH and AcOEt for HPLC, dehydrated THF, and dehydrated DMF were purchased from Wako Pure Chemical Industries, Ltd. and used without purification. CH_2Cl_2 was distilled from calcium hydride. All other reagents were purchased from commercial sources and used without further purification. Flash column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM), or Kanto Chemical Co., Inc. 60N (63–210 μm spherical, neutral). ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL AL 400 spectrometer or JEOL EX 400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts (δ) are expressed in parts per million and are internally referenced (0.00 ppm for TMS for $CDCl_3$ for ^{1}H NMR and 77.0 ppm for $CDCl_3$ for ^{13}C NMR). EI and FAB mass spectra were taken on a JEOL JMS-SX102A instrument.

4.2. Synthesis of the substrate

4.2.1. 1-Bromo-4-(2-propenyloxy)benzene (11c).[13] To a solution of 4-bromophenol (1.73 g, 10.0 mmol) and potassium carbonate (1.52 g, 11.0 mmol) in acetone (10.0 mL) was added allylbromide (0.96 mL, 11.0 mmol) and refluxed for 8 h. Et_2O (30 mL) and water (30 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (30 mL) and the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford **11c** in 93% yield (1.98 g) as a colorless oil. ^{1}H NMR spectrum of **11c** was identical to that in the literature.[14]

4.2.2. Synthesis of benzyl ester.[11c] To a solution of carboxylic acid (10.0 mmol), EDC·HCl (2.30 g, 12.0 mmol), and DMAP (122 mg, 1.00 mmol) in CH_2Cl_2 (15 mL) was added benzyl alcohol (1.04 g, 10.0 mmol). After a certain reaction time, chloroform (50 mL) and water (50 mL) were added and the layers were separated. The aqueous layer was extracted with chloroform (50 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford **14c** or **14d**.

4.2.2.1. (2*E*,4*E*)-Benzyl hexa-2,4-dienoate (14c). Obtained from sorbic acid (1.12 g, 10.0 mmol), EDC·HCl (1.92 g, 10.0 mmol), DMAP (122 mg, 1.00 mmol), and benzyl alcohol (1.04 mL, 10.0 mmol) according to the general procedure for the synthesis of the substrate (Section 4.2.2) after 48 h of the reaction followed by flash column chromatography on silica gel (*n*-hexane) in 90% yield (1.82 g) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.38–7.26 (m, 6H), 6.20–6.15 (m, 2H), 5.82 (d, 1H, J=15.9 Hz), 5.19 (s, 2H), 1.85 (d, 3H, J=5.6 Hz); MS (EI) *m*/*z* 202 (M^+, 15), 157 (25), 91 (100); HRMS (EI) Calcd for $C_{13}H_{14}O_2$ (M^+): 202.0994. Found: 202.0985.

4.2.2.2. Benzyl vinylbenzoate (14d).[11c] Obtained from 4-vinylbenzoic acid (500 mg, 3.37 mmol), EDC·HCl (959 mg, 5.00 mmol), DMAP (61.1 mg, 0.500 mmol), and benzyl alcohol (0.350 mL, 3.38 mmol) according to the general procedure for the synthesis of the substrate (Section 4.2.2) after 43 h of the reaction followed by flash column chromatography on silica gel (*n*-hexane→*n*-hexane/Et_2O=

4/1) in 92% yield (737 mg) as a colorless oil. ^{1}H NMR spectrum of **14d** was identical to that in the literature.[11c]

4.2.3. Synthesis of *N*-Cbz protecting group.[11c] To a solution of the amine (5.00 mmol) in THF was added *N*-(benzyloxycarbonyloxy)succinimide (1.45 g, 6.00 mmol). After a certain reaction time, AcOEt (150 mL) and water (100 mL) were added and the layers were separated. The organic layer was washed successively with water (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. If necessary, the residue was applied to flash column chromatography on silica gel to afford **15a**–**15c**.

4.2.3.1. Benzyl diallylcarbamate (16a).[11c] Obtained from diallylamine (1.23 mL, 10.0 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (2.91 g, 12.0 mmol) according to the general procedure for the synthesis of the substrate (Section 4.2.3) after 67 h of the reaction followed by flash column chromatography on silica gel (*n*-hexane) in 97% yield (2.24 g) as a colorless oil. ^{1}H NMR spectrum of **16a** was identical to that in the literature.[11c]

4.2.3.2. Benzyl 4-vinylphenylcarbamate (16b).[11c] Obtained from 4-vinylaniline (1.00 g, 8.39 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (2.45 g, 10.1 mmol) according to the general procedure for the synthesis of the substrate (Section 4.2.3) after 7 h of the reaction without any purification in 92% yield (1.99 g) as a pale yellow solid. ^{1}H NMR spectrum of **16b** was identical with that in the literature.[11c]

4.2.3.3. Benzyl allylphenylcarbamate (16c).[11c] Obtained from *N*-allylaniline (1.33 g, 10.0 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (2.91 g, 12.0 mmol) according to the general procedure for the synthesis of the substrate (Section 4.2.3) after 7 h of the reaction followed by flash column chromatography on silica gel (*n*-hexane) in 81% yield (2.18 g) as a colorless oil. ^{1}H NMR spectrum of **16c** was identical with that in the literature.[11c]

4.2.3.4. 5-Azide-1,2,3-trimethoxybenzene (19a).[15] To a solution of 3,4,5-trimethoxyaniline (916 mg, 5.00 mmol) and concentrated hydrochloric acid (11.3 mL) in water (20 mL) was added dropwise a solution of sodium nitrite (362 mg, 5.20 mmol) in water (12.5 mL) at 0–5 °C and the mixture was stirred at 0–5 °C. After 1 h, the mixture was filtered and the filtrate was added to a solution of sodium azide (325 g, 12.5 mmol) in water (12.5 mL) and stirred for 6 h. The mixture was filtered to afford **19a** in 76% yield (795 mg) as a pale yellow solid. ^{1}H NMR spectrum of **19a** was identical with that in the literature.[16]

4.3. Optimization of the reaction conditions (Table 1)

Compound **1a** (208 mg, 1.00 mmol), 10% Pd/C (20.8 mg, 10 wt % of **1a**), an additive (0.01 mmol), and MeOH (2.0 mL) were added to a test tube and the system was sealed with a septum. After two vacuum/H_2 cycles to replace the air inside with hydrogen, the mixture was vigorously stirred at room temperature (ca. 20 °C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm) to afford the mixture of **1a**–**4a**. The ratio of the mixture was determined by ^{1}H NMR analysis.

4.4. Typical procedure for the chemoselective hydrogenation of olefins in the presence of Ph_2S as a catalyst poison (Tables 2, 5–9, and Scheme 3)

Substrate (500 μmol), 10% Pd/C (10 wt % of the substrate), diphenylsulfide (0.84 μL, 5.00 μmol), and MeOH (2.0 mL) were added to a test tube and the system was sealed with a septum. After two vacuum/H_2 cycles to replace the air inside with hydrogen, the mixture was vigorously stirred at room temperature (ca. 20 °C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and the filtrate was concentrated to provide the product.

4.5. Procedure for Table 3

Compound **3a** (81.1 mg, 500 μmol), 10% Pd/C (8.2 mg, 10 wt % of **3a**), diphenylsulfide (0.84 μL, 5.00 μmol), and solvent (2.0 mL) were added to a test tube and the system was sealed with a septum. After two vacuum/H_2 cycles to replace the air inside with hydrogen, the mixture was vigorously stirred at room temperature (ca. 20 °C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and the filtrate was concentrated to provide the product.

4.6. Investigation of solvent effect on the hydrogenation of aromatic aldehyde (Table 4)

Substrate (500 μmol), 10% Pd/C (10 wt % of the substrate), diphenylsulfide (0.84 μL, 5.00 μmol), and AcOEt (2.0 mL) were added to a test tube and the system was sealed with a septum. After two vacuum/H_2 cycles to replace the air inside with hydrogen, the mixture was vigorously stirred at room temperature (ca. 20 °C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a membrane filter (Millipore, Millex®-LH, 0.45 μm) and the filtrate was concentrated to provide the product.

4.7. Procedure for reuse of Pd/C (Table 10)

In entry 1, **14e** (200 mg, 839 μmol), 10% Pd/C (20 mg, 10 wt % of **14e**), diphenylsulfide (1.38 μL, 8.39 μmol), and MeOH (2.0 mL) were added to a test tube and the system was sealed with a septum. After two vacuum/H_2 cycles to replace the air inside with hydrogen, the mixture was vigorously stirred at room temperature (ca. 20 °C) under ordinary hydrogen pressure (balloon) for 24 h. The reaction mixture was filtered using a Kiriyama funnel (8 mm diameter, filter paper 5C, 1 μm, Kiriyama Glass Works Co.), the filtrate was concentrated to provide the product, and filtered Pd/C was dried under reduced pressure for 24 h. In entries 2–4, according to the procedure in entry 1, the reaction was carried out without the addition of Ph_2S.

References and notes

1. (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, NY, 1999; (b) Nishimura, S.

Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis; Wiley-Interscience: New York, NY, 2001; (c) Hudlickey, M. *Reductions in Organic Chemistry*, 2nd ed.; ACS: Washington, DC, 1996; (d) Rylander, P. N. *Hydrogenation Methods*; Academic: New York, NY, 1985.

2. (a) Sajiki, H. *Tetrahedron Lett.* **1995**, *36*, 3465–3468; (b) Sajiki, H.; Kuno, H.; Hirota, K. *Tetrahedron Lett.* **1997**, *38*, 399–402; (c) Sajiki, H.; Kuno, H.; Hirota, K. *Tetrahedron Lett.* **1998**, *39*, 7127–7130; (d) Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981–13996; (e) Sajiki, H. *Yakugaku Zasshi* **2000**, *120*, 1091–1103; (f) Sajiki, H.; Hirota, K. *Chem. Pharm. Bull.* **2003**, *51*, 320–324.
3. (a) Sajiki, H.; Hattori, K.; Hirota, K. *J. Org. Chem.* **1998**, *63*, 7990–7992; (b) Sajiki, H.; Hattori, K.; Hirota, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4043–4044; (c) Sajiki, H.; Hattori, K.; Hirota, K. *Chem. Commun.* **1999**, 1041–1042; (d) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron Lett.* **2000**, *41*, 5711–5714; (e) Sajiki, H.; Hattori, K.; Hirota, K. *Chem.—Eur. J.* **2000**, *6*, 2200–2204; (f) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2000**, *56*, 8433–8441; (g) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2001**, *57*, 2109–2114; (h) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2001**, *57*, 4817–4824; (i) Sajiki, H.; Hirota, K. *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 109–120.
4. (a) Rosenmund, K. W. *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 585–598; (b) Rosenmund, K. W.; Zetzsche, F. *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 425–437; (c) Mosettig, E.; Mozingo, R. *Org. React.* **1948**, *4*, 362–377.
5. Oelschläger, H. *Arch. Pharmacol.* **1960**, *293*, 442–451.
6. Dovell, F. S.; Greenfield, H. *J. Am. Chem. Soc.* **1965**, *87*, 2767–2768.
7. Preliminary results were reported as a communication, Mori, A.; Miyakawa, Y.; Ohashi, E.; Haga, T.; Maegawa, T.; Sajiki, H. *Org. Lett.* **2006**, *8*, 3279–3281.
8. (a) Sajiki, H.; Ikawa, T.; Hattori, K.; Hirota, K. *Chem. Commun.* **2003**, 654–655; (b) Ikawa, T.; Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2004**, *60*, 6901–6911.
9. (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, NY, 1999; (b) Kocieński, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, 2005.
10. Misiti, D.; Zappia, G.; Monach, G. D. *Synthesis* **1999**, 873–877.
11. (a) Sajiki, H.; Ikawa, T.; Yamada, H.; Tsubouchi, K.; Hirota, K. *Tetrahedron Lett.* **2003**, *44*, 171–174; (b) Sajiki, H.; Ikawa, T.; Hirota, K. *Tetrahedron Lett.* **2003**, *44*, 8437–8439; (c) Ikawa, T.; Sajiki, H.; Hirota, K. *Tetrahedron* **2005**, *61*, 2217–2231.
12. (a) Reetz, M. T.; Frömbgen, C. *Synthesis* **1999**, 1555–1557; (b) Bae, J. W.; Cho, Y. J.; Lee, S. H.; Yoon, C. M. *Tetrahedron Lett.* **2000**, *41*, 175–177; (c) Deshpande, R. M.; Mahajan, A. N.; Diwakar, M. M.; Ozarde, P. S.; Chaudhari, R. V. *J. Org. Chem.* **2004**, *69*, 4835–4838; (d) Chen, Y.; Wang, C.; Liu, H.; Qiu, J.; Bao, X. *Chem. Commun.* **2005**, 5298–5300.
13. Allen, C. F. H.; Gates, J. W., Jr. *Organic Synthesis*; Wiley: New York, NY, 1955; Collect. Vol. 3, pp 140–141.
14. Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112–8113.
15. Smith, P. A. S.; Boyer, J. H. *Organic Synthesis*; Wiley: New York, NY, 1963; Collect. Vol. 4, pp 75–78.
16. Kita, Y.; Tohma, H.; Hatanaka, K.; Takeda, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684–3691.