Reliable and Safe, Gram-Scale Hydrogenation and Hydrogenolysis of *O*-Benzyl Ether Groups with In Situ Pd^0/C Catalyst

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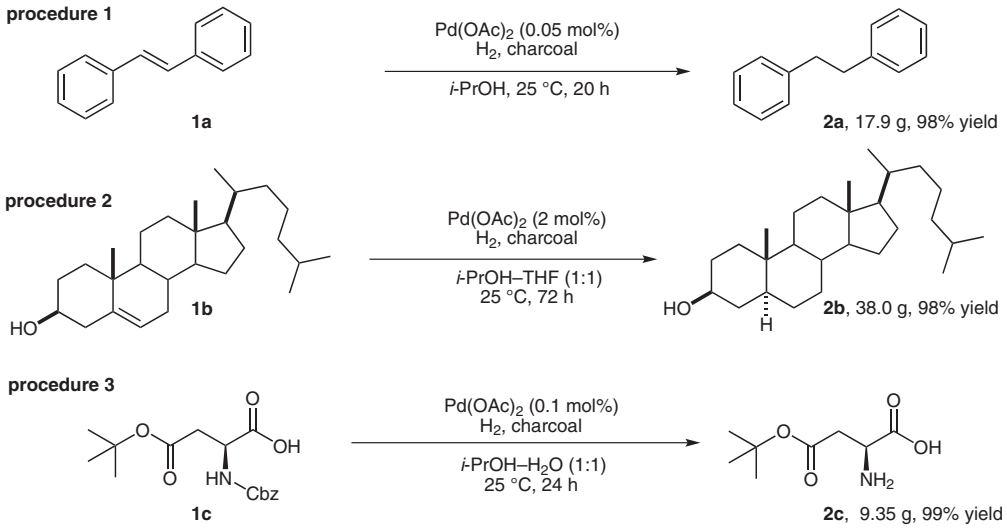
Abstract: Hydrogenation of alkenes, alkynes, and hydrogenolysis of *O*-benzyl ethers with Pd^0/C catalyst generated in situ can be readily scaled up under safer conditions than with traditional procedures. The precise control of the palladium loading and the mild conditions developed allow the formation of a very active and reliable Pd^0/C catalyst, leading to highly reproducible results.

Key words: hydrogenation, hydrogenolysis, palladium, charcoal, gram-scale synthesis



Scheme 1 Typical procedures for hydrogenations and hydrogenolyses

Metal-mediated reductive processes, including hydrogenation and hydrogenolysis, are indispensable methods in the tool box of synthetic chemists.[2] Among the different metals that are active in reductive processes, palladium supported on activated carbon (Pd/C) catalysts have become a standard in both industrial and academic laboratories.[3] For instance, it is estimated that approximately 75% of industrial hydrogenations involves the use of a Pd/C catalyst. The denomination 'Pd/C' is quite evasive and confusing because Pd/C catalysts can have many different forms, according to the palladium loading, size distribution, dispersion, and degree of oxidation. The nature of the charcoal (i.e., surface area, porosity, water content, etc.) may also have a role in the catalytic efficiency.[4] Unfortunately, these important properties are rarely available for commercial Pd/C catalysts due to the unpredictable quality of batches. Moreover, the random distribution and size of palladium nanoparticles on the charcoal frequently led to discrepancies in the catalytic activity, forcing chemists to frequently use high loadings of catalysts (~5 mol%).

In order to address these issues, we devised a cost-effective and reliable procedure for hydrogenations and hydrogenolyses by taking advantage of a Pd^0/C catalyst generated in situ with perfectly controlled properties.[5] The Pd^0/C catalyst was generated in situ by reduction of palladium(II) acetate, one of the cheapest sources of palladium, followed by deposition of the palladium nanoparticles formed onto charcoal during the reaction. By using such an approach, we observed a high level of reproducibility because the properties of Pd^0/C are perfectly controlled. Moreover, we also observed that the quality of palladium(II) acetate is relatively consistent over time, regardless of the commercial source.

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In this paper, we report our optimisation studies for gram-scale (50–100 mmol) hydrogenations of alkenes and alkynes as well as hydrogenolyses of *O*-benzyl ethers.

Under our original conditions on a laboratory scale (1–5 mmol), we used methanol as the sole solvent. However, although setting up and starting the reaction did not require special handling, because Pd/C was formed in situ from palladium(II) acetate and charcoal, the filtration step proved to be more risky. Indeed, Pd/C is highly pyrophoric and even spontaneously flammable in the presence of oxygen and methanol vapours. To address this issue for multigram-scale procedures, we selected isopropanol as solvent instead of methanol. Moreover, we also observed that, for substrates that are weakly soluble in alcoholic solvents, the stirring process can be interrupted, particularly in gram-scale syntheses. Based on these observations, we revisited our procedure and we are now able to propose three different procedures according to the nature of the reducible substrate (Scheme 1).[6] For compounds that are fairly soluble in isopropanol, procedure 1 was developed. On the other hand, with substrates that are insoluble in isopropanol, we observed irreproducible results with this procedure due to difficulties with stirring. After extensive solvent screening it was found that, for highly lipophilic compounds, tetrahydrofuran could be added as co-solvent (procedure 2), whereas for hydrophilic compounds, water should be preferred as co-solvent (procedure 3). We opted for palladium(II) acetate as palladium source instead of palladium(II) chloride because it is highly soluble in most organic solvents and does not produce salts that would need to be be specifically treated on industrial scales and that could react with sensitive functional groups.

With these three procedures in hand, we screened the reduction of a representative variety of alkenes, alkynes, and *O*-benzyl ethers on multigram scales (50–100 mmol;

Table 1 Reduction of Alkenes, Alkynes, and *O*-Benzyl Ethers

Entry	Substrate	Product	Procedure	Scale (mmol)	Pd loading (mol%)	Time (h)	Yield (%)
1	**1a**	**2a**	1	100	0.05	20	98
2	**1b**	**2b**	2	100	2	72	98
3	**1c**	**2c**	3	50	0.05	24	99
4	**1d**	**2d**	1	100	0.1	48	98
5	**1e**	**2e**	1	100	0.1	15	92
6	**1f**	**2f**	1	100	0.05	22	97
7	**1g**	**2g**	1	100	0.1	14	99
8	**1h**	**2h**	3	50	0.05	15	99
9	**1i**	**2i**	1	100	0.3	48	97

Table 1). The reduction of unhindered alkynes and alkenes using procedure 1 was carried out with very low loading of palladium (0.05–0.1 mol%) at room temperature under one atmosphere of hydrogen (Table 1, entries 1 and 3–9). Similarly, *O*-benzyl ether cleavage proceeded smoothly to give the corresponding alcohol (entry 5), acid (entry 7), or amine (entries 3 and 8). With substrates having multiple reduction sites, such as benzyl cinnamate (**1i**), procedure 1 still proved to be very efficient. On the other hand, hydrogenation of highly lipophilic cholesterol **1b** into 5α-cholestan-3β-ol **2b** required tetrahydrofuran as co-solvent for convenient stirring (procedure 2). With such a challenging olefin, a higher loading (2 mol%) was required, but, compared to literature precedents reported on laboratory scales, this catalytic system is still very competitive.[7] With highly hydrophilic substrates, the addition of water as co-solvent did not hamper the catalytic activity and avoided the precipitation of the deprotected amino acids **2c** and **2h** into the solvent. All compounds reported in Table 1 were isolated in high purity (>98%; determined by ^{1}H NMR and HPLC analyses) after simple filtration over a nylon membrane followed by evaporation of volatiles.

We also analysed the content of palladium residues in the isolated product by inductively coupled plasma mass spectrometry (ICP-MS). To our great pleasure, the concentration of residual palladium species polluting the products typically ranged from 0.4 to 16.8 ppb, indicating that 99.9% of palladium initially introduced had been adsorbed onto the charcoal (Table 2). The only exceptions observed concerned amino acids **2c** and **2h**, for which we found, respectively, 10.6 and 6.7 ppm metal residue. The discrepancy could be explained by the amino acid function that could act as a pincer ligand for palladium. We explained the high activity and reproducibility of our catalytic system by the excellent control in the dispersion, size distribution, and spherical shape of the palladium nanoparticles adsorbed on charcoal.[5]

Table 2 Palladium Content in the Isolated Product Measured by ICP-MS

Entry	Product	Procedure	Pd loading (mol%)	ICP-MS (ppb)
1	**2a**	1	0.05	1.1
2	**2b**	2	2	0.4
3	**2c**	3	0.1	10.6 ppm
4	**2d**	1	0.1	4.4
5	**2e**	1	0.1	10.8
6	**2f**	1	0.05	2.1
7	**2g**	1	0.1	11.2
8	**2h**	3	0.1	6.7 ppm
9	**2i**	1	0.3	16.8

In summary, we have reported scalable procedures for the hydrogenation of alkenes and alkynes, as well as hydrogenolysis of *O*-benzyl ethers. The main procedure involves the formation of a highly active Pd^0/C catalyst in situ from palladium(II) acetate and charcoal in isopropanol. However, with weakly soluble substrates in isopropanol, we recommend the use of a co-solvent in order to ensure good stirring and reproducible results. For lipophilic compounds, tetrahydrofuran has been found to be an excellent co-solvent, whereas with hydrophilic compounds, water should be preferred. These procedures allow the isolation of reduced compounds with high purity that are free of palladium residues, and should find applications for biologically active compounds for which metal contamination is closely monitored.

All reactions were carried out under a hydrogen atmosphere (1 atm). All starting materials were commercially available and used as received without further purification. The progress of the reactions were monitored by TLC analyses and by ^{1}H NMR analysis of the crude mixture. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 spectrometer; chemical shifts were referenced using residual solvent peak. Yields refer to isolated compounds estimated to be >98% pure as determined by ^{1}H NMR spectroscopic and HPLC analyses. HPLC analyses were performed with a Luna 5 μm C18–2 column (Phenomenex), 250 × 46 mm; flow rate: 1 mL/min; UV detection (254 nm).

Dibenzyl (2a); Typical Procedure 1

To a stirred solution of stilbene (**1a**; 18 g, 100 mmol) in *i*-PrOH (120 mL) were added charcoal (100 mg, 90% wt/Pd) and $Pd(OAc)_2$ (11.2 mg, 0.05 mol%) at 25 °C. The resulting mixture was stirred for 20 h at 25 °C under H_2 (1 atm) and then filtered. The catalyst was washed with EtOAc (2 × 15 mL) and the clear solution was concentrated under reduced pressure to give dibenzyl (**2a**) with high purity after filtration.

Yield: 17.9 g (98%); white solid; mp 52 °C (Lit.[8] 51 °C); HPLC (MeCN–H_2O, 80:20): t_R = 9.33 min.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.06 (s, 4 H), 7.30–7.44 (m, 10 H).[5]

5α-Cholestan-3β-ol (2b); Typical Procedure 2

To a stirred solution of cholesterol **1b** (38.6 g, 100 mmol) in *i*-PrOH (60 mL) and THF (60 mL) were added charcoal (4 g, 90% wt/Pd) and $Pd(OAc)_2$ (448 mg, 2 mol%) at 25 °C. The resulting mixture was stirred for 72 h at 25 °C under H_2 (1 atm) and then filtered. The catalyst was washed with EtOAc (2 × 15 mL) and the clear solution was concentrated under reduced pressure to give 5α-Cholestan-3β-ol **2b** with high purity after filtration.

Yield: 38.0 g (98%); white solid; mp 141 °C (Lit.[9] 141 °C).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.59–0.69 (m, 1 H), 0.66 (s, 3 H), 0.82 (s, 3 H), 0.88 (d, *J* = 6.6 Hz, 6 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.79–1.82 (m, 30 H), 1.94–2.00 (m, 1 H), 3.55–3.64 (m, 1 H).[5]

4-*tert*-Butyl L-Aspartate (2c); Typical Procedure 3

To a stirred solution of Z-Asp(O*t*-Bu)-OH **1c** (16.17 g, 50 mmol) in *i*-PrOH (30 mL) and H_2O (30 mL) were added charcoal (100 mg, 90% wt/Pd) and $Pd(OAc)_2$ (11.2 mg, 0.1 mol%) at 25 °C. The resulting mixture was stirred for 24 h at 25 °C under H_2 (1 atm) and then filtered. The catalyst was washed with EtOAc (2 × 10 mL) and the clear solution was concentrated under reduced pressure to give 4-*tert*-butyl L-aspartate (**2c**) with high purity after filtration.

Yield: 9.35 g (99%); white solid; mp 190 °C (Lit.[10] 177–178 °C).

^{1}H NMR (D_2O, 300 MHz): δ = 1.44 (s, 9 H), 2.91 (d, *J* = 5.5 Hz, 2 H), 3.96 (t, *J* = 5.5 Hz, 1 H).[5]

Methyl 3-Phenylpropanoate (2d)

Following procedure 1, methyl cinnamate (**1d**; 16.2 g, 100 mmol) in *i*-PrOH (120 mL) was reduced under H_2 (1 atm) with charcoal (100 mg, 90% wt/Pd) and $Pd(OAc)_2$ (11.2 mg, 0.05 mol%) for 48 h, into dihydrocinnamic acid **2d**, which was isolated with high purity after filtration.

Yield: 16.1 g (98%); colourless oil; HPLC (MeCN–H_2O, 70:30): t_R = 5.72 min.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.64 (t, *J* = 7.5 Hz, 2 H), 2.99 (t, *J* = 7.5 Hz, 2 H), 3.68 (s, 3 H), 7.19–7.33 (m, 5 H).[5]

3-Phenylpropan-1-ol (2e)

Following procedure 1, cinnamyl alcohol (**1e**; 13.4 g, 100 mmol) in *i*-PrOH (120 mL) was reduced under H_2 (1 atm) with charcoal (200 mg, 90% wt/Pd) and $Pd(OAc)_2$ (22.4 mg, 0.1 mol%) for 15 h, into hydrocinnamyl alcohol **2d**, which was isolated with high purity after filtration.

Yield: 12.5 g (92%); colourless oil; HPLC (MeCN–H_2O, 50:50): t_R = 5.56 min.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.64 (br s, 1 H), 1.86–1.95 (m, 2 H), 2.72 (t, *J* = 7.5 Hz, 2 H), 3.68 (t, *J* = 6.4 Hz, 2 H), 7.18–7.32 (m, 5 H).[5]

Benzoic Acid (2g)

Following procedure 1, benzyl benzoate (**1g**; 21.2 g, 100 mmol) in *i*-PrOH (120 mL) was hydrogenolysed under H_2 (1 atm) with charcoal (200 mg, 90% wt/Pd) and $Pd(OAc)_2$ (22.4 mg, 0.1 mol%) for 14 h, into benzoic acid (**2g**), which was isolated with high purity after filtration.

Yield: 12.1 g (99%); white solid; mp 122 °C (Lit.[11] 121.5 °C); HPLC (MeCN–H_2O, 5:95): t_R = 20 min.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.49 (t, *J* = 7.7 Hz, 2 H), 7.63 (t, *J* = 7.4 Hz, 1 H), 8.13 (d, *J* = 8.5 Hz, 2 H), 9.75 (br s, 1 H).[5]

L-Proline (2h)

Following procedure 3, Cbz-proline **1h** (g, 50 mmol) in *i*-PrOH (30 mL) and H_2O (30 mL) was reduced under H_2 (1 atm) with charcoal (100 mg, 90% wt/Pd) and $Pd(OAc)_2$ (11.2 mg, 0.1 mol%) for 15 h, into proline (**2h**), which was isolated with high purity after filtration.

Yield: 4.98 g (99%); white solid; mp 220 °C (Lit.[12] 220–222 °C).

^{1}H NMR (CD_3OD, 200 MHz): δ = 1.87–2.37 (m, 4 H), 3.16–3.43 (m, 2 H), 3.97 (dd, *J* = 6.0, 8.4 Hz, 1 H).[5]

Dihydrocinnamic Acid (2i)

Following procedure 1, benzyl cinnamate (**1i**; 23.8 g, 100 mmol) in *i*-PrOH (120 mL) was reduced under H_2 (1 atm) with charcoal (600 mg, 90% wt/Pd) and $Pd(OAc)_2$ (67.2 mg, 0.3 mol%) for 48 h, into dihydrocinnamic acid (**2i**), which was isolated with high purity after filtration.

Yield: 14.5 g (97%); white solid; mp 46 °C (Lit.[13] 46.4–46.8 °C); HPLC (MeCN–H_2O, 70:30): t_R = 3.42 min.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.72 (dd, *J* = 7.0, 8.1 Hz, 2 H), 2.99 (t, *J* = 7.5 Hz, 2 H), 7.23–7.36 (m, 5 H), 11.0 (br s, 1 H).[5]

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