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A Useful, Reliable and Safer Protocol for Hydrogenation and the Hydrogenolysis of *O*-Benzyl Groups: The In Situ Preparation of an Active Pd^0/C Catalyst with Well-Defined Properties

François-Xavier Felpin* and Eric Fouquet[a]

Dedicated to Professor Jacques Lebreton on the occasion of his 50th birthday

Abstract: A simple, highly reproducible protocol for the hydrogenation of alkenes and alkynes and for the hydrogenolysis of *O*-benzyl ethers has been developed. The method features the in situ preparation of an active Pd^0/C catalyst from $Pd(OAc)_2$ and charcoal, in methanol. The mild reaction conditions (25 °C) and low catalyst loading required (0.025 mol %), as well as the absence of contamination of the product by palladium residues (< 4 ppb), make this a sustainable, useful process for organic chemists. Alternatively, the protocol can be carried out under microwave activation, to shorten the reaction times, with cyclohexene as the hydrogen source.

Keywords: heterogeneous catalysis • hydrogenation • hydrogenolysis • palladium • supported catalysts • sustainable chemistry

Introduction

Palladium on carbon (Pd/C) has been known, for more than a century, to be an effective catalyst for reductive processes and it is estimated that 75 % of industrial hydrogenation processes are performed with Pd/C catalysts.[1] More recently, its scope has been diversified, by synthetic chemists, to include many applications in coupling reactions for carbon–carbon and carbon–heteroatom bond formation.[2] Our laboratory has also reported its own contributions over the last five years.[3]

In conventional hydrogenation protocols, the Pd/C catalyst is used as received in its commercially available form. Many different forms of Pd/C, more or less expensive, can be purchased from suppliers according to several parameters, including catalyst loading, size, distribution, dispersion, degree of oxidation (Pd^0 or Pd^{II}) of the palladium nanoparticles and water content of the charcoal, as well as other properties. Generally, the rate of hydrogenation is, at least in part, dependent upon these parameters.[4] Despite the number of applications described in the literature, including industrial processes,[5] hydrogenation following a standard protocol displays several drawbacks. For instance, from a safety perspective, Pd/C is highly pyrophoric and, thus, spontaneously flammable in the presence of oxygen and methanol vapours, causing serious handling issues. Furthermore, the unpredictable quality of commercially available batches of Pd/C and the random distribution and size of palladium nanoparticles over the charcoal in the same batch force chemists to use quite a high loading of catalyst, usually 5 wt % or 5 mol %. In order to address these issues we have devised a simple and reliable protocol, in which the loading of palladium can be accurately controlled and lowered to "homeopathic" doses. Our protocol generates, in situ, the Pd/C catalyst from charcoal and a homogeneous source of palladium, that is, $Pd(OAc)_2$. This idea was inspired by our recent work on one-pot reactions that uses a multi-task, in situ generated, Pd/C catalyst.[6]

Results and Discussion

Our optimisation studies employed the combination of $Pd(OAc)_2$ and charcoal in methanol under an atmosphere of hydrogen (balloon, 1 atm). Under these conditions the reduction of stilbene (**1**) to dibenzyl **2** was studied at various

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[a] Dr. F.-X. Felpin, Prof. E. Fouquet
Université de Bordeaux, CNRS-UMR 5255
Institut des Sciences Moléculaires (ISM)
351, Cours de la Libération, Talence, 33405 (France)
Fax: (+33) 540-006-286
E-mail: fx.felpin@ism.u-bordeaux1.fr

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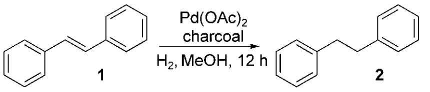
palladium loadings and temperatures (Table 1). We found that the reduction is ideally carried out at room temperature (25 °C) with a catalyst loading of 0.05 mol % palladium.

Table 1. Optimisation studies.[a]



Entry	Temperature [°C]	Pd loading [mol %]	Yield[b] [%]
1	65	1	99
2	65	0.5	99
3	65	0.1	99
4	65	0.05	99
5	45	0.05	99
6	25	0.05	99[c]
7[d]	25	0.05	99
8	25	0.005	18
9	25	0	3

[a] Reaction conditions: stilbene (5 mmol), $Pd(OAc)_2$, charcoal (90 wt %/$Pd(OAc)_2$), MeOH (6.5 mL), H_2 (1 atm, balloon), 12 h. [b] Yield of isolated product. [c] Contamination of the solvent <0.2 ppb (see text). [d] Charcoal was omitted from this reaction.

Working at higher temperatures does not allow lower catalyst loadings. We adjusted the amount of support in order to have a 10:90 (wt:wt) $Pd(OAc)_2$/charcoal ratio, resulting in an approximate 5 wt % loading of palladium metal. We have also shown that the background reaction resulting from traces of palladium on the magnetic stirring bar and/or glassware is negligible (Table 1, entry 9). Inductively coupled plasma mass spectrometry (ICP-MS) analyses show very little contamination of the solvent by palladium residues, with levels as low as 0.2 ppb. This result indicates that virtually all of the palladium species (>99.99 %) have been adsorbed onto the charcoal and confirms the quantity of palladium metal loaded onto the charcoal (≈ 5 wt % Pd/C).

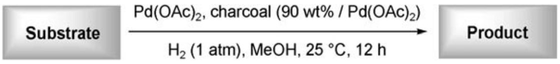
Our new protocol allows excellent reproducibility of results, since the quantity of palladium introduced can be accurately controlled by using a home-made stock solution of $Pd(OAc)_2$ in THF. This alternative is particularly convenient for reactions conducted at low loadings of palladium, especially on a laboratory scale. Although we screened various batches of $Pd(OAc)_2$ from different sealers, we consistently reproduced our results. This can be explained by the highly stable nature of $Pd(OAc)_2$, which does not decompose over time. On the other hand, the use of low loadings of commercially available Pd/C, on a laboratory scale (0.1–10 mmol) requires the weighing of small quantities of the heterogeneous catalyst, which leads to irreproducible results. Indeed, the quality of batches and precision of the weighing of small quantities (0.1–5 mg), as well as the disparity in palladium distribution over the charcoal, are all aspects that are addressed by our protocol (vide infra). In addition, from a safety perspective, the launch of the reaction does not require any special handling, since, in contrast to Pd/C catalysts, $Pd(OAc)_2$ is not pyrophoric. The quantity of charcoal used in our protocol has a limited influence on the reaction outcome (Table 1, entry 7).[7] Essentially, it sequesters Pd^0 nanoparticles and prevents contamination of the solvent and product by palladium residues. In other words, inaccuracy in the charcoal weighing has no effect upon the reproducibility of the reaction.

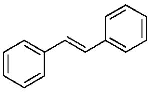
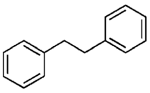
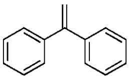
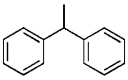
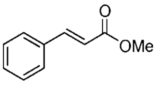
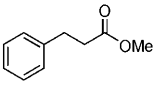
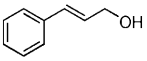
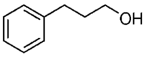
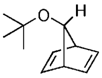
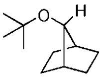
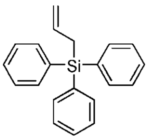
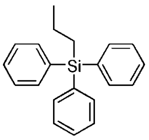
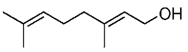
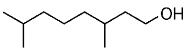
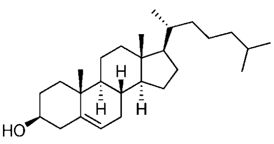
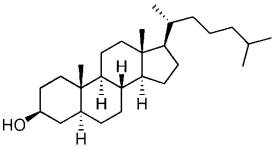
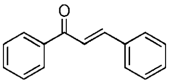
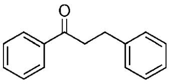
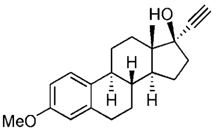
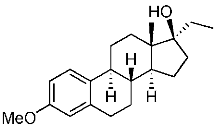
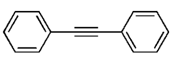
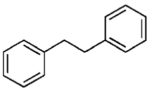
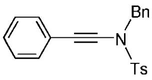
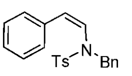
With the optimised conditions in hand, we screened for activity in the hydrogenation reactions of a variety of substrates possessing an alkene or an alkyne functionality (Table 2). Whatever the nature of the alkene, the hydrogenation reaction can be carried out at room temperature (25 °C), under mild conditions, with a catalyst loading as low as 0.025 mol %. Only the reduction of extremely hindered cholesterol (**15**) to 5α-cholestan-3β-ol (**16**) required a higher loading of palladium (1 mol %), but still at room temperature and under 1 atm of hydrogen (Table 2, entry 8). Although a higher palladium loading was necessary for the reduction of cholesterol (**15**), a brief survey of the literature for the use of palladium-based catalysts for this reaction makes our protocol highly competitive.[8] Such mild conditions allow the selective reduction of chalcone **17** without significantly affecting the carbonyl group, which is usually prone to reduction (Table 2, entry 9). Alkynes are also easily reduced to the corresponding alkane at low palladium loadings (Table 2, entries 10 and 11). To our surprise, ynamide **22**[9] proved to be averse to hydrogenation and only the corresponding enamide, **23**, can be isolated at a loading of 1.5 mol % palladium, as an inseparable mixture of isomers (*E*/*Z*, ≈10:90). Similar behaviour has already been observed with Lindlar's catalyst.[10]

To evaluate the added value of our in situ prepared catalyst, we evaluated (Table 3) the catalytic activity of various commercially available Pd/C catalysts for the reduction of cholesterol (**15**) to 5α-cholestan-3β-ol (**16**) at a Pd loading of 1 mol %. As expected, dramatic differences in catalytic activity are observed, depending upon the Pd source, giving low to good conversions. However, to the credit of our protocol, none of the commercial Pd/C catalysts, in our hands, were as active as our home-made catalyst. Moreover, it should be noted that $Pd(OAc)_2$ is one of the cheapest sources of Pd that competes favourably against most of the commercial Pd/C catalysts. As a consequence, this protocol would also be particularly convenient on a preparative scale from both economic and safety perspectives (palladium acetate in not pyrophoric).

Next, we investigated the hydrogenolysis of *O*-benzyl protecting groups by using a similar catalyst system (Table 4). Benzyl ethers are commonly employed in synthetic chemistry as transient protecting groups for alcohols, carboxylic acids and amines (through a carboxybenzyl (Cbz) group). Although many reaction conditions for their cleavage have been described in the literature with bases, Lewis acids and oxidising or reducing agents under forced conditions, the combination of hydrogen and a Pd/C catalyst has proved to be the mildest and most effective system.[11] We were pleased to find that the in situ prepared Pd/C catalyst was able to smoothly catalyse the cleavage of the *O*-benzyl pro-

Table 2. Scope of the hydrogenation.[a]



Entry	Substrate	Product	Pd loading [mol %]	Yield[b] [%]
1	 **1**	 **2**	0.05	99
2	 **3**	 **4**	0.1	99
3	 **5**	 **6**	0.025	99
4	 **7**	 **8**	0.05	99
5	 **9**	 **10**	0.1	85[c]
6	 **11**	 **12**	0.05	99
7	 **13**	 **14**	0.1	75[c]
8	 **15**	 **16**	1	99
9	 **11**	 **18**	0.05	89[d]
10	 **19**	 **20**	0.05	99
11	 **21**	 **2**	0.05	99
12	 **22**	 **23**	1.5	91

[a] Reaction conditions: substrate (5 mmol), $Pd(OAc)_2$, charcoal (90 wt%/$Pd(OAc)_2$), MeOH (6.5 mL), H_2 (1 atm, balloon), 12 h. [b] Yield of isolated product. [c] Volatile compound. [d] After 6 h of stirring, 6% of the alcohol was also isolated.

tecting group of carboxylic acids (Table 4, entries 1 and 2) and alcohols (Table 4, entries 3 and 4) at quite low loadings (0.1–0.3 mol% Pd) and under mild conditions (25 °C, 1 atm H_2).

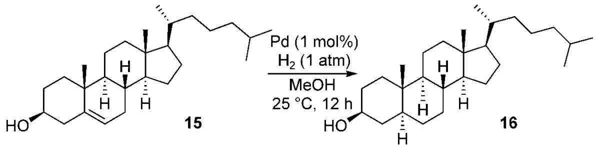
Surprisingly, benzyl-2-naphthyl ether (**30**) was found to be averse to hydrogenolysis under our reaction conditions and we only obtained partial conversion to the targeted, unstable 2-naphthol (**31**), along with unidentified degradation products (Table 4, entry 5). On the other hand, Cbz protecting groups were easily cleaved with only 0.05 mol% palladium loadings, to give the corresponding free amines (Table 4, entries 6–8).

Subsequently, we wondered whether olefins could be selectively hydrogenated in the presence of a benzyl protecting group. With activated olefins, such as α,β-unsaturated ester **26**, both functionalities (i.e., alkene and benzyl ether) were affected by 0.2 mol% palladium. On the other hand, lower catalyst loadings, with quantities as low as 0.025 mol%, allow the selective hydrogenation of the olefin without affecting the benzyl ether functionality, to give compound **38** (Scheme 1). With non-activated olefin **29** we were unable to selectively hydrogenate the double bond by adjusting the palladium loading. Indeed, at low catalyst loadings (<0.1 mol% Pd) the targeted benzyl ether **39** was accompanied by unreacted starting material. At higher palladium loadings (0.1–0.25 mol% Pd) variable amounts of fully reduced 3-phenylpropanol (**8**) were isolated, along with the expected product **39**. Fortunately, the presence of triethylamine inhibited the hydrogenolysis of the benzyl ether, while the double bond was selectively reduced at 0.1 mol% Pd to give compound **39**.[12]

The use of microwave activation in heterogeneous palladium-catalysed hydrogenations and cross-coupling reactions has been intensively studied over the last ten years.[13] Although the "microwaves effect" is still a subject of debate, we expected that the heterogeneous catalyst should strongly absorb microwaves and, therefore, exhibit different reactivity compared with the "classical" thermal reactions described above.

In Table 5 we report the microwave reactions of substrates already studied under thermal conditions (except for Table 5, entry 5) in order to compare the results obtained under microwave activation. As the reaction was carried out in a sealed tube, we used cyclohexene (6 equiv) as the hydrogen donor, at 150 °C for 15 min. Comparisons with the

Table 3. Evaluation of the Pd/C source for catalytic activity.[a]

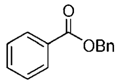
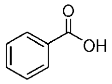
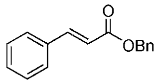
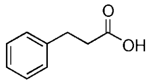
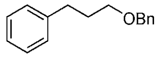
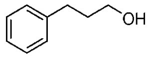
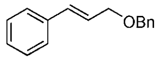
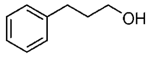
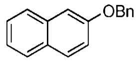
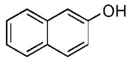
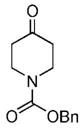
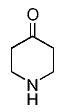
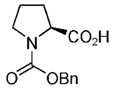
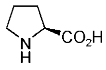
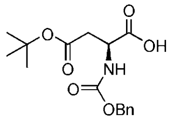
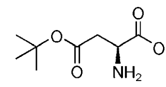


Entry	Palladium	Conversion[b] [%]	Yield[c] [%]
1	Pd(OAc)$_2$/charcoal	100	99
2	10% Pd/C (Aldrich)	40	–
3	3% Pd/C (Aldrich)	85	–
4	10% Pd/C (Alfa)	60	–
5	5% Pd/C (Degussa)	95	93

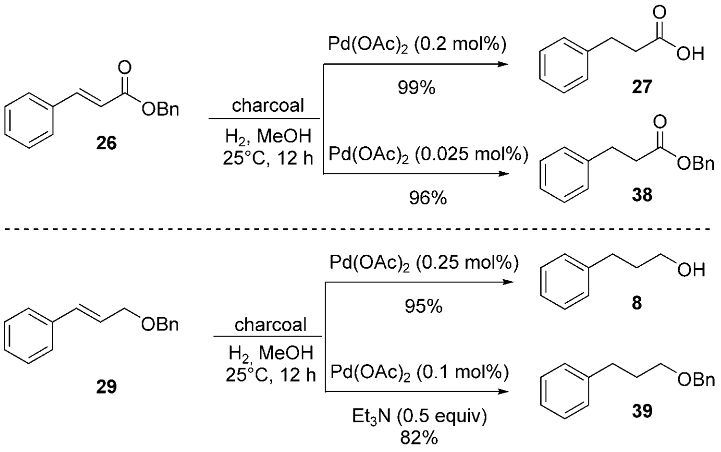
[a] Reaction conditions: substrate (5 mmol), Pd (1 mol%), MeOH (6.5 mL), H_2 (1 atm, balloon), 25 °C, 12 h. [b] Conversion calculated by ^{1}H NMR spectroscopy. [c] Yield of isolated product.

Table 4. Scope of the hydrogenolysis of *O*-benzyl ethers.[a]

$$\text{Substrate} \xrightarrow[\text{H}_2\text{ (1 atm), MeOH, 25 °C, 12 h}]{\text{Pd(OAc)}_2\text{, charcoal (90 wt\% / Pd(OAc)}_2\text{)}} \text{Product}$$

Entry	Substrate	Product	Pd loading [mol%]	Yield[b] [%]
1	 **24**	 **25**	0.1	99
2	 **26**	 **27**	0.2	99
3	 **28**	 **8**	0.25	97
4	 **29**	 **8**	0.3	99
5	 **30**	 **31**	1.5	66[c]
6	 **32**	 **33**	0.05	99[d]
7	 **34**	 **35**	0.05	99
8	 **36**	 **37**	0.05	99

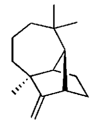
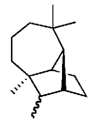
[a] Reaction conditions: substrate (5 mmol), Pd(OAc)$_2$, charcoal (90 wt%/Pd(OAc)$_2$), MeOH (6.5 mL), H_2 (1 atm, balloon), 12 h. [b] Yield of isolated product. [c] Conversion determined by NMR spectroscopy. Significant decomposition was observed. [d] GC yield due to volatility.



Scheme 1. Selective hydrogenations in the presence of benzyl ethers.

Table 5. Scope of the MW-assisted hydrogenation and hydrogenolysis.[a]

$$\text{Substrate} \xrightarrow[\text{cyclohexene (6 equiv), MeOH, MW, 150 °C, 15 min}]{\text{Pd(OAc)}_2\text{, charcoal (90 wt\% / Pd(OAc)}_2\text{)}} \text{Product}$$

Entry	Substrate	Product	Pd loading [mol%]	Yield[b] [%]
1	**1**	**2**	0.5	99
2	**3**	**4**	0.5	99
3	**5**	**6**	0.5	99
4	**7**	**8**	0.5	–[c]
5	 **40**	 **41**	2	–[d]
6	**11**	**12**	0.5	–[c]
7	**17**	**18**	0.5	99
8	**19**	**20**	0.5	–[d]
9	**21**	**2**	2	99
10	**24**	**25**	0.5	99
11	**26**	**27**	1	99
12	**29**	**8**	1	–[c]

[a] Reaction conditions: substrate (5 mmol), Pd(OAc)$_2$, charcoal (90 wt%/Pd(OAc)$_2$), MeOH (6.5 mL), H_2 (1 atm, balloon), 12 h. [b] Yield of isolated product. [c] Decomposition. [d] No reaction, starting material was recovered.

results reported in Tables 2 and 4 clearly show that higher palladium loadings are required in the microwave-activated reaction for optimal conversion to occur. Moreover, we noticed a more limited scope with these conditions. Indeed, thermally sensitive substrates were rapidly degraded (Table 5, entries 4 and 6), whereas hindered, reducible functionalities remained unaffected (Table 5, entries 5 and 8). Surprisingly, we also noticed difficulties in reducing alkynes, in that they required high palladium loadings even for structurally simple diphenylacetylene (**21**). Similar trends were also observed for the hydrogenolysis processes (Table 5, entries 10–12), rendering the scope of the microwave-assisted reaction quite limited. However, to the credit of this protocol, we observed short reaction times (15 min) and low contamination of the solvent and product by palladium residues, thereby confirming the formation of a heterogeneous Pd/C catalyst (see Table 5).

Expecting the in situ formation of Pd^0/C during the reaction, we measured the palladium concentration in solution by ICP-MS after separation of the charcoal by filtration.

The measurements were repeated for five different sets of conditions, including olefin reductions and debenzylation reactions under thermal and MW conditions (Table 6). To our delight, we observed only trace amounts, in the ppb range, of palladium species in solution, indicating that virtually all of the palladium introduced was adsorbed onto charcoal. This feature renders the catalysis more valuable from both an economic and an environmental perspective, since the palladium can be exhaustively recovered.

Table 6. Measurement of the palladium leaching into the solvent.

Entry	Substrate	Product	Pd loading [mol %]	Conditions[a]	Pd leaching[b] [ppb]
1	**1**	**2**	0.05	A	0.19
2	**13**	**14**	0.1	A	1.45
3	**26**	**27**	0.2	A	1.24
4	**1**	**2**	0.5	B	3.71
5	**24**	**25**	0.5	B	0.19

[a] Conditions A: substrate (5 mmol), $Pd(OAc)_2$, charcoal (90 wt %/$Pd(OAc)_2$), MeOH (6.5 mL), H_2 (1 atm, balloon), 25 °C, 12 h. Conditions B: substrate (5 mmol), $Pd(OAc)_2$, charcoal (90 wt %/$Pd(OAc)_2$), MeOH (6.5 mL), cyclohexene (6 equiv), MW, 150 °C, 15 min. [b] Determined by ICP-MS.

Having observed that palladium was adsorbed onto charcoal with great efficiency, we were interested in utilising transmission electron microscopy (TEM) for further characterisation of the Pd^0/C formed (Figure 1). The catalyst exhibits a uniform distribution of palladium nanoparticles, which have an average size of 4.4 nm (Figure 2). It is expected the mild conditions used in these reactions preclude any sintering processes that could lead to the formation of colloidal particles of higher size and lower catalytic activity. These observations contrast with commercially available catalysts that we have characterised previously,[3e,f] which show a high dispersion in nanoparticle size. Our home-made Pd^0/C catalyst shows exceptional control of the size and spherical shape of the palladium nanoparticles, despite our extremely simple experimental conditions.

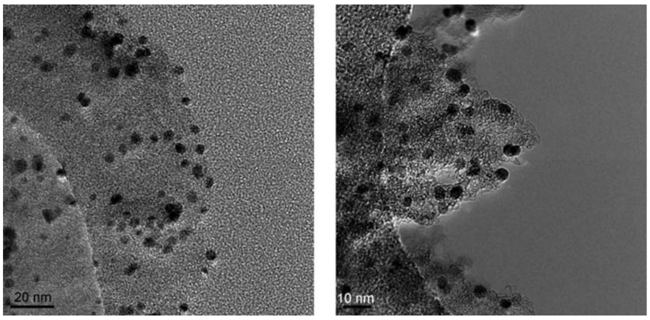


Figure 1. Transmission electron microscopy (TEM) images of the in situ generated Pd^0/C catalyst at two different magnifications.

Lastly, having a Pd^0/C catalyst with well-defined and controlled properties, we explored its reusability in the reduction of stilbene (**1**) to dibenzyl **2**. Evidently, since we are aware of the pyrophoric nature of Pd^0/C catalysts, we carefully degassed the methanolic solution prior to catalyst introduction. In order to show the potential of our home-made Pd^0/C catalyst, we performed these tests on a 0.1 mol scale (19 g of starting material). At such an unusual laboratory scale, we were able to use the Pd^0/C catalyst in at least eight consecutive runs with virtually identical yields (97–99 %). For each run, the catalyst recovery, by simple filtration, was excellent (≈95 %) and allows convenient and efficient recycling.

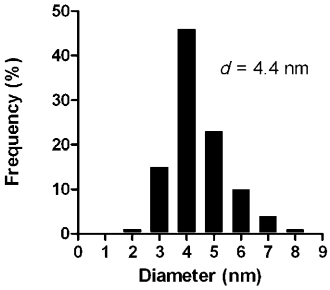


Figure 2. Palladium nanoparticle diameter distributions measured from the TEM images.

Conclusion

We have reported a convenient protocol for the hydrogenation of alkenes and alkynes and for the hydrogenolysis of *O*-benzyl ethers using a home-made Pd^0/C catalyst. The originality of this work lies in the in situ preparation of the catalyst from a homogeneous source of palladium ($Pd(OAc)_2$) concomitant to the progress of the reaction, leaving products and solvents virtually free of palladium residue (<4 ppb). Our protocol allows low palladium loadings (0.025 mol %) and mild conditions (25 °C) and has proved to be reliable on a multigram scale (0.1 mol). Furthermore, we have shown that microwave irradiation can shorten the reaction time (15 min vs. 12 h), but thermally sensitive substrates are not well tolerated and higher palladium loadings are required. We believe that this work will be of interest for synthetic and medicinal chemists that are concerned with cost effective, sustainable processes. Extension of the scope of the in situ generated Pd/C catalyst to other reductive processes is currently underway in our laboratory.

Experimental Section

General procedure for the hydrogenation of alkenes and alkynes and the hydrogenolysis of *O*-benzyl ethers under thermal conditions (Table 2 and Table 4): Charcoal (90 wt %/Pd) and $Pd(OAc)_2$ (THF solution, 0.05–1.5 mol %, see the corresponding Tables) were added to a stirred solution of the substrate (5 mmol) in MeOH (6.5 mL) at 25 °C. The resulting mixture was stirred for 12 h under H_2 atmosphere (1 atm, balloon), filtered and concentrated under reduced pressure. The crude was usually isolated with analytical purity. In some cases it was purified by flash column chromatography to give the corresponding product.

General procedure for the hydrogenation of alkenes and alkynes and the hydrogenolysis of *O*-benzyl ethers under microwave conditions (Table 5): Charcoal (90 wt %/Pd), $Pd(OAc)_2$ (THF solution, 0.5–2 mol %, see Table 5), and cyclohexene (30 mmol) were added to a stirred solution of the substrate (5 mmol) in MeOH (6.5 mL) at 25 °C. The resulting mixture was stirred for 15 min at 150 °C under microwave irradiation, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography to give the corresponding product.

See the Supporting Information for more experimental details.

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