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Mild and Selective Hydrogenation of Nitro Compounds using Palladium Nanoparticles Supported on Amino-Functionalized Mesocellular Foam

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We present the utilization of a heterogeneous catalyst comprised of Pd nanoparticles supported on aminopropyl-functionalized siliceous mesocellular foam (Pd^0–AmP–MCF) for the selective hydrogenation of aromatic, aliphatic, and heterocyclic nitro compounds to the corresponding amines. In general, the catalytic protocol exclusively affords the desired amine products in excellent yields within short reaction times with the reactions performed at room temperature under ambient pressure of H_2. Moreover, the reported Pd nanocatalyst displayed excellent structural integrity for this transformation as it could be recycled multiple times without any observable loss of activity or leaching of metal. In addition, the Pd nanocatalyst could be easily integrated into a continuous-flow device and used for the hydrogenation of 4-nitroanisole on a 2.5 g scale, where the product *p*-anisidine was obtained in 95% yield within 2 h with a Pd content of less than 1 ppm.

Introduction

Aromatic and heterocyclic amines are fundamental building blocks in industrial-scale organic synthesis, as they are frequently used as intermediates for the production of various dyes, pharmaceuticals, pigments, and polymers.[1] Classical methods for the preparation of amines involve the reduction of the corresponding nitro compounds by the use of stoichiometric Fe[2] or Zn[3] reagents in the presence of various proton sources, or by other catalytic protocols employing toxic reducing agents, such as H_2S,[4] N_2H_4,[5] or $NaBH_4$.[6] During the past decades, catalytic hydrogenation protocols utilizing Pd/C, Pt/C, or Raney Ni as catalysts have become the methods of choice for the reduction of nitro compounds.[7] Although these heterogeneous catalysts generally display good performance in nitro group reduction, they are unfortunately associated with chemoselectivity issues if other reducible groups are present in the substrate.

Consequently, significant attention has been dedicated to the development of new catalytic hydrogenation systems that display higher selectivity towards the reduction of the nitro functionality.[7,8] More recently, metal-nanoparticle-based catalysts have emerged as attractive and green alternatives for the hydrogenation of nitro compounds, as they have shown to exhibit excellent activities and selectivities under mild reaction conditions and low H_2 pressures.[9] In addition, heterogeneously supported nanocatalysts offer several practical advantages, such as simpler procedures for separation and recycling, as well as reduced amount of metal impurities in the final products, which make these catalysts attractive from an economic and environmental point of view.[10] Furthermore, an appropriately chosen support material for the nanometal species can provide an opportunity for the catalyst to be integrated into a device for flow chemistry, which enables the catalytic protocol to be scaled-up and streamlined.

Our group recently reported on the development of a heterogeneous catalyst comprised of Pd nanoparticles immobilized on amino-functionalized siliceous mesocellular foam (Pd^0–AmP–MCF, Figure 1a) and its successful application in a wide range of organic transformations.[11] In all cases, the Pd nanocatalyst has exhibited excellent activity and recyclability, which can be ascribed to its small and well-dispersed Pd nanoparticles, predominantly in the size range of 1.5–3.0 nm (Figure 1b), and the ideal properties of the mesoporous MCF material. The MCF support consists of a three-dimensional network of pores, which provides a large surface area that enables high catalyst loadings, together with shielding of the Pd nanoparticles from mechanical grinding, thus reducing the leaching of metal into solution. Moreover, the large pore windows ($\approx$14 nm) of the MCF allow for efficient transfer of organic molecules in and out of the material, granting unhindered access to the Pd nanoparticles supported within the pores.

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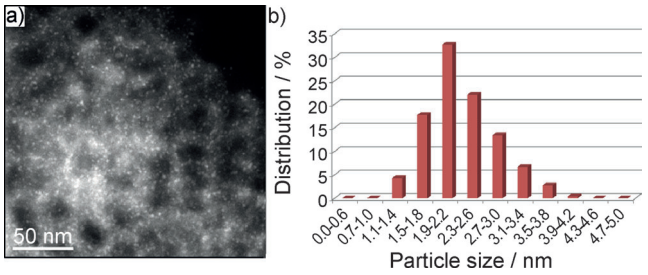


Figure 1. a) Image of the Pd^0–AmP–MCF nanocatalyst taken by high-angle annular dark-field (HAADF)-STEM, showing well-dispersed Pd nanoparticles. b) Particle size distribution of the Pd^0–AmP–MCF nanocatalyst determined by HAADF-STEM.

Recently, we disclosed the use of Pd^0–AmP–MCF as a selective and recyclable catalyst for the transfer hydrogenation of a variety of nitro compounds into the corresponding amines, utilizing the cheap and readily available natural product γ-terpinene as the hydrogen donor.[11a] Although, the catalytic protocol displayed satisfying activity for most of the tested substrates, it required the use of elevated temperatures (80 °C) and an excess of the hydrogen donor to give high yields of the desired amine products. Moreover, this protocol was not ideal from an atom-economical perspective because *p*-cymene was formed as the byproduct in stoichiometric quantities, which required the use of column chromatography for obtaining the pure amine products. To circumvent this problem and concurrently achieve a more efficient and eco-friendly catalytic system for the reduction of nitro compounds, we therefore sought to evaluate the performance of the Pd^0–AmP–MCF in combination with H_2 as the reducing agent.

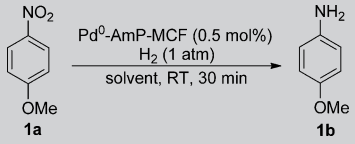
In this work, we report on the use of Pd^0–AmP–MCF as a highly efficient catalyst for the hydrogenation of a wide range of nitro compounds into the corresponding amines. All reactions were performed at room temperature under an atmospheric pressure of H_2, under which the amine products were generally obtained in excellent yields and high purity after only a simple separation of the Pd nanocatalyst by centrifugation and concentration of the reaction solution in vacuo. Furthermore, the Pd nanocatalyst proved suitable for integration into continuous-flow hydrogenation reactors, which enabled the present catalytic protocol to be scaled up in a straightforward fashion.

Results and Discussion

Initial screening

The catalytic evaluation of the Pd nanocatalyst commenced with a solvent screening, using 4-nitroanisole (**1 a**) as the model substrate (Table 1). In a typical reaction, **1 a** (1.60 mmol) and Pd nanocatalyst (0.5 mol%) were suspended in a 2 mL volume of solvent and vigorously stirred under 1 atm of H_2 at room temperature. The conversion of each reaction was determined after 30 min by the withdrawal of an aliquot, which was analyzed by ^{1}H NMR spectroscopy. In general, the Pd nanocatalyst was found to be compatible with a broad range of solvents, including both polar and unpolar solvents. Interestingly, the green solvents[12] 2-methyltetrahydrofuran (Me-THF) and EtOAc were demonstrated to be some of the most efficient ones for this catalytic system, affording 62% and 64% conversion, respectively (Table 1, entries 1 and 2). The hydrogenation was also found to proceed efficiently in solvents such as toluene, α,α,α-trifluorotoluene (TFT) and MeCN, which all resulted in conversions exceeding 50% (entries 3–5). Moderate conversions were obtained in the alcoholic solvents MeOH, EtOH, and 2-BuOH (entries 6–8), whereas solvents such as DMF, dioxane, and H_2O gave significantly lower amounts of amine **1 b** (entries 9–11).

Table 1. Solvent screening of the Pd^0–AmP–MCF-catalyzed hydrogenation of 4-nitroanisole (**1 a**).[a]



Entry	Solvent	Conv. [%][b]
1	Me-THF	62
2	EtOAc	64
3	MeCN	63
4	toluene	57
5	TFT	54
6	MeOH	44
7	EtOH	38
8	2-BuOH	30
9	DMF	21
10	dioxane	17
11	H_2O	17
12[c]	toluene	14
13[d]	toluene	0

[a] Reaction conditions: substrate **1 a** (1.60 mmol) and Pd^0–AmP–MCF (0.5 mol% with respect to Pd content) were suspended in solvent (2 mL), and the reaction was vigorously stirred at room temperature for 30 min under 1 atm of H_2 (using balloon). [b] Conversion determined by ^{1}H NMR analyses [conv. (%) = (integral amine **1 b**)(integral nitro compound **1 a** + integral amine **1 b**)$^{-1}$ × 100%]. [c] Performed with 0.5 mol% Pd/C. Two different batches (one 5 wt% and one 10 wt% Pd) were tested and both gave similar results. [d] Performed without Pd^0–AmP–MCF.

A control reaction with commercially available Pd/C was performed in toluene to allow for a direct comparison of its activity with that of Pd^0–AmP–MCF (Table 1, entry 12). Pd/C displayed a substantially lower activity than the Pd nanocatalyst, demonstrating the advantage of using a heterogeneous catalyst that possesses a well-defined nanostructure and a higher surface-to-volume ratio of metal. In addition, a blank experiment without the Pd nanocatalyst was performed, and as expected it resulted in no conversion of the starting material (Table 1, entry 13).

Reaction scope

Having identified EtOAc as the most suitable solvent for this catalytic system, we next chose to study the substrate scope, which was designed to cover a range of aromatic, aliphatic, and heteroaromatic nitro compounds (Table 2). Generally, the

Table 2. Substrate scope of the Pd^0–AmP–MCF-catalyzed hydrogenation of nitro compounds.[a]

$$R\text{-}NO_2 \xrightarrow[H_2\ (1\ atm),\ RT,\ EtOAc]{Pd^0\text{-}AmP\text{-}MCF\ (cat.)} R\text{-}NH_2$$

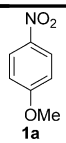
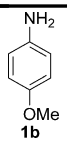
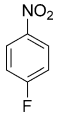
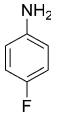
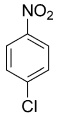
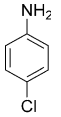
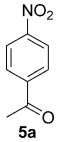
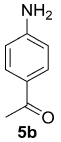
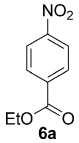
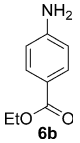
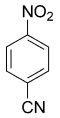
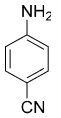
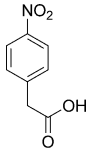
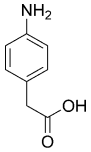
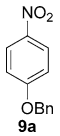
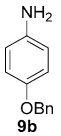
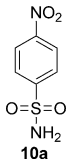
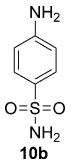
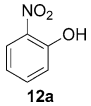
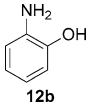
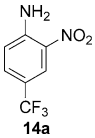
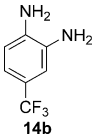
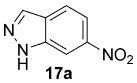
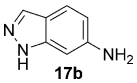
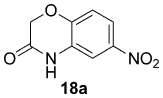
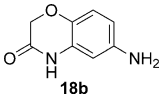
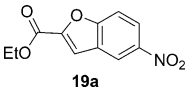
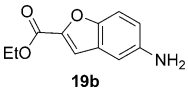
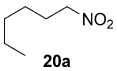
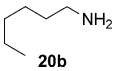
Entry	Substrate	Product	Time [h]	Yield [%][b]
1	 **1a**	 **1b**	1	99
2	 **2a**	 **2b**	0.75	90
3	 **3a**	 **3b**	1	97
4	 **4a**	 **4b**	2	91[c]
5	 **5a**	 **5b**	0.75	99
6	 **6a**	 **6b**	0.75	98
7	 **7a**	 **7b**	2	99
8	 **8a**	 **8b**	1.5	99
9[d,e]	 **9a**	 **9b**	8	96
10[d,f]	 **10a**	 **10b**	4	99
11	 **11a**	 **11b**	1	99
12	 **12a**	 **12b**	2	99

Table 2. (Continued)

Entry	Substrate	Product	Time [h]	Yield [%][b]
13	 **13a**	 **13b**	5	99
14	 **14a**	 **14b**	2	95
15[d,e]	 **15a**	 **15b**	7	97
16	 **16a**	 **16b**	2	99
17[d,e,g]	 **17a**	 **17b**	14	96
18[h,i]	 **18a**	 **18b**	7	98
19[d,e,i]	 **19a**	 **19b**	4	99
20	 **20a**	 **20b**	2	>95[j]

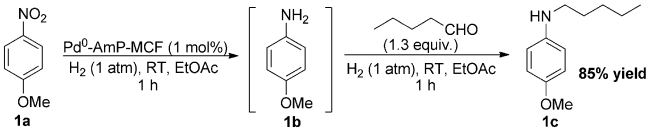
[a] Reaction conditions unless otherwise noted: nitroarenes (1.60 mmol) and Pd^0–AmP–MCF (0.5 mol% with respect to Pd content) were suspended in EtOAc (2 mL) and the reaction was stirred under 1 atm of H_2 (using balloon) at room temperature for the time given in the table. [b] Isolated yields. [c] 6% of aniline **2b** present alongside the desired 4-chloroaniline **4b** (i.e., 97% total yield of both aniline products). [d] Substrate amount of 0.80 mmol was used. [e] 1 mol% Pd^0–AmP–MCF was used. [f] Reaction performed in a 1:1 mixture of EtOAc/MeOH (2 mL). [g] Reaction performed in a 1:1 mixture of EtOAc/EtOH (2 mL). [h] Substrate amount of 0.40 mmol was used. [i] Reaction performed in a 1:1 mixture of EtOAc/DMF (2 mL). [j] Yield determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

amine products were obtained in excellent yields and high purities after a simple purification procedure involving separation of the Pd nanocatalyst by centrifugation and concentration of the reaction solution in vacuo. This straightforward purification of the reaction was made possible by the high selectivity exhibited by Pd nanocatalyst, which allowed for the exclusive formation of the desired amines over other intermediary reduction products such as azo compounds, hydroxyl amines, oximes, and nitrones.

For the reaction of model substrate **1a**, it was possible to achieve a quantitative yield of **1b** by simply extending the reaction time to 1 h (Table 2, entry 1). In the case of unsubstituted nitrobenzene **2a**, the hydrogenation was found to proceed faster and full conversion was reached already after only 45 min; however, as a result of the volatility of product **2b** it could only be isolated in a yield of 90% (entry 2). The catalytic system was shown to tolerate a variety of *para*-substituted nitrobenzene derivatives, bearing fluoro, chloro, ketone, ester,

cyano, and carboxylic acid functional groups, giving the corresponding anilines **3**–**8b** in excellent yields within short reaction times ranging from 45 min to 2 h (entries 3–8). Interestingly, in the case of substrate **9a** having a *p*-benzyloxy group, the Pd nanocatalyst was found to selectively reduce the nitro group without giving rise to any debenzylated products, and consequently aniline **9b** could be obtained in 96% yield after 8 h (entry 9). By performing the hydrogenation for 4 h under slightly diluted conditions in a 1:1 mixture of EtOAc/MeOH, it was also possible to quantitatively reduce 4-nitrobenzenesulfonamide **10a** into 4-aminobenzenesulfonamide **10b**, which constitute an important fragment in several antimicrobial agents (entry 10).[13] Nitroarenes substituted in one or both *ortho* positions, as exemplified with 2-nitro-1,1′-biphenyl **11a**, 2-nitrophenol **12a**, 1,3-dimethyl-2-nitrobenzene **13a**, and 2-nitro-4-(trifluoromethyl)aniline **14a**, could all be converted to the corresponding aniline products **11b**–**14b** in 95–99% yield (entry 11–14). Among these substrates, the doubly *ortho*-methylated **13a** gave the slowest reaction and needed 5 h to reach completion, demonstrating the importance of unhindered access of the nitro functionality to the catalyst surface. Consequently, the hydrogenation of the bulky 1-nitronapthalene **15a** was also found to proceed slowly, requiring the use of elevated catalyst loadings and longer reaction times to give satisfactory yields of **15b** (entry 15). To our delight, the catalytic protocol also proved effective in the hydrogenation of both heterocyclic and aliphatic nitro compounds, allowing for the preparation of amines **16b**–**20b** in excellent yields (Table 2, entries 16–20). In the case of the heterocyclic substrates **17a**–**19a**, the slower rate of reduction can be ascribed to a combination of large steric bulk and inhibition of the Pd nanocatalyst by the additional heteroatom functions.

Unfortunately, the Pd nanocatalyst proved to be incapable of selectively reducing the nitro group of substrates containing olefin, acetylene, bromo, or formyl substituents under the optimized reaction conditions (results not shown in Table 2). In the hydrogenations of 4-nitrophenylacetylene and 3-nitrostyrene, the carbon–carbon multiple bonds were found to undergo a faster reduction than the nitro functionality and consequently the corresponding ethyl nitroarenes were formed almost exclusively after 5–10 min as determined by ^{1}H NMR spectroscopy.[14] For the reaction of 1-bromo-4-nitrobenzene, nitro group reduction and debromination were observed to occur simultaneously, and thus it was only possible to obtain aniline **2b** selectively. The selective formation of aminobenzaldehydes in adequate yields by this catalytic protocol was prevented by a fast condensation reaction between amine- and formyl-containing products, which resulted in a complex mixture of polymeric byproducts. However, we identified that this latter reactivity could be exploited to yield monoalkylated amine products as previously demonstrated by Sreedhar et al. using gum acacia stabilized Pd nanoparticles.[15] To demonstrate that our Pd^0–AmP–MCF could also function as a catalyst for this transformation, a reaction was set up in which nitroarene **1a** was first reduced into the corresponding aniline **1b** by using the standard conditions, which was followed by addition of pentanal (1.3 equiv) to form the imine condensation product that was rapidly reduced by the Pd nanocatalyst into the desired monoalkylated amine in 85% yield (Scheme 1).



Scheme 1. Pd^0–AmP–MCF-catalyzed one-pot sequential transformation to access monoalkylated amine **1c** from nitroarenes **1a**.

Recyclability, kinetic, and stability studies

To provide for an initial assessment on the reusability of the Pd nanocatalyst, a recycling study was conducted in which the hydrogenation of nitroarene **1a** was investigated over five cycles in EtOAc for 1 h. In conformity with our previous work on the Pd^0–AmP–MCF,[11] an excellent recyclability was observed also for this transformation because the catalyst afforded amine **1b** quantitatively over all cycles. Furthermore, to gain insights into how the rate of the reaction was affected upon consecutive reuse of the Pd nanocatalyst, a kinetic study was conducted on the first and fifth cycle, in which the conversion of **1a** was monitored over time (see the Supporting Information, Figure S2). By comparing the slope of the two curves during the first 30 min, it could be concluded that the recycled Pd^0–AmP–MCF maintained approximately 88% of the original activity, demonstrating its high stability under the present reaction conditions. Another interesting observation that can be made upon inspection of Figure S2 is that the kinetic profile belonging to the reaction of the unused catalyst seems to remain linear up to 95% conversion. This behavior is uncommon for catalytic reactions, which normally display an exponential decline in reaction rate over time as the substrate concentration gets lower. A possible explanation for the zero-order kinetics is that the nitro substrate binds strongly to the catalyst surface, and in this way the catalyst may become saturated. The rate of the reaction is thus proportional to the substrate bound to the catalyst, and this amount would then become constant and independent of the substrate concentration between 0 and 95% conversion. By following the reactions by ^{1}H NMR spectroscopy over time, we could in almost all cases observe that the unreacted nitro compound and the product amine constituted the major species in solution during the entire course of the reaction, whereas the corresponding nitroso and hydroxylamine intermediates were typically present in trace amounts at most. This observation suggests that these intermediates are not readily released into solution by the catalyst, and once formed they are most likely quickly reduced all the way to the aniline product.

Further evidence for the robustness of the Pd^0–AmP–MCF was obtained from TEM analyses of catalyst recovered from the fifth cycle. As depicted in Figure S1, the majority of the Pd nanoparticles were still found to be in the 1.5–3.0 nm size range and only a small degree of agglomeration into larger clusters could be seen. The retained Pd nanoparticle size indicates that

the reaction proceeds through a heterogeneous mechanism. A "boomerang"-type mechanism,[16] in which homogeneous and catalytically active Pd species are continuously released and redeposited seems less likely. This hypothesis was further supported by Inductively Coupled Plasma Optical Emission Spectroscopy (ICP–OES) analysis of a liquid aliquot taken from the Pd^0–AmP–MCF-catalyzed hydrogenation of **1a**, which showed no detectable amounts of Pd in the reaction solution (<0.1 ppm).

Flow study

To demonstrate the practical utility and scalability of the developed catalytic protocol, we chose to evaluate the applicability of the Pd^0–AmP–MCF nanocatalyst for integration into a continuous-flow hydrogenation reactor (H-Cube, ThalesNano, Figure 2).[17] The substrate solution (**1a**, 2.50 g, in EtOAc, 165 mL) was delivered into the device through an HPLC-like platform, the H_2 was generated in situ by electrolysis of water and the cartridge container was charged with a catalyst amount of 70 mg of Pd^0–AmP–MCF (12 wt% Pd, 0.48 mol% Pd) and equipped with a heating device. The substrate solution was mixed with H_2 in the reactor before it was allowed to flow through the Pd nanocatalyst, which was prepacked in replaceable cartridges (30 mm × 8 mm), at a flow rate of 1.5 mL min^{-1}. Gratifyingly, this methodology furnished aniline **1b** in excellent yield (1.90 g, 95%) and purity after concentration of the collected liquid phase in vacuo. Furthermore, ICP–OES analysis of the isolated amine product determined the Pd content to 0.2 ppm, demonstrating that the Pd^0–AmP–MCF is highly stable under these continuous flow conditions and only leaches negligible amounts of Pd.

Comparison with other catalytic nitro reduction systems

The Pd^0–AmP–MCF nanocatalyst compares favorably with previously reported systems for the hydrogenation of nitro compounds. It has the advantage of working efficiently under mild reaction conditions, whereas some of the other catalytic systems require elevated temperatures and long reaction times to give high yields of the desired amine products.[8] Moreover, the Pd nanocatalyst constitutes an environmentally friendly option as it allows for hydrogen gas to be utilized as the reducing agent, in contrast to many other catalytic systems that require the use of less green alternatives, such as H_2S,[4] N_2H_4,[5] $NaBH_4$,[6] and silanes.[18] Another benefit of the present catalytic system is that it shows a relatively broad substrate scope, enabling for instance both heterocyclic and aliphatic nitro compounds to be reduced into the corresponding amines. This substrate scope has not been demonstrated with some of the previously reported hydrogenation protocols, which have only been evaluated for the reduction of nitroarenes.[9b,c–g,i,j]

Conclusions

The application of a heterogeneous catalyst consisting of Pd nanoparticles immobilized on aminopropyl-functionalized siliceous mesocellular foam (Pd^0–AmP–MCF) is reported for the selective hydrogenation of a wide range of nitro compounds to amines in green solvents at room temperature and under ambient pressure of hydrogen gas. The catalytic protocol used is highly efficient and environmentally friendly as the desired amine products could be obtained in excellent yield and purity after a simple purification procedure involving separation of the catalyst by centrifugation and subsequent concentration of the reaction solution in vacuo. Moreover, the Pd nanocatalyst exhibited high stability and low metal leaching, which allowed it to be reused multiple times without any significant loss of activity. Additionally, the Pd nanocatalyst could be easily integrated into a continuous-flow hydrogenation reactor, which makes it a highly attractive and economical process for nitro compound reduction on an industrial scale. Future work in our group will be dedicated to the continued examination of this Pd nanocatalyst for other chemical transformations in flow.

Experimental Section

General information

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Flash chromatography was performed on an automated flash chromatography instrument using silica-based cartridges with UV detection for fraction collection. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR measurements were recorded on a Bruker Avance 400 MHz instrument. Chemical shifts in ^{1}H NMR and ^{13}C NMR spectra are reported in ppm, relative to solvent peaks (^{1}H δ_H: $CDCl_3$ 7.26 or [D_6]DMSO 2.50 and ^{13}C δ_C: $CDCl_3$ 77.0 or [D_6]DMSO 39.5). Chemical shifts in ^{19}F NMR spectra are reported in ppm, relative to the internal standard fluoroben-

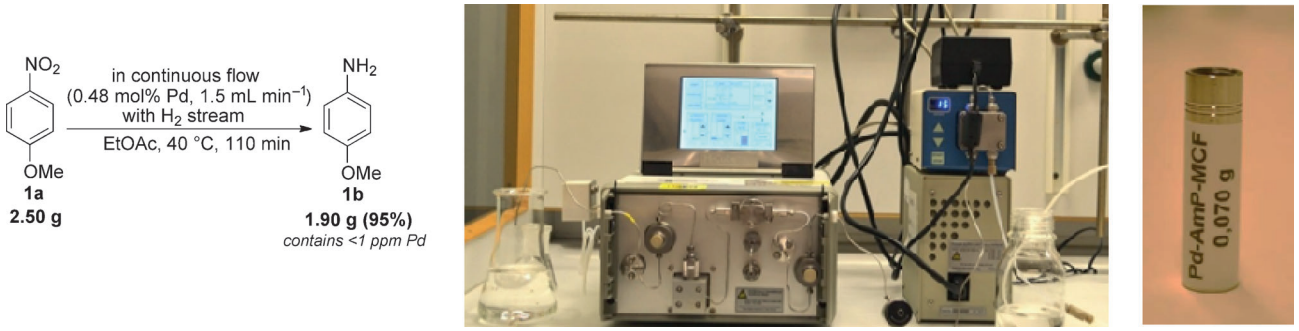


Figure 2. Continuous-flow chemistry experiment using an H-Cube hydrogenation reactor and prepacked cartridge with Pd^0–AmP–MCF nanocatalyst.

zene (^{19}F δ_F: −113.2). The following abbreviations were used to explain multiplicities: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HRMS data were recorded by using time-of-flight ESI detection. The Pd^0–AmP–MCF catalyst (7.90 wt% Pd) was analyzed for palladium leaching by ICP–OES (Medac Ltd, Analytical and Chemical Consultancy Services, UK) and the size/distribution of the palladium nanoparticles was determined by STEM. The HAADF-STEM images, also known as Z-contrast images, were taken at RT using a JEOL JEM-2100F field-emission microscope equipped with a JEOL ADF detector. The microscope was operated at 200 kV. The probe size and camera length used were 0.20 nm and 8 cm, respectively. Flow experiments were performed in an H-Cube provided by ThalesNano. The cartridge used in the flow experiment was packed by ThalesNano with Pd^0–AmP–MCF (70 mg Pd nanocatalyst containing 12 wt% Pd). Consequently, a Pd amount of 0.48 mol% in regards to the substrate 4-nitroanisole **1a** was used in the flow experiment.

Solvent screen of the Pd^0–AmP–MCF-catalyzed hydrogenation of 1-nitroanisole (Table 1)

General procedure: 4-Nitroanisole (1.60 mmol) and Pd^0–AmP–MCF (7.90 wt% Pd, 12.7 mg Pd nanocatalyst, 8.0 μmol Pd, 0.50 mol% Pd to substrate) were suspended in the appropriate solvent (2 mL) in a screw-capped Radley carousel tube. The reaction vessel was then evacuated and filled with hydrogen gas from a balloon, in three repeating cycles. The reaction was allowed to vigorously stir at RT for 30 min with the H_2 balloon attached, after which the reaction was stopped, diluted with $CDCl_3$ (2 mL), transferred to a 50 mL Falcon tube and centrifuged for 5 min at 4000 rpm. An aliquot was withdrawn from the supernatant and the outcome of the reaction was determined by ^1H NMR spectroscopy [Eq. (1)]:

$$\text{Conv. } (\%) = \frac{\text{integral amine } \mathbf{1b}}{\text{integral nitro compound } \mathbf{1a} + \text{integral amine } \mathbf{1b}} \times 100 \quad (1)$$

Substrate scope investigation of the Pd^0–AmP–MCF catalyzed hydrogenation of 1-nitroanisole (Table 2)

General procedure: Nitro compound (0.40–1.60 mmol) and Pd^0–AmP–MCF (7.90 wt% Pd, 3.2–12.7 mg Pd nanocatalyst, 2.0–8.0 μmol Pd, 0.50–1.00 mol% to substrate) were suspended in EtOAc (2 mL) (a few entries were run with other solvents, see the Supporting Information) in a screw-capped Radley carousel tube. The reaction vessel was then evacuated and filled with hydrogen gas from a balloon, in three repeating cycles. The reaction was allowed to vigorously stir at RT for an appropriate time with the H_2 balloon attached, after which the reaction was stopped, transferred to a 50 mL Falcon tube and centrifuged for 5 min at 4000 rpm. The supernatant was collected and the Pd^0–AmP–MCF was washed with EtOAc (2×10 mL) (in some entries another solvent was used, see the Supporting Information) by using centrifugation technique. The wash fractions were combined with the original supernatant and the combined organic solution was concentrated in vacuo to yield the pure amine product (no further purification required). The alipathic amine **20b** was not isolated because of its high volatility and instead it was quantified by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene that was used as an internal standard. Shown in the Supporting Information, Table S1, is a list of all relevant experimental parameters that were used in the reactions of each substrate.

Synthesis of N-(4-methoxyphenyl)-N-pentylamine 1c through a one-pot sequential reaction

4-Nitroanisole (1.60 mmol) and Pd^0–AmP–MCF (7.90 wt% Pd, 12.7 mg Pd nanocatalyst, 8.0 μmol Pd, 0.50 mol% Pd to substrate) were suspended in EtOAc (2 mL) in a shortened screw-capped Radley carousel tube. The reaction vessel was then evacuated and filled with hydrogen gas from a balloon, in three repeating cycles. The reaction was allowed to vigorously stir at RT for 60 min with the H_2 balloon attached, after which pentanal (2.08 mmol) in EtOAC (0.5 mL) was injected and the reaction was allowed to stir for an additional hour. The reaction was transferred to a round-bottomed flask, concentrated in vacuo and diluted with dichloromethane (4 mL), before it was charged onto a silica column cartridge. Purification by column chromatography was performed on an automated flash chromatography instrument with UV detection for fraction collection, using a Pentane/EtOAc solvent gradient (90:10→80:20→0:100). The desired *N*-(4-methoxyphenyl)-*N*-pentylamine **1c** was afforded as a yellow oil (263 mg) in 85% yield.

Flow experiment

A 0.1 M solution of 4-nitroanisole **1a** (2.50 g, 16.3 mmol) was prepared in EtOAc (165 mL) and passed through the H-Cube (ThalesNano), equipped with a cartridge packed with Pd^0–AmP–MCF (12 wt% Pd, 70 mg Pd nanocatalyst, 0.48 mol% Pd), at 40 °C and 1 atm in situ hydrogen pressure (full hydrogen mode, 30 mL H_2 per min) with a flow rate of 1.5 mL min^{-1}. After passing through the flow instrument, the solution was collected and solvents were removed in vacuo to afford pure 4-methoxyaniline **1b** (1.90 g, 15.4 mmol, 95%) without the need of any further purification.

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Keywords: amines · hydrogenation · nanoparticles · palladium · supported catalysts

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[14] It is also possible to achieve full reduction of both functional groups and afford the corresponding ethyl anilines by simply allowing the hydrogenation to continue for prolonged reaction times.

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