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Nanopalladium-Catalyzed Conjugate Reduction of Michael Acceptors – Application in Flow

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A continuous-flow approach towards the selective nanopalladium-catalyzed hydrogenation of the olefinic bond in various Michael acceptors, which could lead to a greener and more sustainable process, has been developed. The nanopalladium is supported on aminofunctionalized mesocellular foam. Both aromatic and aliphatic substrates, covering a variation of functional groups such as acids, aldehydes, esters, ketones, and nitriles were selectively hydrogenated in high to excellent yields using two different flow-devices (H-Cube® and Vapourtec). The catalyst was able to hydrogenate cinnamaldehyde continuously for 24 h (in total hydrogenating 19 g cinnanmaldehyde using 70 mg of catalyst in the H-cube®) without showing any significant decrease in activity or selectivity. Furthermore, the metal leaching of the catalyst was found to be very low (ppb amounts) in the two flow devices.

Introduction

Catalytic hydrogenation is undoubtedly an indispensable tool in organic synthesis both in academia and in industry.[1, 2] In 2013 approximately 25% of compounds in clinical trials and marketed drugs had at least one hydrogenation step in their synthetic route.[3] The chemoselective hydrogenation of the olefinic bond in various Michael acceptors, in particular ketones and aldehydes, are of high interest for the manufacturers of fragrances and other fine chemicals.[4, 5] Therefore, safe, simple and selective procedures that are high yielding are required in order to obtain sustainable processes by minimizing waste and energy consumption. Many elegant protocols using heterogeneous catalysis have been developed for the chemoselective hydrogenation of various α,β-unsaturated carbonyl compounds.[6-18] Most of these protocols are standard batch procedures employing either an excess of a hydride donor or H_2 as the hydrogen source. Although the use of H_2 in catalysis covers two of the "twelve principles of green chemistry" (catalysis and atom economy),[19, 20] batch hydrogenation reactions are cumbersome as they require special safety precautions, pressurized vessels and sometimes autoclave conditions.[2, 21, 22] These limitations can be circumvented by applying catalytic hydrogenation in continuous flow. Since the reactants are introduced in small channels and the residence time on the catalyst is minimized,[23] the risk of explosions are reduced hence covering the twelfth principle (inherently safer chemistry for accident prevention). Other advantages associated with continuous flow are a higher throughput per unit volume and time due to better mass transfer, simple scale up, and better temperature control.[23, 24] Zhang *et al.* have reported on a continuous-flow hydrogenation using Pd/C.[18] This protocol, however, focuses mainly on cinnamaldehyde and the reaction kinetics for the hydrogenation. Kobayashi *et al.*[6,25] have also studied hydrogenation under flow conditions. In one protocol various alkenes were investigated, among them it was only one substrate that contained an α,β-unsaturation.[25] Selective hydrogenation in small scale using microfluid reactors has also been accomplished in good yields.[6, 14, 16]

Recently, the interest of nanotechnology in catalysis has increased as numerous reactions have been performed under milder conditions. The Bäckvall group has recently reported on the preparation and application of a heterogeneous Pd nanocatalyst supported on aminofunctionalized mesocellular foam, Pd^0-AmP-MCF (Figure 1).[26, 27] The nanoparticles are well dispersed on the solid support and are usually around 1-5 nm in size with a palladium loading between 8 and 12 wt%. The catalyst has successfully been employed in a wide range of organic transformations and in general allowing for low catalyst loadings, exhibiting high recyclability and low leaching.[26-33] Herein we wish to report the use of Pd^0-AmP-MCF in the chemoselective hydrogenation of various Michael acceptors in continuous flow.

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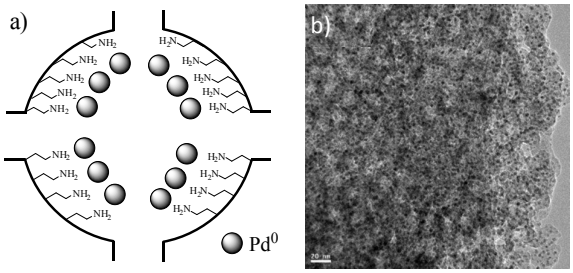


Figure 1. a) A schematic view of the catalyst b) Transmission electron microscopy (TEM) of Pd^0-AmP-MCF.

Results and discussions

Materials

For the primary studies, H-Cube® was used as the continuous-flow device.[34] The instrument is based on an HPLC-like platform and enables temperatures and pressures up to 100 °C and 100 bar respectively. The hydrogen is generated *in situ* by electrolysis of distilled water and mixed together with the liquid phase before flowing through the Pd^0-AmP-MCF (70 mg Pd^0-AmP-MCF with 12 wt% Pd) which is pre-packed in replaceable cartridges (30 × 8 mm) that are placed in a cartridge holder equipped with a heating device. A simplified schematic overview of the hydrogenation set up for the H-Cube® and the Vapourtec is depicted in Figure 2.

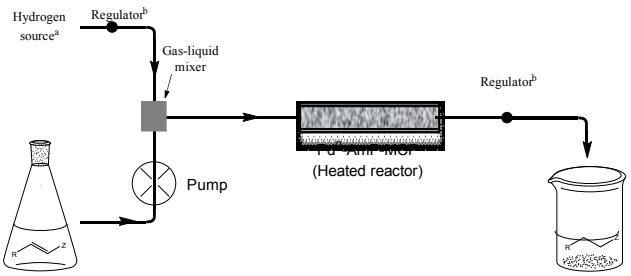
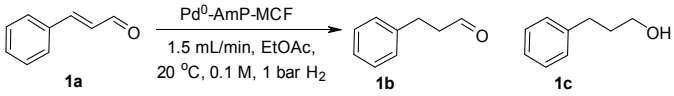


Figure 2. a) For the H-Cube® the hydrogen is generated electrochemically and for the Vapourtec commercial hydrogen is used. b) For the H-Cube® pressure sensors/check valves are an integral part of the instrument while 40 psi back pressure regulators are used for the Vapourtec experiments

Optimization

The selective hydrogenation of cinnamaldehyde (**1a**) to the corresponding 3-phenylpropanal (**1b**) was employed as the model reaction for the initial experiments. As a starting point, the effects of different solvents in terms of conversion and selectivity were investigated. The H-Cube® was set to operate at 1 bar H_2 pressure (Table 1). The highest conversions were obtained in EtOAc, THF and toluene. Among these solvents, the highest selectivity towards **1b** was observed in EtOAc (entry 1). Employing dioxane or CH_3CN as solvents resulted in lower conversions and selectivities (entries 4-5). Other solvents such as acetone or EtOH were examined for this transformation as well. These solvents, however, created high back pressures in the device.[35] Since the best results were obtained in EtOAc, it was chosen as the solvent for further studies.

Table 1. Solvent screening.[a]



Entry	Solvent	Conversion **1b**:**1c** (%)	**1a** (%)
1	EtOAc	85:15	0
2	THF	77:23	0
3	Toluene	80:20	0
4	Dioxane	69:14	17
5	CH3CN	73:13	14

[a] Flow conditions: A 0.1 M solution of **1a** in the solvent indicated was injected in the H-Cube® at a flow rate of 1.5 mL/min and 1 bar H_2 (full H_2 mode, 30 mL H_2/min) at 20 °C. A sample was collected and diluted with $CDCl_3$ and the conversions were determined by ^{1}H NMR analysis.

Substrate scope

In separate experiments we found that the desired product **1b** was stable even under more forcing conditions (50 °C and 50 bar of H_2 pressure) in the described catalytic system, while the double bond in the conceivable intermediate (*E*)-3-phenylprop-2-en-1-ol was saturated under the same conditions to give 3-phenylpropanol (**1c**). Subsequently, we set out to investigate the generality of the described method. Pleasingly, the protocol proved to be selective towards the olefinic bond and various Michael acceptors could be hydrogenated in high to excellent yields under flow conditions (Table 2). The hydrogenation of cinnamaldehyde proceeded with reasonable selectivity and the corresponding 3-phenylpropanal was obtained as a 85:15 mixture of **1b** and **1c** (entry 1). The selective hydrogenation of this particular substrate without using any additives is indeed a challenging task[7, 10, 18] and as a consequence good selectivities (heterogeneous protocols yielding >90% of **1b**) are, to the best of our knowledge, only obtained in batch procedures.[8, 9, 12, 13, 36] Changing the substrate to the closely related enone **2a** resulted in excellent selectivity and the corresponding product (**2b**) was isolated in 98% yield (entry 2). Subjecting enone **3a** to the same hydrogenation conditions resulted in a slight decrease of selectivity and the products **3b** and **3c** were obtained in 90% and 10% yields (entry 3). Furthermore, the protocol was compatible with other α,β-unsaturated systems containing acid (**4a**), ester (**5a**) and cyano (**6a**) functionalities and the corresponding β-saturated products were isolated in excellent yields, nitrile **6a** required a slightly lower flow rate (1.4 mL/min) (entries 4-6). Next, a series of aliphatic α,β-unsaturated Michael acceptors were investigated. For (*E*)-hex-2-enal (**7a**), the system exhibited complete selectivity and hexanal (**7b**) was obtained in 94% yield with no detectable

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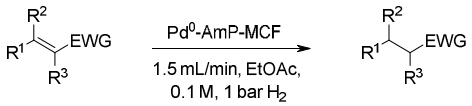
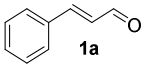
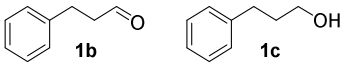
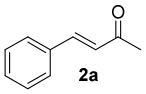
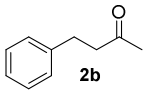
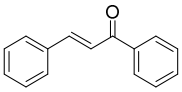
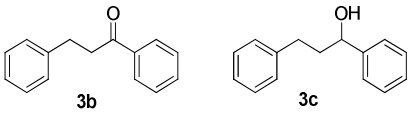
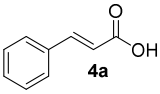
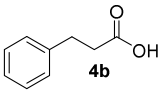
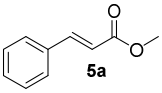
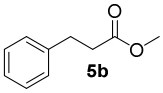
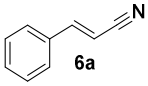
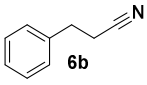
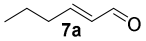
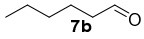
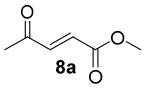
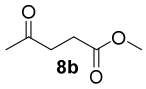
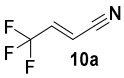
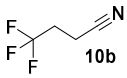
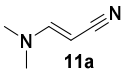
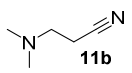
hexan-1-ol (entry 7). Substrate **7b** is of particular interest as it can be used as a component of antibacterial flavor, and fragrance compositions.[37] *α,β*-Unsaturated *γ*-ketoester **8a**, but-2-enenitrile (**9a**) and the electron deficient 4,4,4-trifluorobut-2-enenitrile (**10a**) were also selectively hydrogenated in excellent yields (entries 8-10). Interestingly, the nitrile substituent in enamine **11a** was unaffected under the standard conditions while hydrogenation of the closely related **12a** resulted in **12c** as the only product and **12c** was obtained in 65% yield at 60 °C (entry 12).[38] The olefinic bond was selectively hydrogenated in the cyclic *α,β*-unsaturated ketone **13a** and the corresponding saturated compound was obtained in high yield as a *cis*/*trans* mixture (entry 13). In the hydrogenation of compound **13a**, the corresponding oxidized product **13c** (thymol), resulting from disproportionation, was also obtained in 5% yield. On the contrary, the selective hydrogenation of cyclohexenone **14a** proceeded smoothly and cyclohexanone (**14b**) was obtained in quantitative yield (entry 14). Both of these protocols could represent industrially important processes. For instance, **13b** may be used for obtaining mint-like flavors after resolution.[39] As an interesting extension of this protocol, we investigated the reactivity of the challenging *E*-(2-nitrovinyl)benzene under flow conditions. Although analysis of the crude ^{1}H NMR spectrum indicated full consumption of starting material the presence of the expected (2-nitroethyl)benzene could not be confirmed and a mixture was obtained that we did not explore further. Additionally, it should be noted that the catalyst was highly stable and the same cartridge was used for the majority of the substrates in the scope.

Table 2. Substrate scope using H-Cube®.[a]



Entry	Substrate	Product	Temp. (˚C)	**b**(%)[b]	**c**(%)[c]
1	 **1a**	 **1b** **1c**	20	85[c]	15
2	 **2a**	 **2b**	20	98	-
3	 **3a**	 **3b** **3c**	20	90[c]	10
4	 **4a**	 **4b**	20	97	-
5	 **5a**	 **5b**	20	99	-
6	 **6a**	 **6b**	30	99[d]	-
7	 **7a**	 **7b**	20	94[c]	-
8	 **8a**	 **8b**	20	97	-
9	 **9a**	 **9b**	20	>99[c]	-
10	 **10a**	 **10b**	20	>99[c]	-
11	 **11a**	 **11b**	20	-	-

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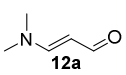
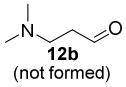
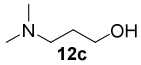
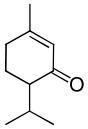
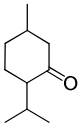
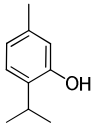
12	 **12a**	 **12b** (not formed)	 **12c**	60	-	70
13	 **13a**	 **13b**	 **13c**	50	90[c,e]	5[e]
14	 **14a**	 **14b**		20	>99	-

[a] Conditions (isolation): A 0.1 M solution of the substrate in EtOAc was injected in the H-Cube® loaded with a cartridge filled with Pd^0-AmP-MCF (70-80 mg with 12wt% Pd giving 0,08 - 0,09 mmol Pd) at a flow rate of 1.5 mL/min and 1 bar H_2 (full H_2, where H_2 was introduced at 30 mL/min) at the indicated temperature. After removal of the solvent from the eluent, the residue was weighed and analyzed. [b] Isolated yield. [c] The value is based on analysis of the ^{1}H NMR spectrum eluent (without removal of the solvent) using 1,3,5-trimethoxybenzene (added before the hydrogenation) as internal standard. [d] Flow rate: 1.4 mL/min. [e] Hydrogenation occurs to give a 77:23 molar ratio of cis and trans isomeric ketones. Disproportionation (5%) was also found to take place.

To further extend the utility of the presented method, a selected number of substrates were subjected to hydrogenation in another continuous-flow device, i.e. Vapourtec R-series (see Figure 2 for schematic setup) equipped with a standard column reactor. The column was charged with 226-236 mg Pd^0-AmP-MCF and thus a higher throughput than the H-Cube® could be achieved.[40] By taking advantage of this higher capacity more concentrated solutions could also be used. Delivering hydrogen to the column was initially attempted to take place via a gas/liquid membrane reactor (tube in tube) in which hydrogen is delivered in a controlled manner to the reaction mixture via an inner (hydrogen permeable) tube. We found that the capacity of the system became limited due to the low solubility of hydrogen in organic solvents.[41] By replacing the gas/liquid membrane reactor with a T-piece in combination with a back pressure regulator rated at 40 psi it was possible to obtain a steady surplus of hydrogen. After some optimization, stable results with cinnamaldehyde using 1 M solutions were obtained. As can be seen from Table 3, a higher selectivity was observed for substrate **1a** in the Vapourtec than in the H-Cube® and **1b** could now be obtained in 94:6 ratio over **1c** (entry 1). Substrate concentrations for cinnamaldehyde of up to 4 M[42] were also partly successful but with the increased viscosity and need for optimization of each substrate in mind a 1 M solution was chosen for the Vapourtec hydrogenations. Hydrogenation of neat cinnamaldehyde led to clogging of the system. The hydrogenation of **7a** proceeded smoothly and **7b** was obtained in quantitative yield (entry 2). Interestingly, for the cyclic substrates **13a** and **14a**, disproportionation of the substrate occurred at 50 °C and both the corresponding saturated cyclic ketone and phenol were obtained in substantial amounts.[43] Satisfyingly, this disproportionation could be avoided by performing the reaction at lower temperatures (30 °C and 20 °C), providing **13b** and **14b** in excellent yields (entries 3 and 4).

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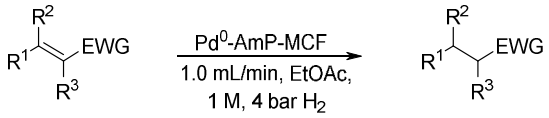
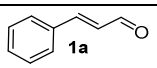
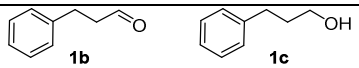
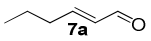
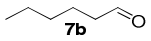
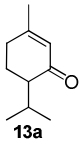
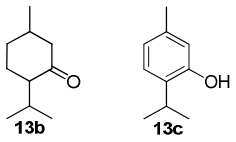
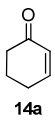
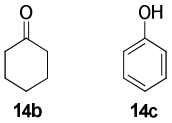
Table 3. Substrate scope using Vapourtec.[a]



Entry	Substrate	Product	Temp. (˚C)	**b**(%)	**c**(%)
1			50	94	6
2			50	>99	0[b]
3			30	95	3[c]
4			20	99.5	0.5[d]

[a] A sample was collected at the out-flow, diluted with $CDCl_3$ and quantified by analysis of the crude ^1H NMR spectrum using 1,3,5-trimethoxybenzene as internal standard. [b] Hydrogenation was performed at 6 bar. [c] Starting material (2%) remained in the mixture. [d] Flow rate: 0.5 mL/min.

Stability and Leaching

A high stability of the presented catalytic system is an essential aspect in the context of "greenness" and sustainability as it will allow for a high substrate/catalyst ratio without decrease in activity. With this in mind we investigated the stability of the Pd^0-AmP-MCF by hydrogenating substrate **1a** as 0.1 M solutions in EtOAc using the H-Cube® and analyzing the eluent by ^1H NMR periodically for extended amounts of time. Two different[43] runs at different pressures were investigated for 24 h at 20 ˚C with a flow rate of 1 mL/min, in one run 18 g substrate (TON 1510) was hydrogenated at 10 bar and in another run 19 g substrate (TON 1594) was hydrogenated at 50 bar. To our delight, the catalyst could efficiently hydrogenate **1a** without any significant decrease in activity or selectivity towards **1b** in both cases.

A constant challenge in heterogeneous catalysis is to minimize the leaching of metal species from the catalyst support into the solution. In order to avoid additional purification steps, a low or negligible metal residue in the final product is desirable. Gratifyingly, ICP-OES analysis (Inductively Coupled Plasma Optical Emission Spectroscopy) of the eluent from the H-Cube® resulting from hydrogenation of **14a** showed less than 2 ppb Pd, giving a total leaching of only 4.4×10^{-7} mmol in this system. This is 5.2×10^{-4}% of the total amount of Pd leached out in the solution. Furthermore, analysis after concentration of the eluent resulting from the hydrogenation in Vapourtec of **1a** showed a minimal 6 ppb Pd, giving a total leaching of only 2.9×10^{-7} mmol in this system which is 1.13×10^{-4}% of the total amount Pd used in the system. The used catalyst was submitted to HAADF-STEM and TEM analysis, which showed formation of few large (>200 nm) MCF particles, although most of the sample showed similar morphology to that of fresh catalyst.[43]

Conclusions

The presented protocol describes an efficient route towards the selective hydrogenation of the olefinic moiety in various Michael acceptors using two different continuous-flow devices. In comparison with current batch protocols the presented method this could be a greener and more sustainable alternative. The catalytic system proved to be highly tolerant towards both aromatic and aliphatic substrates containing functional groups such as aldehyde, ketone, ester and nitriles. The catalyst exhibited high stability as large amounts of cinnamaldehyde (19 g in H-Cube® using a cartridge charged with 70 mg 12% Pd^0-AmP-MCF) could be

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hydrogenated to 3-phenylpropanal without any decrease in catalyst activity or selectivity. Additionally, only negligible metal contamination (ppb amounts) was detected in the final products in both flow devices.

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