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Continuous Flow Hydrogenation of Functionalized Pyridines

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The heterogeneous hydrogenation of substituted pyridines has been accomplished by employing a continuous flow hydrogenation device that incorporates in situ hydrogen generation by electrolysis of H_2O and pre-packed catalyst cartridges. In general, the hydrogenation reactions proceeded smoothly regardless of the supported precious metal catalyst (Pd/C, Pt/C, or Rh/C). By using 30–80 bar of hydrogen pressure at 60–80 °C full conversion was typically achieved in all cases at a flow rate of 0.5 mL min^{-1}, providing the corresponding piperidines in high yields. For disubstituted pyridines, variations in stereoselectivity were observed depending on both the metal catalyst and the temperature/pressure of the hydrogenation reaction. For ethyl nicotinate the selectivity between partial and full hydrogenation could be tuned depending on the hydrogen pressure, solvent, and the choice of supported metal catalyst. Changing the hydrogen source from H_2O to D_2O allowed the preparation of deuteriated derivatives.
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Introduction

Catalytic heterogeneous hydrogenation processes arguably are the most valuable synthetic transformations known.[1] The hydrogenation of organic compounds by addition and/or hydrogenolysis using molecular hydrogen, typically carried out in the presence of a suitable precious metal catalyst, is of great significance, not only in research laboratories, but also in the chemical and pharmaceutical industries.[1] The hydrogenation of substituted pyridines is of particular interest to organic/medicinal chemists[2,3] as the resulting functionalized piperidines are important building blocks and intermediates in the synthesis of both natural products and pharmaceuticals.[4] Because of the aromatic character of the pyridine nucleus, the hydrogenation of these heterocyclic substrates often requires the use of significant hydrogen pressures in combination with elevated temperatures and extended reaction times.[1,2]

In the past few years, interest in the use of microwave heating technology for performing hydrogenation reactions has increased.[5–8] Both single-mode and multimode microwave batch reactors have recently been commercialized that typically allow pre-pressurization of the reaction vessel with reactive gases up to 20 bar.[9,10] For heterogeneous hydrogenation reactions, the use of microwave heating appears to be particularly attractive because the supported metal catalyst (e.g., Pd/C) is often strongly microwave-absorbing.[11] Therefore, selective heating of the catalyst by microwave irradiation will occur under certain conditions, which may result in differences in reaction rates and selectivities compared with experiments performed by using conductive heating.[5–8] On the other hand, the presence of a strongly microwave-absorbing heterogeneous material can lead to intense arcing phenomena,[12] which, in combination with hydrogen gas, poses a severe operational hazard.

In this context, continuous flow hydrogenation technology presents an attractive alternative to batch processing and the recent introduction of the H-Cube, a continuous flow hydrogenation device that incorporates in situ hydrogen generation and pre-packed catalyst cartridges, has provided a safe and reliable method for performing hydrogenation reactions under pressure.[13–16] In this article we investigate the hydrogenation of substituted pyridines under continuous flow conditions and make a qualitative comparison with reaction rates and selectivities recently reported for batch hydrogenation reactions performed by utilizing microwave heating.[7]

Results and Discussion

As a starting point in our investigations we evaluated the hydrogenation of ethyl cinnamate (**1**) as a model substrate by using microwave batch and continuous flow conditions (Scheme 1). As recently demonstrated by Vanier, this type of substrate can be readily hydrogenated over Pd/C on a

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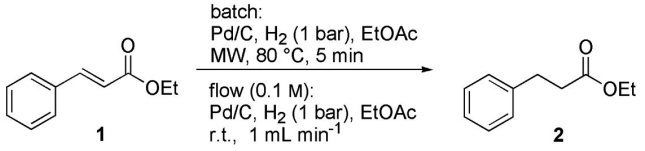
small scale in a single-mode batch microwave system (80 °C, 3 min) by using ethyl acetate as the solvent and around 3.5 bar hydrogen pressure.[6] In our hands this hydrogenation reaction also proceeded well without pre-pressurizing the microwave vial by simply flushing the sealed 10 mL vessel with hydrogen gas through the Teflon septum before insertion into the microwave cavity. In this case, the amount of alkene substrate needs to be kept comparatively small to ensure that a sufficient amount of hydrogen gas for complete conversion is contained in the sealed 10 mL reaction vessel.[6] After 5 min at 80 °C full conversion on a 0.1 mmol scale was obtained by employing 2 mol-% of Pd/C (10% w/w) catalyst, providing the expected propanoic acid ester **2** in 86% isolated yield (TON = 50, TOF = 600 h^{-1}).



Scheme 1. Hydrogenation of ethyl cinnamate under batch and continuous flow conditions.

In subsequent experiments the same hydrogenation reaction was performed by using flow conditions in the H-Cube.[13] In the case of ethyl cinnamate (**1**) clean hydrogenation over a standard Pd/C catalyst (10% w/w) was obtained by using a 0.01 M stock solution (ethyl acetate) at a flow rate of 0.5 mL min^{-1} at room temperature under atmospheric hydrogen pressure (1 bar). The degree of conversion was readily established by monitoring the composition of the reaction mixture after being exposed to the hydrogenation conditions by HPLC analysis. Increasing the concentration to 0.05 and 0.1 M still provided full conversion at room temperature when a 0.5 mL min^{-1} flow rate was applied. From a preparative experiment performed on a 1.5 mmol scale (0.1 M concentration, 0.5 mL min^{-1} flow rate) the desired propanoate **2** was isolated in 89% yield. Trace analysis by ICP-MS confirmed that no significant amount of Pd metal was contained in the hydrogenated sample (Pd content <0.1 μg) and that therefore no substantial leaching of Pd from the catalyst cartridge containing around 15 mg of Pd had occurred. On increasing the flow rate to above 2.0 mL min^{-1} for a 0.1 M ethyl cinnamate concentration, the conversion ultimately started to decrease (Figure 1, a).

To increase the sample throughput we subsequently increased the reaction temperature of the flow hydrogenation process. Recent results presented by Ley and co-workers suggested that increasing the temperature of the catalyst cartridge in H-Cube hydrogenations has a significant effect on maintaining catalyst activity.[14] Therefore, the hydrogenation of ethyl cinnamate (**1**) was additionally performed at higher temperatures. At reaction temperatures ≥80 °C, the flow rate with a more concentrated 0.2 M solution could be increased to 3.0 mL min^{-1} to give full conversion (Figure 1, b). Under these optimized conditions the processing of a sample of ethyl cinnamate (**1**; ca. 2.0 g, 60 mL solution, ca. 10 mmol) was achieved within around 20 min by using a single (and fresh) catalyst cartridge. After around 25 min the conversion in this flow hydrogenation started to slowly decrease and the experiment was terminated.[17] A higher sample throughput can potentially be achieved by using similar flow hydrogenators fitted with larger catalyst cartridges to increase residence times.[18] Based on the measured dead volume of around 140 μL of the catalyst cartridge (30 × 4 mm i.d., 150 mg Pd/C), a residence time of less than 3 s for hydrogenation over the catalyst can be calculated by applying a 3.0 mL min^{-1} flow rate (the residence time in the complete H-Cube system is around 50 s at this flow rate). It has to be emphasized that one of the key differences between the catalytic hydrogenations performed by the batch and continuous flow methods described herein lies in the fact that the amount of heterogeneous "catalyst" is significantly higher in flow processing using the H-Cube than it is in a typical batch experiment (e.g., 150 vs. 2 mg in the experiments described in Scheme 1). In the flow approach, the TON of the catalyst is dependent on how much material is actually processed through the catalyst cartridge. For an experiment on a 1 mmol scale giving full conversion the formal TON is only 7.

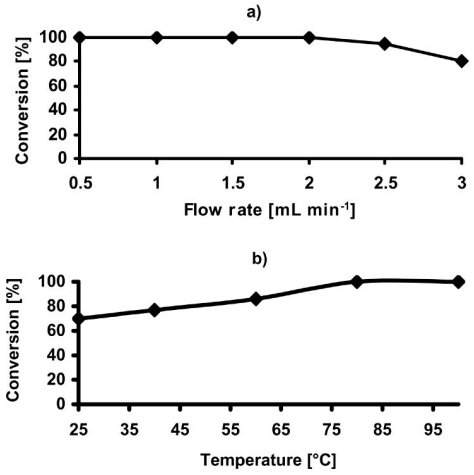


Figure 1. Flow hydrogenation of ethyl cinnamate (**1**) in ethyl acetate over 10% Pd/C (see Scheme 1): a) dependence of conversion on flow rate (0.1 M solution, room temperature); b) dependence of conversion on temperature (0.2 M solution, 3.0 mL min^{-1} flow rate).

Having established the transfer of conditions from microwave batch to flow hydrogenation for the model substrate ethyl cinnamate (**1**), we were interested in investigating more challenging pyridine substrates. Holzgrabe and co-workers (EtOH, 25 bar H_2, 125 °C, 1 h)[5] and Vanier (EtOH, 7 bar H_2, 80 °C, 10 min)[6] succeeded in hydrogenating picolinic acid (**3**) to pipecolic acid (**4**) under microwave batch conditions by employing PtO_2 as catalyst. In both cases full conversion and high isolated product yields were obtained,[5,6] comparing very favorably with classic autoclave hydrogenations. On going from batch to flow conditions the solubility of both the substrate and the product play an important role. Our initial flow experiments involved ethyl acetate as the solvent and full conversion to

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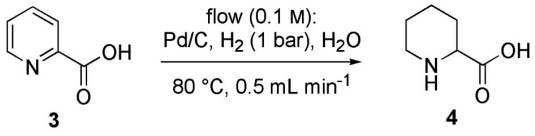
pipecolic acid (**4**) over Pd/C (10% w/w) was obtained with 0.01 M picolinic acid at room temperature by employing a flow rate of 1 mL min^{-1} (1 bar H_2). At higher concentrations the limited solubility of the amino acid product **4** in ethyl acetate became an issue and in addition we found that elevated temperatures needed to be employed to effect complete hydrogenation. Switching to ethanol as the solvent to some extent alleviated the problem and full hydrogenation of picolinic acid could be achieved at a concentration of 0.1 M at 80 °C by employing a flow rate of 0.5 mL min^{-1}. Ultimately, water[19] proved to be the best solvent for the hydrogenation of picolinic acid (**3**) to pipecolic acid (**4**) because both the starting material and the product are sufficiently soluble in this solvent. At 80 °C and 1 bar hydrogen pressure complete conversion could be maintained up to a flow rate of 1.5 mL min^{-1} (0.1 M concentration). Pipecolic acid was isolated in a yield of 97% from a preparative experiment (1.0 mmol) at a flow rate of 0.5 mL min^{-1} (Scheme 2).



Scheme 2. Hydrogenation of picolinic acid under continuous flow conditions.

We were initially surprised that the aromatic pyridine ring in picolinic acid could be fully hydrogenated by using a standard Pd/C catalyst. Typically, metal catalysts such as Pt, Rh, Ru, or Ni are employed to effect the hydrogenation of pyridines,[1,2,5,6] although in a few cases the use of Pd catalysts has also been reported.[3,7,20,21] To evaluate the performance of different supported metal catalysts on the saturation of pyridine rings, flow hydrogenation experiments were performed with a variety of substituted pyridines (**5a**–**g**; Table 1). We were particularly interested in investigating the influence of both the metal catalyst and the temperature/pressure on the hydrogenation of disubstituted pyridines like **5e** and **5f**, in which the stereoselectivity of the obtained piperidines could vary. We also wanted to compare these results with data recently obtained in the microwave-assisted batch hydrogenation of pyridines **5b**–**f**.[7] Because heterogeneous catalytic hydrogenation reactions of pyridines are usually performed in acidic media,[1,2] we selected acetic acid as the solvent of choice for all subsequent studies. Protonation not only activates the pyridines for hydrogenation, but also suppresses catalyst poisoning by the resulting secondary amines.[1] As shown in Table 1, hydrogenation reactions involving pyridines **5a**–**g** in general performed equally well regardless of whether a supported Pd, Pt, or Rh catalyst was employed. By using 30–80 bar of hydrogen pressure at 60–80 °C, full conversion at a flow rate of 0.5 mL min^{-1} was typically achieved in all cases (the use of atmospheric hydrogen conditions was not effective). For example, methyl pyridine-4-carboxylate (**5a**) was successfully hydrogenated over Pt/C, Rh/C, and Pd/C at 80 °C by applying a 30 bar hydrogen pressure (entries 1–3). For this pyridine derivative bearing an electron-withdrawing substituent at C-4, even a hydrogen pressure of 10 bar led to an 81% conversion to piperidine **6a** over Pt/C. Successful flow hydrogenation reactions were also performed on pyridines bearing acid-labile and/or -sensitive protection groups (entries 4–8, **5b** and **5c**). Even at 80 °C in acetic acid these hydrogenation reactions remained clean with no byproducts being observed by careful reaction monitoring by GC–MS/FID analysis. For substituted pyridines bearing simple alkyl groups, a higher hydrogen pressure generally had to be applied to ensure full hydrogenation in one pass through the catalyst cartridge. In the case of pyridine-2-acetic ester **5d** a hydrogen pressure of 80–90 bar at 80 °C was required to achieve full conversion over Pt/C (entry 9). Reducing the hydrogen pressure to 50 bar led to a significant drop in conversion (70%, entry 11). Raising the temperature from 80 to 100 °C at the same pressure only led to a minor improvement in the conversion (76 vs. 70%, compare entries 12 and 11). The flow hydrogenation of pyridine-2-acetic ester **5d** could also be carried out in comparable efficiency by using a Pd catalyst, with $Pd(OH)_2$/C providing the best results (entry 13).

For the disubstituted pyridine-2,5-dicarboxylate **5e**, flow hydrogenation over Pt/C proved to be stereoselective, similar to the analogous batch experiment.[7] Regardless of the type of catalyst employed for the hydrogenation (Pt, Pd, Rh), the *cis* isomer of piperidine diester **6e** was obtained in all cases with around 99% selectivity (entries 14–18). The corresponding *trans* isomer could only be detected in trace amounts (ca. 1%) by GC–MS/FID monitoring.[7] Variation in temperature (60–80 °C) and pressure (30–90 °C) also had no detectable influence on the stereoselectivity. Owing to the electron-deficient nature of the pyridine nucleus in **5e** complete hydrogenation could be performed under comparatively mild conditions [60 °C, 30 bar H_2, $Pd(OH)_2$/C, entry 17].

Another interesting case in this study proved to be the hydrogenation of unsymmetrically disubstituted pyridine **5f** to the corresponding piperidine **6f** (entries 19–27). Hydrogenation by the microwave batch mode using PtO_2 as the catalyst at 80 °C (4 bar H_2) in acetic acid resulted in an approximate 1:1 mixture of the *cis* and *trans* isomers.[7] Flow hydrogenation over Pt/C at 80 °C in the same solvent also produced an approximate 1:1 mixture of diastereoisomers at 30 bar hydrogen pressure (entry 19), albeit only at 80% conversion. Notably, when the pressure in the flow hydrogenation was increased from 30 to 80 bar, not only was full conversion achieved, but the diastereoisomeric ratio was now in favor of the *cis* isomer (1.7:1, compare entries 19, 20, and 21). Switching to a Rh/C (5% w/w) catalyst provided similar diastereoisomeric ratios to those obtained with Pt/C (10% w/w), but the Rh system appeared to have slightly higher catalytic activity allowing the full hydrogenation of pyridine **5f** to piperidine **6f** at 60 °C using 40–50 bar hydrogen pressure (e.g., entry 22). When a Pd/C catalyst was used we were surprised to find that the diastereoisomeric ratio of the piperidine product **6f** was now changed in favor of the *trans* isomer (entries 23–27). In addition, we

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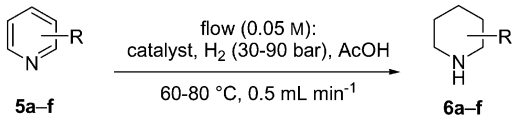
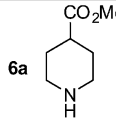
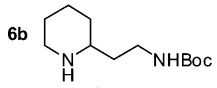
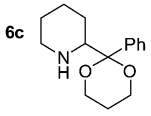
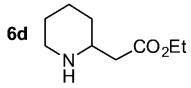
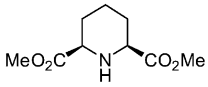
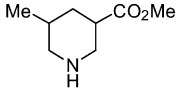
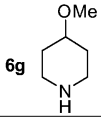
Table 1. Influence of catalyst and hydrogen pressure on the flow hydrogenation of functionalized pyridines **5**.[a]



5a–f **6a–f**

Entry	Catalyst	Temp. [°C]	Pressure [bar]	Piperidine	Conversion [%][b]
1	Pd/C (10 % w/w)	80	30		>99
2	Pt/C (10 % w/w)	80	30		>99 (93)[c]
3	Rh/C (5 % w/w)	80	30	**6a**	>99
4	Pt/C (10 % w/w)	80	30		>99 (74)[c]
5	Pt/C (10 % w/w)	80	50	**6b**	>99
6	Pt/C (10 % w/w)	80	90		>99 (81)[c]
7	Pt/C (10 % w/w)	80	50	**6c**	>99
8	Rh/C (5 % w/w)	70	50		>99
9	Pt/C (10 % w/w)	80	90		>99
10	Pt/C (10 % w/w)	80	100		>99 (92)[c]
11	Pt/C (10 % w/w)	80	50	**6d**	70
12	Pt/C (10 % w/w)	100	50		76
13	$Pd(OH)_2$/C (10 % w/w)	70	70		>99
14	Pt/C (10 % w/w)	80	40		>99
15	Pt/C (10 % w/w)	80	90		>99 (89)[c]
16	Pd/C (10 % w/w)	80	50		98
17	$Pd(OH)_2$/C (10 % w/w)	60	30		>99
18	Rh/C (5 % w/w)	60	50	**6e** (*cis*)	>99
19	Pt/C (10 % w/w)	80	30		80 (*dr* 1:1.1)[d]
20	Pt/C (10 % w/w)	80	50		>99 (*dr* 1.3:1)[d] (89)[c]
21	Pt/C (10 % w/w)	80	80		>99 (*dr* 1.7:1)[d]
22	Rh/C (5 % w/w)	60	50		>99 (*dr* 1.3:1)[d]
23	Pd/C (10 % w/w)	80	50		>99 (*dr* 1:1.3)[d]
24	Pd/C (10 % w/w)	80	40		>99 (*dr* 1:1.7)[d]
25	Pd/C (10 % w/w)	70	30	**6f** (*cis*/*trans* mixture)	>99 (*dr* 1:1.8)[d]
26	Pd/C (10 % w/w)	50	30		63 (*dr* 1:2)[d]
27	$Pd(OH)_2$/C (10 % w/w)	60	30		>99 (*dr* 1:1.8)[d]
28	Pt/C (10 % w/w)	80	30		>99 (91)[c]
29	Pt/C (10 % w/w)	80	10	**6g**	34

[a] H-Cube, substrate in AcOH (concentration 0.05 M), 30 × 4 mm i.d. catalyst cartridge, 150 mg catalyst. [b] Determined by GC-FID. [c] Isolated yield of the pure compound (^{1}H NMR) after dilution with $CHCl_3$, addition of K_2CO_3, filtration, and evaporation (0.5 mmol scale). [d] Determined by ^{1}H NMR spectroscopy.

observed a small but significant influence of both hydrogenation temperature and pressure on the diastereoisomeric product ratio. The lower the temperature (compare entries 25 and 26) and hydrogen pressure (compare entries 23 and 24) the higher the selectivity for the *trans* diastereoisomer. At 50 °C and 30 bar hydrogen pressure the ratio was 2:1 in favor of the *trans* isomer (63% conversion). It can therefore be concluded that in the hydrogenation of substituted pyridine **5f** a Pt catalyst in combination with a high temperature and pressure favors the formation of the *cis* product, whereas the use of a Pd catalyst at lower temperatures and pressures favors the formation of the *trans* product.

As a final example in this series we studied the hydrogenation of 4-methoxypyridine (**5g**). Similar to the more electron-deficient pyridines **5a**–**f**, complete hydrogenation of this electron-rich analogue was accomplished by using Pt/C (10% w/w) at 80 °C and 30 bar of hydrogen pressure (Table 1, entries 28 and 29).

To investigate the possibility of performing stepwise (partial) hydrogenation reactions under flow conditions, additional hydrogenation experiments were performed with

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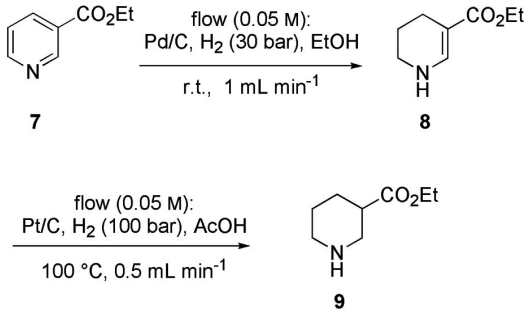
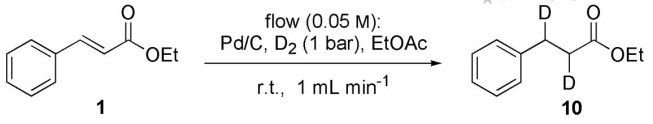
ethyl pyridine-3-carboxylate (ethyl nicotinate, **7**). The partial hydrogenation product is the vinylogous carbamate **8** (Scheme 3), which is stabilized by conjugation of the lone-pair of electrons on the nitrogen atom with the C=C bond and the carbonyl group.[21] This conjugation allows the hydrogenation to be stopped at this stage under suitable conditions. By using ethanol as the solvent and a Pd/C catalyst,[21] high selectivity for the partial hydrogenation **7** → **8** was obtained at room temperature and 30 bar of hydrogen pressure (flow rate 1.0 mL min^{-1}). By applying these settings, around 95% selectivity for the vinylogous carbamate **8** was consistently achieved, a significant improvement compared with the selectivity reported for the corresponding batch hydrogenations.[21] Small amounts of unreacted **7** and the fully hydrogenated byproduct **9** were selectively removed by extraction with 10% citric acid[21] to provide **8** in 85% isolated yield. Subsequent conversion of the partially hydrogenated intermediate **8** to the fully hydrogenated piperidine substrate **9** was unsuccessful using the ethanol/Pd/C conditions. Increasing the pressure (100 bar) and temperature (100 °C) provided only around 50% selectivity for piperidine **9**. However, by switching the solvent to acetic acid and the catalyst to Pt/C (see above), we were able to obtain the desired fully hydrogenated piperidine **9** with complete selectivity at 100 bar hydrogen pressure and 100 °C (flow rate 0.5 mL min^{-1}). By using the same conditions piperidine **9** could also be obtained directly from pyridine **7** in 92% isolated yield.



Scheme 3. Tuning the selectivities between partial and full hydrogenation of pyridine-3-carboxylate **7** under continuous flow conditions.

As hydrogen gas in the H-Cube is generated in situ by electrolysis of H_2O, it is also possible to generate D_2 by simply replacing H_2O by D_2O in the electrolysis cell, a technique to the best of our knowledge not described so far in the published literature. For this purpose, the H_2O reservoir and system lines of the flow reactor must be meticulously cleaned and dried to achieve a high degree of deuteriation. We have generated the known[22] dideuterio analogue of ethyl 3-phenylpropanoate (i.e., **10**) in 92% yield by flow deuteriation of ethyl cinnamate (**1**) using the same conditions as applied for the hydrogenation **1** → **2** (Scheme 4). Analysis of **10** by GC–MS[23] and ^{1}H NMR spectroscopy revealed a degree of deuteriation of around 95%.



Scheme 4. Deuteriation of ethyl cinnamate under continuous flow conditions.

Conclusions

In this article we have demonstrated that hydrogenation reactions of functionalized pyridines can be carried out conveniently under continuous flow conditions in a dedicated high-pressure reactor. Comparing the results shown in Table 1 with published data from microwave batch hydrogenation reactions[7] it can be seen that the selectivity and isolated product yields are very similar. It has to be stressed, however, that a more direct comparison between microwave batch and flow hydrogenations is not possible because the catalyst loadings and hydrogen pressures are vastly different in the two methods (see above). The optimization studies shown in Table 1 and in Schemes 1, 2, 3, and 4 were conducted in a comparatively short time frame as changes in temperature, hydrogen pressure, and flow rate can be made "on-the-fly" without having to stop the actual experiment.[13] As both the injection of samples[14,15] and the change/replacement of the catalyst cartridge can be fully automated[18] flow hydrogenation reactions of this type can likely be performed much more efficiently (and safer) then batch hydrogenation reactions. We have additionally shown that flow hydrogenation reactions are easily scalable because once conditions have been optimized the amount of material generated is mainly a function of the processing time.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker 360 MHz instrument at 360 and 90 MHz, respectively. Low-resolution mass spectra were obtained with an Agilent 1100 LC/MS instrument using atmospheric pressure chemical ionization (APCI) in positive or negative mode. Analytical HPLC analysis was carried out with a Shimadzu LC-10 instrument using a LiChrospher 100 C18 reversed-phase analytical column (119 × 3 mm, 5 μm particle size) at 25 °C, mobile phase A [water/MeCN (9:1, v/v) + 0.1% TFA] and phase B (MeCN + 0.1% TFA), a linear gradient from 30–100% B in 8 min and 2 min with 100% phase B. GC-FID analysis was performed with a Trace-GC (ThermoFisher) equipped with a flame ionization detector using a HP5 column (30 m × 0.250 mm i.d.). After 1 min at 50 °C the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 4 min. The detector gas for the flame ionization was H_2 and compressed air (5.0 quality). Microwave irradiation experiments were carried out with a Biotage Initiator Eight system. All products synthesized in this study are known in the literature and have been characterized by ^{1}H NMR and MS analysis. All starting materials except **5c** are commercially available and were used as received. Starting material **5c** was prepared according to a published literature procedure.[24] Flow hydrogenations were performed at least three times (using

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fresh cartridges) with the results being identical within experimental error.

Batch Hydrogenation Under Microwave Conditions. Ethyl 3-Phenylpropanoate (2): A mixture containing ethyl cinnamate (**1**; 17.6 mg, 0.1 mmol) and Pd/C (2 mol-%, 0.002 mmol, 10% w/w, Aldrich 205699) was suspended in ethyl acetate (2.0 mL) in a 2–5 mL (filling volume) Pyrex microwave vial equipped with a magnetic stirring bar. After sealing the vial, hydrogen gas was flushed through the vial for 5 min at atmospheric pressure at room temperature. The vial was subsequently heated for 5 min at 80 °C in a single-mode microwave reactor. Thereafter the crude reaction mixture was filtered through a sintered glass crucible. Evaporation of the solvent under reduced pressure delivered 15.3 mg (89%) of ethyl 3-phenylpropanoate (**2**) as a colorless oil. For ^{1}H NMR and MS data, see below.

Flow Hydrogenations in the H-Cube. General Procedure: A stock solution of the corresponding starting material (**1**, **3**, **5a**–**g**, **7**, **8**) at a concentration of 0.01–0.2 M in the appropriate solvent was prepared in a glass vial. The reaction parameters (temperature, flow rate, and hydrogen pressure) were selected on the H-Cube fitted with the appropriate CatCart and the processing was started, whereby initially only pure solvent was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was assured. At that point the sample inlet line was switched to the vial containing the substrate. The reaction was monitored (including monitoring in response to "on-the-fly" changes in reaction parameters) by constant HPLC or GC analysis of the processed reaction mixture. For preparative experiments, the total reaction mixture was collected and the cartridge subsequently washed with pure solvent for 5 min to remove any substrate/product still adsorbed on the catalyst. Evaporation of the solvent provides the desired products (**2**, **4**, **9**, **10**). In the case of piperidines **6a**–**g**, $CHCl_3$ (5 mL) was added to the crude material. After addition of K_2CO_3 and stirring for 10 min the solution was filtered and the solvent removed under vacuum to provide the pure products. For vinylogous carbamate **8**, the residue was taken up in CH_2Cl_2 (15 mL) and washed with 10% aqueous citric acid. Subsequent drying of the organic phase with anhydrous Na_2SO_4 and evaporation yielded the pure product.

Ethyl 3-Phenylpropanoate (2):[25] Compound **1** (1.5 mmol) in EtOAc (0.1 M), room temp., 1 bar H_2, 0.5 mL min^{-1} flow rate. Colorless liquid (154 mg, 87%). HPLC: $R_{t,product}$ = 4.7 min (215 nm). ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, J = 7.1 Hz, 3 H), 2.61 (t, J = 7.6 Hz, 2 H), 2.94 (t, J = 7.6 Hz, 2 H), 4.11 (q, J = 7.1 Hz, 2 H), 7.21–7.32 (m, 5 H) ppm. MS (pos. APCI): m/z = 179 (100) [M + 1]$^+$.

Pipecolic Acid (4):[26] Compound **3** (1.0 mmol) in H_2O (0.05 M), 80 °C, 1 bar H_2, 0.5 mL min^{-1} flow rate. Colorless crystals (50 mg, 97%). M.p. 272 °C [ref.[27] m.p. 270–274 °C]. ^{1}H NMR (D_2O): δ = 1.43–1.75 (m, 5 H), 2.10 (m, 1 H), 2.8 (m, 1 H), 3.26 (m, 1 H), 3.46 (m, 1 H) ppm. MS (pos. APCI): m/z = 130 (100) [M + 1]$^+$.

Methyl Piperidine-4-carboxylate (6a):[28] Compound **5a** (0.5 mmol) in AcOH (0.05 M), 80 °C, 30 bar H_2, 0.5 mL min^{-1} flow rate. Colorless oil (66.7 mg, 93%). HPLC: $R_{t,product}$ = 0.8 min (215 nm). ^{1}H NMR ($CDCl_3$): δ = 1.86–1.94 (m, 2 H), 2.01–2.06 (m, 2 H), 2.49–2.57 (m, 1 H), 2.78–2.85 (m, 1 H), 3.20 (t, J = 4.2 Hz, 1 H), 3.24 (t, J = 4.3 Hz, 1 H), 3.7 (s, 3 H) ppm. MS (pos. APCI): m/z = 144 (100) [M + 1]$^+$.

***tert*-Butyl *N*-[2-(Piperidin-2-yl)ethyl]carbamate (6b):**[7] Compound **5b** (0.5 mmol) in AcOH (0.05 M), 80 °C, 30 bar, 0.5 mL min^{-1} flow rate. Colorless oil (84.5 mg, 74%). GC-FID: $R_{t,product}$ = 8.51 min. ^{1}H NMR ($CDCl_3$): δ = 1.35 (s, 9 H), 1.37–1.81 (m, 9 H), 2.48–2.69 (m, 3 H), 3.13 (m, 2 H), 4.52 (br. s, 1 H), 5.48 (br. s, 1 H) ppm. MS (pos. APCI): m/z = 229 (100) [M + 1]$^+$.

2-(2-Phenyl-1,3-dioxan-2-yl)piperidine (6c):[7] Compound **5c** (0.5 mmol) in AcOH (0.05 M), 80 °C, 90 bar, 0.5 mL min^{-1} flow rate. Colorless oil (100 mg, 81%). GC-FID: $R_{t,product}$ = 9.51 min. ^{1}H NMR ($CDCl_3$): δ = 1.04–1.65 (m, 6 H), 1.63 (br. s, 1 H), 2.06–2.09 (m, 2 H), 2.44 (m, 2 H), 3.03 (dd, J_1 = 1.6, J_2 = 9.6 Hz, 1 H), 3.69–3.84 (m, 4 H), 7.26 (m, 3 H), 7.33 (d, J = 4.4 Hz, 2 H) ppm. MS (pos. APCI): m/z = 248 (100) [M + 1]$^+$.

Ethyl 2-(Piperidin-2-yl)acetate (6d):[7] Compound **5d** (0.5 mmol) in AcOH (0.05 M), 80 °C, 100 bar, 0.5 mL min^{-1} flow rate. Yellow oil (78.5 mg, 92%). GC-FID: $R_{t,product}$ = 6.44 min. ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, J = 7.9 Hz, 3 H), 1.74–1.85 (m, 6 H), 2.80–3.99 (m, 3 H), 3.36 (m, 2 H), 4.14 (q, J = 7.8 Hz, 2 H), 4.98 (br. s, 1 H) ppm. MS (pos. APCI): m/z = 172 (100) [M + 1]$^+$.

***cis*-2,6-Bis(methoxycarbonyl)piperidine (6e):**[7] Compound **5e** (0.5 mmol) in AcOH (0.05 M), 80 °C, 90 bar, 0.5 mL min^{-1} flow rate. Yellow solid (89.5 mg, 89%). GC-FID $R_{t,product}$ = 7.61 min. ^{1}H NMR ($CDCl_3$): δ = 1.31–1.50 (m, 3 H), 1.90–1.98 (m, 3 H), 2.30 (br. s, 1 H), 3.69 (s, 6 H), 3.75 (dd, J_1 = 12.6, J_2 = 2.3 Hz, 2 H) ppm. MS (pos. APCI): m/z = 202 (100) [M + 1]$^+$.

Methyl 5-Methylpiperidine-3-carboxylate (6f):[7] Compound **5f** (0.5 mmol) in AcOH (0.05 M), 80 °C, 50 bar, 0.5 mL min^{-1} flow rate. Colorless solid (70 mg, 89%). GC-FID: $R_{t,product}$ = 6.02 min (*trans*); 6.15 min (*cis*). ^{1}H NMR ($CDCl_3$): δ = 1.32 (d, J = 14.0 Hz, 3 H), 1.37 (d, J = 4.8 Hz, 3 H), 2.18–2.29 (m, 2 H), 2.55 (m, 2 H), 2.67 (m, 4 H), 2.55–3.05 (m, AB system, 4 H), 2.92–3.33 (m, AB system, 4 H), 3.63 (s, 3 H), 3.65 (s, 3 H), 5.74 (br. s, 1 H), 5.90 (br. s, 1 H) ppm. MS (pos. APCI): m/z = 152 (100) [M + 1]$^+$. The configuration of both isomers was established by gDQCOSY measurements of the *N*-tosylated analogues: ^{1}H NMR ($CDCl_3$) *cis*: δ = 0.87 (d, J = 6 Hz, 3 H), 0.91 (m, 1 H), 1.53 (m, 1 H), 1.71 (m, 1 H), 2.02 (d, J = 13.2 Hz, 1 H), 2.17 (t, J = 11.6 Hz, 1 H), 2.41 (s, 3 H), 2.65 (m, 1 H), 3.64 (s, 3 H), 3.72 (d, J = 8.8 Hz, 1 H), 4.01 (dd, J_1 = 2, J_2 = 11.6 Hz, 1 H), 7.30 (d, J = 7.6 Hz, 2 H), 7.62 (d, J = 7.6 Hz, 2 H) ppm. ^{1}H NMR ($CDCl_3$) *trans*: δ = 0.95 (d, J = 6 Hz, 3 H), 1.30 (m, 1 H), 1.87 (m, 1 H), 2.01 (m, 1 H), 2.40 (s, 3 H), 2.74 (t, J = 10.4 Hz, 1 H), 2.74 (m, 1 H), 2.99–3.10 (m, AB system, 2 H), 3.37 (m, 1 H), 3.68 (s, 3 H), 7.29 (d, J = 7.6 Hz, 2 H), 7.61 (d, J = 7.6 Hz, 2 H) ppm.

4-Methoxypiperidine (6g):[27] Compound **5g** (0.5 mmol) in AcOH (0.05 M), 80 °C, 30 bar H_2, 0.5 mL min^{-1} flow rate. Colorless oil (52.3 mg, 91%). GC-FID: $R_{t,product}$ = 4.55 min. ^{1}H NMR (D_2O): δ = 1.61–1.70 (m, 2 H), 1.94–2.05 (m, 2 H), 2.93–3.06 (m, 2 H), 3.17–3.22 (m, 2 H), 3.24 (s, 3 H), 3.50–3.54 (m, 1 H) ppm. MS (pos. APCI): m/z = 116 (100) [M + 1]$^+$.

Ethyl 1,4,5,6-Tetrahydropyridine-3-carboxylate (8):[21] Compound **7** (0.5 mmol) in EtOH (0.05 M), room temp., 30 bar H_2, 1.0 mL min^{-1} flow rate. Yellow oil (65.8 mg, 85%). GC-FID: $R_{t,product}$: 7.65 min. ^{1}H NMR ($CDCl_3$): δ = 1.22 (t, J = 6.8 Hz, 3 H), 1.75–1.81 (m, 2 H), 2.30 (t, J = 6.18 Hz, 2 H), 3.16–3.19 (m, 2 H), 4.1 (q, J = 7.1 Hz, 2 H), 4.56 (s, 1 H), 7.46 (s, 1 H) ppm. MS (pos. APCI): m/z = 156 (100) [M + 1]$^+$.

Ethyl Piperidine-3-carboxylate (9):[28] Compound **8** (0.5 mmol) (or **7**) in AcOH (0.05 M), 100 °C, 100 bar H_2, 0.5 mL min^{-1} flow rate. Yellow oil (72.3 mg, 92%). GC-FID: $R_{t,product}$ = 6.14 min. ^{1}H NMR (D_2O): δ = 1.13 (t, J = 7.1 Hz, 3 H), 1.62–1.75 (m, 4 H), 1.94–2.0 (m, 1 H), 2.76–2.81 (m, 1 H), 2.90–2.96 (m, 1 H), 3.09–3.16 (m, 2 H), 3.32–3.37 (dd, J_1 = 3.45, J_2 = 12.45 Hz, 1 H), 4.03–4.11 (m, 2 H) ppm. MS (pos. APCI): m/z = 158 (100) [M + 1]$^+$.

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Ethyl [2,3-H_2]-3-Phenylpropanoate (10):[22] The deuteriation experiment was performed similarly to the general flow hydrogenation protocol described above, except that the water reservoir in the H-Cube™ was filled with D_2O (99.96% D) and kept under nitrogen to reduce the moisture content. The electrolysis cell was purged with D_2O several times to minimize the presence of H_2O inside the system before starting the experiment. Conditions: **1** (0.5 mmol) in EtOAc (0.05 M), room temp., 1 bar D_2, 1 mL min^{-1} flow rate. Colorless liquid (82.8 mg, 92%). GC–MS: $R_{t,product}$ = 6.23 min. ^{1}H NMR ($CDCl_3$): δ = 1.22 (t, J = 7.1 Hz, 3 H), 2.6 (d, J = 6.6 Hz, 1 H), 2.92 (d, J = 6.6 Hz, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 7.20 (m, 3 H), 7.27 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.4, 30.8 (t, J_{CF} = 19.6 Hz), 35.8 (t, J_{CF} = 19.6 Hz), 60.6, 126.4, 128.5, 128.7, 140.7, 173.1 ppm. MS (pos. APCI): m/z = 181 (100) $[M + 1]^+$.

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