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The First Continuous Flow Hydrogenation of Amides to Amines

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Amines are a versatile class of compounds with applications ranging from dyes, solvents and detergents to the pharmaceutical industry. Amine functionalities are often introduced by initial amide formation followed by a reduction step using reducing agents such as $LiAlH_4$ or boranes. These reducing agents are, however, hazardous and difficult to handle, particularly on large scale, and their use often involves complex and wasteful workup procedures. Thus, routes to selective and environmentally benign amide reduction are sought after, and for this reason, the American Chemical Society Green Chemistry Institute (GCI) and members of the Pharmaceutical Round Table have shortlisted amide hydrogenation as one of their three most desirable reactions for development.[1] Although a number of successful amide reductions through catalytic hydrosilylation have been reported,[2] catalytic hydrogenation represents a promising alternative, as water is generated as the only by-product. The groups of Saito,[3] Milstein,[4] and Bergens[5] reported homogeneously catalysed hydrogenation of amides, but in all cases, the reduction proceeds either through C–N bond cleavage to give amines and alcohols or through monohydrogenation to give hemiaminals. We recently reported the first successful homogeneous Ru-based catalyst capable of selectively hydrogenating amides to amines without C–N bond cleavage, even in the presence of aromatic ring systems.[6] The scope of this reaction is, however, currently limited to substrates containing a phenyl ring directly attached to the N atom and to primary amides. A number of bimetallic heterogeneous hydrogenation catalysts have been reported by the groups of Fuchikami[7] and Whyman[8] to give good conversions of amides into amines, but they generally require fairly harsh operating conditions. More recently, promising bimetallic graphite-supported Pd–Re and TiO_2-supported Pt–Re based catalysts capable of promoting amide hydrogenations under mild reaction conditions were reported independently by the groups of Breit[9] and Hardacre.[10] Although the use of a heterogeneous catalyst for amide hydrogenation is currently limited to nonaromatic substrates owing to the complication of unwanted ring hydrogenation, the ease of catalyst separation associated with such systems is a great advantage to their implementation in continuous flow systems for industrial applications. Herein, we report the first selective catalytic hydrogenation of amides to amines in continuous flow by using a bimetallic TiO_2-supported Pt–Re-based catalyst.[10]

The air-stable 4 % Pt–4 % Re/TiO_2 catalyst employed in this study was first reported by some of us to be catalytically active towards amide hydrogenation.[10] A range of bimetallic Pt–Re-based catalysts supported on $CeZrO_4$, TiO_2 and Al_2O_3 were tested for the selective hydrogenation of *N*-methylpyrrolidin-2-one to *N*-methylpyrrolidine in hexane under an atmosphere of hydrogen (20 bar, 1 bar = 100 kPa) at 120 °C. Under these conditions, 4 % Pt–4 % Re/TiO_2 displayed the highest activity and gave almost full conversion after 24 h. For this system, the nature of the solvent was shown to play an important role, and the rate of the reaction was found to decrease in the order: hexane > tetrahydrofuran ≈ diethyl ether > methanol > methyl *tert*-butyl ether.[10]

To assess the performance of this catalyst under continuous flow conditions, we developed a versatile flow reactor. The reactor is vertical with an upwards flow and has the facility to flow liquids, gases and CO_2 simultaneously through the vertical-packed bed reactor containing the catalyst. The flowing stream is then decompressed, and the products are collected free from the catalyst and other impurities apart from side products, solvent, and unreacted substrates. A schematic of the reactor is shown in Figure 1.

Prior to testing 4 % Pt–4 % Re/TiO_2 in continuous flow, the catalyst was tested in batch mode with an aromatic substrate to determine the tolerance of this catalyst towards arene functionalities. Acetanilide, a substrate that performed very well with the homogeneous [Ru(acac)$_3$]/triphos [acac = acetylacetonate, triphos = 1,1,1-tris(diphenylphosphinomethyl)-ethane] system (Table 1, entry 1), was used as a test substrate.[6a] Acetanilide (5 mmol) in hexane was heated at 120 °C in the presence of 4 % Pt–4 % Re/TiO_2 (1.6 mol % in metal) under an atmosphere of hydrogen (20 bar, RT) for 16 h (Table 1, entry 4). Although this resulted in hydrogenation of 36 % of the amide functionality, ring hydrogenation occurred for both the final amine as well as the remaining substrate to give a mixture of *N*-cyclohexyl-*N*-ethylamine (**2**) and *N*-cyclohexylacetamide (**3**) as the final products (Scheme 1). In addition, minor amounts of *N*-cyclohexylamine (**4**) and ethanol (**5**) were produced as a result of C–N bond cleavage.

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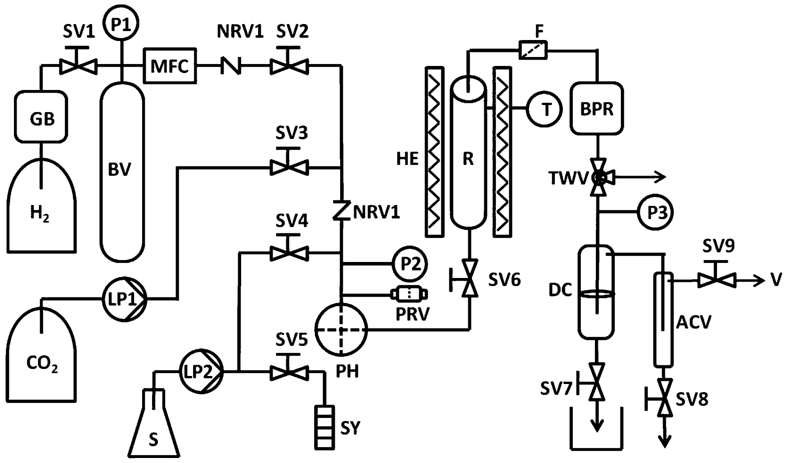
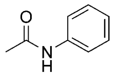
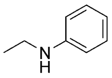
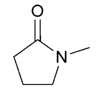
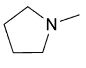
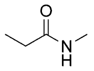
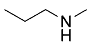
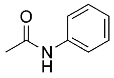
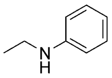
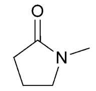
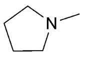
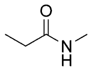
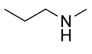


ACV: *auxiliary collection vessel*
BPR: *back pressure regulator*
BV: *ballast vessel*
DC: *decompression chamber*
F: *filter*
GB: *gas booster*
HE: *heater*
LP: *liquid pump*
MFC: *flow controller*
NRV: *non return valve*
P: *pressure transducer*
PCV: *pressure control valve*
PH: *pre-heater*
PRV: *pressure relief valve*
R: *reactor*
S: *substrate*
SV: *screw-down valve*
SY: *purge syringe*
T: *thermocouple*
TWV: *three-way valve*
V: *vent*

Figure 1. Schematic drawing of the continuous flow reactor.

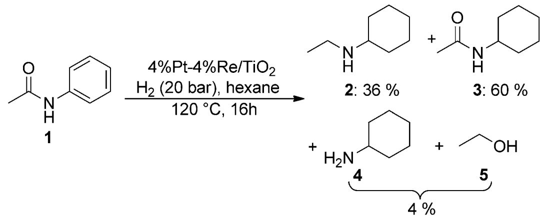
Table 1. A comparison between the homogeneous and heterogeneous catalytic systems in the hydrogenation of amides to amines in batch mode.

Entry	Substrate	Catalyst	*t* [h]	Product	Conv. [%]	Sel. [%]
Homogeneous system[a]						
1		$[Ru(acac)_3]$/triphos	16		100	92
2		$[Ru(acac)_3]$/triphos	16		0	0
3		$[Ru(acac)_3]$/triphos	16		67	45[b]
Heterogeneous system[c]						
4		4 % Pt–4 % Re/TiO_2	16		100	0
5		4 % Pt–4 % Re/TiO_2	16		100	100
6		4 % Pt–4 % Re/TiO_2	16		97	74

[a] Conditions: Amide (5 mmol), $[Ru(acac)_3]$ (1 mol %), triphos (2 mol %), THF (10 mL), methanesulfonic acid (MSA; 1.5 mol %), H_2 (15 bar), 220 °C, Hastelloy autoclave. [b] The main side products were methyldipropylamine (25 %) and dimethylpropylamine (12 %). [c] Conditions: Amide (5 mmol), 4 % Pt–4 % Re/TiO_2 (1.6 mol % in metal), hexane (15 mL), H_2 (20 bar), 120 °C, Hastelloy autoclave.

Despite the fact that this catalyst is not suitable for the hydrogenation of amide substrates containing arene functionalities, it is very effective in catalysing the hydrogenation of aliphatic amides such as *N*-methylpyrrolidin-2-one and *N*-methylpropanamide. This catalytic system can be viewed as complementary to our previously reported homogeneous system in which aliphatic substrates such as *N*-methylpyrrolidin-2-one and *N*-methylpropanamide performed rather poorly and gave either no conversion (Table 1, entry 2) or poor selectivity (Table 1, entry 3).[6a] Conversely, hydrogenation of *N*-methylpyrrolidone or *N*-methylpropanamide in batch mode with 4 % Pt–4 % Re/TiO_2 under an atmosphere of H_2 (20 bar) at 120 °C gave 92–100 % conversion with 75–100 % selectivity towards the desired amine (Table 1, entries 5 and 6).

Using the flow reactor described in Figure 1 and 4 % Pt–4 % Re/TiO_2 as the catalyst, *N*-methylpyrrolidin-2-one could be hydrogenated smoothly under continuous flow to produce *N*-methylpyrrolidine as the only product. Upon passing a solution of *N*-methylpyrrolidin-2-one in hexane (0.33 M, solution flow rate = 0.06 mL min^{-1}) over a fixed catalyst bed of 4 % Pt–4 % Re/TiO_2 at 120 °C, together with hydrogen (flow rate = 190 mL min^{-1}) under a total pressure of 20 bar, full conversion with 100 % selectivity towards *N*-methylpyrrolidine was achieved over 8 h on stream (Figure 2, ●).[11] Pumping *N*-methylpyrrolidin-2-one either neat (Figure 2, □) or as an emulsion in supercritical CO_2 (total pressure in this case increased to 100 bar; Figure 2, ▲) led to no catalytic activity. In the first instance, this was presumably due to the polarity of neat *N*-methylpyrrolidin-2-one, and in the second instance, this could be due to the low solubility of the substrate in supercritical CO_2. If the original *N*-methylpyrrolidin-2-one solution in hexane (0.33 M) was again passed over the same catalyst bed (Figure 2, ○), a decrease in the activity was observed, and this suggests that the use of supercritical CO_2 or neat substrate leads to some deactivation of the catalyst over time. This is attributable to strong adsorption of the amide on the surface, which has also



Scheme 1. Catalytic hydrogenation of acetanilide in batch mode with the use of 4 % Pt–4 % Re/TiO_2.

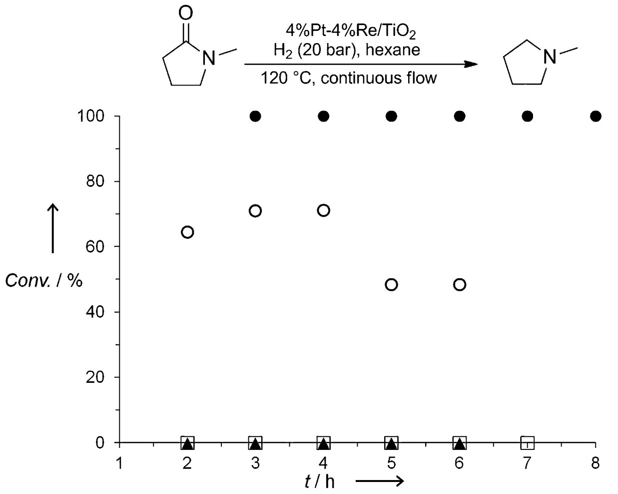


Figure 2. Hydrogenation of *N*-methylpyrrolidin-2-one with 4 % Pt–4 % Re/TiO_2 as the catalyst under continuous flow with hexane (●), neat (□), supercritical CO_2 (▲) and hexane again (○).[11]

been demonstrated in batch experiments by pre-treating the catalyst with *N*-methylpyrrolidin-2-one in hexane for 3 h prior to the addition of H_2.[10]

The temperature-programmed oxidation (TPO) profile (Figure 3 a) of used 4 % Pt–4 % Re/TiO_2 shows an additional broad peak (300–500 °C) in comparison to the profile of the fresh catalyst, which is likely to be attributed to adsorbed organic molecules on the surface. The temperature-programmed reduction (TPR) profile of the fresh catalyst shows low-temperature reduction of ReO_x (≈260 °C), which can be attributed to the strong electronic perturbation of Re by Pt. On the contrary, the TPR profile of the used catalyst indicates decreased interaction between Pt and Re, which gives rise to an additional higher temperature reduction peak for ReO_x (470 °C).

For a 0.67 M solution of *N*-methylpyrrolidin-2-one in hexane under H_2 flow of 190 mL min^{-1}, a temperature of 120 °C and a total pressure of 20 bar, the substrate solution flow rate could be increased to 0.12 mL min^{-1} without any drop in conversion or selectivity. If the substrate solution flow rate was again doubled (0.24 mL min^{-1}) to give even shorter residence times, a sharp drop in the conversion was observed (Figure 4).

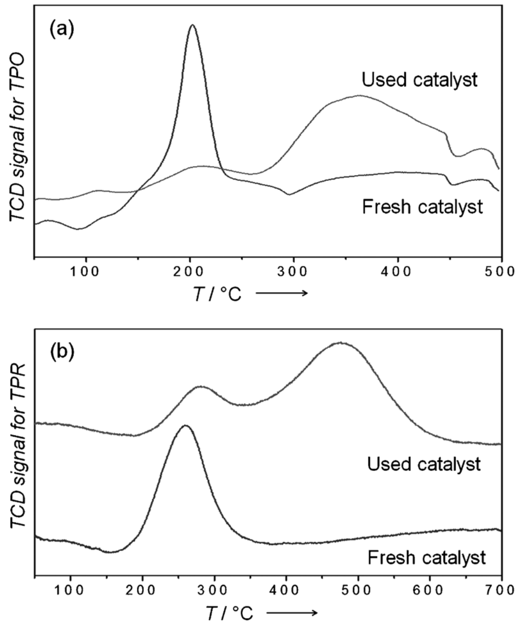


Figure 3. Temperature-programmed oxidation (a) and reduction (b) profiles for fresh and used 4 % Pt–4 % Re/TiO_2 as the catalyst.

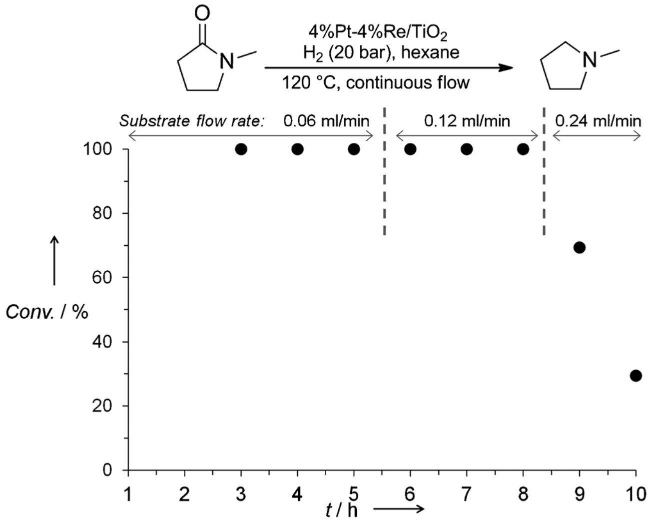


Figure 4. Hydrogenation of *N*-methylpyrrolidin-2-one with 4 % Pt–4 % Re/TiO_2 as the catalyst under continuous flow with variation of the substrate flow rate.[11] In each case, the selectivity was 100 % to *N*-methylpyrrole.

Using the same slightly deactivated catalyst bed as that used during earlier continuous flow experiments with supercritical CO_2, *N*-methylpropanamide could also be hydrogenated successfully under continuous flow. Owing to the low solubility of *N*-methylpropanamide in hexane, the substrate was passed over the catalyst bed at 120 °C as an emulsion (0.94 mL substrate in 85 mL hexane; substrate emulsion flow rate = 0.12 mL min^{-1}) together with H_2 (flow rate = 190 mL min^{-1}) under a total pressure of 20 bar. Under these conditions, high conversion (75–99 %) and selectivity towards the secondary amine (80–86 %) were achieved continuously over 8 h on stream (Figure 5); 1-propanol was obtained as the major side product. Notably, given that *N*-methylpropanamide was fed as an emulsion in hexane, there were some difficulties in maintaining a constant and homogeneous substrate feed despite

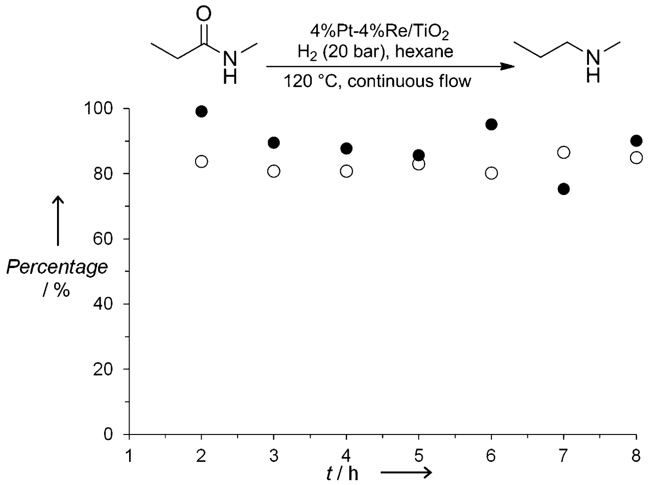


Figure 5. The conversion (●) and selectivity (○) for the catalytic hydrogenation of *N*-methylpropanamide with 4 % Pt–4 % Re/TiO_2 as the catalyst under continuous flow over an 8 h period on stream by using a recycled catalyst bed.[11]

vigorous stirring. Owing to this complication, the conversion for this reaction varies slightly over time on stream.

The low boiling point of hexane resulted in poor mass recovery for continuous flow reactions with this solvent. Thus, decane was employed as a less volatile and more environmentally benign alternative. With decane as the solvent, a mass recovery of greater than 90 % could be maintained for the hydrogenation of *N*-methylpyrrolidin-2-one under flow over a 10 h period on stream (Figure 6, ▲). To evaluate the stability of the catalyst over time, the catalytic hydrogenation of *N*-methylpyrrolidin-2-one in decane was performed under low conversion with a shorter residence time (substrate solution flow rate = 0.24 mL min^{-1}, H_2 flow = 190 mL min^{-1}). Under these conditions, gradual catalyst deactivation was observed with time on stream, and the greatest deactivation (observed as a sharp drop in conversion) occurred within the first four hours on stream (Figure 6, ●).

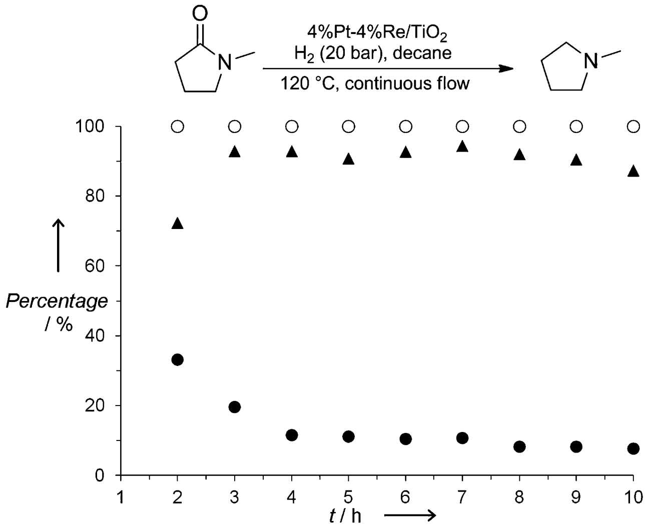


Figure 6. The stability of the 4 % Pt–4 % Re/TiO_2 catalyst during the hydrogenation of *N*-methylpyrrolidin-2-one over a 10 h period on stream showing the conversion (●), mass recovery (▲) and selectivity (○).[11]

A number of samples taken at different time intervals were analysed for metal content by using inductively coupled plasma mass spectrometry (ICP-MS). In all cases, metal leaching was negligible, and the values measured were generally below the detection limit (1 ppm; Table S1, Supporting Information). Under batch conditions, recycling of the catalyst also resulted in significant deactivation.[10] This was attributed to the loss of Pt–Re interactions as observed in the TPR profile, probably as a result of the exposure of the catalyst to air upon recycling, which caused an exotherm on the partially reduced surface. Under flow conditions, the catalyst is maintained under reducing conditions at all times Therefore, the observed deactivation is likely to be caused by the presence of a strongly adsorbed material blocking the surface sites, as observed in the TPO profile.

In conclusion, we have demonstrated the first catalytic hydrogenation of amides to amines under continuous flow conditions. Aliphatic amides such as *N*-methylpyrrolidin-2-one and *N*-methylpropanamide were hydrogenated successfully under mild conditions in continuous flow by using the heterogeneous bimetallic catalyst 4 % Pt–4 % Re/TiO_2.

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Keywords: amides · amines · continuous flow · heterogeneous catalysis · hydrogenation

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[11] Please note that no conversion is shown over the first 2 hrs on stream for reactions done with a fresh catalyst bed, and 1 h for reactions performed with a recycled catalyst bed. This is because no products flow out at beginning of the reaction until the reactor has filled up, with the fill-up time dependant on the substrate solution flow rate. For reactions performed with a recycled catalyst bed, the fill-up times were shorter despite prior washing of the catalyst bed with hexane and thorough purging under a flow of H_2 for 1–2 hrs.

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