Enantioselective hydrogenation of polar substrates in inverted supercritical CO_2/aqueous biphasic media†

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An inverted supercritical CO_2/aqueous biphasic catalytic system allows highly enantioselective hydrogenation of polar water-soluble substrates and efficient recycling of the CO_2-philic catalysts.

In the field of homogeneous catalysis, new concepts for catalyst recycling and product separation are among the most important targets. The currently most successful approach in this field is multiphase catalysis, where a suitably modified catalyst resides in one liquid phase and substrates and products partition into a second immiscible fluid phase.[1] In all industrial processes and in the vast majority of scientific studies based on this concept to date the catalyst compartment is a highly polar phase such as water,[2] limiting the applications to products that are sufficiently hydrophobic or non-polar to partition into the second phase. Fine chemicals and biologically active compounds are, however, often densely functionalised molecules, many of which are highly polar and even water soluble. Surprisingly little effort has been made to develop so-called "inverted" biphasic systems, where the catalyst resides in a non-polar phase and substrates/products are contained in an aqueous medium.[3,4] In the present communication, we demonstrate that an inverted biphasic catalyst system using environmentally benign supercritical carbon dioxide ($scCO_2$)[5,6] as the stationary catalyst phase and water as the substrate/product phase makes it possible to combine rapid and highly enantioselective catalytic hydrogenation of very polar substrates with simple product isolation and efficient catalyst recycling (Fig. 1).[7]

The development of inverted biphasic systems based on classical organic media as catalyst phase is hampered by the difficulty in identifying solvents which provide sufficient interfacial exchange for high reaction rates and yet do not result in any cross contamination into the aqueous product stream. For reactions involving gaseous substrates, such systems are triphasic (g/l/l) in nature, resulting in additional mass transfer limitations. In contrast, the inverted $scCO_2$/aqueous system is always truly biphasic owing to the miscibility of the gases with the supercritical phase (Fig. 1). Cross contamination is not an issue in this case, as the solubility of CO_2 in water leads to the formation of carbonic acid (*vide infra*), but not to any impurities in the product stream. Another interesting aspect of this concept is the fact that the supercritical phase is never depressurised resulting in considerable reduction of operating costs as compared to multiphase systems employing $scCO_2$ as the mobile phase.

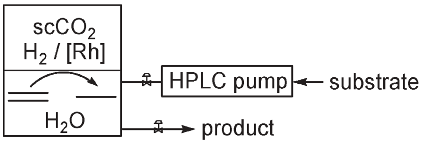
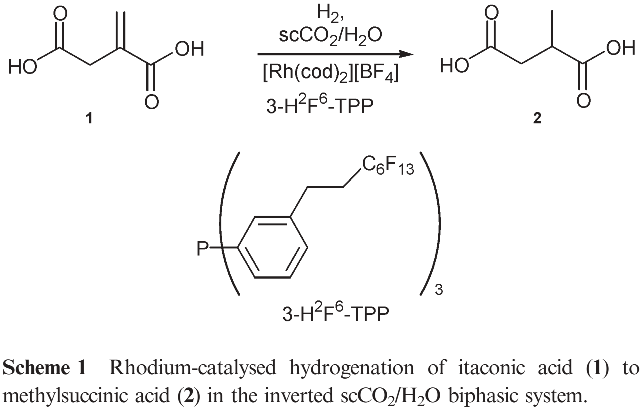


Fig. 1 The inverted $scCO_2$/aqueous biphasic system for rhodium-catalysed hydrogenation.

Inverted $scCO_2/H_2O$ biphasic catalytic systems have been used previously for the palladium-catalysed generation of aqueous H_2O_2 from H_2 and O_2,[8] and the rhodium catalysed hydroformylation of water soluble olefins.[9] In both cases, the acidic conditions in the CO_2/water system were found to limit catalyst stability at least partly. We therefore turned our attention to hydrogenation reactions, where catalysts are known to tolerate acidic conditions in many cases. Enantioselective hydrogenation appeared to be an especially interesting target reaction for the inverted $scCO_2/H_2O$ approach as it would allow the generation of enantiomerically enriched biologically active compounds directly and cleanly in an aqueous environment.

The rhodium-catalysed hydrogenation of itaconic acid (**1**) to methylsuccinic acid (**2**) was chosen as a benchmark reaction involving prototypical hydrophilic compounds. Initially, a rhodium catalyst consisting of the precursor complex $[Rh(cod)_2][BF_4]$ (cod = 1,5-cyclooctadiene) and the achiral CO_2-philic phosphine ligand tri-[3-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoroctyl)phenyl]phosphane (3-H^2F^6-TPP)[10] was used to validate the approach and to optimise the reaction conditions (Scheme 1).

The catalyst was preformed from the metal precursor and the ligand in the appropriate ratio in a small amount of organic



Scheme 1 Rhodium-catalysed hydrogenation of itaconic acid (**1**) to methylsuccinic acid (**2**) in the inverted $scCO_2/H_2O$ biphasic system.

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† Dedicated to Prof. Dr Henri Brunner on the occasion of his 70th birthday.

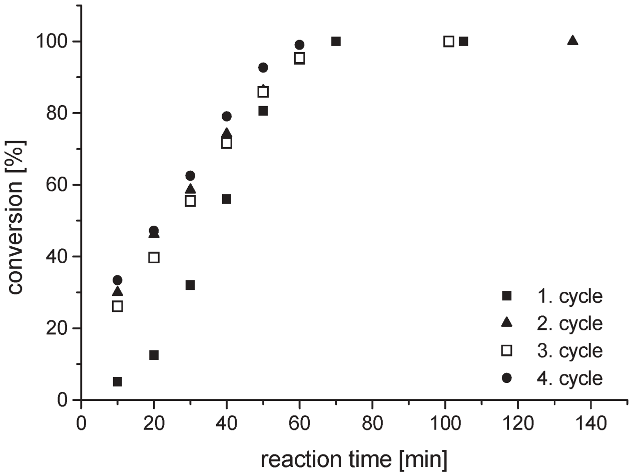

Fig. 2 Conversion/time profiles of recycling experiments for the hydrogenation of **1** using the catalyst system $[Rh(cod)_2][BF_4]$/3-H^2F^6-TPP in the inverted $scCO_2/H_2O$ biphasic system. – Reaction conditions see Table 1.

solvent. After removal of the solvent under reduced pressure, the catalyst was redissolved in a mixture of $scCO_2$ and compressed hydrogen at the desired reaction temperature. Then, an aqueous solution of **1** was brought into the autoclave against the pressure using an HPLC-pump. No residual solid material or colouration of the aqueous phase could be observed by visual inspection at this stage if more than 40 g CO_2 were charged in the reactor. Magnetic stirring at 1000 rpm caused the two phases to form an intimate emulsion-type mixture, which separated immediately when agitation was stopped. The aqueous phase could be removed partly or in total through a needle valve at the bottom of the reactor for offline analysis. The recovery of the substrate/product mixture from the autoclave ranged from 85 to 90% of the theoretical amount and conversions were reproducible within ± 3.5% under typical conditions.‡

As seen from Fig. 2, a marked induction period was present in the first reaction cycle, after which a $TOF_{max} = 252\ h^{-1}$ was reached as derived from the maximum slope of the conversion/time profile. The following three cycles showed a slightly lower, but constant reaction rate and no further significant loss of activity was detected (Fig. 2, Table 1). It was also found that the P : Rh ratio is very important for the recycling process with the catalytic system based on the 3-H^2F^6-TPP ligand and stable performance as in Fig. 2 was observed only at P : Rh $\geqslant$ 5.

Table 1 Rhodium and phosphorus leaching given as contamination of the product layer and percentage of the originally charged amount of catalyst during the recycling experiment summarised in Fig. 1[a]

		Rh leaching[c]		P leaching[c]	
Cycle	$TOF_{max.}$[b]$[h^{-1}]$	[ppm]	[%]	[ppm]	[%]
1	252	14.2	14.0	6.23	4.02
2	194	3.55	3.50	0.75	0.48
3	192	0.95	0.94	0.96	0.62
4	192	0.63	0.62	0.83	0.54

[a] *Reaction conditions:* $[Rh(cod)_2][BF_4]$ (0.02 mmol), 3-H^2F^6-TPP (0.1 mmol), **1** (4.0 mmol, 0.2 M in H_2O, 20 mL), V_{tot} = 100 mL, $m(CO_2)$ = 50 g, $p(H_2)$ = 30 bar, T = 40 °C, t = 1 h @ 1000 rpm. [b] From the maximum slopes of the conversion/time profiles shown in Fig. 2. [c] Determined by inductively coupled plasma atomic emission spectrometry (ICP).

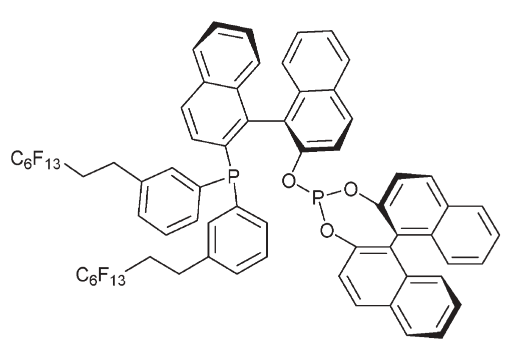

Fig. 3 (*R*,*S*)-3-H^2F^6-BINAPHOS.

The leaching data summarised in Table 1 are consistent with this behaviour. Considerable amounts of rhodium and phosphorus were detected in the aqueous phase after the first cycle. The much higher rhodium contamination indicates that some non ligand-modified species were present in the first run and partitioned to a large extent into the water layer. However, the leaching of both catalyst components dropped below 1 ppm in the third cycle and remained low in the subsequent cycle, indicating that a stable and highly active phosphine complex was effectively immobilised in the $scCO_2$ phase at this stage.

The CO_2-philic ligand (*R*,*S*)-3-H^2F^6-BINAPHOS[11] (Fig. 3) was chosen to extend the concept to enantioselective hydrogenation. The chiral phosphine–phosphite framework of BINAPHOS was originally designed for asymmetric hydroformylation reactions,[12] but recent research has demonstrated its potential also for enantioselective hydrogenation, especially in $scCO_2$ media.[13] The complex $[Rh(cod)_2]$BARF containing the CO_2-philic counterion tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate (BARF) was used in this case and the catalyst was preformed as before using a ligand to rhodium ratio of only 1.5 : 1 however. Again, visual inspection gave no evidence for undissolved material and only the $scCO_2$ phase showed the yellow colour typical of rhodium phosphine complexes.

Enantioselective hydrogenation of itaconic acid (**1**) was quantitative under standard conditions and 93.6% *ee* for the *S*-enantiomer of **2** was reached. The metal and phosphorus contamination in the aqueous phase was only 1.6 ppm and 4.9 ppm respectively, indicating an even better retention in the $scCO_2$ phase than for the achiral catalyst system. There are two effects that are likely to contribute to a better retention of the (*R*,*S*)-3-H^2F^6-BINAPHOS derived catalyst. On the one hand, the use of the BARF anion is expected to increase the solubility of the rhodium complex in $scCO_2$ as compared to the BF_4 analog.[14] On the other hand, the bidentate chelation with the chiral ligand makes it more difficult for unmodified rhodium to leach into the aqueous phase.

Full conversion and an *ee* of 97.3% (*R*) were achieved within one hour (not optimised) also for the hydrogenation of methyl 2-acetamidoacrylate (**3**) as another benchmark substrate (Fig. 4). It is important to note that the protected amino acid partitioned almost exclusively into the aqueous phase and the product was isolated in quantitative yield directly from the water layer that was removed from the reactor. Fig. 4 shows the results of five subsequent cycles with substrate **3** demonstrating the efficient recycling of the catalytic system under these conditions.

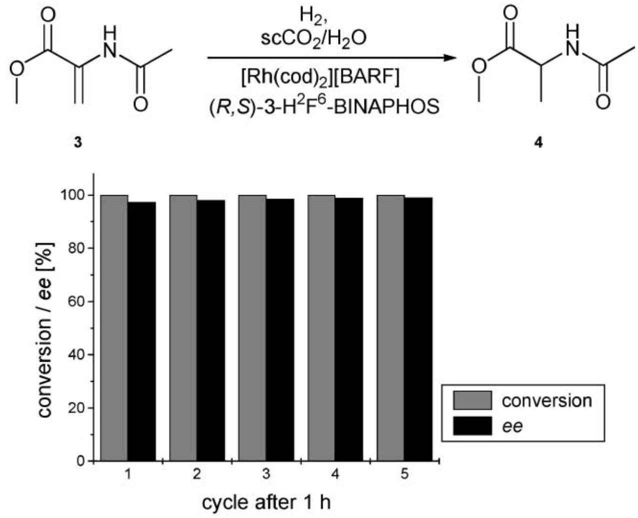

Fig. 4 Enantioselective hydrogenation of methyl 2-acetamidoacrylate **3** using a (*R,S*)-3-H^2F^6-BINAPHOS-modified rhodium catalyst. *Reaction conditions*: $[Rh(cod)_2]$BARF (0.02 mmol), (*R,S*)-3-H^2F^6-BINAPHOS (0.03 mmol), **3** (4.0 mmol, 0.2 M in H_2O, 20 mL), $V_{tot} = 100$ mL, $m(CO_2) = 55$ g, $p(H_2) = 30$ bar, $T = 56$ °C, $t = 1$ h @ 1000 rpm.

A total of 1000 turnovers was achieved and the lower limit for the TOF was 200 h^{-1} in each cycle. An excellent asymmetric induction of 99.1% (*R*) was obtained in the fifth cycle and the average value for the enantiomeric excess of the isolated (*R*) enantiomer was 98.4 ($\pm$0.6)%. Leaching of rhodium and phosphorus into the aqueous layer was 1.4 ppm and 5.2 ppm during the first cycle. For all following cycles the contamination was below the detection limit.

In summary, it was demonstrated that the inverted biphasic system $scCO_2/H_2O$ provides a promising approach to the hydrogenation of highly polar water-soluble compounds. Achiral and chiral rhodium complexes can be immobilised efficiently in the $scCO_2$ phase using "CO_2-philic" ligands.[15] Reasonable turnover rates and excellent enantioselectivities were observed. This method allows the straightforward generation of aqueous solutions of almost enantiomerically pure products without any solvent impurities. Contamination of the aqueous phase with metal and phosphorus was strongly dependent on the catalyst system and the reaction conditions, and could be supressed below the detection limits of ICP in favourable cases.

The large body of know-how in supercritical/liquid extraction[16] makes it attractive to consider inverted $scCO_2/H_2O$ biphasic systems also for continuous operation. In such a scenario, the supercritical phase is never depressurised, saving the most energy and cost intensive step of supercritical processing. Details of intrinsic kinetics and mass transfer rates are currently being studied and the long term stability of the catalytic systems is being investigated as part of this development.

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Notes and references

‡ **Procedure for a typical catalytic run:** $[Rh(cod)_2][BF_4]$ (8.3 mg, 0.02 mmol) and 3-H^2F^6TPP (130 mg, 0.1 mmol) were placed in a small Schlenk tube and dissolved in dichloromethane (3 mL). After stirring for 10 min, the orange solution was transferred *via* cannula into a 100 mL window-equipped autoclave and the solvent was removed under reduced pressure. The reactor was pressurised with H_2 (30 bar) and then filled with CO_2 (50–60 g) by means of a compressor. After the mixture was allowed to equilibrate at the reaction temperature of 40–60 °C, a solution of **1** in water (0.2 M, 20 mL) was added to the autoclave using an HPLC pump. The reaction was started by turning on the magnetic stirrer at 1000 rpm. Amounts of ligand, precursor, and substrate were adjusted as given in the legends of the figures. Samples of the reaction mixture were taken by stopping the stirring and removing *ca.* 0.5 mL of the lower water solution from the autoclave using a capillary needle valve at the bottom of the reactor. The sample was worked up by removing the water under reduced pressure. Conversion was determined by ^{1}H NMR spectroscopy of the crude product in D_2O and – if appropriate – the *ee* was measured by GC after conversion of the acid into the dimethyl ester. Rhodium and phosphorus content was determined directly in the aqueous samples by inductively coupled plasma atomic emission spectrometry (ICP). Recycling experiments were carried out by removing the water layer from the reactor completely and adding a new batch of substrate solution to the autoclave using an HPLC pump. Small amounts of CO_2 were added after the third run to re-adjust the total pressure accounting for its loss as carbonic acid. The loss of hydrogen through chemical consumption and dissolution in the water layer is negligible under the present conditions.

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