



Inverted Supercritical Carbon Dioxide/Aqueous Biphasic Media for Rhodium-Catalyzed Hydrogenation Reactions

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Abstract: An inverted supercritical carbon dioxide (scCO₂)/aqueous biphasic system has been used as reaction media for Rh-catalysed hydrogenation of polar substrates. Chiral and achiral CO₂-philic catalysts were efficiently immobilised in scCO₂ as the stationary phase, while the polar substrates and products were contained in water as the mobile phase. Notably, product separation and catalyst recycling were conducted without depressurisation of the autoclave. The catalyst phase was reused several times with high conver-

sion and product recovery of more than 85 %. Loss of rhodium and phosphorus by leaching were found to be below the detection limit after the first two cycles in the majority of repetitive experiments. The reaction conditions were optimised with a minimum of experiments by using a simplex algorithm in a sequential optimisation. Total turn-

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over numbers (TTNs) of up to 1600, turnover frequencies (TOFs) of up to 340 h⁻¹ and *ee*'s up to 99% were obtained in repetitive batch operations. The scope of the devised catalytic system has been investigated and a semicontinuous reaction setup has been implemented. The chiral ligand (*R,S*)-3-H²F⁶-BINAPHOS allowed highly enantioselective hydrogenation of itaconic acid and methyl-2-acetamidoacrylate combined with a considerable catalyst stability in these reaction media.

Introduction

Multiphase catalysis represents a key technology for the immobilisation of homogeneous catalysts and product separation.^[1] Among all possible solvent combinations for multiphase systems, aqueous-phase catalysis occupies a prominent role as evidenced by the industrial success of the Ruhrchemie/Rhône-Poulenc oxo process (RCH/RP) for the hydroformylation of propene.^[2,3] In this process, a water-soluble rhodium catalyst is immobilised in the stationary aqueous phase, whereas the products form a second phase that can be easily separated. The gaseous reactants CO and H₂ constitute the third phase in this multi-ton-scale process.

The use of supercritical carbon dioxide (scCO₂) as reaction medium for catalysis continues to attract interest from

academia.^[4,5] Also industrial applications were recently accomplished.^[6] In contrast to most conventional organic solvents, scCO₂ is non-toxic, non-flammable and environmentally benign. It enables fast mass transfer due to gas-like diffusivity and at the same time offers a tuneable liquid-like dissolving power. Mass-transfer limitations are strongly reduced for most gaseous reactants as they are fully miscible with CO₂. Therefore, hydrogenation reactions have been investigated intensively using CO₂ as the only reaction medium or in biphasic systems.^[7] When used in combination with a second (immiscible) solvent, CO₂ constitutes generally the mobile phase, replacing the organic solvent.^[8,9] Some examples of biphasic aqueous/CO₂ systems have been reported in which the water layer containing a hydrophilic catalyst forms the stationary phase.^[10,11] These systems are truly biphasic (sc/l) in nature. However, the scope of such systems is limited to non-polar and/or volatile products, which can be readily extracted by CO₂ from the aqueous catalyst phase.

The majority of products in the focus of the fine chemical and pharmaceutical industry are densely functionalised molecules of low-to-medium polarity. For such compounds, it seems attractive to devise an inverted aqueous biphasic system, in which water is used as the product phase. Howev-

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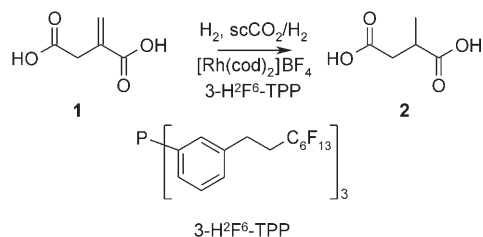
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er, very few examples are known in which the catalyst is immobilised in an organic phase and the polar substrates and products reside in the aqueous phase.^[12] The use of classical organic solvents as the catalyst phase causes significant cross contamination of the aqueous product phase and the resulting waste water stream. To enable the conversion of polar compounds without losing the advantages of the combination of water and scCO_2 , we have recently proposed the inverted system $\text{scCO}_2/\text{H}_2\text{O}$.^[13] Rhodium-catalysed hydroformylation of water-soluble substrates was used to demonstrate that this approach allows catalyst recycling and product isolation from the aqueous layer.^[14] Another example has been reported where a CO_2 -soluble palladium catalyst allowed the synthesis of aqueous H_2O_2 from H_2 and O_2 in $\text{scCO}_2/\text{H}_2\text{O}$ media.^[15] Furthermore, the same group showed that H_2O_2 generated in such a system can be used in situ as the oxidant for the epoxidation of alkenes.^[16]

Herein, we present the application of an inverted supercritical CO_2 /aqueous biphasic system for the hydrogenation of $\text{C}=\text{C}$ double bonds in polar substrates.^[17] The system is based on “ CO_2 -philic” rhodium catalysts that are immobilised in scCO_2 as the stationary phase, while substrates and products are contained in water as the mobile phase. Achiral and chiral catalysts are utilised efficiently and the potential for continuous-flow operation is demonstrated.

Results and Discussion

Recycling experiments and kinetic investigations: As a first benchmark system, phosphine-modified rhodium catalysts were prepared from $[\text{Rh}(\text{cod})_2]\text{BF}_4$ (cod = 1,5-cyclooctadiene) and tri-[3-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)phenyl]phosphane ($3\text{-H}^2\text{F}^6\text{-TPP}$)^[18] for the hydrogenation of itaconic acid (**1**) as a prototypical substrate (Scheme 1). The catalysts were prepared in situ by mixing the ligand and the metal complex in CH_2Cl_2 . After evaporation of the solvent, the residual solid was re-dissolved in scCO_2 and subsequently the solution was pressurised with hydrogen.



Scheme 1. Rhodium-catalysed hydrogenation of itaconic acid **1**.

Then, an aqueous solution of itaconic acid **1** was dosed into the reactor with a high-pressure pump (Figure 1). The reaction progress was monitored by taking samples of the water layer through a needle valve at the bottom of the reactor.

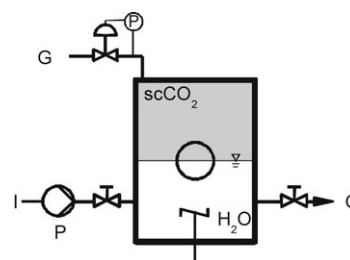


Figure 1. Schematic experimental setup of the high pressure window equipped autoclave (I: inlet, G: gas inlet, P: dosing pump, O: outlet).

This catalytic system was reused in a repetitive batch sequence by using the following procedure: After quantitative conversion or after a given time, the aqueous phase was removed and a new batch of substrate was pumped into the reactor without depressurisation of the autoclave. Variation of the ligand-to-rhodium ratio (L:Rh) from 3:1 to 5:1 at constant reaction time of one hour led to a significant increase in conversion as well as catalyst retention. At an L/Rh ratio of 3:1, the conversion decreased from 34% after one hour in the initial reaction cycle to 8% in the fourth run (Table 1, entries 1–4). In contrast, an L/Rh ratio of 5:1 led to a constant conversion of 95% per cycle. The catalyst could be recycled three times without apparent loss of activity (Table 1, entries 5–8). Leaching of rhodium and phospho-

Table 1. Rhodium-catalysed hydrogenation of itaconic acid: recycling experiments.^[a]

Entry	L/Rh/S	Cycle	Conversion [%]	TOF _{max} ^[b] [h ⁻¹]	Rh leaching ^[c] [ppm]	P leaching ^[c] [%]	P leaching ^[c] [ppm]	P leaching ^[c] [%]
1	3:1:200	1	34	70	19.5	18.9	0.6	0.6
2	3:1:200	2	20	24	4.4	4.3	0.6	0.6
3	3:1:200	3	14	20	2.1	2.0	0.9	1.0
4	3:1:200	4	8	14	2.0	1.9	0.8	0.8
5	5:1:200	1	95	252	14.2	14.0	6.2	4.0
6	5:1:200	2	95	194	3.6	3.5	0.8	0.5
7	5:1:200	3	95	192	1.0	0.9	1.0	0.6
8	5:1:200	4	95	192	0.6	0.6	0.8	0.5

[a] Reaction conditions: Rh = $[\text{Rh}(\text{cod})_2]\text{BF}_4$ 0.02 mmol, L = $3\text{-H}^2\text{F}^6\text{-TPP}$, substrate **1** (4.0 mmol, 0.2 M in H_2O , 20 mL), V_{tot} = 100 mL, $m(\text{CO}_2)$ = 50 g, $p(\text{H}_2)$ = 30 bar, T = 40 °C, t = 1 h @ 1000 rpm. [b] Compare Figure 2. [c] Rh and P content measured by ICP methods.

rus into the aqueous layer was determined by inductively coupled plasma (ICP) atomic emission spectrometry (Table 1). Significant amounts of rhodium and phosphorus leached to the aqueous layer when an L/Rh = 3:1 ratio was used. By utilising a larger excess of ligand (L/Rh = 5:1) the leaching decreased below 1 ppm in the second and third cycle for phosphorus and rhodium, respectively, and remained low in the following cycles.

A series of experiments with short sampling intervals were conducted to investigate the reaction course during the repetitive runs. It was found that a short induction period occurred during the first reaction cycle. The reaction rates in following cycles are comparable within the experimental error and no loss of activity is apparent. A total turnover number (TTN) of 1000 was achieved within the four cycles with a maximum turnover frequency of 252 h^{-1} (Figure 2).

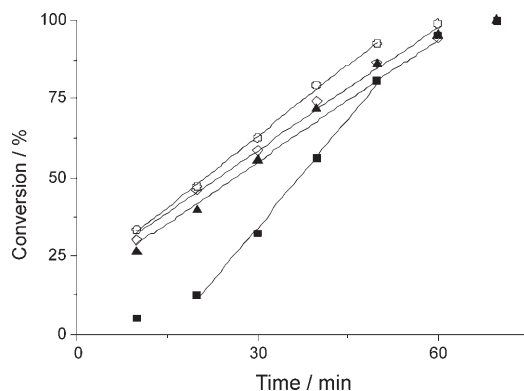


Figure 2. Conversion/time profiles of repetitive batch hydrogenations of itaconic acid **1** (experimental: points (symbol/entry in Table 1: square:5, caret:6, triangles:7, circles:8, maximum reaction rates: lines).

Optimisation of reaction conditions: A simplex algorithm for function minimisation according to Nelder and Mead was used for the optimisation of the reaction conditions.^[19] Maximised conversion was set as the target parameter of the optimisation. The amounts of CO_2 and hydrogen, the temperature, and the L/Rh ratio were selected as the optimisation parameters to be varied within reasonable limits. Substrate, rhodium amount, stirring speed, and reaction time were kept constant. The conditions of the five initial experiments were randomly calculated.^[20] The subsequent experiments were obtained by applying the algorithm as reflection of the experimental conditions with the least favourable result at the hyperplane given by the other parameter sets (Table 2).

Within six experiments, an increase of conversion from 8% to 86% could be achieved. The optimisation procedure

Table 2. Parameters for the hydrogenation of **1** obtained by simplex optimisation.^[a]

Entry	$m(\text{CO}_2)$ [g]	T [°C]	L/Rh	$p(\text{H}_2)$ [bar]	Conv. [%]
1	50	40	5.0	30	8
2	60	40	5.0	30	9
3	55	58	5.0	30	65
4	55	46	5.8	30	17
5	55	46	5.2	38	22
6	62	56	5.6	34	86

[a] Reaction conditions: $[\text{Rh}(\text{cod})_2][\text{BF}_4]$ 0.02 mmol, L = 3- $\text{H}^2\text{F}^6\text{TPP}$, substrate 4 mmol in 20 mL H_2O , 30 min, 1000 rpm.

was not iterated further as the next calculated parameter set would have exceeded the maximum autoclave pressure. Several conclusions about the influence of individual parameters can be drawn from this set of experiments. In general, higher conversions were obtained by increasing the amount of CO_2 at constant temperature. This can be attributed to higher substrate availability due to increasing solvent power of the dense CO_2 and the decrease of hydrogen partial pressure which act as an anti-solvent in the given system. If the temperature is increased at a given CO_2 amount, the acceleration of the catalytic cycle surpasses potential negative effects of a reduced CO_2 density. The L/Rh ratio and the hydrogen concentration seem to be close to optimum values and are not changed significantly.

Hydrogenation of other polar substrates: The successful application of this catalyst system to further substrates depends both on the intrinsic reactivity and on the partition coefficient of each particular substrate within the biphasic system. Table 3 presents the hydrogenation results of some

Table 3. Hydrogenation of other substrates.^[a]

Substrate	Conversion [%]
Z-2-butenic acid	50
tiglic acid	> 99
maleic acid	15
methyl-2-acetamidoacrylate (3) ^[b]	> 99
2-acetamidoacrylic acid ^[c]	20
fumaric acid ^[c]	> 99
α -acetamidocinnamic acid	> 99

[a] Reaction conditions: $[\text{Rh}(\text{cod})_2][\text{BF}_4]$ 0.02 mmol, 3- $\text{H}^2\text{F}^6\text{TPP}$ 1.12 mmol, substrate 4 mmol in 20 mL H_2O , $V_{\text{tot}} = 100 \text{ mL}$, $m(\text{CO}_2) = 62 \text{ g}$, $p(\text{H}_2) = 30 \text{ bar}$, $T = 56^\circ\text{C}$, Reaction time = 1 h@1000 rpm. [b] Catalyst was reused four times (see Table 4). [c] Catalyst was reused four times (data not shown).

selected polar substrates in the inverted $\text{scCO}_2/\text{H}_2\text{O}$ biphasic system.

The highest efficacy was achieved with methyl-2-acetamidoacrylate (**3**). Both, favourable partition and quantitative conversion is achieved in hydrogenation of this substrate. The catalyst could be recycled four times without noticeable deterioration of performance, reaching a TTN of 750. The leaching of rhodium and phosphorus decreased with the number of repetitive batches performed (Table 4).

Semi-continuous reaction: Encouraged by the promising results of the batchwise recycling, a semi-continuous reaction was carried out to assess the possibility of continuous processing. The hydrogenation of itaconic acid (**1**) was performed in a 35 mL reactor with a catalyst/substrate ratio of 1:60, an L/Rh ratio of 6.2:1 and a substrate concentration of 0.1 mol L^{-1} . A fixed amount of aqueous non-reactive phase was replaced at regular time intervals with the same volume of a substrate solution without depressurisation. The shorter the intervals compared to the averaged residence time are, the closer the system approaches the characteristic of a con-

Table 4. Hydrogenation of methyl-2-acetamidoacrylate **3** with catalyst recycling.^[a]

Cycle	1 h	Conv. [%] 2 h	Leaching [ppm]	
			Rh	P
1	78	81	2.3	4.9
2	61	92	1.7	2.1
3	>99	>99	0.5	1.5
4	>99	>99	0.5	0.4
5	>99	>99	0.3	0.5

[a] Reaction conditions: see footnote [a] in Table 3.

tinuously stirred tank reactor (CSTR). In these experiments, a third of the total aqueous solution volume was replaced every 30 min. After an induction period of approximately 1.5 h, a stable conversion of 87% ($\pm 3\%$) was achieved for the residual duration of the experiment (five hours in total; Figure 3).

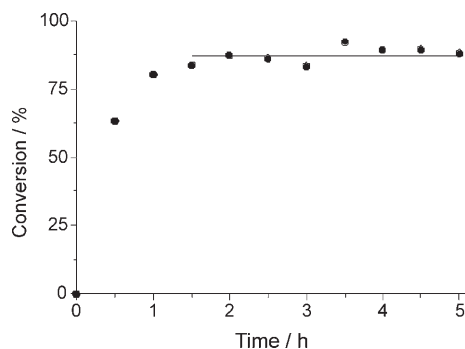
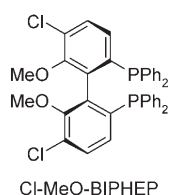


Figure 3. Semi-continuous hydrogenation of itaconic acid **1** (experimental points: circles; average conversion after 1.5 h: straight line).

Asymmetric hydrogenation reactions: To extend this approach to enantioselective hydrogenation, the chiral bis-phosphane ligand Cl-MeO-BIPHEP^[21] was tested in the enantioselective hydrogenation in the inverted biphasic system $\text{scCO}_2/\text{H}_2\text{O}$.



Although the ligand itself is poorly soluble in scCO_2 , a sufficient solubility of the resulting rhodium complex could be achieved by using the CO_2 -philic

BARF (BARF = tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate) as the counterion^[22] and through the addition of 3 vol % benzotrifluoride as co-solvent.^[23] Hydrogenation of **1** was performed under the previously optimised conditions except that an L/Rh ratio of 3:2 was employed, considering the fact that Cl-MeO-BIPHEP is a bidentate ligand. In the first cycle, a conversion of 89% and an *ee* of 53% (*S*) were

obtained. Recycling of the catalyst phase resulted in a decrease of both conversion and enantioselectivity (Figure 4). The instability of this system does not seem to result from

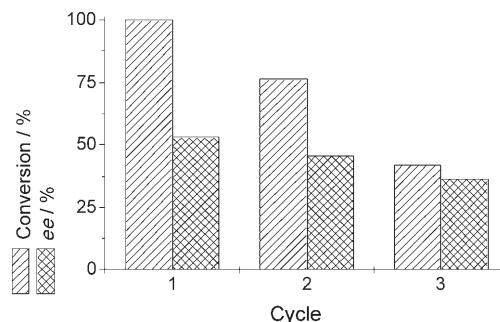


Figure 4. Conversion and enantiomeric excess (*ee*) of the hydrogenation of itaconic acid **1** with (*R*)-Cl-MeO-BIPHEP-modified rhodium catalyst.

catalyst leaching, as no contamination of rhodium and phosphorus in the aqueous phase was detectable.

Stable performance was achieved with the same catalyst for the hydrogenation of **3** leading to quantitative conversion throughout five cycles. The enantioselectivity was only modest (about 40% in all cycles; Figure 5). Also in these ex-

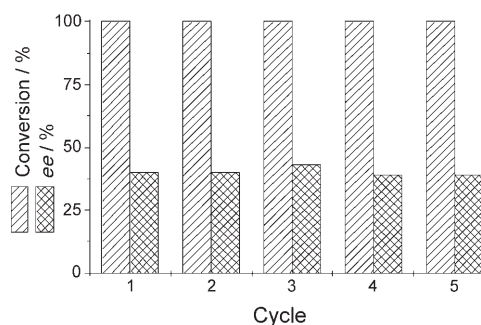
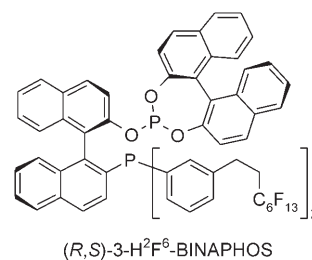


Figure 5. Conversion and enantiomeric excess (*ee*) of the hydrogenation of methyl-2-acetamidoacrylate **3** with (*R*)-Cl-MeO-BIPHEP-modified rhodium catalyst.

periments, no leaching of rhodium and phosphorus into the product phase was measurable.

The CO_2 -philic ligand (*R,S*)-3- H^2F^6 -BINAPHOS was then tested in the same reaction.^[24] The chiral phosphane-phosphite framework of BINAPHOS was originally designed for



hydroformylation reactions,^[25] but recent research has demonstrated its potential also for enantioselective hydrogenation, especially in scCO_2 media.^[26,27]

Again, the complex $[\text{Rh}(\text{cod})_2]\text{BARF}$ was used as the precursor and the catalyst was preformed as before. No undissolved material was detected by visual inspection and the water layer remained colourless, whereas the scCO_2 phase showed the yellow colour typical of rhodium–phosphane complexes. Enantioselective hydrogenation of **1** led to quantitative conversion under standard conditions with an *ee* of 94% (*S*) (Figure 6). Recycling of the catalyst was straight-

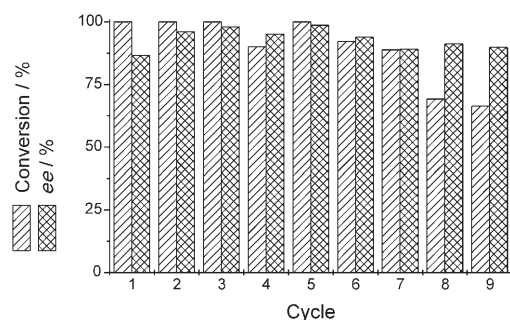


Figure 6. Conversion and enantiomeric excess (*ee*) of the hydrogenation of itaconic acid **1** with (*R,S*)-3- H^2F^6 -BINAPHOS-modified rhodium catalyst.

forward, and only after seven cycles and a long hold up time did the activity start to decrease. A TTN > 1600 was reached in the repetitive batch series. These data are encouraging as they demonstrate a noticeable stability of the potential sensitive catalytic system in the unconventional and fairly acidic medium (pH 3 under experimental conditions).^[28]

With the (*R,S*)-3- H^2F^6 -BINAPHOS-based system, leaching of rhodium and phosphorus into the aqueous layer was found to be 1.6 and 4.9 ppm, respectively. This indicates a better retention in the scCO_2 phase of the latter catalyst compared to the previous achiral catalyst system. Two effects are likely to contribute to the better retention of the (*R,S*)-3- H^2F^6 -BINAPHOS-derived catalyst. One is the use of the BARF anion, which is expected to increase the solubility of the metal complex in scCO_2 relative to the tetrafluoroborate analogue and which is not susceptible to hydrolysis. The second is the enhanced catalyst stability due to the chelation of the bidentate ligand.

For the hydrogenation of **3**, quantitative conversion and an *ee* of 97.3% (*R*) were achieved in the first run (Figure 7). Again, the product was easily isolated in quantitative yield directly from the water layer and the scCO_2 phase could be re-used several times. TTN = 1000 and TOF = 200 h^{-1} were achieved and the enantiomeric excess increased from 97 to 99% (*R*) over the course of five cycles. The contamination of the aqueous layer with rhodium and phosphorus was low for the initial experiment (1.4 ppm and 5.2 ppm, respectively) and below the detection limit for the successive experiments.

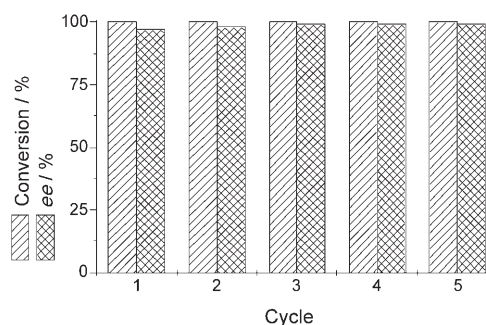


Figure 7. Conversion and enantiomeric excess (*ee*) of the hydrogenation of methyl-2-acetamidoacrylate **3** with (*R,S*)-3- H^2F^6 -BINAPHOS-modified rhodium catalyst.

Conclusion

The inverted biphasic system $\text{scCO}_2/\text{H}_2\text{O}$ provides a promising approach to combine efficient transformation and separation for organometallic catalytic processes leading to highly polar and water-soluble products. Immobilisation of the catalyst in the scCO_2 phase can be achieved utilising established concepts to design achiral or chiral “ CO_2 -philic” catalysts.^[29] The system is completely VOC-free and the product-containing water phase is readily isolated with very low levels of contamination of catalyst components (below ICP detection limits in favourable cases). Continuous processing is possible for which no energy consuming pressure cycle of a scCO_2 -phase is required and liquid water constitutes the mobile phase in this system. The resulting relatively low operating costs, the high reaction rates (TOF $\approx 10^2 \text{ h}^{-1}$), excellent asymmetric induction (up to 99% *ee*) and a remarkable long-term stability are salient features of this novel approach to multiphase catalysis.

Experimental Section

General: Reactions involving air-sensitive materials were performed under an atmosphere of dry argon using standard Schlenk techniques. Water was distilled and degassed before use. Hydrogen (99.999%), argon (99.995%) and carbon dioxide (99.9995%) were purchased from Messer Griesheim. 3- $\text{H}^2\text{F}^6\text{TPP}$,^[30] Cl-MeO-BIPHEP,^[21] and (*R,S*)-3- H^2F^6 -BINAPHOS^[26] were synthesised according to literature procedures. NMR spectra were recorded on a Bruker DPX 300 spectrometer. Rhodium and phosphorus contents were determined by inductively coupled plasma (ICP) atomic emission spectrometry (average value over five replicates; error ± 0.1 ppm, detection limit typically 0.7 to 1.2 ppm depending on the amount of sample available).

Caution: Working with highly compressed gases must be carried out only using suitable equipment and with appropriate safety precautions.

General procedure for batch and repetitive batch hydrogenation experiments: Ligand and rhodium precursor (see text and Tables for details) were dissolved in dichloromethane (3 mL) and stirred at room temperature for 30 min. This solution was transferred into a window-equipped 100 mL autoclave ($T_{\text{max}} = 120^\circ\text{C}$; $p_{\text{max}} = 200$ bar) and the solvent was removed under reduced pressure. Alternatively, the ligand and rhodium precursor were introduced in the autoclave as solids. No significant difference was observed between these two procedures. The reactor was pressurised with H_2 (typically 30 bar) and then filled with CO_2 (typically

50 g). The reaction mixture was heated to 40 °C and the aqueous solution of the substrate (20 mL, 0.2 mol L⁻¹) was added to the autoclave. The reaction was started by stirring at 1000 rpm, at which a highly disperse scCO₂/water mixture is formed rapidly. Samples of the reaction mixture (≈0.5 mL) were withdrawn periodically from a needle valve placed at the bottom of the reactor. The stirrer was switched off during sampling to allow for complete phase separation. The products were isolated simply by removing the water under reduced pressure and the conversion was determined by ¹H NMR spectroscopy. The recovery of the substrate/product mixture from the autoclave ranged from 85 to 90%. The repetitive batch experiments were carried out by removing the water phase completely and exchanging it with a substrate solution using a HPLC pump.

Simplex optimisation: the conversion of **1** was defined as the target for the optimisation sequence. The amount of CO₂, the reaction temperature, the H₂ pressure and the ligand-to-rhodium ratio were chosen as the variable parameters [Eq. (1)].

$$\chi = f \left[m(\text{CO}_2), T, p(\text{H}_2), \left(\frac{n(\text{L})}{n(\text{Rh})} \right) \right] \quad (1)$$

The amount of itaconic acid (4 mmol, 0.2 mol L⁻¹) and of rhodium precursor (5 mol%), stirring speed (1000 rpm) and reaction time (30 min) were kept constant throughout the optimisation study. To calculate the starting simplex, the initial conditions and the interval for each variable have been set (Table 5). By using Equation (2) and the *kF* values accord-

Table 5. Starting conditions of the simplex optimisation.

Parameter	X ₀	ΔX
<i>m</i> (CO ₂) [g]	50	10
<i>T</i> [°C]	40	20
L/Rh	5	1
<i>p</i> (H ₂) [bar]	30	10

Table 6. Values of *kF* of the simplex optimisation.

Entry	<i>kF</i> value for			
	<i>m</i> (CO ₂)	<i>T</i>	L/Rh	<i>p</i> (H ₂)
1	0			
2	1.00	0		
3	0.50	0.87	0	
4	0.50	0.29	0.82	0
5	0.05	0.29	0.20	0.79

ing to the algorithm shown in Table 6, the first five working points were calculated.

$$X_i = X_0 + (kF \Delta X) \quad (2)$$

The obtained results were then listed in descending order relative to the conversion and the barycentre of the best four experiments is calculated according to Equation (3).

$$\vec{S}_{a,b,c,d} = \frac{1}{4}(\vec{a} + \vec{b} + \vec{c} + \vec{d}) \quad (3)$$

The following experiment was calculated [Eq. (4)] by reflection of the point of lowest conversion onto the barycentre calculated before

$$X_{\text{new}} = 2S_{a,b,c,d} - e \quad (4)$$

Semi-continuous hydrogenation: 3-H²F⁶TPP (217.2 mg, 0.167 mmol) and [Rh(cod)₂]BF₄ (10.9 mg, 0.027 mmol) were dissolved in dichloromethane (3 mL). This solution was transferred into a 35 mL window-equipped autoclave (*T*_{max} = 120 °C; *p*_{max} = 400 bar) and the solvent was removed under reduced pressure. The reactor was pressurised with H₂ (40 bar), and heated to 55 °C. An aqueous solution of itaconic acid (15 mL, 0.1 mol L⁻¹) was added. The reactor was then filled with CO₂ until a total pressure of 260 bar was reached. The reaction was started by stirring (500 rpm). Every thirty minutes the stirrer was turned off and 5 mL of the water phase was withdrawn and replaced with the same volume of fresh substrate solution. The pressure was readjusted to the initial value by addition of CO₂. The hydrogen consumption was considered as negligible. The reaction was restarted by stirring. Quantification was carried out as described above for batch experiments.

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