Continuous-Flow Asymmetric Hydrogenation of the β-Keto Ester Methyl Propionylacetate in Ionic Liquid–Supercritical Carbon Dioxide Biphasic Systems

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Abstract: A continuous-flow process for the asymmetric hydrogenation of methyl propionylacetate as a prototypical β-keto ester in a biphasic system of ionic liquid and supercritical carbon dioxide (scCO$_2$) is presented. An established ruthenium/2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) catalyst was immobilised in an imidazolium-based ionic liquid while scCO$_2$ was used as mobile phase transporting reactants in and products out of the reactor. The use of acidic additives led to significantly higher reaction rates and enhanced catalyst stability albeit at slightly reduced enantioselectivity. High single pass conversions (>90%) and good enantioselectivity (80–82% *ee*) were achieved in the first 80 h. The initial catalyst activity was retained to 91% after 100 h and to 69% after 150 h time-on-stream, whereas the enantioselectivity remained practically constant during the entire process. A total turnover number of ~21,000 and an averaged space-time yield (STY$_{av}$) of 149 g L^{-1} h^{-1} were reached in a long-term experiment. No ruthenium and phosphorus contaminants could be detected *via* inductively coupled plasma optical emission spectrometry (ICP-OES) in the product stream and almost quantitative retention by the analysis of the stationary phase was confirmed. A comparison between batch-wise and continuous-flow operation on the basis of these data is provided.

Keywords: asymmetric ketone hydrogenation; BINAP; carbon dioxide; continuous flow; ionic liquids; ruthenium; supercritical fluids

Introduction

Homogeneous transition metal-catalysed asymmetric hydrogenation is an important method for the synthesis of high value chiral chemicals under mild reaction conditions.[1] The application of this technology, however, is still facing typical obstacles associated with homogeneous catalysed processes such as product separation and catalyst recycling: Often, product isolation requires resource-, time-, and labour-intensive downstream processing to ensure complete removal of catalyst residues. Moreover, recovery and recycling of the often expensive ligands and precious metals are essential to achieve acceptable production costs.[2]

Different approaches have emerged in recent years to circumvent the aforementioned hurdles[3] and biphasic reaction systems based on ionic liquids (ILs) and compressed carbon dioxide (scCO$_2$) have been identified as a promising solution.[4,5] The complementary properties of these media result in a biphasic reaction system that combines rapid mass transfer with essentially quantitative phase separation. This allows for an effective integration of catalytic reaction and product separation in a single-step process.[6] Under continuous flow conditions, the use of compressed carbon dioxide as transport vector permits metal- and solvent-free product isolation and even fractionation,[7,8] which can meet the strict purity criteria of the pharmaceutical industry. The potential of this approach has been successfully demonstrated so far in hydroformylation,[9] C=C hydrogenation,[10] hydrovinylation,[11] and alkene metathesis.[12]

In this work, we have investigated the continuous flow asymmetric hydrogenation of β-keto esters to β-hydroxy esters, which are useful building blocks for flavours and pharmaceuticals, for example, as key chiral intermediate in the synthesis of atorvastatin calcium (Lipitor).[13] The aim was to elucidate the funda-

mental molecular and physico-chemical parameters for the adjustment of the well-established Ru/BINAP catalysts to this system as a basis for a fully integrated reaction/separation process under stable long-term operation.

Results and Discussion

Hydrogenation of MPA in Ionic Liquids

The hydrogenation of the β-keto ester methyl propionylacetate (MPA) to the corresponding hydroxy ester (MHP) was studied as the model system and readily available ruthenium-BINAP complexes were selected as the catalysts (Scheme 1). Literature data indicate that the hydrogenation of β-keto esters in the presence of ionic liquid (Figure 1) is possible although it is often necessary to add protic co-solvents in order to promote the reaction and/or to achieve acceptable enantioselectivities.[14] Only few attempts to use ionic liquid as the only solvent were undertaken and poor
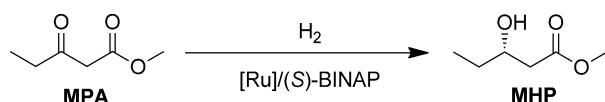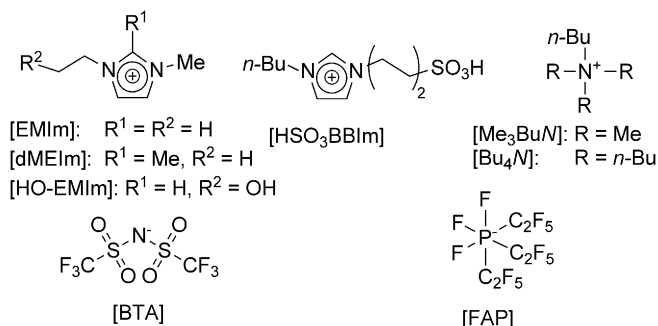
reaction rates and low enantioselectivity were observed in most cases.[14e,15]

Thus, a series of batch experiments was carried out using the ionic liquid [dMEIm][BTA] without co-solvents to identify an appropriate catalyst precursor (Table 1).

Catalyst **A**, prepared *in situ* from [Ru(benzene)Cl$_2$]$_2$ and (*S*)-BINAP by Noyori's procedure,[16] resulted in high enantioselectivity (95% *ee*). In line with the literature reports,[15] reduced activity (TOF = 56 h^{-1}) was observed in IL as compared with the reaction in protic solvents. Similar results were obtained with the preformed chloride-containing complex **B** (entry 2), while the iodide-containing complex **C** led to lower enantioselectivity as well as activity (entry 3), reflecting the importance of the nature of the halide ligands.[17] Halide-free complexes **D**[18] and **E**[19] were twice to ten times more active than complex **B**, respectively. Unfortunately, both complexes resulted in very low enantioselectivities and in the case of complex **E** even reversed enantioselectivity was achieved, again underlining the pivotal role of the halide co-ligands for the catalyst performance.[17b]

Ionic liquids with different anions and cations were then tested as solvents in the hydrogenation of MPA using catalyst **A** (Table 2). Imidazolium-based ILs gave superior results over ammonium-based solvents (entries 1–4 *vs.* 5), but in general no drastic effects on catalysis outcome were observed upon IL variation. Using [HO-EMIm][BTA], a task-specific ionic liquid bearing a hydroxy functionality and having a polarity similar to that of methanol, did also not effect any improvement in the activity (entry 4). It was therefore decided to explore the use of additives as a way to improve the catalyst performance

Scheme 1. Hydrogenation of the β-keto ester methyl propionylacetate MPA.

Figure 1. Ionic liquids used in the hydrogenation of MPA as solvent and/or additive.

Additives in the Hydrogenation of MPA in IL

Water is used as additive in the hydrogenation of keto esters in alcoholic solvents to reduce acetal formation.[17a,20] The hydrogenation of ketones can even be performed in pure water with high reaction rates and very good enantioselectivities.[21] In ionic liquids, how-

Table 1. Hydrogenation of MPA in [dMEIm][BTA] with different Ru/(*S*)-BINAP precursors[a]

Entry	Catalyst	p(H$_2$) [bar]	TOF [h^{-1}]	Conv. [%]	*ee* [%]
1	[Ru(benzene)Cl$_2$]$_2$/PP, **A**	90	56	45	95(*S*)
2	[Ru(*p*-cymene)ClPP]Cl, **B**	100	65	52	95(*S*)
3	[Ru(*p*-cymene)IPP)]I, **C**	100	21	17	89(*S*)
4[b]	[Ru(η^5-2,4-dimethylpentadienyl)PPCH$_3$CN][BTA], **D**	60	138	99	10(*S*)
5[c]	[Ru(η^6-cot)HPP)][BF$_4$], **E**	60	≥660	≥99	13(*R*)

[a] PP = (*S*)-BINAP; IL = 1.26 mL; MPA = 1.88 mmol; MPA/Cat = 500; *T* = 60 °C, *t* = 4 h.
[b] *t* = 3.6 h.
[c] *t* = 0.75 h.

Table 2. Hydrogenation of MPA in different ILs.[a]

Entry	IL	$p(H_2)$ [bar]	TOF [h^{-1}]	Conv. [%]	ee[b] [%]
1	[EMIm][BTA]	100	56	45	97
2	[EMIm][FAP]	90	53	42	90
3	[dMEIm][BTA]	90	56	45	95
4	[HOEMIm][BTA]	100	41	33	93
5	[Me$_3$BuN][BTA]	90	26	21	90

[a] Catalyst = **A**; IL = 1.26 mL; MPA = 1.88 mmol; MPA/**A** = 500; T = 60 °C, t = 4 h.
[b] *S*-enantiomer.

ever, even small amounts of water can have a strong negative effect on catalyst activity and even more on enantioselectivity.[15b,22] Indeed, the addition of degassed water (4.0 equiv. with respect to the catalyst) in virtually dry [dMEIm][BTA] (water content: 8 ppm) resulted in a drop in conversion and enantioselectivity from 47% to 12% and 95% to 76% *ee*, respectively (Table 3 entries 1 *vs.* 2). For this reason, careful drying of all reaction components is essential to obtain good and reproducible results in ionic liquids in the present system.

The beneficial effect of acidic additives in the hydrogenation of β-keto ester was first reported by King.[23] Addition of small amounts of hydrochloric acid significantly enhanced the reaction rate of the hydrogenation of methyl propionylacetate catalysed by [Et$_2$NH$_2$][Ru$_2$Cl$_5$(BINAP)$_2$]. Later, it was found that other acidic additives like sulphuric acid and *para*-toluenesulphonic acid (*p*-TsOH)[24] led also to significant improvements of reaction rates in conventional solvents without any loss of enantioselectivity.

According to these findings, the addition of acids was evaluated in the hydrogenation of MPA in ionic liquid solutions. Whereas the addition of tetrafluoroboric acid caused a reduced catalyst activity and re-

sulted in the formation of many side products (entry 3), the use of *p*-TsOH led to an enhancement of the reaction rate by a factor of 2.6 reaching a TOF of 156 h^{-1} (entry 4). This increase in activity was accompanied by a slightly reduced enantioselectivity and an *ee* of 81% was obtained. The addition of up to 40 equivalents of *p*-TsOH enhanced the reaction rate by nearly 400% (entry 6), while higher amounts of acid apparently did not affect further the reaction outcome.

The same effect as with *p*-TsOH could be achieved when the acid-functionalised IL 1-butyl-3-(4-sulfobutyl)-imidazolium bis(trifluoromethanesulphonyl)-amide ([HSO$_3$BBIm][BTA]) was employed as acidic additive[25] resulting in increased reaction rates (TOF = 102 h^{-1}) and slightly lowered enantioselectivity (82% *ee*, entry 7).

Chloride-containing additives were also tested in the hydrogenation of MPA. Higher TOF of 98 and 85 h^{-1} rates were observed by adding 10–20 equiv. of [*N*Bu$_4$]Cl and [OMIm]Cl, respectively (entries 8 and 9). Slightly enhanced *ee* values of 97% were achieved confirming the beneficial effects of chloride anions.[26,27]

Finally, a combination of *p*-TsOH and [*N*Bu$_4$]Cl was used as additive to evaluate whether the activity *and* the enantioselectivity can be simultaneously improved. This mixture, however, did not lead to a synergistic effect and resulted in a TOF of 74 h^{-1} and *ee* values of 82% (entry 10).

In summary, these results confirm the feasibility of the use of catalyst **A** in a stationary IL phase, whereby the role of the acidic additives requires special attention for activity and long-term stability.

Table 3. Hydogenation of MPA in [dMEIm][BTA] with different additives.[a]

Entry	Additive (equiv.)	t [h]	TOF [h^{-1}]	Conv. [%]	ee[b] [%]
1	–	4	59	47	95
2[c]	H$_2$O (4)	4	15	12	76
3[d]	HBF$_4$·Et$_2$O (11)	4	43	34	69
4	*p*-TsOH (11)	1	156	62	81
5	*p*-TsOH (20)	1	237	48	80
6	*p*-TsOH (40)	1	270	55	80
7	[HSO$_3$BBIm][BTA] (11)	4	102	82	82
8	[Bu$_4$N]Cl (11)	4	98	77	97
9	[OMIm]Cl (11)	4	85	65	97
10	*p*-TsOH (40)/[*N*Bu$_4$]Cl (10)	1	74	15	82

[a] IL = 1.26 mL; Catalyst = **A**; MPA = 1.88 mmol; MPA/**A** = 500:1; T = 60 °C; $p(H_2)$ = 90 bar.
[b] *S*-enantiomer.
[c] $p(H_2)$ = 100 bar; H$_2$O/**A** = 4:1.
[d] Side products formed.

Phase Behaviour and Partitioning in the System IL–CO$_2$

A sufficient CO$_2$-solubility of the reagents as well as a favourable partitioning of the products between mobile and catalytic phase are prerequisites for the use of CO$_2$ as transport medium in a continuous flow system. Organic compounds pressurised with CO$_2$ can exhibit complex phase behaviour, which have been classified following practical criteria.[28] Upon pressurising the substrate MPA with CO$_2$ to $p = 80$ bar at $T = 40\,°C$, a large volume expansion of up to 500% was observed indicating that MPA clearly belongs to class II liquids. At higher CO$_2$ pressures only one homogeneous phase could be observed.

The partitioning of product and substrate between ionic liquid and carbon dioxide expressed by the partition coefficient K$_N$ was determined *via* high-pressure NMR. A high-pressure sapphire NMR tube (V$_{tot} = 0.93$ mL) was loaded with 0.35 mL of an equimolar mixture of MPA and MHP in the ionic liquid [dMEIm][BTA] ($c_i = 1.25$ mol/L) mimicking a reaction mixture at 50% conversion. The total substance concentration in the IL was chosen to be of the same order of magnitude used later on in the continuous reactions. ^{1}H NMR spectra were recorded at 40 °C prior and after pressurisation with CO$_2$ (86 bar). The residual concentration of both compounds in the ionic liquid (bottom phase) after pressurisation with CO$_2$ was measured using the signals of the ionic liquid as an internal standard assuming a negligible volume expansion of the IL-phase in the presence of CO$_2$.[29] The concentration in the CO$_2$ phase was deduced from the difference. Applying Eq. (1), the partition

$$K_{N,i} = \frac{c_i(CO_2)}{c_i(IL)} \qquad (1)$$

coefficients $K_{N,\text{MPA}} = 0.18$ and $K_{N,\text{MHP}} = 0.23$ were determined. These data indicate that both compounds are dissolved preferentially in the ionic liquid phase. However, the product displays a higher affinity (*ca.* 30%) for the CO$_2$-rich phase with respect to the substrate. These solubility profiles meet the most favourable situation for continuous flow operation, where the product will be extracted preferentially by the mobile phase from the catalytic phase.

Hydrogenation in Presence of CO$_2$

The effect of carbon dioxide on the hydrogenation of MPA in [dMEIm][BTA] was examined in the next step (Figure 2). Conversion after 4 h reaction time increased from 55% to 78% upon addition of 60 bar
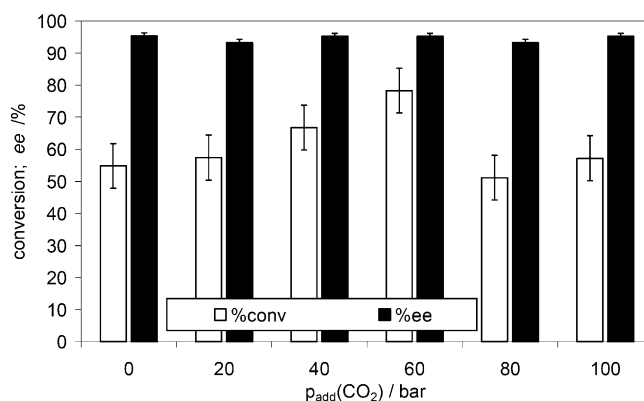

Figure 2. Variation of CO$_2$ partial pressure in the hydrogenation of MPA in [dMEIm][BTA], V(IL) = 1.03 mL, catalyst = **A**, MPA = 3.62 mmol, MPA/**A** = 500:1, $T = 60\,°C$, $t = 4$ h, 90 bar H$_2$. Error bars determined from the standard deviation of 3 experiments.

CO$_2$. Enhanced hydrogen solubility[30] and reduced viscosity of the ionic liquid phase[31] leading to improved mass transfer can explain this trend on the basis of increased hydrogen availability in the reactive phase. Increasing the partial pressure further resulted in lower conversion (51%). This can be rationalised by the increased density of CO$_2$, resulting in partial extraction of the substrate from the catalyst to the carbon dioxide phase in accordance with the partition coefficient data (*vide supra*). The enantioselectivity was not affected by the presence of carbon dioxide and ~95% *ee* was obtained over the whole pressure range examined (Figure 2).

The positive effect of CO$_2$ at moderate pressures was even more pronounced when the hydrogenation was carried out in the presence of *p*-TsOH (25 equivalents). After 1 h reaction time in presence of carbon dioxide (50 bar) a substrate conversion of 73% was reached corresponding to a four-fold increase of the TOF to 363 h^{-1}. Again a lower enantioselectivity was obtained in the presence of the acid (*ee* 82%).

Reactor Set-up for Continuous Flow Hydrogenation

Based on previous experience,[32] a dedicated reactor set-up was built for the continuous flow hydrogenation experiments (Figure 3). The program LabView™ (National Instruments) was used to record all data, control flows and pressures, and to monitor safety parameters for automatic shutdown procedure. Substrate delivery was accomplished by a double piston HPLC pump capable of realising flows down to 0.001 mL min^{-1} (E-5) and monitored by recording the weight loss of the substrate container (I-6). Carbon dioxide flow was controlled *via* a heated, compressed air regulated needle membrane valve connected to
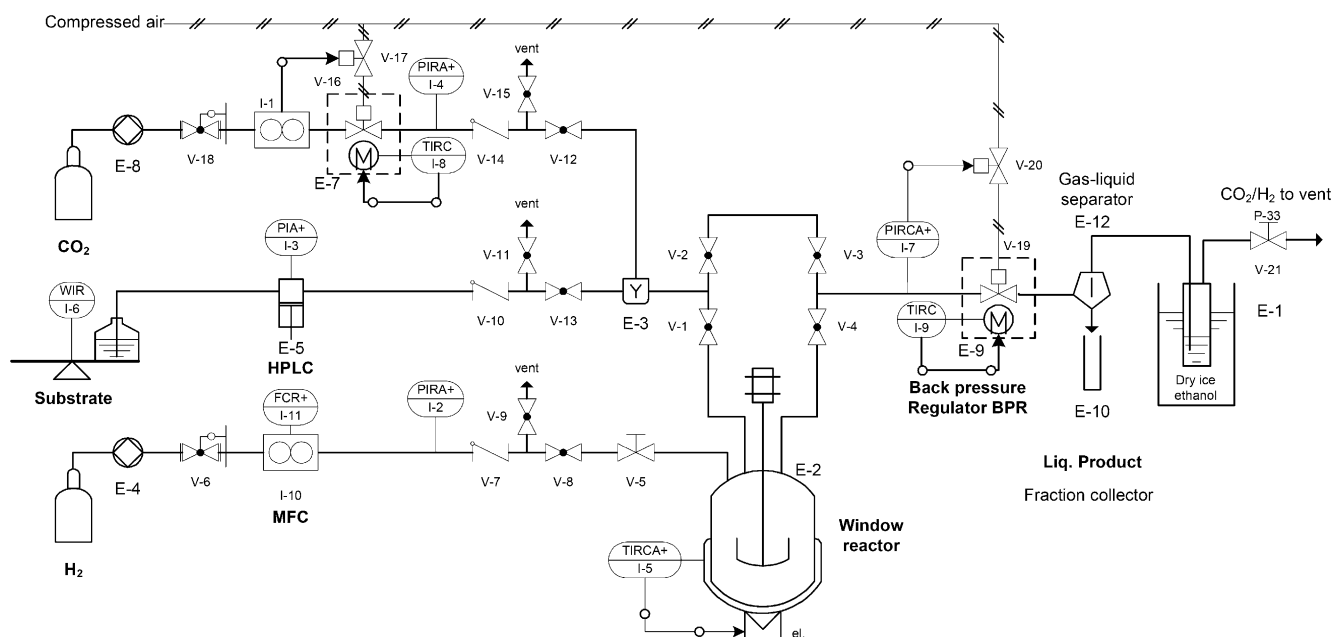
Figure 3. Flow scheme of the reactor for continuous flow reactions. E-7: CO_2 dosing unit, MFC: hydrogen mass flow controller, E-2: window reactor, E-9: back pressure regulator, E-12: gas-liquid separator, E-10: Fraction collector.

a calibrated liquid-flow device (E-7). Hydrogen flow was regulated by a mass-flow controller (I-10).

A stainless steel autoclave (10 mL) equipped with two thick-glass windows and a magnetic stirring bar was used as central reactor unit (E-2). Capillaries for incoming and outcoming flow were connected to the upper part of the autoclave. The total pressure in the system was controlled *via* a back pressure regulator consisting of a compressed air regulated and heated needle membrane valve (E-9).

The product was separated from the effluent CO_2 flow by customised gas-liquid separator (E-12). The use of the separator allowed for continuous time-resolved sampling of the product mixture in a fraction collector (E-10). The outgoing gas stream from the separator was then passed through a cooling trap containing toluene at $-80\,°C$ (E-1). Mass balance could be closed up to 95% at the end of each continuous experiment.

Continuous Hydrogenation Experiments

In a preliminary experiment, the density of the mobile phase $(0.49 \pm 0.01\ g\,mL^{-1})$ and the partial pressure of H_2 (pH_2 of 57 ± 3.5 bar) were determined under the typical conditions used for the continuous flow catalytic experiments (H_2 flow $= 3.3$ L_s/h, CO_2 flow $= 9.3$ L_s/h, $T = 60\,°C$; $p_{tot} = 250$ bar).[33] Catalyst **A** was dissolved in [dMEIm][BTA] (3 mL), MPA (1.6 mL, S/C $= 500$) added, and the resulting solution introduced in the reactor. After setting temperature,

CO_2 and H_2 flows, and total pressure, the delivery of MPA was started with a rate of 0.6 g/h. Under these conditions, a residence time of 17 min can be estimated for the 10-mL reactor volume.[34]

Figure 4 shows the results obtained without any additive at two different catalyst loadings (run 1: 15 μmol; run 2: 30 μmol). Conversion reached a maximum after 5 h time-on-stream (18% in run 1, 35% in run 2) and slowly decreased afterwards. At the beginning, high enantioselectivities of up to 96% *ee* were obtained, which also decreased in the course of the experiments (Figure 4). The average TOF_{av} calculated
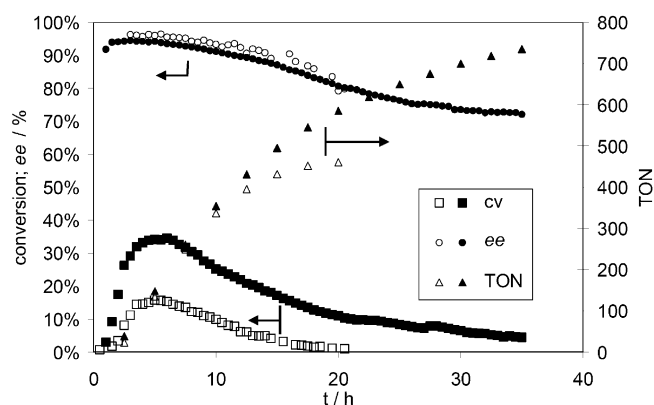

Figure 4. Continuous hydrogenation of MPA in [dMEIm][BTA]/scCO₂ in the absence of additives. *Conditions:* IL $= 3$ mL; V/t(H_2) $= 3.3$ L_s/h, V/t(CO_2) $= 9.3$ L_s/h, m/t(MPA) $= 0.6$ g/h, $T = 60\,°C$, $p_{tot} = 250$ bar; open symbols: **A** $= 15$ μmol; closed symbols: **A** $= 30$ μmol.

from the slope of accumulated turnovers in the first 8 h on stream was identical in both runs (49 h^{-1}).

Product samples obtained in the first phase of the reaction had a slightly yellow colour, but no IL contamination could be detected by ^{1}H NMR spectroscopy. Similarly, ruthenium content in the product fraction never exceeded the detection limit of 5 ppm of the ICP-OES analysis. High retention of Ru-BINAP species was confirmed by ^{31}P NMR analysis of the reactor content showing a set of signals in the characteristic region between 35–45 ppm. No evidence for the formation of phosphine oxides[35] or for trimeric Ru-BINAP complexes[17b] could be detected, ruling out such transformations as major source for deactivation.

Similar to the situation under batch conditions, the addition of *p*-TsOH as acidic additive strongly enhanced catalyst activity and stability. In the presence of 5 equiv. of *p*-TsOH, conversions >50% were achieved over 165 h reaching a maximum value of 73% after 55 h (Figure 5, open symbols). The TOF$_{av}$ (101 h^{-1}) was increased two-fold as compared to experiments without additives corresponding to a space-time yield (STY) of 114 g L^{-1} h^{-1}.[36] Notably, nearly constant levels of enantioselectivity between 85% and 79% *ee* were obtained over the entire experiment.

By doubling the amount of *p*-TsOH to 10 equiv.$_{cat}$ a further increase in activity (TOF$_{av}$ = 122 h^{-1}) and catalyst lifetime could be obtained. After a short induction period, stable conversion of 81–83% was observed for over 70 h time-on-stream. Afterwards, the conversion decreased similarly to the previous experiment but was still 40% after 185 h time-on-stream. Again, stable enantioselectivities around 80% *ee* were registered over the entire experiment. A total turnover number (TON) of ~19,000 with a STY of 132 g L^{-1} h^{-1} was achieved in this experiment (TON = 21,000 and STY = 149 g L^{-1} h^{-1} including residual product in the reactor and cooling traps).
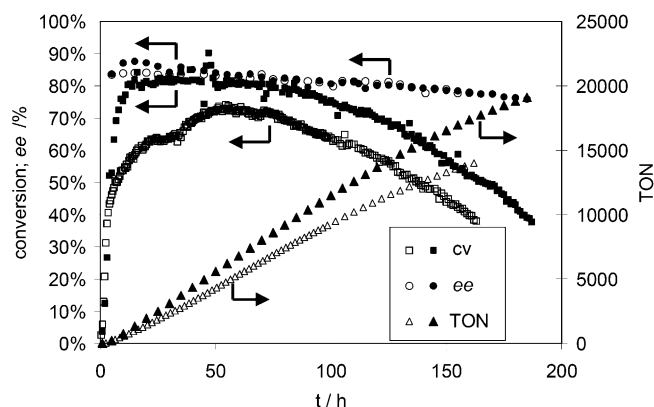
Again, no phosphorus and ruthenium could be detected in the collected samples *via* ICP-OES measurement. In the ^{1}H NMR spectrum of the ionic liquid solution recorded after reaction, the signals of the aromatic protons of *p*-TsOH at $\delta = 7.38$ and 7.75 ppm were no longer present. This indicates that the additive was depleted from the catalyst phase by CO$_2$ extraction over the extended reaction period.

To prevent extraction of the additive, the acid-functionalised IL [HSO$_3$BBIm][BTA] was used (Figure 6). Gratifyingly, an even higher single pass conversion of 95% was observed with 80% *ee* after 10 h time-on-stream, corresponding to a maximum TOF of 138 h^{-1} and STY of 168 g L^{-1} h^{-1}. Switching off the stirrer in the reactor unit led to a rapid but fully reversible decrease of turnover rate, reflecting the importance of mass transport in the biphasic reaction system.

The permanent immobilisation of the acidic additive was confirmed by ^{1}H NMR analysis of the stationary phase after 140 h. Nevertheless, the deactivation behaviour was very similar to that observed with *p*-TsOH, as conversion had steadily decreased to 40% (TON = 18,900) at this stage with a constant *ee* of 80–82%. These results indicate that the acid plays a major role in the initial phase of the reaction for the formation of the active species, but has a less direct influence on its performance and stability under turnover conditions.

Similarly to all previous runs, also in this continuous flow experiment no traces of ionic liquid or catalyst components were detected *via* ^{1}H and ^{31}P NMR in the collected samples. The analysis of the catalyst solution before and after the continuous flow experiment showed no difference in metal and phosphorus content within the accuracy of the measurement and Ru and P mass-balance could be closed for all experiments within the error margins.

As ligand oxidation, cluster formation, catalyst leaching and additive depletion can all be ruled out as

Figure 5. Continuous hydrogenation of MPA with *p*-TsOH as additive. Conditions: see Figure 4, **A** = 30 µmol. Open symbols: *p*-TsOH = 5 equiv.; closed symbols: *p*-TsOH = 10 equiv.
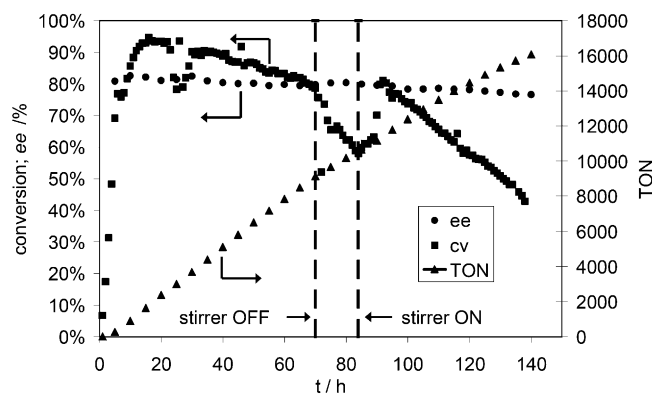
Figure 6. Continuous hydrogenation of MPA with [HSO$_3$BBIm][BTA] as additive. *Conditions:* see Figure 4, **A** = 30 µmol; [HSO$_3$BBIm][BTA] = 10.5 equiv.
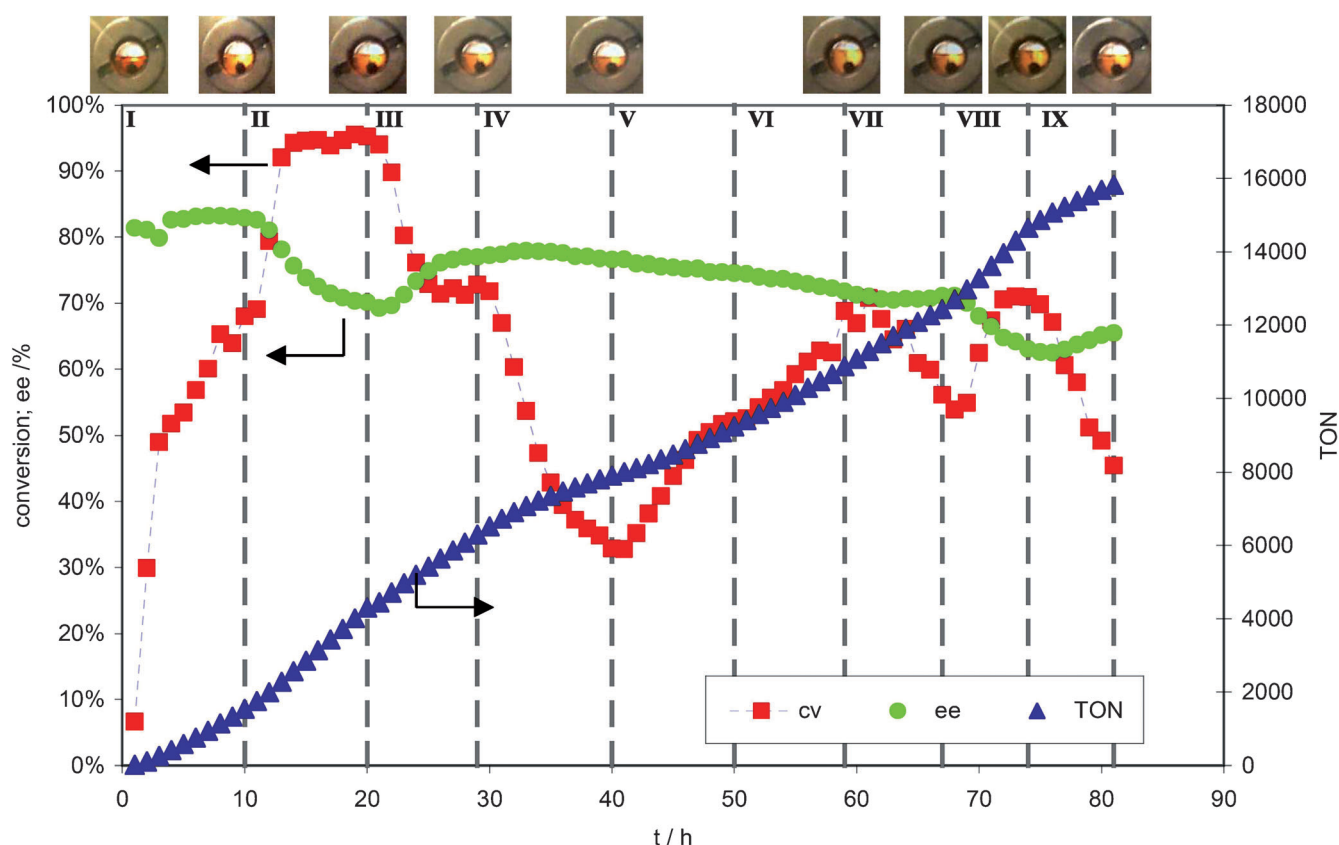
Figure 7. Continuous hydrogenation of MPA in [EMIm][BTA]/scCO$_2$. *Conditions:* **A** = 14 μmol; IL = 3 mL [HSO$_3$BBIm] [BTA] = 10 equiv. Variation of reaction conditions every 8–10 h. *Standard conditions* (**I**, **III**; **V**, **VII**, **IX**): V/t(H$_2$) = 3.3 L$_s$/h, V/t(CO$_2$) = 10.5 L$_s$/h, m/t(MPA) = 0.6 g/h, T = 60 °C, p$_{tot}$ = 250 bar. *Variations*: (**II**): T = 70 °C, (**IV**): V/t(H$_2$) = 1.7 L$_s$/h; (**VI**): V/t(H$_2$) = 1.7 L$_s$/h, V/t(CO$_2$) = 5.4 L$_s$/h; (**VIII**): m/t(MPA) = 0.9 g/h, T = 70 °C.

major source for deactivation, the introduction of water into the reactive phase remains most likely the limiting factor. Water is constantly delivered as a contaminant of the substrate (60–110 ppm) and of the CO$_2$ stream (≤ 5 ppm) contacting or even accumulating in the catalyst phase. A 25-fold excess relative to the catalyst amount is estimated over a typical run. As shown in the batch experiments, water is deleterious for the catalyst performance and even a four-fold excess resulted already in a clear depletion of the catalyst activity. Thus, water is most probably the main source of catalyst deactivation in the long term.

To explore the limits for optimisation, the response of the system to the variation of different reaction parameters was investigated. Temperature, hydrogen flow, and residence time were varied in 8–10 h periods. Conversion, enantioselectivity, and the phase behaviour in the reactor at the end/beginning of a period were monitored and are depicted in Figure 7. The catalyst concentration was set to 14 μmol to enable positive and negative variation of single pass conversion.

In the first 10 h time-on-stream (period **I**) a maximum conversion of 69% and an *ee* value of 83% were

achieved. From the accumulated TON an average TOF of 203 h^{-1} was calculated. Raising the temperature by 10 °C in period **II** led to an increase of conversion to 95% (TOF 290 h^{-1}) accompanied by a drop in *ee* to 70%. Restoring initial conditions after 10 h (period **III**) resulted in similar conversion (71%) and slightly reduced enantioselectivity level (*ee* 77%) as before in period **I**.

In the next step (period **IV**), hydrogen flow was set to 1.7 L$_s$/h corresponding to a reduction of the H$_2$ partial pressure by 50% in the mobile phase. Conversion dropped to ~33% over 10 h, consistent with a first order rate dependence in hydrogen pressure. After switching back to standard conditions (period **V**), a maximum conversion of only 52% was observed (*cf.* period **V** and **III**). This indicates that catalyst stability is somewhat reduced under lower H$_2$ pressure.

Next, carbon dioxide and hydrogen flows were reduced by 50% leaving the substrate flow unchanged (period **VI**). Visual inspection revealed a constant rise of the filling level in the reactor resulting from insufficient extraction of the substrate/product mixture under these conditions. Thus, the actual residence time in the reactor is no longer determined by the

flow rates, and therefore no steady operating mode could be adjusted. The conversion measured at the outlet increased steadily, but this apparent "activation" reflects merely the increasing contact time between substrate and catalyst.

By switching back to standard conditions (period **VII**) the product mixture could be extracted and the volume of the catalyst phase reduced to the initial level. Similar conversion and enantioselectivity as at the end of period **V** were observed, indicating no significant catalyst deactivation during the last 20 h time-on-stream.

In period **VIII**, the substrate flow was increased to 0.9 g h^{-1} and the temperature to 70 °C, under otherwise identical conditions. As expected, enantioselectivity dropped from 71% to 63%, whereas single pass conversion increased to 71%. This corresponds to an apparent TOF of 307 h^{-1} that exceeds the initial maximum despite the significant deactivation resulting from more than 70 h time-on-stream. Again a slight volume increase of the catalyst phase was observed at the end of period **VIII** indicating that the extraction capacity of the mobile phase was not able to balance the incoming flow completely.

Restoring the initial conditions (period **IX**) led to a decrease in conversion and slightly higher enantioselectivity. The comparison of the conversion values at the end of zone **I** (69%) and zone **IX** (45%) indicates a rate of catalyst deactivation by 35% over the 80 h time-on-stream, which is fully consistent with the results obtained under constant conditions.

Conclusions

The present study demonstrates that enantioselective hydrogenation of β-keto esters can be conducted under continuous-flow conditions in ionic liquid/scCO$_2$ biphasic systems using established Ru-BINAP catalysts. Using methyl propionylacetate as example for this class of compounds, a representative methodology for a systematic approach to successful implementation has been developed. The key elements of this strategy are the integrated evaluation and optimisation of the catalytic system on the molecular level (catalyst and transformation), the *meso*-scale (solubility and phase behaviour,) and the macro-scale (reactor unit and process scheme).[6a] This approach can be readily adopted to other targets of this substrate class, providing an efficient general outline for the validation of continuous-flow methods in specific synthetic applications.

The highest activity and stability was observed with a catalyst prepared according to the Noyori *in situ* method[16] using [dMEIm][BTA] as stationary phase and [HSO₃BBIm][BTA] as acidic additive. Maximum space-time yields of 180 g L^{-1} h^{-1} were obtained at

Table 4. Calculated figures for the production of 100 kg of MHP through batch[16b] and continuous-flow hydrogenation.

	Batch	Continuous flow
Number of batch	4	1
Reactor unit	50 L	5.4 L
Reaction solvent[a]	100 L	2.7 L
Catalyst **A**[a]	350 g	25 g
Reaction time	4×6 h	96 h
Processing time]	1–2 weeks	<1 week
Pressure	4 bar (H$_2$)	250 bar (H$_2$/CO$_2$)
Temperature	100 °C	60 °C

[a] Cumulative values for four batches.

almost quantitative single pass conversion and 80–82% *ee*. No contamination of IL or catalyst components was detected in the product. The initial catalyst activity was retained at 91% after 100 h and 69% after 150 h time-on-stream, with traces of water as the most likely source for deactivation.

Based on these data, it can be estimated that 100 kg of product can be produced within less than a week using 25 g of Ru/BINAP catalyst in 2.7 L of IL in a simple compact processing unit comprising a 5.4-L reactor (Table 4). To yield the same amount of product under conventional condition, four batches of 6 h reaction time in a 50-L reaction vessel would be necessary, each requiring 87.5 g of catalyst and 25 L of MeOH as solvent. Including all processing steps of make-up and downstream purification comprising separation of solvent and catalyst, a conservative estimate leads to a total working time of approximately one to two weeks to isolate the product. Thus, the continuous-flow process is considerably more resource efficient and requires much less man power for operation. It is conducted at considerably higher pressure but this is offset largely by a ten times reduced equipment size.

Whereas the mobile phase is vented in the laboratory set-up described here, it could be easily recycled at the scale of Table 4. Commercially available equipment designed for small-scale natural product extraction could be readily adapted to this kind of processing scale. A major factor of operating costs and energy requirement are the compression cycles for CO$_2$ between isolation and reaction.[37] Using temperature as separation variable[7] or adsorption and absorption processes[4b] would allow nearly isobaric operation conditions, however.

The major drawback of the present case study is the reduced enantioselectivity of the Ru/BINAP catalyst in the acidic IL matrix (80–82% *vs.* 97–98% in methanol). Although acceptable for certain agrochemicals[38] and API's intermediates,[39] this may necessitate more efforts to obtain the required optical purity for pharmaceutical end products.

Although a detailed economic analysis will depend strongly on an individual company framework, these basic data suggest that continuous-flow asymmetric hydrogenation in IL/scCO$_2$ can offer a viable process alternative to classical batch operation. Critical factors to be addressed include the product extraction efficiencies and the method for product isolation from the CO$_2$ stream on a process level and the control of catalyst performance by immobilisation matrix on a molecular level.

Experimental Section

Caution: High-pressure experiments with compressed gases are potentially dangerous and must be carried out with suitable equipment under appropriate safety regulation only.

All manipulations of air- and moisture-sensitive material were carried out under an argon atmosphere using Schlenk techniques. Solvents were dried and purified according to standard methodologies prior to use. The gases H$_2$ (99.999%) and CO$_2$ (99.995%) were used without further purification. Methyl propionylacetate was dried over 3 Å molecular sieves, decanted, distilled and degassed *via* three freeze-pump-thaw cycles prior to use. Dry methanol was used as received and stored under argon on 3 Å molecular sieves. [dMEIm][BTA] was prepared *via* a halide-free route according to the literature.[40] [EMIm][BTA], [EMIm][FAP] and [Me$_3$BuN][BTA] were purchased from Solvent Innovation (Merck). [HO-EMIm][BTA] was prepared according to a described procedure.[41] Prior to use, the ionic liquids were dried and degassed under vacuum ($<10^{-3}$ mbar) at 60°C for 48 h. Water content could by reduced to a minimum of 5 ppm except for the case of [HOEMIm][BTA] (340 ppm). Water content was determined by a Metrohm KF 756 as average from two independent measurements. NMR spectra were measured on a Bruker AV-400 spectrometer. Chemical shifts are given relative to TMS by using the solvent signal as internal reference for ^{1}H NMR as well as for ^{13}C NMR and H$_3$PO$_4$ (85%) as external reference for ^{31}P NMR spectroscopy. Ruthenium and phosphorus content were determined *via* ICP-OES (Thermo Scientific, Iris Intrepid) at the University of Dortmund.

Catalyst Preparation

Catalyst **A** was prepared *in situ* following a reported procedure.[16] Volatiles were removed under reduced pressure and the resulting solid material was used without further purification. Complexes **B**,[17b] **C**,[17b] **D**[18] and **E**[19] were prepared according to literature procedures.

General Procedure for Batch Catalysis

Catalyst **A** (3.5 mg 3.75 μmol), MPA (0.24 mL, 1.88 mmol), ionic liquid (1.26 mL) and, additive were placed in a Schlenk tube and stirred for at least 1 h until a homogenous orange solution was obtained. The solution was transferred *via* a syringe to a 10-mL stainless steel autoclave, which was previously evacuated and purged with argon (3 cycles). The autoclave was equipped with a magnetic stirring bar, needle

valve, pressure read-out, and two thick-glass borosilicate windows allowing for visual observation. After heating the autoclave at 60°C, it was pressurised with CO$_2$ and then with H$_2$, and the stirrer was switched on (750 rpm). After the reaction time was over, the autoclave was cooled to room temperature, slowly vented, and the reaction mixture analysed.

General Procedure for Continuous Flow Experiments

The system was purged with a flow of carbon dioxide for at least 2 h at 120 bar to exclude any oxygen from the apparatus (Figure 3). Afterwards, pressure was reduced to 0.2 bar and a preformed mixture of precatalyst, additive and substrate (2 mL) dissolved in ionic liquid (3 mL) was filled into the reactor. The system was pressurised with carbon dioxide to 250 bar. Substrate, hydrogen, and carbon dioxide flows were set to the desired value, and stirrer (500 rpm) and product sampling at fraction collector was started. See captions of Figure 4 to Figure 7 for details.

Determination of Conversion and Enantiomeric Purity

In batch experiments, conversion was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. In continuous flow experiments, conversion was determined by GC analysis and validated by ^{1}H NMR spectroscopy.

The enantiomeric purity of MHP was determined from the corresponding TMS-derivative using following procedure: an aliquot of the product mixture (*ca.* 4 mg) was dissolved in CH$_2$Cl$_2$ (1 mL), treated with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (50 μL) and analysed *via* GC (Chiraldex CB).

Acknowledgements

References

[1] J. G. de Vries, C. J. Elsevier, (Eds.), *Handbook of Homogeneous Hydrogenation*, Wiley-VCH, Weinheim, **2006**.

[2] H. U. Blaser, E. Schmid, *Asymmetric catalysis on industrial scale*, Vol. 1, Wiley-VCH, Weinheim, **2004**.

[3] a) D. J. Cole-Hamilton, R. P. Tooze, (Eds.), *Catalyst Separation, Recovery and Recycling – Chemistry & Process Design*, Springer, Heidlberg, Berlin, **2006**; b) D. J. Cole-Hamilton, *Science* **2003**, *299*, 1702–1706.

[4] a) *Multiphase Homogeneous Catalysis*, 1st edn., (Eds.: B. Cornils, W. A. Herrmann, I. T. Horváth, W. Leitner, S. Mecking, H. Olivier-Bourbigou, D. Vogt), Wiley-

VCH, Weinheim, **2005**; b) *Handbook of Green Chemistry*, Vol. 4, *Supercritical Solvents*, (Eds.: W. Leitner, P. G. Jessop), Wiley-VCH, Weinheim, **2010**.

[5] W. Leitner, *Acc. Chem. Res.* **2002**, *35*, 746–756.

[6] a) U. Hintermair, G. Franciò, W. Leitner, *Chem. Commun.* **2011**, *47*, 3691–3701; b) M. I. Burguete, E. Garciá-Verdugo, S. V. Luis, *Beilstein J. Org. Chem.* **2011**, *7*, 1347–1359.

[7] T. Harwardt, G. Franciò, W. Leitner, *Chem. Commun.* **2010**, 6669–6671.

[8] M. T. Reetz, W. Wiesenhöfer, G. Franciò, W. Leitner, *Adv. Synth. Catal.* **2003**, *345*, 1221–1228.

[9] a) M. F. Sellin, P. B. Webb, D. J. Cole-Hamilton, *Chem. Commun.* **2001**, 781–782; b) P. B. Webb, M. F. Sellin, T. E. Kunene, S. Williamson, A. M. Z. Slawin, D. J. Cole-Hamilton, *J. Am. Chem. Soc.* **2003**, *125*, 15577–15588; c) A. C. Frisch, P. B. Webb, G. Zhao, M. J. Muldoon, P. J. Pogorzelec, D. J. Cole-Hamilton, *Dalton Trans.* **2007**, *47*, 5531–5538; d) U. Hintermair, G. Zhao, C. C. Santini, M. J. Muldoon, D. J. Cole-Hamilton, *Chem. Commun.* **2007**, 1462–1464; e) U. Hintermair, Z. Gong, A. Serbanovic, M. J. Muldoon, C. C. Santini, D. J. Cole-Hamilton, *Dalton Trans.* **2010**, *39*, 8501–8510.

[10] U. Hintermair, T. Höfener, T. Pullmann, G. Franciò, W. Leitner, *ChemCatChem* **2010**, *2*, 150–154.

[11] A. Bösmann, G. Franciò, E. Janssen, M. Solinas, W. Leitner, P. Wasserscheid, *Angew. Chem.* **2001**, *113*, 2769–2771; *Angew. Chem. Int. Ed.* **2001**, *40*, 2697–2699.

[12] R. Duque, E. Öchsner, H. Clavier, F. Caijo, S. P. Nolan, M. Mauduit, D. J. Cole-Hamilton, *Green Chem.* **2011**, *13*, 1187–1195.

[13] a) H. Shimizu, I. Nagasaki, K. Matsumura, N. Sayo, T. Saito, *Acc. Chem. Res.* **2007**, *40*, 1385–1393; b) M. A. Schwindt, M. P. Fleming, Y.-K. Han, L. M. Hodges, D. A. Johnston, R. P. Micheli, C. R. Roberts, R. Snyder, R. J. Topping, K. Püntener, M. Scalone, *Org. Process Res. Dev.* **2007**, *11*, 524–533; c) A. Korostylev, V. Andrushko, N. Andrushko, V. I. Tararov, G. König, A. Börner *Eur. J. Org. Chem.* **2008**, 840–846; d) N. Andrushko, V. Andrushko, V. Tararov, A. Korostylev, G. König, A. Börner, *Chirality*, **2010**, *22*, 534–541.

[14] a) H. L. Ngo, A. Hu, W. Lin, *Chem. Commun.* **2003**, 1912–1913; b) A. Hu, H. L. Ngo, W. Lin, *Angew. Chem.* **2004**, *116*, 2555–2558; *Angew. Chem. Int. Ed.* **2004**, *43*, 2501–2504; c) K. H. Lam, L. Xu, L. Feng, J. Ruan, Q. Fan, A. S. C. Chan, *Can. J. Chem.* **2005**, *83*, 903–908; d) E. Öchsner, K. Schneiders, K. Junge, M. Beller, P. Wasserscheid, *Appl. Catal. A: Gen.* **2009**, *364*, 8–14; e) E. V. Starodubtseva, M. G. Vinogradov, V. A. Pavlov, L. S. Gorshkova, V. A. Ferapontov, *Russ. Chem. Bull. Int. Ed.* **2004**, *53*, 2172–2174.

[15] a) T. Floris, P. Kluson, L. Bartek, H. Pelantova, *Appl. Catal. A: Gen.* **2009**, *366*, 160–165; b) M. Berthod, J.-M. Joerger, G. Mignani, M. Vaultier, M. Lemaire, *Tetrahedron: Asymmetry* **2004**, *15*, 2219–2221.

[16] a) M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, *Tetrahedron Lett.* **1991**, *32*, 4163–4166; b) M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, *Org. Synth.* **1993**, *71*, 1.

[17] a) K. Mashima, K.-h. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, *J. Org. Chem.* **1994**, *59*,

3064–3076; b) K. Mashima, T. Hino, H. Takaya, *J. Chem. Soc. Dalton Trans.* **1992**, 2099–2107; c) K. Mashima, K. Kusano, T. Ohta, R. Noyori, H. Takaya, *J. Chem. Soc. Chem. Commun.* **1989**, 1208–1210.

[18] J. A. Wiles, C. J. A. Daley, R. J. Hamilton, C. G. Leong, S. H. Bergens, *Organometallics* **2004**, *23*, 4564–4568.

[19] A. Doppiu, A. Salzer, *Eur. J. Inorg. Chem.* **2004**, 2244–2252.

[20] a) A. Wolfson, I. F. J. Vankelecom, P. A. Jacobs, *J. Organomet. Chem.* **2005**, *690*, 3558–3566; b) L. Bartek, M. Drobek, M. Kuzma, P. Kluson, L. Cerveny, *Catal. Commun.* **2005**, *6*, 61–65.

[21] a) M. Berthod, C. Saluzzo, G. Mignani, M. Lemaire, *Tetrahedron: Asymmetry* **2004**, *15*, 639–645; b) T. Lamouille, C. Saluzzo, R. ter Halle, F. Le Guyader, M. Lemaire, *Tetrahedron Lett.* **2001**, *42*, 663–664.

[22] Often the negative effect of water was attributed to the generation of HF by hydrolysis of fluorinated ionic liquids anions like BF_4 and PF_6. In our experiments, however, FAP and BTA anions were used, which are regarded as inert against hydrolysis.

[23] S. A. King, A. S. Thompson, A. O. King, T. R. Verhoeven, *J. Org. Chem.* **1992**, *57*, 6689–6691.

[24] a) M. Kitamura, M. Yoshimura, N. Kanda, R. Noyori, *Tetrahedron* **1999**, *55*, 8769–8785; b) A. E. Sollewijn Gelpke, H. Kooijman, A. L. Spek, H. Hiemstra, *Chem. Eur. J.* **1999**, *5*, 2472–2482; c) A. Wolfson, I. F. J. Vankelecom, S. Geresh, P. A. Jacobs, *J. Mol. Catal. A: Chem.* **2004**, *217*, 21–26; d) V. A. Pavlov, E. V. Starodubtseva, M. G. Vinogradov, V. A. Ferapontov, O. R. Malyshev, G. L. Heise, *Russ. Chem. Bull. Int. Ed.* **2000**, *49*, 728–731.

[25] F. M. A. Geilen, B. Engendahl, A. Harwardt, W. Marquardt, J. Klankermayer, W. Leitner, *Angew. Chem.* **2010**, *122*, 5642–5646; *Angew. Chem. Int. Ed.* **2010**, *49*, 5510–5514.

[26] R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1987**, *109*, 5856–5858.

[27] D. B. Williams, M. E. Stoll, B. L. Scott, D. A. Costa, W. J. Oldham Jr, *Chem. Commun.* **2005**, 1438–1440.

[28] U. Hintermair, W. Leitner, P. G. Jessop, in: *Handbook of Green Chemistry*, Vol. 4, *Supercritical Solvents*, (Eds.: W. Leitner, P. G. Jessop), Wiley-VCH, Weinheim, **2010**, pp 103–120.

[29] S. N. V. K. Aki, B. R. Mellein, E. M. Saurer, J. F. Brennecke, *J. Phys. Chem. B* **2004**, *108*, 20355–20365.

[30] M. Solinas, A. Pfaltz, P. G. Cozzi, W. Leitner, *J. Am. Chem. Soc.* **2004**, *126*, 16142.

[31] A. Ahosseini, E. Ortega, B. Sensenich, A. M. Scurto, *Fluid Phase Equilib.* **2009**, *286*, 72–78.

[32] a) C. Roosen, J.-L. Muller, M. Kaever, H. Kronenberg, R. Thelen, S. Aey, T. Harwardt, W. Leitner, L. Greiner, *J. Supercrit. Fluids* **2009**, *48*, 33–35; b) U. Hintermair, C. Roosen, M. Kaever, H. Kronenberg, R. Thelen, S. Aey, W. Leitner, L. Greiner, *Org. Process Res. Dev.* **2011**, *15*, 1275–1280.

[33] The density was directly determined by weighing the reactor filled the mobile phase. The NIST SuperTrapp™ program was used to calculate the CO_2/H_2 ratio from the mixture density.

[34] Considering the high solubility of CO_2 in the IL, the entire reactor volume including the IL-phase was considered for the calculation of the residence time.

[35] 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl monoxide: ^{31}P NMR (CDCl$_3$): $\delta = -14.1$ (s), 28.7 (s); 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl oxide: ^{31}P NMR (CDCl$_3$): $\delta = 29.4$ ppm.

[36] In analogy to heterogeneous catalytic systems, we define the space-time yield (STY) for biphasic systems as the mass flow of the product per volume of the catalyst phase ($g\,h^{-1}\,L_{rV}^{-1}$). For simplicity, the initial volume of the ionic liquid phase is considered.

[37] C. M. Gordon, W. Leitner, in: *Catalyst Separation, Recovery and Recycling – Chemistry & Process Design*, (Eds.: D. J. Cole-Hamilton, R. P. Tooze), Springer, Heidleberg, Berlin, **2006**, p 215.

[38] H.-U Blaser, W. Brieden, B. Pugin, F. Spindler, M. Studer, A. Togni, *Topics in Catalysis* **2002**, *19*, 3–16.

[39] J. Klosin, C. R. Landis, *Acc. Chem. Res.* **2007**, *40*, 1251–1259.

[40] J. D. Holbrey, W. M. Reichert, R. P. Swatloski, G. A. Broker, W. R. Pitner, K. R. Seddon, R. D. Rogers, *Green Chem.* **2002**, *4*, 407–413.

[41] K. Shimojo, N. Kamiya, F. Tani, H. Naganawa, Y. Naruta, M. Goto, *Anal. Chem.* **2006**, *78*, 7735–7742.