Continuous-flow homogeneous catalysis using the temperature-controlled solvent properties of supercritical carbon dioxide[†]

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A fully integrated continuous process for homogeneous catalysed reactions in $scCO_2$ has been developed exploiting the tunable solvent properties of $scCO_2$. A heated condenser situated above the reaction zone leads to a phase split under isobaric conditions resulting in efficient catalyst retention and recirculation. Continuous isomerisation of allylic alcohols was carried out for over 200 hours time-on-stream demonstrating the viability of this approach.

Homogeneous catalysis is an attractive technology for advanced synthesis and offers highly selective access to fine chemicals and pharmaceuticals.¹ However, separation and reuse of the high-value catalysts is one major challenge for industrial scale applications. Moreover, the stringent regulations for (noble) metal residues in chemical and especially pharmaceutical products must be taken into account for the proper design of processes and the choice of the separation sequence.²

Multiphase catalysis has proven to be a viable approach to catalyst immobilisation with high stability and low levels of leaching, and some of these techniques have been established on an industrial scale.³ The concept relies on the presence of two immiscible phases with distinct solvent properties for the catalyst and the products, creating an effective physicochemical barrier that leads to separation and retention of the catalyst. In recent years, supercritical carbon dioxide (scCO₂) has received increasing interest as a mobile phase in continuous flow multiphase catalysis.⁴ A range of highly polar and/or low volatile solvents form two phase systems with scCO₂, which can be exploited to immobilize catalysts under scCO₂-flow in liquid⁵ or supported liquid phases.⁶ This concept has been demonstrated using for example ionic liquids,⁷ polyethyleneglycol,⁸ or high boiling products⁹ as the liquid phase containing the catalyst.¹⁰

However, catalyst separation can be also achieved in $scCO_2$ alone without the need of a permanent separate phase. In a two-step process, the reaction is carried out under single phase conditions and then a switch to a biphasic product/CO₂ system is induced upon density reduction during the extraction of the products with fresh CO₂ (CESS procedure).¹¹ Excellent levels of separation between products and catalysts have been obtained with this technique, but the need to operate the reaction and separation step under different sets of parameters is a major restriction for the design of continuous-flow processes.¹²

In the present contribution, we describe a novel approach for continuous flow catalysis which integrates reaction and separation into one unit operation by exploiting the tuneable solvent properties of $scCO_2$. While the catalytic transformation occurs under homogeneous single phase conditions in the bottom part of the apparatus (reaction zone), efficient catalyst separation and recirculation is achieved by a phase split in the upper part (separation zone). The phase split is induced by a temperature increase under isobaric conditions resulting in a reduced density. This is achieved using a special reactor design incorporating a built-in heat-exchanger (Fig. 1) similar to the "hot finger" described by Zosel in his seminal investigation on separation processes with supercritical fluids.¹³

The isomerisation of allylic alcohols yielding carbonyl compounds catalysed by metal-phosphine complexes (Scheme 1) was chosen as a test reaction for validating the process



Fig. 1 Principle of continuous-flow homogeneous catalysis by integrated reaction and catalyst separation using temperature-controlled $\rm CO_2$ -solubility.



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Scheme 1 Catalytic isomerisation of allylic alcohols.

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concept. This atom-economical transformation finds application in a variety of natural product synthesis as well as in bulkchemical production.¹⁴ As model substrates 3-butene-2-ol (1a) and 1-octene-3-ol (1b) were selected, which have analogous substitution pattern at the terminal double bond, but very distinct volatilities (bp 96–97 °C for 1a and 180 °C for 1b).

The integrated reactor/separator unit for continuous synthesis under high-pressure conditions was established with the necessary periphery for precise dosing of fluids and pressure control.¹⁵ The central part of this set-up provides the possibility to define a temperature gradient between the bottom (reaction zone) and the upper part (separation zone) of the reactor (Fig. 2). The reaction zone consists of a 20 mL window autoclave. On the top of it, a heat exchanger with a volume of ca. 150 mL is connected constituting the separation zone. Its layout consists of an inverted pipe-in-pipe system and allows for visual monitoring of the state of operation through high-pressure windows in the outer wall. The inner tube is heated by a circulating heating fluid, whereas the outer wall can be heated electrically or cooled by ventilation. After the back-pressure regulator, the exit stream passes through a cold trap, where the products are collected.

In preliminary experiments, the isomerisation of 3-butene-2-ol in $scCO_2$ was studied in batch mode to identify a suitable catalyst. The combination of $[Rh(cod)_2]BArF$ as the metal precursor and the CO₂-philic fluorinated ligand $3-H^2F^6-TPP^{11}$ yielded a soluble and active catalyst to conduct the target reaction under single phase conditions (Scheme 1). A ligand-to-metal ratio of 3.5 led to the highest TOF (145 h⁻¹) at 50 °C and was therefore applied in the continuous flow experiments.

In a representative continuous flow experiment a catalyst loading of 15 mg (0.013 mmol) Rh precursor and 58 mg (0.045 mmol) phosphine ligand was applied. Feed rates were adjusted to 3.9 g h⁻¹ (89 mmol h⁻¹) for CO₂ and 0.11 g h⁻¹ (1.5 mmol h⁻¹) for **1a**, corresponding to a substrate content of 2.7 weight% and a residence time of 6 h. The system pressure in the integrated reactor/separator unit was held constant at 200 bar throughout the experiment. The temperature of the reaction zone was kept at $T_r = 35$ °C, whereas the temperature of the separation zone was set to $T_{sep} = 120$ °C. Under these conditions, a single phase was observed throughout the unit



Fig. 2 Flow sheet of the continuous-flow set-up (left) and photograph of the integrated reactor/separator unit with the built-in heat exchanger (right).

with a calculated density of $ca. 0.71 \text{ g mL}^{-1}$ in the reaction zone, which is strongly lowered to $ca. 0.17 \text{ g mL}^{-1}$ in the separation zone by the temperature gradient. The sample collected from the exit stream after 24 h showed almost full conversion, whereas after 48 h only 50% of the substrate was transformed. After 72 h almost no conversion was observed anymore (Fig. 4). Product samples were largely colourless indicating that the temperature-induced density gradient served as an efficient barrier to prevent the catalyst from escaping the reactor. Indeed, close inspection of the dismounted unit after the reaction revealed that the catalyst was deposited as a yellow film in the hot separation zone, while the reaction zone was virtually catalyst-free. This proves that the catalyst was efficiently precipitated upon density reduction, but it was not transported back into the reaction zone leading to a gradual decrease and ultimately stop of conversion (Fig. 2).

In order to establish a "vehicle" for recirculating the catalyst, the formation of liquid phase droplets in the separation zone falling down to the reaction zone was envisaged. Zosel described in his work on "destraction" with supercritical fluids already the possibility to generate a reflux by means of a heated condenser ("hot finger").¹³ In contrast to conventional reflux conditions, where a liquid phase is formed by cooling a vapour phase, the liquid phase is generated by temperature *increase* from the supercritical fluid in this case.

For 3-butene-2-ol **1a** no reflux could be achieved under various conditions since the low boiling point of this substrate prohibited the formation of a liquid phase. In contrast, the phase behaviour of 1-octene-3-ol **1b**/CO₂ mixtures showed that the formation of a liquid phase upon temperature increase under isobaric conditions is possible for this substrate. Fig. 3 shows the dew point curve for defined mixtures of CO₂ and **1b** monitored visually in a window-equipped autoclave at 125 bar. Phase separation was observed already at 85 °C at 3 weight% content and at 65 °C at 5 weight% content. The temperature for the phase separation did not change significantly upon increasing the content of **1b** up to 20 weight%.¹⁶

Consequently, the process parameters for the continuous flow isomerisation of **1b** were adjusted to maintain a single phase in the reaction zone (Fig. 3, one phase region) and to induce a phase split in the separation zone through a suitable temperature gradient (Fig. 3, two phase region). A typical continuous isomerisation of **1b** was performed at 132 bar, setting a reaction temperature of $T_r = 80$ °C, a separation temperature of $T_{sep} = 100$ °C and a substrate content in the feed stream of 4.2 weight%. A catalyst system,¹⁷ generated



Fig. 3 Phase behaviour of $CO_2/1$ -octen-3-ol mixtures at 150 bar.



Fig. 4 Time/conversion profiles of the continuous isomerisation of 3-butene-2-ol **1a** (\blacktriangle) and 1-octene-3-ol **1b** (\bigcirc) under reflux conditions in scCO₂.



Fig. 5 Refluxing liquid at the heat exchanger during the continuous isomerisation of **1b**.

in situ from [RuCp(MeCN)₃]PF₆ and 4-H²F⁸-TPP, was used for these experiments (Scheme 1). Already by applying this relatively low temperature gradient of 20 °C, condensation of a liquid phase occurred on the hot condenser surface and a reflux was observed (Fig. 5). As seen in Fig. 5, the yellow colour of the refluxing liquid indicates that it effectively dissolves the catalyst and recycles it back into the reaction zone, where the droplets merge instantaneously with the homogeneous high density supercritical phase. Stationary reflux operation was maintained over a considerable time period at feed rates of 18.3 g h⁻¹ (0.42 mol h⁻¹) for CO₂ and 0.8 g h⁻¹ (2.8 mmol h⁻¹) for **1b**, corresponding to a residence time of 5 hours.

Under these conditions significant stability of the catalyst performance over a long time could be achieved. The time/ conversion profile of an experiment with more than 200 hours time-on-stream shows that after a short start-up period of a few residence times a stationary level of nearly full conversion was maintained over 72 hours (circles in Fig. 4). Conversion decreased only after 96 hours and was still in the range of 50% after 200 h. ICP-OES measurements revealed an upper limit for the contamination of the colourless product stream of 10 to 25 ppm for Ru and 5 to 7 ppm for the residual phosphor content.

In conclusion, the integration of reaction and catalyst separation for continuous homogeneous catalysis using $scCO_2$ as the only reaction medium and separation fluid has been demonstrated for the Rh- and Ru-catalysed isomerisation of allylic alcohols. The concept relies on a temperature induced

density gradient of the supercritical phase between the reaction and the separation zone of an integrated unit under isobaric conditions. The dramatically reduced solubility of the catalyst in the separation zone accounts for efficient catalyst retention. The formation of a liquid phase at the heat exchanger allows to recirculate the catalyst. This situation could be maintained stable for over 200 hours time-on-stream demonstrating the viability for long term operation. This approach avoids the use of any additional solvent to constitute the catalyst phase and operates under fully homogeneous conditions in the reaction zone, defining a unique scenario in the area of multiphase catalysis.

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