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A Versatile Lab to Pilot Scale Continuous Reaction System for Supercritical Fluid Processing

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Supporting Information

ABSTRACT: A compact and versatile continuous reaction system for supercritical fluids as mobile phase was realised using commercially available components where possible. All process parameters of particular importance to the specific properties of near- or supercritical fluids such as pressure, temperature, and composition (p, T, x) can be accurately controlled over a wide flow range. The setup is completely automated by the help of computerised control and features a view cell for inline phase behavior observation. Coupling to supercritical fluid chromatography permits sampling under process conditions for reaction monitoring. Potential applications include continuous flow synthesis and catalysis, extractions, and other operations demanding controlled application of compressible gases. Highly efficient continuous flow asymmetric hydrogenation catalysis with integrated product separation is demonstrated.

INTRODUCTION

Compressible gases as near- or supercritical fluids (SCFs)[1] are highly attractive media for many applications including chromatography,[2] material syntheses,[3] polymer processing,[4,5] extractions,[6] solvent recovery,[7] formulation,[8] synthesis,[9] and catalysis[10−12] on both laboratory and industrial scale.[13] Exploiting the beneficial properties of compressible gases requires highly accurate control of temperature, pressure, and composition due to the nonlinear response to parameter variations[14] and complex phase behavior with solutes.[15] In order to transfer promising results from academic research to industrially viable processes, accurate process control is of crucial importance. On small scale as used for early-on catalyst testing and process evaluation, control over compressible gases is complicated by issues of heat loss caused by high surface to volume ratios and technical limitations of dosing, especially in continuous flow mode. Reactor setups that offer sufficient accuracy and precision are still not commercially available to date, thus hampering process development in this promising area.[16]

Following up previous development,[17] we here report on a compact and highly integrated continuous flow high pressure setup for near- or supercritical fluids. It was realised by combination of mainly commercially available components at very reasonable overall costs. The setup offers high accuracy of process control in continuous operation mode over a wide range of conditions. In addition, it allows automated experimentation and monitoring of phase behavior under process conditions. This is exemplified using supercritical carbon dioxide ($scCO_2$) as prototypical SCF, as it is the most commonly used compressed gas for reasons of toxicity, safety, and availability.

RESULTS AND DISCUSSION

We aimed at establishing a compact yet flexible continuous flow system capable of processing supercritical fluids with maximum process control. Accurate flow, pressure, and temperature regulation with a focus on long-term stability were the basic prerequisites, but reasonable response times to parameter variations should be possible to allow for efficient process optimization. As the first target was development and evaluation of immobilised homogeneous catalysts, a gaseous and a liquid cofeed had to be incorporated to continuously dose substrates to the mobile SCF phase. Reaction gases may include hydrogen, oxygen, carbon monoxide, or mixtures thereof. Liquids should include premolten solids to be fed under inert atmosphere with high accuracy even at low flow rates. Recovery of solutes from the SFC after the reactor is achieved by controlled depressurization. Eventually, an automated computer-based control system was needed in order to ensure maximum utility and safety for unsupervised long-term operation. The flow scheme in Figure 1 illustrates the setup (for details see Supporting Information).

A key prerequisite for continuous flow processing with compressible gases is independent and pulsation-free control of flow and pressure. As commercial mass flow controllers for such conditions are not available and thermostatted syringe pumps commonly used for dosage of compressed CO_2 have limited capacities, a continuous dosing unit was developed consisting of an electrically heated and pneumatically actuated needle valve (SITEC, k_v = 0.01) and a high pressure liquid flow meter (Bronkhorst, LiquiFlow L). Heating of the valve socket

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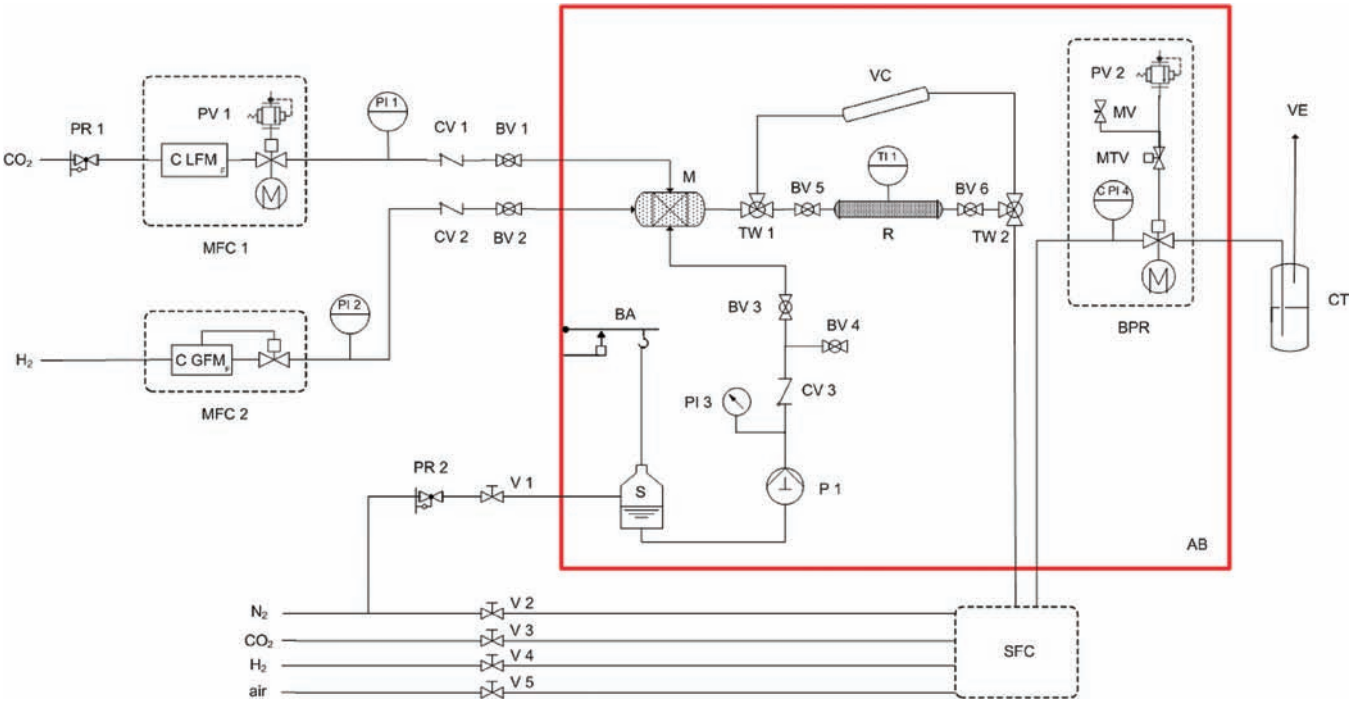

Figure 1. Flow scheme of the continuous reaction system for supercritical fluid processing (PR = pressure reducing valve, MFC = mass flow controller, LFM = liquid flow meter, GFM = gas flow meter, PI = pressure indicator, PV = proportional valve, CV = check valve, BV = ball valve, AB = air bath, V = screw-down valve, M = mixing chamber, S = substrate reservoir, BA = balance, P = piston pump, TW = three-way valve, R = reactor, VC = high pressure view cell, TI = temperature indicator, BPR = back pressure regulator, MTV = magnetic trigger valve, MV = metering valve, CT = cooling trap, VE = vent, SFC = supercritical fluid chromatograph).

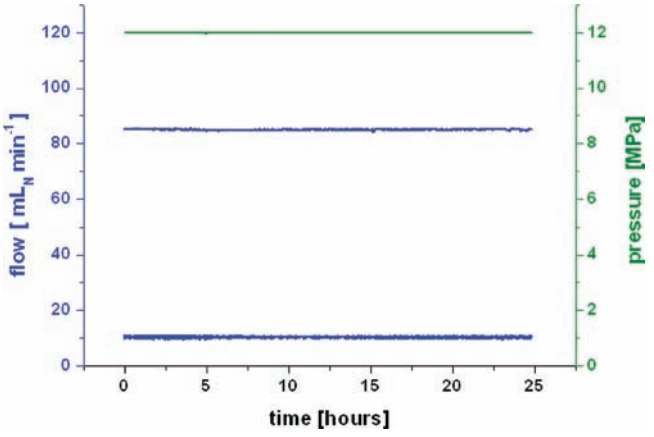

Figure 2. Regulation of pressure (set point 12.0 MPa) and flow (set points 85 $mL_N\ min^{-1}$ CO_2, 10 $mL_N\ min^{-1}$ H_2) at 313 K (inlet pressure 25 MPa).

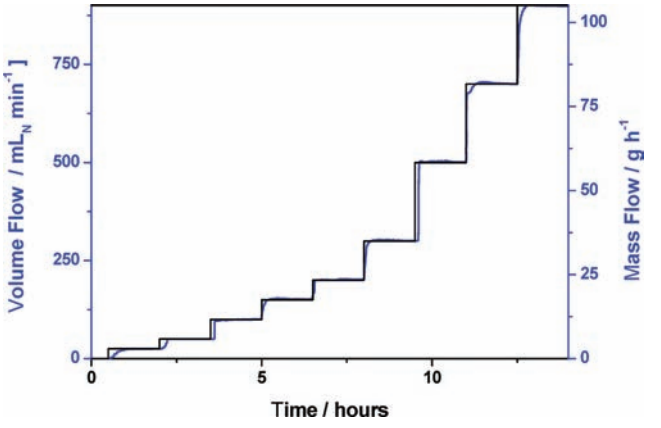

Figure 3. Set point variation (steps) of CO_2 flow at 14.0 MPa and 313 K using the bypass (PID parameters were adapted for flows higher than 300 and 700 $mL_N\ min^{-1}$).

was found to be mandatory to compensate for the Joule-Thompson effect. PID regulation of the valve was realised via computer (see below), and the regulation parameters were optimized for stability in continuous operation. As precision turned out to be dependent on inlet pressure (see Supporting Information), the installation of a high pressure reservoir and an upstream pressure reducing valve (HOKE) proved necessary to allow pressure and flow control with less than 0.01 MPa and 0.2 $mL_N\ min^{-1}$ (equivalent volume flow in mL at normal pressure and temperature per time) deviation from the set point, respectively (Figure 2). Co-dosing of hydrogen was achieved with commercial equipment (Brooks, Smart Mass Flow 5800).

This initial configuration allowed accurate CO_2 dosing up to 115 $mL_N\ min^{-1}$ (13 $g\ h^{-1}$).[17] With additional precision control of the pneumatic actuator (Festo, VPPM proportional valve) the accessible flow range could be considerably extended by a factor of 8 to up to 900 $mL_N\ min^{-1}$ (100 $g\ h^{-1}$), allowing both the use of small scale reactors for early-on catalyst testing and kinetic studies as well as pilot scale production capacities. Adaptive regulation parametrization afforded excellent dynamic behavior with flow deviations of less than 5% within 0.5 h after alteration of set points (Figure 3).

System pressure was maintained by a back pressure regulator (BPR) consisting of a similar combination of the heated

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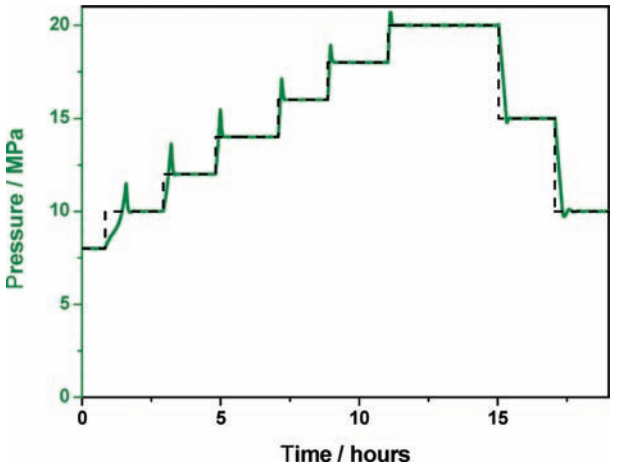

Figure 4. Set point variation (dashed line) of CO_2 pressure at 50 mL_N min^{-1} flow and 313 K using the bypass.

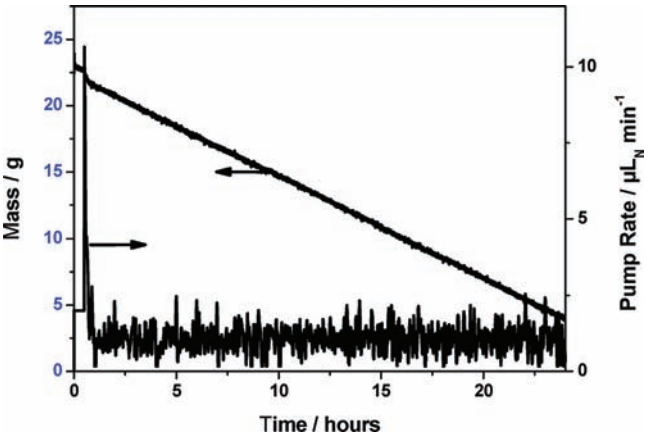

Figure 5. Substrate reservoir mass and pump rate of the piston pump as controlled by the hanging balance at 313 K against 12.0 MPa CO_2 (set point 0.78 g h^{-1}, corresponding theoretical volume flow 0.01 mL_N min^{-1}). In the first 30 min the PID regulation is bypassed with a fixed volume flow (here 0.02 mL_N min^{-1}) to generate an initial data array.

pneumatic needle valve for dosing and a digital pressure transducer (WIKA) instead of a flow meter. The pneumatic signal for the needle valve was pulsed by a magnetic trigger valve (Bürkert) and the decay of the pulses attenuated with the help of a metering valve (HOKE, Milli-Mite) to achieve a floating pulsation of the needle in order to prevent blocking. Similar to the MFC unit, the dynamic range of the back pressure unit could be extended by using a proportional valve. Step changes of the set point show initial deviations of up to 1.5 MPa with steady-state deviations of less than 0.01 MPa for which the PID parameters were optimized (Figure 4). Overshooting is dependent on flow, pressure, and temperature as well as on the overall pressurized volume and thus the reactor configuration. Overshooting could be minimized by applying a time ramp for the set point, as demonstrated for depressurization where typically 0.3 MPa min^{-1} were applied.

Isobaric variations of temperature directly influence density and thus solvent power of SCFs.[18] While this unique feature may be used for the realization of integrated separation processes based on controlled temperature swings,[19] it cannot be ignored if not desired. Pressure throughout the setup is typically very close to uniform because of the low viscosity of SCFs and thus low flow resistances. Uniform temperature is more difficult to ensure over a physically extended installation consisting of multiple components with different heat conductivities. Especially for small scale apparatus the high surface to volume ratio may lead to temperature gradients that locally change phase behaviour. Such effects are known to interfere with reaction and/or extraction kinetics,[20] and uniform heating of all parts and components must thus be ensured. For this purpose we inserted all parts to be kept at process temperature in an air bath (Incubator Binder BF 115). Customized ducts of 30 mm diameter (insulated with glass wool) were placed in both side walls to guide high pressure capillaries and electrical wiring (see Supporting Information). An inner glass door allowed for visual inspection of all contained parts during operation without measurable temperature perturbation. When both doors were opened for a typical switch or refill interval of 30 s temperature deviation was within 6 K and returned to ±0.3 K of the set point within 1 min (see Supporting Information). To avoid potential hazards by leakage of reactive gases (e.g., hydrogen) or organic substrates, the power supply of the air bath was interfaced by a sniff probe detecting combustible compounds inside the incubator.[21] The outlet of the air recirculation was connected to a passive exhaust, preventing potential CO_2 accumulation in the room. All components installed inside the air bath were found to work reliably over more than 10^4 h (data not shown). In addition to enhanced temperature control the use of an air bath instead of electrical heating tapes greatly facilitated handling and surveillance even during operation. The application range was also extended as the reactor configuration could be altered without the need for customised heating devices.

A particular practical concern in applications using SCFs as carriers for liquid solutes is the controlled dosage of the solute to the SCF. We decided to use a double-piston HPLC pump (Knauer, K-120 with 10 mL head) for this purpose. When installing the substrate reservoir and the pump mechanics inside the air bath and separating the pump electronics outside at room temperature, the pump could be used up to 333 K, allowing for dosing of substances liquid under reaction conditions. Furthermore, accuracy of dosing was greatly improved by monitoring the mass flow from the substrate reservoir (500 mL glass funnel under inert N_2 atmosphere) with a hanging balance (HiTec Zang, GraDo 0−1000 g with digital amplifier GraDoAMP-1D). The linear slope of a trimmed moving time average was used as mass flow signal to control the pump. The resolution of ±25 mg allowed substrate dosing as low as 0.50 g h^{-1} at accuracy better than 5% (Figure 5). With a 500 g reservoir up to 40 days of continuous operation could be sustained without refill. Noteworthy, this regulation based solely on mass flow is temperature-independent and allows dosage of mixtures of unknown density.

The number of phases in multicomponent systems depends on composition as well as temperature and pressure, and only above the mixture critical point is a single supercritical phase obtained.[22] To date, the phase behaviour of mixtures containing compressible gases cannot be predicted reliably, and experimental data for systems of synthetic interest are often not available. By including a sapphire tube (l = 12 cm, i.d. = 3 mm, glued 1 cm deep into HOKE steel fittings with TEK Eccobond 104, tested up to 25 MPa)[23] in the bypass as flow-through view cell, the phase behaviour of the mobile phase could be directly observed (Figure 6). The influence of the relative amount of each component (Table 1) could thus be probed under process

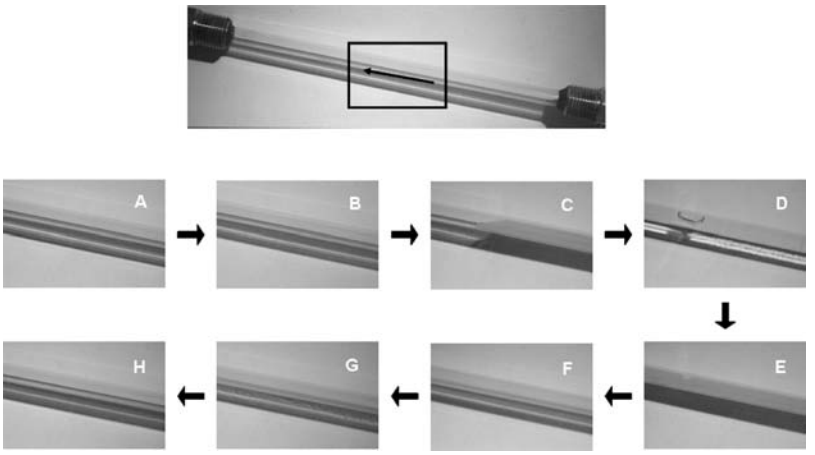

Figure 6. Photographs of the view cell in the marked section (flow from right to left as indicated by the arrow) showing the change of phase behavior through composition variation at constant temperature and pressure (for conditions see Table 1).

Table 1. Relative Amounts of CO_2, H_2, and dimethylitaconate (DMI) as Flow Values at Constant 12.0 MPa and 313 K Corresponding to the Photographs in Figure *6*

photograph	CO_2 [mL_N min^{-1}]	H_2 [mL_N min^{-1}]	DMI [mL_N min^{-1}]	no. of phases
A	85	10	0	1
B	85	10	0.02	1
C → D	85	10	0.1	2
E → F	150	10	0.1	1
G	150	50	0.1	2
H	250	50	0.1	1

conditions, greatly substantiating interpretation of results from parameter variations.[24]

The regulation of the MFCs, the BPR, heating and the HPLC pump was realized on a standard PC using LabVIEW 8.2 (National Instruments) under Windows XP (Microsoft) (see Supporting Information). All values of flow, temperature, and pressure were recorded and monitored with automated shutdown procedures for secure long-term operation without supervision. Specific variations of process parameters such as residence time or substrate concentrations could be preprogrammed as operation units that will automatically be executed after a given time or when preset conditions are met. This automation allowed efficient screening of parameter space and reliable reproduction of standardized procedures (e.g., startup).

To demonstrate closure of mass balance, the recovery of dimethylitaconate (DMI) from $scCO_2$ was monitored (Figure 7). The initial delay in extraction caused by saturation of the rig is a function of the volume ratio of reactor and flow rate used, and the difference could be quantitatively recovered by flushing with CO_2. In the reactor setup used after 4 h similar inlet and outlet concentration was obtained. However, the conditions for quantitative recovery strongly depend on the physical properties of the compounds at hand and the flow rates used.[25] For the low-volatile DMI the effluent was passed through a single cooling trap filled with dichloromethane and 2 mm glass beads.

As demonstration of performance of the equipment in applied research, the results of continuous flow catalysis using a chiral phosphine-phosphoramidite rhodium complex (QUINAPHOS)[26]

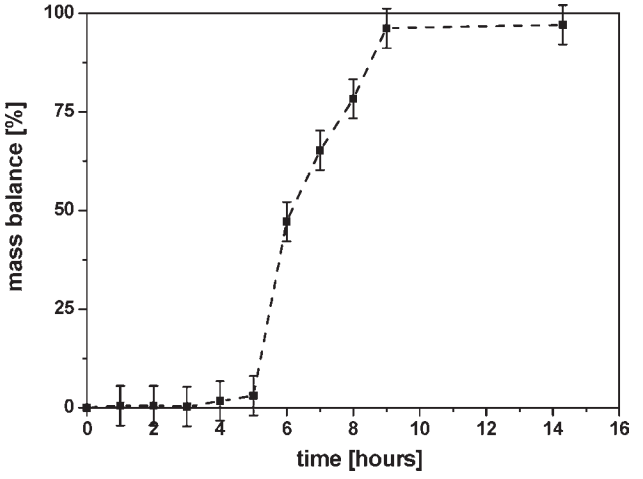

Figure 7. Recovery of dimethylitaconate (DMI) from continuous $scCO_2$ extraction (p = 12.0 MPa, T = 313 K, V_{CO_2} = 85 mL_N min^{-1}, V_{DMI} = 0.78 g h^{-1}) by gravimetry.

immobilized in supported ionic liquid phase (SILP)[27] on silica was employed.[28] The enantioselective hydrogenation of DMI was carried out with $scCO_2$ as the mobile phase for substrates and products affording fully integrated product separation (Figure 8). The decreased slope up to 4 h matches the time needed to obtain steady state (see above).

The amounts of precious catalyst could be minimised to less than 1 g of SILP material supporting 1.4 μmol of Rh-QUINAPHOS in 0.20 mL of ionic liquid. Turnover numbers of 70×10^3 (108 kg product per gram Rh) at enantioselectivity of more than 98% ee were obtained. Highly pure product samples free of any solvent or contamination (rhodium leaching <1 ppm) were withdrawn from the process operating at space-time yields of up to 0.78 kg L^{-1} h^{-1} at full conversion. After 30 h on stream catalyst deactivation became apparent. Noteworthy, the scale of the experiment shown in Figure 8 could be raised by 1 order of magnitude to produce 1.3 kg product per week without compromise in process control and needless of any changes in the peripherals.

The setup was extended with online supercritical fluid chromatography (SFC) to yield direct insight into catalyst

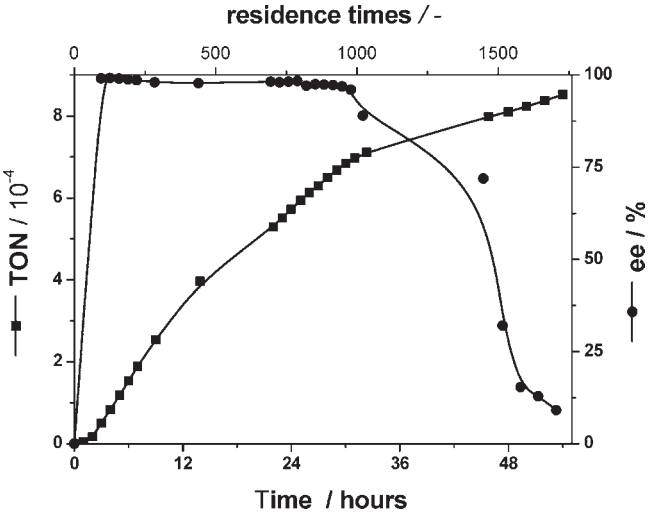

Figure 8. Turnover number (TON, ■) and enantioselectivity (ee, ●) of a chiral SILP catalyst in the continuous hydrogenation of dimethylitaconate over time on stream (p = 12.0 MPa, T = 313 K, V_{CO_2} = 85 mL_N min^{-1}, V_{H_2} = 10 mL_N min^{-1}, V_{DMI} = 0.78 g h^{-1}, lines as visual aids only).

performance without extraction delays or potential loss of minor components during sample workup.[29,30] A capillary supercritical fluid chromatograph (Carlo Erba SFC 3000) equipped with an air-driven high pressure 4-port switching valve with a sample loop (VICI) was connected after the reactor and before the BPR for sampling close to reaction conditions (see Supporting Information for details). A capillary or open-tubular column SFC[31,32] was chosen as it can be combined with flame ionization detection (FID) of non-UV-absorbing molecules such as DMI. Interfacing to LabVIEW was achieved by automatic reading of customized result files, opening up attractive automated regulation possibilities.[33] Future extension with suitable chiral phases would even permit analysis of enantiomeric ratio.[34−37]

■ CONCLUSION

We have shown how by combination of commercially available parts a compact and highly flexible continuous reaction system for continuous flow SCF processing can be established. It permits high process control at both minimum flow rates for research and development in early on testing and kilogram-quantity production. With equilibration times in the order of 1 h and automated monitoring and control, experimental conditions can be varied to gain insight into the experimental system. The phase behaviour can be visually inspected under reaction conditions and capillary SFC with FID was successfully integrated for online analysis.

■ ASSOCIATED CONTENT

Supporting Information. Further details of the setup. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The use of a gas detector or sniff probe is state of the art and standard practice in gas chromatography with hydrogen as carrier or detection gas. Typically, a detection limit of half the lower explosion limit (LEL) is safe and allows for leak detection without immediate shutdown of the apparatus.
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(23) The glue is after curing as resistant as ceramics. The glue used is in our experience the only tight solution for the application with CO_2. Here, alternatives such as O-rings of all tested materials tend to swell and decompose during or after decompression. PTFE tends to alter during use. Furthermore, all tested polymeric materials do not reliably block leakage of hydrogen. As the glue has been used in high pressure NMR for almost two decades with all kinds of solvent systems, we are pretty confident that the glue can be considered safe and practical for this purpose.

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