## Green Chemistry

## A Cartridge System for Organometallic Catalysis: Sequential Catalysis and Separation Using Supercritical Carbon Dioxide to Switch Phases\*\*

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There is continued interest in homogeneous organometallic catalysis<sup>[1]</sup> as an important synthetic tool in the research and production of fine chemicals and pharmaceuticals. As a consequence, effective separation techniques are needed increasingly for the clean isolation of products and catalyst recycling.<sup>[2,3]</sup> A promising approach toward this goal is provided by regulated systems in which a defined substitution pattern in the periphery of the metal's coordination sphere affects the catalyst's solubility, making it possible to switch between two states: the catalyst is homogeneously dissolved during the reaction and precipitates quantitatively in the separation stage.<sup>[4]</sup> The most commonly used parameters to induce the precipitation are temperature,<sup>[5]</sup> solvent polarity,<sup>[6]</sup> and pH of the solution.<sup>[7]</sup> It has been shown also that compressed and in particular supercritical carbon dioxide<sup>[8]</sup>  $(scCO_2, T_c = 31.0 \degree C, p_c = 73.75 \text{ bar})$  can be used to control the solubility of transition-metal catalysts, such that one can switch from the reaction mode to the separation stage in certain cases.<sup>[9,10]</sup>

Ideally, in a regulated system all reaction components are removed from the precipitated catalyst quantitatively under mild conditions to ensure that the catalyst remains available for repeated application in homogenous form after redissolving. In particular, it would be attractive to devise a "catalyst cartridge" with a single catalyst batch for a range of transition-metal-catalyzed conversions utilizing different substrates or even different reaction types in the same apparatus

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with an integrated separation technique.<sup>[11]</sup> Several limitations hamper the development of efficient systems for cartridge catalysts based on the more conventional regulated systems:

- Thermal and/or chemical stress can lead to deactivation of the organometallic catalyst.
- Additives used to induce precipitation may accumulate in the catalyst compartment or require additional operations for purification of the product stream.
- Reaction and separation are difficult to integrate if pressurized gases are used as reagents.
- 4) As the catalyst must be soluble in a broad range of reaction mixtures of different polarities, it can be difficult or even impossible to find a suitable solvent for separation without cross-contamination and catalyst leaching.

We report here on the design and application of a system approaching the cartridge-catalyst ideal based on the use of a poly(ethyleneglycol) (PEG) modified phosphine ligand in a  $CO_2$ -regulated reaction/separation sequence (Figure 1).

In contrast to liquid solvent systems, separation with  $scCO_2$  can be regulated through a combination of polarity and volatility.<sup>[12]</sup> The design of ligand  $\mathbf{1}^{(13)}$  reflects this principle. A PEG chain of moderate length ( $M_w = 750$ , n = 16) was used having a medium polarity compatible with a broad range of chemical environments and an almost negligible vapor pressure considerably below that of typical reaction products in fine-chemical applications. This substitution pattern makes catalysts based on ligand  $\mathbf{1}$  soluble in a variety of organic substrates without the need for additional solvents; at the same time they are expected to be completely insoluble in  $scCO_2$  even at high density.

We chose the hydroformylation of 1-octene (2a) initially as our benchmark reaction to validate these considerations



**a**:  $R = n \cdot C_6 H_{13}$ ; **b**:  $R = n \cdot C_8 H_{17}$ ; **c**:  $R = n \cdot C_{12} H_{13}$ ; **d**:  $R = C_4 H_8 - \bigvee_{j}^{O}$ ; **e**: R = Ph

**Scheme 1.** Hydroformylation as a benchmark reaction to validate the cartridge catalyst system  $1/[Rh(acac)(CO)_2]/scCO_2$ .

(Scheme 1). In a first set of experiments we found that the hydroformylation of **2a** catalyzed by a catalyst formed in situ from **1** and [Rh(acac)(CO)<sub>2</sub>] (acac = acetylacetonate; P/Rh = 5:1) could be "switched off" completely by the introduction of CO<sub>2</sub> into the reactor. Thus, conversion achieved within two hours' reaction time (T = 70 °C,  $p(H_2/CO) = 50$  bar) dropped from 99% in the absence of CO<sub>2</sub> to 66.4% at a density  $d(CO_2) = 0.35$  g mL<sup>-1</sup> to 0% at  $d(CO_2) = 0.57$  g mL<sup>-1</sup>. Visual inspection revealed that this complete stop of the reaction was accompanied by precipitation of a yellow-orange solid, demonstrating the perfect separation of the catalyst and substrate **2a**.<sup>[14]</sup> When CO<sub>2</sub> was introduced after the two-hour reaction time, the same efficient separation was induced in the product mixture (Figure 2). A mixture of **3a** and **4a** 



**Figure 2.**  $CO_2$ -induced quantitative precipitation of the rhodium catalyst formed from 1 and [Rh(acac)(CO)<sub>2</sub>] during hydroformylation of **2a**. a) Reaction mixture without CO<sub>2</sub>, b) during addition of CO<sub>2</sub>, and c) after introduction of CO<sub>2</sub> at a density of approximately 0.5 g mL<sup>-1</sup>.



**Figure 1.** The cartridge catalyst system should be flexible enough such that any of a variety of transition-metal-catalyzed conversions of substrates  $S_i$  with different reagents  $R_x$  can give the desired product  $P_{ix}$  by means of one single catalyst batch with the same apparatus and separation techniques. In the present case, a PEG-modified phosphine ligand defines the solubility properties of a rhodium catalyst, and scCO<sub>2</sub> is used to switch from the reaction stage (homogeneously dissolved catalyst) to the separation/extraction stage (precipitated catalyst).

(n/iso = 2.5:1) was isolated quantitatively in solvent-free form with low levels of metal contamination (ca. 5 ppm, vide infra) by extraction with scCO<sub>2</sub>. The reaction/separation sequence was repeated successfully six times with no significant changes in conversion or selectivity (conversion: 99.3–99.7%, *n/iso*: 2.3:1–2.5:1, isomerization: 1.6–2.5%, recovery of organic material: 91–103%).

Based on these findings, a catalyst cartridge based on  $1/[Rh(acac)(CO)_2]$  (P/Rh=5:1) was successfully implemented for the hydroformylation of a set of structurally diverse olefins **2a–e** using scCO<sub>2</sub> to induce a phase switch and mass separation (Table 1).<sup>[11]</sup> After a recycling experiment

impossible, to achieve a comparable efficient separation by standard solvent extraction owing to the similarities in polarity between catalyst and some of the substrates.

Encouraged by the promising performance of the cartridge system  $1/[Rh(acac)(CO)_2]/scCO_2$  for hydroformylation, we wanted to extend our approach to a series of different reaction types. It is now necessary that the precipitated catalyst is able to enter different catalytic cycles independent of its previous history. The hydrogenation, hydroformylation, and hydroboration of styrene **2e** were chosen as test reactions for our catalyst cartridge (Scheme 2). All three reactions involve phosphine rhodium hydride

catalytic cycles.

 $(acac)(CO)_2]/scCO_2$ .

were

results

fragments as part of the active intermediates, providing a reason-

able chance of linking the different

extended periods of time independent of the starting point and the order of the subsequent reac-

tions. Figure 3 shows the results of

a representative series starting with hydroboration and following the

We were very pleased to find that the reaction sequence shown in Scheme 2 can be indeed realized with the cartridge system 1/[Rh

obtained

Excellent

over

Table 1: Hydroformylation of 2 a-e using MeOPEG<sub>750</sub>-PPh<sub>2</sub> (1)/[Rh(acac)(CO)<sub>2</sub>]/scCO<sub>2</sub>.

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Cycle <sup>[a]</sup>	Substr.	Substr./Rh	Conv. [%]	Prod., sel. [%]	scCO <sub>2</sub> extraction <sup>[b]</sup> T [°C]/p [bar]/V [L]	Recov. [%]
1	2a	984	>99	<b>3 a</b> , 73.7	45-50/80-96/130	87.0
2	2a	1010	>99	<b>3 a</b> , 72.2	45-50/85-95/140	92.7
3	2c	1018	>99	<b>3 c</b> , 70.6	45-50/120-130/188	99.8
4	2c	1003	>99	<b>3 c</b> , 70.6	45-50/120-140/200	100
5	2 d	997	>99	<b>3 d</b> , 68.8	45-50/90-100/120	100
6	2 d	1010	>99	<b>3 d</b> , 68.9	45-50/95-105/130	100
7	2e	1039	>99	<b>4e</b> , 90.0	45-50/86-95/115	91.0
8	2e	1015	>99	<b>4e</b> , 89.8	45-50/88-100/120	91.0
9	2a	1056	94.1	<b>3</b> a, 73.0	45-50/80-100/100	86.2

[a] For details see the Experimental Section. [b] The exit flow was maintained at 0.5–0.7 Lmin<sup>-1</sup>; the total volume of  $CO_2$  is given as a liter of gas at standard conditions.

with **2a** as described above, the substrate was changed to **2b**, which was equally well converted and isolated in two subsequent runs. The same was shown for styrene (**2e**) and the functionalized olefin **2d**. In cycle 9 substrate **2a** was employed again; the results demonstrated that the catalyst had largely preserved its high activity and selectivity throughout the procedure. This was further confirmed by an additional run in which the **2a**/Rh ratio was increased to 3000:1; the resulting turnover frequency was 852 h<sup>-1</sup> and the selectivity for **3a** was 72.2%.

The conditions of the extraction step were not optimized in detail, albeit slightly higher pressures and longer extraction times were applied for the less volatile products. The products were collected from the CO2 stream upon depressurization in two sequential cold traps kept at -60 °C. Small amounts of the more volatile products 3a and 4e were lost by evaporation in this simple setup, but in general the recovery of organic material was good to excellent. Most importantly, the products of the individual reactions were obtained without any significant cross-contamination of material from the previous runs (<0.5% according to GC analysis). A total turnover number of almost 11000 was achieved over the nine consecutive reactions. Rhodium and phosphorous contamination in all samples was determined by ICP MS (inductively coupled plasma mass spectrometry), and the total loss of the original catalyst amounted to 1.2% for rhodium and 2.4% of phosphorous over the entire sequence. It is important to note that none of the products 3a-e/4a-e would be amenable to isolation by distillation without thermal decomposition of the catalyst. Furthermore, it would be very difficult, if not



**Scheme 2.** A series of different catalytic reactions carried out sequentially with the cartridge catalyst system  $1/[Rh(acac)(CO)_2]/scCO_2$ ; pinBH = pinacolborane.

reaction/separation sequence of Scheme 2 in a clockwise manner

The series of reactions was carried out in a 24-mL stainless steel reactor equipped with a window. The substrate-to-metal ratio 2e/Rh was adjusted to approximately 1000:1 in all cases, and no additional solvent was used. The catalyst was formed in situ in the first run from 1 and  $[Rh(acac)(CO)_2]$  (P/Rh = 5:1). As the initial reaction a hydroboration of 2e was carried out with pinacol borane at room temperature for (3 h)



Figure 3. Representative example for a series of different catalytic reactions linked sequentially with the cartridge system  $1/[Rh(acac)(CO)_2]/scCO_2$  (see Scheme 2 and text for details).

followed by extraction of all organic material with scCO<sub>2</sub> (45°C/60–100 bar). The conversion of 2e was 87%, the two regioisomeric borane adducts 5 and 6 were the only significant products (7 was formed in 1% yield), and the selectivity for the branched product 5 was 84%. A new batch of 2e was added to the material remaining in the reactor, and a hydroformylation was carried out and worked up as described above (see Table 1, entry 8). Complete conversion with a selectivity of 90% for 4e was achieved. In the third catalytic process, hydrogenation of **2e** (T = 50 °C,  $p(H_2) = 50$  bar, t =2 h) and subsequent extraction with  $scCO_2$  (45 °C/80 bar) gave ethylbenzene (7) in practically quantitative yield. Finally, the sequence was completed with a hydroboration, which gave results identical to those from the initial run (89%) conversion, 83% selectivity for 5). All samples were analyzed for their rhodium and phosphorous content; the total loss over all four reactions was only 0.16 and 1.3%, respectively.

In summary, we have demonstrated for a series of rhodium-catalyzed reactions that the combination of a PEG-modified phosphine ligand and scCO<sub>2</sub> as phase switch provides an efficient cartridge system for organometallic catalysis. As all reactions examined here were carried out neat and proceeded as 100% atom-efficient addition reactions, no solvent waste or by-products were generated and the products were isolated directly in high purity. The equipment required for handling the supercritical fluid is largely identical to that established in supercritical extraction or chromatography. Thus it would be possible to retrofit a commercially available technology platform to accommodate this reaction-separation system. The method is readily scalable to small- or medium-size production, and can be automated and even parallelized for the generation of libraries of structural diversity on a laboratory scale. This seems particularly intriguing for reactions involving pressurized gases, for which the integration of reaction and separation in one operation unit is notoriously difficult in the context of conventional homogeneous catalysis.

Although the metal contamination (ca. 5 ppm) achieved under the nonoptimized conditions reported here would be too high for larger scale production in many cases, it may be acceptable in synthetic laboratory-scale applications. Further reduction of the catalyst leaching seems possible by improved engineering and optimization of the extraction conditions. Another limitation of the system at its current stage of development is imposed by the range of catalytic transformations that can be achieved with the ligand type 1. However, the synthetically straightforward modification of achiral or chiral ligands with PEG chains together with the significant solubility of a large body of organic compounds in scCO<sub>2</sub> suggest that this strategy can be extended also to other broadly applicable catalytic systems. Side chains other than PEG may also be envisaged to provide similar solubility properties, for example, ionic groups such as those reported recently for continuous-flow hydroformylation of propene.<sup>[10e]</sup>

## **Experimental Section**

Safety warning: Experiments using compressed gases must be carried out only with appropriate equipment and under rigorous safety precautions.

Typical procedure for the catalysis/separation sequence, exemplified by the hydroformylation of 2a-e. A window-equipped stainless steel reactor (V = 24 mL) was charged under argon atmosphere with  $[Rh(acac)(CO)_2]$  (0.01 mmol) and ligand  $\mathbf{1}^{[13]}$  (0.05 mmol). Substrate 2a (10 mmol) was added under argon to give a clear orange solution, and the reactor was heated to 70 °C. The reaction was started by introduction of synthesis gas ( $H_2/CO = 1:1$ , 50 bar) and allowed to proceed for two hours during which the color of the reaction mixture changed to dark red. At the end of the reaction, the autoclave was cooled to 50°C, and carbon dioxide was added to reach a density of approximately 0.5-0.6 gmL<sup>-1</sup>. An orange solid precipitated and most of the liquid product dissolved. The extraction was performed by flushing CO<sub>2</sub> through the reactor at a flow rate of approximately 0.5-0.7 mLmin<sup>-1</sup> (STP); the reactor was maintained at a temperature between 45 and 50 °C and a pressure between 80 and 100 bar. After exiting the reactor, the CO2 stream was vented to ambient pressure through a series of two cold traps ( $-60^{\circ}$ C). The extraction process was monitored visually through the windows of the reactor and continued for twice the time after which no liquid product was visible in the reactor. The contents of the cold traps were combined and collected for off-line analysis, and the reactor was charged again with a new batch of substrate for the next cycle.

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- [14] It is important to note that rhodium catalysts based on other very poorly CO<sub>2</sub>-soluble ligands tend to give some background reaction under similar conditions either through formation of liquid phases<sup>[10a]</sup> or through small amounts of unmodified soluble rhodium carbonyl complexes.<sup>[9c]</sup> These ligands cannot be recycled with the high efficiency required for cartridge catalysts as experimentally verified for the hydroformylation of **2a** with the system PPh<sub>3</sub>/[Rh(acac)(CO)<sub>2</sub>]/scCO<sub>2</sub>, where the selectivity and activity were found to decrease significantly upon recycling.