Recent advances in catalyst immobilization using supercritical carbon dioxide*

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Abstract: Homogeneous organometallic catalysts have a great potential for the development of sustainable synthetic processes. There is, however, an urgent need for the development of new techniques to separate products and catalysts efficiently, allowing for recycling and reuse of the precious catalyst. The unique solvent properties of supercritical carbon dioxide offer new approaches for the immobilization of organometallic catalysts, many of which are suitable for efficient continuous-flow operation. Recent research in this field tries to combine the molecular nature of organometallic catalysts with the reaction-engineering aspect of multi-phase catalysis.

INTRODUCTION

Catalysis is the key technology for an environmentally benign and economically successful “green” chemistry [1]. Industrial chemical production depends to more than three-quarters on the phenomenon of catalysis, and the number approaches 90% for newly implemented processes. Although the fundamental principles of catalysis are identical for the different approaches, three scientific areas of heterogeneous, homogeneous and bio-catalysis have emerged. This historic distinction results from the different techniques and research methodologies applied in the corresponding disciplines, which provide most of the input to catalyst development and process design (Table 1).

Table 1 The chemical disciplines that contribute mainly to catalyst development and process design in the three areas of catalysis research.

<table>
<thead>
<tr>
<th></th>
<th>Heterogeneous catalysis</th>
<th>Biocatalysis</th>
<th>Homogeneous catalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Catalyst development</strong></td>
<td>Solid-state inorganic chemistry</td>
<td>Biochemistry/molecular biology</td>
<td>Organometallic chemistry</td>
</tr>
<tr>
<td><strong>Process design</strong></td>
<td>Chemical engineering</td>
<td>Biotechnology</td>
<td>Organic synthesis</td>
</tr>
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</table>

Most of the existing industrial catalytic processes are found in petrochemistry and the bulk and commodity business. They are based on the use of solid heterogeneous catalysts, because these can be implemented in a variety of sophisticated process designs resulting in continuous-flow operation. Reaction rates and selectivities can often be influenced strongly by engineering parameters such as flow rates, residence time, and the like. Owing to the solid nature of the catalyst, our understanding of the transformations on a molecular level lags far behind their applications. Therefore, catalyst development


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is still very much dependent on trial and error with high-throughput techniques gaining increasing importance in recent times.

In contrast, homogeneous catalysis is based on well-defined organometallic species that can be investigated in detail with the spectroscopic techniques of molecular chemistry. In many cases, we have at least a good working hypothesis for the catalytic cycle, and catalyst development can be achieved by systematic and, in favorable cases, even rational modification of the molecular structure. The most obvious result of this difference between homogeneous and heterogeneous catalysis is found in enantioselective catalysis, where a plethora of successful organometallic catalysts for various transformations is contrasted by the single case of alkaloid-modified heterogeneous hydrogenation catalysts.

For industrial applications, the attractive opportunities of molecular catalysis are partly offset by the inherent difficulties for reaction engineering. The homogeneous nature of the organometallic catalyst makes separation from the products and recycling difficult, and reactions are usually carried out in batch mode, requiring large amounts of solvents during reaction and separation steps. Consequently, space–time yields are often unnecessarily low considering the remarkable activity of many homogeneous catalysts. Multiphase catalysis where the catalyst resides in one phase while substrates and products are contained in a second immiscible liquid phase offer an intriguing opportunity to solve this problem [2]. Although this approach is often referred to as “biphasic catalysis”, reaction systems are in fact triphasic in nature if gaseous reagents are involved, as shown in Fig. 1a.

Two important boundary conditions have to be considered in the design and development of multiphase systems for organometallic catalysis. During the chemical transformation, mass transfer between the various phases must be high enough to allow for sufficiently high reaction rates. For efficient separation and immobilization, cross-contamination between the catalyst phase and the continuous substrate/product phase must be kept to a minimum to avoid catalyst leaching and impurities in the products. Obviously, these two constraints are contradicting and need to be compromised in real systems. In the present short review, we will discuss the role of supercritical carbon dioxide (scCO₂) in the design of efficient multiphase systems for organometallic catalysis. In particular, we will highlight two recent developments from our laboratories at the Max Planck Institute for Coal Research in Mülheim and the Institute for Technical and Macromolecular Chemistry of the RWTH Aachen. In one case, the catalyst is immobilized in an ionic liquid and scCO₂ forms the mobile phase (Fig. 1b). In the second approach, the supercritical fluid is used as the stationary catalyst phase and water is used as the mobile phase for very polar substrates and products (Fig. 1c).

![Fig. 1](image_url)  
**Fig. 1** Systems for multiphase organometallic catalysis discussed in this paper: (a) classical “biphasic” catalysis based on two immiscible liquids; (b) ionic liquid/scCO₂ catalysis for CO₂-soluble substrates and products; (c) inverted scCO₂/aqueous phase catalysis for highly polar substrates and products.
SUPERCRITICAL CARBON DIOXIDE AS A REACTION AND SEPARATION MEDIUM FOR MULTIPHASE CATALYSIS

Supercritical fluids (SCFs) are substances heated above their critical temperature \( T_c \) and compressed above their critical pressure \( p_c \) [3]. At temperatures greater than \( T_c \), isothermic compression results in a continuous increase of the fluid density without condensing it into a liquid. Just like gases, supercritical fluids fill the entire space available, have negligible surface tension, and are miscible with other gases. At the same time, they can act as solvents for liquid and solid materials, a typical liquid-like property. The solvent properties can be “tuned” over a wide range by adjusting the fluid density through comparably small changes of temperature and/or pressure.

Carbon dioxide has very mild critical data \( (T_c = 31.0\, ^\circ C, p_c = 73.75\, \text{bar}) \) and is by far the most widely used supercritical fluid. It is nontoxic, nonflammable and can be handled safely on laboratory and industrial scales [4]. A commercial-scale multipurpose plant for heterogeneous catalysis with scCO\(_2\) as the continuous phase has been opened in the United Kingdom recently [5]. General aspects of the use of these fascinating reaction medium for organometallic catalysis have been reviewed in detail [3,6] and a short review comparing some CO\(_2\)-based immobilization techniques for hydroformylation as a common benchmark reaction is available [7]. As many of the potential benefits of CO\(_2\) for multiphase catalysis are also retained in the near-critical liquid region, operation at temperatures slightly below the critical temperature can also be envisaged. In the present article, we will use the term “supercritical” universally to describe general aspects of the methods and techniques. Some of the applications described below were carried out at near-critical conditions, however, and we will point this out as appropriate.

The use of scCO\(_2\) for multiphase catalysis reduces the number of phase boundaries and results in truly biphasic systems as seen from Figs. 1b and 1c. Together with an actual increase of solubilities in the liquid phase, this can significantly increase the availability of substrates at the catalytically active center. For continuous processing, scCO\(_2\) is an ideal mobile phase that can be removed from the products downstream by simple pressure reduction or other techniques known from supercritical fluid extraction [4]. The nature of the catalyst-containing liquid phase, which will be the stationary phase in continuous flow operation according to Fig. 1b, becomes the crucial design parameter for these systems [8]. The key properties required for this phase are (i) low volatility, (ii) minimum solubility in CO\(_2\), (iii) good solubility properties for organometallic compounds, and (iv) compatibility with catalytically active intermediates. Ionic liquids (ILs) match this characterization in an almost perfect way [9].

ILs are molten salts that are liquid at temperatures below 100 °C. Typical combinations of cations and anions are summarized in Fig. 2, together with a schematic representation of the unique phase behavior of their binary mixtures with compressed CO\(_2\) [10]. Owing to their ionic nature and negligible vapor pressure, typical ILs are insoluble in pure carbon dioxide under practical reaction conditions. Carbon dioxide is, however, remarkably soluble in the IL phase, resulting in solutions containing up to 0.6 mole fractions of CO\(_2\) under typical supercritical conditions. In contrast to many organic solvents that can swell dramatically under CO\(_2\) pressure, these IL solutions do not exhibit a major increase in volume of the liquid phase. Other properties of the liquid phase such as viscosity, diffusion rates, and gas solubilities can change significantly, but fortunately in the desired way for multiphase catalysis in all cases [11].

The potential of this unique phase behavior for multiphase catalysis has been recognized immediately, and several groups have demonstrated the first examples shortly after the seminal paper by Brennecne and Beckman [10] had been published. The Jessop group was first to present their results on enantioselective hydrogenation reactions in ILs followed by separation of the product with scCO\(_2\) extraction and recycling of the catalyst containing IL phase [12]. Tumas and Baker carried out the catalytic hydrogenation of CO\(_2\) itself in a biphasic IL/scCO\(_2\) medium [13]. The reaction requires the presence of a secondary amine, resulting in the corresponding dialkyl formamides as the final products. The IL phase was used to solubilize and stabilize intermediately formed carbamates and could thus broaden...
the scope of this reaction type beyond the pure scCO$_2$ system. Cole-Hamilton and coworkers investigated the hydroformylation of long-chain olefins as a prototypical reaction of industrial importance [14]. They noted that certain ILs and ligand types were not compatible, but with the right choice of the catalyst system, they were able to establish a first example for continuous-flow processing in IL/scCO$_2$.

Our strategy was to capitalize on the potential benefits from a chemical interaction of the IL with the catalytically active species and to combine this molecular role of the catalyst support with continuous-flow operation. In collaboration with the group of Peter Wasserscheid at the RWTH Aachen, the nickel-catalyzed enantioselective hydrovinylation was chosen as a first benchmark reaction (Scheme 1) [15]. The reaction is a transformation of considerable, yet largely unexplored potential for organic synthesis, creating chiral allyl moieties as interesting building blocks [16]. The development of efficient

![Scheme 1](image-url)
ligand systems for this reaction still is a field of ongoing interest, which has seen promising developments most recently [17]. For the present investigation, we relied on the Wilke catalyst (3) [18], which we had shown to be compatible with carbon dioxide as a reaction medium previously [19].

Complex 3 is not the actual catalyst for the hydrovinylation, but needs to be activated in the presence of a suitable cocatalyst. The role of this additive is to abstract the chloride ion from the nickel center to generate a cationic allyl complex that further converts to the catalytically active nickel hydride species. These active intermediates are highly reactive and extremely sensitive so that reactions in conventional solvents need to be carried out at low temperatures, typically –60 °C and below. The use of the sodium salt of tetrakis-[3,5-bis(trifluormethyl)phenyl]borate (BARF) as activator was found to generate an active catalyst from 13 giving high yields and enantioselectivities in liquefied and supercritical CO2 (Table 2) [19]. The chemo- and enantioselectivities in CO2 were considerably higher than those obtained in conventional solvents at the same temperatures. Catalyst recycling by selective extraction of the products with low-density CO2 was met with limited success, however, owing to extreme instability of the active species especially in the absence of the substrates.

Table 2 Enantioselective hydrovinylation of substituted styrenes 1a-c using the catalyst 3/NaBARF in compressed CO2 (data taken from ref. [19]).

<table>
<thead>
<tr>
<th>Substrate/ product</th>
<th>R</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Conversion (%)</th>
<th>Selectivitya (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a/2a</td>
<td>H</td>
<td>1</td>
<td>15</td>
<td>&gt;99</td>
<td>88.9</td>
<td>86.2(R)</td>
</tr>
<tr>
<td>1a/2a</td>
<td>H</td>
<td>23</td>
<td>15</td>
<td>&gt;99</td>
<td>71.4</td>
<td>85.6(R)</td>
</tr>
<tr>
<td>1a/2a</td>
<td>H</td>
<td>40</td>
<td>15</td>
<td>&gt;99</td>
<td>74.9</td>
<td>83.6(R)</td>
</tr>
<tr>
<td>1a/2a</td>
<td>H</td>
<td>35</td>
<td>30</td>
<td>&gt;99</td>
<td>38.9</td>
<td>91.6(R)</td>
</tr>
<tr>
<td>1b/2b</td>
<td>Cl</td>
<td>40</td>
<td>15</td>
<td>&gt;99</td>
<td>80.5</td>
<td>81.0(–)</td>
</tr>
<tr>
<td>1b/2b</td>
<td>Cl</td>
<td>24</td>
<td>15</td>
<td>&gt;99</td>
<td>87.0</td>
<td>81.3(–)</td>
</tr>
<tr>
<td>1c/2c</td>
<td>Br</td>
<td>21</td>
<td>15</td>
<td>&gt;99</td>
<td>82.4</td>
<td>81.8(–)</td>
</tr>
<tr>
<td>1d/2d</td>
<td>sec-Bu</td>
<td>35</td>
<td>50</td>
<td>&gt;99</td>
<td>44.4</td>
<td>89.4(R)</td>
</tr>
<tr>
<td>1d/2d</td>
<td>sec-Bu</td>
<td>20</td>
<td>50</td>
<td>75.8</td>
<td>71.4</td>
<td>76.6(R)</td>
</tr>
</tbody>
</table>

aTypical side-products were 2-phenyl-2-butenes and hydrovinylation products of 2.

By transferring this reaction in an IL/scCO2 system, we envisaged that the ionic liquid might serve as the catalyst phase and the cocatalyst at the same time. Indeed, it was found that dissolving complex 3 in various ILs resulted in activation without the need for additional cocatalysts. As shown in Fig. 3 for various salts of the 1-ethyl-3-methylimidazolium cation (EMIM), the catalyst support is effective for the generation of the active species, whereby the choice of the counterion has a dramatic influence on the activity and selectivity of the cationic nickel center. The level of conversion drops in the order BARF > Al[OC(CF3)2Ph]4 > Tf2N > BF4 consistent with the estimated coordination strength of these anions. The high activity of catalyst 3 in [EMIM][BARF] leads to a significant amount of consecutive isomerization and oligomerization under the nonoptimized conditions, but could probably be avoided by shorter contact times.

The results summarized in Fig. 3 demonstrate for the first time that the molecular nature of the IL phase can directly influence the performance of an organometallic complex for multiphase catalysis in the presence of CO2. However, attempts to recycle the catalyst solution batch-wise after removing the product by CO2 extraction were again frustrated by the notorious instability of the nickel species. As we hypothesized that the absence of excess substrate was one of the major reasons for the deactivation during batch-wise recycling, continuous-flow operation was hoped to ameliorate this limitation. In a first set of experiments, [EMIM][Tf2N] was used as the ionic liquid to activate, tune, and immobilize catalyst 3. CO2, the liquid substrate 1a, and ethylene were delivered from a compressor unit, an HPLC pump, and a gas-dosing module, respectively. After passing through a mixer (in its simplest form, a
four-port joint), the substrate flow was fed into the reactor where it bubbled through the ionic liquid solution containing complex 3. Substrate 1a was converted to product 2a with high activity and selectivity, and the CO2 stream transported the product from the reactor into the separation chamber. Upon pressure reduction, 2a separated from the CO2 stream and was isolated as a colorless liquid in pure form. Although not implemented on the laboratory scale of our experiments, the CO2 could be compressed and recycled into the process.

Figure 4 summarizes the remarkable long-term stability of this catalytic system under continuous-flow operation. At a reaction temperature of 0 °C, conversion remained practically constant over 60 h. The short induction period can be associated with the time required to reach the saturation concentration of substrates and products in the IL. After reaching steady-state conditions, the enantiomeric excess showed a marginal decrease from around 65 to 60%. Intriguingly, this system is open for optimization on both the molecular and the engineering level. For example, matching the IL and catalyst even better according to the results of Fig. 3 can be expected to yield products with higher ee’s at bet-

Fig. 3 Influence of the anions of 1-ethyl-3-methylimidazolium (EMIM)-based ionic liquids on the performance of 3 for the hydrovinylation of 1a in IL/CO2 (data taken from ref. [15]).

Fig. 4 Continuous-flow hydrovinylation of 1a with 3 in IL/CO2 (data taken from ref. [15]).
ter conversion. At the same time, controlling the residence time now becomes an option for homogeneous catalysis, allowing, for example, the suppression of consecutive reactions. With the number of successful examples increasing [20], it is expected that these general advantages of continuous-flow multiphase catalysis in IL/scCO_2 will be exploited further, making this a viable option also for fine chemical production.

It is important to note that the application of IL/scCO_2 systems is by no means limited to organometallic catalysts. In cooperation with the group of Manfred Reetz at the MPI for Coal Research, we have demonstrated that the approach can be utilized also for enzyme catalysis [21,22]. Transesterification reactions of alcohols using various modifications of the lipase _candida antarctica_ (Cal-B) were found to occur with high rates under continuous-flow conditions. High space–time velocities could be achieved, and the biocatalyst proved remarkably robust in this unconventional reaction medium.

Lipase-catalyzed kinetic resolution of chiral racemic secondary alcohols such as 4 occurred with excellent enantiodifferentiation (Scheme 2) [23]. As a new approach to isolate the two enantiomers separately, it was envisaged to precipitate ester and alcohol sequentially by step-wise reduction of the CO_2 density in the downstream processing. In the case of simple acetates, the ester 6a is better soluble in scCO_2 than alcohol 4. Therefore, alcohol 4 precipitates in the first separation chamber, whereas ester 6a is isolated after the second density reduction. The differences in solubility are, however, not large enough to allow for synthetically useful separations in this simple scheme. If vinyl laureate 5b is used as the transesterification reagent, the solubilities of ester and alcohol are inverted. Owing to the low volatility of ester 6b, it is now less soluble than the alcohol 4 and precipitates in the first separation chamber. In this case, the solubility difference is large enough to yield excellent separation efficiency, providing ultimately both enantiomers of 4 in very high purity from a continuous process. Again, this example emphasizes the crucial importance of a fruitful interplay of molecular design and reaction engineering for “green” chemical processes.

![Scheme 2](image)

The development of the IL/scCO_2 system is still in its infancy and offers numerous possibilities for further research. There is, however, an inherent limitation that is intrinsic to this approach and all other techniques employing scCO_2 as the mobile phase: Naturally, substrates and/or products have to exhibit sufficiently high solubility in scCO_2 under practical conditions. Although numerous low-molecular-weight organic compounds used in organic synthesis will fall under this category, a large body of highly polar or hydrophilic substrates cannot be processed with these methodologies. In order to make the advantages of multiphase catalysis using supercritical fluids also available for processes involving these classes of compounds, we have developed an “inverted” system, where the catalyst resides in the scCO_2 phase and substrates/products are contained in an aqueous phase (Fig. 1c) [24].

Specific boundary conditions apply also for multiphase catalysis with water and CO_2, as known from classical system where the catalyst is contained in the aqueous phase. Mass transfer between water and scCO_2 can be expected to be sufficient for many catalytic reactions and can be enhanced with surfactants if necessary [25]. Furthermore, the pH of the aqueous phase will be around 3 in the presence

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of the compressed CO₂ phase, requiring that substrates, products, and catalysts tolerate such acidic conditions. If necessary, buffer systems can be applied to control the pH even up to slightly basic values [26]. The solubility of water in CO₂ is below 1% under typical conditions, but some CO₂ will be lost with the aqueous phase. Cross-contamination between the two solvent systems and resulting impurities in the products can be tolerated, however, as both are environmentally and toxicologically benign. A very attractive and unique feature of the inverted aqueous/scCO₂ system is that the stationary supercritical phase is never depressurized, and hence the large energy input required for recompression is avoided.

The key prerequisite to immobilize the catalyst in the carbon dioxide phase is the availability of sufficiently “CO₂-philic” organometallic compounds [27]. The catalysts must have a significant absolute solubility in scCO₂ as well as an extremely high partitioning preference in the biphasic system. A common strategy for the design of CO₂ soluble catalysts is the use of highly fluorinated ligands and anions [28]. Gratifyingly, this approach proved successful also for the inverted aqueous/scCO₂ system [24,29]. A fluoralkyl-substituted derivative of triphenylphosphine, 4-H₆F₆-TPP (9) was used to generate a rhodium catalyst for hydroformylation of the unsaturated carboxylic acid 7 (Scheme 3).

![Scheme 3](image)

As can be seen from Table 3, unmodified rhodium catalysts did not lead to active and stable systems, even though unmodified rhodium catalysts are known to form very soluble and active catalysts in pure scCO₂ [30]. Presumably, both the partitioning in the biphasic system, as well as the stability under the acidic conditions, is not sufficient for this type of catalyst. The phosphine-modified system resulted in reasonable turnover rates, and the catalyst could be recycled well at high-enough catalyst loadings. A total turnover number of 1500 was achieved in three consecutive runs. This could be increased to over 4500 at lower catalyst concentrations, albeit at the expense of noticeable deactivation during each recycling step. As catalyst leaching was measured to be very small, the loss of activity at lower catalyst

<table>
<thead>
<tr>
<th>Runa</th>
<th>Rh-precursorb</th>
<th>c(Rh) in CO₂ (mmol/l)</th>
<th>Conv. (%)</th>
<th>TONc</th>
<th>c(Rh) in H₂O (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>[Rh(CO)₂(hfacac)]</td>
<td>0.2</td>
<td>14</td>
<td>70</td>
<td>68.3</td>
</tr>
<tr>
<td>1b</td>
<td>[Rh(CO)₂(acac)]</td>
<td>0.2</td>
<td>&gt;99</td>
<td>500</td>
<td>0.26</td>
</tr>
<tr>
<td>2a</td>
<td>[Rh(CO)₂(hfacac)]</td>
<td>0.2</td>
<td>1:10:500</td>
<td>6.4</td>
<td>32</td>
</tr>
<tr>
<td>2b</td>
<td>[Rh(CO)₂(acac)]</td>
<td>0.2</td>
<td>&gt;99</td>
<td>500</td>
<td>0.16</td>
</tr>
<tr>
<td>2c</td>
<td>[Rh(CO)₂(acac)]</td>
<td>0.05</td>
<td>1:10:2000</td>
<td>79</td>
<td>1580</td>
</tr>
<tr>
<td>3a</td>
<td>[Rh(CO)₂(acac)]</td>
<td>0.05</td>
<td>93</td>
<td>1860</td>
<td>0.05</td>
</tr>
<tr>
<td>3b</td>
<td>[Rh(CO)₂(acac)]</td>
<td>0.05</td>
<td>60</td>
<td>1200</td>
<td>0.08</td>
</tr>
</tbody>
</table>

a,b,c refer to recycling experiments with the same catalyst batch.
bhfacac = hexafluoroacetylacetone; acac = acetylacetone.
cTurnover number for isomeric aldehydes 8 per run after 20 h.
loading must be again attributed to catalyst decomposition. Despite these practical shortcomings, the present system demonstrates the principal applicability of the inverted aqueous/scCO₂ system for multi-phase catalysis with highly polar products.

CONCLUSION AND OUTLOOK

Any method for the immobilization of organometallic catalysts faces the paradoxical condition of the need for intimate contact of reagents and catalyst during the reaction stage with a maximum of discrimination at the separation stage. Supercritical fluids and, in particular, scCO₂ can open innovative and distinct approaches in this field. The two methods described in this paper are representative examples for a rapidly growing toolbox of techniques that have emerged during the last five years. The two approaches are complementary in the substrates/products that can be processed: the IL/scCO₂ system is best applicable to compounds of medium to low polarity, whereas the scCO₂/water system is designed for very polar species. The examples described herein emphasize in particular the need for a close interaction between molecular design and reaction engineering in multiphase catalysis. This opens new and challenging avenues for fundamental research in chemistry that will finally contribute to the development of sustainable industrial processes and green synthetic chemistry.

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