

Supercritical Carbon Dioxide as a Green Reaction Medium for Catalysis

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ABSTRACT

Carbon dioxide in its liquid or supercritical state (scCO₂) has a prodigious potential as an environmentally benign reaction medium for sustainable chemical synthesis. Since the mid-1990s, rapidly increasing research efforts have shown that scCO₂ can replace conventional and potentially hazardous solvents in a wide range of processes. There is also increasing evidence that the application of scCO₂ can broaden the scope of catalytic synthetic methodologies. On the basis of the experience in our laboratories, this report analyzes the impact of scCO₂ on green organometallic catalysis.

1. Introduction

The countless opportunities for molecular transformation remain a major driving force for chemical research ever since the origin of organic synthesis in the late 19th century. The second half of the 20th century, however, saw also a growing awareness of the ecological impact of chemical production. It is now widely recognized that the development of inherently clean synthetic methodologies can offer new avenues to benign and cost-effective processes. This quest for “Green Chemistry” engenders a tremendous challenge for fundamental research in chemistry, chemical engineering, and their neighboring areas.¹

One important aspect of research toward more sustainable processes for chemical synthesis is the scientific evaluation of potential replacements for volatile organic compounds (VOCs) as solvents and reaction media.² In fine chemical production in particular, syntheses are mainly carried out in solution phase, and organic solvents

are usually the first choice. These solvents are often problematic owing to their toxicity, flammability, or environmental hazards. Isolation of the pure product(s), recycling of reagents or catalysts, and solvent makeup or disposal are important cost factors for downstream processing in solution-phase synthesis. On the other hand, the solvent can play a crucial role in the stabilization of reactive intermediates and often has a decisive influence on the rate and selectivity of a particular reaction. Therefore, the choice of solvent is generally made in an early stage of development and is usually not questioned unless dramatic problems are encountered during up-scaling. In other words, the solvent is a strategic parameter for the planning of a synthesis already in the initial stage and “green” solvents should be considered in contemporary preparative chemistry already on a laboratory scale.

The quest for new reaction media is acutely challenging in the field of homogeneous catalysis with transition metal complexes. The possibility of activating substrates under mild conditions and of controlling the chemo-, regio-, and stereoselectivity of their transformations with small amounts of a well-defined chemical multiplier is most intriguing from an ecological and economical view. Ironically, the molecular structure and the homogeneously dissolved nature of these catalysts are at the same time the most severe limitations for their application in practical catalysis. The development of innovative separation schemes based on environmentally benign reaction media is, therefore, a field of utmost importance for homogeneous catalysis in the future. Research in this field is particularly exciting if these alternative media are sufficiently different from organic solvents to exploit some of their specific features for reaction tuning or even new chemistry.

Compressed (liquefied or supercritical) carbon dioxide (Figure 1) is one of the frequently discussed alternative reaction media for chemical synthesis.³ The critical point marks the end point of the evaporation line in the phase diagram and is characterized for CO₂ by the critical temperature $T_c = 31.0$ °C, the critical pressure $p_c = 73.8$ bar, and the corresponding critical density $d_c = 0.466$ g mL⁻¹. Beyond this point, no distinct liquid or vapor phase can exist, and the new supercritical phase exhibits properties that are reminiscent of both states. The unique physicochemical properties of supercritical fluids (SCFs) are described in detail elsewhere and do not need to be reiterated here.^{3,4}

Mild critical data, a truly benign character, and the low costs of the material itself make CO₂ particularly attractive, although various other SCFs, such as water, hydrocarbons, or hydrofluorocarbons, also hold considerable promise for chemical synthesis. Importantly, there is an existing technology platform for the use supercritical carbon dioxide (scCO₂) in the food and nutrition industry, in which today's large-scale applications in the extraction of caffeine or hops aroma are based on the pioneering work

Walter Leitner was born in Pfarrkirchen, Bavaria, in 1963. He studied Chemistry at the University of Regensburg, where he received his PhD in 1989 with H. Brunner. In 1990, he worked as a postdoctoral fellow with J. M. Brown at the University of Oxford. He returned to Regensburg as a Liebig scholar of the Fonds der Chemischen Industrie, working on metal-catalyzed activation of carbon dioxide. In 1992, he joined the working group “CO₂ Chemistry” of the Max-Planck-Society, which was directed by E. Dinjus at the Friedrich-Schiller-University of Jena. In 1995, he received his habilitation for Inorganic Chemistry at Jena University and moved to the Max-Planck-Institute for Coal Research in Mülheim an der Ruhr as a group leader in the department of Organic Synthesis (M. T. Reetz), where he became supervisor of the Technical Laboratories in 1998. In February 2002, he was appointed Professor for Technical Chemistry and Petrochemistry at the RWTH Aachen as successor to W. Keim. His scientific interests are centered around homogeneous catalysis with transition metal complexes and the use of supercritical carbon dioxide for environmentally benign chemical processes. He received the Gerhard-Hess-Award of the Deutsche Forschungsgemeinschaft in 1997 and the Otto Roelen Medal of DECHEMA in 2001.

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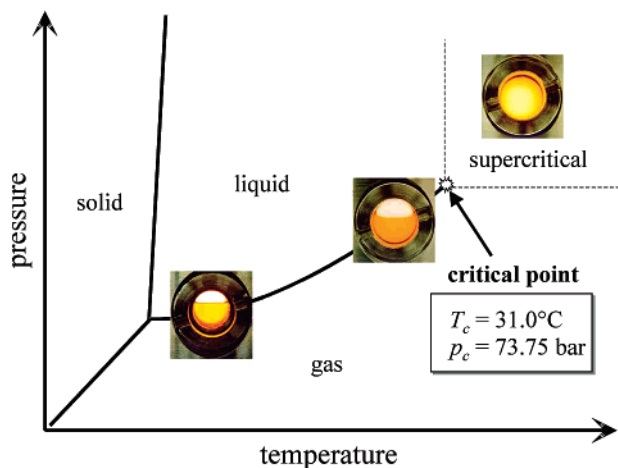


FIGURE 1. Schematic phase diagram of CO₂ with snapshots of the transition from the liquid/gas region to the supercritical region (a bright orange “CO₂-philic” rhodium complex was added for better contrast and to illustrate the solvent properties of the liquid and the supercritical phase).

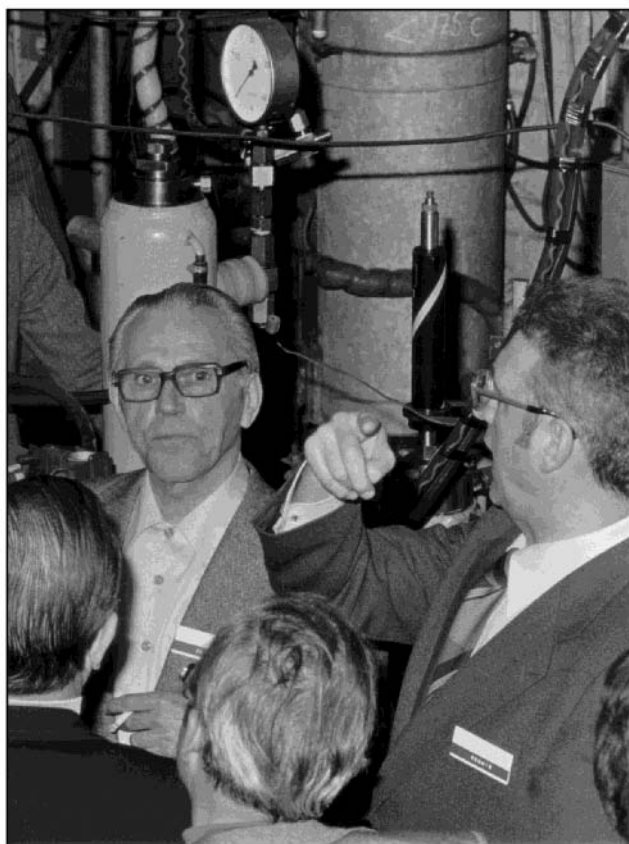
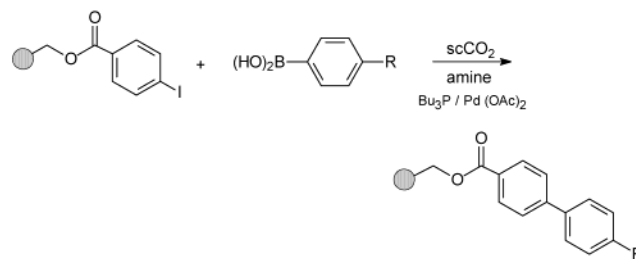


FIGURE 2. Dr. Kurt Zosel (1913–1989) in the Technikum of the Max-Planck-Institut für Kohlenforschung on the occasion of a press conference announcing the first commercial decaffeination process utilizing scCO₂ as the solvent.

of Kurt Zosel at the Max-Planck-Institut für Kohlenforschung in the 1960s (Figure 2).⁵ More recently, this unique solvent has found considerable commercial interest in applications as diverse as dry cleaning, metal degreasing, polymer modification, and pharmaceutical processing.⁶ Industrial activities in the field of radical polymerization⁷

Scheme 1. Pd-Catalyzed Suzuki Coupling of Polymer-Supported Substrates in scCO₂



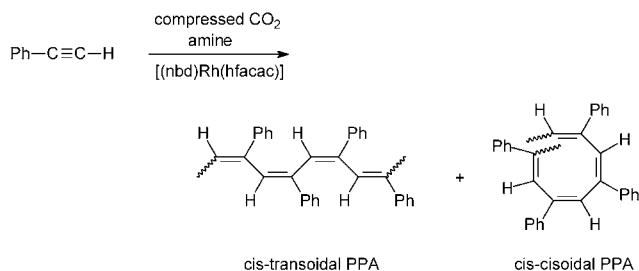
and heterogeneous hydrogenation⁸ demonstrate the economic viability of scCO₂ as a solvent for chemical reactions, as well. Researchers in organometallic catalysis started to contemplate a broader use of CO₂ as a solvent in the mid-1990s,^{9,10} especially after sufficiently “CO₂-philic” organometallic catalysts became more generally available.¹¹

In the present Account, we shall discuss systematically the possible consequences for the sustainability of a reaction or process upon substitution of organic solvents by CO₂. The material will be based on recent examples from our own group and a selection of contributions from other research laboratories. There will be a strong focus on organometallic catalysis, but other approaches may be included where appropriate. We hope that this personal selection will be useful in the ongoing discussions concerning the need for “added benefits” of benign solvents.

2. Potential Benefits Arising from the Use of Compressed Carbon Dioxide as a “Green” Reaction Medium for Chemical Reactions and Processes

2.1 Solvent Replacement. The most general driving force for replacing organic solvents by scCO₂ is the benign character of this medium. Even in large-scale use, no environmental risk would arise in case of accidental contamination of the immediate environment with the nontoxic and innocuous solvent CO₂. Note that the application of carbon dioxide as a solvent does not, of course, increase the anthropogenic greenhouse gas emission, as it does not generate any additional CO₂.

Palladium-catalyzed C–C coupling reactions are finding increasing importance for industrial synthesis of fine chemicals, including biologically active compounds. In scCO₂, such coupling processes occur at high rates and with excellent selectivities.¹² Most recently, palladium nanoparticles encapsulated in fluorinated CO₂-philic dendrimers were found to be highly active catalysts for coupling reactions under single phase conditions in scCO₂, yielding a unique selectivity for the 2-phenylacrylate product.¹³ A particularly intriguing development is the use of soluble catalysts, such as Pd(OAc)₂/P^tBu₃ for coupling reactions on solid-phase-bound substrates (Scheme 1).¹⁴ The plasticizing and swelling effects of compressed CO₂ on polymeric compounds ensure rapid mass transfer between the solid and the supercritical reaction phases. Excess reagents and catalysts can be readily stripped off

Scheme 2. Rhodium-Catalyzed Synthesis of Poly(phenylacetylene)(PPA) in scCO₂

with scCO₂, yielding the solid-phase-bound product without the need for subsequent drying or purification steps. Interesting applications of this technique for parallel or high-throughput synthesis of biologically active compounds can be envisaged.

Plasticizing and swelling of polymers by scCO₂ also play a role in metal-catalyzed polymerization reactions in compressed CO₂. Successful examples include ruthenium-catalyzed ring-opening metathesis polymerization (ROMP),^{15,16} palladium-catalyzed olefin copolymerization,¹⁷ nickel-catalyzed olefin/CO copolymerization,¹⁸ and rhodium-catalyzed formation of polyphenylacetylene (PPA, Scheme 2).¹⁹ The low solubility of high-molecular-weight hydrocarbons leads to precipitation polymerization processes in all cases. Rapid mass transfer between polymer and bulk supercritical phase ensures high polymerization rates even under these conditions. Further improvements of these protocols for better control of molecular weight distributions and polymer morphology should be possible with CO₂-philic surfactants similar to those developed for radical polymerization processes.²⁰

The plasticizing effect results from the solubility of CO₂ in the polymer. Similarly, a considerable melting point depression results for many organic solids in the presence of compressed CO₂. Thus, "solventless" syntheses become possible in liquefied mixtures at temperatures way below the regular melting points of substrates and products. Subcritical²¹ and supercritical²² pressures can be applied as exemplified for the hydroformylation of vinylnaphthalene. The use of so-called gas-expanded solvents for catalytic synthesis utilizes the same fundamental principle, leading to a reduction of the required amount of solvent rather than its complete replacement.²³ A special need for solvent replacement is encountered in catalytic C–H activation processes in which conventional solvents cannot be used, because they are also prone to attack by the reactive organometallic species.²⁴ Ethane has been used as supercritical solvent and substrate for C–H activation simultaneously, but this approach is limited to alkanes with the appropriate critical data or boiling points.²⁵ Compressed CO₂ can be applied more generally, allowing even the photochemical functionalization of methane under single-phase conditions.²⁶

2.2 Catalyst Immobilization and Downstream Processing. One of the most intriguing possibilities when replacing organic solvents with scCO₂ is the possibility of facilitating downstream processing by applying the es-

tablished technology of supercritical fluid extraction (SFE) for product isolation.⁴ The solvent properties of scCO₂ depend strongly on its density and can be tuned very precisely by fine adjustment of pressure, temperature, or both. Selective separation processes based on these phenomena can be applied even for high-boiling-point products for which distillation is either not practical or puts too much thermal stress on sensitive components. Furthermore, purification of the product from unreacted starting material or side products is possible during extraction from the catalyst whereby even small structural differences can be sufficient for significant enrichment or separation. In the present section, hydroformylation is used as a common case study to exemplify various strategies for the separation and immobilization of organometallic catalysts involving scCO₂.

In its simplest form, the SFE workup can just follow a conventional hydroformylation process using scCO₂-insoluble catalysts. The SFE step can be used to strip away high-boiling long-chain aldehydes²⁷ or even the so-called "high-end" side products of propene hydroformylation,²⁸ regenerating the precious catalysts. In contrast, the direct combination of fully homogeneous reaction and subsequent separation relies on the use of sufficiently CO₂-soluble phosphine-modified hydroformylation catalysts.²⁹ Once the reaction has reached the desired conversion, the external parameters of pressure or temperature are changed to achieve phase separation into a "supercritical" and a liquid phase. The more volatile organic components partition between the two phases, whereas the considerably less volatile organometallic compounds remain exclusively in the condensed phase. Extraction under these conditions yields the product in solvent-free form, leaving the catalyst behind for further use. Continuous processing can be readily envisaged using loop technologies. This particular sequence has been referred to as catalysis and extraction using supercritical solutions (CESS), but this acronym may be applied in a more general sense to all techniques described in this section.

Figure 3 exemplifies the CESS approach for batchwise asymmetric hydroformylation of styrene using the CO₂-philic chiral ligand 3-H²F⁶-BINAPHOS.²² Eight successive runs were performed, with conversion and regioselectivity remaining uniformly high, even after more than 12 000 catalytic turnovers. A certain decrease of the enantiomeric excess was encountered after the fourth run, but the initial high level of enantioselectivity could be fully restored by an addition of small amounts of ligand in the last cycle. The solvent-free product was recovered quantitatively, with rhodium contents ranging from 0.36 to 1.94 ppm as determined by atomic absorption measurements. Because the branched aldehyde formed upon hydroformylation of vinylnaphthalene is considerably more soluble in scCO₂ than its linear isomer, the branched-to-linear ratio for this product increased from ~90:10 in the liquid phase to up to 98:2 in the CO₂ phase in a single extraction step.²²

The use of scCO₂ as reaction and separation phase also offers new opportunities for classical approaches to catalyst immobilization, such as supported catalysts or

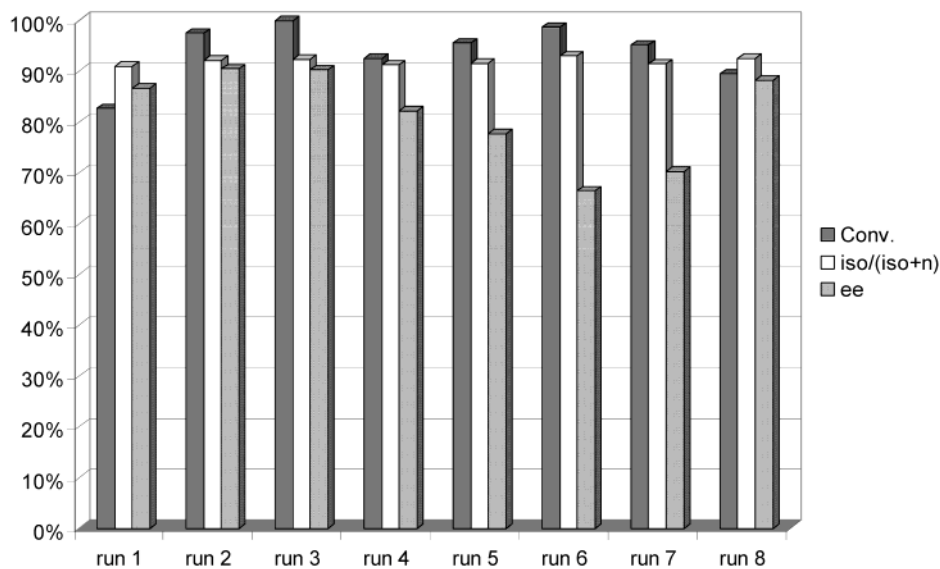
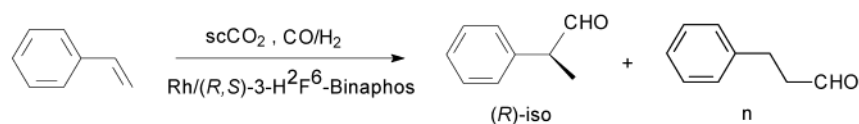
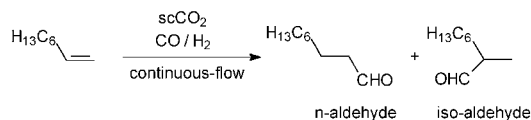


FIGURE 3. Product isolation and catalyst recycling applying a batch-wise CESS procedure for the hydroformylation of styrene with the CO₂-philic in situ catalyst 3-H₂F₆-BINAPHOS/[Rh(acac)(CO)₂] (2:1).

Scheme 3. Continuous-Flow Hydroformylation of Long-Chain Olefins Using a Catalyst Immobilized on Silica or in Ionic Liquids



Rh / Xantphos on silica: TOF = 160 h⁻¹, n/iso = 33, conv. = 14%
 Rh / TPPDS in ionic liquid: TOF = 13 h⁻¹, n/iso = 3, conv. = 5%

liquid biphasic systems.³⁰ With supported catalysts, the miscibility of scCO₂ with reaction gases reduces the number of phase boundaries from gas/liquid/solid to supercritical/solid in processes such as hydrogenation,³¹ carbonylation,³² or oxidation etc. This reduction of potential mass transfer barriers can lead to increased reaction rates and selectivities. Most importantly, these immobilized systems can be readily implemented for continuous operation in flow-type reactors.³³ For the hydroformylation reaction depicted in Scheme 3, the rhodium catalyst was immobilized using classical sol-gel techniques, and the specific structure of the Xantphos-ligand framework ensured high selectivity for the linear aldehyde.

Another intriguing approach to catalyst immobilization is based on the combination of ionic liquids (ILs) and supercritical CO₂. Ionic liquids are low melting (<100 °C) salts of organic cations, which have no measurable vapor pressure.³⁴ Consequently, they exhibit no detectable solubility in scCO₂. Carbon dioxide, however, is remarkably soluble in some ILs and can be used to extract even high-boiling-point organic substances very efficiently.³⁵ Such systems can be applied to facilitating product isolation and batch-wise catalyst recycling as exemplified for hydrogenation reactions using achiral³⁶ and chiral³⁷ cata-

lysts. A rhodium catalyst based on the double sulfonated triphenylphosphine ligand TPPDS was effectively immobilized in ILs for continuous flow hydroformylation (Scheme 3).³⁸ The small amounts of ILs required in such continuous flow applications resemble a catalyst support rather than a “solvent”.

The use of ILs and compressed CO₂ for continuous flow organometallic catalysis is particularly intriguing in cases in which molecular interactions between the “support” and the active species are possible. The nickel complex shown in Figure 4 is a catalyst precursor for the hydrovinylation reaction, a highly enantioselective and atom-economic C–C bond forming process. ILs such as [EMIM]–[(CF₃SO₃)₂N] (EMIM = 1-ethyl-3-methylimidazolium) can act simultaneously as solvents and chloride abstracting agents to “switch on” the catalysis in the presence of scCO₂.³⁹ The choice of the anion has a decisive influence on the performance of the active species. Thus, the catalyst is effectively immobilized in active and selective form by simply dissolving the stable precursor in the IL. This system showed stable performance over 60 h under continuous flow conditions with compressed CO₂ as the mobile phase. It is interesting to note that the highly sensitive nature of this particular nickel catalyst limited its recycling in batch-wise experiments using the CESS approach.⁴⁰

The combination of the two innocuous solvents water and CO₂ is another attractive approach to “green” solutions for catalyst immobilization. Catalysts can be immobilized in the aqueous phase as colloids⁴¹ or using water-soluble complexes based on the trisulfonated TPPTS ligand.⁴² Particularly high reaction rates are obtained with surfactant-stabilized microemulsions and emulsions that

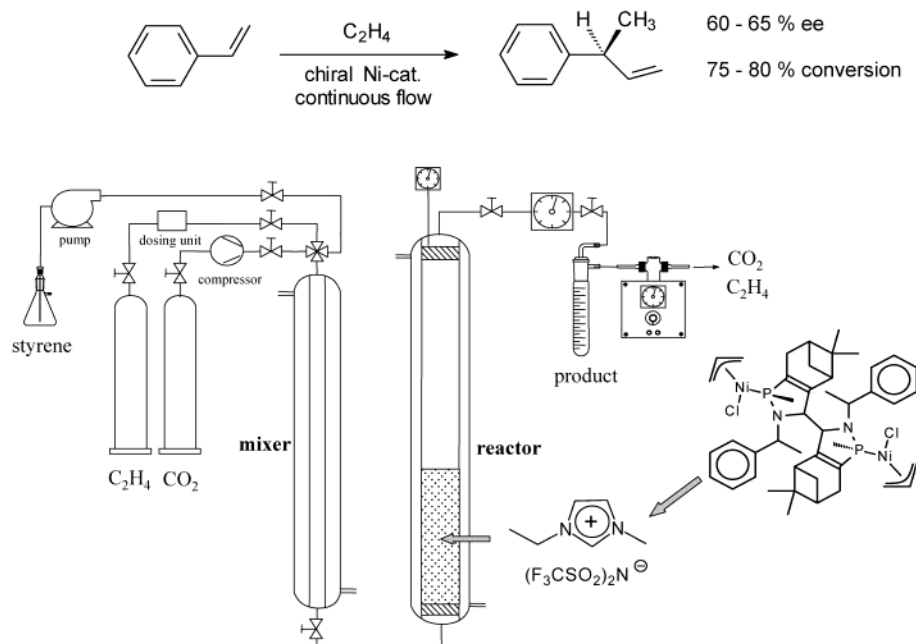


FIGURE 4. A chiral nickel catalyst for asymmetric hydrovinylation is activated, tuned, and immobilized in a IL/CO₂ continuous flow system.

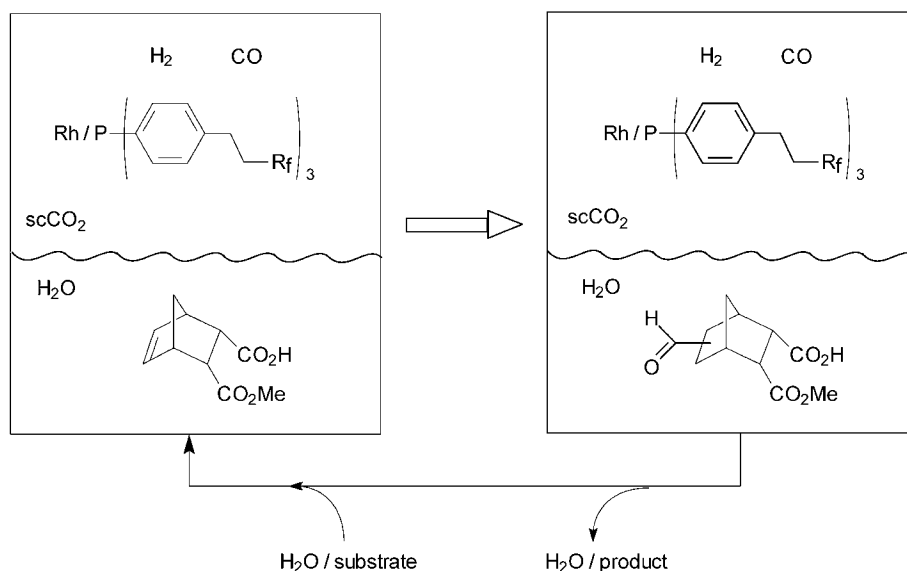


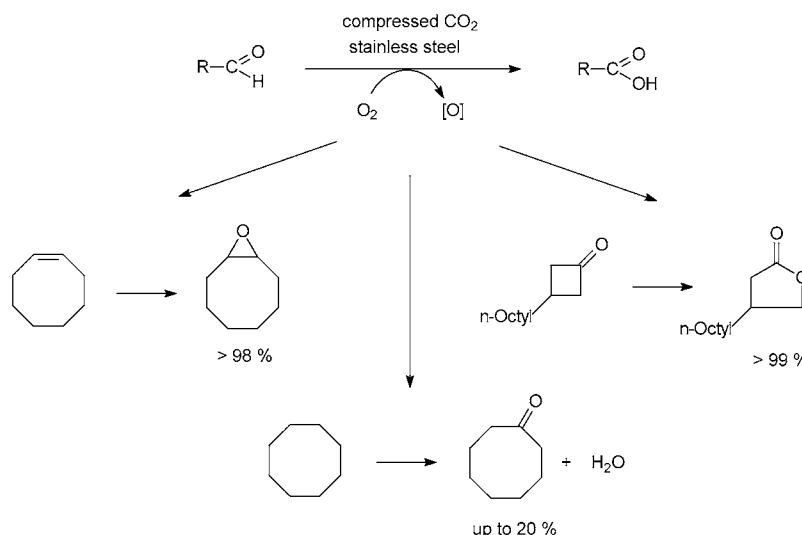
FIGURE 5. Hydroformylation of a water soluble olefin using an “inverted” water/CO₂ system.

allow for intimate contact of all reagents with the catalyst during the reaction.⁴³ The emulsions separate readily into two phases by small pressure changes and the CO₂ phase is then vented to isolate the products.

All techniques discussed up to now use CO₂ as the mobile phase for substrates and products. Naturally, this restricts the applications to relatively nonpolar and volatile materials with sufficient solubility in the supercritical medium. An intriguing alternative for processing highly polar reactants and products is “inverted” aqueous systems. In this approach, a CO₂-philic catalyst resides in the nonpolar CO₂ phase, and the water-soluble substrates, products, or both are contained in the aqueous layer.^{44,45} The product stream of these systems is obtained without the need for depressurization of the CO₂ phase, which is an important cost factor in SCF processing. Furthermore,

the aqueous solution is not contaminated with any organic solvent or catalyst residues, which is particularly important if the product is a fine chemical for direct further use in aqueous solution. The principle is illustrated in Figure 5 for a prototypical hydroformylation reaction.⁴⁵

2.3 Process Safety. The use of nonexplosive and nonflammable scCO₂ as a solvent (i.e., in a large excess compared to all other components) greatly reduces potential risks and hazards in many reaction types involving highly reactive reactants or gases. Pressurized gases such as hydrogen, carbon monoxide, or oxygen can be handled much more safely after “dilution” with CO₂. Single-phase reaction conditions ensure at the same time optimum availability of these gases without any mass transfer restrictions. In oxidation reactions, the oxygen/substrate ratio can thus be considerably increased while still

Scheme 4. Steel-Promoted Selective Oxidation Processes Using Molecular Oxygen with Aldehydes as Sacrificial Co-Reductants in scCO₂

improving the safety of the process as a result of expanded explosion limits. The excellent heat transport capacity of scCO₂ enables effective heat control, avoiding hot spots or runaway scenarios in highly exothermic reactions. In addition, side products from oxidation of the solvent are a priori avoided in this medium. The homogeneously palladium-catalyzed synthesis of H₂O₂ directly from H₂ and O₂ provides an impressive confirmation of these arguments.⁴⁴

A frequently used method of activating molecular oxygen in metal-mediated oxidations is the addition of an aldehyde as a sacrificial co-reductant. Under the high-pressure conditions associated with the use of compressed CO₂, the stainless steel from the walls of high-pressure reactors is sufficient to trigger the formation of peroxy acyl radicals from RCHO/O₂ mixtures in scCO₂.⁴⁶ These species can initiate an oxidation pathway directly or after conversion to peracids by H-abstraction of another aldehyde molecule. A third option for oxygen transfer with these systems is the formation of metaloxo species if appropriate catalysts were present. Ultimately, the aldehyde is converted to the corresponding acid in all cases. The catalyst-free oxidation system can be applied for highly selective epoxidations,⁴⁶ oxidation of alkanes,⁴⁷ and Baeyer–Villiger oxidations⁴⁸ (Scheme 4). Reaction rates and selectivities are at least comparable, and in many cases significantly higher than with related systems in conventional solvents.

2.4 Improved Reaction Rates. The replacement of organic solvents by scCO₂ as a reaction medium can be expected to lead to changes in the reaction rates, sometimes for worse but often for better. In favorable cases, the resulting changes can be rationalized on the basis of the physicochemical properties of the supercritical state. Enhanced mass transfer properties may often be involved when increased reaction rates are observed in multiphase systems, such as those described in Section 2.2. Similarly, high gas availability may be responsible for increased rates under single-phase gas conditions. Rate enhancements in supercritical CO₂ are, however, not restricted to reactions with gaseous reagents. Large negative activation volumes

and local composition enhancements can contribute to significantly higher rates and also to rate control by pressure tuning.

For single-phase reactions, the potential benefits arising from the miscibility with reaction gases are exemplified nicely in the pioneering work on CO₂ hydrogenation.⁴⁹ Similar arguments may apply for the significantly enhanced hydroformylation rates observed with unmodified rhodium catalysts.²⁹ Note, however, that hydroformylation rates with phosphine-modified systems are similar for organic solvents and scCO₂.²⁹ This comparison illustrates the subtle interplay between catalytic system, reaction medium, and kinetics.

It is important to note that increased gas availability does not necessarily result in higher rates. The elementary steps of a catalytic cycle are often reversible and can be influenced by gas availability in different ways. A significant increase in the overall reaction rate will result only if a forward reaction with a gaseous partner constitutes the rate-limiting step. This is the case for most hydrogenation pathways, but other gases, such as CO, have a large tendency to block vacant coordination sites and, consequently, higher availability may even retard reactions. Finally, the change of reaction medium can induce a shift of the rate-determining step in the overall cycle, resulting in a kinetic response different from that anticipated from a mechanism that was established for conventional solution.

The hydrogenation of imines in scCO₂ shows a remarkable enhancement of catalyst efficiency that cannot be related only to gas availability.⁵⁰ The time required for full conversion is ~20 times shorter in scCO₂, as compared to CH₂Cl₂. This remarkable improvement is largely due to differences in reaction profiles rather than in initial rates. As shown in Figure 6, the turnover rate is largely independent of conversion in scCO₂, whereas the reaction slows down considerably as it proceeds in CH₂Cl₂. The apparent zero-order kinetics in scCO₂ indicate that substrate binding is quantitative and much faster than the reaction with hydrogen, whereas the rates of both pro-

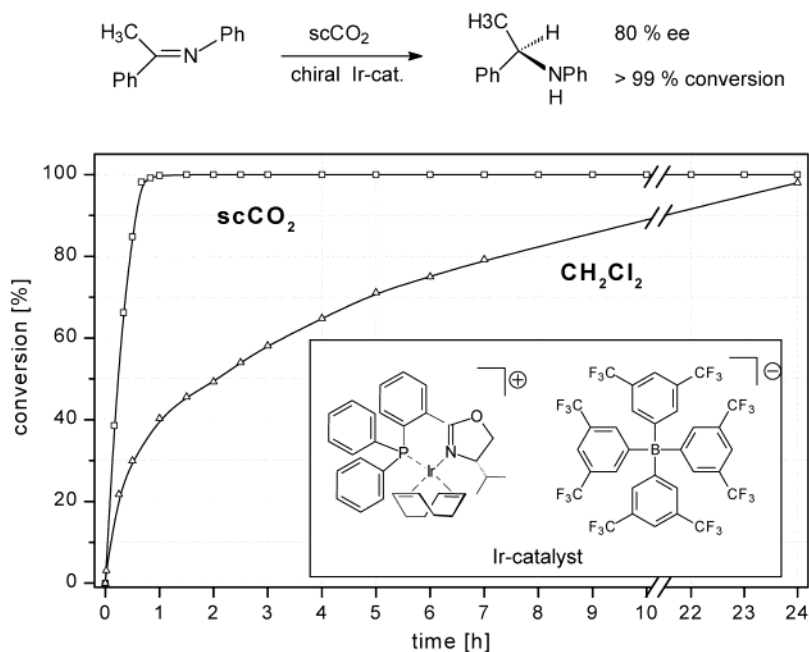


FIGURE 6. Reaction profile for the enantioselective hydrogenation of *N*-(1-phenylethylidene)aniline in scCO_2 and CH_2Cl_2 .

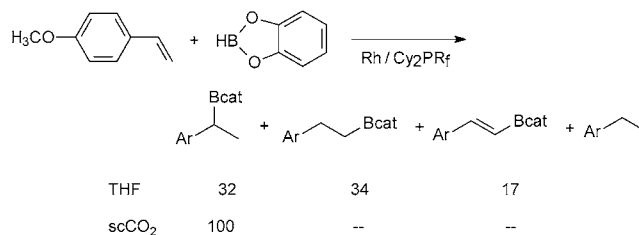
cesses appear to be of similar magnitude under conventional conditions.

2.5 Selectivity Control. The transfer of a reaction from an organic solvent to scCO_2 has been found to induce significant changes in the chemo-, regio-, or stereoselectivity in a number of processes. Such selectivity changes may result not only from the solvent, but also from the structural modifications of the CO_2 -philic catalyst as compared to the parent compounds. In favorable cases, these effects are in line with established models of organometallic catalysis, allowing a rational design of suitable derivatives.²² In the present section, however, the discussion will be restricted to examples in which changes in selectivity result from the change of the reaction medium only. The related issue of using CO_2 as a temporary protecting group will be discussed separately in section 2.6.

A significant improvement in regioselectivity for the desired linear aldehyde was noted in the pioneering work on hydroformylation of propene using $[\text{Co}_2(\text{CO})_8]$ as the catalyst precursor.⁵¹ More recently, the linear/branched ratio in this system was reported to increase from 2.7:1 to 4.3:1 as the CO_2 pressure is increased from 92 to 184 bar.⁵² A higher linear-to-branched ratio was also observed for the hydroformylation in scCO_2 using a rhodium trialkylphosphine catalyst.⁵³ Chemoselectivity is improved in the case of unmodified rhodium catalysts that give rise to less isomerization during hydroformylation in scCO_2 , because the interception of the intermediates with CO is more effective under these conditions.²⁹

A remarkable solvent effect on chemo- and regioselectivity was observed in the rhodium-catalyzed hydroboration of vinyl arenes (Scheme 5).⁵⁴ Mixtures of all four possible products were obtained in liquid solvents such as THF, but a single isomer was produced selectively with the same catalyst in scCO_2 . Drastic changes were also

Scheme 5. Increased Selectivity during Rhodium-Catalyzed Hydroboration in scCO_2

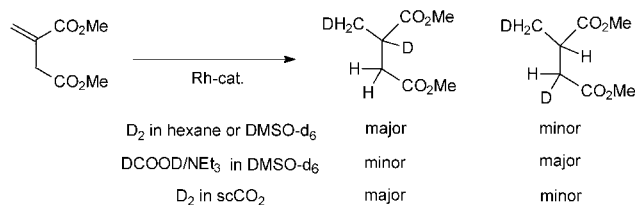


noted for the regioselectivity of the Pd-nanoparticle-catalyzed Mizoroki–Heck reaction¹³ and for the stereoregularity of PPA obtained with unmodified Rh catalysts (Section 2.1).¹⁹ An unusual density-dependent diastereoselectivity was reported for the S-oxidation of cysteine derivatives in scCO_2 .⁵⁵

Significantly higher enantioselectivities were obtained in scCO_2 , as compared to methanol, in the asymmetric hydrogenation of β,β -disubstituted enamides with chiral rhodium catalysts.⁵⁶ In the asymmetric hydrogenation of itaconates, the enantiomeric excess decreased upon lowering the H_2 pressure in hexane but remained stable in scCO_2 .⁵⁷ A detailed mechanistic investigation revealed that the catalytic pathway was largely identical in both solvents. In particular, the formation of metal formate intermediates by insertion of CO_2 into Rh–H bonds was unambiguously ruled out on the basis of their characteristic deuterium isotope pattern (Scheme 6).^{57,58} The most plausible explanation for the different response on H_2 pressure in the two media is that the extremely active catalysts “starve” for hydrogen in conventional solution at low partial pressures, whereas H_2 availability remains sufficient in the supercritical medium.

Density variations can have a strong impact on chemical equilibria and reaction rates in highly compressible supercritical media, sometimes providing additional con-

Scheme 6. Characteristic Deuterium Pattern of the Main *d*₂-Isotopomers Obtained from Rhodium-Catalyzed Enantioselective Reduction of Dimethyl Itaconate under Various Conditions



trol over yield or selectivity that is not available in conventional liquids. For example, the competition between ruthenium-catalyzed ring closing metathesis and acyclic diene metathesis can be controlled entirely by adjusting the density of scCO₂ (Figure 7).¹⁶ At low density, the intermolecular reaction can be favored by local composition enhancement.⁵⁹ High density, on the other hand, leads to effective dilution by reducing the mole fraction (and, hence, the activity or fugacity) of the reactants in the reaction medium.¹⁶

2.6 ScCO₂ as a Protective Medium. All applications discussed so far utilize CO₂ as an inert reaction medium that undergoes no chemical reaction with either the catalyst or the substrate. In some cases, such as C–H activation or oxidation processes, this inert character is actually a major driving force for its application. Carbon dioxide does, however, interact with certain functional groups and can thus impact the chemical transformation. For example, the formation of carbamic acids or carbamates can be used to “mask” sufficiently basic amines in CO₂ solution.

The ruthenium catalysts used for RCM (Section 2.5) are deactivated irreversibly by basic N–H groups, and substrates containing this type of functional group cannot be cyclized in conventional solvents unless they contain suitable protecting groups. Therefore, the conventional RCM route to cyclic amines involves three steps (protection/cyclization/deprotection) and has a low atom efficiency because of the protecting group manipulation. In scCO₂, however, the reversible formation of the carbamic acid results in a temporary protection of the amine, and no additional protecting group is necessary.¹⁶ Upon pressure release, the carbamic acid is converted back spontaneously to the free amine, which is isolated directly without the need for further manipulation.

The use of CO₂ as a protective medium for amines also allows control of the product distribution during the hydroaminomethylation sequence of allylic amines.⁶⁰ In conventional solvents, the nucleophilicity of the nitrogen center leads to direct ring closure at the rhodium acyl intermediate of the catalytic cycle (Scheme 7, pathway B). Therefore, cyclic amides are formed as the sole products. Conducting the same reaction in scCO₂ cuts off pathway B effectively and directs the reaction almost exclusively through pathway A (Scheme 7). Consequently, saturated heterocyclic products are formed with high selectivity under these conditions.

2.7 Simultaneous Use of scCO₂ as a Reaction Medium and a C1 Building Block. The use of CO₂ as a cheap,

nontoxic, and readily available C1 building block is of itself a highly attractive approach to “Green Chemistry”, because it would allow use of a (arguably small) portion of a major waste material of human activities to replace considerably less benign reagents, such as carbon monoxide or phosgene. The highly attractive scenario of using carbon dioxide as solvent and “activating” it simultaneously by a suitable catalyst for chemical reactions was recognized early on.^{49,61} More recently, the use of scCO₂ as a solvent and a reagent is finding increasing interest as a possible strategy for the synthesis of organic carbonates^{62,63} and urethanes⁶⁴ via nonphosgene routes. High rates and conversions were observed under pressures and temperatures beyond the critical point of CO₂. The initial carbamate formation may play an important role in these processes, depending on the nature of the amine used (vide supra). Most of the reactions form water or halide salts, which can be expected to be insoluble in scCO₂, opening opportunities for workup and separation schemes.

Epoxides react with CO₂ to give cyclic carbonates or polycarbonates, depending on the structure of the oxirane ring, the nature of the catalyst, and the reaction conditions. The formation of styrene carbonate from styrene oxide and CO₂ in the presence of catalytic amounts of DMF was investigated as a function of phase behavior and CO₂ pressure.⁶⁵ A sharp maximum of the yield was observed in the vicinity of the transition of biphasic to single-phase conditions. The copolymerization of propylene oxide and carbon dioxide occurs when the homogeneous supercritical phase is contacted with a heterogeneous zinc catalyst.⁶⁶ In general, however, the copolymerization of epoxides with CO₂ is the domain of alicyclic substrates, such as cyclohexene oxide, owing to the potential materials application of the resulting polymers. CO₂-soluble zinc⁶⁷ and chromium⁶⁸ catalysts perform extremely well to give high-molecular-weight polymers with narrow-molecular-weight distributions under initially monophasic conditions (Scheme 8).

With the notable exception of telomerization processes,^{61,69} investigations toward C–C bond formation reactions using scCO₂ as solvent and building block are still scarce. Similar to the situation with dialkyl carbonates, this reflects more a fundamental lack of suitable catalysts and reaction pathways than an incompatibility of scCO₂ as a solvent. Clearly, there is a need for specific catalyst development in this highly promising area, which has to take into account the molecular transformation and the application in the supercritical fluid at the same time.

3. Conclusion

From the selected examples discussed in this review, it can already be seen that a large variety of synthetically useful reactions can be performed in scCO₂ with results that are similar and sometimes even better than in conventional organic solvents. A detailed economic comparison of a given reaction in a conventional solvent and in scCO₂ is, however, not possible on the basis of these data alone. Most importantly, the largest part of this

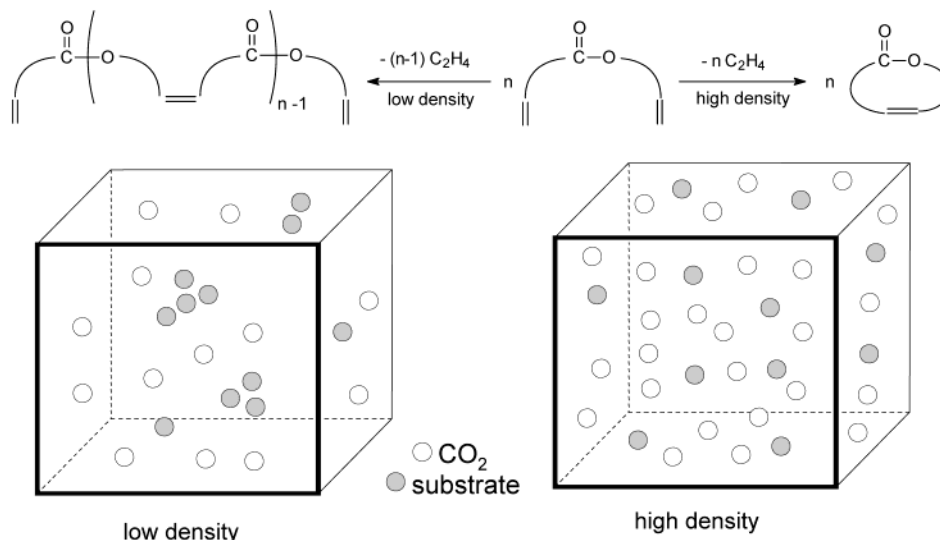
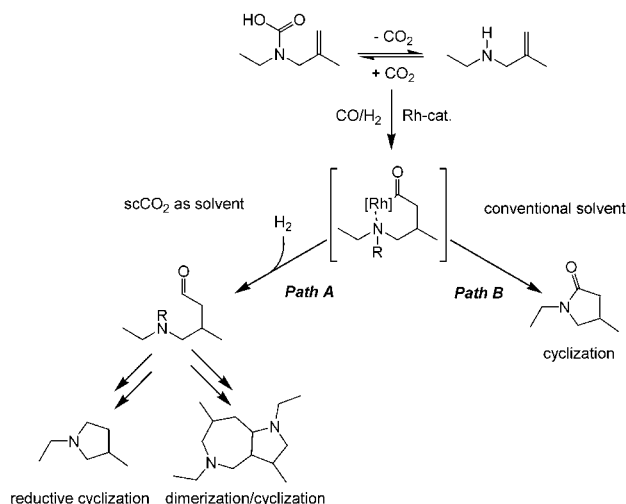
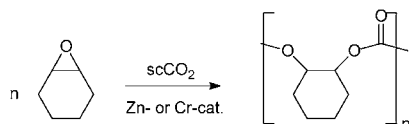


FIGURE 7. Density effect on intermolecular and intramolecular pathways in ruthenium-catalyzed olefin metathesis and schematic representation of its origin.

Scheme 7. Reversible Carbamic Acid Formation Controls the Principal Reaction Pathway under Hydroaminomethylation Conditions



Scheme 8. Homogeneously Catalyzed Copolymerization of Cyclohexene Oxide with ScCO₂



exploratory work has been conducted in batch reactors so far, whereas continuous processing would be the method of choice for industrial SCF reactions on any scale. Furthermore, downstream processing in scCO₂ can be entirely different from that of classical synthesis making, for example, new approaches for catalyst immobilization possible. Benefits such as increased rates and selectivities or the use of CO₂ as protecting group or reagent are also becoming evident in more specific cases. The scope of these effects is not yet explored in any detail, and our current understanding does not (yet) allow us to use such features generally for process or reaction design. Significant progress has been made, however, during the short

history of organometallic catalysis in scCO₂, and reactions that are more or less likely to benefit from such additional features can at least be identified.

In practical terms, CO₂ is not regulated as a VOC (volatile organic chemicals, i.e., organic compounds that participate in atmospheric photoreactions) and has a GRAS status (generally regarded as safe). Both aspects facilitate greatly the authorization procedure for processes in which CO₂ replaces an organic solvent. Nevertheless, the advantages of this benign medium need to be balanced against the installation and use of high-pressure equipment, which is generally perceived as costly and safety intensive. The commercial success of replacing CH₂Cl₂ with CO₂ for the decaffeination of coffee indicates, however, that such investments may pay off even in the unfavorable case of a large volume batch process.

Taken together, the current status of this field convincingly substantiates the potential of scCO₂ as an alternative solvent for Green Chemistry. Increasing research efforts are urgently needed to improve our fundamental knowledge and to broaden the scope of the basic methodology. At the same time, reaction engineering becomes more and more important to evaluate various process designs in terms of efficiency and costs. Interdisciplinary efforts involving preparative chemists, researchers in catalysis, physicochemists, and chemical engineers appear to have the highest chances to meet this challenge.

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