

39

Supercritical and Compressed Carbon Dioxide as Reaction Medium and Mass Separating Agent for Hydrogenation Reactions using Organometallic Catalysts

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39.1

Introduction

Compressed and (in particular) supercritical carbon dioxide (scCO₂) is finding increasing interest as alternative solvent system to replace classical volatile organic chemicals (VOC) in chemical processes [1]. During the past decade, research with this medium and other supercritical fluids (SCFs) has shown that the potential of these “green solvents” reaches far beyond the substitution of potentially harmful substances and offers new opportunities for the control of chemical reactions on both molecular and engineering levels. This chapter will summarize recent advances in this field for the specific example of hydrogenation reactions using organometallic complex catalysts.

Hydrogenation using SCFs has already found considerable industrial interest and application using typical heterogeneous catalysts. Hoffmann LaRoche has operated scCO₂ technology for a key step in a vitamin synthesis [2]. Likewise, research teams at Degussa [3] and in Scandinavia [4] have conducted intensive investigations into the hydrogenation of fatty acid esters in scCO₂ and sc-propane, respectively, including the recent development of a demonstration plant [5]. The multipurpose plant opened by Thomas Swan in the UK in 2002, based on their collaboration with the group of Poliakoff at the University of Nottingham, is probably the most advanced example for hydrogenation with scCO₂ at present, allowing an annual production capacity of up to 1000 tonnes [6]. These examples demonstrate that SCF technology is a viable option for hydrogenation reactions in the fine chemical and pharmaceutical industries. The combination of the advanced reaction engineering of compressed CO₂ and other SCFs with the molecular design of organometallic complex catalysis seems therefore highly attractive.

The fundamental properties of SCFs and their relation to organometallic catalysis have been reviewed extensively in recent years, and will not be re-iterated here [1, 7]. The term “supercritical” indicates that the substance used as reaction medium or solvent is heated and compressed beyond its critical temperature and pressure. For CO₂, which is the most widely used SCF in hydrogenation reactions, these values are $T_c=31.04^\circ\text{C}$ and $p_c=73.83\text{ bar}$. Owing to the complex

phase behavior of multicomponent reaction mixtures as encountered in hydrogenation processes, this notation includes truly monophasic as well as multiphasic systems. For simplicity, we will use the term “supercritical” for general discussions in this chapter, and specify the nature of mixtures if necessary. We will furthermore refer to “homogeneous catalysts” in this chapter only for truly monophasic systems, whereas we will use “organometallic catalysts” as notation for the active species in general.

One of the most attractive features of using novel solvent systems for organometallic hydrogenation is the development of new separation and immobilization concepts. A number of interesting approaches has been investigated very recently by exploiting the physico-chemical properties of compressed (supercritical or subcritical) CO₂. We will extend the discussion in this chapter to these systems, and highlight similarities and differences between the various methods. Clearly, many of these techniques are still in their very early stages of development and have been demonstrated often for singular examples only. With this chapter, we hope to stimulate further research in the area in order to validate the individual techniques for potential applications.

39.2

The Molecular and Reaction Engineering Basis of Organometallic-Catalyzed Hydrogenations using Compressed and scCO₂

39.2.1

Control of Hydrogen Availability

Hydrogenation reactions carried out with soluble organometallic catalysts are often very sensitive to the availability of H₂ in the catalyst phase. The availability of the gaseous reagent at the active center is limited by the maximum solubility of H₂ and the rate of its diffusion into the catalyst phase. This may affect reaction rates as well as selectivities in hydrogenation reactions [8, 9]. Both, solubility and mass transfer are strongly influenced by compressed and scCO₂-based media, offering an additional control parameter in hydrogenation reactions. Figure 39.1 depicts the situation for a conventional hydrogenation set-up, for a biphasic scCO₂/liquid system, and for a single-phase reaction mixture, assuming that all components (including the catalyst) are sufficiently soluble in scCO₂ to reach a single phase.

Organic liquids often show very high solubilities for CO₂, associated with a very significant volume expansion (Fig. 39.1, center). Such “expanded liquids” [10] are formed in the presence of scCO₂ from solutions or also from neat liquid substrates. The physico-chemical properties of these phases can differ significantly from those of the non-expanded liquids. Viscosity and surface tension are reduced, increasing therefore the rate of mass transfer between the liquid and the supercritical phase. The solubility of H₂ in the expanded liquid phase is also increased. Under single-phase conditions (Fig. 39.1, right), all mass transfer barriers (gas/liquid) have disappeared completely and the reactive gas is fully mis-

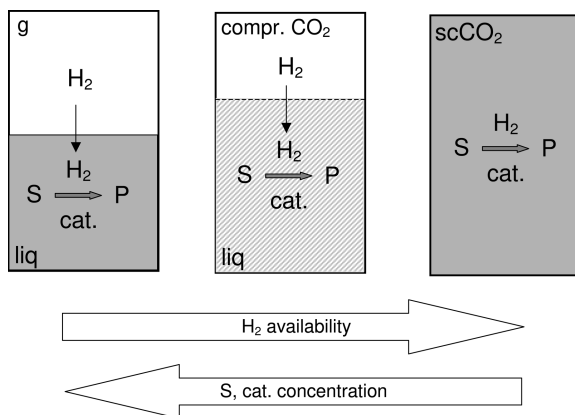


Fig. 39.1 Organometallic complex-catalyzed hydrogenation under conventional conditions, in liquids expanded with compressed (super- or subcritical) CO₂ and under monophasic supercritical conditions.

cible with the reactive phase. This situation ensures the maximum availability of H₂ for the reaction. However, as the liquid phase expands and finally dissolves completely in the SCF phase, the catalyst and substrate become distributed over a larger volume. Depending on the reaction order of each component in the rate law of the reaction, the overall rate and selectivity can therefore have a fairly complex dependence on the phase behavior of such systems [11, 12].

Other liquid phases such as ionic liquids (ILs) or poly(ethyleneglycol) (PEG) also show very high CO₂ affinities, albeit the volume expansion is generally less pronounced. Hydrogen solubility in ILs as a function of additional CO₂ has been measured using high-pressure ¹H-NMR spectroscopy, and an increase by a factor of three to five has been noted at typical operating pressures. These data could be corroborated with the preparative results of the iridium-catalyzed imine hydrogenation in IL/scCO₂ mixtures (see Section 39.2.3), where reactions were often sluggish in the pure ionic liquid, but occurred smoothly in the biphasic system at identical H₂ partial pressure [13]. Such systems are of particular interest as they allow for continuous-flow operation of organometallic hydrogenation without the use of any additional organic solvent (*vide infra*).

39.2.2

Catalyst Recycling and Immobilization

Owing to the large synthetic importance of hydrogenation reactions, many individual techniques have been developed to address the fundamental problem of catalyst recycling and immobilization by using compressed gases and SCFs. The following general pattern emerges from these investigations to date [14], and will be reflected also in the examples to be discussed in detail in Section 39.2.3.

39.2.2.1 Solubility Control for Separation

Compressed CO₂ can be used to control the solubility of suitably modified organometallic complexes in reaction mixtures, thus allowing selective separation processes. Three different scenarios can be envisaged for hydrogenation reactions:

- CO₂ as anti-solvent: The introduction of CO₂ to a reaction mixture selectively precipitates the organometallic hydrogenation catalysts, followed by SCF extraction of the products and recovery of the catalyst in active form.
- CO₂ as adjustable-solvent: In this case, the reaction is carried out in scCO₂ under truly monophasic conditions and the catalyst is selectively precipitated through a change in temperature and/or pressure. Again, product isolation is achieved by SCF extraction.
- CO₂ as co-solvent: Here, CO₂ is used to solubilize a catalyst, which is insoluble in the pure organic liquid, in an expanded organic phase. Once the CO₂ is removed at the end of the reaction, the catalyst precipitates and can be removed by filtration.

39.2.2.2 Membrane Separation

CO₂-philic catalysts that allow operation under fully homogeneous supercritical conditions are usually much larger than typical organic products, and can be retained by suitably size-selective membranes.

39.2.2.3 Biphasic Liquid/Supercritical Systems

As with classical multiphase catalysis, the organometallic catalyst is retained here in a liquid phase that is immiscible with the second phase containing substrates and/or products. For hydrogenation, the liquid/SCF system is always biphasic, whereas conventional systems are usually triphasic (liquid-1/liquid-2/H₂). The liquid phase must provide a stable environment for the organometallic catalyst and should be insoluble in the SCF phase. Water, ILs and PEG have been used successfully for this purpose, together with scCO₂ as the mobile phase. Again, the products must not be too polar in order to be effectively extracted if CO₂ is used as the SCF.

39.2.2.4 Inverted Biphasic Systems

Biphasic systems that contain the catalyst in the supercritical phase and the substrates/products in a second liquid phase can also be implemented. With water as the polar phase, these “inverted” systems are particularly attractive for the conversion of highly polar and/or low-volatile hydrophilic substrates with limited solubility in typical SCFs such as scCO₂.

39.2.2.5 Solid-Supported Catalysts

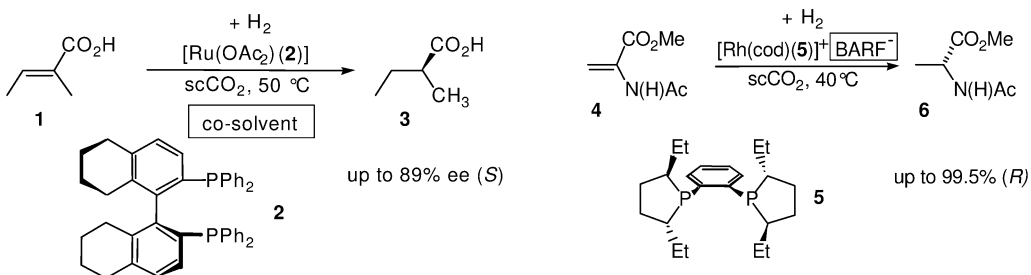
The heterogenization of organometallic catalysts on inorganic or organic solids has been extensively studied with traditional organic solvents. Mass transfer limitations and metal leaching have been identified as major obstacles for the practical use of this approach. Both factors might be reduced if an SCF is used as the mobile phase, albeit systematic studies are currently not yet available.

39.2.3

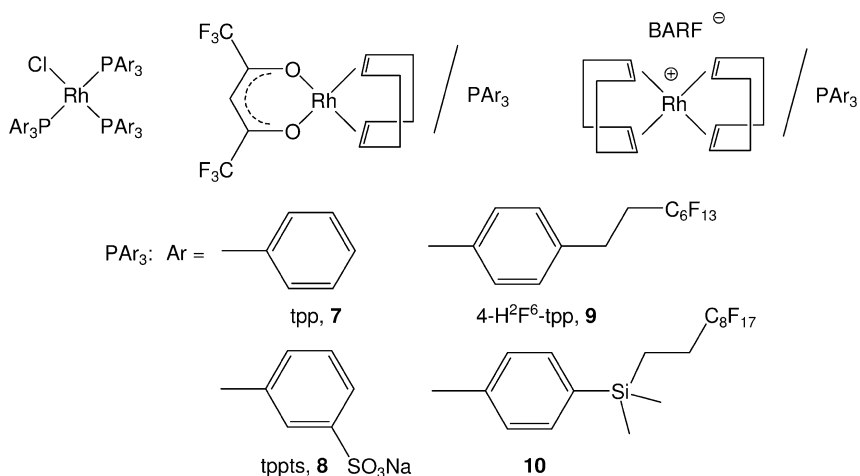
Catalytic Systems for Hydrogenation using SCFs, and their Synthetic Applications

The area of organometallic-catalyzed hydrogenation in SCFs was pioneered during the mid-1990s by studies on the hydrogenation of CO₂ itself to yield formic acid or derivatives such as formamides [15, 16]. Although the phase behavior of the multicomponent reaction mixtures is probably more complex than anticipated in these early studies, these investigations showed that the high availability of hydrogen under supercritical conditions can be exploited to achieve very high turnover frequencies (TOFs) with sufficiently CO₂-soluble metal catalysts. The generally low solubility of organometallic catalysts in scCO₂ was identified as a major limitation upon attempts to extend this methodology to asymmetric hydrogenation of C=C double bonds. For example, a ruthenium catalyst containing partly hydrogenated BINAP **2** as ligand required the presence of a co-solvent in the hydrogenation of dehydroamino acids in scCO₂ (Scheme 39.1) [17]. The cationic rhodium catalyst based on Et-DuPHOS (**5**) was rendered sufficiently CO₂-soluble in combination with the perfluoroalkyl substituted anion tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF) [18].

The most general approach to generate highly CO₂-soluble catalysts is the attachment of a "CO₂-philic" [19] side group at the periphery of a ligand in the organometallic catalyst [20]. Until now, fluor-containing groups have been used most widely to generate hydrogenation catalysts. Fluorinated aryl phosphines have been investigated for Ru-catalyzed chemoselective hydrogenation of α,β -unsaturated aldehydes in scCO₂ [21]. CO₂-soluble hydrogenation catalysts bearing a large number of perfluoroalkyl group [22] or extended fluorinated polymers [23] are extremely soluble, and they reach a size where they can be efficiently retained by membrane



Scheme 39.1 Early examples for enantioselective hydrogenation in scCO₂.

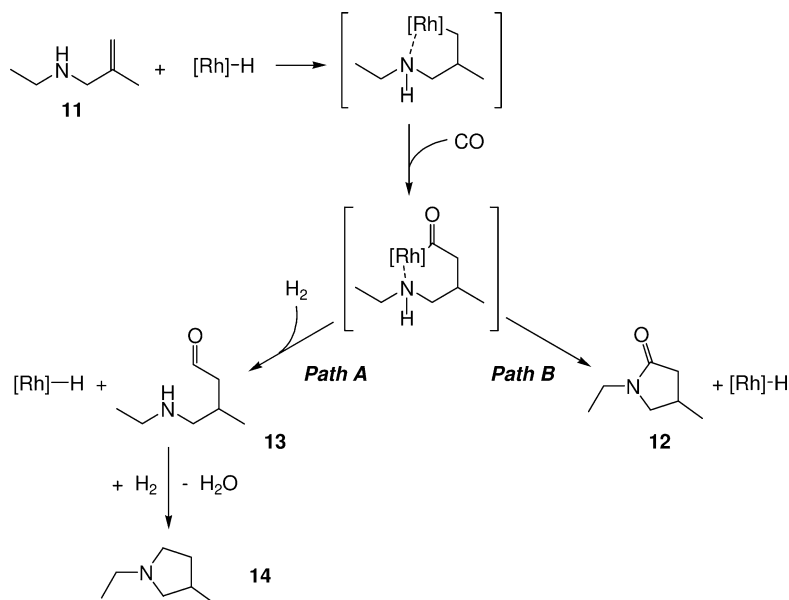


Scheme 39.2 Examples of typical rhodium-based catalyst systems and modified derivatives of triphenylphosphine as used to control their solubility with scCO_2 in homogeneous or multiphase systems (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate).

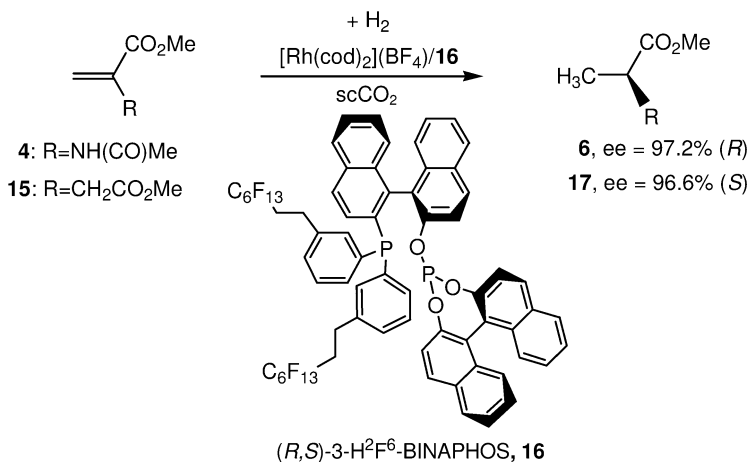
filtration. For example, the rhodium-catalyzed hydrogenation of butene as a model reaction has been carried out successfully in a continuous membrane reactor using the perfluoroalkyl-substituted derivative of triphenylphosphine **10** (Scheme 39.2) to generate an analogue of Wilkinson's catalyst [22].

The reaction sequence of hydroformylation and reductive amination (hydroaminomethylation) of the allylamine **11** provides an illustrative example for additional reaction control in scCO_2 (Scheme 39.3). Under conventional conditions, path B is preferred, leading to pyrrolidone **12** as the major product. In scCO_2 , however, the secondary amine is temporarily protected as the corresponding carbamic acid and the hydrogen availability is strongly increased. Therefore, path A prevails, leading first to the hydroformylation product **13** and finally to the saturated heterocycle **14** as the major product. The application of the rhodium-based catalytic system for this reaction under scCO_2 conditions was made possible by the use of the CO_2 -philic derivative of triphenylphosphine **9** [24].

Chiral ligand frameworks that have been modified with perfluoroalkyl groups and applied to asymmetric hydrogenation include chelating ligands such as BINAP [25–27], BINAPHOS [28–30], phosphino-oxazolines [31], and phosphonites [32], as well as monodentate phosphoramidites and phosphites [27, 33]. The application of 3-H²F⁶-(R,S)-BINAPHOS (**16**) in the asymmetric hydrogenation of α,β -unsaturated carboxylic acid derivatives is shown in Scheme 39.4. Owing to the relatively high molecular weight of the chiral framework, ligand **16** has a fairly low fluorine content of only 34%. This is sufficient, however, to render the ligand highly CO_2 -philic, allowing for example investigation of the reactivity of its rhodium complexes in scCO_2 by high-pressure multinuclear NMR spec-



Scheme 39.3 Product control by affecting the relative rates of competing reaction pathways in scCO₂. Path A is preferred in scCO₂, whereas path B prevails in conventional solvents.



Scheme 39.4 Enantioselective hydrogenation in scCO₂ using a CO₂-philic derivative of BINAPHOS.

troscopy [28b]. In combination with the cationic precursor $[\text{Rh}(\text{cod})_2][\text{BF}_4]$, high conversion and excellent ee-values were obtained for substrates 4 and 15. Visual inspection of the reaction mixture indicated that fully homogeneous conditions could be achieved with 15, whereas small amounts of substrate 4 remained al-

ways undissolved under the used conditions. The catalytic active species was, however, contained predominantly in the scCO_2 phase, as indicated by the typical yellow-orange color.

It is apparent from these prototypical results that the solubility of both catalysts and substrates can place certain constraints on the hydrogenation in scCO_2 under truly homogeneous conditions. Co-solvents such as methanol or trifluorotoluene (benzotrifluoromethane, BTF) can be used to overcome these limitations, but they partly offset the purpose of using a VOC-free system. Most recently, supercritical hydrofluorocarbons such as 1,1,1,2-tetrafluoroethane have been suggested as possible alternatives to scCO_2 , with an improved solubility profile for polar substrates and catalysts [34]. A very attractive approach utilizing a combination of two benign solvents is the application of an inverted $\text{scCO}_2/\text{H}_2\text{O}$ biphasic system, where the limited solubility of the polar substrates and products is turned into an advantage allowing simple and efficient separation and recycling of the catalyst [30].

The principle of the inverted system is depicted in Figure 39.2, together with typical results. The CO_2 -philic catalyst, which is generated in the same way as above, is contained in the scCO_2 phase, whereas the polar product partitions preferentially into the aqueous phase. Using a rhodium catalyst formed with the chiral BINAPHOS-derivative **16**, reasonable reaction rates and excellent *ee*-values were observed with substrate **4**. The catalyst was recycled without loss of activity or selectivity, leading to an average value of $98.4 \pm 0.6\%$ *ee* in five consecutive runs. Metal and phosphorus leaching into the aqueous phase was below the detection limit of 1 ppm, and recovery of product **6** was nearly quantitative. Similar results were obtained with itaconic acid (**18**) as another prototypical substrate [30].

Continuous-flow hydrogenation processes using scCO_2 as the mobile substrate/product phase can be envisaged also in systems where the catalyst is immobilized in the liquid phase. The hydrogenation of styrene (Scheme 39.5) is often used as a first benchmark reaction to evaluate such immobilization methods. Water is only sparingly soluble in scCO_2 and can be applied as a catalyst compartment with typical sulfonated water-soluble phosphine ligands such as *tppts* (**8**) [35]. Despite the use of a SCF as the substrate/product phase, the system seems to be operating under mass transfer limitations, and surfactants have been used to generate emulsion- and microemulsion-type reaction mix-

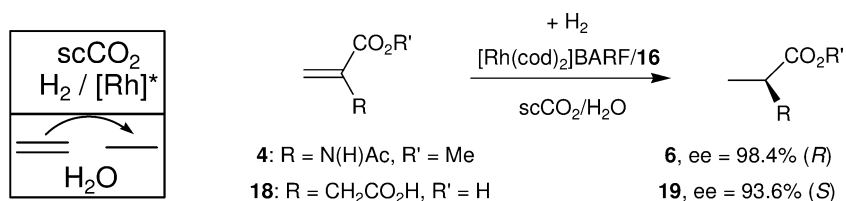
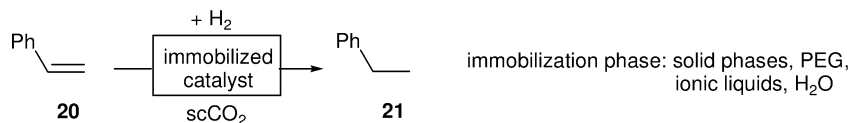


Fig. 39.2 Enantioselective hydrogenation of polar substrates in an inverted scCO_2 /water biphasic system.

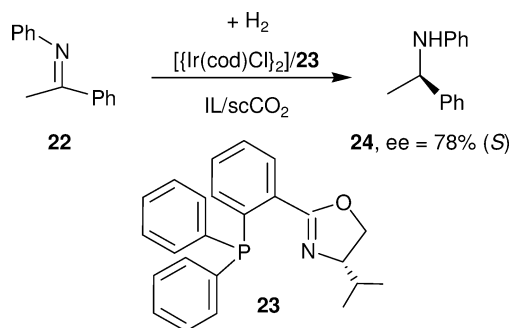


Scheme 39.5 Hydrogenation of styrene as a test reaction for immobilization methods, using scCO₂ as the mobile phase.

tures for enhanced performance in these systems [36]. High molecular-weight PEG has been demonstrated as a catalyst immobilization phase for organometallic hydrogenation with the same test reaction [37]. Although this catalyst phase would be a solid at the reaction temperature, it melts in the presence of scCO₂ as the compressed gas dissolves in the polymer. An attractive feature of this system is that no catalyst modification is necessary with triphenylphosphine (7)-based catalysts, suggesting that many chiral catalysts might also operate under the same conditions.

Ionic liquids (ILs) form also biphasic mixtures with scCO₂, and can serve as catalyst reservoirs for hydrogenation processes. The hydrogenation of supercritical CO₂ to formamides was used to investigate the possibility of controlling consecutive reaction pathways in such biphasic mixtures [38]. Asymmetric hydrogenation with ruthenium–BINAP catalysts similar to **2** in ILs allowed recycling of the chiral catalyst after extraction of the product with scCO₂ [39]. The iridium-catalyzed asymmetric hydrogenation of imines revealed a synergistic effect of the use of both media in this combination as compared to the individual solvent systems (Scheme 39.6) [13].

The secondary aryl amine **24** is far less basic than primary or secondary alkyl amines, and does not form the carbamic acid to any detectable extent in the presence of scCO₂ [31]. Therefore, **24** is extracted readily from the catalyst-containing IL phase, which can be recycled without noticeable loss of activity and selectivity [13]. In fact, it transpires that the active species is more stable towards oxygen in the IL than in organic solvents. Furthermore, the choice of anion of the IL largely controls the performance of the active cationic species, allowing even the use of an otherwise inactive iridium chloride precursor [$\{\text{Ir}(\text{cod})\text{Cl}\}_2$] to form *in-situ* catalysts



Scheme 39.6 Enantiomeric hydrogenation of imine **22** in an IL/scCO₂ biphasic system using an *in-situ*-activated iridium catalyst.

in such media. This allows a rapid variation and screening of ligands with alternative structures to **23**. As mentioned in Section 39.2.1, the inherent problems of low H₂ solubility and low viscosity of some ILs is overcome in the biphasic system through the beneficial effects of scCO₂.

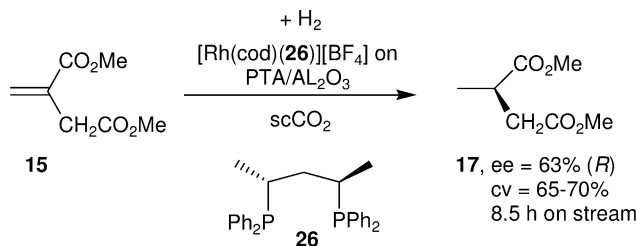
The presence of compressed CO₂ can also enhance the mass transport properties in liquid/supercritical reaction mixtures where the catalyst resides in the neat substrate. A striking example is the hydrogenation of vinyl arenes using Wilkinson's catalyst [RhCl(7)₃] at temperatures below the melting point of the solid substrates, where the presence of even subcritical CO₂ induces a significant melting point depression [40]. High rates and enantioselectivities were reported also for a ruthenium-catalyzed hydrogenation of β -keto esters [41] and a rhodium-catalyzed cascade reaction sequence involving hydrogenation as a key step under conditions where a liquid substrate/scCO₂ biphasic system is likely to be present [42].

The effects of added CO₂ on mass transfer properties and solubility were assessed in some detail for the catalytic asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl) acrylic acid to (*S*)-naproxen using Ru-(*S*)-BINAP-type catalysts in methanolic solution. The catalytic studies showed that a higher reaction rate was observed under a total CO₂/H₂ pressure of ca. 100 bar (*p*H₂=50 bar) than under a pressure of 50 bar H₂ alone. Upon further increase of the CO₂ pressure, the catalyst could be precipitated and solvent and product were removed, at least partly by supercritical extraction. Unfortunately, attempts to re-use the catalyst were hampered by its deactivation during the recycling process [11].

Most recently, a catalyst system based on PEG-modified phosphine ligands was reported to allow for a highly effective CO₂-induced separation procedure. In this case, the scCO₂ was used only at the separation stage to precipitate the catalyst and extract the products. The hydrogenation of styrene to ethyl benzene was used as a benchmark reaction, and it was shown that the catalytic active species could be recovered and not only re-used for another hydrogenation but also be subjected as a "cartridge" to a series of different transformations [43].

It should be noted, however, that CO₂ cannot be used only to precipitate, but also to solubilize catalysts in organic solvents. Not surprisingly, this method again relies on the application of CO₂-philic catalysts. As outlined above, these complexes are often highly fluorinated and hence, in certain cases, are immiscible with organic solvents. When expanded with CO₂, the liquid phase becomes increasingly "fluorophilic" until the catalyst finally dissolves. Release of CO₂ reverses the process and leads to precipitation of the catalyst. This method was demonstrated again for the hydrogenation of styrene to ethylbenzene using [RhCl(9)₃] as the catalyst precursor and cyclohexane as solvent. To facilitate the handling of the dissolved and re-precipitated catalyst, fluorosilica gel was used as a catalyst "sponge". In recycling experiments employing this system, the fluorosilica Wilkinson's catalyst showed only marginal activity decrease over five cycles [44].

Control of product solubility by compressed CO₂ is also possible. Primary and secondary alkylamines form carbamic acids or ammonium carbamates in the



Scheme 39.7 Continuous-flow hydrogenation of dimethyl itaconate (**15**) using a solid-supported chiral catalyst and scCO_2 as the mobile phase (PTA = $\text{H}_3\text{P}_{40}\text{PW}_{12}$).

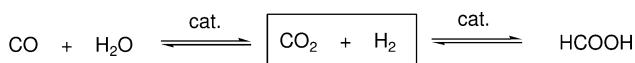
presence of compressed CO_2 . It has been shown that this reaction can be used to modulate the reactivity of such species in scCO_2 solution in reductive amination reactions (cf. Scheme 39.3) [24]. Depending on their substitution pattern and the exact solvent system, however, these compounds may also precipitate from the reaction mixture upon their formation by hydrogenation of the corresponding imines [31] or nitriles [45]. In favorable cases, this can be used for a simple catalyst separation scheme with organometallic catalysts in expanded solvent systems [45].

Finally, SCFs and scCO_2 allow for continuous-flow fixed-bed hydrogenations with heterogenized solid-supported catalysts. The application of ruthenium complexes that were linked covalently to solid supports was demonstrated early on in CO_2 hydrogenation [46, 47]. Ruthenium complexes were also supported on silica in combination with ligand **8** using the supported-aqueous-phase (SAP) approach [35]. Application of scCO_2 yielded better conversions for the hydrogenation of cinnamaldehyde than using toluene with the same method. A silica-adsorbed Wilkinson catalyst $[\text{RhCl}(\text{7})_3]/\text{SBA-15}$ was investigated recently for the hydrogenation of simple olefins, as shown in Scheme 39.5 [48]. For asymmetric hydrogenation, true continuous-flow operation was demonstrated most recently with a Skewphos (**26**)-based cationic rhodium catalyst that was anchored to alumina by electrostatic interaction via a polyoxometallate anion. Steady-state conversion and enantioselectivity was observed for the hydrogenation of dimethyl itaconate (**15**) over a period of more than 8 h (Scheme 39.7) [49].

39.2.4

Mechanistic Aspects

The large body of examples discussed in the previous section indicates that SCFs, and in particular scCO_2 , offer a broad potential for applications in hydrogenation reactions. Very little is known, however, about possible interactions between the catalytically active species and the reaction medium in such systems. In particular, two possible transformations of CO_2 in the presence of hydrogen must be considered, which are also transition metal-catalyzed (Scheme 39.8). The water gas shift (WGS) reaction can lead to the formation of CO , and has

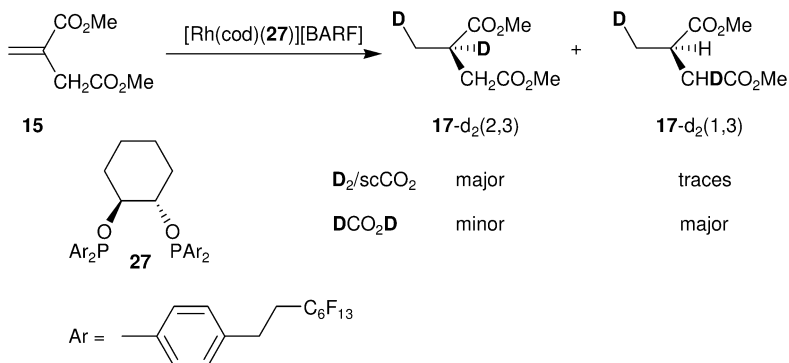


Scheme 39.8 Possible reactions of CO₂ in the presence of H₂ under transition metal-catalyzed hydrogenation conditions.

been observed as a major deactivation and poisoning pathway with heterogeneous catalysts in a number of cases [50]. Successful hydroformylation/hydrogenation sequences, such as that shown in Scheme 39.3, indicate that organometallic transition metal hydrogenation catalysts can tolerate CO in certain cases. Nevertheless, activities and selectivities might be expected to be altered in the presence of this additional ligand, though to date no such cases have been reported.

The second reaction to be considered is the formation of formic acid from H₂ and CO₂. This reaction is very effectively catalyzed by rhodium and ruthenium hydride complexes similar to those involved in C=C or C=O hydrogenation reactions. As formic acid itself is a widely used hydrogen transfer reagent, a hydrogenation carried out in scCO₂ may actually follow a transfer hydrogenation pathway involving formate intermediates rather than the classical hydride route. The hydrogenation of dimethyl itaconate **15** using a cationic CO₂-philic rhodium catalyst formed with ligand **27** was used as a probe reaction to distinguish between these two possibilities (Scheme 39.9) [32].

The distribution of isotopomers **17-d_n** obtained from the reaction of **15** with D₂ in scCO₂ and other media was used as a diagnostic tool. In particular, the 2,3- and 1,3-pattern in the dideutero products **17-d₂** differs significantly from the classical hydrogenation and the transfer hydrogenation pathway owing to a shift in relative rates between rearrangement and hydrogen transfer processes [51]. The 2,3-addition is largely preferred in the hydrogenation pathway, whereas the 1,3-isomer is the major product obtained from transfer hydrogenation. The



Scheme 39.9 Deuterium labeling as a mechanistic probe for hydrogenation pathways in scCO₂.

pattern observed in scCO_2 was largely identical to that observed with D_2 in hexane or sc -ethane, revealing a preferred 2,3-addition mode with no significant incorporation at C-1. It was therefore concluded that formate intermediates are unlikely to play a major role in the productive catalytic cycle. This was further supported by parahydrogen-induced polarization (PHIP)-NMR measurements indicating that the two H atoms are transferred pairwise without significant scrambling which would be unlikely for a formic acid pathway.

Interestingly, the enantioselectivity of the hydrogenation shown in Scheme 39.9 exhibited a large dependence on the partial pressure of hydrogen in conventional solvents, whereas it was almost independent of this parameter in scCO_2 . As fundamental differences in the hydrogenation pathways were ruled out by the above-mentioned experiments, it seems most likely that the availability of hydrogen (see Section 39.2.1) is the controlling factor for this observation.

39.3

Conclusions and Outlook

Compressed and, in particular, supercritical CO_2 offers great potential as reaction medium and/or mass-separating agent for organometallic hydrogenation reactions. Especially, the design of integrated reaction and separation processes represents a highly attractive development for the future. There is increasing evidence that flexible and small-scale engineering solutions are possible that would allow the advantages of molecular catalyst design to be combined with continuous-flow operation. Indeed, such modular “cartridge” systems offer an interesting alternative to the classical batch-wise processing of the fine chemical and pharmaceutical industries, especially for the high-pressure reactions often encountered with hydrogenation.

As the factors that control the reaction rates and selectivities of these systems become better understood, the design of highly effective catalytic systems may also become increasingly rational. At present, the control of hydrogen availability and chemical interactions with amine groups in substrates and products are emerging as general themes. However, many additional options to regulate the structure, solubility, phase behavior, and chemical interactions on all levels can undoubtedly be discovered through interdisciplinary efforts by molecular scientists and engineers in this field.

Finally, it should be stressed that CO_2 is not the only SCF to demonstrate potential use in hydrogenation reactions. While the established technology platform and largely benign character of scCO_2 make it the current preferred choice, other SCFs may possess complementary properties in terms of polarity, solvation, and reactivities. In future, it is possible that alkanes (e.g., ethane and propane), fluorohydrocarbons and more reactive SCFs such as N_2O – or even water – may also be envisaged for this purpose.

Abbreviations

BTF	benzotrifluoromethane
IL	ionic liquid
PEG	poly(ethyleneglycol)
SAP	supported-aqueous-phase
scCO ₂	supercritical carbon dioxide
SCF	supercritical fluid
VOC	volatile organic chemical

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