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Homogeneous Catalysis in Supercritical Fluids

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I. Introduction

Why perform a homogeneously catalyzed reaction in a supercritical medium? Other than environmental and technical benefits, are there any advantages to using such an unusual “solvent”? This review has been written to show that the chemistry of these reactions can be changed for the better by this change in medium.

Transition metal based homogeneous catalysts are renowned for their great tunability. In comparison to heterogeneous catalysts, homogeneous catalysts have the advantages of greater selectivity, ease of spectroscopic monitoring, and, above all, controlled and tunable reaction sites. To optimize reaction rate and selectivity, their steric and electronic properties can be adjusted through an infinite range of variations because of diverse reactivities of metallic elements and unlimited structural permutabilitiy of organic ligands. Ligand design allows for the modification of the shape of the reactive site, resulting in greater selectivity or even asymmetric catalysis.[1−3] Addition of reactive groups among the ancillary ligands allows for ligand−substrate “secondary” interactions (e.g., hydrogen bonding, electrostatic interaction,[4] or π-stacking[5]), resulting in greater rates and selectivity for substrates with the appropriate functional groups (e.g., hydrogen bond acceptors).[6−8] Modification of the electron donating or accepting properties of ligands allows for the optimization of the electronic properties of the metal center.[9−13] In ligand-accelerated catalysis, this results in greater rates. Even the solubility of the metal complexes can be tuned by adjustment of hydrophilic,[14−17] lipophilic, or fluorophilic[18−20] groups, as needed for use in various media. Thus molecular design of catalyst structure renders homogeneous catalysts both tunable and selective, far beyond the level possible with heterogeneous catalysts. Only enzymes are capable of greater selectivity, but the number of enzymes available is limited. Thus, it seems only natural that homogeneous catalysts be coupled with supercritical fluids (SCFs), for the latter are the tunable analogues of liquid solvents.[21] The use of homogeneous catalysts in SCFs should then allow the chemist the greatest ability to tune the reaction system.

Among the advantages of SCFs, which are discussed in greater detail in other contributions to this special edition, is the miscibility of gases in these media compared to the very limited solubility of gases in liquid solvents. There is no doubt that this can improve the performance of homogeneous catalysts, particularly for those reactions which are first order in the concentration of the gaseous reagent. In addition to the benefits for the chemistry, the use of SCFs as reaction media may help us to solve the “Achilles heel” of homogeneous catalysis; namely the

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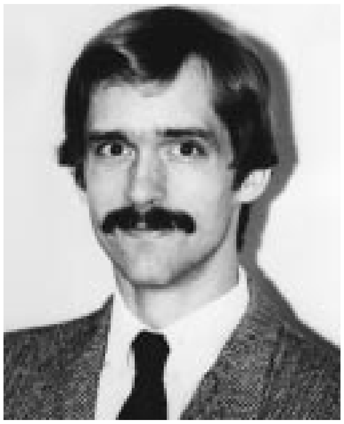


Philip G. Jessop, born in Ottawa, received his B.Sc. from the University of Waterloo in 1986 and his Ph.D. from the University of British Columbia in 1991. His doctoral research, performed under the supervision of Professor Brian R. James, concerned the kinetics of reactions of hydrido- and thiolatoruthenium complexes. During a postdoctoral appointment with Professor Robert H. Morris at the University of Toronto, he studied molecular hydrogen complexes and, in a separate project, the properties of deuterated polymers. At ERATO with Professor R. Noyori, he investigated the hydrogenation of carbon dioxide and other reactions in supercritical carbon dioxide. Since taking up the position of assistant professor at the University of California, Davis, he has directed his research toward two projects: the effect of pressure on asymmetric syntheses in supercritical fluids and the reactions of supercritical nitrous oxide.

Takao Ikariya, born in Matsumoto, Japan, in 1948, completed his Ph.D. degree in 1976 at Tokyo Institute of Technology under the direction of Professor Akio Yamamoto and then was appointed assistant professor in the Department of Synthetic Chemistry at the University of Tokyo. He worked with Professor Sadao Yoshikawa on asymmetric reactions catalyzed by ruthenium–BINAP complexes. He spent one and a half years in 1979–1981 as a postdoctoral fellow in Professor Robert H. Grubbs' group at Caltech. In 1985 he moved to the central research center of NKK Corp. where he developed a carbonylation reaction of nitrobenzene. In 1991 he joined in the ERATO Molecular Catalysis Project of Japan Science and Technology Corporation which was directed by Professor Ryoji Noyori and he was promoted to professor at Tokyo Institute of Technology in 1997. His current research interests include homogeneous catalysis in both liquid solvents and supercritical fluids.

Ryoji Noyori, born in Kobe, Japan, in 1938, completed his undergraduate and Master's degree at Kyoto University and became Research Associate at the same university in 1963. He received his Ph.D. degree (Professor H. Nozaki) in 1967, and in the following year, he was appointed Associate Professor in the Department of Chemistry at Nagoya University. He spent a postdoctoral year at Harvard (Professor E. J. Corey) in 1969–1970 and, shortly after returning to Nagoya, was promoted to Professor in 1972. From 1991 to 1996, he directed the ERATO Molecular Catalysis Project, a research project of the governmental agency, Japan Science and Technology Corporation. He now serves as Dean of Graduate School of Science, Nagoya University, and President of the Synthetic Organic Chemistry, Japan. His current research interests include homogeneous catalysis, particular asymmetric catalysis, using organometallic molecular catalysts and its synthetic applications. His achievement have been recognized with The Chemical Society of Japan Award for 1985, The J. G. Kirkwood Award (1991), The Asahi Prize for 1992, the Tetrahedron Prize (1993), The Japan Academy Prize (1995), and The Arthur C. Cope Award (1997) among others.

problem of recovery of the expensive transition metal containing species in solution (the "catalyst"). The results of the past century of research into the SCF extraction and purification of compounds from mixtures can be applied to the separation of the transition metal complexes from the product stream downstream from the reaction vessel. For example, controlled pressure reduction could be used to selectively precipitate the catalyst precursor and active catalyst, assuming that these species have distinctly lower solubility than the products in the SCF at lower densities. Alternative techniques such as retrograde crystallization could also be applied (section II.B).

SCFs can affect the outcome of a homogeneously catalyzed reaction in a number of ways. SCFs can allow the deliberate control of the phase behavior, dissolution of the reactants, or precipitation of the products or catalysts with moderate changes in temperature and pressure. They also offer the opportunity to tune reaction rate and selectivity with very small changes in operating conditions. Physical properties of SCFs could uniquely and subtly influence the nature of the molecules and molecular associates.[22] These factors have already been demonstrated for a number of simple stoichiometric reactions,[23] but their application to homogeneous catalysis is far more complicated. The principles developed with stoichiometric reactions, if applied to the product-determining or turnover-limiting step of the catalytic cycle, should allow one to explain the effect of supercritical conditions on homogeneous catalysis.

Although homogeneous catalysis in SCFs is considered a relatively new field, only gaining wide attention since around 1990, it has been around for a lot longer. For example, Ipatiev in 1913 used $AlCl_3$ as a catalyst for the oligomerization of supercritical ethene at 240 °C.[24] However, homogeneous catalysis in $scCO_2$, an ideal medium, has not been the subject of serious study until more recently. Part of the reason for this is the poor solubilizing power of $scCO_2$, which has restricted the choice of catalysts, reagents, and substrates to a narrow range of nonpolar, nonionic, and low molecular weight compounds. This restriction has been lifted recently with the development of surfactants, cosolvents, and other reagents which can dramatically increase the solubility of polar or charged species in $scCO_2$. One can expect that this development will fuel even greater interest in the field during the next decade.

This review was written to emphasize reactions which are homogeneously catalyzed by metal-containing complexes, although some heterogeneously catalyzed reactions will be mentioned for illustrative purposes. The reader is referred to other works in this special issue for discussion of polymerization, uncatalyzed reactions, and reactions in scH_2O such as pyrolysis and destructive oxidation. It should become obvious to the reader that far too little work has been done in the field of this review, although at the present interest level the field will advance very rapidly.

II. Experimental Considerations

A. Pressure and Density

Increasing pressure leads to increasing density (Figure 1) and consequently greater solubility, both for the catalyst precursor and the other reactants (Figure 2). The pressure required to properly dissolve some catalyst precursors should not be underestimated. Thus, solubility considerations set a lower limit on the pressures which can be used, and economic considerations usually determine the upper limit. Higher pressures increase the costs both industrially and for the academic researcher. Thus the average researcher without need for the special properties of SCFs should not be encouraged to invest time or funds in attempts to see if a reaction "works" in SCFs. However, for those reactions in which there is a definite advantage to operating under supercritical conditions, high pressure should not be a hindrance to either research or commercialization. For example, the Haber–Bosch process and the polymerization of ethene have been performed on very large scales and at high pressures for most of this century.

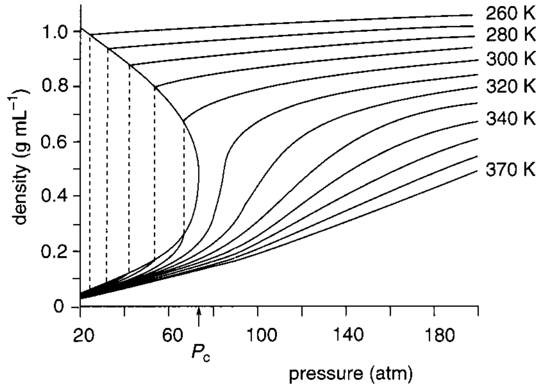


Figure 1. The density of pure CO_2 as a function of pressure and temperature.[25]

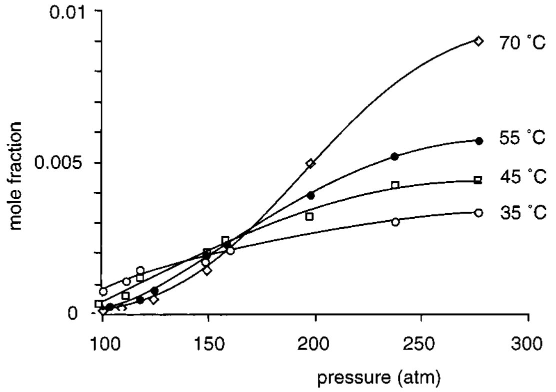


Figure 2. Mole fraction solubility of benzoic acid in $scCO_2$ as a function of pressure and temperature. The crossover pressure is approximately 160 atm.[26]

The question of activation volumes in SCFs has been greatly discussed,[23] and there is no doubt that unusual pressure effects have been seen for stoichiometric reactions in SCFs. There has been virtually no work yet on the effect of unusual activation volumes on the rates and selectivities of homogeneously catalyzed reactions in SCFs, but this is sure to change soon.

On a practical point, researchers should note that the use of CO_2 tanks with a helium head pressure can decrease the density of the $scCO_2$ and hence decrease the solubility of reagents or catalysts.[27] Reproducibility of experimental results may also suffer.[28] CO_2 cylinders with helium head pressures are not necessary if the pump is cooled.

B. Temperature

As in liquid solvents, catalytic reactions in SCFs can only be performed in a rather narrow temperature range. Too low a temperature gives unacceptably low rates, while too high a temperature causes loss of selectivity or catalyst decomposition. The acceptable temperature range, of course, varies with the reaction system, and it greatly restricts the choices of SCFs. One must choose a SCF that has a T_c below or within the desired temperature range (Figure 3). However, one should avoid selecting a SCF with a T_c far below the desired temperature range, because this will then require the use of very high pressures to obtain reasonable solvent densities (Figure 1). Thus, pressurized N_2 gas is rarely considered a SCF at room temperature, although it is one, because

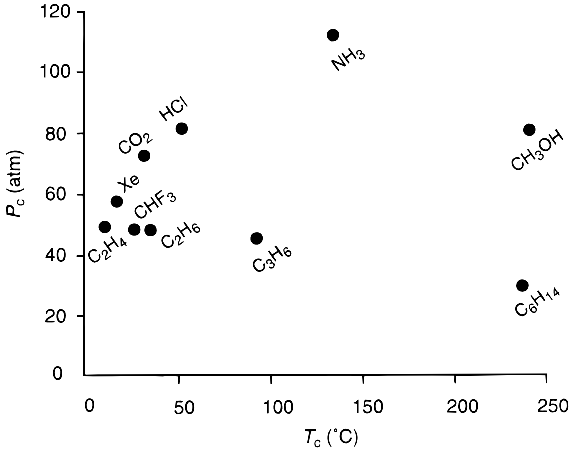


Figure 3. The critical points of selected solvents. Water (374.0 °C and 217.8 atm) and methane (−82.6 °C and 45.4 atm) are offscale.[29]

extremely high pressures would be required to allow it to dissolve anything but other gases.

Temperature also affects solubility, and this is not only of importance in selecting reaction conditions but also could potentially be used to advantage in catalyst recovery. Below a "crossover pressure", increasing temperature decreases the solubility of compounds (Figure 2) because the SCF density decreases. This phenomenon is referred to as retrograde behavior. Above the crossover pressure, increasing temperature increases the solubility of the solute because the volatility of the solute increases.[30−32] For solutes of low volatility, this crossover pressure can be quite high. For example, naphthalene has a crossover pressure in $scCO_2$ of 120 atm, while that for phenanthrene is 230 atm.[31]

The following speculation is offered as an example of how the properties of SCFs could be used to recover transition metal containing complexes or catalysts from the product mixtures of reactions. The technique of retrograde crystallization[30−32] involves the separation of mixtures of two solids by adjusting the temperature at a constant pressure between the crossover pressures of the solids. For example, naphthalene can be precipitated from a $scCO_2$ solution of naphthalene and phenanthrene by lowering the temperature at a constant pressure between 120 and 230 atm. Raising the temperature would precipitate the phenanthrene. Of course, this separation technique would only be possible for mixtures of solids which differ significantly in volatility and therefore crossover pressure. The technique might therefore be applicable to the recovery of a transition metal containing complex after catalytic reactions, assuming that the complex is much less volatile than the organic product. Research of the possibilities for catalyst recovery by SCF techniques would be a useful contribution to this field, but the present authors are unaware of any published reports on this topic.

C. Density-Dependent Properties of SCFs

The dielectric constant, viscosity, and other physical properties of the SCF medium are functions of density, and since density varies with pressure, these properties are also strongly pressure-dependent. One such property that has attracted interest from researchers is the dielectric constant. The name of the property is unfortunate, given the fact that the dielectric constant is far from constant (Figure 4). Although all SCFs have variable dielectric constants, the range over which it varies is large only for the more polar SCFs such as $scNH_3$, scH_2O, and the partially fluorinated methanes and ethanes. The variation of the dielectric constant with pressure has the potential of affecting homogeneous catalysis. Many reactions which have polarized reactants, products or transition states or which exhibit solvent effects in liquids are in fact affected primarily by the polarity of the medium; this is the basis for the Hughes−Ingold rules for reaction rates.[33] These reactions should then have pressure-dependent rates or selectivities in polar SCFs such as $scCHF_3$.[34]

The viscosity of SCFs is generally much lower and the diffusivity much higher than those of liquids, but this should have little effect on all but the very fastest homogeneously catalyzed reactions. Exceptions to this may include paired radical reactions[38] and reactions in which mass transfer between the SCF and another phase is rate-limiting. For example, reactions involving polymeric substrates or polymer-supported "heterogenized" catalysts may have greater rates if performed in SCFs rather than liquid solvents. Preliminary work in this direction includes tests of the effectiveness of $scCO_2$ as a solvent for impregnating polymers with transition metal complexes.[39−43]

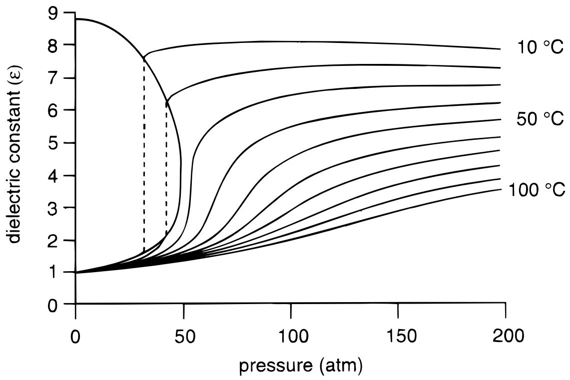


Figure 4. The dielectric constant of fluoroform, calculated from published densities[35,36] using the equation of Rhodes et al. which is most accurate above T_c.[37]

D. Reactivity of SCFs

Supercritical fluids are not always inert reaction media. In fact, all SCFs will react under at least some conditions and with some reagents. The results can be useful processes for the activation and utilization of SCFs or they can be hazardous uncontrolled reactions.

In the hazardous category are $CH{\equiv}CH$ and $CF_2{=}CF_2$, which are prone to explosive deflagration or polymerization upon pressurization,[44] and SiH_4, which spontaneously ignites upon leaking from pressurized vessels.[45] At higher temperatures, even alkanes can become thermodynamically unstable; supercritical hexane was found to explosively decompose at 500 °C.[46] Nitrous oxide supports explosive combustion if used as a solvent for significant quantities of combustible materials.[47,48]

Less hazardous reactions can either be beneficial or a hindrance. The controlled polymerization of scC_2H_4 is an important industrial process.[49] Partially fluorinated methanes and ethanes such as $scCHF_3$ are acidic enough to be deprotonated by strong bases,[50,51] preventing these SCFs from being used as media for reactions involving reagents such as LiR, NaH, or KOR, but opening up the possibility that $scCHF_3$ may one day be used as a solvent for trifluoromethylation reactions. While supercritical alkanes are generally unreactive, stoichiometric C−H bond activation reactions of $scCH_4$ and scC_2H_6 have been reported.[52] Even $scCO_2$ can be quite reactive; it inserts readily into M−H, M−R, M−OR, or $M{-}NR_2$ bonds in transition metal complexes[53] and reacts with secondary or primary amines to form carbamate salts.[54,55] The coordination chemistry of supercritical noble gases is also actively being studied.[56] It seems likely, on the basis of these stoichiometric reactions and the many examples of the fixation of $scCO_2$,[57−61] that the reactivity of SCFs will continue to be explored as an opportunity for the fixation of gases.

E. Solubility of Catalyst Precursors

Most of the SCFs that have critical points below 100 °C are very nonpolar (Figure 3). The few exceptions are either expensive (CHF_3, CH_3F) or toxic (CO, PF_3). By far the most popular choice is $scCO_2$, in which only nonpolar catalysts will dissolve. The many first-row transition metal complexes, and the very few second- or third-row transition metal complexes for which solubility data are available are listed in Table 1. Note that all of these data describe solubility in $scCO_2$ only. There is certainly a need for solubility data for inorganic compounds in other SCFs. Transition metal complexes known to dissolve in $scCO_2$, but for which quantitative data are unavailable include phosphine complexes,[60] porphyrin complexes,[74,75] metallocenes,[76−78] carbonyls,[79] and metal oxinates.[80] Polar complexes, charged complexes, and even nonpolar complexes with many aryl-substituted ligands often have insufficient solubility to be used as catalysts.

Ligand modification is one of several approaches which have been developed to increase the solubility of transition metal complexes. Ligands containing aryl substituents have been replaced with ligands containing alkyl groups.[60] Even further improvement can be obtained by replacing alkyl groups with perfluoroalkyl groups. The effect on solubility can be quite dramatic; for example, the solubility of $Cu(hfacac)_2$ is 200 times greater than that of $Cu(acac)_2$ in $scCO_2$ at 205 atm and 40 °C [acac, pentane-2,4-dionate; hfacac, bis(1,1,1,6,6,6-hexafluoropentane-2,4-dionate)].[71] Metals in higher oxidation states allow for more fluorinated anionic ligands; thus the solubility of hfacac complexes of M^{3+} metals is greater than that of M^{2+} metals.[73] Addition of CO_2-philic “ponytails” such as polyfluoroalkyl, fluoro ether, or silicone groups, often as substituents on aryl rings can increase the solubility of metal complexes.[77,81−83] The longer the fluorinated alkyl chain, the better the solubility.[84] Often, the first two carbons in the ponytail are unfluorinated, so that the electron-withdrawing effect of the group is mitigated.[82,85] Leitner’s group found that $Rh(hfacac)(R_2PCH_2CH_2PR_2)$ was insoluble in $scCO_2$ for $R = C_6H_5$, sparingly soluble for R = cyclohexyl, and seven times more soluble for $R = C_6H_4$-*p*-$(CH_2)_2(CF_2)_7CF_3$.[83] Other groups[86,87] have reported the use of other fluorinated phosphine ligands such as $P(C_6F_5)_3$, $P(C_6H_3$-3,5-$(CF_3)_2)_3$, and $P(C_6H_5)(CH_2CH_2C_6F_{13})_2$. The syntheses of these highly fluorinated ligands are of interest to both researchers of reactions in SCFs and those studying catalysis in fluorous phases.[18]

Table 1. Mole Fraction Solubility (x) of Transition Metal Complexes in $scCO_2$[a]

complex	P, atm	T, °C	d, g mL^{-1}	x	ref
Group 4					
$TiCl_4$	100	76	0.23	0.09	62
Group 6					
$Cr(acac)_3$	200	60	0.73	1.2×10^{-4}	63
$Cr(acac)_3$	200	40	0.85	1.1×10^{-4}	64
$Cr(acacBr)_3$	200	40	0.85	1.3×10^{-5}	64
$Cr(thd)_3$	200	40	0.85	4.5×10^{-3}	64
mer-$Cr(tfa)_3$	200	40	0.85	2.0×10^{-3}	64
fac-$Cr(tfa)_3$	200	40	0.85	1.4×10^{-3}	64
$Mo(CO)_6$	103	51	0.39	9.2×10^{-3}	65
Group 7					
$Mn(acac)_3$	290	60	0.83	1.9×10^{-7}	66
$Mn(acac)_2$	290	60	0.83	8.5×10^{-8}	66
$CpMn(CO)_3$	100	40	0.62	8.1×10^{-3}	67
Group 8					
$Fe(C_5H_5)_2$	241	50	0.83	4.0×10^{-3}	68,69
Group 9					
$Co(fddc)_2$	100	50	0.41	8.8×10^{-5}	70,71
$Co(ddc)_2$	100	50	0.41	2.6×10^{-7}	70,71
$Co(acac)_3$	290	60	0.83	9.4×10^{-8}	66
$Co(acac)_2$	290	60	0.83	5.2×10^{-8}	66
Group 10					
$Ni(fddc)_2$	100	50	0.41	7.9×10^{-5}	70,71
$Ni(ddc)_2$	100	50	0.41	9.4×10^{-8}	70,71
$Ni(hfa)_2$	200	60	0.73	4.9×10^{-4}	63
$NiCl_2[P(C_6H_5)_3]_2$	220	45	0.83	3.6×10^{-6}	72
Group 11					
$Cu(fddc)_2$	100	50	0.41	1.0×10^{-4}	70,71
$Cu(ddc)_2$	100	50	0.41	1.2×10^{-7}	70,71
$Cu(acac)_2$	290	60	0.83	4.3×10^{-8}	66
$Cu(acac)_2$	200	40	0.85	1.8×10^{-5}	64
$Cu(bzac)_2$	200	40	0.85	6.0×10^{-6}	64
$Cu(tfbzm)_2$	200	40	0.85	2.1×10^{-5}	64
$Cu(dmhd)_2$	200	40	0.85	2.1×10^{-4}	64
$Cu(dibm)_2$	200	40	0.85	4.6×10^{-4}	64
$Cu(thd)_2$	200	40	0.85	5.8×10^{-4}	64
$Cu(tod)_2$	200	40	0.85	1.1×10^{-3}	64
$Cu(hfa)_2$	200	40	0.85	3.8×10^{-3}	64
$Cu(tfa)_2$	200	40	0.85	4.2×10^{-4}	64
$Cu(hfa)_2 \cdot H_2O$	100	40	0.62	8.1×10^{-3}	67
Group 12					
$Zn[SCSN(n\text{-}C_4H_9)_2]_2$	237	55	0.80	3.0×10^{-5}	73
$Zn[SCSN(C_2H_5)_2]_2$	237	55	0.80	1.9×10^{-6}	73
$Zn(SCSNC_4H_8)_2$	237	55	0.80	2.8×10^{-7}	73
$Zn(acac)_2$	290	60	0.83	2.1×10^{-7}	66
$Hg(fddc)_2$	100	50	0.41	5.5×10^{-4}	70
$Hg(ddc)_2$	100	50	0.41	9.0×10^{-7}	70

[a] Abbreviations: acac, pentane-2,4-dionate; acacBr, 3-bromopentane-2,4-dionate; bzac, 1-phenylpentane-1,3-dionate; ddc, diethyldithiocarbamate; dibm, 2,6-dimethylheptane-3,5-dionate; dmhd, 1,1-dimethylhexane-3,5-dionate; fddc, bis(trifluoroethyl)dithiocarbamate; hfa, 1,1,1,6,6,6-hexafluoropentane-2,4-dionate; tfa, 1,1,1-trifluoropentane-2,4-dionate; tfbzm, 1,1,1-trifluoro-4-phenylbutane-2,4-dionate; thd, 2,2,6,6-tetramethylheptane-3,5-dionate; tod, 2,2,7-trimethyloctane-3,5-dionate; tta, 1-thienyl-4,4,4-trifluoropentane-1,3-dionate.

A second approach to increasing the solubility of complexes is the addition of cosolvents, an approach which was already known to increase the solubility of aromatic reagents.[88,89] Lin et al.[77] found that 5% methanol quadrupled the solubility of bis(diethyldithiocarbamato)mercury(II) in $scCO_2$, while Cowey et al.[75] found that 10% methanol greatly increased the solubility of a nickel complex with a cyclic tetraamine ligand, 5,7,12,14-tetramethyl-2,3,9,10-dibenzo[*b*,*i*][1,4,8,11]tetraazacyclotetradecine. This Ni(II) complex was virtually insoluble in $scCO_2$ in the absence of methanol.

Although charged complexes are generally insoluble in $scCO_2$, careful choice of counterions can greatly increase the solubility of charged complexes. Burk et al.[90] cite $[(3,5\text{-}(CF_3)_2C_6H_3)_4B]^-$ (“BArF$^-$”)[91,92]

and $CF_3SO_3^-$ as anions which enhanced the solubility of their cationic rhodium complexes. Information on the solubility of anionic complexes is even scarcer, but studies have shown that tetraalkylammonium[93] or morpholinium cations[94] can enhance the solubility of main-group or organic anions. Presumably perfluorotetraalkylammonium cations would be even more effective.

Finally, surfactants have been developed which can create aqueous reverse micelles in $scCO_2$,[95,96] and hence solubilize hydrophilic reagents such as $KMnO_4$.[97,98] The surfactants generally have siloxane[99] or fluorinated lipophilic tails to increase their solubility in $scCO_2$,[94] although nonfluorinated surfactants are more appropriate for use in scC_2H_6.[100,101]

III. Homogeneous Catalysis

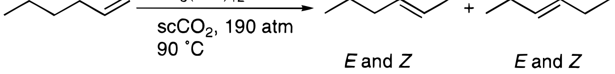
A. Isomerization

Examples of heterogeneously catalyzed isomerizations under supercritical conditions date back at least as far as Ipatiev's 1911 report of the isomerization of cyclohexane to methylcyclopentane at 500 °C over Al_2O_3.[46] However, there has been very little work done on homogeneously catalyzed isomerization reactions in SCFs.

In 1975, Kramer and Leder patented, on behalf of Exxon, the isomerization of *n*-hexane to methylpentane or dimethylbutane catalyzed by $AlBr_3$ in a supercritical hexane/CO_2 mixture.[102] The researchers suggested in the patent that $AlCl_3$ has insufficient solubility in the supercritical mixture. The reactions were performed at 40−150 °C and typically at 140 atm. This was one of the first reports to cite the benefits of the high miscibility of H_2 with $scCO_2$. Adding H_2 at high concentration increased the selectivity for isomerization over cracking. The use of a SCF as the solvent allowed a greater percentage (i.e., 100%) of the hydrogen to be present in the reaction phase. Supercritical hexane/HCl or hexane/HBr mixtures were also effective solvents, for similar reasons.

The isomerization of olefins in SCFs has not been thoroughly studied. Initial tests have shown that $Fe_3(CO)_{12}$, a known isomerization catalyst,[103,104] is effective in isomerizing 1-hexene to primarily 2-hexene in $scCO_2$ at 90 °C (78% yield of 2-hexene after 90 min) but not at 64 °C (Scheme 1).[105] The reaction in $scCO_2$ requires a higher temperature than the same reaction in neat alkene under argon; the reason for this is unknown but one could speculate that it is a dilution effect.

Scheme 1



B. Hydrogenation

Most transition metal catalyzed homogeneous hydrogenation reactions take place by either an insertion mechanism or a hydrogen atom transfer (radical) mechanism, depending on the nature of the catalyst and the substrate. The insertion mechanism is more common for hydridic MH complexes where M = rhodium, ruthenium, etc., while the radical mechanism is more common for acidic MH compounds such as $MnH(CO)_5$ and $CoH(CO)_4$.[106,107]

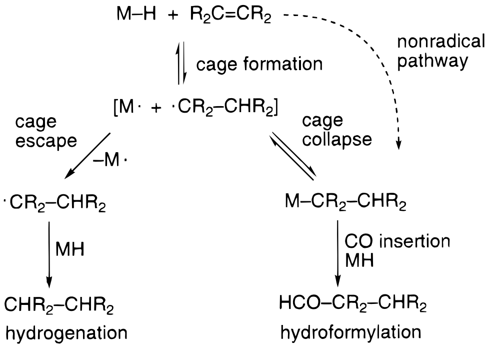


Figure 5. The mechanism for hydrogenation and hydroformylation of olefins by $MnH(CO)_5$ and related complexes.

The complete miscibility between H_2 and SCFs such as CO_2[108] is particularly beneficial for hydrogenation reactions. The rates of many but not all hydrogenation reactions in liquids are proportional to hydrogen concentration and are sometimes limited by the rate of diffusion of H_2 from the gas to the liquid phase.[109] Both problems are solved by the use of SCFs as hydrogenation media. However, one must note that the insertion of CO_2 into the metal−hydride bond of catalytic species to produce formate complexes[59,60] could potentially inhibit hydrogenation reactions in $scCO_2$, depending on the ability of the formate complexes to revert back to hydride and CO_2.[105] This is more likely to inhibit hydrogenation by hydridic rather than acidic complexes.

To our knowledge, the first report of homogeneous hydrogenation of organic substrates in a SCF was a patent describing the hydrogenation of coal extracts in scH_2O.[110] The liquid hydrocarbons were extracted from the coal into the scH_2O, which also contained added H_2 and dissolved catalysts such as NaOH, Na_4SiO_4, or KBO_2. The reaction was performed above the T_c and P_c of scH_2O, and the catalysts were recovered by precipitation induced by a pressure reduction. Compared to the earlier Bergius process,[111] which used liquid oils as the solvent, the use of scH_2O prevented the caking together of the coal, facilitated the separation of the hydrocarbon products from the solvent, and rendered the coal residue more porous. The yield of liquid hydrocarbons was up to 50 wt %.

The first example in $scCO_2$ was the hydrogenation of a cyclopropene by $MnH(CO)_5$ via a radical mechanism (Figure 5).[112] This reaction can be performed either catalytically (in the presence of H_2 and CO) or stoichiometrically (in the absence of H_2 and CO).[113] With the Mn complex or $CoH(CO)_4$, olefins are either hydrogenated or hydroformylated, depending on the olefin. Activated olefins typically are hydroformylated, although for some, such as 3,3-dimethyl-1,2-diphenylcyclopropene, both hydrogenation and hydroformylation products are observed (Scheme 2). In these cases the selectivity for hydrogenation over hydroformylation has been used as a measure of the strength of the solvent cage, with stronger cages favoring hydroformylation. For example, the reaction

Scheme 2

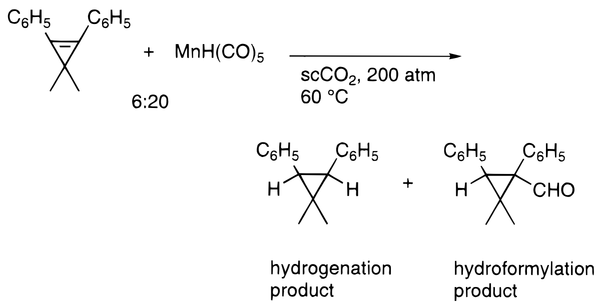


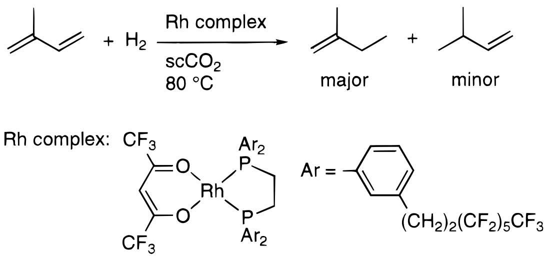
Table 2. Reactions of $MnH(CO)_5$ with 3,3-Dimethyl-1,2-diphenylcyclopropene

solvent	gas, (atm)	[M]/[olefin], mM	T, °C	t, h	product yield, % al-kane	product yield, % alde-hyde	ref
micelle	CO	8/2	50	15	8	92	114
pentane	Ar or CO	89/87	60	2−4	63	37	113
hexane	CO	3200/1100	55	5	66	34	115
none	CO_2 (5)	20/6	60	4	66	34	112
$scCO_2$	CO_2 (200)	20/6	60	3.5	66	34	112

in a micellar solution (0.4 M sodium dodecyl sulfate in water), where sequestering should be strong, gave only 7% hydrogenation, the remainder being hydroformylation (Table 2).[114] The reaction in pentane or hexane gave 63−66% hydrogenation. The observed selectivity in $scCO_2$ was 66−70%,[112] close to the selectivity observed in alkanes, and suggesting a solvent cage strength comparable to that of liquid alkanes. Alternatively, the aldehydes may be formed by nonradical pathways which are independent of solvent viscosity.

The ponytail complex Rh(hfacac)($R_2PCH_2CH_2PR_2$) (where R = C_6H_4-*m*-$(CH_2)_2(CF_2)_5CF_3$) was shown by the Leitner group to be an active catalyst for the hydrogenation of isoprene (Scheme 3). The reaction in $scCO_2$ was considerably slower than the hydrogenation by the analogous dppp (1,3-bis(diphenylphosphino)propane) complex in organic solvents.[116] Reasons for the decreased rate were not identified, but the present authors suggest that they could include CO_2 insertion into Rh−H bonds, insufficient solubility of the catalyst, or dilution effects. Also, the decomposition of Rh hydrogenation catalysts under similar conditions has been reported previously.[59]

Scheme 3



Heterogeneously catalyzed hydrogenations have also been tested,[117−122] but this topic is more appropriately covered in another contribution to this issue.[123] Use of heterogeneous catalysts in a continuous-flow reaction system allows for the hydrogenation of large volumes of material with only a relatively small vessel,[120] a potentially very useful feature for a scaled-up process.

On the basis of the amount of work that has been published, as summarized in this section and the following two sections, it is clear that hydrogenation reactions are the most important class of homogeneously catalyzed reactions being studied in SCFs. It may be only a matter of a year or two before studies of a wide range of hydrogenation catalysts in $scCO_2$ are reported; it is clear that several groups are working in this direction.

C. Asymmetric Hydrogenation

The enantioselectivity of asymmetric hydrogenation of a prochiral olefin often depends strongly on the hydrogen concentration. Using higher hydrogen concentrations can lead to higher, lower, or even reversed enantioselectivity, depending on the reaction system.[1] The possibility that the miscibility of H_2 in SCFs might lead to better enantioselectivity occurred independently to two groups of researchers.

A team put together by Burk and Tumas[90] studied the asymmetric hydrogenation of several α-enamides in $scCO_2$ using a cationic Rh complex containing the Et-DuPHOS ligand (Scheme 4). The reaction proceeds homogeneously under the reaction conditions tested (40 °C, H_2 partial pressure 14 atm, total pressure 340 atm). The enantiomeric excesses (ee's) were fair to excellent and generally comparable to those obtained in conventional solvents, although in the case of a valine derivative, the ee was superior to that obtained in either methanol or hexane (Table 3). The same high ee could not be obtained by running the reaction in hexane, even by increasing the H_2 pressure or by adding a high pressure of an

Scheme 4

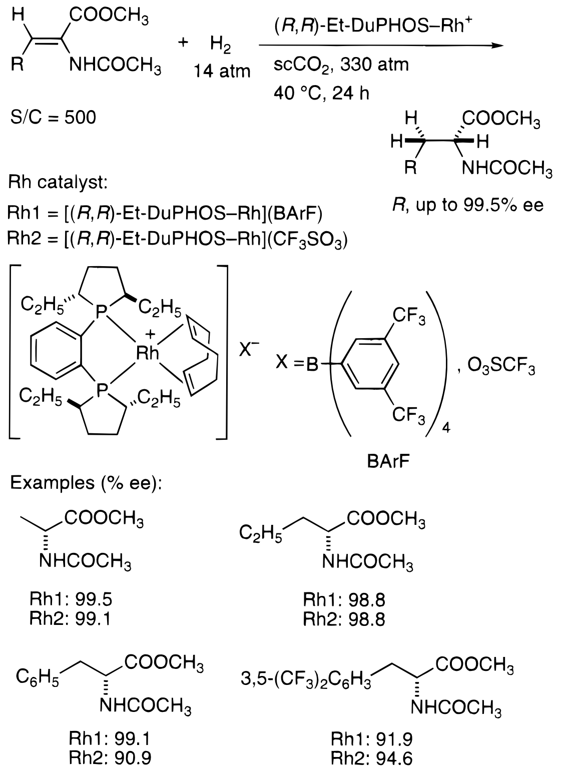
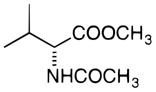
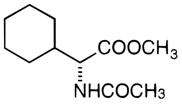


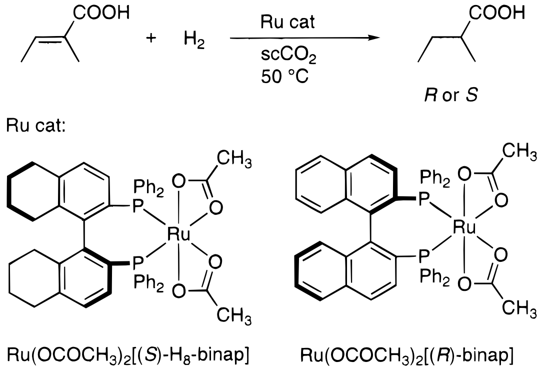
Table 3. Product Ee's for the Hydrogenation of *β*,*β*-Disubstituted α-Enamides Catalyzed by [Rh((*R*,*R*)-Et-Duphos)(cod)][B(C_6H_3-3,5-$(CF_3)_2)_4$] in $scCO_2$ and Other Media[90]

product	% ee		
	$scCO_2$	CH_3OH	hexane
	96.8	81.8	76.2
	84.7	62.6	69.5

inert gas, N_2. Note that the H_2 pressure used in the liquid solvents was lower than that used in the SCFs. Although the H_2 partial pressure effect on the enantioselectivity of asymmetric hydrogenation in $scCO_2$ is not fully understood, it is clear that the use of $scCO_2$ rather than a liquid solvent can greatly increase the selectivity for some substrates.

Noyori et al. found that $Ru(OCOCH_3)_2(H_8\text{-binap})$ is active as a catalyst in $scCO_2$ for the hydrogenation of α,*β*-unsaturated carboxylic acids such as tiglic acid (Scheme 5).[124] The ee of the product prepared in $scCO_2$ (81%) was comparable to that in methanol (82%) and greater than that in hexane (73%), all at 50 °C and 30 atm H_2. Lowering the H_2 partial pressure increased the ee in methanol[125] but not in $scCO_2$ (Table 4). Addition of the fluorinated alcohol $CF_3(CF_2)_6CH_2OH$ to the reaction in $scCO_2$ increased both the conversion (to 99%) and the enantioselectivity (to 89%). The alcohol may have served to increase the solubility of the catalyst or it may have allowed a change in the mechanism.

Scheme 5

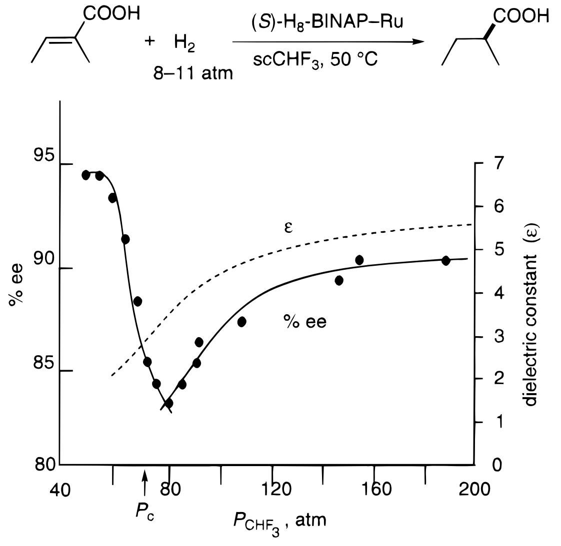


There is preliminary data to show that the hydrogenation of tiglic acid by $Ru(OCOCH_3)_2(H_8\text{-binap})$ in $scCHF_3$ is dependent not only on the H_2 partial pressure but also on the pressure of the inert SCF itself. The ee of the product is higher at 188 atm CHF_3 than it is at 82 atm (H_2 partial pressure constant at 12 atm).[126] As shown in Figure 6, this change in the selectivity correlates well with the change in the dielectric constant of the solvent as observed in conventional liquid solvents.[127] The notable pressure effect in the hydrogenation in CH_3OH on the enantioselectivity[128] indicates the coexistence of a highly stereoselective monohydride mechanism and a less selective polyhydride mechanism. The increase in enantioselectivity with the increase of polarity of the SCF phase is ascribable to the enhanced contribution of the monohydride mechanism that requires heterolytic cleavage of H_2. At high pressures, the dielectric constant is approximately 6 at 50 °C while closer to the critical pressure the dielectric constant is around 3. The critical point for this reaction mixture has not yet been located, so it is difficult to evaluate the contribution of "near-critical" phenomena to this pressure effect. Visual inspection of the reaction mixture demonstrated that tiglic acid and the product were dissolved in the SCF phase at pressures above 68 atm, but it was not possible to determine the extent of catalyst dissolution. Below that pressure, a liquid phase formed and the ee values of the product increase to 93%.

Table 4. Asymmetric Hydrogenation of Tiglic Acid by Chiral Ru(II) Complexes in $scCO_2$ and Other Media[124,a]

catalyst	medium	H_2 atm	product	
			yield %	% ee (confign)
(*S*)-H_8-BINAP−Ru	$scCO_2$	33	99	81 (*S*)
(*S*)-H_8-BINAP−Ru	$scCO_2$	7	23	71 (*S*)
(*S*)-H_8-BINAP−Ru	$scCO_2/R_FOH$	5	99	89 (*S*)
(*S*)-H_8-BINAP−Ru	CH_3OH	30	100	82 (*S*)
(*S*)-H_8-BINAP−Ru	hexane	30	100	73 (*S*)
(*R*)-BINAP−Ru	$scCO_2$	33	50	37 (*R*)

[a] Conditions: cat 4.4−4.7 μmol, S/C = 150−160, CO_2 170−180 atm, 50 °C, time 12−15, R_FOH = $CF_3(CF_2)_6CH_2OH$, 1.5 mmol, CH_3OH, 7.4 mmol.



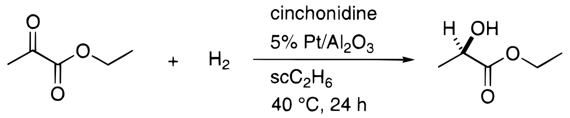
Conditions: 4.5 μmol $Ru(OCOCH_3)_2[(S)\text{-}H_8\text{-binap}]$, olefin/catalyst = 150–160, 8–11 atm H_2, at 50 °C, in 50-mL reactor.

Figure 6. Asymmetric hydrogenation of tiglic acid in $scCHF_3$.[124] The equation used to generate this plot underestimates the dielectric constant under some conditions.[36b]

It is instructive to compare the approaches taken by the two teams to ensure the solubility of the catalysts in $scCO_2$. The Burk and Tumas team used a diphosphine with alkyl rather than aryl substituents, and carefully selected counterions, either $CF_3SO_3^-$ or $BArF^-$, which would impart greater solubility upon the catalyst.[90] These features rendered the catalyst fairly soluble in $scCO_2$ despite the fact that the complex was cationic. The Noyori team used a neutral complex and a partially hydrogenated derivative of the BINAP ligand to maximize the solubility of the catalyst.[124] Indeed, the analogous BINAP-containing catalyst was far less effective, probably because of insufficient solubility.

For comparison, it is worth pointing out that the enantioselectivity of heterogeneously catalyzed reactions are also dependent on H_2 concentration. The enantioselectivity of the hydrogenation of ethyl pyruvate using cinchonidine-modified Pt on alumina in scC_2H_6 was equal to that in toluene and greater than that in ethanol (Scheme 6).[118] The observed ee increased with increasing H_2 partial pressure up to 60 atm (74% ee), beyond which no further increase in the ee value was observed. In $scCO_2$, however, the reaction was slower because of the reduction of the $scCO_2$ to CO on the surface of the catalyst.[129]

Scheme 6



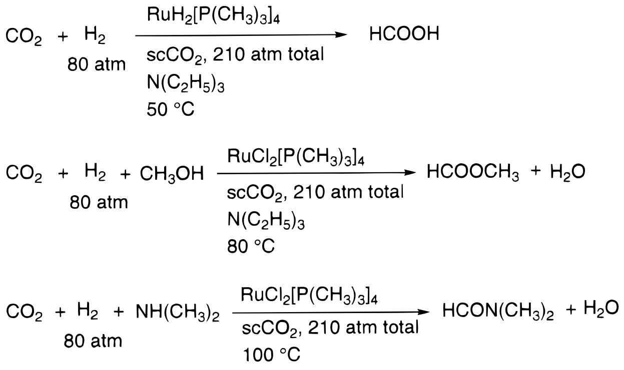
Future work in this field should investigate those substrates for which high H_2 partial pressure or concentration gives greater enantioselectivity in liquid solvents.[1] Can this lead to even greater selectivity in $scCO_2$, given the miscibility of H_2 in $scCO_2$? Also, the reasons for the unusually high enantioselectivity in some of the Burk–Tumas systems need to be identified.

D. Hydrogenation of CO_2

Carbon dioxide hydrogenation using H_2 from solar or hydrothermally powered electrolysis would result in a future promising synthetic method for the production of common chemicals such as HCO_2H, CH_3OH, and hydrocarbons because CO_2 is the cheapest and most abundant C_1 resource. The products of CO_2 hydrogenation depend on the conditions and catalyst.[53] High-temperature hydrogenation conditions, usually along with heterogeneous catalysis, produce CO, CH_3OH, or CH_4. Mild conditions usually give formic acid or closely related products such as alkyl formates or formamides. Performing this reaction in $scCO_2$ allows one to take advantage of the miscibility of H_2 in $scCO_2$. The team led by Noyori[59,60,130,131] showed that dissolving $N(C_2H_5)_3$, 0.0006 equiv of $RuH_2[P(CH_3)_3]_4$, and 85 atm of H_2 in 50 mL of $scCO_2$ (total pressure 210 atm) leads to rapid production of formic acid, as the 2:1 adduct with the amine, at a turnover frequency (TOF, mole product per mole of catalyst per hour) of 680 h^{-1} at 50 °C (Scheme 7). A comparison of different catalyst precursors showed that $RuH_2[P(C_6H_5)_3]_4$ is less active than $RuH_2[P(CH_3)_3]_4$, that $RuCl_2[P(CH_3)_3]_4$ has an induction period but is very active thereafter, and that Rh complexes decompose under these conditions.

The rate of the reaction in $scCO_2$ is also highly dependent on the temperature, the pressure, and the reagent concentrations. The dependence of rate on reagent concentration seems to be more a function of phase behavior than a function of the stoichiometry of the rate-determining step. Although the reaction system is homogeneous at the start, the product precipitates as the reaction proceeds. Adding 0.02 equiv of water doubles the rate of the reaction to 1400 h^{-1} (Figure 7). Adding a small quantity of methanol into the supercritical solution is even more effective at accelerating the reaction (over 4000 h^{-1}), but adding too much water or methanol causes the rate to drop dramatically. This result was attributed to the formation of a liquid water or methanol phase. The rate is also dependent on the amount of $N(C_2H_5)_3$ in the vessel; the rate increases with increasing amounts of $N(C_2H_5)_3$ up to a limit, beyond which the mixture is no longer homogeneous and the rate drops 60-fold. Surprisingly, addition of DMSO accelerates the reaction so much that the researchers were unable to determine whether the single-phase (dissolved DMSO) or the biphasic (liquid DMSO) conditions led to the higher rate.

Scheme 7



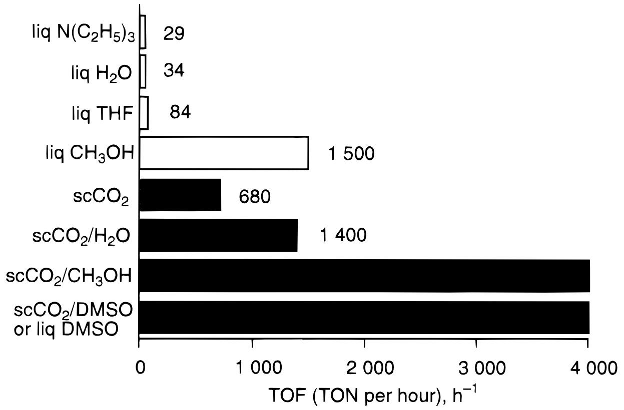


Figure 7. The initial rate of hydrogenation of $scCO_2$ in various media. The reactions in liquid DMSO, $scCO_2/CH_3OH$, and $scCO_2$/DMSO were all complete within 0.5 h, so the true initial TOF could not be determined but must be significantly greater than 4000 h^{-1}.[60] Conditions: 3 μmol $RuH_2[P(CH_3)_3]_4$, 5.0 mmol $N(C_2H_5)_3$, 0.1 mmol H_2O, 85 atm H_2, total pressure 210 atm, 50 °C, 0.5 or 1 h.

At higher temperatures the situation changes in many ways. $RuCl_2[P(CH_3)_3]_4$ becomes the preferred catalyst precursor, due to its greater stability. The use of methanol as an additive at 80 °C leads to the synthesis of methyl formate in addition to formic acid (Scheme 7),[60,132,133] and the use of biphasic conditions (liquid methanol) causes an increase, not a decrease, in the rate of hydrogenation of $scCO_2$.[60]

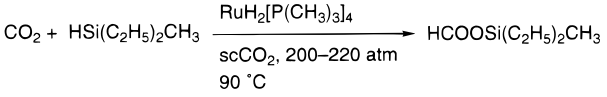
With primary or secondary amines as the base for $scCO_2$ hydrogenation at 100 °C, mono- or dialkylformamides can be synthesized in turnover numbers (TON, mole of product per mole of catalyst) up to 420 000, far higher than any previously reported (Scheme 7).[60,131,134,135] This system is complicated by the fact that the secondary or primary amine forms a liquid carbamate salt on contact with CO_2. Thus, two phases were in the vessel right from the start of each reaction, the $scCO_2$ phase and a liquid salt phase. Although it was not possible to determine if the catalyst remained in the $scCO_2$ phase throughout the reaction, the $RuCl_2[P(CH_3)_3]_4$ catalyst precursor was shown to be soluble in $scCO_2$ and not in the liquid carbamate. Several factors probably contributed to the high activity, including the favorable electronic properties of the catalyst and the ability of the SCF to dissolve both H_2 and the product DMF.

Subsequent studies by the group of Baiker[136] demonstrated that a heterogenized analogue of $RuCl_2[P(CH_3)_3]_4$ supported by a sol–gel-derived silica matrix was also very active for the synthesis of DMF, giving a TON of up to 110 800. The catalyst was prepared by the co-condensation of $RuCl_2[P(CH_3)_2(CH_2)_2Si(OC_2H_5)_3]_3$ with $Si(OC_2H_5)_4$. Supported Ir, Pd, Pt, and Rh catalysts were not as effective; the Rh complex was reduced to metal as had been observed in the homogeneous studies by Noyori.[60] The complex $RuCl_2(dppe)_2$ (dppe = 1,2-bis(diphenylphosphino)ethane) was an even better catalyst, showing higher rates of reaction (up to 740 000 TON in only 2 h).[137] The researchers also showed that lower but still reasonable rates of DMF formation could be obtained at subcritical pressures with $RuCl_2(dppe)_2$. This catalyst was insoluble in $scCO_2$. The length of the carbon backbone in the diphosphine ligand affected the catalytic activity, with catalysts containing dppm (bis(diphenylphosphino)methane) and especially dppp being inferior to the catalyst containing dppe. These results confirmed that the properties of the ligands have very strong effects on catalytic activity.

E. Hydrosilylation of CO_2

Although the hydrosilylation of olefins or ketones in a SCF has yet to be reported, the hydrosilylation of CO_2 has been observed. The complex $RuH_2[P(CH_3)_3]_4$ catalyzes the formation of silyl formate esters in $scCO_2$ (Scheme 8).[105,138] The TON was 62, higher than the literature results with related complexes in liquid solvents[139] but lower than those with anionic catalysts.[140] It is possible but not probable that the rate of the reaction was enhanced by the high concentration of CO_2 in the reaction phase relative to the concentration one would find in a liquid organic solvent. If the oxidative addition of the Si–H bond to the Ru center is the rate-limiting step, then the rate should be independent of CO_2 concentration. No rate measurements were made to test this.

Scheme 8



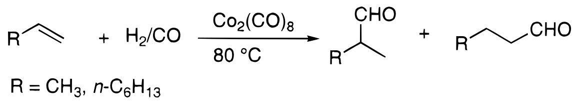
$$CO_2 + HSi(C_2H_5)_2CH_3 \xrightarrow[\text{scCO}_2\text{, 200–220 atm, 90 °C}]{RuH_2[P(CH_3)_3]_4} HCOOSi(C_2H_5)_2CH_3$$

F. Hydroformylation and Related Reactions

Hydroformylation of olefins is one of the most important industrial homogeneously catalyzed reactions. The catalytic cycle proposed by Heck and Breslow[141] consists of a number of elementary steps such as a dissociation of CO from $CoH(CO)_4$ to form the catalyst $CoH(CO)_3$, olefin insertion into the Co–H bond, migratory insertion of CO into the Co–alkyl bond, and aldehyde elimination with H_2, and regeneration of $CoH(CO)_3$ species. If the use of a SCF is to accelerate the reaction, it must influence the rate-limiting step. Depending on the catalyst and other factors, the rate-limiting step can be the reaction with H_2;[142] thus a rate increase could be observed for some hydroformylation systems in SCFs.

In 1991, Rathke and co-workers[143] described the first example of homogeneous hydroformylation in $scCO_2$ (Scheme 9). The reaction of propene with a Co catalyst, $Co_2(CO)_8$, at 80 °C at $P_{H_2} = P_{CO} = 56$ atm occurs at a slightly lower rate in $scCO_2$ ($d = 0.5$ g mL^{-1}) than in hydrocarbon solvents such as methylcyclohexane and heptane. The selectivity for the desired linear aldehyde, butanal, 88%, is higher than the value, 83% measured in benzene at slightly higher pressures ($P_{H_2} = P_{CO} = 80$ atm). The linear-to-branch ratio is slightly influenced by the pressure and temperature.[144] When the temperature is constant at 88 °C, the linear product selectivity increases from 73 to 81% as the pressure doubles (Table 5). One possible explanation for the change in the selectivity is a steric effect of a CO_2 molecule coordinated to the central metal as observed in the $CoH(CO)_3[P(C_4H_9)_3]$ or $Rh–P(C_6H_5)_3$ catalyst systems.[142] The effect of the temperature on the selectivity is similar to that in organic solvents. A detailed kinetic study of this reaction conducted at 108.9 and 163.3 atm indicated that the activation energy obtained in $scCO_2$ is 23 ± 1.4 kcal mol^{-1}, which is comparable to or somewhat

Scheme 9



olefin	medium	H_2, atm	CO, atm	d[aldehyde]/dt, M s^{-1}
propene	$scCO_2$, 165 atm	56	56	0.77×10^{-5}
1-octene	c-$C_6H_{11}CH_3$	48	48	1.2×10^{-5}

Table 5. Dependence of Selectivity on Temperature and CO_2 Pressure in Propene Hydroformylation Catalyzed by $Co_2(CO)_8$ in $scCO_2$[144]

P_{CO_2}, atm	T, °C	linear %	P_{CO_2}, atm	T, °C	linear %
163	78	81	92	88	73
163	88	80	112	88	75
163	98	76	143	88	81
163	108	73	184	88	81

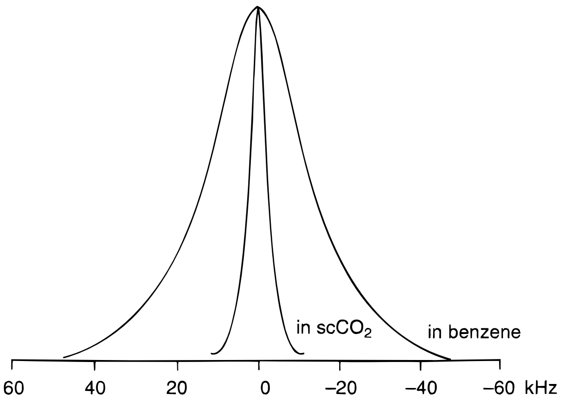
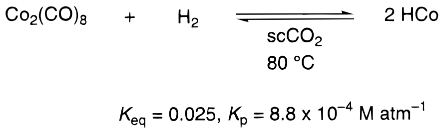


Figure 8. ^{59}Co NMR spectra of $Co_2(CO)_8$ 0.04 M, comparing widths at half-height for $scCO_2$ at 32 °C and benzene solution at 25 °C. Line width: $scCO_2$ 5.1 kHz, benzene 30 kHz.[143]

lower than those measured in organic solvents, 27−35 kcal mol^{-1}.

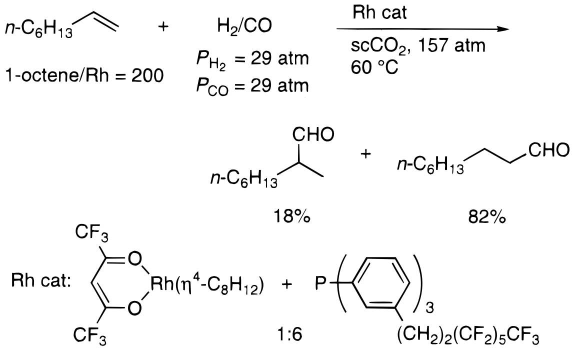
The major advantages of using SCFs are the elimination of gas-to-liquid mass-transfer problems and the order-of-magnitude lower viscosity of $scCO_2$ compared to typical liquids. The low viscosity has a beneficial line-narrowing effect on quadrupolar nuclei in NMR analysis. Figure 8 contrasts the narrow line widths of the ^{59}Co NMR spectra obtained in $scCO_2$ ($d = 0.5$ g mL^{-1}) at 32 °C with the broad spectrum measured in C_6D_6 at 25 °C. This narrowing effect allowed the detection of $Co_2(CO)_8$, $HCo(CO)_4$, and even the intermediate acyl complex $RCOCo(CO)_4$ in $scCO_2$.[143,145,146] High-pressure NMR studies of the reaction revealed that equilibration between $Co_2(CO)_8 + H_2$ and $HCo(CO)_4$ in $scCO_2$ occurs reproducibly (Scheme 10). The equilibrium constants, $K_{eq} = 0.025$, $K_p = 8.8 \times 10^{-4}$ M atm^{-1}, obtained in $scCO_2$ at 80 °C are in close agreement with those ($K_{eq} = 0.124$, $K_p = 7.7 \times 10^{-4}$ M atm^{-1}) obtained by using Penninger's experimental results[147] and H_2 solubility data[148] in heptane, and the rate constants of forward and reverse reactions for hydrogenation of $Co_2(CO)_8$ are also comparable to those measured in typical hydroformylation solvents. These are not surprising results because the rate of $CoH(CO)_4$ formation is independent of CO pressure above 25 atm in liquids[148] and the rate-limiting step for the hydroformylation in liquids is the reaction of olefin and $CoH(CO)_4$ or the reaction of acyl complex to liberate the product aldehyde.[147] The high miscibility of CO in SCF is therefore not necessarily a major factor determining the rate of the hydroformylation. Surprisingly, the rate of hydrogen atom transfer between $CoH(CO)_4$ and $Co_2(CO)_8$ is many orders of magnitude higher than the transfer rate of the same hydride moiety to olefin in hydroformylation.[143,145,146] This is evidence for the intermediacy of $Co(CO)_4$ radicals in the hydrogen atom transfer reaction and possibly also in the hydroformylation itself.[146]

Scheme 10



Recently Leitner found that a CO_2-soluble Rh complex with a polyfluoroalkyl-substituted triarylphosphine ligand (Rh/phosphine 1:6) in $scCO_2$ also effected hydroformylation of 1-octene to give a linear aldehyde in a good yield and with 82% selectivity (Scheme 11). The reaction proceeds smoothly in the homogeneous supercritical phase without any side reactions such as hydrogenation or isomerization of the olefin. The introduction of fluorinated side chains on the aromatic rings of the phosphine ligands results in an increase of the solubilities of the complexes in $scCO_2$, quantified by UV/vis spectroscopy of the Rh hexafluoroacetylacetonate complexes with these ligands (Figure 9).[83] Under supercritical conditions at 45 °C and 91 atm ($d = 0.55$ g mL^{-1}) complexes A and B give bright yellow solutions with saturation concentration of 6.3×10^{-5} and 7.5×10^{-5} mol L^{-1}, respectively. These values are 5−7 times higher than that of complex C without any polyfluorinated phosphine ligand. Increasing the density of CO_2 enhances the solubility of complex A to a concentration of 4.4 $\times 10^{-3}$ mol L^{-1} at $d = 0.75$ g mL^{-1}.

Scheme 11



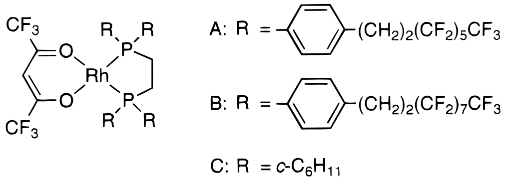


Figure 9. $scCO_2$ soluble Rh phosphine complexes.[83]

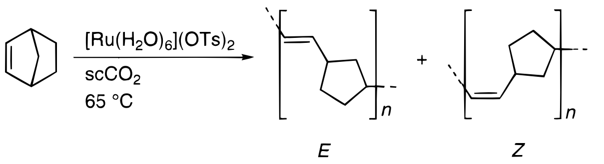
Photochemical carbonylation of the C−H bonds of liquid propane was achieved by Sakakura et al.[149] with the use of $RhCl(CO)(PMe_3)_2$ catalyst and 3 atm of CO at 15 °C. Excellent selectivity for linear butanal (97% selectivity, 20 TON after 48 h) was obtained with only traces of 2-methylpropanal and acetaldehyde being observed. The carbonylation of benzene in $scCO_2$ was also mentioned, with the details of that reaction to be reported separately.

G. Olefin Metathesis

Olefin metathesis has been a very important subject of research from both academic and industrial points of view.[150] Of particular interest has been the development of the mutual alkylidene exchange reaction of alkenes and the ring-opening metathesis polymerization (ROMP) of cyclic olefins in synthetic organic chemistry.[151,152] Recent results demonstrate that supercritical fluids can be useful reaction media for the metathesis of olefins.

DeSimone found that $[Ru(H_2O)_6](OTs)_2$ (Ts = *p*-toluenesulfonyl) catalyzed the ROMP of norbornene at 65 °C in $scCO_2$ (67–296 atm). The product, an off-white spongy-textured polymer, was isolated by just venting the CO_2 (Scheme 12).[153] CO_2 does not participate in the reaction. The chemical yield and molecular weight of the polymers are comparable to those in conventional solvents. Norbornene is quite soluble in CO_2 under the reaction conditions, although the Ru catalyst is not completely soluble. The change in the color of the reaction mixture, from clear colorless at the beginning to orange during the reaction, strongly indicates that the catalyst is sufficiently soluble for the completion of the reaction. In the presence of added methanol cosolvent, the catalyst dissolved. The polymers obtained in $scCO_2$ have a very high cis olefin content, 83%, but doping with methanol in $scCO_2$ results in a decrease in the cis content to 30%. This result indicates that the microstructure of the polymer is controllable by adjusting the polarity of the CO_2 medium with methanol.

Scheme 12



The isolable metal–carbene complexes shown in Figure 10[151,152] are also highly effective for the ROMP of norbornene.[154] The activities of these catalysts in $scCO_2$ are considerably higher than that of $[Ru(H_2O)_6](OTs)_2$ in the same medium.[153] Although the Ru carbene complex in Figure 10 retains catalytic activity even under aqueous emulsion conditions,[155] $scCO_2$ is another environmentally responsible solvent besides H_2O and offers the possibility of developing new polymer syntheses without solvent waste.

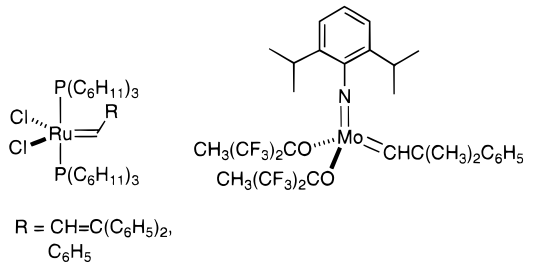
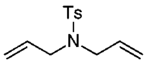
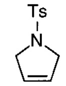
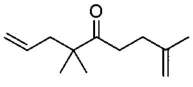
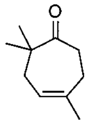
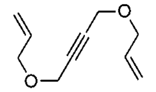
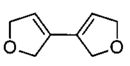
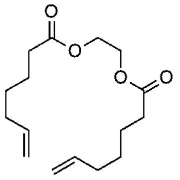
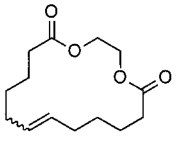
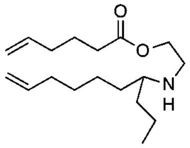
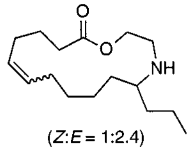


Figure 10. Isolable metal–carbene complexes for olefin metathesis in $scCO_2$.[151,152]

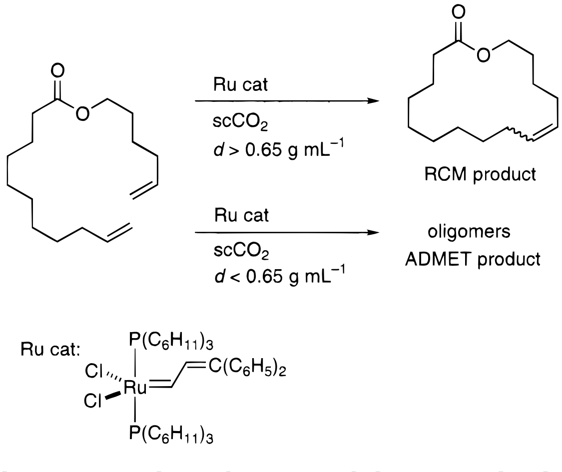
Table 6. Ring-Closing Metathesis of Dienes in $scCO_2$[154]

substrate	cat	CO_2 d, g mL^{-1}	product	yield %
	Ru	0.76		93
	Mo[a]	0.76		62
	Ru	0.76		62
	Ru	0.62		67
	Ru[b]	0.76	 (Z:E = 1:2.4)	74

Conditions: Ru and Mo cat refer to the Ru (R = $CH{=}C(C_6H_5)_2$) and the Mo complexes shown in Figure 10, catalyst 1 mol %, 40 °C, 72 h.
[a] cat 5 mol %, [b] 170 h.

Fürstner and Leitner found that these same carbene complexes effected ring-closing metathesis (RCM) of dienes to cyclic olefins.[116,154] Table 6 lists some examples of RCM in $scCO_2$. Even dienes with functionalized groups can be converted, leading to carbo- and heterocyclic compounds in good yields. The reaction of a diene bearing an N–H group (Table 6) produces an azamaclolide smoothly without the need for protection; possibly because it reversibly reacts with CO_2, giving it in situ protection. In conventional solvents, it can be cyclized only in protonated or otherwise protected form. The density of the $scCO_2$ significantly affects the reaction pathway. As shown in Scheme 13, an acyclic diene leads to 16-membered cyclic compounds with RCM, while its acyclic diene metathesis (ADMET) gives polymer or oligomer. At densities of CO_2, $d > 0.65$ g mL^{-1}, the cyclic compound is produced in an excellent yield, while mainly oligomers are obtainable at lower densities. The density effect on the reaction pathway is not fully understood but may be caused by the compressibility of the supercritical phase. Fürstner et al. speculated that increasing the density at constant volume leads to a high dilution reaction condition, favoring the intramolecular reaction pathway. The present re-

Scheme 13

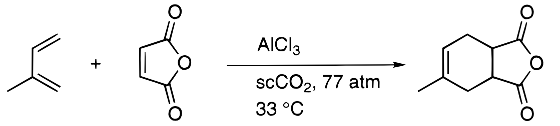


viewers suggest that clustering at the lower densities may have created a local concentration of diene higher than the bulk concentration, favoring the intermolecular pathway.

H. Cyclization and Other C–C Bond Forming Reactions

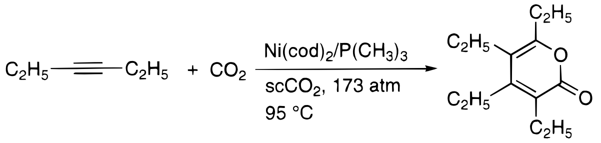
Diels–Alder reactions have been extensively investigated in SCFs.[23] At least one of the studies involved Lewis acid catalysis.[156] In situ monitoring by FTIR of an $AlCl_3$-catalyzed Diels–Alder reaction in $scCO_2$ (Scheme 14) suggested the presence of an unidentified intermediate, consistent with a nonconcerted, two-step mechanism, but further studies were needed before definitive conclusions could be reached. The controversy between the concerted and stepwise mechanisms has been a facet of liquid-phase Diels–Alder chemistry for the past decade.[157–160] There was also weak evidence in the $scCO_2$-phase study for a small increase in rate at higher CO_2 pressures.

Scheme 14



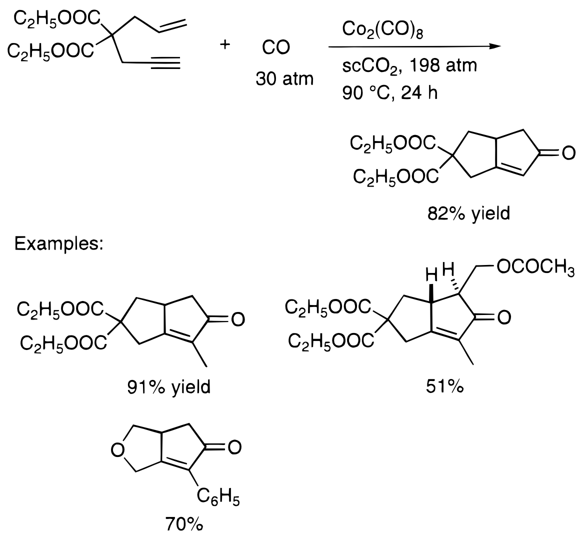
After some initial phase behavior problems,[61] a study of the coupling of alkynes with CO_2 has shown that the synthesis of 2-pyrones can be catalyzed by $Ni(cod)_2/P(CH_3)_3$ in $scCO_2$ (Scheme 15).[61] The selectivity was over 90% and a TON of almost 3 was obtained within 50 h at 40 °C. This selectivity, but not the rate, was greater than that obtainable in a THF/acetonitrile solution. The rate in $scCO_2$ could be improved by increasing the temperature; at 95 °C, a TON of 9 was obtained after about 9 h. In comparison, the catalyst $Ni(cod)_2$/dppb (dppb = 1,4-bis(diphenylphosphino)butane) had inferior activity probably because of poor solubility in $scCO_2$. FTIR measurements[79] showed that some catalyst deactivation was occurring by the formation of nickel carbonyl complexes. The source of the CO was believed to be nickel-catalyzed reduction of the CO_2 by $P(CH_3)_3$. This is certainly an undesired result which could have serious consequences for processes involving trialkylphosphines in $scCO_2$.

Scheme 15



The Pauson–Khand reaction, a catalytic cocyclization of alkynes with alkenes and carbon monoxide, proceeds smoothly in $scCO_2$ to give cyclopentenones.[161] As shown in Scheme 16, the ene-ynes react with carbon monoxide in the presence of 2–5 mol % of $Co_2(CO)_8$ as the catalyst, yielding the products in moderate to good yields. Temperatures of 90–100 °C, well beyond T_c, and CO pressures of 15–30 atm are required. The high CO pressure prevented the deactivation of the catalyst and subsequent precipitation of an unidentified white solid. This observation is rather surprising, considering that a study of these reactions in liquids had stated that high pressures of CO decreased the yield.[162] Allylpropargylamines with tosyl and cbz protecting groups, which work well in conventional solvents, are inert under these conditions probably because of poor solubility. The solubilities of the ene-ynes in $scCO_2$ and phase behavior during the reaction were not reported.

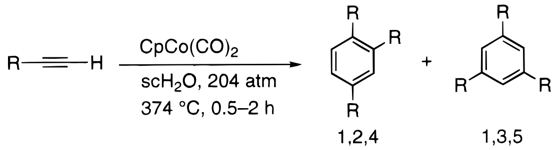
Scheme 16



Conditions: 3–5 mol % $Co_2(CO)_8$, substrate/catalyst = 20–40, 24–48 h, 90–94 °C, CO_2 pressure, 110–120 atm at 36–39 °C

Cyclotrimerization of alkynes to substituted benzene derivatives is homogeneously promoted by $CpCo(CO)_2$ in scH_2O (Scheme 17).[163] Thermal decomposition of the complex is not a problem even at the high temperature of scH_2O. Selectivity for the 1,2,4-isomer of the product is comparable to that found in organic solvents. In comparison, liquid H_2O at 140 °C was an inferior medium, causing significant side reactions.

Scheme 17

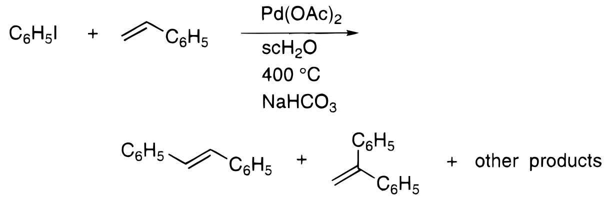


alkyne	yield, %	benzene isomer 1,2,4:1,3,5
n-C_4H_9—≡—H	>95	1:3
C_6H_5—≡—H	>95	1:6

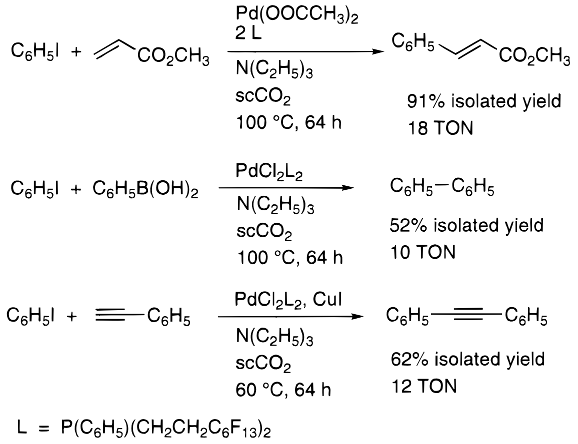
Very recent communications have described the use of $scCO_2$ and scH_2O as media for various coupling reactions. The Pd-catalyzed coupling reaction of iodobenzene with styrene (Scheme 18) proceeds in scH_2O, although in this case the yield of diphenylethenes, 23% and selectivity were lower than those at subcritical temperatures.[164]

Carroll and Holmes[87] prepared unusual polyfluoroalkylphosphine ligands to enhance the solubility of

Scheme 18



Scheme 19



Scheme 20

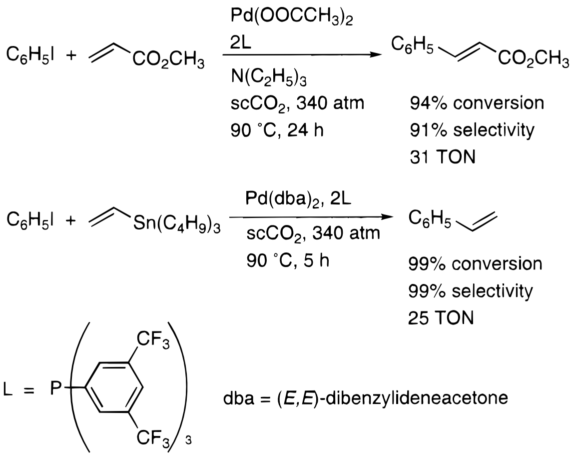


Table 7. The Initial Rate of Stille Coupling of Phenyl Iodide with Tributyl(vinyl)tin at 75 °C[86]

ligand	k, s^{-1}	
	CO_2 (306 atm)	toluene
$P(C_6H_5)_3$	2.7×10^{-4}	5.7×10^{-4}
$P[C_6H_3\text{-}3,5\text{-}(CF_3)_2]_3$	6.0×10^{-4}	9.5×10^{-4}

Pd(II) catalysts for coupling reactions of phenyl iodide (Scheme 19). While $PdCl_2[P(C_6H_5)_3]_2$ and $Pd(O_2CCH_3)_2[P(C_6H_5)_3]_2$ were insoluble in $scCO_2$, their analogues containing $P(C_6H_5)_{3-n}(CH_2CH_2C_6F_{13})_n$ (n = 1 or 2) ligands were at least somewhat soluble in $scCO_2$. This is a significant achievement because Pd catalysts are among the most important in the field of homogeneous catalysis, and unfortunately heretofore among the least soluble in $scCO_2$. Their Suzuki coupling of phenylboronic acid in $scCO_2$ at 100 °C gave a 52% yield of biphenyl after 64 h, while Suzuki's original reaction in liquid benzene at 80 °C gave a 32% yield after only 6 h.[165] The Sonogashira coupling of phenylacetylene in $scCO_2$ at 60 °C gave a 62% yield of diphenylacetylene after 64 h, compared to Sonogashira's original reaction in neat liquid diethylamine at room temperature which yielded 85% after only 6 h.[166] Thus for these two reactions there is as yet no evidence of improvements obtained by performing the reactions in $scCO_2$. However, the Heck coupling of electron-poor alkenes gave greater yields (but not greater TON) in $scCO_2$ than in liquid solvents.[167] For example, the reaction of methyl acrylate and phenyl iodide gave 91% conversion in $scCO_2$ (5 mol % catalyst, 18 TON)[87] but only 50% in acetonitrile (1 mol % catalyst, 50 TON)[168] at the same temperature. The cause of the improved yield has not been identified, but further investigation of this promising result is certainly warranted.

Tumas' group[86] also studied coupling reactions of phenyl iodide (Scheme 20). Their catalyst for the Heck reaction, however, used $P(C_6F_5)_3$ or $P(C_6H_3\text{-}3,5\text{-}(CF_3)_2)_3$ ligands for the same solubility reasons. They noticed that even with these ligands, the Heck reaction phases were "dark and opaque", preventing them from visually determining whether the solutions were homogeneous. The yield of the reaction in $scCO_2$ was similar to that obtained in toluene. It seems likely to these reviewers, on the basis of some experiments of our own, that the reaction might have been heterogeneous, with the reaction taking place in the liquid phase. Polar aprotic solvents are typically used for this reaction.[169] The same researchers found that the Stille coupling of tributyl(vinyl)tin was slower in $scCO_2$ than in toluene or hexane,[86] regardless of the phosphine used. When $P(C_6H_5)_3$ was used as the ligand, they observed precipitation, presumably of Pd complexes. This precipitation was avoided if the fluorinated phosphines were used. However, it was shown that greater initial rate of reaction observed when $P(C_6H_5)_3$ was replaced by $P(C_6H_3\text{-}3,5\text{-}(CF_3)_2)_3$ was due to electronic effects; the rate doubled in both toluene and in $scCO_2$ (Table 7).

In general, the few studies done so far suggest that most cyclization and coupling reactions are not faster and do not offer greater yields in $scCO_2$ than in liquid solvents, with the possible exception of the Heck reaction. This may not be surprising, because the coupling reactions as performed thus far do not benefit from any of the unique properties of SCFs. The potential advantage to using SCFs for these reactions may lie in the tunable dielectric constant[34] or local solute/solute clustering effects which have been beneficial in noncatalyzed reactions.[170,171] Such clustering causes an increase in the local concentration of one reactant around another, resulting in a rate acceleration. These aspects may be among the topics of future work.

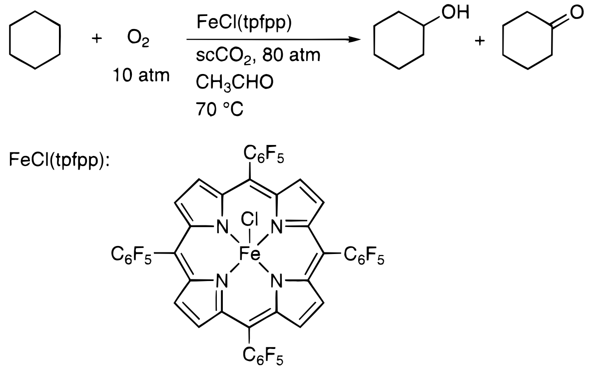
I. Oxidation

Despite the nonflammability of $scCO_2$, the miscibility of O_2 with SCFs, and the abundance of studies of heterogeneously catalyzed oxidations in SCFs, there have been surprisingly few homogeneously catalyzed oxidations in these media. The heterogeneously catalyzed oxidation reactions include the steel-catalyzed oxidation of cumene to cumyl hydroperoxide by O_2 in $scCO_2$ and scXe at 110 °C,[172] the CoOcatalyzed oxidation of toluene to benzaldehyde in $scCO_2$,[173] and many examples of the oxidative destruction of wastes in scH_2O.[174,175] Interest in homogeneously catalyzed supercritical phase oxidations has picked up greatly in the past two years.

Perhaps the first report of a homogeneously catalyzed oxidation in a SCF described the oxidative degradation of *p*-chlorophenol in scH_2O by O_2 catalyzed by Mn^{2+} and Cu^{2+} serendipitously leached from the steel vessel walls.[176]

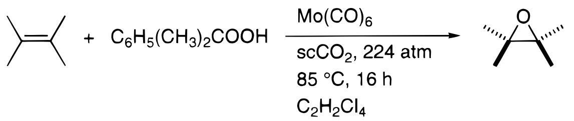
The functionalization of alkanes by oxidation has been of interest both in liquid solvents and in SCFs. The uncatalyzed oxidation of cyclohexane by O_2 in $scCO_2$ was reported in 1994;[177] after 5 h at 200 atm and 160 °C, 3% of the cyclohexane is oxidized, mostly to cyclohexanone. The same reaction, but catalyzed by FeCl(tpfpp) (TPFPP = 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin)[178] has recently been tested in $scCO_2$ by Koda (Scheme 21). It was hoped that the perfluorophenyl groups would increase the solubility of the catalyst in $scCO_2$, but the solubility was not measured. The reaction required the presence of stoichiometric quantities of a sacrificial aldehyde, which serves as a co-reductant for the O_2. Under the conditions, the acetaldehyde is first oxidized to peracetic acid and then acetic acid. At 70 °C and 10 atm O_2, the dependence of the rate on the CO_2 partial pressure was quite unusual; the reaction was fastest at 80 atm CO_2 (20% conversion after 1 h, based on aldehyde initial concentration), the lowest partial pressure at which the reaction mixture was visually mostly homogeneous. The present authors suggest that the catalyst is unlikely to have been dissolved in the $scCO_2$ under these conditions because the SCF density would have been only 0.18 g mL^{-1}.[25] At 50 °C, the CO_2 pressure effect was somewhat less pronounced, with a maximum at ~60 atm CO_2, lower than the pressure required for a visually homogeneous solution. The reasons for the pressure effect are not yet clear, but are probably closely related to the phase behavior of the system. The pressure did not affect the cyclohexanol/cyclohexanone product ratio, which remained relatively close to 1:1 at all pressures. The greatest yield obtained was 20% after 1 h at 70 °C, based on aldehyde initial concentration. In comparison, the reaction's discoverer, Murahashi, reported a yield of 85% after 24 h at the same temperature in liquid ethyl acetate.[179] Murahashi used Ru, Mn, or Co complexes of TPFPP, rather than the Fe complex, but found that there was little difference in effectiveness between the three catalysts. It seems that the rate of the reaction in $scCO_2$ is comparable to that in a liquid solvent. There is a remarkable difference in selectivity, however. In contrast to Koda's result, Murahashi obtained primarily cyclohexanone (80−92% selectivity) in the liquid-phase reaction.

Scheme 21



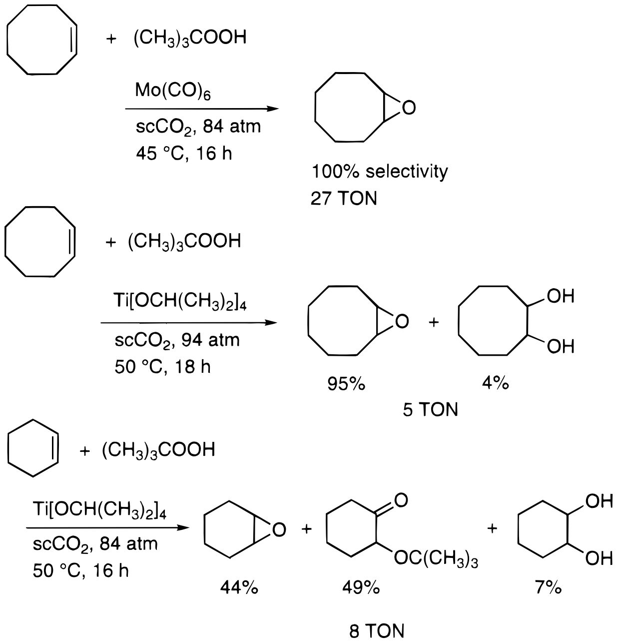
Epoxidations of alkenes by hydroperoxides in $scCO_2$ in the presence of $Mo(CO)_6$ have been tested independently by three groups. These reactions are more typically performed in benzene at reflux or neat olefin at 85 °C.[180,181] These reactions have attracted attention from SCF chemists because nonpolar solvents usually give higher yields[181] and because the solubility of $Mo(CO)_6$ in $scCO_2$ is known to be reasonable (Table 1).[72] Noyori's group performed the epoxidation of 2,3-dimethylbutene by cumene hydroperoxide in $scCO_2$ with 1,1,2,2-tetrachloroethane as a cosolvent (Scheme 22).[105,138] Although the cosolvent was not necessary for solubility reasons, it helped to maintain good mass balance in experiments with very small quantities of the volatile olefin. No cyclic carbonates were formed as byproducts in these epoxidation reactions, although such compounds have been prepared in the past by the oxidation of alkenes by O_2 in the presence of CO_2.[182,183]

Scheme 22



Walther's group[79] in Germany found that cyclooctene could be epoxidized by $(CH_3)_3COOH$ and $Mo(CO)_6$ with complete selectivity at the much lower temperature of 45 °C (Scheme 23). However, when $Ti[OCH(CH_3)_2]_4$ was used as the catalyst, conversion to the epoxide was accompanied by formation of small

Scheme 23



Scheme 24

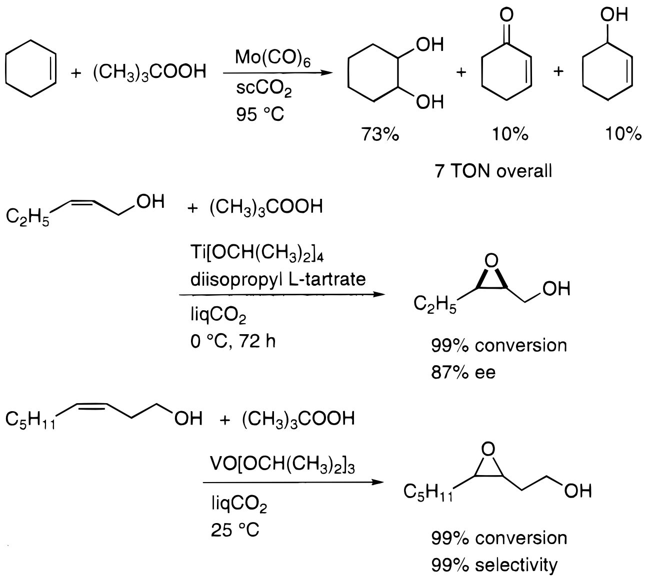


Table 8. The Rate of Epoxidation of (*Z*)-Non-3-en-1-ol by $(CH_3)_3COOH$ in Liquids CO_2 at 24 °C in the Presence of $VO[OCH(CH_3)_2]_2$[184]

solvent	k, M^{-1} s^{-1}
CH_2Cl_2	30
CH_3CN	18
$C_6H_5CH_3$	17
CO_2	9
CCl_4	5
n-C_6H_{14}	3

quantities of cyclooctane-1,2-diol. Using the Ti catalyst for the epoxidation of cyclohexene generated a roughly 1:1 mixture of the epoxide and a condensation product 2-*tert*-butoxycyclohexanone.

Tumas' group[184] tested the oxidation of cyclohexene by wet $(CH_3)_3COOH$ to primarily 1,2-cyclohexanediol (Scheme 24). The immediate product of the oxidation was presumably cyclohexene oxide, which then underwent hydrolysis. Byproducts also formed via allylic oxidation. Tests in $scCO_2$ and in hexane showed that greater rates of oxidation were obtained if aqueous hydroperoxide were used rather than the anhydrous analogue. The oxidation products in the absence of water were not identified, and the conversion was only 15%.

The same report from Tumas' group also described several epoxidations of homoallylic and allylic alcohols performed in liquid CO_2, such as the $VO[OCH(CH_3)_2]_2$-catalyzed oxidation of (*Z*)-non-3-en-1-ol (Scheme 24 and Table 8). While complete conversions and good selectivity were observed, the rate of reaction in liquid CO_2 compared unfavorably with all but the most nonpolar liquid solvents.

Asymmetric epoxidation of allylic alcohols is typically performed at low temperatures.[185] Thus liquid CO_2 is preferable to $scCO_2$. Early results by Tumas' group[184] found that at 0 °C, an ee of 87% could be obtained for the epoxidation of (*E*)-hex-2-en-1-ol by $(CH_3)_3COOH$ with $Ti[OCH(CH_3)_2]_4$ and diisopropyl L-tartrate (Scheme 24). Although the ee's typically obtained with allylic alcohols in liquid CH_2Cl_2 are higher,[185] an ee as high as 87% at such an early stage in the research suggests that liquid CO_2 is a promising solvent for low-temperature asymmetric catalysis. If the benefits of a SCF are needed at such a low temperature, then other SCFs with lower T_c's will have to be used.

IV. Phase-Transfer Catalysis

A few examples of phase-transfer catalysis between a supercritical phase and a second phase have been reported. In the case of the halide exchange reaction between benzyl chloride and solid KBr (Figure 11), the second phase was solid. Tetraheptylammonium bromide (THAB) was superior to 18-crown-6 as a phase-transfer catalyst because the crown ether/KBr adduct was virtually insoluble. The mole fraction solubility of the THAB salt in $scCO_2$ with 5% acetone cosolvent was 1.6×10^{-5} at 50 °C and 204 atm. The rate of the reaction was first order in THAB concentration, while in the absence of any catalyst, the reaction was very slow.[93] Stirring of the solid phase was required to avoid mass transfer limited rates.

Reactions involving a $scCO_2$ phase and an aqueous phase have met with mixed success. Tetraalkylammonium halide catalysts were used in a patented process for the carbonation of ethylene glycol in $scCO_2$ and the subsequent $scCO_2$/aqueous dual-phase hydrolysis.[186] The Tumas team reported a phase-transfer oxidation of cyclohexene to adipic acid with inorganic oxidants in the aqueous phase and RuO_4 as the phase-transfer catalyst (Figure 12).[187] The low TON observed (never more than 5) may have been due to complexation of the catalyst by bicarbonate, which was formed by the reaction between water and CO_2. Obviously, this is a problem that would not be encountered if a liquid or a different SCF were the nonpolar solvent. $NaIO_4$, Ce^{4+}, and peroxyacetic acid

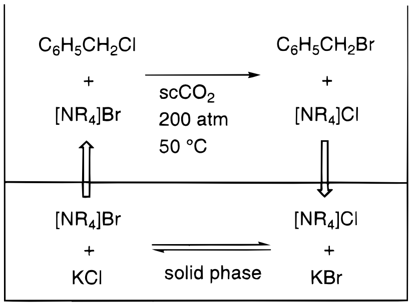


Figure 11. Phase-transfer reaction in $scCO_2$. Nucleophilic displacement of the chloride ion of a benzyl chloride with a bromide ion.[93]

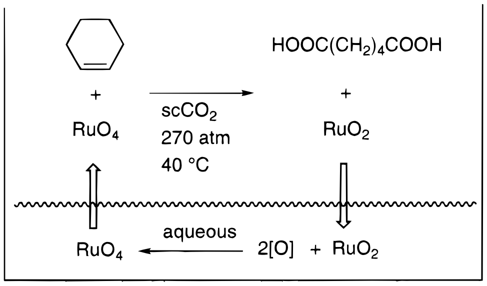


Figure 12. Phase-transfer oxidation of cyclohexene in an aqueous/$scCO_2$ medium.[187]

were suitable oxidants, but use of NaOCl resulted in the formation of 1,2-dichlorocyclohexane.

Future research in the field of scCO_2/aqueous phase-transfer catalysis must address the problem of acidity, unless we are to be restricted to only those reactions which can be operated under acidic conditions. There may be some remedy in the use of buffers, but these are likely to be overpowered at high CO_2 pressures. Alternative SCFs should be considered.

V. Conclusions and Future Directions

Why perform homogeneous catalysis in SCFs? The ideal catalytic reaction would have high rates of reaction because of the high solubility of the reactant gases in SCFs, high mass-transfer rates, and weak catalyst or substrate solvation. Obviously, the access to high performance must overcome the disadvantages frequently encountered with this unique phase such as lower solubility of catalyst and substrates and the requirement for high pressure. Optimization of the rate and selectivity would be facilitated by the tunability of the SCF's solvent properties and the tunability of the molecular catalyst's ligands. Spectroscopic measurements would be easier because of narrower NMR line widths. Finally, separation of catalyst and product could be performed using supercritical fluid extraction technology. The results described in this review clearly demonstrate the potential that SCFs have as reaction media for homogeneous catalysis. Many of the reactions are examples of these tangible benefits of the use of supercritical media. These early successes will encourage more research in the field.

On the other hand, there are also many examples cited above in which no discernible benefit was obtained by performing the reaction under supercritical conditions, and indeed one could have predicted a priori that no benefit beyond environmental considerations should be obtained. Chemists considering entering the field should first evaluate the potential for improvement in their reaction systems before committing time and research funds.

The following future trends seem likely.

Catalysts will be designed specifically for use in SCFs. Most of the catalysts have been adopted from liquid solution studies without change. There have been a few examples of catalysts modified for use in scCO_2, but the benefits of designing catalysts specifically for this new medium have only begun to be realized.

There will be further work in the catalyzed reactions of gases dissolved in SCFs. Miscibility of SCFs with H_2 has been cited many times as a favorable factor, but there has been almost no work in which the miscibility of other reagent gases in scCO_2 has been cited as advantageous. This may be one of the factors which will motivate researchers of aerobic oxidations in scCO_2, in addition to the nonflammability of the SCF.

Cage and clustering effects in SCFs have not yet been utilized to improve catalyst performance in terms of selectivity or activity. An increase in the local concentration of reagents around the catalyst, or specific molecular association should allow an improvement of the catalytic acitvity.

Development of surfactants for the solubilization of hydrophilic reagents in scCO_2 should allow for the use of polar or charged catalysts and/or reagents in that medium. This should result in a broadening of the range of reactions for which homogeneous catalysis in scCO_2 is an option.

The use of SCFs for the separation of homogeneous catalysts from the product stream will be explored. This could be advantageous for systems in which a SCF was the reaction solvent as well as for systems in which a liquid was the reaction solvent.

High-pressure operations would be facilitated in large-scale production processes and continuous-flow systems for which SCFs are well suited. Industry, in the end, may opt to use SCFs for the environmental and technical benefits they offer, but researchers should not be satisfied with these benefits alone. Instead, every effort should be made to explore the other properties of SCFs such as phase behavior control and the improvements they may make in the rate, yield, or selectivity of chemical synthesis.

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