The use of supercritical fluids in synthetic organic chemistry

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1 Introduction

This article is intended to provide organic chemists with an up to date review of the use of supercritical fluids in synthesis. Because of the unusual nature of this reaction medium, an initial brief introduction on supercritical fluids (SCFs) is included to aid the understanding of the subsequent discussion of reactions. The major part of the review is centred on reactions which are likely to be of most interest to the synthetic organic chemistry community, with an emphasis on the most recent publications up to September 2000, and those examples which demonstrate the use of SCFs to be particularly advantageous. A number of previous reviews have been published in this area describing topics such as homogeneous catalysis,[1,2] heterogeneous catalysis,[3] and SCFs as solvent replacements in chemical synthesis.[4] Other reviews are referenced in appropriate places throughout the text. There are also two recent books published in the area, one of which describes many aspects of synthetic chemistry in SCFs,[5] whilst the other concentrates on more physical aspects.[6]

A global increase in environmental awareness has led to an ever-increasing control over the use and disposal of hazardous materials by the chemical industry. This in turn has meant that the chemical industry is continually searching for new "cleaner" alternatives to its current processes.[7,8] One obvious target area is the solvent. Suitable candidates for the replacement of conventional organic solvents include supercritical fluids (particularly CO_2), ionic liquids,[9] perfluorinated hydrocarbons,[10] and water,[11] or alternatively reactions may be carried out neat in the absence of solvent.[12]

Most chemical processes are carried out in dilute solution in order to homogenise reactants, increase reaction control and selectivity, provide a means of temperature control and allow simple product isolation. This does, however, mean that vast amounts of waste solvents are created in the production of relatively small amounts of products, particularly in the fine chemical and pharmaceutical areas.[13]

SCFs have already established themselves as useful solvents for extraction, chromatography and a few specialised reactions.

SCFs are employed on an industrial scale for the extraction of hops, spices, flavours, perfumes and for the decaffeination of coffee.[14] They have also been used on a laboratory preparative scale in the extraction of natural product pharmaceuticals such as Taxol.[15] The use of SCFs as reaction media has gained recognition in the polymer industry with polyethylene being produced at levels of over 500 million lb/yr world wide. More recently, the use of supercritical carbon dioxide (scCO$_2$) as a polymerisation solvent has been exploited in the manufacture of polymethylmethacrylate and polystyrene (Xerox; Toronto, Canada),[16] and DuPont (USA) are reported to be investing in a pilot plant for the production of fluoro-polymers.[17] Other important large scale uses for scCO$_2$ are emerging such as dry cleaning,[18] and spray painting,[19] which will play a crucial role in the adaptation and acceptability of such technologies.

Green or environmentally friendly chemistry is, however, much more than simply replacing hazardous materials (solvents or reagents) with less hazardous ones and can be defined as elegant chemistry on the basis of three factors:[8] being environmentally friendly; being chemically efficient (selective); being economically viable.

The environmentally friendly factor can simply be considered as a product of the amount of waste effluent and the toxicity (ease of disposal) of that effluent. The chemical efficiency refers to the selectivity and elegance of the chemistry. Elegant chemistry uses a minimum of reagents to selectively produce a single product in quantitative yield, reducing the amount of by-products or the need for purification steps. Finally, if the chemistry is to be considered elegant, it must also be economically viable once all other factors have been considered; this is the major driving force for industry. If either a generic green process, or a totally new chemical process is to be developed, then when all the above factors have been considered, it must be the most effective route possible for it to be commercially viable.

2 Fundamentals of supercritical fluids

A SCF is defined as a substance above its critical temperature (T_C) and critical pressure (P_C). This definition should arguably include the clause "but below the pressure required for condensation into a solid", however this is commonly omitted as the pressure required to condense a SCF into a solid is generally impracticably high.[6] The critical point represents the highest temperature and pressure at which the substance can exist as a vapour and liquid in equilibrium. The phenomenon can be easily explained with reference to the phase diagram for pure carbon dioxide (Fig. 1). This shows the areas where carbon dioxide exists as a gas, liquid, solid or as a SCF. The curves represent the temperatures and pressures where two phases coexist in equilibrium (at the triple point, the three phases coexist). The gas–liquid coexistence curve is known as the boiling curve. If we move upwards along the boiling curve, increasing both temperature and pressure, then the liquid becomes less dense due to thermal expansion and the gas becomes more dense as the pressure rises. Eventually, the densities of the two phases converge and become identical, the distinction between gas and liquid disappears, and the boiling curve comes to an end at the critical point. The critical point for carbon dioxide occurs at a pressure of 73.8 bar and a temperature of 31.1 °C. Other important supercritical fluids for reaction chemistry[6] include fluoroform (T_c = 25.9 °C, T_p = 48.2 bar), and water (T_c = 374.0 °C, T_p = 220.6 bar), although the high critical parameters for the latter significantly limit the degree of constructive reactions which can be carried out. A variety of units are used to define pressure in the literature and in this review. Conversion factors are as follows: 1 atmosphere = 1.01 bar = 14.7 psi (pounds per square inch) = 0.101 MPa (megapascal).[5]
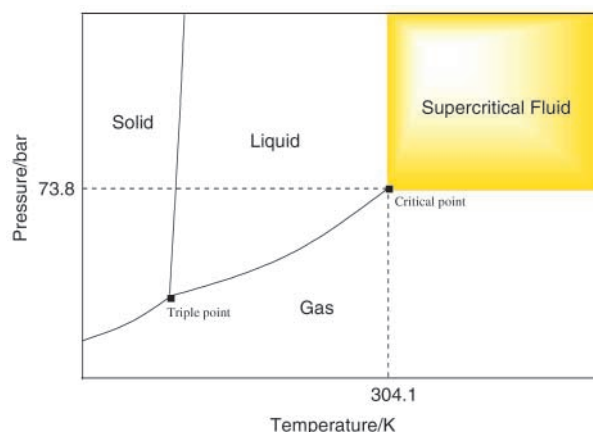

**Fig. 1** Phase diagram for pure carbon dioxide.

The disappearance of the distinction between liquid and gas phases can be demonstrated visually in an autoclave with a window, in which the meniscus between liquid and gas can be seen to disappear as the critical point is reached (Fig. 2). Photograph (a) shows a two phase liquid–gas system, with a clearly defined meniscus. As the temperature and pressure of the system are increased, the meniscus is less well defined (photograph (b)). This is due to the decrease in the difference between the densities of the two phases. Finally, in photograph (c), no meniscus is present and the system is now a single homogeneous SCF. This process can be viewed as a video *via* the Leeds Cleaner Synthesis Group web page.[20]

It should be emphasised that as reagents or cosolvents are added to a SCF, its properties can change significantly. Although in many literature examples CO$_2$ is described as being supercritical, this may not be the case for solutions with significant concentrations of additional reagents, and so the term should be treated with caution. Often the term "dense phase CO$_2$" is used, particularly when there is some uncertainty regarding the actual phase of a mixture.

A SCF has physical properties intermediate to those of gases and liquids. This definition is in reality a little simplistic as the properties of a substance may vary dramatically within the SCF phase boundaries, as its temperature and pressure are changed.[6] Around the critical point, the density of carbon dioxide is approximately 0.4 g ml^{-1}. However, if the pressure is increased, the density of the fluid dramatically increases so that at approximately twice the critical pressure the SCF now has a density comparable to that of liquid carbon dioxide (Fig. 3).

Modification of the density (and hence solvent power) of this reaction medium may exhibit some control over reaction pathways. A number of reactions have been reported in which product selectivity is controlled by variation in SCF density, in some cases, with results far superior to anything possible using conventional solvents (*vide infra*).

Table 1 shows a comparison of typical values for physical properties of a pure substance in different phases, including that of a SCF around the critical point.[5] It can be seen that the density of a SCF is approximately two orders of magnitude higher than that of the gas but still less than half that of a conventional liquid phase. The viscosity and diffusivity (which is strongly related to viscosity) are also temperature and pressure dependent, and are in general at least an order of magnitude lower and higher, respectively, compared to the liquid phase. If a chemical reaction is particularly fast, then it is feasible that diffusion could be rate limiting, and an increase in the diffusivity could lead to reaction rate enhancement. This principle is particularly applicable to unimolecular fission reactions (where increased diffusion allows an increase in radical separation rather than recombination) and highly efficient bimolecular processes such as free radical or enzymatic reactions.[21]
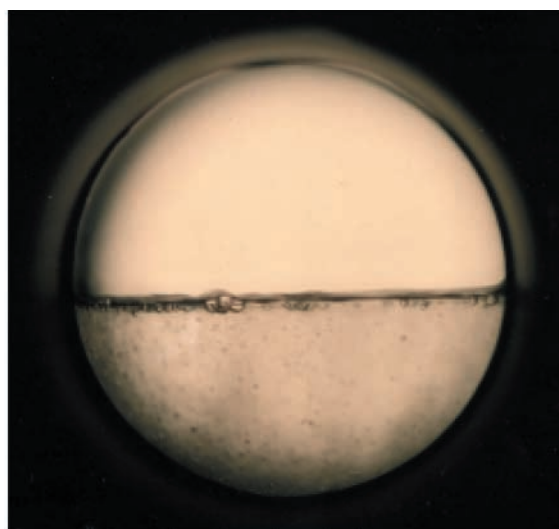
Photograph a. Two phase liquid-gas system
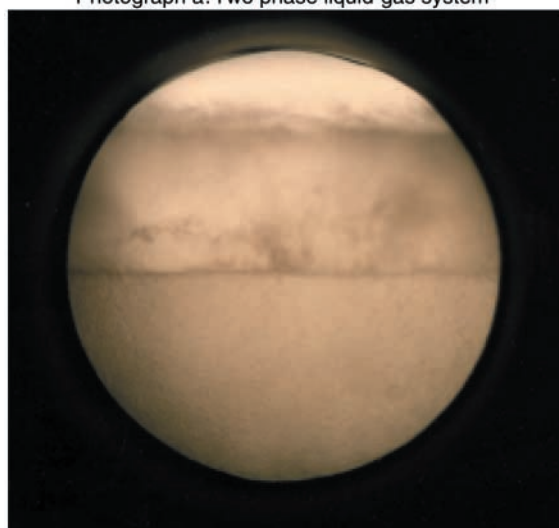
Photograph b. Meniscus less well defined
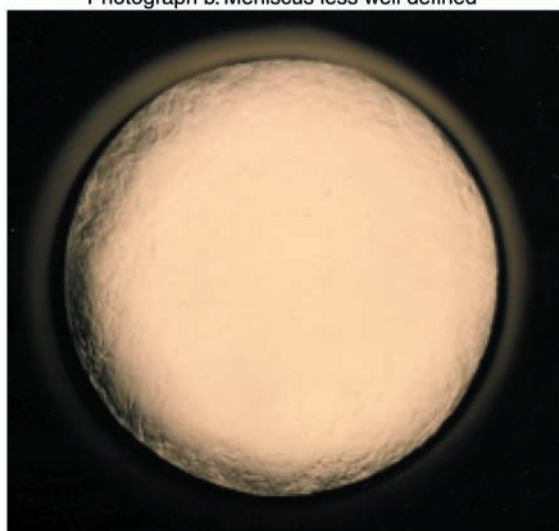
Photograph c. Homogeneous supercritical fluid

Fig. 2 Photographs demonstrating the disappearance of the meniscus as the critical point is reached for a pure substance.

The relative permittivity (ε) can also increase sharply with pressure in the compressible region for the majority of SCFs. This behaviour mirrors the change in density to some extent. The magnitude of the increase depends on the nature of the SCF, with non-polar substances such as scCO$_2$ seeing very little variation, whereas more polar SCFs such as water or fluoroform show a dramatic increase in relative permittivity with pressure (Fig. 4).[6]

Table 1 Comparison of the physical properties of gases, liquids and SCFs[5]

Property	Gas	SCF	Liquid
Density/g ml^{-1}	10^{-3}	0.4	1
Viscosity/Pa s	10^{-5}	10^{-4}	10^{-3}
Diffusivity/cm^2 s^{-1}	0.1	10^{-3}	10^{-5}–10^{-6}
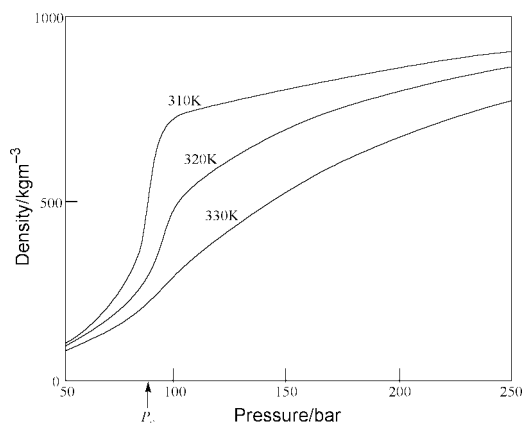
Fig. 3 Variation of density with pressure for pure carbon dioxide above the critical temperature.[6]
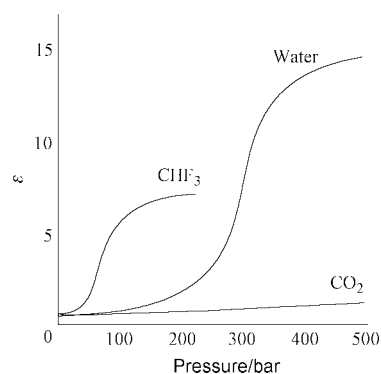
Fig. 4 Variation of relative permittivity (ε) as a function of pressure for various SCFs at their critical temperatures.[6]

SCFs are gas-like in that having no surface tension, they diffuse rapidly to occupy the entire volume of the system. This also means that if other gases are introduced, they too will diffuse to fill the entire volume and the two substances will mix perfectly. Gases are therefore totally miscible with SCFs and can be said to have perfect solubility. This is in contrast to the solubility of gases in liquid solvents, which is relatively low and also decreases as temperature increases. The concentration of hydrogen in a supercritical mixture of hydrogen (85 bar) and carbon dioxide (120 bar) at 50 °C is 3.2 M, whereas the concentration of hydrogen in tetrahydrofuran under the same pressure is merely 0.4 M.[22] There is therefore potential for much improved chemical processes where gaseous reagents have traditionally been used in solution phase.

SCFs are considered useful as reaction media because of the surprisingly high solubility of liquid and solid solutes, particularly when compressed to liquid-like densities. As solubility is related to density, this medium has the added benefit of being solubility tuneable, and hence the solubility of an organic solute can be directly controlled. This offers the potential for reaction control by precipitation of a product, or for purification by selective precipitation of products. In addition, the ability to dissolve gaseous, liquid and solid materials and
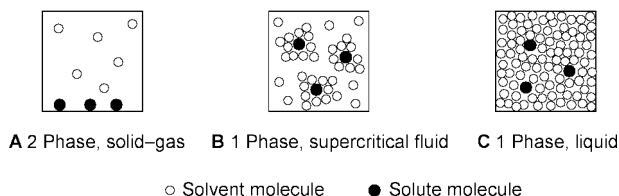
A 2 Phase, solid–gas   **B** 1 Phase, supercritical fluid   **C** 1 Phase, liquid

○ Solvent molecule   ● Solute molecule

Fig. 5 Reagent clustering in a supercritical fluid.

hence homogenise reaction mixtures in the SCF phase is particularly powerful.[23] This phenomenon is potentially extremely important to the bulk chemicals industry for such reactions as hydrogenation, hydroformylation and oxidation, where traditionally the solubility of the gaseous reagent in the liquid solvent has been rate limiting.

An additional feature of SCFs, which enhances solubilities at moderate densities is solute–solvent clustering.[24] In Fig. 5, (A) demonstrates a two phase system in which a solid solute is under a pressure of a gas. Interactions between the molecules are very weak and no significant solvation occurs. In (C), the system is now in the liquid phase, the bulk density is high, offering high solvation and we therefore see a single phase. (B) represents SCF conditions. The bulk density is moderate, higher than the gas phase but much lower than that of a liquid. Solvent clustering around the solute molecules does however mean that the local density is relatively high and therefore a moderate solvation is offered and we observe a one phase system for low concentration solutions.[6,25]

2.1 Enhancement of solubilities in supercritical carbon dioxide

Carbon dioxide is a non-polar molecule and therefore the solubility of non-polar solutes is significantly higher than for polar molecules. However, because of its large molecular quadrupole, $scCO_2$ has a higher affinity for polar solutes than a true non-polar solvent such as pentane.[6] Solubility can still be a problem, but can be enhanced in one or a combination of ways: increasing the bulk density of the SCF; addition of a co-solvent; modification of the solute.

Increasing the bulk density of the SCF is simple but not always desired. The solvent power can be increased by addition of a co-solvent to modify the characteristics of the SCF to be more like the substrate.[6] Modifiers (*e.g.* MeOH, toluene) can therefore be added to increase or decrease polarity, or to increase affinity for aromatic species, however, the more modifier that is added, the further $scCO_2$ moves away from being the ideal green solvent. Reagents themselves may also in effect act as cosolvents, enhancing the solubility of other more polar solutes in the reaction medium. Hence, while measuring solubility of reagents in pure CO_2 is helpful, it can only act as an indicator—it is the solubility of a reagent in the reaction mixture as a whole which is the most crucial factor.

An alternative approach is to modify the solute to make it more CO_2-philic. Molecules with hydrocarbon chains show greater solubility than aromatic or polar substrates. Of special interest, however, is the greater solubility of organic fluorocarbons and silanes in $scCO_2$, compared with the corresponding hydrocarbon. The nature of this increased solubility is not as yet fully understood, however computational and NMR studies have suggested that an increase in solute–solvent van der Waals interactions as the fluorocarbon character is increased, combined with a lower solute–solute attraction, may account for this.[26] The effect of the increased solubility of fluorocarbon species has been used to good effect in the design of CO_2-philic surfactants, chelating agents, and ligands in order to enhance the solubility of polymers, metals and catalysts, respectively.[5,27] Recent reports of cheaper, more sustainable approaches to solubility enhancement are likely to have a significant impact in the future.[28]

2.2 Carbon dioxide as a replacement solvent

Potentially $scCO_2$ is the ideal green solvent. It is non-toxic to the environment and non-toxic to personnel, however it is an asphyxiant and a large accidental release could be problematic. At atmospheric pressure carbon dioxide is gaseous, which means that simple depressurisation will leave no hazardous solvent effluent requiring complex and/or expensive waste treatment. Carbon dioxide is a greenhouse gas, however, it can be obtained in large quantities as a by-product of fermentation, combustion and ammonia synthesis. It is relatively cheap and is readily available on an industrial scale in a very pure form (>99.9% purity). On a laboratory scale, high grade carbon dioxide is available in >99.995% purity, at a cost of approximately £70 per 25 kg.[29]

There are also a number of practical advantages associated with the use of $scCO_2$ as a solvent. Product isolation to total dryness is achieved by simple evaporation. This could prove to be particularly useful in the final steps of pharmaceutical syntheses where even trace amounts of solvent residues are considered problematic. There are also two complementary routes to particle formation with SCFs and $scCO_2$ in particular, rapid expansion of supercritical solutions (RESS)[30] and supercritical anti-solvent precipitation (SASP).[31] Together these techniques allow the processing of a wide range of solid materials with a high control of morphology. Although beyond the scope of this review, they are particularly relevant in pharmaceutical formulation, and anyone involved in such areas is encouraged to consult recent reviews.[30,31]

There are also a number of potentially interesting and useful properties of $scCO_2$ media in terms of the chemistry which can be achieved. Carbon dioxide is chemically inert to most conditions. It is non-flammable, non-protic, not strongly Lewis acidic or basic, and is inert to radical and oxidising conditions.[32] It can react with nucleophiles (*e.g.* carbamic acid formation from amines), although this can be reversible, and can be exploited synthetically.[33] This general lack of reactivity is essential to the success of $scCO_2$ as a common replacement for more conventional solvents.

3 Synthetic reactions in supercritical carbon dioxide

The concept of SCFs is not a new one, and a vast amount of literature exists on their use in extraction[15] and materials applications.[34] In comparison, the use of SCFs as reaction solvents is an area which has until relatively recently received much less attention, with very little literature existing before 1990. This is, however, an area which is gaining an ever-increasing amount of attention, with approximately 80% of all published synthetic applications being reported in the last 5 years. This review will concentrate mainly on the use of $scCO_2$ as this has tended to be the solvent of choice for investigation to date because it is cheap, plentiful and has relatively mild critical parameters, however, other SCFs will also be included when appropriate. This review will describe a wide range of chemistries which we consider to be of the greatest value to the synthetic organic chemist, with an emphasis on recent publications, and those which demonstrate the use of SCFs to be advantageous.

3.1 Hydrogenation in supercritical carbon dioxide

Gases such as hydrogen are totally miscible with SCFs, and many liquid and solid substances also have significant solubility. Thus the ability of a SCF to bring together gases, reagents and catalysts in a single homogeneous phase offers a significant potential rate advantage for hydrogenation reactions over more conventional processes. This theory was the driving force behind much of the early work on reactions in SCFs.

3.1.1 Homogeneous catalytic hydrogenation of supercritical carbon dioxide

The use of carbon dioxide as a starting material for the synthesis of organic compounds has long been a goal for synthetic chemists. The hydrogenation of carbon dioxide to formic acid, methanol and other organic substances is particularly attractive but has remained difficult under conventional gas phase conditions.

In 1994, Noyori reported one of the first synthetically useful processes involving scCO$_2$ as both solvent and as substrate.[35] The system involves the use of homogeneous ruthenium(II) phosphine catalysts **1** or **2**, for the hydrogenation of carbon dioxide to formic acid **3** (Scheme 1). The catalysts were chosen for their known solubility in non-polar solvents such as hexane, and were shown to be superior to RuH$_2$(P(C$_6$H$_5$)$_3$)$_4$ which was considered to be the most active catalyst in benzene solution.
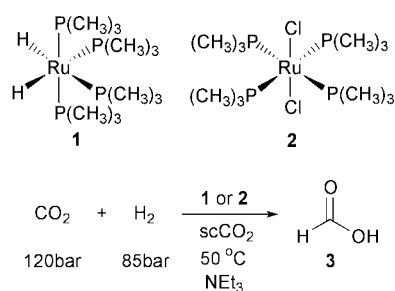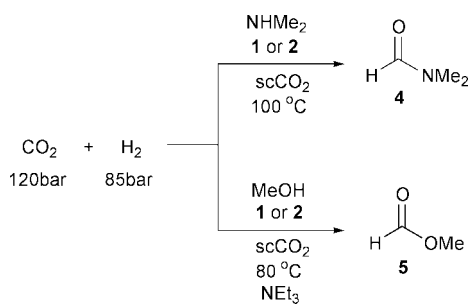

Scheme 1

The formic acid production is performed under 85 bar of hydrogen, pressurised up to a total pressure of 200–220 bar with carbon dioxide. The reaction is driven by the presence of triethylamine which forms a salt with the formic acid, and without which the equilibrium is unfavourable.

The reaction is very rapid and proceeds with a turnover frequency of 1400 h^{-1} (catalyst **1**) over the first hour, and 1040 h^{-1} for catalyst **2**. The initial rate with **2** is slow, and it is considered that this catalyst is not initially present in its active form. However, once this induction period has passed, the greatest conversions were achieved using catalyst **2**, with turnover numbers of 7200 being recorded. These rates compare favourably with those achieved in conventional solvents, as the reaction proceeds 18 times faster in scCO$_2$ using **1** at 50 °C, than in THF under otherwise identical conditions.

The high performance of this formic acid production is explained as a phenomena of the SCF, with its increased mass transfer capability and the high miscibility of hydrogen, and not by the high concentration of carbon dioxide. This was demonstrated by repeating the reaction utilising similar conditions, but at a reduced temperature of 15 °C, under liquid CO$_2$ conditions. The turnover frequency dropped dramatically to 1.3 h^{-1}, with a turnover number of just 20.

This methodology was utilised in the one-pot production of both DMF **4** and methyl formate **5**, from carbon dioxide (Scheme 2).[22] The conversion proceeds in two steps and is two

phase. The initial catalytic hydrogenation of carbon dioxide to formic acid takes place very efficiently in scCO$_2$, whereas the thermal condensation (to form the amide or ester) is rate limiting and takes place in a liquid phase.

Using catalyst **2**, scCO$_2$ reacts with hydrogen and dimethylamine to yield DMF with turnover numbers (TON) as high as 370 000. This catalytic efficiency was two orders of magnitude greater than any reported in liquid solvent (3400 TON, 73% yield), giving 99% selectivity to DMF production, with a conversion of dimethylamine of 99%.[36] The dimethylamine acts as base during the first step, and leads to an increased efficiency for carbon dioxide fixation. This is further helped by the condensation reaction which leads to the production of water and an aqueous phase, which in turn prevents dissolution of the non-polar catalyst.

Using catalysts **1** and **2**, methyl formate is produced with turnover numbers of 3500 at 80 °C, with a selectivity of 35%.[37] The amine, which is necessary for good conversions in the hydrogenation step, is an inhibitor of the esterification, which in turn requires high temperatures whereas the hydrogenation is favoured by lower temperatures. The selectivity for methyl formate therefore increases with temperature, but the maximum yield is obtained at the intermediate temperature of 80 °C.

3.1.2 Asymmetric hydrogenation in supercritical fluids
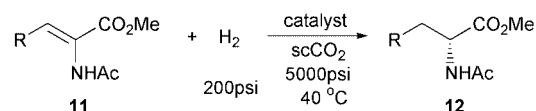
The asymmetric hydrogenation of ethyl pyruvate **6** to ethyl (R)-lactate **7**, under SCF conditions was investigated by Minder et al. in 1995,[38] using a heterogeneous catalytic system (Scheme 3). The enantioselectivity is derived from a chiral cinchonidine modifier which is adsorbed on the surface of a supported platinum.
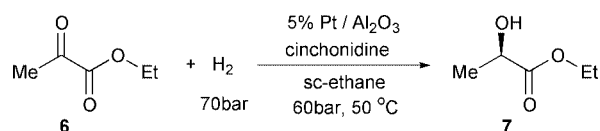
Scheme 3

The reaction proceeded significantly faster in supercritical ethane, compared with the rate in toluene solution, by a factor of >3.5. The enantioselectivity was found to be comparable, with ee's of around 75%. A strong catalyst deactivation was observed in the enantioselective hydrogenation in scCO$_2$. This was shown to be due to CO poisoning of the Pt, following the reduction of CO$_2$ to CO, on the catalyst surface.

Tumas et al. developed a homogeneous catalytic system for the enantioselective hydrogenation of prochiral α-enamides **11** in scCO$_2$ (Scheme 4).[39] The catalyst is a cationic rhodium species **8**, which incorporates the chiral bidentate DuPHOS ligand **9** and the tetrakis[3,5-bis(trifluoromethyl)phenyl] borate (BARF) counter ion **10**. The enantioselectivities achieved with this catalytic system (0.2 mol%) in scCO$_2$ were found to be very high, and comparable to those achieved in conventional solvents (methanol, hexane).


R = H, 99.5% ee (scCO$_2$); 98.7% ee (methanol); 96.2% ee (hexane)
R = Ph, 99.1% ee (scCO$_2$); 97.5% ee (methanol); 98.3% ee (hexane)
R = Et, 98.8% ee (scCO$_2$); 98.7% ee (methanol); 96.8% ee (hexane)

Scheme 4

The asymmetric hydrogenation of β,β-disubstituted enamide **13** in scCO$_2$, gave the valine derivative (R)-**14** (Scheme 5) in 85% ee. This compares very favourably to results obtained in

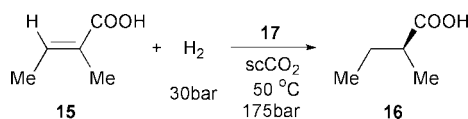**Scheme 2**

8

9

10
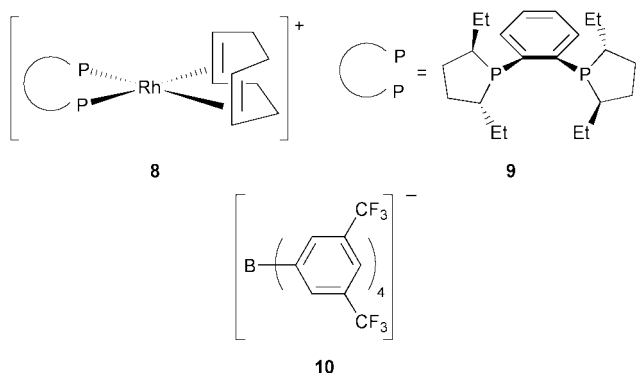
conventional solvents, with the highest reported enantioselectivity for this substrate previously being 55% ee. A study of this reaction in hexane, pressurised to 5000 psi with nitrogen, indicated that this enhancement of enantioselectivity was not simply a pressure effect, but is specifically associated with the use of scCO$_2$.
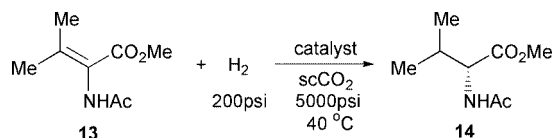

Scheme 5

Noyori has also demonstrated a homogeneous catalytic asymmetric hydrogenation reaction in scCO$_2$. (*E*)-2-Methylbut-2-enoic acid **15** was hydrogenated to give (*S*)-2-methylbutanoic acid **16** in >99% yield with up to 81% ee (Scheme 6), catalysed by ruthenium complex **17**.[40] This conversion and selectivity is comparable to the best obtained in a conventional organic solvent (methanol, 100% yield, 82% ee).
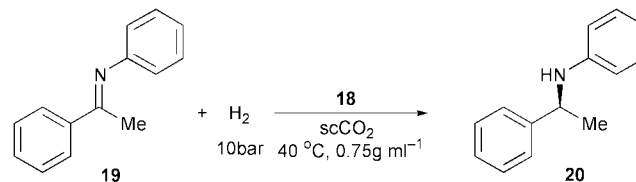

Scheme 6
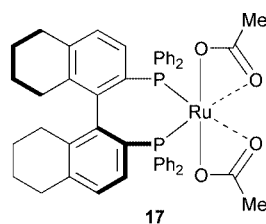
17
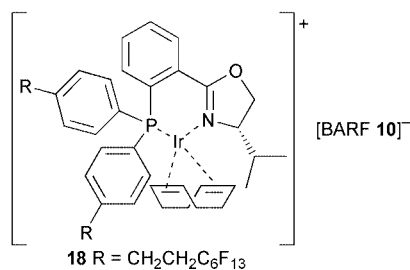
18 R = CH$_2$CH$_2$C$_6$F$_{13}$

The partially hydrogenated BINAP catalyst **17** showed increased solubility in scCO$_2$ over the fully aromatic version, which gave a poorer rate and selectivity (50% yield, 37% ee). The introduction of perfluorinated alcohol CF$_3$(CF$_2$)$_6$CH$_2$OH, also offered solubility enhancement and caused an increase in both conversion (100%, at 5 bar H$_2$ pressure) and enantioselectivity (89% ee). The reaction in liquid CO$_2$ at 20 °C afforded no hydrogenated product.

Leitner and Pfaltz have reported the use of scCO$_2$ as a reaction medium for the homogeneous iridium catalysed enantioselective hydrogenation of prochiral imines.[41] Cationic iridium(I) complexes with chiral phosphinodihydrooxazoles, modified with perfluoroalkyl groups for increased CO$_2$-philicity **18**, were synthesised and tested in the hydrogenation of *N*-(1-phenylethylidene)aniline **19** (Scheme 7). The complex with the BARF counter-ion **10** led to the highest asymmetric induction, with (*R*)-*N*-phenyl-1-phenylethylamine **20** being formed quantitatively with an 81% ee, using 0.078 mol% of catalyst.
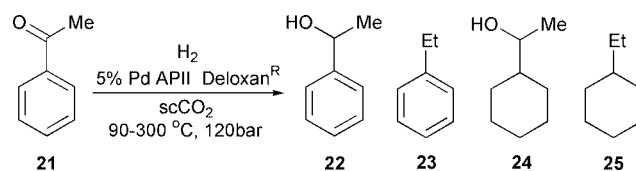

Scheme 7

In scCO$_2$, the rate remained stable with low catalyst loadings. A >90% conversion of the imine (>6800 TON) was achieved in 6 h in scCO$_2$, whereas more than 22 h was required in dichloromethane, using a 5 times larger amount of catalyst (1400 TON).

3.1.3 Continuous hydrogenation in supercritical fluids

Poliakoff has developed a system for the continuous hydrogenation in SCFs, with a polysiloxane supported palladium catalyst.[42] Initial investigations demonstrated that cyclohexene could be quantitatively reduced in scCO$_2$, using a 5 ml reactor with a throughput of 1200 ml h^{-1}. By adjusting the reactor temperature and hydrogen concentration, reaction control in the hydrogenation of acetophenone **21** was achieved (Scheme 8). At a temperature of 90 °C, with 2 equivalents of hydrogen, alcohol **22** is produced in >90% yield, whereas if the temperature is increased to 300 °C and the hydrogen ratio to 6 : 1, the fully reduced product **25** is produced with a >95% yield. At the intermediate temperature of 200 °C, products **23** and **24** are predominant, with their actual ratios being dependent on the hydrogen concentration used. The selective hydrogenation of a number of organic functionalities including aromatic and aliphatic alcohols, aldehydes, ketones, nitro-compounds, imines, oximes, olefins and acetylenes have been performed by this continuous system.[43]
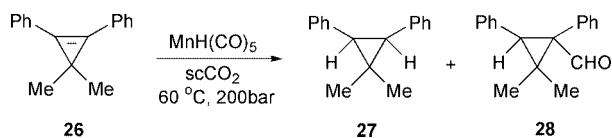

Scheme 8

3.2 Hydroformylation in supercritical carbon dioxide

Hydroformylation reactions are similar to hydrogenation processes, traditionally using liquid solvents, gaseous reagents (hydrogen and carbon monoxide) and solid catalysts (either homogeneous or heterogeneous). The benefits of using SCFs as a reaction medium are potentially as applicable to this system as they have been shown to be with hydrogenation.

In 1991, Rathke *et al.* reported the cobalt carbonyl catalysed hydroformylation of propylene using scCO$_2$ as a reaction solvent in order to avoid gas–liquid mixing problems.[44] Propylene hydroformylation proceeded cleanly at 80 °C in scCO$_2$ (d = 0.5 g ml^{-1}) with Co$_2$(CO)$_8$ (10 mol%), hydrogen (42 bar) and carbon monoxide (42 bar), giving *n*-butyraldehyde (88%). This compared favourably with the 83% obtained in benzene solution at higher pressures (80 bar H$_2$ and CO) and catalyst concentration (Co$_2$(CO)$_8$ 15 mol%).

Noyori used scCO$_2$ and liquid solvents for hydrogenation and hydroformylation in order to investigate the reaction mechanisms. The stoichiometric reaction of olefin **26** with MnH(CO)$_5$ in scCO$_2$, gave similar selectivity for the hydroformylation product **28**, over the hydrogenation product **27**, to that found in alkane solvents (Scheme 9).[45] This suggested that the aldehyde **28** was primarily formed by non-radical pathways, which were independent of solvent viscosity.

Scheme 9

Leitner and Erkey independently developed fluorinated hydroformylation catalysts in order to enhance their CO$_2$-philicity and hence catalytic activity in scCO$_2$. Erkey produced *trans*-RhCl(CO)(P(p-CF$_3$C$_6$H$_4$)$_3$)$_2$ **29** and RhH(CO)(P(p-CF$_3$-C$_6$H$_4$)$_3$)$_3$ **30** which had solubilities 2 orders of magnitude higher than the conventional metal-triphenylphosphine catalysts, and showed equivalent activity in scCO$_2$ to the conventional catalyst in benzene.[46,47]

Leitner synthesised arylphosphine ligand **31** with perfluoro-alkyl chains and inserted methylene spacers in order to prevent modification of the electronic properties of the ligands.[48] Hydroformylation of oct-1-ene **32** gave a conversion of 95% and a linear **33** to branched **34** product ratio of 8.5 : 1 (Scheme 10).[49] This compared favourably with the use of conventional triphenylphosphine ligands (26% yield, **33** : **34** 3.5 : 1). In liquid carbon dioxide solution at 25 °C, a conversion of 5% was achieved.
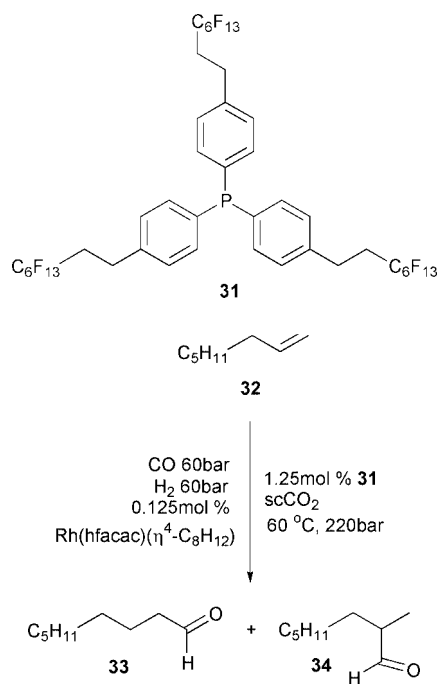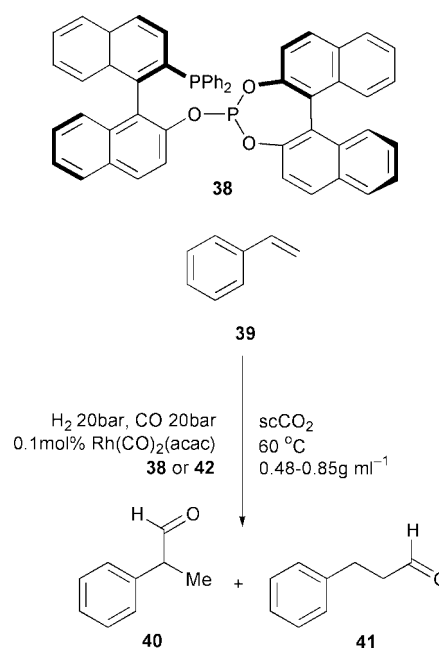
Scheme 10

Cole-Hamilton has reported a rhodium catalysed hydroformylation reaction in scCO$_2$, using trialkylphosphines as simple alternatives to fluorinated arylphosphines, in order to achieve solubility.[50] The catalyst prepared *in situ* from Rh$_2$(OAc)$_4$ (0.75 mol%) and PEt$_3$ (4 mol%) gave complete conversion of hex-1-ene within 2 hours at 100 °C (2.5 : 1 linear to branched product ratio, TOF 57 h^{-1}). The equivalent reaction in toluene solution showed an equivalent rate, but a poorer product ratio of 2.1 : 1.

The product selectivity of octacarbonyldicobalt catalysed hydroformylation of propylene **35**, in scCO$_2$ was reported by Akgerman.[51] At a constant temperature of 88 °C, rate increased with pressure from 1300 psi to 2100 psi before levelling off to give quantitative conversion after 12 hours. Linear **36** to branched **37** product selectivity also showed a pressure dependency (Scheme 11). At 88 °C, selectivity increased with pressure, from 1.6 : 1 (90 bar) to 2.6 : 1 (190 bar). The selectivity also had an inverse dependency on temperature at a constant pressure of 167 bar, decreasing from 3.5 : 1 (69 °C) to 2.3 : 1 (88 °C). These changes in product selectivity are explained in terms of the differences in partial molar volumes and partial molar enthalpies of the two isomers.[52]
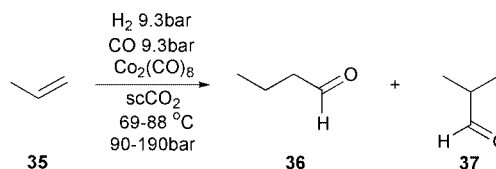
Scheme 11

The asymmetric hydroformylation of styrene **39** using Rh(CO)$_2$(acac) and (*R,S*)-BINAPHOS **38** as catalyst ligand in dense phase CO$_2$ was reported by Leitner in 1998.[53] At 60 °C, with a CO$_2$ density of 0.48 g ml^{-1} (close to the critical density), branched product **40**, favoured in the asymmetric hydroformylation, was formed in ratios of 6 : 1 to 8 : 1, over its achiral regioisomer **41**, with an appreciable asymmetric induction 66% ee (Scheme 12). It was, however, observed that as the scCO$_2$ density was increased, the asymmetric induction decreased (*d* = 0.75 g ml^{-1}, <10% ee). This was explained by phase behaviour. At low density a true single phase SCF is not observed and enantioselective hydroformylation takes place in a liquid phase. At higher density, the chiral ligand **38** is only sparingly soluble in the single scCO$_2$ phase, and background hydroformylation catalysed by the unmodified rhodium catalyst gives a near racemic product.

Scheme 12

The ligand solubility problem was addressed by the addition of fluorinated chains, leading to the development of the fluorinated BINAPHOS ligand **42**. Use of this ligand with Rh-(CO)$_2$(acac), led to increased levels of enantioselectivity compared with ligand **38** (>90% ee for **40**, in scCO$_2$, Scheme 12),

and greater regioselectivity both in conventional benzene solvent and in scCO$_2$ with quantitative conversions (17 hours, 60 °C, 0.1 mol% cat., 0.2 mol% **42**).[54]


42
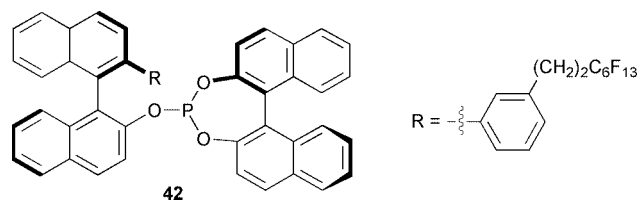
### 3.3 Photochemical and radical reactions in supercritical carbon dioxide

As SCFs are low density fluids with low viscosity resulting in high rates of diffusion, they offer potential benefits for radical processes. A significant proportion of the radical reactions studied have been in polymerisation type applications and will be covered later. Other radical processes have been used as models for kinetic studies, particularly studies of solvent–solute interactions and solvent clustering.[24] Although radical reactions were some of the first synthetic processes to be considered in SCFs, relatively few literature examples exist.

As early as 1987, Aida and Squires demonstrated how pressure and hence density manipulation of scCO$_2$, could change the outcome of a chemical reaction.[55] Studying the photoisomerisation of (*E*)-stilbene **43** (Scheme 13), it was observed that increasing the pressure at constant temperature (25 °C) in liquid CO$_2$, facilitated a slight increase in conversion of **43** to (*Z*)-stilbene **44** (**44** : **43**, 5.5 : 1 at 83 bar, 6.8 : 1 at 214 bar). However, under supercritical conditions, the same pressure change gave a more pronounced variation (1.4 : 1 to 7.0 : 1). This was due to the greater density change observed on increasing the pressure of the more compressible SCF.

The photodimerisation of isophorone **45** in scCO$_2$ and scCHF$_3$ was reported by Johnston.[56] The reaction is a [2+2]
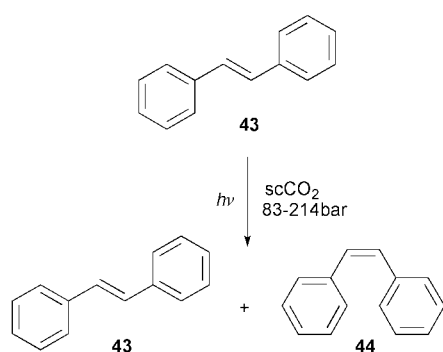
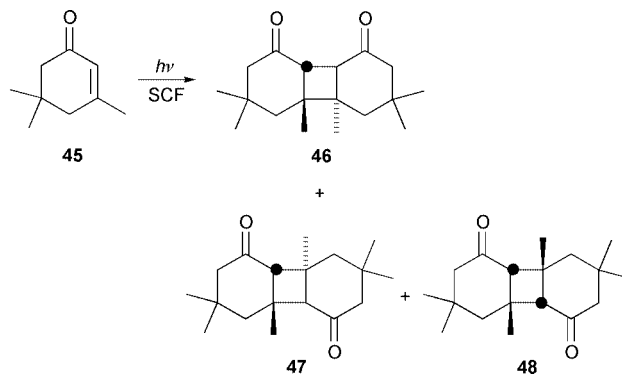**Scheme 13**
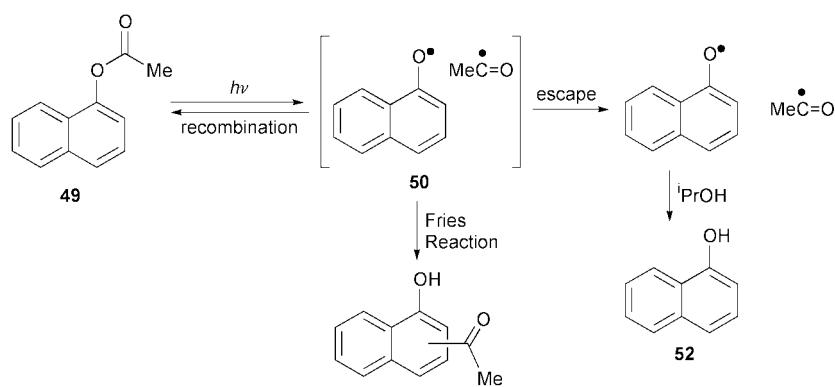
cycloaddition and produces three isomeric products depending on the orientation of the addition: head to head **46**, head to tail (*anti*) **47**, and head to tail (*syn*) **48** (Scheme 14). It had previously been demonstrated that this product ratio was dependent on solvent polarity, as **46** is significantly more polar than **47** and **48** (**47** and **48** are produced equally).

Scheme 14

As discussed previously, the relative permittivity of scCHF$_3$ changes dramatically with pressure (Fig. 4). The photodimerisation of **45** in scCHF$_3$ (35 °C) was shown to be pressure dependent with the product ratio of **46** : (**47** + **48**) varying from 0.75 : 1 to 1.0 : 1, with increasing pressure. In scCO$_2$ (38 °C), the ratio was independent of pressure and lower than that observed in scCHF$_3$ (0.1 : 1 in scCO$_2$), as expected, with the relative permittivity of scCO$_2$ being low and essentially constant across the pressure range. Interestingly, the *syn* to *anti* ratio appeared to be pressure dependent in both SCF solvents. The *anti*-isomer **47** is formed preferentially at higher pressures. This is explained as a solvation effect, with **47** having similar solvent–solute interactions to **45**, whereas formation of **48** requires a significant desolvation.

Weedon studied the photo-Fries rearrangement of 1-naphthyl acetate **49** in scCO$_2$ with propan-2-ol present as a hydrogen donor.[57] Photolysis of **49** gives a radical caged pair **50**, which, depending on the strength of the solvent cage, can react in three ways (Scheme 15): in-cage recombination to reform **49**; in-cage reaction to form photo-Fries products **51**; cage escape to form 1-naphthol **52** by hydrogen abstraction from propan-2-ol.

In liquid CO$_2$ (27 °C), the ratio of Fries product **51** to 1-naphthol **52** was constant at 4 : 1 over the pressure range of 75–345 bar. However in scCO$_2$ at 35 °C and 47 °C, the initial ratio is 4 : 1, but leaps to 12–13 : 1 as the critical density is approached, before returning to 4 : 1 on further pressure increase. This suggests that there is an enhancement of the cage effect around the critical density of SCFs, where the existence

Scheme 15

of solvent–solute clusters have a lifetime comparable with, or longer than that of the radical pair **50**.

3.3.1 Free radical halogenation reactions in supercritical carbon dioxide

Tanko suggested that scCO$_2$ was potentially an ideal environmentally benign replacement for carbon tetrachloride in free radical halogenation reactions. The reaction of molecular bromine with toluene **53** and ethyl benzene **56**, forming the corresponding benzylic bromides (**54** 74%, **57** 95% respectively) was studied (Scheme 16).[32] In the case of **53**, a small amount of *p*-bromotoluene **55** was also formed (11%), arising from the competitive electrophilic aromatic substitution. In the competitive bromination of **53** and **56**, the observed selectivities in scCO$_2$ were similar to those observed in conventional organic solvent. This suggests that there is no change in the mechanism, with a bromine radical acting as the chain carrier.
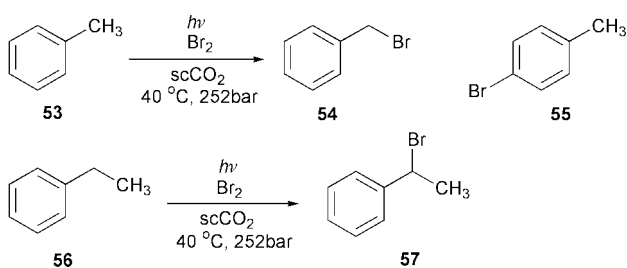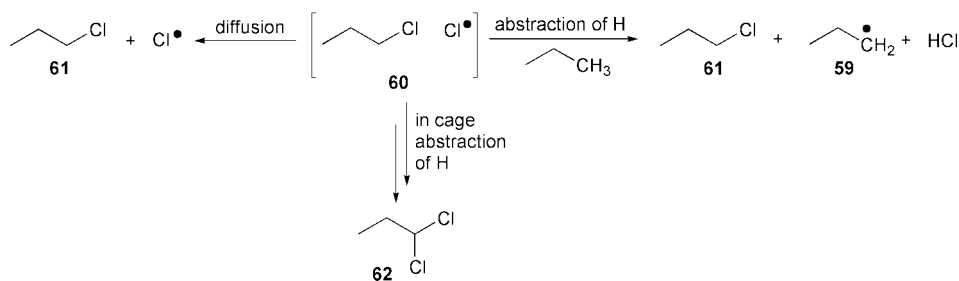

Scheme 16

The Ziegler bromination of **53** and **56** was also investigated. *N*-Bromosuccinimide (NBS) serves to provide a low steady state concentration of bromine and the limited solubility of NBS is crucial. Reaction with **53** at 40 °C gave **54** quantitatively. The competitive bromination of **53** and **56**, was again as observed in carbon tetrachloride suggesting no mechanism change.

The radical chlorination of propane **58** was also studied in order to determine the extent of viscosity effects in scCO$_2$.[58] The mechanism involves a chlorine atom abstracting hydrogen from **58**, yielding an alkyl radical **59** and HCl. Alkyl radical **59** subsequently reacts with molecular chlorine to yield the product **61** and regenerate a chlorine radical (Scheme 17).
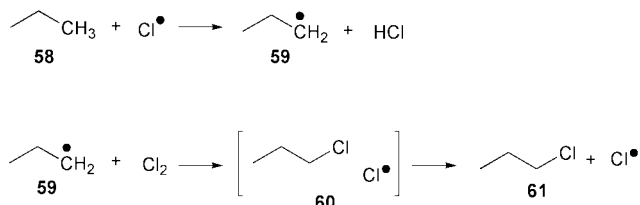
Scheme 17

It is suggested that **61** and the chlorine radical exist as a caged pair **60** and as with the Fries rearrangement, the pair can follow three different pathways (Scheme 18): diffusion out of the

cage, leading to monochlorinated product **61**; abstraction of hydrogen from a molecule of **58** in the cage wall, leading to the monochlorinated product **61**; an in-cage abstraction of a second hydrogen leading to polychlorination product **62**.

In conventional solvent, the product ratio (**61** : **62**) depends on solvent viscosity. The product ratio in scCO$_2$ was also observed to vary with increased density and hence viscosity as expected. However, no evidence was found in this case for an increased cage effect attributable to solvent–solute clustering in scCO$_2$. The results did, however, demonstrate that scCO$_2$ provides a "tuneable" reaction medium.

3.3.2 Thermally initiated radical reactions in supercritical carbon dioxide

In 1997, Beckman and Curran reported a number of radical reactions using tin hydride reagents in scCO$_2$.[59] Both tributyltin hydride **65** and tris(2-(perfluorohexyl)ethyl)tin hydride **66** were investigated, **66** being miscible under reaction conditions (90 °C and 4000 psi) whereas **65** was insoluble. Bromoadamantane **63** was reduced by **66** (initiated by AIBN) under scCO$_2$ conditions to give **64** in 90% yield after 3 hours (Scheme 19). The work-up for this reaction is particularly clean by partitioning between benzene and perfluorohexane. Surprisingly, despite its insolubility, **65** also facilitated reduction, with **64** being isolated in 88% yield. Reaction of steroidal bromides, iodides and selenides with **65** and **66** also gave the corresponding reduced products in high yields (85–98%).
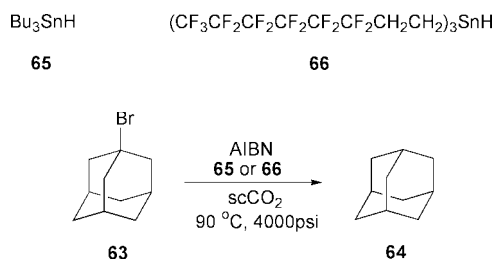
Scheme 19

Several radical cyclisation reactions were also studied. Reduction of 1,1-diphenyl-6-bromohex-1-ene **67** with **66** gave the 5-*exo* product **68** in 87% yield (Scheme 20). A small amount of the reduced product **69** was also formed (7%), which does not occur in conventional solvent. This is attributed to the higher diffusion rates in scCO$_2$, which allows the bimolecular reduction to compete more efficiently with the cyclisation. Similarly, reduction of aryl iodide **70** with **66** gave quantitative conversion to cyclised product **71** (Scheme 20). Interestingly, no reaction was observed with **65** in either case.

The standard Giese reaction of iodoadamantane **72** with acrylonitrile **73** was also facilitated by **66** in scCO$_2$, giving the radical adduct **74** in 81% yield (Scheme 21). It is suggested that the use of fluorous reagents in scCO$_2$, combined with fluorous phase work-up could provide a new clean approach to synthetic chemistry.
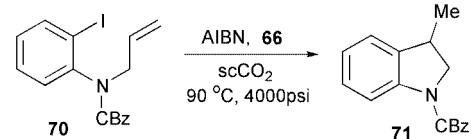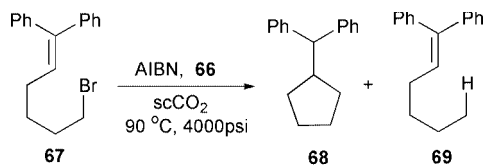
Scheme 18
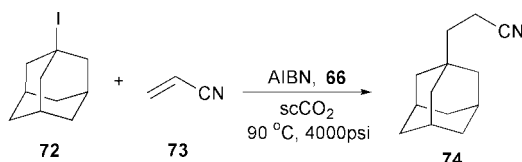
Scheme 20
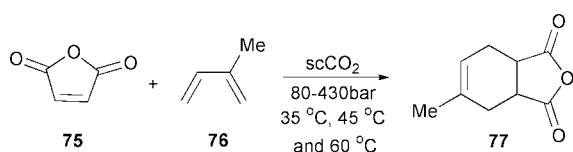

Scheme 21

3.4 Diels–Alder cycloaddition reactions in supercritical carbon dioxide

The Diels–Alder reaction has been the subject of numerous studies in scCO$_2$ media. The effects of fluid pressure and density on rates and selectivities have been investigated by several groups with in some cases conflicting results and conclusions. This review describes the findings and conclusions of the many publications in chronological order.

In 1987, Paulaitis and Alexander reported a Diels–Alder reaction in scCO$_2$ which was one of the earliest reported synthetic reactions in SCF media.[60] The object of the study was to investigate the effect of SCF solvent pressure on reaction rates. The Diels–Alder reaction of maleic anhydride **75** and isoprene **76** (Scheme 22) was chosen as it was considered that the mechanism of this reaction was the same irrespective of whether it was performed neat, in the gas phase, or in an inert liquid solvent. The second order rate constant was measured over a range of pressures (80–430 bar) at three temperatures (35, 45 and 60 °C). In general, the rate increased slightly with pressure, as observed in liquid solvents. However at 35 °C, at pressures around the critical pressure, a large variation in rate was observed. This was explained as a result of a dramatic change in activation volume on approaching the critical point.
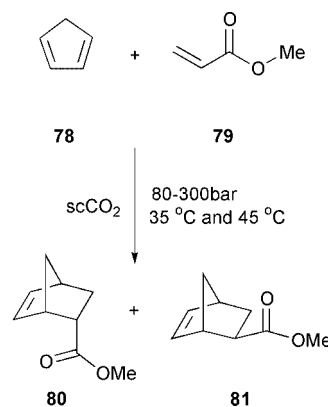

Scheme 22

In 1988, Kim and Johnston reported that the selectivity of the Diels–Alder reaction could be adjusted by modification of the SCF density.[61] In the Diels–Alder reaction between cyclopentadiene **78** and methyl acrylate **79**, two isomeric products are formed, the *endo*-adduct **80** and the *exo*-adduct **81** (Scheme 23). The selectivity for **80** increases as pressure (or density) increases, at constant temperature. At constant pressure, the selectivity decreases with temperature. The change in selectivity is explained in terms of the difference in dipole moment of the two products, with **80** being more polar than **81**. The difference in dipole of the two products means that selectivity increases with solvent power, which is achieved in scCO$_2$ by increasing density. The increase in selectivity is, however, only small, with the product ratio **80** : **81** increasing from 2.83 : 1 to 2.90 : 1 on increasing the pressure from 80–300 bar at 35 °C.

Table 2 Product distribution *versus* pressure for Diels–Alder reaction between **76** and **79** in scCO$_2$

Pressure/MPa	Product distribution	
	% **82**	% **83**
4.90	67.1	32.9
7.45	38.9	61.1
11.77	71.3	28.7
15.69	75.5	24.5
19.12	81.0	19.0
20.60	85.9	14.1

Scheme 23

Ikushima reported the cycloaddition of methyl acrylate **79** with isoprene **76** in scCO$_2$ and in conventional organic solvent (Scheme 24).[62] Increasing the pressure of the scCO$_2$ solvent was found to enhance the reaction rate, with the rate constant increasing from 0.022 h^{-1} at 7.45 MPa, to 0.099 h^{-1} at 19.1 MPa at 40 °C. This increase in rate was later described in terms of transition state theory and the solubility parameter.[63]
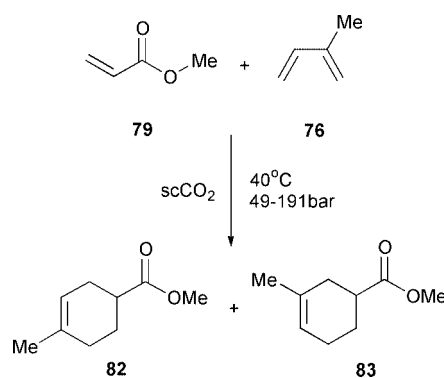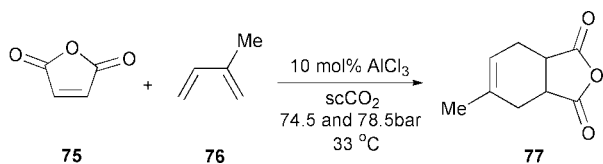

Scheme 24

The product distribution is also reliant on SCF pressure. In conventional solvents at atmospheric pressure, the 1,4-product **82** predominates over the 1,3-product **83** (>98% **82**). In scCO$_2$, the ratio varies with pressure, with **82** being generally favoured, but in less dramatic ratios (75% at 15.69 MPa, 40 °C and 86% at 20.60 MPa, 40 °C, Table 2). However, around the critical pressure of CO$_2$, at 7.45 MPa and 40 °C, the selectivity is reversed with **83** now observed as the major product formed in 61% yield.

Ikushima also studied the Diels–Alder reaction between maleic anhydride **75** and isoprene **76**,[64] previously reported by Paulaitis and Alexander.[60] The reaction was now conducted using aluminium chloride as a Lewis acid catalyst at 33 °C and at two pressures, 74.5 bar and 78.5 bar, and was analysed by high pressure FT-IR (Scheme 25). The concentration of **76** was found to decrease exponentially, whereas **75** gradually decreased at first, before decreasing rapidly to be fully con-

sumed at the same time as **76**. The product **77** was formed steadily at first and then remained constant before increasing rapidly again until reaching a steady concentration. These results were explained by suggesting a modification to the generally accepted concerted mechanism, with the product being formed in a two-step sequence of sigma bond formation, followed by cyclisation. The observations were similar at both pressures, with the rate increasing slightly on increasing the pressure.
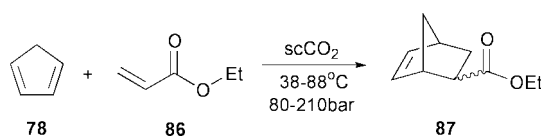

Scheme 25

In a study by Isaacs and Keating, kinetic measurements were made for the cycloaddition of cyclopentadiene **78** and *p*-benzoquinone **84** in liquid CO_2 and $scCO_2$ (Scheme 26).[65] The reaction was performed with a large excess of **78**, over a range of temperatures (25–40 °C), with adjustment of the pressure in order to maintain a fluid density of 0.8 g ml^{-1}. Pseudo first order rates were observed across the temperature range with no fluctuation around the critical point. In general, the rates were 20% faster than those observed in liquid diethyl ether solvent.
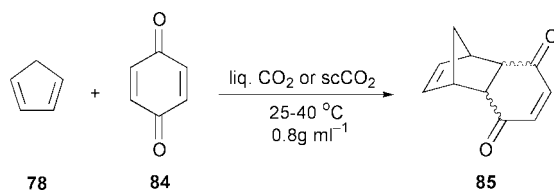
Scheme 26

Danheiser *et al.* reported a kinetic correlation for the cycloaddition of cyclopentadiene **78** and ethyl acrylate **86**, over a pressure range of 80–210 bar and at temperatures from 38–88 °C (Scheme 27). The reactions were performed at very dilute concentrations and pure CO_2 fluid conditions were assumed. Normalisation of the rate constant to the rate constant at the same temperature and a fixed density of 0.5 g ml^{-1}, was shown to give a linear function of density.[66] The calculations were also repeated for the data from previous work by Ikushima,[62] and Paulaitis and Alexander,[60] and gave good agreement, demonstrating that the density of the fluid was more significant than the pressure.
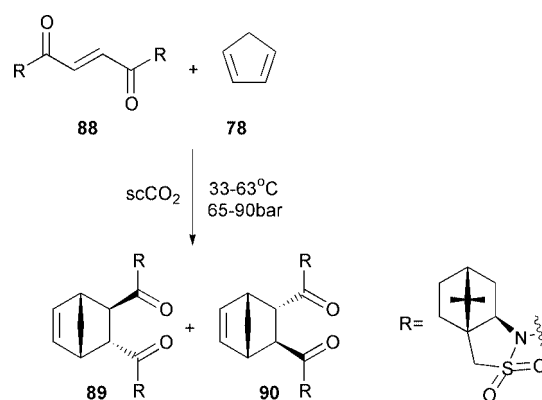

Scheme 27

The regiochemical selectivity of Diels–Alder reactions was also investigated.[67] A sapphire window was employed to allow visual inspection of the phase behaviour during the reaction. On examining the methyl acrylate–isoprene system investigated by Ikushima,[62] under identical conditions, a two phase system was observed. On analysis of the total reaction mixture, similar selectivity was observed to that achieved in conventional solvent, with no dramatic reversal in selectivity. Similarly, on performing the reaction at 50 °C and 92.5 bar under single phase conditions, no deviation from the normal selectivity was observed.

Using a series of alternative dienes and dienophiles, with differing steric and electronic properties, the Diels–Alder reaction was investigated in $scCO_2$. In all of the investigated cases, regioselectivity similar to that observed in conventional solvent was achieved, with no dramatic variation on modification of the pressure.
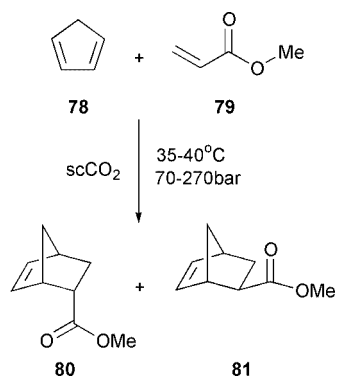
In 1998, Chapuis *et al.* reported the first Diels–Alder reaction in $scCO_2$ controlled by a chiral auxiliary.[68] As part of a study into solvent effects (particularly solvent polarity) on stereoselectivity, the reaction between cyclopentadiene **78** and dienophile **88** was performed in $scCO_2$ (Scheme 28). In conventional solvent, the de generally increased with polarity (58% de in CCl_4, 92% de in water), although several anomalies were observed such as diethyl ether (87% de) and hexane (70% de). For these anomalies, the reaction was not homogeneous as the product crystallised out, and the high selectivity was attributed to reaction at the solid–liquid interface. In $scCO_2$, the best selectivity was observed around the critical point (65% conversion, 93% de at 33 °C, 74 bar) although a similar result was obtained at slightly higher temperature and pressure (100% conversion, 92% de at 43 °C, 78 bar). Although no real trend in selectivity with pressure was observed, the reaction was particularly poor below the critical point (1.4% conversion, 56% de at 33 °C, 65 bar). The conversions and selectivities in $scCO_2$ are generally high (equivalent to the highest observed), although it was not known if the mixture was homogeneous or whether precipitation occurred as observed in some organic solvents.


Scheme 28

In our own laboratories, reaction control and potential tuning in the Diels–Alder reaction between cyclopentadiene **78** and methyl acrylate **79** in $scCO_2$ was investigated.[69] The theoretical explanation is based on a tuning function, as follows: transition state theory describes two reagents forming an activated complex in a rapid equilibrium, which in turn forms the product. It is suggested that if the reagents can form two different products *via* competing transition states, then the selectivity depends on the ratio of the two rate constants. The rate of change of the rate coefficient ratio depends on the tuning function of the two transition states, which is dependent on interactions between solvent molecules and the transition states and is therefore a function of density. Calculation using this tuning function suggested that a maximum in selectivity would occur at a density of 0.540 g ml^{-1}, significantly above the critical density of 0.465 g ml^{-1}.

The experimental study (Scheme 29) was based on that reported by Kim and Johnston,[61] however, on investigation of the phase behaviour, it was considered that this previous work had been performed with compositions well below the critical point and in the liquid phase. A much lower concentration was therefore used in order to guarantee single phase behaviour within the SCF region. The product ratio, **80** : **81**, was found to be density dependent, going through a maximum (or a minimum for **81** : **80**). The maximum ratio did not occur at the critical density but was in good agreement with the theoretical values.
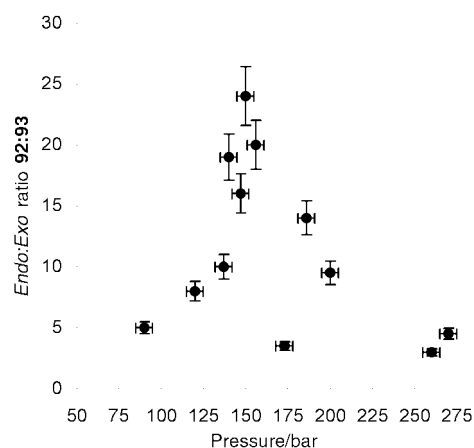
Scheme 29

Fig. 6 Variation of *endo : exo* selectivity with pressure for the Diels–Alder reaction between cyclopentadiene and *n*-butyl acrylate catalysed by scandium triflate.

The poor rates and selectivities in this uncatalysed Diels–Alder reaction, however, limited its synthetic value. In order to improve this situation a Lewis acid catalysed Diels–Alder system was developed using scandium trifluoromethanesulfonate as a mild CO_2-philic Lewis acid.[70] Optimisation of the catalytic system for the reaction between *n*-butyl acrylate **91** and cyclopentadiene **78** showed that quantitative conversion was achieved at a temperature of 50 °C, in 15 hours with a catalyst loading of 6.5 mol% (Scheme 30). On increasing the temperature to 80 °C, complete conversion was achieved with a reduced catalyst loading of 1 mol%. The reaction was, however, very slow in the absence of the catalyst, with a conversion of <10% being observed.

Scheme 30
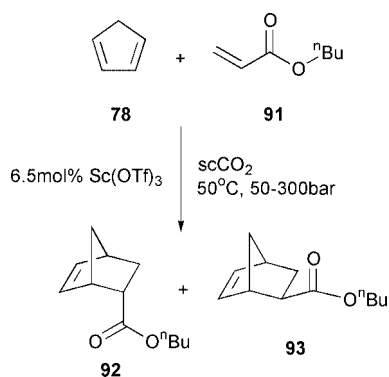
On investigation of this reaction at a range of pressures and hence SCF densities, a more dramatic product control was observed. The *endo* to *exo* product ratio **92** : **93** increased with pressure to a maximum of 24 : 1, before falling on further pressure increase (Fig. 6). Optimisation of the product selectivity means that the maximum achieved in $scCO_2$ is significantly higher than that observed in conventional toluene or chloroform solvents (10 : 1 and 11 : 1 respectively).

Improved selectivities compared to those observed in conventional solvents were also observed on optimisation of the $scCO_2$ solvent conditions for other dienophiles (methyl acrylate **79** >9 : 1 and phenyl acrylate **94** >8 : 1). The Lewis acid catalysed diastereoselective Diels–Alder reaction between (−)-menthyl acrylate **95** and cyclopentadiene **78** was also investigated using this catalytic system (Scheme 31).[71] A moderate diastereocontrol was observed which was once again optimised by tuning the pressure of the $scCO_2$ solvent. At a pressure of 155 bar and a temperature of 50 °C, an *endo* to *exo* ratio of 9.25 : 1 was achieved with a diastereomeric ratio of 3.6 : 1 which when combined means that the major diastereoisomer accounted for 71% of the overall yield.

Kobayashi also reported the use of scandium perfluoroalkanesulfonates as Lewis acid catalysts for Diels–Alder reactions in $scCO_2$.[72] A number of simple reactions were reported in which it was concluded that the catalyst activity was improved
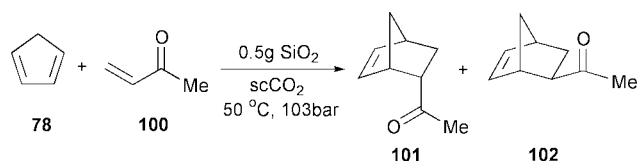

Scheme 31
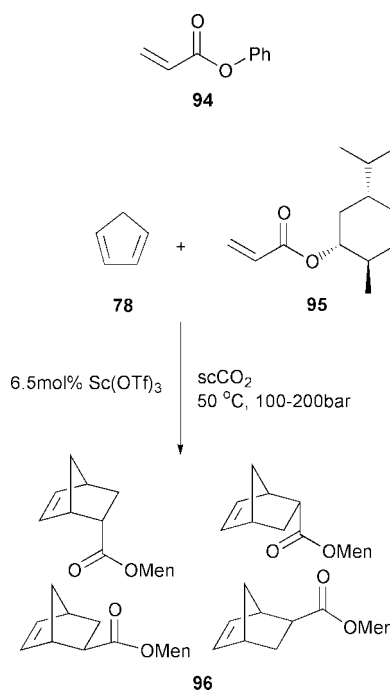
by increasing the length of the perfluoroalkyl chain, and hence its solubility. The optimum catalyst, $Sc(OSO_2C_8F_{17})_3$, was used to demonstrate the Lewis acid catalysed aza-Diels–Alder reaction in $scCO_2$. Danishefsky's diene **97** reacted with imine **98** to give the aza-Diels–Alder adduct **99** in 99% yield (Scheme 32).

Scheme 32
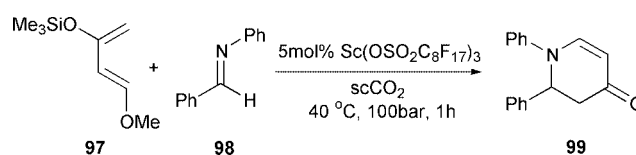
Danheiser *et al.* have reported a silica catalysed Diels–Alder reaction in $scCO_2$.[73] Studying a number of diene–dienophile pairs, the silica catalysed reaction was found to significantly enhance rate and selectivity. For the uncatalysed reaction between cyclopentadiene **78** and methyl vinyl ketone **100** at 50 °C over 4 h (Scheme 33), the yield was 29% and the product ratio **101** : **102** was 82 : 18. However if silica was added as catalyst, the yield increased to 82% and the selectivity to 92 : 8. The selectivity of the reaction was found to be independent of pressure, although the yield was found to decrease on

Scheme 33

increasing the pressure. This was explained as an increase in solubility of the reactants with pressure, meaning that less of the reactants are adsorbed on the catalyst surface, causing a shift away from the catalysed process.

Roberts investigated the effect of pressure on the bimolecular rate constant of the Diels–Alder reaction between maleic anhydride **75** and isoprene **76**, in scCO$_2$ at 35 °C.[74] Predictions of the thermodynamic pressure effect were also made using transition state theory and the Peng–Robinson equation of state. The rate was found to increase with pressure as observed previously,[60,66] with a linear dependence on density, and agreed closely with the thermodynamic pressure effect predictions over the entire pressure range.

### 3.5 Oxidation reactions in supercritical carbon dioxide

A significant proportion of the research effort for oxidation processes in SCFs has been in non-synthetic areas, utilising the homogenising properties of SCFs to enhance the total aerobic oxidation of organics.[75] This review will, however, focus on the synthetic oxidation processes which have been reported in scCO$_2$ media.

#### 3.5.1 Catalytic aerobic/dioxygen oxidation in supercritical carbon dioxide

Dioxygen and air are seen to be ideal oxidants as they are inexpensive, readily available and produce water as the only by-product. The high miscibility of gases with scCO$_2$ potentially offers rate benefits as observed for hydrogenation and hydroformylation. The aerobic oxidation of cyclohexane in the presence of an iron-porphyrin catalyst and acetaldehyde in scCO$_2$ was reported by Koda.[76] The main products of the reaction were cyclohexanol and cyclohexanone, but conversions were very poor.

Tumas developed halogenated porphyrin systems for the aerobic oxidation of cyclohexene in scCO$_2$.[77] Metalloporphyrins **103** and **104**, were active catalysts for formation of epoxidation and allylic oxidation products. In 12 hours at 80 °C, up to 350 and 580 turnovers were observed for **103** and **104**, respectively. Selectivity for epoxide formation is higher in scCO$_2$ (up to 34%) than in dichloromethane solution (up to 21%), however a number of allylic oxidation products are also formed.

Jiang has reported a palladium(II) catalysed oxidation of acrylic esters to acetals in scCO$_2$.[78] Methyl acrylate **79** is oxidised

103 R = H, **104** R = Br
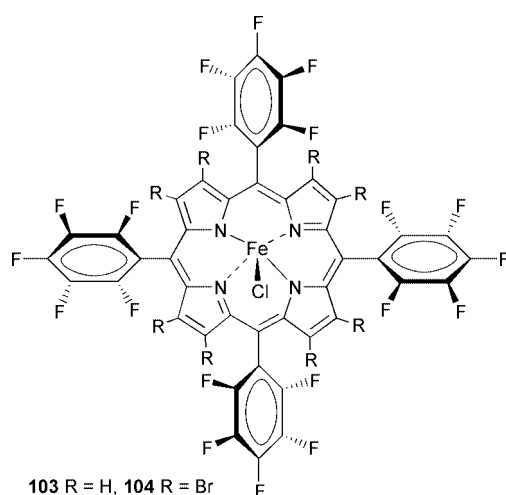
by dioxygen in the presence of excess methanol, catalysed by PdCl$_2$ with CuCl or CuCl$_2$ as co-catalyst to give the dimethyl-acetal **105** as the major product (Scheme 34). The reaction gave good conversion (93%) and selectivity for **105** (>93%) at 40 °C with an oxygen pressure of 1 bar. Increasing the oxygen pressure to 10 bar, increased both conversion (99.4%) and selectivity (96.6%). The identical reaction in DME solution gave only 46% conversion although addition of HMPA increased this to 92%.
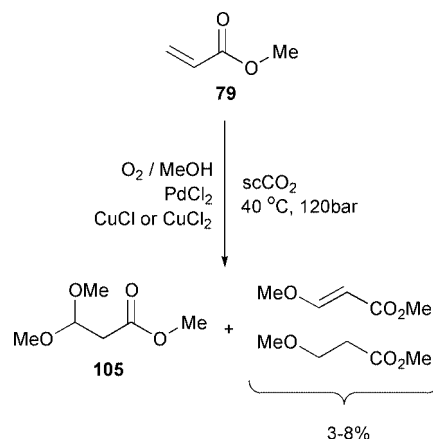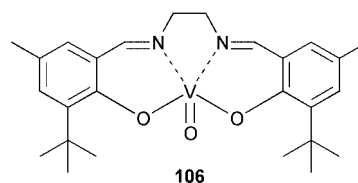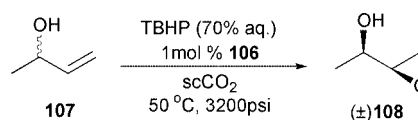

Scheme 34

3.5.2 Oxidation by alkyl peroxide in supercritical carbon dioxide

Kolis investigated olefin epoxidation in scCO$_2$, using *tert*-butyl hydroperoxide (TBHP) and catalytic Mo(CO)$_6$.[79] Using aqueous TBHP solution (70 wt%), *trans*-diols were formed, whereas if anhydrous decane solutions of TBHP were used then the epoxide was formed. (Z)-Alkenes gave much faster rates than (E)-alkenes, with cyclooctene giving quantitative conversion to the epoxide (3 hours, 86 °C, 3200 psi). No reaction was observed with (E)-hept-2-ene or (E)-stilbene.

The diastereoselective epoxidation of olefins in scCO$_2$ has also been reported. By combining the Jacobsen type salen ligand with the vanadyl system, a salen catalyst **106**, which is re-oxidised by stoichiometric TBHP, was developed.[80]

106

A number of allylic alcohols were epoxidised using this catalytic system giving good yields (50–100%) at 40 °C after 24 hours. Good diastereoselectivity for the *erythro* product was observed for olefins with secondary alcohols (Scheme 35). Epoxide **108** was formed in 76% yield with a 69% de.

Scheme 35

Tumas investigated a number of transition metal catalysts for oxidation of olefins with TBHP in liquid CO$_2$.[81] The oxidation of activated olefins by anhydrous TBHP and catalytic oxo-vanadium(V) tri(isopropoxide) gave quantitative conversion and excellent selectivity for epoxide formation (85–100%) in liquid CO$_2$ at 25 °C. The rate was found to be 3 times faster than that in hexane solution.

Using titanium(IV) tetra(isopropoxide) in the presence of chiral diisopropyl L-tartrate ligand **109**, Tumas performed a Sharpless type asymmetric epoxidation of allylic alcohols in liquid CO_2 (Scheme 36). Epoxidation of allylic alcohol **110** at 25 °C gave a poor enantioselectivity (16% ee, 93% yield), however at 0 °C this was improved to 87% ee, with a quantitative conversion after 72 hours.
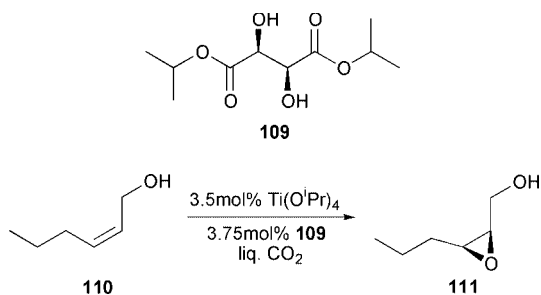
Scheme 36

Within our own laboratories we have investigated the selective oxidation of sulfides to cleanly form sulfoxides with no over oxidation to the sulfone. Using TBHP as the oxidant and Amberlyst™ 15 as a heterogeneous acid catalyst, a range of alkyl, aryl and benzyl sulfides have been selectively oxidised to the sulfoxide in quantitative yield.[71]

Using the above described sulfoxidation methodology, the diastereoselective sulfoxidation of cysteine derivatives in $scCO_2$ was investigated.[82] The oxidation of cysteine derivative **112** in conventional solvents (toluene and dichloromethane) led to mixtures of the diastereomeric products with no selectivity. However, on transferring the reaction to $scCO_2$, it proceeded in a quantitative yield, giving the *anti*-diastereomer **113** as the major product (Scheme 37).
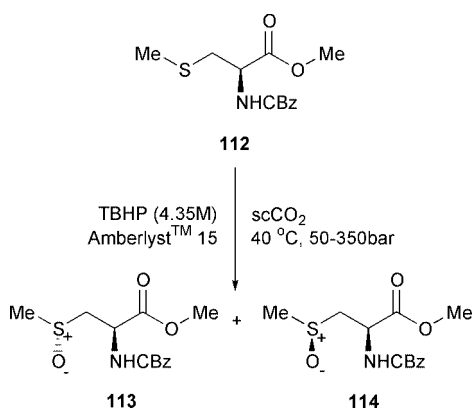
Scheme 37

Optimisation of the SCF conditions by adjustment of the pressure led to a dramatic enhancement of the diastereoselectivity. The selectivity increased with pressure to a maximum of >95% de at 185 bar, before falling to approximately 30% de at >300 bar pressure (Fig. 7). The maximum observed selectivity of >95% de in $scCO_2$ is a dramatic improvement on the 1 : 1 mixture of diastereomers observed when the reaction was performed in conventional liquid solvents.

A number of other substrates and catalytic systems were also investigated, and although the optimisation and selectivities were less dramatic, in all cases an improved selectivity was observed on transferring the reaction to $scCO_2$ conditions and tuning the pressure accordingly.[71]

3.6 Palladium mediated coupling reactions in supercritical carbon dioxide

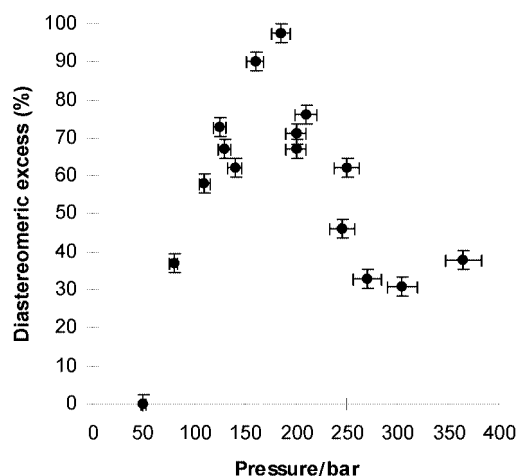Palladium catalysed coupling reactions in $scCO_2$ have received

Fig. 7 Variation of diastereomeric excess with pressure for oxidation of **112**.

much recent attention. Holmes observed that the solubility of phosphine ligands, traditionally used in conjunction with palladium catalysts such as $Pd(OAc)_2$, was low in $scCO_2$. A fluorinated phosphine ligand **115** was synthesised, which gave a palladium complex with dramatically enhanced solubility.[83]

The Heck reaction between iodobenzene **116** and methyl acrylate **79** (Scheme 38), catalysed by $Pd(OAc)_2$ in the presence of ligand **115**, gave a superior yield of methyl cinnamate **117** (92%), than reported in conventional solvent. Examples of other intermolecular Heck reactions, intramolecular Heck reactions, Suzuki and Sonogashira couplings were also reported, giving comparable yields to those obtained in conventional organic solvents. The work-up procedures for these reactions was significantly easier than those associated with standard reaction conditions. A simple pressure change facilitates separation, thus eliminating liquid–liquid partitioning.

Scheme 38
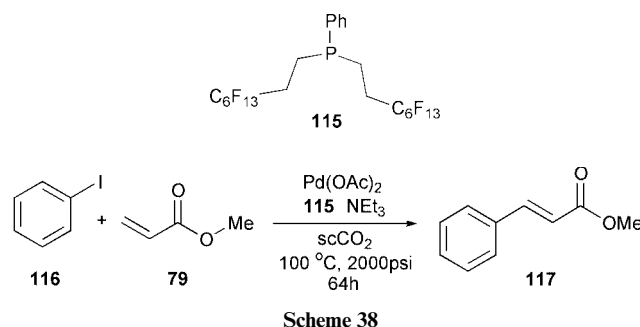
Around the same time, but independently, Tumas also developed the Heck and Stille coupling reactions in $scCO_2$.[84] The Stille cross-coupling reaction between iodobenzene **116** and vinyl(tributyl)tin **118** was investigated with a number of alternative ligands using $Pd_2(dba)_3$ as the source of palladium (Scheme 39). The nature of the ligand was found to significantly affect the yield. Using PPh_3, a 49% conversion was achieved, which was only slightly better than that observed with no ligand present (38%). However, tris(2-furyl)phosphine showed good activity (86% conversion), and a quantitative conversion (>99%) was achieved with ligand **119**. The differing conversions were suggested to be an effect of solubility, with PPh_3 being virtually insoluble in $scCO_2$.

Scheme 39

119   **120**
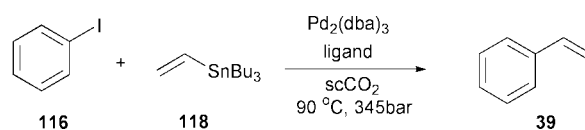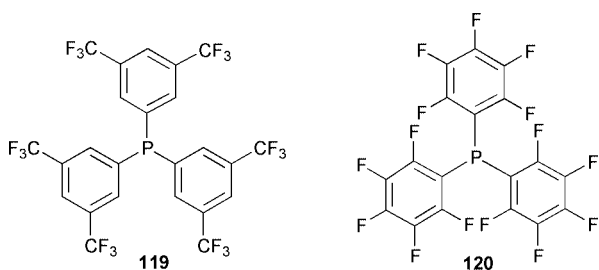
The Heck reaction between iodobenzene **116** and both methyl acrylate **79** and styrene **39** (Scheme 40) was also investigated. The use of fluorinated ligands **119** or **120**, resulted in high conversions (>94%), comparable to the highest reported yields in conventional solvent.
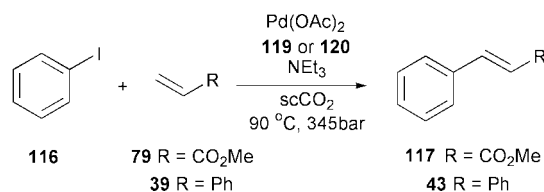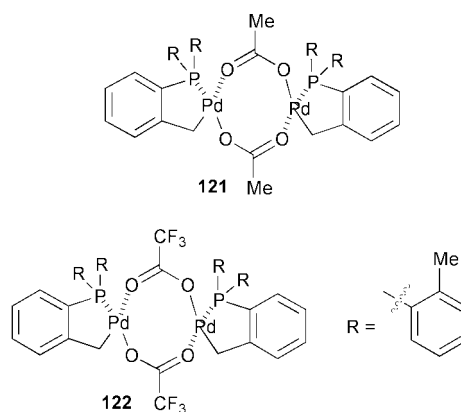

Scheme 40

In our own laboratories, a series of palladium catalysed coupling reactions in scCO$_2$, using commercially available ligands have been investigated. This is considered to be important if the procedures are to be widely adopted.[85] The nature of the initial palladium source is crucial. A series was investigated, including several fluorinated species. Using Pd(OAc)$_2$ as the palladium source, both triphenylphosphine and tris(2-furyl)phosphine ligands (TFP) gave promising results for the Heck reaction of methyl acrylate **79** and iodobenzene **116** (Scheme 41). However, high catalyst loadings (14 mol%) and prolonged reaction times (40 h) were required for complete conversion. Changing the base from triethylamine to diisopropylethylamine gave a modest improvement.
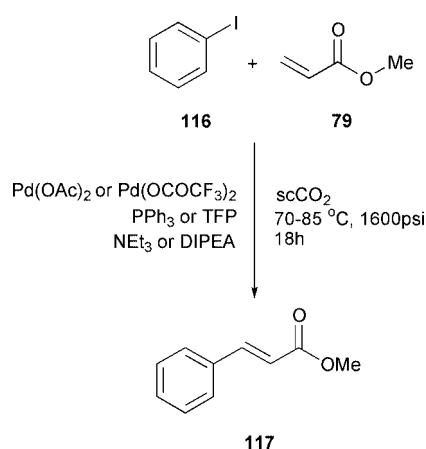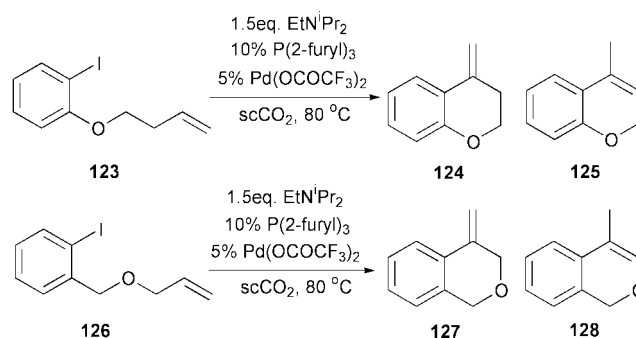

Scheme 41

Palladium trifluoroacetate and palladium hexafluoracetyl-acetanoate were investigated as catalysts. It was considered that they would have enhanced solubility in scCO$_2$, as would have any free ligands dissociated from the metal centre. These catalysts were found to be much more active, allowing lower catalyst loadings (2%), with TFP still being the best ligand. However, other ligands now gave acceptable conversions, including those often considered to be poor when used for Heck reactions (PBu$_3$, PCy$_3$). With a moderate increase in catalyst loading (6%), the reaction proceeded in the absence of ligands. The activity of metallocycles **121** developed by Hermann, was also reported (4 mol%, 43% conversion). Once again, replacement of acetate groups by trifluoroacetate **122** significantly enhanced

the conversion (2 mol%, >95% conversion). The optimised catalytic systems were also used to perform other Heck, Suzuki and Stille coupling reactions, giving superior results to those previously reported, with low catalyst loadings and moderate temperatures.

121

122

The intramolecular Heck cyclisation reaction of two related substrates **123** and **126** were also studied (Scheme 42).[86] It is known that in many such cases, double bond isomerisation to form thermodynamically more favoured alkenes is a serious problem which can only be alleviated by the addition of expensive silver salts or toxic thallium salts, which have obvious limitations for scale-up. Cyclisation of **123** and **126** in acetonitrile solvent gave complete conversion, however the isomerised endocyclic products **125** and **128** account for 76% and 80% of the yields, respectively. It has, however, been shown that by carrying out the reaction in scCO$_2$, not only is a complete conversion achieved, but also suppression of the double bond isomerisation reaction is observed. The desired exocyclic products **124** and **127** account for 83% and 93% of the yield respectively.
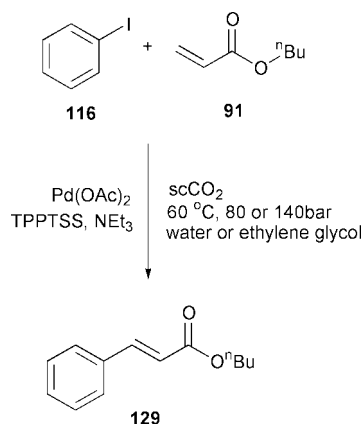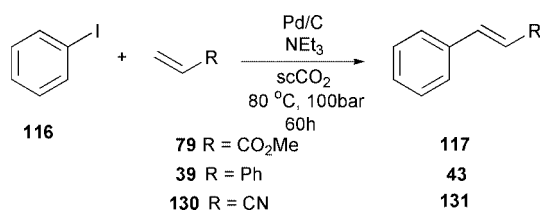

Scheme 42

Arai reported a Heck reaction using water soluble catalysts in scCO$_2$–water biphasic systems.[87] The coupling of iodobenzene **116** with butyl acrylate **91** in scCO$_2$ was investigated using Pd(OAc)$_2$ and triphenylphosphine trisulfonate sodium salt (TPPTSS) as water soluble ligands (Scheme 43). In the absence of co-solvent, the catalyst remains insoluble and yields are low (<5% at 80 bar). Addition of a polar co-solvent such as water increases the rate, with conversions up to 18% with TON of 36. Use of a more CO$_2$-philic co-solvent such as ethylene glycol offered further enhancement (conversion 29%, TON of 58 at 80 bar). Importantly, no catalyst leaching occurred.

Cacchi investigated the reaction of aryl iodides with a variety of olefins in scCO$_2$ in the presence of triethylamine and a heterogeneous catalyst of palladium on carbon.[88] Without optimisation of SCF conditions, the palladium catalysed vinylic coupling of methyl acrylate **79**, styrene **39** and acrylonitrile **130** with iodobenzene **116** and a range of other aryl iodides was achieved in moderate yields (Scheme 44).
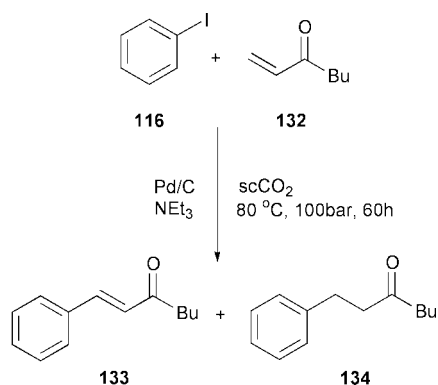
Scheme 43

79 R = CO₂Me   117
39 R = Ph   43
130 R = CN   131

Scheme 44

The reaction of aryl iodides with butenone **132** was also reported, with a mixture of the vinylic substitution product **133** and the hydroarylation product **134** being formed in an approximate 85 : 15 ratio (Scheme 45). The ratio of the two products was found to be independent of solvent following investigation of the reaction in more conventional media, however, the yields were found to be significantly reduced (benzene 18%, THF 15%, DMF 66%).

Scheme 45

Noyori investigated the palladium catalysed carbonylation of aryl halides in scCO₂.[89] The intramolecular carbonylation of 2-iodobenzyl alcohol **135**, catalysed by PdCl₂(MeCN)₂ in scCO₂, proceeded efficiently to give phthalide **136** with a TON of 1880 after 18 h (Scheme 46). Changing the ligand to the more soluble triethylphosphite gave an increase in rate with a TON of 5000 after 18 h. Even at CO pressures as low as 1 bar, the TON was still 4650, compared with a TON of 3100 at this pressure in toluene solution, showing that the rate of reaction is faster than in conventional organic solvent.
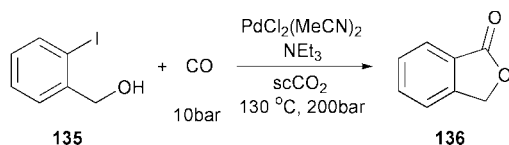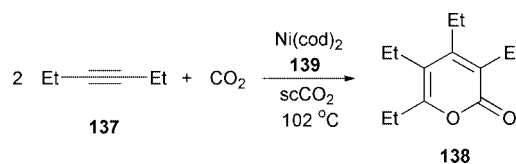

Scheme 46

3.7 Miscellaneous catalytic synthetic reactions in supercritical fluids

A number of miscellaneous catalytic synthetic processes, utilising scCO₂ and other SCFs as reaction media have been reported. Although these topics have not received as much attention as those previously discussed, several important synthetic transformations have been reported, and a number of interesting observations and new strategies in the use of SCFs as solvents have been demonstrated.

3.7.1 Nickel catalysed 2-pyrone formation in supercritical carbon dioxide

The coupling of two alkyne molecules with CO₂ in the presence of nickel gives 2-pyrones. Reetz *et al.* investigated this process in scCO₂, combining hex-3-yne **137** and CO₂ to form tetra-ethyl-2-pyrone **138** (Scheme 47).[90] The catalyst is generated *in situ* from Ni(cod)₂ and the bidentate diphosphine 1,4-diphenyl-phosphinobutane [Ph₂P(CH₂)₄PPh₂] **139**. The selectivity and TON of 7, although only moderate, was similar to those reported in conventional solvent. Changing from **139** to tri-methylphosphine as ligand increased the activity and allowed lower temperatures (51 °C) to be used and a higher TON of 18. The catalyst did, however, have a shorter lifetime in scCO₂ compared with conventional solvent, having a TON of 60 in THF.[5]

Scheme 47

3.7.2 Catalytic Pauson–Khand reaction in supercritical carbon dioxide

The co-cyclisation of an alkyne with an alkene and carbon monoxide leading to cyclopentanones is known as the Pauson–Khand reaction. In 1997, Jeong reported several examples of the Pauson–Khand reaction in scCO₂, catalysed by octacarbonyldicobalt.[91] The intramolecular reaction of enyne **139** was optimised to give a yield of 85% of **140** using 2.5% catalyst loading, a CO pressure of 15 bar, a total pressure of 180 bar and a temperature of 69 °C (Scheme 48). The reaction was also successful for a number of substituted enynes.
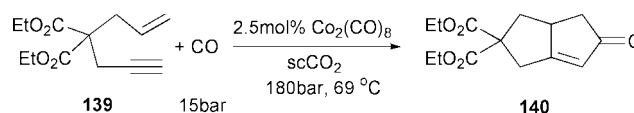
Scheme 48

An intermolecular reaction was also demonstrated, with phenyl acetylene **141** coupled to an excess of norbornadiene† **142** to give **143** in 87% yield (Scheme 49).
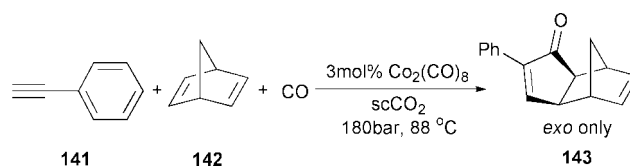
Scheme 49

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† The IUPAC name for norbornadiene is bicyclo[2.2.1]heptadiene.

3.7.3 Olefin metathesis in compressed carbon dioxide

Furstner and Leitner reported transition metal catalysed olefin metathesis reactions in compressed CO_2 media.[33] Using conventional metathesis catalysts **144** and **145**, ring opening metathesis polymerisation (ROMP) of norbornene and cyclo-octene gave the corresponding polymers in excellent yields in both liquid CO_2 and $scCO_2$ (*vide infra*). Ring-closing metathesis (RCM) was also investigated and remarkable observations were made.[33] It was found that the RCM of **146** was extremely sensitive to density, with the 16-membered ring **147** being formed in excellent yield (>90%) at densities >0.65 g ml^{-1}, whereas mainly oligomers (70% with 10% **147**) were produced at low densities (Scheme 50). This density dependence was explained as a dilution effect, as at higher densities, there are in effect more solvent molecules and the more dilute conditions favour the intramolecular reaction and *vice-versa*. A number of other cyclisations were performed in good yield. An interesting observation was that catalyst **144** which is normally deactivated in the presence of basic N–H groups, was active under such conditions in CO_2 solution. This was attributed to the *in situ* protection of the amine by reversible formation of the corresponding carbamic acid.

144a R= CH=CPh$_2$
**144b** R= Ph

145

Scheme 50
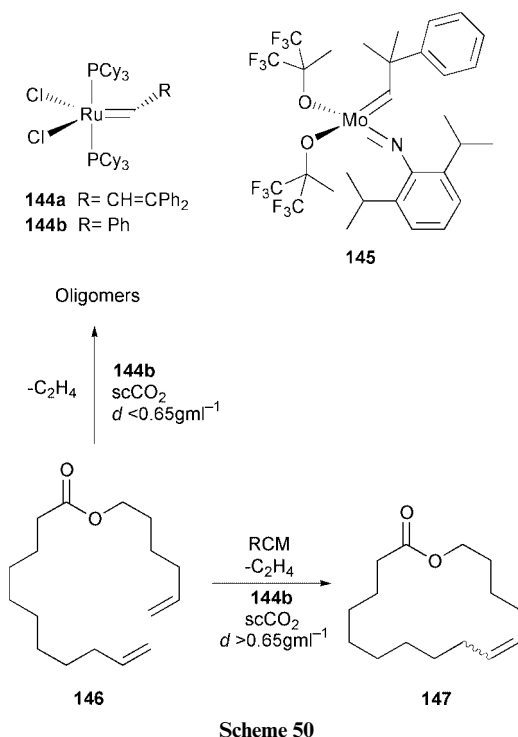
3.7.4 Friedel–Crafts alkylation in supercritical fluids

Poliakoff has previously reported the continuous hydrogenation using a SCF flow reactor.[42,43] Using the same flow cell, with a fixed bed heterogeneous polysiloxane supported acid catalyst, continuous Friedel–Crafts alkylation of aromatics has been performed in SCF media.[92] Mesitylene **148** was alkylated in sc-propene ($T_c = 91.9$ °C, $P_c = 46.0$ bar), which acted both as solvent and alkylating agent (Scheme 51). Temperatures required were high (160 °C), however because of the short residence time, and although the mono-alkylated species **149** is the major product (25% yield, 6% **150**), selectivity is poor. Selectivity is, however, much improved if $scCO_2$ is used as the reaction medium with propan-2-ol as the alkylating agent. At a molar ratio **148** to propan-2-ol of 2 : 1, a pressure of 200 bar, catalyst temperature of 250 °C and a flow rate of 0.60 g min^{-1}, **149** is produced as the only product with a conversion of 42%, at a rate of 0.13 g min^{-1}. Alkylation of anisole also gave similar results, with increased selectivity achieved in the $scCO_2$–propan-2-ol system.
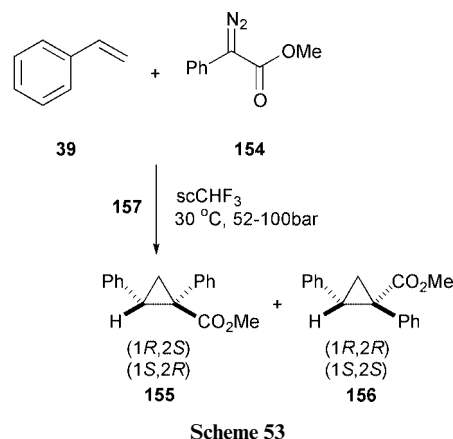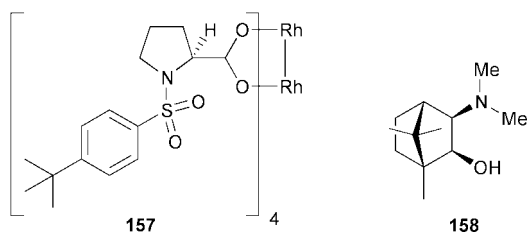

Scheme 51
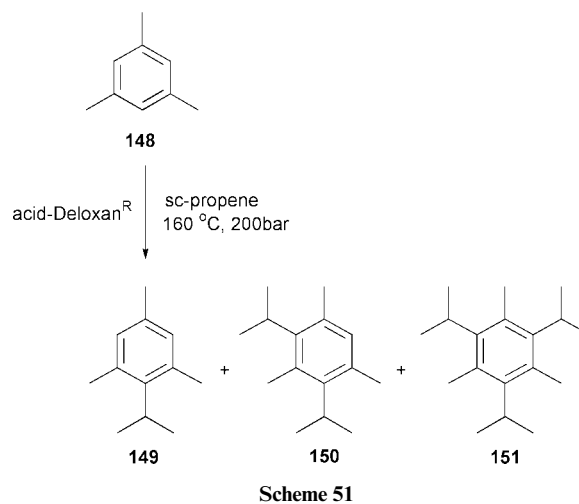
Using the same continuous flow reactor apparatus, the acid catalysed dehydration of alcohols in $scCO_2$ was also investigated.[93] The dehydration of butane-1,4-diol **152** gave THF **153** with a quantitative conversion at a flow rate of 0.5 ml min^{-1} through the 10 ml reactor (Scheme 52). The dehydration of a number of other diols, to give various cyclic ethers and acetals in more moderate yields, were also reported.

Scheme 52
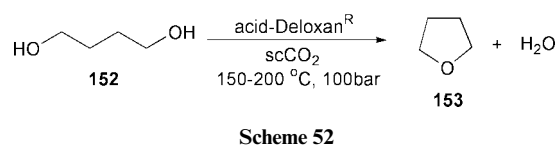
3.7.5 Catalytic asymmetric cyclopropanation in supercritical fluids

In 1999, Jessop reported a homogeneous catalytic asymmetric cyclopropanation reaction in $scCHF_3$, which was dependent on fluid pressure.[94] The cyclopropanation reaction between styrene **39** and methyl phenyldiazoacetate **154**, catalysed by dirhodium species **157** gave diastereomeric products **155** and **156** (Scheme 53). In conventional solvent, the ee of the major product **155** increased as solvent polarity decreased (61% in CH_2Cl_2, 85% in pentane). However, in $scCHF_3$ the relative permittivity of the fluid changes significantly with pressure, particularly around the critical point. This was demonstrated experimentally as the selectivity of this reaction changes from 40% ee at 100 bar, to 77% ee at 52 bar, in $scCHF_3$ at 30 °C. This effect was shown to be one of polarity, as the reaction was repeated in $scCO_2$ over a similar pressure range. Although selectivity was excellent (84% ee is equivalent to the best reported in conventional solvent), no dramatic pressure dependence was observed, which is expected as the relative permittivity of $scCO_2$ is not affected by pressure.

Scheme 53

157 **158**

The asymmetric alkylation of benzaldehyde **159**, catalysed by **158** was also reported.[95] Preliminary investigations of the alkylation of **159** by diethylzinc in scCHF$_3$, showed that the enantioselectivity was again pressure dependent (Scheme 54), although further details were not given.
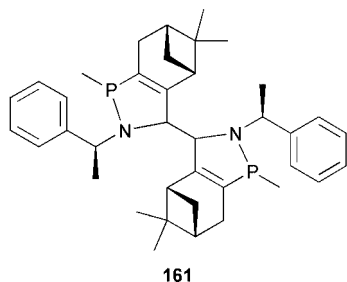

**159** **160**
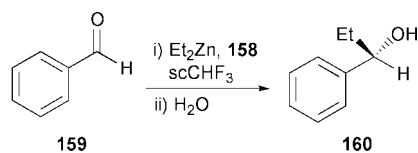
Scheme 54

3.7.6 Catalytic enantioselective hydrovinylation of styrenes in supercritical carbon dioxide

Leitner has reported the catalytic enantioselective hydrovinylation of styrenes in scCO$_2$, using a catalytic system of η^3-allyl-Ni(**161**)(**10**), where **161** is a dimeric azaphospholene ligand and **10** is the BARF anion.[96]

161

Hydrovinylation of styrene **39** with ethylene using the catalytic system described above was performed in both liquid CO$_2$ and scCO$_2$ at low to moderate temperatures (0–40 °C). Quantitative conversion, high regioselectivity (>70% and higher than in CH$_2$Cl$_2$ at the higher temperatures) and excellent enantioselectivity (83.2–91.6%) were achieved, with turnover numbers of 5500 and turnover frequencies of >1200 h^{-1} (Scheme 55).


39 **162**
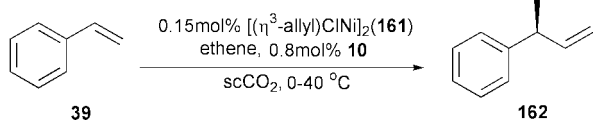
Scheme 55

3.7.7 Catalytic production of urethanes in supercritical carbon dioxide

Yoshida *et al.* have reported the use of scCO$_2$ both as the reaction media and carbonyl source for the production of urethanes from amines (Scheme 56).[97] Using potassium carbonate in conjunction with an ammonium salt catalyst, a number of primary and secondary aliphatic, as well as aromatic amines reacted well with butyl chloride to give the corresponding urethane in yields in the range of 72–90%.

Use of potassium phosphate in place of the potassium carbonate demonstrated that the carbonyl source was the CO$_2$
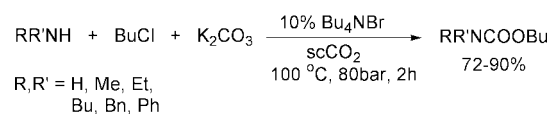
Scheme 56

and not the carbonate. This novel methodology is an attractive catalytic one-pot alternative to the use of phosgene in urethane synthesis.

3.7.8 Asymmetric Mukaiyama aldol reaction in supercritical fluoroform

Ikariya has reported the catalytic asymmetric Mukaiyama aldol reaction of a ketene silyl acetal of a thioester in scCHF$_3$.[98] Catalysed by a chiral binaphthol–titanium(IV) catalyst **163**, the reaction of ketene silyl acetal **164** with aldehyde **165** proceeded to give the silylated aldol product **166** in moderate yields (20–46%, Scheme 57). The maximum observed enantioselectivity for the reaction in scCHF$_3$ was 88% ee compared with a maximum of 72% ee for the equivalent reaction using a conventional toluene solution.

163

164 **165** **166**
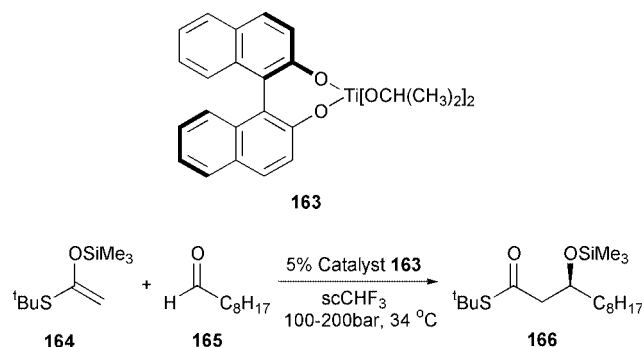
Scheme 57

3.7.9 Catalytic alkene hydroboration in supercritical carbon dioxide

Tumas reported a rhodium catalysed alkene hydroboration reaction in scCO$_2$.[99] Hydroboration of the styrene **169** with catecholborane (HBcat), rhodium catalyst precursor **167** and phosphorus ligand **168**, gave a quantitative conversion in scCO$_2$ (Scheme 58). Reactivities with other ligands were also reported but gave lower yields and/or selectivities.

(hfacac)Rh(cyclooctene)$_2$ Cy$_2$P(CH$_2$CH$_2$C$_6$F$_{13}$)

167 **168**

169 **170**
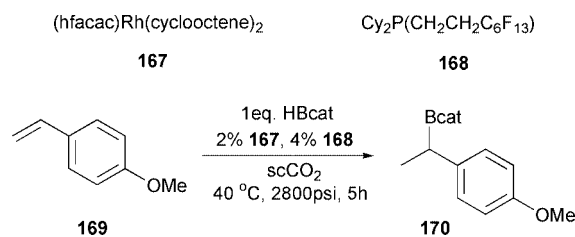
Scheme 58

The catalytic reaction is homogeneous and exhibits higher rates and regioselectivity compared with the equivalent reaction performed in liquid perfluoromethylcyclohexane or THF solvents.

3.8 Biotransformations in supercritical carbon dioxide

The prospect of using enzymes as heterogeneous catalysts in SCF media has created a significant interest since the mid 1980s. The low viscosity and high diffusion rates offer the potential to increase the rate of mass-transfer controlled reactions, and because enzymes are not soluble in SCFs, dispersion

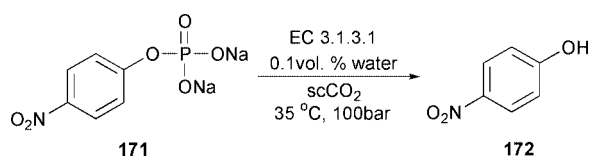of the free enzyme potentially allows simple separation without the need for immobilisation.[21]
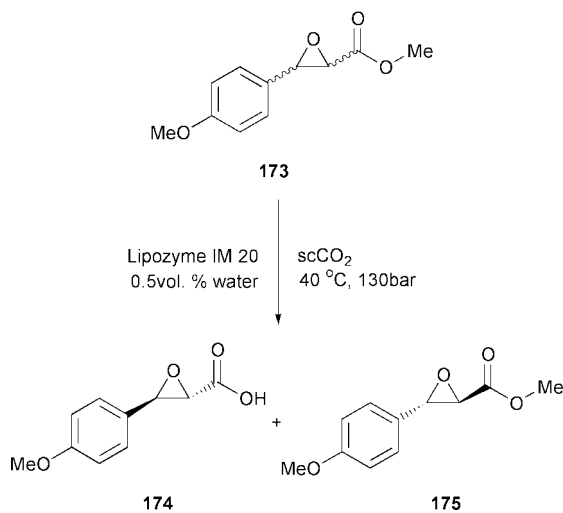
A large amount of literature exists, reporting enzymatic catalysis in scCO₂, performing hydrolyses, oxidations, esterifications and transesterification reactions. A number of factors and questions have been covered within the literature, such as the stability of enzymes in SCFs, the role of water in an essentially non-aqueous environment, temperature and pressure effects and the potential enhancement due to high diffusivity. This review will address these issues, however, it must be emphasised that many of these points are not fully understood and a number of contradictory results have been reported. Further information, particularly regarding experimental procedures and theoretical kinetics can be obtained from alternative recent reviews.[5,21]

3.8.1   Enzymatic hydrolysis in supercritical carbon dioxide

In 1985, Randolph reported the first enzyme catalysed reaction under SCF conditions. The enzyme alkaline phosphatase EC 3.1.3.1 was found to be active in scCO₂ for the hydrolytic formation of p-nitrophenol **172** from disodium p-nitrophenylphosphate **171**, at 35 °C and 100 bar, with a 0.1 vol% water concentration (Scheme 59).[100] p-Nitrophenol **172** was produced in a 71% yield after a reaction time of 5 hours. The rate was found to be independent of enzyme concentration, showing that the limiting factor was the rate of dissolution of **171** into scCO₂ solution. The enzyme was recovered after 24 hours in scCO₂ and still showed activity. In control experiments, no reaction was observed after 24 hours if the enzyme was absent.

the stereoselectivity of the reaction. The reaction rate was found to be considerably faster than that in a toluene–water mixture, where a 75% ee was observed after 21 hours, corresponding to a 5-fold increase in rate in scCO₂. No reaction was observed in a control experiment in the absence of the enzyme.

3.8.2   Enzymatic transesterification reactions in supercritical carbon dioxide

Carrea investigated the transesterification of N-acetyl-L-phenylalanine chloroethyl ester **176** with ethanol catalysed by *subtilisin Carlsberg*, in scCO₂ (Scheme 61).[102] A range of ethanol concentrations were investigated (0.5 vol%–5.0 vol%) at 45 °C and 150 bar. The highest activity was observed with an intermediate concentration of 2.5 vol% ethanol, which gave quantitative conversion after 45 min. No reaction was observed in the absence of ethanol. The enzyme was recovered and was used in repeated transformations with no appreciable loss of activity after 3 cycles. Enzyme stability was further confirmed by the increase in rate observed with an increase of temperature to 80 °C. Comparison of the rate with that obtained in conventional organic solvent showed that the reaction is significantly faster in scCO₂. The highest observed conversion was 89% after 2 hours in *tert*-amyl alcohol. The increase in rate under SCF conditions was attributed to the higher diffusion rates and lower resistance to mass transfer. Interestingly, increasing the ethanol concentration in organic media increased the reaction rate where the adverse was observed in scCO₂. This may be due to the decrease in diffusivity in the SCF by addition of a more viscous co-solvent.
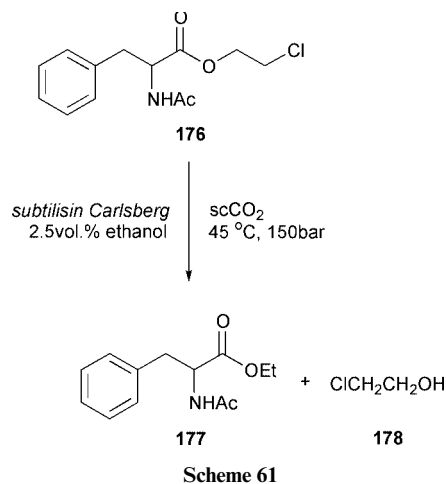

Scheme 59

Aaltonen reported the kinetic resolution of racemic 3-(4-methoxyphenyl)glycidic acid methyl ester **173** by immobilised *Mucor miehei* lipase (Lipozyme IM 20) in scCO₂ (Scheme 60).[101] The reaction was performed at 40 °C, 130 bar, with a water concentration of 0.5 vol%. The initial hydrolysis rate of the (2S,3R)-form was faster than that of the (2R,3S)-form, giving **174** with an 87% ee at a conversion of 53%, after 5 hours. A range of substrate and water concentrations (0.15 vol% to 0.5 vol%) were investigated, and were found to have no effect on

Scheme 61

Mori reported the use of lipid-coated β-D-galactosidase (prepared from *Bacillus circulans*) in scCO₂.[103] The lipid-coated enzyme (LCE) was found to be soluble over a wide range of temperatures and pressures (32–60 °C, 74–200 bar). In the transesterification of 1-O-p-nitrophenyl-β-D-galactopyranoside **179** with 5-phenylpentan-1-ol **180**, the reaction was 25-fold faster in scCO₂ (40 °C, 150 bar), than in diisopropyl ether, producing **181** in 72% yield after 3 hours (Scheme 62). On replacement of the LCE with the native β-D-galactosidase, no reaction was observed. FT-IR analysis suggested that the structure of LCE in scCO₂ is not significantly changed from that of the free enzyme in aqueous buffer solution. Temperature and pressure were shown to have a dramatic effect around the critical point. Decreasing the temperature at constant pressure (150 bar), so that the medium was now liquid CO₂ drastically reduced the rate of reaction, an effect not observed over this temperature range in aqueous solution. This effect is presumably again due to increased mass transfer limitations of the liquid state compared to the SCF. Similarly, decreasing the pressure below that of the critical pressure saw a large drop in activity.

Scheme 60

Scheme 62
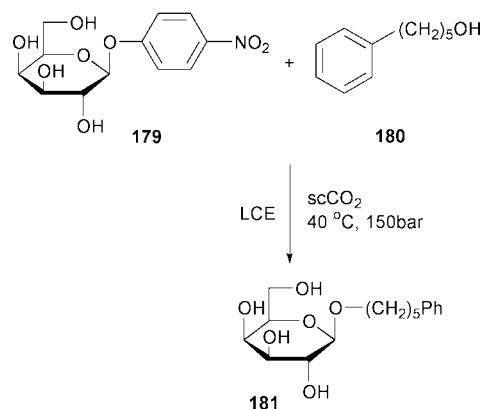
3.8.3 Enzymatic esterification in supercritical carbon dioxide

Using an alternative LCE (prepared from *Rhizopus delemar*), Mori investigated triglyceride synthesis in scCO$_2$.[104] The enzymatic esterification of lauric acid **182** with glyceride **183** at 40 °C, proceeded 5 to 10-fold faster in scCO$_2$ (200 bar) than in benzene at atmospheric pressure (Scheme 63). In scCO$_2$ di and tri-glycerides **184** and **185** were produced in 90% yield after 3 hours. The free lipase was found to be inactive under SCF conditions, whereas the LCE was found to maintain stability for over 80 hours. If the temperature was reduced below 31 °C, at constant pressure (200 bar), the esterification almost ceased. The solution under these conditions was then liquid phase and the LCE had a much reduced solubility. Reactivity increased with temperature until 45 °C, where it started to fall. This was attributed to denaturation at elevated temperatures. Rate also increased with pressure from 75 bar to 150 bar (at constant temperature of 40 °C), before falling on further pressure increase. By modifying temperature and pressure, it was observed that the enzyme activity could be reversibly controlled for at least 5 cycles.

Scheme 63
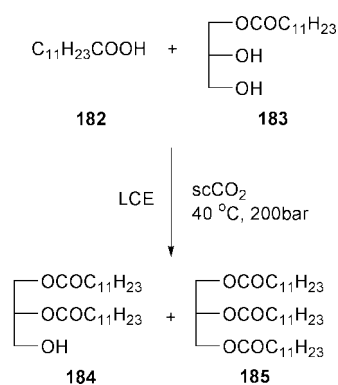
Ikushima reported the syntheses of terpene esters from primary terpene alcohols and acyl donors in scCO$_2$, catalysed by *Candida cylindracea* lipase (CCL).[105] The rate of esterification of *n*-valeric acid **186** with citronellol **187** in scCO$_2$ (Scheme 64) at constant temperature (35 °C) showed a dramatic pressure dependence around the critical pressure. The rate of reaction increased from around 120 μmol h^{-1} at 7.0 MPa, to a maximum of 282 μmol h^{-1} at 7.55 MPa, before falling to 130 μmol h^{-1} at 10.5 MPa and gradually dropping to 101 μmol h^{-1} at 24.5 MPa. The pressure dependence of the α-value of scCO$_2$ (a measure of the electron accepting power of scCO$_2$) followed an almost identical path to that of the rate dependence. It was proposed therefore that the mechanism of this esterification in scCO$_2$ involved CO$_2$ interacting with, and activating the enzyme in a Lewis acidic manner.
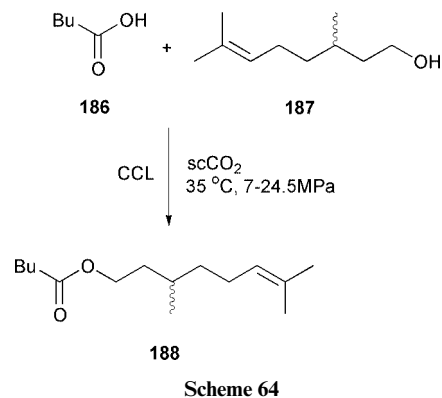
Scheme 64

In the CCL catalysed esterification of oleic acid **189** with citronellol **187** in scCO$_2$ forming 3,7-dimethyloct-6-enyl ester **190** (Scheme 65), the stereoselectivity exhibited a similar pressure dependence. Around the critical pressure, moderate selectivity was observed (26% ee at 7.58 MPa), increasing dramatically to >98% ee at 8.41 MPa, before falling to 4% ee at 10.15 MPa. The weight of the CCL was found to change significantly over the pressure range, showing a large increase in the 7.7–8.7 MPa region, suggesting that a large number of CO$_2$ molecules were becoming reversibly absorbed by the enzyme. FT-IR experiments also suggest a significant change in structure over this pressure range, and the authors suggested that this corresponded to a change in conformation whereby the α-helix "lid" covering the active site swung wide open and allowed easier access for the substrate.
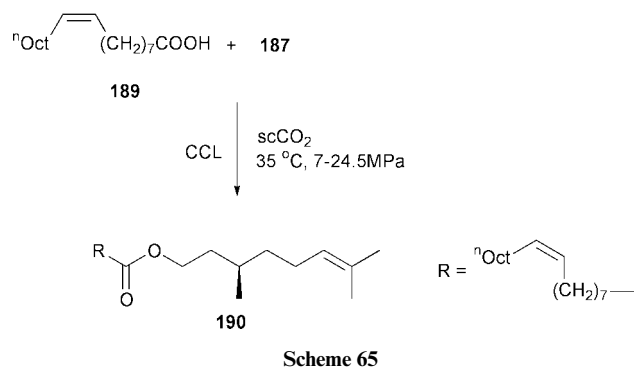
Scheme 65

Brunner studied the reaction rate and selectivity of the enzymatic kinetic resolution of 1-phenylethanol **191** with vinyl acetate **192**, in scCO$_2$ over a range of temperatures from 40 °C to 160 °C (Scheme 66).[106] The activity of the enzyme (Novozym 435, EC 3.1.1.3 from *Candida antarctica* B) was found to be temperature dependent at constant pressure and concentration, increasing with temperature to give a maximum conversion of **191** of 26.8 mmol h^{-1} at 92 °C, before falling steadily to be inactive at temperatures >160 °C. This rate was similar to the best achieved in an organic solvent. At a constant temperature of 60 °C, the enzyme activity was found to be pressure dependent, with the maximum reactivity observed at 15–20 MPa. The stereoselectivity was found to be excellent and independent of temperature, with methyl (*R*)-1-phenylethyl acetate **193** produced in >99% ee achieved at 50% conversion.

Cernia reported the enantioselective acetylation of a number of racemic alcohols using an immobilised lipase (*Pseudomonas*

Scheme 66
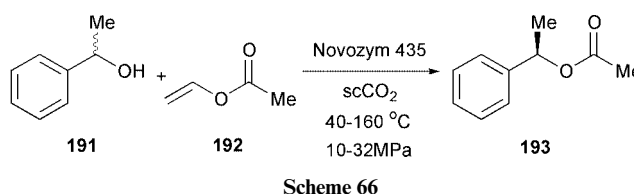
sp. from Amano P) in scCO$_2$.[107] The immobilised lipase was found to have almost double the activity of the free enzyme along with a greater thermal stability (37–60 °C). This stability was higher than that observed in conventional organic solvents (83% residual activity in scCO$_2$ after 5 hours, compared with 59% in hexane and 62% in benzene). The lipase was also found to be stable over a large pressure range (15–25 MPa). The rate of reaction for the esterification of a range of alcohols was found to be significantly faster in scCO$_2$ than in conventional solvent in all cases. The reaction of racemic (E)-pent-3-en-2-ol 194 reaches 50% conversion after 250 minutes at 40 °C, compared with the rate in toluene (best of the organic solvents) where <20% conversion is achieved in this time (Scheme 67). The enantioselectivity was also higher in scCO$_2$, with 196 being produced with an 89% ee, at 53% conversion, compared with a 65% ee at 19% conversion in toluene. These rate and selectivity enhancements were mirrored across the range of alcohols investigated.
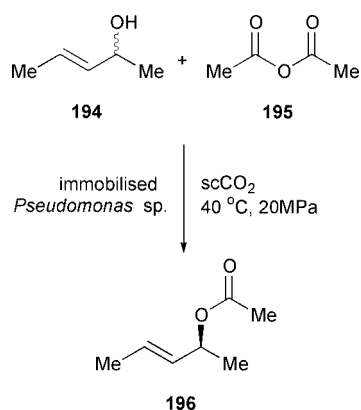
Scheme 67

### 3.9 Polymerisation reactions in supercritical carbon dioxide

A significant amount of the current literature on reactions in SCF solvents and particularly using scCO$_2$ as reaction media, involve polymerisation processes. The controllability of fluid properties, combined with the inertness to radical conditions, ability to plasticise glassy polymers, associated processing techniques and environmental friendliness makes scCO$_2$ a unique solvent in which to perform polymer synthesis. This is reflected in the commercialisation of a number of polymerisation processes utilising scCO$_2$ as the reaction solvent. This review will outline several recent examples which demonstrate the principles and potential advantages in performing various polymerisation methods in scCO$_2$. More information can be found in dedicated reviews by DeSimone, who is responsible for a large proportion of the research in this area.[5,108]

3.9.1 Homogeneous free radical polymerisation in supercritical carbon dioxide

Fluoropolymers are generally insoluble in conventional organic solvents and are often synthesised using CFCs as solvent. As discussed previously, fluorinated species have an enhanced solubility in scCO$_2$ and these materials are soluble in scCO$_2$ under mild conditions. ScCO$_2$ therefore potentially offers an environmentally benign alternative solvent for high molecular mass fluoropolymer synthesis.

In 1992, DeSimone reported the free radical chain growth polymerisation of 1,1-dihydroperfluorooctyl acrylate 197, initiated by AIBN in scCO$_2$.[109] The rate of decomposition of AIBN in scCO$_2$ was investigated and was found to be 2.5 times slower than in benzene solution. This was attributed to the lower relative permittivity of scCO$_2$, which offered less stabilisation to the transition state of the primary scission reaction. The decomposition in scCO$_2$ was also dependent on pressure, with a

maximum observed at around 250 bar.[110] Despite the slower decomposition, AIBN was found to be a more efficient radical generator in scCO$_2$, due to the absence of a cage effect in the less dense medium. The homopolymerisation of 197 in scCO$_2$ (59.4 °C, 207 bar), gave perfluoropolymer 198 in 65% yield, with a molar weight of 270 000 g mol^{-1} (Scheme 68). The reaction mixture remained homogeneous throughout.
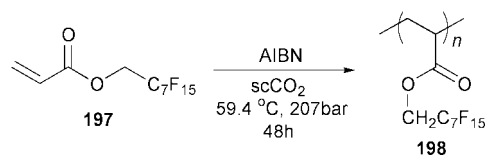
Scheme 68

The formation of statistical copolymers of fluorinated monomers with hydrocarbon comonomers such as methyl methacrylate was also investigated. The corresponding homopolymers of the hydrocarbon monomers were insoluble in scCO$_2$, however, the copolymerisations were homogeneous throughout.
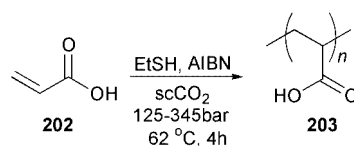
The telomerisation of 1,1-difluoroethylene 200 with perfluorobutyl iodide 199 was also reported (Scheme 69).[111] The distribution of telomers was highest at low degrees of telomerisation (degree of polymerisation (DP) = 2 or 3), extending to products up to DP = 9, with conversions of around 35%. The selectivity for normal (head–tail) addition was relatively constant across the range (20 : 1). The molar mass distribution appeared to be pressure dependent, with telomers of higher molar mass produced at higher pressures. This was explained as a result of the negative activation volume associated with the propagation.
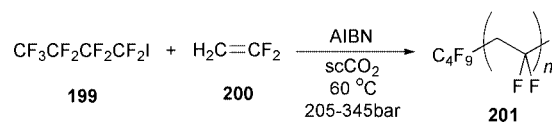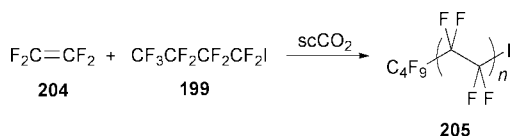

Scheme 69

3.9.2 Free radical precipitation polymerisation in supercritical carbon dioxide

Precipitation polymerisation is a form of heterogeneous polymer formation. The monomer is totally soluble in the reaction medium, however, even low molecular weight polymers are essentially insoluble and precipitate out on formation. DeSimone reported the precipitation polymerisation of acrylic acid 202 in scCO$_2$, using AIBN as radical initiator (Scheme 70).[112] No chain transfer to CO$_2$ was observed and the mass transfer rates of the monomer 202 were found to be significantly enhanced compared with those obtained in conventional solvents. The reaction began as a homogeneous solution, but on the onset of polymerisation the formation of solid particles was observed. Performing the reactions at a range of pressures (125–345 bar) indicated that there were no pressure effects on product molecular weight (~150 kg mol^{-1}), molecular weight distribution (3.8–3.9), particle size or morphology. Comparison of micrographs of the polyacrylic acid product 203 formed in scCO$_2$ and that synthesised in conventional solvent show the morphology to be similar. Molecular weight control could be achieved by use of varying amounts of chain transfer agent, ethanethiol.
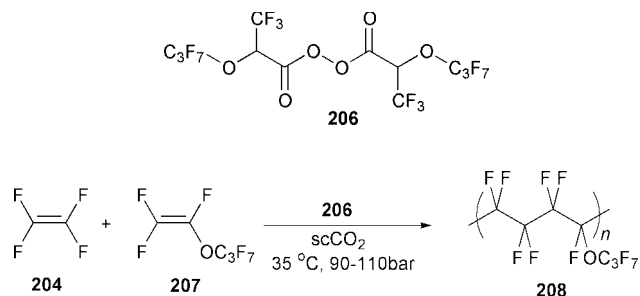

Scheme 70

The free radical telomerisation of tetrafluoroethylene **204** with perfluorobutyl iodide **199** was also reported.[113] Tetrafluoroethylene is explosive but can be stored safely under pressure of CO_2, therefore the use of $scCO_2$ as a reaction solvent is particularly practical. The telomerisation was performed both thermally and with AIBN initiation (Scheme 71). The thermal reaction (180 °C) remained homogeneous throughout, however, at the lower temperature of the AIBN reaction (68 °C), precipitation occurred on polymer formation. This precipitation was due to the relatively high crystallinity of the telomer product **205**.
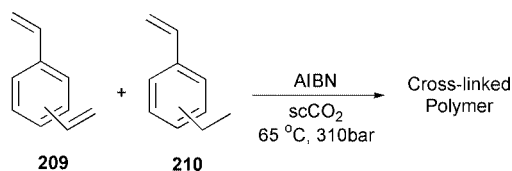

Scheme 71

The copolymerisation of tetrafluoroethylene **204** with perfluoro(propyl vinyl ether) **207** was also reported in $scCO_2$, using bis(perfluoro-2-propoxypropionyl) peroxide **206** as initiator (Scheme 72).[114] Under the reaction conditions (35 °C, 90–110 bar) the initial mixture was homogeneous and again, the polymer product **208** was observed to precipitate on formation. The polymer **208** was produced in 100% yield. Generally, an excess of **207** was required to perform this copolymerisation due to the lower reactivity of **207** than **204**. However, in $scCO_2$, the desired incorporation of **207** in the polymer was achieved at reduced monomer concentrations.

Scheme 72

Holmes *et al.* reported the synthesis of cross-linked polymers based on divinylbenzene (1,3- and 1,4-isomers) **209** and incorporating ethylvinylbenzene (1,3- and 1,4-isomers) **210** by precipitation polymerisation in $scCO_2$ (Scheme 73).[115] The polymer product was isolated in the form of discrete microspheres of diameter 1.5–5.0 μm, in yields of >90%. Under the reaction conditions (65 °C, 310 bar), much of the monomer mixture was insoluble and the reaction occurred as an unstabilised suspension polymerisation.
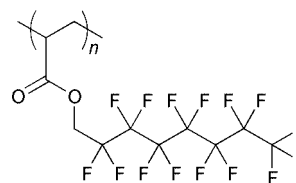

Scheme 73

3.9.3 Free radical dispersion polymerisation in supercritical carbon dioxide

Conventional dispersion polymerisation of unsaturated monomers is performed in dispersing media with the addition of interfacially active agents to stabilise the colloidal dispersion which forms. This stabilisation is usually a steric stabilisation,

by amphipathic macromolecules, which contain an anchoring segment which attaches to the polymer particle by physical adsorption, and a steric stabilising moiety which is soluble in the continuous phase. Successful stabilisation results in the formation of high molar mass polymers with high rates of polymerisation.

DeSimone developed a fluoropolymer stabiliser **211** for the dispersion polymerisation of methyl methacrylate **212** in $scCO_2$.[27] The stabiliser has a lipophilic acrylic-like backbone with a series of long CO_2-philic fluorocarbon chains.


211

The polymerisation of **212** was carried out both with and without stabiliser (Scheme 74). All the polymerisations were initially homogeneous. In the absence of stabiliser, poly(methyl methacrylate) **213** accumulated as a thick irregular film as precipitation polymerisation occurred, giving low yields (39%) of low molecular mass polymer (149 kg mol⁻¹). In contrast, polymerisation in the presence of a stabiliser **211** (either low molecular weight 110 kg mol⁻¹, LMW, or high molecular weight 200 kg mol⁻¹, HMW) formed a kinetically stable colloidal dispersion. High yields (85–95%) were obtained with improved molar masses (up to 321 kg mol⁻¹ using 4% of HMW) and the resulting product was easily isolated as a free flowing powder. No dependence on pressure was observed.[116]
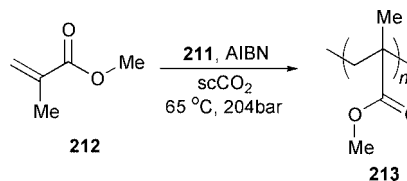
Scheme 74

Holmes *et al.* synthesised well defined AB block copolymers for use as surfactants (stabilisers) in the dispersion polymerisation of methyl methacrylate **212** in $scCO_2$.[117] Block copolymers can exhibit micelle-like aggregation if they are dissolved in a solvent which is more selective to one of the blocks. Copolymer **214** has a perfluorinated block which will have a high affinity for $scCO_2$ and a methyl methacrylate block which will stabilise the monomer.

$R = CH_2CH_2(CF_2)_5CF_3$
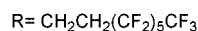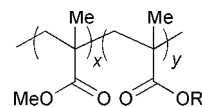
214

In the polymerisation of methyl methacrylate **212** (Scheme 75), significantly higher yields were obtained for poly(methyl methacrylate) **213** when surfactant **214** (1 wt%) was added (79–91% compared with 16%).[118] The molecular mass of the polymer was also increased by the presence of **214** (up to 340 kg mol⁻¹ compared with 22 kg mol⁻¹). The molecular weight and molecular weight distribution of the product was found to be dependent on the block ratio and molecular weight of the surfactant. Use of a low molecular weight surfactant did not prevent particle aggregation whereas if a high molecular weight
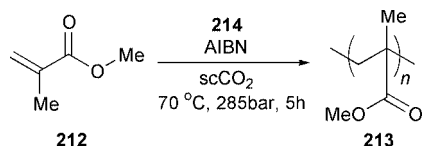
Scheme 75

surfactant was used, the product was isolated as a free flowing powder. The molecular weight of polymer **213** increased dramatically (160–340 kg mol⁻¹) on increasing the $y : x$ ratio of **214** from 1.0 to 1.3.

The copolymerisation of **209** and **210** (Scheme 73) was also investigated using **214** as a stabilising surfactant.[115,119] In the presence of **214** (3 wt%), much smaller poly(divinyl-benzene) particles were formed (0.29–0.50 μm compared with 1.5–5.0 μm for the unstabilised polymerisation), with a narrow particle size distribution, in an excellent yield (>95%). The phase behaviour was considered consistent with emulsion polymerisation. Thermal analysis showed the cross-linked resins to have high thermal stability with almost no thermal decomposition observed below 400 °C. The particle size and particle size distribution were found to be dependent on stabiliser concentration. With just 0.25% of surfactant, the particle size was reduced, however, the distribution was still large (0.5–3.5 μm). Increasing the concentration of surfactant to 1% further reduced the particle size along with the distri-bution (0.4–1.6 μm), however, the optimum concentration of surfactant was considered to be 3%, as small and highly uniform particles were produced (0.41 μm) and no aggregation was observed.

3.9.4 Cationic polymerisation in supercritical carbon dioxide

DeSimone investigated the cationic polymerisation of vinyl ethers and oxetanes in scCO₂.[120] Polymerisation of isobutyl vinyl ether **215**, catalysed by ethylaluminium dichloride and initiated by isobutyl vinyl ether adduct **219** was initially homo-genous in scCO₂, but became heterogeneous as the polymer **217** was formed (Scheme 76). Ethyl acetate was added as a mild Lewis base deactivator, and the reaction was quenched using sodium ethoxide. The equivalent reaction in cyclohexane was homogeneous throughout. The yield of polymerisation was high and equivalent to that achieved in cyclohexane solu-tion, giving predictable molar masses, although the molecular weight distributions were slightly higher than those achieved in hexane (1.8 *versus* 1.2). Molecular weight control was lost above temperatures of 40 °C. In the absence of initiator **219**, polymers of high molar masses and large molecular weight distributions were obtained.

215 R = CH₂CH(CH₃)₂ 217
216 R = (CH₂)₂N(C₃H₇)SO₂C₈F₁₇ 218
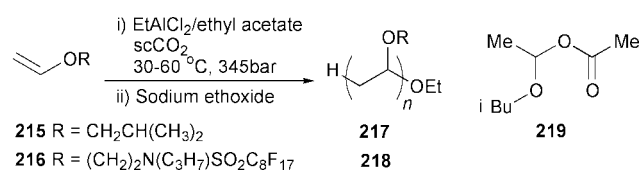
Scheme 76

Polymerisation of fluorinated vinyl ether **216** with ethyl-aluminium dichloride in the absence of initiator **219**, led to a homogeneous reaction giving polymer product **218** with a narrow molecular weight distribution (1.6). This suggested that the precipitation of the hydrocarbon polymer during the course of the reaction and continued propagation in the biphasic system was the cause of the broad molar mass distribution.

Polymerisation of oxetane **220** with boron trifluoride catalyst in both dichloromethane solution and in liquid CO₂, at −10 °C, exercised similar phase behaviour to that of the vinyl ether,

with polymer **221** being precipitated in the case of liquid CO₂ (Scheme 77). The yields (around 70%) and molecular weights were similar for the two alternative media, but mol-ecular weight distribution was slightly broader in liquid CO₂ (2.7 *versus* 1.9).

220 R = CH₂OCH₂CH₃ 221
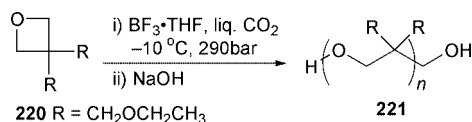
Scheme 77

3.9.5 Metal catalysed polymerisation in supercritical carbon dioxide

Furstner and Leitner reported the ring opening metathesis polymerisation (ROMP) of a number of cyclic olefins in both liquid CO₂ and scCO₂.[33] Using conventional metathesis cat-alysts **144** and **145**, ROMP of norbornene **222** gave the corre-sponding polymer in excellent yields (up to 97%) after short reaction times (Scheme 78). The yield and *cis* : *trans* ratio were similar in both liquid CO₂ and scCO₂, however, the molecular weight distribution was narrower in scCO₂ (2.0 *versus* 3.2 in liquid CO₂ and 2.3 in dichloromethane). During the course of the reaction, the polymer precipitated from the CO₂ phase. The *cis* : *trans* ratio was dependent on the catalyst with **144** favour-ing the *trans* geometry (25 : 75), whereas **145** gave a majority of the *cis* (82 : 18). Complete conversion of the monomer was observed after 1 hour even with a substrate to catalyst ratio of 5350 : 1.
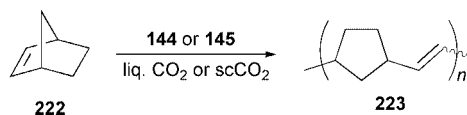
Scheme 78

Leitner has also reported the polymerisation of phenyl-acetylene **141** using rhodium catalysts in liquid CO₂ and scCO₂.[121] The polymerisation is performed using the complex (norborna-2,5-diene)rhodium acetylacetanoate as a catalyst precursor, either unmodified, or modified with phosphine ligand **31** (Scheme 79). The unmodified catalyst was insoluble in liquid CO₂, however, the polymerisation proceeded efficiently, giving mainly the *cis-cisoidal* product **224** (83 : 17) in a 65% yield after 1 hour. The reaction was significantly slower in THF solution, with a yield of 75% after 18 hours, of exclusively the *cis-transoidal* product **225**.
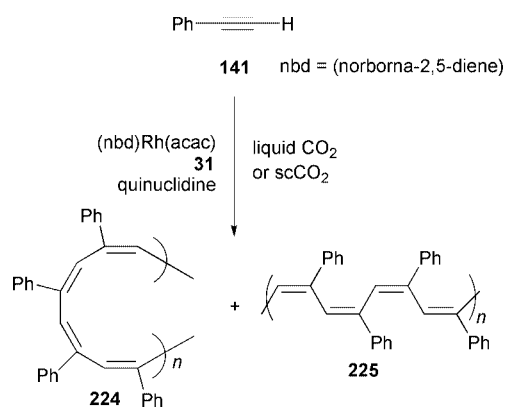
Scheme 79

Reaction of phenylacetylene using the modified catalyst system, was initially homogeneous, with the fluorinated phos-phine ligands enhancing the solubility of the rhodium catalyst.

Precipitation rapidly occurred as polymerisation took place. After a reaction time of 1 hour, the polymer was recovered in a 62–76% yield, with a molecular weight of 3.5–5.8 × 10⁴ and a molecular weight distribution of 7.7–10.1. These values were similar to those obtained with unmodified catalysts in CO_2 solution or in conventional organic solvent. However, the presence of the ligand had a significant effect on the stereoselectivity of the resulting polymer. The amount of *cis-transoidal* polymer **225** increased with addition of the ligand. By modification of the conditions, the product ratio could be changed from favouring production of the *cis-cisoidal* polymer (no ligand, 81% **224**) to producing the *cis-transoidal* polymer as the major product (ligand to catalyst 2 : 1, 58% **225**). This effect was particularly evident in liquid CO_2.

4 Summary and conclusions

Supercritical carbon dioxide is rapidly emerging as a versatile medium for carrying out a diverse range of synthetic reactions. The fundamental differences between supercritical fluids and conventional solvents open up many different avenues for potential exploitation, which can only lead to increased interest in using scCO₂. To exploit its potential to the full, we must also understand the fundamental principles behind the effects we are observing. To do this requires true interdisciplinary research involving academic synthetic chemists and industrial process chemists, physical chemists, and chemical engineers, all of whom have an important role to play. Although scCO₂ requires relatively high pressures, we are already seeing applications in consumer areas such as natural product extraction (decaffeination), polymer synthesis and dry cleaning, and the establishment of this technology will undoubtedly lead to further applications. Whilst there are limitations to using supercritical fluids for synthesis, there is no doubt that they are a fascinating medium for carrying out synthetic organic chemistry, and we are only just beginning to see the real potential and benefits they offer in addition to environmental aspects. Just how important it becomes remains to be seen, but we hope this article will stimulate further interest in this area.

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