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The Potential of Carbon Dioxide in Synthetic Organic Chemistry

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Abstract:

The aim of this review is to demonstrate, using examples developed in our own laboratories, that carbon dioxide has real potential in synthetic organic process chemistry. As well as potential environmental benefits, it offers opportunities for enhanced diastereo- and enantioselectivity compared to processes in conventional solvents. Fine control of reagent and product solubilities can lead to selective product separation and novel CO_2-induced reactions. Pd-mediated cross-coupling reactions in $scCO_2$ can give increased yields and selectivities, especially in the presence of usually incompatible functionality such as amines, which are protected in situ by reaction with CO_2. Useful reactions can also be carried out at subcritical pressures utilising either the Lewis acidity of CO_2 or the Brønsted acidity of carbonic acid formed in aqueous solutions under an atmosphere of CO_2. Finally, product processing (extraction, chromatography, crystallisation) can also be carried out using CO_2 without significant amounts of conventional solvents. We believe that the principles demonstrated here can be applied to a wide variety of procedures of relevance to organic process chemistry, and that the use of $scCO_2$ as a solvent, whilst currently in its infancy in this area, will be of increasing importance in the future.

1. Aim of This Review

The aim of this review is convey some of the potential of carbon dioxide technology in synthetic organic chemistry. In order to illustrate this, I have chosen examples of chemistry developed from within our group over the past 10 years or so, since we actively began research in this area. Some contributions from others active in the field will also be mentioned where appropriate, but this is a personal, rather than a comprehensive, account of developments in the area; thus, I apologise in advance to anyone who believes their contributions have been omitted. It is also beyond the scope of this review to provide anything more than a brief introduction to the fundamental properties of carbon dioxide. Fortunately, there are numerous recent reviews[1−4] and books[5−7] that have been published in this area, some specific to supercritical fluids, others covering more general aspects of alternative solvents, and the reader is strongly encouraged to look at these in more detail to get a broader coverage of the literature and background.

2. Introduction

There can be little doubt that CO_2 currently has the highest public profile of any molecule in the history of mankind and that this will continue for the foreseeable future. In the mid-1990s it became clear to us that environmental aspects of many things, including synthetic chemistry, were going to be of greater significance in the future.[8] Since then, ever increasing legislation, rising oil prices, political instability, and a general consensus that global warming is upon us with enormous potential ramifications have led to a marked increase in environmental awareness in the chemical community,[9] and of course, elsewhere.[10]

Our work with carbon dioxide came out of a short project utilising supercritical CO_2 ($scCO_2$) to extract various taxanes from yew tree clippings, and analyse them using supercritical fluid chromatography (SFC).[11] This was in collaboration with Tony Clifford and Keith Bartle, who had for many years established Leeds as a leading centre for CO_2 extraction and chromatography research, respectively. The taxane work was particularly pertinent to us, as many of the original taxanes were first isolated and characterised in Leeds by Professor Basil Lythgoe (now retired) in the early 1960s,[12] and became an area of intense interest in the early 1990s due to their anticancer activity.[13,14] Indeed, it is as an extraction solvent that CO_2 has found many of its commercial applications being particularly powerful in penetrating solid matrices to extract small organic molecules but also having variable solvating power (vide infra) which gives opportunities for selectivity often not possible when using conventional solvent extraction.[15] Particularly important commercial examples of extraction include coffee decaffeination[16] and extraction of

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(13) Kingston, D. G. I. *Anticancer Agents Nat. Prod.* **2005**, 89−122.
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hops for brewing. Other commercial applications of CO_2 technology are described in a recent review by Beckman,[17] and it is clear that, as the technology becomes more widespread, many of the perceived barriers to implementation will begin to fade. There remain, however, significant barriers that still need to be overcome in many potential applications.

We reasoned that in a high-value industry such as pharmaceuticals and fine chemicals $scCO_2$ would also have considerable potential; however, relatively little was known at the time about what could really be achieved by using such an unusual reaction medium as a supercritical fluid. We were fortunate to be given funding from a consortium of fine chemical and pharmaceutical companies (then Pfizer, GlaxoWellcome, SmithKline Beecham, Aventis, and Solvay Interox) to investigate new chemistries in $scCO_2$ to really see what was possible. We thus set out on what has been a very rewarding and academically challenging 10 years, where we have discovered some particularly notable facets to CO_2 chemistry, many of which were unexpected and beyond what we could have realistically hoped for.

It is particularly relevant in this review to give some comment on my opinion of commercial aspects of CO_2 chemistry in the pharmaceutical industry. General issues have been discussed in an extensive recent review, although relatively little from the perspective of the pharmaceutical industry.[17] Supercritical fluid chromatography (SFC) is now widely used throughout the industry,[18] and I anticipate that familiarity and the necessary facilities (viz. high-pressure CO_2 supply) will facilitate other applications of CO_2 technology. Small-scale reaction facilities are relatively inexpensive to purchase, although relevant expertise is also desirable. However, for large-scale facilities, capital investment is much more significant, and powerful drivers, mostly economic, will be required for commercialisation. At present, current environmental regulations are not sufficient in themselves but will undoubtedly play an increasing role in the future.[17] Fortunately, regulations appear to be evolving that will allow some of the best available emerging technologies to be more realistically considered for process implementation; however, the first real example in the pharmaceutical industry remains elusive. What we now have, though, is a much better appreciation of some of the benefits that chemistry in $scCO_2$ can offer, which should enable potential areas of application to be more readily identified.

There are a limited number of commercial examples where CO_2 is used as a reaction solvent, one of the most notable being in the manufacture of fluoropolymers (which previously relied on chlorofluorocarbons which are no longer available after their environmental impact was realised).[17] In addition, Thomas Swan Ltd. in the United Kingdom have a commercial continuous flow reactor for large-scale reactions, particularly hydrogenations and alkylations.[19] Reactions involving light gases (hydrogen,[20−22] CO,[23] and oxygen[24]) have been the subject of intense study because of their total miscibility with $scCO_2$, compared to their only limited solubility in conventional solvents.[25]

In principle, continuous reactors are particularly attractive for such high-pressure reactions, as they maximise process intensification and help keep costs to a minimum. However, our approach has concentrated on batch processes mainly due to solubility issues when working with drug-like molecules (which are often relatively polar compounds of appreciable solubility in water) in CO_2, and for ease of comparison with established methods. It became clear to us early on that there were likely to be solubility issues when working with CO_2; during initial studies on sulfur oxidation (vide infra), whilst the starting sulfides had reasonable but finite solubility in $scCO_2$, the relatively polar sulfoxide products did not and rapidly precipitated out of solution as soon as they were formed. Such a reaction in a flow system would have been problematic to say the least, and we wished to concentrate on understanding and developing new chemistry without this additional complication.

It is often possible to enhance solubility of substrates in $scCO_2$ by adding cosolvents (often just a few percent of solvents such as MeOH or toluene); it is also possible to modify compounds to enhance solubility in $scCO_2$, often by increasing the lipophilicity or adding perfluorinated chains or siloxane groups.[4,26] Whilst this is generally achievable for catalysts and ligands (although this raises other issues such as cost and sustainability), scope for such variability in a final active structure is much more limited, although there may be more potential for variation of substituents in intermediate structures. Perhaps less obvious, but potentially more important, is that it is also possible that less polar solutes in a reaction mixture can enhance solubility of more polar solutes. Hence, it is the solubility of a reaction mixture as a whole and not just that of individual components which is of greatest importance.

This having been said, most of the interesting effects we have observed have been around the limits of solubility (vide infra), and we have always tried to avoid situations where we are specifically trying to substantially modify systems to enhance solubility as this would detract from the main aim of the study and its generality.

3. Fundamental Properties of CO_2

Whilst it is beyond the scope of this article to give a full description of the fundamental properties of CO_2, some information is provided to give the reader the basic information required to understand the following sections. More extensive introductions are given in numerous recent reviews and books.[5,7,17]

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(21) Clarke, D.; Ali, M. A.; Clifford, A. A.; Parratt, A.; Rose, P. M.; Schwinn, D.; Bannwarth, W.; Rayner, C. M. *Curr. Top. Med. Chem.* **2004**, *4*, 729−71.
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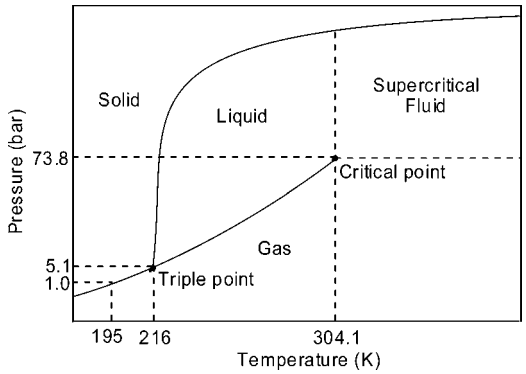


Figure 1. **Phase diagram for pure CO_2.**

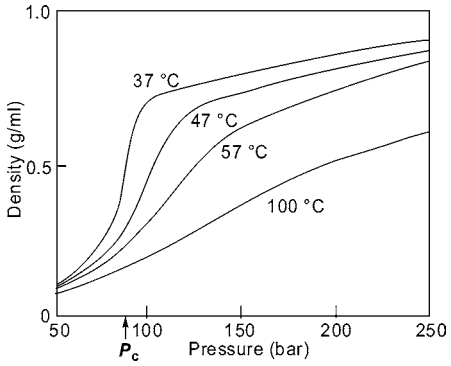


Figure 2. **Variation of CO_2 density with temperaure and pressure.**

There are two main points that one really needs to understand to have an appreciation of the potential of $scCO_2$ as a solvent in synthetic chemistry. First the nature of a supercritical fluid (SCF) and second the tuneability of its solvent properties. A SCF can be considered to be a dense-phase gas, which in principle can solvate a mixture of gases, liquids, and solids into a single homogeneous phase which occupies the whole of a reaction vessel. Increasing pressure increases the density of the $scCO_2$, reaching a liquid-like density, but a distinct liquid layer is not observed. For $scCO_2$, a minimum temperature of 31 °C and pressure of 74 bar is required (Figure 1); we typically work between 35 and 100 °C and at pressures up to 150 bar. Although higher pressures are possible and routinely available, most of the interesting effects we have observed have been in the 100−120 bar region. It is important to note that, although many organic reactions are accelerated by pressure (e.g., Diels−Alder reactions), they are usually pressures at least 1 order of magnitude higher than what we are typically working at, with consequent increase in equipment limitations.[27] Hence, any rate accelerations are unlikely to be due to pressure acceleration but instead are likely to be due to the unusual aspects of reactions in supercritical fluids, such as high diffusion rates, low solvent viscosity, and limited solvation of reacting species.

The second main point about $scCO_2$ is its tuneability as a solvent. Varying temperature and pressure allows manipulation of the density of CO_2 which determines much of its power as a solvent (Figure 2). At its critical point (31 °C, 74 bar), CO_2 has a density of 0.46 g/mL, which when compared to conventional solvents may be expected to be a relatively weak solvent. Increasing pressure increases the density of the CO_2 for a given temperature, such that at pressures of, for example 120 bar at 40 °C, densities of around 0.7 are typical. Beyond such densities, however, SCFs tend to lose some of their "magic" properties; many of the subtle fine-tuning opportunities are no longer possible, and from our experience, reaction outcomes tend to resemble those in conventional solvents.

For a given density, increasing the temperature increases the pressure (there is no change in density, as it is a sealed system). Care should be taken when heating pressure vessels that are charged at or around room temperature, as a large increase in pressure would be expected. For example a system at 40 °C, 100 bar pressure, and density of 0.70, on heating to 120 °C increases pressure to approximately 400 bar, which is above the safe operating limit of many pressure vessels. At high temperatures, density for a given pressure can be lower that expected; for example at 100 °C and 120 bar the density of CO_2 is approximately 0.24 g/mL; consequently, much higher pressures are often required at higher temperatures for appreciable solvation of solutes. Note that all of these figures are for pure CO_2 and will differ once solutes are added, but they are useful guides for a first approximation and are readily accessible.[28] A number of pressure units are used in the literature: conversion factors are as follows: 1 atm = 1.01 bar = 14.7 psi (pounds per square inch) = 0.101 MPa (megaPascal).

A final comment on reactions in terms of phase behaviour. Much is made of achieving a homogeneous SCF mixture; however, this is frequently not necessary, especially in batch processes. What is more important is that phase behaviour is understood—which reagents are in or out of solution, and if the reaction is occurring in the $scCO_2$ or as a neat liquid phase at the bottom of the reactor. Use of reactors with windows (which we refer to as view cells) and appropriately located sampling ports help greatly in establishing phase behaviour and observation of constituent parts in the various phases.

4. Reactions in Supercritical CO_2

The previous section was intended to provide a basic introduction to the physical properties of CO_2 and some of the most important considerations when assessing its potential for use in fine chemical and pharmaceutical synthesis. The following sections give an overview of many of the results we have achieved over the last 10 years or so working in this area and give a perspective of our approach. In almost all cases, the unusual properties of $scCO_2$ have helped us to develop reactions where specific advantages can be apparent over comparable processes in conventional solvents. Although the reactions themselves may not be of direct relevance to the reader, the underlying principles of what can be achieved are most important, and the reader is encouraged to consider how these may impact their own chemistry and lead to improvements in their processes. It is

(27) Matsumoto, K.; Acheson, R. M. *Organic Synthesis at High Pressures*; Wiley and Sons: New York, 1991.
(28) http://webbook.nist.gov/chemistry/fluid/.

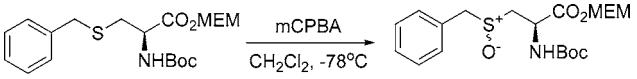
these kinds of advantages that we believe will lead to initial phases of adaptation of such technology in industry.

5. Enhancement of Stereochemical Control by Solvent Tuning

As a synthetic organic chemist, one of my main areas of interest has been the development of new reactions which allow a high degree of stereocontrol during formation of the product. This could be in terms of diastereocontrol, where the outcome of the reaction is determined by pre-existing chirality in a molecule, or enantiocontrol, where the reaction usually involves use of a chiral catalyst for controlling absolute stereochemistry of a new chiral centre.

5.1. Diastereoselective Processes under Kinetic Control. A long-term interest in organosulfur chemistry led us to consider sulfur oxidation as a potential candidate for investigation in $scCO_2$.[29] At the time, very few reactions had actually been reported in $scCO_2$, and it was necessary first of all to develop a procedure compatible with such reaction conditions. We chose *tert*-butyl hydroperoxide (TBHP) in toluene, with Amberlyst sulfonic acid ion-exchange resin as a catalyst. This worked exceptionally well for a variety of simple sulfides, giving high yields of clean products with no overoxidation to the sulfone. The sulfones could be prepared using TBHP in the presence of SiO_2.[29] A close inspection of the literature revealed relatively few examples of diastereocontrolled sulfur oxidation, and those that gave appreciable levels of selectivity were at low temperatures (−78 °C, Scheme 1);[30] we were well aware that we needed to work at temperatures above 31 °C if we were to have $scCO_2$ and be able to access the tuneability potential we thought could be important. At lower temperatures we would be dealing with liquid CO_2 which shows relatively little variation of density with temperature and pressure compared to the highly compressible supercritical fluid.

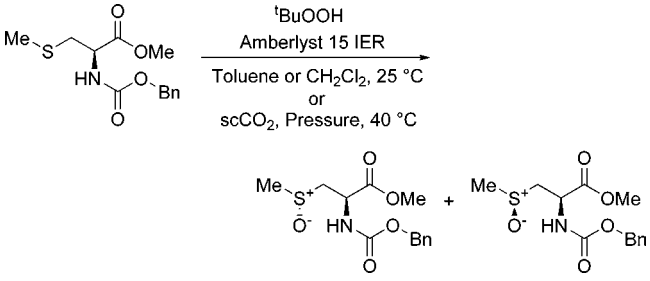
Scheme 1. **Diastereoslective *S*-oxidation in conventional solvents**



We chose a relatively simple system to investigate based on protected *S*-methyl cysteine and carried out some preliminary studies using the oxidation procedure we had developed. In conventional solvents (e.g., CH_2Cl_2 or toluene) at room temperature, no appreciable selectivity was observed, which was consistent with literature precedent at such temperatures (Scheme 2). We then investigated the selectivity in $scCO_2$ at a variety of pressures to see if there was any scope for optimisation. The results, shown in Figure 3, were astounding and totally unexpected.[31]

Essentially by switching from conventional solvents to $scCO_2$ and optimising the density of the CO_2 (in this case the optimum was around 0.7 g/mL), we had been able to go

Scheme 2. **Diastereoselective oxidation in CO_2**



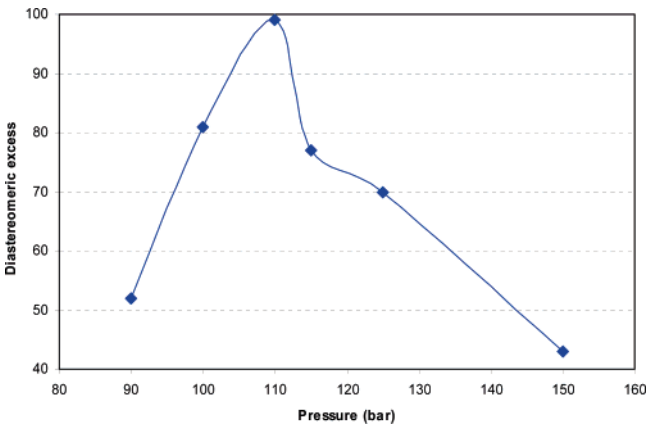


Figure 3. **Variation of *S*-oxidation diastereoselectivity with pressure.**

from no selectivity to near complete selectivity in favour of the *trans* isomer. This remains one of the most outstanding examples of selectivity enhancement when using $scCO_2$. We also investigated a range of other substrates.[29,31] In many cases, a selectivity enhancement was observed, however, not as pronounced as the above example. It is clear from our results that outstanding results are possible, but they depend very much on structure of substrate. Further studies also revealed concentration and temperature effects, which are no doubt linked to phase behaviour. During this reaction, the polar sulfoxide could clearly be seen precipitating as the reaction proceeded, which complicates full analysis of phase behaviour. However, model studies indicated that the pressure which gave optimum selectivity was also the lowest pressure at which the reaction mixture was homogeneous (at least at the beginning of the reaction, i.e., when the system was near to the two-phase/one-phase boundary) and was therefore at the limits of substrate solubility. Note this optimum was ∼36 bar higher than the critical point of pure CO_2 and occurred at a density of approximately 0.69 g/mL, which is significantly higher than the critical density of pure CO_2 (0.46 g/mL).[32] It is important to emphasise we were working at temperatures of 40 °C, whereas earlier literature only achieved reasonable selectivities at very low temperature (−78 °C), and no selectivity was observed in conventional solvents. There was therefore something very special about this reaction in $scCO_2$ which warranted further investigation.

The most likely explanation for these effects was the interaction of CO_2 with solute molecules. It is known that

(29) Oakes, R. S. Ph.D. Thesis. University of Leeds, 2000.
(30) Nakamura, S.; Goto, K.; Kondo, M.; Naito, S.; Bando, M.; Kido, M.; Shishido, K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 937−940.
(31) Oakes, R. S.; Clifford, A. A.; Bartle, K. D.; Thornton-Pett, M.; Rayner, C. M. *Chem. Commun.* **1999**, 247−248.
(32) Following our initial publication, it was found that pressures originally quoted were inaccurate due to equipment problems, and those reported here are correct.

CO_2 is mildly Lewis acidic, interacting with Lewis basic sites (often carbonyl groups) in a solute, liberating approximately 1 kcal/mol per interaction.[33−39] This is at a maximum at the critical point (which for a multicomponent mixture like ours would be related to the two-phase/one-phase transition region),[39,40] and so optimum interaction between CO_2 and carbonyl groups in the substrate may be expected to be at a maximum at this point, consistent with our optimum selectivity. Such an interaction would enhance the effective steric bulk of the carbonyl group(s), leading to enhanced conformational rigidity and increasing their ability to determine the direction of reagent approach (Figure 4). We are currently undertaking spectroscopic studies to understand and be able to quantify this effect in more detail and to correlate it with our observed results.

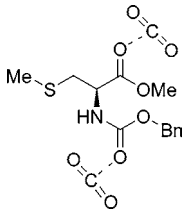
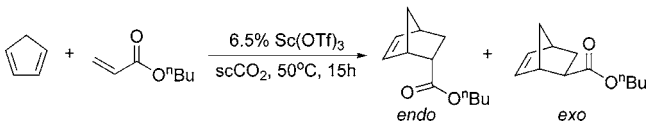


Figure 4. **Possible interactions between substrate and CO_2.**

Although this effect was extremely encouraging, we were concerned about its generality and thus investigated fundamentally different reactions to see whether the effect was more general. Earlier results had shown that changes in *endo/exo* ratios in cycloaddition reactions were possible by solvent tuning; however, improvements were modest, and chemical yields of the reactions were low. Nevertheless, this did provide the basis for theoretical work using the Diels−Alder reaction between cyclopentadiene and an acrylate.[41]

We then went on to demonstrate that scandium triflate was an excellent Lewis acid catalyst for this reaction and was particularly convenient (Scheme 3).[42] Its fluorinated

Scheme 3. **$Sc(OTf)_3$-catalysed Diels−Alder reaction of *n*-butyl acrylate with cyclopentadiene in $scCO_2$**



nature gave it reasonable solubility in $scCO_2$; it was commercially available and relatively inexpensive. It gave greatly improved yields and higher *endo/exo* selectivity as would be expected for a Lewis acid-catalysed Diels−Alder reaction.[2] We were able to show that the optimum *endo/exo* selectivity for the reaction between *n*-butyl acrylate and cyclopentadiene was 16:1 at 100 bar, 50 °C and a density of 0.60 g/mL (Figure 5), measured by accurately weighing the reactor. Again, this maximum was at the density corresponding to the one-phase/two-phase boundary of the initial reaction mixture. As with the sulfur oxidation work, this effect was substrate dependent, and we are currently working to understand the system requirements for maximum optimisation potential.

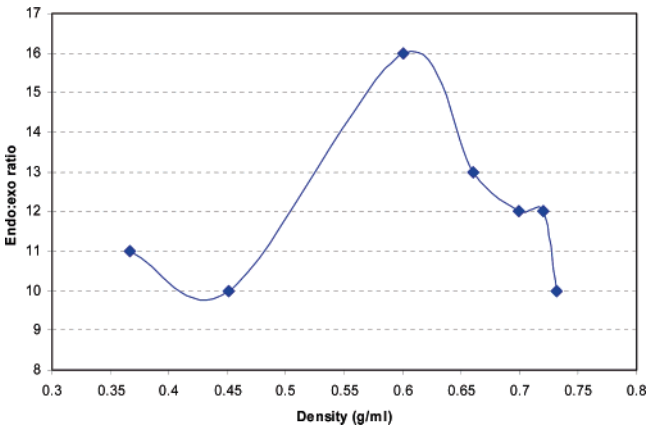


Figure 5. **Variation of *endo/exo* selectivity with $scCO_2$ density.**

5.2. Diastereoselective Processes under Kinetic and/or Thermodynamic Control. Thus far, all the selectivity variations we had observed were with reactions which are under kinetic control. In order to investigate reactions under thermodynamic control, we chose to look in some detail at the Henry (nitro-aldol) reaction.

The Henry reaction is a particularly useful carbon−carbon bond-forming reaction giving highly functionalised products of considerable synthetic utility.[43] One of the most attractive features of the Henry reaction is its potential for stereocontrol. Varying levels of diastereoselectivity have been reported[44] although this is generally modest, even with modern complex asymmetric reactions.[45] Hence, there remains considerable scope for improvement, which can be best achieved if a greater understanding of the factors controlling the stereochemical outcome of the reaction can be obtained. The Henry reaction is also known to be an equilibrium process[46] and is promoted by very high pressure (8 kbar—nearly 2 orders of magnitude greater than we typically use with CO_2).[47]

For simplicity, we chose NEt_3 as the catalyst as it is well established for simple Henry reactions and is very soluble in $scCO_2$.[25] Initial studies in $scCO_2$ showed an interesting contrast when compared with reactions under more conventional conditions (solventless, MeCN, or toluene). In all

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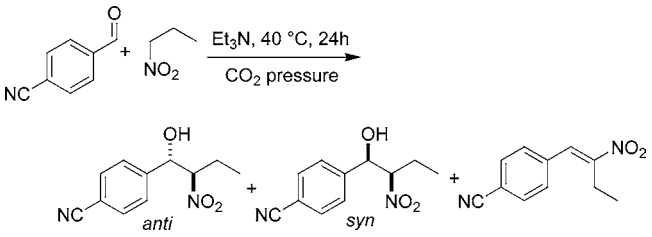
cases, use of $scCO_2$ (at around 90 bar) showed a significant shift in stereoselectivity away from the more usual *anti* isomer, towards the *syn* (Scheme 4). Although this change

Scheme 4. **Henry reaction in $scCO_2$**



in selectivity could be due to a simple solvent effect, we decided to investigate one specific example in detail, that of reaction of *p*-cyanobenzaldehyde with 1-nitropropane at a variety of pressures, including subcritical (Figure 6).

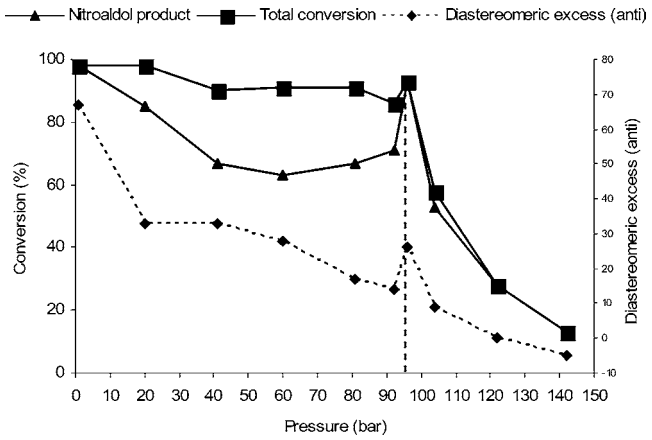


Figure 6. **Control of Henry reaction by change of CO_2 pressure.**

Studies in a high-pressure view cell showed this reaction to be homogeneous above approximately 100 bar at 40 °C (indicated by the vertical dotted line on the graph). Around this pressure, the conversion was optimum (Figure 6), but as pressure increased, a significant decrease in rate was observed. A similar trend was also observed in our studies on the Morita−Baylis−Hillman reaction (vide infra).[48] This rate change may be attributed, at least in part, to the $scCO_2$ achieving more liquid-like densities at higher pressures; the conversion at 140 bar is similar to what is observed in toluene at a similar concentration.

At pressures below 100 bar, we observed two distinct phases, a neat (or CO_2-expanded) liquid layer, where the reaction was probably proceeding, under an atmosphere of super- or subcritical CO_2. Overall conversions at this lower pressure were excellent and comparable to neat reactions, but interestingly, significant amounts of dehydration product (∼30%, represented by the difference between total conversion (▲) and proportion of nitroaldol (◆)) were also observed which only occurred in the presence of CO_2. As with the sulfur oxidation work, this may be a result of the Lewis acidity of CO_2. In this case, it would be dissolved in the neat reaction aiding the dehydration process, which would also be facilitated by the polar nature of the neat reaction medium.

The most interesting aspect of this study was the stereoselectivity. It can be seen (Figure 6) that there was a gradual shift from ∼70% *anti* to 5% *syn* on going from 1 to 140 bar of CO_2 pressure. It was also intriguing to note that this effect occurs almost linearly with pressure and independently of phase, other than a slight dip around 20 bar (which may be due to facile dehydration of the *anti* isomer), and an enhancement around the one-phase/two-phase transition region (in this case, probably due to reagent clustering).[49]

To explain these observations, it is necessary to consider the reaction in more detail. The Henry reaction is reversible, and in this case what we are observing is competing kinetic vs thermodynamic control. At low CO_2 pressures, we have a neat reaction which is rapid, which also allows for rapid equilibration of the kinetic product mixture to the thermodynamically more stable *anti* isomer. However, at higher pressures, the reaction is significantly slower, particularly under supercritical conditions, and kinetic control of the reaction begins to take effect, with the product distribution under complete kinetic control tending towards ∼10% in favour of the *syn* isomer, although, of course, conversions are now greatly reduced. Such control has not been reported before for the Henry reaction and provides valuable mechanistic insight into the factors controlling diastereoselectivity, which remains a problem even in some recent, elegant asymmetric processes.[50] This is an excellent example of how fundamental studies in $scCO_2$ can lead to results of more widespread importance.

The final point on which to comment is the variation of stereocontrol at subcritical pressures. These reactions were all performed for 24 h to aid comparison with other results, but such neat reactions are usually "complete" in terms of conversion within a few hours. However, they will continue to equilibrate for the remaining period, with such equilibration being apparently more facile at lower pressures. A possible explanation for this again is the ability of CO_2 to interact with Lewis bases, in this case, either NEt_3, or perhaps less likely, the nitronate/nitronol nucleophile. It is known that CO_2 has a high affinity for NEt_3, forming expanded solutions,[25] and spectroscopic studies have also provided evidence for a weak Lewis acid−Lewis base interaction which would be expected to influence the efficiency of the base and would be pressure dependent.[51]

5.3. Enantioselective Processes. Our most recent work in this area has been investigating the potential for optimisation of the enantioselectivity of asymmetric processes in $scCO_2$.[52] We have chosen to concentrate on processes controlled by chiral bis-oxazoline (Box) ligands, as this offers many opportunities for investigating a wide range of different

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(50) Risgaard, T.; Gothelf, K. V.; Jorgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153−156.

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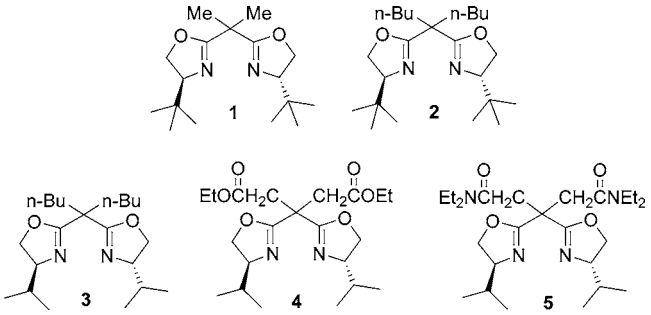
(52) Brough, S.; Woods, M.; Rayner, C. M. Unpublished results.

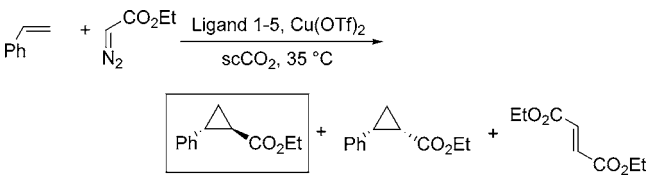
processes.[53,54]



The Box ligand **1** is the classic ligand utilised in many key asymmetric reactions and gives high enantioselectivities for a wide range of asymmetric processes, mainly due to the large steric bulk of the two *tert*-butyl groups.[55] It is a useful reference point for our studies but has two main limitations from our point of view. First, it often gives ee's above 90% which leaves little scope for observing any real optimisation effects; second, it is derived from *tert*-leucinol, which is roughly an order of magnitude more expensive than other aminoalcohols derived from natural α-aminoacids. Thus, we also synthesised a range of ligands (**3**−**5**) derived from the less expensive valinol, which are also reported to give relatively modest ee's[55] (although for this reason they have not been investigated as extensively as **1**), and therefore offer significant opportunities for improvement. We also chose to investigate ligands which have different substituents on the central methylene carbon, first to improve ligand solubility but also investigate potential for interaction with CO_2 via Lewis acid−Lewis base complexes similar to that proposed in the diastereoselective sulfur oxidation chemistry. Hence, the *n*-butyl chain in ligands **2** and **3** would increase the lipophilicity and increase solubility in $scCO_2$, whereas the ester and amide groups in **4** and **5** would show if there was any other effect due to CO_2 coordination (which could also enhance solubility). Although one might expect these relatively remote substituents to have little effect on the enantioselectivity (which is clearly not the case, vide infra), it has been shown that the bite angle of the Box ligand can affect enantioselectivity,[56] and such an effect may operate in this case.

One of the best reactions to illustrate the potential for solvent tuning of enantioselectivity is asymmetric cyclopropanation (Scheme 5).[55] This had previously been investigated

Scheme 5. **Asymmetric cyclopropanation in $scCO_2$**



(53) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.
(54) Rechavi, D.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 3467.
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(56) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875.

Table 1. **Optimum cyclopropanation enantioselectivity in $scCO_2$ and conventional solvents.**

ligand	% optimum ee (conventional solvent)	% optimum ee $scCO_2$ (pressure)
1	96 (hexane)	90 (115 bar)
2	90 ($CHCl_3$)	92 (75 bar)
3	57 (hexane)	63 (95 bar)
4	70 (hexane)	80 (125 bar)
5	62 (toluene)	72 (125 bar)

by Jessop et al., but this study concentrated on the use of supercritical fluoroform, mainly due to problems of catalyst solubility in $scCO_2$.[57] Fortunately, our ligands showed no such limitation in $scCO_2$, and even the unmodified ligand **1** had sufficient solubility under typical reaction conditions to give high levels of enantioselectivity. The results (enantioselectivity for formation of *trans*-cyclopropane) of the reaction between ethyl diazoacetate and styrene are summarised in Figure 7 and Table 1, and it can clearly be seen that there is considerable variation in enantioselectivity with CO_2 pressure.

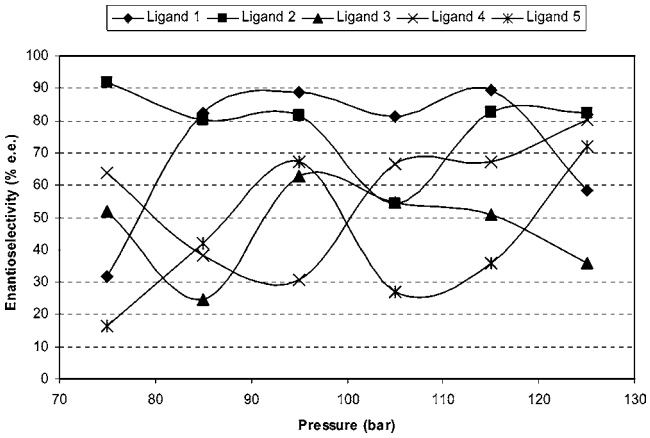


Figure 7. **Variation of cyclopropanation enantioselectivity with $scCO_2$ pressure and Box ligand.**

As expected the *tert*-leucinol derived ligands **1** and **2**, gave high enantioselectivity. It is interesting to note, however, that only ligand **1** gave highest enantioselectivity in conventional solvents ($CHCl_3$, hexane, toluene or neat), whereas for all the others, higher enantioselectivity could be observed in $scCO_2$ after optimisation (Table 1). With the valinol-derived ligands, lower enantioselectivity was generally observed as would be expected, but with optimisation, respectable levels of enantiocontrol were achieved (up to 80% ee with **4**), particularly considering the relative costs of ligand precursors. Even in conventional solvents such as hexane these ligands gave reasonable levels of enantioselectivity, something that would perhaps not have been appreciated without this study. Note that in the $scCO_2$ reactions the optimum selectivities vary considerably and are not necessarily at the one-phase/two-phase boundary observed in many of the previous reactions. The majority of these reactions are single phase, with only the 75 bar reactions showing an additional

(57) Wynne, D. C.; Olmstead, M. M.; Jessop, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 7638.

liquid layer at the bottom of the reactor. It is clear that the substituents on the methylene carbon have a significant effect on the enantioselectivity (cf. ligands **3** and **4**) and that the pressure for optimum selectivity depends very much on the ligand, with quite a complex range of effects operating. We are currently carrying out spectroscopic studies to help quantify interactions between CO_2 and solutes, which we believe will provide further information to help promote our understanding of the processes involved.[58]

6. Product Solubility Control and CO_2-Induced Reactions

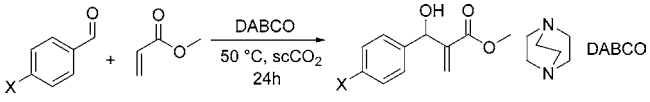
The ability to fine-tune the density of $scCO_2$ also allows fine control of reagent and product solubility. This can have some obvious benefits but also some less obvious ones as we found during our studies on the Morita−Baylis−Hillman reaction in $scCO_2$, which also provided an elegant example of CO_2-induced reaction processes.

6.1. The Morita−Baylis−Hillman Reaction in $scCO_2$. The Morita−Baylis−Hillman (MBH) reaction is a very useful C−C bond-forming reaction, whose products are particularly versatile synthetically as they contain a high degree of functionality.[59] However, it can also be a very demanding reaction—it often gives very low conversions in solution—but in the absence of solvent or use of a very concentrated solution it can give efficient reactions on a small scale. The reaction also has a high negative volume of activation, and hence rates would be increased by high pressure, although as with the Henry and Diels−Alder reactions, significant effects require much higher pressures than we typically use for $scCO_2$.[60,61] As such, we believed there may be opportunities for interesting solvent effects in $scCO_2$, although we did not predict what we observed.

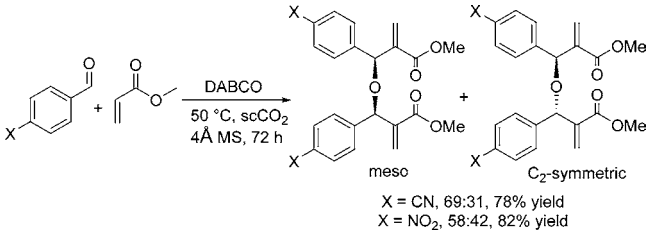
Initial studies focussed on carrying out simple MBH reactions in $scCO_2$ with the commonly used 1,4-diazabicyclo-[2.2.2]octane (DABCO) as catalyst (Scheme 6).[48] In general, the reactions proceeded normally but generally gave conversions better than those in comparable solution-phase reactions. However, it was also noted that, on occasion, unanticipated by-products were formed to varying degrees, particularly after prolonged reaction times. These were eventually identified as symmetrical dimers of the initial MBH reaction products (Scheme 7); the formation of such products was unprecedented in conventional solvents with any similar precursors (other than when formaldehyde was used as the aldehyde component).[62] However, yields were variable, and the origin and mechanism for their formation was unclear. In keeping with previous studies, a more detailed understanding of the effect of pressure on the outcome of the reaction would provide valuable information as to what was happening.

We chose to focus on the MBH reaction of *p*-nitrobenzaldehyde with methyl acrylate, catalysed by DABCO at 50 °C.[48] The results of this study are shown in Figure 8. There

Scheme 6. **Morita−Baylis−Hillman reaction in $scCO_2$**



Scheme 7. **Dimer formation in the Morita−Baylis−Hillman reaction in $scCO_2$**



are two main products, the normal MBH product, and the dimer (as a mixture of diastereoisomers). It can be seen that at high pressure, the relative rate of reaction decreases such that by 170 bar the conversion to the MBH product (denoted ■) is now very low—in fact it is now about the same as is observed in an equivalent volume of a conventional solvent such as toluene. As pressure is decreased to around 110 bar, the conversion increases to reasonable levels but is predominantly the expected MBH product (region A). Our laboratory experimental set-up allows us to monitor phase behaviour over a period of time, using time lapse photography. At pressures below approximately 110 bar (to the left of the dotted line) as the reaction proceeded, there was a phase separation at some time during the reaction. It was noted that only under these conditions was the dimer product formed (region B, denoted ▲) alongside the initial MBH product—the phase separation and subsequent dimerisation reactions were connected. Control studies demonstrated that the presence of both CO_2 and DABCO were required for dimerisation and that the dimerisation reaction itself was actually occurring in the neat oily layer at the bottom of the reactor, and not in the supercritical solution. Thus, the solubility of the initially formed MBH product was key to the success of this reaction, and it could be finely controlled by variation of CO_2 pressure.

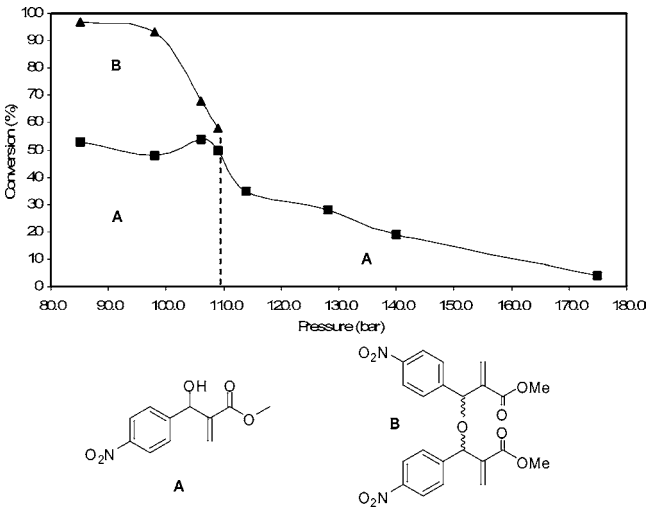
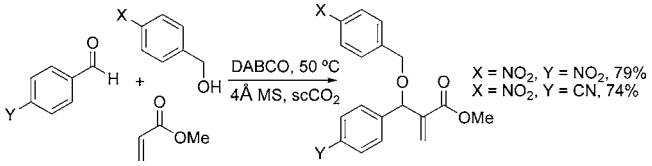


Figure 8. **Variation of product distribution with pressure for the Morita−Baylis−Hillman reaction in $scCO_2$.**

(58) Arai, M.; Rayner, C. M.; Brough, S.; Fujita, S. Unpublished results.
(59) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
(60) Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015.
(61) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241.
(62) Drewes, S. E.; Loizou, G.; Roos, G. H. P. *Synth. Commun.* **1987**, *17*, 291−8.

Whilst this dimerisation was novel, it was of limited synthetic utility. What would be much more useful would be if the reaction could be used to synthesise unsymmetrical ethers by getting the initial MBH products to react with another alcohol. In keeping with our suggestion above that the etherification was occurring in the oily layer, use of CO_2-soluble alcohols failed to lead to unsymmetrical ether formation; however, use of alcohols only sparingly soluble in $scCO_2$ (e.g., *p*-nitrobenzyl alcohol) led to very good yields, providing further evidence for phase reactivity, and also better yields that were observed for the simple MBH reactions (Scheme 8).[48,63] One possible explanation for this is that MBH reactions are a series of equilibria; however, we believe the final etherification step is essentially irreversible, which would displace all previous equilibria giving enhanced yields of products. Thus, understanding the phase behaviour and fundamental reactivity of CO_2 has allowed us to develop a potentially useful one-pot three-component coupling reaction, which gives higher yields than the corresponding MBH reaction.[48]

Scheme 8. **Unsymmetric ether formation during the Morita−Baylis−Hillman reaction in $scCO_2$**



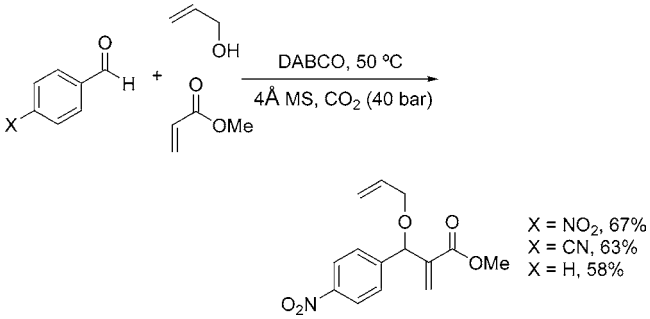
There remained one major limitation in this three-component reaction; that is the use of CO_2-soluble alcohols in the final etherification step. These were too soluble in $scCO_2$ and were held out of contact from the separated MBH product, preventing reaction. From our control studies we knew that CO_2 and DABCO were required and that the reaction proceeded neat under an atmosphere of CO_2. According to our mechanistic proposal, there was no particular reason why the CO_2 had to be supercritical, so we investigated the neat MBH reactions under an atmosphere of *subcritical* CO_2, i.e. just gaseous CO_2 above the neat reaction.[63] After brief pressure optimisation it was found that, at 40 bar, acceptable yields of unsymmetrical ethers could be obtained (67% for allyl alcohol, methylacrylate, and *p*-nitrobenzaldehyde), including relatively unreactive aldehydes (58% for allyl alcohol, methylacrylate, and benzaldehyde) (Scheme 9).

This work represents a relatively unexplored area of CO_2-induced chemistry, combining the subtle Lewis acidic properties of CO_2 with potentially incompatible functionality (e.g., amines, alcohols) at pressures which would be more accessible for large-scale work than some of the earlier processes discussed.

7. Pd-Mediated Couplings in $scCO_2$

Palladium-catalysed coupling reactions are fundamentally important C−C bond-forming processes and are used extensively in the pharmaceutical and fine chemical industries.[64] It is therefore not surprising that considerable attention has been paid to developing methods that allow them to be carried out in $scCO_2$, including the usual range of Heck, Stille, Suzuki, and Sonagashira couplings. This is, however, quite challenging in that the ubiquitous ligand, PPh_3 has only low solubility in $scCO_2$, and this problem is exacerbated when a number of such ligands surround a metal centre such as Pd. Similarly, a typical palladium source such as $Pd(OAc)_2$ is also insoluble in $scCO_2$. To overcome these problems, a range of fluorinated phosphines of enhanced solubility has been developed for use in $scCO_2$;[21,65−67] similarly, we have developed $scCO_2$-soluble siloxane-based ligands.[26] These approaches generally work well and also allow a degree of recycling. However, throughout our studies we have tried to minimise reagent modification, restricting ourselves to easily accessible, relatively inexpensive, simple reagents wherever possible. We were able to show in our original work that, when used in conjunction with commercially available $Pd(OCOCF_3)_2$, a range of simple ligands was successful, including tris-2-furylphosphine (TFP), and tricyclohexylphosphine.[68−70] We have also recently shown that 1,1′-bis(diphenylphosphino)ferrocene (dppf) is particularly useful for coupling of aryl bromides rather than iodides.[71] However, simply being able to carry out Pd-mediated coupling reactions in $scCO_2$ is likely to have limited impact; again, significant advantages are required, and two examples are provided in the following sections.

Scheme 9. **Unsymmetric ether formation using $scCO_2$-soluble alcohols**



7.1. Reduction of Double Bond Isomerisation during Pd-Mediated Coupling Reactions in $scCO_2$.[70] A common side reaction in some Heck coupling reactions is isomerisation of the double bond in the initially formed product. This can be particularly problematic if the isomerised product is thermodynamically favoured. As an example (Scheme 10),[70] cyclisation of the iodoalkene under conventional conditions ($Pd(OAc)_2$, PPh_3, NEt_3, toluene) gives roughly a 1:1 mixture of the initially formed exocylic alkene and the

(63) Rose, P. M. Ph.D. Thesis, University of Leeds, 2003.

(64) King, A. O.; Yasuda, N. *Top. Organomet. Chem.* **2004**, *6*, 205−245.
(65) Morita, D. K.; David, S. A.; Tumas, W.; Pesiri, D. R.; Glaze, W. H. *Chem. Commun.* **1998**, 1397−1398.
(66) Carroll, M. A.; Holmes, A. B. *Chem. Commun.* **1998**, 1395−1396.
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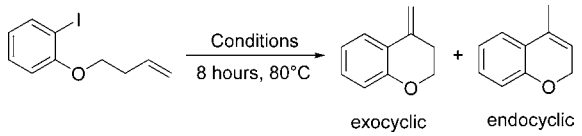
(68) Shezad, N.; Oakes, R. S.; Clifford, A. A.; Rayner, C. M. *Tetrahedron Lett.* **1999**, *40*, 2221−2224.
(69) Shezad, N.; Clifford, A. A.; Rayner, C. M. *Green Chem.* **2002**, *4*, 64−67.
(70) Shezad, N.; Clifford, A. A.; Rayner, C. M. *Tetrahedron Lett.* **2001**, *42*, 323−325.
(71) Raynel, G., Lobedan, L., Ravenscroft, P., Rayner, C. M. Unpublished results. Raynel, G. Ph.D. Thesis, University of Leeds, 2004.

Table 2. **Suppression of double bond isomerisation in intramolecular Heck reactions.**

entry	reagents	ratio exocyclic/endocyclic	conversion (%)
1	$Pd(OAc)_2$, PPh_3, NEt_3, toluene	49:51	25
2	$Pd(OAc)_2$, PPh_3, NEt_3, MeCN	36:64	67
3	$Pd(OCOCF_3)_2$, TFP, DIPEA, toluene	45:55	85
4	$Pd(OCOCF_3)_2$, TFP, DIPEA, MeCN	24:76	>95
5	$Pd(OCOCF_3)_2$, TFP, DIPEA, $scCO_2$, 90 bar	83:17	>95

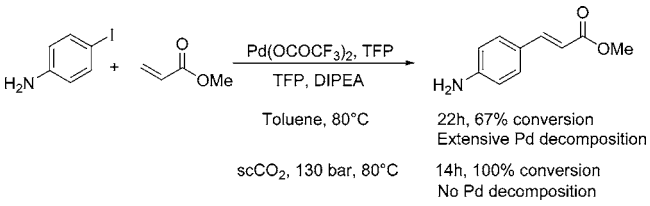
Scheme 10. **Double bond isomerisation in intramolecular Heck reactions**



isomerised endocylic product (Table 2). If the reaction is carried out in MeCN, a higher conversion is obtained, but a larger degree of isomerisation is also observed. These effects are mirrored if $Pd(OCOCF_3)_2$, TFP, and diisopropylethylamine (DIPEA) are used. However, if this latter reagent system is used in $scCO_2$, a dramatic reduction in the amount of isomerisation is observed, such that the major product is the exocyclic alkene (83:17). The actual reason for this effect has not been proven, but we believe the most likely explanation is due to rapid separation of the product from the catalyst as soon as it is formed (the isomerisation reaction is usually caused by Pd−H species derived from the coupling catalyst). At 90 bar and 80 °C the density of CO_2 is relatively low (∼0.2 g/mL),[28] and the reaction is not homogeneous. The catalyst and starting materials are likely to be part of a liquid layer at the bottom of the reactor, under an atmosphere of $scCO_2$. The product would, however, be expected to have higher solubility in $scCO_2$ than the catalyst or starting materials, such that as soon as it is formed it is removed from contact with the Pd-catalyst system which prevents subsequent isomerisation. Thus, this provides an example of product/catalyst separation which could potentially apply to a range of reactions where the initial product is unstable and needs to be rapidly removed from the reaction mixture to prevent degradation.

7.2. Use of CO_2 as a Temporary N-Protecting Group during Pd-Mediated Coupling Reactions in $scCO_2$. The potential for CO_2 to interact with Lewis basic sites has already been mentioned as being a potentially important feature of many of the reactions we have investigated. With primary and secondary amines, CO_2 can also react further to form carbamic acids or carbamate salts which remain during the reaction, but undergo decarboxylation on depressurisation to liberate the free amine.[72−76] This is potentially very powerful as there are numerous reactions where the presence of a free amine functionality can have a dramatic effect on the efficiency of a reaction. One of the early examples of this was by Fürstner et al., whilst investigating alkene metathesis in $scCO_2$ using catalysts which were sensitive to the presence of basic heteroatom functionality.[73] In situ protection of the nitrogen allowed the reaction to proceed efficiently. We have also used this principle in our Pd-catalysed coupling reactions in $scCO_2$. The classic coupling of iodobenzene with methyl acrylate proceeds very efficiently using our $Pd(OCOCF_3)_2$/TFP reagent system in both toluene and $scCO_2$. However, with 4-iodoaniline, the reaction is significantly slower in toluene, and only reaches 67% conversion after 22 h with extensive Pd decomposition (Scheme 11). If the equivalent reaction is carried out in

Scheme 11. **Effect of CO_2 on Heck reactions of Iodoanilines**



$scCO_2$, it is complete within 14 h, with no sign of Pd decomposition. In this case, it is unlikely that a formal carbamate derivative is formed; no such intermediate could be detected by high-pressure NMR in our hands, or by others.[77] More likely is the formation of a Lewis acid−Lewis base complex between the CO_2 and aniline. This has two effects. First, it dramatically reduces the possibility of the aniline nitrogen coordinating to Pd and reducing its efficiency. Second, if the aniline lone pair is coordinated to CO_2, then its donation of electron density into the benzene ring is reduced. As it is known that electron-rich iodoarenes react significantly more slowly in Heck reactions than electron-deficient ones, then again this effect should promote the coupling reaction.

Similar observations can be made for the coupling of aryl bromides, although in this case dppf is used as ligand rather than TFP (Scheme 12).[71] Thus, coupling of 4-aminostyrene to bromobenzene occurs efficiently in $scCO_2$ but gives negligible yields in toluene or in the absence of solvent. Similarly, the Suzuki reaction between benzeneboronic acid

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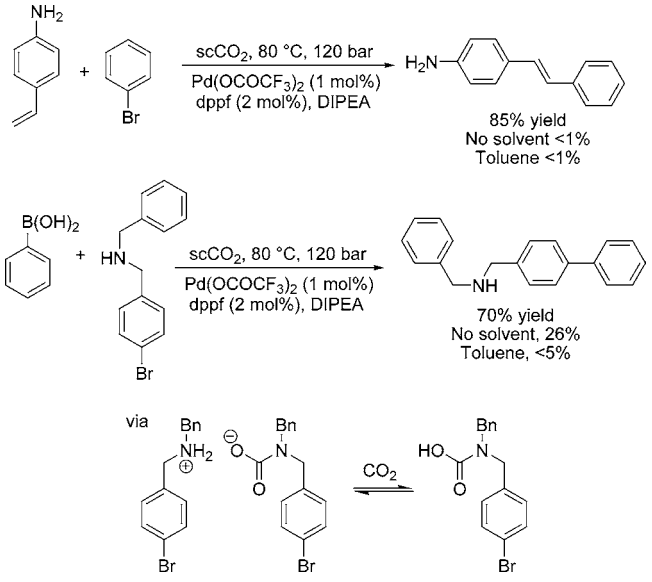
and 4-bromodibenzylamine works well in $scCO_2$ but again gives negligible yields in toluene and only a low yield in the absence of solvent. In the latter case, we were able to prove in situ carbamate formation in CO_2 using high-pressure ^1H NMR.[78] Because nitrogen functionality is ubiquitous in pharmaceutical synthesis, we believe that using CO_2 as a temporary protecting or modifying group represents a fascinating area for study with real potential.

Scheme 12. **Effect of CO_2 on coupling reactions of aryl bromides in the presence of amine functionality**



8. Use of Carbonic Acid in Synthetic Organic Chemistry and Novel Reaction Work-up Procedures

8.1. Carbonic Acid-Catalysed Reactions. Many chemical processes are acid catalysed but on a large scale can generate significant amounts of acid waste which requires neutralisation and/or disposal. In principle, water under an atmosphere of CO_2 is mildly acidic, due to formation of carbonic acid (Scheme 13), and should be capable of catalysing a range of reactions. Simple pressure release at the end of the reaction raises the pH back to levels which require minimal neutralisation.[79] Note in this case, we are not dealing with $scCO_2$ (although this would lower the pH of a lower water layer), but gaseous CO_2 usually at a pressure of around 20 bar. This helps reduce equipment requirements, but also ensures that organic substrates remain in contact with the aqueous phase, rather than in a separate supercritical phase, although we have recently reported the use of natural surfactants which allow the formation of stable emulsions which would alleviate this to a degree.[80] Note that although CO_2 has appreciable solubility in water, the converse is not the case and usually separate water and CO_2 layers are observed.

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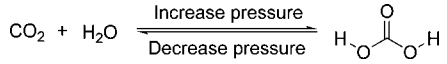
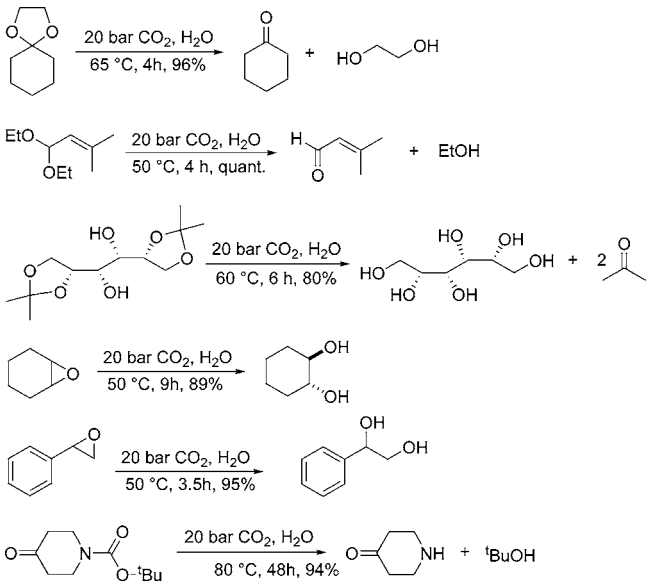
Scheme 13. **Carbonic acid formation**



Some representative examples of simple transformations to illustrate carbonic acid-catalysed reactions are shown in Scheme 14.[81] Thus, mixing a ketal with water, pressurising with 20 bar CO_2, and heating to 65 °C give complete hydrolysis to cyclohexanone and ethylene glycol within 4 h. This is also successful with more complex ketals such as those derived from D-mannitol, and acetals of unsaturated aldehydes. Similarly, epoxides also undergo hydrolysis to diols, and the Boc-protected amine undergoes deprotection.[82] In all cases, little or no reaction was observed under comparable conditions in the absence of CO_2.

Scheme 14. **Carbonic acid-catalysed hydrolysis of ketals, acetals, and epoxides**



8.2. Product Extraction Using $scCO_2$. The hydrolysis of cyclohexanone-derived ketal (Scheme 14) provides an interesting example of reaction work-up and product separation using $scCO_2$.[83−87] The crude product mixture contains water, ethylene glycol, and cyclohexanone; of these, only the ketone has appreciable solubility in $scCO_2$.[81] Thus after reaction, if the CO_2 pressure is increased to supercritical conditions (120 bar) and temperature kept at 45 °C, then by bubbling $scCO_2$ through the crude aqueous layer the desired ketone can be selectively extracted in >90% yield. Utilising $scCO_2$ in this way represents one of the most attractive opportunities for replacement of conventional solvents, as

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(82) Unfortunately, other Boc-protected amines were unreactive under these conditions.
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often the amount of solvent used in product purification is much larger than that used as a reaction medium.

8.3. Hyphenated Preparative $scCO_2$ Reactions and Chromatography Procedures. As with the extraction procedure described above, one of the main uses of solvent in organic synthesis is in purification of products rather than as a reaction medium. This is particularly true in the case of reactions requiring chromatography to purify products. $scCO_2$ is now widely used throughout the pharmaceutical industry for analytical HPLC and is also being used increasingly for preparative work.[88−90] With this in mind, we have constructed a single system which allows reactions to be carried out in $scCO_2$, and then, rather than any conventional work-up, the crude product mixture is loaded onto a high-pressure column packed with normal flash silica simply by opening a tap and increasing the pressure of CO_2 (Figure 9).[91] For most

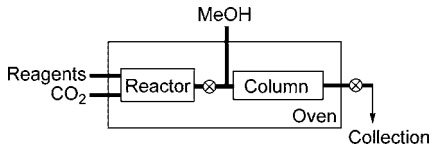

Figure 9. **Hyphenated $scCO_2$ reaction and chromatography equipment.**

substrates $scCO_2$ is sufficiently nonpolar that very little elution of products takes place. However, if $scCO_2$ is continually pumped through the system and a second HPLC pump is used to introduce 1−5% MeOH as a polar modifier, then chromatographic elution and efficient separation are observed. In our reactions we have typically worked on scales of 100−500 mg, but in principle the whole process could be done on a significantly larger scale if required. We have demonstrated that this process works in a wide range of reactions including Diels−Alder, Heck, Henry, Morita−Baylis−Hillman, and ketene cycloaddition reactions.

9. The Potential of CO_2 in Synthetic Organic Chemistry

The main aim of this review was to use chemistry we have developed to illustrate some of the potential of CO_2 in synthetic organic chemistry. It is important to appreciate that it is the underlying principles rather than the specific examples that are most important here, and it is envisaged that the reader will now consider what potential this may have in the specific areas they are involved in. There remain many opportunities to be explored further, particularly in terms of the control of reaction selectivity, product purification (as an example, we are currently working on novel crystallisations utilising CO_2), using CO_2 as a C-1 building block,[92−94] and applying the principles we have developed to real examples of pharmaceutical synthesis, and we would welcome opportunities to discuss potential new projects in these areas. CO_2 technology is certainly going to be of increasing importance in the future. It remains to be seen what the impact will be in fine chemical and pharmaceutical synthesis, but we believe it offers real advantages in terms of reaction control, product purification, and environmental issues, such that its day will come.

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