A critical look at reactions in class I and II gas-expanded liquids using CO_2 and other gases

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This short review aims to give a summary of the publications on reactions in class I and II gas-expanded liquids (GXLs) (those with organic or aqueous liquid components), and to draw conclusions from the trends in the current literature.

Introduction

For many years, there has been interest in performing reactions in supercritical fluids (SCFs),[1–24] one of the main advantages being their complete miscibility with gases such as H_2 or O_2. The non-toxicity of CO_2 and its low cost are also appealing when choosing environmentally acceptable replacements for traditional solvents. However, the relatively high pressures[3] ($P_c(CO_2) = 73.8$ bar) and low solvent power have discouraged their application. This lack of solvent power is a key issue preventing the use of SCFs in the pharmaceutical industry, where the molecules of interest are often strongly basic and usually not very soluble in conventional organic solvents, let alone in SCFs. Despite this, the relatively low production volumes typical of pharma are well-suited to using SCFs, and SCFs have been successfully applied to the micronisation of drugs[25–29] and supercritical fluid chromatography, both for analytical and preparative purposes.[30–32]

Our research group at the University of Nottingham has been working hard to overcome these solubility problems by the use of appropriate co-solvents. This approach is promising, as for example in the continuous selective hydrogenation of sertraline imine using THF as a co-solvent, where it was possible to improve on the diastereoselectivity compared with the published Pfizer process.[33]

We are now developing this co-solvent approach further and this has inevitably drawn us into the field of gas-expanded liquids (GXLs). These liquids and their applications were extensively reviewed by Jessop *et al.* two years ago,[34] and more recently by Arai *et al.* in a more limited sense.[35] However, our project required a more detailed survey of the recent literature on reactions in GXLs, leading to some quite interesting conclusions. We felt that our findings might be of some use to others, so the purpose of this short review is to publish these conclusions and to provide an easily accessible tabulation of the papers for those who wish to follow particular points in greater depth.

This review focuses on reactions in class I and class II GXLs (defined later) since the non-volatility of class III liquids such as CO_2+ionic liquids (ILs) or polymers requires a very different approach to reactions. In addition, both CO_2+ILs[36–40] and CO_2+polymers[41] have been reviewed in their own right.

For those reading the HTML version, this review also demonstrates the power of the RSC Project Prospect to enhance the information available to the reader.

What are GXLs?

Interest in GXLs has increased rapidly in the last 10 years, but the precise definition of a GXL is still not clear-cut. As a working definition,[42] a GXL is a liquid the volume of which is increased when pressurised with a condensable gas such as CO_2. Due to the variety of different behaviours of liquids with expanding gases, a classification system has been proposed by Jessop *et al.*[34] A class I GXL is one where the expanding gas has a low solubility in the liquid, and which does not expand much (such as CO_2+water). A class II GXL is one where the solubility of the expanding gas is high and the expansion is large, *e.g.* CO_2+THF. Class III GXLs are liquids where the gas is moderately soluble but the expansion is small *e.g.* CO_2+ILs or liquid polymers.

Several definitions have been put forward since the concept of a GXL was first suggested, with the definitions changing slightly over time. One of the more recent was proposed by Jessop *et al.* where a GXL was defined[34] as "a mixed solvent composed of a compressible gas…dissolved in an organic solvent". This definition is probably too broad because it encapsulates an extremely large number of reactions carried out in SCFs, where only small volumes (<5 vol%) of co-solvent are used. A slightly

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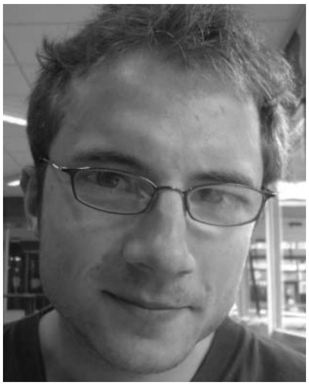

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more refined definition has been put forward by Eckert *et al.* who suggest that a CO_2-expanded liquid (CXL) be any mixture of CO_2 and an organic solvent at conditions below the mixture critical point.[43] Both of these definitions inadverdently exclude systems where the reactants are liquid at the reaction conditions without the need for additional co-solvents, so the definition should be extended to incorporate these. As will be seen in this review, there are just as many CXLs which do not use any solvent compared to those which do. The Eckert *et al.* definition also includes low pressure and high temperature mixtures which can best be described as a vapour, which probably should not be included in the GXL definition. In contrast to Jessop *et al.*,[34] we believe that an enhanced fluidity liquid (EFL) (one where the gas is completely dissolved in the liquid[44]) resembles a liquid more closely than an SCF since, under high pressures, the compressibility of an EFL is much less than that of an SCF. Because of these issues, we think that the definition of a GXL should be either broadened or narrowed, instead of currently occupying an ambiguously-defined middle ground.

We favour the broader definition of a GXL, which is applied in this review. In defining a GXL it is more useful to use pressure–composition diagrams at constant temperature than the more usual pressure–temperature diagrams at a constant composition, since the composition of a mixture can change when it is pressurised with CO_2. For convenience sake we also use the critical composition to describe the composition corresponding to the critical pressure and temperature.

A GXL would therefore be a mixture of a condensible gas with other components such that there are at least 2 fluid phases or, a single phase above the bubble point curve but below the critical composition, where the properties of the liquid phase(s) are substantially different from those at atmospheric pressure. This then excludes all mixtures which are adjacent to the dew point curve, but includes mixtures where the components are solid at atmospheric pressure. A clearer diagram of this is shown in Fig. 1. The separation between an EFL and an SCF at the top of the diagram is certainly an artificial one, but is perhaps the most practical way of properly defining a GXL.

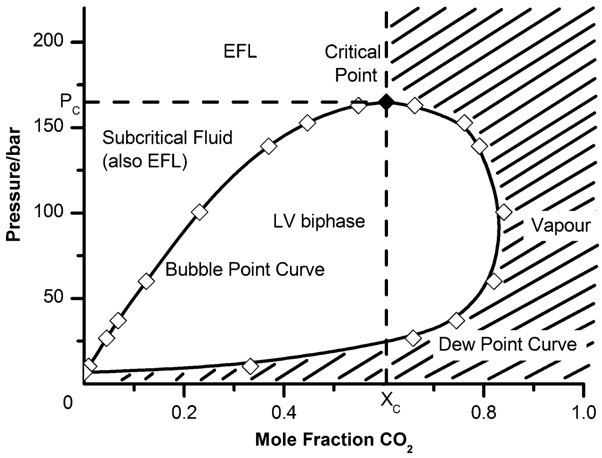

Fig. 1 Definitions of different phase regions, using an isotherm for the CO_2+methanol binary system at 121.1 °C as an example.[45] The hashed region represents the area which the GXL definition is intended to exclude. Note that the position of the critical point on the phase envelope will vary from one binary system to another.

In other words, a GXL encompasses systems with >1 fluid phase, subcritical fluids (both the pressure and composition are below their critical values) and EFLs.[46] On the other hand, a narrower and simpler definition would only require that a liquid be *saturated* with a gas which expands it, *i.e.* excluding EFLs and subcritical fluids outside of the biphasic region. Note that this would not necessarily require the presence of a separate vapour phase.

What happens on expansion?

The typical expansion behaviour of a class II GXL is shown in Fig. 2, using CO_2+THF as the example.[47]

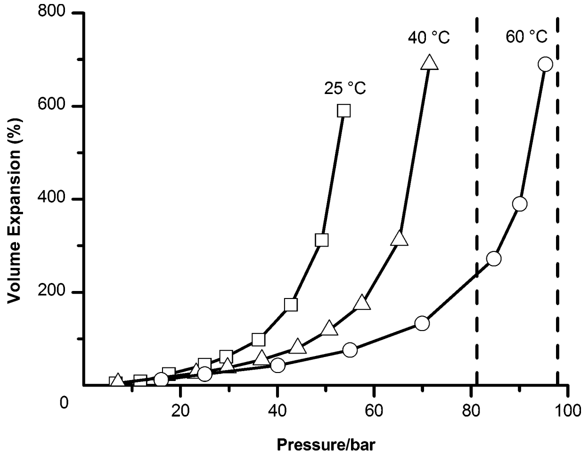

Fig. 2 Volume expansion of THF with varying CO_2 pressure at different temperatures, as measured visually in a Jerguson view cell.[47] The expansion increases rapidly towards the mixture critical point (shown with dashed lines).[48]

The expansion increases with pressure, rising almost exponentially towards the critical point. When the expansion is plotted against the CO_2 mole fraction in the liquid phase, it is largely independent of the pressure or temperature.[42] This expansion changes both the solvent character and the physical properties of the liquid. When CO_2 dissolves into the liquid, it reduces both the polarity and the hydrogen-bonding abilities of the expanded liquid.[43,49–59] However, the solvent power is maintained for longer than expected, compared to simple dilution by CO_2, since the more polar solvent molecules can cluster dynamically around the solute. This leads to both an increase in the proportion of solvent molecules in the cybotactic region, but also an increase in the local density too.[60–84] Although class I GXLs expand negligibly since CO_2 is not very soluble in them, when CO_2 is added, it can form carbonic acid *in situ*,[26,85–93] lowering the pH to less than 3.

A rarely considered point is that the maximum expansion of a GXL depends on the initial amount of liquid in the vessel. Typically, <2 mol% of the solvent is dissolved in the CO_2-rich phase. If the cell is under-filled, increasing the pressure increases the density of the CO_2-rich vapour phase enough to start dissolving significant quantities of the solvent, so that the expansion decreases instead[94] until the dew point is reached. If the cell is over-filled, then increasing the pressure will increase the amount of CO_2 in the liquid phase until all of the vapour will have dissolved, *i.e.* at the bubble point. At lower pressures where CO_2

is a much poorer solvent, the expansion level is not significantly affected by the amount of liquid initially in the cell, but at higher expansions ($>500\%$) this can be important. The normal working definition of the critical point is defined as the merging of the co-existing liquid and vapour phases when the properties of the two phases (density, composition *etc.*) are identical. This means that, for a pure substance, the meniscus must be at half the volume of the vessel.[95] In contrast for GXLs, the maximum possible liquid expansion can only be achieved if the critical point is observed with the meniscus at the top of the sealed vessel.

Like SCFs, GXLs have been shown to have improved mass transfer through reduced viscosity,[64,69,71,87,96–109] increased solute diffusivity[44,97,104,107–110] and decreased interfacial tension.[111–131] However, studies into actual mass transfer coefficients have been limited, with only four different systems being investigated, and most studies are on CO_2+H_2O under conditions relevant to deep-sea CO_2 sequestration.[132–141] The mass transfer rates for H_2 and CO into CO_2-expanded 1-octene have been measured, but unfortunately they were not compared with data obtained under comparable conditions in the absence of CO_2.[141]

The use of GXLs can in principle also lead to an overall reduction in solvent usage; the usually quoted reduction[10,142] being "up to 80%". This figure comes from a comparison of *e.g.* 5 mL solvent *versus* 1 mL of solvent expanded five-fold.

More controversially, it has been suggested that gases such as H_2, O_2 and CO have an increased solubility in CXLs. Several authors have shown that the H_2 mole fraction,[34,117,118,124,126–128,131,143] concentration[130] (mol dm^{-3}) or ratio of H_2 : reactant[111] increases with increasing pressure, expansion[116,122] or mole fraction CO_2 (we have ignored articles where there were no ternary VLE data to correlate the models used). There is much less data on O_2 and CO solubility,[34,115,116,121] and the solubility enhancements for these gases in CXLs are generally smaller than for H_2.[121,131] Unfortunately, rather few authors have made true comparisons of gas solubility with or without CO_2. Complicating matters further, there are two main ways of comparing solubilities, as shown in Fig. 3.

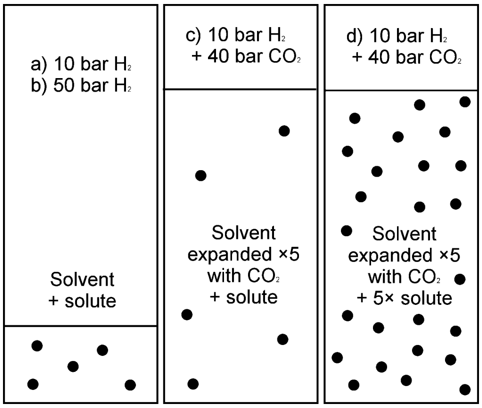

Fig. 3 A schematic of the four different ways of describing the gas solubility in a CXL compared to the solvent in the absence of CO_2. Absolute values are for illustrative purposes only.

In case 1, the enhancement in the gas solubility can be compared in the absence and presence of CO_2 at the *same* gas fugacity—as in Fig. 3 with (a) *versus* (c) or (d). In case 2, one can also compare them at the same *total* pressure—(b) *versus* (c) or (d). Most of the authors who have included solubilities of the pure gas for comparison have so far only used case 1 to compare their data, and it appears that in general, CO_2 enhances the solubility of the gas by this definition.[34,124] Far fewer authors make direct comparisons using case 2,[118,127,143] and only in select cases does the H_2 solubility exceed that achievable with H_2 alone at the same *total* pressure.

A few authors also compare their H_2 solubilities by the ratio of the solvent to the H_2,[122] taking into account the effect of the volume expansion. It is also noteworthy that only small quantities of CO_2 are necessary to achieve a 20–30% solubility enhancement (as compared by case 2), one study requiring only a 10–20% partial pressure of CO_2 to do this.[127] Only one study has investigated the gas solubility enhancements with different expanding gases, the authors comparing the H_2 solubility in CO_2- and propane-expanded *iso*-propanol.[126] Under most of the conditions tested, the H_2 solubility was increased substantially by propane pressurisation as compared by case 2 (up to seven-fold enhancement as by case 1). The authors also studied CO_2-expanded *iso*-propanol and found similar enhancements[126,131] (~1.5–2.5) as compared by case 1.

It has been suggested that, as the solvent expands with increasing CO_2 pressure, although the H_2 mole fraction may only increase slightly, the expansion will reduce the volumetric concentration of the solute, and therefore the ratio of H_2 : solute will increase. Whether this has any effect will depend on the kinetics of the particular reaction involved. This also implies the dilution of the solute where it is not necessary. If a process runs well in 10 mL methanol, but runs slightly better in 10 mL methanol expanded five-fold, there is no overall reduction in solvent use—one of the purported benefits of using CXLs. The reduction can only be achieved if less methanol or more solute is used instead (as in Fig. 3(d)).

Selection criteria

In any review one has to be selective rather than encyclopedic. Since the terms "GXL" or "CXL" are often not used in the relevant articles, selecting papers becomes difficult. Papers have been included where they feature reactions with a CO_2 partial pressure of >15 bar and are also shown to be biphasic (excluding emulsions). If there is no information on the phase behaviour, articles are included if the CO_2 partial pressure is subcritical (<73.8 bar) or if there is >1 vol% H_2O, since H_2O rarely has a greater solubility than this under typical reaction conditions.[144] Papers are also included if the temperature is relatively low (≤ 40 °C) and the pressure is high (≥ 150 bar), *i.e.* an EFL.

The use of CO_2 as a C_1 building block[145–148] has been widely investigated to make a variety of chemicals such as carboxylic acids,[149] carbonates,[150] carbamates[151] and ureas.[152] The literature on this subject is so extensive that a systematic review is beyond the scope of this article. However, if there was an accompanying systematic investigation of the phase behaviour of the system, or if the results were particularly interesting in their own right, then they have been included. Polymerisation and the modification of polymers have also been excluded for similar reasons.[153–162]

All of the reactions in class I and II CXLs have been ordered alphabetically by reaction type in Table 1 and, by increasing complexity of the reactants within each reaction type. The range of temperatures and pressures studied for each example is included but are not always indicative of the number of phases, since phase behaviour data are rarely given for the whole range of reaction conditions studied. All reactions were performed in batch mode unless otherwise stated and, the reader is referred to the relevant article for more details.

The headings in Table 1 are intended to give the maximum amount of useful information without being unnecessarily lengthy. We have pointed out where comparisons have been made of the CXL with comparable supercritical operation, but only where there is a clear advantage for one type of phase behaviour over another. Frequently, one of the phase systems offers better selectivity for a reaction, with the other giving better conversion, or *vice versa.*

Table 2 is much shorter and contains the few examples of reactions in GXLs where expanding gases other than CO_2 have been used. Note that although N_2O has critical parameters[3] similar to CO_2 ($P_C = 72.5$ bar and $T_C = 36.4$ °C), **N_2O should never be used with organic compounds** at high pressure because it is a potentially strong oxidising agent and severe explosions have been reported.[163,164]

Conclusions

Unusually, we present our conclusions before our two Tables. These Tables show that there is a now a sufficiently large number of studies for general conclusions to be drawn. There are still many questions that remain unanswered but we believe that the following points from Tables 1 and 2 are a starting point for summarising the current state of the art.

1 There are many ways of using GXLs as reaction media. For instance, the catalyst need not be in the liquid phase, but in the dense fluid phase,[165–167] or the whole reaction need not occur in the liquid phase either.[168,169]

2 Apart from the Thomas Swan[170] and Idemitsu[3] plants, all entries in the Tables feature laboratory-scale reactors. A wide range of reactor types and modes other than batch mode have been tested with CXLs, *e.g.* semi-batch where the catalyst is retained in the CO_2-rich phase and the liquid phase is removed without unnecessarily reducing the pressure.[165–167] There is one example of a continuously-fed stirred batch reactor (CSTR) where the vapour phase is continuously removed and the inlet feed carefully controlled to maintain the correct liquid level inside the vessel,[171] However, no one so far appears to have used a CSTR with continuous liquid phase removal. There have also been many examples of reactions in continuous flow fixed bed reactors.[123,170,172–192]

3 Many of the reactions involve gaseous reagents such as H_2, O_2 or CO probably because these are the most atom economical. This may also be because of the perceived large increase in gas solubility with CO_2 pressure, but this is not borne out by experiments which usually only show a small increase in solubility.[121,131]

4 The number of papers is overwhelmingly skewed in favour of hydrogenation, with these making up nearly half of all the entries in Table 1.

5 Relatively few of the reactions are multi-step/component. The current trend in organic chemistry is to perform multi-step/component reactions in one pot,[193–196] and this trend is not reflected in the CXL literature. Since the use of high pressures increases the energy costs, being able to run multiple reactions without depressurisation would go some way to mitigating these costs.

6 The molecular complexity of the reactants is relatively low, with most substrates having only one reactive functional group, and rarely more than two. This is perhaps surprising because one could use more complex substrates with lower solubility in GXLs. One of the strengths of GXLs is that their solvent power is much higher than in the corresponding SCF—this advantage has so far mainly been exploited to dissolve homogeneous catalysts, and not as often for reactants with a low solubility.

7 Over half of the reactions in Table 1 do not use any additional solvent at all. This is partly due to the solvent being a reactant, *e.g.* MeOH or ethylene glycol in acetal formation,[197] but more often it is the result of the reactants already being liquids.

8 CO_2 can reduce the lower temperature limit for performing reactions; reactions of naphthalene,[198] 2-vinylnaphthalene, methyl 2-acetamidoacrylate[199] and 2-butyne-1,4-diol[200] involve solid reactants which are only liquid at the reaction temperature when pressurised with CO_2—CO_2 is crucial in reducing the melting point of the solid phase so that a reaction takes place without solvent. The concept can also work for reactions in which the product is a solid at the reaction temperature.[201]

9 CO_2 can also increase the upper temperature limit; butadiene is a gas at ambient pressure and temperature and the CO_2 pressure allows liquid operation with a dissolved homogeneous catalyst at higher temperatures.[202]

10 The range of catalysts used is very broad, and very few of the reactions use stoichiometric reagents—nicely adhering to the 9th principle of green chemistry.[203] For ease of scale-up, heterogeneous catalysts are to be preferred, but homogeneous ones may be more selective.

11 The separation of the catalyst from GXL reaction mixtures has not been considered enough where homogeneous catalysts have been used. Two general approaches have been identified to separate the catalyst from the reaction mixture after the reaction is complete: (a) increase the pressure and hence expand the liquid to precipitate the catalyst, whether the reaction was carried out either in a GXL[115] or at ambient pressure,[204] or (b) release the pressure and expand the gas to separate the phases.[205] This lack of proven catalyst separation strategies is a serious shortcoming which needs to be remedied since precious metal-catalysed processes will rarely be economically viable unless the catalyst can be properly recycled.[206]

12 Where conventional solvents are used, they are often polar, *e.g.* water, alcohols or acetonitrile (MeCN). This strategy is a sensible one, with CO_2 being used to tune the solvent power across the largest possible polarity range.

13 The pressure range is quite varied, but too few researchers cover a wide enough pressure range within their experiments, *e.g.* 30–300 bar.

14 A large number of the reactions in Table 1 do not include comparable experiments with a single phase—be it supercritical or otherwise. This is often because the poor solvent power of $scCO_2$ means that it is not practical to run the reaction in an SCF.

15 Where satisfactory comparisons have been made, there is no general consensus, even for a particular reaction type, on whether it is better to run the reactions in two phases or a single phase. This is perhaps because of the wide continuum of

properties that is achievable as a liquid-like single phase through to a vapour-like single phase.

16 There are surprisingly few control experiments at ambient conditions or in the absence of CO_2—less than half of the papers included these types of experiments. It would be good to have more comparisons in the future. Those that do include comparisons with ambient conditions nearly always find that CXLs are superior. Those that report otherwise do not always give a plausible reason for the difference in performance.

17 One of the oft-cited advantages of SCFs is that the absence of phase boundaries increases the rate of mass transfer in the solvent.[4] However, it is not always necessary to remove the phase boundaries since mass transfer (particularly at higher expansions) is not necessarily the rate-limiting process in a reaction.[128,207,208] In some cases it may be that the rate of the reaction is the limiting factor.

18 In many cases, expansion with CO_2 decreases (rather than increases) the miscibility of two liquids. This occurs typically when one liquid is water and the other is a water-miscible organic (*e.g.* THF); expansion with CO_2 promotes the separation of the organic- and water-rich phases. Sometimes two (or more) liquid phases are present, in addition to the usual CO_2-rich vapour phase. CO_2 can also increase the miscibility of certain liquids normally immiscible at ambient conditions, *e.g.* glycerol monostearate and MeOH.[209] In one particular case involving alkenes and aqueous H_2O_2, it was possible to render the two phases completely miscible.[210]

19 Where the phase behaviour changes drastically over the course of the reaction, particularly in the condensation of small molecules, *e.g.* propylene oxide + CO_2[211] or H_2 + O_2,[168,169] it is difficult to draw firm conclusions about the role of GXLs in that reaction.

20 Those reactions in the Tables which have been scaled-up,[111,170,172,178,202,212] have always had more thorough investigations into the phase behaviour.

21 There is great potential in combining product separation with the chemical reaction while under pressure, *e.g.* liquid–liquid separation with levulinic acid hydrogenation,[188] or in the particle formation of Cu(indomethacin) using the anti-solvent properties of CO_2.[213]

22 CO_2 cannot always be considered as an inert solvent—it can form carbonic acid which may deactivate enzyme catalysts,[214] carbamates which can either help or hinder reactions,[151,215–219] or even CO *via* the reverse water gas shift reaction at higher temperatures.[220–222]

23 The use of CO_2 as an *in situ* acid catalyst has considerable potential when weakly acidic catalysis is required. When the reaction mixture is depressurised there is no residual salt waste that needs to be removed, as in conventional acid-catalysed reactions.[57,197,223–226]

24 It is not always necessary to use large amounts of CO_2 to improve a reaction.[123,127] In the hydrogenation of tetralin in a continuous flow fixed bed reactor, it was found that the optimum conditions were achieved with only 25 wt% CO_2 in the H_2 feed.[123] This has interesting implications for hydroprocessing worldwide, where unit operations are already run at high pressure and the addition of relatively small amounts of CO_2 to the feed might help improve performance. Similarly, the optimum performance in the selective hydrogenation of *p*-chloronitrobenzene required a CO_2 partial pressure of only 17% of the total pressure.[127]

25 In the majority of papers, the expanding gas is CO_2, despite the lower solvent power of CO_2, and the higher pressures required to achieve a particular level of expansion. For example, 440% expansion of ethyl acetate at 25 °C with CO_2 needs 53.4 bar, but with ethane only 31.7 bar is required.[42] This preference for CO_2 amongst the authors is probably the result of its low toxicity, non-flammability, cost and the fact that explosion-proof electrical systems are not necessarily required.

26 Different expanding gases have usually been chosen for chemical reasons, *e.g.* the use of CO_2 to form carbonic acid to accelerate the reaction,[197] the use of ethane to avoid the formation of CO which can poison the catalysts.[227,228] However, another important reason is for solubility where the low polarity of CO_2 is not enough to dissolve large molecules like fatty acid methyl esters[229] or more polar ones like carboxylic acids.[230] Other expanding gases, such as propane or fluoroform, are much better solvents than CO_2. This means that the pressures needed to reach single phase conditions with the pure fluid are accessible enough to negate the low pressure advantage normally associate with GXLs.

Table 1 Reactions in class I and II CXLs

Reaction	Substrate(s)	Added solvent(s)	Catalyst(s)	$T/°C$	P/bar	CXL> SCF?[a]	>ambient P?[b]	Comment(s)	Ref.
Acetal formation	Cyclohexanone + MeOH or ethylene glycol	—	*In situ* carbonic acid	25–50	1–60	—	Yes	Increasing the pressure too high reduces the liquid phase polarity, which hinders the carbonic acid dissociation equilibrium and therefore the reaction rate.	197
Acylation	Anisole + acetic anhydride	—	Various solid acids	50–90	50–155	—	No	Continuous-mode slurry reactor, catalyst could be reactivated completely by treating with boiling 40% $HNO_{3(aq)}$.	231
Aldol Condensation	Propionaldehyde	—	None, MgO, or MgO with H_2O or dilute $HCl_{(aq)}$	80	1–170	—	—	Single phase operation favours the enal product and CXL operation the aldol.	232
Aldol Condensation + Hydrogenation	Crotonaldehyde + H_2	—	1 wt% Pd/Amberlyst-15	60	40–160	No	—	Continuous flow fixed bed, catalyst deactivated over time.	189,191
Alkylation	1-Butene + isobutene	—	SiO_2-supported Nafions or a zeolite	75–95	79–166	No	—	Continuous-mode slurry reactor; best performance was with periodic pressure increases to extract coke from the catalyst.	233

Table 1 *(Contd.)*

Reaction	Substrate(s)	Added solvent(s)	Catalyst(s)	$T/°C$	P/bar	CXL> SCF?[a]	>ambient P?[b]	Comment(s)	Ref.
Alkylation	Phenol + cyclohexanol or cyclohexene	—	γ-Al_2O_3	275–300	100–150	No	—	Continuous fixed bed, second phase formed from water by-product probably responsible for catalyst deactivation	190
Alkylation	Anisole + ^nPrOH	—	Various solid acids	100–250	200–400	—	—	Continuous flow fixed bed; pressure dependence depended on the catalyst support.	181
Alkylation	Triphenylmethanol + anisole	—	TFA or AcOH	23–118	1–346.7	Yes	No	Solventless operation at ambient pressure gave the highest conversion but reaction was very exothermic so unsuitable for scale-up.	234
Carboxylation	Pyrrole + CO_2 (+ NH_4OAc to deprotonate the product)	KH_2PO_4 aqueous buffer	*Bacillus megaterium* PYR 2910 decarboxylase	40	65	—	—	Conducted both in batch and in continuous upflow.	192
Carboxylation	Range of ketones + CO_2	Neat (no added solvent), THF or MeOH	DBU	0–40	20–60	—	—	Competing decarboxylation is less in the absence of solvent; one-pot carboxylation-hydrogenation also attempted.	235
Complexation	Indomethacin + $Cu(OAc)_2$	DMF	—	25	59	—	—	Precipitation of product drives equilibrium and simultaneously micronises the product for pharmaceutical application.	213
Condensation	2,3,6-Trimethylhydroquinone + isophytol	—	CO_2-soluble fluorinated Brønsted acids, or solid acids	100	1–350	No	Yes	Presence of a (polar) liquid phase leads to production of undesired side-products.	236
Coupling	Butadiene + CO_2	—	$[(\eta^5\text{-}C_5H_5)Pd(\eta^3\text{-}C_3H_5)]$ + nitrile substituted phosphine ligands + BTD	60–85	46.3–143	Yes	—	Scaled up to 1 L reactor size; reaction could not be run as a single phase due to low catalyst solubility.	202
Coupling	Diazodiphenylmethane + H_2O or various alcohols or glycols	Acetone	*In situ* carbonic acid	23–40	15–100	—	—	Used to infer the presence of carbonic or alkylcarbonic acids formed *in situ* from CO_2 + H_2O.	57,223
Coupling	Phenyl iodide + diphenylacetylene + phenylboronic acid + CsOAc	MeOH	$PdCl_2$	100	0–100	—	Yes	Increasing pressure increased the yield up to a threshold pressure of 60 bar after which no further changes were observed.	237
Coupling (Heck)	Styrene or butyl acrylate + iodobenzene	H_2O or ethylene glycol	$Pd(OAc)_2$ with TPPTS and NEt_3	60	1–140	Yes	—	Higher conversions at ambient pressure but less leaching as a CXL than without CO_2; on depressurisation catalyst is in a separate liquid phase to the product.	238
Coupling (Heck)	Methyl acrylate + aryl bromides + NEt_3	Toluene	$Pd(OAc)_2$ + PPh_3	130	1–130	—	—	Pressure effect was highly substrate-dependent.	239
Dehydration	1,4-Butanediol	H_2O	–	250–300	97–112	—	Yes	Includes mechanistic study using other solid acid catalysts to determine the role of CO_2.	240
Dehydration	Diols or triols	H_2O	*In situ* carbonic acid	300	177–255	—	Yes	Presence of CO_2 substantially accelerated the reaction.	241,242
Dehydrogenation	1-Phenylethanol	—	0.5 wt% Pd/Al_2O_3	80–165	25–190	Yes	—	Continuous flow fixed bed reactor, no catalyst deactivation over 300 hours.	182
Diazotisation + Coupling	*N*-heterocycle + substituted aminobenzene + sodium or isoamyl nitrite	H_2O	*In situ* carbonic acid	35–40	5–65	—	—	Early example of intentional *in situ* acid catalysis with pressurised CO_2.	243
Diazotisation + Coupling	*N*,*N*-diethylaniline + *p*-nitroaniline + $NaNO_2$	H_2O	*In situ* carbonic acid	10–80	1–214	—	Yes	*In situ* acid catalysis meant that the use of the usual high concentrations of mineral acids could be avoided.	244
Diazotisation + Coupling	Aniline + isoamyl nitrite or $NaNO_2$, then + *N*,*N*-dimethylaniline or KI (one-pot synthesis)	MeOH, THF or neat	*In situ* carbonic acid	5–50	10–47	—	—	Higher temperatures reduced the product yield; presumably due to decomposition of the intermediate diazobenzene.	225
Diels–Alder	Isoprene + methyl acrylate, methyl vinyl ketone or acrolein	Toluene or EtOH	SiO_2–Al_2O_3	80	1–160	Yes	No	Authors suggest that the change in reactivity is due to changes in the interactions of the reactants with CO_2 as observed *via* FTIR.	239

Table 1 *(Contd.)*

Reaction	Substrate(s)	Added solvent(s)	Catalyst(s)	T/°C	P/bar	CXL> SCF?[a]	>ambient P?[b]	Comment(s)	Ref.
Direct reaction	$H_2 + O_2$	Aqueous stabilisers	Homogeneous CO_2-soluble Pd(0) or (II)	22–25	172	—	—	Reaction takes place in the vapour phase with H_2O_2 condensing into the aqueous phase; dilution of vapour phase by CO_2 reduces explosion risks; see also cyclohexene epoxidation below.	168,169
Electro-carboxylation	Butadiene or 1,4-dibromobut-2-ene (Bu_4NBr or Bu_4NBF_4 as supporting electrolytes)	DMF	—	25	1–40	—	Yes	Poor yields due to competing reactions; different cathode materials (Pb, Cu or stainless steel) gave significantly different product distributions.	245
Electro-carboxylation	1,4-Dibromoperfluoro-butane, trifluoromethyl iodide or perfluorobutyl iodide (Bu_4NBF_4 as supporting electrolyte)	MeOH	—	25–50	30–50	—	—	Increased CO_2 pressure did not improve yields much since the rate of addition of CO_2 to the fluorinated anion intermediate was too slow.	246
Electro-carboxylation	Benzyl chloride (BuN_4ClO_4 or $(decyl)_4NBPh_4$ as supporting electrolytes)	DMF or neat	—	40	1–120	Yes	Yes	Yields and selectivities much poorer when performed without DMF.	247
Epoxidation	Cyclohexene + O_2 or PhIO	MeCN	TPPFeCl or PFTPPFeCl homogenous, or MCM-41-immobilised PFTPPFeCl	25–80	1–127	Yes	Yes	Leaching was less with the CXL than in the absence of CO_2.	115,142,248,249
Epoxidation	Propene + H_2O_2	MeOH, MeCN, ^{i}PrOH or ^{t}BuOH	$MeReO_3$, optionally with *N*-bases	25–70	2.7–49.3	—	No	Pressurisation with N_2 was more effective than with CO_2.	125,129
Epoxidation	Cyclohexene + H_2O_2 (formed *in situ* from H_2 + O_2)	Neat or with $CHCl_3$	Homogeneous Pd(0) or (II) or 1 wt% Pd/C + zeolite TS-1	25	131	—	—	H_2O_2 forms in CO_2-rich phase and then condenses into the aqueous phase.	168,169
Epoxidation	Cyclohexene + H_2O_2, optionally with $NaHCO_3$ or hydroxy-1,1-ethanephosphinic acid (HEDP)	Neat, H_2O, DMF, DMA, MeOH, PC or MeCN	None or $NaHCO_3$	40	120	—	—	Peroxycarbonic acid formed *in situ* catalyses reaction.	250
Epoxidation	3-Cyclohexen-1-carbxylate sodium salt + H_2O_2 + hydroquinone as stabiliser	H_2O, optionally with DMF	None or $NaHCO_3$	40	120	—	—	Peroxycarbonic acid formed *in situ* catalyses reaction—used to show reaction takes place in aqueous phase.	250
Epoxidation	Alkene + H_2O_2	EtOH + $NaOH_{(aq)}$ buffer, with or without an ionic surfactant	None or tetraheptyl ammonium bromide	23–24	241	—	—	Reaction believed to go *via* a peroxycarbonate intermediate.	169
Epoxidation	Alkene + H_2O_2	H_2O, optionally with MeCN, THF or ^{t}BuOH	Pyridine or pyridine-*N*-oxide	30–40	48–60	Yes	—	CO_2 used to homogenise organic and aqueous components; *in situ* peroxycarbonic acid formation cited as the reason for the good performance.	210
Epoxidation	Cyclohexene + pivaldehyde + O_2	FC-75–90% fluorinated butyltetra-hydrofuran	Co(II) carboxylate	25	0–70	—	—	CO_2 used to render catalyst (fluorous) and reactant (organic) phases miscible for reaction, and then depressurised to separate the phases for catalyst recycling	251
Esterification	AcOH + EtOH	—	*In situ* carbonic acid	60	58.6	—	—	Shifts equilibrium due to CO_2 extraction of EtOAc from liquid into vapour phase	252
Esterification	AcOH + EtOH	—	*p*-TsOH	60	60–160	Yes	Yes	Shifts equilibrium due to CO_2 extraction of EtOAc from liquid into vapour phase.	253

Table 1 *(Contd.)*

Reaction	Substrate(s)	Added solvent(s)	Catalyst(s)	$T/°C$	P/bar	CXL> SCF?[a]	>ambient P?[b]	Comment(s)	Ref.
Esterification	Ethylene glycol + propionic acid	—	*p*-TsOH	50	0–200	—	—	Phase behaviour dictates equilibrium concentrations.	254
Esterification	Oleic acid + 1-dodecanol	—	Lipozyme RM IM (immobilised lipase from *Rhizomucor miehei*)	60	60–410	Yes	—	Phase behaviour of reaction investigated thoroughly.	255
Esterification	Glycerol + acetic acid	—	Amberlyst 15	100–150	65–300	—	—	Continuous flow fixed bed reactor; catalyst stable over 25 h on stream.	256
Esterification	Citronellol + lauric acid	Acetone, *n*-heptane, or 2-methyl-2-butanol	Immobilised lipase Novozym 435 (*Candida Antarctica*)	50–70	80–200	—	—	Water immiscibility of acetone (under CO_2 pressure) blamed for poorer performance compared to other co-solvents.	257
Esterification	Glucose + palmitic acid	Acetone	Novozym 435	40–60	1–105	—	Yes	Suggested mechanism has the reaction taking place in the vapour phase (where there is less H_2O) to allow the equilibrium to be shifted.	258
Esterification	Caffeic acid + sucrose	$K_3PO_{4(aq)}$ buffer	Sucrose phosphorylase	42	0–250	—	No	*In situ* carbonic acid believed to deactivate enzyme catalyst.	214
Etherification	1,6-Hexanediol or 1,4-propandiol + MeOH, EtOH or ^nPrOH	—	Amberlyst 15	110–170	40–425	—	—	Continuous flow fixed bed reactor; CXL favours di-etherification and $scCO_2$ mono-etherification.	183
Etherification (cyclisation)	1,4-Butandiol	MeOH	Deloxan ASP	100–200	60–200	—	—	Continuous flow fixed bed reactor.	174
Formylation	Morpholine + CO_2 + H_2	Neat, H_2O or NEt_3	$RuCl_2(dppe)_2$	100	215	—	—	Initial part of reaction not a CXL as only solid and vapour phases present—increasing quantities of product result in an additional liquid phase.	259
Hydration	Cyclohexene + H_2O	—	*In situ* carbonic acid	300	0–55	—	Yes	CO_2 enhances reaction rate.	260
Hydroformylation	1-Hexene + CO + H_2	Toluene	Homogeneous or SiO_2-immobilised $Rh(acac)_3$ + $PEtPh_2$	75	181.6	Yes	Yes	*n*/*iso* ratio largely unchanged in the presence of CO_2.	261
Hydroformylation	1-Octene + CO + H_2	Acetone or neat	Various homogeneous Rh	30–90	6–210	Yes	Yes	Increasing the CO_2 pressure at the end of the reaction precipitates the catalyst so it can be separated and reused.	124,262
Hydroformylation	1-Octene + CO + H_2	—	$Rh(acac)(CO)_2$ + ionic tri-alkylphosphine ligands	100	125–140	—	—	Continuously fed batch vessel with CO_2-assisted extraction of products from catalyst-containing liquid phase; Rh leaching could be kept very low.	171
Hydroformylation	Cyclohexene + CO_2 + H_2	Neat or NMP	$Ru_3(CO)_{12}$ with or without LiCl	50–150	20–80	—	—	CO formed *in situ* from CO_2 hydrogenation.	221
Hydroformylation	Styrene or 2-vinylnapthalene + CO + H_2	—	$[Rh(cod)_4](BF_4)$ + (*R*,*S*)-3-H^2F^6-BINAPHOS	45	205–220	—	—	CO_2 reduces melting point of 2-vinylnaphthalene; ligand designed to reduce the required fluorination.	199
Hydroformylation	Functionalised bicyclic internal alkene + CO + H_2	H_2O with or without MOPS buffer	$Rh(acac)(CO)_2$ with and without $P(C_6H_4\text{-}p\text{-}(CH_2)_2C_6F_{13})_3$, or $Rh(hfac)(CO)_2$	60	n/a	—	—	Semi-batch operation with catalyst retained in CO_2-rich phase; H_2O-rich liquid phase could be periodically replaced with fresh reactants.	165
Hydrogenation	Cyclohexene + H_2	—	5 wt% Pd + 5% wt% Pt/Deloxan APII	>100	60–80	—	—	Continuous flow fixed bed reactor.	173
Hydrogenation	Cyclohexene + H_2	—	1 wt% Pd/Amberlyst 15	60	40–180	No	—	Catalyst activity good long-term.	191
Hydrogenation	Cyclohexene + H_2	—	1 wt% Pd/SiO_2	40	0–140	No	Yes	Catalyst leaching during CXL operation was comparable to conventional organic solvents.	263
Hydrogenation	Tetralin + H_2	—	5 wt% Rh/C or Al_2O_3	60	60–340	—	—	Single phase favours higher conversion but lower selectivity.	264

Table 1 *(Contd.)*

Reaction	Substrate(s)	Added solvent(s)	Catalyst(s)	T/°C	P/bar	CXL> SCF?[a]	>ambient P?[b]	Comment(s)	Ref.
Hydrogenation	Tetralin + H_2	Decane	0.5 wt% $Pt/\gamma\text{-}Al_2O_3$	260–320	34.5–89.6	Yes	Yes	Continuous fixed bed reactor; also run with CO_2 in the absence of a vapour phase in upflow ("liquid-full mode") to decouple mass transfer effects from kinetics; a relatively small amount of CO_2 is required in the gas feed for optimum benefits (25 wt% CO_2).	123
Hydrogenation	Naphthalene + H_2	—	5 wt% Rh/C	60	110–280	—	—	Single phase favours higher conversion but lower selectivity; CO_2 lowers melting point of naphthalene so that it is a liquid under reaction conditions.	198
Hydrogenation	Styrene + H_2	H_2O	$RhCl(TPPDS)_3$	40	275.9	—	Yes	CXL was not as good as a CO_2+H_2O emulsion.	265
Hydrogenation	Styrene, citral or nitrobenzene + H_2	—	5 wt% Pd/C	50	0–130	—	Yes	Conversion did not change significantly between CO_2, N_2 or H_2 vapour phases.	266
Hydrogenation	Styrene + H_2	Cyclohexane	$[RhCl(P(C_6H_4\text{-}p\text{-}CH_2CH_2(CF_2)_2F)_3)_3]$ + fluorous silica	40	90	—	—	CO_2 pressure also used to precipitate catalyst so that it sticks to the fluorous silica, ready for re-use in further reactions.	204
Hydrogenation	α-Methylstyrene + H_2 2	—	1 wt% Pd/C	50	70–130	—	—	Improved rate of reaction believed to be due to increased H_2 solubility in liquid phase.	267
Hydrogenation	Limonene + H_2	—	1 wt% Pd or Pt/C	50	125–160	Yes	—	Batch vessel with liquid phase continuously recirculated through a fixed bed reactor; limonene concentration in liquid phase a more important factor than the H_2 concentration in the liquid phase.	128,130
Hydrogenation	α-Pinene	—	1 or 10 wt% Pt/C	50	70–170	Yes	—	Batch vessel with liquid phase continuously recirculated through a fixed bed reactor; α-pinene adsorption on to the catalyst is the rate-determining step at single-phase conditions—not the availability of H_2.	207,208
Hydrogenation	Phenylacetylene + H_2	—	Amorphous $Pd_{81}Si_{19}$	55–85	50–200	No	—	Continuous flow fixed bed reactor; H_2 excess needed to be minimised for single-phase conditions to be reasonably accessible.	175
Hydrogenation	Dehydroisophytol + H_2	—	Amorphous $Pd_{81}Si_{19}$	42–120	50–250	No	—	Continuous flow fixed bed reactor.	178
Hydrogenation	Benzaldehyde + H_2	—	5 wt% Pt/C	50	100–200	—	No	FTIR studies on interactions of benzaldehyde with CO_2.	119
Hydrogenation	Acetophenone + H_2	—	5 wt% Pd/Deloxan APII	240	40–140	—	—	Different pressures favoured different products	173
Hydrogenation	1- or 2-phenylethanol + H_2	—	5 wt% Pt, Pd, Rh or Ru/C or $\gamma\text{-}Al_2O_3$	50	80–230	No	—	5 wt% Ru/C had the highest selectivity to the desired cyclohexylethanols.	268
Hydrogenation	Allyl alcohol + H_2	FC-40 (95% perfluorinated tributylamine)	Fluorous-soluble dendrimer encapsulated Pd^0 nanoparticles	25	0–70	—	Yes	CO_2 used to make catalyst (fluorous) and reactant (organic) phases miscible for reaction, then depressurised to separate the phases for catalyst recycling.	251
Hydrogenation	Maleic anhydride + H_2	—	$RuCl_2(PPh_3)_3$	140–200	0–160	No	Yes	CO_2 extracted out product from the H_2O produced in reaction—reducing hydrolysis.	269
Hydrogenation	Maleic anhydride + H_2	—	1 wt% Pd/Al_2O_3	100–225	42–141	No	Yes	Catalyst loses selectivity after recycling more than 7 times.	270,271
Hydrogenation	Levulinic acid + H_2	H_2O	5 wt% Pd/Al_2O_3	180–200	100	—	—	Continuous flow fixed bed reactor; γ-valerolactone can be separated conveniently from the H_2O *via* phase separation post-reactor without depressurisation.	188
Hydrogenation	2-Butyne-1,4-diol + H_2	—	Ni and Mn contained in SS 316 reactor wall	50	100–200	—	—	CO_2 lowers melting point of 2-butyne-1,4 diol so that it can be a liquid at the reaction conditions.	200

Table 1 *(Contd.)*

Reaction	Substrate(s)	Added solvent(s)	Catalyst(s)	$T/°C$	P/bar	CXL> SCF?[a]	>ambient P?[b]	Comment(s)	Ref.
Hydrogenation	2-Butylphenol	—	5 wt% Rh/C with or without HCl	40–80	0–220	No	Yes	Presence of HCl improves selectivity for the *cis* product.	272
Hydrogenation	Benzophenone imine + H_2	THF	$[Rh(cod)(PPh_3)_2]^+[PF_6]^-$	23–25	0–30	Yes	—	CO_2 protects amines *in situ* from further reaction to produce secondary amines.	216
Hydrogenation	Benzonitrile or phenylacetonitrile + H_2	THF	$RhH(P^iPr_3)_3$	23–25	0–25	—	—	CO_2 presented as an easily removable alternative protecting group to di-*tert*-butyl carbonate.	216
Hydrogenation	Nitrobenzene + H_2	—	5 wt% Pt, Pd, Ru or Rh/C, SiO_2 or Al_2O_3	35	100–180	—	—	Single phase improves selectivity but reduces conversion.	273,274
Hydrogenation	*p*-Chloronitrobenzene + H_2	MeOH	Ni-B nanoparticles	70–90	35.4–70.9	—	Yes	CO_2 shown to enhance reactivity by comparing the reaction with different partial pressures of CO_2 (the balance being H_2) at the same *total* pressure.	127
Hydrogenation	*o*-Chloronitrobenzene + H_2	—	5 wt% Pd/C	35	0–200	—	Yes	Selectivity to *o*-chloroaniline increased when performed in a single-phase.	275
Hydrogenation	*o*-Chloronitrobenzene + H_2	—	1 wt% Pt/C	40	0–161	No	Yes	Presence of CO_2 suppressed dechlorination.	276
Hydrogenation	Substituted nitrobenzenes + H_2	—	5 wt% Pt/C	50	90–180	No	Yes	Selectivity and conversion improved under single phase conditions.	277
Hydrogenation	2-Cyclohexen-1-one	—	1 wt% Pt/MCM-48	40	90–160	No	—	Selectivity significantly improves under single phase conditions.	278
Hydrogenation	Isophorone + H_2	—	2 wt% supported Pd or 5 wt% Pd/Deloxan	70–116	~120	Yes	—	Continuous flow fixed bed—reaction successfully scaled-up to 1000 tonnes per annum.	170,279
Hydrogenation	4-Oxoisophorone + H_2	—	1 wt% Pd/Al_2O_3	50–200	99–212	No	Yes	Catalyst deactivated more slowly in the presence of CO_2 than in MeOH.	280
Hydrogenation	Cinnamaldehyde + H_2	H_2O	$RuCl_3$ + PPh_3, $Pd(OAc)_2$ or $RhCl_3$ + TPPTS	40–50	40–140	Yes	Yes	Different products could be formed selectively with different catalysts.	281
Hydrogenation	Cinnamaldehyde + H_2	Neat, H_2O or DMF	$RuCl_3$ + PPh_3, $PPh_2(C_6F_5)$, $PPh(C_6F_5)_2$ or TPPTS	50–70	60–220	Yes	Yes	Reaction run in different configurations with 1, 2 or 3 fluid phases.	120
Hydrogenation	Cinnamaldehyde + H_2	H_2O	$Ru(H)(Cl)(TPPTS)_3$ or $Ru(H)_2(TPPTS)_4$	70	120–200	Yes	—	Reaction run in either 2 or 3 fluid phases.	282
Hydrogenation	Cinnamaldehyde + H_2	—	$RuCl_3$ + $PPh(C_6F_5)_2$	50	125–200	Yes	Yes	Both conversion and selectivity superior in a CXL.	283
Hydrogenation	Cinnamaldehyde + H_2	—	5 wt% Pt/C	50	100–200	No	Yes	FTIR studies on interactions of cinnamaldehyde with CO_2.	119
Hydrogenation	Cinnamaldehyde + H_2	—	Pt/Al, Si or Ti-modified MCM-48 (or unmodified)	20–80	7–210	—	—	Different catalysts performed better in different phase systems, and all catalysts could be easily recycled with minimal deactivation.	284–286
Hydrogenation	Cinnamaldehyde + H_2	—	10 wt% Pd/C, optionally with KOAc or K_2CO_3	50	40–180	—	Yes	Conversion good but selectivity moderate.	287
Hydrogenation	Cinnamaldehyde + H_2	—	Ru–Pt/MCM-48	50	100–210	Yes	Yes	Catalyst very selective for formation of the unsaturated alcohol.	288
Hydrogenation	α,β-Unsaturated aldehyde + H_2	—	1 wt% Pt/Al_2O_3	50	70–220	No	—	Selectivity showed strong pressure dependence.	289,290
Hydrogenation	Citral + H_2	—	$RuCl_3$, $RhCl_3$, $Pd(OAc)_2$ or $Ni(OAc)_2$ with PPh_3	65	60–160	No	—	$RuCl_3$ + PPh_3 particularly selective for the unsaturated alcohols.	291
Hydrogenation	Citral + H_2	—	1 wt% Pt/MCM-41	35–80	40–170	—	—	Possible to tune product selectivity between *cis*- and *trans*-products by changing the CO_2 density.	292
Hydrogenation	Citral + H_2	—	1 wt% Pd/MCM-48	50	110–210	—	Yes	Complete hydrogenation of both of the C=C bonds in citral possible.	293

Table 1 *(Contd.)*

Reaction	Substrate(s)	Added solvent(s)	Catalyst(s)	$T/°C$	P/bar	CXL> SCF?[a]	>ambient P?[b]	Comment(s)	Ref.
Hydrogenation	Citral + H_2	—	1 wt% Pt or 3.5 wt% Pt + Ru/MCM-48	35–70	100–210	—	—	Negligible catalyst deactivation; different catalysts preferred different numbers of phases.	294
Hydrogenation	Citral + H_2	—	5 wt% Pd/Al_2O_3	40	30–190	No	—	Performed in batch and continuous flow fixed bed reactors; the batch reaction resulted in much less hydrogenation of the isolated C=C bond in citral.	179
Hydrogenation	Unsaturated aldehyde + H_2	—	0.5 or 1 wt% Pd/Al_2O_3 (3 mm egg-shell pellets)	50–300	120–200	—	—	Kinetics from a Berty-type differential internal recycle reactor; applied to a pilot scale 2 m long (4 L volume) continuous flow fixed bed reactor (downflow).	111,172,212
Hydrogenation	Methyl 2-acetamidoacrylate + H_2	—	$[Rh(cod)_2](BF_4)$ + (R,S)-3-H^2F^6-BINAPHOS	40	n/a	—	—	Asymmetric hydrogenation; CO_2 reduces melting point of solid substrate; ligand designed to reduce necessary fluorination.	199
Hydrogenation	Polar alkenes + H_2	H_2O	$[Rh(cod)_2](BF_4)$ optionally with fluorinated phosphines	40–58	~260	—	—	Catalyst in CO_2-rich phase and reactants in aqueous phase; catalyst could be recycled up to 9 times without depressurisation.	166,167
Hydrogenation	2-(6′-Methoxy-2′-napthyl)acrylic acid + H_2	MeOH	[(S)-Ru(BINAP)Cl]Cl + p-cymene + NEt_3	5–45	95–128	—	—	Catalyst believed to have deactivated with the trace O_2 present in the CO_2.	295,296
Hydrogenation	*rac*-Sertraline imine + H_2	THF	5 wt% $Pd/CaCO_3$, 5 wt% Pd or Pt/C	25–120	0–175	—	Yes	Very high diastereoselectivity; performance better than published Pfizer process.	33
Hydrolysis	β-Pinene + H_2O	MeOH, EtOH or acetone	*In situ* carbonic acid	25–75	14–21	—	Yes	Probably LLV phase system with CO_2 enhancing miscibility of the two liquid phases.	224
Hydrolysis	Sunflower or soybean oil + H_2O	Phosphate buffer	Lipase 100T (from *Aspergillus niger*)	30–60	0–200	—	Yes	Continuous flow membrane reactor; membranes used to retain enzyme inside reactor.	297
Hydrolysis	Carboxymethylcellulose + H_2O	Phosphate buffer	Cellulase from *Humicola insolens* immobilised on polysulfon membrane	45	0–100	—	Yes	Continuous flow tubular membrane reactor; catalyst immobilised on membrane which simultaneously separates the products from unreacted substrates.	297
Oxidation	Cyclohexane + O_2	—	PFTPPFeCl	32–70	1–190	Yes	Yes	Best reaction outcome is close to the critical pressure.	298
Oxidation	Cyclohexane + O_2	—	MnAPO-5 molecular sieve	125	N/A	—	—	Conversion increased in a CXL, but selectivity better when a single phase.	299
Oxidation	Cyclohexane or various cyclic alkenes or aromatics + O_2	AcOH	$Co(OAc)_2$ or Co(salen) + N-hydroxysuccinamide	21–125	8.3–65.8	—	Yes	CO_2 reduces induction period, some unexpected yet selective products formed.	300
Oxidation	Xylenes + O_2	AcOH + H_2O	$Co(OAc)_2$ + $Mn(OAc)_2$ + HBr	185–195	28	—	Yes	O_2 + CO_2 believed to form a peroxycarbonate complex *in situ*.	301–303
Oxidation	Toluene or p-toluic acid + O_2	AcOH	$Co(OAc)_2$ and mixtures with other metal acetates and ketones	80	60	—	Yes	CO_2 reduced the induction period substantially.	304
Oxidation	DTBP + O_2	MeCN or CH_2Cl_2	Co^{II}(salen), Co^{II}(salen*) or Co^{II}(acacen), with optional basic axial ligands	25–90	1–207	Yes	Yes	Increased polarity of CXL *versus* $scCO_2$ improves conversion by stabilising the transition state; includes mechanistic studies.	115,116,142,248,305

Table 1 *(Contd.)*

Reaction	Substrate(s)	Added solvent(s)	Catalyst(s)	$T/°C$	P/bar	CXL> SCF?[a]	>ambient P?[b]	Comment(s)	Ref.
Oxidation	DTBP + O_2	MeCN	Co^{II}(salen)-based, co-polymerised into PMMA	35–80	1–125	No	—	Catalyst nature meant that the superior mass transport properties of $scCO_2$ were necessary for good conversions.	306
Oxidation	2- or 1-octanol + O_2	—	0.5 wt% Pd/Al_2O_3	80–140	75–125	—	Yes	Continuous flow fixed bed; all reactions performed under a biphasic system; no deactivation observed.	176
Oxidation	Benzyl alcohol + O_2	Neat or toluene	0.5 wt% Pd/Al_2O_3 (optionally with 0.05 wt% Pb) or C, or 0.5% Pt or Ru/Al_2O_3	60–100	65–170	No	—	Continuous flow fixed bed; no catalyst deactivation observed; *in situ* XAS and ATR-IR of catalyst; transmission IR of fluid phases.	177,180,184,187
Oxidation	Cinnamyl alcohol + O_2	Toluene, THF or acetone	0.5 wt% Pd, Pt or Ru/Al_2O_3	80	90–170	Yes	—	Continuous flow fixed bed; *in situ* ATR-IR, transmission IR, XANES and EXAFS.	185
Oxidation	Geraniol + O_2	—	5 wt% Pd/Al_2O_3 or SiO_2	80	30–195	Yes	—	Continuous flow fixed bed, *in situ* ATR-IR and transmission IR; significant coking meant conversion and selectivity never stabilised properly.	186
Oxidation	Benzyl alcohol, geraniol or 1-octanol + O_2	—	1 wt% Au/TiO_2, C or Fe_2O_3	80–120	133–167	Yes	Yes	Base not required for reaction; observation of reaction by transmission IR.	307
Oxidation	Cyclohexane + H_2O_2	Neat, AcOH, EtOH or acetone	Zeolite TS-1	60–80	0–180	—	—	Increasing CO_2 pressure increases yield in three-phase region until transition to two phases where further influence is limited.	94
Oxidation	Cyclohexene + $NaIO_4$, Ce(IV) with AcOOH, or NaOCl	H_2O	RuO_4	40	166.5–275.9	—	—	Bicarbonate produced from CO_2 dissolution in aqueous phase believed to be responsible for poor catalyst activity.	308
Oxybromin-ation	Phenols or anilines + NaBr, KBr, NH_4Br or Bu_4NBr + H_2O_2 (optionally with $NaHCO_3$)	H_2O	—	40	100–110	—	Yes	*In situ* formation of peroxycarbonic acid[309] believed to be responsible for the improvement in performance.	250
Reduction	Aryl alcohols + Fe	H_2O	—	130–150	0–220	—	—	Addition of buffer solution used to show *in situ* carbonic acid did not affect reaction outcome.	310
Reduction	Benzonitrile or phenylacetonitrile + $NaBH_4$	EtOH	$NiCl_2$	30	30	—	—	CO_2 protects amines *in situ* from further reaction to produce secondary amines.	216
Sequential	Alkyne + CO + H_2O	1,4-dioxane	PdI_2 + KI	80	40–50	—	—	CO_2 interferes in the catalytic cycle by acting as an H-acceptor.	311
Synthesis of carbonates	MeOH + MeI + CO_2	—	K_2CO_3	80–120	~113–146	—	—	Reaction rate is higher in the critical region (*i.e.* either side of the critical point).	312
Synthesis of carbonates	MeOH or a dimethyl acetal + CO_2	—	$Bu_2Sn(OMe)_3$	180	15.2–2027	No	Yes	Rate continues to increase linearly with increasing pressure after the critical point (304 bar).	313
Synthesis of carbonates	Alcohol + MeI or EtI + CO_2	—	Inorganic carbonate base	70	0–150	Yes	Yes	Increasing pressure reduces formation of Me_2O by-product.	314
Synthesis of cyclic carbonates	Ethylene oxide + CO_2	—	(salen)AlX (X = Cl, Et or OMe) with TBAB, TBACl or TBAI	10–120	40–160	—	—	Temperature drastically changes partitioning of reactants between liquid and vapour phases; phase transitions as a function of conversion result in different rates of reaction at different stages.	315
Synthesis of cyclic carbonates	Propylene oxide + CO_2	—	SiO_2-immobilised $Zn_2Br_2(py)_2$	64–149	110	Yes	Yes	Phase behaviour changes significantly as propylene carbonate is formed.	211
Synthesis of cyclic carbonates	Propylene or styrene epoxides + CO_2	—	Mn^{III}(substituted salen) homogeneous or immobilised	50–200	N/A	Yes	—	Extensive IR and XAS study on liquid phase and catalyst.	316,317
Synthesis of cyclic carbonates	Styrene + O_2 + CO_2	THF or toluene	Rh^1 homogeneous	~40–80	1–50	—	No	Styrene oxide formed *in situ* then coupled with CO_2.	318
Synthesis of cyclic carbonates	Styrene + ^tBuOOH or H_2O_2 + CO_2	—	TBAB	60–90	0–180	—	—	Complicated dependence on pressure due to the way the phase behaviour alters with conversion.	319

Table 1 *(Contd.)*

Reaction	Substrate(s)	Added solvent(s)	Catalyst(s)	*T*/°C	*P*/bar	CXL> SCF?[a]	>ambient *P*?[b]	Comment(s)	Ref.
Synthesis of 2-oxa-zolidinones	Various aminoalcohols + CO_2, DCC as dehydrating agent	—	—	20–40	150	No		Solid carbamic acid/carbamate phase usually present.	215
Synthesis of alkyl-carbamates	3,4-Dimethoxy-phenethylamine + DMC or DBC	—	—	1–190	1–190	—	Yes	Yields were moderate.	320
Synthesis of alkyl-carbamates + Acyl-Pictet–Spengler	3,4-Dimethoxy-phenethylamine + DMC or DBC, then aldehyde + 9 mol dm^{-3} H_2SO_4 or 50 v/v % $TFA_{(aq)}$	—	—	130	140–160	—	—	Three phases present: H_2O-rich liquid, DMC-rich liquid, and CO_2-rich vapour phase.	320
Synthesis of methyl-carbamates	DMC + various primary amines (some hydroxy-substituted)	—	—	5–200	130	Yes	Yes	Three phases present: DMC-rich liquid, molten carbamate-rich liquid, and CO_2-rich vapour phase; mechanistic study.	217
Trans-esterification	Glycerol monostearate + MeOH	—	Concentrated $H_2SO_{4(aq)}$	60–70	65–105	—	Yes	CO_2 improves mutual miscibility of the 2-liquid phases compared to ambient.	209

[a] Does the reaction run better in 2 phases (CXL) than as a single phase with or without the added solvent? [b] Does the reaction work better in 2 phases than under “ambient” conditions (*i.e.* open to atmosphere, 1 bar CO_2, or a high pressure of an inert gas)?

Table 2 Reactions in class I and II GXLs using gases other than CO_2

Reaction	Substrate(s)	Added solvent(s)	Catalyst(s)	*T*/°C	*P*/bar	GXL> SCF?[a]	>ambient P?[b]	Comment(s)	Ref.
Acetal formation	Cyclohexanone + MeOH	CO_2 or ethane	*In situ* carbonic acid	25	40	—	—	Reaction does not occur in the absence of CO_2 as it is needed to form the acid catalyst *in situ*.	197
Epoxidation	Ethylene + 50% $H_2O_{2(aq)}$	MeOH	$MeReO_3$ + pyridine *N*-oxide	20–40	16–50	—	—	Lower temperatures meant no decomposition of H_2O_2 to form O_2 as in the conventional process—this would lead to hazardous flammable gas mixtures	321
Hydration	1- and 2-butene mixture + H_2O	—	—	200	200	—	—	Butene in vapour phase strips out 2-butanol from aqueous phase to shift equilibrium.	3
Hydrogenation	CO_2+H_2	Neat, ethane, or CHF_3 with MeOH + NEt_3	$[RuCl(OAc)(PMe_3)_4]$	50	0–60	—	—	Ethane reduced TON relative to neat CO_2, but fluoroform increased it by ~15%; other solvent additives tried with limited success.	149
Hydrogenation	Ethyl pyruvate + H_2	Ethane or CO_2	Cinchonidine-modified 5 wt% Pt/Al_2O_3	25–140	40–125	No	—	Continuous flow fixed bed reactor; CO_2 a poorer choice of solvent due to formation of poisoning CO from CO_2 hydrogenation	227,228
Hydrogenation	Fatty acid methyl esters + H_2	Propane	Cu-based (Cu-1985 T) then 2 wt% Pd/SiO_2-Al_2O_3 zeolite (2 steps)	280	150	No	—	Rapid drop in reaction rate with condensation of a liquid phase.	229
Protonation	Sodium acetate, propionate or butanoate	H_2O with CO_2 + Me_2O	—	60–90	120–220	—	—	*In situ* carbonic acid protonates the acid salt so it is soluble enough in the vapour phase to be extracted out.	230

[a] Does the reaction run better in 2 phases (GXL) than as a single phase with or without the added solvent? [b] Does the reaction work better in 2 phases than under “ambient” conditions (*i.e.* open to atmosphere, 1 bar CO_2, or a high pressure of an inert gas)?

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