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Heterogeneous Catalysis for Fine Chemicals in Dense Phase Carbon Dioxide

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Abstract: An increasing number of fine chemicals is being produced using heterogeneously catalysed reactions in supercritical carbon dioxide with significant improvements in terms of process selectivity and purity of the products thereby obtained. A selection of examples and of recent findings shows the large potential of this technology for the synthetic chemistry of the future.

Keywords: carbon dioxide; continuous flow processes; fine chemicals; heterogeneous catalysis; supercritical fluids

1 Introduction

In the last 20 years carbon dioxide, an abundant, cheap and non-flammable solvent, has been investigated extensively in both academic and industrial settings as replacement for a wide variety of organic solvents. However, CO_2 is actually a rather feeble solvent compared to alkanes, thus requiring the design of CO_2-philic materials, namely of compounds that dissolve in CO_2 at significantly lower pressures than do their alkyl analogues.[1] These CO_2-philes, initially expensive fluoropolymers but later materials that are better suited than fluorinated analogues and containing no fluorine,[2] opened up a host of new applications for CO_2 as chemical solvent, including heterogeneous polymerisation, protein extraction and homogeneous catalysis.[3]

In catalysis for fine chemicals a major approach resides in the heterogenisation of homogeneous catalytic processes.[4] Often the heterogeneous catalytic production of fine chemicals in dense phase (or "supercritical") carbon dioxide ($scCO_2$) provides unique advantages which justify a switch to the high-pressure reactor. For example, not only is a solid heterogeneous catalyst easily separated from the products and reactants, but the physico-chemical properties of the supercritical fluid enable high-throughput heterogeneous continuous processes in small reactors that are, indeed, those practiced at industrial level. A recent review on the potential of carbon dioxide in synthetic organic chemistry concluded that "applications in the pharmaceutical industry remain elusive" because of high capital investment".[5] Referring to selected examples of fine chemicals syntheses in dense phase carbon dioxide, we show in the following the large potential of this technology for the synthetic chemistry of the future.

2 Principles

The replacement of the volatile organic solvents used as reaction medium with water or with other environmentally benign solvents such as supercritical fluids is one of the primary objectives of current research in chemistry.[3] Solvents, in addition to their impact through use and final disposal, have a considerable life-cycle impact and their broader total costs are high and increasing.[6]

Dense phase carbon dioxide as an alternative reaction medium shows several advantageous physical and chemical properties:[10] (i) low critical temperature

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($T_c = 31\,°C$) and critical pressure ($P_c = 73.8$ bar); (ii) excellent miscibility with reagents such as O_2 and H_2; (iii) lack of flammability in the presence of O_2; and (iv) low viscosity and superior mass transport properties (absence of a gas-liquid phase boundary).

Furthermore, carbon dioxide is cheap and abundantly available from multiple sources. Its separation and reuse is facile and efficient; CO_2 is non-toxic (but it is an asphyxiate at concentrations of $>5\%$ and can cause death, it is as well the major component of "greenhouse" gases) and does not present any significant end-of-life concerns.[7]

All this generally holds true for pure CO_2. The major limitation resides in the fact that $scCO_2$ is a poor solvent for many compounds especially in the case of drug-like substances. Around the critical point, the density of carbon dioxide is approximately $0.4\,g\,mL^{-1}$. The density, however, dramatically increases with pressure (Figure 1) and so does the solvent capacity of carbon dioxide. Hence, in order to ensure full solubilisation of reactants, commercial reactions in $scCO_2$ are typically carried out at pressure >100 bar (requiring higher investment and operating costs), and in a very narrow temperature window

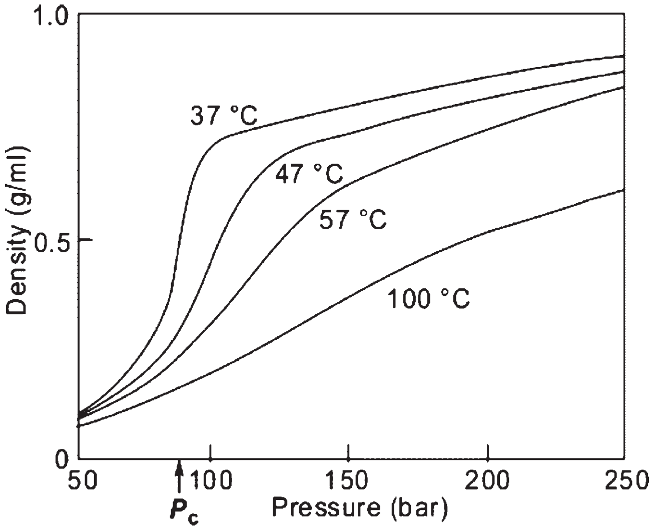

Figure 1. Variation of CO_2 density with temperaure and pressure (reproduced from ref.[5] with permission).

(<70 °C) where the solubility is high enough to run reactions on a commercial scale.

A major advantage of using dense phase carbon dioxide as solvent resides in the possibility to carry out unique continuous processes using small, high-throughput reactors where the CO_2 is recycled while the substrates are converted.[8]

In contrast to batch reactions in conventional solvents in which the products are those of thermodynamic equilibrium, continuous processes often favour kinetically controlled conversions. Hence, the kinetics of the different reactions taking place in $scCO_2$ can be adjusted by selecting the reaction parameters, i.e., one can select a set of conditions under which the desired reaction is favoured and the rest are suppressed. Such a continuous reactor system provides a simple means of increasing the yield from a supercritical reaction without increasing the overall size of the apparatus. In place of the conventional conversion of substrates in solution over an heterogeneous catalyst with a reactant at high pressure controlled by the transport rate of reactants (the reactant diffuses from the gas phase into the liquid and then through the liquid to the active sites in the pores of the catalyst), here the reactant and organic substrate dissolve in the supercritical CO_2 creating a single phase and thereby eliminating gas-liquid mass transfer resistance.

Upon the combined consideration of solubility, adsorption and diffusion characteristics and their tunability, it emerges[9] that, for adsorption processes and heterogeneously catalysed reactions in supercritical fluids, solids of intermediate pore size and a supercritical fluid (SCF) of intermediate density (around $1\,g\,mL^{-1}$) are best suited. In general, by careful optimisation it is possible to find temperatures and pressures where the density is in an intermediate range, so the solvent power of the SCF is strong enough to dissolve reasonable amounts of reactants but the diffusivity is not reduced too much.

As the capillary critical temperatures (critical temperature within the pore) depend on the pore size, it is also crucial to choose the "right" support material for the catalytically active species. For instance, recent investigations[10] of the mechanism of benzyl alcohol oxidation to benzaldehyde with O_2 over Pd/Al_2O_3 show that pressure has a strong influence on the reaction rate. There is a sharp increase in activity correlated to a transition from a biphasic to a monophasic reaction mixture when increasing the pressure from 140 to 150 bar. In the single phase region, both oxygen and benzyl alcohol are dissolved in the $scCO_2$ phase, which leads to a reduction of the mass transport resistances in the catalyst pores, and thus to a high reaction rate.

3 Commercial Production Processes

Hydrogenation over commercial catalysts was among the first heterogeneous reactions in $scCO_2$ to be commercialised, in the early 2000s, due to the advantages in terms of efficiency and selectivity obtained by the U.K. manufacturer Thomas Swan.[11] Hydrogenation in $scCO_2$, furthermore, often affords quantitative conversion and enables the use of stoichiometric amounts of expensive hydrogen.

Reaction parameters such as temperature, pressure, flow rate, and hydrogen concentration are controlled independently, the most important being temperature and H_2 concentration. Hence, by simple variation of these parameters (and of pressure) one may achieve high selectivity for a particular product in reactions where several products can be generated. The reduction of acetophenone over a Pd catalyst which gives 1-phenylethanol at low pressure, 1-cyclohexylethanol at higher pressure and ethylcyclohexane at higher temperature, exemplifies the concept (Figure 2).[12]

A wide range of organic functional groups can be hydrogenated with very high conversion and selectivity. Using a palladium catalyst on aminopolysiloxane (Deloxan, a commercial polyaminosiloxane catalyst support), the supercritical hydrogenation of a variety of organic compounds, including alkenes, alkynes, aliphatic and aromatic ketones and aldehydes, epoxides, phenols, oximes, nitrobenzenes, Schiff bases and nitriles, takes place selectively with only a small excess of hydrogen reducing the C=C double bond in the presence of other reducible groups (Figure 3).[13]

Production of TMCH (3,3,5-trimethylcyclohexanone, a market of several hundreds tonnes per year) by hydrogenation of isophorone in $scCO_2$ was thus readily commercialised (Figure 4).[14]

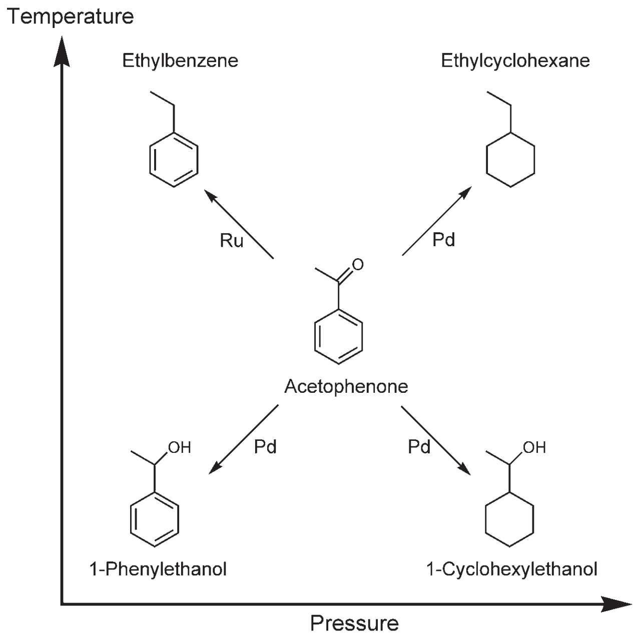

Figure 2. By varying temperature and pressure the selectivity of reactions in $scCO_2$ can be largely controlled (reproduced with permission from Dr. R. Clarke, Thomas Swan Ltd.).

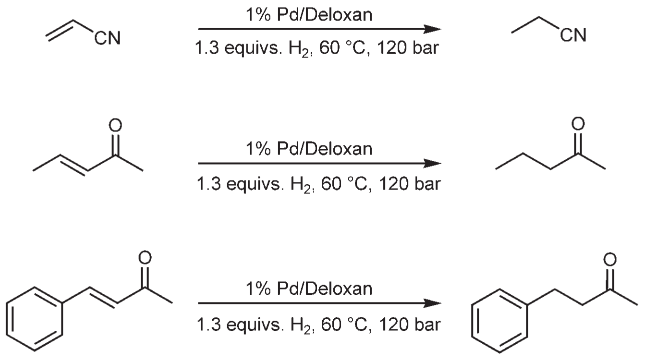

Figure 3. Selective reduction of C=C double bonds in $scCO_2$ (reproduced with permission from Dr. R. Clarke, Thomas Swan Ltd.).

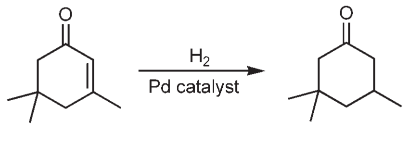

Figure 4. Hydrogenation of isophorone in $scCO_2$ affords uniquely TMCH (reproduced with permission from ref.[14]).

The reaction in acetone is slow (>4 h), affords conversion only up to 70% and requires additional solvent (acetone), whereas in the gas phase (>200 °C) the process proceeds with poor selectivity (reduction of the C=O bond to the corresponding cyclohexanol) and limited stability of the Pd catalyst. Furthermore, the starting material, the desired product and the unwanted by-product all have very similar boiling points and are difficult to separate. In $scCO_2$, conversely, the reaction takes place rapidly with 100% conversion and *ca.* 100% selectivity whereas the catalyst lifetime increases by a factor of 30 with 1 g of catalyst being efficient enough to hydrogenate more than 7.5 kg of isophorone before losing activity.

4 Potential Applications

A number of catalytic processes in $scCO_2$ show large commercial potential. For instance, the low viscosity of $scCO_2$ enables efficient microfluidic reactions as shown by the fast continuous hydrogenation of cyclohexene in a microchannel reactor over supported Pd.[15] As organic synthesis in microreactors is envisaged to find widespread use in synthetic chemistry,[16] applications using $scCO_2$ as reaction solvent in similar reactors are likely to flourish.

Recently the continuous quantitative hydrogenation of levulinic acid to γ-valerolactone over a ruthenium catalyst immobilised on silica using water and supercritical CO_2 as the solvent system was reported.[17] By controlling the pressure in a separation chamber, pure γ-valerolactone can be separated from the reaction mixture without the need of an expensive conventional distillation.

Another example is catalytic hydroformylation. Current problems with traditional hydroformylation in organic solvents (catalyst separation in homogeneous systems, leaching in heterogeneous systems), are all smoothly overcome by carrying out the hydroformylation of alkenes to aldehydes in $scCO_2$ in a continuous process. The aldehyde product is extracted with supercritical CO_2 as it is formed, whereas the catalyst which is insoluble in CO_2 remains in the reactor.[18] For example, octene is first mixed with nonanal (to solubilise the Rh catalyst) and the catalyst precursors in the reaction chamber. The soluble rhodium catalyst forms *in situ* while the reactor is being pressurised with H_2, CO and CO_2. Once the reaction begins, supercritical CO_2 continuously transports the reactants into the reactor. Since nonanal is highly soluble in CO_2 it can be efficiently removed from the reactor as it forms and then easily separated from gaseous carbon dioxide.

Friedel–Crafts alkylation or acylation reactions of aromatic substrates also proceed in $scCO_2$ with a number of unique benefits.[19] The classic Friedel–Crafts alkylation reaction usually requires either $AlCl_3$ or HF as a catalyst, both of which create serious waste issues; while the alkylating agent is usually an alkyl halide, with further cost and waste implications. Moreover, it is very difficult to control the degree of alkylation, particularly so as to get only the mono-alkylated product.

When the alkylation is conducted in $scCO_2$ (Figure 5) over a catalytic support such as Deloxan ASP or alumina using an alcohol as alkylating agent (cheaper and environmentally better than an alkyl halide), it is possible to achieve selective mono-alkylation and the only by-product is water. Hence, for example, thymol can be synthesised by continuous catalytic alkylation of *m*-cresol with different alkylating agents over Al_2O_3.[20]

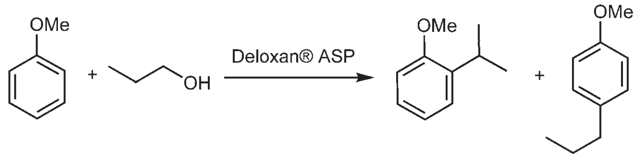

Figure 5. Alkylation of aromatics in $scCO_2$ with alcohol as alkylating agent takes place selectively (reproduced with permission from Dr. R. Clarke, Thomas Swan Ltd.).

Quantitative etherifications in $scCO_2$ using solid acid catalysts proceed with a high selectivity for linear alkyl ethers with little rearrangement (common in conventional syntheses) to give branched ethers. Again, the selectivity of the continuous reaction can be tuned by varying the pressure and thus the phase state of the reaction mixture, with monophasic conditions favouring the mono-ether and biphasic conditions favouring the bis-ether. The etherification has not been carried out commercially although the dehydration of butanediol to THF was carried out successfully on a large scale in the Thomas Swan plant.[21]

Finally, the heterogeneously catalysed oxidative dehydrogenation of alcohols in $scCO_2$ is also of great interest as it would replace traditional stoichiometric conversions carried out with chromium salts in volatile, toxic organic solvents. For example, organically modified sol-gel silicates doped with TPAP (tetra-*n*-propylammonium perruthenate) are a truly off-the-shelf catalytic series suitable for the conversion of widely different alcohols with the unique selectivity of Ru-based oxidation catalysis. Benzyl, allyl and aliphatic alcohols are smoothly and selectively oxidised with O_2 into the corresponding carbonyl compounds using alkyl-modified,[22] fluorinated[23] and supported ionic liquids[24] silica matrixes doped with this highly selective commercial catalyst (Figure 6).

Similarly, the oxidation of benzyl alcohol to benzaldehyde with O_2 proceeds selectively using PEG-modified silica-supported Pd nanoparticles.[25]

Selective oxidation for the production of odorant molecules in carbon dioxide might soon find practical applications. Indeed $scCO_2$ is increasingly being employed as extracting agent of volatile oils and fragrance compounds.[26] As number of small modern $scCO_2$ extraction plants are being installed worldwide,[27] adding a small high-throughput reactor to these plants would not be problematic once synthetic processes are on place. Vanillin, for instance, has largely different prices depending on whether it is of natural or synthetic origin. Synthetically, it can be obtained by oxidation of the *p*-cresol precursor to the *p*-hydroxybenzaldehyde precursor in an organic solvent.[28] The process, however, leaves solvent residues that blind taste testing panels can distinguish. Heterogeneously catalysed production of vanillin and other fragrances in $scCO_2$ by aerobic oxidation over a supported catalyst would eliminate any solvent residue.

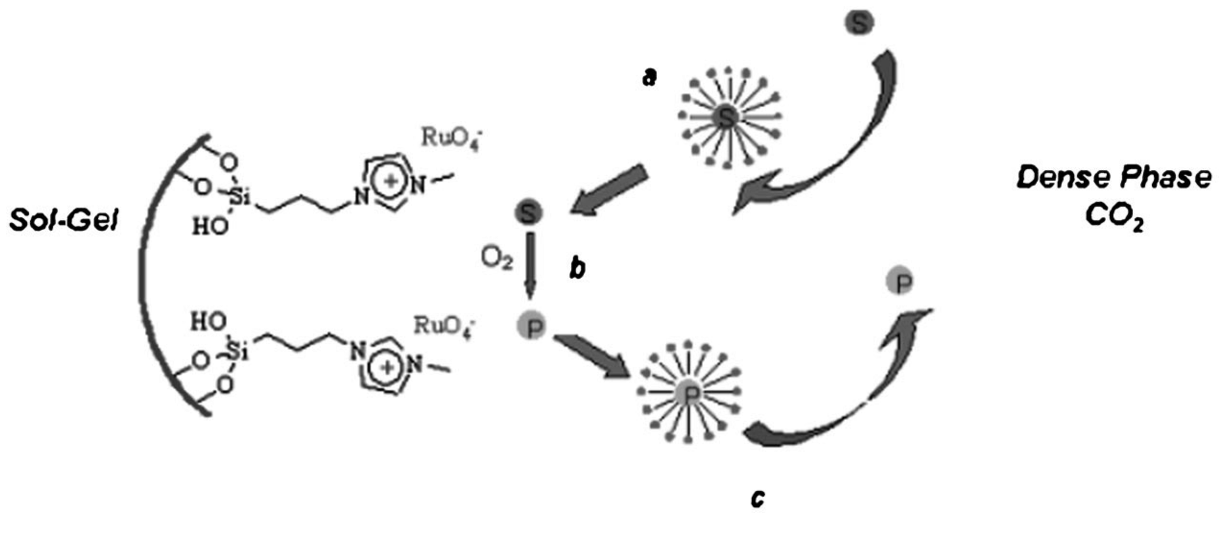

Figure 6. Supported ionic liquid Ru-based catalysis in $scCO_2$ ensures smooth oxidative dehydrogenation of a variety of alcohols (reproduced from ref.[24] with permission).

5 Outlook and Perspective

Reactions in dense phase carbon dioxide are versatile, efficient and selective.[29] In addition, the reduced size of high-throughput process lowers costs. On the other hand, bringing CO_2 to supercritical state adds cost as it requires substantial amounts of increasingly expensive energy, and capital investment for the high-pressure equipment. Hence, opting for production in $scCO_2$ will depend on specific evaluation whether the benefits in terms of product purity and process selectivity outweigh the enhanced cost of the SCF process. This is often the case, and several fine chemicals are already being commercially synthesised in compressed carbon dioxide. Economic factors and increasingly demanding environmental and health requirements are likely to make the production of fine chemicals in dense phase carbon dioxide a relevant commercial technology of tomorrow's chemical industry.

Acknowledgements

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