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Carbon dioxide as an environmentally benign reaction medium for chemical synthesis†

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This contribution highlights recent developments from our research efforts at the Max-Planck-Institute for Coal Research concerning the use of compressed (liquid or supercritical) carbon dioxide as a solvent for environmentally friendly synthesis of fine chemicals. Representative examples discussed here include steel-promoted epoxidation using molecular oxygen as the primary oxidant and transition-metal-catalysed asymmetric C—C bond forming reactions. Copyright © 2000 John Wiley & Sons, Ltd.

Keywords: supercritical carbon dioxide; catalysis; hydroformylation; hydrovinylation; oxidation

INTRODUCTION

CO_2 is the most abundant waste product of our industrialized society. The significant increase of the CO_2 concentration in the atmosphere over the last 120 years appears to be directly related to anthropogenic CO_2 emission and its possible impact on the global climate has caused much concern. A number of possible ways for CO_2 mitigation and utilization have been proposed and many of them are discussed throughout this volume. The present contribution deals with a fairly different approach to the utilization of CO_2, namely the use of compressed (liquid or supercritical) carbon dioxide as a solvent for fine chemical synthesis. Obviously, this kind of application cannot have any significant impact on the global CO_2 emission problem, as no CO_2 is consumed in most cases and the required quantities are negligible compared with the huge emissions of CO_2 resulting from human activities. However, using the abundant and cheap waste material carbon dioxide as a replacement for toxic, carcinogenic, flammable or otherwise potentially hazardous organic solvents seems a very attractive approach to 'green chemistry' and environmentally benign synthesis.[1]

As seen from the schematic phase diagram in Fig. 1, pure CO_2 can be liquefied by compression only at temperatures below 31°C. Above this *critical temperature* T_c and the corresponding critical pressure p_c, no distinct liquid or gaseous phases exist and the new phase is referred to as a *supercritical fluid (SCF)*. At densities above the critical density d_c, supercritical carbon dioxide ($scCO_2$) has an appreciable solvent power for many organic substances. $ScCO_2$ has already found various technical applications as a solvent for

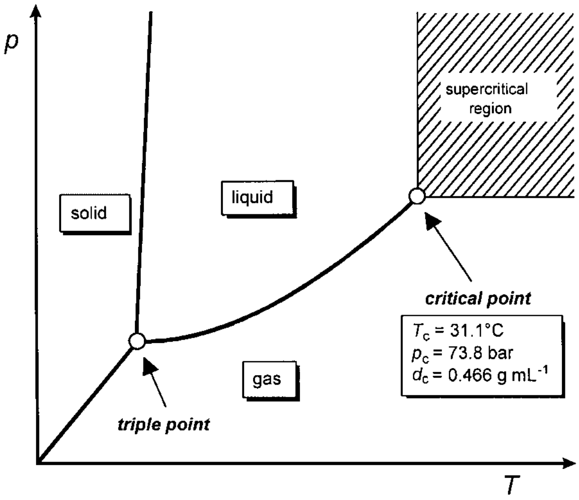

Figure 1 Schematic phase diagram of carbon dioxide.

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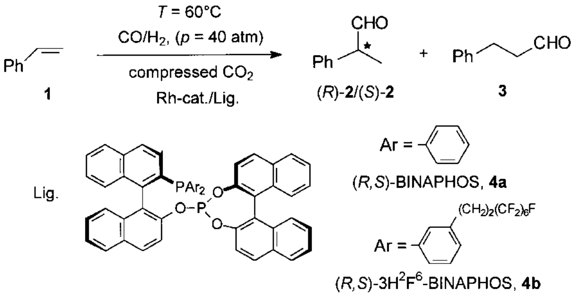
purification and natural product extraction processes such as the decaffeination of green coffee beans.[2,3]

In addition to the environmental and safety aspects discussed above, a number of benefits may arise from the unique physico-chemical properties of $scCO_2$ when using it as a reaction medium for chemical synthesis.[4–7] The presence of a single supercritical phase can be highly advantageous for chemical reactions involving gaseous substrates because mass transport limitations at the gas–liquid phase boundary are avoided. Therefore, it may come as no surprise that all examples presented in this paper involve at least one gaseous substrate. Other beneficial effects, which will not be discussed here, result from the chemical reactivity of the solvent CO_2 which allows it to be used simultaneously as a C_1 building block[8] or an *in situ* protecting group.[9] Furthermore, the high compressibility of SCFs provides the opportunity to explore density as an additional reaction parameter.[9,10] Finally, the established separation techniques utilizing $scCO_2$ may be fruitfully integrated into synthetic processes allowing, for example, the development of new recycling techniques for homogeneous catalysts.[7]

SELECTED RECENT EXAMPLES FOR CHEMICAL SYNTHESIS IN COMPRESSED CO_2

Rhodium-catalysed asymmetric hydroformylation

Asymmetric hydroformylation is a highly attractive synthetic methodology for the preparation of optically active aldehydes,[11] providing for example a viable route from readily available vinyl arenes to important anti-inflammatory drugs like ibuprofen® or naproxen®. Rhodium catalysts based on the chiral bidentate phosphorus ligand (*R,S*)-BINAPHOS (**4a**)[12] are known to allow outstanding levels of enantiocontrol in this reaction (Scheme 1), but the established protocols require application of ecological and toxicological hazardous organic solvents, in particular benzene. Furthermore, the catalysts based on **4a** give only a moderate regioselectivity of 88% towards the desired branched aldehydes such as **2**.



Scheme 1 Asymmetric hydroformylation of styrene (**1**) using BINAPHOS-type ligands **4a, b**. Catalysts were formed *in situ* using $[(CO)_2Rh(acac)]$ as the source of rhodium.

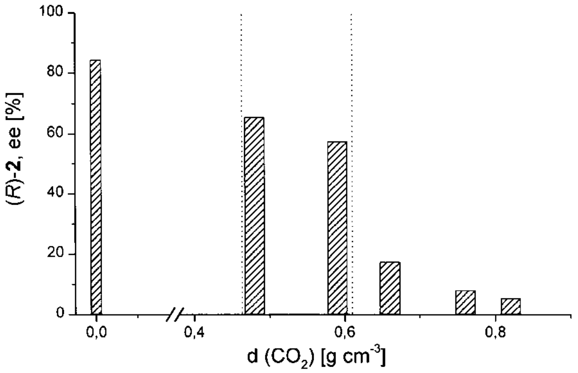
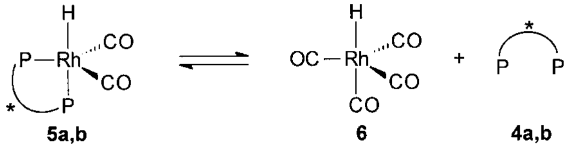


Figure 2 Enantiomeric excess *ee* of product (*R*)-**2** as a function of the density of CO_2, when hydroformylation of **1** was carried out using a catalyst formed *in situ* from $[(CO)_2Rh(acac)]$ and **4a**. The dotted lines mark the area where small amounts of a liquid phase could be visually detected during some stages of the reaction.

Initial attempts to utilize $scCO_2$ as a solvent for the hydroformylation of styrene (**1**) using a catalyst formed in situ from $[(CO)_2Rh(acac)]$ (acac = acetylacetonate) and **4a** in a molar ratio of approximately 1:1 gave good yields of the branched (**2**) and linear (**3**) aldehydes under various reaction conditions.[13,14] However, the enantiomeric excess *ee* of the desired product **2** was highly dependent on the density of the reaction medium (Fig. 2), with appreciable asymmetric induction (up to 66% *ee*) being observed only at densities close to the critical density of pure CO_2. The maximum *ee* achieved in the presence of compressed CO_2 was considerably lower than that observed in neat **1** under otherwise identical conditions (84%). Most notably, small amounts of an additional liquid phase could be detected by visual inspection in all cases where high *ee*s were achieved in the presence of compressed CO_2.[13]



Scheme 2 Equilibrium between ligand-modified and unmodified rhodium species under hydroformylation conditions. The formula [(CO)$_4$RhH] (**6**) is used to summarize all phosphine-free hydrido carbonyl species that might be catalytically active.

These results are best rationalized by taking into account the equilibrium between unmodified and ligand-modified rhodium species, which is well established for ligand **4a** under hydroformylation conditions in conventional solvents (Scheme 2).[12] The ligand itself, and any ligand-modified rhodium complex, can be expected to have a very low (if any) solubility in a fully homogeneous supercritical CO$_2$ phase.[15] Therefore, intermediates of the catalytic cycle, such as **5a**, can operate only in the presence of small amounts of a liquid phase. However, ligand free—and hence achiral—rhodium species like **6** are highly soluble in scCO$_2$ and act as very efficient hydroformylation catalysts under these conditions,[16] leading to the formation of racemic **2**. The possibility to form a liquid phase for **5a** can be expected to decrease with increasing density of the reaction mixture,[2,3] resulting in the observed decrease of the overall enantioselectivity at higher CO$_2$ density and pressure.

It was shown recently that the introduction of perfluoroalkyl substituents like (CH$_2$)$_2$(CF$_2$)$_6$F into aryl phosphorous compounds greatly enhances their CO$_2$ solubility, making catalysts derived from such ligands available for general application in this medium.[15–17] Encouraged by this precedence, we set out to synthesize the perfluoroalkyl-substituted BINAPHOS derivative **4b** and used it for asymmetric hydroformylation in compressed CO$_2$ (Scheme 1). This ligand provides now the first catalytic system that allows highly efficient enantioselective hydroformylation of **1** and related vinyl arenes in compressed (liquid or supercritical) CO$_2$.[18] The reaction rates and the *ee*s compare well with those observed with **4a** in conventional solvents. Most remarkably, the selectivity for the desired branched aldehyde **2** over the achiral byproduct **3** is significantly higher under the new conditions (Fig. 3).

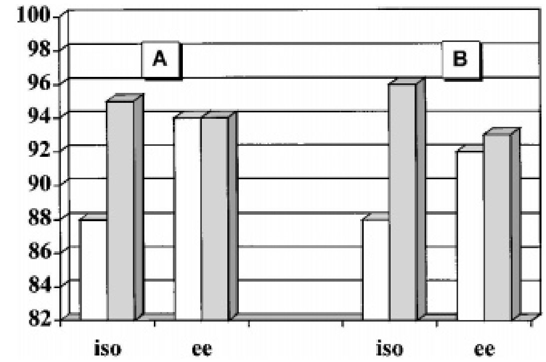
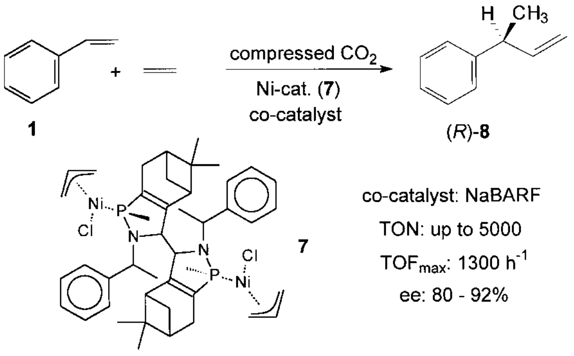


Figure 3 Comparison of the regioselectivity towards the branched aldehydes of type **2** [iso (%)] and the enantioselectivity [*ee* (%)] obtained from asymmetric hydroformylation of vinyl arenes (A = styrene, **1**; B = *p*-^{i}Bu-styrene) using ligand **4a** in benzene (white bars) and ligand **4b** in compressed CO$_2$ (grey bars). Data are taken from Refs[12] and[18] respectively.

Detailed control experiments revealed that the enhanced regioselectivity is mainly due to the presence of the substituent in the ligand rather than to the change of solvent. This observation is consistent with the formation of the hydrido carbonyl complex **5b** as the actual catalyst precursor in the supercritical phase, which was experimentally established most recently by high-pressure NMR spectroscopy.[19] Owing to the enhanced solubility of **4b** in scCO$_2$, the equilibrium shown in Scheme 2 is effectively shifted to the left regardless of the phase behaviour of the reaction medium.

Nickel-catalysed asymmetric hydrovinylation

The metal-catalysed co-dimerization of alkenes with ethene yielding 3-substituted 1-butenes (hy-



Scheme 3 Nickel-catalysed asymmetric hydroformylation in compressed CO$_2$.

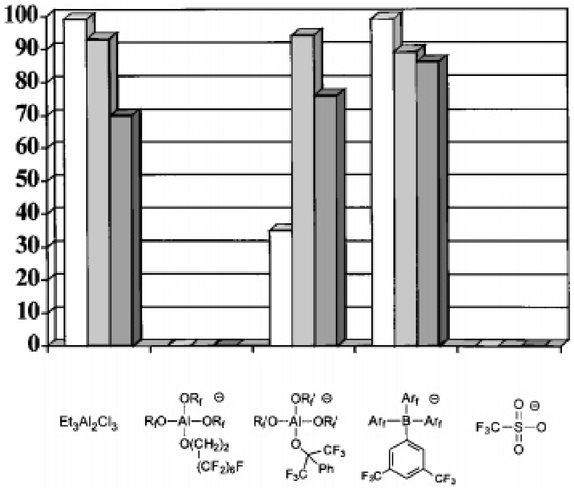


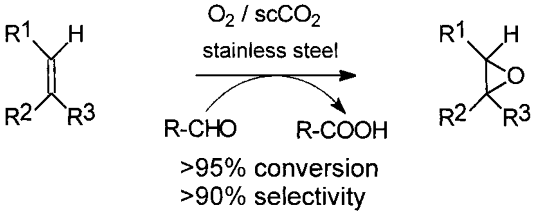
Figure 4 Influence of the co-catalyst on conversion (white bar), chemoselectivity (grey bar) and enantioselectivity ((*R*)-**8**, black bar) of the asymmetric hydrovinylation of styrene (**1**) in compressed CO_2 using catalyst **3** according to Scheme 3. All anions were employed as their sodium salts. Data are taken from Ref 21.

drovinylation) is a particularly intriguing carbon–carbon bond forming reaction because both starting materials are incorporated entirely in the product and the resulting new double bond can be used for further transformations to highly functionalized molecules.[20] Wilke introduced the (η^3-allyl)-nickel(II) complex **7** containing a chiral 1,2-substituted 1-azaphospholene ligand as a catalyst precursor for the *asymmetric* hydrovinylation of vinyl arenes (Scheme 3) and other olefins.[20a] Complex **7** catalyses the enantioselective hydrovinylation of **1** to give **8** at extremely high rates and with unrivalled chemo-, regio- and enantio-selectivity, but it needs to be activated by an excess of highly flammable $Et_3Al_2Cl_3$. Furthermore, the reaction requires temperatures below −60 °C and the use of toxicologically disreputable CH_2Cl_2 as a solvent. Therefore, the use of compressed CO_2 as an alternative medium is highly attractive for this reaction.[21]

Initial attempts using the original catalyst recipe with $scCO_2$ showed promising results, but the difficult handling of $Et_3Al_2Cl_3$ and corrosion problems with the high-pressure equipment made this approach impractical. It is generally accepted that the role of the co-catalyst in this reaction is to abstract a chloride ion from **7** to provide a vacant co-ordination site on a cationic nickel centre. We therefore anticipated that a suitable salt of a non-coordinating anion should have a similar promoting effect in $scCO_2$,[20a] provided that sufficient solubility of all species except the resulting chloride salt could be achieved in the reaction mixture. Based on these considerations, the sodium salt of the tetrakis-[3,5-bis(trifluormethyl)phenyl]borate anion (BARF) seemed to be the logical choice for a suitable co-catalyst.[17e,20b,22] Indeed, excellent results were achieved in the hydrovinylation of **1** using a catalyst generated from **7** and NaBARF in liquid or supercritical CO_2. Other fluorinated anions were considerably less effective than the borate (Fig. 4).

Steel-promoted epoxidation of olefins

The miscibility of the supercritical phase with reactant gases, together with the oxidation stability of the CO_2 molecule, make $scCO_2$ a particularly interesting reaction medium for selective oxidation of organic substrates with molecular oxygen.[6b,23] Previous attempts to apply $scCO_2$ for metal-catalysed oxidations using O_2 led only to moderate yields of the desired products.[23,24] We have therefore turned our interest to the epoxidation of olefins with oxygen in the presence of aldehydes as sacrificial oxygen transfer agents (Mukaiyama conditions).[25] It soon became apparent that the epoxidation of substrates with internal double bonds occurs under these conditions in $scCO_2$ with excellent yields and selectivities *even in the absence of any additional catalyst* (Scheme 4).[26] Other olefins were oxidized with somewhat lower efficiency. Depending on the substitution pattern at



$R^1, R^2 = -(CH_2)_6-, R^3 = H$
$R^1, R^2 = -(CH_2)_4-, R^3 = H$
$R^1 = R^3 = Et, R^2 = H$

Scheme 4 Steel-promoted epoxidation of internal double bounds using oxygen as the primary oxidant, aldehydes ($R = {}^iPr, {}^tBu$) as sacrificial co-oxidants, and $scCO_2$ as the reaction medium.

the double bond, either epoxidation or vinylic oxidation was the prevailing pathway in these cases.

Detailed control experiments revealed that the stainless steel of the reactor walls plays a crucial role for the epoxidation of internal double bonds. Presumably, the steel surface promotes the formation of acylperoxy radicals $RC(O)OO^{\cdot}$ from the reaction of the aldehyde with oxygen.[27,28] These radicals can act as the actual oxygenating species for the olefin, whereby they are ultimately converted to the corresponding carboxylic acids. The $RC(O)OO^{\cdot}$ radicals are regenerated in the presence of oxygen during this process. This oxidation cycle does not require an additional catalyst and operates very effectively and selectively in $scCO_2$ as the reaction medium. One of the most intriguing options arising from these results is the principal possibility to combine the oxidation of olefins with the coupling of epoxides and CO_2 to give either cyclic or polymeric carbonates.[29] Exploration of this approach is part of our ongoing efforts in this area.

CONCLUSION

Compressed CO_2 is a readily available and technically feasible solvent, providing fascinating opportunities for applications in chemical synthesis. Especially in the supercritical state, CO_2 has unique properties that may be beneficial for various synthetic transformations. Metal-catalysed processes involving gaseous substrates occur with high rates and selectivities if the organometallic catalysts are suitably adjusted to this reaction medium. Oxidation reactions are particularly attractive targets for the application of $scCO_2$ and are, as yet, largely unexplored. The possibility of radical pathways initiated by stainless steel from the reactor walls must be considered as a background reaction in such studies, and may even be utilized for an efficient epoxidation process of olefins with internal double bonds. Further studies in this field seem highly rewarding for the development of environmentally benign synthetic methodologies.

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