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Catalytic asymmetric hydroformylation in the presence of compressed carbon dioxide

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The asymmetric hydroformylation of styrene using [$(CO)_2Rh(acac)$]/(R, S)-BINAPHOS as catalyst precursor occurs smoothly in the presence of compressed CO_2 to give appreciable asymmetric induction (ee = 66% (R)) under conditions close to the critical data of pure CO_2, but very low ees are obtained at high CO_2 densities. The phase behaviour of the reaction medium and the different solubilities of the unmodified and ligand-modified catalytically active species in the supercritical phase provide a possible rationalisation of the results.

Keywords: asymmetric catalysis, hydroformylation, supercritical carbon dioxide, rhodium catalysts

Asymmetric hydroformylation using chiral transition metal catalysts is an efficient and well established strategy for the synthesis of functionalised non-racemic organic compounds, providing, for example, viable routes to important anti-inflammatory drugs starting from simple vinyl arenes [1]. The chiral phosphine/phosphite ligand (R, S)-BINAPHOS (**2**) allows rhodium-catalysed asymmetric hydroformylation of vinyl arenes with outstanding levels of enantiocontrol [2], but the established protocols require application of ecological and toxicological hazardous organic solvents. Supercritical carbon dioxide has been introduced recently as an environmentally friendly solvent with unique properties for metal-catalysed processes [3] and has been applied to hydroformylation reactions in the presence of cobalt [4], manganese [5], and rhodium [6] complexes or catalysts. The homogeneously catalysed enantioselective hydrogenation of dehydroamino acids has also been achieved in this medium [7], and it seems, therefore, attractive to use $scCO_2$ as a reaction medium for efficient asymmetric hydroformylation in $scCO_2$ as well. We herein disclose preliminary experimental results on the use of ligand **2** for asymmetric hydroformylation in the presence of compressed CO_2, which emphasise the importance of the relationship between the physico-chemical properties of the supercritical reaction medium and the structure of the enantioselective catalysts.

The hydroformylation of styrene (**3**) using [$(CO)_2Rh$ (acac)] (acac = acetylacetonate, **1**) as the catalyst precursor and **2** as the source of chirality was chosen as a test reaction (scheme 1). Initial experiments were carried out at temperatures and pressures far beyond the critical data of pure CO_2 ($T_c = 31\,^\circ C$, $p_c = 73$ atm, $d_c = 0.468$ g/ml) to ensure high densities and formation of a presumably supercritical reaction mixture. At 60 °C and CO_2 densities between 0.70 and 0.82 g/ml (initial pressure of the reaction mixture $p^0 = 210$–295 atm), no liquid-phase or solid material was observed by visual inspection of the reactor, but very small amounts would probably not have been detectable. Within a standard reaction time of 22 h, **3** was consumed completely ($c\nu > 98\%$) to produce mixtures of the chiral aldehyde **4** and its achiral regioisomer **5** in ratios between 6 : 1 and 8 : 1. Excellent chemoselectivity for aldehyde formation was achieved and $\leqslant 1\%$ ethylbenzene was formed via hydrogenation of **3**. The enantiomeric excess, however, was disappointingly low under these conditions (5–35%) with (R)-**4** being the slightly favoured enantiomer (figure 1). The sense of optical induction is identical to the one observed in conventional solvents [2] or in neat **3** (*vide infra*).

A control experiment was carried out in order to probe whether the low ee might arise from rapid racemisation of **4** in the reaction mixture [1,2]. The ee of an independently synthesised sample of (R)-**4** lowered from 79 to 72% within 22 h and further to 55% over a total of 52 h in the presence of **1**/**2** under typical reaction conditions ($T = 60\,^\circ C$, $p(H_2/CO) = 40$ atm, $d(CO_2) = 0.68$ g/ml). Hence, there is a tendency of **4** to racemise under hydroformylation conditions in the presence of **1**/**2** and compressed CO_2, but racemisation is far too slow to account for the very low ees observed in catalytic runs.

Upon variation of the reaction conditions, we noticed a considerable increase of the enantiomeric excess at lower CO_2 densities. Most intriguingly, the highest ee in the presence of CO_2 was achieved with 66% (R)-**4** at a CO_2 density of 0.48 g/ml ($p^0 = 155$ atm), i.e., very close to the critical density of pure CO_2 (figure 1). In the initial state of this reaction, no inhomogeneities were detected by visual inspection of this reaction mixture, but appreciable amounts of a strongly coloured liquid phase could be observed after approximately 1.5 h. Similar phase separations occurred

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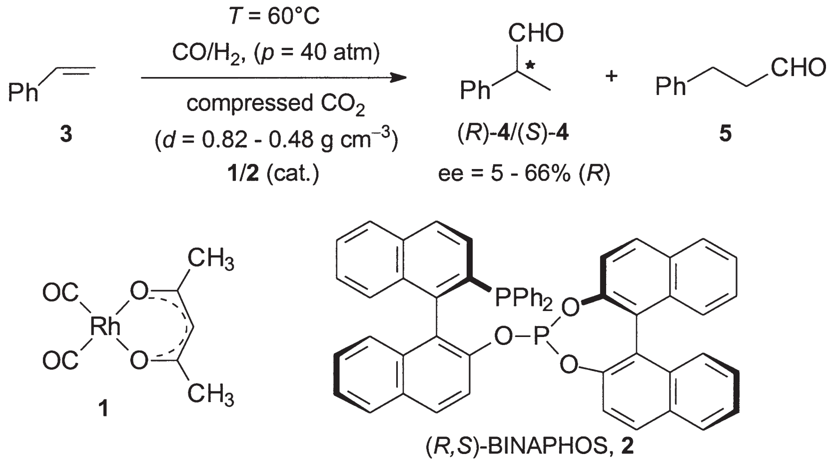

Scheme 1.

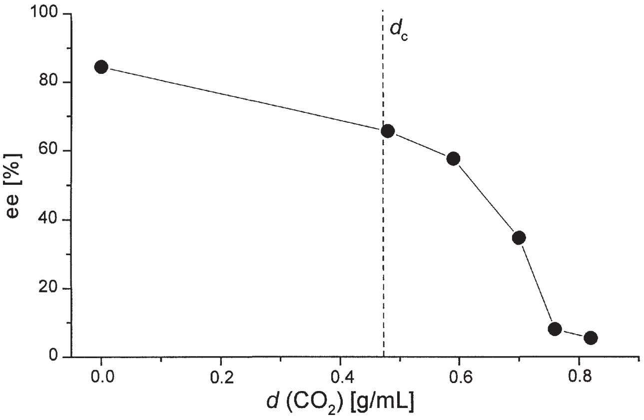

Figure 1. Influence of compressed CO$_2$ on the enantiomeric excess (ee) of 3-phenylpropanal (**4**) obtained from hydroformylation of styrene (**3**) in the presence of the rhodium complex [(acac)Rh(CO)$_2$] (**1**) and the chiral ligand (R,S)-BINAPHOS (**2**). The ee decreases dramatically above the critical density of pure CO$_2$ ($d_c = 0.468$ g/ml, dashed line) and is below 30% when homogeneous mixtures of CO$_2$ and all reactants are observed thoughout the reaction ($d > 0.7$ g/ml).

at some stages in all reactions leading to high conversion *and* good levels of enantiocontrol. Efforts are underway to quantitatively corroborate the appearance of this coloured phases with conversion and/or ee.

Current literature data predict a very low solubility of **2** and its complexes in pure scCO$_2$ [6a,7,8]. Together with the above observations, this strongly suggests that the ligand-modified rhodium catalyst operates primarily in a CO$_2$-rich liquid phase consisting of unreacted olefin and product aldehyde. In a parallel catalytic cycle, ligand-free – and hence achiral – rhodium species could lead to the formation of racemic **4** in the supercritical phase (*vide infra*). The equilibrium between unmodified and ligand-modified rhodium species is well established under hydroformylation conditions when **1** and **2** are used in equimolar amounts in conventional solvents [2]. The tendency to form a liquid phase can be expected to decrease with increasing density of the supercritical mixture [9] resulting in the observed decrease of the overall enantioselectivity at higher CO$_2$ pressure.

In agreement with these considerations, complex **1** catalyses the hydroformylation of **3** very efficiently in supercritical CO$_2$ *in the absence of ligand* **2**, leading quantitatively to a mixture of **5** and racemic **4** with very similar regioselectivity (**4** : **5** $\approx$ 7 : 1). In fact, the hydroformylation of olefins with unmodified rhodium catalysts in scCO$_2$ is very general and is considerably faster than in liquid phases as described in detail elsewhere [6b]. Furthermore, we found that hydroformylation of *neat* **3** *catalysed by* **1**/**2** *in the absence of CO$_2$* proceeded quantitatively to give (R)-**4** with a similar regioselectivity and with a high ee of 84% (figure 1).

Thus, all experimental results obtained up to now are in agreement with the assumption that the efficiency of this asymmetric catalytic process is largely determined by phase behaviour of and solubility in the supercritical fluid. However, we would like to note that extrapolation of solubility data from pure scCO$_2$ to a multicomponent system consisting of CO$_2$ and the reactant gases together with **3**, **4** and **5** in variable amounts is very difficult. It is known that aromatic compounds can act as co-solvents in supercritical fluids enhancing the solubility of otherwise insoluble materials [9]. Therefore, we cannot rule out completely that a rhodium complex containing ligand **2** might be homogenously dissolved in such a supercritical reaction medium even at low densities. However, the remarkable variation of the enantioselectivity with density (or pressure) of the compressed "solvent gas" remains intriguing in this case.

In summary, we have demonstrated that chiral rhodium catalysts are in principle compatible with the hydroformylation reaction in the presence of compressed CO$_2$. Even more important, however, the results nicely exemplify the complex interplay of density, phase behaviour, and solubility properties in multicomponent reaction systems involving transition metal catalysts and compressed CO$_2$. These factors represent a major complication in attempts to simply adopt highly effective systems based on classical aryl phosphorus ligands for utilisation in scCO$_2$, especially when both ligand-modified and unmodified systems are potentially catalytically active as in the present case. The development of chiral "CO_2-philic" ligands [6,10] seems, therefore, urgently required to allow the exploitation of all potential benefits associated with the application of well defined supercritical phases in homogeneous catalysis.

Experimental

In a typical experiment, the catalyst was formed in a window-equipped high pressure reactor ($V = 10$ ml) by stirring equimolar amounts (0.02×10^{-4} mol) of **1** and **2** in CH_2Cl_2 (3 ml) at room temperature for approximately 10 min under argon atmosphere. The solvent was removed *in vacuo* and **3** (0.18 ml, 1.57×10^{-3} mol) was introduced resulting in apparent dissolution of the catalyst material. The reactor was pressurised with a $1:1$ mixture of H_2 and CO to 40–45 bar and a weighed amount of CO_2 was introduced using a compressor to adjust the desired density. The reaction mixture was heated to 60 °C within 5–10 min and stirring was continued at this temperature for a standard reaction time of 22 h.

After cooling, the reactor was carefully vented through a cold trap and the products were collected for NMR and GC analysis by extraction of the reactor and the trap with toluene. The conversion of **3** was found to be $>$98% in all cases. The enantiomeric excess of **4** (ee% $= 100 \times [(R)\text{-}\mathbf{4} - (S)\text{-}\mathbf{4}]/[(R)\text{-}\mathbf{4} + (S)\text{-}\mathbf{4}]$) was determined by GC without further derivatisation using 20% 6-tbudimeSi-2,3-dime-β-CD/80% SE54 or 30% 6-tbudimeSi-2,3-dime-β-CD/70% OV1701 (IVADEX 5) as chiral stationary phases consisting.

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