Continuous platinum-catalyzed enantioselective hydrogenation in 'supercritical' solvents

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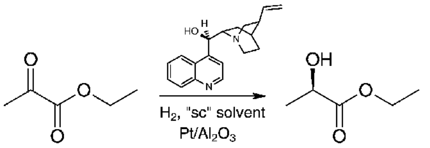
Hydrogenation of ethyl pyruvate in 'supercritical' ethane in a fixed bed reactor over cinchona-modified Pt/Al_2O_3 affords good ee at an exceptionally high rate, whereas in carbon dioxide the catalytic performance under similar conditions is inferior.

Application of supercritical (sc) fluids as solvents and reactants has great potential for optimizing chemical reactions.[1–3] The continuous hydrogenation of organic compounds in sc CO_2 or propane has recently been reported by Poliakoff and co-workers.[4] Here we show the first example of a continuous asymmetric hydrogenation in a 'sc' fluid. The well studied enantioselective hydrogenation of ethyl pyruvate (EP)[5] over cinchonidine (CD)-modified Pt/Al_2O_3 has been chosen as a model reaction (Scheme 1) to demonstrate the feasibility of the process. A crucial point is that trace amounts of the chiral modifier have to be fed continuously to the reactor in order to maintain a good ee with time-on-stream.[6] We show that the application of 'sc'ethane as a solvent affords a remarkable increase in reaction rate compared to the best conventional solvent, toluene. Note that the widely used term supercritical is deprived of any meaning in multi-component systems since phase separation is still possible at conditions beyond the mixture critical point or the critical point of the pure components.[7] For convenience, 'sc' is used here in quotes for the solvent-rich phase at temperatures exceeding its mixture critical point, irrespective of further liquid phases present.



Scheme 1

Catalytic studies were carried out in a continuous stainless steel tubular fixed-bed reactor with 12.5 mm inner diameter.[6] A mechanical mixture of 100 mg 5 wt% Pt/Al_2O_3 (Engelhard 4759, metal dispersion: 0.27) and 900 mg Al_2O_3 (110 $m^2\ g^{-1}$ surface area) as diluent was employed, resulting in a catalyst bed length of 15 mm. The catalyst was prereduced *in situ* at 400 °C in H_2. A flow of 1.0 ml min^{-1} EP (Fluka, 97%) was mixed with ethane (99.5%) or CO_2 (99.995%) and H_2 (99.999%) in a static mixer before entering the reactor. CD (Fluka, > 98%) was fed together with EP (Fluka, 97%) at a molar ratio EP : CD of 2500 : 1. The corresponding solution was prepared immediately before the reaction and kept cool and in the dark to minimize side-reactions. Conversion and ee were determined by GC analysis without derivatization. Chemoselectivity to ethyl lactate was always 100%. Enantiomeric excess is defined as $([R] - [S])/([R] + [S])$.†

Preliminary studies using CO_2 and ethane as solvents indicated that the latter is a better solvent for EP hydrogenation. Fig. 1 shows the changes in conversion and ee induced during continuous hydrogenation of EP when the solvent is changed from dense CO_2 to ethane. Note the prominent increase in reaction rate and enantioselectivity with ethane. A similar but reversed behaviour was observed when the sequence of solvents was changed. The poor performance in CO_2 is not completely understood yet. A possible explanation is partial poisoning of the platinum catalyst due to the formation of CO *via* the reverse water gas shift reaction ($CO_2 + H_2 \rightleftharpoons CO + H_2O$).[8] As a consequence of these comparative studies further investigations were performed in ethane.

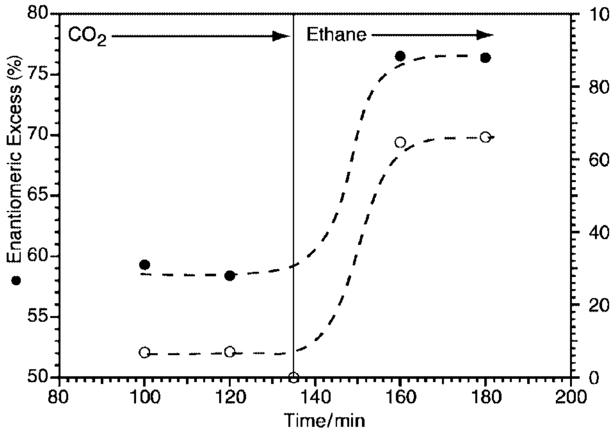


Fig. 1 Conversion (○) and ee (●) of EP hydrogenation in dense CO_2 and ethane at 30 °C and 100 bar. Molar ratio of solvent : EP : H_2 = 500 : 1 : 10. EP-flow was 4.3 mmol min^{-1}.

Careful consideration of the phase behavior under reaction conditions is critical for understanding the outcome of the reaction. The phase behavior of the system under reaction conditions was investigated in a computer controlled high-pressure view cell of variable volume (23–63 ml), equipped with on-line digital video imaging and recording. The magnetically stirred cell consisted of a horizontal cylinder equipped with a sapphire window covering the entire diameter and an opposite, horizontally moving piston equipped with another sapphire window for illumination of the system. The basic setup of the computer-based approach and video imaging has been described before.[9]

The reaction mixture ethane–EP–H_2 exhibited a three-phase LLV equilibrium (EP–rich liquid, ethane-rich liquid and ethane–H_2-rich gaseous phase) at 30 and 40 °C. The upper two ethane-rich phases critically merged at around 40 °C and 70 bar. Beyond this upper critical endpoint of the coexistence of the ethane-rich phases, the system exhibited a two-phase equilibrium of a liquid EP-rich phase and a dense fluid ('sc') ethane-rich phase, continuously blending to one phase with increasing pressure. The pressure required for this transition depended strongly on temperature (20–50 °C) and H_2 concentration (1–9%) in the system. A similar phase behavior was found in the system ethane–ethyl lactate–H_2 as well as in the system ethane–ethyl pyruvate–ethyl lactate–H_2. On this basis we assume that the whole conversion range can be well modelled by the ethane–EP–H_2 system discussed above.

At low H_2 concentration, the transition from a multiphase to a homogeneous fluid phase (single phase) was accompanied by a pronounced increase in EP conversion (Fig. 2, k = 2). In

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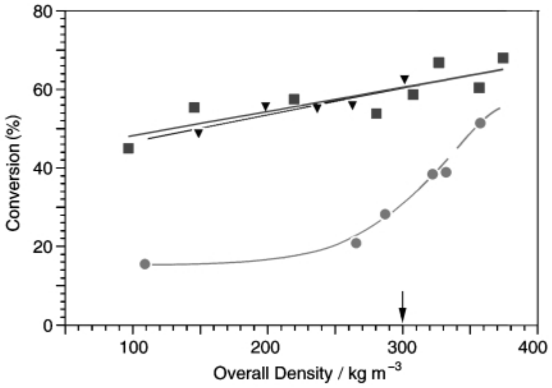

Fig. 2 Conversion of EP at 40 °C as a function of overall density at various H_2 concentrations. Ethane : EP : H_2 molar ratio = 200 : 1 : k, (○) k = 2, (■) k = 10, (▼) k = 20. Arrow marks density required for merging of fluid phases to homogeneous phase.

contrast, at higher H_2 concentration the conversion changed continuously with density, irrespective of changes in phase behavior. This behavior clearly corroborates the often made assumption that a homogeneous fluid phase affords remarkably higher reaction rates, which only holds true under conditions where mass transfer of the limiting reactant is enhanced due to elimination of phase boundaries. Enantiomeric excess to (*R*)-ethyl lactate was in the range 55–75%, depending on the temperature and H_2 concentration. Representative results illustrating the influence of pressure and reactant ratio (H_2 : EP) at 40 °C are listed in Table 1. Note that full conversion could easily be attained by increasing the contact time. Lower conversions are shown here to illustrate the effect of reaction conditions on reaction rate (conversion).

The continuous enantioselective hydrogenation in 'sc' ethane afforded a remarkably fast reaction with good ee. At best, a TOF of 15 s^{-1} was obtained at 70% conversion and ambient temperature. Using toluene as solvent provided the highest TOF of 1.8 s^{-1} under otherwise comparable conditions and optimal H_2 concentration. The process in 'sc' ethane furthermore facilitated an easy and complete separation of the solvent from the reactants by simple expansion of the reaction mixture.

Table 1 Conversion, ee and number of phases present at different pressures and feed compositions, for the enantioselective hydrogenation of EP in dense ethane at 40°C

Feed ratio	*p*/bar	Number of phases	ee (%)	Conv. (%)
	62	3	66	49
H_2 : EP = 20	88	2	65	55
	114	1	63	59
	62	3	68	20
H_2 : EP = 2	88	1	71	37
	114	1	72	50

The phase behavior of the system can be understood in terms of immiscibility of the EP-rich and ethane-rich dense phases at intermediate temperature. The solubility of EP in the ethane-rich dense phase depends mainly on the density of this phase in the temperature range investigated.[10] In fact, complete solvation of EP occurred at a density of around 300 kg m^{-3} (indicated in Fig. 2) for all temperatures and H_2 concentrations, resulting in a saturated ethane-rich dense phase under these conditions. The higher the H_2 concentration in the system, the higher was the pressure required to achieve a density of 300 kg m^{-3} and thus complete solubility of EP in the dense ethane-rich phase. Note that coexistence of two phases was observed at values well above the critical parameters of ethane (ethane, T_c = 32.2 °C, p_c = 48.8 bar). This observation illustrates the danger of assuming that the phase behavior of a multi-component system is similar to that of the pure solvent.

In conclusion, we have shown the feasibility of continuous enantioselective hydrogenation of an α-ketoester in dense ('sc') ethane by continuous dosing of a minute quantity of the chiral modifier CD. High reaction rates combined with good enantioselectivity and easy separation of products are beneficial features of this process.

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Notes and references

† Safety note: the experiments described in this paper involve the use of relatively high pressure and require equipment with the appropriate pressure rating.

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