Ruthenium-catalysed asymmetric hydrogenation with fluoroalkylated BINAP ligands in supercritical CO₂

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Abstract
Fluoroalkylated BINAP ligands have been evaluated in the ruthenium-catalysed asymmetric hydrogenation of dimethyl itaconate in both MeOH and supercritical CO₂. The reaction proceeds slower and gives a lower enantioselectivity in the latter, which is probably due to the lower polarity of scCO₂.

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1. Introduction
In the search for more environmentally friendly chemical processes, the use of supercritical fluids (SCFs) as reaction media has received a great deal of attention in both academia and industry [1–3]. The potential of SCFs is clearly seen in the recent launch of a scCO₂-based commercial hydrogenation process by Thomas Swan on the basis of Polyaokoff’s research [4]. The key advantages of SCFs arise from their tuneable polarity, high mass transport rates and environmental compatibility. By far most studies have been carried out using scCO₂ because of the easily accessible critical constants, cost and lack of toxicity of the solvent. However, the apolarity of scCO₂ restricts the application of many, “conventional”, metal-based catalysts, in particular, those that contain chiral ligands, which are generally more complex in structure and, hence, more difficult to render soluble in scCO₂. The introduction of perfluoroalkyl substituents, colloquially called “fluorous ponytails”, can enhance ligand and catalyst solubilities in scCO₂, and we have developed simple and efficient catalytic methods for the synthesis of a series of fluoroalkylated binaphthyl-based chiral ligands (Scheme 1) [5–7], including preliminary data on the ruthenium-catalysed hydrogenation of dimethyl itaconate in MeOH using 2 and 3 [5].

Whilst a spectrum of reactions have been studied in scCO₂, the number of examples of asymmetric induction are few [1–3]. Asymmetric hydrogenation of α, β-unsaturated carboxylic acids, e.g. tiglic acid, by [Ru(OAc)₂(BINAP)] in scCO₂ was shown to give low conversion and low enantioselectivity; but enhanced conversion and ee’s were observed when BINAP was made more CO₂-philic by saturating two of the naphthyl rings [8]. Asymmetric hydrogenation of α-enamides with a cationic Rh-DuPHOS catalyst was made possible by using a highly fluorinated, CO₂-philic, anion [9], and a similar approach has been adopted for the enantioselective hydrogenation of an imine with a cationic iridium catalyst [10]. We have shown that the rhodium-catalysed asymmetric hydrogenation of dimethyl itaconate in scCO₂ with the monodentate ligands 4–7 offers low conversions and low enantioselectivities in comparison to the same catalysts in CH₂Cl₂ [7]. However, very recently, the enantioselective hydrogenation of tiglic acid in scCO₂ was revisited, employing a OCF₃-substituted BINAP ligand in which the low ee of 25–35% in scCO₂ could be increased to 50–60% by the addition of MeOH [11]. This prompted us to report our results using fluoroalkylated BINAP ligands for enantioselective hydrogenation in scCO₂.

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2. Results and discussion

We have been investigating the application of perfluoroalkylated phosphorus(III) ligands for catalysis under fluorous biphasic conditions [12–16] and in scCO$_2$ [5,17,18], and have synthesised a series of fluoroalkylated binaphthyl-based chiral ligands, aiming to confer solubility on these catalysts based on these ligands for use in scCO$_2$ (Scheme 1) [5–7]. Herein we detail our results on the asymmetric hydrogenation of dimethyl itaconate using ruthenium and the ligands 2 and 3 as catalyst.

The ruthenium-catalysed hydrogenation was first evaluated in the most-often used solvent methanol [19]. The catalysts, Ru-2 and Ru-3, were prepared by reacting [RuCl$_2$(benzene)]$_2$ with 2 and 3 in DMF, respectively, according to the method of Noyori [20]. The hydrogenation was performed at ambient temperature under 50 bar H$_2$ with a substrate/catalyst ratio of 2000. As can be seen from Table 1, the direct attachment of the perfluoroalkyl groups has an influence on the rate of reaction (entries 1–3), as expected since it is well established that electron withdrawing and donating substituents have a direct effect on both catalyst activity and enantioselectivity [21,22]. This is ameliorated by the inclusion of the additional C$_2$H$_4$ spacer unit, whereby 3 affords a similar or faster rate compared to that obtained with BINAP 1. Crucially, the introduction of the

<table>
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<th>Time (h)</th>
<th>Conversion (%)</th>
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</table>

$^a$ Assuming that all the substrate was dissolved in mol dm$^{-3}$.

$^{b}$ 20 bar H$_2$.

$^c$ 0.2 mL MeOH was introduced following by H$_2$ and CO$_2$.

$^d$ The reaction was quenched with a dry ice bath immediately after the CO$_2$ pressure reached 150 bar.
fluorouralkyl groups has a negligible effect on the enantioselectivity of the reaction, with excellent ee values obtained with both Ru-2 and Ru-3.

In scCO2 these derivatised ligands show poor reactivities and enantioselectivities. Thus, as shown in Table 1, a much longer reaction time was necessary for a complete conversion when the ligands 2 or 3 was employed at 100 bar CO2 and a higher temperature of 80 °C, and considerably reduced ee values were observed (entries 4 and 5). This decrease in ee is not caused by the increase in reaction temperature, as high enantioselectivities were observed in MeOH at both low and high temperature (vide infra). Interestingly, increasing the CO2 pressure to 150 bar for Ru-3 resulted in an even lower conversion (entry 6). The conversion increased at higher temperatures, but at the expense of enantioselectivity (entry 7), whilst decreasing the temperature gave a much lower conversion without affecting the ee (entry 8). The last entry in the table shows that the ee values observed with scCO2 resemble that observed without any solvent (71.6%) [7], and those with the OCF3-substituted Ru-BINAP catalyst [11], where reduced activity and enantioselectivity were recorded on going from a liquid solvent to scCO2.

There are two possible explanations for the poor reactivity and enantioselectivity in scCO2: (i) catalyst solubility and (ii) polarity of the solvent. For (i), a phase study showed that, under the catalytic conditions at 80 °C (S/C = 1000, [Ru] = 0.11 M), two distinct phases existed at 100 bar CO2, that the liquid phase did not disappear until a pressure of ca 140 bar CO2 was reached, and that a few small liquid droplets were visible even at 150 bar CO2, apparently due to undissolved catalyst. Thus, under these conditions, there is a possibility that the reaction may have, to some degree, taken place in the liquid phase. To address this problem, a reaction was performed at a lower substrate and catalyst concentration (S/C = 2000, [Ru] = 0.022 M, entry 9), under which a single homogeneous phase was observed. Contrary to what one might expect, a much reduced enantioselectivity was obtained, and this trend continued at higher CO2 pressure (180 bar, entry 10). These observations suggest that it is not the solubility of catalyst that dictates the activity and enantioselectivity of the catalyst in scCO2.

For (ii), it is well established that the Ru-BINAP catalysts normally give their best performance in polar, protic solvents, such as MeOH [19]. In contrast to such solvents, scCO2 is apolar and non-protic. Thus, the results presented in Table 1 tend to support the view that it is the apolarity of CO2 that is responsible for the low catalyst activity and enantioselectivity in scCO2. Alcohol additives have previously been shown to enhance the enantioselectivity of hydrogenation of tiglic acid by ruthenium catalysts containing a modified BINAP in scCO2 [8]. Bearing this in mind, a hydrogenation reaction was carried out, in which 0.2 mL MeOH was introduced into the autoclave at room temperature followed by heating and introducing H2 and CO2. The subsequent hydrogenation with Ru-3 under scCO2 conditions indeed afforded a delightful conversion (92%) and ee (93.6%) in the short reaction time of 3 h (entry 11). However, a control experiment showed that most of the hydrogenation had occurred before the conditions for scCO2 had been reached. Thus, when the hydrogenation was quenched immediately after 150 bar CO2 had been introduced, a conversion of 82% alongside an ee of 94.5% was detected (entry 12). This experiment also suggests that caution should be exercised when explaining results arising from the use of co-solvents alongside scCO2, as these could arise from reactions occurring in a CO2-saturated liquid solvent.

The results shown in Table 2 further demonstrate the importance of polarity. The asymmetric hydrogenation of dimethyl itaconate was carried out in MeOH under various CO2 pressures. As can be seen, when the hydrogenation was conducted in methanol under a low pressure of CO2 (<30 bar), no noticeable effects from CO2 were observed, with the ee values similar to that observed in MeOH without CO2. However, further increases in CO2 pressure led to significant deterioration of both the reactions rates and ee's. Thus, the enantioselectivity decreased to ca 80% accompanied with an incomplete reaction when 60 bar CO2 was present (entry 4). This result could be explained as a consequence of decreased solvent polarity due to the expansion of methanol by the apolar CO2. A more dramatic demonstration of the CO2 effect is seen in the reaction where methanol was introduced when the autoclave was already pressurised with 120 bar CO2; a very low conversion of 13% and an ee value close to those in the absence of CH3OH (Table 1) were

<table>
<thead>
<tr>
<th>Entry</th>
<th>P CO2 (bar)</th>
<th>P CH3OH (bar)</th>
<th>Temperature (°C)</th>
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<th>Time (h)</th>
<th>Conversion (%)</th>
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</tbody>
</table>

* Methanol was introduced at room temperature before hydrogenation took place. Two hundred milligram (1.3 mmol) substrate was used with S/C = 2000.

* Methanol was introduced under scCO2 conditions via a sample loop.
and the Ru-L catalysts were prepared according to published methods. Conversions and ee values were determined by a Varian CP-3380 GC equipped with a Chiraldex G-TA (40 mm × 0.25 mm) column. Hydrogenation in scCO$_2$ was carried out in a Parr 71 mL high-pressure stainless steel reactor equipped with a glass liner (actual reactor volume = 56 mL) and a magnetic stirrer. In a typical experiment, dimethyl itaconate (6.3 mmol) and a Ru-L catalyst (3 μmol) were introduced. The autoclave was then sealed, degassed and heated to the reaction temperature (80 °C) under an atmosphere of CO$_2$. After the introduction of H$_2$ (50 bar), liquid CO$_2$ was transferred into the autoclave using a head-cooled HPLC pump to give a total pressure of 200 bar. The mixture was stirred for 24 h, after which the autoclave was allowed to cool in a dry ice bath. The CO$_2$ was then carefully vented. The product was collected and analysed by GC. When the hydrogenation was performed in the presence of MeOH, the CO$_2$ was first introduced into the autoclave followed by H$_2$ (Table 2, P$_{CO_2}$ < 100 bar).

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References