Ruthenium-catalysed asymmetric hydrogenation with fluoroalkylated BINAP ligands in supercritical CO_2

Yulai Hu [a], David J. Birdsall [b], Alison M. Stuart [b], Eric G. Hope [b], Jianliang Xiao [a],*

[a] Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK
[b] Department of Chemistry, University of Leicester, Leicester LE1 7RH, UK

Abstract

Fluoroalkylated BINAP ligands have been evaluated in the ruthenium-catalysed asymmetric hydrogenation of dimethyl itaconate in both MeOH and supercritical CO_2 (scCO_2). The reaction proceeds slower and gives a lower enantioselectivity in the latter, which is probably due to the lower polarity of scCO_2.
© 2004 Elsevier B.V. All rights reserved.

Keywords: Supercritical CO_2; Asymmetric hydrogenation; BINAP; Ruthenium catalysts; Fluorous

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 scCO_2-based commercial hydrogenation process by Thomas Swan on the basis of Poliaokoff'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 scCO_2 because of the easily accessible critical constants, cost and lack of toxicity of the solvent. However, the apolarity of scCO_2 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 scCO_2. The introduction of perfluoroalkyl substituents, colloquially called "fluorous ponytails", can enhance ligand and catalyst solubilities in scCO_2, 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 scCO_2, 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 scCO_2 was shown to give low conversion and low enantioselectivity; but enhanced conversion and ee's were observed when BINAP was made more CO_2-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, CO_2-philic, anion [9], and a similar approach has been adopted for the enantioselective hydrogenation of an imine with an cationic iridium catalyst [10]. We have shown that the rhodium-catalysed asymmetric hydrogenation of dimethyl itaconate in scCO_2 with the monodentate ligands **4–7** offers low conversions and low enantioselectivities in comparison to the same catalysts in CH_2Cl_2 [7]. However, very recently, the enantioselective hydrogenation of tiglic acid in scCO_2 was revisited, employing a OCF_3-substituted BINAP ligand in which the low ee of 25–35% in scCO_2 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 scCO_2.

* Corresponding author. Tel.: +44 151 794 2937;
fax: +44 151 794 3589.
E-mail address: j.xiao@liv.ac.uk (J. Xiao).
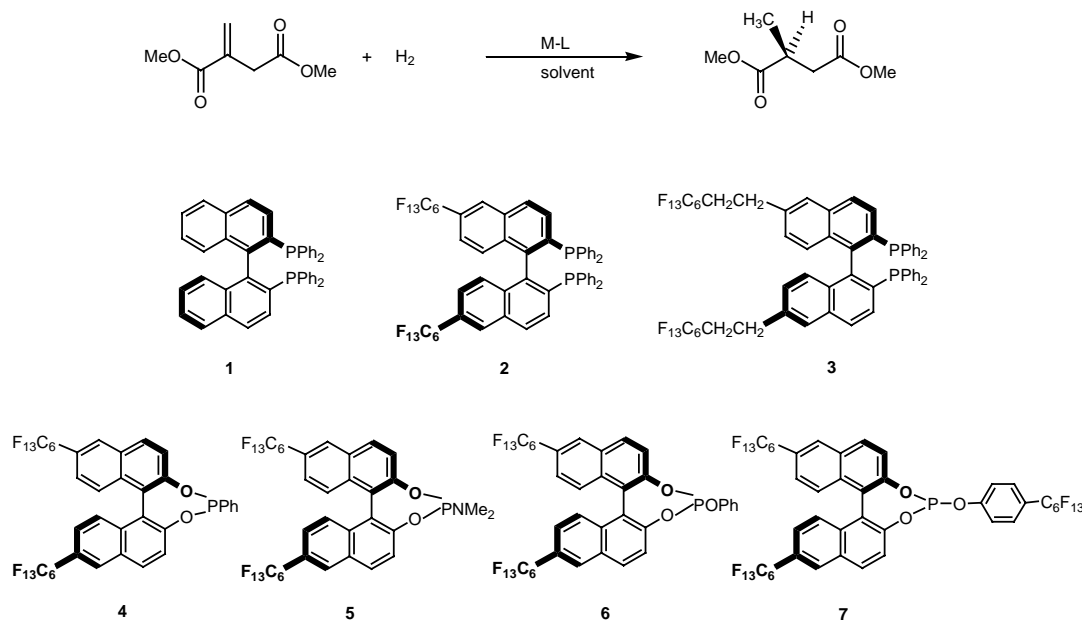
Scheme 1. Asymmetric hydrogenation with ligands 1–7 scCO$_2$ or common solvents.

2. Results and discussion

We have been investigating the application of perfluoroalkylated phosphorus(III) ligands for catalysis under fluorous biphase 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 1
Asymmetric hydrogenation of dimethyl itaconate by the catalysts Ru-L

Entry	Ligand	Solvent	P$_{CO_2}$ (bar)	S/C	[Olefin][a]	Temperature (°C)	Time (h)	Conversion (%)	ee (%)
1	1	Methanol		2000	6.3	22	0.25	97	95.4
2	2	Methanol		2000	6.3	22	0.25	75	95.3
3	3	Methanol		2000	6.3	22	0.25	100	95.7
4	2	CO$_2$	100	1000	0.11	80	24	100	73.0
5	3	CO$_2$	100	1000	0.11	80	24	100	74.0
6	3	CO$_2$	150	1000	0.11	80	24	94	76.0
7	3	CO$_2$	150	1000	0.11	100	24	100	70.6
8	3	CO$_2$	150	1000	0.11	50	24	29	75.0
9	3	CO$_2$	150	2000	0.022	80	3	19	56.1
10	3	CO$_2$	180[b]	2000	0.022	80	3	7	36.7
11	3	CO$_2$[c]	150	1000	0.11	80	3	92	93.6
12	3	CO$_2$[c,d]	150	1000	0.11	80	0.17	82	94.5
13	3	None		1000	Neat	80	1	74	71.6

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

[b] 20 bar H$_2$.

[c] 0.2 mL MeOH was introduced followed 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.

fluoroalkyl groups has a negligible effect on the enantioselectivity of the reaction, with excellent ee values obtained with both Ru-**2** and Ru-**3**.

In scCO$_2$ 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 CO$_2$ 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 CO$_2$ 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 scCO$_2$ resemble that observed without any solvent (71.6%) (entry 13). These observations are reminiscent of those observed with the rhodium catalysts containing **4**, **5**, **6**, or **7** [7], and those with the OCF$_3$-substituted Ru-BINAP catalyst [11], where reduced activity and enantioselectivity were recorded on going from a liquid solvent to scCO$_2$.

There are two possible explanations for the poor reactivity and enantioselectivity in scCO$_2$: (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, [olefin] = 0.11 M), two distinct phases existed at 100 bar CO$_2$, that the liquid phase did not disappear until a pressure of ca 140 bar CO$_2$ was reached, and that a few small liquid droplets were visible even at 150 bar CO$_2$, 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, [olefin] = 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 CO$_2$ 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 scCO$_2$.

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, scCO$_2$ is apolar and non-protic. Thus, the results presented in Table 1 tend to support the view that it is the apolarity of CO$_2$ that is responsible for the low catalyst activity and enantioselectivity in scCO$_2$. Alcohol additives have previously been shown to enhance the enantioselectivity of hydrogenation of tiglic acid by ruthenium catalysts containing a modified BINAP in scCO$_2$ [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 H$_2$ and CO$_2$. The subsequent hydrogenation with Ru-**3** under scCO$_2$ 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 scCO$_2$ had been reached. Thus, when the hydrogenation was quenched immediately after 150 bar CO$_2$ 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 scCO$_2$, as these could arise from reactions occurring in a CO$_2$-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 CO$_2$ pressures. As can be seen, when the hydrogenation was conducted in methanol under a low pressure of CO$_2$ (<30 bar), no noticeable effects from CO$_2$ were observed, with the ee values similar to that observed in MeOH without CO$_2$. However, further increases in CO$_2$ 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 CO$_2$ 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 CO$_2$. A more dramatic demonstration of the CO$_2$ effect is seen in the reaction where methanol was introduced when the autoclave was already pressurised with 120 bar CO$_2$; a very low conversion of 13% and an ee value close to those in the absence of CH$_3$OH (Table 1) were

Table 2
Effect of CO$_2$ on asymmetric hydrogenation of dimethyl itaconate with Ru-**3**[a]

Entry	P_{H_2} (bar)	P_{CO_2} (bar)	Temperature (°C)	CH$_3$OH (mL)	Time (h)	Conversion (%)	ee (%)
1	50	10	80	0.20	1	100	95.2
2	50	20	80	0.20	1	100	96.2
3	50	40	80	0.20	1	100	92.0
4	50	60	80	0.20	1	95	79.8
5	50	100	80	0.20	1	65	84.6
6	50	150	80	0.24[b]	3	13	73.6

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

[b] Methanol was introduced under scCO$_2$ conditions via a sample loop.

observed (entry 6), suggesting that the decrease in solvent polarity or loss of solvating solvent shell at the transition state is to a great degree responsible for the low catalyst activity and selectivity. Hydrogenation of the itaconate by the ruthenium catalysts probably involves heterolytic splitting of H_2 and hydrogenolysis of a Ru–C bond [23], and it is likely that both steps would be slowed down in an apoplar, non-protic medium. In addition, when catalysis is carried out in MeOH, the solvent molecules take part in the reaction by coordinating to unsaturated ruthenium species. This becomes impossible in $scCO_2$ or less probable in the $scCO_2$–MeOH mixture. There is another possibility, that is a polyhydride ruthenium species [23] might have been generated in $scCO_2$, altering the reaction mechanism under our conditions where the hydrogen concentration is higher than that achievable in MeOH.

3. Conclusions

Fluoroalkylated BINAPs have been shown to form excellent ruthenium catalysts for the enantioselective hydrogenation of methyl itaconate in MeOH. However, the same catalysts displayed both reduced activity and enantioselectivity when used for the same hydrogenation in $scCO_2$. This is probably a result of reduced solvent polarity, and indicates that new strategies beyond simple fluorination of ligands must be sought if $scCO_2$ is to be used to facilitate reactions that are sensitive to solvent polarity. Although the mechanistic details for the decrease in enantioselectivity in $scCO_2$ remain to be delineated, our experiments establish that asymmetric hydrogenation with fluorous BINAP-type ligands in $scCO_2$ will not be an efficient process in terms of productivity and enantioselectivity.

4. Experimental

CO_2 (99.995%) and H_2 (99.995%) were obtained from BOC Gases and used without further purification. Dimethyl itaconate and the BINAP ligand **1** were purchased from Aldrich and used as received. The fluorous ligands **2** and **3** [5] and the Ru-L catalysts [20] 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).

Acknowledgements

References

[1] P.G. Jessop, T. Ikariya, R. Noyori, Chem. Rev. 99 (1999) 475.
[2] T. Ikariya, Y. Kayaki, Catal. Surv. Jpn. 4 (2000) 39.
[3] W. Leitner, Acc. Chem. Res. 35 (2002) 746.
[4] S.K. Ritter, C and EN 16 (July) (2001) 26.
[5] D.J. Birdsall, E. Hope, A.M. Stuart, W. Chen, Y. Hu, A.M. Stuart, J. Xiao, Tetrahedron Lett. 42 (2001) 8551.
[6] W. Chen, L. Xu, Y. Hu, A.M. Banet, J. Xiao, Tetrahedron 58 (2002) 3889.
[7] D.J. Adams, W. Chen, E.G. Hope, A. West, J. Xiao, A.M. Stuart, Green Chem. 5 (2003) 118.
[8] J. Xiao, S.C.A. Nefkens, P.G. Jessop, T. Ikariya, R. Noyori, Tetrahedron Lett. 37 (1996) 2813.
[9] M.J. Burk, S. Feng, M.F. Gross, W. Tumas, J. Am. Chem. Soc. 117 (1995) 8277.
[10] S. Kainz, A. Brinkmann, W. Leitner, A. Pfaltz, J. Am. Chem. Soc. 121 (1999) 1999.
[11] X. Dong, C. Erkey, J. Mol. Catal. A: Chem. 211 (2004) 73.
[12] P. Bhattacharyya, D. Gudmunsen, E.G. Hope, R.D.W. Kemmitt, D.R. Paige, A.M. Stuart, J. Chem. Soc. Perkin Trans. I (1997) 3609.
[13] E.G. Hope, R.D.W. Kemmitt, D.R. Paige, A.M. Stuart, J. Fluorine Chem. 99 (1999) 197.
[14] W. Chen, L. Xu, J. Xiao, Chem. Commun. (2000) 839.
[15] D.F. Foster, D. Gudmunsen, D.J. Adams, A.M. Stuart, E.G. Hope, D.J. Cole-Hamilton, G.P. Schwarz, P. Pogorzelec, Tetrahedron 58 (2002) 3901.
[16] D.F. Foster, D.J. Adams, D. Gudmunsen, A.M. Stuart, E.G. Hope, D.J. Cole-Hamilton, Chem. Commun. (2002) 722.
[17] A. Banet, W.Chen, E.G. Hope, R.D.W. Kemmitt, D.R. Paige, A.M. Stuart, J. Xiao, L. Xu, J. Chem. Soc., Dalton Trans. (2000) 4052.
[18] Y. Hu, W. Chen, A.M. Banet Osuna, A.M. Stuart, E.G. Hope, J. Xiao, Chem. Commun. (2001) 725.
[19] R. Noyori, Asymmetric Catalysis in Organic Synthesis, Wiley, New York, 1994.
[20] M. Kitamura, M. Tokunaga, T. Ohkuma, R. Noyori, Tetrahedron Lett. 32 (1991) 4163.
[21] Y.-Y. Yan, T.V. RajanBabu, Org. Lett. 2 (2000) 4137.
[22] K. Matsumura, H. Shimizu, T. Saito, H. Kumobayashi, Adv. Synth. Catal. 345 (2003) 180.
[23] M. Kitamura, M. Tsukamoto, Y. Bessho, M. Yoshimura, U. Kobs, M. Widhalm, R. Noyori, J. Am. Chem. Soc. 124 (2002) 6649.