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Continuous Asymmetric Hydrogenation in Supercritical Carbon Dioxide using an Immobilised Homogeneous Catalyst

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Abstract: Continuous flow supercritical carbon dioxide ($scCO_2$) has previously been shown (P. Stephenson, P. Licence, S. K. Ross, M. Poliakoff, *Green Chem.* **2004**, *6*, 521) to be a viable medium for conducting continuous asymmetric hydrogenation when it is combined with an appropriate enantioselective catalyst. Here we examine the use of a composite catalyst immobilisation system modified with several different types of asymmetric bisphosphine ligands in continuous flow $scCO_2$. In particular, proprietary ligands from Solvias AG were found to be the most successful, with *Josiphos 001* improving the enantiomeric excess (*ee*) to > 80% in the asymmetric hydrogenation of dimethyl itaconate (DMIT); this *ee* is higher than that reported for the batch hydrogenation of DMIT using a homogeneous catalyst fully dissolved in $scCO_2$ (S. Lange, A. Brinkmann, P. Trautner, K. Woelk, J. Bargon, W. Leitner, *Chirality* **2000**, *12*, 450).

Keywords: asymmetric hydrogenation; continuous reactions; immobilized homogeneous catalyst; multiphase catalysis; supercritical carbon dioxide

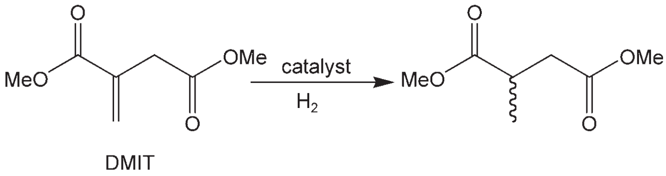
Introduction

Increasing environmental awareness and regulation have placed constraints on the use of 'traditional' chlorinated solvents and volatile organic compounds (VOCs). Alternative solvents such as ionic liquids and supercritical fluids (SCFs) are becoming increasingly accepted as viable alternative reaction media for conducting synthetically valuable chemical transformations.[1–4] SCFs, particularly supercritical carbon dioxide ($scCO_2$), are attractive alternative solvents because of their unique combination of gas-like and liquid-like physical properties. The solubility of many reagents, including gases and high diffusivity can lead to increased reaction rates.[5] Also, product recovery is facile by simple depressurisation of the reaction mixture. In addition, when combined with a fixed catalyst bed SCFs can also be used in continuous flow regimes which are highly efficient[6] and often favoured by industry.[7]

Catalytic asymmetric hydrogenation reactions for the production of enantio-enriched and enantio-pure compounds have also received significant interest over the past two decades.[8,9] A wide variety of chiral ligands has been developed for use in transition metal-based catalysis.[10] However, there are surprisingly few examples of the combination of asymmetric catalysis and SCFs. The reactions that have been successfully demonstrated include hydrogenations,[11–14] hydroformylations,[15,16] oxidations,[17,18] cyclopropanation,[19] hydrovinylation[20] and addition reactions of organozinc[21] and a single example of an aldol reaction.[22] The vast majority of these reactions have been conducted under batch conditions. Exceptions to this include the hydrovinylation of styrene[23] using a nickel catalyst immobilised in an ionic liquid by Leitner et al. that produced enantiomeric excess (*ee*) values up to 95%. Recently, Leitner has also demonstrated outstanding enantioselectivities (*ee* > 95%) in an inverted CO_2/aqueous biphasic semi-continuous flow media.[24] However, the first example of continuous asymmetric hydrogenation in SCFs was reported by Baiker and co-workers[25] who used cinchonidine-modified Pt in the continuous asymmetric hydrogenation of ethyl pyruvate, to achieve an *ee* of up to 75% in supercritical C_2H_6. However, enantioselectivities in $scCO_2$ were not as encouraging.

Perhaps the main reason for the lack of asymmetric transformations in supercritical continuous flow regimes is the fact that reliable immobilisation of a homogeneous catalyst is difficult to achieve. There are several criteria that have to be satisfied if a catalyst immobilisation method is to be considered a success; the method of support has to be strong enough to withstand the reaction conditions but subtle enough not to interfere with the catalytic cycle, similarly the immobilisation system must not interfere with the asymmetric modifier otherwise the stereoselectivity of the system could be reduced. This 'balancing act' between immobilisation and catalytic effect is all the more crucial in any continuous flow system. If the immobilisation method is too weak, either the entire catalyst or just the asymmetric ligand will be flushed away in the passing reaction mixture. Detachment is less of a problem in batch reactions because, in principle at least, the catalyst has the opportunity to reattach itself to the support. As no single ligand is suitable for all asymmetric transformations, a further criterion must be added, namely that the immobilised catalyst should be usable with a variety of ligands and, indeed, be able to be screened for use with specific substrates. Finally, smaller continuous flow reactors are commercially more viable;[2b] therefore the reactor temperature is usually elevated to increase productivity, placing additional demands on the thermal stability of both catalyst and support.

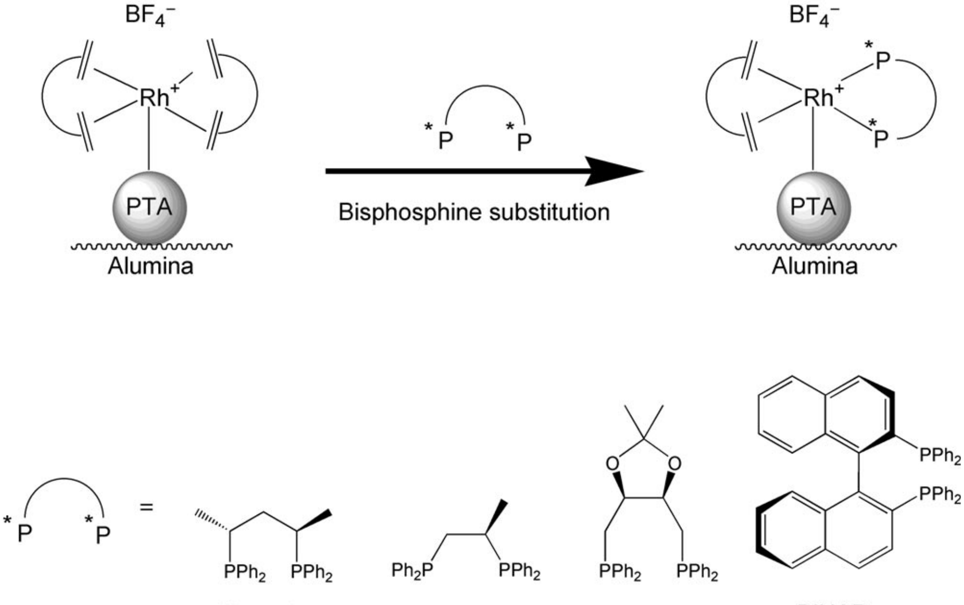
Previously we have reported the asymmetric hydrogenation of dimethyl itaconate[26] (DMIT), using an established immobilised homogeneous asymmetric catalyst,[27] in continuous flow $scCO_2$, Scheme 1.



Scheme 1. The catalytic asymmetric hydrogenation of DMIT using the immobilised homogeneous catalyst.

DMIT is often used as a prototypical molecule when evaluating new asymmetric hydrogenation systems.[28] In this particular case,[26] we used the catalyst $[Rh(S,S\text{-Skewphos})(nbd)]^+[BF_4]^-$ immobilized[27] on γ-alumina *via* a phosphotungstic acid linker $H_3O_{40}PW_{12}$. Although respectable conversions (66 %) and *ee* (63 %) were achieved[26] the true power of this composite catalyst system lies in the fact that it can be used with a wide range of chiral bisphosphine ligands, Scheme 2.

In this paper, we expand the scope of this investigation by screening other chiral bisphosphine ligands, to improve the hydrogenation of dimethyl itaconate, with the ultimate goal of increasing enantioselectivity and improving *ee.* Achieving high conversions was not of such a high priority. Provided that the reaction rate is sufficient for a reaction to occur, low conversions can be improved simply by increasing the residence time of the reactor. In principle, any bisphosphine ligand can be incorporated into this composite system by the ligand substitution reaction in Scheme 2



Scheme 2. The ligand substitution of a diene with the bisphosphine ligands shown. The diene ligand used in this paper was cycloctadiene (COD); PTA = phosphotungstic acid, $H_3O_{40}PW_{12}$.

Results and Discussion

The hydrogenation of DMIT was used to investigate the performance of the ligands shown in Scheme 2. The results are presented in Table 1. The goal of this study was to obtain enantioselectivities as high as possible, therefore for conciseness, the results are presented as a range. For each point in the range, the value was confirmed by maintaining the experiment under steady state conditions over several hours and taking repeat samples every 20 min. Importantly neither conversion nor *ee* were observed to degrade over time, under steady state conditions. This resulted in minimum catalyst turnover numbers (TONs) of 250 for all samples, the maximum recorded is 4600 [moles product][moles Rh]$^{-1}$ at 60 °C and 10 MPa and this corresponds to a turnover frequency (TOF) of 560 [moles product][moles Rh]$^{-1}$ h^{-1} for an 8-hour run.

Table 1. Hydrogenation of DMIT with various bisphosphine ligands combined with the CATAXA® immobilised catalyst system.[a]

Entry	Ligand	Temp. [°C]	Pressure [MPa]	Conv.[b] [%]	*ee* [%][c]
1	Skewphos	40–80	10	10–66	5–63
2	Skewphos	30–70	17	20–65	9–68[e]
3	Prophos	40–70	10	30–34	0–1
4	Prophos	50–70	20	14–37	0–1
5	DIOP	35–55	10	42–61	10–18
6	DIOP	35–55	16	45–67	10–12
7	BINAP	30–50	10	5–19	0–11
8	BINAP	30–50	20	20–26	9
9	COD[d]	40	10	58	0

[a] *Reaction conditions:* CO_2 flow rate 0.5 mL min^{-1} (liquefied at −10 °C), substrate flow rate 0.15 mL min^{-1} (2.5 M solution in 2-propanol), H_2:substrate ratio 2.5:1, dosed with a 5 MPa overpressure.

[b] Low temperatures correspond to low conversions, with increasing reactor temperature the conversions increased accordingly. Reactants and products were quantified using a Shimadzu GC-2010 GLC equipped with a β-DEX 110 chiral column supplied by Supelco®.

[c] The % enantiomeric excess (*ee*) was calculated from GC peak areas = 100 × [Area(A) − Area (B)]/[Area(A) + Area(B)].

[d] The unmodified CATAXA® (Entry 9) is included as a control reaction.

[e] Maximum *ee* was observed at 30 °C with a corresponding conversion of 20%.

A number of points are clear from Table 1. (i) Skewphos (Entries 1 and 2) gives the best *ee* values yet with conversions that can be as high as that of the unmodified CATAXA® (Entry 9). (ii) The system pressure does not have a significant effect on either *ee* or conversion (Entries 1 and 2); a similar lack of pressure effect has been reported[32] for the batch asymmetric hydrogenation of DMIT in $scCO_2$, presumably because under these conditions the system is not limited by mass transport of H_2. (iii) Skewphos (Entries 1 and 2) gave a maximum *ee*, 68% at 17 MPa, this is comparable to the *ee* (72%) reported by Leitner and co-workers in their batch hydrogenation with a fully homogeneous catalyst.[32] (iv) Prophos has a structure closely related to that of Skewphos so it is quite surprising that Prophos gave essentially racemic product (Entries 3 and 4); it is unlikely that the Prophos was leaching from the catalyst since it gave less conversion than the control experiment without phosphines (Entry 9). This was supported by ICP-MS data which indicated that at 60 °C very little Rh leaching occurs (i.e., [Rh] < 1 ppm) but that at 100 °C leaching became significant ([Rh] = 8.6 ppm). Although clearly less sensitive, ^{31}P NMR of selected samples collected at 60 °C showed no traces of phosphine present. (v) Neither DIOP nor BINAP were particularly successful ligands in terms of asymmetric hydrogenation (Entries 5–8), although DIOP gave much higher conversions than BINAP; this result is somewhat unexpected because both ligands perform successfully in conventional solvents.[29] Possibly, the difference in behaviour in $scCO_2$ may be due to the low dielectric constant of this solvent.[33] However, it is known that hydrogenation under these conditions in $scCO_2$ is usually a multi-phase process with both a liquid and gas phase.[7b] The bulk of the substrate is found in the condensed phase but the high CO_2 concentration in this phase could still lead to a reduction in the dielectric constant of this phase when compared to pure organic. Also it is possible that, in our experiments, DIOP and BINAP could have been oxidised by trace impurities (in this case < 0.01% wt) in the flowing $scCO_2$.

The second part of our investigation involved bisphosphine ligands, Figure 1, based on a highly stable ferrocenyl backbone, which have been highly successful in asymmetric hydrogenation in conventional solvents.[30] The results obtained using these ligands in $scCO_2$ are summarised in Table 2.

It can immediately be seen from Table 2 that the overall activity of these ligands was generally lower than those listed in Table 1. However, like those ligands there was a range of asymmetric induction. The ligands incorporating nitrogen moieties, BoPhoz, Taniaphos and Mandyphos all gave very low *ee*. It is not clear why, although CO_2 can react with primary amines to form carbamates and, if wet, could in principle form carbonates with any amine. BoPhoz is interesting, as it is essentially inactive until temperatures of *ca.* 100 °C and then the product formed is racemic (Entry 2). The lack of enantioselectivity is probably to be expected because of the high temperature; indeed, it is possible that the ligand decomplexes. The inactivity of BoPhoz is surprising since there are only

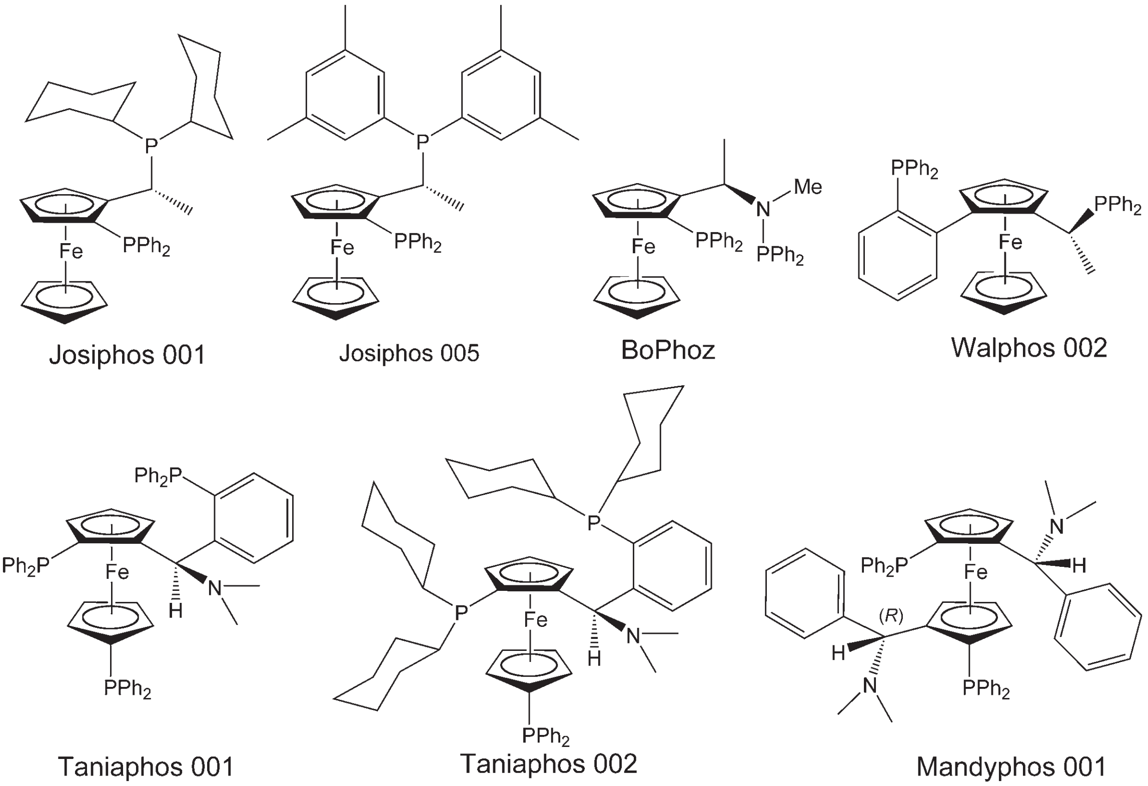


Figure 1. Structures of the ferrocenyl-based ligands used in Table 2.

Table 2. Results for the continuous hydrogenation of DMIT using ferrocenyl-type catalysts.[a]

Entry	Ligand	Temperature [°C]	Pressure [MPa]	Conversion [%][b]	*ee* [%]
1	BoPhoz	30–100	10	0–12	0
2	BoPhoz	30–100	20	0–15	0
3	Josiphos 005	35–55	10	6–12	5–37
4	Josiphos 005	35–55	17	1–3	1–9
5	Walphos 002	35–55	10	46–59	43–57
6	Walphos 002	35–55	17	22–42	23–44
7	Mandyphos 001	35–55	10	12–14	1–2
8	Mandyphos 001	35–55	17	11–17	1–3
9	Taniaphos 001	35–55	10	14–56	6–10
10	Taniaphos 001	35–55	17	41–57	7–8
11	Taniaphos 002	35–55	10	20–55	9–15
12	Taniaphos 002	35–55	17	3–28	3–15
13	Josiphos 001	35–55	10	0–19	0–51
14	Josiphos 001	35–55	16	24–35	58–83[c]

[a] Using the same reaction conditions and analytical method as in Table 1.

[b] Low temperatures correspond to low conversions, with increasing reactor temperature the conversions increased accordingly.

[c] Maximum *ee* was observed at 35 °C with a corresponding conversion of 24 %.

relatively small structural differences between BoPhoz and Josiphos, and both ligands give good *ee* in the asymmetric hydrogenation of DMIT in conventional solvents such as ethanol.[31] It is therefore quite possible that the polarity of the solvent has an effect on the *ee* produced in the reactions.

Throughout this investigation it was hoped that ligands with a stronger chiral motif would exert a greater effect on the metal centre. This effect was expected to reduce conversion but lead to an increase in *ee*. However, this is not necessarily the case; e.g., Mandyphos 001 (Entries 7/8) gives low conversion *combined with* low *ee*. The best results were obtained with Walphos 002 (Entries 5/6) and Josiphos 001 (Entries 13/14). There was some effect of pressure; for Walphos 002, higher pressures appear to give slightly higher *ee* but the effect may not be significant. The most important observation is that Josiphos gave an *ee* of 83% at 55 °C (Entry 14). This is a higher *ee* than reported[32] for the fully homogeneous hydrogenation of DMIT in $scCO_2$, albeit with a different chiral bisphosphine.

Conclusions

This study has highlighted the fact that immobilising an asymmetric catalyst and retaining high enantioselectivity is by no means a trivial task, especially when the catalyst is to be used in a solvent as unusual as $scCO_2$. Combining this with the elevated temperatures typically employed in a continuous flow $scCO_2$ reactor these problems are compounded. We have shown that the CATAXA® approach can be used with a wide range of different chiral bisphosphine ligands and is therefore a powerful tool for immobilised asymmetric catalysis.

From the results presented in this paper, it can be seen that the delicate balancing act of catalytic activity and enantioselectivity is further strained by being placed in a continuous flow $scCO_2$ solvent. Although the majority of ligands were unsuccessful, Josiphos 001 has produced an *ee* of 83% at 55 °C. This clearly demonstrates that a good *ee* is achievable in a continuous flow $scCO_2$ hydrogenation reactor. With further optimisation, this value can most probably be increased.

Experimental Section

Safety note: All supercritical experiments involve the use of relatively high pressures and require equipment with the appropriate pressure rating. It is the responsibility of individual researchers to verify that their particular apparatus meets the necessary safety requirements. The individual components that we describe work well, but they are not necessarily the only equipment of this type available nor the most suitable for the purpose.

Continuous Flow Hydrogenation Apparatus

The apparatus for small-scale continuous flow reactions has been described previously.[26] The system is essentially modular, made from commercially available components. A schematic diagram of the reactor and its components can be seen in Figure 2.

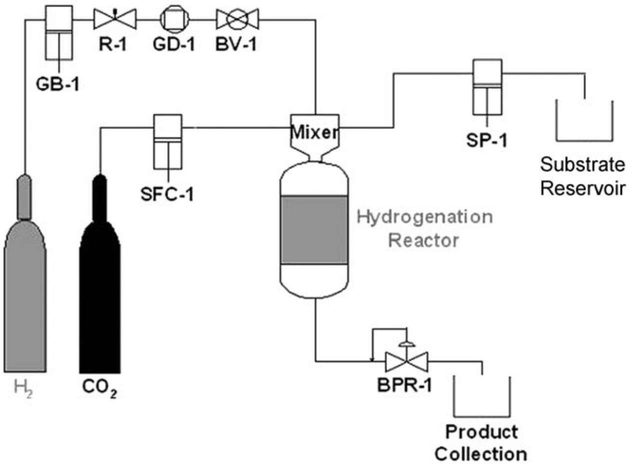


Figure 2. Schematic of the reactor and components; hydrogen gas is pressurised to a constant pressure using a gas booster, GB-1 [NWA GmbH, CU-105], and regulator, R-1, before being dosed into the reactor by a gas dosage unit, GD-1 [Rheodyne 7000 L]; the supply is isolable using the ball valve (BV-1). The CO_2 is pressurised and delivered by SCF-1 [Jasco PU-1580-CO2]. The organic substrate is delivered via a standard HPLC pump, SP-1 [Jasco PU-980], all components are connected by 1/16 inch 316 stainless steel tubing. The tubular reactor holds approximately 0.1 g of catalyst.

Catalyst Preparation

All the catalyst preparations were performed under an inert atmosphere using appropriate Schlenk techniques.[27] $[Rh(COD)_2]^+[BF_4]^-$/PTA/alumina (0.25 g, 8.75×10^{-3} mmol Rh; supplied until recently by Johnson Matthey under the trade name, CATAXA®) and 13×10^{-2} mmol of ligand (supplied by Johnson Matthey or Solvias AG) were added to 30 mL of ethanol and the solution was left to stir overnight. The ethanol was removed and the catalyst washed with 3 × 15 mL of ethanol. The wash solution was removed by cannula and the remaining solid was dried under vacuum to yield a free flowing powder, usually with a pale yellow colouration.

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