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Asymmetric Catalytic Synthesis of Organic Compounds using Metal Complexes in Supercritical Fluids

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Abstract: The applications of metal-based catalysts for the asymmetric synthesis of organic compounds in supercritical fluids are reviewed. Much of the work discussed concerns hydrogenation and hydroformylation of alkenes, but dihydoxylation and cyclopropanation reactions of alkenes are discussed as are asymmetric Diels–Alder reactions and aldol condensations. Supercritical fluids remove the need for harmful volatile organic solvents, but their use in separating the products from the catalyst by pressure swings or multiphasic systems is also described.

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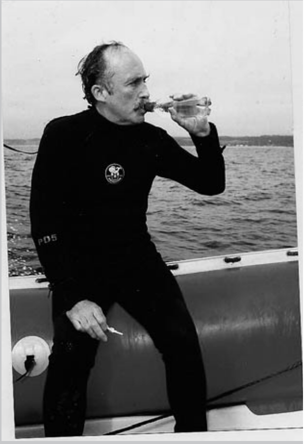
Keywords: asymmetric catalysis; catalyst separation; flow systems; supercritical fluids

1 Introduction

Many pharmaceutical, agricultural or fragrance products are chiral; that is they exist as only one of two isomers (enantiomers) which are identical apart from being non-superimposable mirror images of one another. Traditionally, chiral compounds are extracted from natural sources or are synthesised as racemic mixtures (mixtures of both mirror images) and separated by complex processes. Sometimes they are applied as racemic mixtures, with the disadvantage that twice as much material must be used than is necessary. In some cases, the isomer that is not active for the desired effect can be extremely detrimental, as in the case of thalidomide where one isomer was excellent for treating morning sickness, whilst the other caused foetal deformities. Environmental, legislative and economic considerations mean that it is desirable or obligatory to use only the isomer which has the beneficial effect, so there is considerable interest in synthesising single enantiomers of chiral compounds. One way of doing this is to use asymmetric catalysis, in which a chiral catalyst is used selectively to transfer its chirality during a catalytic reaction so that only the desired enantiomer of a chiral product is formed. The first chiral catalytic reactions giving high enantiomeric excess were described by Knowles for the enantioselective hydrogenation of α-amidocinammic acids as part of a route to the anti-Parkinson's disease drug, L-DOPA (L-dihydroxyphenylalanine).[1] Knowles was awarded the Nobel Prize for this work, along with other pioneers of asymmetric catalysis, Sharpless and Noyori, in 2001.

The catalysts used for asymmetric catalysis are almost exclusively soluble metal complexes, so they suffer from the same problems as most homogeneous catalytic reactions in that they are usually carried out in volatile organic compounds (VOCs), emissions of which are environmentally damaging and there is a severe problem with the separation of the product from the catalyst.[2–6] In many cases, the catalyst must be destroyed in order to separate it from the product, causing loss of the metal centre and chiral ligand with the consequent economic disadvantages. In addition, it can be very hard to remove the last residues of the catalyst from the product, which is a major problem for pharmaceutical applications because the heavy metal-containing catalysts can be highly toxic. There is, therefore, considerable interest in developing new processes for carrying out the separation, recovery and recycling of homogeneous catalysts, with many new protocols being developed over the last few years.[3,4] In this review, we consider the use of supercritical fluids as benign alternatives to VOCs as solvents for asymmetric catalytic reactions using metal complexes and as the basis of methodologies for the



David Cole-Hamilton has been Irvine Professor of Chemistry at the University of St. Andrews in Scotland since 1985. His main current research interests are in the use of highly electron-rich metal complexes in catalysis, in new methodologies for the separation of the products of homogeneous catalytic reactions from the starting materials and any solvent and in the synthesis and study of semiconductor nanoparticles.

separation of catalyst and product in such a way that the catalyst can be reused or can be used under continuous flow operation. In both cases the total number of turnovers the catalyst makes before it must be replaced is greatly increased.

When a liquid is heated its density falls. When a gas is compressed, its density rises. At the critical point, the densities of the liquid and of the gas are the same, the interface disappears and a supercritical fluid is formed. Supercritical fluids cannot be liquefied by compression and have both liquid-like (they can dissolve many organic compounds) and gas like (they fill all the space available to them, do not fall under gravity and flow like gases) properties. These properties have attracted the attention of a large number of chemists, including those involved in homogeneous catalysis.[7–9] The most striking example of a commercial use of a supercritical fluid is in the decaffeination of coffee, in which caffeine is extracted from coffee beans using supercritical carbon dioxide (critical point: 73.8 bar, 31.1 °C). This process is carried out in extractors of up to 20 m in length and 2 m in diameter.

Initial studies on the use of supercritical fluids for asymmetric, as well as other, catalytic reactions centred around rendering the catalyst soluble in $scCO_2$, since most usual homogeneous catalysts are not. This allowed the removal of the VOCs, but did not greatly assist the catalyst/product separation because both were usually soluble in the $scCO_2$. Pressure and temperature swings (the CESS process)[10] were successfully used for selective precipitation of first the catalyst and then the product, but more recently this problem has been addressed by using the $scCO_2$ as a continuously flowing medium to transport the substrates to and remove the products from the catalyst immobilised either on a solid support[11,12] or in an ionic liquid.[13–16] Immobilisation by dissolving the catalyst in liquid polymers[17] or in the reaction product[18] has also been demonstrated, but not in asymmetric catalysis.

We now discuss the progress made in the use of supercritical fluids in asymmetric catalysis, dividing the review by reaction type. In principle, tacticity control in polymerisation reactions is also an asymmetric reaction, but those kinds of reaction are beyond the scope of this review.

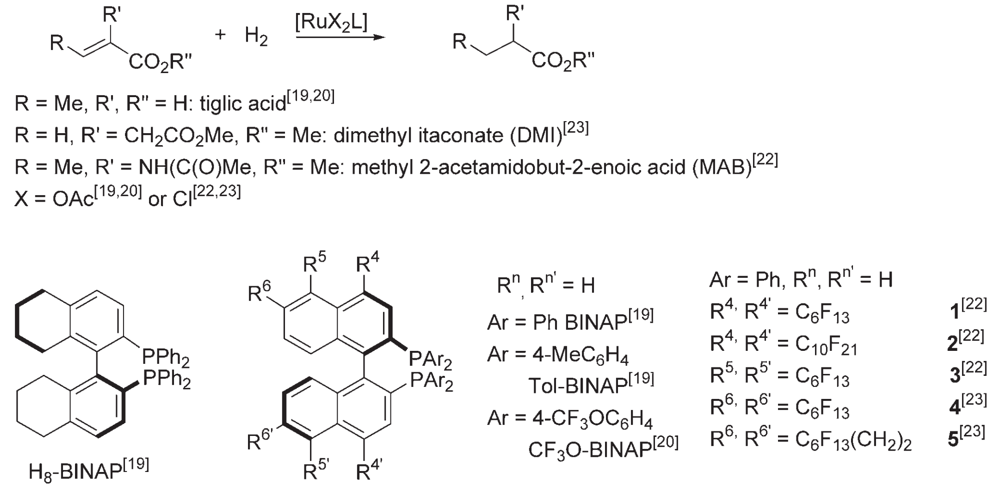
2 Catalytic Reactions in Supercritical Fluids

2.1 Asymmetric Hydrogenation in Supercritical Fluids

In the hydrogenation of tiglic acid (*E*-2-methybut-2-enoic acid) using catalysts based on ruthenium complexes of the well known chiral ligand 2,2′-bis-diphenylphosphino-1,1′-binaphthyl (BINAP, Scheme 1), enantiomeric excesses (*ee*s) were similar in $scCO_2$ to those obtained in methanol or hexane (*ca.* 80 %), but reduced slightly at lower pressure, whereas in conventional solvents they increase to *ca.* 95 % at 5 bar.[19] The conversion and enantioselectivity decreased in the order H_8BINAP > Tol-BINAP > BINAP because of the relative solubilities of the ligands in $scCO_2$. However, none of the ruthenium complexes was sufficiently soluble for solubility measurements to be made. Addition of fluorinated alcohols, which are known to increase the solubility of aromatic compounds in $scCO_2$ by forming micelles, increased the conversion and *ee* (to 89 %) when using H_8-BINAP at low H_2 pressure (see Table 1).

Attempts to improve the reaction further involved the used of fluorinated substituents on the BINAP ligand. Using CF_3O-BINAP, which rendered the ruthenium complex soluble in dense CO_2, the enantioselectivity was disappointing at *ca.* 25–35 % (*cf.* 90 % in methanol alone) In $scCO_2$ containing methanol intermediate results were obtained (50–60 % *ee*, Table 1) with hydrogen partial pressures between 0.7 and 50 bar, with the rate being increased at 30 bar relative to 50 bar.[20]

Unsubstituted BINAP has also been used for the final step in the synthesis of the anti-inflammatory drug, naproxen, which requires the asymmetric hydrogenation of an α-naphthyl methylacrylate, in methanol expanded with dense CO_2.[21] (Scheme 2, Table 1) The reaction rate and enantioselectivity were again less for the system containing CO_2 and reduced further with increasing CO_2 partial pressure (and temperature). UV-VIS studies suggested that solvent clustering around the substrate molecules in the presence of CO_2, as indicated by a significant increase in the



Scheme 1. Asymmetric hydrogenation of acrylic acids and esters using ruthenium BINAP and related catalysts.

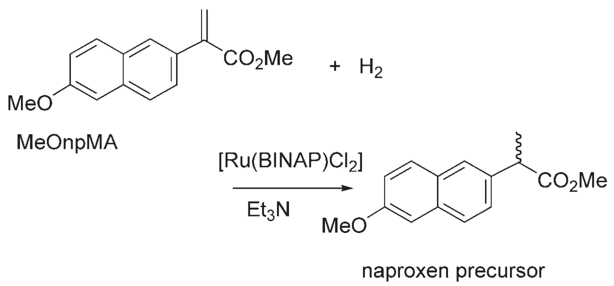
Table 1. Asymmetric hydrogenation using Ru BINAP and related complexes.[a],[19]

Substrate	Ligand	Solvent	$P(H_2)$ [bar]	Yield [%]	*ee* [%]	Ref.
tiglic acid	*(S)*-H_8-BINAP	$CO_{2\,(l)}$[b]	30	0		[19]
tiglic acid	*(S)*-H_8-BINAP	$scCO_2$	33	99	81	[19]
tiglic acid	*(S)*-H_8-BINAP	$scCO_2$	7	23	71	[19]
tiglic acid	*(S)*-H_8-BINAP	$scCO_2$[c]	5	99	89	[19]
tiglic acid	*(S)*-H_8-BINAP	methanol[d]	30	100	82	[19]
tiglic acid	*(S)*-H_8-BINAP	hexane	30	100	73	[19]
tiglic acid	*(R)*-BINAP	$scCO_2$	33	50	37	[19)
tiglic acid	*(R)*-Tol-BINAP	$scCO_2$	29	100	36	[19]
tiglic acid	CF_3O-BINAP	$scCO_2$	30		25	[20]
tiglic acid	CF_3O-BINAP	methanol	27.2		82	[20]
tiglic acid	CF_3O-BINAP	$scCO_2$/methanol	30		54	[20]
MAB	**1**	$scCO_2$	20	0	0	[22]
MAB	**1**	$scCO_2/(CF_3)_2OH$	20	100	63	[22]
MAB	**1**	$scCO_2/CF_3C_6H_5$	20	100	74	[22]
MAB	**2**	$scCO_2$	20	0	0	[22]
MAB	**3**	$scCO_2$	20	0	0	[22]
MAB	**3**	$scCO_2/(CF_3)_2OH$	20	100	64	[22]
MAB	**3**	$scCO_2/CF_3C_6H_5$	20	100	74	[22]
DMI	**4**	$scCO_2$	50	100	73	[23]
DMI	**4**	methanol[b]	50	75	95.3	[23]
DMI	**5**	$scCO_2$	50	100	74	[23]
DMI	**5**	methanol[b]	50	100	95.7	[23]
DMI	**5**	$scCO_2$/methanol	50	92	93.6	[23]
DMI	**5**	none	50	74	71.6	[23]
MeOnpMA	BINAP	methanol/CO_2	60		92	[21]
MeOnpMA	BINAP	methanol[c]	60		97	[21]
MeOnpMA	BINAP	methanol/CO_2[d]	60		84	[21]
MeOnpMA	BINAP	methanol[d]	60		93	[21]

[a] For conditions see original references.
[b] At 25 °C *cf.* 80 °C for reactions in $scCO_2$.
[c] At 5 °C.
[d] At 35 °C.

extinction coefficient, might be responsible for the lower reaction rates, although the presence of adventitious dissolved oxygen was seen as the most likely cause of the poor results.

Longer fluorous ponytails have also been added to BINAP in the 4,4′-,[22] 5,5′-,[22] or 6,6′-positions[23] of the binaphthyl ring, (Scheme 1) and the resulting ligands used in the enantioselective hydrogenation of

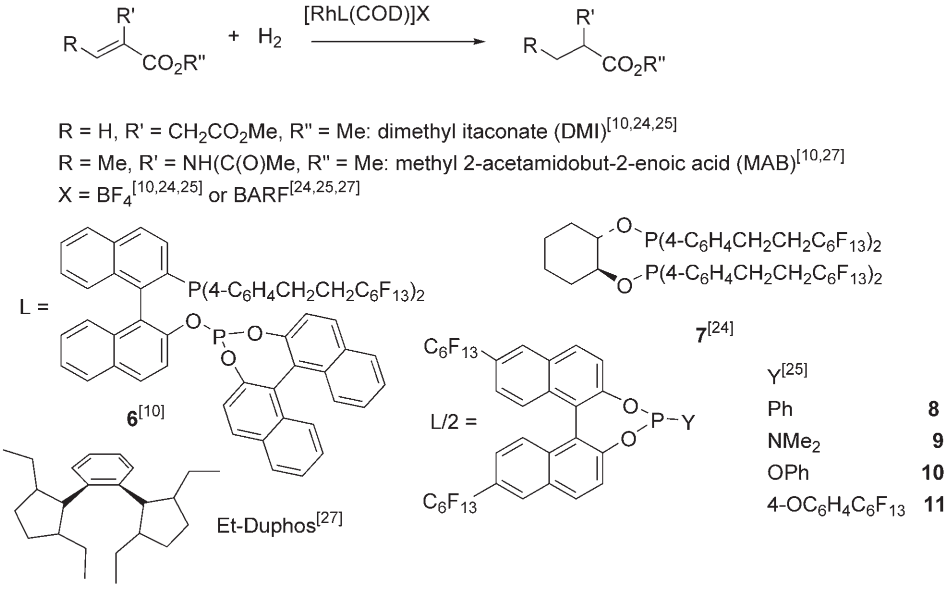


Scheme 2. Formation of naproxen by asymmetric hydrogenation.

dimethyl itaconate (6,6′) or methyl *(Z)*-2-acetylaminobut-2-enoate using chlororuthenium complexes (Table 1). A comparison of the 6,6′-substituted ligands with BINAP itself in methanol shows that the rate is reduced if the substituents are C_6F_{13}, but recovers if an ethanediyl spacer is used ($C_6F_{13}CH_2CH_2$-). The *ee* is constant at 95%. In $scCO_2$, the reactions are much slower (24 rather than 0.25 h for complete conversion) and the *ee*s are much lower (*ca.* 75%) than in methanol, although they can be restored by the addition of methanol with an intermediate reaction time of 2 h (Table 1).[23] The hydrocarbon spacer makes little difference to the results. The poorer results in $scCO_2$ are attributed to the polarity of the reaction medium as well as the lower concentration of catalyst and substrate. A reaction carried out in the neat substrate had a high rate (74% conversion in 1 h) but low *ee* (72%), confirming the adverse effect of the low polarity medium on the *ee*. The reactions in $scCO_2$ were only homogeneous above 200 bar (50 bar H_2, 150 bar CO_2), when using high catalyst (0.11 mmol dm^{-3}) and substrate (0.11 mol dm^{-3}) loadings, but when the loadings were reduced ([catalyst] = 0.011 mmol dm^{-3}, [substrate] = 0.022 mol dm^{-3}) to ensure homogeneity, the *ee* was even lower (56%).

C_6F_{13} substiuents in the 4,4′- or 5,5′-positions of BINAP (Scheme 1, Table 1) did not confer sufficient solubility in $scCO_2$ (100 bar) containing H_2 (20 bar) for ruthenium-catalysed hydrogenation of methyl *(Z)*-2-acetylaminobut-2-enoate (MAB) to occur at 50 °C.[22] Addition of 1,1,1,3,3,3-hexafluoro-2-propanol or trifluoromethylbenzene did allow high conversions, but the *ee*s were only 50–70%. This contrasts with using the same catalysts for the hydrogenation of ethyl acetoacetate in methanol or ethanol, where the *ee*s were uniformly 96–99%, perhaps again highlighting the importance of polar media in these reactions.

Fluorous ponytails [$C_6F_{13}(CH_2)_2$-] have also been added to the arylphosphine groups of BINAPHOS,[10] a ligand that has found extensive use in asymmetric hydroformylation reactions, although it had not previously been found to be effective for asymmetric hydrogenation. During studies of asymmetric hydroformylation reactions (see below), it was found that the fluorinated ligand (**6**, Scheme 3) could promote the asymmetric hydrogenation of methyl acrylate substituted in the 2-position by −NHC(Me)O or $-CH_2CO_2Me$ (dimethyl itaconate, Scheme 3).[10] Using cationic rhodium-based complexes derived from $[Rh(cod)_2]BF_4$ (cod = 1,5-cyclooctadiene), full conversion and high *ee*s (97%) were obtained for both substrates in 16 h. For dimethyl itaconate the reaction was homogeneous, whilst for the dehydroamino acid, it was biphasic throughout. Using a diaryl diphosphinite derived from 1,2-cyclohexanediol (aryl = 4-$C_6F_{13}CH_2CH_2C_6H_4$), **7** (Scheme 3) and $[Rh(cod)_2]X$ {X = BF_4 or BARF = $[3,5\text{-}(CF_3)_2C_6H_3]_4B$}, complete



Scheme 3. Asymmetric hydrogenation catalysed by cationic rhodium complexes of fluorous derivatised ligands.

hydrogenation of dimethyl itaconate was obtained after 20 h at 40 °C and 200–240 bar (20–35 bar H_2), but the *ee* was much higher when using BARF (72 %), than when using BF_4 (13 %).[24] The difference was attributed to the lower solubility of the BF_4 complex because the *ee* increased to 73 % when the $C_6F_6CH_2CH_2OH$ was added to the reaction using BF_4 as anion. Using BARF as the anion, the *ee* was found to be high (65–72 %) in non-polar solvents such as $scCO_2$, sc-ethane or hexane, but low in methanol or THF. The reaction rates were high in liquid solvents, but an order of magnitude lower in supercritical solvents, perhaps because the concentrations of the catalyst and substrates were much reduced. Even so, turnover frequencies of 6,000 h^{-1} were obtained in $scCO_2$. The *ee* was insensitive to the partial pressure of hydrogen for reactions in $scCO_2$, but increased from $<10\,\%$ to $>70\,\%$ on increasing $P(H_2)$ from 10 to 20 bar for reactions in hexane. This presumably reflects the absence of mass transfer effects in the monophasic supercritical solution. Para-hydrogen-induced polarisation NMR and deuterium labelling studies showed that the reaction pathway in $scCO_2$ containing trifluoromethylbenzene to enhance the solubility of the catalyst is similar to that in hexane. The only significant difference is that the H migration is rapidly reversible, leading to increased H/D scrambling into the methyl group, for the reactions in hexane. No evidence was found for reactions of the hydridorhodium intermediates with CO_2 to form metal-bound formates.[24]

Dimethyl itaconate has also been hydrogenated using monodentate phosphites containing bidentate naphthadiolate substituted by 6,6′-C_6F_{13} chains and the same rhodium precursor (Scheme 3, Table 2).[25] The third substituent on the phosphite has a marked effect on the *ee* of reactions carried out in CH_2Cl_2, with $-NMe_2$ giving the best results ($>99\,\%$ *ee*).The results in $scCO_2$ are much less impressive with the highest *ee* (65 % at 28 % conversion) being obtained using a ligand with 4-$C_6F_{13}C_6H_4O$- and added NaBARF, which is known to increase the solubility of ionic compounds of this kind in $scCO_2$. The poor results are partially attributable to poor solubility of the catalysts in $scCO_2$, but also to the low polarity of the medium. However, this last conclusion is not supported by the observation that the ligand containing $-NMe_2$ gives 92 % *ee* when the reaction is carried out in hexane.[25]

Table 2. Asymmetric hydrogenation of dimethyl itaconate in $scCO_2$ catalysed by $[Rh(cod)L_2]BF_4$.[a],[25]

Ligand, L	Additive	Conversion [%]	ee [%]
8		9	8
9		11	10
9	NaBARF	85	15
9	NaBARF/$C_6F_{13}(CH_2)_2OH$	67	1
10		8	7
11		21	34
11	NaBARF	28	65

[a] Conditions as in ref.[25]

Similar reactions were carried out in monophasic sc-1,1,1,2-tetrafluoroethane using $[Rh((R)\text{-}monophos)_2(cod)]BF_4$ Quantitative conversion was obtained above a threshold pressure (see Table 3), and, in contrast to the results obtained in $scCO_2$, *ee*s were generally high (*ca.* 90 %), as in conventional solvents, and independent of variables such as the nature of R and R' (Scheme 3), $P(H_2)$ and the total pressure.[26]

Table 3. Asymmetric hydrogenation using $\{Rh[(R)\text{-}monophos]_2(cod)\}BF_4$[a] in sc-1,1,1,2-tetrafluoroethane.[26]

Substrate	Threshold pressure [bar][b]	*ee* at threshold pressure [%]
itaconic acid	30	91
DMI	100	87
α-acetamidocinnamic acid	130	88

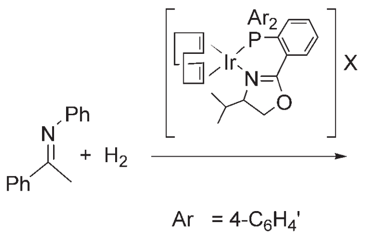
[a] The original paper[26] refers to the ligand as monophos, (structure as for **8–11**, Scheme 3), but the nature of Y does not appear to have been defined.

[b] Pressure at which conversion is > 90 %

As indicated by the reactions with H_8-BINAP, fluorous ponytails are not essential for conferring solubility in $scCO_2$, especially if rhodium complexes with BARF anions are used. The first reported asymmetric hydrogenation reactions in a supercritical fluid involved catalysts based on [Rh(cod)(Et-Duphos)]X [X = BARF or CF_3SO_3, Et-Duphos = bis-(*2R,3R*)-2,5-diethylphospholanebenzene, Scheme 3], which are sufficiently soluble in $scCO_2$ (for BARF, 0.03 mmol dm^{-3} at 40 °C and 330 bar).[27] These complexes have been used very successfully for the asymmetric hydrogenation of α-amidoacrylic acids (*ee* typically 99 %) even when the β-C atom is disubstituted (*ee* 85–97 %). These results are comparable to or better than those obtained in conventional solvents, suggesting that the low polarity of $scCO_2$ is not always detrimental to catalytic hydrogenation reactions.

All of the reactions described so far have been aimed at obtaining homogeneous catalysis by rendering the catalyst and substrate soluble in the supercritical phase. Although this overcomes problems associated with VOCs, it does not address the more serious problem of product/catalyst separation.

In one case, changes in the nature of the iridium based catalyst (Scheme 4) during the enantioselective



R	X	Conversion [%]	*ee* [%]
H	PF_6	99.9	37
$C_6F_{13}(CH_2)_2$	PF_6	100	26
H	BPh_4	11	26
$C_6F_{13}(CH_2)_2$	BPh_4	99.8	68
H	BARF	100	81
$C_6F_{13}(CH_2)_2$	BARF	100	80

Scheme 4. Asymmetric hydrogenation of imines.[28]

hydrogenation of prochiral imines led to precipitation of the catalyst once all the substrate had been consumed.[28] This allowed the reaction to be carried out and the product separated from the catalyst. Once complete conversion had occurred, the reactor was flushed with $scCO_2$ (110 bar, 40 °C, the same conditions as used for the reaction) for 1 h to extract the product quantitatively whilst leaving the catalyst within the reactor (< 5 ppm of iridium in the recovered product). Addition of fresh substrate, H_2 and CO_2 allowed the reaction to be repeated 4 times with no loss in activity or selectivity. Further repetitions required longer reaction times for complete conversion, possibly because of catalyst oxidation by O_2 introduced accidentally during the recharging process, but the *ee* remained > 70 %. Overall, the catalyst produced 10,000 turnovers with an average *ee* of 76 %. The nature of the counteranion plays a crucial role in determining the enantioselectivity of the reaction, with BARF providing the highest *ee* (80 %, Scheme 4), comparable to those obtained for all anions in CH_2Cl_2 (70–87 %).[28] Further improvements were obtained by carrying out the hydrogenation of prochiral imines in an ionic liquid-$scCO_2$ biphasic system.[29] In this case, the catalyst was designed to be soluble in the IL and insoluble in $scCO_2$. Once again the anion, this time of the ionic liquid, since it also acts as the counterion for the iridium-based catalyst formed *in situ* from $[Ir(cod)Cl]_2$ and the ligand, has a marked effect on the success (especially enantioselectivity) of the reaction, with BARF (*ee* 78 %) again being the best. The presence of $scCO_2$ considerably enhanced the reaction rate relative to that obtained in the ionic liquid, for example, 1-ethyl-3-methylimidazolium triflamide, alone; possibly because the solubility of hydrogen in the ionic liquid was increased, as determined by ^1H NMR studies, and because $scCO_2$, which is highly soluble in ionic liquids, reduces the viscosity. Using the repetitive batch process in which the product of a reaction in $[BMIM]PF_6$ (BMIM = 1-butyl-3-methylimidazolium) was removed with $scCO_2$ at the same pressure and temperature as used in the reaction and the reactor charged with fresh substrate and hydrogen, the reaction was repeated 7 times without loss of activity (> 90 % conversion in 3 h) or selectivity (*ee* 62 % throughout) because the catalyst is markedly less air-sensitive in ionic liquids than in $scCO_2$ alone. Depressurisation of the $scCO_2$ allowed the quantitative collection of the white crystalline amine product in analytically pure form (< 1 ppm iridium, no IL detected by NMR). Total catalyst turnovers exceeded 3000.[29] Continuous flow operation for this system would be feasible and should give more efficient use of CO_2.

The very first reaction to be described using ionic liquids and supercritical fluids involved the asymmetric hydrogenation of tiglic acid in $[BMIM]PF_6$ containing water catalysed by a ruthenium Tol BINAP complex (Scheme 1), which proceeded to essentially full conversion (98 %) with high *ee* (85 %).[30] The product was then extracted using $scCO_2$ before depressurising, recharging with substrate and H_2 and repeating the reaction. This repetitive batch reaction was repeated 3 more times. In the second and subsequent runs, the conversion remained high (97–98 %) and the *ee* (87–91 %) was somewhat enhanced compared with the first run

An alternative to immobilising the catalyst within an ionic liquid for a continuous flow process using $scCO_2$ as the mobile phase, which does not appear to have been demonstrated for asymmetric hydrogenation, is to support the catalyst on a solid support.

Using $[Rh(norbornadiene)(skewphos)]BF_4$ [skewphos = *(S,S)*-2,4-bis(diphenylphosphino)pentane] on an alumina support with a phosphotungstic acid ($[H_3O]_{40}PW_{12}$) linker,[31] the hydrogenation of dimethyl itaconate has been demonstrated with the transport of substrates and products being effected by flowing $scCO_2$ (60–120 bar). The best results were obtained at 60 °C (conversion = 66.5 %, *ee* = 63 %) and continued unchanged for at least 8 h. Neither rhodium nor tungsten (< 1 ppm) was detected in the product recovered by decompression of the $scCO_2$, although catalyst leaching (Rh 7 ppm, W 1 ppm) did occur at higher temperatures (100 °C).[31]

More conventional heterogeneous catalysts (cinchonidine-modified Pt on alumina) have been employed for the continuous hydrogenation of ethyl pyruvate using "supercritical" ethane (T_c: 32 °C, P_c: 48 bar) as the transport vector.[32] In fact, the system exhibited regions in which it was monophasic and regions where it was biphasic (a liquid phase was present) even well above the critical parameters of pure ethane. At low $P(H_2)$ there was a significant rate enhancement on passing from the biphasic to the monophasic region, as a result of improved mass transport of hydrogen to the catalyst surface, whilst at high $P(H_2)$ there was no discontinuity, just a gradual increase in rate with ethane pressure, attributable to an increased rate of reaction in the supercritical phase. The *ee* was generally between 60 and 70%, varying slightly with the temperature, $P(H_2)$ and total pressure, possibly because higher *ee*s are favoured in the ethane-rich phase.[32] The good enantioselectivities observed in this system have been attributed to a hydrogen bonded interaction between the N–H of the adsorbed cinchonidine and the two carbonyl groups of the ethyl pyruvate on the basis of reflection absorption infrared spectroscopic studies (Figure 1).[33]

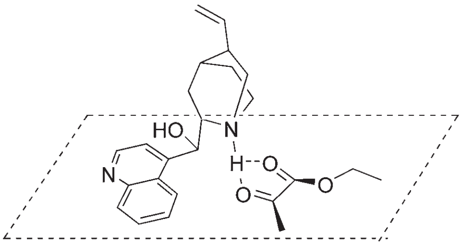
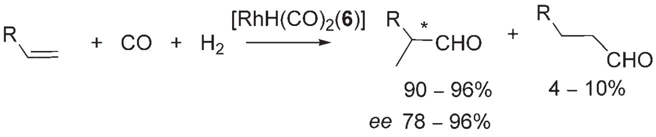


Figure 1. Surface-bound, hydrogen-bonded adduct responsible for asymmetric induction in the heterogeneous hydrogenation of ethyl pyruvate in sc-ethane catalysed by cinchonidine-modified Pt/Al_2O_3.[33]

2.2 Asymmetric Hydroformylation in Supercritical Fluids

The hydroformylation of alkenes to give aldehydes is one of the highest volume homogeneous catalytic processes to be carried out commercially.[6,34] The commercial processes target linear aldehydes, which are not chiral. There is considerable interest, however, in the hydroformylation of substrates such as styrene and related vinylaromatic compounds or of vinyl esters such as vinyl acetate. For these substrates, electronic and anchimeric effects generally provide good selectivity to the branched aldehyde and there is considerable scope for asymmetric catalysis. The products from styrene and related substrates are of interest as precursors to anti-inflammatory drugs such as naproxen or ibruprofen, whilst the asymmetric hydroformylation of vinyl acetate provides a potential route to lactic acid esters or chiral 1,2-propanediol.

One of the most successful ligands to be used for asymmetric hydroformylation is the bidentate phosphine-phoshite ligand BINAPHOS. In order to render it soluble in $scCO_2$, it has been modified by attaching fluorous ponytails (**6**, Scheme 3). With $C_6F_{13}C_2H_4$- groups on the phenyl rings of the phosphine moiety, the rhodium catalyst precursor, [RhH(CO)$_2$(**6**)] was sufficiently soluble in $scCO_2$ for ^{31}P NMR studies to reveal that it exists exclusively with the P atoms occupying one axial (phosphite P) and one equatorial site (phosphine P), like its unfluorinated analogue.[10] There is no interaction of the hydride with CO_2. Using a variety of vinylarene substrates, asymmetric hydroformylation (Scheme 5) was achieved in $scCO_2$ with high conversion (generally > 90%) and excellent *ee* (generally > 90%).[10,35] In addition, the regioselectivity towards the branched product (generally 93:7) was higher than for unsubstituted BINAPHOS in benzene. Since this increased regioselectivity was also observed when using BINAPHOS' in benzene, it was attributed to the ligand, in particular the weakly electron-donating ability of the $C_6F_{13}C_2H_4$- groups, rather than to the reaction medium. With vinyl acetate as substrate, the *ee* (95%) was higher in $scCO_2$ than in benzene (90%), whilst, both allyl acetate and indene only gave good *ee*s at low temperature where the reaction rate was low.[10]



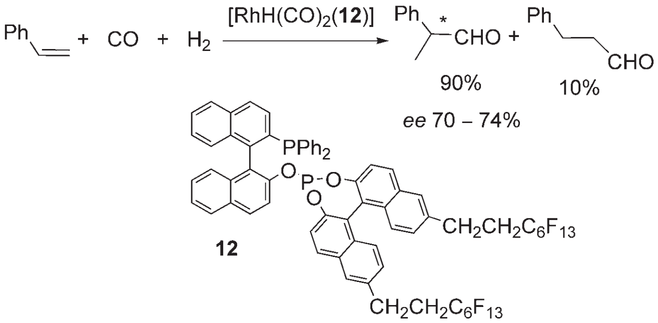
R = Ph, 4-ClC$_6$H$_4$, 4-(Me$_2$)CHCH$_2$C$_6$H$_4$, 2-naphthyl,OC(O)Me, CH$_2$OC(O)Me,

Scheme 5. Asymmetric hydroformylation of a variety of substrates in $scCO_2$ catalysed by rhodium complexes of fluorinated BINAPHOS, **6**, see Scheme 3.[10]

On cooling a reaction mixture after the asymmetric hydroformylation of styrene to room temperature and releasing some CO_2, a liquid phase and a gaseous phase formed. The catalyst was predominantly in the liquid phase, whilst the product was distributed between the two phase. By passing CO_2 into the bottom of the reactor and releasing it from the top, keeping the temperature and pressure constant, it was possible to remove the product leaving the catalyst in the reactor. After addition of further substrate, CO, H_2 and CO_2 the reaction could be repeated. This combination of catalysis and extraction using supercritical solutions (CESS), was repeated 8 times with the conversion and regioselectivity remaining constant and high. The *ee* dropped from 90.4% in the second run to 70.2% in the 7th, partly as a result of product racemisation over the longer reaction times. The *ee* could be restored to 88.2% by the addition of one equivalent of ligand. 12,000 catalyst turnovers had been achieved by the end of the reaction. Rhodium leaching of 1–2 ppm was observed in all runs.[10] A more detailed description of the use of the CESS process for this reaction has appeared.[7]

Interestingly BINAPHOS, itself, also gave good results for the asymmetric hydroformylation of styrene at low CO_2 pressures, where the reaction occurred in liquid styrene or product, but the *ee* dropped markedly at pressures above the critical pressure of CO_2.[36,37] It is possible that the *in situ* formation of the catalyst does not occur at these higher pressures because the ligand is insoluble in $scCO_2$ but the unmodified rhodium is soluble. This would explain the high conversions but poorer regio- and stereoselectivities observed at these higher pressures, since they are very similar to those obtained when using $[Rh(acac)(CO)_2]$ (acacH = 2,4-pentanedione), the rhodium-containing catalyst precursor alone under similar conditions.[36]

BINAPHOS has also been modified by the addition of fluorous tails (with hydrocarbon spacers) to the binaphthyl moieties (Scheme 6).[38] These complexes are also soluble in $scCO_2$, but they gave poorer *ee*s than those described above for styrene hydroformylation and than were obtained using the same ligand in benzene. The poorer performance has been attributed to racemisation of the product aldehyde under the reaction conditions.[38]



12

Scheme 6. Asymmetric hydroformylation of styrene in $scCO_2$ catalysed by rhodium complexes of BINAPHOS fluorinated on the phosphite moiety, **12**.[38]

BINAPHOS has been supported on cross-linked polystyrene by copolymerisation of a vinyl-functionalised BINAPHOS with styrene and divinylbenzene, for the asymmetric hydroformylation of alkenes. Gaseous alkenes could be hydroformylated in a simple flow system, but less volatile substrates such as vinyl acetate and styrene were hydroformylated in flowing $scCO_2$.[39] After incubation of the catalyst under CO/H_2 in $scCO_2$, styrene was injected and allowed to react for 30 min. The products were then swept from the reactor using a higher pressure of CO_2 (120 bar). This process was repeated up to 7 times. Conversion, selectivities to the branched isomer (80 %) and *ee*s (80–85 %) were all reasonably constant, with the conversion being increased (90 %) at 120 bar total pressure compared with 80 bar (85 %), although they were slightly inferior to the results obtained using benzene as the solvent (99 % conversion, 89 % branched selectivity, 92 % *ee*). This is almost certainly related to the solvent polarity as the results in hexane are similar to those in $scCO_2$. The same $scCO_2$ flow system was used for the sequential asymmetric hydroformylation of a variety of substrates, with good results in most cases (see Table 4). Injecting styrene in runs 1, 5 and 8 showed that the catalyst was not deteriorating with continuous use.[39]

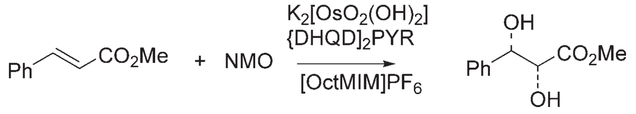
Table 4. Sequential hydroformylation of alkenes catalysed by supported Rh/BINAPHOS complexes carried out in pulsed flowing $scCO_2$.[39]

Run No	Substrate	Conversion [%]	Ratio b:l	*ee* [%]
1	styrene	49	82:18	77
2	vinyl acetate	3	70:30	74
3	1-octene	47	21:79	72
4	1-hexene	40	21:79	60
5	styrene	36	81:19	82
6	$C_6F_5CH{=}CH_2$	27	89:11	88
7	$C_6F_{13}CH{=}CH_2$	21	91:9	78
8	styrene	54	80:20	80

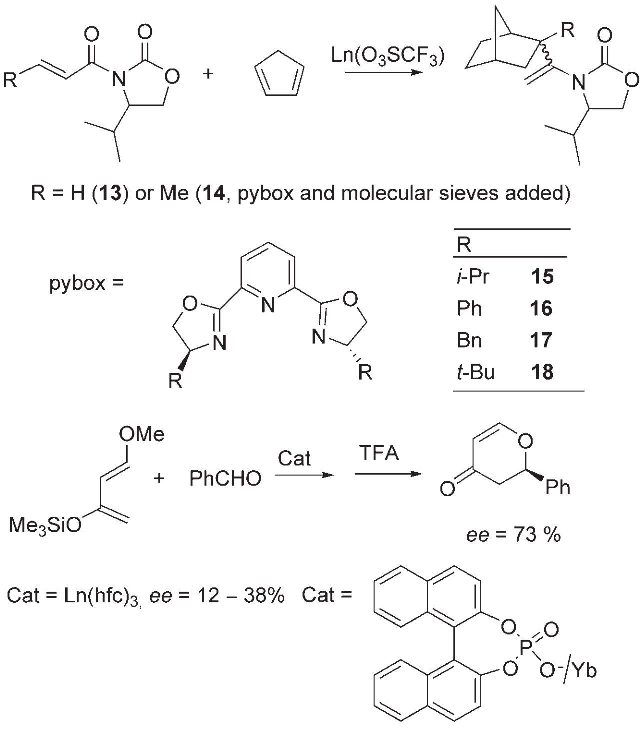
Density functional theory calculations have been used to predict that [Ru(cod)(Et-Duphos)]BARF should be suitable for the asymmetric hydroformylation of styrene, with high enantioselctivity being predicted if the rate-determining step is hydride migration, but low *ee* would be expected if the rate-determining step is before hydride migration (alkene coordination or hydrogen activation).[40] Experimental results confirm that no enatioselectivity occurs under any of the reaction conditions studied.[41]

2.3 Other Asymmetric Catalytic Reactions in Supercritical Fluids

One of the most successful asymmetric catalytic reactions is the dihydroxylation of alkenes catalysed by osmium complexes of *Cinchona* alkaloids. This reaction has been performed on methyl *E*-cinnamic acid esters in ionic liquids, with the product recovery involving extraction with $scCO_2$.[42,43] [1-Octyl-3-methyl imadozlium]PF_6 ([octMIM]PF_6) or 1-butyl-2,3-dimethylIM]PF_6 were studied with catalysts prepared *in situ* from $K_2[OsO_2(OH)_4]$, $[DHQD]_2PYR$ and *N*-methylmorpholine oxide (NMO) as co-oxidant over 24 h (Scheme 7). Extraction with $scCO_2$ was carried out at 125 bar and 40 °C, with [octMIM]PF_6 giving the best results (88 % yield, < 0.05 % Os). The reaction and extraction were repeated 6 times, with addition of fresh substrate and oxidant each time. Yields were consistently in the range 85–91 % with *ee*s of 80–85 % after the first run (77 %). Osmium was not detectable in the product (< 0.03 %). These results are superior to those achieved by extraction of the product using



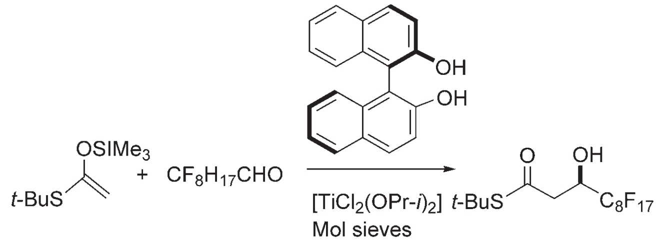
Scheme 7. Asymmetric dihydroxylation of methyl cinnamate catalysed by osmium complexes in an ionic liquid. The product was removed by extraction with $scCO_2$.[43]



Scheme 8. Asymmetric Diels–Alder reactions catalysed by lanthanide complexes in $scCO_2$. hfcH = $CF_3C(O)CH_2C(O)CF_3$.[44]

Table 5. Asymmetric Diels–Alder reactions catalysed by lanthanum complexes (Scheme 8).[44]

Substrate	$Ln(O_3SCF_3)$	Solvent	Conversion [%]	*endo/exo*	*de* (*endo*) [%]
13	La	$scCO_2$	84	70/30	59
13	La	CH_2Cl_2	92	74/26	38
13	La	hexane	34	80/20	46
13	La	toluene	48	83/17	40
13	La	$C_6F_5CF_3$	92	70/30	38
13	Yb	$scCO_2$	91	76/24	50
13	Sc	$scCO_2$	95	83/17	49
13	Eu(hfc)	$scCO_2$	60	92/8	69
14	Sc/**15**	$scCO_2$	71	93/7	88
14	Sc/**16**	$scCO_2$	75	95/5	41
14	Sc/**17**	$scCO_2$	33	88/12/	54
14	Sc/**18**	$scCO_2$	41	92/8	70
14	Y/**15**	$scCO_2$	21	89/11	25
14	La/**15**	$scCO_2$	trace	-	-
14	Sm/**15**	$scCO_2$	trace	-	-



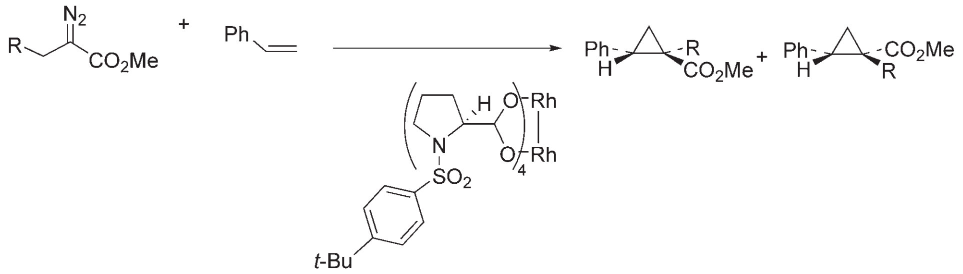
Scheme 9. Asymmetric Mukaiyama aldol reaction catalysed by a titanium complex in supercritical fluids.[45]

organic solvents, which invariably led to low extraction efficiencies, although osmium was not detected in the product.[43]

Diels–Alder reactions (Scheme 8, Table 5) have been catalysed by lanthanide metal complexes in $scCO_2$ using chiral or prochiral dienophiles.[44] Diasteromeric excesses (*de*s) when using the chiral dienophile were generally superior in $scCO_2$ (49–60%) than in organic solvents and were only little affected by the reaction pressure, except in liquid CO_2 at room temperature where they fell markedly. The *ee*s when using benzaldehyde as the dienophile were comparable or poorer in $scCO_2$ than in conventional solvents, although the reaction yield was generally enhanced.

A binaphthol-based titanium complex has been used for the asymmetric Mukaiyama aldol reaction in sc-CF_3Cl or $scCO_2$ (Scheme 9).[45] At low catalyst loadings, the reaction did not occur in conventional solvents (toluene or CH_2Cl_2), but proceeded smoothly in the supercritical solvents. Conversions were modest (20–46% in CF_3Cl, 8% in $scCO_2$), but enantioselectivites could be as high as 88% (72% in $scCO_2$). The results, obtained at 34 °C and 50–200 bar were comparable to the best obtained in conventional solvents with high catalyst loadings, although in these cases, the reactions had to be carried out at 0 °C to obtain the highest *ee*s (92%).

As in several other reactions, the ***ee*** for the product of the cyclopropanation of styrene catalysed by tetrakis{1-[(4-*t*-BuC_6H_4)sulphonyl]*(2S)*-pyrrolidinecarboxylate}rhodium(II) was found to depend on the dielectric constant of the reaction medium (Scheme 10).[46] In CF_3Cl, the *ee* fell significantly as the pressure was raised through the critical point, but levelled out thereafter. A plot of *ee* against dielectric constant is shown in Figure 2. As expected on the basis of their dielectric constants, the *ee* was higher for reactions in $scCO_2$ (> 80%) than in fluoroform (< 65%).



Scheme 10. Asymmetric cyclopropanation catalysed by a rhodium complex in $scCF_3Cl$ or $scCO_2$. R = Ph or CH=CHPh.[46]

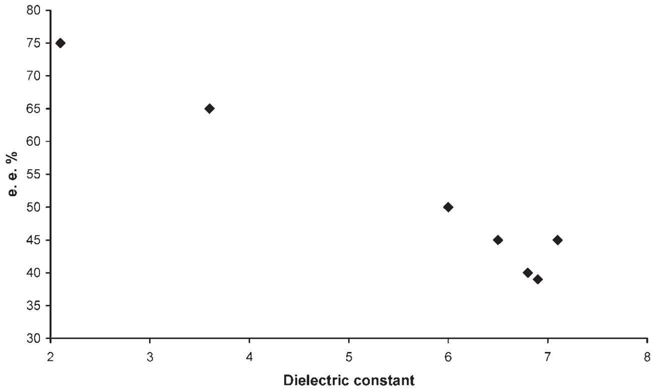


Figure 2. Dependence of *ee* of a cyclopropanation reaction on the dielectric constant of solvent $scCF_3Cl$, which was varied by varying the pressure.[46]

3 Conclusions

Fluorous functionalisation of ligands, known to be active for a variety of asymmetric catalytic reactions, has allowed the reactions to be carried out in a single supercritical phase, usually of CO_2. Excellent results can be obtained in terms of activity and selectivity, especially when conventional solvents suffer from problems associated with transport of hydrogen across the liquid-gas interface. In many cases, *ee*s are lower in $scCO_2$ than in polar organic solvents but in the cyclopropanation of styrene, the reverse is true. Catalyst/product separation has been demonstrated by using pressure and temperature swings (the CESS process), but more effective separation can be obtained by using catalysts immobilised either in an ionic liquid or on an insoluble support with the substrates and products being transported dissolved in the supercritical fluid. Although there is potential for these biphasic systems to be used in continuous flow processes, such processes remain unexplored for asymmetric catalytic reactions.

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