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Fluorous chiral ligands for novel catalytic systems

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Contents

Abstract

The relatively new fields of fluorous biphasic (FB) and supercritical catalysis, with their advantageous recycling properties, are quickly expanding to include examples of asymmetric catalysis. In order that catalysts are preferentially soluble in these media, various chiral ligands with perfluoroalkyl chains attached have been synthesised and studied. The use of these ligands, the effect of the perfluoroalkyl chains and reaction solvent on the activity and selectivity of the catalysts are herein discussed.

Keywords: Asymmetric catalysis; Biphasic catalysis; Perfluoroalkylation; Supercritical fluid

1. Introduction

The continuing drive toward 'Greener' chemistry has led to a growing interest in the use of catalytic processes to enhance the activity and selectivity of organic reactions and thus increase their efficiency. Particular attention has been paid to homogeneous catalysis due to the high selectivities achievable. In particular, catalytically active chiral enantiopure organometallic complexes can be used to accomplish asymmetric transformations with high enantioselectivities. The inherent problem with homogeneous catalysis is separating the catalyst, without decomposition, from the other reaction components once the process has gone to completion. This is important both for facilitating the purification of the products and for recycling of the catalyst. Indeed, contamination with transition metals (even in traces) is unacceptable for many compounds, e.g. pharmaceuticals, and homogeneous catalysts can be relatively difficult and expensive to make, as in the case of chiral complexes.

Abbreviations: BARF, tetrakis(3,5-bis(trifluoromethyl)phenyl)-borate; BINAP, 2,2′-bis(diphenylphosphino)-1-1′-binaphthyl; BINAPHOS, 2-(diphenylphosphino)-1,1′-binaphthalen-2′-yl-1,1′-binaphthalene-2,2′-diyl phosphite; BINOL, 1,1′-bi(2-naphthol); FB, fluorous biphasic; MOP, 2-(diphenylphosphino)-2′-alkoxy-1,1′-binaphthyl; $scCO_2$, supercritical carbon dioxide.

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This has led to the development of several techniques that facilitate the separation of catalyst and product, such as the immobilisation of catalytically active organometallic complexes onto organic or inorganic polymers by covalent or non-covalent interactions [1], or the synthesis of dendritic and micellar complexes which can be recovered by ultra- or nanofiltration due to their molecular size [2]. Besides these approaches, the use of novel reaction media (aqueous biphasic systems [3,4], ionic liquids [5,6], supercritical fluids [7,8] and fluorous systems [9–11]) in which homogeneous catalysts can effectively operate and then be easily recovered by simple phase separation is currently attracting considerable interest. Research in this last field is also stimulated by the unusual selectivities and increased activities which are sometimes observed for catalytic reactions. These improvements can be related to the peculiar solvation environment, but also to the molecular structure of the catalyst which, with the notable exception of ionic liquids, must be specifically tailored for use in one of these reaction media. The development of highly fluorinated ligands to be used in liquid–liquid biphasic systems and supercritical CO_2 nicely illustrates these points. In this paper we will summarize the ongoing efforts to design and use chiral ligands bearing perfluoroalkyl substituents for asymmetric catalysis.

1.1. Fluorous biphasic catalysis

Horváth and Rábai pioneered the relatively new field of fluorous biphasic (FB) catalysis. They used fluorocarbons with their many unusual chemical and physical properties, such as low isoelectric constants, chemical and thermal stability and lack of toxicity, as solvents for catalytic reactions usually carried out in organic solvents [12,13]. The word fluorous was proposed in analogy to the word aqueous, to emphasize the peculiar phase properties of the reaction system. Indeed, the low miscibility of fluorocarbons with most organic solvents and water offered a means of separation of a catalyst designed to dissolve preferentially in fluorocarbons from reaction products showing the usual affinity for organic solvents. In a seminal paper, Horváth and Rábai described the hydroformylation of 1-decene with perfluoro(methylcyclohexane) as the fluorous phase and toluene as the organic phase, catalysed by a Rhodium complex of the phosphine $P[CH_2CH_2(CF_2)_5CF_3]$ [12]. The presence of the perfluoroalkyl chains ('fluorous ponytails') made the catalyst highly soluble in perfluorocarbons and insoluble in toluene at room temperature. Reaction conditions ($T = 100\ ^\circ C$, $P = 150$ psi) favoured the mutual miscibility of the organic and perfluorinated solvent which is highly temperature-dependent and therefore the efficient mass-transfer required for high catalytic activities. Upon completion of the reaction, the reactor was cooled and depressurised, so that the solvents once again become immiscible with the catalyst in the fluorocarbon layer and the products in the hydrocarbon layer. Recycling required only the decanting off of the lower fluorous phase to which a fresh solution of olefin in toluene was added after separation of the upper solution of aldehydes.

The research field opened in 1994 quickly expanded to include many other catalytic reactions and separation techniques [14]. The meaning of the adjective 'fluorous' also became broader and it now also indicates perfluoroalkyl-labeled species or highly fluorinated organic materials based upon sp^3-hybridized carbon: it will be used accordingly in the present paper [15].

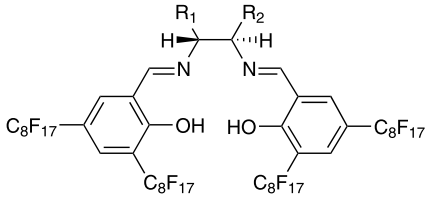
1.2. Fluorous catalysts in supercritical carbon dioxide

At the same time as fluorous solvent systems have been developed for catalysis so have supercritical fluid systems and in particular those based on supercritical carbon dioxide ($scCO_2$), because of its mild critical temperature and pressure ($Tc = 31\ ^\circ C$, $Pc = 74$ bar), low cost and benign character. Another advantage of the use of $scCO_2$ is that its solvent properties are tuneable by changing temperature and pressure allowing the separation of catalyst and products in downstream processing [16]. However, the solvent properties of $scCO_2$ are roughly comparable to those of hexane and only relatively nonpolar and volatile materials show sufficient solubility in this medium, so most organometallic catalysts developed for homogeneous reactions in organic solvents are not suitable for use in $scCO_2$. The high affinity of fluorinated compounds for $scCO_2$ offers the opportunity to overcome limitations arising from the poor solubility of polar organic compounds. Structural modifications of organometallic complexes by incorporation of 'CO_2-philic' fluorinated moieties represents an elegant approach which is particularly effective in the case of asymmetric catalysis in $scCO_2$. The highly lipophilic fluorinated counteranion tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BARF) was introduced at first in order to enhance the solubility of cationic Rhodium complexes of the chiral ligand (*R*,*R*)-1,2-bis(*trans*-2,5-diethylphospholano)benzene [17], but more recently fluorous ligands have been also developed for use in $scCO_2$ [18].

2. Fluorous ligands

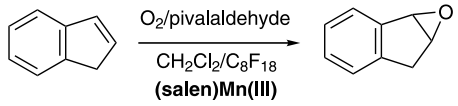
2.1. Nitrogen ligands

Asymmetric transformations were soon recognized as a potential area of application of FB catalytic systems [12], but this concept was substantiated only a few years later when fluorous chiral ligands were first made available [19]. Salen ligands **1** and **2** (Fig. 1) were



Ligand	R_1	R_2
1		
2	Ph	Ph

Fig. 1. First-generation fluorous chiral salen ligands.



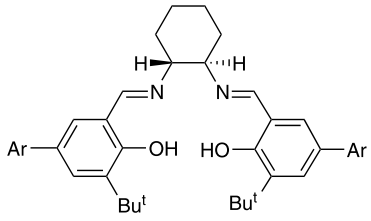
Scheme 1. Example of epoxidation reaction under FB conditions.

developed in 1998 and were used to form manganese(III) complexes, fluorous equivalents of the Jacobsen–Katsuki catalysts, able to catalyze the asymmetric epoxidation of terminal alkenes using molecular oxygen and pivalaldeyde under FB conditions [19,20].

A high yield (83%) and enantioselectivity (e.e. = 92%) were achieved for indene (Scheme 1), however other alkenes gave low enantioselectivities (e.e.s $\leq$ 10%) and under FB conditions the catalyst could only be recycled once.

Despite the limited success in catalysis, it was shown that fluorous chiral ligands can be easily prepared by attaching fluorous building blocks to an existing chiral scaffold and this remains the most general and convenient approach to the synthesis of new fluorous chiral ligands. The subtle influence of fluorous ponytails on the level of enantioselection of a chiral catalyst was also highlighted. It should be noted that perfluoroalkyl substituents are highly electron withdrawing and when they are attached to ligands they can decrease the electron density at the donor sites, thus affecting the catalytic activities of the corresponding metal complexes. In the case of achiral fluorous complexes, adverse electron withdrawing effects had been successfully modulated by the use of simple spacers such as methylene chains and phenyl rings between the fluorous ponytails and the donor sites [12,21]. Things proved to be more complicated in the case of fluorous chiral complexes for which both electronic insulation of the metal centre and steric requirements must be taken into account.

Second generation fluorous salen ligands such as **3** and **4** (Fig. 2) with bulky tertiary butyl groups in the 5,5′



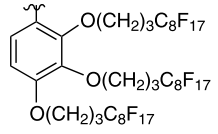
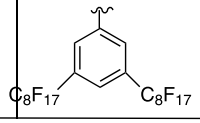
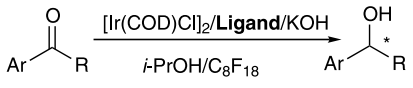
Ligand	Ar
3	
4	

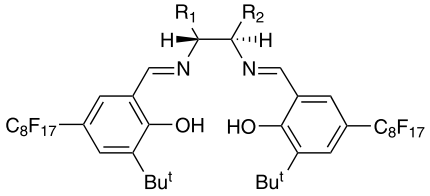
Fig. 2. Second-generation fluorous chiral salen ligands.

positions and more fluorous ponytails further from the metal centre were synthesised on these premises and their Mn(III) complexes featuring the fluorinated $C_7F_{15}COO^-$ counteranion were used for epoxidation with iodosylbenzene and pyridine *N*-oxide under FB conditions (*n*-perfluorooctane/CH_3CN) [22,23]. Similar activities and improved enantioselectivities (50–90%) for several alkenes were achieved and the fluorous layer could be recycled three times before a drop in activity due to bleaching of the catalyst by the oxidising system, analogously to what was reported in the case of non-fluorous, immobilised (salen)Mn(III) complexes [24]. In this catalytic system enantioselectivity and reaction yields increased with temperature, the best results being obtained at 100 °C, corresponding to the boiling point of *n*-perfluorooctane. Blank experiments indicated that only traces of epoxide were formed at this temperature in the absence of the fluorous catalysts. Although the FB mixture did not become homogeneous at 100 °C, the contact among the components of the catalytic system was obviously facilitated by the increased miscibility of the two layers. The emergence of temperature-dependent micellar effects cannot be ruled out either.

Fluorous chiral salen ligands are not limited to epoxidation, they were also tested for enantioselective hydrogen transfer reduction of ketones after reaction in situ with $[Ir(COD)Cl]_2$ to form the catalyst, and used in a FB system with the hydrogen donor isopropanol acting also as the organic solvent (Scheme 2) [25].



Scheme 2. Hydrogen-transfer reduction of ketones under FB conditions.



Ligand	R_1	R_2
5	Ph	Ph
7		

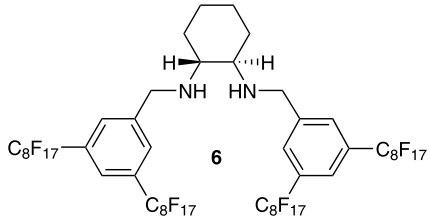


Fig. 3. Fluorous chiral ligands for the hydrogen-transfer reduction of ketones.

Enantioselectivities of up to 60% were achieved in the case of ligand **5** (Fig. 3) which were slightly higher than the respective reaction using chiral non-perfluorinated aldimines under homogeneous conditions. Unfortunately it was not possible to recycle effectively these catalysts as the ligands partly decomposed and iridium was massively lost into the organic phase. Therefore, the fluorous salen ligands were modified by reduction to the respective diamines, which are much more stable under the reaction conditions [26]. Even more stable were diamines without chelating hydroxyl groups in the 1,1′ positions as shown by the results obtained with ligand **6** (Fig. 3) which gave similar activities to salen **5** and enantioselectivities up to 79% in the hydrogen transfer reduction of acetophenone. The catalytically active fluorous layer could be recycled up to four times with moderate loss of iridium (4% in the first run, then $\leq 1\%$).

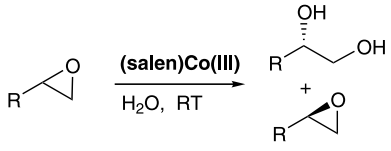
Cobalt(III) complexes of chiral fluorous salen ligands **1**, **5** and **7** (Fig. 3) have also been used for hydrolytic kinetic resolution of terminal epoxides in homogenous systems where the epoxide acted as the solvent to give the diol and the epoxide in high yields (almost 50% each) and enantioselectivities (up to 99%) (Scheme 3) [27].

The Co(II) complexes of the salen ligands were oxidised by air prior to the reaction in the presence of $C_8F_{17}COOH$ as a promoter to give catalytically active Co(III) complexes. As already observed by Ready and Jacobsen for the asymmetric ring-opening of terminal epoxides with phenols catalyzed by non-fluorous (salen)Co(III) complexes [28], the presence of a fluorinated counteranion enhanced the activity of the cationic fluorous catalysts, among which the complex prepared from ligand **7** gave the best results. This catalyst could be recycled by distilling the products off, but attempts to recycle it according to the classical FB approach were foiled by the lack of sufficient fluorine, preventing preferential partition into fluorous solvents. As **7** belongs to the family of 'light-fluorous' compounds defined, specific techniques (continuous fluorous extraction [29], filtration on fluorous reverse-phase silica [13]) were also tested. Although unsuccessful for recycling of the catalyst, these methods were very efficient for the separation of the catalysts from the reaction products.

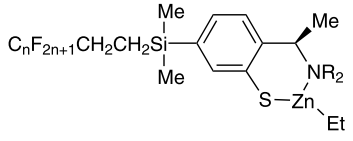
Fluorous chiral ethylzinc arenethiolates **8**–**10** (Fig. 4) have been proposed as catalysts for the asymmetric addition of diethylzinc to benzaldehyde (Scheme 4) by van Koten and coworkers [30]. The reaction was carried out in hexane and the fluorous catalysts gave higher enantioselectivities (e.e.s up to 94%) compared to the non-fluorous equivalents (e.e. = 72%), clearly showing the positive effects brought about by the insertion of the fluorous ponytails. These catalysts were also tested under FB conditions (octane/perfluoromethylcyclohexane), and the best results were obtained with **10** (e.e. = 92%). The fluorous layer could be reused, but a significant drop in enantioselectivity (e.e. = 76%) was already observed in the third consecutive run.

2.2. Oxygen ligands

Fluorous 1,1′-bi(2-naphthol) (BINOL) derivative **11** (Fig. 5) was first developed by Takeuchi and coworkers as a chiral proton source for the asymmetric protonation of Samarium enolates (Scheme 5) [31]. This reaction had been previously studied under FB conditions (THF/perfluorohexane) in the presence of a stoichiometric amount of the highly fluorinated achiral alcohol tris-

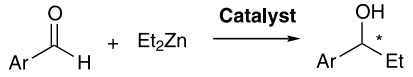


Scheme 3. Hydrolytic kinetic resolution of epoxides.

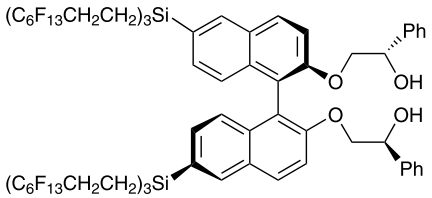


8 n = 6 R = Me
9 n = 10 R = Me
10 n = 10 R_2 = -$(CH_2)_4$-

Fig. 4. Fluorous chiral ethylzinc arenethiolates.

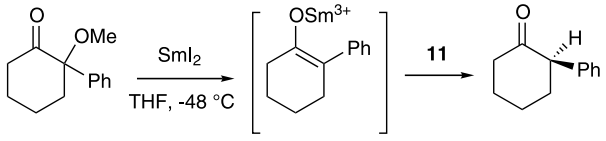


Scheme 4. Addition of diethylzinc to aromatic aldehydes.



11

Fig. 5. A chiral fluorous proton source.



Scheme 5. Asymmetric protonation of Samarium enolates.

[perfluorohexyl)ethyl]methanol as the bulk proton source and (*S*)-2-bis-[perfluorohexyl)ethyl]-2-methoxy-1-phenylethanol, which is soluble in THF, as the catalyst [32].

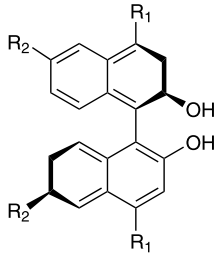
Fluorous BINOL **11** was used in excess as the only proton source showing higher enantioselectivity (e.e. = 95%) than the equivalent non-fluorous alcohol (e.e. = 87%) in reactions carried out in THF. It was not possible to recycle **11** by simple fluorous extraction as it was not preferentially soluble in perfluorocarbons. However, the catalyst could be separated from the reaction mixture by solid phase extraction with fluorous reverse phase silica gel, eluting first with CH_3CN and then perfluorohexane. The recovery of **11** from the perfluorohexane fractions was almost quantitative ($\geq$ 97%).

Takeuchi and coworkers also synthesised the BINOL derivatives **12** and **13** (Fig. 6) and used them as ligands for the titanium-catalysed asymmetric addition of diethylzinc to aromatic aldehydes (Scheme 4) [33,34].

The lengths of the fluorous ponytails influenced the partition coefficients of **12** and **13** between toluene and perfluorohexane to a limited extent and both ligands seemed to be suitable for FB applications. However, attempts to recycle **12** after the addition of diethylzinc to benzaldehyde carried out in a FB system (toluene + hexane/perfluorohexane) showed that about 10% of the fluorous ligand leached into the organic phase. Among organic solvents hexane has one of the highest affinities for perfluorocarbons and thus had a beneficial effect on the efficiency of the catalytic FB system, but it was also responsible for the massive leaching of **12** into the organic phase. This was demonstrated by experiments carried out in toluene/perfluorohexane where the amount of ligand leached into the toluene layer was less than 1% and the enantioselectivities were only slightly lowered. In the case of **13**, the presence of hexane did not have any particular effect, leaching into the organic phase was consistently $< 1\%$ and the fluorous layer was recovered and recycled showing a slight activity decrease in the third run. Good yields (86–97%) and enantioselectivities (e.e. = 78–91%) were achieved with both ligands for various aromatic aldehydes using TFT (trifluorotoluene) as the monophasic solvent. After evaporation of the solvent, the residue was placed on the top of a reverse phase silica gel plug and washed successively with acetonitrile and perfluorohexane. The ligand isolated in the fluorous washings could be recycled at least four times and the active catalyst reformed by the addition of Ti(*i*-PrO)$_4$ after each run. This system proved to be useful also for simultaneous substrate screening: five starting aldehydes were reacted in one vessel and their products analysed by GC after purification by solid phase extraction with fluorous reverse phase silica gel [34].

Chan's group independently synthesised the highly fluorinated BINOL ligand **14** bearing four C_8F_{17} ponytails directly linked to the binaphthyl moiety (Fig. 6). This ligand was also used with titanium for addition of diethylzinc to aromatic aldehydes (Scheme 4), the best results being obtained with benzaldehyde [35]. The solvent system was perfluoro(methyldecalin) and hexane and the fluorous phase in which the ligand was immobilised could be recycled up to nine times affording 1-phenylpropanol in 80% yield and e.e.s = 60–55%. Again Ti(*i*-PrO)$_4$ had to be added after each cycle to maintain high activity and selectivity.

Later on, the same group reported the synthesis of BINOL ligands **15**–**18** (as well as their enantiomers) with varying numbers of fluorous ponytails of several



Ligand	R_1	R_2
12	H	$(C_6F_{13}CH_2CH_2)_3Si$
13	H	$(C_8F_{17}CH_2CH_2)_3Si$
14	C_8F_{17}	C_8F_{17}
15	C_4F_9	C_4F_9
16	C_4F_9	H
17	H	C_4F_9
18	H	C_8F_{17}

Fig. 6. Fluorous BINOLs.

different lengths (Fig. 6) [36]. These fluorous chiral ligands gave lower e.e.s (70–77%) than (*R*)-BINOL (88%) when tested in the titanium-catalyzed addition of diethylzinc to benzaldehyde in CH_2Cl_2. Moreover, increasing fluorine content of the ligand resulted in lower enantioselectivities. Only ligand **14** could be conveniently used in FB reactions, since all the other ligands were also partly soluble in hexane; the yields and enantioselectivities were influenced by the working temperature in the same way as observed in the FB epoxidation of alkenes [22].

Ethylation of aromatic aldehydes with triethylaluminium was carried out at 53 °C in perfluoro(methyldecalin)/hexane in the presence of ligand **14** and Ti(*i*-PrO)$_4$. Higher e.e.s (up to 82%) were achieved in the case of benzaldehyde in comparison with diethylzinc addition, but only minor differences were observed with other substrates [36].

2.3. Phosphorus ligands

2.3.1. Phosphorus ligands for supercritical CO_2 applications

Fluorous phosphines were the first class of compounds designed for catalysis in FB systems. [9] This is not surprising due to the extensive use of phosphorus-based ligands in homogeneous catalysis. However, fluorous chiral phosphorus ligands were first developed for applications in $scCO_2$ by Leitner and Franciò who prepared the chiral phosphine/phosphite ligand **19** (Fig. 7), an analogue of (*R*,*S*)-BINAPHOS, and used it in the rhodium-catalysed asymmetric hydroformylation of vinyl arenes in liquid or $scCO_2$ (Scheme 6) [37].

Higher catalytic activity and, more strikingly, regio- and enantioselectivity were observed in comparison to reactions carried out in benzene in the presence of (*R*,*S*)-BINAPHOS. Control experiments with **19** in benzene proved that these beneficial effects arise from the presence of fluorous ponytails and not from the use of CO_2 as a reaction medium. The physical state of CO_2 (liquid or supercritical) did not influence the outcome of the reaction to a large extent, at least in the case of styrene.

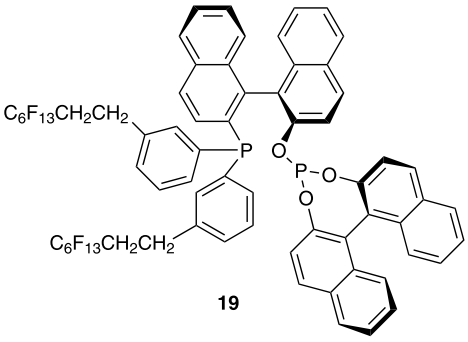
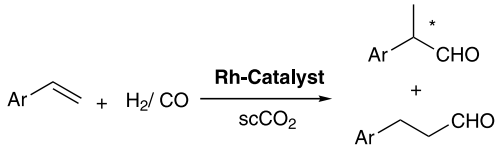


Fig. 7. Fluorous (*R*,*S*)-BINAPHOS.

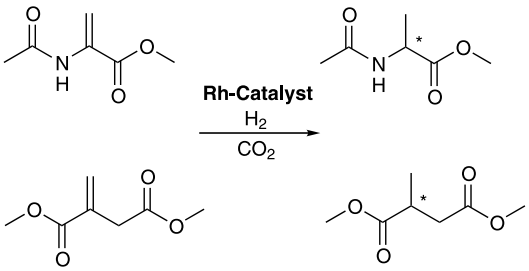


Scheme 6. Hydroformylation of vinyl arenes.

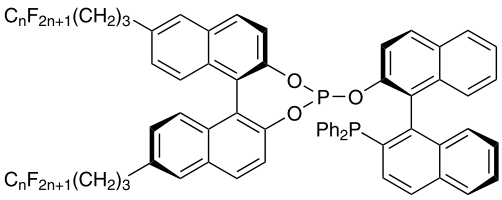
The results obtained with vinyl arenes are valid for a wide range of olefins which were hydroformylated with good conversions (70–99%) regioselectivities (up to 95/5 branched to linear aldehyde) and enantioselectivities (e.e.s up to 95%) [38]. Recycling of the rhodium catalyst based on ligand **19** was demonstrated for the enantioselective hydroformylation of styrene. The catalyst could be separated from the product and reused by lowering the density of the $scCO_2$ in the reactor so a liquid phase formed, in which the catalyst was preferentially soluble while the product could be evaporated off by flushing with nitrogen. Three successive runs were possible before the enantioselectivity of the reaction slowly decreased. Rhodium leaching was usually lower than 1 ppm for each run. Ligand **19** was also used for asymmetric hydrogenation of 2-acetamido methylacrylate and dimethyl itaconate in compressed CO_2 (Scheme 7). Both substrates where reduced quantitatively and with high enantioselectivities (e.e. = 97%) [38].

The rhodium-catalysed hydroformylation of styrene in $scCO_2$ has also been investigated by Ojima who recently reported the synthesis of the BINAPHOS-like ligands **20**, **21** (Fig. 8, (*R*,*S*) configuration) and **22** ((*S*,*R*) configuration) [39].

The three ligands were used to form Rhodium catalysts by reacting them in situ with Rh(acac)(CO)$_2$; their catalytic activity was tested at first in benzene, the standard solvent for the hydroformylation catalysed by Rh–BINAPHOS complexes. The fluorous catalysts showed good activity (styrene conversion = 84–100%) and selectivity for aldehydes (100%), with a ratio of branched to linear 9/1 and e.e.s = 88–95%, in good agreement with figures reported with ligand **19** or BINAPHOS in the same solvent. However, when the hydroformylation was carried out in $scCO_2$, e.e.s dropped to 70–74%. Preliminary data concerning the use of ligands **20**–**22** in FB systems showed that



Scheme 7. Asymmetric hydrogenation of 2-acetamido methylacrylate (up) and dimethyl itaconate (down).



Ligand	n
20	4
21	6
22	8

Fig. 8. Fluorous analogues of BINAPHOS.

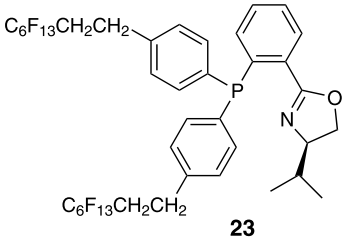
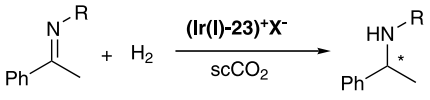


Fig. 9. A fluorous chiral phosphinodihydrooxazole.

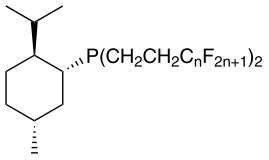
enantioselectivities were in the same range as those observed in benzene. Unfortunately, with small amount of fluorine these ligands were not preferentially soluble in perfluorocarbons and their recycling by fluorous techniques would probably be tricky.

A third example of 'CO_2-philic' phosphorus ligands bearing long fluorous ponytails is due to Leitner, Pfaltz and coworkers [40]. Cationic iridium(I) complexes with the fluorous chiral phosphinodihydrooxazole **23** (Fig. 9) were prepared and tested for the enantioselective hydrogenation of prochiral imines in CH_2Cl_2 or $scCO_2$ (Scheme 8).

The nature of the counter anion X^- (PF_6^-, Ph_4B^- or BARF) had little influence on the hydrogenation of *N*-(1-phenylethylidene)aniline in CH_2Cl_2, which occurred with quantitative conversions and e.e.s = 80–86%, as observed in reactions catalysed by similar iridium(I) complexes of the non-fluorous analogue of **23**. The latter proved to be less active than the fluorous complexes for reactions carried out in $scCO_2$. Such a difference almost disappeared for complexes containing the BARF anion. Also the level of enantioselection strongly depended on the counter anion and not on the



Scheme 8. Asymmetric hydrogenation of prochiral imines in $scCO_2$.



Ligand	n
24	6
25	8

Fig. 10. Monodentate chiral fluorous phosphines.

nature of the ligand, with high e.e.s (80%) only being seen when the counter anion was BARF.

2.3.2. *Mono and bidentate phosphorus ligands for fluorous systems*

The first example of monodentate chiral fluorous phosphine was reported by Klose and Gladysz who prepared ligands **24** and **25** based on L-menthyl (Fig. 10) and the corresponding iridium complexes [41]. Catalytic applications of these compounds were not disclosed.

Enantiopure 2-(diphenylphosphino)-2′-alkoxy-1,1′-binaphthyls (MOPs) are useful ligands for several metal-catalysed asymmetric transformations. Cavazzini et al. combined the standard approach to the synthesis of MOPs with the introduction of fluorous ponytails onto aromatic compounds via ether bond formation and prepared the enantiopure fluorous MOP ligand **26** (Fig. 11) which was used to carry out the Pd^0-catalysed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with several nucleophiles (Scheme 9) [42].

Two other fluorous MOP ligands **27** and **28** (Fig. 12) have been developed independently by Sinou and coworkers and tested for the same reaction [43]. While all these ligands gave the substitution products in almost quantitative yield under optimised conditions, only the use of **26** resulted in high enantioselectivities (e.e.s up to 87% using dimethyl malonate as a nucleophile, activated

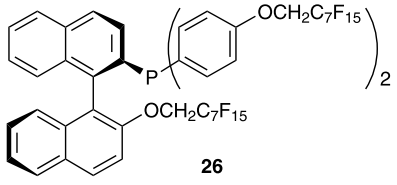
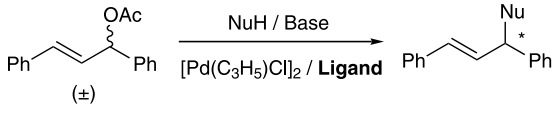
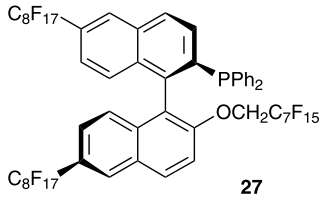


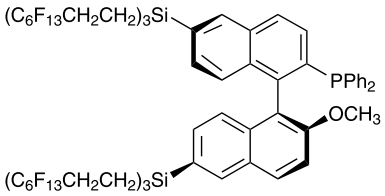
Fig. 11. Enantiopure MOP with fluorous ponytails attached via O-alkylation of aromatic rings.



Scheme 9. Pd^0-catalysed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate.



27

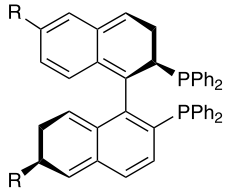


28

Fig. 12. Enantiopure MOP with fluorous ponytails attached to the binaphthyl moiety.

by bis(trimethylsilyl)acetamide and potassium acetate, in benzotrifluoride as a solvent) [42]. Palladium complexes of ligands **27** and **28** showed poor enantioselectivities (e.e.s max = 37 and 24%, respectively) and the use of a strong base such as NaH was required to activate dimethyl malonate.

Preliminary attempts at using **27** and **28** as rhodium ligands for the hydrogenation of α-acetamidocinnamic acid methyl ester and for the hydroformylation of styrene also gave low enantioselectivities (e.e.s = 14 and 5%, respectively) [43]. It appears that the introduction of fluorous ponytails onto the binaphthyl moiety of the MOP ligands has a negative effect on the level of enantioselection, possibly due to steric effects arising from mutual interaction of the perfluoroalkyl chains. Indeed electron withdrawing effects are not the determining factor as the interposition of $-CH_2CH_2Si-$ insulating spacers does not improve the enantioselectivities obtained with ligand **28** in comparison to those obtained with **27**.



Ligand	R
29	C_6F_{13}
30	$C_6F_{13}CH_2CH_2$
31	$(C_6F_{13}CH_2CH_2)_3Si$

Fig. 13. Bidentate fluorous chiral phosphines.

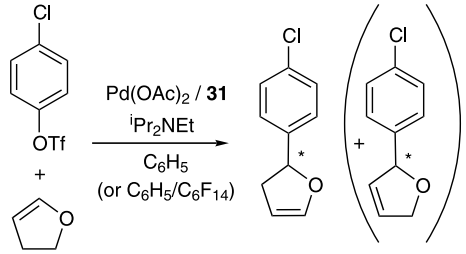
None of the complexes contained enough fluorine to be used in an FB system, but they did have enough fluorine to separate them from the product using liquid–liquid extraction with perfluorooctane. When **26** was isolated in this way and reused, the catalyst was inactive probably due to the oxidation of the phosphine to the phosphine oxide.

Enantiopure 2,2′-bis(diphenylphosphino)-1-1′-binaphthyl (BINAP) ligands **29** and **30** (Fig. 13) bearing two perfluoroalkyl chains with and without an ethylene spacer, respectively, were synthesised by Stuart and coworkers [44].

Ruthenium complexes of these two fluorous ligands where used for the asymmetric hydrogenation of dimethyl itaconate (see Scheme 7) in methanol as a solvent and the results were compared to those obtained with BINAP. Enantiomeric excess for the three ligands **29**, **30** and BINAP was, respectively 95.3, 95.7 and 95.4% therefore fluorous ponytails on the binaphthyl framework have no effect on the enantioselectivity of the ligands. More interestingly, conversion of the substrate after 15 min was, respectively 42, 83 and 88% which clearly shows that for this reaction electron withdrawing fluorous ponytails lower the activity of the hydrogenation catalyst. This deactivation can be mostly avoided using an ethylene spacer between the ponytail and the binaphthyl framework. The fluorous ligands **29** and **30** have not as yet been tested under FB conditions.

The highly fluorinated fluorous ligand **31** (Fig. 13) with six fluorous ponytails attached via silicon atoms to the binaphthyl moiety has recently been disclosed [45]. The asymmetric Heck reaction pictured in Scheme 10 was chosen for preliminary catalytic tests that were carried out reacting the ligand in situ with $Pd(OAc)_2$ to form the active species.

Ligand **31** was tested under homogeneous conditions either in benzotrifluoride or benzene and compared to BINAP. In the first solvent, the fluorous ligand had a lower activity (overall yields of the two substituted dihydrofurans = 59%) and selectivity (88/12) for the desired isomer compared to BINAP (yield = 67, isomer ratio = 92/8), but a higher enantiomeric excess was generated (e.e.s = 90 and 76%, respectively), similar to that obtained with BINAP in benzene. The fluorous



Scheme 10. Asymmetric Heck reaction under homogeneous or FB conditions.

ligand could be used in a FB system benzene/perfluorohexane affording the desired isomer with e.e. = 93%, but again the activity and the selectivity were lower than both the BINAP and the fluorous ligand in a monophasic system. Attempts to reuse the fluorous phase in further reactions failed due to the oxidation of the ligand to the corresponding phosphine oxide, which was inactive.

3. Conclusions

In the last 4 years various examples of chiral fluorous ligands and their application to many reactions have appeared in the literature. These reactions have been carried out in fluorinated solvents and in supercritical carbon dioxide with good activity and enantioselectivity. Slowly the effects of these solvent systems and the addition of fluorous ponytails to catalysts are being understood. It is clear that detailed studies of the phase behaviour of reaction mixture in $scCO_2$ and perfluorocarbons are required to acquire a better knowledge of the influence of these media on the activity and selectivity of catalytic systems. A good example is given by the unexpected observation that in FB systems enantioselectivity can be improved by heating the reaction to increase miscibility and therefore the contact between substrate and catalyst.

Far more important is the addition of the fluorous ponytails whose electron withdrawing properties often deactivate the catalyst and can reduce its selectivity. However, by careful design of the catalyst and the use of spacers this can be mostly avoided. On the other hand, electron withdrawing properties can have beneficial effects in some reactions as demonstrated by the increased regioselectivity of fluorous catalyst in the hydroformylation of styrene derivatives.

It is often possible to recover and recycle catalysts based on chiral fluorous ligands taking advantage of their phase properties, but after a limited number of recycles catalytic activity is lost. These are similar results to other supported systems and have to be improved for fluorous catalysts to have industrial applications. Again this can be achieved by systematic catalyst design, not only by increasing the number of fluorous ponytails attached to a ligand, but also the position and length of these ponytails is important. For instance, the more widely spread they are around the catalyst the greater the shielding of the hydrocarbon centre and the greater the solubility of the catalyst in fluorous solvents. Therefore, there are still many avenues to be researched in this fast expanding field in order to tailor fluorous ligands to the demanding requirements of recyclable asymmetric catalysts.

Acknowledgements

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References

[1] D.E. De Vos, I.F.J. Vankelecom, P.A. Yamamoto (Eds.), Chiral Catalyst Immobilization and Recycling, Wiley-VCH, Weinheim, 2000.
[2] H.P. Djikstra, G.P.M. van Klink, G. van Koten, Acc. Chem. Res. 35 (2002) 798.
[3] B. Cornils, W.A. Herrmann (Eds.), Aqueous-Phase Organometallic Catalysis. Concepts and Applications, Wiley-VCH, Weinheim, 1998.
[4] F. Joó, Aqueous Organometallic Catalysis, Kluwer, Dordrecht, 2001.
[5] R. Sheldon, Chem. Commun. (2001) 2399.
[6] H. Olivier-Bourbigou, L. Magna, J. Mol. Cat. A 182–183 (2002) 419.
[7] P.G. Jessop, T. Ikariya, R. Noyori, Chem. Rev. 99 (1999) 475.
[8] W. Leitner, Acc. Chem. Rev. 35 (2002) 746.
[9] I.T. Horváth, Acc. Chem. Rev. 31 (1998) 641.
[10] L.P. Barthel-Rosa, J.A. Gladysz, Coord. Chem. Rev. 192 (1999) 587.
[11] R.H. Fish, Chem. Eur. J. 5 (1999) 1677.
[12] I.T. Horváth, J. Rabai, Science 266 (1994) 72.
[13] I.T. Horváth, J. Rábai (Exxon Comp.), U.S. Pat. 5,463,082, 1995.
[14] D.P. Curran, Green Chem. 3 (2001) G3.
[15] J.A. Gladysz, D.P. Curran, Tetrahedron 58 (2002) 3823.
[16] C.A. Eckert, B.L. Knutson, P.G. Debenedetti, Nature 383 (1996) 313.
[17] M.J. Burk, S. Feng, M.F. Gross, W. Tumas, J. Am. Chem. Soc. 117 (1995) 8277.
[18] S. Kainz, D. Koch, W. Baumann, W. Leitner, Angew. Chem. Int. Ed. Engl. 36 (1997) 1628.
[19] G. Pozzi, F. Cinato, F. Montanari, S. Quici, Chem. Commun. (1998) 877.
[20] G. Pozzi, M. Cavazzini, F. Cinato, F. Montanari, S. Quici, Eur. J. Org. Chem. (1999) 1947.
[21] P. Bhattacharyya, D. Gudmunsen, E.G. Hope, R.D.W. Kemmit, D.R. Paige, A.M. Stuart, J. Chem. Soc. Perkin Trans. 1 (1997) 3609.
[22] M. Cavazzini, A. Manfredi, F. Montanari, S. Quici, G. Pozzi, Chem. Commun. (2000) 2171.
[23] M. Cavazzini, A. Manfredi, F. Montanari, S. Quici, G. Pozzi, Eur. J. Org. (2001) 4639.
[24] T.S. Reger, K.D. Janda, J. Am. Chem. Soc. 122 (2000) 6929.
[25] D. Maillard, C. Nguefack, G. Pozzi, S. Quici, B. Valadé, D. Sinou, Tetrahedron: Asymmetry 11 (2000) 2881.
[26] D. Maillard, G. Pozzi, S. Quici, D. Sinou, Tetrahedron 58 (2002) 3971.
[27] M. Cavazzini, S. Quici, G. Pozzi, Tetrahedron 58 (2002) 3943.
[28] J.M. Ready, E.N. Jacobsen, J. Am. Chem. Soc. 121 (1999) 6086.
[29] D. Crich, X. Hao, M. Lucas, Tetrahedron 55 (1999) 14261.
[30] H. Kleijn, E. Rijnberg, J.T.B.H. Jastrzebski, G. van Koten, Org. Lett. 1 (1999) 853.
[31] Y. Nakamura, S. Takeuchi, Y. Ohgo, D.P. Curran, Tetrahedron 56 (2000) 351.

[32] S. Takeuchi, Y. Nakamura, Y. Ohgo, D.P. Curran, Tetrahedron Lett. 39 (1998) 8691.
[33] Y. Nakamura, Y. Takeuchi, Y. Ohgo, D.P. Curran, Tetrahedron Lett. 41 (2000) 57.
[34] Y. Nakamura, S. Takeuchi, K. Okumura, Y. Ohgo, D.P. Curran, Tetrahedron 58 (2002) 3963.
[35] Y. Tian, K.S. Chan, Tetrahedron Lett. 41 (2000) 8813.
[36] Y. Tian, Q.C. Yang, T.C.W. Mak, K.S. Chan, Tetrahedron 58 (2002) 3951.
[37] G. Franciò, W. Leitner, Chem. Commun. (1999) 1663.
[38] G. Franciò, K. Wittmann, W. Leitner, J. Organomet. Chem. 621 (2001) 130.
[39] D. Bonafoux, Z. Hua, B. Wang, I. Ojima, J. Fluorine Chem. 112 (2001) 101.
[40] S. Kainz, A. Brinkmann, W. Leitner, A. Pfaltz, J. Am. Chem. Sect. S 121 (1999) 6421.
[41] A. Klose, J.A. Gladysz, Tetrahedron: Asymmetry 10 (1999) 2665.
[42] M. Cavazzini, S. Quici, G. Pozzi, D. Maillard, D. Sinou, Chem. Commun. (2001) 1220.
[43] D. Maillard, J. Bayardon, J.D. Kurichiparambil, C. Nguefack-Fournier, D. Sinou, Tetrahedron: Asymmetry 13 (2002) 1449.
[44] D.J. Birdsall, E.G. Hope, A.M. Stuart, W. Chen, Y. Hu, J. Xiao, Tetrahedron Lett. 42 (2001) 8551.
[45] Y. Nakamura, S. Takeuchi, S. Zhang, K. Okumura, Y. Ohgo, Tetrahedron Lett. 43 (2002) 3053.