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Asymmetric fluorous catalysis: the particular case of nitrogen-containing chiral auxiliaries

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Asymmetric fluorous biphasic (FB) catalysis has been developed in the last decade in the perspective of creating new recyclable catalytic systems, easy to separate from the reaction products. This approach came after other concepts for the heterogenization of homogeneous ligands, developed for the same purpose. We focus this paper on fluorous nitrogen-containing ligands and compare them to the unfluorinated ones and, when possible, to the same ligands heterogenized in another way. The future of the FB technique is discussed.

Introduction

In 1994, Horváth and Rabái[1] published the fluorous biphase hydroformylation of olefins, leading to a facile catalyst separation. The term fluorous was introduced for the first time as the analogue of aqueous and since this seminal work, numerous papers dealing with fluorous phase chemistry have appeared. The development of this area was so rapid and extensive that the concept needed to be clarified. Therefore, Gladysz and Curran[2] proposed in an article definitions of different terms such as fluorous, fluorous tag, fluorous chemistry, *etc.*, now commonly used but which did not belong to the vocabulary of chemists nine years ago!

What is the basic concept of fluorous chemistry? Fluorous solvents are immiscible at 20 °C with both organic and aqueous solvents, forming two distinct layers. When heated to a temperature that depends on the nature of the solvents, only one phase is obtained. For example, when a catalyst mainly soluble in the fluorous solvent and classical reagents soluble in the organic phase are used, heating to the appropriate temperature allows to perform the reaction under homogeneous conditions. Cooling down to room temperature leads to the starting two phases, which allows an easy separation of the organic final products from the catalyst. In some cases, the catalyst can be recycled.

This basic but brilliant concept has been considerably extended from liquid-liquid extraction to numerous other separation techniques. For example, commonly used reagents that cause purification problems, such as the Mitsunobu one,[3] have been synthesized in their fluorinated form, leading to easy separation; silica gel modified by fluorocarbon chains is used for solid-liquid extraction;[4] and fluorous chemistry also finds applications in combinatorial chemistry and parallel synthesis.[5] This list is not exhaustive and the purpose of this article is not to review all that has been published in fluorous chemistry (for reviews on the subject, see ref. 6)

One field particularly attractive for fluorous chemistry is catalysis as most organometallic reagents are inert towards fluorous solvents. More specifically, asymmetric catalysis, which most of the time uses expensive chiral ligands, can take advantage of a technique that allows easy separation and recycling of these ligands. To ensure affinity of the latter with the fluorous phase, it is necessary to add fluorous tags; some classical chiral ligands such as BINOL[7] and BINAP[8] already have fluorous analogues. Taking into account our experience in asymmetric catalysis with nitrogen-containing ligands,[9] we have examined the possibilities of asymmetric catalysis with such ligands under fluorous conditions. Two reviews on chiral fluorous catalysts have been recently published but they are not exclusively devoted to nitrogen ligands and therefore not exhaustive.[10] Moreover, numerous catalytic systems have already been modified in other ways like supported catalysis or heterogenization of homogeneous systems, with the purpose of easy separation and recycling. When possible, we will compare the homogeneous catalytic system, its fluorous counterpart and also these modified systems when they exist. We will also discuss the advantages of these different approaches.

In this paper, for the sake of clarity, the results are classified according to the type of new bond formed.

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C–H bond formation

Hydrogen as reducing agent

The enantioselective reduction of the C=N double bond leads to the formation of chiral amines, an important class of

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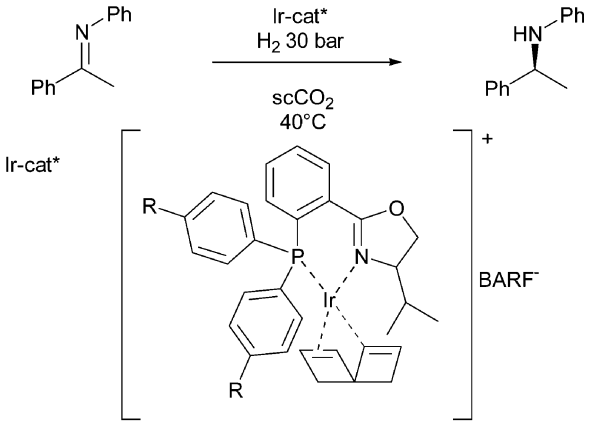


1: **a** R = H; 81% ee with 0.14 mol% catalyst
b R = $CH_2CH_2C_6F_{13}$; 80% ee with 0.09 mol% catalyst

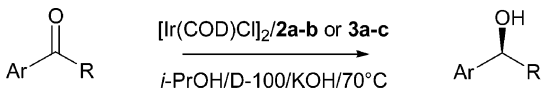
Scheme 1 Enantioselective hydrogenation of imines with cationic iridium complexes.

compounds used in numerous syntheses of products of biological interest. Iridium is particularly efficient for such reactions under hydrogen pressure. A Ciba-Geigy research group developed the first industrial application of an imine hydrogenation using a ferrocenylphosphine iridium complex for the synthesis of an herbicide.[11] Taking into account the economical interest of such a reaction, a search for a "green" medium was performed and supercritical (sc) CO_2 was tested with success, using cationic iridium and phosphinodihydrooxazoles **1** as ligands[12] (Scheme 1).

The nature of the anion has a high influence on the reactivity and tetrakis-3,5-bis(trifluoromethyl)phenylborate (BARF) led to the highest asymmetric induction. Working in $scCO_2$ allows efficient product isolation and cocatalyst recycling. Nevertheless, the introduction of a polyfluoroalkyl chain on the ligand (**1b**) did not have a beneficial influence on the enantioselectivity.

Hydride transfer reduction

Hydride transfer reduction is another widely developed method to form new chiral C–H bonds. Ketones have been reduced by this way using diimines (salen-type ligands **2a**,**2b** and **3a**–**3c**) or diamines (**4a**,**4b**) bearing fluorous ponytails in a perfluoroalkane (D-100)–isopropanol mixture (Schemes 2 and 3).[13] An ee of up to 56% was measured with ligand **2b** for the reduction of acetophenone. Recycling of the fluorous phase led to a significant loss of both activity and selectivity. The organic phase led to high conversion but 0% ee. This could be due to the low fluorine content of the ligand (47.2%), which makes it soluble mainly in the organic phase. Moreover, diimine ligands are unstable under the reaction conditions. Thus,[14] ligand **4b** with a higher fluorine content (65.7%) allowed recycling of the catalytic system and enantioselectivities of up to 79% were measured for the second run (for 69% ee at the first cycle), which was higher than those obtained with nonfluorinated ligand in isopropanol only. Two further recyclings of the fluorous phase were performed but with a decrease in both activity and selectivity. With ligand **4a**, significant iridium leaching was observed, probably due to the presence of two reactive OH groups.



Ar = C_6H_5; Br-C_6H_4; *p*-NO_2-C_6H_4; *p*-CN- C_6H_4 ; *p*-MeO-C_6H_4
R = Me; Et; *i*Pr

Scheme 2 Hydride transfer reduction of ketones.

For comparison, we can look at the work of Lemaire *et al.*[15] who have copolymerized diimines of type **3** with styrene and divinylbenzene (R_1 = R_3 = H, main chain polymer in R_2) and tested them in the same reaction with iridium. Up to 70% ee was obtained. The second cycle led to almost the same results but the third one saw a drop of both activity and selectivity. In this case, as with polyfluorinated imines, leaching of iridium could explain the disappointing recycling results.

C–C bond formation

Allylic substitution

Pd-catalyzed allylic substitution, named the Tsuji–Trost reaction, allows the formation of a new C–C bond. Numerous chiral ligands have been successfully used in such a reaction, among which are nitrogen-containing ligands such as bisoxazolines. Bayardon and Sinou[16] synthesized fluorous bisoxazolines **5b** and **5c** bearing polyfluorinated chains in place of the traditionally occurring gem dimethyl in **5a**. They were used in the classical test reaction, the allylic alkylation of 1,3-diphenylprop-2-enyl acetate using dimethyl malonate as nucleophile and a catalytic amount of $[Pd(C_3H_5)Cl]_2$ (Scheme 4). The same results were obtained with ligands **5b** and **5c** in CH_2Cl_2: up to 94% ee for quantitative yields, which is similar to what was measured with the nonfluorinated ligand **5a**. Nevertheless, in this case, the reaction went faster. Working in BTF (benzenetrifluoride) led to the same values but required longer reaction times. Recycling of the catalytic system was not possible as black palladium precipitated but the ligand was recovered after extraction with FC72 and reused successfully one time with fresh Pd (up to 98% ee).

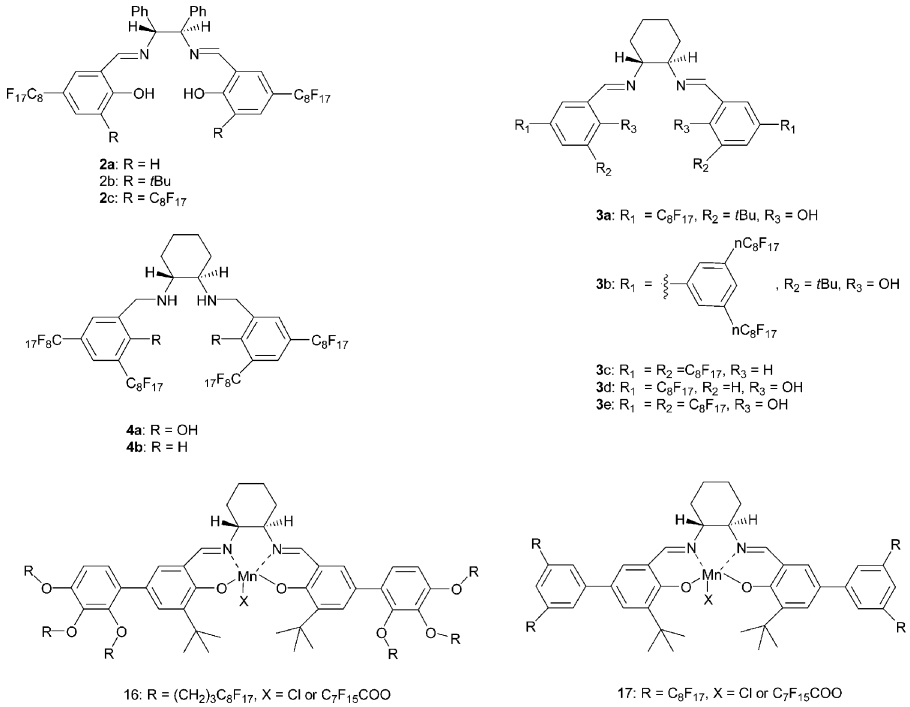
For comparison, with the heterogenized ligand **5d**, Hallman and Moberg[17] obtained the same results: good enantioselectivity at the first run with precipitation of the catalyst, which prevented recycling. After washing, the polymer was reused up to 5 times with fresh palladium added each time without any loss of selectivity (94% ee).

Cyclopropanation

Other fluorinated bisoxazolines (F-box) were used in the cyclopropanation of styrene with CuOTf[18] (Scheme 5). Ligand **6** in a CH_2Cl_2–perfluorooctanes (1 : 1) mixture led to 55% yield with a *trans* : *cis* ratio of 73 : 27 and 60% ee on the *trans* isomer, whereas ligand **7** in CH_2Cl_2 led to 68% yield with a 65 : 35 mixture of the *trans* : *cis* cyclopropane and 78% ee on the *trans* isomer. These values have to be compared to the 99% ee obtained with the *gem*-dimethyl-substituted box.[19]

Despite a similar fluorine content (55.5% for **6** and 49.2% for **7**) their solubilities are different and **6** was recovered after Cu decomplexation by liquid-liquid separation whereas **7** was recovered by chromatography. Recycling was also possible but with lower activity and selectivity. Moreover, the recovered ligands were contaminated by the decomposition product of the diazoacetate.

Ligand **6** can be compared to the insoluble polymer **8**, which in the same reaction showed lower activity (36% yield) but higher enantioselectivity (78% ee).[20] **8** could be recycled twice after filtration with only a slight decrease in activity and selectivity but without the need of further decomplexation/addition of copper. Soluble polymer supported PEG-box **9**,[21] which can be compared to **7**, led to 96% yield and 95% ee and was easily recycled after simple precipitation and filtration. Finally, F-box ligands, while stable under reaction conditions, were not proven to be good candidates to compete with other existing recyclable systems.

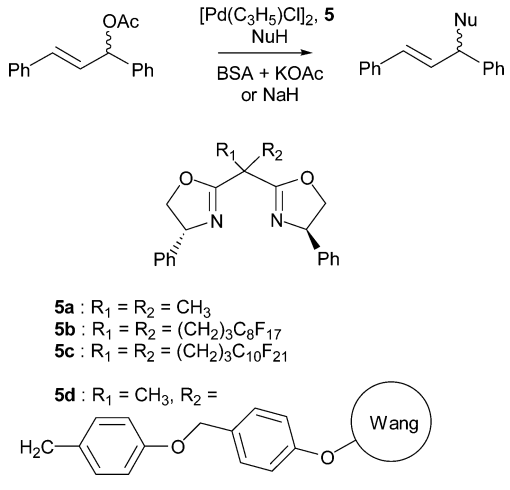


Scheme 3 Salen-type ligands.

Ene reaction

The ene reaction between α-methylstyrene and ethyl glyoxalate was performed using $Cu(OTf)_2$ and bis(oxazoline) ligands bearing perfluoroalkyl substituents (F-box)[18] (Scheme 6). Ligand **7** afforded better results than ligand **6**, 99% isolated yield and 67% ee *versus* respectively 64% and 26%, which was nevertheless poorer than that obtained with the nonfluorinated box analogues (89% ee).[22] To explain this difference of behaviour, the electronic effects of the fluorinated ponytails on the box nitrogen atoms were not in this case a plausible hypothesis due to the long spacer separating the two parts. Nevertheless, both steric and electronic repulsion between the two fluorinated chains could diminish the bite angle of the box moiety and thus reduce its chelation ability. This could explain why ligand **6** led to a poorer ee than **7**, in which these interactions are minimized or suppressed.

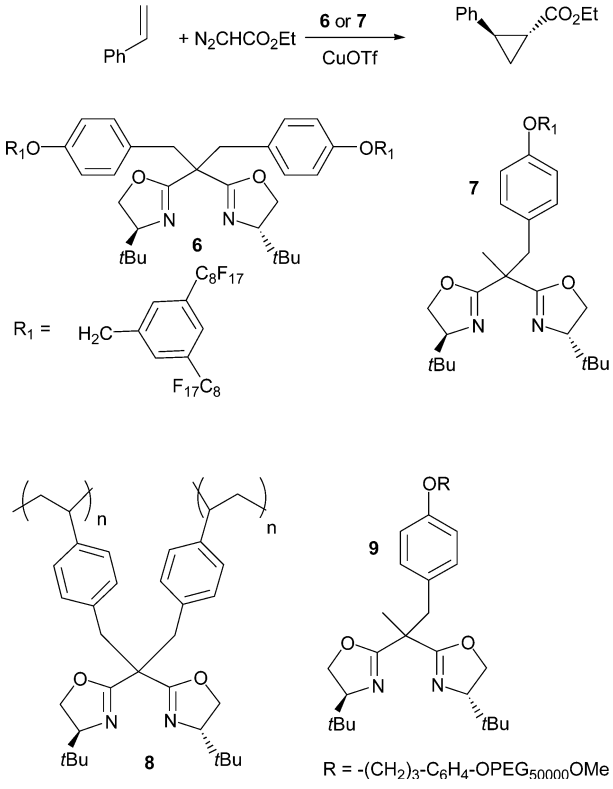
Recovery of the F-boxes was performed as already described for cyclopropanation. Recycling was thus possible once with similar results. Nevertheless, other existing recyclable systems like PEG-box **9** afforded higher performances (up to 95% ee).



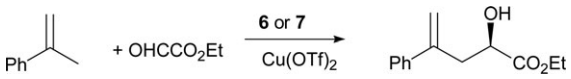
Scheme 4 Allylic substitution.

Diels–Alder reaction

The Diels–Alder reaction is a powerful method that is in perfect agreement with the concept of atom economy, like other condensation reactions. Numerous catalytic systems have been developed for this reaction, among which are optically active nitrogen-containing ligands that led to particularly good results, probably because of their high stability. The use of organocatalysts,[23] which avoids metals, was also proposed for this reaction. More specifically, base-catalyzed



Scheme 5 Cyclopropanation reaction with various bisoxazoline ligands.



Scheme 6 Ene reaction.

Diels–Alder reactions were developed by Kagan *et al.* in 1989 using cinchona derivatives.[24] In the perspective of developing "green" chemistry, the use of both approaches, fluorous biphase catalysis and organocatalysis, is particularly attractive. The fluorous version of these results was published by Fache and Piva.[25] (Scheme 7).

Because of the relatively low fluorine content of these amino alcohols **10** (around 45%) it was not possible to work in FB conditions. Nevertheless, in BTF, the same activity and selectivity as with Kagan's system were measured (quantitative yield, 40% ee). Moreover, a large proportion of the final product (75%) precipitated in the solvent and was recovered by simple filtration with 59% ee instead of 40% for the totality of the product (precipitate + filtrate). The fluorinated organocatalyst, soluble in BTF whereas the natural amino alcohol is not, was contained in the filtrate and recycled once but with lower selectivity (20% ee).

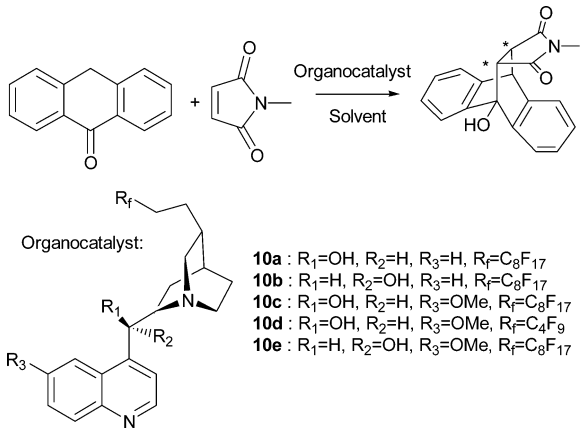
Cinchona alkaloids have been bound to numerous polymers[26] but, to our knowledge, none of these systems has been tested in this base-catalyzed Diels–Alder reaction.

Aldol reaction

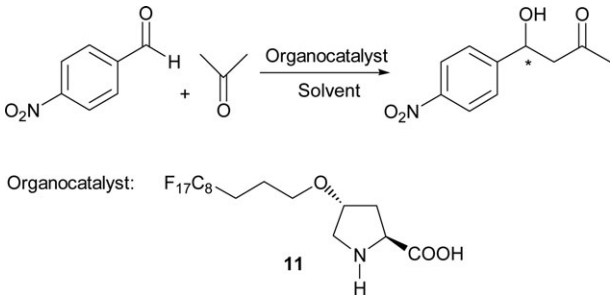
Numerous asymmetric catalytic systems have been developed for this powerful reaction, one of the most important C–C bond forming reactions used in organic synthesis. Since the beginning of the '70s, when Hajos and Parrish[27] reported the first proline catalyzed intramolecular aldol reactions, numerous versions of this system have been published. We synthesized a proline derivative bearing a fluorous side chain and tested it in the intermolecular aldolization reaction between acetone and *p*-nitrobenzaldehyde[28] (Scheme 8).

Despite the relatively high fluorine content of ligand **11** (54%) it was not possible to work in biphasic conditions. BTF turned out to be the best solvent for such a reaction with the fluorinated proline instead of DMSO in the case of natural proline. The main advantage of this fluorous organocatalyzed system was that it was easier to get rid of the solvent at the end of the reaction. As for the activity and enantioselectivity, the same results were obtained for both systems (72% isolated yield, 73% ee for the fluorous proline, 68% isolated yield, 76% ee for proline). No recycling was possible.

Proline was incorporated into double layered hydroxides (LDHs) in order to synthesize a heterogeneous version of this



Scheme 7 Asymmetric base catalysed Diels–Alder reaction.



Scheme 8 Aldolisation reaction using an organocatalyst.

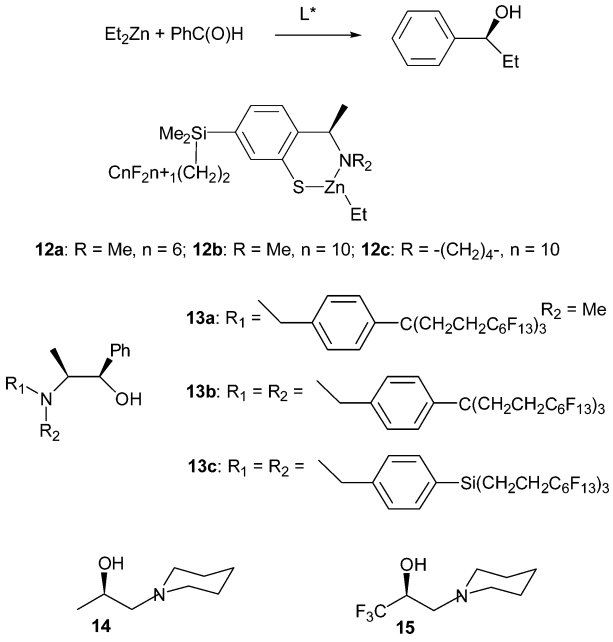
product.[29] The aldol products were obtained selectively in excellent yields but with low enantioselectivities (<10% ee). The catalyst was recovered by simple filtration and reused for 5 runs with consistent activity. If we compare the two possibilities of synthesizing proline derivatives with the possibility of recovery and recycling, we can see that the fluorinated system is superior in terms of enantioselectivity but the supported one is better for activity and recycling.

Nucleophilic addition of diethyl zinc reagents

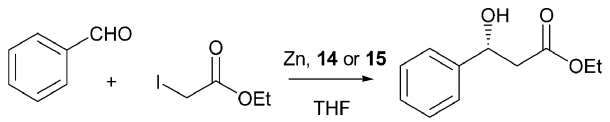
This reaction, which leads to secondary alcohols, is limited by the access to alkyl zinc derivatives other than methyl or ethyl. Nevertheless, it has been extensively studied and numerous nitrogen-containing ligands, mainly β-amino alcohols, have been developed. In 1999, van Koten *et al.*[30] published the first example of a two-phase organic–fluorous enantioselective catalytic system using ligands **12a**–**12c** in the enantioselective zinc-mediated 1,2-addition of diethyl zinc to aldehydes (Scheme 9).

Up to 94% ee was reached with **12c** in hexane *versus* 92% in the biphasic hexane–perfluoromethylcyclohexane system. The system was recycled twice by a simple liquid-liquid extraction without a significant loss of enantioselectivity. The authors showed that lengthening the perfluoroalkylchain does not have a positive effect on the recycling of the catalyst. Moreover, ligand **12c** led to higher activity and selectivity in hexane than its nonfluorinated analogue.

Compounds**13** prepared from ephedrine[31] were also tested for the same reaction with an ee of up to 84% with **13a**. The



Scheme 9 Addition of diethyl zinc catalyzed by amino alcohols.



Scheme 10 Reformatsky reaction catalysed by trifluoromethyl amino acohols.

catalytic system was in that case recovered by filtration through a fluorous reverse phase silica gel and reused without purification up to ten times. It has to be mentioned that the reaction was performed in a toluene–hexane mixture without fluorous solvent, the fluorous part of the ligand being thus only necessary for the final purification. Ephedrine has been heterogenized through different methods. Thus, Laspéras *et al.*[32] reported its immobilization on inorganic mesoporous templated silica. Only 40% ee was measured, which has to be compared to the 67% ee obtained with ephedrine. This poor result was ascribed to either a possible participation of uncovered surface in the racemic alkyl transfer or to a lack of accessibility of the catalytic asymmetric sites. No recycling experiment was described. Soai *et al.*[33] reported 93% ee with dendrimers based on ephedrine. The system was recycled twice with similar activity and enantioselectivity. In the case of ephedrine, it seems that the fluorous system leads to the best results in terms of recycling. Nevertheless, the economical interest of ephedrine recycling compared to the cost of its polyfluoration can be addressed.

Another family of ligands was shown to be efficient for this reaction: trifluoromethylated amino alcohols.[34] These compounds can hardly be considered as fluorinated derivatives due to their low fluorine content. Nevertheless, in the specific case of diethyl zinc addition, they ensure a higher aggregation of the zinc species than their methyl analogues, which has a positive effect on the asymmetric induction. Thus, ligand **15** induced 90% ee *versus* only 20% ee for ligand **14** under the same conditions. Even if the mechanistic reasons of this behaviour are not clear yet, it seems that again the electron-withdrawing effect of the trifluoromethyl group has to be taken into account.

Reformatsky reaction

Another reaction that takes advantage of the association of zinc species is the Reformatsky reaction[35] (Scheme 10). Similarly, ligand **15** led to a better enantioselectivity than its methylated analogue **14** and in THF up to 90% ee was reached, which was the best result ever obtained in this reaction.

These two examples (diethyl zinc addition and Reformatsky reaction) tend to prove that the negatively charged nature of the fluoromethyl group makes trifluoromethylated ligands particularly effective for stereoselective alkylation with a carbanion species.

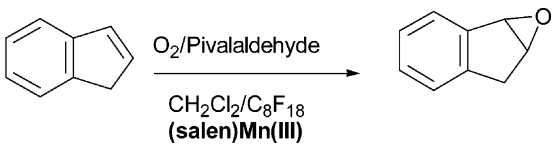
C–O bond formation

Epoxidation of C=C

Asymmetric epoxidation of C=C is a powerful method, which gives access to valuable chiral intermediates. Jacobsen and Katsuki developed catalytic systems based on chiral salen metal complexes able to perform such a reaction. The fluorous version of these systems was first tested in 1998.[36] Thus, salen bearing perfluoroalkyl ponytails were synthesized and tested in biphasic systems (ligands **2a**, **2c**, **3d**, **3e** in Scheme 3). Only ligands **2c** and **3e** with a fluorine content of respectively 59% and 62% were soluble in perfluorocarbon, which allowed their easy isolation from the organic reaction mixture. They were tested under the conditions depicted in Scheme 11 with various alkenes.

Only indene gave a good ee (up to 92%), but the catalytic system was recycled only once. It is important to notice that ligands **2c** and **3e**, which led to good enantioselectivity, bore substituents at the 3,3′ and 5,5′ positions like the best salen ligands used in classical homogeneous catalysis, with *t*-butyl groups at these positions. Nevertheless, the electron-withdrawing effect of the fluorous alkyl chain was supposed to affect the catalytic activity of the corresponding metal complex. Therefore, a second generation of salen ligands was synthesized with *t*-butyl groups in the 5,5′ positions and several fluorous ponytails in the 3,3′ positions far enough from the metal centre to prevent the electron-withdrawing effect (ligands **16** and **17**).[37] This time, using the oxidating system PhIO–pyridine *N*-oxide in the perfluorooctane–CH_3CN biphasic system, good to excellent enantioselectivities were obtained (50–92% ee). Moreover, the system was recycled 3 times before oxidative decomposition of the catalyst. This feature was commonly encountered with other immobilized (salen)Mn systems. These results tend to prove that both steric and electronic factors must be taken into account. It has to be noticed that the use of the fluorinated counterion $C_7F_{15}COO^-$ enhances the solubility of the fluorous complex in the fluorous phase and this is in favour of a better activity.

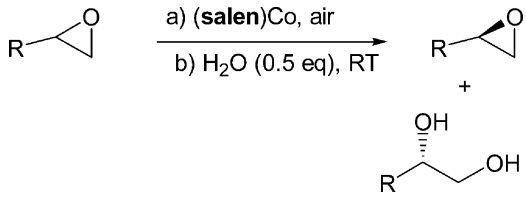
Numerous salen complexes have been supported on various inorganic supports such as silica gel[38] or mesoporous materials[39] and tested in the asymmetric epoxidation of alkenes. Soluble and insoluble polymeric matrices have also been used for such a reaction.[40] In most cases, the catalytic system could be reused several times with constant activity and selectivity. Usually, after three to five runs leaching occurred due to salen oxidative degradation. In this case, both approaches, the fluorous biphase one and the supported one, lead to the same results and suffer from the same drawback, the instability of the salen under the reaction conditions.



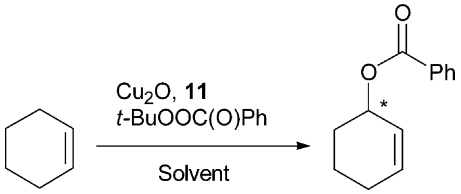
Scheme 11 Asymmetric epoxidation using salen type ligands.

Hydrolytic kinetic resolution of terminal epoxides

Another application of fluorous salen ligands could be the hydrolytic kinetic resolution of terminal epoxides (Scheme 12). This reaction, described by Jacobsen in 1997, was performed under mild conditions using Co complexes. In this way, decomposition of the catalytic system could be avoided. Two types of ligands were tested: light fluorous ones (F < 50%)[41] such as **2b** and **3a** (respectively 45.3 and 48.6% F) soluble in CH_2Cl_2 and toluene but insoluble in perfluorocarbons at room temperature; and a richer fluorous one (F = 63%),[42] **3e**, insoluble in these organic solvents and slightly soluble in perfluorocarbons at room temperature. Prior to the reaction, the Co(II) complexes first have to be oxidized into the catalytically active Co(III) species, and once again, $C_8F_{17}COO^-$ as a counterion played a beneficial role, leading to an increase of activity. The salen Co(III) complexes thus obtained were solu-



Scheme 12 Hydrolytic kinetic resolution of epoxides.



Scheme 13 Allylic oxidation of cyclohexene.

ble in the starting epoxides and the reaction was performed without solvent. Finally, **3a** turned out to be the best-performing ligand and more than 99% ee on both the diol and the epoxide was measured. Moreover, the catalyst was recycled 3 times with only minor loss in activity and selectivity. Recycling was made possible by distillation of the organic products. A standard fluorous biphasic procedure was not possible due to the light fluorous content of this ligand ($F < 60\%$) and its insolubility in fluorous media. The separation on fluorous reverse-phase silica of the organic products from the catalyst was possible but the recovery of the catalyst was incomplete. The heavily fluorinated chiral salen **3b** led to excellent enantioselectivity too ($>99\%$ ee for 1-hexene oxide) in the biphasic epoxide–perfluorooctane mixture but recycling caused a loss in catalytic activity with the same enantioselectivity. Polystyrene- and silica-bound chiral Co(salen) complexes[43] were used for the heterogeneous version of this reaction. These materials were easy to separate from the reaction mixture and could be reused several times with the same activity and selectivity as their homogeneous counterpart.

Due to its high affinity for the fluorous modified silica, ligand **3a** complexed with Co was adsorbed on this material and tested in the same hydrolytic kinetic resolution of 1-hexene oxide, but no reaction occurred. This could be due either to isolation of the catalytic sites (whereas a cooperative bimetallic mechanism is proposed) or to the difficulty encountered by water to access the catalytic site, due to the hydrophobic character of the fluorous silica.

Allylic oxidation

Enantioselective allylic oxidation of olefins with *t*-butyl perbenzoate, known as the Kharasch–Sosnovsky reaction (Scheme 13), is a possible approach to allylic alcohols. Among the different catalytic systems described in the literature, only the proline–Cu one developed by Levina and Muzart[44] has been developed in its fluorous version.[45] Once again, it has not been possible to work in FBS, even if Le Bras and Muzart[46] recently published the successful use of BTF with a racemic cationic cupper complex. Hexafluoroisopropanol (HFIP)[45] was the best solvent in the case of fluorous proline. In 2 h, 77% isolated yield and 20% ee were obtained instead of 59% isolated yield and 45% ee with proline in benzene. Recycling was possible but with both loss in activity and selectivity (54% and 13%, respectively, for the second run).

Conclusion and perspectives

The numerous results published since 1994 and the seminal work of Horváth and Rabái clearly show that asymmetric catalysis with fluorine containing ligands is now well-established. Nevertheless, the scope and limitations of this approach are far from being assessed. The results reported in this article prove that fluorous nitrogen-containing ligands are widely used in asymmetric catalysis. Because this approach is still "young", all the potential applications of these ligands have not yet been tested nor have fluorous versions of all the existing powerful nitrogen-containing ligands been synthesized.

Nevertheless, we can already draw preliminary conclusions and list several conditions that fluorinated ligands must meet in order to be efficient. First of all, it is difficult to apply a real fluorous biphasic technique as most of the time fluorinated ligands are soluble in organic solvents, due to their low fluorine content. It must be superior to 60% to ensure good solubility in fluorous solvents and exploit the possibilities of biphasic catalysis and/or easy separation. Moreover, it is better to have several polyfluoroalkyl chains judiciously spread around the carbon skeleton than only one chain, even if the overall fluorine content is the same. This crucial observation was at the origin of numerous so-called second generation ligands. In the case of light fluorous ligands it is not possible to perform the reaction in fluorous media but the separation between the products and the catalytic system is possible by chromatography techniques, thanks to the difference of polarity induced by the fluorinated part of the ligand. In addition, the electron-withdrawing properties of fluorine often deactivate the catalyst, but the use of carefully chosen spacers allows this problem to be avoided. Moreover, in some cases, this effect has a beneficial impact, as in the nucleophilic addition of diethyl zinc.

All these points have to be taken into account for the conception of good fluorous ligands but they alone are not enough. For example, the spatial arrangement of the different fluorous chains around the metal centre is still not well-established and can have a great impact on both activity and selectivity. The influence of the fluorous solvent itself on the reaction is still a matter to be addressed. These general remarks are valuable for every type of ligand, and especially in the case of fluorous nitrogen-containing ligands.

The primary objective of using fluorous ligands was to synthesize catalytic systems that are easy to separate and recyclable thanks to their difference of solubility between fluorous and organic solvents. This approach comes after the concepts of "supported" catalysis or heterogeneous catalysis, which have the same purpose. We have focussed our review on fluorous nitrogen-containing ligands first because, like their nonfluorous counterparts, they have interesting intrinsic properties due to the nitrogen atom(s) and second because the heterogenization of nitrogen-containing ligands is widely illustrated with organic and inorganic supports, contrary to phosphine, and thus comparisons between the two approaches are possible. In most cases, fluorous catalytic systems are recyclable at most one or two times with the same activity and selectivity. After a few runs, the ligand is decomposed, poisoned and/or there is metal leaching. Generally, the same problems are encountered with their supported or heterogenized counterparts. Concerning the separation of the catalytic system from the reaction mixture, in both approaches precipitation techniques, filtration or chromatography allow to recover the catalyst, reusable or not. This is particularly interesting in the case of pharmaceutical products, for example, when extremely high purities have to be obtained. Whatever the type of fluorous ligand, light or heavy, the choice of the appropriate solvent allows solubilization of the catalytic system and thus avoids the problems of diffusion encountered in heterogeneous catalysis. To prevent this problem, soluble organic supports, mainly polymers, are used in supported catalysis. Thus, it seems that the two concepts, heterogenization or fluorination of existing systems, suffer from the same drawbacks and are not as performant as they were planned to be!

Supercritic conditions have also been tested with fluorous ligands but it seems that fluorination is not always necessary to ensure good activity and selectivity.

nitrogen-containing functional groups are particularly appropriate for combinatorial chemistry and solution phase mixture synthesis with fluorous compounds could be one of the possible applications of fluorous nitrogen ligands.[47] Nevertheless, in our opinion an important parameter not already explored in asymmetric catalysis is the intrinsic properties of

fluorinated solvents. Numerous examples have been published in organic synthesis that show the positive effect of fluorous solvents on activity and selectivity.[48] It might be better to choose first the fluorinated solvent and then to adapt the ligand. It seems that this factor has not been thoroughly examined in asymmetric catalysis.

Every time a new concept appears many people rush to work in the field but are rapidly disappointed and stop working on the subject. This has been the case for fluorous biphasic catalysis. This approach is not as simple as it first seems but good results have already been obtained. Plenty of work remains to be done, numerous directions are still unexplored. In this short review we have tried to show the drawbacks, the advantages and the potentialities of fluorous biphasic catalysis and fluorous nitrogen-containing molecules. We really do believe that there is a future for such a chemistry and we are currently working in this direction.

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