

Chiral fluorous catalysts: synthesis and purposes

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Abstract

Despite the growing number of applications of fluorous biphasic catalysis and related techniques, only a few examples of asymmetric reactions carried out under these conditions have been reported up to now. Scope and limitation of this approach are thus far to be assessed. Our efforts toward this goal will be presented here, with emphasis on the design of efficient chiral fluorous catalysts. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Environmental and safety concerns are spurring the search for alternatives to the most common organic solvents. Accordingly, the use of novel reaction media such as supercritical fluids [1], ionic liquids [2], and liquid biphasic systems (aqueous/organic [3] as well as purely organic [4]) in synthetic organic chemistry is now thoroughly investigated [5]. Besides offering the possibility of cleaner technology for the chemical industry, these reaction media sometimes promote reactions that are not attainable in common organic solvents, along with selectivity improvements related to the unique solvation environment [6,7]. Perfluorocarbons are particularly promising in this regard, because of their distinctive chemical and physical properties (e.g. low dielectric constant, chemical inertness, non-toxicity, low miscibility with common organic solvents and water) [8,9]. Following

the pioneering work of Horváth and Rábai [10], a number of reagents and catalysts bearing appropriate perfluoroalkyl substituents (“fluorous compounds”) have been prepared and used in “fluorous biphasic chemistry”. This expression has been coined to label the whole set of stoichiometric and catalytic reactions, phase separation and immobilization techniques that profit of perfluorinated media [11].¹ In particular, catalytic reactions in fluorous biphasic systems show several advantages over classical homogeneous systems, including easy product separation and catalysts recycling. Thus fluorous chemistry seems to have a great potential for enantioselective transformations, for which recovery of precious chiral reagents or catalysts and peculiar solvation effects can have critical importance [10,14]. As it will be discussed in the present report, only a few chiral fluorous compounds have been prepared so far and the results obtained in asymmetric reactions in perfluorinated media are not conclusive yet. However, the fluorous biphasic

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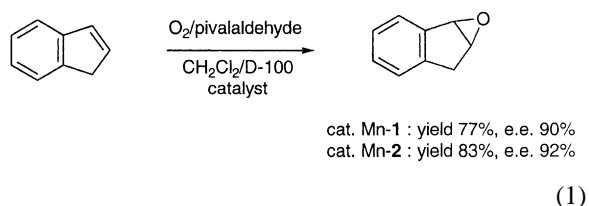
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¹ Principles and applications of fluorous biphasic chemistry are described in several reviews. See for instance Refs. [12,13].

approach can now stand the comparison with more popular methods of immobilization of chiral catalysts at least in the case of the asymmetric epoxidation of unfunctionalized alkenes.

2. Discussion

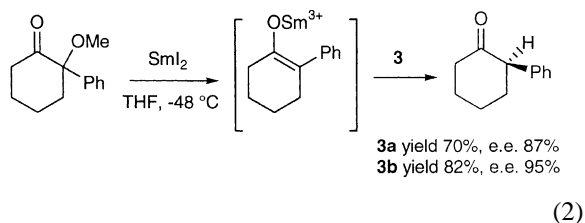
The first enantioselective reaction under fluororous biphasic conditions was described in 1998 [15]. C₂ nitrogen-based ligands were singled out as the most promising candidates for developing efficient and selective fluororous chiral catalysts. Indeed, the asymmetric epoxidation of indene in the presence of two different optically active fluororous (salen)manganese(III) complexes (Jacobsen–Katsuki catalysts Mn-1 and Mn-2, Fig. 1) was demonstrated (Eq. (1)).



Enantiomeric excesses up to 90% were obtained and recycling of the catalyst was also achieved, but other substrates gave low e.e.'s, even when they were structurally close to indene as in the case of dihydronaphthalene and benzosuberene [16].

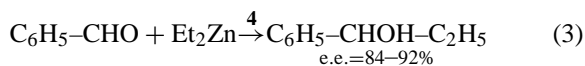
At the same time, Takeuchi et al. [17] reported the enantioselective protonation of a samarium enolate in the presence of a stoichiometric amount of an achiral alcohol soluble in perfluorohexane, and a chiral alcohol soluble in THF as the catalyst. The maximum enantioselectivity obtained in reactions carried out

in a fluororous biphasic system THF/perfluorohexane (e.e. = 60%) was higher than that attained in pure THF (e.e. = 43%). However, with a more enantioselective non-fluororous alcohol, the results were independent of the solvent system (e.e. = 90%). Later, the same reaction was described in the presence of an excess of the chiral fluororous BINOL derivative **3** as the only proton source (Eq. (2)) (Fig. 2) [18].



The use of the fluororous BINOL derivative **3b** resulted in a higher enantioselectivity (e.e. = 95%) than that obtained using the original non-fluororous analogue **3a** (e.e. = 87%).

van Koten and co-workers [19] have recently synthesized three fluororous chiral ethylzinc arenethiolates **4a–c** (Fig. 2). Experiments carried out in hexane as the solvent showed that these compounds are active catalysts in the 1,2-addition of diethylzinc to benzaldehyde (Eq. (3)).



The insertion of an R_FCH₂CH₂(Me₂)Si- ponytail enhanced both the activity and the enantioselectivity of the fluororous catalysts (e.e. up to 94% with respect to 72% obtained with a similar catalyst without the perfluoroalkyl substituent). Further experiments in a fluororous biphasic system demonstrated the

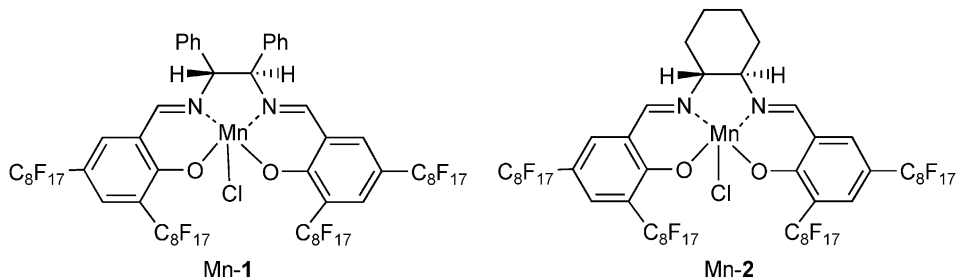


Fig. 1. First-generation chiral fluororous (salen) manganese (III) complexes.

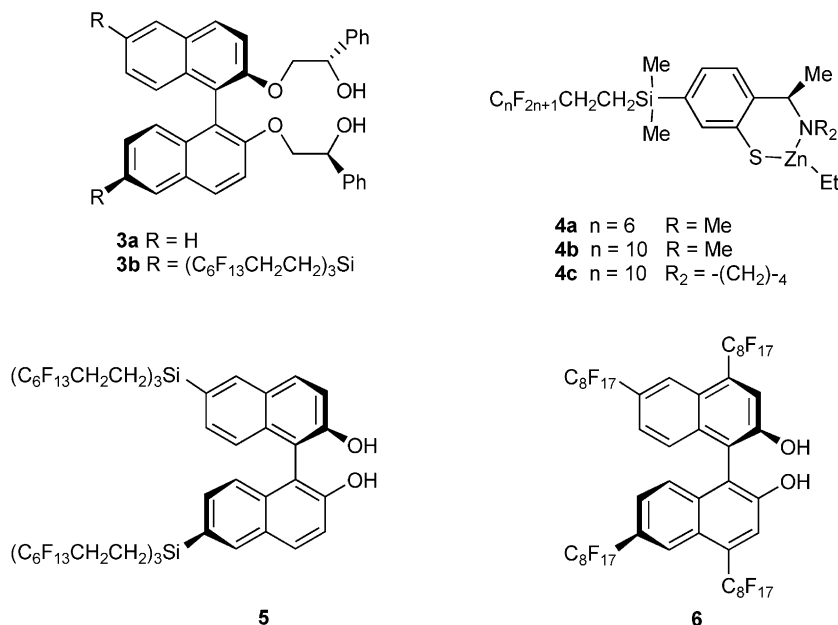


Fig. 2. Chiral fluororous ligands for the asymmetric addition of diethylzinc to arylaldehydes.

possibility of catalysts recycling, although a significant drop in enantioselectivity was generally observed after two runs.

The enantioselective 1,2-addition of diethylzinc to benzaldehyde in a fluororous biphasic system (toluene + hexane/perfluorohexane) was also reported by Takeuchi et al. [20]. The catalyst (a titanium complex generated in situ from Ti(O-*i*-Pr)₄ and the fluororous chiral BINOL **5**, Fig. 2) partitioned between the organic and the fluororous phase. Indeed, after each run about 10% of the fluororous ligand was recovered from the organic phase after acidic workup of the reaction mixture. Nevertheless, five consecutive runs were carried out using the ligand recovered from the fluororous phase only, without any apparent loss of enantioselectivity (e.e. = 80–83%) and catalytic activity. The presence of hexane in the reaction mixture enhanced the solubility of the fluororous catalyst in the organic phase and allowed to reach the same enantioselectivity observed for reactions catalyzed by non-fluororous titanium–BINOL in toluene. A similar approach was devised by Tian and Chan [21], who used of the highly fluorinated BINOL derivative **6** (Fig. 2) with Ti(O-*i*-Pr)₄ for the asymmetric diethylzinc addition to arylaldehydes in perfluoromethyldecalin/hexane.

After nine consecutive reaction/recovery cycles, the fluororous phase trapping the chiral ligand did not show any significant decrease of catalytic activity. However, despite the rather large amount of chiral ligand required (20 mol% with respect to the aldehyde), the catalytic system showed only moderate enantioselectivity (e.e. = 37–58%).

In the meantime, we have been pursuing the synthesis of new fluororous C₂ nitrogen-based ligands that were designed taking into account the drawbacks of first-generation salen catalysts [22]. Indeed, the low enantioselectivity levels observed in the fluororous epoxidation of alkenes catalysed by Mn-**1** and Mn-**2** (Fig. 1) were tentatively ascribed to: (a) the inadequate electronic insulation of the metal site from the strong electron-withdrawing effect of the perfluoroalkyl substituents (R_F); (b) the low steric hindrance ensured by R_F substituents placed in the key 3,3' and 5,5' positions of the ligands.

Second-generation fluororous (salen)manganese(III) complexes Mn-**7** and Mn-**8** (Fig. 3), in which the 3,3' positions of the ligand are occupied by *tert*-butyl substituents and perfluoroalkyl-substituted aryl moieties attached to the 5,5' positions, were thus synthesized. It should be noted that the biaryl frame offers

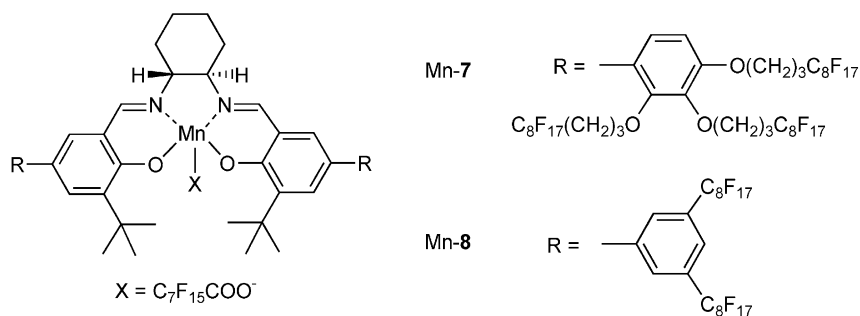


Fig. 3. Second-generation chiral fluoros (salen) manganese (III) complexes.

additional flexibility in salen ligands design. The overall number of R_F ponytails can be increased to attain the sought preferential solubility in perfluorocarbons and proper spacers can be inserted between R_F and the core structure of the ligand, in order to finely tuning the electron-withdrawing effect. The biaryl frame was also expected to have some influence on the three-dimensional structure of the catalyst and to generate more steric hindrance, possibly enhancing the enantioselectivity.

It is now widely accepted that a fluorine content of at least 60% is required to ensure preferential solubility of a catalyst or reagent in perfluorocarbons. The behaviour of Mn-7 and Mn-8 (% F = 56.9 and 57.9, respectively) represents an interesting exception to this rule of thumb. Indeed, partition coefficients for the two complexes between perfluorooctane and CH_3CN exceed 1000 and this makes possible their use under classical fluoros biphasic conditions. The nature of the counter anion is also crucial to get this result: it was observed that Mn-7 and Mn-8 quickly precipitate from the fluoros phase in the presence of Cl^- instead of $C_7F_{15}COO^-$, and this is probably due to aggregation phenomena.

The new catalysts were successfully employed in the asymmetric epoxidation of several alkenes under fluoros biphasic conditions (perfluorooctane/ CH_3CN). Both reaction yield and enantioselectivity rose with temperature and the best results were obtained at $100^\circ C$, corresponding to the boiling point of *n*-perfluorooctane, as exemplified in the case of 1,2-dihydronaphthalene (Fig. 4).

Blank experiments evidenced that only traces of epoxide were formed at this temperature in the

absence of the fluoros catalysts. Although the fluoros biphasic mixture did not become homogeneous at $100^\circ C$, the contact among the components of the catalytic system was obviously facilitated by the increased miscibility of the two layers. Emergence of temperature-dependent micellar effects cannot be ruled out either. The fluoros layer, easily separated upon cooling, could be reused up to three times after the first run. Catalytic activity generally dropped in the fourth run. Bleaching of the catalyst rather than leaching into the organic phase was responsible for this behaviour, as evidenced by the progressive disappearance of the characteristic UV-Vis absorption bands of the catalyst in the fluoros phase and by

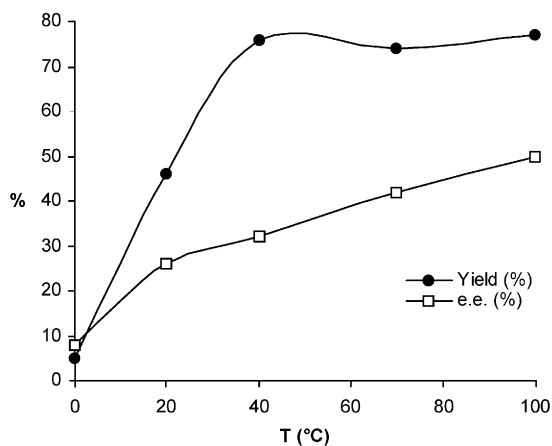
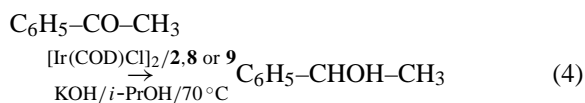


Fig. 4. Influence of the temperature on the yield and the enantioselectivity in the fluoros biphasic epoxidation of 1,2-dihydronaphthalene catalyzed by Mn-8.

the absence of such bands in the organic phase. This trend is in agreement with other investigations on the stability of immobilized (salen)Mn(III) complexes [23,24]. It was recently claimed by Reger and Janda [25,26] that immobilization of (salen)Mn(III) complexes onto gel-type resins offered an improvement over earlier immobilization systems and that it may find utility in high-throughput organic synthesis. Such supported catalysts afforded yields in epoxide ranging between 69 and 84%, with e.e. = 51–90%, and they could be generally used just twice before a decrease in yield and enantioselectivity was observed. One of the catalysts could be used for three subsequent reaction/recovery cycles only for two substrates. Epoxide yields (67–98%) and e.e. (50–87%) obtained with the fluororous biphasic approach are very close to those reported by Reger and Janda (Table 1). Moreover,

recycling of the fluororous catalysts is more effective and experimentally easier.

The good results obtained in the asymmetric epoxidation prompted us to check whether fluororous salen ligands might be conveniently used in other fluororous biphasic reactions. Ligands **2**, **8** and **9** (Fig. 5) associated with [Ir(COD)Cl]₂, were tested as catalysts for the asymmetric reduction of various ketones via hydrogen transfer (Eq. (4)) [27].



Reactions were carried out in a biphasic mixture isopropanol/perfluorooctane, affording alcohols with enantioselectivities ranging from 5 to 60%. Although not impressive, these values were consistently higher than those obtained in isopropanol alone using non-perfluorinated aldimines. On the other hand, recycling of the fluororous phase was unsuccessful probably due to the poor stability of these ligands under the reaction conditions. In order to circumvent this limitation, we are currently investigating the use of fluororous C₂ chiral diamines as ligands. Preliminary results are encouraging since, as expected, the stability of diamines towards solvolysis increases the service-life of the fluororous phase.

As phosphorous-based chiral ligands are extensively used in catalytic reaction, many efforts has been devoted to the synthesis of their fluororous analogues. However, such enantiopure compounds are not easily available, mainly because of purification problems. For example, Klose and Gladysz [28] described the synthesis of the chiral ligand **10** derived from menthol (Fig. 5), without any application in catalysis. A straightforward synthetic pathway was devised to prepare compound **11** which is a suitable ligand for “light fluororous” applications (Fig. 5) [29]. “Light fluororous” reagents and catalysts are characterised by partition coefficients between a perfluorocarbon and a common organic solvent that are too low to apply the fluororous biphasic protocol as such. In this case, alternative techniques based on the recovery of fluorinated molecules by liquid–liquid or solid-phase extraction have been proposed [30]. The feasibility of this approach has been tested by using **11** as a ligand in the Pd(0)-catalyzed asymmetric allylic alkylation

Table 1
Asymmetric epoxidation of various alkenes with PhIO/PNO in CH₃CN/perfluorooctane at 100 °C catalyzed by Mn-**8**^a

Run	Substrate	Yield (%) ^b	e.e. (%) ^c
1	1,2-Dihydronaphthalene	77	50
2		67	46
3		63	45
4		19	40
1	Benzosuberene	92	68
2		92	66
3		83	64
4		43	60
1	1-Methylindene	98	77
2		99	77
3		82	76
4		42	57
1	1-Methylcyclohexene	91	58
2		87	53
3		76	40
4		45	25
1	Triphenylethylene	98	87 ^d
2		96	85 ^d
3		92	83 ^d
4		80	71 ^d

^a PNO = pyridine *N*-oxide; *T* = 100 °C, time = 30 min; PhIO/PNO/substrate/catalyst = 1.5/0.25/1/0.05.

^b Determined by GC analysis (HP-5, 5% phenyl methyl siloxane column), internal standard method.

^c Determined by GC analysis (cyclodex-B chiral column).

^d Determined by ¹H NMR spectroscopy in the presence of the chiral shift reagent Eu(hfc)₃.

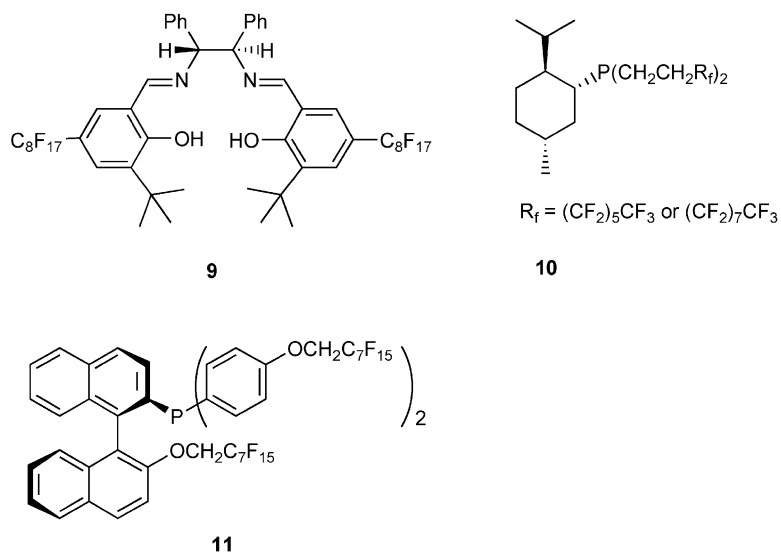
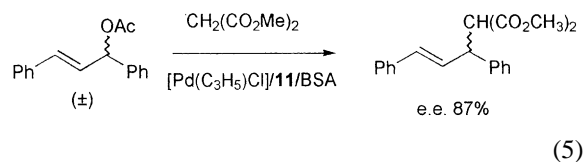


Fig. 5. Nitrogen- and phosphorus-containing chiral fluororous ligands.

of 1,3-diphenyl-2-propenyl acetate (Eq. (5)).



Reactions were carried out in toluene or benzotrifluoride under homogeneous conditions, affording e.e. up to 87% in the case of alkylation with dimethyl malonate. When toluene was used the solvent, the liquid–liquid extraction of the reaction mixture with perfluorooctane allowed the complete removal of the fluororous ligand and of the corresponding palladium derivatives. Although the recovered material lost its catalytic activity, as also observed in the case of achiral “light fluororous” phosphines [30], the easy separation of the organometallic compounds from the reaction mixture, together with the use of standard reaction conditions, make this approach very appealing.

3. Conclusions

Over the last 3 years, there has been rapidly increasing interest in the subject of asymmetric catalysis in fluorinated media. Remarkable progresses in this field have been obtained, although relatively slowly

due to the lack of available chiral fluororous ligand. Moreover, a better design of asymmetric fluororous catalytic systems is now possible since a few basic requirements have been identified. For instance, location and number of the perfluoroalkyl substituents in the ligand structure must be carefully chosen and in most cases shielding of the metal site from the electron-withdrawing effect of these substituents must be ensured. The nature of the counterion in the case of charged fluororous complexes should be taken into account and the choice of proper reaction conditions is also very important in order to achieve satisfactory results. In order to switch an homogeneous asymmetric catalytic reaction into its fluororous biphasic version, many parameters must be adjusted, and not always according to the chemist’s common sense as exemplified by the striking increase in enantioselectivity observed upon raising the temperature in the fluororous biphasic epoxidation of alkenes. Some of the potential advantages of chiral fluororous catalysis have been experimentally confirmed and this technique is likely to become much more popular in the next years.

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