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Second-generation fluorous chiral (salen) manganese complexes

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Sterically hindered chiral (salen)manganese complexes bearing long perfluoroalkyl substituents are synthesized and successfully employed as catalysts in the enantioselective (ee = 50–87%) epoxidation of alkenes under fluorous biphasic conditions.

Following the pioneering work of Horváth and Rábai,[1] a number of reagents and catalysts bearing appropriate perfluoroalkyl substituents ('fluorous compounds') have been prepared and used in 'fluorous biphase chemistry'.[2] Catalytic reactions in fluorous biphasic systems present several advantages over their classical homogeneous counterparts.[3] Fluorous chemistry has also a great potential for enantioselective transformations, offering both an easy way to recover precious chiral reagents or catalysts and unusual solvation effects. Nevertheless, only a few chiral fluorous compounds have been prepared to date and the actual influence of perfluoroalkyl substituents (R_F) and perfluorocarbon solvents on the outcome of asymmetric reactions is virtually unknown.[4] We have reported the first example of a fluorous biphasic enantioselective reaction, namely the epoxidation of alkenes in the presence of the optically active fluorous (salen)Mn^{III} complexes Mn-**1** and Mn-**2** (Jacobsen–Katsuki catalysts, Fig. 1).[4a] Good chemoselectivity and efficiency were observed in the epoxidation of several substrates, and recycling of the catalysts was also demonstrated. However, high levels of enantioselectivity were not attained, except in the epoxidation of indene (ee = 90%). This behaviour was tentatively ascribed to the low steric hindrance of the R_F groups in the 3,3'- and 5,5'-positions of the ligands and to the inadequate electronic shielding of the metal site from the strong electron-withdrawing effect of these substituents.[4c]

Second-generation (salen)Mn^{III} complexes Mn-**3** and Mn-**4** (Fig. 1) were designed with these assumptions in mind. In order to better shield the metal site, the R_F substituents in 5,5'-positions were replaced by perfluoroalkyl-substituted aryl moieties. Moreover, sterically demanding *tert*-butyl substituents were introduced in the key-positions 3,3' of ligands **3** and **4**.

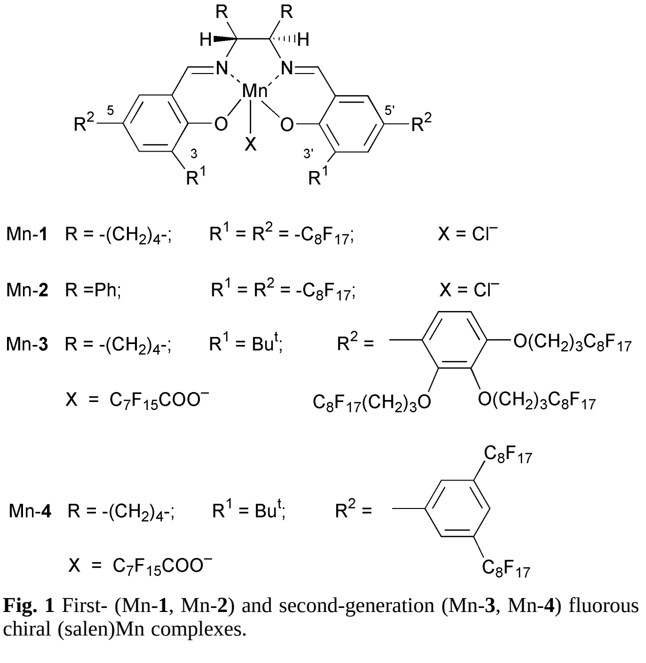
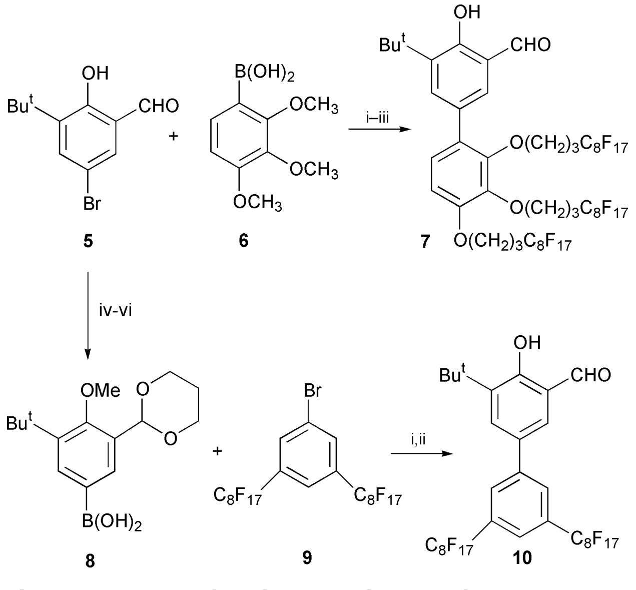


Fig. 1 First- (Mn-**1**, Mn-**2**) and second-generation (Mn-**3**, Mn-**4**) fluorous chiral (salen)Mn complexes.

Both salicylaldehydes **7** and **10**, the key intermediates for the synthesis of ligands **3** and **4**, were prepared starting from aldehyde **5**,[5] as shown in Scheme 1. Pd^0-catalyzed cross-coupling reaction of **5** with boronic acid **6** (yield = 86%),[6] followed by *O*-deprotection (89%) and *O*-alkylation with $C_8F_{17}(CH_2)_3I$ (37%), afforded the fluorous salicylaldehyde **7**. Mono- and bis-*O*-alkylated biaryl compounds were isolated from the reaction mixture by column chromatography and reused in following runs.

In the case of salicylaldehyde **10,** aldehyde **5** was used as a precursor of aryl boronic acid **8**, whereas perfluoroalkyl-substituted aryl bromide **9** was prepared by copper-mediated cross-coupling reaction of 1,3,5-tribromobenzene with 2 equiv. of $C_8F_{17}I$. The bis(perfluoroalkyl) derivative was obtained as the main product and isolated in reasonable yields (60%) after crystallization from CH_2Cl_2 and then from Et_2O. Pd^0-catalyzed cross-coupling reaction of crude aryl boronic acid **8** with **9**, followed by deprotection with BBr_3 gave the desired salicylaldehyde **10** in 62% yield.

Condensation of two equivalents of salicylaldehyde **7** or **10** with (1*R*,2*R*)-(−)-1,2-diaminocyclohexane in boiling ethanol afforded the fluorous salen ligands **3** (72%) and **4** (95%), respectively.[7] Mn^{III} complexes Mn-**3** and Mn-**4** were prepared by reaction of the corresponding ligand with an excess of $Mn(OAc)_2{\cdot}4H_2O$ in refluxing ethanol under aerobic conditions, followed by anion exchange with LiCl and then $C_7F_{15}COONH_4$. The exchange of Cl^- for the fluorophilic



Scheme 1 *Reagents and conditions*: i, $Pd(OAc)_2/PPh_3$, Pr^iOH, aqueous Na_2CO_3, 110 °C; ii, BBr_3, CH_2Cl_2, 0 °C; iii, $C_8F_{17}(CH_2)_3I$, K_2CO_3, CH_3CN, 70 °C; iv, $(CH_3)_2SO_4$, K_2CO_3, acetone, r.t.; v, $HO(CH_2)_3OH$, *p*-TsOH, toluene, reflux; vi, BuLi, −78 °C, THF, 45 min, then $B(OCH_3)_3$, −78 to 0 °C, aqueous HCl.

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$C_7F_{15}COO^-$ anion resulted in the sought preferential solubility of Mn-**3** and Mn-**4** in perfluorocarbons, as verified by partition experiments in biphasic mixtures *n*-perfluorooctane/organic solvents. Partition coefficients, determined by UV–Vis spectroscopy at 25 °C,[8] were found to be quite similar for the two complexes, ranging from 1.21 for Mn-**3** in *n*-perfluorooctane/hexane, to >1000 for Mn-**3** and Mn-**4** in *n*-perfluorooctane/CH_3CN and *n*-perfluorooctane/toluene.

First- and second-generation (salen)Mn^{III} complexes were initially compared in the homogeneous epoxidation of 1,2-dihydronaphthalene in CH_2Cl_2/benzotrifluoride, using *meta*-chloroperbenzoic acid/ *N*-methylmorpholine *N*-oxide (*m*-CPBA/NMO) as the oxidant at −50 °C.[9] Second-generation catalysts afforded ee values much higher than those obtained with Mn-**1** and Mn-**2** (63% *vs*. 16 and 12%, respectively) and slightly improved epoxide yields (70% with Mn-**3** and Mn-**4** *vs*. 60% with Mn-**1** and Mn-**2**). Other oxidising agents commonly used in association with (salen)Mn^{III} complexes were also tested and the superiority of the new complexes was confirmed.

PhIO together with small amounts of pyridine *N*-oxide (PNO) was used as the oxidising system in the next fluorous biphasic reactions that were run in *n*-perfluorooctane/CH_3CN (Table 1).† This set of conditions was chosen taking into account the favourable partition coefficients of the catalysts and considering that homogeneous epoxidation reactions with PhIO/PNO are conveniently carried out in CH_3CN at 0–25 °C.[10] Both reaction yield and enantioselectivity rose with temperature under fluorous biphasic conditions: the best results were obtained at 100 °C, corresponding to the boiling point of *n*-perfluorooctane (Table 1, entries 1–5). Blank experiments evidenced that only traces of epoxide are formed at this temperature in the absence of the fluorous catalysts. The results obtained in the fluorous biphasic epoxidation of 1,2-dihydronaphthalene with PhIO/PNO at 100 °C (entry 5) compare favourably to those reported for the same reaction in CH_3CN in the presence of Jacobsen's catalyst, a commercially available, standard (salen)Mn^{III} complex (yield = 70%, ee = 46%).[11]

The fluorous layer, easily separated upon cooling, could be reused up to three times after the first run as exemplified in the case of triphenylethylene (entries 8–10). Catalytic activity generally dropped in the fourth run due to the oxidative decomposition of the catalyst, as evidenced by the progressive disappearance of the characteristic UV–Vis absorption bands of the (salen)Mn^{III} in the fluorous phase and by the absence of such bands in the organic phase. Such behaviour is in agreement with previous literature reports dealing with (salen)Mn^{III} complexes immobilised by other techniques.[11]

Table 1 Asymmetric epoxidation of alkenes with PhIO/PNO in CH_3CN/perfluorooctane.[a]

Entry	Catalyst	Substrate	T/°C	t/h	Yield[b](%)	Ee[c](%)
1	Mn-**4**	1,2-dihydronaphthalene	0	3	4.5	8
2	Mn-**4**	1,2-dihydronaphthalene	20	3	46	26
3	Mn-**4**	1,2-dihydronaphthalene	40	3	76	32
4	Mn-**4**	1,2-dihydronaphthalene	70	2	74	42
5	Mn-**4**	1,2-dihydronaphthalene	100	1	77	50
6	Mn-**3**	1,2-dihydronaphthalene	100	1	68	50
7	Mn-**4**	triphenylethylene	100	0.5	98	87[g]
8	Mn-**4**[d]	triphenylethylene	100	0.5	96	85[g]
9	Mn-**4**[e]	triphenylethylene	100	0.5	92	83[g]
10	Mn-**4**[f]	triphenylethylene	100	1	80	71[g]
11	Mn-**3**	triphenylethylene	100	0.5	98	80[g]
12	Mn-**4**	benzosuberene	100	0.5	92	68
13	Mn-**3**	benzosuberene	100	0.5	84	69
14	Mn-**4**	1-methylindene	100	0.5	98	77
15	Mn-**3**	1-methylindene	100	0.5	96	70
16	Mn-**4**	1-methylcyclohexene	100	0.5	91	58
17	Mn-**3**	1-methylcyclohexene	100	0.5	95	52

[a] See footnote †. [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] First, [e] second and [f] third reuse of the fluorous layer. [g] Determined by ^1H NMR spectroscopy in the presence of the chiral shift reagent Eu(hfc)$_3$.

The use of the second-generation (salen)Mn^{III} complexes considerably widen the scope of the fluorous biphasic epoxidation reaction, since these catalysts not only afford good epoxide yields, but also ee ranging from 50 to 87% with several substrates. This finding strongly supports our aforementioned hypotheses about the role of R_F substituents on the catalytic activity of (salen)Mn^{III} complexes. The relative importance of electronic and steric effects in determining the enantioselectivity of fluorous (salen)Mn^{III} complexes and the design of new chiral fluorous catalysts are currently investigated in this laboratory.

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Notes and references

† General procedure for the asymmetric epoxidation of alkenes under fluorous biphasic conditions: in a 10 ml Schlenk vessel placed in a thermoregulated bath at 100 °C, 1 ml of a 0.2 M solution of alkene in CH_3CN containing *o*-dichlorobenzene (0.1 M, internal standard for GC) and 0.2 ml of a 0.25 M solution of pyridine *N*-oxide (PNO) in CH_3CN were added under nitrogen to 1 ml of a solution of the catalyst in *n*-perfluorooctane. PhIO (67 mg, 0.3 mmol) was quickly added under a nitrogen stream. The two-phase mixture was magnetically stirred at 1300 ± 50 rpm and cooled to room temperature at the end of the reaction. The brown fluorous layer was separated, washed with CH_3CN (2×0.5 ml) and reused in further runs (see Table 1). The combined organic layers were washed with saturated aqueous Na_2SO_3 (1 ml), brine (1 ml) and dried ($MgSO_4$). Epoxide yield and enantiomeric excess were determined by gas-chromatographic analysis of the organic solution.

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