Efficient aerobic epoxidation of alkenes in perfluorinated solvents catalysed by chiral (salen) Mn complexes

Gianluca Pozzi,*† Flavio Cinato, Fernando Montanari and Silvio Quici

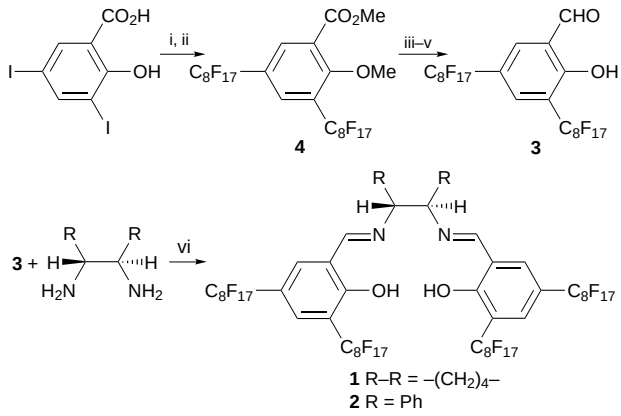
Centro CNR and Dipartimento di Chimica Organica e Industriale dell'Università, Via Golgi 19, I-20133 Milano, Italy

Chiral complexes selectively soluble in perfluorocarbons have been synthesized for the first time and tested as catalysts for the epoxidation of alkenes under fluorous biphasic conditions.

The use of perfluorocarbons as reaction media in preparative organic chemistry and homogeneous catalysis is a topic of growing interest.[1] In particular, the value of a new phase-separation and immobilization technique known as FBS (Fluorous Biphase Systems), developed by Horváth and Rábai,[2] is now becoming evident to both academic and industrial researchers. Principles and current achievements of this technique have been recently reviewed.[3] The introduction of FBS raises a number of questions, among them the possible application to enantioselective reactions. Besides helping recovery and reuse of precious chiral reagents or catalysts, it has been repeatedly proposed that the unique solvation environment provided by perfluorocarbons might have unforeseen beneficial effects on the selectivity of the reactions.[4] However, neither examples of enantioselective FBS reactions nor feasibility studies have been reported so far. Metal complexes of salen ligands are able to catalyse the epoxidation of unfunctionalized alkenes.[5] The synthetic route to salen ligands is straightforward and can be adapted to the preparation of many different compounds, including chiral ones.[6] This offers the opportunity to increase the very limited number of known catalysts for FBS oxidations,[7,8] and also to begin assessing the true potential of FBS in enantioselective catalysis. For these reasons we have synthesized two optically active (salen)Mn^{III} complexes (Jacobsen–Katsuki catalysts) selectively soluble in fluorocarbons (Scheme 1). They were tested as catalysts in the epoxidation of alkenes under FBS conditions, in the presence of various oxygen donors.

Both C_2 symmetric salen ligands **1** and **2** were obtained in good yields (75 and 82%, respectively) by the condensation of 2 equiv. of the perfluoroalkylated salicylaldehyde **3** with the proper chiral 1,2-diamine (Scheme 1).‡ The synthesis of the key compound **3** was easily achieved following the pathway reported in the same scheme. The free OH groups of 3,5-diiodosalicyclic acid were protected by methylation with Me_2SO_4 (quantitative yield) before the coupling reaction with 2 equiv. of $C_8F_{17}I$ mediated by Cu powder (65% yield).[9] The ester **4** was converted into **3** by reduction to benzylic alcohol (70% yield) followed by oxidation (85% yield) and demethylation (88% yield). The use of trifluoromethylbenzene as solvent greatly improved the yield of the oxidative step,[10] which was conveniently carried out under aqueous-organic two-phase conditions according to a procedure already reported by us.[11] The free salen ligands were soluble in cold perfluorocarbons,§ CCl_2FCF_2Cl and Et_2O, soluble in hot EtOH and only sparingly soluble in cold halogenated solvents. The corresponding manganese complexes (Mn–**1** and Mn–**2**), obtained in quantitative yield by refluxing an ethanolic solution of ligand with an excess of $Mn(OAc)_2{\cdot}4H_2O$, were soluble in cold perfluorocarbons and CCl_2FCF_2Cl, but completely insoluble in common organic solvents.

Mukaiyama and co-workers have shown that optically active (salen)Mn complexes catalyse the enantioselective epoxidation of alkenes in the presence of molecular oxygen and a sacrificial aldehyde.[12] Fluorocarbons dissolve large quantities of molecular oxygen and this property has been exploited in oxidation reactions, including the epoxidation of alkenes under FBS conditions in the presence of aliphatic aldehydes.[7a,8b] Complexes Mn–**1** and Mn–**2** were thus first tested adapting Mukaiyama conditions to a typical FBS procedure (see Table 1 for results and conditions). Reactions were carried out in the dark at 20 °C under atmospheric pressure of O_2, with Mn–**1** and Mn–**2** immobilized in the fluorinated phase. In the absence of the catalyst, conversions were negligible. As already reported in



Scheme 1 *Reagents and conditions*: i, Me_2SO_4, K_2CO_3, acetone, reflux; ii, $C_8F_{17}I$, Cu, DMF, 125 °C; iii, LAH, Et_2O, 0 °C; iv, aq. NaOCl, KBr (10 mol%), TEMPO, $PhCF_3$, 5 °C; v, BBr_3, CH_2Cl_2 −78 °C, then toom temp.; vi, EtOH, reflux

Table 1 Expoxidation of alkenes with O_2–pivalaldehyde catalysed by chiral (salen)Mn complexes under FBS conditions[a]

Catalyst	Substrate	*t*/h	Conversion (%)[b]	Yield (%)[c]	Ee (%)
Mn–**1**[d]	Indene	2	100	83	92[e]
Mn–**1**[d]	1,2-Dihydronaphthalene	8	85	70	10[e]
Mn–**1**[d]	Styrene	5	100	86	n.d.[e]
Mn–**1**[f]	3-Nitrostyrene	12	70	36	n.d.[e]
Mn–**1**[d]	*trans*-β-Methylstyrene	5	100	75	n.d.[g]
Mn–**1**[d]	*trans*-Stilbene	12	80	78	n.d.[g]
Mn–**1**[d]	*cis*-Stilbene	12	88	85[h]	—
Mn–**2**[d]	Indene	3	100	77	90[e]
Mn–**2**[d]	1,2-Dihydronaphthalene	8	95	73	13[e]
Mn–**2**[d]	Styrene	5	100	81	n.d.[e]

[a] Conditions: [catalyst] = 0.005 M in D-100; [substrate] = 0.33 M in CH_2Cl_2; [pivalaldehyde] = 1 M in CH_2Cl_2; [*N*-hexylimidazole] = 0.033 M in CH_2Cl_2; volume of D-100 = 3 ml; volume of CH_2Cl_2 = 3 ml. *T* = 20 °C. Stirring rate = 1300 rpm. [b] Determined by capillary GC integration against an external standard (dichlorobenzene). [c] Isolated epoxide. [d] A second run with the recovered perfluorocarbon layer gave almost the same results. [e] Determined by capillary GC using a Cyclodex-B chiral column. n.d. = not detected. [f] The catalyst bleached in the first run. [g] Determined by ^1H NMR spectroscopy in the presence of Eu(hfc)$_3$. [h] *cis* : *trans* epoxide = 3 : 1.

Table 2 Epoxidation of 1,2-dihydronaphthalene catalysed by Mn–**1** under FBS conditions[a]

Oxidant	Solvent	*t*/h	*T*/°C	Conversion (%)[b]	Yield (%)[b]	Ee (%)[c]
30% H_2O_2[d]	MeCN	0.5	20	—	—	—
PhIO	MeCN	24	20	85	65	6
Bu_4NHSO_5	CH_2Cl_2	10	20	95	89	8
MCPBA–NMO[e]	CH_2Cl_2	4	−78	10	9	5
MCPBA–NMO[e]	CH_2Cl_2	6	−50	70	56	7
MCPBA–NMO[e]	CH_2Cl_2	6	−20	98	86	5
MCPBA–NMO[e,f]	CH_2Cl_2	4	−50	90	85	71

[a] Conditions: [catalyst] = 0.005 M in D-100; [substrate] = 0.1 M in CH_2Cl_2; volume of D-100 = 1 ml; volume of CH_2Cl_2 = 1 ml; oxidant: 0.2 mmol. Stirring rate = 1300 rpm. [b] Determined by capillary GC integration against an internal standard (dichlorobenzene). [c] Determined by capillary GC using a Cyclodex-B chiral column. [d] The catalyst bleached in 30 min. [e] NMO = *N*-methylmorpholine *N*-oxide (0.5 mmol). Addition of the oxidant was carried out according to the procedure described in ref. 13. [f] Substrate = indene.

the case of the cobalt complex of a perfluoroalkylated tetraarylporphyrin, the presence of two distinct phases did not preclude the oxidation of the substrate dissolved in the organic solvent.[7a] Both complexes were found to be active catalysts, affording epoxides in isolated yields up to 85%. Moreover we were able to use the catalysts in substantially lower amounts than those required under homogenous conditions (catalyst = 1.5% with respect to the alkene, instead of 12%).[12] The brown perfluorocarbon layer recovered by simple decantation could be generally recycled in a second run without appreciable decrease of activity. Rather surprisingly, only indene was epoxidized with high enantioselectivity (> 90%). All the other alkenes that we tested gave low (15%) or even 0% ee. The same trend was observed when reactions were carried out in the presence of other oxygen donors more commonly used in combination with chiral (salen)Mn. Results are exemplified in Table 2 for the epoxidation of 1,2-dihydronaphthalene and indene catalysed by Mn–**1**. Epoxidations with the couple *m*-chloroperbenzoic acid–*N*-methylmorpholine *N*-oxide (MCPBA–NMO) were very slow at −78 °C, probably because of hindered mass-transfer between the two liquid phases. Although still lower than in the case of homogeneous systems,[13] reaction rates in the FBS became reasonable at −50 °C. Catalyst Mn–**2** gave lower ee (58%) and conversion (50%) with respect to Mn–**1** in the MCPBA–NMO epoxidation of indene. In the case of 1,2-dihydronaphthalene ee was improved (15 *vs*. 7%), but conversion of the substrate was not satisfactory (45% after 5 h).

Despite the low enantioselectivities generally observed with our prototype catalysts, the FBS approach described here offers distinct advantages over other reported methods of immobilization of salen complexes. Note that in just one case the reported activities, chemoselectivities and ees of heterogenized Jacobsen–Katsuki catalysts were as high as those obtained with one of the best homogeneous chiral (salen)Mn complexes.[14] Stability of the catalyst immobilized in the fluorocarbon layer toward bleaching is increased and its activity remains high. The easy separation of the products from the catalyst which can be readily reused is another considerable benefit that was not given, for instance, by embedding salen complexes into the pores of zeolites.[15] The present results show that an improvement in enantioselectivity does not necessarily follow from the use of FBS versions of chiral catalysts. In this context, the behaviour of Mn–**1** and Mn–**2** is coherent with a strong electron-withdrawing effect exerted by the four perfluoroalkyl chains on the Mn–oxo intermediate responsible for the oxygen transfer.[16,17] Further synthetic efforts are required in order to improve enantiofacial discrimination, still maintaining the peculiar solubility of the catalysts in fluorocarbons.

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Notes and References

† E-mail: lupo@iumchz.chimorg.unimi.it

‡ *Selected data* for **1**: mp 108–109 °C; $[\alpha]_D^{20}$ −105.2 (*c* 0.5 in Et_2O); δ_H(300 MHz, $CDCl_3$) 13.45 (br s, 2 H), 8.29 (s, 2 H), 7.65 (d, *J* 2.1, 2 H), 7.47 (d, *J* 2.1, 2 H), 3.48–3.37 (m, 2 H), 2.16–1.68 (m, 8 H); δ_F(282 MHz, $CDCl_3$) −81.3 (t, *J* 10, 3 F), −106.9 (t, *J* 15, 2 F), −120.2 (br s, 2 F), −122.1 (m, 6 F), −123.2 (br s, 2 F), −126.6 (br s, 2 F). For Mn–**1**: $[\alpha]_D^{20}$ −780 (*c* 0.01 in CCl_2FCF_2Cl); λ_{max}(CCl_2FCF_2Cl)/nm 465, 385, 335. For **2**: mp 48–50 °C; $[\alpha]_D^{20}$ −8.8 (*c* 0.5 in Et_2O); δ_H($CDCl_3$) 13.24 (br s, 2 H), 8.44 (s, 2 H), 7.65 (d, *J* 2.1, 2 H), 7.52 (d, *J* 2.1, 2 H), 7.27–7.05 (m, 10 H), 4.82 (s, 2 H); δ_F(282 MHz, $CDCl_3$) −81.1 (t, *J* 10, 3 F), −106.8 (t, *J* 14, 2 F), −120.3 (br s, 2 F), −121.9 (m, 6 F), −123.8 (br s, 2 F), −126.6 (br s, 2 F). For Mn–**2**: $[\alpha]_D^{20}$ +90 (*c* 0.01 in CCl_2FCF_2Cl); λ_{max}(CCl_2FCF_2Cl)/nm 480, 385, 330.

§ The following commercially available perfluorocarbons were tested as solvents: FC-72 (3M, mainly perfluorohexanes, bp 56 °C), FC-75 (3M, mainly perfluoro-*n*-butyltetrahydrofuran, bp 102 °C), D-100 (Ausimont, mainly *n*-perfluorooctane, bp 100 °C).

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