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A macrocyclic chiral manganese(III) Schiff base complex as an efficient catalyst for the asymmetric epoxidation of olefins

Alexandre Martinez, Catherine Hemmert *, Bernard Meunier *

Laboratoire de Chimie de Coordination du CNRS, 205 route de Narbonne, 31077 Toulouse cedex 4, France

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Abstract

A new chiral macrocyclic Mn(III)-salen complex has been prepared with two salicylidene moieties linked together to their 3 and 3′ positions by an aliphatic polyether bridge. This complex provides a highly enantioselective (up to 93%) catalyst for epoxidation of *cis*-disubstituted olefins with sodium hypochlorite as an oxygen atom donor and can be recycled up to three times without significant loss in performance.

Keywords: Schiff base; Manganese; N, O ligands; Asymmetric catalysis; Epoxidation

1. Introduction

Chiral epoxides are important synthetic intermediates in the development of new drugs, and there is much interest in designing efficient catalysts for asymmetric olefin epoxidation [1]. In 1990, Jacobsen [2] and Katsuki [3] independently reported efficient optically active Mn(salen) catalysts for enantioselective epoxidation. Since then, several chiral Mn(salen) complexes have been developed, and high enantioselectivities have been achieved in the epoxidation of conjugated *cis*-di-, *cis*-tri-, and some tetra-substituted olefins [1,4]. But because these catalysts are associated with an oxygen atom donor, the epoxidation generally proceeds with relatively low turnover numbers, and most are unstable to prolonged oxidative conditions and thus are not recyclable [5]. Homogeneous chiral catalysts have been immobilized either by anchoring the catalyst on a solid support or by using a two-phase system [6]; however, both of these methods lead to partial loss of activity and/or enantioselectivity in all but a few examples [7].

We recently developed another approach to creating more robust catalysts, involving cyclization of the Jacobsen-type ligand. Macrocyclization of the ligand is expected to enhance the stability of the corresponding complexes in catalytic conditions in comparison with open-chain analogs (e.g., Jacobsen's catalyst Scheme 1), because of the macrocyclic effect. We have already reported preliminary results on the synthesis and catalytic activity of a first series of macrocyclic chiral Mn(salen) (e.g., complex **1**, Scheme 1) complexes for asymmetric epoxidation of *cis*-disubstituted olefins [8]. But these first macrocyclic chiral Mn(III)-salen complexes had two major drawbacks: (i) the enantiomeric excess values obtained in the asymmetric epoxidation of *cis*-disubstituted olefins were modest (with the best *ee* values ranging from 42 to 74%), probably due to the absence of bulky substituents in close proximity to positions 3 and 3′, and (ii) the catalysts were not recyclable. The presence of an additional oxygen atom at positions 3 and 3′ of the ligand, making an electron-rich aromatic ring easily oxidable, could explain the fragility of these complexes in catalytic conditions.

Taking into account these first results, we report here on the preparation and catalytic activity of a new, more robust macrocyclic chiral Mn(III)-salen complex (e.g., complex **2**,

* Corresponding authors. Fax: +33-5-61-553003.
E-mail address: hemmert@lcc-toulouse.fr (C. Hemmert).

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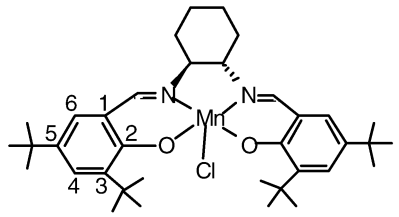
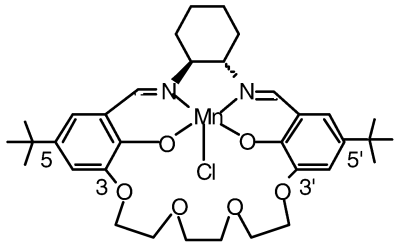


The Jacobsen's catalyst



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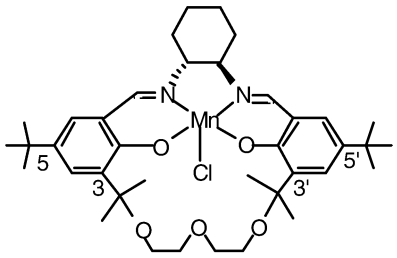

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Scheme 1. Macrocylic catalysts of first (**1**) and second (**2**) generations.

Scheme 1). Three criteria directed our choice: (i) we retained the key features of the ligand (the chiral diimine, the bulky substituents at the 5,5′ positions, the C_2 axis, and macrocyclization of the ligand); (ii) reinforced the steric hindrance in the "south part" of the ligand by introducing bulky substituents; and (iii) suppressed oxygen atoms present in the ligand of complex **1** at positions 3 and 3′. Moreover, we already showed that the length of the linker is an especially important factor in the catalytic properties of these macrocyclic complexes, and so we chose a rather long and flexible bridge to allow a nonplanar conformation, which is required for the high-valent (salen)Mn^{V}=O species [8].

2. Experimental

2.1. Instrumentation

Mass spectrometry analysis was performed on a Perkin-Elmer SCIEX Api 365 (ES in MeOH) spectrophotometer. The UV–vis spectrum was obtained on a Hewlett-Packard 8452A diode array spectrophotometer. The infrared spectrum was recorded on a Perkin-Elmer GX 2000 spectrophotometer. Optical rotation was measured with a Perkin-Elmer 241 polarimeter. Gas chromatography (GC) analyses were performed on a Hewlett-Packard HP4890A chromatograph equipped with a flame ionization detector and a Supelco cyclodextrin-β capillary column (β-dex 120, 30 m × 0.25 mm, 0.25 μm film) and coupled to a Hewlett-Packard HP3395 integrator. 1,4-Dibromobenzene or *n*-decane was used as an internal standard for the GC analyses. The epoxides were identified by comparing the GC data with data obtained from reaction of the corresponding olefin with *m*-chloroperbenzoic acid.

2.2. Synthesis of complex **2**

Compound **7** (80 mg, 0.1475 mmol) was dissolved in 50 ml EtOH under a nitrogen atmosphere. To the resulting solution was added, in succession, (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane (17 mg, 0.1475 mmol) and manganese (II) diacetate tetrahydrate (36.4 mg, 0.1475 mmol). After stirring overnight, air was bubbled through the solution for 4 h. The reaction mixture was concentrated to 20 ml, treated with 20 ml of brine, and extracted with 2 × 50 ml of CH_2Cl_2. The organic layer was washed with 100 ml of H_2O and dried over Na_2SO_4. After evaporation of the solvent and drying under vacuum, 85 mg (82%) of complex **2** was obtained as a dark-brown microcrystalline solid, $C_{38}H_{54}N_2O_5ClMn$ (709): calcd. C 64.35, H 7.67, N 3.95, Mn 7.75, Cl 5.00; found C 64.66, H 7.61, N 3.54, Mn 7.75, Cl 5.39. MS (ES): $m/z = 673.55$ [M–Cl^-]$^+$. IR (KBr, cm^{-1}): 1631(C=N). UV–vis (CH_3OH): $\lambda(\varepsilon) = 274$ nm (14,000 $l\,mol^{-1}\,cm^{-1}$), 290 (13210), 318 (8928), 354 (5714), 416 (4103). $[\alpha]_D^{20} = -0.0231°$ (589 nm, 20 °C, 0.039 g/dm^{-3} in CH_3OH, 10 cm path).

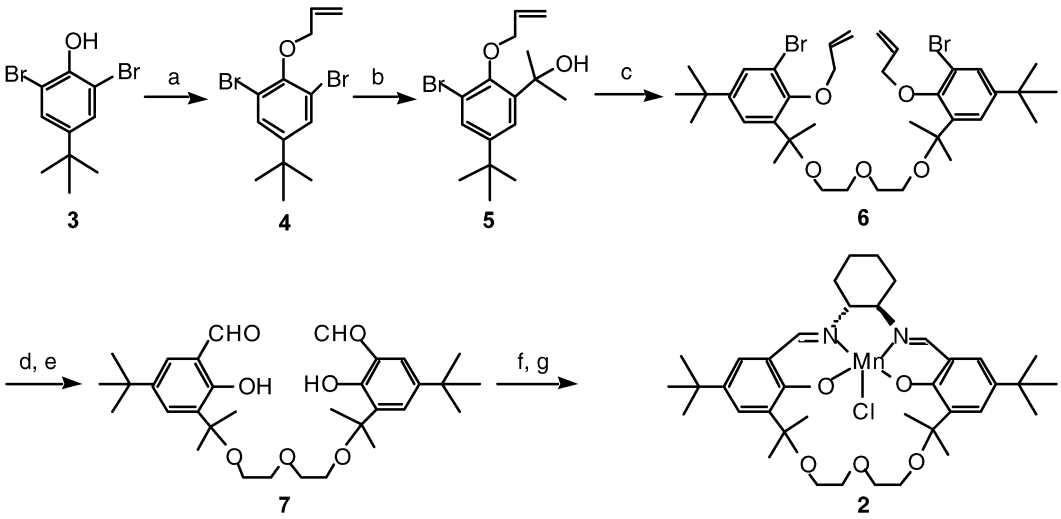
2.3. Representative catalytic experimental procedure

A typical reaction mixture contained 16 μl of 2,2′-dimethylchromene (0.1 mmol) and internal standard (23.6 mg of 1,4-dibromobenzene, 0.1 mmol) in 0.5 ml CH_2Cl_2, 5 μmol of the appropriate catalyst precursor (0.5 ml of a 10 mmol CH_2Cl_2 stock solution; catalyst/substrate ratio = 5%), and 4-phenylpyridine *N*-oxide (4.3 mg, 25 μmol). After stirring at 0 °C for 10 min, 0.2 mmol NaOCl (0.4 ml of a 0.5 mol aqueous NaOCl solution in 0.16 ml of a 0.05 mol aqueous Na_2HPO_4 solution; 2 eq. of oxidant with respect to the substrate) was added. After vigorous stirring for 2 h, the reaction was diluted with water (2 ml) and CH_2Cl_2 (2 ml). The layers were separated, and the organic phase was dried over Na_2SO_4, filtered, concentrated to approximately 1 ml, and analyzed by chiral GC.

3. Results and discussion

3.1. Synthesis of catalyst **2**

The synthesis of catalyst **2** is summarized in Scheme 2 [9]. The synthesis of 2,4-dibromo-4-*tert*-butylphenol (**3**) was done as described previously [10]. The phenolic function



Scheme 2. Synthesis of complex **2**. (a) Allyl bromide, CH_2Cl_2–H_2O, *n*-Bu_4NOH, 95%; (b) *n*-BuLi, Et_2O, $(CH_3)_2CO$, −78 °C, 65%; (c) NAH-THF, diethylene glycol ditosylate, DMF, 55%; (d) TMEDA, *n*-BuLi, Et_2O, DMF, −90 °C, 40%; (e) $Pd(PPh_3)_4$, MeOH, K_2CO_3, 86%; (f) (1*R*,2*R*)-(−)-diaminocyclohexane, $Mn(OAc)_2 \cdot 4H_2O$, EtOH; (g) air, NaCl, 82%.

of **3** was protected with an allyl group to yield **4** [11]. Lithiation of **4** with *n*-BuLi followed by quenching with acetone produced **5** [12]. This key step corresponds to introduction of the bulky substituents in positions 3 and 3′ of the final salen ligand. The polyether linker was introduced by a Williamson reaction to yield **6** [13]. A diformylation reaction followed by the deprotection of the phenol group under mild conditions led to **7** [10,14]. The template synthesis of complex **2** was achieved by mixing stoichiometric amounts of **7**, (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane, and $Mn(OAc)_2 \cdot 4H_2O$, with subsequent air oxidation and axial ligand exchange.

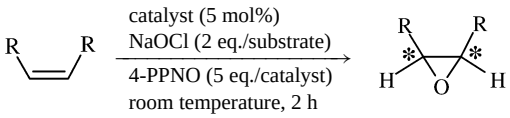
3.2. Enantioselective epoxidation of cis-disubstituted olefins

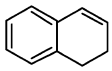
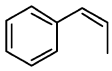
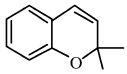
An evaluation of the catalytic activity of complex **2** was performed with three *cis*-disubstituted olefins. Typical reaction conditions were complex **2** (5 mol%), substrate (1 eq.), an oxygen atom donor (NaOCl, PhIO, 2 eq. or H_2O_2, 3 eq.), and the axial ligand 4-phenylpyridine *N*-oxide (4-PPNO, 5 eq. with respect to the catalyst). The reactions were carried out at 0 °C for 2 h; the results are reported in Table 1. With the three olefins used and sodium hypochlorite as oxidant, asymmetric induction was obviously increased for complex **2** compared with catalyst **1** (Table 1, entries 1–2, 7–8, and 9–10). This is due mainly to the introduction of bulky substituents in the close proximity to positions 3 and 3′ of the ligand. With 1,2-dihydronaphthalene as substrate, the yields of epoxide and naphthalene are in the same range for both catalysts (entries 1–2). Naphthalene is the main byproduct in this catalytic oxidation and results from a dehydrogenation reaction [15]. For *cis*-β-methylstyrene and 2,2′-dimethylchromene as substrates, catalyst **2** gives slightly better conversions and epoxide yields (entries 7–8 and 9–10, respectively). In the case of *cis*-β-methylstyrene, an acyclic olefin conjugated to an aryl group, the epoxidation is nonstereospecific and affords a mixture of *cis*- and *trans*-epoxides. A stepwise process with formation of a radical intermediate was proposed to rationalize these results [16,17]. Using chromene as substrate, we tested the catalytic activities of complex **2** with several oxygen atom donors (Table 1, entries 10, 15, and 16). We obtained the best results with sodium hypochlorite in a quantitative yield with a 100% selective formation of the corresponding epoxide and an enantiomeric excess of 93% (Table 1, entry 10). The *ee* values were 81% with PhIO and 82% with H_2O_2 (Table 1, entries 15 and 16), the reaction being rather slow with the green oxidant H_2O_2. In a general trend, the best *ee* values were obtained with NaOCl as an oxygen atom donor for complex **2** (Table 1, entries 2 and 10), whereas complex **1** gave a better stereoinduction with PhIO as oxidant (Table 1, entries 5 and 14). These results suggest that the nature of the active high-valent species will differ depending on the nature of the catalyst and the oxidant. In the case of complex **1** associated with PhIO, the PhI group could be involved in the transition state of the "Mn(salen)-oxo like" species (PhIO–(salen)Mn^{V}=O or (salen)Mn^{IV}–OIPh), thus inducing a better stereoinduction than with NaOCl. With catalyst **2** bearing bulky substituents in positions 3 and 3′ of the ligand, such species are perhaps less involved, because of steric hindrance, and a pure (salen)Mn^{V}=O could be the major oxygen-transfer agent. But several other minor oxidizing species should be involved, as proposed in the literature [17], explaining the differences observed for the enantiomeric excesses.

3.3. Recyclability of catalyst 2

We also tested the stability under the oxidative conditions of complex **2**. We have already reported that complex **1** was not recyclable. The reuse of catalyst **2** was im-

Table 1
Asymmetric epoxidation of *cis*-disubstituted olefins with 5% molar of catalyst and an oxygen atom donor



Entry	Run	Catalyst	Substrate	Oxidant	Conversion (%)	Yield[a] (%)	*ee*[b] (%)
1[c]	1	**1**		NaOCl	90	56 (19)	28
2	1	**2**		NaOCl	80	55 (23)	60
3	2	**2**		NaOCl	70	55 (16)	60
4	3	**2**		NaOCl	70	55 (16)	58
5[c]	1	**1**		PhIO	93	62 (19)	42
6	1	**2**		PhIO	49	35 (15)	35
7[c]	1	**1**		NaOCl	10	4 (4)	0
8	1	**2**		NaOCl	67	51 (11)	73
9[c]	1	**1**		NaOCl	86	64	56
10	1	**2**		NaOCl	100	100	93
11	2	**2**		NaOCl	100	100	91
12	3	**2**		NaOCl	100	95	90
13	4	**2**		NaOCl	100	88	80
14[c]	1	**1**		PhIO	68	51	74
15	1	**2**		PhIO	68	51	81
16[d]	1	**2**		H_2O_2	18	18	82

Reactions were carried out with substrate (0.1 mmol), catalyst (5 μmol) and oxidant (0.2 mmol) at 0 °C in the presence of 5 eq. of 4-PPNO with respect to the catalyst.

[a] Epoxide yield (naphthalene or *trans*-β-methylstyrene oxide yield).

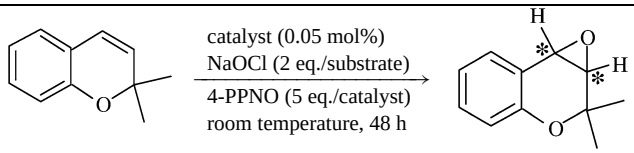
[b] *ee* were determined by GC on a chiral capillary column (Supelco cyclodextrin-β); epoxide configurations are (1*R*,2*S*) for 1,2-dihydronaphthalene and *cis*-β-methylstyrene and (3*R*,4*R*) for 2,2′-dimethylchromene.

[c] Ref. [8].

[d] 0.3 mmol of oxidant was used.

proved with two substrates, 2,2′-dimethylchromene and 1,2-dihydronaphtalene, and sodium hypochlorite as oxidant; attempts to recycle complex **2** with *cis*-β-methylstyrene failed. At the end of each run, the complex was recovered after a workup by precipitation in hexane and then analyzed by mass spectrometry. The catalyst **2** (5 mol%) can be used three times in the epoxidation of 2,2′-dimethylchromene and 1,2-dihydronaphtalene without lost of conversion, yield, selectivity, or enantioselectivity (Table 1, entries 2–4 and 10–13). But a decrease of the yield and of the enantiomeric excess was observed during the fourth run for the asymmetric epoxidation of 2,2′-dimethylchromene, because catalyst **2** underwent a partial oxidative decomposition (i.e, slight decoloration of the organic phase due to leaching). We also compared complex **2** and the commercially available (*S*,*S*)-Jacobsen's catalyst (Table 2). To estimate the turnover numbers of the Jacobsen's catalyst and complex **2**, we decreased the amount of catalyst in the next two experiments. First, we reduced the amount of catalyst to 0.05 mol% for the asymmetric epoxidation of 2,2′-dimethylchromene with NaOCl as oxidant at room temperature. The obtained conversion, epoxide yield, and *ee* value were 61, 59, and 96%, respectively, for the Jacobsen's catalyst and 52, 50, and 86%, respectively, for catalyst **2** (Table 2, entries 1–2). If the *ee* value was better for the Jacobsen's catalyst, then the selectivities (97 to 95%) (Table 2, entries 1–2) and turnover numbers (1220 to 1040) (Table 2, entries 1–2) were in the same range for both catalysts. Note that Katsuki previously reported a very efficient metallosalen catalyst with a carboxylate group on the ethylene diimine moiety [18]. This catalyst associated with iodosylbenzene as oxidant gave *ee* values as high as 99% and a very high turnover number (9200; 8 days) for the asymmetric epoxidation of 2,2′-chromene derivatives [18]. Because, in terms of epoxide yields and *ee* values, 2,2′-dimethylchromene usually provides good results with a wide variety of Mn(salen) catalysts, we chose 1,2-dihydronaphtalene as the substrate for the second experiment (Table 3, entries 1–5). The reactions were performed with 1 mol% of catalyst and NaOCl as oxidant at room temperature for 3 h. The Jacobsen's catalyst lost activity quickly and was quite ineffective after the first run, whereas catalyst **2** could be recycled without loss in activity (Table 3, entries 1–2 and 3–5, respectively). However, a significant drop in epoxide yield was observed with catalyst **2** for the third run (Table 3, entry 5). The corresponding turnover numbers were 136 for the Jacobsen's catalyst and 231 for catalyst **2**.

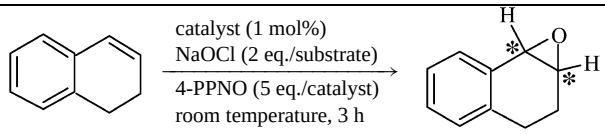
Table 2
Comparison of the Jacobsen's catalyst and catalyst **2**: asymmetric epoxidation of 2,2′-dimethylchromene with 0.05% molar of catalyst and sodium hypochlorite



Entry	Catalyst	Conversion (%)	Yield[a] (%)	Selectivity (%)	*ee*[b] (%)
1	Jacobsen's catalyst	61	59	97	96
2	Catalyst **2**	52	50	96	86

Reactions were carried out with 2,2′-dimethylchromene (0.1 mmol), catalyst (0.05 μmol) and NaOCl (0.2 mmol) at room temperature in the presence of 5 eq. of 4-PPNO with respect to the catalyst.
[a] Epoxide yield.
[b] *ee* were determined by chiral GC; major enantiomers: (3*S*,4*S*)-2,2′-dimethyl-3,4-epoxychromane with the Jacobsen's catalyst and (3*R*,4*R*)-2,2′-dimethyl-3,4-epoxychromane with catalyst **2**.

Table 3
Recycling of Jacobsen's catalyst and catalyst **2** (1% molar) in the asymmetric epoxidation of 1,2-dihydronaphthalene with sodium hypochlorite



Entry	Run	Catalyst	Conversion (%)	Yield[a] (%)	Selectivity[b] (%)	*ee*[c] (%)
1	1	Jacobsen's catalyst	100	73 (27)	73	72
2	2		31	24 (0)	67	68
3	1	Catalyst **2**	100	75 (25)	69	55
4	2		100	73 (26)	73	54
5	3		31	21 (4)	68	52

Reactions were carried out with 1,2-dihydronaphthalene (0.1 mmol), catalyst (1 μmol) and NaOCl (0.2 mmol) at room temperature in the presence of 5 eq. of 4-PPNO with respect to the catalyst.
[a] Epoxide yield (naphthalene yield).
[b] Selectivity of the epoxide.
[c] *ee* were determined by chiral GC; major enantiomers: (1*S*,2*R*)-1,2-dihydronaphthalene oxide with the Jacobsen's catalyst and (1*R*,2*S*)-1,2-dihydronaphthalene oxide with catalyst **2**.

In conclusion, we have prepared a new macrocyclic chiral Schiff base (complex **2**), involving a polyether bridge with substituents to generate steric constrains and linked to the 3 and 3′ positions of the salicylidene moieties. This catalyst, associated with NaOCl as oxidant, promotes highly enantioselective catalytic epoxidation reaction (*ee* values up to 93%) with *cis*-disubstituted olefins. In addition, catalyst **2** can be used two to three times, depending on the substrate used, without significant loss in performance. With 1,2-dihydronaphthalene as substrate, the macrocyclic complex **2** displays a better robustness in oxidizing conditions than the Jacobsen's catalyst. These results validate the ligand macrocyclization strategy. Moreover, the synthetic strategy developed here allows the modulation of the different key groups, particularly the bulky substituents in positions 3 and 3′ and the linker used to macrocyclize the ligand. For example, introduction of bulkier substituents could enhance stereoinduction, and a functionalized bridging arm could be used to immobilize the corresponding catalyst on a solid support. So structural variations on the catalyst (to increase activity and enantioselectivity) could be readily available, thus facilitating tuning of the catalytic properties. Extension of this strategy to the design of new chiral macrocyclic Mn^{III} (salen) catalysts is currently underway.

Acknowledgments

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Supplementary material

The online version of this article contains additional supplementary material.

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