Synthesis of New Macrocyclic Chiral Manganese(III) Schiff Bases as Catalysts for Asymmetric Epoxidation

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We describe a general synthetic strategy for the preparation of a series of macrocyclic chiral manganese(III) salen complexes. The developed reaction pathway allows the modulation of the different key groups, namely, the chiral diimine, the bulky substituents in positions 3 and 3′, and the linker used in the macrocyclization of the Schiff base. The different complexes presented here illustrate these readily available structural variations. The catalytic properties of the catalysts (5 mol %) were improved for the asymmetric epoxidation of 2,2′-dimethylchromene with NaOCl or H2O2 as oxygen atom donor. A large range of enantiomeric excesses was obtained (ee values from 30% to 96%), depending on the features and the stability of the complexes. The most efficient catalyst, in terms of stereoinduction (ee value = 96%), contains a diiminocyclohexyl moiety, ethyl groups in positions 3 and 3′, and a short polyether junction arm.

Introduction

Cytochrome P-450 enzymes represent a class of biological oxidation catalysts able to perform enantioselective epoxidation of prochiral olefins.1,2 Synthetic metalloporphyrins3,4 have been developed for enantioselective epoxidation, and in the same way, metallosalens,4 since Schiff bases and porphyrin ligands have common features such as planar structures and electronic properties. Optically active metallosalens are among the widely used catalysts for asymmetric synthesis. This is mainly due to their facile preparation, the easy construction of a highly asymmetric coordination sphere, and their versatile catalytic activity, depending on the nature of the metal chelated by the salen ligands. At about the same time, Jacobsen5 and Katsuki6 have reported the use of chiral manganese(III)-salen catalysts in asymmetric epoxidations. The Jacobsen–Katsuki reaction is universally recognized as one of the most useful and widely applicable methods for the epoxidation of unfunctionalized olefins, and Jacobsen’s catalyst (Figure 1) is now commercially available. EnantiomERICALLY pure epoxides are key intermediates in organic chemistry because they can undergo stereospecific ring-opening reactions, giving rise to a wide range of biologically and pharmacologically active compounds.5–7,12 During the past 15 years, many different chiral manganese-salen catalysts have been reported for homogeneous or supported asymmetric

highest ee value was 74% with 2,2′-cis a linker between the 3 and 3′ positions, bridging linker, and chiral diimine, can be easily tuned (Figure 2). The catalytic activity of these new chiral complexes was evaluated in the asymmetric epoxidation of 2,2′-dimethylchromene with sodium hypochlorite or hydrogen peroxide as oxygen atom donors.

Results and Discussion

The scaffold of these macrocyclic salen complexes contains a linker between the 3 and 3′ positions, a chiral diimine, and bulky substituents in the “south part” of the ligand, in positions 3, 3′ and 5, 5′, to induce the approach of the olefin by the “north face” in the vicinity of the chiral diimine. The ligands retain a C	extsubscript{2} symmetry to have the same stereoinduction on both faces of the catalyst.

The macrocyclization of the Schiff bases was generated by introducing a symmetrical junction arm in the 3 and 3′ positions. Reinoudt et al. have previously reported macrocyclic achiral Schiff bases containing aliphatic polyether linkers. However, such a strategy has not been employed for chiral Mn(III)-salen catalysts. The macrocyclization of the ligand is expected to increase the stability of the corresponding complexes in asymmetric catalysis due to the macrocyclic effect. We have previously prepared a first generation of macrocyclic chiral Mn(III)-salen catalysts (one example is depicted in Figure 3). The synthesis of this first generation of chiral macrocyclic complexes was convenient and was realized in three steps, starting from 4-tert-butylcatechol. Unfortunately, the enantioselective excess values obtained in the asymmetric epoxidation of cis-disubstituted olefins were modest for these catalysts; the highest ee value was 74% with 2,2′-dimethylchromene as substrate and iodosylbenzene as oxidant. This result was probably due to the absence of bulky substituents in the close proximity of positions 3 and 3′. Moreover, the presence of two oxygen atoms on the aromatic entities of the ligand, making an electron-rich easily oxidizable ligand, could explain the fragility of the complexes under oxidative conditions.

This prompted us to develop a new and more elaborated synthetic strategy. The synthetic pathway for the synthesis of one representative complex of the second generation (complex 7) is illustrated in Scheme 1 and involves seven steps. The aromatic electrophilic substitution (compound 1) was already described in the literature. In the next step, the protection of the phenol function (compound 2) was necessary for the further introduction of the bridging linker leading to compound 4, thus avoiding the formation of undesired intracyclic byproduct. The choice of this group, allyl in our case, was important because the deprotection conditions have to be mild. First attempts involving a methoxymethyl as protecting group were disappointing. All the experimental methods reported in the literature for the deprotection of this group were unsuccessful (HBr 6 M, MeOH, rt; BF	extsubscript{3}/Et	extsubscript{2}O, MeOH, rt; BB	extsubscript{3}, CH	extsubscript{2}Cl	extsubscript{2}, −78 °C; Ph	extsubscript{3}CBF	extsubscript{4}, rt; LiCl, collidine, 160°C; AcOH 0.2 M, MeOH, reflux) and led either to the deprotected starting material or to complicated unseparable mixtures. Compound 3 was obtained, after a metal−halogen exchange, by the addition of a ketone, acetone in this case. This is the key step in the preparation of these macrocyclic chiral salen ligands, since it corresponds to the insertion of the bulky substituents in positions 3 and 3′ of the final complex. The introduction of the junction arm was performed by a Williamson reaction. The formylation step required the presence of TMEDA to obtain the dialdehyde. The deprotection of the phenol group was achieved under mild conditions at room temperature, and the reaction was highly chemo-selective since no cleavage of the ether bond of the linker was observed. Finally, the template synthesis of complex 7 was achieved by mixing stoichiometric amounts of the dialdehyde, the chiral diamine, and manganese(II) diacetate. An air oxidation, followed by NaCl treatment to introduce a chloro axial ligand, produced complex 7.
SCHEME 1. Synthesis of Complex 7

SCHEME 2. General Synthetic Pathway Allowing Modulation of the Different Building Blocks of These Macrocyclic Schiff Base Complexes

<table>
<thead>
<tr>
<th>Complex</th>
<th>Ketone ((R_2)C\equiv O)</th>
<th>Ditosylate</th>
<th>Diamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>(R = CH_3)</td>
<td>diethylene glycol ditosylate</td>
<td>((S),2,3)-diaminopropionic acid</td>
</tr>
<tr>
<td>11</td>
<td>(R = CH_3)</td>
<td>triethylene glycol ditosylate</td>
<td>((1S,2S))(+)-1,2-diaminocyclohexane</td>
</tr>
<tr>
<td>12</td>
<td>(R = CH_3)</td>
<td>triethylene glycol ditosylate</td>
<td>((1R,2R))(-)-diphenylethlenediamine</td>
</tr>
<tr>
<td>16</td>
<td>(R = CH_3)</td>
<td>5-allyloxy-1,3-benzenedimethyl ditosylate</td>
<td>((1S,2S))(+)-1,2-diaminocyclohexane</td>
</tr>
<tr>
<td>21</td>
<td>(R = C_6H_4F)</td>
<td>diethylene glycol ditosylate</td>
<td>((1S,2S))(+)-1,2-diaminocyclohexane</td>
</tr>
<tr>
<td>26</td>
<td>(R = CH_2CH_3)</td>
<td>diethylene glycol ditosylate</td>
<td>((1S,2S))(+)-1,2-diaminocyclohexane</td>
</tr>
<tr>
<td>30</td>
<td>(R = CH_2CH_3)</td>
<td>triethylene glycol ditosylate</td>
<td>((S))-((-))-1,1'-binaphthyl-2,2'-diamine</td>
</tr>
</tbody>
</table>
This general strategy is original because it made it possible to modulate the different building blocks of the molecule, namely, the ketone with bulky substituents, the ditosylate containing the junction arm, and the chiral diamine (Scheme 3), and thus gives rise to a new family of chiral macrocyclic salen complexes (Scheme 3). For example, bulky substituents such as methyl (complexes 8, 11, 12, and 16), ethyl (complexes 26 and 30) or halogenated aryl (complex 21, Scheme 3) can be introduced. In the same way, simple polyether linkers of different lengths (see complexes 8 and 11 for example, Scheme 3) can be employed for homogeneous catalysis. A functionalized linker can also be included (complex 16, Scheme 3) in order to have the possibility of grafting the corresponding catalyst on solid supports such as silica or dendrimers. Katsuki et al. have reported a metallosalen catalyst having a carboxylate group on the ethylene diamine moiety. This catalyst associated with iodosylbenzene as oxidant was found to be efficient for the asymmetric epoxidation of 2,2′-chromene derivatives (ee values up to 99%) with a very high turnover number of 9200. The high catalytic activity of this complex was partly explained by the fact that it does not require any additional axial ligand, generally used in excess, and thus it possesses a free axial coordination site. This prompted us to synthesize complex 8 (Scheme 3), starting from (S)-2,3-diaminopropionic acid hydrogen chloride instead of the most common (1S,2S)-1,2-diaminocyclohexane, to study the influence of the carboxylate group in asymmetric epoxidation reactions. Complex 8 involved a ligand without a C₂ symmetry. Finally, three different chiral C₂-symmetric amines (namely, (1R,2R)-(−)-1,2-diaminocyclohexane or (1S,2S)-(−)-1,2-diaminocyclohexane, (1R,2R)-(−)-1,2-diphenylethylenediamine, and (S)-(−)-1,1′-binaphthyl-2,2′-diamine) have been used in the template synthesis of these chiral macrocyclic manganese(II) Schiff bases (complexes 11, 12, and 30 for example, Scheme 3). These three complexes differed in terms of size and rigidity, and one can expect to observe different behaviors in catalytic reactions.

In Table 1 are summarized the comparative catalytic activities of the various macrocyclic Schiff base complexes in the asymmetric epoxidation of three cis-disubstituted olefins, namely, 2,2′-dimethylchromene, cis-β-methylstyrene, and 1,2-dihydronaphthalene and sodium hypochlorite as oxygen atom donor (except for catalyst 8). The epoxidations reactions were typically performed with a substrate/oxidant/catalyst molar ratio of 1/2/0.05 in a biphasic system, in the presence of an excess of 4-phenylpyridine-N-oxide (5 equiv with respect to the caralyst, except for catalyst 8) at 0 °C. In the case of complex 8, involving a carboxylate on the diethylenediamine moiety, no additional axial ligand was used and the reaction was conducted in an organic medium with the attractive hydrogen peroxide oxidant (3.4 equiv with respect to the substrate). As expected for these chiral macrocyclic metallosalen catalysts of second generation, the asymmetric induction is efficiently increased, giving rise to enantiomeric excesses up to 96% (Table 1, entry 6), when compared to those of the first series (ee = 74% with iodosylbenzene as oxidant). This a general trend with the three substrates employed. Complex 7, with methyl groups as bulky substituents, a short polyether bridging arm and a cyclohexyl diamine, gave a highly selective epoxidation reaction (entry 1, yield and selectivity of the epoxycrohylene derivative = 100%). The best stereoinduction was achieved with the efficient catalyst 26, analogous to complex 7 but bearing ethyl groups instead of methyl groups (entry 6, ee = 96%). Moreover, the asymmetric epoxidation proceeded more rapidly with catalyst 26 (30 min) than with the other complexes, whereas 2 h were required to obtain a complete conversion of the olefin. By lengthening the linker of the catalyst in order to study the influence of the flexibility of the macrocycle in the high-valent salen-MnV species, the selectivity in epoxide remained excellent (100%) but the ee value slightly decreased (entry 2, ee = 85%, catalyst 11). In the same way, the presence of an aromatic linker gave similar results (entry 4, ee = 85%, catalyst 16). In addition, catalyst 16 is interesting because the phenol group could act as an axial ligand while still keeping the C₂ symmetry for enantioselective epoxidation. This functionalized linker could also serve to graft the corresponding catalyst on a solid support for heterogeneous asymmetric catalysis. Introducing the bulkier diiminothylene entity has not a strong influence on the enantioselectivity (entries 2 and 3 to be compared, ee = 83% and 85% for catalysts 11 and 12, respectively). However, complex 30 containing the bulk and rigid diiminodiphenyl backbone showed a poor catalytic activity (entry 7), when compared to the cyclohexyl-based analogues. Surprisingly, catalyst 21 with bulky fluorinated aromatic groups in 3 and 3′ positions gave a significantly lower enantiomeric excess (ee value = 59%, entry 5, catalyst 21).

This unexpected result could be explained by the presence of these sterically hindered substituents that probably block the C2 axis of the ligand by conformational constraints and create the possibility of having diastereomeric complexes. The less efficient catalyst was the unsymmetrical complex 8 with the carboxylate group on the diethylendiamine (entry 10 to be compared with entry 9 or entry 19 to be compared with entry 18). These two later results suggested that the C2 symmetry of the ligand constitutes one of the key factors to have a good stereoinduction with these chiral macrocyclic metallosalen catalysts. To summarize these results, complexes 7 and 26 are the most efficient in terms of stereoinduction (entries 1 and 6, 11 and 16, and 18 and 24) for the asymmetric epoxidation of cis-disubstituted olefins and can be compared to the commercially available Jacobsen’s catalyst (entries 8, 17, and 25).

Conclusion

In summary, we have developed a new family of macrocyclic chiral manganese(III) Schiff bases. The strategy consists of the macrorylization of the ligand via the 3 and 3’ positions, to have efficient and robust catalysts in oxidative conditions. Enantiomeric excesses up to 96% have been obtained in the asymmetric epoxidation of 2,2’-dimethylchromene with NaOCl as oxidant, associated with a quantitative conversion of the olefin. Moreover, the same synthetic pathway allowed the modulation of the key groups of the molecule: the bulky substituents in the south part of the catalyst, which are necessary for a good orientation of the olefin and the bridging linker, which can be more or less flexible or functionalized for the fixation on a solid support.

Experimental Section

Synthesis of Ligands and Complexes. 1,3-Dibromo-5-(1,1-dimethyl)2-(2-propen-1-olxy)benzene (2). To a solution of 1 (3.82 g, 0.0124 mol) in 30 mL of CH3Cl/H2O (10:7 v/v) and 8.52 mL of a 40 wt% solution of nBu4NOH in water was added an excess of allylbromide (13.4 mL, 0.062 mol) at room temperature. The reaction mixture was stirred vigorously for 24 h. Addition of 200 mL of NaOH (1 M) was followed by extraction with CH2Cl2 (3 × 100 mL). The combined organic extracts were washed with NaOH (1 M) and water (2 × 200 mL), dried (MgSO4), filtered, and concentrated. The crude product was dissolved in CH2Cl2 and the ammonium salt was precipitated by addition of CH2Cl2 and the ammonium salt was precipitated by addition of diethyl ether (20 mL) under nitrogen at 0 °C in the presence of 5 equiv of 4-PPNO with respect to the catalyst.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>substrate</th>
<th>conversion(%)</th>
<th>yield (%)</th>
<th>selectivity (%)</th>
<th>ee(%)</th>
</tr>
</thead>
</table>

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[2-Bromo-5-(1,1-dimethyl)2-(2-propen-1-olxy)phenyl]-2-propanol (3). To a solution of 2 (6.05 g, 0.017 mol) in anhydrous diethyl ether (20 mL) under nitrogen at −78 °C was added dropwise n-BuLi (1.6 M, 13 mL, 0.0204 mol). After stirring for 1 h at −78 °C, acetone (1.65 mL, 0.0221 mol) in anhydrous Et2O (10 mL) was added dropwise at −78 °C. The solution was allowed to warm
to room temperature and stirred for 1 h. Water (15 mL) was added to the solution at 5 °C. The mixture was extracted with ether (3 × 100 mL), and the combined organic layers were washed with water (2 × 100 mL). The aqueous solution was extracted with CHCl₃ (3 × 20 mL) and dried over MgSO₄. The solvent was removed and the crude product was purified by column chromatography using hexane/ethyl acetate (9/1) as the eluent to give a colorless oil (3.7 g, 65%). ¹H NMR (CDCl₃): δ 1.13 ppm (s, 9H), 1.6 (s, 6H), 3.8 (s, 1H), 4.5 (m, 2H), 5.4–5.5 (m, 2H), 6.3 (m, 1H), 7.32 (d, J = 2.3 Hz, 1H) 7.44 (d, J = 2.3 Hz, 1H). ¹³C NMR (63 MHz, CDCl₃): δ 31.2, 34.3, 73.2, 74.3, 117.2, 118.3, 122.9, 129.8, 133.0, 142.2, 148.2, 152.0. C₃₆ H₅₂ O₅ Br₂  (328): calcd C 58.72, H 7.08; found C 58.49, H 7.09. MS (EI): m/z = 673.55 [M + Cl]⁺. IR (KBr cm⁻¹): 1631 (C=N). UV–vis (CH₂Cl₂): λ (e) = 274 nm (16430 L mol⁻¹ cm⁻¹), 290 (13210), 318 (8928), 354 (5714), 416 (4103). [α]₀D₂ = −0.0231 (589 nm, 0.039 g/dm³ in CH₂Cl₂, 1 cm path).

**Mn³⁺-Salen Complex 8.** Two equivalents of sodium hydroxide (18.8 mg, 0.47 mmol in EtOH (10 mL) were added slowly to a suspension of 6 (107.8 mg, 0.24 mmol) and (S)-2,3-diaminopropionic acid hydrogen chloride (33.1 mg, 0.24 mmol) in EtOH (50 mL). After stirring for 2 h under nitrogen, Mn(OAc)₂·4H₂O (58.0 mg, 0.24 mmol) in EtOH (10 mL) was added to the mixture. After stirring overnight, air was bubbled through the solution for 4 h. The solvent was evaporated and the residue was dissolved in 50 mL of CH₂Cl₂. The organic layer was washed with H₂O (2 × 100 mL), dried over Na₂SO₄, filtered and evaporated to dryness. The residue was purified by column chromatography using hexane/ethyl acetate (9/1) as the eluent to obtain a colorless solid (2.3 g, 55%). ¹H NMR (CDCl₃): δ 1.26 ppm (s, 18 H), 1.62 (s, 6H), 3.43 (t, J = 55 Hz, 4H), 3.66 (t, J = 5.5 Hz, 4H), 4.48 (m, 4H), 5.24–5.48 (m, 4H), 6.10 (m, 2H), 7.43 (d, J = 2.9 Hz, 2H), 7.48 (d, J = 2.9 Hz, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 28.3, 31.3, 62.1, 71.0, 73.8, 77.5, 117.4, 118.4, 124.7, 129.3, 136.9, 137.9, 149.7, 151.3. C₃₆ H₅₂ O₅ Br₂  (726.6): calcd C 59.51, H 7.52. MS (ES): mL/z = 742 [M + NH₄]⁺.

3.3-[Oxybis(2,1-ethanediol-2,2-propenylidene)bis[5-(1,1-dimethyl-2-hydroxybenzaldehyde)] (11). To a well-stirred solution of 4 (1.6 g, 2.2 mmol) in anhydrous ether (5 mL) at −90 °C was added dropwise a mixture of TEMDA (330 mg, 2.9 mmol) and n-BuLi (1.6 M, 4.4 mL, 6.4 mmol) in anhydrous ether (5 mL) at −90 °C under nitrogen. The yellow solution was stirred at −90 °C for 1 h. Then a solution of anhydrous DMF (1.8 mL, 22.4 mmol) was added at −90 °C. The reaction mixture was stirring overnight, air was bubbled through the solution for 4 h. The solvent was evaporated and the residue was dissolved in 50 mL of CH₂Cl₂. The mixture was allowed to warm to room temperature and stirred for an other hour. Water (5 mL) was slowly added to the solution at 5 °C. The mixture was extracted with CHCl₃ (3 × 100 mL) and the combined organic layers were washed with water (2 × 100 mL) and dried over MgSO₄. The solvent was removed and the crude product was purified by column chromatography using hexane/ethyl acetate (9/1) as the eluent to give a pale yellow oil (30 mg, 40%). ¹H NMR (CDCl₃): δ 1.29 ppm (s, 18H), 1.65 (s, 12H), 3.45 (t, J = 5.6 Hz, 4H), 3.68 (t, J = 5.6 Hz, 4H), 4.46 (m, 4H), 5.30–5.40 (m, 4H), 6.05 (m, 1H), 7.75 (d, J = 2.8 Hz, 2H) 7.83 (d, J = 2.8 Hz, 2H) 10.28 (s, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 28.1, 31.3, 34.66, 62.1, 70.8, 71.0, 78.9, 117.7, 125.0, 129.7, 131.9, 132.8, 139.2, 142.4, 149.2, 190.6. C₃₆ H₅₂ O₄ (662.85): calcd (+H₂O) C 71.62, H 8.80; found C 71.56, H 9.21. MS (ES) mL/z = 645 [M + Na⁺].

3.3-[Oxybis(2,1-ethanediol-2,2-propenylidene)bis[5-(1,1-dimethyl-2-hydroxy-benzaldehyde)] (6). To a solution of 5 (120 mg, 0.193 mmol) in MeOH (3 mL) was added catalytic amounts of Pd(PPh₃)₄ (111 mg, 0.0098 mmol) under nitrogen. The slightly yellow solution was stirred for 5 min, and K₂CO₃ (160 mg, 1.16 mmol) was added. The reaction was completed within 2 h (monitored by TLC). The reaction mixture was concentrated in a vacuum and the residue was treated with water (20 mL). The aqueous solution was extracted with CHCl₃ (3 × 20 mL) and dried over MgSO₄. The solvent was removed and the crude product was purified by column chromatography using CHCl₃ as the eluent to give a pale yellow oil (90 mg, 86%). ¹H NMR (CDCl₃): δ 1.29 ppm (s, 18H), 1.64 (s, 12H), 3.54 (t, J = 5.0 Hz, 4H), 3.73 (t, J = 5.0 Hz, 4H), 7.50 (d, J = 2.4 Hz, 2H), 7.66 (d, J = 2.4 Hz, 4H), 6.10 (s, 2H), 6.66 (s, 2H). ¹³C NMR (63 MHz, CDCl₃): δ 31.6, 34.5, 62.1, 70.75, 78.0, 121.5, 127.1, 128.4, 141.2, 157.5, 194.8. C₉H₁₀O₂ (542): calcd C 70.82, H 8.54; found C 70.46, H 8.62. MS (ES) mL/z = 565.25 [M + Na⁺].

**Mn³⁺-Salen Complex 7.** The compound 6 (80 mg, 0.148 mmol) was dissolved in 50 mL of EtOH under nitrogen. To the resulting solution was added successively (1R,2R)-(+)-1,2-diaminocyclohexane (17 mg, 0.148 mmol) and manganese(II) diacetate trihydrate (36.4 mg, 0.148 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 CH₂Cl₂. The organic layer was washed with 100 mL of H₂O and dried over Na₂SO₄. After evaporation of the solvent and drying under vacuum, 85 mg (82%) of complex 7 was obtained as a dark brown microcrystalline solid. C₃₆ H₅₄ N₂ O₅ ClMn (709): calcd C 71.62, H 8.80; found C 71.56, H 9.21. MS (ES): mL/z = 685.4 [M + H¹⁺], 685.4 [M + Na¹⁺]. 701.3 [M + K¹⁺]. IR (KBr cm⁻¹): 1619 (C=N). UV–vis (CH₂Cl₂): λ (e) = 274 nm (16430 L mol⁻¹ cm⁻¹), 290 (13210), 318 (8928), 354 (5714), 416 (4103). [α]₀D₂ = −0.0231 (589 nm, 0.039 g/dm³ in CH₂Cl₂, 1 cm path).
eluent to give a pale yellow oil (160 mg, 30%). $^1$H NMR (CDCl$_3$): $\delta$ 1.30 ppm (s, 18H), 1.63 (s, 12H), 3.51 (t, $J$ = 4.8 Hz, 4H), 3.70 (t, $J$ = 4.8 Hz, 4H), 3.72 (s, 4H), 7.49 (d, $J$ = 2.3 Hz, 2H), 7.65 (d, $J$ = 2.3 Hz, 2H), 7.72 (d, $J$ = 2.3 Hz, 2H). $^{13}$C NMR (CDCl$_3$): $\delta$ 26.6, 31.3, 34.1, 61.2, 70.7, 77.9, 121.6, 127.0, 131.8, 132.3, 142.1, 157.5, 194.7. C$_2$H$_5$CO$_2$(568): calculated (+0.4 CH$_2$Cl$_2$) C 66.56, H 8.25; found C 66.98, H 7.81. MS (DCI/NH$_3$) $m/z$ = 604 [M + NH$_4^+$]$^+$. M$^{III}$/Salen Complex 1 (Complex 11). Complex 11 was synthesized as described above for complex 7, starting from 9 (88.0 mg, 0.15 mmol) in 50 mL of EtOH, (1S,2S)-1,2-diaminocyclohexane (17.1 mg, 0.15 mmol), and Mn(OAc)$_2$·4H$_2$O (36.8 mg, 0.15 mmol). Yield: 90 mg, 80% as a dark brown microcrystalline solid. C$_{34}$H$_{50}$O$_8$ (586): calcd (C 73.23, H 7.96; found C 73.25, H 7.88. MS $m/z$: 717.5 [M + Cl]$^-$; IR (KBr, cm$^{-1}$): 1615 (C=N), UV–vis (CH$_2$OH): $\lambda$ (e) = 290 nm (19031 L mol$^{-1}$ cm$^{-1}$), 318 (13379), 356 (8469), 412 (6124). $\alpha$P = 0.0482 (589 nm, 0.108 g dm$^{-3}$ in CH$_2$OH, 10 cm path).

**1.1’-[5-(Ethenoxy)benzene-1,3-diyl]bis(methanediyl-2,2-propanedioxy)-1,2-ethanediyloxy[bis(4-fluorophenyl)methanediyl]-2-(2-propan-1-yloxy)benzene** (13). Compound 13 was prepared as described for 4 starting from NaH (0.60 g, 15.0 mmol, 60% dispersion in oil) in THF (5 mL) and 3 (2.8 g, 8.54 mmol) in THF (5 mL). 5-Allyloxy-1,3-benzenedimethyl ditosylate (2.0 g, 3.98 mmol) in DMF (5 mL) was added in one portion and the mixture was stirred for 48 h. The crude product was purified by column chromatography using hexane/ethyl acetate (95/5) as the eluent to obtained a colorless oil (1.45 g, 42%). $^1$H NMR (CDCl$_3$): $\delta$ 1.22 ppm (s, 18H), 1.70 (s, 12H), 4.31 (s, 4H), 4.48 (m, 4H), 4.52 (m, 2H), 5.23–5.47 (m, 6H), 6.01 (m, 3H), 6.80 (m, 2H), 6.89 (s, 1H), 7.45 (d, $J$ = 2.3 Hz, 2H), 7.52 (d, $J$ = 2.3 Hz, 1H). $^{13}$C NMR (63 MHz, CDCl$_3$): $\delta$ 28.3, 31.2, 32.4, 64.5, 73.7, 77.4, 112.3, 117.2, 118.8, 118.9, 124.3, 129.8, 133.2, 133.3, 139.1, 141.1, 151.3, 158.8. C$_{24}$H$_{20}$O$_2$Br$_2$ (812.7): calculated C 63.55, H 6.95; found C 63.21, H 6.83. MS (DCI/NH$_3$): $m/z$ = 830 [M + NH$_4^+$]$^+$. 3.3’-[5-(Ethenoxy)benzene-1,3-diyl]bis(methanediyl-2,2-propanedioxy)-1,2-ethanediyloxy[bis(4-fluorophenyl)methanediyl]-2-(2-propan-1-yloxy)benzaldehyde** (14). Compound 14 was prepared as described for 5 starting from 13 (0.2 g, 0.39 mmol), TMEDA (350 mg, 2.9 mmol), and n-BuLi (1.6 M, 0.75 mL, 1.2 mmol) in ether (5 mL) and DMF (0.25 mL, 3.25 mmol) at 90 °C. After 5 h, the solvent was removed to give a pale yellow oil (280 mg, 98%). $^1$H NMR (CDCl$_3$): $\delta$ 1.29 ppm (s, 18H), 1.74 (s, 12H), 4.35 (s, 4H), 4.44 (m, 4H), 4.53 (m, 2H), 5.23–5.48 (m, 6H), 6.05 (m, 3H), 6.08 (s, 2H), 6.91 (s, 1H) 7.77 (d, $J$ = 2.4 Hz, 2H) 7.86 (d, $J$ = 2.4 Hz, 2H), 10.09 (s, 2H). $^{13}$C NMR (63 MHz, CDCl$_3$): $\delta$ 28.4, 31.3, 34.7, 64.7, 68.8, 79.0, 112.3, 117.5, 117.7, 118.2, 125.2, 129.8, 131.8, 132.7, 133.3, 138.9, 140.7, 147.0, 190.7. C$_{32}$H$_{20}$O$_2$(711): calculated (+0.4 CH$_2$Cl$_2$) C 72.35, H 7.96; found C 72.35, H 7.88. MS (DCI/NH$_3$): $m/z$ = 728 [M + NH$_4^+$]$^+$. $^{3.3’}$-[5-Hydroxybenzene-1,3-diyl]bis(methanediyl-2,2-propanedioxy)-1,2-ethanediyloxy[bis(4-fluorophenyl)methanediyl]-2-(2-propan-1-yloxy)benzaldehyde** (15). Compound 15 was prepared as described for 6 starting from 14 (280 mg, 0.385 mmol) in MeOH (6 mL). Pd (PPh$_3$)$_2$Cl$_2$ (20.0 mg, 0.06 mmol) and CO (360 mmHg, 2.61 mmol). The crude product was purified by column chromatography using hexane/ethyl acetate (9/1) as the eluent to give a pale yellow oil (145 mg, 64%). $^1$H NMR (CDCl$_3$): $\delta$ 1.26 ppm (s, 18H), 1.70 (s, 12H), 4.40 (s, 4H), 4.81 (s, 1H), 6.83 (s, 2H), 6.93 (s, 1H), 7.49 (d, $J$ = 2.7 Hz, 2H), 7.73 (d, $J$ = 2.7 Hz, 2H) 10.01 (s, 2H), 11.01 (s, 2H). $^{13}$C NMR (63 MHz, CDCl$_3$): $\delta$ 26.8, 31.3, 34.2, 64.7, 78.3, 113.3, 118.1, 121.2, 128.0, 132.1, 132.4, 140.7, 142.2, 156.1, 157.5, 195.6. C$_{34}$H$_{20}$O$_2$(590.76): calculated (+0.7 CH$_2$Cl$_2$) C 67.79, H 7.35; found C 67.90, H 7.26. MS (DCI/NH$_3$): $m/z$ = 608 [M + NH$_4^+$]$^+$.
3.3'-[(Oxybis(2,1-ethanedioloyl)bis(4-fluorophenyl)-methanediyl)]bis[5-(1,1-dimethylthyl)-2-hydroxybenzaldehyde] (20). Compound 20 was prepared as described for 6 starting from 23 (1.0 g, 1.28 mmol), TEMEDA (0.88 mL) and n-BuLi (1.6 M, 3.2 mL, 5.12 mmol) in Et₂O (3 mL) and DMF (0.99 mL, 12.8 mmol) in Et₂O (3 mL). The reaction was realized at −90 °C. The crude product was dissolved in ethyl acetate/hexane (30 mL/30 mL) and the flask was placed at −20 °C overnight. After filtration and drying, the crude product was directly used for the deprotection of the phenol function. 1H NMR (CDCl₃): δ 0.62 ppm (t, 12H), 1.30 (s, 18 H), 1.90−2.10 (m, 8H), 3.45 (t, J = 5.5 Hz, 4H), 3.74 (t, J = 5.5 Hz, 4H), 3.76 (t, 4H), 4.41 (dd, J₁ = 3.7 Hz, J₂ = 1.5 Hz, 4H), 5.29 (dd, J₁ = 9.1 Hz, J₂ = 1.2 Hz, 2H), 5.49 (dd, J₁ = 9.1 Hz, J₂ = 1.2 Hz, 2H), 5.99−6.12 (m, 2H), 7.73 (d, J = 2.9 Hz, 2H) 7.96 (d, J = 2.9 Hz, 2H) 10.26 (s, 2H).

3.3’-[Oxybis(2,1-ethanedioloyl)-3,3-pentanediyl)]bis[5-(1,1-dimethylthyl)-2-hydroxybenzaldehyde] (25). Compound 25 was prepared as described for 6 starting from 24 (530 mg 0.781 mmol) in MeOH (15 mL), Pd(PPh₃)₄ (45.0 mg, 0.391 mmol), and K₂CO₃ (647.4 mg, 4.68 mmol). The crude product was purified by column chromatography using hexane/ethyl acetate (96/4) as the eluent to give a white solid (707 mg, 80%). 1H NMR (CDCl₃): δ 0.65 ppm (t, 12H), 1.29 ppm (s, 18H), 1.88−2.15 (m, 8H), 3.54 (t, J = 5.1 Hz, 4H), 3.84 (t, J = 4.7 Hz, 4H), 7.50 (d, J = 2.5 Hz, 2H), 7.67 (d, J = 2.5 Hz, 2H), 10.11 (s, 2H), 10.81 (s, 2H). 13C NMR (CDCl₃): δ 7.77, 27.01, 32.1, 34.1, 60.3, 70.9, 83.5, 121.3, 126.4, 129.4, 133.7, 141.4, 157.5, 194.7, C₆H₅O₂H (598.8): calc C 72.22, H 9.09; found C 71.93, H 9.37. SM (ES) m/z (%) = 621.8 [M + Na⁺] 17 3 8 7 4 6.378.8 [M + K⁺] 17 3 8 7 4 6.378.8 [M + K⁺].

3.3'-[(Oxybis(2,1-ethanedioloyl)-3,3-pentanediyl)]bis[5-(1,1-dimethylthyl)-2-hydroxybenzaldehyde] (26). Compound 26 was synthesized as described above for complex 7, starting from 25 (80 mg, 0.0134 mmol) in 80 mL of EtOH, (1S,2S)-(+)-1,2-diaminocyclohexane (15.3 mg, 0.0134 mmol), and MnOAc2·4H₂O (32.8 mg, 0.134 mmol). Yield: 87 mg, 85% as a dark brown microcrystalline solid. The crude product was purified by column chromatography using hexane/ethyl acetate (96/4) as the eluent to give a white solid (707 mg, 80%). 1H NMR (CDCl₃): δ 0.65 ppm (t, 12H), 1.29 ppm (s, 18H), 1.88−2.15 (m, 8H), 3.54 (t, J = 5.1 Hz, 4H), 3.84 (t, J = 4.7 Hz, 4H), 7.50 (d, J = 2.5 Hz, 2H), 7.67 (d, J = 2.5 Hz, 2H), 10.11 (s, 2H), 10.81 (s, 2H). 13C NMR (CDCl₃): δ 7.77, 27.01, 32.1, 34.1, 60.3, 70.9, 83.5, 121.3, 126.4, 129.4, 133.7, 141.4, 157.5, 194.7, C₆H₅O₂H (598.8): calc C 72.22, H 9.09; found C 71.93, H 9.37. SM (ES) m/z (%) = 621.8 [M + Na⁺] 17 3 8 7 4 6.378.8 [M + K⁺] 17 3 8 7 4 6.378.8 [M + K⁺].

3.4-Bis-[3-bromo-5-(1,1-dimethylthyl)-2-(2-propen-1-yloxy)phenyl]-4,7,10,13-tetraoxahexadecane (31). Compound 31 was prepared as described for 24 starting from NaH (4.23 g, 105.6 mmol, 60% dispersion in oil, washed with 2 × 25 mL of pentane in THF (35 mL) and DMF (5 mL), and triethyleneglycol dinitrate (5.5 g, 12.0 mmol) in DMF (20 mL) was added in one portion. The reaction was monitored by TLC and after 24 h, a subsequent portion of triethyleneglycol dinitrate (4.4 g, 9.6 mmol) in DMF (15 mL) was added and stirred for 24 h. After workup, the crude product was purified by column chromatography using hexane/ethyl acetate (9/1) as the eluent to give a colorless oil (4.86 g, 49%). 1H NMR (CDCl₃): δ 0.61 ppm (t, 12H), 1.26 (s, 18H), 1.88−2.07 (m, 8H), 3.42 (t, J = 5.4 Hz, 4H), 3.71 (t, J = 5.4 Hz, 4H), 3.73 (s, 4H), 4.49 (d, J = 5.3 Hz, 4H), 5.27 (dd, J₁ = 16 Hz, J₂ = 1.4 Hz, 2H), 5.43 (dd, J₁ = 16 Hz, J₂ = 1.4 Hz, 2H), 7.41 (d, J = 2.5 Hz, 2H), 7.59 (d, J = 2.5 Hz, 2H), 13C NMR (CDCl₃): δ 8.0, 27.5, 31.3, 34.5, 60.3, 71.0, 71.1, 73.4, 82.0, 117.3, 117.4, 126.7, 129.7, 133.6, 137.6, 147.2, 150.6, C₆H₅O₂Br₂ (778.3): calc C 61.54, H 7.77, found C 61.80, H 7.79. SM (FAB, MBNA): m/z (%) = 803 [M + Na⁺] 17 3 8 7 4 6.378.8 [M + Na⁺] 17 3 8 7 4 6.378.8 [M + Na⁺].

3.4-[(1,1,12,12-Tetraethyl-2,5,8,11-tetraoxadodecan-1,12-diyloxy)]bis(5-(1,1-dimethylthyl)-2-(2-propenyl)benzaldehyde) (28). Compound 28 was prepared as described for 5 starting from 27 (2.25 g, 2.73 mmol) in Et₂O (155 mL), TEMEDA (1.9 mL, 12.5 mmol) and n-BuLi (1.6 M, 6.9 mL, 11.0 mmol) in Et₂O (6.5 mL), and DMF (2.12 mL, 27.3 mmol) in Et₂O (6.5 mL). The reaction was realized at −90 °C. After workup and drying, the crude product (colorless oil) was directly used for the deprotection of the phenol function. 1H NMR (CDCl₃): δ 0.62 ppm (t, 12H), 1.30 (s,
18H), 1.90–2.10 (m, 8H), 3.45 (t, \( J = 5.5 \) Hz, 4H), 3.74 (t, \( J = 5.5 \) Hz, 4H), 5.29 (dd, \( J = 9.1 \) Hz, \( J = 1.2 \) Hz, 2H), 5.49 (dd, \( J = 9.1 \) Hz, \( J = 1.2 \) Hz, 2H), 5.99–6.12 (m, 2H), 7.73 (d, \( J = 2.9 \) Hz, 2H) 7.96 (d, \( J = 2.9 \) Hz, 2H). 3,3′-(1,1,12,12-Tetraethyl-2,5,8,11-tetraoxadodecane-1,12-diyl)-bis[5-(1,1-dimethylethyl)-2-hydroxybenzaldehyde] (29). Compound 29 was prepared as described for 6 starting from 28 (1.98 g, 2.74 mmol) in MeOH (56 mL), Pd(PPH 3 ) 4 (158.2 mg, 0.137 mmol), and K 2 CO 3 (2.27 g, 16.44 mmol). The crude product was purified by column chromatography using hexane/ethyl acetate (9/1) as the eluent to give a colorless oil (1.43 g, 81%). 1 H NMR (CDCl 3 ): δ 0.64 ppm (t, 12H), 1.28 ppm (s, 18H), 1.88–2.12 (m, 8H), 3.50 (t, \( J = 4.9 \) Hz, 4H), 3.75 (t, \( J = 4.9 \) Hz, 4H), 3.75 (s, 4H), 7.49 (d, \( J = 2.4 \) Hz, 2H), 7.66 (d, \( J = 2.4 \) Hz, 2H), 10.10 (s, 2H), 10.80 (s, 2H). 13 C NMR (63 MHz, CDCl 3 ): δ 7.7, 26.9, 31.2, 34.1, 60.2, 70.6, 71.0, 83.4, 121.3, 126.4, 129.5, 133.7, 141.5, 157.5, 194.7. C 38 H 58 O 8 (642.9): calcd C 71.00, H 9.09; found C 70.79, H 9.28. SM (ES) m/z (%): 665.85 [M + Na]+, 681.65 [M + K]+.

Catalytic Epoxidation Procedures. With NaOCl as Oxidant. A typical reaction mixture contained substrate (16 \( \mu \)L of 2,2′-dimethylchromene, 0.1 mmol) and internal standart (23.6 mg of 1,4-dibromobenzene, 0.1 mmol) in 0.5 mL of CH 2 Cl 2, 5 μmol of the appropriate catalyst (0.5 mL of a 10 mM CH 2 Cl 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 M solution in 0.16 mL of a 0.05 M aqueous NaHPO 4 solution, 2 equiv 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 2 Cl 2 (2 mL). The layers were separated, the organic phase dried over Na 2 SO 4, concentrated to ≈1 mL and analyzed by gas chromatography.

With Hydrogen Peroxide as Oxidant. The reaction mixture was prepared according to the procedure described above. After stirring at 0 °C for 10 min, 35% aqueous H 2 O 2 (30 μL, 0.34 mmol, 3.4 equiv of oxidant with respect to the substrate) was added in four portions during 40 min. After stirring for 2 h, the reaction mixture was diluted with water (2 mL) and CH 2 Cl 2 (2 mL). The filtrate was worked up as previously described and analyzed by chiral GC as described above.

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Supporting Information Available: Copies of 1 H NMR and proton-decoupled 13 C NMR spectra for compounds 6, 10, 15, 20, and 25. This material is available free of charge via the Internet at http://pubs.acs.org.

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