Synthesis and characterization of 'calixsalens': a new class of macrocyclic chiral ligands

Zengmin Li and Chet Jablonski*

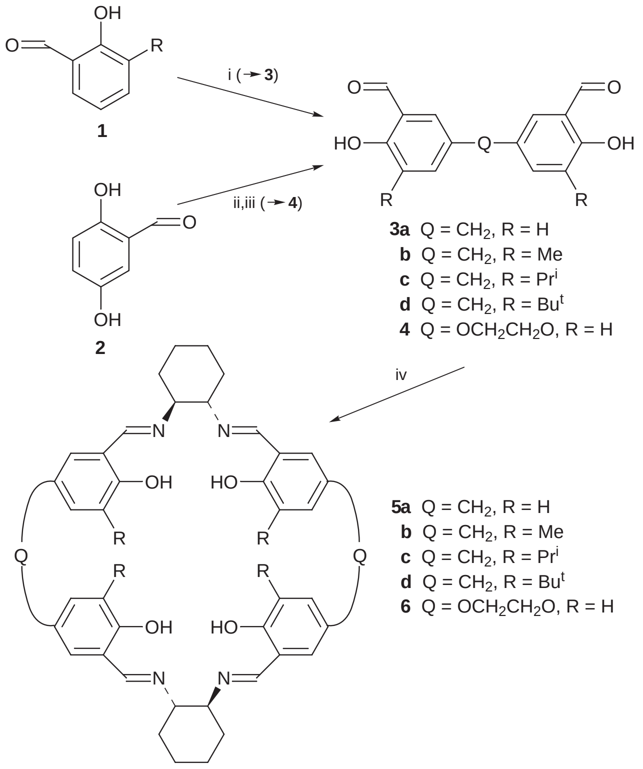
Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1B 3X7.
E-mail: cjablons@morgan.ucs.mun.ca

Received (in Corvallis, OR, USA) 4th January 1999, Accepted 7th June 1999

Template directed reaction of dialdehydes and (*R*,*R*)- or (*S*,*S*)-1,2-diaminocyclohexane affords a practical route to chiral, metal-free macrocyclic salen dimers which have a novel calixarene-like structure and show catalytic activity for enantioselective epoxidation of unfunctionalized alkenes in the presence of Mn^{III}–NaOCl (aq.).

Chiral Schiff base ligands are efficient chiral auxiliaries for a wide range of enantioselective epoxidations.[1] Our search strategy for new asymmetric catalysts, particularly for asymmetric epoxidation of unfunctionalized alkenes,[1–4] has focussed on development of chiral macrocycles bearing two salen-based metal binding sites[5] which can act co-operatively[6a,7] within an enzyme-like chiral cavity. This approach is based on the expectation that non-covalent interactions,[8] which are the sole determinants of stereochemical outcome for enantioselective reactions of unfunctionalized substrates,[2a,9] can be maximized within a chiral host–guest paradigm.[6] The macrocycles reported herein are simple chiral salen dimers (Scheme 1) containing two tetradentate metal binding sites coupled by one- or four-atom linking groups which determine ring size.

The 26- or 32-membered salen macrocycles **5** and **6** were synthesized by template-induced cyclization (Scheme 1) of *trans*-(*R,R*) or *trans*-(*S,S*)-1,2-diaminocyclohexane and an appropriate dialdehyde (**3a**–**d** or **4**), prepared from the corresponding aldehydes.[10] Three products, identified as the dimer **5d** (*m/z* 893), along with the corresponding trimer (*m/z* 1339) and tetramer, were isolated from condensation of dialdehyde **3d** and *trans*-(*R*,*R*)-(−)-1,2 diaminocyclohexane. Two major products were obtained from cyclization of **3a**–**c** with the (*R*,*R*)-diamine. The higher TLC R_f product in each case was confirmed to be macrocyclic dimer **6a**–**c** (*m/z* 668, 725 and 837). Relatively simple and similar ^1H NMR spectra of the dimer and the corresponding trimer or tetramer suggested a highly symmetric structure. ^{13}C NMR revealed seven low field signals assigned to the four equivalent imine C=N carbons and six of the twenty-four aromatic carbons of **5a**–**d**. Consistent with overall D_2 symmetry, four (**5a**), five (**5b**) or six (**5c**,**d**) high field ^{13}C NMR signals were observed for the remaining carbon atoms.



Scheme 1 *Reagents and conditions*: i, $(CH_2O)_3$, H_2SO_4, AcOH, 70 °C; ii, NaH, $(TsOCH_2)_2$; iii, HCl; iv, 1,2-diaminocyclohexane, $Ba(ClO_4)_2$, MeOH–THF.

A single crystal X-ray study† of **5a**·DMF confirms the D_2 symmetric structure (Fig. 1) inferred from solution spectroscopy. The four benzene rings of **5a**·DMF form a well-defined cavity and adopt a 1,3-dialternate conformation with a striking calixarene-like[11] structure, hence we have introduced the name 'calixsalen' to describe these macrocycles. The two opposing face-to-face benzene rings are nearly coplanar and lie 7.57 Å apart and, as a consequence of the preferred 1,3-dialternate conformation, the hydroxy groups are twisted away from the 'salen' plane so that hydrogen-bonding between adjacent OH groups is precluded.

In contrast, the ambient temperature 500 MHz ^1H NMR spectrum of the 32-membered salen macrocycle **6**, obtained as a single TLC band from cyclization of **4** with the (*R*,*R*)-diamine (*cf*. Scheme 1), showed four imine signals (8.12, 8.10, 8.09 and 8.07 ppm) in a ratio of 2 : 4 : 8 : 30 which were assigned to four slowly-interconverting conformers. NMR and mass spectral (*m/z* 761) evidence are consistent with the dimeric structure **6**. ^{13}C NMR showed two imine carbon signals (164.74, 164.51 ppm) in an approximate ratio of 10 : 30 corresponding to the two most stable conformers. Eleven pairs of ^{13}C resonances for the two major conformers, tentatively assigned as the D_2 symmetric 1,3-alternate and C_2 symmetric 1,2-alternate conformers in slow exchange, were observed. Although a maximum of eleven ^{13}C resonances are expected for the D_2 symmetric 1,3-alternate conformation, the 1,2-alternate or any of the remaining

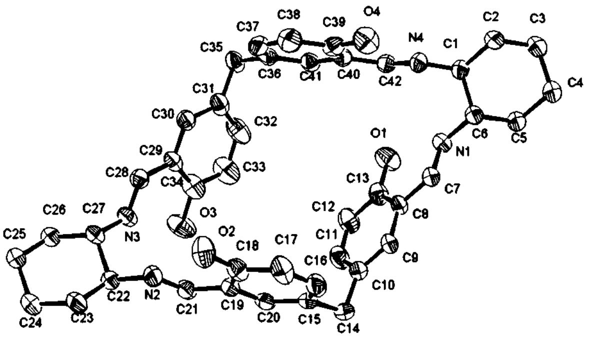


Fig. 1 ORTEP representation (30% ellipsoids) for **5a**·DMF (DMF and hydrogen atoms removed for clarity).

conformations should show a total of 22 resonances. We conclude that some degree of flexibility, made possible by the ethylene glycol links, establishes a second, time-average C_2 axis. Warming to 55 °C results in collapse of the two ^{13}C imine resonances into a single peak at 165.04 ppm, possibly as a result of 1,3-alternate $\leftrightarrow$ 1,2-alternate exchange which becomes fast on the NMR time scale.

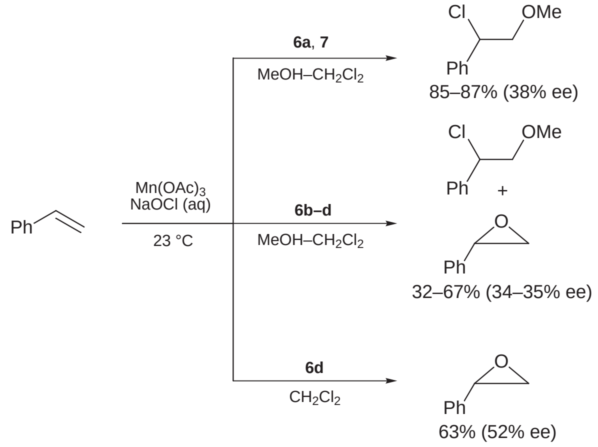
Although the solid state conformation of **5a**·DMF appears ill-disposed to provide two tetradentate salen coordination sites, reaction with Mn^{III} salts is facile. Addition of a solution of $Mn(OAc)_3$ to solutions of the salen dimers **5** or **6** caused an immediate colour change from yellow to deep brown. An electrospray mass spectrum of a methanolic solution of the dark brown product obtained by treatment of **5d** with $Mn(OAc)_3$ showed strong peaks at *m/z* 1093 [(**5d** −4H)Mn_2·2MeOH·CH_2O]$^+$, 1063 [(**5d** −4H)Mn_2·2MeOH]$^+$, 1045 [(**5d** −4H)Mn_2·HCO_2H]$^+$, 999 [(**5d** −4H)Mn_2]$^+$ and 893 [**5d**]$^+$, consistent with the formation of a bimetallic complex.

Preliminary tests of the brown Mn^{II} macrocyclic salen complexes as catalysts for the epoxidation of styrene, the most challenging enantioselective version of this type of reaction thus far,[12] were conducted at room temperature (23 °C) using NaOCl (aq) as terminal oxidant (Scheme 2). Both ring-opened chloromethyl ether and epoxide products were obtained with modest enantioselectivity (Scheme 2) in methanolic solvent. Chemoselectivity responds to the steric requirements of the R groups**.** For example, *tert*-butyl substituted macrocycle **5d** gave epoxide : chloro ether in the ratio 100 : 3 but only one product (85–87% chemical yield), identified as 1-phenyl-1-chloro-2-methoxy ethane by mass spectrometric analysis and comparison of NMR data with 1-phenyl-1-methoxy-2-chloroethane (obtained through direct chlorination of styrene in MeOH), was isolated in the presence of unsubstituted dimer **5a** or **6**. Interestingly, both epoxide and chlorinated products (chloro ether or chlorohydrin) in a ratio of 10 : 1 are obtained with catalyst **5b** (R = CH_3).

The ring opened products obtained were uniquely *anti*-Markownikoff, hence Scheme 2 may have some important synthetic applications.[13] Reversed regioselective chlorination of alkenes has previously been observed in alkoxychlorination of allylamines with Wacker type catalysts[14] but Markownikoff addition was found for all other alkenes tested.

Unlike mononuclear salen catalysts,[2*a*] the enantioselectivity of the macrocyclic Mn^{III}–calixsalen systems reported in this work appears unrelated to the steric requirements of the R groups on the *ortho* position of the phenol in the salen frame (Scheme 2). We therefore speculate that the observed enantioselectivity is controlled by host–guest intra-cavity interactions.

The dimanganese complex isolated from ligand **5d**, which unlike that from **5a** was soluble in CH_2Cl_2, allows direct comparison of the enantioselectivity of the bimetallic calixsalen complexes reported in this work with the well characterized Jacobsen catalysts. Aqueous NaOCl oxidation of styrene in the presence of the brown dimanganese complex of **5d** in CH_2Cl_2 gave only epoxide product with 52% ee in 63% isolated chemical yield at 25 °C. This result compares favourably with the best value of 59% ee at 23 °C in CH_2Cl_2 for a mononuclear Mn^{III} salen catalyst reported by Jacobsen.[12]



Scheme 2

C. J. acknowledges the Natural Science and Engineering Council of Canada (NSERC) for a grant in aid of research. Z. L. acknowledges Memorial University for financial support. We thank Professor M. McGlinchey and MacMaster University for 500 MHz NMR data reported for compound **6** and Mr David Miller, Memorial University Crystallography Laboratory, for determination of the molecular structure of **5a**.

Notes and references

† *Crystal data* for **6a**: $C_{42}H_{40}O_4N_4$·DMF, yellow, monoclinic, space group $P2_1/c$ (#14), a = 14.640(3), b = 25.679(4), c = 11.045(6) Å, β = 81.97(2)°, V = 4112(4) Å^3, Z = 4, 5858 unique reflections, R = 0.077, R_w = 0.045, GOF = 1.80. CCDC 182/1289.

1 W. Zhang and E. N. Jacobsen, *J. Org. Chem.*, 1991, **56**, 2296; S. H. Zhao, P. R. Ortiz, B. A. Keys and K. G. Davenport, *Tetrahedron Lett.*, 1996, **37**, 2725; P. J. Pospisil, D. H. Carsten and E. N. Jacobsen, *Chem. Eur. J.*, 1996, **2**, 974; T. Hamada, T. Fukuda, H. Imanishi and T. Katsuki, *Tetrahedron*, 1996, **52**, 515; T. Nagata, K. Imagawa, T. Yamada and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 1455; K. D. S. Bernardo, A. Robert, F. Dahan and B. Meunier, *New J. Chem.*, 1995, **19**, 129; T. Kuroki, T. Hamada and T. Katsuki, *Chem. Lett.*, 1995, 339; K. G. Rasmussen, D. S. Thomsen and K. A. Jorgensen, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2009; I. Fernández, J. R. Pedro and R. Delasalud, *Tetrahedron*, 1996, **52**, 12 031.

2 (*a*) E. N. Jacobsen, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1993, p. 159; (*b*) J. P. Collman, X. Zhang, V. J. Lee, E. S. Uffelman and J. I. Brauman, *Science*, 1993, **261**, 1404; (*c*) V. Schurig and F. Betschinger, *Chem. Rev.*, 1992, **92**, 873; (*d*) T. Katsuki, *Coord. Chem. Rev.*, 1995, **140**, 189.

3 K. B. M. Janssen, I. Laquiere, W. Dehaen, R. F. Parton, I. F. J. Vankelecom and P. A. Jacobs, *Tetrahedron: Asymmetry*, 1997, **8**, 3481.

4 B. B. De, B. B. Lohray, S. Sivaram and P. K. Dhal, *J. Polym. Sci. Part A: Polym. Chem.*, 1997, **35**, 1809.

5 H. Brunner and H. Schiessling, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 125; C. Fraser, R. Ostrander, A. L. Rheingold, C. White and B. Bosnich, *Inorg. Chem.*, 1994, **33**, 324; C. Fraser and B. Bosnich, *Inorg. Chem.*, 1994, **33**, 338; F. C. J. M. van Veggel, W. Verboom and D. Reinhoudt, *Chem. Rev*., 1994, **94**, 279.

6 (*a*) J. M. Lehn, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 89; (*b*) H. L. Anderson and J. K. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2223; (*c*) A. J. Kirby, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 707.

7 P. Scrimin, P. Tecilla, U. Tonellato and A. Veronese, *Molecular Design and Bioorganic Catalysis*, ed. C. S. Wilcox and A. D. Hamilton, Kluwer, Dordrecht, 1996, p. 211.

8 D. J. Cram, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1009.

9 R. W. Quan, Z. Li and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1996, **118**, 8156.

10 G. Casiraghi, G. Casnati, M. Corina, A. Pochini, G. Puglia, G. Sartori and R. J. Ungaro, *J. Chem. Soc., Perkin Trans. 1*, 1978, 318; C. S. Marvel and N. Tarköy, *J. Am. Chem. Soc.*, 1957, **79**, 6000; A. R. van Doorn, R. Shaafstra, M. Bos, S. Harkema, J.-V. Erden, W. Verboom and D. N. Reinhoudt, *J. Org. Chem.*, 1991, **56**, 6083.

11 C. Wieser, C. B. Dieleman and D. Matt, *Coord. Chem. Rev.*, 1997, **165**, 93.

12 M. Palucki, P. J. Pospisil, W. Zhang and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1994, **116**, 9333.

13 A. El-Qisairi, O. Hamed and P. M. Henry, *J. Org. Chem.*, 1998, **63**, 2790; J. Y. Lai, F. S. Wang, G. Z. Guo and L. X. Dai, *J. Org. Chem.*, 1993, **58**, 6944; H. Nakamura, M. Sekido, M. Ito and Y. Yamamoto, *J. Am. Chem. Soc.*, 1998, **120**, 6838.

14 J. Y. Lai, X. X. Shi and X. Dai, *J. Org. Chem.*, 1992, **57**, 3485.

Communication 9/00018F