



Synthesis and structures of novel enantiopure inherently chiral calix[4]arene-derived salphen ligands and their transition-metal complexes

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ABSTRACT

Synthesis and structures of two pairs of novel enantiopure inherently chiral calix[4]arene-derived salphen ligands were described. Several Zn²⁺, Ni²⁺, and Cu²⁺ complexes of the chiral ligands were also prepared, and their structures were characterized by NMR, IR, CD, and HRMS spectra.

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In the past decades, significant advances have been made in the development of chiral salen ligands and the use of their optically pure metal complexes as asymmetric catalysts.¹ Similarly, the salphen (*N,N*-phenylene-salicylidene) ligands, which create nearly planar, rigid NOON coordination geometry with a vacant axial coordination sites, have also been widely studied in coordination and supramolecular chemistry owing to the easy synthetic accessibility of a large variety of different structures.² However, synthesis of the chiral salphen ligands still remains a significant challenge, which thus impeded their practical applications in material science and asymmetric catalysis.^{3,4}

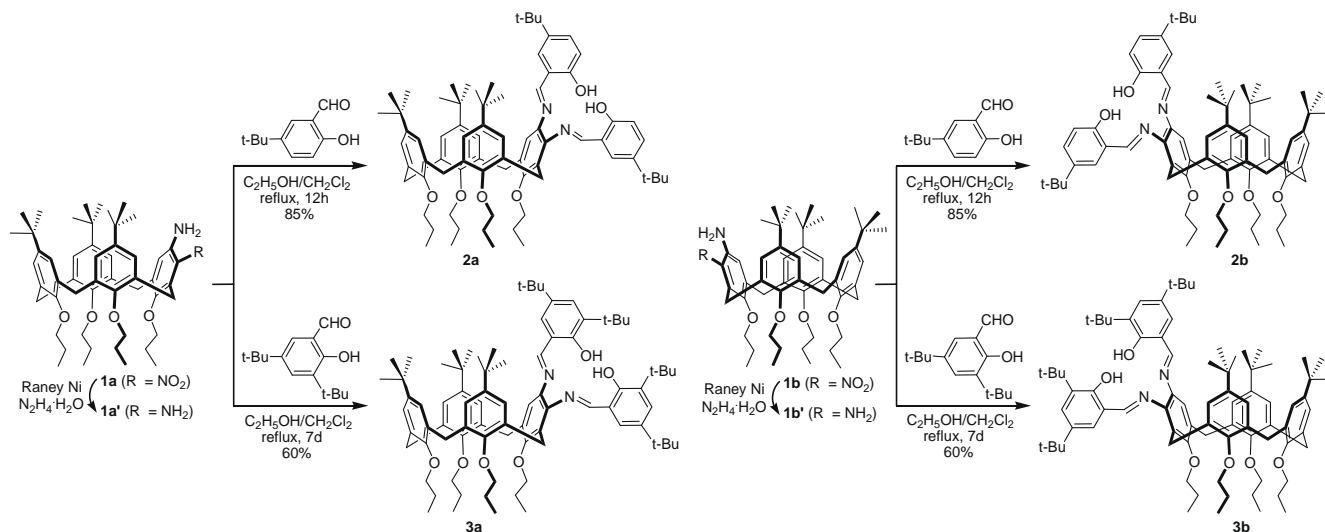
Inherently chiral calixarenes⁵ are a class of chiral macrocyclic compounds with their chiralities based on the asymmetric array of achiral groups upon the three-dimensional calix-skeletons. Since the first example⁶ of inherently chiral calix[4]arene reported by Gutsche et al. in 1982, significant efforts have been devoted to the synthesis of inherently chiral calixarenes for their unique structures and potential applications in chiral recognition⁷ and asymmetric catalysis.⁸ In recent years, we⁹ and other groups¹⁰ developed an effective resolution approach to the enantiopure inherently chiral calixarenes by introduction of a chiral auxiliary. More recently, we reported a more convenient approach¹¹ to the enantiopure *meta*-substituted inherently chiral aminocalix[4]are-

nes based on the dual functions of Boc-*L*-proline auxiliary. Especially, we¹² further found that Boc-*L*-proline could also be used as the chiral acylating reagent for the enantioselective acylation of the racemic *meta*-nitro substituted aminocalix[4]arenes, which thus provided us an opportunity to developing chiral salphen ligands. Herein, we report the synthesis and structures of a class of novel enantiopure inherently chiral calix[4]arene-based salphen ligands and their metal complexes.

Synthesis of the salphen ligands is depicted in Scheme 1.^{13,14} Starting from the optical pure inherently chiral calix[4]arenes (*cS*)-**1a** and (*cR*)-**1b**, the *meta*-amino substituted inherently chiral aminocalix[4]arenes **1a'** and **1b'** were then obtained by the reduction of **1a** or **1b** with Raney Ni in the presence of hydrazine hydrate, respectively. Reaction of **1a'**/**1b'** with the commercially available 3-*tert*-butylsalicylaldehyde or 3,5-di-*tert*-butylsalicylaldehyde in CH₂Cl₂ and C₂H₅OH at reflux temperature gave the salphen ligands (*cS*)-**2a** and (*cR*)-**2b**, and (*cS*)-**3a** and (*cR*)-**3b**, respectively, in good yields.

The two pairs of novel salphen ligands were all air-stable, and soluble in common organic solvents. Due to the inherently chiral calix[4]arene backbone, ¹H NMR spectra of ligands **2a** and **2b** showed two singlet signals for the phenol protons at the downfield of 12.91/12.14, and 12.89/12.13 ppm, respectively, which was probably due to the hydrogen bonding interactions between the phenol protons and the imine nitrogen atoms. For the protons of two imine groups, two singlet signals at 8.25 and 7.67 ppm were

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Scheme 1. Synthesis of inherently chiral calix[4]arene-derived salphen ligands.

observed, meanwhile the *t*-Bu groups showed five distinct signals for **2a** or **2b**, respectively. In the cases of (*cS*)-**3a** and (*cR*)-**3b**, similar ¹H NMR spectral features were also observed.¹⁴ Moreover, circular dichroism (CD) spectroscopy of (*cS*)-**2a** ($[\alpha]_D^{25} -180^\circ$)/(*cR*)-**2b** ($[\alpha]_D^{25} +180^\circ$), and (*cS*)-**3a** ($[\alpha]_D^{25} -155^\circ$)/(*cR*)-**3b** ($[\alpha]_D^{25} +155^\circ$) showed excellent mirror images, indicating their each inherent chirality (Fig. 1).

We have also obtained the single crystals of (*cS*)-**2a** and (*cR*)-**3b** suitable for X-ray diffraction by slow evaporation of their mixture solution of CH₂Cl₂ and MeOH, and the single crystals of (*cS*)-**3a** from the acetone solution.¹⁵ The crystal structures provided further evidences for formation of the chiral salphen ligands. As shown in Figure 2, both the macrocyclic frameworks in (*cS*)-**3a** and (*cR*)-**3b** adopt the cone conformation of the calix[4]arene, with dihedral angles between the opposite phenoxy rings of 3.95° and 84.72° for (*cS*)-**3a**, and 1.67° and 84.87° for (*cR*)-**3b**, respectively. Moreover, the intramolecular hydrogen bonding interactions between the phenol protons and the imine nitrogen atoms with the distances of 1.877 and 1.833 Å for (*cS*)-**3a**, and 1.860 and 1.814 Å for (*cR*)-**3b**, respectively, were also found, which are consistent with the results in solution.

With the optical pure chiral salphen ligands in hand, the synthesis of their metal complexes was then carried out according to the known procedure.^{3d,16} We first tested the reactions of **2a** and **2b** with metal acetate reagents in 1:6 (v/v) CH₂Cl₂/MeOH, and found that the salphen complexes **4–6** could be synthesized in good isolated yields (Scheme 2). However, under the same conditions as described above, the metal complexes of the salphen

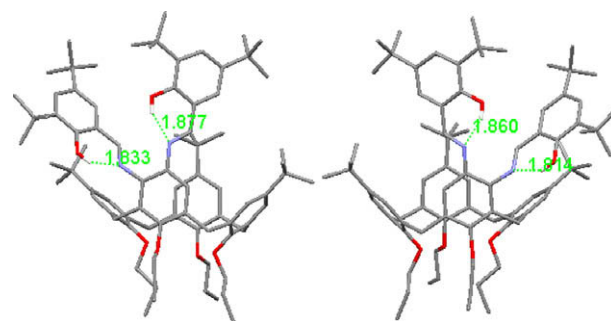


Figure 2. Crystal structures of (left) compound (*cS*)-**3a** and (right) compound (*cR*)-**3b**.

ligands **3a** and **3b** could not be expectedly obtained probably owing to the steric effects of 3-positioned *t*-Bu groups in the ligands.

Formation of the metallo-salphen complexes first came from the obvious color changes of the reaction mixture. For **4a/4b**, the color changed from yellow of the ligands to deep red, while for **5a/5b** and **6a/6b**, orange or gray green of the complexes could be observed, respectively. The complexes **4–6** were further characterized by the IR, NMR, and HRMS spectra. Compared with the free salphen, lower C=N stretches in the IR spectra of the complexes were expectedly observed.^{14,17} In the ¹H NMR spectra of complexes **4a/4b** and **5a/5b**, it was found that two OH proton signals were disappeared, while the imine proton signals shifted downfield¹⁴

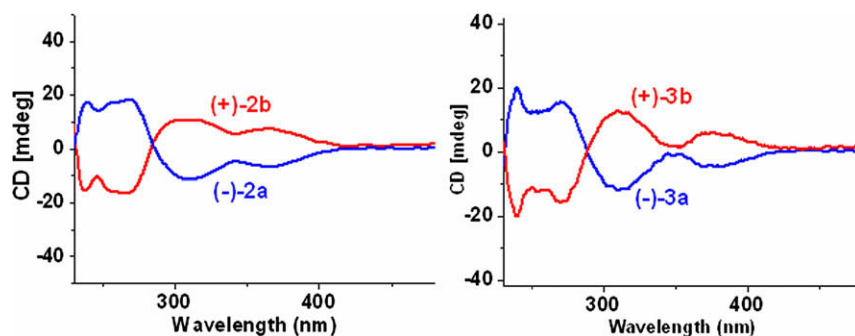
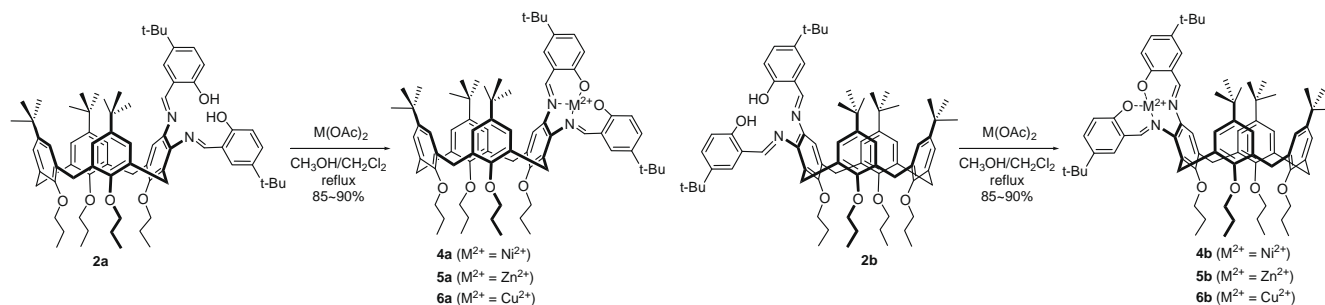


Figure 1. CD spectra of (left) (*cS*)-**2a**/*cR*)-**2b**, and (right) (*cS*)-**3a**/*cR*)-**3b** in CH₂Cl₂ at 25 °C; *c* = 2 × 10^{−5} M.



Scheme 2. Synthesis of the complexes.

probably due to the Lewis acidity of the metal center of the complexes. The HRMS spectra¹⁴ were also measured, which provided further evidences for formation of the complexes. For the complexes **4a/4b** and **5a/5b**, the peaks at m/z 1167.6697/1167.6689 or 1174.6691/1174.6627 for $[M+H]^+$ were observed. Meanwhile the peaks at m/z 1194.6467 and 1194.6458, corresponding to $[M+Na]^+$, were shown for the complex **6a** or **6b**, respectively. Moreover, it was also found that the CD spectra (Fig. 3) of (cS)-**4a** ($[\alpha]_D^{25} -223^\circ$)/(cR)-**4b** ($[\alpha]_D^{25} +223^\circ$), (cS)-**5a** ($[\alpha]_D^{25} +55^\circ$)/(cR)-**5b** ($[\alpha]_D^{25} -55^\circ$), and (cS)-**6a** ($[\alpha]_D^{25} -133^\circ$)/(cR)-**6b** ($[\alpha]_D^{25} +133^\circ$) all showed excellent mirror images, indicating their each purity and inherently chirality.

In conclusion, we have synthesized two pairs of novel optically pure inherently chiral calix[4]arene-derived salphen ligands and three pairs of the chiral salphen-based complexes, and also characterized their structures by NMR, CD, HRMS spectra, and X-ray crystallographic analyses. We believe that these novel chiral salphen ligands and their metal complexes will be found practical

applications in enantioselective polymerization¹⁸ of epoxides and lactones, and asymmetric synthesis,¹⁹ which are now in process in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data (Synthetic procedures and characterization data of new compounds. Copies of IR and HRMS spectra. Crystal data of (cS)-**2a**, (cS)-**3a**, and (cR)-**3b**.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.064.

References and notes

- (a) Larrow, J. F.; Jacobsen, E. N. *Top. Organomet. Chem.* **2004**, *6*, 123–152; (b) Cozzi, P. G. *Chem. Soc. Rev.* **2004**, *33*, 410–421; (c) McGarrige, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563–1602.
- (a) Vigato, P. A.; Tamburini, S. *Coord. Chem. Rev.* **2004**, *248*, 1717–2128. and references therein; (b) Hirahata, W.; Thomas, R. M.; Iobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2008**, *130*, 17658–17659; (c) Kleij, A. W.; Wezenberg, S. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 2–14; (d) Kleij, A. W. *Chem. Eur. J.* **2008**, *14*, 10520–10529; (e) Kleij, A. W.; Lutz, M.; Spek, A. L.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Commun.* **2005**, 3661–3663; (f) Kleij, A. W.; Reek, J. N. H. *Chem. Eur. J.* **2006**, *12*, 4218–4227; (g) Das, S.; Nag, A.; Goswami, D.; Bharadwaj, P. K. *J. Am. Chem. Soc.* **2006**, *128*, 402–403.
- Examples for the synthesis of asymmetric metallo-salphen complexes, see: (a) Kleij, A. W.; Tooke, D. M.; Spek, A. L.; Reek, J. N. H. *Eur. J. Inorg. Chem.* **2005**, 4626–4634; (b) Lin, H. C.; Huang, C.-C.; Shi, C.-H.; Liao, Y.-H.; Chen, C.-C.; Lin, Y.-C.; Liu, Y.-H. *Dalton Trans.* **2007**, 781–791; (c) Kleij, A. W.; Kuli, M.; Lutz, M.; Tooke, D. M.; Spek, A. L.; Kamer, P. C. J.; Leeuwen, P. W. N. M.; Reek, J. N. H. *Inorg. Chim. Acta* **2006**, *359*, 1807–1814; (d) Curreli, S.; Escudero-Adan, E. C.; Benet-Buchholz, J.; Kleij, A. M. J. *Org. Chem.* **2007**, *72*, 7018–7021; (e) Wu, X. H.; Gorden, A. E. V.; Tonks, S. A.; Vilseck, J. Z. *J. Org. Chem.* **2007**, *72*, 8691–8699.
- (a) Chen, Z. H.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170–2171; (b) Chen, Z. H.; Yakura, K.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 3239–3242.
- Gutsche, C. D. *Calixarenes Revisited*; RSC: Cambridge, UK, 1998.
- No, K. H.; Gutsche, C. D. *J. Org. Chem.* **1982**, *47*, 2713–2719.
- (a) Araki, K.; Inada, K.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 72–74; (b) Jin, T.; Monde, K. *Chem. Commun.* **1998**, 1357–1358; (c) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2005**, *61*, 8517–8528; (d) Shirakawa, S.; Moriyama, A.; Shimizu, S. *Org. Lett.* **2007**, *9*, 3117–3119.
- (a) Dieleman, C.; Steyer, S.; Jeunesse, C.; Matt, D. *J. Chem. Soc., Dalton Trans.* **2001**, 2508–2517; (b) Xu, Z.-X.; Li, G.-K.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2008**, *67*, 8668–8675; (c) Shirakawa, S.; Kimura, T.; Murata, S.; Shimizu, S. *J. Org. Chem.* **2009**, *74*, 1288–1296.
- (a) Cao, Y.-D.; Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Wang, M.-X.; Huang, Z.-T. *J. Org. Chem.* **2004**, *69*, 206–208; (b) Li, S.-Y.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron: Asymmetry* **2005**, *16*, 641–645; (c) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Chem. Eur. J.* **2005**, *11*, 5917–5928; (d) Mao, R.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *J. Org. Chem.* **2005**, *70*, 7662–7671.
- (a) Narumi, F.; Yamabuki, W.; Hattori, T.; Kameyama, H.; Miyano, S. *Chem. Lett.* **2003**, *32*, 320–321; (b) Narumi, F.; Hattori, T.; Yamabuki, W.; Kabutso, C.; Kameyama, H. *Tetrahedron: Asymmetry* **2005**, *16*, 793–800; (c) Narumi, F.;

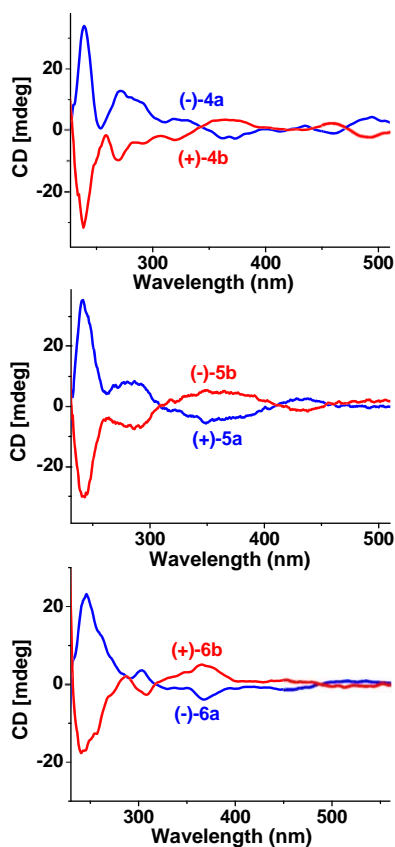


Figure 3. CD spectra of (top) **4a/4b**, (middle) **5a/5b**, and (down) **6a/6b** in CH_2Cl_2 at 25°C ; $c = 2 \times 10^{-5}$ M.

- Hattori, T.; Matsumura, N.; Onodera, T.; Katagiri, C.; Kabutto, C.; Kameyama, H. *Tetrahedron* **2004**, *60*, 7827–7833; (d) Boyko, V. I.; Shivanyuk, A.; Pyrozhenko, V. V.; Zubatyuk, R. I.; Shishkin, O. V.; Kalchenko, V. I. *Tetrahedron Lett.* **2006**, *47*, 7775–7778.
- Xu, Z.-X.; Zhang, C.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2007**, *9*, 4447–4450.
 - Xu, Z.-X.; Zhang, C.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Org. Lett.* **2008**, *10*, 477–479.
 - General synthetic procedure for ligands (**cS**)-**2a**, **3a** and (**cR**)-**2b**, **3b**. To a suspension of (**cS**)-**1a**/**(cR)**-**1b** (428 mg, 0.52 mmol) and a catalytic amount of Raney Ni in THF (40 mL) was added hydrazine hydrate (2.1 mL) dropwise. After the mixture was refluxed 2 h under argon, the Raney Ni was filtered over Hyflo and the solvent was evaporated. The residue was taken up in CH₂Cl₂ (50 mL), washed with H₂O (30 mL) and brine (30 mL), dried over anhydrous Na₂SO₄. After evaporation of the solvent, a white solid was obtained and dissolved in a mixture of C₂H₅OH/CH₂Cl₂ (15:1 v/v) without any purification. The solution was refluxed under N₂ for 12 h after the addition of 2 equiv 3-*tert*-butylsalicylaldehyde or 3,5-di(*tert*-butyl)salicylaldehyde. The yellow precipitate was filtered off after the removal of half of the solvent under reduced pressure.
 - See [Supplementary data](#) for details.
 - CCDC 734918, CCDC 734919, and CCDC 734920 contain the supplementary crystallographic data for (**cS**)-**2a**, (**cS**)-**3a**, and (**cR**)-**3b**, respectively. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.
 - General synthetic procedure for complexes **4–6**. To a solution of ligand **2a** or **2b** in a mixture of MeOH/CH₂Cl₂ (5:1 v/v, 6 mL) was slowly added another solution of metal acetate in MeOH (1 mL). After the reaction mixture was refluxed for 48 h, the isolation of the product was accomplished by adding two volumes of H₂O to the crude reaction mixture, and then filtering the precipitate.
 - (a) DiMauro, E. F.; Kozłowski, M. C. *Organometallics* **2002**, *21*, 1454–1461; (b) Chen, Z. H.; Morimoto, H.; Matsunaga, S.; Shibazaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170–2171.
 - (a) Nomura, N.; Aoyama, T.; Ishii, R.; Kondo, T. *Macromolecules* **2005**, *38*, 5363–5366; (b) Zintl, M.; Molnar, F.; Urban, T.; Bernhart, V.; Preishuber-Pflügl, P.; Rieger, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 3458–3460.
 - (a) Richeter, S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 16280–16281; (b) Purse, B. W.; Tran, L. H.; Piera, J.; Åkermark, B.; Bäckvall, J. E. *Chem. Eur. J.* **2008**, *14*, 7500–7503.