

Minimalist End Groups for Control of Absolute Helicity in Salen- and Salophen-Based Metallofoldamers

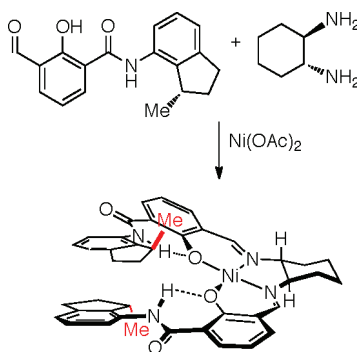
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ABSTRACT



(*S*)-1-Methylindan end groups are effective controllers of absolute helicity in Ni-salen- and Ni-salophen-based foldamers derived from (*R,R*)-*trans*-1,2-cyclohexanediamine and 1,2-phenylenediamine, respectively. Evidence for the helicity of the described complexes was provided through X-ray crystallography and study of chiroptical properties in solution. The chiral end groups control the absolute sense of helicity for the salen complexes, even in a case where the helical bias of the end group is mismatched relative to that of the internal diamine.

The design of foldamers—unnatural molecules that fold into distinct secondary structures—has been inspired by natural strategies for creating three-dimensional structure in macromolecules.¹ As the unnatural analogues of metalloptides, single-stranded metallofoldamers^{2,3} present intriguing possibilities for the study of asymmetric catalysts. In particular, the ability to control the three-dimensional structure of metallofoldamers presents a unique tool for understanding the role of secondary structure in enantioselective catalysis.

Our group has been engaged in the use of metallofoldamers as tools for probing the role of helicity in asymmetric

induction by metal-salen catalysts.⁴ Previously, we described the properties of a number of large metallofoldamers such as **1** and **2** (Figure 1), and we determined that stereocenters at the periphery of the foldamers can control the absolute sense of helicity.^{4c} In **2**, the end group overwhelms the chiral

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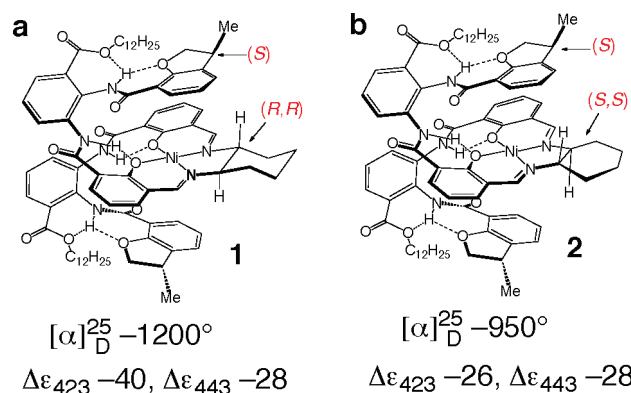


Figure 1. Chiral end groups control the sense of helicity in metallofoldamers. Diastereomeric complexes **1** and **2** fold as (*M*)-helical diastereomers. In **2**, the directing ability of the end group completely overwhelms the influence of the chiral diamine, which ordinarily directs for a (*P*)-helix. As for **1**, the (*M*)-helicity of **2** results in significant chiroptical properties.

diamine, which ordinarily directs for the opposite helical diastereomer.

In foldamers **1** and **2**, the metal center is embedded within the helix. To design foldamers that can be used in catalysis, it will be necessary to utilize analogues in which the metal center is not blocked by the ends of the helices. Accordingly, we envisioned salen and salophen foldamers with “minimalist” end groups, which retain virtue of peripheral control over helicity⁵ without precluding the possibility of axial coordination. Herein, we describe the synthesis and properties

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(5) Lead examples of abiotic foldamers where absolute helicity is controlled by stereocenters at the termini: (a) Moore, J. S. *Acc. Chem. Res.* **1997**, *30*, 402. (b) Mamula, O.; von Zelewsky, A. *Coord. Chem. Rev.* **2003**, *242*, 87. (c) Baum, G.; Constable, E. C.; Fenske, D.; Housecroft, C. E.; Kulke, T.; Neuburger, M.; Zehnder, M. *J. Chem. Soc., Dalton Trans.* **2000**, 945. (d) Yagi, S.; Morinaga, T.; Nomura, T.; Takagishi, T.; Mizutani, T.; Kitagawa, S.; Ogoshi, H. *J. Org. Chem.* **2001**, *66*, 3848. (e) Hofacker, A. L.; Parquette, J. R. *Proc. R. Soc. London, Ser. A* **2010**, *466*, 1469. (f) Hu, H.-Y.; Xue, W.; Hu, Z.-Q.; Xiang, J.-F.; Chen, C.-F.; He, S.-G. *J. Org. Chem.* **2009**, *74*, 4949. (g) Naidu, V. R.; Kim, M. C.; Suk, J.-m.; Kim, H.-J.; Lee, M.; Sim, E.; Jeong, K.-S. *Org. Lett.* **2008**, *10*, 5373. (h) Akazome, M.; Ishii, Y.; Nireki, T.; Ogura, K. *Tetrahedron Lett.* **2008**, *49*, 4430. (i) Petitjean, A.; Cuccia, L. A.; Schmutz, M.; Lehn, J.-M. *J. Org. Chem.* **2008**, *73*, 2481. (j) Clayden, J.; Lemiègre, L.; Morris, G. A.; Pickworth, M.; Snape, T. J.; Jones, L. H. *J. Am. Chem. Soc.* **2008**, *130*, 15193. (k) Hu, H.; Xiang, J.-F.; Yang, Y.; Chen, C.-F. *Org. Lett.* **2008**, *10*, 1275. (l) Li, C.; Wang, G.; Yi, H.; Jiang, X.; Li, Z.; Wang, R. *Org. Lett.* **2007**, *9*, 1797. (m) Maurizot, V.; Dolain, C.; Huc, I. *Eur. J. Org. Chem.* **2005**, 1293. (n) Dolain, C.; Jiang, H.; Leger, J.-M.; Guenneau, P.; Huc, I. *J. Am. Chem. Soc.* **2005**, *127*, 12943.

of a new class of foldamers with structure **3**, in which small chiral end groups are able to control the absolute sense of helicity. Asymmetry is derived from chiral 1-methylindanol groups at the periphery of the foldamer (Figure 2a), and

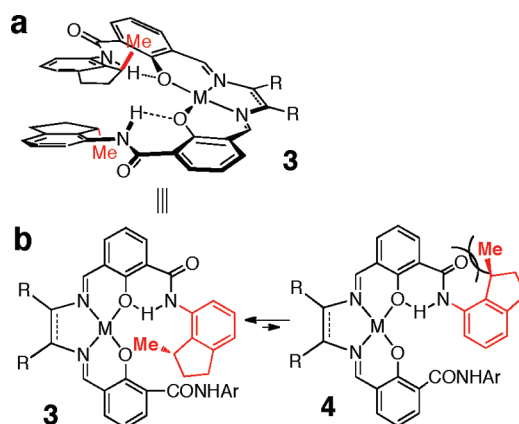


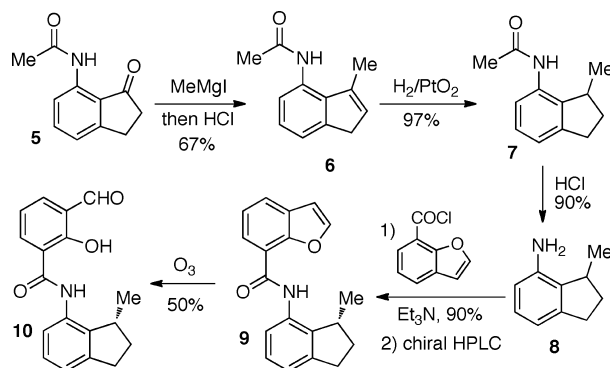
Figure 2. Design of metallofoldamers with minimalist end groups.

control over absolute helicity is predicted, as shown in Figure 2b. It is speculated that conformer **4** will be disfavored as a result of a steric interaction, which causes deviation from planarity and consequently disrupts π -stacking interactions with the underlying ring.

The goal of this study was to demonstrate the ability of the chiral end groups to enforce absolute helicity in metallofoldamers of structure **3**. Because the chiroptical signatures of folding are well understood for Ni-salen foldamers and Ni-salophen foldamers, we focused initial studies on Ni complexes of **3**.⁴ We demonstrate that these complexes adopt helical structures in solution and the crystalline state. The absolute sense of helicity is dominated by stereocenters at the periphery for all of these metallofoldamers, including those in which the end group chirality is mismatched relative to the diamine chirality.

Foldamers **3** were synthesized from salicylaldehyde **10**, which was prepared as outlined in Scheme 1. The known

Scheme 1. Salicylaldehyde Synthesis



compound **5** was readily prepared from commercially available 4-aminoindan.⁶

Grignard addition followed by dehydration of compound **5** provided compound **6**. Hydrogenation of **6** at 30 psi provided compound **7**, and subsequent deacetylation gave **8**. Coupling to benzofuran-8-carbonyl chloride^{4,7} gave racemic **9** in excellent yield. Compound **9** was separated on semipreparative scale using chiral chromatography (Chiral Technologies, AD column): the slower eluting enantiomer was determined to have the *S*-configuration. Ozonolysis of (*S*)-**9** and (*R*)-**9** generated the enantiomerically pure salicylaldehydes (*S*)-**10** and (*R*)-**10**, respectively.

Combination of (*S*)-**10** with 1,2-phenylenediamine and Ni(OAc)₂ produced **3a**, which crystallized and was analyzed by X-ray diffraction. A helical structure was observed with the terminal methyl group pointing to the outside of the helix. Upon refinement of Flack parameters based on anomalous dispersion, it was possible to assign (*P*)-helicity to the structure (Figure 3). In solution studies, it was observed that

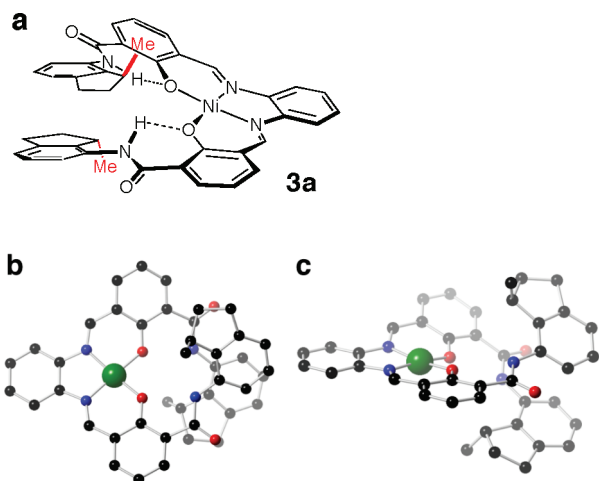


Figure 3. (a) Salophen **3a**. X-ray structure; (b) top view and (c) side view.

the magnitudes of the specific rotation ($[\alpha]_D^{25} +1500$) and the CD spectrum are both large (Figure 4). The significant chiroptical properties of complex **3a** suggests that there is a dominant (*P*)-helix in the solution.

Compound **3a** was also analyzed in solution by variable-temperature ¹H NMR (see Supporting Information). In our prior work on Ni-salen and salophen foldamers, the inter-conversion between two helical conformers was observed in VT-NMR experiments with coalescence observed at -10 to -25 °C.^{4b,c} In contrast, the ¹H NMR spectrum of **3a** in CD₂Cl₂ does not broaden upon cooling to -100 °C. This may be consistent with a single helical diastereomer for **3a**

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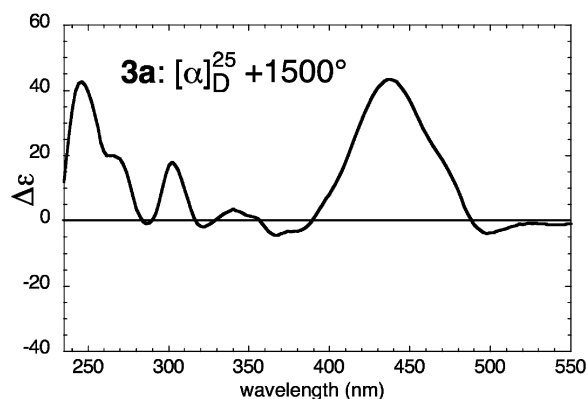
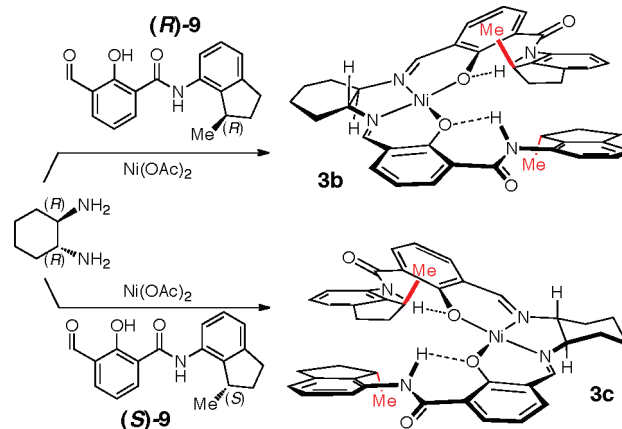


Figure 4. CD spectrum of **3a**.

in solution. However, it cannot be ruled out that another conformer is not present in small amounts, as complex **3a** may have a barrier to helical inversion that is rapid on the NMR time scale even at -100 °C. Nonetheless, the large magnitude of the chiroptical properties implies that the (*P*)-helix is the thermodynamically dominant conformation for **3a** in solution.

Combination of (*R*)-**9** with (*R,R*)-*trans*-cyclohexane-1,2-diamine and Ni(OAc)₂ gave the “matched” complex **3b** upon reaction with Ni(OAc)₂ (Scheme 2). In **3b**, the diamine and

Scheme 2. Synthesis of Matched Complex **3b** and Mismatched Complex **3c**



the end group both bias for (*M*)-helicity. The structure of **3b** was determined by crystallography (Figure 5) and found to be (*M*)-helical and structurally analogous to **3a**. The combination of (*R*)-**9** with (*R,R*)-*trans*-cyclohexane-1,2-diamine and Ni(OAc)₂ gave the mismatched complex **3c**, in which the chiral diamine biases for an (*M*)-helix, but the end group biases for a (*P*)-helix. The magnitude of the chiroptical properties of **3b** and **3c** are similar to those observed previously in **1** and **2**, which were shown to be dominated by a single helical diastereomer in solution.

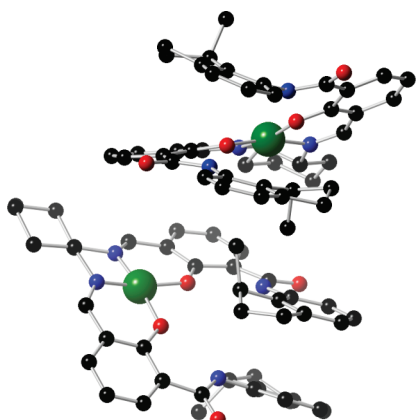


Figure 5. X-ray crystal structure of **3b**. The unit cell contained two very similar, but symmetry unique molecules.

Consistent with end group control over the absolute sense of helicity, the chiroptical properties of **3b** and **3c** are comparable in magnitude but opposite in sign. Thus, the specific rotation of **3b** is $[\alpha]_D^{25} -1100$, whereas the specific rotation of **3c** is $[\alpha]_D^{25} +970$. The CD spectrum (Figure 6) of the matched complex **3b** is dominated by strongly negative dichroisms, as expected for a chiral structure with (*M*)-helicity. For **3c**, the sign of the dichroisms is reversed, indicating (*P*)-helicity.

In Ni-salen complexes, the long wavelength dichroisms above 400 nm are attributed to MLCT bands,^{4,8} and the intensity of these dichroisms is an indicator of helicity.

As the secondary structures of compounds **1** and **2** (Scheme 1) are established to be highly helical, the CD spectra^{4b,c} of these compounds serve as convenient benchmarks for comparison. Complex **3b** was compared to **1**, as both have end groups and diamines with matched chirality (Figure 6). For **3b**, the dichroisms at 416 nm ($\Delta\epsilon -35$) and 442 nm ($\Delta\epsilon -34$) are similar in intensity to the dichroisms at 421 ($\Delta\epsilon -40$) and 446 nm ($\Delta\epsilon -28$) in **1**, indicating that **3b** is predominantly (*M*)-helical. We also compared the long wavelength dichroisms of **3c** and **2**, as both of these complexes have end groups with mismatched chirality. For **3c**, the dichroisms at 416 nm ($\Delta\epsilon 22$) and 435 nm ($\Delta\epsilon 28$) are similar in intensity to the dichroisms at 423 ($\Delta\epsilon -26$) and 443 nm ($\Delta\epsilon -28$) in **2**. This comparison implies that **3c**

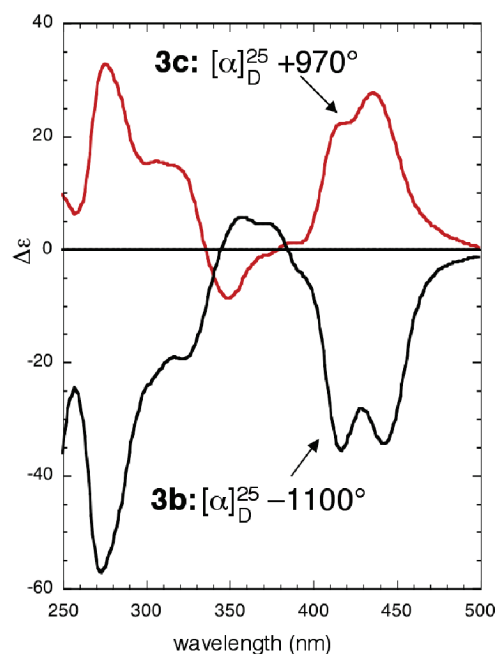


Figure 6. CD spectra and specific rotations for **3b** and **3c**.

is predominantly (*P*)-helical. Overall, these observations are consistent with helical structures for **3b** and **3c** in which the sense of absolute helicity is dominated by the end group and not the chiral diamine.

In conclusion, a new class of metallofoldamers has been described in which small end groups control the sense of helical folding, even in a case where the helical bias of the end group is mismatched relative to that of the internal diamine. Applications of these and related complexes in asymmetric catalysis are the focus of current study.

Acknowledgment. For financial support of this work, we thank the NSF (CHE-0547865). NMR spectra were obtained with instrumentation supported by NSF CRIF:MU Grant CHE 0840401.

Supporting Information Available: Full experimental details, ^1H and ^{13}C NMR spectra, and X-ray data for compounds **3a** and **3b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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