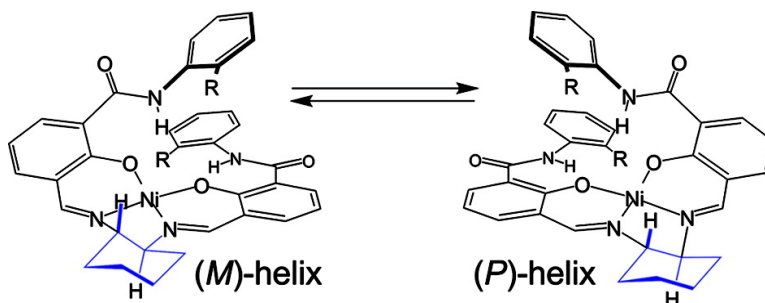


trans-Cyclohexane-1,2-diamine Is a Weak Director of Absolute Helicity in Chiral Nickel–Salen Complexes

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***trans*-Cyclohexane-1,2-diamine Is a Weak Director of Absolute Helicity in Chiral Nickel–Salen Complexes**

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Abstract: The interconversion between helical diastereomers of nickel–salen-based foldamers can be observed on a NMR time scale. Such complexes provide quantitative information about the propensity of different elements of central chirality to control the absolute sense of folding. *trans*-Cyclohexane-1,2-diamine—a common component of chiral salen catalysts—is a surprisingly weak director of absolute helicity in nickel–salen foldamers. Implications for asymmetric catalysis are discussed.

Introduction

Chiral salens are exceptionally useful ligands for asymmetric catalysis,¹ and the origin of asymmetric induction in reactions catalyzed by chiral metal–salen complexes has been a topic of considerable interest.^{2–5} Many models for asymmetric induction by salen–metal catalysts have focused on the role of central chirality, in which stereogenic centers within the catalyst backbone directly influence the approach of a substrate to one enantiotopic face of the catalyst.² However, central chirality can also induce helicity in salen–metal complexes, and in some models for asymmetric induction, it has been argued that helical^{6,7} chirality plays a critical role in asymmetric catalysis.^{3–5} For example, elegant studies by Katsuki have demonstrated that chiral donor ligands can induce a high enantioselectivity in epoxidations catalyzed by achiral manganese–salen catalysts.^{1b,c,3c} Computational studies on the manganese–salen catalyzed epoxidation have also connected asymmetric induction to folding of the salen ligand.⁵ More recently, Rawal and co-workers hypothesized that helicity plays a role in cobalt–salen catalyzed asymmetric Diels–Alder reactions, and this hypothesis guided the design of a more effective generation of catalysts.⁴

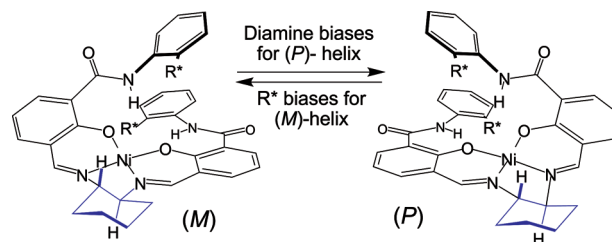


Figure 1. Mismatched chirality in metallofoldamers as a probe for helical bias.

Implicit to models that invoke helicity to explain asymmetric induction is that an element of central chirality (typically a chiral diamine) creates a bias for one sense of folding in metal–salen complexes. However, two helical diastereomers are possible for metal–salens derived from chiral diamines. Under catalytic conditions, it is possible that these diastereomers would equilibrate and that Curtin–Hammett kinetics would be relevant. Currently, tools for directly measuring such ratios of helical diastereomers are lacking. We hypothesized that ratios of helical diastereomers could be measured by juxtaposing different elements of chirality within salen complexes that are predisposed to fold (Figure 1). In this scenario, the chiral end-group (R^*) would bias for the formation of a (*M*)-helix, whereas the diamine would bias for the diastereomeric metallofoldamer of (*P*)-helicity. Spectroscopic and crystallographic studies of such complexes would provide a measure of the ability of the chiral diamine to control helicity relative to the end-group.

Previously, we described helical nickel–salophens **1** and **2**, in which absolute helicity is determined by chiral end-groups A and B (Figure 2).^{8,9} For **1**, two conformers of opposite helicity interconvert on the NMR time scale with a slight (~2:1) bias for the (*M*)-helix over the (*P*)-helix. By contrast, **2** is dominated by an (*M*)-helix that is stabilized by 3-point hydrogen bonds.

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- (6) We consider chiral stepped conformations¹ of salens to be encompassed within the definition of helical chirality.
- (7) It has been demonstrated that multiple elements of chirality can work synergistically to induce asymmetry in metal–salen catalyzed transformations. See ref 1b,c and (a) Walsh, P. J.; Lurain, A. E.; Balsells, J. *Chem. Rev.* **2003**, *103*, 3297. (b) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1641.

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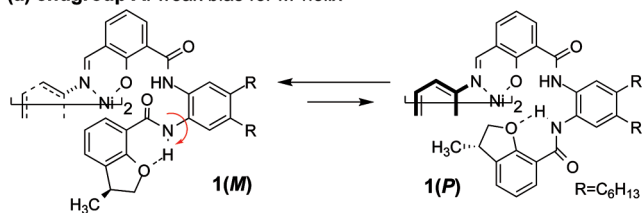
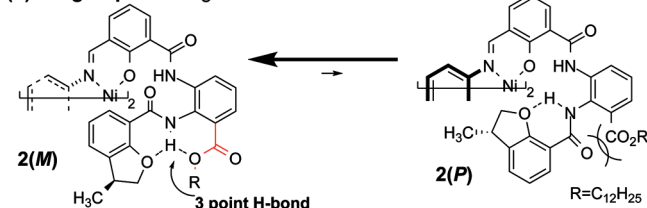
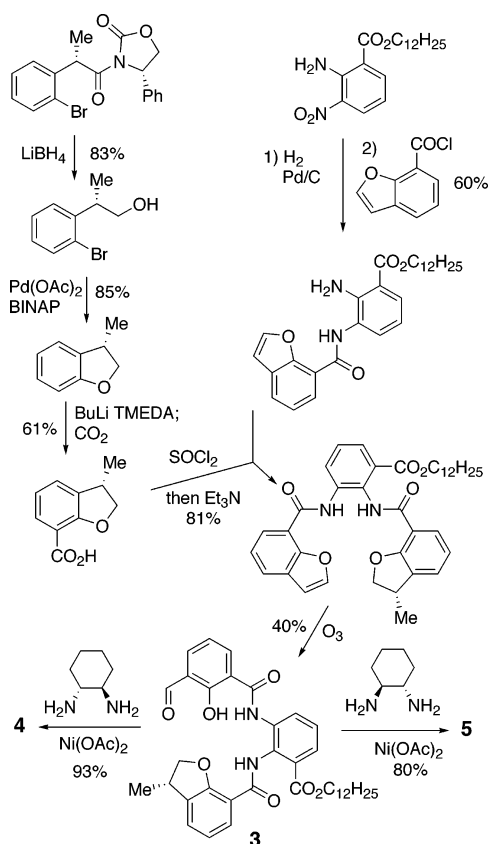
(a) endgroup A: weak bias for *M*-helix(b) endgroup B: strong bias for *M*-helix

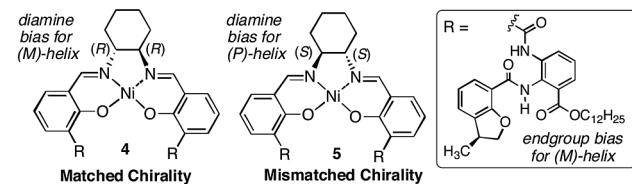
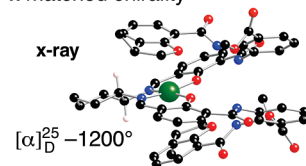
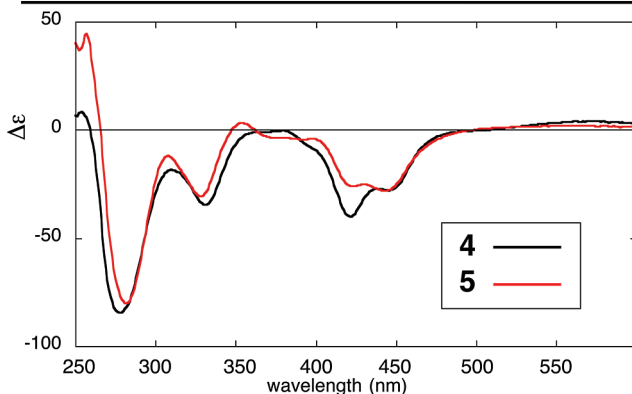
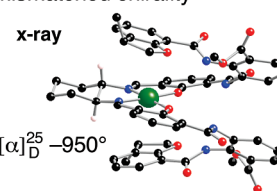
Figure 2. End-group directors of absolute helicity in salophen foldamers.

Scheme 1



Thus, end-group B can be considered to be a strong director of absolute helicity in salophen foldamers, whereas end-group A provides only a weak bias.

Herein, it is demonstrated that *trans*-cyclohexane-1,2-diamine—a common component of chiral salen catalysts—is a surprisingly weak director of absolute helicity in nickel–salen metallofoldamers. This is demonstrated not only for foldamers that contain competing elements of chirality (as depicted in Figure 1) but also for a foldamer in which the diamine is the only element of central chirality. For models that invoke helicity to explain asymmetric induction by metal–salen catalysts, an implication is that both helical diastereomers are viable.

Scheme 2. Chiroptical Data and X-ray Crystal Structures for **4** and **5** Show That Absolute Sense of Helicity Is Determined by the End-Group and Not the Diamine^a**4**: matched chirality**5**: mismatched chirality

^a Displayed CD spectra are those from CH₂Cl₂ solutions of **4** (3.6×10^{-4} M) and **5** (3.6×10^{-4} M). C₁₂H₂₅ side chains are not displayed in the X-ray structures.

Results and Discussion

To measure the ability of *trans*-cyclohexanediamine to control absolute helicity, salens **4** and **5** were prepared from salicylaldehyde **3**^{8b} using the ozonolysis approach^{8a} outlined in Scheme 1. This synthetic approach, which parallels our earlier approach to foldamer **2**,^{8b} takes advantage of Pd catalyzed C–O bond formation¹⁰ and the differential reactivity of the amino groups of dodecyl-2,3-diaminobenzoate toward acylhalides.

Spectroscopic and X-ray crystallographic properties of **4** and **5** are displayed in Scheme 2. In **4**, the helical bias of the diamine is matched to that of the end-group B. As expected, the chiroptical properties of **4** indicate the formation of an (*M*)-helix: a strong, negative CD signal and a large specific rotation ($[\alpha]_D -1200^\circ$) were observed. In **5**, the chirality of the diamine and the end-group are mismatched: the diamine biases for a (*P*)-helix, whereas the end-group biases for an (*M*)-helix. Strikingly, the chiroptical data indicate that the end-group completely overrides the diamine. Thus, the specific rotation (-950°) and the magnitude and shape of the CD spectrum are similar to those of **4** and are indicative of (*M*)-helicity. CD spectroscopy also indicates that the folding of **4** and **5** is not disrupted by the addition of MeOH. Thus, the spectra of **4** and **5** in 1:1 MeOH/CH₂Cl₂ (displayed in the Supporting Information) were nearly identical to those displayed in Scheme 2.

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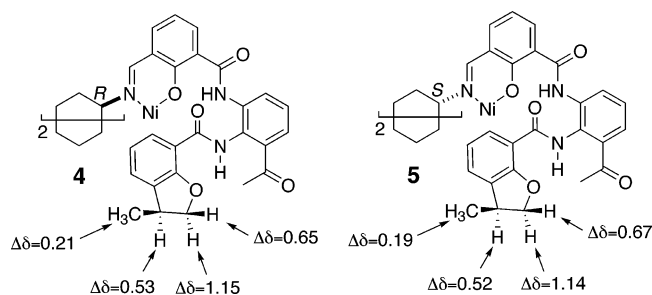
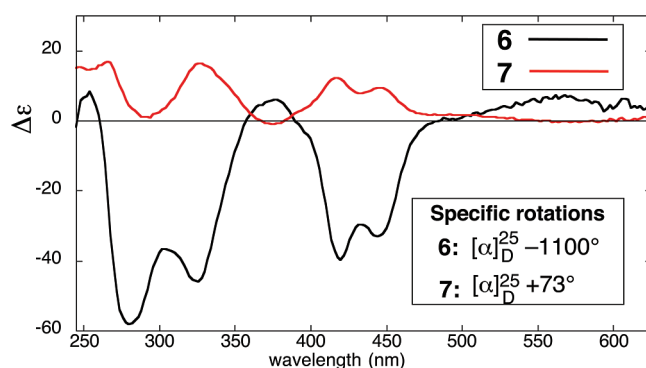
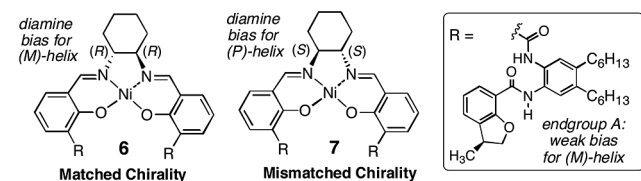


Figure 3. Comparison of ^1H NMR chemical shifts of **4** and **5** against salicylaldehyde precursor **3**. The $\Delta\delta$ values refer to upfield chemical shifts relative to **3**. Large chemical shift anisotropies were also observed for foldamers **6–8**.

Scheme 3. Chiroptical Data for **6** and **7**^a



^a CD spectra are those from CH_2Cl_2 solutions of **6** (3.8×10^{-4} M) and **7** (3.8×10^{-4} M).

The X-ray crystal structures of **4** and **5** were also determined (Scheme 1). Both structures are helical with an (*M*)-configuration. The structures are highly analogous and resemble those determined previously for **2**. In accord with the conclusion of chiroptical studies in solution, the absolute configuration of **5** is governed by the end-group and not by the diamine.

Chemical shift anisotropies in the ^1H NMR spectra of **4** and **5** also support that their structures are helical (Figure 3). In previous studies on salophen **2**, significant upfield chemical shifts were associated with the aliphatic hydrogens of the dihydrobenzofuran ring.^{8b} Upfield chemical shifts of similar magnitudes were observed for salens **4** and **5** as compared to their salicylaldehyde precursor **3**.

Using procedures that mirrored those in Scheme 1, salen compounds **6** and **7** were prepared. These salen complexes also combined elements of chirality from *trans*-cyclohexanediamine and end-group A, a weak director of absolute helicity (vide supra) (Scheme 3). Chemical shift anisotropies suggest that both **6** and **7** have helical structures (see Supporting Information). As expected, the chiroptical data indicate a strong bias for the (*M*)-helix in **6** ($[\alpha]_{\text{D}}^{25} -1100^\circ$) as the chirality of the end-group is matched to that of the diamine. In the mismatched **7**, the positive dichroisms in the CD spectrum indicate a reversal in helicity. However, the peaks in the CD of **7** are only $\sim 30\%$ as intense of those of **4–6**, and the rotation ($[\alpha]_{\text{D}}^{25} +73^\circ$) of **7** is

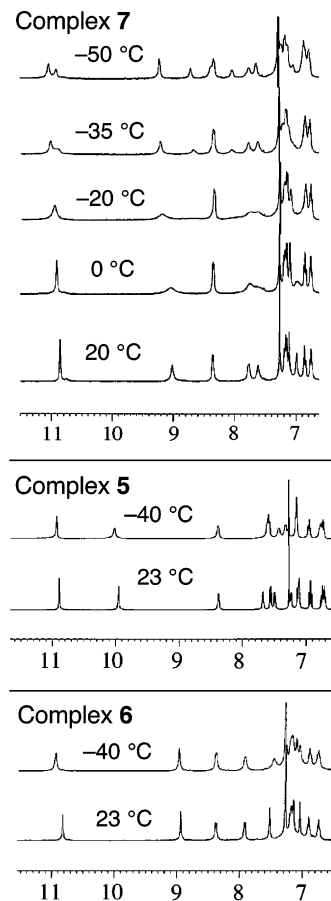


Figure 4. VT-NMR spectra of **5–7** (CDCl_3).

small. Thus, the chiroptical data suggest only a modest preference for the (*P*)-helix in **7**.

VT-NMR also suggests that **7** is a mixture of conformers. In previous VT-NMR studies on **1**, a chemical exchange with coalescence at -25°C was assigned to the equilibrium between two diastereomers of opposing helicity as shown in Figure 2. For **7**, a chemical exchange occurs with a similar coalescence temperature (Figure 4). Two conformers are detected in a 3:2 ratio. By contrast, chemical exchange is not observed in this temperature range for **5** and **6**. We propose that the two conformers of **7** are diastereomers of opposite helicity.

CD spectroscopy also supports that the diminished chiroptical properties of **7** result from a mixture of two helical diastereomers and not from unfolding of the helix. Only very minor differences in the CD spectra of **7** are noted upon changing the solvent from CH_2Cl_2 to DMSO (Figure 5). Furthermore, the CD spectrum of **7** in DMSO is nearly superimposable with the spectrum recorded in 10:1 DMSO/ H_2O (**7** precipitated from DMSO containing higher proportions of water). These data suggest that the helical structures are conserved across solvents with dramatically different abilities to disrupt hydrogen bonding.

The studies on **4–7** suggested that it would be possible to detect helical diastereomers for foldamers in which (*R,R*)-cyclohexanediamine is the only element of central chirality. To test this hypothesis, we synthesized Ni complex **8**—an analogue of **4** with achiral end-groups (Scheme 4). ^1H NMR chemical shift anisotropy (Supporting Information) and NOESY studies suggest that **8** is helical. The *trans*-helix internuclear distances that were measured to be less than 4.5 \AA by NOE are displayed

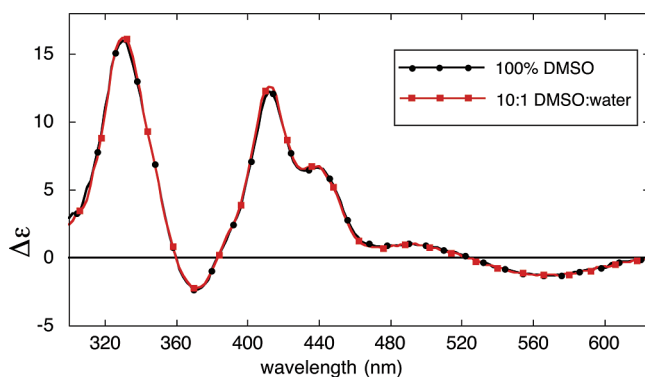
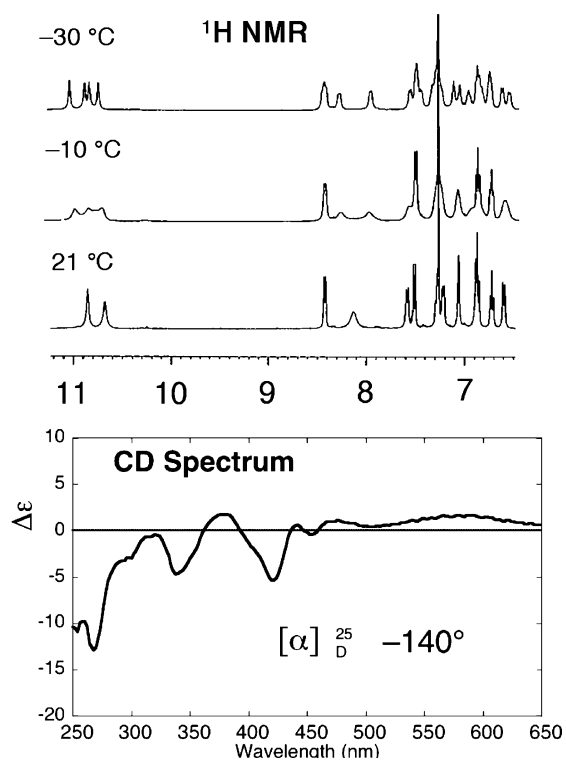
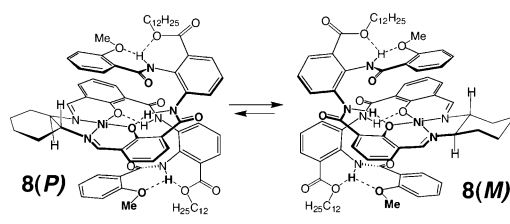


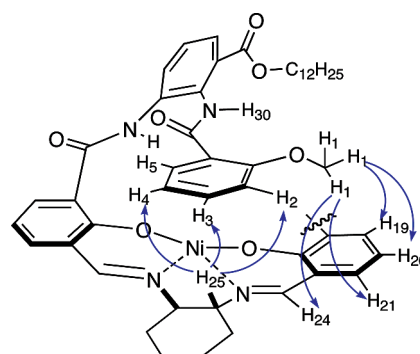
Figure 5. CD spectra of **7** in DMSO (7.7×10^{-4} M) and in 10:1 DMSO/ H_2O (7.0×10^{-4} M).

Scheme 4. Salen **8** Is an Equilibrating Mixture of Helical Diastereomers^a



^a ^1H NMR spectra were measured in CDCl_3 , and CD spectrum was measured in CH_2Cl_2 (2.0×10^{-4} M).

in Figure 6. In particular, short internuclear distances were measured between the cyclohexanediamine methine hydrogens (H-25) and hydrogens on the terminal anisoyl ring (3.4 and 3.3 Å for H-3 and H-4, respectively). Short distances were also measured between the hydrogens of the terminal methoxy groups (H-1) and the underlying aromatic ring (3.4, 3.3, and 3.9 Å for H-19, H-20, and H-21, respectively). These data are



Proton Pair	Distance (NOE) Å
H1-H19	3.4
H1-H20	3.3
H1-H21	3.9
H1-H24	4.4
H25-H2	4.2
H25-H3	3.4
H25-H4	3.3
H19-H30	4.4
H2-H24	4.4
H2-H20	4.0

Figure 6. Selected NOE signals that were observed for **8**.

consistent with prior NOESY studies on **2**^{sb} and provide strong support that **8** is helical in solution.

While NMR studies suggest that **8** is helical, the CD and specific rotation ($[\alpha]_{\text{D}} -140^\circ$) of **8** are weak (Scheme 4). In the VT-NMR spectrum, coalescence is observed at -10°C . Our interpretation of this data is that two diastereomers [**8**(*M*) and **8**(*P*)] are in equilibrium, with only a slight (5:4) bias for the *M*-helix.

Conclusion

Salen-based metallofoldamers are useful tools for studying the influence of central chirality on the absolute sense of helical induction, as the interconversion between helical diastereomers can be observed on the NMR time scale. End-group chirality can dominate the sense of absolute helicity in nickel–salen derivatives that are predisposed to fold into helices. However, it is concluded that *trans*-cyclohexanediamine is only a weak director of absolute helicity in similar foldamers. Both helical diastereomers should be considered in any models that invoke helicity to explain asymmetric induction with chiral salens.

Acknowledgment. This work was supported by the NSF CAREER Award CHE-0547865. Questions regarding the X-rays should be addressed to G.P.A.Y. (gpyap@chem.udel.edu).

Supporting Information Available: Experimental and characterization details and ^1H and ^{13}C NMR spectra for new compounds. CD spectra, UV–vis spectra, and chemical shift anisotropy data for **4–8** and NOE data for **8**. CIF files for **4** and **5**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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