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Stereoselective UV Sensing of 1,2-Diaminocyclohexane Isomers Based on Ligand Displacement with a Diacridylnaphthalene *N,N′*-Dioxide Scandium Complex

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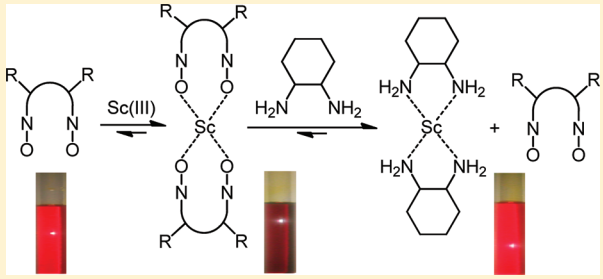
Supporting Information

ABSTRACT: Stereoselective displacement of diacridylnaphthalene *N,N′*-dioxide ligands, **1**, from a scandium(III) complex can be used for quantitative detection of 1,2-diaminocyclohexane isomers. The diastereoselective sensing assay with Sc(*syn*-**1**)$_2$ shows excellent linearity between the sample de and the measured UV absorption change, and sensing of mixtures comprising both low and high de values gave results within 5% accuracy. All three stereoisomers of 1,2-diaminocyclohexane can be differentiated using Sc[*anti*-(−)-**1**]$_2$ in the same ligand displacement assay.



The high demand for pure stereoisomers by the pharmaceutical, agrochemical, and other industries has been accompanied by significant progress in asymmetric synthesis[1] and by the development of analytical techniques for the determination of the stereochemical purity of organic compounds.[2] Stereoselective analysis is very important to verify the purity and the stability to racemization or diastereomerization of fine chemicals and drugs. It also plays an integral part in the development of new asymmetric reactions. High-throughput screening (HTS) efforts utilizing chiral chromatography for the evaluation of one-pot multisubstrate experiments can provide detailed information on yields and stereoselectivity.[3] However, the use of HPLC for HTS of large numbers of samples is generally too time-consuming and produces substantial amounts of solvent waste. Accordingly, real-time analysis of minute sample amounts with carefully designed sensors that translate a molecular recognition event into a quantifiable signal seems to be more promising to complement the advance in automated parallel synthesis and combinatorial methods.

The simplicity, sensitivity, and potential for automation and real-time analysis make UV- and fluorescence-based assays particularly attractive for the development of stereoselective sensing methods. This venue has been pursued by several groups, and intriguing sensors have been reported in recent years. For example, Wang, Zhao, James, and Kubik found that chiral boronic acids can be used for stereoselective recognition and quantitative detection of monosaccharides and α-hydroxy acids.[4] Anslyn, Corradini, and others have demonstrated the usefulness of diaminocyclohexane- and β-cyclodextrin-derived copper(II) complexes for enantioselective colorimetric and fluorescent sensing.[5] Anslyn also introduced compelling indicator-displacement assays suitable for the determination of concentration and quantity of chiral α-hydroxy acids and amino acids.[6] Several molecular and supramolecular fluorosensors derived from BINOL have been used for chiral recognition of α-hydroxy acids and amino acids by Lin's and Pu's groups,[7] while few modified cyclodextrins and calixarenes have been found capable of enantioselective fluorosensing.[8] Our laboratory has developed several C_2-symmetric 1,8-diquinolyl- and 1,8-diacridylnaphthalene selectors for enantioselective UV and fluorescence sensing of minute amounts of a wide range of chiral compounds.[9]

Compared to the variety of enantioselective sensing examples, the analysis of ternary isomeric mixtures, e.g., the enantiomers and the meso isomer of free 1,2-diaminocyclohexane or similar substrates, is an even more complex task. To the best of our knowledge, a UV sensor that can be used to quantitatively distinguish between chiral and meso compounds without prior derivatization has not been reported to date. We now introduce a practical ligand displacement assay (LDA) with a diacridylnaphthalene *N,N′*-dioxide scandium(III) complex that differentiates between the chiral and meso isomers of underivatized diamines.

We have previously shown that 1,8-diacridyl- and 1,8-diquinolylnaphthalenes and their *N,N′*-dioxides can be used for highly enantioselective recognition suitable for quantitative UV and fluorescence detection of chiral amines, amino alcohols, carboxylic acids, α-hydroxy acids, and amino acids in acetonitrile, chloroform, and other organic solvents and even in aqueous solutions.[9] This has been accomplished by using chiral sensor **1** and its analogues in two mechanistically different experiments that either involve (a) stereoselective hydrogen bonding of the analytes to the heteroaryl nitrogen or the heteroaryl *N*-oxide moieties embedded in the chiral cleft of the sensor or (b) ligand exchange with *N,N′*-dioxide-derived

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scandium(III) complexes. We hypothesized that the design of a successful diastereoselective sensor that is expected to recognize a meso substrate in a mixture with chiral isomers should mimic the symmetry of the target and thus exhibit a mirror plane. We therefore began this study with the synthesis of the *syn*-isomer of *N,N′*-dioxide **1** (Figure 1).

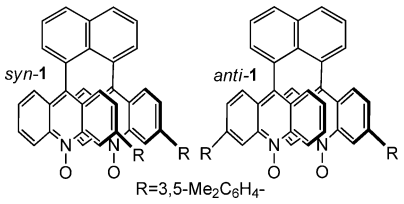


Figure 1. Structures of *syn*- and *anti*-**1**.

Following a previously established synthetic route,[9e] we prepared acridylstannane **3** in four steps via ring construction from commercially available 2-chloro-4-bromobenzoic acid, **2**, in 83% overall yield (Scheme 1). Double Stille coupling with dibromide **4** then produced an equimolar mixture of *syn*- and *anti*-**5** in 89% yield. The diastereomers of **5** were separated by flash chromatography and oxidized with *m*-CPBA to give pure *syn*- and *anti*-isomers of *N,N′*-dioxide **1** in 72−75% yield. After screening of several chiral HPLC columns, we found that the enantiomers of *anti*-**1** can be effectively separated on the WhelkO-1 column. Optimization of HPLC conditions allowed us to separate 20 mg of *anti*-**1** in 7 min or close to 200 mg within 1 h based on repetitive injections (see the Experimental Section).

Having prepared the diastereomers of **1**, we continued with the UV analysis of several transition-metal complexes and found that coordination of *syn*-**1** to indium(III), scandium(III), copper(II), and other metal ions gave characteristic UV charge-transfer bands at 390 nm. Job plot analysis with scandium triflate revealed formation of Sc(*N,N′*-dioxide **1**)$_2$ (see the Experimental Section). We were pleased to observe that this UV absorption fully disappears upon addition of *meso*-1,2-diaminocyclohexane, **6** (Figure 2). Apparently, the change in the UV absorbance at 390 nm is the result of a stepwise displacement of *syn*-**1** from the metal center by the diamine.

The readily observed UV change of Sc(*N,N′*-dioxide **1**)]$_2$ upon addition of diamine **6** then led us to investigate if this

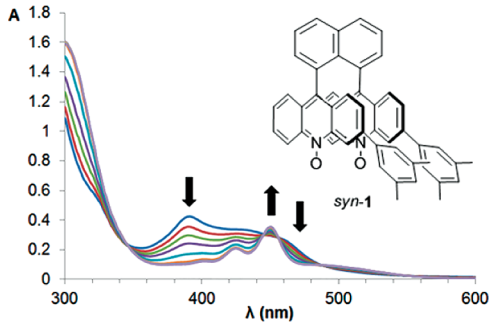


Figure 2. UV spectrum of Sc(*syn*-**1**)$_2$ and disappearance of the charge transfer absorption at 390 nm upon addition of *meso*-**6**. The concentration of the sensor was 1.83 × 10^{-5} M in acetonitrile containing 2% of $CHCl_3$.

ligand displacement reaction could be stereoselective. We assumed that the enantiomers and the meso isomer of diamine **6** are likely to possess different abilities to displace the two *N,N′*-dioxide ligands from the scandium center which would provide a basis for UV analysis of the de of stereoisomeric mixtures of **6**. The titration experiments with meso and racemic diamine **6** are shown in Figure 3. Both diastereoisomers of **6**

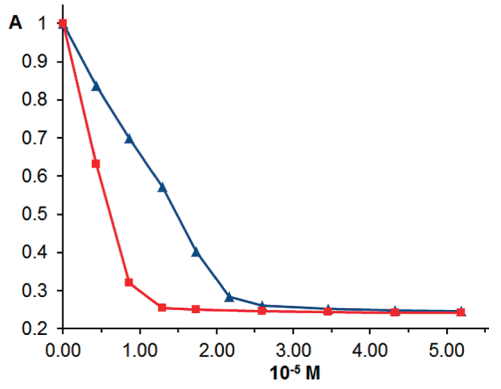
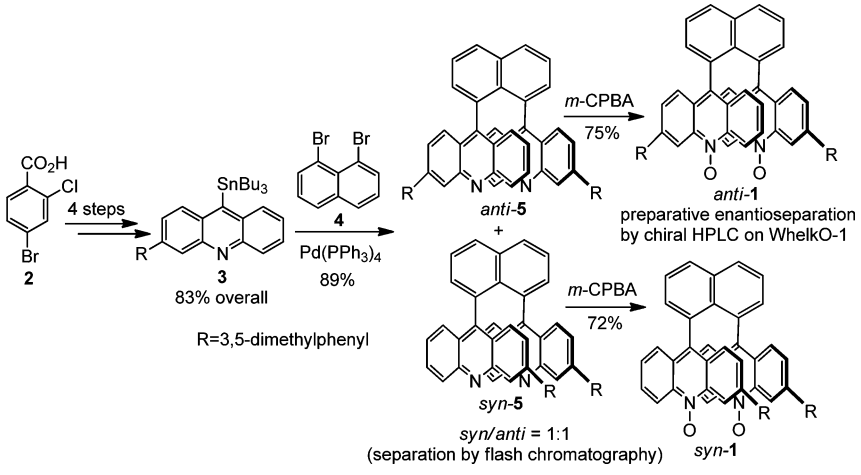


Figure 3. Ligand displacement assay using Sc(*syn*-**1**)$_2$ and *meso*-**6** (blue) and *rac*-**6** (red). The concentration of the sensor was 1.83 × 10^{-5} M in acetonitrile containing 2% of $CHCl_3$. Data were recorded at 390 nm.

Scheme 1. Synthesis of *syn*- and *anti*-1



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replace the *N,N′*-dioxide ligand, and the characteristic UV absorption of Sc(*syn*-**1**)$_2$ at 390 nm disappears almost quantitatively, even when substoichiometric amounts are used. However, the chiral isomers of **6** proved much more effective than the meso diamine. While relatively small amounts of chiral **6** suffice to replace both *N,N′*-dioxide ligands from the scandium center, one needs to add twice as much of the meso isomer to obtain the same UV change. Titration experiments with diastereomeric mixtures of **6** then showed that the remarkably different ligand displacement process can be used to determine the diastereomeric composition of samples with varying de.

To evaluate the practical use of this sensor, three samples of **6** covering a wide de range were analyzed at micromolar concentrations (see Table 1). First, a calibration curve was

Table 1. Experimentally Determined de's of Three Scalemic Samples of 6

actual % de	calcd % de
90	86.4
−50	−45.5
12	16.9

constructed and the comparison of the UV absorption at 390 nm versus % de revealed a perfectly linear relationship. It is noteworthy that a linear correlation between the UV change and the diastereomeric composition of **6** is not necessarily expected.[10] Three mixtures containing **6** in 12, 50, and 90% de, respectively, were then analyzed immediately after mixing with Sc(*syn*-**1**)$_2$ and without further purification. The results obtained by this UV sensing method were in excellent agreement with the theoretical de's. This time-efficient assay gave de's that are generally within 5% of the actual values which is beyond sufficient for HTS purposes.

The formation of Sc(*syn*-**1**)$_2$ and the rapid displacement of the *N,N′*-dioxide ligand from the metal center upon addition of diaminocyclohexane is also evident from ^{1}H NMR and colorimetric analysis (Figure 4). Coordination of free *syn*-**1** to scandium(III) in $CDCl_3$ results in characteristic signal shifts and line broadening. At the same time, the color of the solution changes from bright red to maroon. Upon addition of *rac*-**6**, the free *N,N′*-dioxide is regenerated instantaneously and the original aromatic NMR spectrum and red color can be observed.

We then applied enantiopure Sc[*anti*-(−)-**1**]$_2$ and the isomers of 1,2-diaminocyclohexane in essentially the same assay and realized that this LDA provides an entry to stereoselective UV recognition of the three stereoisomers (Figure 5). In all cases, the full displacement of *anti*-(−)-**1** from the scandium center required 2−3 equiv of the diamine substrate. A comparison of the UV titration curves shows that the meso form of **6** is most effective in this ligand exchange reaction, whereas the UV charge transfer band of Sc[*anti*-(−)-**1**]$_2$ disappears more readily upon addition of (*R,R*)-**6** than in the presence of (*S,S*)-**6**.

Based on our UV and NMR analyses, we assume that the LDA with Sc[*anti*-(−)-**1**]$_2$ is based on a two-step ligand exchange process that is stereoselective because it involves intermediate diastereomeric complexes **8** (Scheme 2). Displacement of the first *N,N′*-dioxide ligand in Sc(*anti*-(−)-**1**)$_2$, **7**, by *meso*-diamine **6**, generates Sc[(*anti*-(−)-**1**)(*meso*-**6**)], **8**. Further addition of the diamine then results in the replacement of the

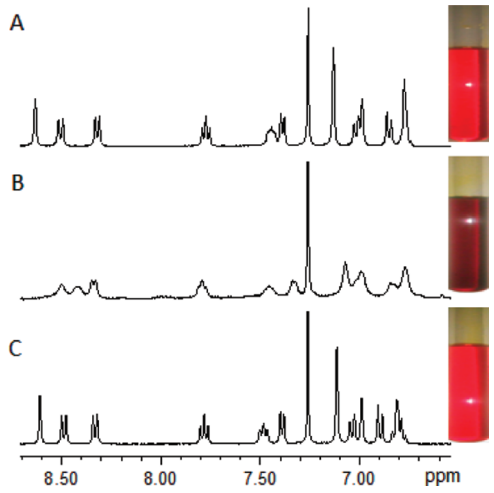


Figure 4. (Left) NMR analysis of the *N,N′*-dioxide displacement in $CDCl_3$: (A) free (*syn*)-**1** at 7.45 mM; (B) (*syn*)-**1** and Sc(OTf)$_3$ at 7.45 mM and 3.75 mM, respectively; (C) (*syn*)-**1**, Sc(OTf)$_3$ and *rac*-**6** at 7.45, 3.75, and 1.87 mM, respectively. (Right) Colorimetric change from bright red (free *N,N′*-dioxide ligand) to maroon (Sc(*syn*-**1**)$_2$) and back to bright red upon addition of **6**.

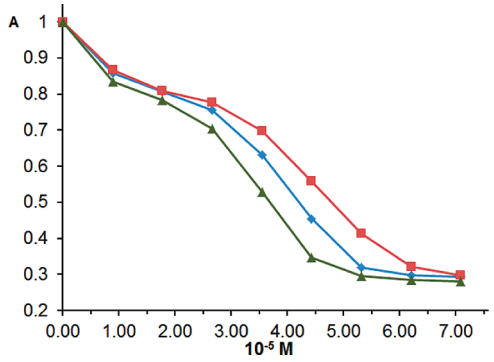
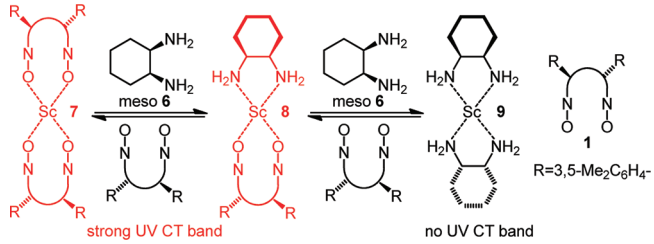


Figure 5. Ligand displacement assay using Sc[(−)-**1**]$_2$ and the isomers of **6**. The concentration of the Sc complex was 1.79 × 10^{-5} M in acetonitrile containing 2% of $CHCl_3$. Data were recorded at 405 nm. The titration curves obtained with (*R,R*)-**6**, (*S,S*)-**6** and *meso*-**6** are shown in blue, red, and green, respectively.

Scheme 2. LDA with 2 equiv of *meso*-6



second *N,N′*-dioxide ligand from the metal center and formation of scandium complex **9**, which is devoid of a UV charge-transfer band at 390 nm (Scheme 2). Accordingly, the ligand exchange results in the disappearance of the intense charge transfer band of the *N,N′*-dioxide-derived scandium complexes **7** and **8**. Assuming that the stereoisomeric complexes of **9** have very similar stabilities, the most striking difference between the LDA with either the meso or the chiral forms of diamine **6** is the structure and stability of the intermediate scandium complex **8**. The stronger displacement

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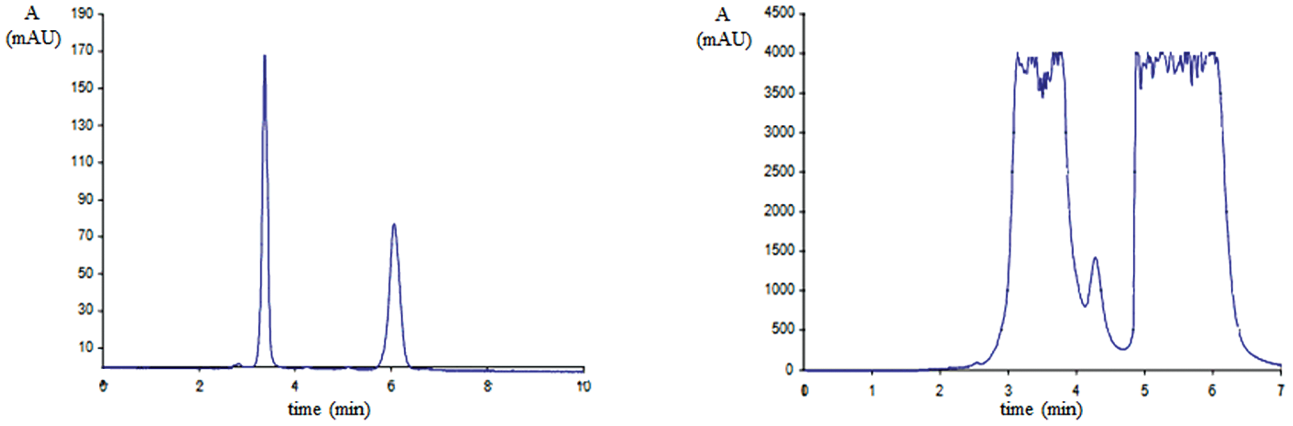

Figure 6. HPLC chromatograms using UV detection at 254 nm for detection of the enantiomers of *anti*-**1**. The two HPLC chromatograms show an analytical (left) and a preparative separation (right).

aptitude of the meso isomer can then be attributed to the formation of a relatively unstable complex **8** due to the steric repulsion between meso **6** and the *N,N′*-dioxide ligand. Although the coordination sphere of **8** is unknown, coordination of a chiral isomer of **6** is expected to result in less steric repulsion and the generation of a more stable intermediate **8** thus impedes removal of the second *N,N′*-dioxide ligand. Accordingly, the chiral isomers are less effective in this LDA and the disappearance of the UV charge transfer band requires higher amounts of the enantiomers of **6**.

In summary, we have demonstrated the first example of UV sensing of enantiomers and diastereomers of an unprotected substrate. The high sensitivity and diastereoselectivity of the ligand displacement assay (LDA) with Sc(*syn*-**1**)$_2$ allows quantitative de analysis of minute sample amounts with sufficient accuracy for high-throughput screening purposes. The use of meso or enantiopure Sc[*N,N′*-dioxide **1**]$_2$ in competitive binding assays seems very promising for the development of practical UV colorimetric assays for rapid analysis of complex ternary mixtures of stereoisomers. The LDA presented is expected to be suitable for automation and has several attractive features: it can be applied to the analysis of minute amounts of underivatized samples which will simplify operation, the UV measurement can be performed immediately after mixing of the sensor and the substrate mixture, and the quantitation is based on sensitive UV spectroscopic detection which minimizes solvent waste.

EXPERIMENTAL SECTION

1. Synthetic Procedures. All reagents and solvents were commercially available and used without further purification. Reaction products were purified by flash chromatography on silica gel (particle size 0.032−0.063 mm). NMR spectra were obtained at 300 or 400 MHz (^{1}H NMR) and 75 or 100 MHz (^{13}C NMR) using $CDCl_3$ as solvent. Chemical shifts are reported in ppm relative to TMS.

*1,8-Bis(3-(3′,5′-dimethylphenyl)-9-acridyl)naphthalene (**5**).*[9h] 1,8-Dibromonaphthalene, **4** (84 mg, 0.293 mmol), CuO (47 mg, 0.585 mmol), and Pd(PPh$_3$)$_4$ (121 mg, 0.11 mmol) were combined under nitrogen in anhydrous DMF (3 mL). The reaction was heated to 130 °C and stirred for 5 min, and then 3-(3′,5′-dimethylphenyl)-9-trimethylstannylacridine, **3** (670 mg, 1.17 mmol), in 3 mL of anhydrous DMF was added in one portion. The reaction proceeded for 40 h at 130 °C, was quenched with saturated sodium bicarbonate water, and was extracted with dichloromethane, and solvents were removed under reduced pressure. The crude material was purified by silica gel column chromatography (2:2:1:1% dichloromethane/hexanes/ethyl acetate triethylamine) to afford the diastereomers of **5** (202 mg, 0.293 mmol) in a 1:1 ratio as yellow crystals in 89% total yield.

anti-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.45 (s, 12 H), 6.62−6.68 (m, 2 H), 6.83−6.86 (m, 4 H), 7.00−7.03 (m, 2 H), 7.07 (s, 2 H), 7.31−7.39 (m, 8 H), 7.67 (d, J = 9.1 Hz, 2 H), 7.73−7.78 (m, 2 H), 7.91 (s, 2 H). 8.31 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 22.3, 124.8, 125.4, 125.5, 125.6, 125.9, 126.2, 126.3, 126.6, 127.0, 129.3, 129.8, 130.1, 130.5, 131.2, 134.2, 134.6, 135.5, 139.0, 140.8, 141.9, 146.1, 147.5, 147.6; mp >275 °C.

syn-Isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.26 (s, 12 H), 6.65−6.70 (m, 2 H), 6.75−6.78 (m, 2 H), 6.85−6.88 (m, 2 H), 6.96−6.99 (m, 4 H), 7.12 (s, 4 H), 7.28−7.31 (m, 2 H), 7.36−7.42 (m, 2 H), 7.69−7.75 (m, 4 H), 7.91 (d, J = 1.7 Hz, 2 H), 8.27 (dd, J = 1.1 Hz, 8.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 22.0, 124.8, 125.3, 125.4, 125.5, 125.8, 126.1, 126.3, 126.4, 126.9, 129.4, 129.7, 130.1, 130.4, 131.1, 134.2, 134.7, 135.5, 138.8, 140.7, 142.1, 146.1, 147.4, 147.5; mp 243−244 °C.

*anti-1,8-Bis(3-(3′,5′-dimethylphenyl)-9-acridyl)naphthalene N,N′-Dioxide (anti-**1**).*[9h] To a solution of *anti*-**5** (100 mg, 0.15 mmol) in 3 mL of THF was added peroxybenzoic acid (68 mg, 0.30 mmol) in 2 mL of THF. The mixture was allowed to stir at room temperature for 5 h, and the solvent was removed under reduced pressure. The residue was dissolved in methylene chloride, washed with 2 N sodium hydroxide, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (100:10 ethyl acetate/ethanol) afforded **1** (80 mg, 1.11 mmol) as a red solid in 75% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.45 (s, 12H), 6.63−6.69 (m, 2H), 6.81 (d, J = 9.1 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 7.09−7.14 (m, 4H), 7.34−7.41 (m, 8H), 7.77 (dd, J = 7.2 Hz, 8.2 Hz, 2H), 8.32 (dd, J = 1.1 Hz, 8.2 Hz 2H), 8.47 (d, J = 9.1 Hz 2H). 8.69 (d, J = 1.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 22.3, 117.6, 120.5, 126.1, 126.5, 126.5, 126.6, 126.7, 126.3, 126.9, 127.5, 130.0, 130.7, 131.0, 132.2, 133.4, 134.1, 135.1, 135.9, 138.6, 138.6, 139.2, 140.2, 143.0; mp 250−251 °C dec.

*syn-1,8-Bis(3-(3′,5′-dimethylphenyl)-9-acridyl)naphthalene N,N′-Dioxide (syn-**1**).* To a solution of *syn*-**5** (38 mg, 0.06 mmol) in 5 mL of THF was added peroxybenzoic acid (102 mg, 77% purity, 0.59 mmol). The mixture was allowed to stir at room temperature for 13 h and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in methylene chloride and washed with 2 N sodium hydroxide, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (100:10 ethyl acetate/ethanol) afforded the hydrate of *syn*-**1** (28 mg, 0.04 mmol) as a red solid in 72% yield. NMR analysis showed that *syn*-**1** cocrystallizes with 3 equivalents of water: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.27 (s, 12H), 6.76−6.79 (m, 4H), 6.85 (d, J = 8.7 Hz, 2H), 6.98−6.7.03 (m, 4H), 7.13 (s, 4H), 7.38 (d, J = 6.9 Hz, 2H), 7.41−7.46 (m, 2H), 7.75−7.79 (m, 2H). 8.32 (d, J = 8.5 Hz, 2H), 8.50 (d, J = 9.1 Hz, 2H), 8.63 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 20.2, 115.8, 118.7, 124.3, 124.4, 124.5, 124.7, 124.8, 124.9, 125.0, 125.1, 125.2, 125.6, 128.5, 129.0, 129.3, 130.5, 131.6, 134.1, 136.8, 136.9, 137.3, 138.3, 141.7; mp 255−256 °C dec.

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Anal. Calcd. for $C_{52}H_{38}N_2O_2 \cdot 3H_2O$: C, 80.39; H, 5.71; N, 3.61. Found: C, 80.01; H, 6.00; N, 3.33.

2. Preparative HPLC Separation of the Enantiomers of *anti*-1. The enantiomers of *anti*-**1** were separated on a preparative (*R,R*)-Whelk-O 1 column (10 mm × 250 mm) using a mobile phase of dichloromethane/ethanol (90:10) and injecting 1 mL of a 0.028 M solution of **1** in dichloromethane/ethanol (20 mg/1 mL). The flow rate was 5 mL/min, and the column temperature was 25 °C. The enantiomers of *anti*-**1** have retention times of approximately 3.5 and 6.0 min, and the levorotatory enantiomer was found to elute first. (Figure 6). With this efficient protocol, 200 mg of the atropisomer was separated in about 1 h. Solvents were removed under reduced pressure, and the enantiomeric purity of each enantiomer was confirmed to be >99% by reinjection on the HPLC using the same separation conditions.

3. UV Spectroscopy Measurements and Characterization of Metal Complexes of *syn*-1. We investigated the formation of a series of metal complexes of *syn*-**1** in acetonitrile at 25 °C (Figure 7). Characteristic charge-transfer bands at 390 nm were observed with In(III), Sn(II), Sc(III), Gd(III). Zn(II), Yb(III), Cu(II), and Cu(I).

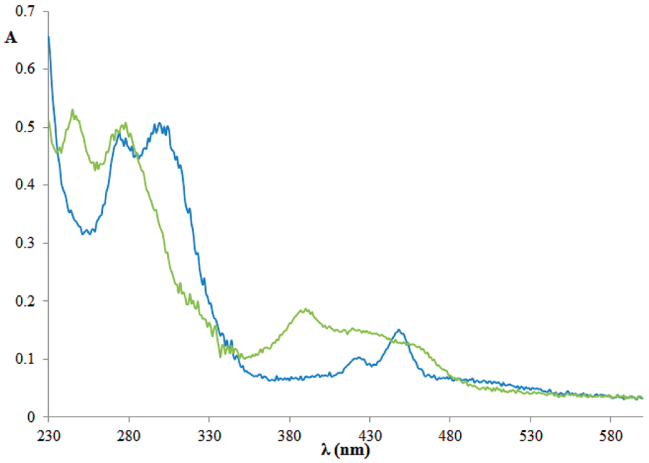

Figure 7. Change in the UV/vis spectra of *syn*-**1** upon addition of $Sc(OTf)_3$. The concentrations of *syn*-**1** and $Sc(OTf)_3$ were 3.48×10^{-5} M and 1.74×10^{-5} M, respectively, in ACN/$CHCl_3$ (49:1). The blue curve represents pure *syn*-**1**, and the green curve represents the complex formed between *syn*-**1** and $Sc(OTf)_3$.

The stoichiometry of the scandium complex of *syn*-**1** was determined by Job plot analysis (Figure 8). It was found that *syn*-**1** forms a 2:1 complex with $Sc(OTf)_3$.

4. Diastereomeric Excess: Calibration Curve and de Determination Using Sc[*syn*-1]$_2$ and 6. In order to evaluate the practical use of Sc[*syn*-**1**]$_2$ for de determination, a calibration curve was constructed using samples of **6** in varying de at 25 °C. A stock solution containing *syn*-**1** at a concentration of 3.52×10^{-5} M and $Sc(OTf)_3$ at a concentration of 1.75×10^{-5} M was prepared in a mixture of acetonitrile:chloroform (49:1). Stock solutions of **6** (1.73×10^{-3} M) with varying de (+100.0, +86.0, +46.0 +16.0 −38.0, −54.0, −88.0, −100.0) were prepared in anhydrous $CHCl_3$. For each ligand displacement assay, 10 μL of the substrate stock solution was added to 2 mL of the Sc[*syn*-**1**]$_2$ stock solution. UV/vis data were collected at 390 nm. The calibration curve shows a linear relationship: $A = 0.0009(\%\ de) + 0.2289$, with $R^2 = 0.9804$ (Figure 9).

Three scalemic samples of **6** were prepared and then treated with Sc[*syn*-**1**]$_2$ as described above. Using the linear regression equation obtained from the calibration curve and the measured UV/vis absorbance at 390 nm, the diastereomeric composition of these samples was determined (Table 1). Experimentally obtained data were within 5% of the actual values.

5. Enantioselective UV Sensing with Sc[*anti*-(−)-1]$_2$. A solution containing *anti*-(−)-**1** at a concentration of 3.49×10^{-5} M and $Sc(OTf)_3$ at a concentration of 1.79×10^{-5} M was prepared in a mixture of acetonitrile/chloroform (49:1). Stock solutions of (*R,R*)-**6**, (*S,S*)-**6**, and *meso*-**6** were prepared in chloroform (1.74×10^{-3} M), and then portions of 10 μL of a substrate stock solution were added to 2 mL of the Sc[*anti*-(−)-**1**]$_2$ solution. Data were recorded at 405 nm and at room temperature.

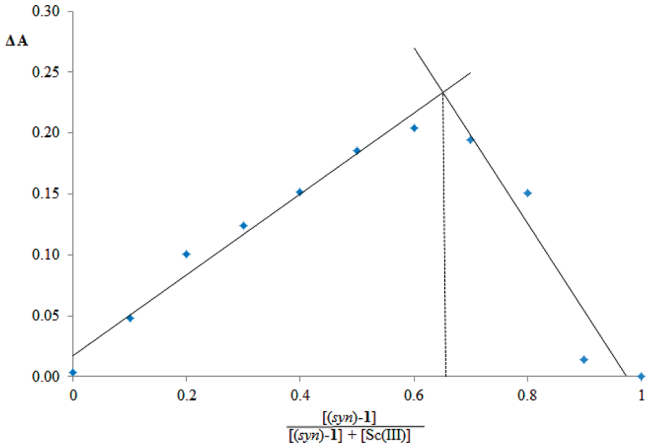

Figure 8. Job plot showing the formation of a 2:1 complex between *syn*-**1** and Sc(III). The total concentration of *syn*-**1** and $Sc(OTf)_3$ was 3.49×10^{-5} M in acetonitrile. The temperature was 25 °C. Data were recorded at 390 nm.

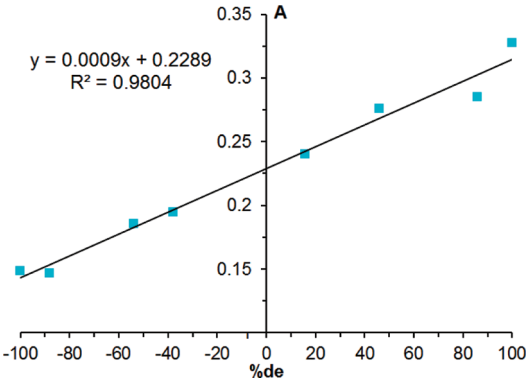

Figure 9. Linear calibration curve for the LDA with Sc[*syn*-**1**]$_2$ and **6**.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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