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# Antenna Biphenols: Development of Extended Wavelength Chiroptical Reporters

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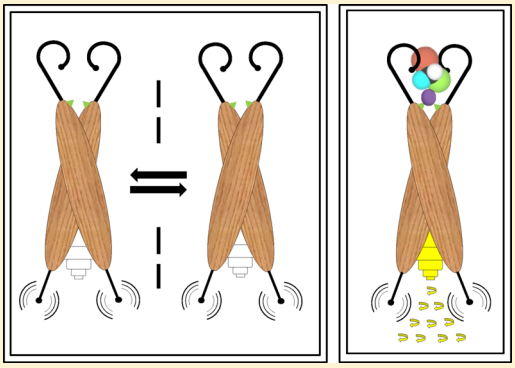
Supporting Information

**ABSTRACT:** Molecular hosts capable of chiroptical sensing of complexed guest molecules offer an attractive alternative to conventional methods for the analysis of the absolute configuration and enantiopurity. Sensors based on the Pfeiffer effect rely on complexation-driven asymmetric transformation of the first kind and can produce a chiroptical signal against an otherwise null background. To be most effective, the wavelength of the induced chiroptical sensor readout should be free and clear of interfering signals coming from the sample under investigation. In this study, we report the introduction of stereodynamic zinc complexes of antenna biphenols, a new class of sensors bearing antenna-like appendages that can extend the wavelength of the chiroptical signal while also improving enantioselective guest recognition.



## INTRODUCTION

Rapid and high-throughput determination of the enantiopurity [enantiomeric excess (ee)] is becoming increasingly important in the pharmaceutical sciences. While chromatography-based approaches are currently dominant,[1] optical sensing has the potential for increased speed and throughput. A number of metal-based chiroptical sensors have been developed,[2] including several that make use of the Pfeiffer effect,[3] where, upon addition of an enantioenriched guest, the equilibrium of rapidly interconverting enantiomeric conformers of the host metal complex is shifted to favor a single enantiomer.[4] This asymmetric transformation of the first kind often results in distinct chiral amplification and a strong circular dichroism response of the host that can be used to determine the absolute configuration and enantiopurity of the guest molecule.[5]

To minimize interference, the detection wavelength for chiroptical sensors should be free and clear of interfering signals coming from the sample under investigation. For pharmaceutical analysis, a CD maximum at >300 nm would therefore be desirable. We herein report the investigation of a design strategy aimed at the systematic tuning and adjustment of the chiroptical reporter readout and other performance characteristics based on the incorporation of arylalkyne substituents into a parent 2,2′-biphenol core by Sonogashira coupling, providing a series of novel sensor candidates with characteristic CD maxima at extended wavelengths (Chart 1).[6] Specifically, we demonstrate with *in silico* screening, CD, and MS analyses that incorporation of extended chromophores adjacent to the metal binding sites of the stereodynamic biphenol core fulfills several purposes, namely, (a) enhancing and red-shifting of the induced chiroptical signals and (b) improving the chiral recognition and amplification processes.

## RESULTS AND DISCUSSION

**Design Strategy.** A variety of design strategies are possible for extending the $\pi$-conjugation of biphenol sensors to shift the maximum CD signal to higher wavelengths where interference from pharmaceutical analytes can be reduced. For example, this can be accomplished with metal complexes carrying biaryl-like ligands where the aromatic moiety is varied from phenyl to naphthyl, phenanthryl, anthryl, or other large $\pi$-residues provided that enantiomer interconversion for the resulting probe remains unconstrained and rapid.[7] However, systematic fine-tuning of the chromophoric properties and reinforcement of the analyte-to-sensor chirality induction to produce a red-shifted and strong CD response of such biaryl CD sensors appear to be less synthetically expedient than an approach in which relatively simple "antenna groups" are appended to a readily available biphenol core using practical Sonagashira[8] or Heck[9] type cross coupling reactions (Figure 1).

*In silico* screening involving computational modeling and calculation of predicted CD signals for a number of biphenol variants allowed the identification of important structural features that could potentially lead to sensors with strongly red-shifted CD signals. Calculations were conducted in the gas phase using Gaussian 09[10] and employing the B3LYP functional and 6-31G** basis set. Time-dependent density

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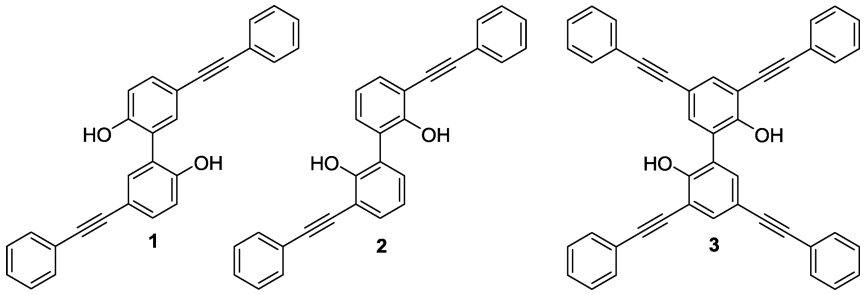
**Chart 1. Structures of Antenna Biphenols**



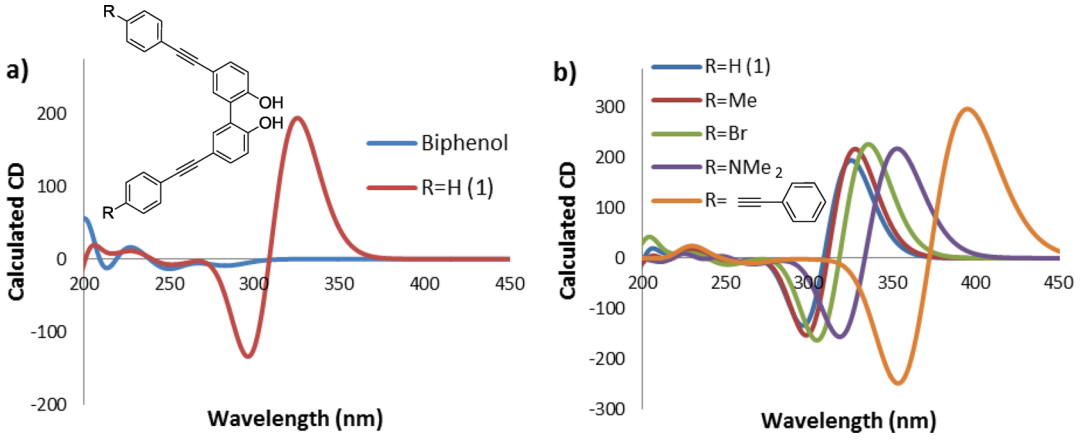
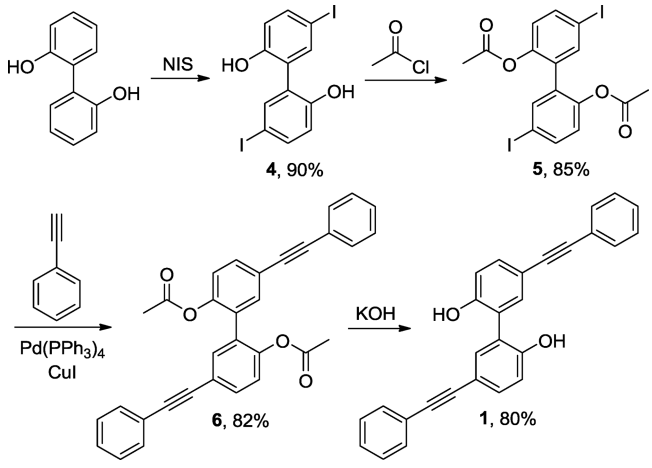




**Figure 1.** (a) Calculated CD spectra for 2,2′-biphenol and the phenylacetylene derivative **1**. (b) Calculated CD spectra for a series of analogues of **1**. In each case, the calculations were performed on the conformation displaying P helicity.

functional theory (TD-DFT) methodology was employed.[11] The calculations were performed on the ligand rather than the metal complex, as a way to guide initial synthetic efforts. In the absence of the metal and chiral guest, the ligand atropisomers interconvert freely, and hence, the calculations were conducted with a torsion angle of 50° between the phenyl chromophores. The CD signals for 2,2′-biphenol and its 4,4′-diphenylacetylene derivative, **1**, were calculated and compared. The calculated biphenol spectrum has very weak CD absorbances above 250 nm, but in the case of **1**, a bisignate curve with a large CD magnitude centered around 330 nm is predicted. Varying the torsion angle between the two chromophores for this compound had only a small impact on the calculated wavelength of the resulting CD signal, and the magnitude of the Cotton effect did not vary substantially within the geometries expected for a bidentate metal complex (see the Supporting Information). *In silico* analysis with the phenylacetylene substituents at the 6,6′ positions of the 2,2′-biphenol core (compound **2**) gave similar results (Supporting Information). As expected, structural variations in the para position of the phenylacetylene antennae (Br, Me, and $Me_2N$) were found to affect both the wavelength and the intensity of the CD signal, as shown in Figure 1b, with the addition of a second conjugated phenylacetylene unit leading to a highly red-shifted CD signal centered around 380 nm.

**Initial Analysis with Prototype 1.** On the basis of these *in silico* modeling studies, we began our investigation with the synthesis of 4,4′-diphenylacetylene-1,1′-dihydroxy-2,2′-biphenyl, **1** (Scheme 1). Iodination of 2,2′-biphenol gave 4,4′-diiodo-1,1′-dihydroxy-2,2′-biphenyl, **4**, in 90% yield. Acylation and double Sonogashira coupling of **5** with phenylacetylene furnished **6** that was finally deprotected with KOH to give **1**

**Scheme 1. Synthesis of Biphenol 1**




in 80% yield. Disappointingly, CD sensing analysis using a zinc biphenolate complex prepared from **1** via reaction with 1 equiv of diethylzinc revealed unsatisfactory CD responses, with weak CD maxima at 325 nm in the presence of stoichiometric amounts of enantiopure 1,2-diphenylethanolamine and 1,2-diphenyldiaminoethane (see the Supporting Information). We hypothesized that this disappointing performance could stem from a relatively poor ability of **1** to sense the chirality of a bound guest, and taking a cue from the classic work of Cram,[12] we proposed that the addition of forward-projecting substituents at the 3,3′ positions could aid in the enantiorecognition of zinc-coordinated analytes. In other words, we believed that our chiroptical sensor should contain, in addition to "antennae" for enhancing and red-shifting chiroptical signals



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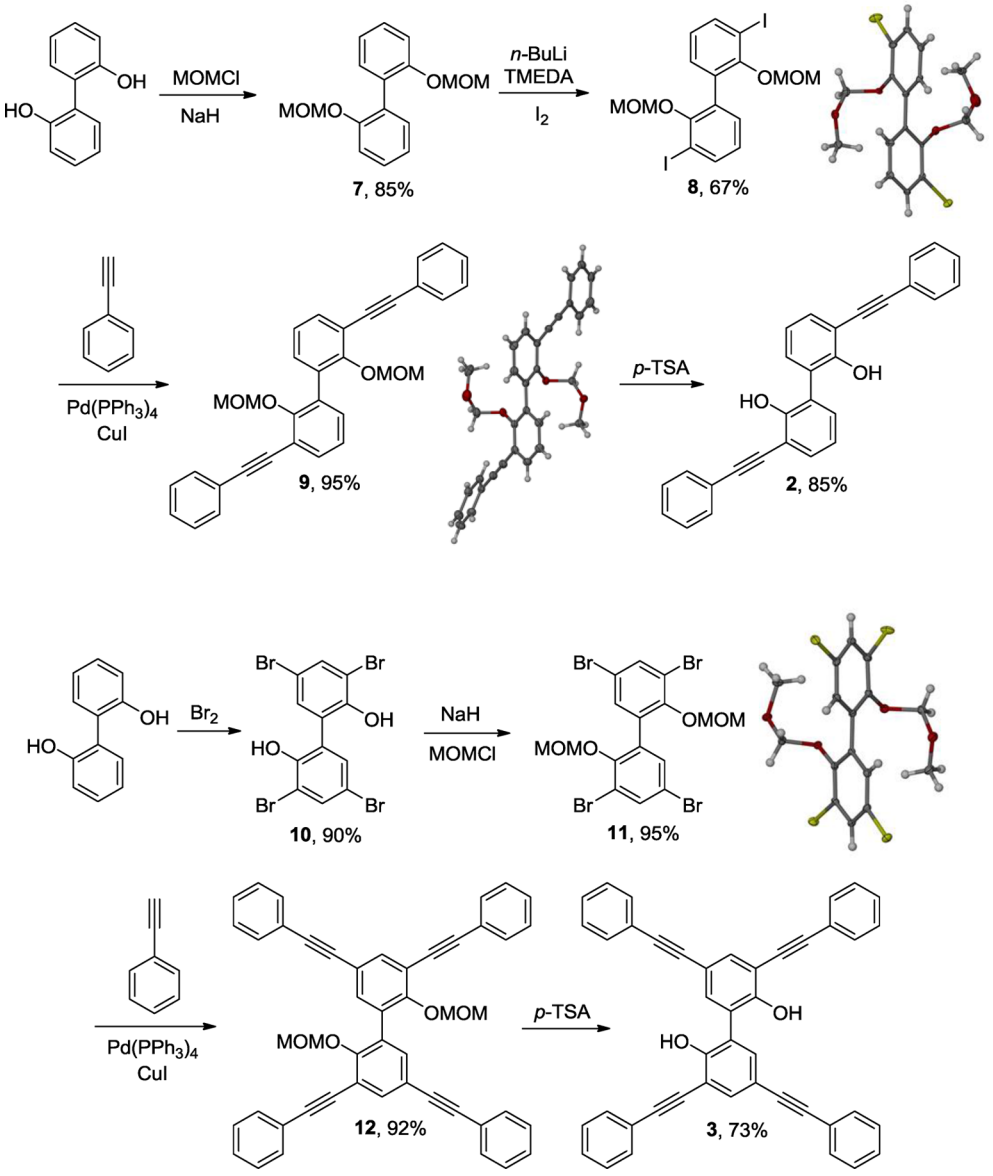
**Scheme 2. Synthesis of Antenna Biphenols 2 and 3 and Crystal Structures of 8, 9, and 11**[a]




[a]The X-ray structures are shown at 50% ellipsoid contour percent probability.

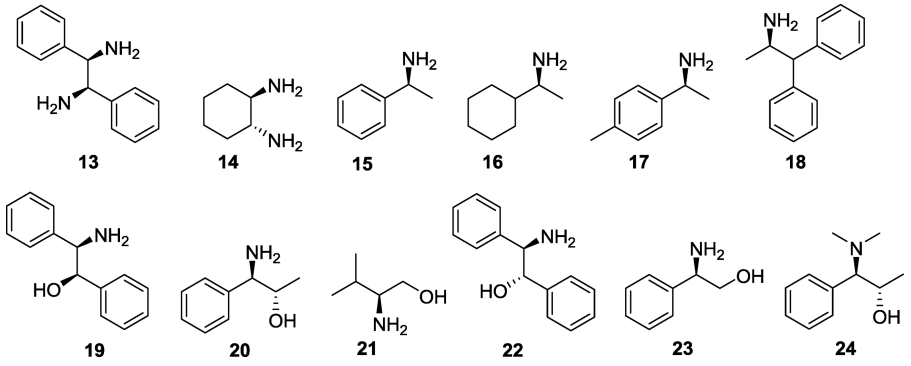



**Figure 2.** Structures of the amines and amino alcohols tested.

(analogous to radio antennae), forward projecting "feelers" (analogous to the antennae of insects) that would increase the number of steric interactions with the guest and thus enhance the chiral induction and CD response.[16]

**Synthesis of 2 and 3 and Chirality Sensing.** The syntheses of two candidate sensors, **2** and **3**, meeting these design criteria are shown in Scheme 2. The synthesis of 1,1′-dihydroxy-6,6′-diphenylacetylene-2,2′-biphenyl, **2**, started with



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MOM protection of 2,2′-biphenol providing **7**, which was lithiated and treated with iodine at −78 °C to generate **8** in 67% yield. Palladium-catalyzed Sonogashira coupling of **8** with phenylacetylene gave almost quantitative amounts of **9**, and deprotection provided **2** in 85% yield. Using similar reactions, we were able to prepare 4,4′,6,6′-tetraphenylacetylene-1,1′-dihydroxy-2,2′-biphenyl, **3**, in four steps. The tetrabromination of 2,2′-biphenol and subsequent MOM protection gave **10** and **11**, respectively, in high yields. Exhaustive alkynylation and deprotection of the phenol units with *p*-toluenesulfonic acid produced **3** in 73% yield.

With these new biphenols in hand, we began to test the possibility of optical chirality sensing of a variety of amines **13**−**18** and amino alcohols **19**−**24** (Figure 2). We were very pleased to find that comparison of the chiroptical response of the zinc biphenolates derived from **2** and **3** in the presence of diamine **13** or amino alcohol **22** indeed showed significantly increased CD amplitudes at higher wavelengths compared to the results obtained with **1** (Figure 3). Overall, the superior

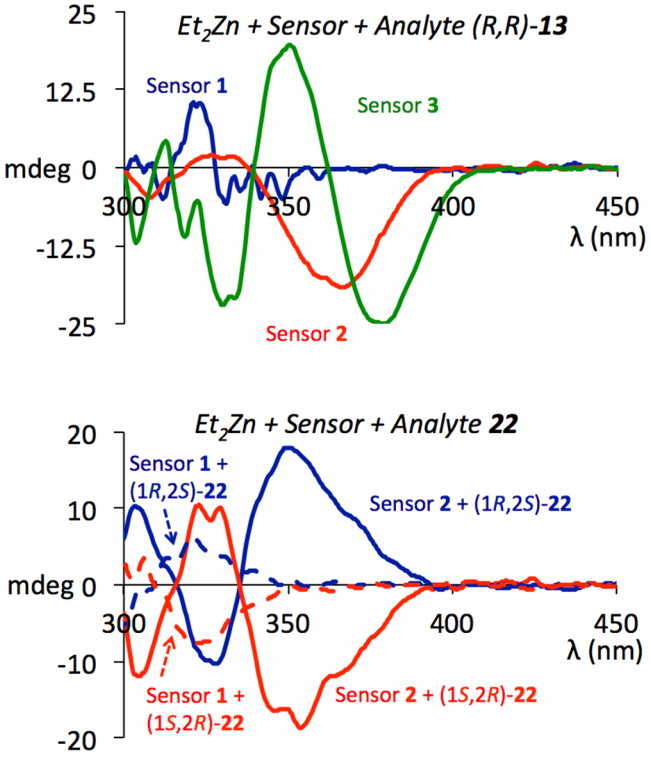


**Figure 3.** CD spectra (top) obtained from **1** (blue), **2** (red), and **3** (green), $Et_2Zn$, and (1*R*,2*R*)-**13**. CD spectra (bottom) obtained from **1**, $Et_2Zn$, and (1*R*,2*S*)-**22** (dashed blue) and (1*S*,2*R*)-**22** (dashed red) and with **2**, $Et_2Zn$, and (1*R*,2*S*)-**22** (solid blue) and (1*S*,2*R*)-**22** (solid red). All measurements were recorded at 6.0 × $10^{-5}$ M in $Et_2O$.

induced circular dichroism (ICD) performance of reporter ligands **2** and **3** compared to that of biphenol is consistent with an improved ability of the forward-projecting antennae to function as mechanical "feelers" as well as conjugation signal enhancers. As expected, CD titration experiments and ESI-MS analysis suggest that diamines **13** and **14** form stoichiometric zinc biphenolate complexes while two analyte molecules coordinate to the zinc center when **15**−**24** are employed (see the Supporting Information).

The general utility of chirality sensing with the antenna biphenol reporter ligands **2** and **3** is further exemplified with the remarkable CD responses of the corresponding zinc biphenolates, which are easily prepared *in situ* by simply mixing the biphenol with 1 equiv of diethylzinc, upon addition of **13** and **19** (Figure 4). In fact, we obtained strong CD responses to all analytes tested (see the Supporting Information).

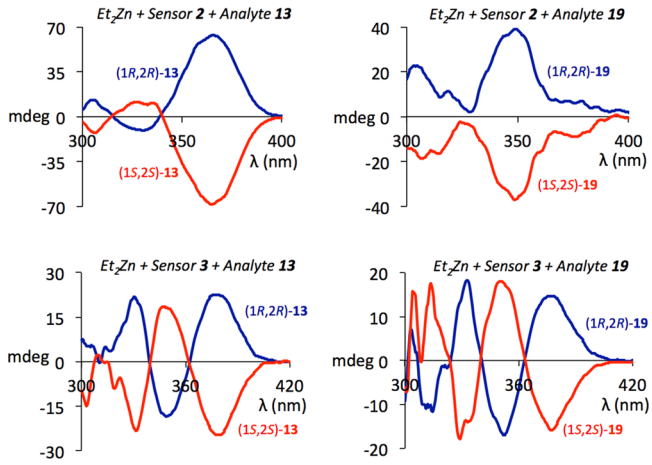


**Figure 4.** CD spectra (top) obtained using **2**, $Et_2Zn$, and (1*R*,2*R*)-**13** (blue) and (1*S*,2*S*)-**13** (red). The response of the same chiroptical reporter to (1*R*,2*R*)-**19** (blue) and (1*S*,2*S*)-**19** (red) is shown on the right. CD spectra (bottom) obtained using **3**, $Et_2Zn$, and (1*R*,2*R*)-**13** (blue) and (1*S*,2*S*)-**13** (red). The response of the same reporter to (1*R*,2*R*)-**19** (blue) and (1*S*,2*S*)-**19** (red) is shown on the right. All measurements were collected at 1.2 × $10^{-4}$ M (sensor **2**) and 6.0 × $10^{-5}$ M (sensor **3**) in $Et_2O$.

We expected that the induced CD responses of the stereodynamic Zn biphenolates might provide a characteristic chiroptical signature that can be used to assign the absolute configuration of the detected analyte, while the CD amplitudes can be correlated to the enantiomeric composition. We therefore determined the CD responses of the zinc biphenolates of **2** and **3** to enantioenriched mixtures of diamine **13** (Figure 5). Interestingly, a slightly nonlinear relationship between the sample ee and the ICD readouts at 325 and 365 nm for **2** and 350 and 378 nm in the case of **3** was obtained. Nonlinear effects in chiroptical sensing with stereodynamic metal complexes have been reported and attributed to coexisting homo- and heterochiral dinuclear zinc species that are expected to make individual contributions to the overall CD readout.[13] Importantly, the nonlinearity in the CD readouts does not interfere with the use of these sensors for the determination of the absolute configuration of the analytes tested and the quantitative analysis of the enantiomeric composition (*vide infra*).

**Chiroptical ee Determination.** To evaluate the utility of our sensing assay, five enantioenriched samples of **13** covering a wide ee range were prepared and subjected to CD analysis with either **2** or **3** and $Et_2Zn$. Following our fast mix-and-measure protocol, the enantiomeric composition of these samples was determined on the basis of the regression equations obtained from the calibration experiments (Supporting Information) and the CD amplitudes recorded with the nonracemic samples at 325 and 365 nm for **2** and 350 and 378 nm in the case of **3**. The qualitative and quantitative chirality sensing with the two stereodynamic Zn probes gave excellent results (Table 1). The sign of the CD responses observed was correctly correlated to the absolute configuration of the major enantiomer, and the


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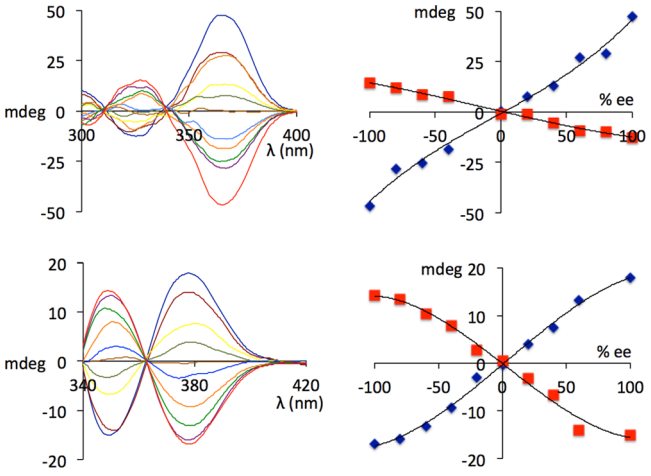


**Figure 5.** CD response (top left) of the zinc biphenolate of **2** in the presence of **13** with varying ee's at $1.2 \times 10^{-4}$ M in diethyl ether. Relationship (top right) between the induced CD amplitudes at 365 nm (blue) and 325 nm (red) and the enantiomeric excess of **13**. CD spectra (bottom left) obtained from **3**, $Et_2Zn$, and scalemic samples of **13** at $1.2 \times 10^{-4}$ M. Relationship (bottom right) between the induced CD amplitudes at 378 nm (blue) and 350 nm (red) and the enantiomeric excess of **13**.

**Table 1. Determination of ee's of Nonracemic Samples of 13 Using Zinc Biphenolates of 2 and 3**

| reporter | actual % ee (1*R*,2*R*)-**13**[a] | calculated % ee at 325 (350) nm (1*R*,2*R*)-**13** | calculated % ee at 365 (378) nm (1*R*,2*R*)-**13** | average % ee (1*R*,2*R*)-**13** |
|---|---|---|---|---|
| **2** | 87.0 | 85.4 | 88.3 | 86.9 |
| **2** | 76.0 | 72.2 | 78.2 | 75.2 |
| **2** | 12.0 | 11.5 | 15.6 | 13.6 |
| **2**[b] | −26.0 | −29.3 | −27.8 | −28.6 |
| **2**[b] | −68.0 | −71.7 | −72.4 | −72.1 |
| **3** | 87.0 | 86.9 | 92.2 | 89.6 |
| **3** | 76.0 | 79.1 | 77.5 | 78.3 |
| **3** | 12.0 | 9.2 | 13.8 | 11.5 |
| **3**[b] | −26.0 | −28.3 | −25.3 | −26.8 |
| **3**[b] | −68.0 | −72.1 | −69.1 | −70.6 |

[a]Nonracemic solutions of the diamine in THF were prepared by carefully weighing out the corresponding amounts of the pure enantiomers of **13**. The enantiomeric excess was determined using CD calibration curves obtained with the zinc biphenolates of **2** and **3** (Supporting Information). [b]The minus sign indicates that (1*R*,2*R*)-**13** was the minor enantiomer.

averaged CD sensing outputs gave ee's that were strikingly close to the actual values. In all cases, variations were small and the values differed by only a few percent for samples of high and of low enantiopurity. For example, the ICD analysis of samples containing **13** in 87.0 and 12.0% ee with the zinc sensor derived from biphenol **2** gave 86.9 and 13.6% ee, respectively. The use of biphenol **3** in the same assay gave very similar results, i.e., 89.6 and 11.5% ee, respectively. The practicality, time efficiency, and accuracy of chirality sensing with **2** and **3** indicate the potential of these rationally developed antenna biphenols for quantitative ee analysis in high-throughput screening applications. The chiroptical analysis with the *in situ*-formed zinc biphenolates used in this study is suitable for automation, and we believe that the accuracy can be further improved with automated liquid handling equipment that is generally available in HTS laboratories.

## CONCLUSION

Antenna biphenol sensors provide excellent chiroptical sensing of a variety of amines, diamines, and amino alcohols. These sensors bear appendages that extend the wavelength of the observed chiroptical signal while improving enantioselective guest recognition. A design approach based on preliminary *in silico* screening was helpful in identifying structural features likely to lead to improved performance. Sonogashira coupling of arylalkyne substituents to a biphenol core afforded a set of potential chiroptical sensors, with evaluation of readily prepared biphenolate complexes of zinc and **2** or **3** showing good performance in both the qualitative assessment of absolute configuration and the quantitative assessment of enantiopurity.

## EXPERIMENTAL SECTION

**Synthetic Procedures and Product Characterization.** All reagents and solvents were used as purchased. NMR spectra were obtained at 400 MHz ($^1$H NMR) and 100 MHz ($^{13}$C NMR) using $CDCl_3$ as a solvent unless stated otherwise. Chemical shifts are reported in parts per million relative to TMS or to the solvent peak when ACN-$d_3$ or DMSO-$d_6$ was used. Reaction products were purified by column chromatography on silica gel (particle sizes of 32−63 μm).

*4,4′-Diphenylacetylene-1,1′-dihydroxy-2,2′-biphenyl (**1**).* A solution of **6** (200 mg, 0.43 mmol) and KOH (238.5 mg, 4.3 mmol) in 12 mL of an ACN/water mixture (5:1) was stirred at 60 °C for 6 h. The reaction was quenched with a saturated $NH_4Cl$ solution and the mixture extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes/EtOAC) afforded 132 mg (0.34 mmol, 80%) of a light brown crystalline solid: mp 113−115 °C; $^1$H NMR $\delta$ 5.59 (s, 2H), 7.02 (d, $J$ = 8.4 Hz, 2H), 7.33−7.37 (m, 6H), 7.50−7.53 (m, 8H); $^{13}$C NMR $\delta$ 91.4, 91.5, 119.5, 119.8, 126.0, 126.2, 130.9, 131.1, 134.2, 136.2, 137.5, 155.6. Anal. Calcd for $C_{28}H_{18}O_2$: C, 87.02; H, 4.70. Found: C, 87.32; H, 4.95.

*1,1′-Dihydroxy-6,6′-diphenylacetylene-2,2′-biphenyl (**2**).* A solution of **9** (200 mg, 0.4 mmol) and *p*-TSA (176 mg, 0.9 mmol) was stirred at room temperature in 5 mL of methanol for 12 h. The reaction was quenched with water and the mixture extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded 138 mg (0.36 mmol, 85%) of a light brown oil: $^1$H NMR $\delta$ 6.21 (s, 2H), 7.01 (dd, $J$ = 7.7, 7.7 Hz, 2H), 7.29−7.37 (m, 8H), 7.48−7.55 (m, 6H); $^{13}$C NMR $\delta$ 83.5, 96.0, 110.7, 120.7, 122.5, 124.1, 126.4, 126.7, 131.6, 131.7, 132.2, 153.5. Anal. Calcd for $C_{28}H_{18}O_2$: C, 87.02; H, 4.70. Found: C, 86.98; H, 4.95.

*4,4′,6,6′-Tetraphenylacetylene-1,1′-dihydroxy-2,2′-biphenyl (**3**).* To a suspension of **12** (400 mg, 0.59 mmol) in 10 mL of methanol was added *p*-toluenesulfonic acid monohydrate (247 mg, 1.30 mmol). The reaction mixture was stirred at 60 °C for 6 h. The reaction was quenched with aqueous $NH_4Cl$ and the mixture extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (4:1 hexanes/EtOAc) afforded 253 mg (0.43 mmol, 73%) of a yellow solid: $^1$H NMR $\delta$ 6.31 (s, 2H), 7.33−7.39 (m, 12H), 7.50−7.56 (m, 10H), 7.69 (s, 2H); $^{13}$C NMR $\delta$ 82.5, 88.1, 88.7, 96.7, 110.0, 111.2, 116.0, 122.1, 123.2, 123.7, 128.1, 128.5, 129.0, 131.5, 131.6, 134.8, 135.3, 153.6. Anal. Calcd for $C_{44}H_{26}O_2$: C, 90.08; H, 4.47. Found: C, 90.41; H, 4.55.

*4,4′-Diiodo-1,1′-dihydroxy-2,2′-biphenyl (**4**).*[14] A solution of 1,1′-dihydroxy-2,2′-biphenyl (200 mg, 1.07 mmol), 450 mg of *p*-toluenesulfonic acid (450 mg, 2.36 mmol) and *N*-iodosuccinimide (532 mg, 2.36 mmol) in 10 mL of ACN was stirred at room temperature for 12 h. The reaction was quenched with water and the mixture extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (3:1 hexanes/EtOAc) afforded 431 mg (0.98 mmol, 92%) of a white solid: $^1$H NMR (ACN-$d_3$) $\delta$ 6.76 (d, $J$ = 8.5 Hz, 2H), 7.13 (s, 2H), 7.51 (d, $J$ = 2.2 Hz, 2H), 7.56 (dd, $J$ =



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8.5, 2.2 Hz, 2H); $^{13}$C NMR (ACN-$d_3$) $\delta$ 81.6 118.8, 127.1, 138.3, 139.9, 154.3.

*1,1′-Biphenyl-4,4′-diiodo-2,2′-diacetate (**5**).*[14] Compound **4** (430 mg, 0.98 mmol) and $NEt_3$ were dissolved in 10 mL of dichloromethane. The mixture was cooled to 0 °C, and acetyl chloride (0.3 mL, 3.93 mmol) was added. The mixture was allowed to warm to room temperature and then stirred for 4 h. The reaction was quenched with water and the mixture extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (4:1 hexanes/EtOAc) afforded 435 mg (0.83 mmol, 85%) of a white solid: $^1$H NMR $\delta$ 2.06 (s, 6H), 6.92 (d, $J$ = 8.5 Hz, 2H), 7.62 (d, $J$ = 2.2 Hz, 2H), 7.71 (dd, $J$ = 8.5 Hz, 2.2 Hz, 2H); $^{13}$C NMR $\delta$ 20.7, 89.8, 124.7, 131.2, 138.3, 139.6, 147.9, 168.7.

*1,1′-Biphenyl-4,4′-diphenylacetylene-2,2′-diacetate (**6**).* A solution of **5** (360 mg, 0.69 mmol), phenylacetylene (0.23 mL, 2.07 mmol), $Pd(PPh_3)_4$ (80.0 mg, 0.07 mmol), CuI (13.1 mg, 0.07 mmol), and $NEt_3$ (0.77 mL, 5.52 mmol) in 5 mL of DMF was stirred at room temperature for 24 h. The reaction was quenched with water and the mixture extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (4:1 hexanes/EtOAc) afforded 268 mg (0.57 mmol, 82%) of a light yellow solid: $^1$H NMR $\delta$ 2.08 (s, 6H), 7.17 (d, $J$ = 8.4 Hz, 2H), 7.34−7.36 (m, 6H), 7.51−7.53 (m, 6H), 7.57 (dd, $J$ = 8.4, 2.1 Hz, 2H); $^{13}$C NMR $\delta$ 23.5, 90.9, 92.7, 124.1, 125.5, 125.7, 131.1, 132.8, 134.3, 135.0, 137.1, 171.6. Anal. Calcd for $C_{32}H_{26}O_4$: C, 80.99; H, 5.52. Found: C, 80.63; H, 5.48.

*1,1′-Dimethoxymethoxy-2,2′-biphenyl (**7**).*[15] 2,2′-Biphenol (500 mg, 2.7 mmol) was dissolved in 15 mL of anhydrous THF and cooled to 0 °C. NaH (161 mg, 6.7 mmol) was added, and the mixture was stirred at 0 °C for 30 min. MOMCl (0.62 mL, 8.1 mmol) was dissolved in 3 mL of THF, and the solution was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water and the mixture extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (4:1 hexanes/EtOAc) afforded 630 mg (2.3 mmol, 85%) of a colorless oil: $^1$H NMR $\delta$ 3.33 (s, 6H), 5.06 (s, 4H), 7.06 (dd, $J$ = 7.3, 7.4 Hz, 2H), 7.20−7.33 (m, 6H); $^{13}$C NMR $\delta$ 55.6, 95.3, 115.6, 121.8, 128.7, 129.2, 131.5, 154.9.

*6,6′-Diiodo-1,1′-dimethoxymethoxy-2,2′-biphenyl (**8**).*[16] A solution of *n*-BuLi (2.5 M in hexanes, 1.1 mL, 2.7 mmol) and TMEDA (0.41 mL, 2.7 mmol) was stirred in 10 mL of diethyl ether for 10 min. Then, **7** (300 mg, 1.1 mmol) dissolved in 10 mL of anhydrous diethyl ether was added dropwise. The mixture was heated to reflux for 2 h, and an orange precipitate appeared. The reaction mixture was then cooled to −78 °C, and $I_2$ (833 mg, 3.3 mmol) dissolved in 10 mL of diethyl ether was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water and the mixture extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded 386 mg (0.73 mmol, 67%) of a light yellow solid: $^1$H NMR $\delta$ 3.04 (s, 6H), 4.80 (s, 4H), 6.92 (dd, $J$ = 7.8, 7.7 Hz, 2H), 7.35 (dd, $J$ = 7.7, 1.6 Hz, 2H), 7.83 (dd, $J$ = 7.8, 1.6 Hz, 2H); $^{13}$C NMR $\delta$ 57.2, 92.9, 99.7, 125.8, 132.2, 133.4, 139.4, 154.7.

*1,1′-Dimethoxymethoxy-6,6′-diphenylacetylene-2,2′-biphenyl (**9**).* A solution of **8** (300 mg, 0.6 mmol), phenylacetylene (0.25 mL, 2.3 mmol), $Pd(PPh_3)_4$ (66 mg, 0.06 mmol), CuI (11 mg, 0.06 mmol), and $NEt_3$ (0.7 mL, 4.6 mmol) was stirred in 10 mL of anhydrous THF at 60 °C for 12 h. The reaction was quenched with water and the mixture extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (4:1 hexanes/EtOAc) afforded 257 mg (0.54 mmol, 95%) of a brown solid: $^1$H NMR $\delta$ 3.04 (s, 6H), 5.09 (s, 4H), 7.18 (dd, $J$ = 7.7, 7.7 Hz, 2H), 7.34−7.40 (m, 8H), 7.52−756 (m, 6H); $^{13}$C NMR $\delta$ 56.8, 86.1, 93.6, 99.3, 110.0, 117.8, 123.3, 123.8, 128.4, 131.5, 132.1, 132.9, 133.1, 156.1. Anal. Calcd for $C_{32}H_{26}O_4$: C, 80.99; H, 5.52. Found: C, 81.22; H, 5.76.

*4,4′,6,6′-Tetrabromo-1,1′-dihydroxy-2,2′-biphenyl (**10**).*[17] 2,2′-Biphenol (200 mg, 1.07 mmol) was dissolved in 5 mL of anhydrous methanol. The solution was cooled to 0 °C, and $Br_2$ (0.27 mL, 5.35 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 8 h. The precipitate was filtered and washed with cold methanol to give 451 mg (0.96 mmol, 90%) of a white solid: $^1$H NMR (DMSO-$d_6$) $\delta$ 7.26 (s, 2H), 7.70 (s, 2H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 110.9, 113.1, 128.5, 133.3, 134.6, 151.7.

*4,4′,6,6′-Tetrabromo-1,1′-dimethoxymethoxy-2,2′-biphenyl (**11**).* A solution of **10** (400 mg, 0.80 mmol) in 10 mL of anhydrous THF was cooled to 0 °C. NaH (60% dispersion in mineral oil, 80 mg, 2.00 mmol) was added, and the mixture was allowed to stir for 30 min. Then, MOMCl (183 $\mu$L, 2.40 mmol) dissolved in 5 mL of THF was added dropwise, and the mixture was stirred overnight at room temperature. The reaction was quenched with water and the mixture extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (4:1 hexanes/EtOAc) afforded 448 mg (0.76 mmol, 95%) of a white crystalline solid: mp 101−104 °C; $^1$H NMR $\delta$ 3.07 (s, 6H), 4.86 (s, 4H), 7.47 (s, 2H), 7.75 (s, 2H); $^{13}$C NMR $\delta$ 57.2, 99.7, 117.1, 118.8, 133.7, 134.3, 135.7, 151.7. Anal. Calcd for $C_{16}H_{14}Br_4O_4$: C, 32.58; H, 2.39. Found: C, 32.67; H, 2.54.

*4,4′,6,6′-Tetraphenylacetylene-1,1′-dimethoxymethoxy-2,2′-biphenyl (**12**).* A solution of **11** (400 mg, 0.68 mmol), phenylacetylene (0.6 mL, 5.44 mmol), $Pd(PPh_3)_4$ (235 mg, 0.20 mmol), CuI (38 mg, 0.20 mmol), and $Et_3N$ (1.52 mL, 10.9 mmol) in 10 mL of THF was stirred at 60 °C for 24 h. The reaction mixture was allowed to cool to room temperature, the reaction quenched with water, and the mixture extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (4:1 hexanes/EtOAc) afforded 422 mg (0.63 mmol, 92%) of a yellow crystalline solid: mp 119−121 °C; $^1$H NMR $\delta$ 3.12 (s, 6H), 5.16 (s, 4H), 7.34−7.37 (m, 12H), 7.51−7.55 (m, 8H), 7.60 (s, 2H), 7.75 (s, 2H); $^{13}$C NMR $\delta$ 57.0, 85.1, 87.9, 89.8, 94.2, 99.4, 118.2, 119.3, 122.9, 123.0, 128.4, 128.4, 128.6, 130.0 131.5, 131.6, 132.4, 134.8, 136.1, 156.0. Anal. Calcd for $C_{48}H_{34}O_4$: C, 85.44; H, 5.08. Found: C, 85.20; H, 5.13.

**Enantioselective Sensing Experiments.** A stock solution of sensor **1**, **2**, or **3** (0.006 M) in THF was prepared, and 0.5 mL portions were transferred to 4 mL vials. Solutions of the substrates (0.15 M) in THF were prepared. To each vial containing 0.5 mL of the sensor stock solution was added 1 equiv (20 $\mu$L, 0.003 mmol) of substrates **13** and **14** or 2 equiv (40 $\mu$L, 0.006 mmol) of substrates **15**−**24**. To each vial was then added $Et_2Zn$ (3 $\mu$L, 0.003 mmol), and the mixtures were allowed to react for 5 min. CD analysis was conducted by adding 20 $\mu$L (sensors **1** and **3**, $6.0 \times 10^{-5}$ M) or 40 $\mu$L (sensor **2**, $1.2 \times 10^{-4}$ M) of the mixtures to 2 mL of diethyl ether. The CD spectra were collected with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a bandwidth of 1 nm, a scanning speed of 500 nm s$^{-1}$, and a response of 0.5 s using a quartz cuvette (1 cm path length). All CD spectra were collected at 25 °C. The data were baseline corrected and smoothed using a binomial equation.

**Quantitative ee Analysis.** The CD response of the zinc biphenolate of **2** or **3** in the presence of **13** with varying ee's was determined. Solutions of the biphenol (0.5 mL, 0.006 M in THF) and of the analyte (0.5 mL, 0.15 M in THF) were prepared. Mixtures of the reporter compound and the analyte at varying enantiomeric compositions (+100, +80, +60, +40, +20, 0, −20, −40, −60, −80, and −100% ee) were generated by adding 20 $\mu$L of the solution containing **13** to a 0.5 mL solution of **2** or **3**. $Et_2Zn$ (3 $\mu$L, 0.003 mmol) was then added, and the mixtures were allowed to stand for 5 min. CD analysis was conducted as described above

**Crystallography.** A single crystal of compound **8** was obtained by slow evaporation of a concentrated chloroform solution. Crystallographic analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo K$\alpha$ radiation ($\lambda$ = 0.71073 Å). Data were integrated and corrected using the Apex 2 program. The structure was determined by direct methods and refined with full-matrix least-squares analysis using SHELX-97-2. Non-hydrogen atoms were refined with anisotropic displacement



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parameters. The asymmetric unit contains two molecules of **8**. Crystal structure data: formula $C_{16}H_{16}I_2O_4$, $M$ = 526.09, crystal dimensions of 0.15 mm × 0.11 mm × 0.13 mm, triclinic, space group $P\bar{1}$, $a$ = 15.0063 Å, $b$ = 18.8148 Å, $c$ = 19.7847 Å, $\alpha$ = 81.12°, $\beta$ = 75.85°, $\gamma$ = 71.58°, $V$ = 5121.2 Å$^3$, $Z$ = 12, and $\rho_{calcd}$ = 2.047 g cm$^{-3}$.

A single crystal of compound **9** was obtained by diffusion of hexanes into a concentrated chloroform solution. The asymmetric unit contains two molecules of **9**. Crystal structure data: formula $C_{32}H_{26}O_4$, $M$ = 474.53, crystal dimensions of 0.21 mm × 0.17 mm × 0.11 mm, monoclinic, space group $P2_1/c$, $a$ = 13.0893 Å, $b$ = 11.2066 Å, $c$ = 17.8513 Å, $\alpha$ = 90.0°, $\beta$ = 107.85°, $\gamma$ = 90°, $V$ = 2492.51 Å$^3$, $Z$ = 4, and $\rho_{calcd}$ = 1.265 g cm$^{-3}$.

A single crystal of compound **11** was obtained by diffusion of hexanes into a concentrated chloroform solution. The asymmetric unit contains one molecule of **10**. Crystal structure data: formula $C_{16}H_{14}Br_4O_2$, $M$ = 589.91, crystal dimensions of 0.19 mm × 0.18 mm × 0.10 mm, triclinic, space group $P\bar{1}$, $a$ = 8.5230 Å, $b$ = 10.0979 Å, $c$ = 12.3744 Å, $\alpha$ = 67.4250°, $\beta$ = 86.1630°, $\gamma$ = 69.1440°, $V$ = 915.95 Å$^3$, $Z$ = 2, and $\rho_{calcd}$ = 2.139 g cm$^{-3}$.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02716.

Full description of CD sensing procedures, theoretical and CD spectral calculations, and MS, NMR and CD spectra (PDF)

Crystallographic details (CIF)

Crystallographic details (CIF)

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### Notes

The authors declare no competing financial interest.

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