Supplemental Information

Chiroptical Sensing of Citronellal: Systematic Development of a Stereodynamic Probe Using the Concept of Isostericity

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1. Synthetic Procedures

All reagents and solvents were commercially available and used without further purification. Reactions were carried out under inert atmosphere and anhydrous conditions. Reaction products were purified by flash chromatography on silica gel (particle size 0.032-0.063 mm). NMR spectra were obtained at 400 MHz (¹H NMR) and 100 MHz (¹³C NMR) using CDCl₃ as solvent. Chemical shifts are reported in ppm relative to TMS. Samples for electrospray ionization mass spectra (ESI-MS) were dissolved in a methanol:chloroform mixture (0.5 mg/mL MeOH:CHCl₃).



1,4-Bis((2-bromophenyl)ethynyl)benzene (4)¹

A solution of 2-iodobromobenzene (3 mL, 23.4 mmol), 1,4-diethynylbenzene (0.999 g, 7.8 mmol), Pd(PPh₃)₄ (0.901 g, 0.78 mmol) and CuI (0.148 g, 0.78 mmol) in 6 mL of acetonitrile:triethylamine (1:1, v/v) was stirred at 80 °C for 12 hours in a closed vessel. The resulting mixture was cooled to room temperature and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂) and recrystallization by slow addition of hexanes to a saturated CH₂Cl₂ solution afforded **4** (3.36 g, 7.73 mmol) as a yellow solid in 99% yield. ¹H NMR: $\delta = 7.18$ (ddd, J = 1.7, 7.6, 7.9 Hz, 2H), 7.29 (ddd, J = 1.1, 7.6, 7.9 Hz, 2H), 7.55 (dd, J =

1.7, 7.6 Hz, 2H), 7.56 (s, 4H), 7.62 (dd, *J* = 1.1, 7.9 Hz, 2H). ¹³C NMR: δ = 89.9, 93.5, 123.1, 125.1, 125.6, 127.0, 129.6, 131.6, 132.5, 133.2.

1,4-Bis(2(2-anilinylethynyl)phenylethynyl)benzene (2)

A solution of **2** (0.400 g, 0.92 mmol), 2-ethynylaniline (0.40 mL, 3.52 mmol), Pd(PPh₃)₄ (0.106 g, 0.092 mmol) and CuI (0.017 g, 0.089 mmol) in 6 mL of acetonitrile:triethylamine (1:1, v/v) was stirred at 90 °C for 24 hours in a closed vessel. The mixture was cooled to room temperature and concentrated in vacuo. Purification by flash chromatography on silica gel (hexanes:CHCl₃, 1:1, v/v gradually changed to pure CHCl₃) afforded **2** (0.206 g, 0.41 mmol) as a yellow solid in 44% yield. NMR analysis showed that **2** cocrystallizes with water in a 2:3 (**2**:H₂O) fashion. ¹H NMR: δ = 4.35 (bs, 4H), 6.66-6.71 (m, 4H), 7.11-7.15 (m, 2H), 7.29-7.39 (m, 6H), 7.61 (s, 4H), 7.57 (dd, *J* = 1.7, 6.4 Hz, 4H). ¹³C NMR: δ = 90.6, 90.8, 92.6, 93.6, 107.4, 114.1, 117.7, 123.0, 124.7, 125.9, 127.8, 128.5, 130.0, 131.5, 131.8, 131.9, 132.0, 148.0. Anal. Calcd. [C₃₈H₂₄N₂]₂·(H₂O)₃: C, 85.21; H, 5.08; N, 5.23 Found: C, 85.23; H, 4.70; N, 4.84.

¹H and ¹³C spectra of **4** in CDCl₃





2. Enantioselective Sensing Experiments

A stock solution of **2** (0.00375 M) in anhydrous CDCl₃ was prepared and 350 μ L aliquots were placed in 4 mL vials. A stock solution of each enantiomer of citronellal, **3**, (0.2626 M in CDCl₃) purchased from Aldrich and used as is was prepared. For each diimine formation, 10 μ L of the substrate stock solution were placed in a vial containing the sensor solution (350 μ L) and molecular sieves (4Å, 8-12 mesh) were added. The reactions were stirred at room temperature for 90 minutes. Prior to each use, the CD instrument was purged with nitrogen for 20 minutes at room temperature. CD spectra were collected with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a band width 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). The data were baseline corrected and smoothed using a binomial equation. The CD analysis was conducted with sample concentrations of 9.38 x 10⁻⁵ M. Control experiments with **3** at concentrations between 1.31 x 10⁻³ M and 6.56 x 10⁻³ M showed that the free substrate is CD silent in the region of interest.



CD Spectra of the diimine obtained using **2** and (*R*)-**3** (blue) or (*S*)-**3** (red) at 9.38 x 10^{-5} M in CHCl₃.

3. Enantiomeric Excess: Calibration curve and ee determination

In order to evaluate the practical use of sensor **2** for ee determination, a calibration curve was constructed using samples of **3** with varying ee. A stock solution of **2** (0.00375 M) in anhydrous CDCl₃ was prepared and aliquots of 350 μ L were placed in 4 mL vials. Stock solutions of **3** (0.2626 M) with varying ee composition (+100.0, +80.0, +60.0, +40.0, +20.0, 0.0, -20.0, -40.0, -60.0, -80.0, -100.0) were prepared in anhydrous CDCl₃. For each diimine formation, 10 μ L of a substrate stock solution were placed in a vial containing the sensor solution (350 μ L) and molecular sieves (4Å, 8-12 mesh) were added. The reactions were stirred at room temperature for 90 minutes. Upon completion, the reaction solution was diluted to 9.38 x 10⁻⁵ M for CD analysis. The data were baseline corrected and smoothed using a binomial equation. The CD amplitudes (mdeg) at 400 nm were plotted versus % ee. The calibration curve shows a linear relationship [mdeg = 0.1659 (% ee) - 1.7798] with R² = 0.9941.



Three scalemic samples of **3** were prepared and then treated with sensor **2** as described above. Using the linear regression equation obtained from the calibration curve and the measured CD amplitudes at 400 nm, the enantiomeric excess of these samples was determined (Table 1). Experimentally obtained data were within 3% of the actual values.

Actual % ee (R)	Calculated % ee (R)
-90.0	-87.6
54.0	51.0
88.0	90.9

Table 1. Experimentally determined ee's of three scalemic samples of **3**.

4. Analysis of Diimine Formation

To monitor the conversion of sensor 2 to its diimine derivative, the condensation reaction between 2 and (*R*)-3 was monitored by IR, NMR, UV and MS. Upon completion of the reaction it is evident that the carbonyl stretching of 3 (1724 cm⁻¹) and the formyl C-H stretching are no longer present while imine stretching absorptions (1613 and 1587 cm⁻¹) have emerged.



IR spectum of 2 under neat conditions.



IR spectum of (R)-3 under neat conditions.



IR spectum of the diimine obtained from 2 and (R)-3 under neat conditions.



Overlaid IR spectra of 3 (blue) and of the diimine (red) obtained from 2 and (R)-3 (red) under neat conditions.

The reaction between **2** and a stoichiometric amount of aldehyde **3** was analyzed by ¹H-NMR spectroscopy in CDCl₃. The disappearance of the formyl signal at 9.7 ppm showed quantitative conversion after 90 minutes. The condensation is also evident from ESI-MS analysis.



¹H-NMR spectrum of the diimine obtained from sensor **2** and (R)-**3**.



The redshift in the UV-Vis spectra of sensor 2 upon the reaction with a stoichiometric amount of substrate (R)-3 after 90 minutes is shown below.



UV-Vis spectra of **2** (blue) and of the diimine obtained using **2** and (*R*)-**3** (red) at 3.75×10^{-5} M in CHCl₃.

5. Crystallographic Data of 2

Single crystals suitable for X-ray diffraction were obtained by slow evaporation of a saturated solution of **2** in chloroform.



Crystal data: $C_{38}H_{24}N_2$, M = 508.59, $0.10 \times 0.11 \times 0.25 \text{ mm}^3$, monoclinic, space group $P2_1/n$, a = 9.8279(11), b = 4.9456(6), c = 27.487(3) Å, $\beta = 96.3450(10)^\circ$, V = 1327.8(3) Å³, Z = 2, $D_c = 1.272 \text{ g/cm}^3$, $F_{000} = 532$, Siemens SMART, Bruker APEXII CCD, MoK α radiation, $\lambda = 0.71073$

Å, T = 296(2)K, $2\theta_{max} = 57.4^{\circ}$, 11300 reflections collected, 3191 unique (R_{int} = 0.0208). Final GooF = 1.071, R1 = 0.0421, wR2 = 0.1109, R indices based on 2598 reflections with I >2sigma(I) (refinement on F^2), 229 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.074$ mm⁻¹.

6. References:

(1) Sanji, T.; Shiraishi, K.; Kashiwabara, T.; Tanaka, M. Org. Lett. 2008, 10, 2689-2692.