Electronic Supplementary Information

Quantitative Chirality Sensing of Amines and Amino Alcohols via Schiff Base Formation with a Stereodynamic UV/CD Probe

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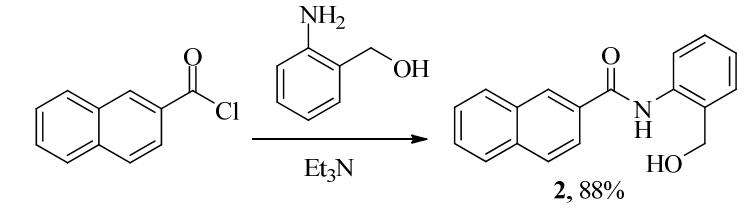
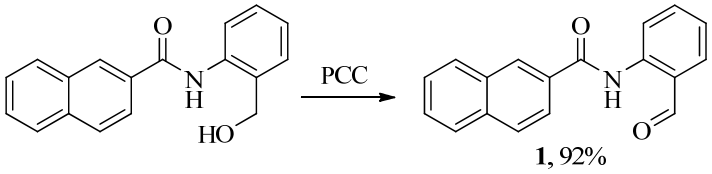
1. Synthetic Procedures

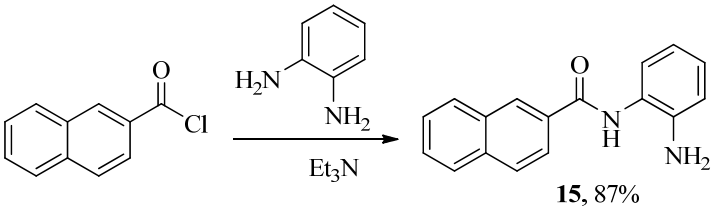
All commercially available reagents and solvents were used without further purification. Reactions were carried out under inert and anhydrous conditions. Flash chromatography was performed on silica gel, particle size 40-63 μm. NMR spectra were obtained at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) using $CDCl_3$ as solvent.



2, 88%



1, 92%



15, 87%

***N*-(2-(Hydroxymethyl)phenyl)-2-naphthamide (2)**

A solution of 2-naphthoyl chloride (100 mg, 0.52 mmol) dissolved in 5 mL of THF was added dropwise to a solution of 2-aminobenzyl alcohol (84 mg, 0.68 mmol) in 5 mL of THF at 0^{o} C. The mixture was allowed to warm to room temperature and was stirred for 18 hours. The resulting mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc:hexanes 1:3) afforded 127 mg (0.50 mmol, 88% yield) of a white solid. ^{1}H NMR: δ = 2.27 (t, *J* = 6.0 Hz, 1H), 4.82 (d, *J* = 6.0 Hz, 2H), 7.09 (dd, *J* = 7.5 Hz, 7.5 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.38 (dd, *J* = 7.0 Hz, 7.0 Hz, 1H), 7.52-7.60 (m, 2H), 7.86-7.97 (m, 4H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.44 (s, 1H), 9.76 (bs, 1H). ^{13}C NMR: δ = 64.9, 109.9, 122.3, 123.4, 124.2, 126.8, 127.7, 127.8, 127.9, 128.6, 129.1, 129.2, 129.3, 131.6, 132.7, 134.9, 137.9, 165.6. Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.69; H, 5.59; N, 5.03.

***N*-(2-Formylphenyl)-2-naphthamide (1)**

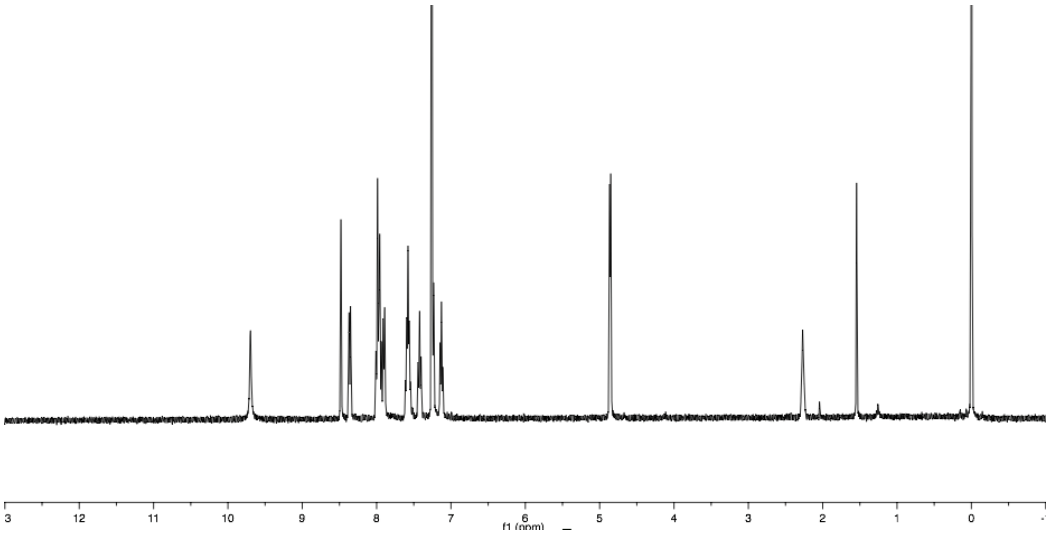
Pyridinum chlorochromate (108 mg, 0.5 mmol) was added into a suspension of **2** (107 mg, 0.39 mmol) in 5 mL of CH_2Cl_2 and Celite (200 mg) and was stirred at room temperature for 18 hours. The resulting mixture was filtered through Celite and the filtrate was concentrated in vacuo. Purification by flash chromatography on silica gel (acetone:hexanes 1:6) afforded 99 mg (0.36 mmol, 92%) of a white solid. ^{1}H NMR: δ = 7.30 (dd, *J* = 8.5 Hz, 8.5 Hz, 1H), 7.56-7.64 (m, 2H), 7.72 (dd, *J* = 8.0 Hz, 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 8.14 (dd, *J* = 8.5 Hz, 8.5 Hz, 1H), 8.62 (s, 1H), 9.02 (d, *J* = 8.5 Hz, 1H), 10.05 (s, 1H), 12.27 (bs, 1H). ^{13}C NMR: δ = 120.0, 122.0, 123.0, 123.6, 126.6, 127.7, 128.0, 128.6, 128.8, 129.4, 131.5, 132.7, 135.1, 136.2, 136.4, 141.3, 168.2, 195.9. Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.64; H, 4.81; N, 5.09.

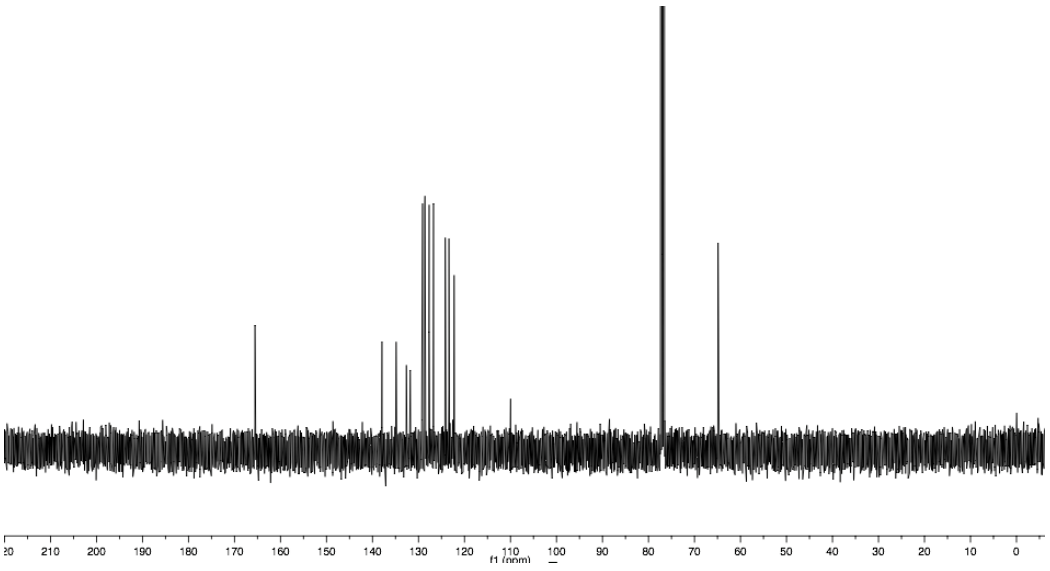
***N*-(2-Aminophenyl)-2-naphthamide (15)**

To a solution of 1,2-diaminobenzene (86.5 mg, 0.80 mmol), triethylamine (89.0 mg, 0.88 mmol) in 3 mL of anhydrous tetrahydrofuran was dropwise added a 3 mL THF solution of 2-naphthoyl chloride (167.7 mg, 0.88 mmol) and the reaction

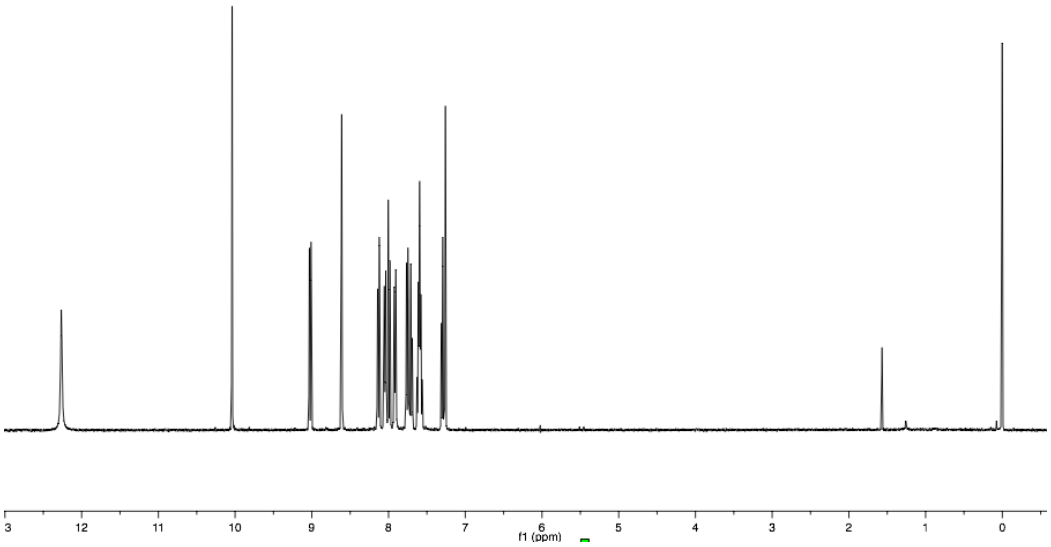
was stirred for 18 hours. The mixture was poured onto brine (40 mL) and extracted with ethyl acetate (3 x 15mL). The combined extracts were dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography on silica gel (EtOAc:hexanes 1:5) afforded a white solid (184.7 mg, 0.70 mmol) in 87% yield (mixture of two amide diastereomers (5:1)). ^{1}H NMR δ = 3.92 (s, 2H), 6.87-6.89 (m, 2H), 7.12 (dd, *J* = 7.8 Hz, 7.8 Hz 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.52 – 7.66 (m, 2H), 7.86 – 8.04 (m, 5H), 8.44 (s, 1H). ^{13}C NMR δ = 157.0, 140.7, 135.0, 132.7, 131.4, 129.0, 128.8, 128.0, 127.9, 127.8, 127.8, 127.3, 127.0, 124.8, 123.7, 119.9, 118.5. Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.62; H, 5.54; N, 10.50.

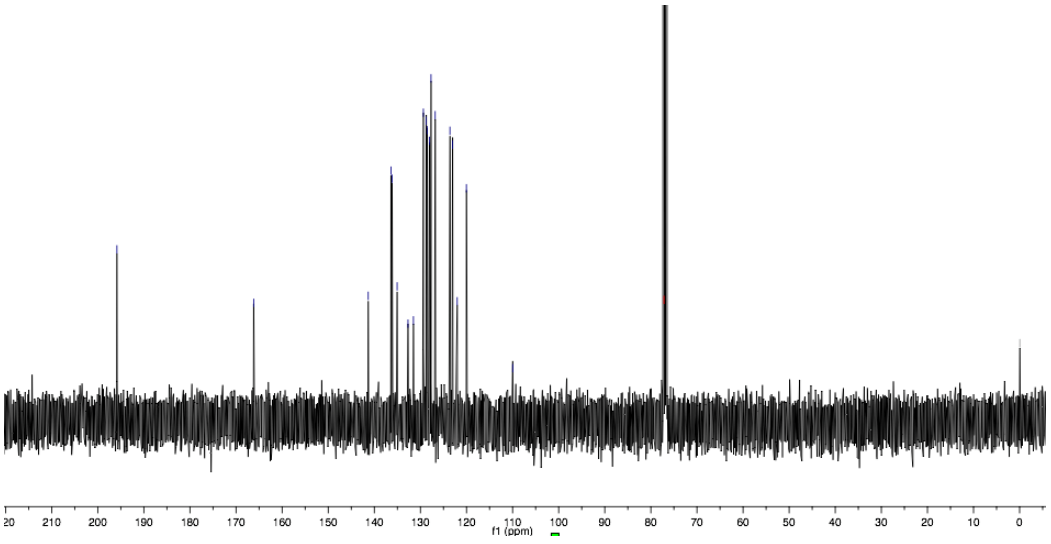
^{1}H and ^{13}C NMR Spectra of **2** in $CDCl_3$.



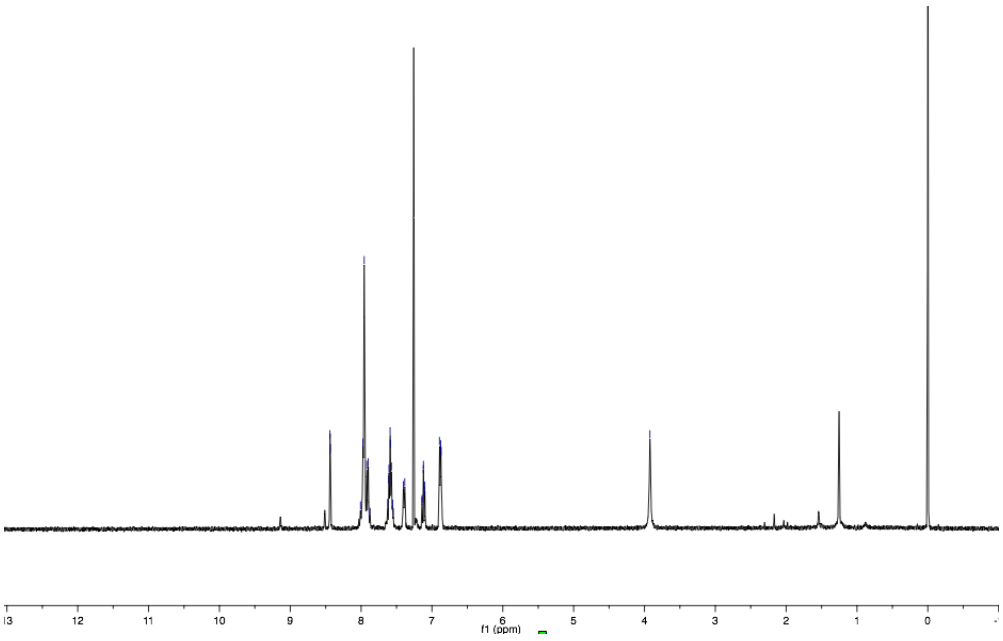


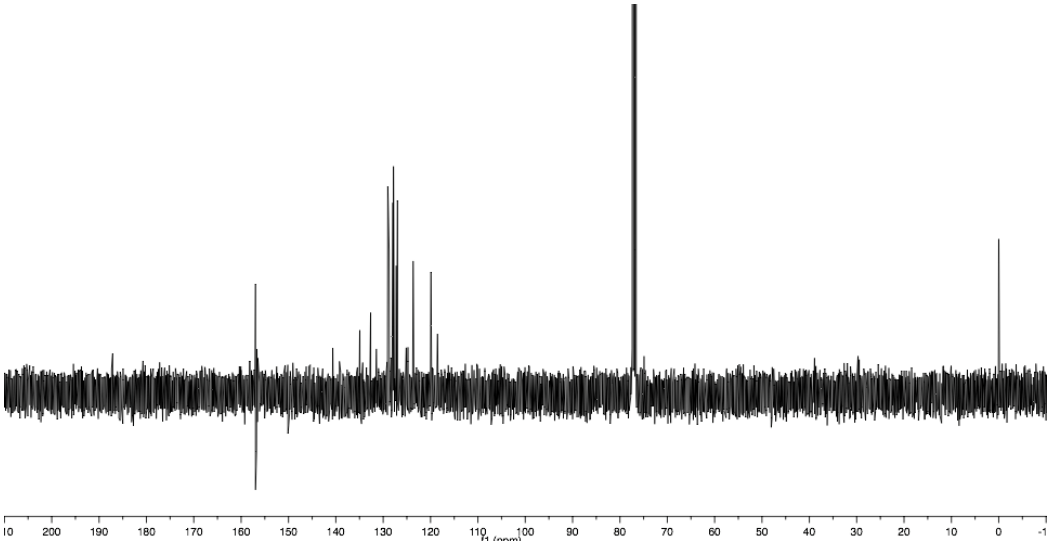
^{1}H and ^{13}C NMR Spectra of **1** in $CDCl_3$.





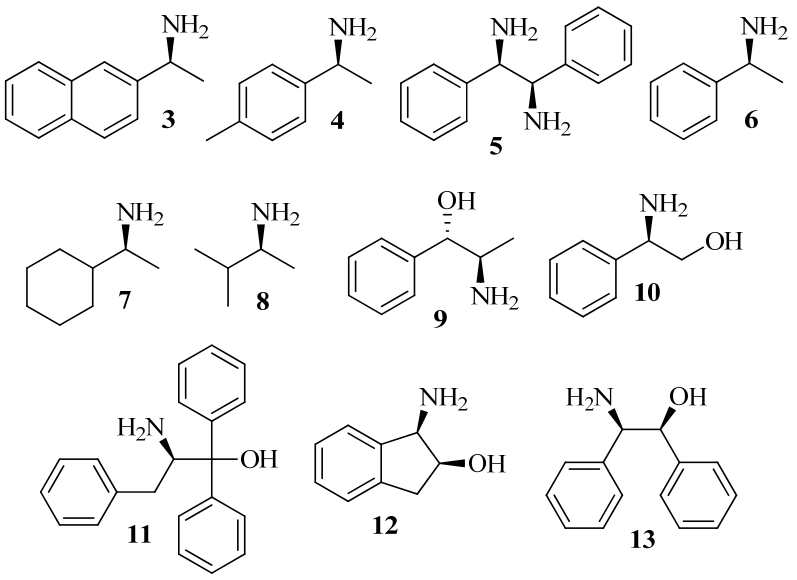
^{1}H and ^{13}C NMR Spectra of **15** in $CDCl_3$.





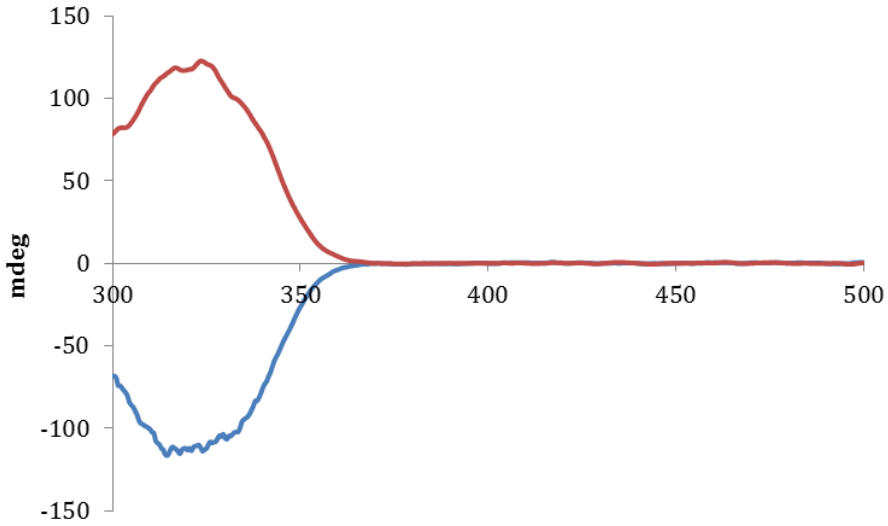
2. Chiroptical sensing

To test the general utility of **1** as enantioselective chemosensor, condensation reactions were performed with amines **3-8** and amino alcohols **9-13** (only one enantiomer shown) and the chiroptical properties of the resulting imines were analyzed by CD spectroscopy.

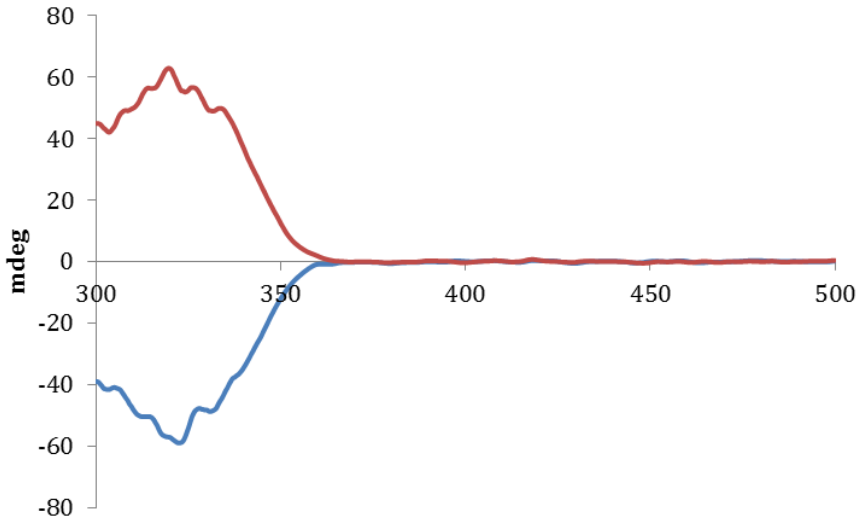


A stock solution of **1** (0.01 M) in CH_3CN was prepared and portions of 500 μL were transferred to 4 mL vials. Solutions of the substrates (0.25 M in CH_3CN) were prepared. To each vial containing 500 μL stock solution was added 1 equivalent (20 μL) of the substrate and molecular sieves (4 Å). The mixture was allowed to react for 5 hours. If necessary, the reaction time can be reduced to 40 minutes by the addition of Ti(O*i*-Pr)$_4$ instead of molecular sieves. The CD analysis was conducted with sample concentrations of 3.0 x 10^{-4} M in CH_3CN. 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. Control experiments with **3-13** showed that the free substrates are CD silent in the region of interest.

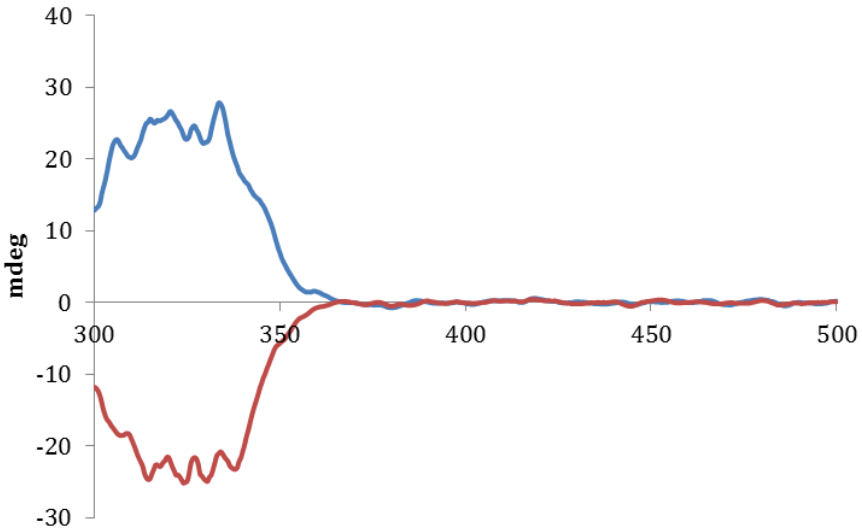
CD Spectra of the imine obtained from **1** and (*R*)-**3** (blue) and (*S*)-**3** (red)



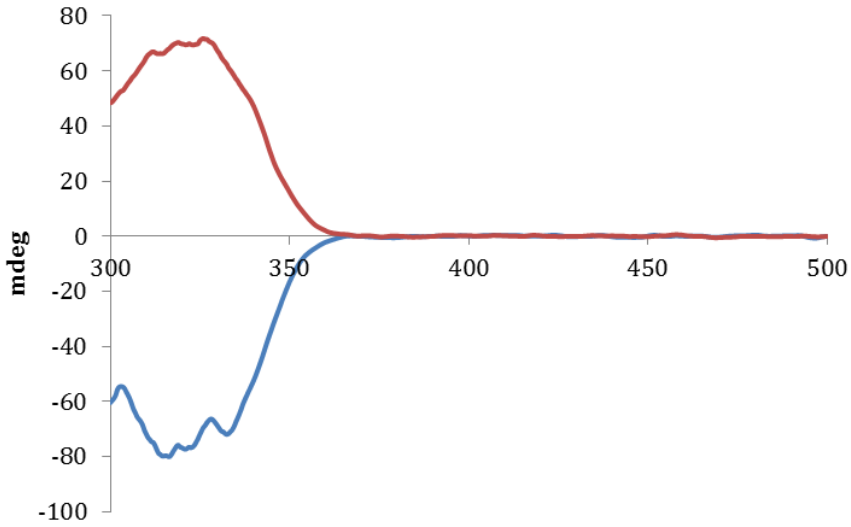
CD Spectra of the imine obtained from **1** and (*R*)-**4** (blue) and (*S*)-**4** (red)



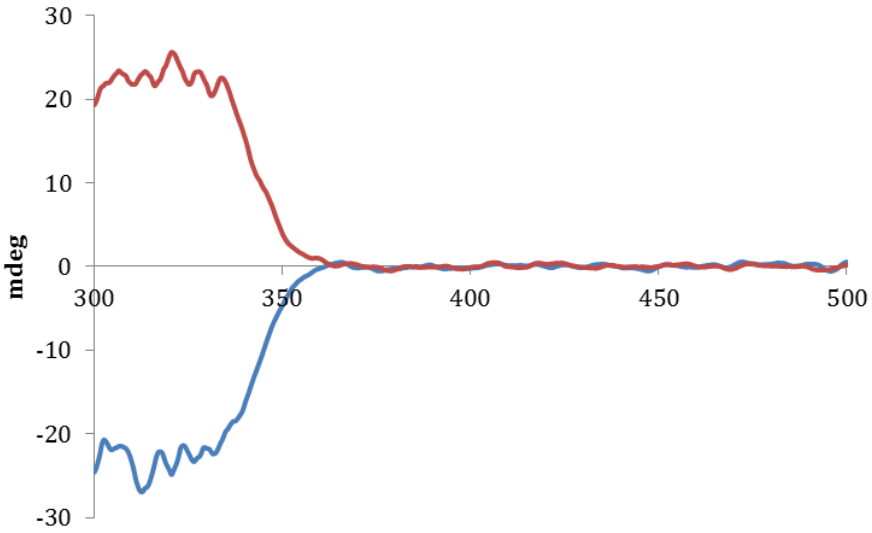
CD Spectra of the imine obtained from **1** and (*R*,*R*)-**5** (blue) and (*S*,*S*)-**5** (red)



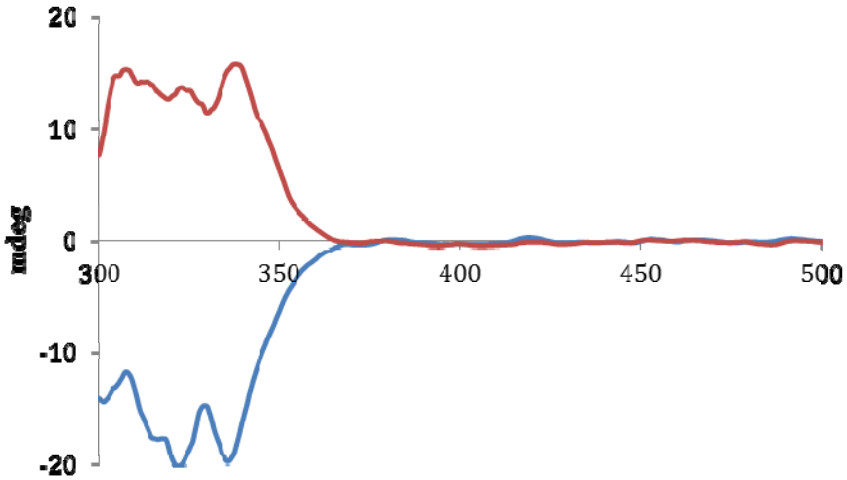
CD Spectra of the imine obtained from **1** and (*R*)-**6** (blue) and (*S*)-**6** (red)



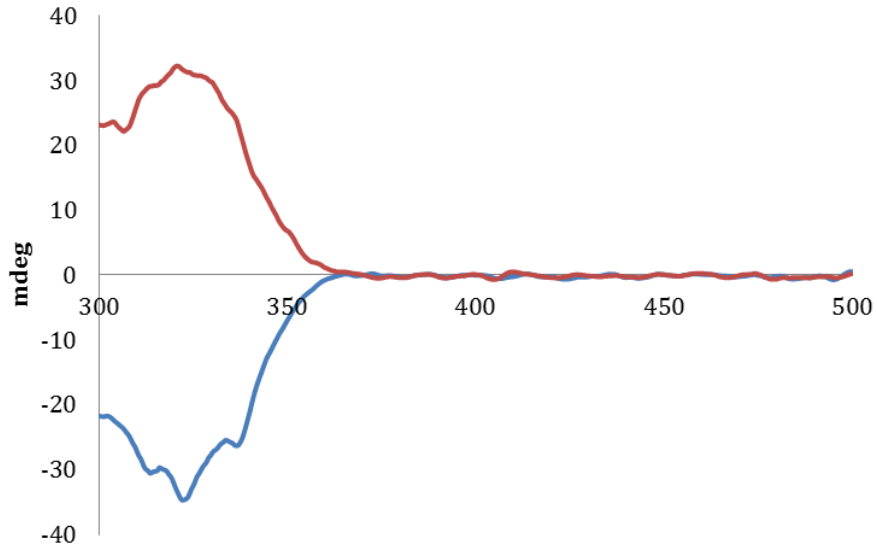
CD Spectra of the imine obtained from **1** and (*R*)-**7** (blue) and (*S*)-**7** (red)



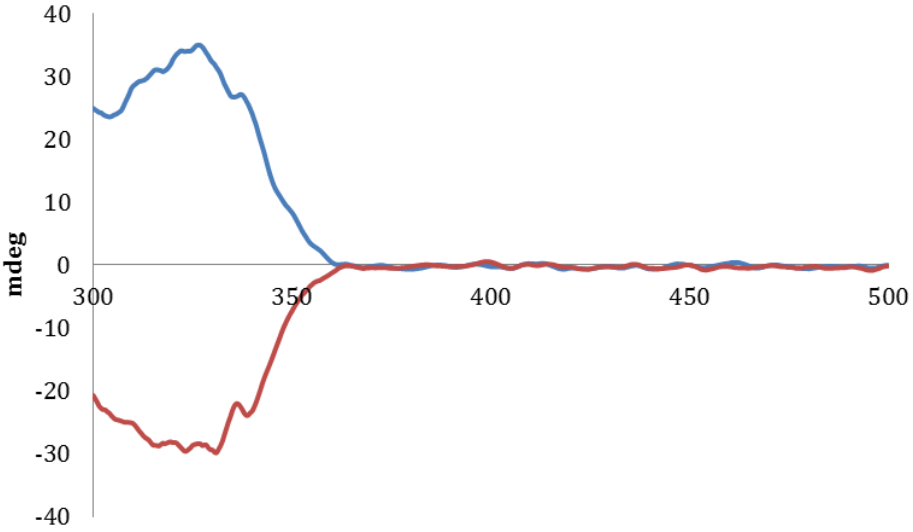
CD Spectra of the imine obtained from **1** and (*R*)-**8** (blue) and (*S*)-**8** (red)



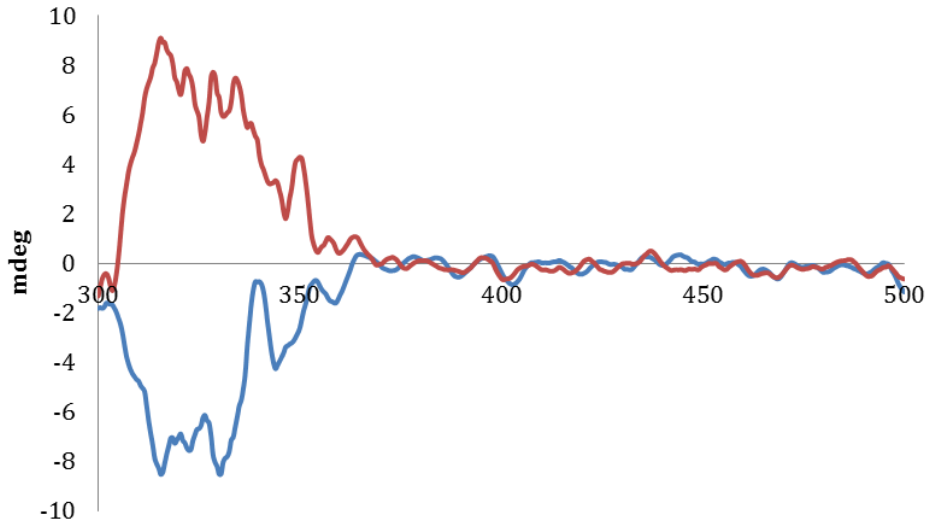
CD Spectra of the imine obtained from **1** and (*S*,*R*)-**9** (blue) and (*R*,*S*)-**9** (red)



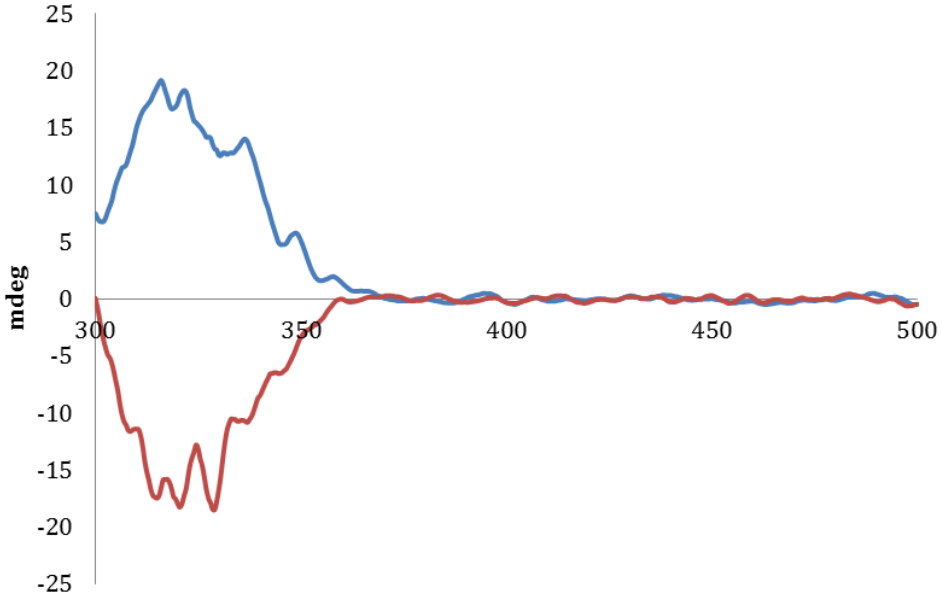
CD Spectra of the imine obtained from **1** and (*R*)-**10** (blue) and (*S*)-**10** (red)



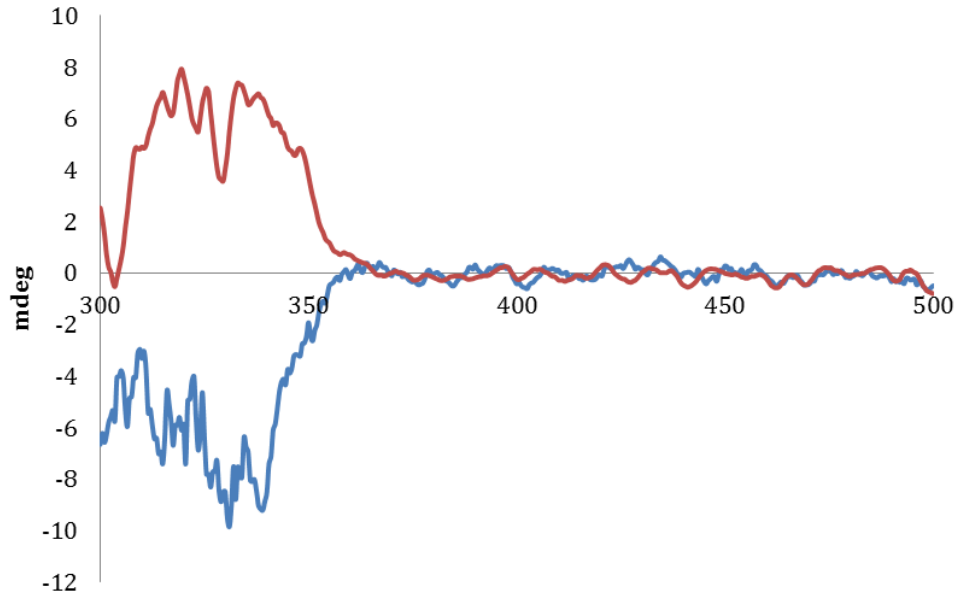
CD Spectra of the imine obtained from **1** and (*R*)-**11** (blue) and (*S*)-**11** (red)



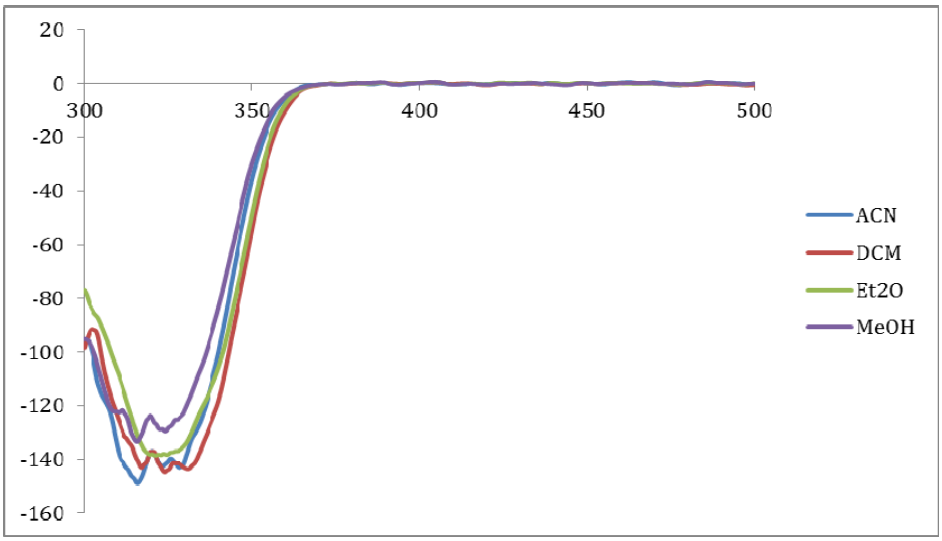
CD Spectra of the imine obtained from **1** and (*R*,*S*)-**12** (blue) and (*S*,*R*)-**12** (red)



CD Spectra of the imine obtained from **1** and (*S*,*R*)-**13** (blue) and (*R*,*S*)-**13** (red)

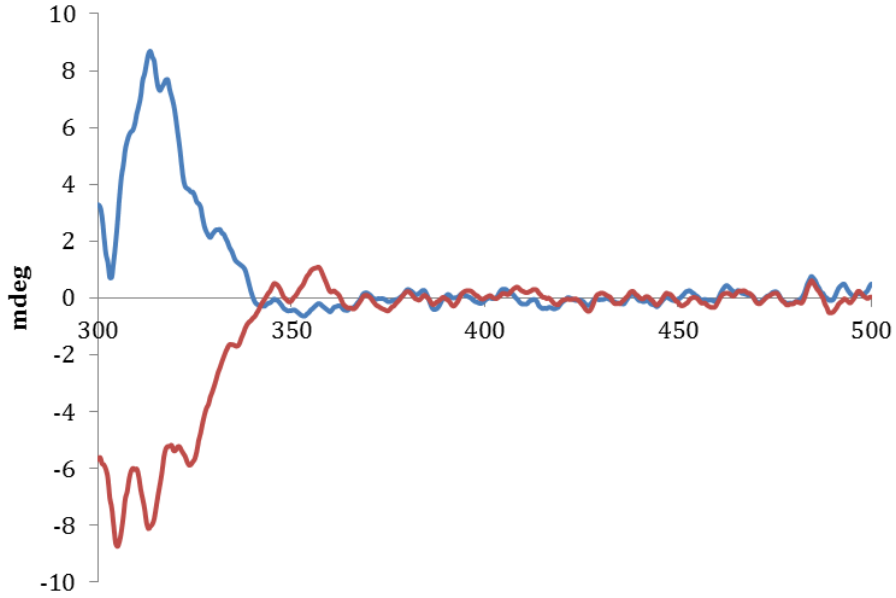


CD spectra of the imine obtained from **1** and (*R*)-**3** in different solvents (0.3mM)



To prove the concept of isostericity, aniline, **15,** was applied to chirality sensing of citronellal, **14**, and the chiroptical properties of the resulting imines were analyzed by CD spectroscopy. The imine was formed by heating a solution of **14** (26.2 mg, 0.10 mmol) and **15** (23.2 mg, 0.15 mmol) in 4 mL of chloroform to 90 ^{o}C in the presence of trifluoroacetic acid (20 mol%) for 18 hours. The formed imine was dissolved at a concentration of 2.0 x 10^{-4} M in $CHCl_3$ for CD analysis that was conducted as described above.

CD spectra of the imine obtained from **15** and (*R*)-**14** (blue) and (*S*)-**14** (red)

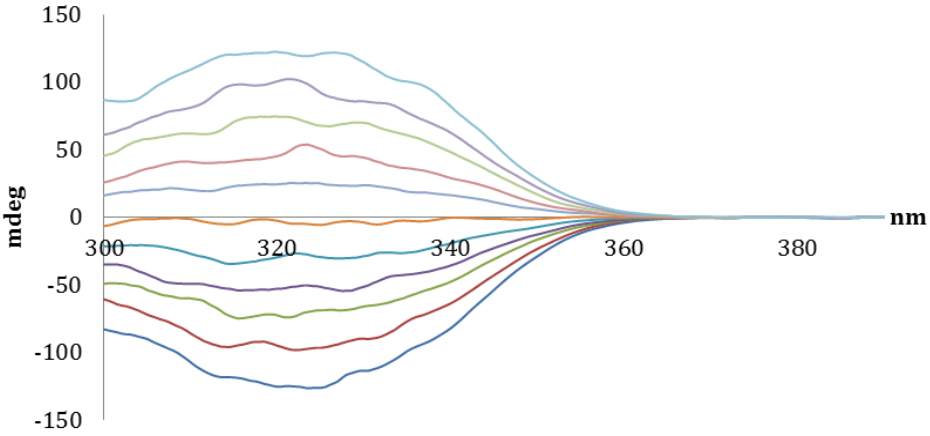


3. Quantitative ee and concentration analysis

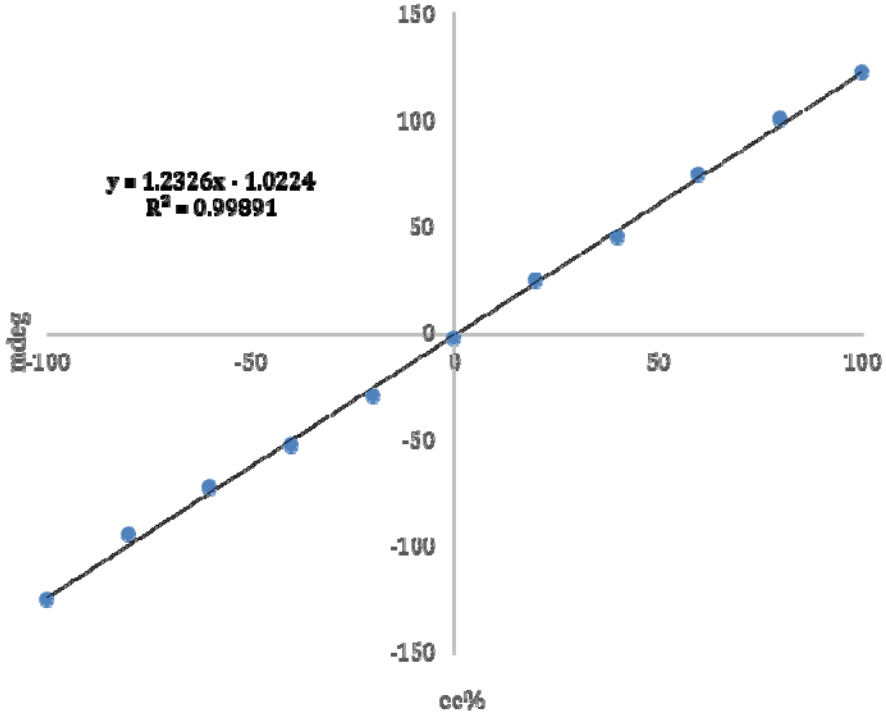
3.1 Calibration curve and ee determination of amine 3 using chemosensor 1

Enantiomers of **3** with identical enantiopurity were purchased. A calibration curve was constructed using nonracemic samples of **3**. A stock solution of **1** (0.01 M in CH_3CN) was prepared and 500 μL portions were placed in 4 mL vials. Solutions of **3** (0.25 M in CH_3CN) with varying ee compositions (+100.0, +80.0, +60.0, +40.0, +20.0 0.0, -20.0, -40.0, -60.0, -80.0, -100.0) were also prepared. To each vial containing 500 μL of the stock solution of **1** was added 1 equivalent (20 μL) of the substrate and molecular sieves (4 Å) and the condensation reaction and CD analysis were carried out as described above. The CD amplitudes measured at 320 nm were plotted against %ee.

CD spectra of the imine obtained from **1** and varying ee compositions of **3**



Linear relationship between the CD amplitude at 320 nm and the enantiomeric excess of **3**



Five scalemic samples of **3** were prepared and then treated with sensor **1** as described above. Using the linear regression equation obtained from the calibration curve and the measured Cotton effect amplitude at 320 nm, the enantiomeric excess of these samples was determined. Experimentally obtained data were within 5.3% of the actual values.

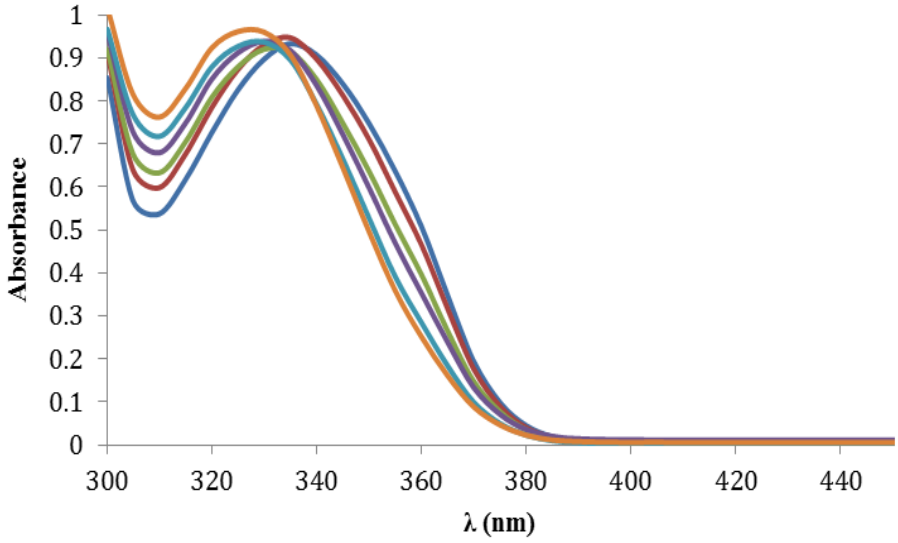
Experimentally determined ee's of five scalemic samples of **3** using the CD maximum at 320 nm

Absolute Configuration	Actual %ee	Absolute Configuration	Calculated %ee
R	-87.0	*R*	-87.6
R	-76.0	*R*	-72.3
R	-12.0	*R*	-8.4
S	26.0	*S*	20.7
S	68.0	*S*	66.9
S	89.0	*S*	89.1

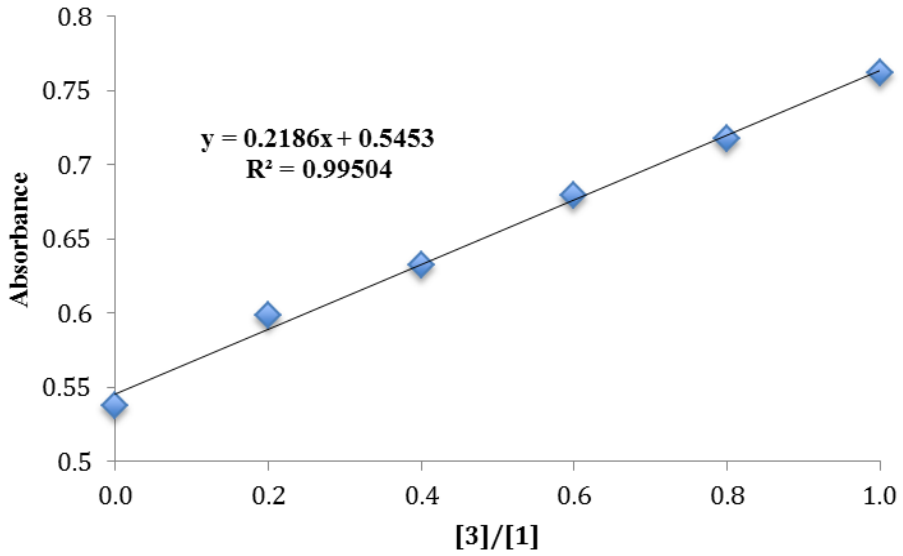
3.2 Determination of the concentration of 3

The change in the UV signature of **1** upon addition of **3** was analyzed. A stock solution of **1** (0.01 M in CH_3CN) was prepared, 500 μL portions were placed in 4 mL vials containing molecular sieves (4 Å). A stock solution of **3** (0.25 M in CH_3CN) was also prepared. To the solutions of **1** was added **3** in varying amounts (0, 20, 40, 60, 80 and 100 mol%). UV spectra were collected with an average scanning time of 0.1 s, a data interval of 1 nm, and a scan rate of 600 nm/min. The UV absorbance at 310 nm increased steadily upon addition of **3**. Plotting and curve fitting of the UV absorbance at 310 nm against the molar ratio of [**3**]/[**1**] from 0 to 100 mol% showed a linear UV response.

UV spectra of **1** upon addition of **3** in varying molar ratios from 0 to 100 mol%



Calibration A: Linear regression analysis of the UV change at 310 nm upon imine formation of **1** and **3** from 0 to 100 mol%

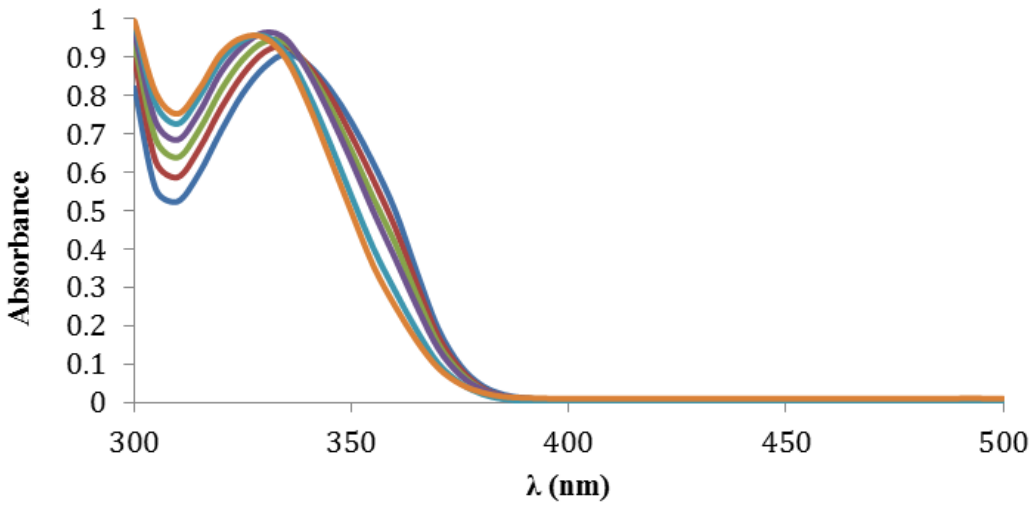


Four solutions of **3** at varying concentrations were prepared and analyzed as described above. Using the regressional equations obtained from the calibration curves and the UV absorbance at 310 nm, the concentration of these samples were determined.

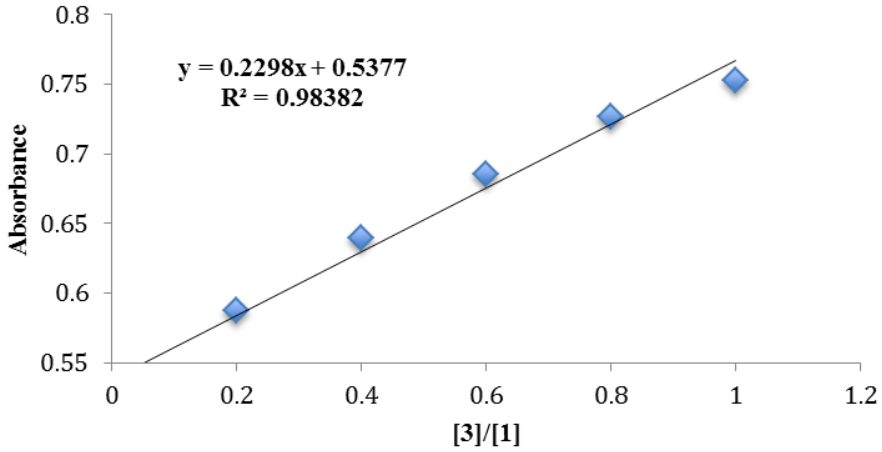
Concentration of **3** ($x10^{-3}$ M)	Sensing result ($x10^{-3}$ M)
1.5	1.5
3.5	3.9
7.0	8.2
9.0	9.2

To prove the reproducibility and practicality, the chemosensing with **1** was repeated. Following the procedures above, five solutions of **3** at varying concentrations were prepared and analyzed with calibration curves obtained at different days. The results obtained with calibration A and B are in good agreement.

Repeated measurements of the UV response of **1** upon addition of **3** in varying molar ratios from 0 to 100 mol%



Calibration B: Linear regression analysis of the UV change at 310 nm upon imine formation of **1** and **3** from 0 to 100 mol%



Concentration of **3** ($x10^{-3}$ M)	Calibration A ($x10^{-3}$ M)	Calibration B ($x10^{-3}$ M)
1.5	1.3	1.6
5.5	5.6	5.7
7.0	6.1	6.1
8.5	8.3	8.3
9.0	8.9	8.8

4. NMR Analysis of the imine formation

To a solution of **1** (1.3 mg, 0.005 mmol) and 1.0 equivalent of (*R*)-**6** in 0.5 mL of $CDCl_3$ was added molecular sieves and the mixture was stirred for 5 hours. The imine formation was evident from NMR analysis showing the disappearance of the formyl signal of **1**.

^{1}H NMR Spectrum of the imine obtained from **1** and (*R*)-**6** in $CDCl_3$.

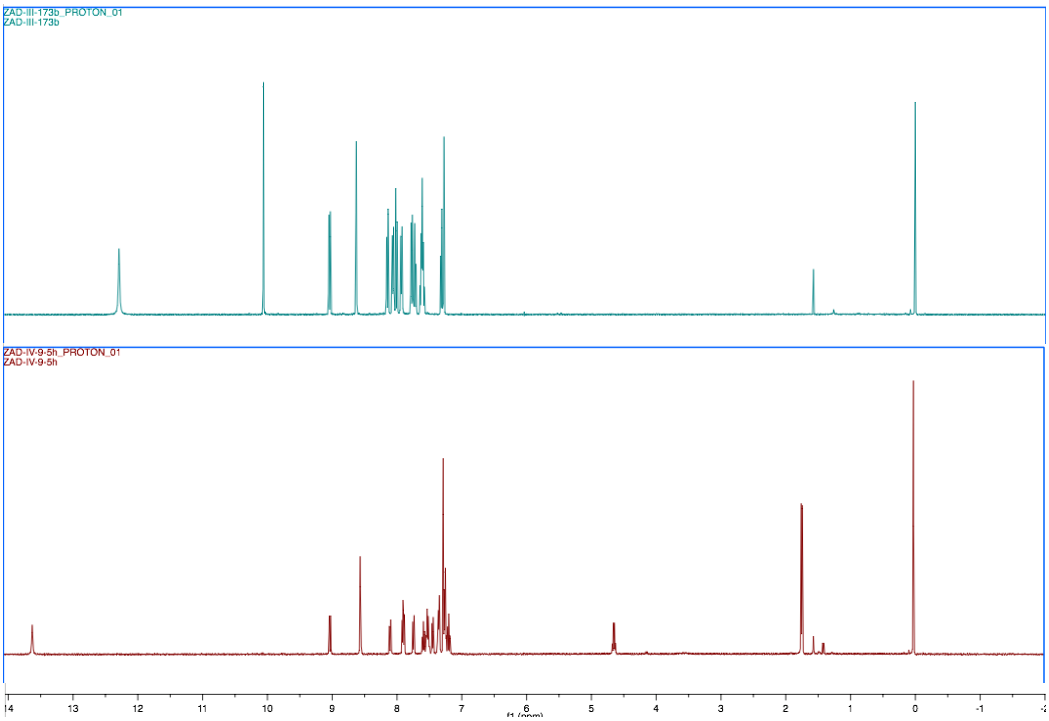


Figure 1 ^{1}H NMR spectra of 1 (teal) and the formed imine (red). Note the disappearance of the formyl peak around 10 ppm.

A solution of **1** (1.3 mg, 0.005 mmol), 1.0 equivalent of (*R*)-**6** in 0.5 ml of $CDCl_3$ and 1.0 equivalent of Ti(O*i*-Pr)$_4$ was stirred for 40 minutes. The imine formation was evident from NMR analysis showing the disappearance of the formyl signal of **1**.

^{1}H NMR Spectrum of the imine obtained from **1** and (*R*)-**6** with Ti(O*i*-Pr)$_4$ as additive in $CDCl_3$.

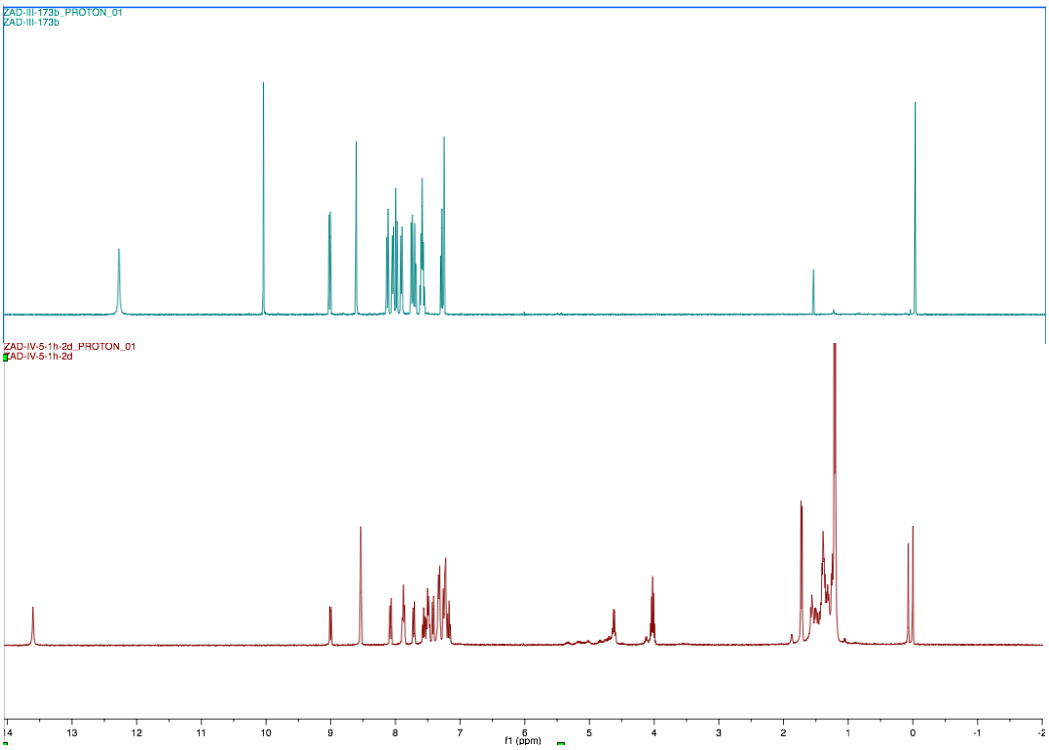
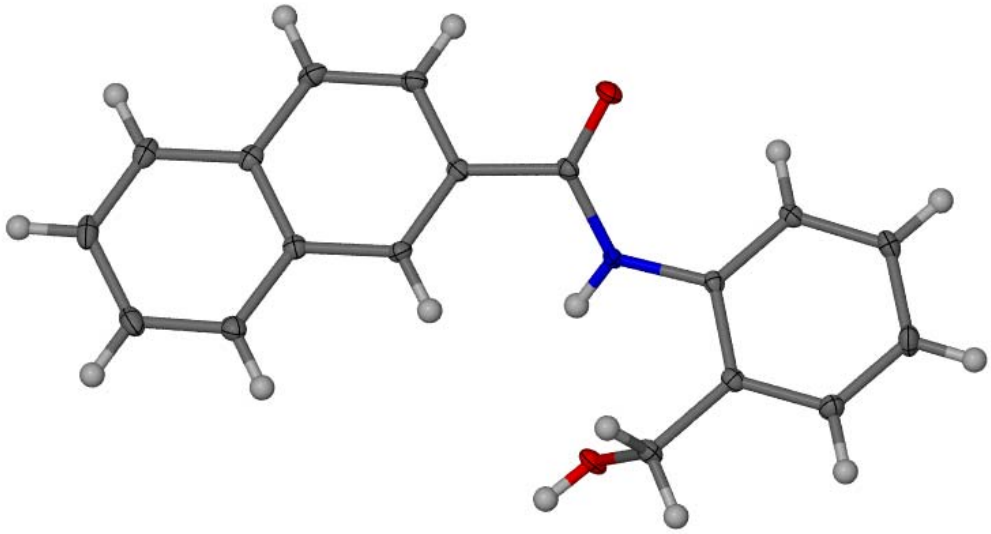


Figure 1 ^{1}H NMR spectra of 1 (teal) and the formed imine (red). Note the disappearance of the formyl peak around 10 ppm.

5. Crystallographic data

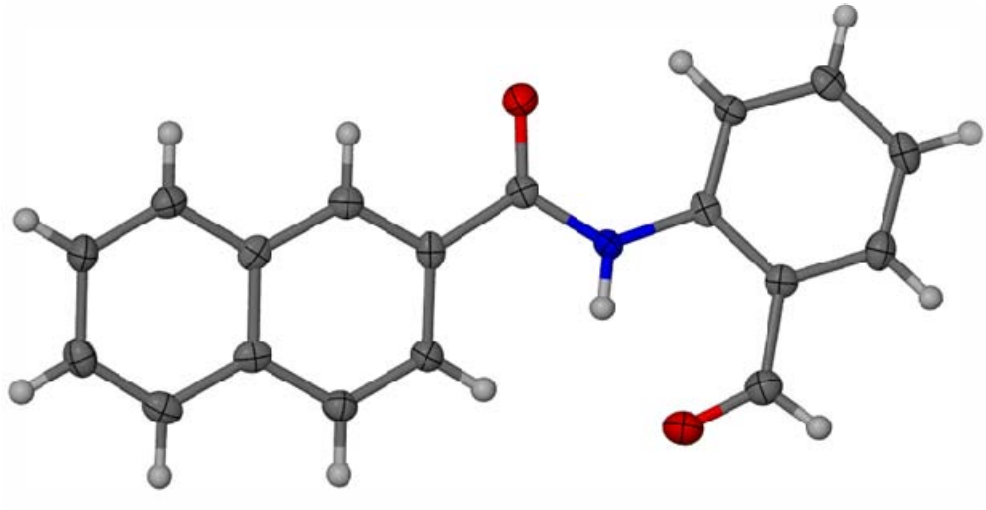
N-(2-(Hydroxymethyl)phenyl)-2-naphthamide

A single crystal was obtained by slow evaporation of a solution of the alcohol in $CDCl_3$. Single crystal X-ray analysis was performed at 296 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 2 program. The structures were solved by intrinsic phasing and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data: $C_{18}H_{15}NO_2$, M = 277.31, colorless needle, 0.10 x 0.06 x 0.06 mm^3, orthorhombic, space group $P2_1/c$, a = 7.1207(5), b = 7.6201(5), c = 25.3427(17) Å, V = 1364.88(16) $Å^3$, Z = 4.



***N*-(2-Formylphenyl)-2-naphthamide**

A single crystal was obtained by slow evaporation of a solution of the aldehyde in CD_3CN. Single crystal X-ray analysis was performed at 296 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 2 program. The structures were solved by intrinsic phasing and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data: $C_{18}H_{13}NO_2$, M = 275.29, colorless needle, 0.06 x 0.04 x 0.02 mm^3, orthorhombic, space group $Pna2_1$, a = 24.4271(14), b = 3.7892(3), c = 14.3031(7) Å, V = 1323.88(14) $Å^3$, Z = 4.



(*R*)-*N*-(2-(((1-(Naphthalen-2-yl)ethyl)imino)methyl)phenyl)-2-naphthamide

A single crystal was obtained by slow evaporation of a solution of the aldehyde in CD_3CN. Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 2 program. The structures were solved by intrinsic phasing and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameter. Crystal data: $C_{30}H_{24}N_2O$, M = 428.51, colorless needle, 0.06 x 0.04 x 0.02 mm^3, orthorhombic, space group $P2_12_12_1$, a = 5.8608(11), b = 13.688(3), c = 27.498(5) Å, V = 2206.0(7) $Å^3$, Z = 4.