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Fluorous Phase-Based Chiral Assay with Circular Dichroism Spectroscopy

Meng Xiao,[a] Shanshan Yu,*[a] Liming Chen,[a] Zeng Huang,[a] Kaili Wen,[a] Yimang Xu,[a] Feng Zhao,[a] Xiaoqi Yu,*[a] and Lin Pu*[a,b]

Abstract: A highly fluorinated molecular probe made of a salicylaldehyde derivative is designed and synthesized for the detection of chiral amines in the fluorous phase. When treated with various chiral amines in a fluorous solvent (perfluorohexyl ethanol), this probe shows intense CD signals at wavelengths greater than 400 nm which has been used to determine the enantiomeric composition of chiral amines, amino alcohols and amino acids. This is the first example to conduct CD recognition of chiral compounds in the fluorous phase which could greatly reduce the undesired interference in the direct assay of asymmetric reactions and catalytic processes.

Introduction

Perfluorocarbon-based molecules and structural units exhibit unique hydrophobic and lipophobic properties and they have been actively utilized for the development of new separation techniques in the past two decades.[1-3] However, in spite of the broad application of the fluorous phase-based chemistry in synthesis and catalysis, very limited study has been done in molecular sensing.[4,5] The first example for the use of a fluorescent sensor to carry out the enantioselective recognition of chiral amino alcohols in the fluorous phase was reported by our laboratory in 2015.[5]

In recent years, extensive work has been conducted on using the circular dichroism (CD) response of molecular receptors to determine the enantiomeric composition of chiral substrates.[6-9] One application of this research is to develop a fast optical analytical method for chiral assay which is potentially useful for high throughput screening of asymmetric reactions.[9] It is our hypothesis that if the CD spectroscopic responses of a molecular receptor toward chiral substrates could be measured in a fluorous solvent, the interference of other species in the screening reactions on the CD measurement should be greatly reduced since most of organic and inorganic substances cannot be dissolved in the fluorous phase. Herein, we report the synthesis of a fluorous phase soluble and CD responsive molecular receptor and the study of its use in the determination of the enantiomeric composition of chiral amines. This is the first example for the use of CD spectroscopy to conduct chiral assay in the fluorous phase.

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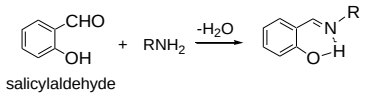
Supporting information for this article, including NMR spectra of the new compounds, additional optical spectra, is given via a link at the end of the document

Results and Discussion

Reaction of salicylaldehyde with an amine can generate a salicylaldimine facilitated by the intramolecular hydrogen bonding between the imine and the *ortho*-hydroxyl group (Scheme 1). This reaction has been used to develop CD and fluorescent sensors for amines.[9f-h,10] In order to conduct the proposed fluorous phase-based CD analysis of chiral amines, we have synthesized a naphthalene derivative of

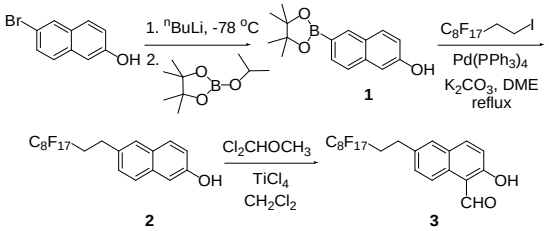
Scheme 1. Reaction of salicylaldehyde with an amine to form a salicylaldimine .



salicylaldehyde

salicyladehyde with the incorporation of a perfluoroalkyl substituent. The use of a naphthalene unit should shift the response of the receptor to a longer wavelength than the absorptions of common aliphatic and aromatic amine substrates to avoid their interference with the CD signals.[11] As shown in Scheme 2, 6-bromo-2-naphthol was converted to the naphthyl boronate **1** by reaction with an excess amount of ^{n}BuLi and then isopropoxyboronic acid pinacol ester.[12] The Suzuki coupling of **1** with 1-(perfluorooctyl)-2-

Scheme 2. Synthesis of a perfluoroalkyl substituted naphthalene-based salicyladehyde **3**.



iodoethane in the presence of $Pd(PPh_3)_4$ gave the perfluoroalkyl substituted naphthol **2**.[13] An aldehyde group

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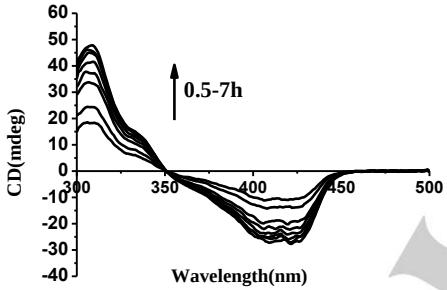
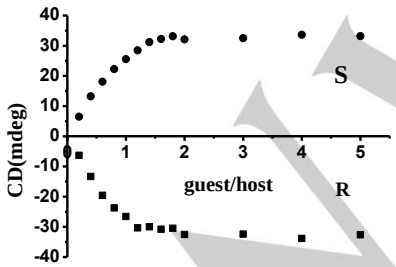
was introduced by treatment of **2** with $TiCl_4$ and dichloromethyl ether to give the desired compound **3**.[14]

Compound **3** is found to be soluble in perfluorohexyl ethanol (PFE), a fluorous solvent, but common organic compounds cannot be dissolved in this solvent (see SI). Therefore, we studied the CD response of **3** toward chiral amines in this fluorous solvent. Figure 1 shows the CD responses of **3** upon reaction with (*R*)-(+)-1-phenylethanamine. When **3** (2.0×10^{-4} M) in the fluorous solvent PFE was treated with the chiral amine (4.0×10^{-4} M, 1.3% CH_2Cl_2 was used to dissolve the amine), CD signals were observed at λ = 309 and 425 nm (Figure 1a). The CD signals reached maximum over 5 h at 25 °C. We also studied the CD response of **3** versus the amine concentration after reaction for 5 h. As shown in Figure 1b, the CD intensity at λ = 425 nm increases as the concentration of the chiral amine increases and the enhancement slows down when the amine is more than 1 equiv with no further increase after 2 equiv. Although the reaction of a salicylaldehyde with an amine normally gives a salicylaldimine product, it also cannot be ruled out that in PFE 2 equiv of an amine could react with **3** to generate compounds such as an aminal besides the expected salicylaldimine. More detailed study will be conducted later to clarify this. Figure 1c gives the g-factor graphs for the CD response of **3** toward the chiral amine.

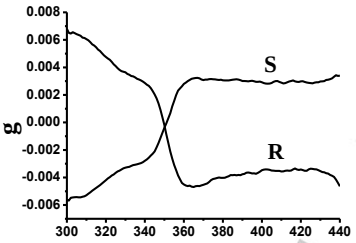
Figure 1. (a) CD responses of **3** (2.0×10^{-4} M) toward (*R*)-(+)-1-phenylethanamine (4.0×10^{-4} M) versus reaction time, (b) the CD intensity at λ = 425 nm versus the amine concentration (4.0×10^{-5} – 1.0×10^{-3} M), and (c) the g-factor graph (solvent: PFE with 1.3% CH_2Cl_2. Temperature: 25 °C).



(a)



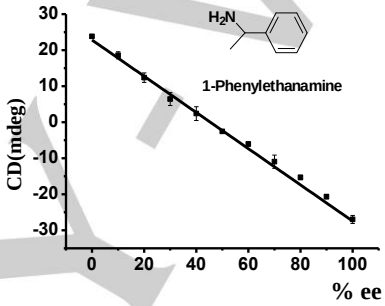
(b)



(c)

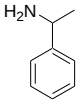
We further investigated the effect of the enantiomeric excess (ee) of the chiral amine on the CD signal of **3**. Compound **3** (2.0×10^{-4} M in PFE) was treated with 1-phenylethanamine (4.0×10^{-4} M) at various ee's. As shown in Figure 2, when the CD intensity at λ = 425 nm is plotted against the ee of the amine, a linear relationship is obtained.

Figure 2. CD intensity of **3** (0.20 mM) at λ = 425 nm versus the ee of 1-phenylethanamine (0.40 mM) (Reaction at 25 °C for 5 h. Solvent: PFE/1.3% CH_2Cl_2.)



We have used the plot of Figure 2 to determine the ee of the chiral amine samples in PFE. As shown in Table 1, the ee's obtained by the CD measurement is very close to the actual ee's of the samples with the absolute errors less than 3%. This demonstrates that compound **3** can be used to determine the ee of the chiral amine in the fluorous phase.

Table 1. Determination of the ee of 1-phenylethanamine samples by using the CD assay.

analyte	actual ee (%)[a]	measured ee (%)	absolute error %
	10.0	8.4	1.6
	20.0	20.7	0.7
	30.0	32.6	2.6
	40.0	40.6	0.6
	50.0	50.5	0.5

a. Calculated by mixing the appropriate amount of the two enantiomers of the chiral amine.

In addition to 1-phenylethanamine, we also studied the CD responses of **3** toward other chiral amines listed in Figure 3 in the fluorous phase. The CD spectra of **3** in the presence of these chiral amines are shown in Figure 4. All the enantiomers of the chiral amines have generated intense CD signals at λ > 300 nm in PFE.

Figure 3. Structures of various chiral amines tested.

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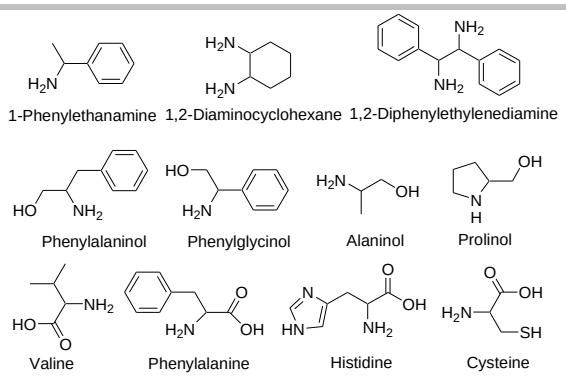
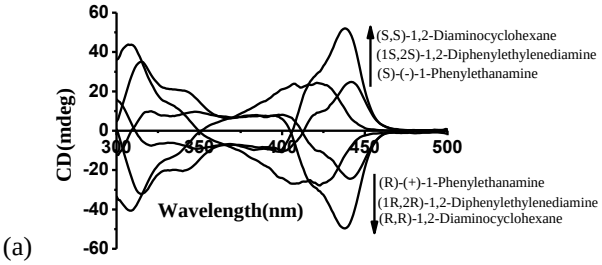
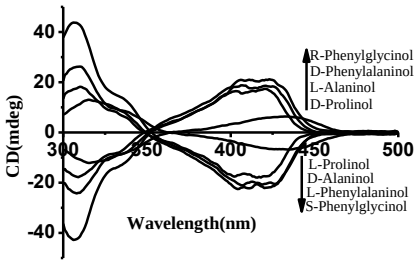


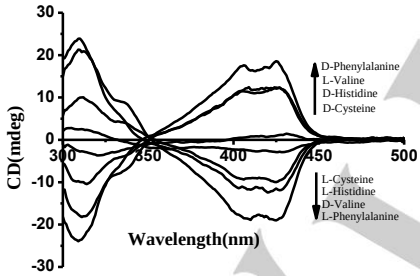
Figure 4. CD spectra of **3** (0.20 mM) with the enantiomers of (a) the monoamines (0.40 mM) in PFE (1.3% CH_2Cl_2) and the diamines (0.12 mM) in PFE (1% MeOH and 0.3% CH_2Cl_2), (b) the amino alcohols (0.40 mM) in PFE (1.3% CH_2Cl_2), and (c) the amino acids (0.4 mM) in PFE (1% MeOH and 0.3 % CH_2Cl_2). (Temperature: 25 ℃)



(a)



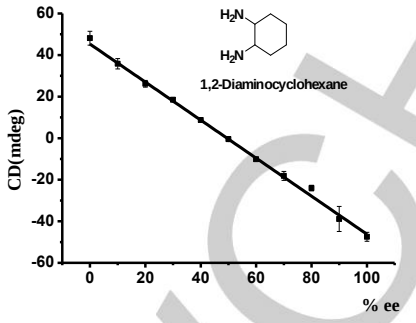
(b)



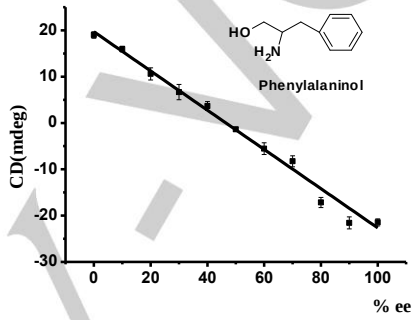
(c)

We studied the CD responses of **3** toward chiral amines of various enantiomeric compositions. As shown in Figure 5, the intensities of the CD signals of **3** at >400 nm are plotted against the ee's of *trans*-1,2-cyclohexanediamine, phenylalaninol and valine which give linear relationships. We have used these plots to determine the ee's of these chiral amines. As the results in Table 2 show, the ee's determined by the CD measurements in the fluorous phase are very close to those the actual ones with the absolute errors < 3%.

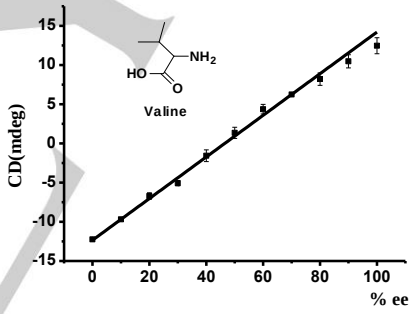
Figure 5. CD intensity of **3** (0.20 mM) (a) at λ = 436 nm versus the ee's of trans-1,2-diaminocyclohexane (0.12 mM) in PFE (1% MeOH and 0.3% CH_2Cl_2), (b) at λ = 424 nm versus the ee's of phenylalaninol (0.40 mM) in PFE (1.3% CH_2Cl_2), and (c) at λ = 426 nm versus the ee's of valine (0.40 mM) in PFE (1% MeOH and 0.3% CH_2Cl_2).



(a)

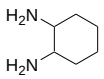
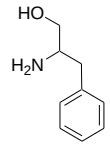
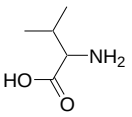


(b)



(c)

Table 2. Determination of the ee's of chiral amines by using the CD assay.

analyte	actual ee (%)[a]	measured ee (%)	absolute error (%)
 *trans*	10.0	10.4	0.4
	20.0	20.9	0.9
	30.0	29.3	0.7
	40.0	40.0	0.0
	50.0	50.0	0.0
	10.0	8.9	1.1
	20.0	21.5	1.5
	30.0	30.8	0.8
	40.0	37.9	2.1
	50.0	49.8	0.2
	10.0	10.0	0.0
	20.0	21.2	1.2
	30.0	27.4	2.6
	40.0	40.6	0.6
	50.0	51.6	1.6

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a. Calculated by mixing the appropriate amount of the two enantiomers of the chiral amine.

Conclusion

A naphthalene-based salicylaldehyde derivative containing highly fluorinated alkyl substituent has been designed and synthesized. This compound is soluble in a fluorous solvent. Intense CD signals at wavelengths greater than 400 nm are observed when this compound is treated with various chiral amines in the fluorous solvent. It can be used to determine the enantiomeric composition of chiral amines, amino alcohols and amino acids. This work represents the first example for the use of a CD sensor in the fluorous phase. Using the fluorous phase-based chiral assay could greatly reduce the interference of other components in the analysis of asymmetric reaction mixtures.

Experimental Section

General Data. Perfluorohexyl ethanol was purchased from Shang Fluoro. All the other chemicals were purchased from Sigma Aldrich Chemical Co. or Alfa Aesar. The amines and amino alcohols were purified before CD measurements. Other chemicals were used without further purification. NMR spectra were obtained with Agilent 400-MR DD2. CD spectra were obtained with the spectrometer by Applied Photophysics. High resolution mass spectroscopic analysis was conducted by using a Shimadzu Corporation LCMS-IT-TOF instrument. All the solvents were either HPLC- or spectroscopic-grade in the optical spectroscopic studies.

Preparation and Characterization of Compound 3. (1) Under argon, 6-bromo-2-naphthol (5.0 g, 21.7 mmol) was dissolved in anhydrous tetrahydrofuran. The solution was cooled to -78 ℃. After 30 min, n-BuLi (33.0 mmol, 2.5 M in hexane, 13 mL) was added dropwise and the mixture was stirred for 1 h. Isopropoxyboronic acid pinacol ester (8.1 g, 43.4 mmol) was then added dropwise still at -78 ℃. After 30 min of stirring at this temperature, the reaction mixture was warmed up to room temperature and further stirred for 1 h. Then, the solvent was removed under vacuum and water (20 mL) was added to the residue. Ethyl acetate (50 mL x 2) was added to extract the aqueous solution, and the organic solution was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with ethyl acetate/petroleum ether (1/4) to afford **1** as a white solid in 25% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.78 (t, J = 7.9 Hz, 2H), 7.65 (d, J = 8.2 Hz, 1H), 7.13 (m, 2H), 5.57 (s, 1H), 1.39 (s, 12H). (2) Under argon atmosphere, compound **1** (0.30 g, 1.1 mmol) and 1-(perfluorooctyl)-2-iodoethane (0.98 g, 1.65 mmol) were dissolved in DME (5 mL) which was combined with $Pd(PPh_3)_4$ (64 mg, 5 mol %) and K_2CO_3 (10 mL, 2 M). The mixture was heated at reflux for 5 h and cooled to room temperature. Ethyl acetate (20 mL) and water (10 mL) were added. The organic layer was separated and washed with water and brine, then dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel eluted with ethyl acetate/dichloromethane (1/20) to afford **2** as a yellow solid in 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.59 (s, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.13 (dt, J = 8.8, 4.9 Hz, 2H), 4.99 (s, 1H), 3.04 (m, 2H), 2.45 (m, 2H). (3) A solution of $TiCl_4$ (0.20 g, 1.06 mmol) and dichloromethyl ether (0.060 g, 0.53 mmol) in anhydrous dichloromethane (1.0 mL) was stirred at 0 ℃ for 15 min. A solution of compound **2** (0.30 g, 0.53 mmol) in anhydrous dichloromethane (2.0 mL) was added dropwise, and the resulting mixture was warmed up to room temperature. The reaction was allowed to stir for 12 h and then quenched with the addition of 1 N HCl (5.0 mL). The aqueous layer was extracted with dichloromethane (3 × 20 mL), and the organic layers were then combined, dried with Na_2SO_4, and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel eluted with dichloromethane /petroleum ether (5/1) to afford **3** as an off yellow solid in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.09 (s, 1H), 10.80 (s, 1H), 8.33 (d, J = 8.6 Hz, 1H), 7.96 (d, J = 9.1 Hz, 1H), 7.64 (s, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 9.1 Hz, 1H), 3.10 (t, J = 8.3 Hz, 2H), 2.46 (m, 2H). ^{13}C NMR (101MHz, $CDCl_3$) δ 193.03, 164.57, 138.48, 135.11, 131.50, 129.58, 128.19, 127.89, 119.50, 119.11, 111.11, 76.84, 76.52, 32.87 (d, J = 22.5 Hz), 32.65, 32.42, 31.26, 30.03, 29.54, 25.99. ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.75 (t, J = 9.9 Hz, 2F), -114.45 (t, J = 13.3 Hz, 2F), -121.86 (d, J = 89.0Hz, 7F), -122.69 (s, 2F), -123.39 (s, 2F), -126.05 (m, 2F). HRMS Calcd for $C_{21}H_{11}F_{17}O_2$-H^+: 617.0409, Found: 617.0423.

Procedure for the preparation of the samples for CD measurements. Compound **3** was purified by column chromatography followed by recrystallization. Stock solutions of **3** were freshly prepared at 0.2 mM in PFE (0.3 CH_2Cl_2) for each measurement. For 1,2-diaminocyclohexane and 1,2-diphenylethylenediamine, 0.012 M stock solutions were freshly prepared in methanol. For monoamines and amino alcohols, 0.04 M stock solutions were freshly prepared in CH_2Cl_2. For amino acids, 0.04 M stock solutions were freshly prepared in methanol with 120 μL tetrabutylammonium hydroxide (1 M). In the measurements, a sensor solution in PFE was mixed with the amines, amino alcohols or amino acids solution in methylene chloride or methanol on a shaking table at 25 ℃. The mixtures containing 1.3% CH_2Cl_2 in PFE formed a stable homogeneous solution after manual shaking. The resulting solution was allowed to shake for 5 h before measurement.

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Keywords: highly fluorinated sensor, circular dichroism,·fluorous phase, chiral amines, salicylaldehyde derivative

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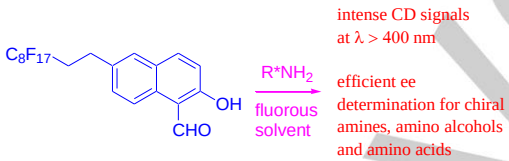

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