Enhanced Enantioselectivity in the Fluorescent Recognition of a Chiral Diamine by Using a Bisbinaphthyl Dialdehyde

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Supporting Information

ABSTRACT: A bisbinaphthyl dialdehyde shows greatly enhanced enantioselective fluorescent response (ef = 10.0) in the fluorescent recognition of a chiral diamine, 1,2-diphenylethylenediamine, over a previously reported monobinaphthyl dialdehyde (ef = 1.1). This compound can be used to determine the enantiomeric composition of the diamine by fluorescence measurement. The NMR and mass spectroscopic studies have demonstrated that the chirality matched reaction of the bisbinaphthyl dialdehyde with the diamine in the presence of Zn(OAc)₂ favors the formation of a macrocyclic product more than the chirality mismatched. This enantioselective cyclocondensation should contribute to the observed highly enantioselective fluorescent response because the macrocyclic Zn(II) complex is proposed to give much greater fluorescence enhancement than the acyclic ones.

INTRODUCTION

Study of the enantioselective fluorescent response of chiral organic compounds is both fundamentally interesting and potentially useful.¹⁻³ For example, an enantioselective fluorescent sensor could provide an analytical method to rapidly assess the enantiomeric composition of a chiral compound, which can facilitate the high throughput screening of asymmetric reactions. In the past 2 decades, a significant amount of research has been conducted in this area and a number of sensitive as well as enantioselective fluorescent probes have been obtained for the recognition of various chiral substrates.¹⁻³ In 2014, we reported the discovery that the 1,1′-bi-2-naphthol (BINOL)-based dialdehyde (S)-1 in combination with Zn(OAc)₂ exhibits highly enantioselective fluorescent enhancement in the presence of a number of chiral functional amines.⁴ However, when (S)-1+Zn(OAc)₂ is used to interact with 1,2-diphenylethylenediamine (2), there is little enantioselectivity in the observed fluorescence enhancement (Figure S4). Chiral diamines have been extensively used in the preparation of chiral ligands for asymmetric catalysis. Fluorescent probes for the enantioselective recognition of chiral diamines will be useful for the synthesis and analysis of these compounds. In order to improve the enantioselectivity in the fluorescent recognition of the chiral diamine, we have studied the use of a bisBINOL-based aldehyde and found greatly enhanced enantioselectivity in the fluorescent recognition of 2. Herein, this result is reported.

RESULTS AND DISCUSSION

Scheme 1 shows the method we have developed for the synthesis of a bisBINOL aldehyde. From the reaction of (S)-BINOL₄ (S)-1

Scheme 1. Synthesis of the BisBINOL Aldehyde

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3, with MOMBr \((\text{MOM} = \text{CH}_3\text{OCH}_2)\) in the presence of disopropylethylamine (DIPEA), the mono-MOM-protected compound \((S)-4\) was obtained in 81% yield. Treatment of \((S)-4\) with excess \(^{6}\text{BuLi}\) at 0 °C followed by warming up to room temperature and addition of DMF gave the aldehyde product \((S)-5\) in 62% yield. Reaction of \((S)-5\) with 1,4-dibromobutane in the presence of \(\text{K}_2\text{CO}_3\) in refluxing acetonitrile followed by deprotection with concentrated HCl gave the desired bisBINOL product \((S)-6\) in 85% yield.5

We studied the fluorescent response of \((S)-6\) toward the two enantiomers of the chiral diamine \((R,R)-\) and \((S,S)-2\) in the presence of \(\text{Zn(OAc)}_2\) in DMSO solution. Compound \((S)-6\) in DMSO showed a weak emission signal at \(\lambda = 499\) nm. When it was treated with \(\text{Zn(OAc)}_2\) (1.0 equiv), almost no change was observed. However, addition of \((R,R)-2\) (2 equiv) to the solution of \((S)-6 + \text{Zn(OAc)}_2\) generated large fluorescence enhancement at \(\lambda = 552\) nm (Figure 1a). When \((S,S)-2\) was used, the fluorescence enhancement was much smaller than the use of \((R,R)-2\). The enantiomeric fluorescence enhancement ratio \((ef)\) is 10.0 (ef = \([I_{RR} - I_0]/[I_{SS} - I_0]\)). \(I_C\): fluorescence intensity of the sensor \((S)-6 + \text{Zn(OAc)}_2\), \(I_{RR}\) and \(I_{SS}\): fluorescence intensity in the presence of \((R,R)-\) and \((S,S)-2\). Thus, \((S)-6\) exhibits excellent enantioselectivity in the fluorescent recognition of this chiral diamine, which is greatly enhanced over that of the monoBINOL aldehyde \((S)-1\) \((ef = 1.1)\). Figure 1b shows that the enantioselective fluorescent response of \((S)-6 + \text{Zn(OAc)}_2\) at \(\lambda = 552\) nm maintains while the equivalences of \((R,R)-\) and \((S,S)-2\) increase.

We prepared the bisBINOL compound \((R,R)-\), the enantiomer of \((S)-6\), from \((R,R)-\)-BINOL. It was found that \((S,S)-2\) enhanced the fluorescence of \((R)-6 + \text{Zn(OAc)}_2\) much greater than \((R,R)-2\) (Figure S6). This mirror-image relationship between the fluorescence responses of \((R)-6\) and \((S)-6\) confirms the observed enantioselective recognition.

The fluorescence response of \((S)-6 + \text{Zn(OAc)}_2\) toward 2 at various enantiomeric composition was studied. As shown in Figure 2, as the amount of \((R,R)-2\) increases in the mixture of \((R,R)-2\) and \((S,S)-2\), the fluorescence intensity of \((S)-6 + \text{Zn(OAc)}_2\) at \(\lambda = 552\) nm increases. This demonstrates that this sensor system can be used to determine the enantiomeric composition of the chiral diamine.

In order to gain a better understanding of the highly enantioselective fluorescent response of \((S)-6\), we studied the \(^1\text{H}\) NMR spectrum of \((S)-6\) upon treatment with \(\text{Zn(OAc)}_2\) and \((R,R)-\) and \((S,S)-2\). As shown in Figure 3, when \((S)-6\) was treated with \(\text{Zn(OAc)}_2\) (1.0 equiv), the \(^1\text{H}\) NMR signals became a little broader but have no significant change in the peak positions except the disappearance of the hydroyl signal of \((S)-6\) at \(\delta = 10.05\) probably because of faster acidic proton exchange. Addition of \((R,R)-2\) (2 equiv) led to continuous reduction of the aldehyde signal at \(\delta = 10.17\) over time, which was accompanied by the growing of a new peak at \(\delta = 8.93\). This new peak can be assigned to an imine proton formed from the condensation of the amine groups of \((R,R)-2\) with the aldehyde groups of \((S)-6\). After 3 h, the aldehyde peak of \((S)-6\) almost completely disappeared, indicating the complete condensation of the aldehyde groups of \((S)-6\) with the diamine.

The mass spectrum of the above product mixture of \((S)-6\), \(\text{Zn(OAc)}_2\) (1 equiv) and \((R,R)-2\) (2 equiv) was obtained (Page S8 in Supporting Information). The base peak at \(m/z = 859.35\) was observed, which can be attributed to that of the macrocyclic product 7 (calcld for \(7 + \text{H}: 859.35\)) formed from the condensation of both of the aldehyde groups of \((S)-6\) with the two amine groups of \((R,R)-2\). A significant peak at \(m/z = 921.40\) was found for the Zn-complex 8 (calcld for \(8 + \text{H}: 921.27\)).
The 1H NMR spectra of (S)-6 with Zn(OAc)$_2$ and (S,S)-2 were also obtained. As shown in Figure 4, the reaction of (S)-6 with Zn(OAc)$_2$ was much less favorable. There was a significant amount of the aldehyde signals remained after 2–12 h of reaction. The mass spectrum of this reaction mixture gave the base peak at m/z = 877.37, which is attributed to that of 9 (calcd for 9 + H: 877.36) formed from the reaction of only one of the aldehyde groups of (S)-6 with the diamine (Page S9 in Supporting Information). Signals corresponding to compounds such as 7 and 8 were also observed but at lower intensities than that of 9. Thus, the condensation of (S)-6 with (S,S)-2 to form the macroyclic product 7 and 8 is not as efficient as that with (R,R)-2, which can be attributed to a mismatched chiral conformation between the two compounds. That is, the chiral configurations of the amino unit and the BINOL units in 9 can strongly influence its intramolecular condensation to form the corresponding macrocycle.

![Image of chemical structures]

On the basis of the above NMR and mass spectroscopic analyses, we can propose the following explanation for the observed enantioselective fluorescent recognition of the chiral diamine by the bisBINOL sensor. When (S)-6 is treated with (R,R)-2 and Zn(OAc)$_2$, formation of the macrocyclic Zn(II) complex 8 is observed. Coordination of the imine nitrogens of 8 with the Zn(II) center can inhibit the excited state proton transfer between the hydroxyl group and the imine nitrogen as well as the excited state isomerization of the imine double bond, both of which can enhance the fluorescence of the compound. In addition, the rigidity of the macrocycle structure of 8 should play a very important role for the greatly enhanced fluorescence. In contrast, when (S)-6 is treated with (S,S)-2, the opposite enantiomer of the diamine, much lower fluorescence enhancement was observed, which could be attributed to the less-favorable cyclocondensation of 9 to form 7 and 8. That is, the mismatched chiral configuration of (S)-6 with (S,S)-2 is not as favorable as that with (R,R)-2 for the formation of the macrocycle.

In conclusion, we have discovered that the bisBINOL aldehyde (S)-6 shows greatly enhanced enantioselectivity in the fluorescent recognition of a chiral diamine over the monoBINOL aldehyde (S)-1. This compound can be used to determine the enantiomeric composition of the diamine by fluorescence measurement. The NMR and mass spectroscopic studies have revealed that the reaction of (S)-6 with the chiral diamine to form a macrocyclic product is enantioselective, which leads to the enantioselective fluorescent response. This study provides new insight to design enantioselective fluorescent sensors.

### EXPERIMENTAL SECTION

**General Data.** All reactions were carried out under N$_2$ unless otherwise noted. All chemicals were purchased from Sigma-Aldrich Chemical Co. or Alfa Aesar. HPLC grade DMSO was used without purification. NMR spectra were obtained on a Varian-600 MHz spectrometer. A Horiba FluoroMax-4 spectrofluorometer was used to acquire the steady-state fluorescence emission spectra. The University of Illinois at Urbana-Champaign (UIUC) Synapt G2SiMass Spectrometry Facility was used to acquire the high and low resolution mass spectra.

**Synthesis and Characterization of Compounds (S)-6.**

1. To a solution of (S)-3 (2.86 g, 10 mmol) in CH$_2$Cl$_2$ (30 mL), DIPEA was added (2.84 g, 22 mmol) at 0 °C, and the mixture was stirred for 3 h. Then, bromomethyl methyl ether (1.87 g, 15 mmol) was added at 0 °C and stirred for 30 min at the same temperature. The reaction was quenched by addition of 2 M-HCl at 0 °C and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluted with hexane/acetone (20/1) to give (S)-4 as a white solid in 81% yield. (2) Under nitrogen, n-BuLi (4.2 mL, 10.5 mmol, 2.5 M solution in hexanes) was added dropwise into a solution of (S)-4 (990 mg, 3.0 mmol) in anhydrous tetrahydrofuran (THF; 40 mL) at 0 °C. The resulting mixture was stirred at room temperature for 2 h, and then, DMF (4.5 mmol, 0.36 mL) was added dropwise. After stirred for 3 h, the reaction was quenched with saturated aqueous NH$_4$Cl, and extracted with methylene chloride. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluted with hexane/acetone (10/1) to give (S)-5 as a yellow solid in 62% yield. (3) To a solution of (S)-5 (895 mg, 2.5 mmol) in acetonitrile (30 mL), K$_2$CO$_3$ (828 mg, 6 mmol) and 1,4-dibromobutane (215 mg, 1 mmol) were added. The mixture was...
heated and stirred at reflux for 24 h. The solvent was then evaporated, and the residue was extracted with ethyl acetate. After removal of ethyl acetate, the combined organic extracts were dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluted with hexane/acetone (5/1) to give a yellow solid in 75% yield. This compound was then dissolved in THF (25 mL), to which concentrated aqueous HCl (32 w/w %, 5.0 mL) was added at 0 °C. After the reaction mixture was stirred at room temperature for 3 h, the solvent was removed under vacuum. The residue was dissolved in methylene chloride, which was washed with saturated aqueous NaHCO3 and dried over anhydrous Na2SO4. After filtration and concentration under vacuum, the residue was purified by flash column chromatography on silica gel eluted with hexane/acetone (5/1) to give (S)-6 as a yellow solid in 85% yield (725 mg). 1H NMR (600 MHz, DMSO-d6) δ 10.23 (s, 2H), 10.06 (s, 2H), 8.51 (s, 2H), 8.02−8.00 (m, 4H), 7.94−7.93 (m, 2H), 7.34−7.29 (m, 8H), 7.23−7.21 (m, 2H), 6.95−6.93 (m, 2H), 6.81−6.79 (m, 2H), 3.65−3.58 (m, 4H), 0.98−0.91 (m, 4H). HRMS (TOF ES+): calcd for C46H34O6 (M+), 683.2434; found, 683.2427. mp 197 °C.

**Preparation of Samples for NMR Measurements.** Stock solutions of 5 mM (S)-1 or (S)-6 and 10 mM 1,2-diphenylethlenediamine in DMSO and 5 mM Zn(OAc)2 in H2O were freshly prepared for each measurement. In the fluorescence enhancement study, the 1,2-diphenylethylenediamine and Zn(OAc)2 solutions with the designated equivalents were added to a 5 mL test tube, which was followed by the addition of the (S)-1 or (S)-6 stock solution. The total volume was maintained at 1 mL with the use of additional DMSO. After the solution was allowed to react at room temperature for 3 h, it was diluted to 5 mL with the addition of DMSO, unless otherwise noted.

**Preparation of Samples for NMR Measurements.** Stock solutions of 5.0 mM (S)-6 and 10.0 mM 1,2-diphenylethlenediamine in DMSO-d6 and 5.0 mM Zn(OAc)2 in D2O were freshly prepared for NMR measurement. In the NMR study, the 1,2-diphenylethylenediamine (2.0 equiv) and Zn(OAc)2 (1.0 equiv) solutions were combined in a NMR tube to which the solution of (S)-6 (1.0 equiv) was added.

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**REFERENCES**

1. (a) Pu, L. Fluorescence of Organic Molecules in Chiral Recognition. *Chem. Rev.* 2004, 104, 1687−1716. (b) Accetta, A.; Corradini, R.; Marchelli, R. Enantioselective sensing by luminescence. *Top. Curr. Chem.* 2010, 300, 175−216. (c) Zhang, X.; Yin, J.; Yoon, J. Recent Advances in Development of Chiral Fluorescent and Colorimetric Sensors. *Chem. Rev.* 2014, 114, 4918−4959. (d) You, L.; Zha, D.; Anslyn, E. V. Recent Advances in Supramolecular Analytical Chemistry Using Optical Sensing. *Chem. Rev.* 2015, 115, 7840−7892.

2. (a) James, T. D.; Samankumara Sandanayake, K. R. A.; Shinkai, S. Chiral discrimination of monosaccharides using a fluorescent molecular sensor. *Nature* 1995, 374, 345−347. (b) Pugh, V. J.; Hu, Q.-S.; Pu, L. The First Dendrimer-Based Enantioselective Fluorescent Sensor for the Recognition of Chiral Amino Alcohols. *Angew. Chem., Int. Ed.* 2000, 39, 3638−3641. (c) Lin, J.; Hu, Q.-S.; Xu, M.-H.; Pu, L. A Practical Enantioselective Fluorescent Sensor for Mandelic Acid. *J. Am. Chem. Soc.* 2002, 124, 2088−2089. (d) Zhao, J.; Fyles, T. M.; James, T. D. Chiral Binol-Bisboronic Acid as Fluorescent Sensor for Sugar Acids. *Angew. Chem., Int. Ed.* 2003, 42, 3461−3464. (e) Zhu, L.; Anslyn, E. V. Facile Quantification of Enantiomeric Excess and Concentration with Indicator-Displacement Assays: An Example in the Analyses of α-Hydroxycids. *J. Am. Chem. Soc.* 2004, 126, 3676−3677. (f) Mei, X.; Wölf, C. Enantioselective Sensing of Chiral Carboxylic Acids. *J. Am. Chem. Soc.* 2004, 126, 14736−14737.

3. (a) Pu, L. Enantioselective Fluorescent Sensors: A Tale of BINOL. *Acc. Chem. Res.* 2012, 45, 150−163. (b) Pu, L. Simultaneous Determination of Concentration and Enantiomeric Composition in Fluorescent Sensing. *Acc. Chem. Res.* 2017, 50, 1032−1040.

4. (a) Huang, Z.; Yu, S.; Wen, K.; Yu, X.; Pu, L. Zn(II) promoted dramatic enhancement in the enantioselective fluorescent recognition of functional chiral amines by a chiral aldehyde. *Chem. Sci.* 2014, 5, 3457−3462.

5. This method improves a previous synthesis and no study on using (S)-6 for fluorescent sensing was reported before: Li, Z.-B.; Pu, L. Synthesis of a new bishinaphthyl macrocycle for enantioselective fluorescent recognition. *J. Mater. Chem. B* 2015, 3, 2860−2864.

6. (a) Barbara, P. F.; Rentzepis, P. M.; Brus, L. E. Photophysical kinetics of salicylideneaniline. *J. Am. Chem. Soc.* 1980, 102, 2786−2791. (b) A review: Formosinho, S. J.; Arnaut, L. G. Excited-state proton transfer reactions II. Intramolecular reactions. *J. Photochem. Photobiol., A* 1993, 75, 21−48.

7. Xu, Z.; Yoon, J.; Spring, D. R. Fluorescent chemosensors for Zn(II). *Chem. Soc. Rev.* 2010, 39, 1996−2006.