Tetrahedron Letters 50 (2009) 5853–5856

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Highly enantioselective fluorescent sensor for chiral recognition of amino acid derivatives

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ARTICLE INFO

Article history:
Received 1 July 2009
Revised 4 August 2009
Accepted 6 August 2009
Available online 9 August 2009

Keywords:
Enantioselective
Fluorescent Sensors
Amino acid derivatives
Binaphthyl derivatives

ABSTRACT

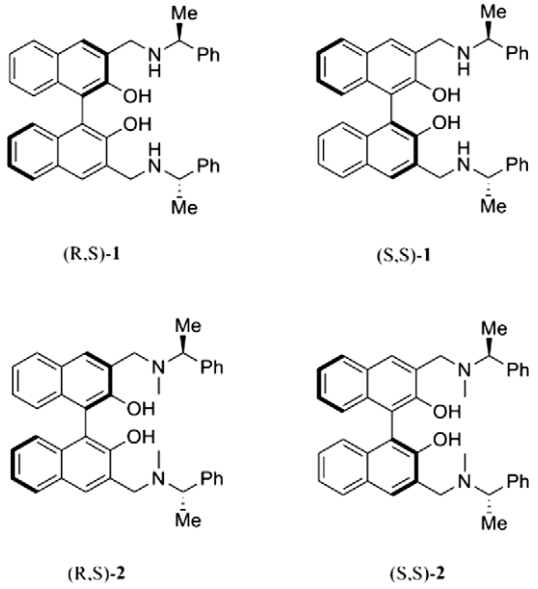
A highly enantioselective fluorescent sensor, containing benzylaminomethyl groups at 3,3′-position of 1,1′-bi-2-naphthol (BINOL), has been used to conduct the chiral recognition of α-amino acid derivatives. It is observed that one enantiomer of *N*-Boc-proline can increase the fluorescence intensity of the binaphthyl fluorophores by over 57-fold, while the other enantiomer can cause only sixfold fluorescence enhancement. Such unusually highly enantioselective response demonstrates that this sensor is potentially useful in the enantioselective recognition of amino acid derivatives.

Molecular recognition, especially chiral recognition, is one of the most fundamental and crucial properties of various natural systems.[1] It is of particular significance for understanding the interactions of biological molecules and for the designing of asymmetric catalysis systems.[2] With the increasingly successful application to smart artificial systems, chiral recognition which is a broader and more commonly used 'tool' for academic research and industry[3] has gained greater scientific maturity.

Amino acids and their derivatives play an important role in a wide variety of biological processes.[4] A number of studies based on various analytical methods for chiral amino acids recognition have been reported, such as capillary electrophoresis,[5] HPLC,[6] absorption spectrometry,[7] and electrochemistry.[8] Fluorescence spectroscopy has only limited reports on chiral amino acid recognition.[9] In 2000, Corradini and co-workers prepared the α-cyclodextrin-based sensor molecules, which could be enantioselective for Pro, Phe, and Trp.[10] Then, Pu and co-workers synthesized and investigated the binaphthol derivatives in the fluorescent recognition of amino acid derivatives.[11] In 2007, our group reported that compounds (*R*,*S*)-**1** and (*R*,*S*)-**2** acted as excellent agents for asymmetric catalysis.[12]

Herein, we describe that compound (*R*,*S*)-**1** shows high enantioselectivity in the fluorescent recognition of a series of amino acid derivatives. Our initial work began with the interaction of the sensor (*R*,*S*)-**1** (Scheme 1) and *N*-Boc-proline (**3**). Recognition **3** was carried out in solutions such as CH_3CN, THF, and MeOH, and no enantioselectivity could be found. Although CH_2Cl_2 was used as the solvent, there was a slight discrimination between *D*-**3** and *L*-**3**.

Then, chiral recognition was investigated under the condition of CH_2Cl_2/hexane (3:7) containing 1.2% THF. THF was added to improve the solubility of **3**. And adding 20% THF had little influence on the whole chiral recognition system. The sensor (*R*,*S*)-**1** was



Scheme 1. Structure of chiral sensors.

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doi:10.1016/j.tetlet.2009.08.006

emitted at a short wavelength of 365 nm and a long wavelength of 434 nm on excitation at 278 nm. To our delight, it showed highly enantioselective fluorescent response to **3** (Fig. 1) at the short wavelength emission band. As showin in Figure 1, the enantiomer *L*-**3** (2×10^{-2} M) enhanced the fluorescence intensity of (*R*,*S*)-**1** 10.4 times more than *D*-**3** (2×10^{-2} M) did, that is, ef = 10.4[11b] (ef: enantiomeric fluorescence difference ratio = $(I_L - I_0)/(I_D - I_0)$, where I_0 is the fluorescence intensity of the receptor, I_D and I_L are the fluorescence intensities of the receptor in the presence of *D*-**3** or *L*-**3**). In addition, (*R*,*S*)-**2** and (*S*,*S*)-**2** were synthesized and used as sensors. Both *L*-**3** and *D*-**3** were found to enhance the fluorescence of (*R*,*S*)-**2** under optimized conditions. But the fluorescence enhancement did not indicate any enantioselectivity.

This result of the chiral recognition arose from three main factors: First, it was quite logical to infer from these experiments that the characteristic enantioselective fluorescence enhancement by the sensor molecule owed its origin to –NH group of sensors and –COOH group of *N*-Boc-amino acids. When –H was taken place by $-CH_3$, it was more difficult for *N*-Boc-amino acids to complex well with the sensor (*R*,*S*)-**2** due to the steric hindrance effect. Second, high polar solution was not favorable for the hydrogen bond formation between sensor and *N*-Boc-amino acids. So, low polar solution was crucial for chiral recognition. Therefore, it was essential that hydrogen bonding interaction contributes for chiral recognition. Third, compound (*R*,*S*)-**1** contained nitrogen atoms adjacent to the naphthyl rings. And the lone pair of electrons of the nitrogen atom was available for photoinduced-electron-transfer (PET)[13] quenching of naphthyl rings. Similarly, the nitrogen atom in amino acids also quenches the fluorescence of the fluorophore. So we introduced the *N*-protecting group into the amino acids to suppress PET quenching.[11b] In the presence of *L*-**3** or *D*-**3**, (*R*,*S*)-**1** exhibited significant fluorescence enhancement owing to the suppressed PET quenching when the acidic proton of *N*-Boc-amino acid interacted with the nitrogen which (*R*,*S*)-**1** contained. Since the interaction of the sensor with the two enantiomers of *N*-Boc-proline would generate two diastereomers, different fluorescence enhancements occurred. Because there was the special cycle structure in *N*-Boc-proline which encouraged the interaction between sensors and *N*-Boc-proline, the result was excellent.

The effect of various concentrations of *D*-**3** or *L*-**3** on the fluorescence of (*R*,*S*)-**1** at 365 nm was investigated (Fig. 2). The error bars shown in Figure 2 were obtained by four independent measurements. These experiments demonstrated that the concentration ranged from 3×10^{-3} M to 2×10^{-2} M, and that the fluorescence

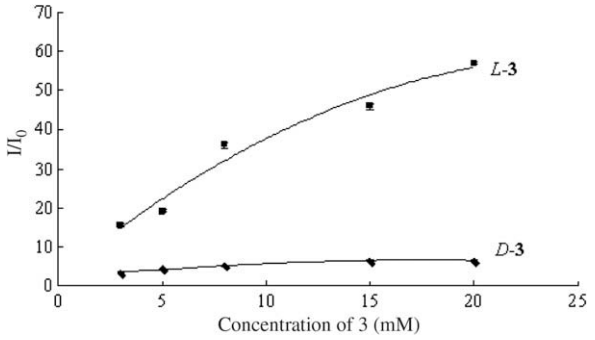

Figure 2. Fluorescence intensity change of (*R*,*S*)-**1** (1×10^{-4} M in CH_2Cl_2/hexane (3:7), containing 1.2% THF) versus concentration of *D*-**3** and *L*-**3**.

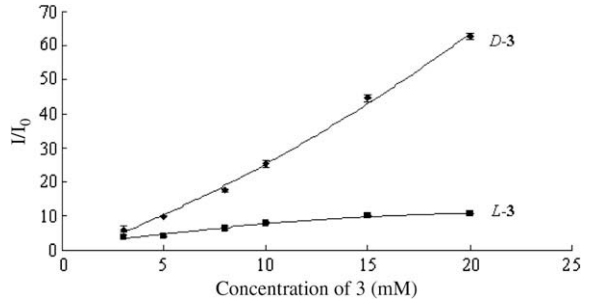

Figure 3. Fluorescence intensity change of (*S*,*S*)-**1** (1×10^{-4} M in CH_2Cl_2/hexane (3:7), containing 1.2% THF) versus concentration of *D*-**3** and *L*-**3**.

intensity was enhanced. While *L*-**3** led to 16–57-fold increase in the fluorescence intensity of (*R*,*S*)-**1**, *D*-**3** caused little change in the fluorescence. Thus, the sensor (*R*,*S*)-**1** proved to be highly enantioselective toward **3**.

Then we changed the axial chirality of the naphthyl rings and studied the interaction of (*S*,*S*)-**1** with *D*-**3** or *L*-**3**. As expected, we noted a 'reverse image' relationship between the fluorescence enhancement of (*R*,*S*)-**1** and (*S*,*S*)-**1** in the presence of *N*-Boc-proline. And the ef observed for the interaction of (*S*,*S*)-**1** and **3** (ef = 6.6) was not as high as that observed for the interaction of (*R*,*S*)-**1** and **3** (ef = 10.4) under the same conditions. The error bars shown in Figure 3 were obtained by four independent measure-

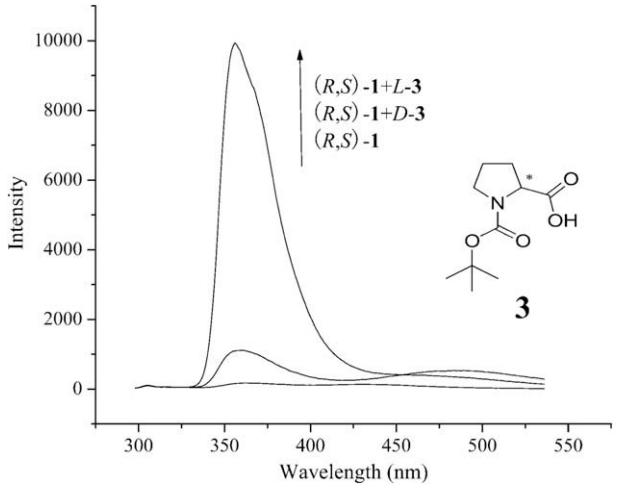

Figure 1. Fluorescence spectra of (*R*,*S*)-**1** (1×10^{-4} M in CH_2Cl_2/hexane (3:7), containing 1.2% THF) with/without *D*-**3** and *L*-**3** (2×10^{-2} M) (λ_{exc} = 278 nm, emission slits = 5.0 nm).

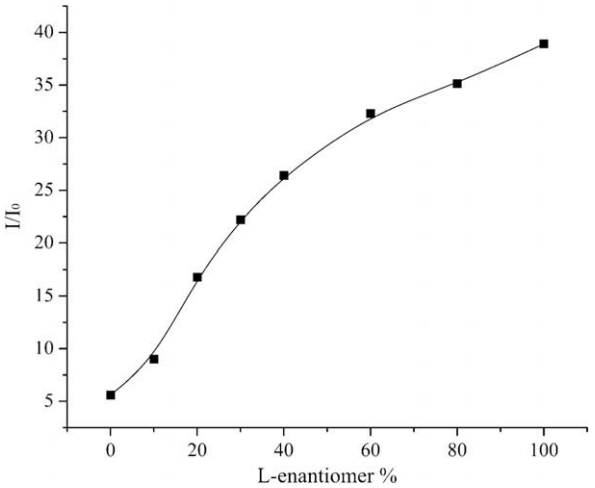

Figure 4. Fluorescence enhancement of (*R*,*S*)-**1** (1×10^{-4} M in CH_2Cl_2/hexane (3:7), containing 1.2% THF) versus the enantiomeric composition of **3** (8×10^{-3} M).

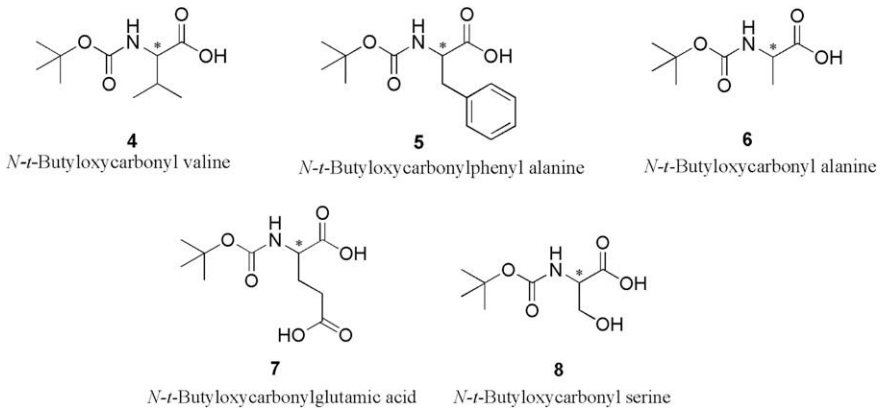

Figure 5. Structures of the amino acid derivatives **4**–**8**.

Table 1
Results for the enantioselective fluorescent responses of (*R*,*S*)-**1** (5×10^{-5} M) to the chiral amino acid derivatives **3**–**8**

Compound	Sensor	Solvent	Concentration (M)	Ef
3	(*R*,*S*)-**1**	CH_2Cl_2/hexane (3:7) containing 1.2% THF	2×10^{-2}	10.4
4	(*R*,*S*)-**1**	CH_2Cl_2/hexane (3:7)	5×10^{-3}	7.9
5	(*R*,*S*)-**1**	CH_2Cl_2/hexane (3:7)	8×10^{-3}	4.0
6	(*R*,*S*)-**1**	CH_2Cl_2/hexane (3:7)	8×10^{-3}	2.5
7	(*S*,*S*)-**1**	CH_2Cl_2/hexane (3:7) containing 4% THF	8×10^{-3}	2.3
8	(*R*,*S*)-**1**	CH_2Cl_2/hexane (3:7) containing 4% THF	8×10^{-3}	1.4

ments with the concentration ranging from 3×10^{-3} M to 2×10^{-2} M. This was confirmed by the enantioselective response of (*S*,*S*)-**1** and (*R*,*S*)-**1** towards the enantiomers of the **3**. And the axial chirality of naphthyl rings was considered to recognize chiral amino acid derivatives. The fluorescence intensity change of (*R*,*S*)-**1** with respect to the enantiomeric composition of **3** was investigated. As shown in Figure 4, the fluorescence intensity of (*R*,*S*)-**1** increased with the increasing *L*-component of **3**. Therefore, (*R*,*S*)-**1** might be used as a fluorescent sensor to readily determine the enantiomeric composition of **3**. Further investigation of the interaction of (*R*,*S*)-**1** or (*S*,*S*)-**1** with other *N*-Boc-amino acids **3**–**8** (Fig. 5) was performed. Table 1 summarizes the highest ef which was observed for the interaction of (*R*,*S*)-**1** or (*S*,*S*)-**1** with the two enantiomers of these *N*-Boc-amino acids. All these compounds enhanced the fluorescence of the binaphthyl fluorophore, respectively. Amino acid **7** showed the opposite enantioselective response to that of others.

In conclusion, we have developed a highly enantioselective fluorescent sensor for the chiral recognition of *N*-Boc-proline and other amino acid derivatives. It is observed that within a certain concentration range, *L*-*N*-Boc-proline could increase the fluorescence intensity of the sensor (*R*,*S*)-**1** by 16–57-fold, while *D*-*N*-Boc-proline led to only sixfold increase. It could be used in ascertaining the enantiomeric composition of *D*- and *L*-*N*-Boc-proline and in finding analytical applications over a definite concentration range.

General procedure: Materials: The *N*-Boc-proline and *N*-Boc-alanine were synthesized and recrystallized. Other *N*-Boc-amino acids were purchased from Aladdin. Compounds (*R*,*S*)-**1**, (*S*,*S*)-**1**, (*R*,*S*)-**2**, and (*S*,*S*)-**2** were synthesized according to the literature procedure.[12] All the solvents were redistilled. The general preparation procedure for the fluorescent measurement is described below:[11b,14] A mixture solvent stock solution of the chiral compound (*R*,*S*)-**1** was freshly prepared before each measurement. Different concentrations stock solution of the chiral *N*-Boc-amino acid in CH_2Cl_2/ hexane (3:7), containing 1.2% THF, was freshly prepared. Then, the sensor solution was mixed with the *N*-Boc-amino acid solution at room temperature in a 5 mL volumetric flask and diluted to the desired concentration. THF was added to improve the solubility of the *N*-Boc-amino acid. The resulting solution was allowed to stand at room temperature for 3 h and the fluorescence was measured on a Hitachi FL spectrophotometer (F-7000).

Acknowledgments

The authors thank the National Natural Science Foundation of China (No. 20732003). We also thank Sichuan University Analytical & Testing Center for NMR analysis.

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