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Highly Enantioselective Fluorescent Recognition of Serine and Other Amino Acid Derivatives

Hai-Lin Liu,[†] Hu-Ping Zhu,[†] Xue-Long Hou,*[,†,‡] and Lin Pu*[,§]

State Key Laboratory of Organometallic Chemistry, Shanghai-Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling Ling Rd, Shanghai 200032, China, and Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904-4319

xlhou@mail.sioc.ac.cn; lp6n@virginia.edu

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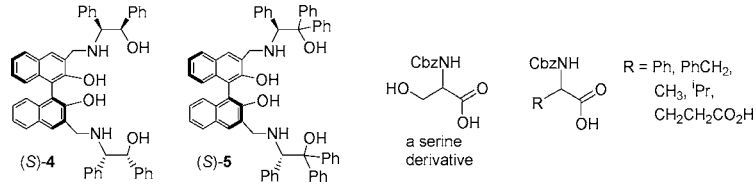
ABSTRACT



The BINOL−amino alcohol compound (*S*)-4 was found to conduct enantioselective fluorescent recognition of a serine derivative with an unprecedented high ef [enantioselective fluorescent enhancement = $(I_D - I_0)/(I_L - I_0)$] of 12.5. Both (*S*)-4 and (*S*)-5 are also found to be highly enantioselective fluorescent sensors for a number of other amino acid derivatives.

Enantioselective fluorescent sensors are potentially useful for real time analysis of the enantiomeric composition of chiral organic compounds, and significant progress has been made in this area in recent years.[1−5] In the fluorescent recognition of chiral carboxylic acids, most of the study has been conducted on sensing α-hydroxycarboxylic acids and α-amino acid derivatives, and a few highly enantioselective sensors have been discovered.[4,5] For example, compounds **2**[5a,b] and **3**[5c] were found to exhibit highly enantioselective fluorescent responses toward a few amino acid derivatives. However, when these sensors are used to interact with **1**, derivatives of the important naturally occurring amino acid serine, only low enantioselectivity was observed.[5b−d] Apparently, the extra β-hydroxyl group of serine made it very different from the other amino acids investigated. This additional hydroxyl group can act as a hydrogen bond

[†] State Key Laboratory of Organometallic Chemistry.
[‡] Shanghai-Hong Kong Joint Laboratory in Chemical Synthesis.
[§] University of Virginia.

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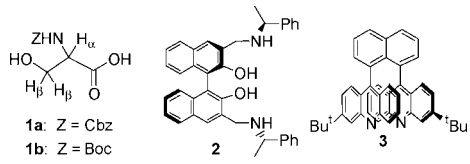
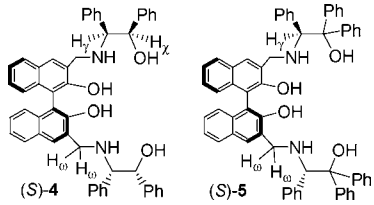


donor and acceptor which might have disturbed the hydrogen bonding interaction between the sensor and the substrate, causing the diminished enantioselectivity.

To improve the enantioselectivity for the recognition of serine and other amino acids, it was proposed to introduce additional hydrogen bond donor or acceptor groups to sensor **2** to enhance the binding with the chirality-matched substrates. Recently, we have synthesized the 1,1′-binaphthol (BINOL)-based amino alcohols (*S*)-**4** and (*S*)-**5** that contain additional hydroxyl groups in comparison with sensor **2**. These compounds were found to be highly enantioselective fluorescent sensors for α-hydroxycarboxylic acids.[6] We have further found that (*S*)-**4** exhibits an unprecedented high enantioselectivity in the fluorescent recognition of the



serine derivative. The additional hydroxyl groups of (*S*)-**4** over **2** have greatly enhanced the enantioselectivity. Herein, the fluorescent recognition of serine and other amino acid derivatives by using the sensors (*S*)-**4** and (*S*)-**5** is reported.

The fluorescence spectra of (*S*)-**4** and (*S*)-**5** in benzene are shown in Figure 1 ("I" in Figures 1−5 stands for fluorescence

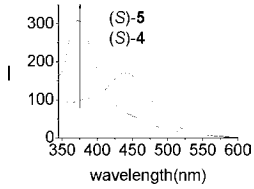


Figure 1. Fluorescence spectra of (*S*)-**4** (λ_{exc} = 341 nm) and (*S*)-**5** (λ_{exc} = 334 nm) (1.0 × 10^{-4} M in benzene, slit = 5.0/5.0 nm).

intensity).[6] In spite of their structural similarity, these two compounds give very different fluorescence spectra. (*S*)-**4** gives predominately excimer emission, but (*S*)-**5** gives predominately monomer emission. This may be due to the increased steric bulkiness of (*S*)-**5** which could reduce the intermolecular interaction to generate the excimer.

When (*S*)-**4** is treated with (*D*)-**1a**, a large fluorescence enhancement at the excimer emission is observed (Figure 2). However, when (*S*)-**4** is treated with the enantiomer (*L*)-

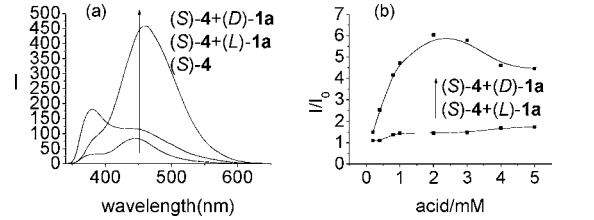


Figure 2. (a) Fluorescence spectra of (*S*)-**4** (5.0 × 10^{-4} M) with (*D*)- and (*L*)-**1a** (2.0 × 10^{-3} M). (b) Fluorescence enhancement of (*S*)-**4** (5.0 × 10^{-4} M) with (*D*)- and (*L*)-**1a** at λ_{em} = 460 nm. (Solvent: benzene/2.5% DME. λ_{exc} = 341 nm, 5.0/5.0 nm.)

1a, very small fluorescence enhancement at the excimer is observed, and the main fluorescence enhancement occurs at the monomer emission. These observations indicate that the binding of (*S*)-**4** with (*D*)-**1a** encourages the association of the excited sensor molecule with the ground state one, leading to the enhanced excimer emission, whereas the binding of (*S*)-**4** with (*L*)-**1a** does not encourage such intermolecular association and only leads to the enhanced monomer emission. In both cases, the fluorescence enhancement could be attributed to the formation of structurally more rigid complexes between the sensor and the acid as well as the protonation of the amine groups of the sensor by the acid to suppress the fluorescence quenching. At the excimer emission of (*S*)-**4** in Figure 2a, the ef value [ef: enantioselective fluorescent enhancement ratio = $[(I_D - I_0)/(I_L - I_0)]$ was 12.5, and I_D/I_0 = 6.0. This is an unprecedented high enantioselectivity for the fluorescent recognition of a serine derivative. Previously, the ef's observed for the use of sensors such as **2** and **3** to recognize the serine derivative **1b** were all less than 2.[5b−d] Figure 2b gives the enantioselective fluorescence response of (*S*)-**4** toward (*D*)- and (*L*)-**1a** at various concentrations in which the highest enantioselectivity is observed at the acid concentration of 2.0 × 10^{-3} M.

Figure 3 gives the fluorescence response of (*S*)-**5** toward (*D*)- and (*L*)-**1a**, and it shows enhancement at both the monomer and excimer emissions. In Figure 3a, the ef at the monomer emission is 3.5, and I_D/I_0 = 3.8. This enantioselectivity is greater than that observed at the monomer

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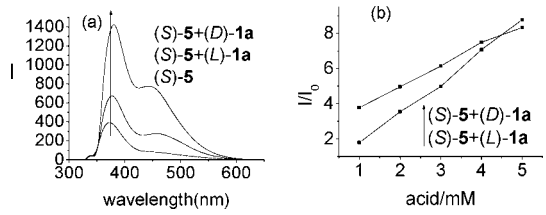
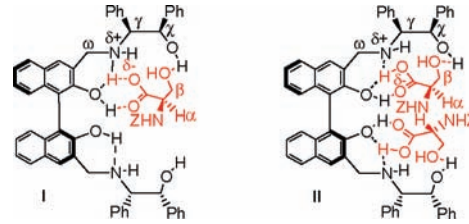


Figure 3. (a) Fluorescence spectra of (*S*)-**5** (2.0×10^{-4} M) with (*L*)- and (*D*)-**1a** at 1.0×10^{-3} M. (b) Fluorescence enhancement of (*S*)-**5** (2.0×10^{-4} M) with (*L*)- and (*D*)-**1a** at $\lambda_{em} = 379$ nm (benzene/2.5% DME; $\lambda_{exc} = 334$ nm, slit = 5.0/5.0 nm).

emission of (*S*)-**4** when (*S*)-**4** is used to interact with **1a** but smaller than that observed at the excimer emission. Figure 3b shows that as the concentration of **1a** increases the enantioselectivity decreases significantly and is even inverted around 4.5×10^{-3} M.

To gain a better understanding for the interaction of the serine derivative with the sensors, we have conducted an ^{1}H NMR spectroscopic investigation. The ^{1}H NMR spectra of the mixtures of (*S*)-**4** and (*D*)-**1a** in C_6D_6/acetone-d_6 (96:4) at various ratios with a constant total concentration of 6.0×10^{-3} M are obtained. It is found that the H_α signal of (*D*)-**1a** undergoes a small upfield shift from δ 4.52 to δ 4.45 in the presence of (*S*)-**4** at (*D*)-**1a**/(*S*)-**4** = 1:10. The two diastereotopic H_β signals of (*D*)-**1a** are observed at δ 3.77 and 3.96, each being a doublet of multiplet, in which one undergoes an upfield shift to δ 3.58 and another a downfield shift to 4.07 at (*D*)-**1a**/(*S*)-**4** = 1:10. This indicates significant interaction of the β-hydroxyl group of the serine substrate with the sensor. When (*D*)-**1a** is treated with (*S*)-**4**, the N−H proton signal of (*D*)-**1a** shifts initially from δ 5.85 to δ 6.01 when (*D*)-**1a**/(*S*)-**4** is about 5:1−10:3. However, no further shift of this signal is observed while other proton signals continuously evolve as the amount of the sensor is further increased to (*D*)-**1a**/(*S*)-**4** = 1:10. This indicates that the N−H proton of (*D*)-**1a** might not participate directly in the hydrogen bonding with the sensor. The H_γ signal of (*S*)-**4** undergoes a large downfield shift from δ 3.80 to δ 4.48 at (*D*)-**1a**/(*S*)-**4** = 10:1. This is consistent with the interaction of the carboxylic acid proton of (*D*)-**1a** with the basic nitrogen atoms of (*S*)-**4**. The H_χ signal of (*S*)-**4** also undergoes a large downfield shift from δ 4.96 to δ 6.15 at (*D*)-**1a**/(*S*)-**4** = 10:1. This unusually large downfield shift of the H_χ signal suggests that the hydroxyl group of the amino alcohol units in (*S*)-**4** should have directly participated in the binding with (*D*)-**1a**, contributing to the greatly enhanced enantioselectivity of (*S*)-**4** over **2**. The two H_ω protons of (*S*)-**4** give two doublets at δ 3.84 and 3.54 in which one undergoes an upfield shift to δ 3.75 and another a downfield shift to δ 4.25 at (*D*)-**1a**/(*S*)-**4** = 10:1, consistent with the acid−amine binding. The Job plot obtained on the basis of the ^{1}H NMR data indicates the formation of a mixture of 1:1 and 1:2 complexes of (*S*)-**4** versus (*D*)-**1a**. Structures **I** and **II** represent the possible structures of the ground state 1:1 and 1:2 complexes, respectively.[6b]



The ^{1}H NMR spectra of the mixtures of (*S*)-**5** and (*D*)-**1a** in C_6D_6/acetone-d_6 (96:4) at various ratios with a constant total concentration of 6.0×10^{-3} M are also obtained. It is found that the H_α signal of (*D*)-**1a** undergoes an upfield shift from δ 4.52 to δ 4.23 in the presence of (*S*)-**5** at (*D*)-**1**/(*S*)-**5** = 1:10. The two H_β protons of (*D*)-**1a** give two doublet of mutiplet signals at δ 3.77 and 3.96 which both shift to around δ 3.44 at (*D*)-**1a**/(*S*)-**5** = 1:10. The NH proton signal of (*D*)-**1a** in the presence of (*S*)-**5** behaves in a way similar to that observed in the presence of (*S*)-**4** and is probably not directly involved in the binding with (*S*)-**5**. The H_γ signal of (*S*)-**5** undergoes a downfield shift from δ 4.64 to δ 4.73 [(*D*)-**1a**/(*S*)-**5** = 10:1]. This downfield shift ($\Delta\delta = 0.09$) is much smaller than that observed for the interaction of (*S*)-**4** with (*D*)-**1a** ($\Delta\delta = 0.68$) which could imply a weaker hydrogen bonding interaction between (*S*)-**5** and (*D*)-**1a** probably due to their greater steric interaction. The two H_ω protons of (*S*)-**5** give two doublets at δ 3.95 and 3.68 which have shifted to δ 3.84 and 3.96 at (*D*)-**1a**/(*S*)-**5** = 10:1. The Job plot on the basis of the ^{1}H NMR data also indicates the formation of a mixture of 1:1 and 1:2 complexes between (*D*)-**1a** and (*S*)-**5**.

We have prepared compound (*S*)-**6** by methylating the hydroxyl groups of the amino alcohol units of (*S*)-**4**. The fluorescence spectrum of (*S*)-**6** in benzene shows predominately excimer emission, similar to that of (*S*)-**4**. The fluorescent response of (*S*)-**6** toward (*D*)- and (*L*)-**1a** is studied. As shown in Figure 4, the

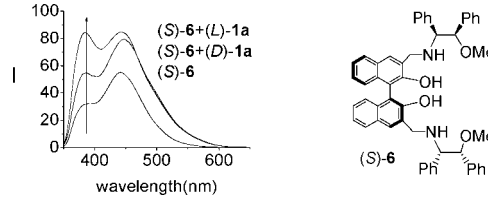


Figure 4. Fluorescence spectra of (*S*)-**6** (5.0×10^{-4} M) with (*L*)- and (*D*)-**1a** (2.0×10^{-3} M). (Solvent: benzene/2.5% DME. $\lambda_{exc} = 341$ nm, slit = 5.0/5.0 nm.)

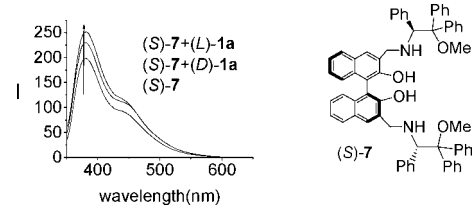
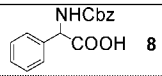
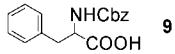
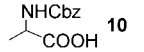
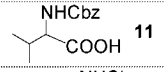
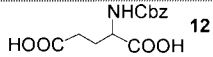


Figure 5. Fluorescence spectra of (*S*)-**7** (2.0×10^{-4} M) with (*L*)- and (*D*)-**1a** (1.0×10^{-3} M). (Solvent: benzene/2.5% DME. $\lambda_{exc} = 334$ nm, slit = 5.0/5.0 nm.)

Table 1. Fluorescent Recognition of Amino Acid Derivates Using (*S*)-**4** (5.0×10^{-4} M) and (*S*)-**5** (2.0×10^{-4} M) in Benzene*

entry	amino acid derivative	acid concentration	sensor	DME (%)	λ_{em} (nm)	I/I_0[a]	ef[b]
1	 **8**	1.0×10^{-3} M	(*S*)-**4**	0.625	376	2.8	10.9
2		4.0×10^{-3} M	(*S*)-**5**	0.625	376	4.8	10.8
3	 **9**	4.0×10^{-3} M	(*S*)-**4**	0.4	377	16.2	5.0
4		4.0×10^{-3} M	(*S*)-**5**	0.4	375	3.6	13.0
5	 **10**	3.0×10^{-3} M	(*S*)-**4**	0.4	376	9.0	6.3
6		4.0×10^{-3} M	(*S*)-**5**	0.4	377	4.5	5.3[c]
7	 **11**	2.0×10^{-3} M	(*S*)-**4**	0.625	377	6.5	9.3
8		4.0×10^{-3} M	(*S*)-**5**	0.625	378	2.4	2.7[c]
9	 **12**	1.0×10^{-3} M	(*S*)-**4**	2.5	380	16.0	2.8
10		1.0×10^{-3} M	(*S*)-**5**	2.5	374	7.8[d]	2.1[e]

* [λ_{exc} = 341 nm for (*S*)-**4** and 334 nm for (*S*)-**5**, 5.0/5.0 nm]. [a] I_D/I_0 unless indicated otherwise. [b] ef = $(I_D - I_0)/(I_L - I_0)$ unless indicated otherwise. [c] I_D/I_L. [d] I_L/I_0. [e] ef = $(I_L - I_0)/(I_D - I_0)$.

enantioselectivity at the excimer emission of (*S*)-**6** toward (*D*)- and (*L*)-**1a** has diminished, and the fluorescence enhancement in the presence of the chirality-matched substrate is also greatly decreased. The enantioselectivity at the monomer emission of (*S*)-**6** is ef = 2.4. This indicates that the hydroxyl protons of the amino alcohol units of (*S*)-**4** probably act as hydrogen bond donors in the interaction with the amino acid derivative and are important for the observed high enantioselectivity and greater fluorescence enhancement at the excimer emission.

The methylated compound (*S*)-**7** is prepared as an analogue of (*S*)-**5**. The fluorescence spectrum of (*S*)-**7** in benzene shows mainly monomer emission, similar to that of (*S*)-**5**. As shown in Figure 5, the enantioselectivity of (*S*)-**6** toward (*D*)- and (*L*)-**1a** has diminished at both the monomer and excimer emissions with little fluorescence enhancement. Thus, the hydroxyl protons of the amino alcohol units of (*S*)-**5** are also very important for the recognition of the serine derivative.

We have further used the fluorescent sensors (*S*)-**4** and (*S*)-**5** to recognize other amino acid derivatives **8**−**12**. As the results summarized in Table 1 show, both (*S*)-**4** and (*S*)-**5** exhibit high enantioselectivity in the fluorescent recognition of divese amino acid derivatives. Unlike the use of (*S*)-**4** to recognize the serine derivative **1a** where the major fluorescence enhancement and enantioselectivty are observed at the excimer emission of the sensor, when (*S*)-**4** and (*S*)-**5** are used to interact with the amino acids **8**−**12** the major fluorescence enhancement and enantioselectivity are all observed at the monomer emission of these sensors. That is, the extra β-hydroxyl group of the serine derivatives might have encouraged the intermolecular interaction of the fluorophore. For the recognition of the phenylglycine derivative **8**, the enantioselectivities of (*S*)-**4** and (*S*)-**5** are the same with a greater fluorescence enhancement observed for (*S*)-**5** in the presence of (*D*)-**8** (entries 1, 2). For the recognition of the phenylalanine derivative **9**, (*S*)-**4** gives greater fluorescence enhancement (entry 3), and (*S*)-**5** shows greater enantioselectivity (entry 4). In the interaction with the alanine derivative **10**, both sensors show good enantioselectivity with greater fluorescence enhancement observed for the interaction of (*S*)-**4** with (*D*)-**10** (entry 5). When (*S*)-**5** was treated with **10**, while there was large fluorescence enhancement in the presence of (*D*)-**10**, a small fluorescence *quenching* was observed with the use of (*L*)-**10** (entry 6). Thus, I_D/I_L rather than ef is used to represent the enantioselectivity. A similar observation was made for the interaction of (*S*)-**5** with the valine derivative **11** (entry 8). Both the fluorescence enhancement and enantioselectivity of (*S*)-**4** in the recognition of **11** are much higher than those of (*S*)-**5** (entry 7). In the presence of the glutamic acid derivative **12**, the γ-carboxylic acid group is expected to interact with the sensors which might have disrupted the chiral recognition leading to the reduced enantioselectivity (entries 9, 10). In addition, the interaction of (*S*)-**5** with **12** gives the inverted enantioselective fluorescent enhancement (entry 10).

In summary, the chiral BINOL−amino alcohol compounds are found to be efficient enantioselective fluorescent sensors for the recognition of various N-protected amino acids. Especially, the high enantioselectivity observed for the serine derivative is unprecedented. The NMR analyses indicate strong interactions between the amino alcohol units of the sensors and the amino acid substrates, leading to the sensitive as well as enantioselective sensing.

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Supporting Information Available: Detailed spectroscopic data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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