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ORIGINAL PAPER

Enantioselective Fluorescent Sensors for Amino Acid Derivatives Based on BINOL Bearing S-tryptophan Unit: Synthesis and Chiral Recognition

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Abstract Four novel derivatives of BINOL bearing S-tryptophan unit have been prepared and the structures of these compounds characterized by IR, MS, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. The enantioselective recognition of these receptors has been studied by fluorescence titration and ^{1}H NMR spectroscopy. The receptors exhibited different chiral recognition abilities towards N-Boc-protected amino acid anions and formed 1:1 complexes between host and guest. Receptors exhibit excellent enantioselective fluorescent recognition ability towards the amino acid derivatives.

Keywords Receptor · Fluorescence · Enantioselective recognition · NMR spectroscopy

Introduction

Chiral recognition of racemic compounds exists extensively in nature. To understand biological process, synthetic chiral receptors were prepared to bind the chiral guest selectively [1–4], these have the ability of discriminating the enantiomers. Many receptors have already been reported; their binding ability to both chiral and achiral anion guests has been studied by ^{1}H NMR, UV–vis spectra, fluorescence and electrochemical analysis [5–7]. Compared with other detection methods, such as NMR, HPLC, CD or capillary electrophoresis, fluorescence techniques have often been used to study the interaction between enantiomers and receptors because of their sensitivity, selectivity, and versatility [8–11]. On the basis of their respective advantages, we attempt to design some receptors with optical response to the enantiomers in the recognition interaction, which may offer a simple method to explore the recognition process for more information. Over the last two decades, 1,1′-bi-2-naphthol(BINOL) and its derivatives have been extensively used in chiral recognition and asymmetric catalysis [12–15]. Because of the fluorescence properties of the naphthalene groups in these compounds, their fluorescence responses toward various chiral molecules have also been investigated [16–18]. In the synthesis of chiral receptors, amino acids or peptides can be employed as chiral sources in building the desired molecules because of their accessibility and biological relevance [19, 20]. The carboxylate group is an anionic entity of prime importance in nature. Enzymes, antibodies, amino acids, and metabolic intermediates contain a range of carboxylate functionalities that account for their characteristic biochemical behavior [21, 22]. Enantioselective recognition of amino acid and its derivatives is important in asymmetric synthesis and drug discovery [23, 24]. Herein, we describe the development of four novel, BINOL derivatives bearing S-tryptophan residues that have similar two-armed structure (Scheme 1); their chiral recognition ability towards amino acid derivatives, two amino acid anions, and two amino alcohols have been explored by fluorimetric titration in $CHCl_3$. ^{1}H NMR experiments suggested that hydrogen-bonding interaction between the host and guest were the main factor in the recognition process.

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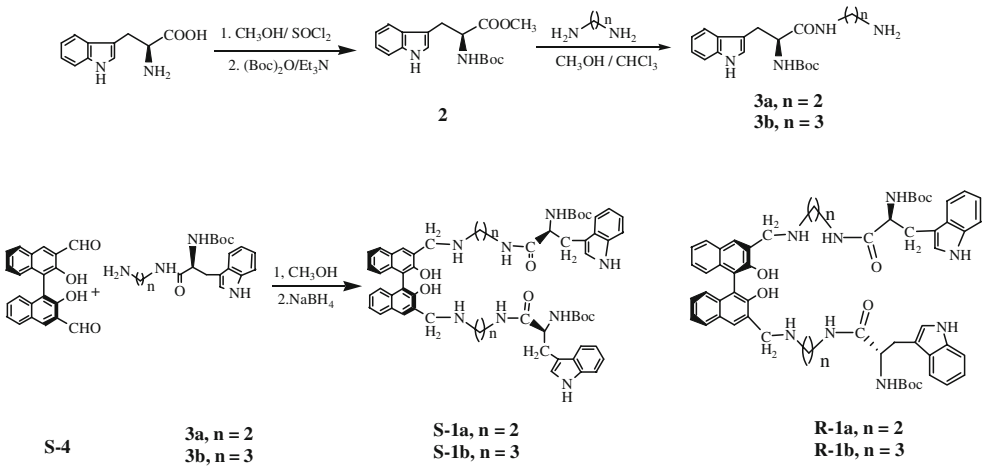
Scheme 1 Synthesis of the receptors S-1a, S-1b and R-1a, R-1b



Results and discussion

Synthesis

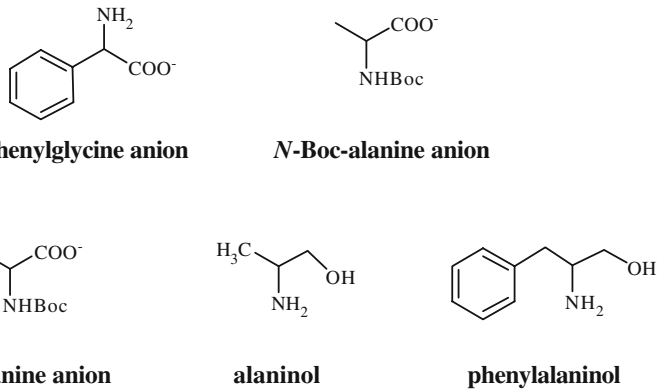
The synthesis of receptors **S-1a**, **S-1b** and **R-1a**, **R-1b** is outlined in Scheme 1. The starting materials binaphthyl dialdehydes were prepared from 1,1′-bi-2-naphthol (BINOL) [25, 26]. N-Boc-protected tryptophan methyl ester (**2**) were synthesized according to the literature started from S-tryptophan with high yield [27], and then reacted with excess amount of diamine to obtain the compounds **3a** or **3b**.

To avoid a cyclic product, the intermediates **3a** or **3b** were prepared by the reaction of compound N-Boc-protected tryptophan methyl ester (**2**) and 5-fold excess of diamine were soluble in large amount of methanol and continued to stir at room temperature. To avoid the partial racemization of **3a** or **3b** in this reaction, at the end of reaction, the solvent and diamine should be evaporated under high vacuum at about 50°C, because a little higher temperature may lead the racemization of compound. Condensation of (S)- or (R)-binaphthyl dialdehydes with compound binaphthyl dialdehyde (**4**) followed by reduction afforded the two disubstituted BINOL **S-1a** or **S-1b** (Scheme 1), respectively. In order to study how the BINOL and amino acid units in **S-1a** or **S-1b** influenced the enantioselective fluorescent recognition, the **R-1a** or **R-1b**, diastereomeric compounds of **S-1a** or **S-1b**, were also prepared. They are readily soluble in common organic solvents such as $CHCl_3$, CH_2Cl_2, CH_3OH, DMSO, and DMF. The structures of all these compounds were characterized by IR, MS, ^1H, and ^{13}C NMR spectroscopy and elemental analysis.

Fluorescence spectra study

The properties of the chiral recognition of receptors **S-1a** and **S-1b** were investigated in the absence and presence of various chiral guests (Fig. 1), such as the (S)- and (R)-α-phenylglycine anion, *N*-Boc-protected alanine anion (Ala) and *N*-Boc-protected phenylalanine anion (Phe), which amino groups were protected by the tert-butyloxycarbonyl functionality. In each case tetrabutylammonium was used as the counter cation, which could increase the reaction between the receptor and guest by hydrogen bondings. We also chose two amino alcohols, namely alaninol and phenylalaninol, as guests to compare the associated abilities of the hosts to bind with neutral molecules. Because there was almost no change

Fig. 1 Structures of the guests



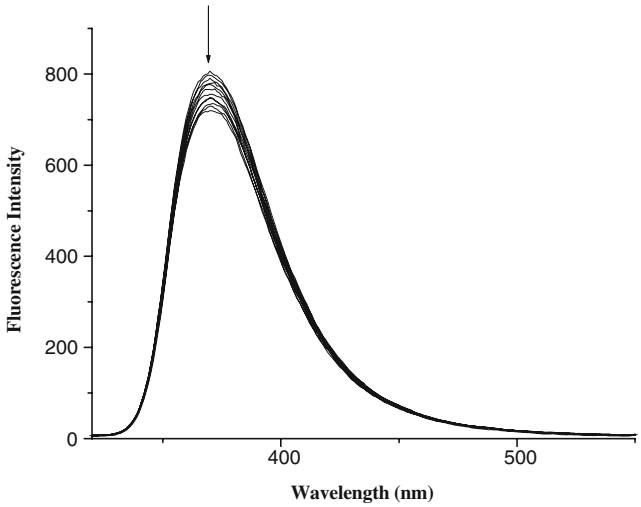


Fig. 2 Fluorescence spectra of receptor S-1a (1.25×10-5 mol L-1) with (R)-Ala anion in $CHCl_3$. The anion equivalents are: 0, 4, 8, 20, 40, 60, 80, 100, 200, 300, 400 and 500. Λex=278 nm

observed on the UV–vis spectra of receptors upon addition of guest anions, the interaction between host and anion was only evaluated by fluorescent spectra.

Figures 2 and 3 show the fluorescence emission spectra of a mixture of **S-1a**(1.25×10^{-5} mol L^{-1}) in $CHCl_3$ and different concentrations of the (R)- or (S)-Ala anion in $CHCl_3$ (λex=278 nm), respectively. The fluorescence emission of **S-1a**(at 371 nm) was slightly quenched by about 10% upon addition of 500 equiv. of (R)-Ala anions (Fig. 2). Figure 3 shows the change in fluorescence emission of **S-1a** upon addition of (S)-Ala anions; the quenching efficiency (at 371 nm) was about 81% for the addition of 500 equiv. of (S)-Ala anions. The different quenching efficiencies indicate that receptor **S-1a** has a excellent enantioselective recognition between (S)- and (R)-Ala anions.

Satisfactory nonlinear curve fitting (the correlation coefficient is over 0.99) confirmed that **S-1a** and the (S)-Ala anion formed a 1:1 complex (see the inset of Fig. 3). For a complex of 1:1 stoichiometry, the association constant(*K*ass) can be calculated by using Eq. 1 from the Origin 7.0 software package [28–31], where X represents the fluorescence intensity, C_H and C_G are the host and guest concentrations, and C_0 is the initial concentration of the host. The association constants (*K*ass) and correlation coefficients (R) obtained by a nonlinear leastsquares analysis of I versus C_H and C_G are listed in Table 1.

$$X = X_0 + (X_{\lim} - X_0)/2C_0 \left\{ C_H + C_G + 1 \Big/ K_{ass} - \left[(C_H + C_G + 1/K_{ass})^2 - 4C_H C_G \right]^{1/2} \right\} \quad (1)$$

The association constant for the interaction of **S-1a** with the (S)-Ala anion is 6.59×10^4 M^{-1}, whereas that for association of **S-1a** with the (R)-Ala anion could not be calculated from this equation owing to the weak response observed in the fluorescence spectra. The dramatically different fluorescent responses and quenching efficiencies observed for the two enantiomers indicate that **S-1a** has excellent enantioselective fluorescent recognition ability towards the Ala anion.

Similar phenomena were observed when (S)- or (R)-Phe anions were added into a solution of **S-1a**. Figure 4 shows the different fluorescence intensity changes when the same equiv. of (S)- or (R)-Phe anion were added to the host **S-1a**, the quenching efficiency was 24.8 % when 8.0 equiv. of (S)-Phe anion was added to the solution of **S-1a**, while the quenching efficiency was only 4.4% when 8.0 equiv. of (R)-Phe anion was added ($\Delta I_S/\Delta I_R$=5.64). The result of a non-linear curve fitting (at 371 nm) indicates that a 1:1 complex was formed between receptor **S-1a** and (S)- or (R)-Phe (see the Table 1). In addition, the association constants (*K*ass) were different (see the Table 1) ($K_{ass(S)}$= $(4.91\pm0.42)\times10^4$ M^{-1}, ΔG_0=−26.78 kJmol^{-1}; $K_{ass(R)}$= $(8.29\pm0.48)\times10^3$ M^{-1}, ΔG_0=−22.37 kJmol^{-1}), yielding a S/R selectivity [$K_{ass(S)}/K_{ass(R)}$] of 5.92 for the Phe anions and a $\Delta\Delta G_0$ value of −4.41 kJmol^{-1}, demonstrating that **S-1a** has good chiral recognition ability towards the enantiomers of Phe anions.

The continuous variation methods were also employed to determine the stoichiometric ratio of the receptor **S-1a** with guests [(S)- and (R)-Phe anions]. The total concentration of host and guest was constant (1.0×10^{-6} mol L^{-1}) in $CHCl_3$, with a continuously variable molar fraction of host ([H]/([H]+[G])). Figure 5 shows the Job plots of receptor **S-1a** with (S)- and (R)-Phe anion (at 371 nm, λex=

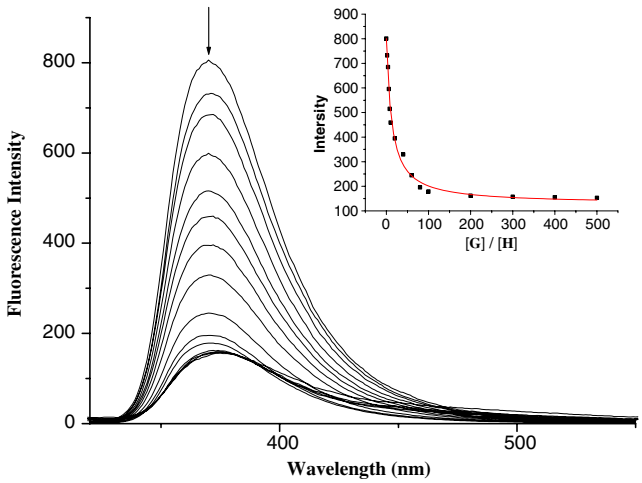


Fig. 3 Fluorescence spectra of receptor S-1a (1.25×10-5 mol L-1) with (S)-Ala anion in $CHCl_3$. The anion equivalents are: 0, 2, 4, 6, 8, 10, 20, 40, 60, 80, 100, 200, 300, 400 and 500. Λex=278 nm. Inset: changes in the fluorescence intensity of S-1a at 371 nm upon addition of (S)-Ala anion. The line shown is a line-fitted curve. The correlation coefficient (R) of the nonlinear curve fitting is 0.9946

Table 1 Association constants (*K*ass), correlation coefficients (*R*), enantioselectivities ($K_{ass(S)}/K_{ass(R)}$), Gibbs free energy changes ($-\Delta G_0$), and $\Delta\Delta G_0$ calculated from ΔG_0 for the complexation of receptors **S-1a**, **S-1b** and **R-1a**, **R-1b** with (S)-/(R)- guests in $CHCl_3$ at 25°C

Entry	Host	Guest	Kass $[M^{-1}]$[a,b]	R	$K_{ass(S)}/K_{ass(R)}$	$-\Delta G_0$ [kJmol^{-1}]	$\Delta\Delta G_0$ [kJmol^{-1}]
1	**S-1a**	(S)-Ala[c]	$(6.60\pm0.57)\times10^4$	0.9946		27.51	
2	**S-1a**	(R)-Ala[c]	[d]				
3	**S-1a**	(S)-Phe[c]	$(4.91\pm0.42)\times10^4$	0.9951		26.78	
4	**S-1a**	(R)-Phe[c]	$(8.29\pm0.48)\times10^3$	0.9986	5.92	22.37	−4.41
5	**S-1a**	(S)-Phenylglycine	$(5.74\pm0.59)\times10^4$	0.9931		27.17	
6	**S-1a**	(R)-Phenylglycine	$(2.01\pm0.19)\times10^4$	0.9917	2.86	24.57	−2.60
7	**S-1a**	(S)-alaninol	$(9.13\pm0.27)\times10^2$	0.9923		16.90	
8	**S-1a**	(R)-alaninol	$(2.24\pm0.05)\times10^2$	0.9902	4.08	13.42	−3.48
9	**S-1a**	(S)-phenylalaninol	$(7.59\pm0.42)\times10^2$	0.9929		16.44	
10	**S-1a**	(R)-phenylalaninol	$(2.09\pm0.18)\times10^2$	0.9907	3.01	13.24	−3.20
11	**S-1b**	(S)- Ala[c]	$(6.14\pm0.71)\times10^4$	0.9942		27.33	
12	**S-1b**	(R)- Ala[c]	[d]				
13	**S-1b**	(S) -Phe[c]	$(4.73\pm0.37)\times10^4$	0.9947		26.69	
14	**S-1b**	(R)- Phe[c]	$(9.22\pm0.08)\times10^3$	0.9974	5.13	22.63	−4.06
15	**S-1b**	(S)-Phenylglycine	$(6.03\pm0.61)\times10^4$	0.9906		27.29	
16	**S-1b**	(R)-Phenylglycine	$(2.29\pm0.22)\times10^4$	0.9940	2.63	24.89	−2.40
17	**S-1b**	(S)-alaninol	$(9.97\pm0.63)\times10^2$	0.9969		15.69	
18	**S-1b**	(R)-alaninol	$(2.50\pm0.12)\times10^2$	0.9919	3.99	13.69	−2.00
19	**S-1b**	(S)-phenylalaninol	$(8.19\pm0.65)\times10^2$	0.9911		16.63	
20	**S-1b**	(R)-phenylalaninol	$(2.76\pm0.15)\times10^2$	0.9916	2.98	13.93	−2.70
21	**R-1a**	(S)- Ala[c]	[d]				
22	**R-1a**	(R)- Ala[c]	$(5.92\pm0.55)\times10^4$	0.9938		27.24	
23	**R-1a**	(S) -Phe[c]	$(7.93\pm0.44)\times10^3$	0.9941		22.26	
24	**R-1a**	(R)- Phe[c]	$(4.11\pm0.24)\times10^4$	0.9957	1/5.18	26.34	4.08
25	**R-1a**	(S)-Phenylglycine	$(2.88\pm0.19)\times10^4$	0.9953		25.46	
26	**R-1a**	(R)-Phenylglycine	$(7.83\pm0.39)\times10^4$	0.9968	1/2.72	27.94	2.48
27	**R-1a**	(S)-alaninol	$(3.51\pm0.14)\times10^2$	0.9917		14.53	
28	**R-1a**	(R)-alaninol	$(8.79\pm0.58)\times10^2$	0.9951	1/1.98	16.22	1.69
29	**R-1a**	(S)-phenylalaninol	$(2.49\pm0.16)\times10^2$	0.9915		13.68	
30	**R-1a**	(R)-phenylalaninol	$(8.81\pm0.61)\times10^2$	0.9930	1/3.54	16.81	3.13
31	**R-1b**	(S)- Ala[c]	[d]				
32	**R-1b**	(R)- Ala[c]	$(5.37\pm0.38)\times10^4$	0.9958		27.00	
33	**R-1b**	(S)-Phe[c]	$(8.93\pm0.68)\times10^3$	0.9972		22.55	
34	**R-1b**	(R)- Phe[c]	$(4.01\pm0.63)\times10^4$	0.9947	1/4.49	26.28	3.73
35	**R-1b**	(S)-Phenylglycine	$(1.98\pm0.17)\times10^4$	0.9944		24.53	
36	**R-1b**	(R)-Phenylglycine	$(5.83\pm0.19)\times10^4$	0.9969	1/2.94	27.21	2.68
37	**R-1b**	(S)-alaninol	$(2.37\pm0.14)\times10^2$	0.9927		13.56	
38	**R-1b**	(R)-alaninol	$(8.99\pm0.47)\times10^2$	0.9936	1/5.21	16.86	3.30
39	**R-1b**	(S)-phenylalaninol	$(2.11\pm0.13)\times10^2$	0.9925		13.27	
40	**R-1b**	(R)-phenylalaninol	$(8.53\pm0.61)\times10^2$	0.9933	1/4.04	16.73	3.46
41	**S-7**	(S)-Ala[c]	$(4.53\pm0.18)\times10^4$	0.9989		26.58	
42	**S-7**	(R)-Ala[c]	$(9.71\pm0.52)\times10^3$	0.9946	4.67	22.76	−3.82
43	**S-7**	(S)-Phe[c]	$(4.19\pm0.24)\times10^4$	0.9938		26.39	
44	**S-7**	(R)-Phe[c]	$(8.62\pm0.29)\times10^3$	0.9913	4.86	22.47	−3.92

[a] The data were calculated from results of fluorescence titrations in $CHCl_3$

[b] All error values were obtained from nonlinear curve fitting

[c] Ala and Phe tetrabutylammonium salts, the amino group was protected by a *tert*-butyloxycarbonyl function

[d] The association constants could not be calculated precisely because the signal change was too small to provide reliable data with tolerable error

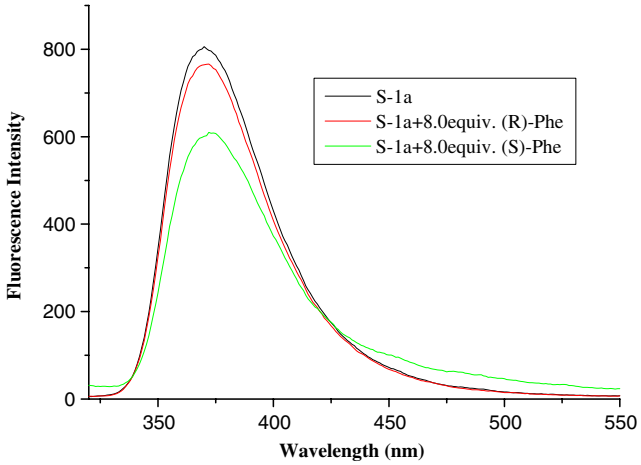


Fig. 4 Fluorescence spectra of host S-1a (1.25×10-5 mol L-1) with 8.0 equiv of (R)- and (S)-Phe anion in $CHCl_3$

278 nm). When the molar fraction of the host was 0.50, the fluorescence intensity reached a maximum, which demonstrated that receptor **S-1a** formed a 1:1 complex with (S)- and (R)-Phe anions, respectively [32].

The binding of **S-1a** with (S)- and (R)-α-Phenylglycine anion was also carried out and the association constants of the host **S-1a** with α-Phenylglycine anion are also listed in Table 1. When **S-1a** interacted with α-Phenylglycine anion, the receptor **S-1a** exhibits weak enantioselective recognition ability to α-Phenylglycine anion we have tested (see the Table 1). Upon the addition of alaninol or phenylalaninol into a solution of **S-1a** in $CHCl_3$, the fluorescence intensity of **S-1a** was slightly quenched by both (S)- and (R)-enantiomers (see the Table 1). This indicates that hydrogen bonding plays an important role in the interaction between the host and guest and leads to the easier signal transductions of chiral recognition by fluorescence method.

Similar phenomena were observed when (R)- or (S)-Ala, Phe, α-Phenylglycine anions, alaninol or phenylalaninol was added into a solution (1.25×10^{-5} M^{-1}) of **S-1b**, respectively. Upon addition of (R)- or (S)- guest, the different fluorescent quenching degree of **S-1b** was observed. The quenching efficiencies of (S)-*N*-Boc-protected amino acid anions were much higher than the (R)-*N*-Boc-protected amino acid anions. Satisfactory nonlinear curve fitting (the correlation coefficient is over 0.99) confirmed that receptor **S-1b** formed a 1:1 complex with the (R)- and (S)-guest anions [31]. Due to the similar structure of **S-1a** and **S-1b**, the fluorescent variations of **S-1a** and **S-1b** showed the same trend. Since there were no changes in the UV-vis spectra of receptors when treated with (S)- or (R)-guests, a PET process might be responsible for the fluorescent quenching [33–36]. Compared with **S-1b**, **S-1a** has a more rigid structure, which causes the enantioselective recognition of **S-1a** with guests to be much higher than those of **S-1b**.

In order to study how the chirality of the (S)-tryptophan residues in **S-1a** and **S-1b** influenced the enantioselective fluorescent recognition, we synthesized compound **S-7** from the reactions of **(S)-4** with compound **6** followed by reduction, respectively. When **S-7** interacted with (R)- or (S)- Ala, Phe anions, similar phenomena to that shown in Fig. 3 were observed when anion guests were added to the solution of **S-7**. The non-linear curve fitting results of the fluorescence intensity (at 371 nm) of the interaction between **S-7** and (R)-, (S)- Ala, Phe anions, are shown in Table 1. The correlation coefficients of the non-linear curve fitting were all large (R>0.99), which indicated that the 1:1 complex between **S-7** and the Ala, Phe anions has been formed [31]. The data in Table 1 illustrate that the association constants (Kass) of **S-7** with (S)- Ala, Phe anion were much higher than those of **S-7** with (R)-Ala, Phe anion. The result of fluorescence titration indicated a matched chirality between the guest anions center and the chiral BINOL unit is the main reason for the enantioselective recognition (Scheme 2).

In order to confirm the chirality of the (S)-tryptophan residues and BINOL groups in **S-1a** and **S-1b** influenced the enantioselective fluorescent recognition, **R-1a** and **R-1b** the diastereomeric compounds of **S-1a** and **S-1b**, were also prepared, and studied its interaction with Ala, Phe, α-Phenylglycine anions, alaninol and phenylalaninol which showed the opposite enantioselectivity. That is, the enantiomer of (R)-guests, quenched the fluorescence of **R-1a** or **R-1b** more efficiently than (S)-guests. The result of fluorescence titration indicated a matched chirality between the guest anions center and the chiral BINOL unit led to the enantioselective recognition. The enantiomers of guest anions interacted with **S-1a**, **S-1b** and **R-1a**, **R-1b** in a same fashion.

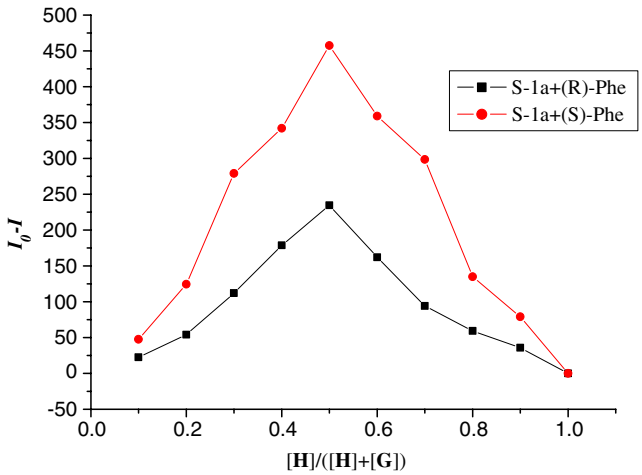
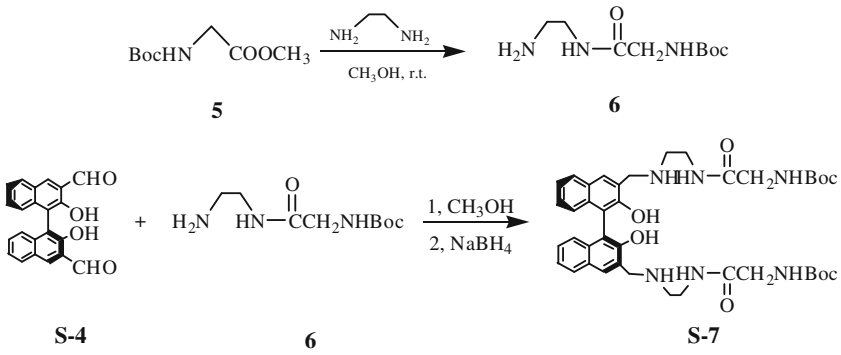


Fig. 5 Job plots of receptor S-1a with (S)- and (R)-Phe anions (371 nm, λ_{ex}=278 nm). The total concentration of the host ([H]) and guest ([G]) is 1.0×10−6 M-1 in $CHCl_3$. I_0: fluorescence intensity of S-1a; I: fluorescence intensity of S-1a in the presence of the guest

Scheme 2 Synthesis of the receptor S-7



According to the Table 1, it indicates that the interaction of **S-1a**, **S-1b** with the (S)-Ala or (S)-Phe anions is better than that with the (R)-Ala or (R)-Phe anions, which is probably due to the (S)-amino acid anions having a more complementary structure with receptors **S-1a**, **S-1b**. The Phe anion has a structure similar to that of the Ala anion, but the association constants for the association of the receptors with the Phe anion are smaller than those for the Ala anion, which could be attributed to the greater steric hindrance of the phenyl ring relative to the methyl group. The receptors **S-1a**, **S-1b** and **R-1a**, **R-1b** all exhibit good chiral recognition ability towards the enantiomers of the Ala and Phe anions, which indicates that the preorganized structure of the chiral center of binaphthyl unit play important roles in the enantioselective recognition process. Interestingly, we found that the association constants for the interactions of **S-1a** or **S-1b** with the (S)-enantiomers were generally larger than those for the (R)-enantiomers, which is probably due to the (S)-enantiomers having a structure more complementary to the hosts. Further research is still being carried out to investigate these phenomena.

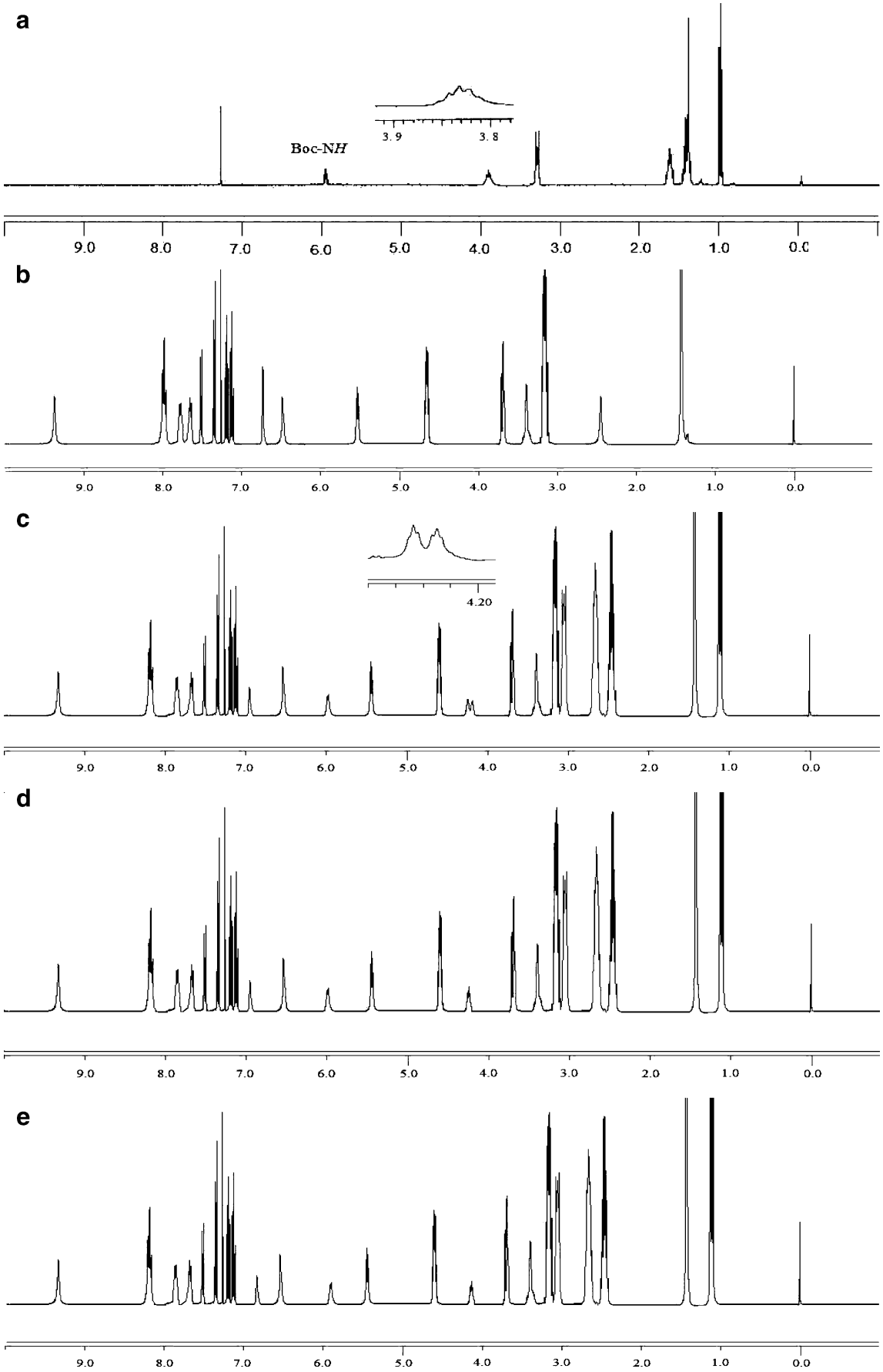
^{1}H NMR study

^{1}H NMR experiments were undertaken to assess the chiral recognition properties between receptor **S-1a** and chiral anionic guest because NMR spectroscopy can provide structural and dynamic information directly [37]. Chiral recognition studies were carried out with a 400 MHz NMR spectrometer using receptor **S-1a** by ^{1}H NMR in $CDCl_3$ as chiral solvating agents at room temperature. The spectra of receptor **S-1a** and its complex with equimolar amounts of racemic Ala anions are shown in Fig. 6. When treated with equimolar amounts of receptor **S-1a**, the CH proton of racemic Ala anion was splitted into a more complicated signal pattern (Fig. 6c) with a downfield shift(from d 3.83 to 4.22 ppm) while that of the host with an upfield shift (from d 5.53 to 5.44). The interaction of receptor **S-1a** with (S)-Ala shown that the CH proton has a larger downfield shift (from δ=3.83 to 4.27 ppm, $\Delta\delta$=0.42 ppm, Fig. 6d) than the CH proton of (R)-enantiomer (from δ=3.83 to 4.14 ppm, $\Delta\delta$=0.29 ppm, Fig. 6e). Moreover, the signals of the -OH proton in the ^{1}H NMR spectra of receptor **S-1a** become weakened obviously and have an downfield shift from 6.57 to 6.89 ppm ($\Delta\delta$=0.32 ppm, Fig. 6d) or 6.74 ppm ($\Delta\delta$=0.17 ppm, Fig. 6e) for (S)- or (R)-Ala anion, respectively, while the signals of the peaks of binaphthyl fragments are downfield shifted and broadened with the addition of the guest. The signal of the amide (N***H***) group of Ala linked to the Boc moiety was also clearly downfield shifted from δ=5.91 to 5.99, ($\Delta\delta$=0.07 ppm, Fig. 6d) 5.93 ppm ($\Delta\delta$=0.02 ppm, Fig. 6e) for (S)- or (R)-Ala anion, respectively. The above results indicate that **S-1** has a stronger interaction with the (S)-Ala anion than with its (R)-enantiomer. This indicated that the interaction between the host and guest also happened by multiple hydrogen bondings. The above results illustrate that the nature of the receptor, multiple hydrogen-bonding interactions, and complementary chiral-centre interactions maybe responsible for the enantiomeric recognition of amino acid anion [38, 39].

Conclusion

In summary, four novel chiral fluorescent receptors **S-1a**, **S-1b** and **R-1a**, **R-1b** were synthesized and their enantioselective recognition was studied by fluorescence titration and ^{1}H NMR spectroscopy. Receptors **S-1a**, **S-1b** and **R-1a**, **R-1b** exhibit different chiral recognition abilities towards some enantiomers of amino acid derivatives and form 1:1 complexes with the guest molecules. It is clear that nature of the receptor, good structural preorganization, multiple hydrogen-bonding interactions and complementary chiral-

Fig. 6 The ^{1}H NMR spectra of **S-1a** and its guest complexes at 25°C ▶ ([**S-1a**] = [guest] = 4.0×10^{-3} mol L^{-1}) in $CDCl_3$ at 400 MHz. **a** Racemic Ala anion; **b** receptor **S-1a**; **c** receptor **S-1a** + racemic Ala anion; **d** receptor **S-1a** + (S)-Ala anion; **e** receptor **S-1a** + (R)-Ala anion


a
Boc-NH
3.9
3.8
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
b
c
4.20
d
e

centre interactions induce may be responsible for the enantiomeric recognition of anionic guests. Receptors **S-1a**, **S-1b** and **R-1a**, **R-1b** are promising in their use as fluorescence sensors for amino acid derivatives. The remarkably different fluorescent responses that result from complexation reveal that **S-1a**, **S-1b** and **R-1a**, **R-1b** could be used as fluorescent chemosensors for the *N*-Boc-protected alanine anion or *N*-Boc-protected phenylalanine anion in the future.

Experimental

Materials and methods

The reagents used were of commercial origin and were employed without further purification. Purifications by column chromatography were carried out over silica gel (230–400mesh). The IR spectra were performed on a Nicolet 670 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer. Mass spectra were determined by ESI recorded on a Esquire 3000 LC–MS mass instrument. Optical rotations were taken on a Perkin–Elmer Model 341 polarimeter. Fluorescence spectra were obtained with a F-7000 FL Spectrophotometer. Elemental analyses were performed by the Vario Elemental CHSN-O microanalyzer. All other commercially available reagents were used without further purification. The anions were used as their tetrabutylammonium salts. The *N*-protected (by the *tert*-butyloxycarbonyl functionality) amino acid derivatives were synthesized according to a literature method [27].

Syntheses

General procedure for the synthesis of compound 3a and 3b

Under nitrogen, excess diamine (10 mmol) in 10 mL CH_3OH was added dropwise into a solution (20 mL) of S-N-Boc-protected tryptophan methyl ester **2** (2 mmol) in $CHCl_3/CH_3OH$ (1:1, v/v) under an ice-bath, then the mixture was stirred at room temperature for 48 h. After evaporation of the solvent and the residual diamine under reduced pressure. Then $CHCl_3$ (30 mL) were added and washed with H_2O (3×30 mL), the organic layer was separated and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give **3a** or **3b** as colorless ropy oil.

3a: yield, 86% $[\alpha]_D^{20} = +21.84$ (c=0.05, $CHCl_3$). IR (film, cm^{-1}): υ 3344, 2982, 1672, 1651, 1528, 1388, 1367, 1175, 1107, 744, 640. ^{1}H NMR ($CDCl_3$): δ=9.51 (s, 1 H, CONH), 7.75 (s, 1 H, Indole-NH), 7.63 (d, J=7.6 Hz, 1 H, Indole-CH), 7.32 (d, J=8.0 Hz, 1 H, Indole-CH), 7.16 (t, J=7.2 Hz, 1 H, Indole-CH), 7.08 (t, J=7.2 Hz, 1 H, Indole-CH), 7.01 (s, 1 H, Indole-CH), 6.59 (s, 1 H, NHBoc), 5.59 (s, 1 H, NC*HCO), 4.38 (d, J=5.1 Hz, 2 H, Indole-CH_2), 3.39 (s, 2 H, NH_2), 3.28–3.23 (m, 2 H, CH_2), 2.97–2.93 (m, 2 H, CH_2), 1.42 (s, 9 H, Boc-*t*Bu) ppm. ^{13}C NMR ($CDCl_3$): δ=174.6, 157.8, 138.4, 129.1, 127.5, 124.1, 122.6, 119.3, 114.8, 112.7, 54.2, 41.9, 40.7, 29.2, 28.3 ppm. ESI-MS *m*/*z*: 347 (M+1). $C_{18}H_{26}N_4O_3$: calcd. C 62.41, H 7.56, N 16.17; found C 62.35, H 7.58, N 16.12.

3b: yield, 91% $[\alpha]_D^{20} = +20.09$ (c=0.05, $CHCl_3$). IR (film, cm^{-1}): υ 3342, 2981, 2929, 1689, 1652, 1528, 1387, 1369, 1325, 1247, 1175, 1111, 744, 641. ^{1}H NMR ($CDCl_3$): δ=9.48 (s, 1 H, CONH), 7.72 (s, 1 H, Indole-NH), 7.61 (d, J=7.6 Hz, 1 H, Indole-CH), 7.32 (d, J=8.0 Hz, 1 H, Indole-CH), 7.15 (t, J=7.2 Hz, 1 H, Indole-CH), 7.07 (t, J=7.2 Hz, 1 H, Indole-CH), 7.01 (s, 1 H, Indole-CH), 6.59 (s, 1 H, NHBoc), 5.57 (s, 1 H, NC*HCO), 4.36 (d, J=5.1 Hz, 2 H, Indole-CH_2), 3.38 (s, 2 H, NH_2), 3.28–3.23 (m, 2 H, CH_2), 2.97–2.93 (m, 2 H, CH_2), 2.17−2.11 (m, 2 H, CH_2), 1.42 (s, 9 H, Boc-*t*Bu) ppm. ^{13}C NMR ($CDCl_3$): δ=174.8, 155.3, 136.4, 127.2, 124.7, 121.1, 119.0, 118.6, 111.5, 110.3, 54.2, 41.1, 40.1, 37.7, 29.2, 28.7 ppm. ESI-MS *m*/*z*: 361 (M+1). $C_{19}H_{28}N_4O_3$: calcd. C 63.31, H 7.83, N 15.54; found C 62.28, H 7.86, N 15.51.

Preparation and characterization of compound 6

The preparation procedure was the same as that of **3a or 3b** by starting with N-Boc-protected glycine methyl ester. This gave **6** as a colorless oil in 95% yield. ^{1}H NMR ($CDCl_3$): δ=7.11 (s, 1 H, CON**H**), 5.57 (s, 1 H, N**H**Boc), 3.74 (s, 2H, CH_2), 3.39 (t, J=6.4 Hz, 2H, CH_2), 2.86 (t, J=8.0 Hz, 2H, CH_2), 1.74(s, 2 H, NH_2), 1.44 (s, 9 H, CH_3), ^{13}C NMR ($CDCl_3$): δ=173.3, 155.9, 78.1, 55.7, 41.9, 40.7, 28.9 ppm. ESI-MS: *m*/*z* (%) =218 (M+1). $C_9H_{19}N_3O_3$: calcd. C 49.75, H 8.81, N19.34; found C 49.57, H 8.89, N 19.22.

General procedure for the synthesis of compound R-1a, R-1b, S-1a and 1b

A mixture of the (R) or (S)-binaphthyl dialdehyde (0.34 g, 1 mmol) and compound **3a** or **3b** (2.2 mmol) in dry $CHCl_3$ (30 mL) was stirred for 48 h under N_2 at room temperature until TLC showed the disappearance of the starting material. $NaBH_4$ (0.19 g, 5 mmol) was then added to the mixture in three portions over 3 h, after which it was stirred under nitrogen for another 6 h at 50°C. The mixture was poured into 30 mL 10% $NaHCO_3$ after removed the solvent under reduced pressure, and extracted with $CHCl_3$ for three times. The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure and the residue was

purified by column chromatography on silica gel [eluent: $CHCl_3/CH_3CH_2OH$ = 30:1 (v/v)]. The pure product was obtained as a pale yellow solid.

S-1a: yield: 77%; $[\alpha]_D^{20} = -27.96$(c=0.05, $CHCl_3$); **R-1a:** yield: 79%; $[\alpha]_D^{20} = +35.42$(c=0.05, $CHCl_3$). IR (film, cm^{-1}): υ 3432, 3353, 3259, 3216, 3061, 1640, 1271, 1196, 1074, 1049, 822, 748. ^{1}H NMR ($CDCl_3$) δ=9.35 (s, 2H, CONH), 7.94 (d, J=8.0 Hz, 2H, Ar–H), 7.91(d, J=9.8 Hz, 2H, Ar–H), 7.74 (d, J=7.6 Hz, 2 H, Ar–H), 7.63 (d, J= 7.8 Hz, 2 H, Indole-NH), 7.52(d, J=8.1 Hz, 2 H, Indole), 7.35 (d, J=7.2 Hz, 2H, Ar–H), 7.23−7.19 (m, 4H, Ar–H), 7.16−7.11 (m, 6H, Ar–H), 6.72 (s, 2H, OH), 6.45 (s, 2H, Boc-NH), 5.53(s, 2 H,NC*HCO), 4.65 (d, J=8.0 Hz, 4H, Ar-C**H**$_2$), 3.38 (m, 4H, Indole-CH_2), 3.12–3.21 (m, 8H, NCH_2C), 2.43 (s, 2H, NH), 1.42(s, 18 H, Boc-tBu) ppm**;** ^{13}C NMR ($CDCl_3$): δ=28.6, 34.4, 38.5, 39.3, 43.8, 57.4, 76.1, 82.1, 115.4, 119.6, 121.4, 122.6, 123.8, 124.3, 125.6, 126.2, 126.8, 127.6, 128.6, 127.9, 129.1,132.9, 140.2, 142.1, 142.6, 149.7, 151.0, 155.6, 169.6, 172.7 ppm, ESI-MS m/z: 1025 $(M+Na)^+$. $C_{58}H_{66}N_8O_8$: calcd. C 69.44, H 6.63, N 11.17; **S-1a:** found C 69.21, H 6.71, N 11.01; **R-1a:** found C 69.18, H 6.72, N 11.04;

S-1b: yield: 72.4%; $[\alpha]_D^{20} = -25.62$ (c=0.05, $CHCl_3$). **R-1b:** yield: 78.2%; $[\alpha]_D^{20} = +32.09$ (c=0.05, $CHCl_3$). IR (film, cm^{-1}): υ 3434, 3357, 3259, 3218, 3065, 1642, 1270, 1196, 1078, 1049, 822, 747. ^{1}H NMR ($CDCl_3$) δ (ppm): 9.32 (s, 2H, CONH), 7.91 (d, J=8.0 Hz, 2H, Ar–H), 7.88(d, J=9.8 Hz, 2H, Ar–H), 7.72 (d, J=7.6 Hz, 2 H, Ar–H), 7.60 (d, J=7.8 Hz, 2 H, Indole-NH), 7.56(d, J=8.1 Hz, 2 H, Indole), 7.39 (d, J=7.2 Hz, 2H, Ar–H), 7.21−7.15 (m, 4H, Ar–H), 7.14−7.08 (m, 6H, Ar–H), 6.72 (s, 2H, OH), 6.46 (s, 2H, Boc-NH), 5.51(s, 2 H,NC*HCO), 4.62 (d, J= 8.0 Hz, 4H, Ar-C**H**$_2$), 3.36 (m, 4H, Indole-CH_2), 3.12–3.21 (m, 8H, CH_2), 2.43 (s, 2H, NH), 2.22−2.11 (m, 4H, CH_2), 1.42(s, 18 H, Boc-tBu), ^{13}C NMR ($CDCl_3$): δ=28.6,29.9, 34.6, 38.7, 39.7, 43.9, 57.6, 76.4, 82.0, 115.2, 119.3, 121.1, 122.2, 123.2, 124.1, 125.8, 126.0, 126.7, 127.9, 128.1, 128.9, 129.4,132.6, 140.5, 142.6, 142.9, 149.3, 151.2, 155.1, 169.0, 172.1 ppm, ESI-MS m/z: 1053 $(M+Na^+)$. $C_{60}H_{70}N_8O_8$: calcd. C 69.88, H 6.84, N 10.87; **S-1b:** found C 69.61, H 6.89, N 10.75; **R-1b:** found C 69.65, H 6.90, N 11.72;

Preparation and characterization of compound S-7

The preparation procedure was the same as that of **S-1 or R-1** by starting with compound **6**. After workup, the crude product was purified by column chromatography on silica gel [eluent: $CHCl_3/CH_3CH_2OH$ = 50:1 (v/v)]. The pure product was obtained as a pale yellow solid. yield: 79.6%; $[\alpha]_D^{20} = -68.32$(c=0.05, $CHCl_3$); IR (film, cm^{-1}): υ 3402, 3092, 2969, 1679, 1529, 1268, 1234, 752. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.89 (s, 2H, CONH), 7.87 (d, J= 8.0 Hz, 2H, Ar–H), 7.79 (d, J=9.6 Hz, 2H, Ar–H), 7.64 (d, J=8.1 Hz, 2H, Ar–H), 7.22 (d, J=7.6 Hz, 2H, Ar–H), 7.19 (d, J=7.2 Hz, 2H, Ar–H), 7.17−7.13 (t, J=4.8 Hz, 2H, Ar–H), 6.55 (s, 2H, OH), 4.12 (d, J=8.0 Hz, 4H, Ar-C**H**$_2$), 3.88 (s, 4H, CH_2), 3.03–2.95 (m, 4H, C**H**$_2$), 2.79−2.70 (m, 4H, C**H**$_2$), 2.38 (s, 2H, NH), 1.44 (s, 18H, CH_3), ^{13}C NMR ($CDCl_3$): δ=174.03, 153.59, 153.31, 134.99, 133.96, 133.44, 133.17, 132.54, 131.06, 130.86, 130.58, 129.91, 128.71, 127.53, 126.62, 126.01, 125.93, 125.85, 125.73, 124.58, 74.09, 58.39, 58.49, 39.89, 24.92 ppm. ESI-MS: m/z (%) =767. $[M+Na]^+$. $C_{40}H_{52}N_6O_8$: calcd. C 64.50, H 7.04, N 11.28; found C 64.29, H 7.09, N 11.19;

Preparation of samples for fluorescence measurement

All solutions were prepared using volumetric syringes, pipettes, and volumetric flasks. The tetrabutylammonium salts were prepared by adding 1 equiv. of tetrabutylammonium hydroxide in methanol to a solution of the corresponding carboxylic acid in methanol and stock solutions of the salts were prepared in $CHCl_3$. The resulting syrup was dried under high vacuum for 24 h, analyzed by NMR spectroscopy, and stored in a desiccator. The compounds **S-1a**, **S-1b**, **R-1a**, **R-1b** and **S-7** were prepared as stock solutions in $CHCl_3$. The test solutions were prepared by adding different volumes of anion solution to a series of test tubes and then the same amount of stock solution of the host compound was added to each of the test tubes and diluted to 3.0 mL with $CHCl_3$. After being shaken for several minutes, the test solutions were analyzed immediately.

Job plots

Stock solutions of host **S-1a** and the (S)-Phe, (R)-Phe tetrabutylammonium salts in $CHCl_3$ system (the total concentration of the host and guest is 1.0×10^{-6} mol L^{-1}) were freshly prepared. The receptor and Phe solutions were added to the test tubes in ratios of 9:1, 8:2 to 0:10, respectively. After being shaken for several minutes, the work solution could be measured immediately.

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