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PAPER

Enantioselective fluorescent recognition of mandelic acid by unsymmetrical salalen and salan sensors†

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As sensors with multiple chiral centers, salalen **1** and salan **2** composed of *trans*-cyclohexane-1,2-diamine (*trans*-DACH) and 1,1′-bi-2-naphthol (BINOL) units were designed and synthesized. Fluorescent recognition studies of resulting sensors towards mandelic acid (MA) reveal that salan **2a** containing (*R*)-BINOL and (*R*,*R*)-DACH exhibits highly sensitive and enantioselective response towards MA. The relationship between the chirality combination and the enantioselectivity is discussed. Based on the studies of concentration and solvent effect on the recognition process of **2a**, it was found that the sensitivity and enantioselectivity could be enhanced *via* changing the concentration of sensors or altering the polarity of solvents. To explain why higher enantioselectivity can be achieved in moderate polar solvent other than in nonpolar or polar solvent, a solvent-guest competition mechanism, which may shed a light on the enhancement of the enantioselectivity of chiral recognition and noncovalent asymmetric catalysis, has been proposed and validated.

Introduction

As one of the most fundamental and significant processes in nature systems, chiral recognition plays an important role in many fields of science and technology.[1] For the studies on chiral recognition might contribute to the understanding of living systems, numerous efforts have been devoted to the design and synthesis of artificial receptors and their applications.[2] 1,1′-Bi-2-naphthol (BINOL) and *trans*-cyclohexane-1,2-diamine (*trans*-DACH) and their derivatives have been widely used in molecular recognition and asymmetric catalysis.[3] Many enantioselective fluorescence sensors using BINOL or its derivatives as building-block and fluorophore have been reported, and some of them have high fluorescence efficiency and enantioselectivity.[4]

As ligand or catalyst, chiral salen and salan compounds have wide application in asymmetry catalysis.[5] Recent studies demonstrate that unsymmetrical chiral salen ligands possess important advantages,[6] and their corresponding metal complexes could exhibit better enantioselectivities for several asymmetry reactions in comparison with their symmetrical counterparts.[6f,6g] Moreover, significant progress has been made on the organocatalysis using unsymmetrical substituted *trans*-DACH derivatives as catalyst.[7] Thus, we expected that the unsymmetrical salalen or salan ligand would establish a unique asymmetric recognition site which induces a high extent of asymmetry.

However, we found that sensors composed of single unsymmetrical substituted *trans*-DACH only exhibit insignificant fluorescence response and enantioselectivity due to the lack of multiple-point interactions[8] which is indispensable for chiral recognition. One viable method for the increase of interaction points is to link two unsymmetrical salalen or salan units together. BINOL derivatives, which can be used as not only linkers but also fluorophores and can bring forth sensors with multiple interaction points and chiral centers, provoked our interests. Furthermore, it is important and interesting to discuss the relationship between the enantioselectivity and the chirality combination of a sensor with multiple chiral centers. In addition, given that unsymmetrical salalen and salan ligands can exhibit distinction in asymmetric catalysis,[6i–6k] the investigation of the difference between them in molecule recognition is also of value. Keeping these in mind, we designed and synthesized chiral sensors salalen **1** and salan **2** possessing multiple interaction points and chiral centers.

Since mandelic acid (MA)[9] is an important chiral α-hydroxycarboxylic acid which can be used as an antibacterial compound,[9a] a skincare modality,[9b] a useful precursor for the pharmaceutical synthetic industry[9c–9e] and most of all a representative and frequently used sensing substrate for molecule recognition researches,[4a–4e,9f–9j] in this paper, we chose MA as sensing substrate and the chiral recognition of sensors **1** and **2** towards the enantiomers of MA has been studied.

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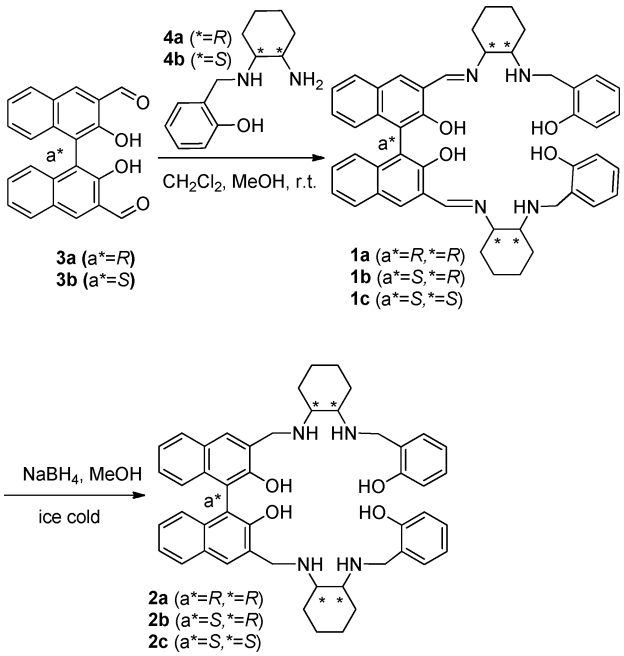
Results and discussion

1. Synthesis of sensors 1 and 2

The synthesis routes of **1** and **2** are shown in Scheme 1. First, optically pure BINOL was protected with methoxymethyl by reacting with chloro(methoxymethoxy)methane. Then after the treatment with *n*-BuLi and followed by the addition of DMF and hydrolysis, 2,2′-dihydroxy-1,1′binaphthalenyl-3,3′-dicarbaldehyde (**3**) was obtained.[10]



Scheme 1 Synthesis routes of sensors **1** and **2**.

The synthesis of 2-((1*R*,2*R*)-2-Amino-cyclohexylamino)-methylphenol (**4a**) was finished by a one-pot reaction of (1*R*,2*R*)-1-aminocyclohexanaminium chloride[11] with salicylal followed by $NaBH_4$ reduction and hydrolysis. **4b** was prepared by the same way.

1 was obtained by reacting **3** with **4**. Whereas **1** trends to decompose while passing through the chromatography column, in order to improve the yield, **2** was obtained by a one pot reaction in which the produced **1** was directly reduced with $NaBH_4$ *in situ* without separation.

2. Optical spectroscopic studies of 1a, 1b, 2a and 2b

Fig. 1 and 2 show the UV-Vis and fluorescence spectra of **1a**, **1b**, **2a** and **2b** in toluene, respectively. The UV-Vis spectra of both **2a** and **2b** are similar to that of BINOL.[12] However, the longest absorption band of **1a** and **1b** situate at 388 nm, which can be attributed to the conjugation of imine with aromatic ring. There are no obvious differences between the UV-Vis spectra of **1a** and **1b**, **2a** and **2b**, respectively, which indicates that the stereo configurations have no influence on UV-Vis absorptions.

In contrast, though the fluorescence spectra of **1a** and **1b** are almost the same, the fluorescence intensity of **2b** is obviously stronger than that of **2a**, which may be ascribed to the difference between the spatial structures of **2a** and **2b**. Meanwhile, **2b**

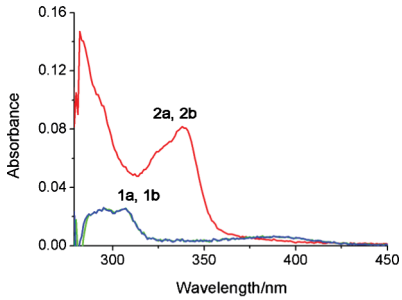


Fig. 1 UV-Vis spectra of **1a**, **1b**, **2a** and **2b** (1×10^{-6} mol L^{-1} in toluene).

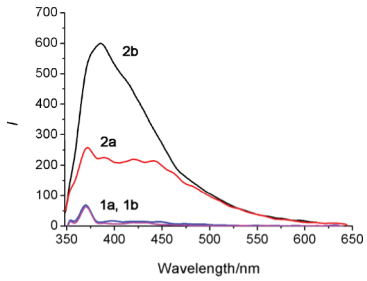


Fig. 2 Fluorescence spectra of **1a**, **1b**, **2a**, and **2b** (1×10^{-6} mol L^{-1} in toluene, $\lambda_{ex} = 331$ nm).

mainly shows the emission of monomers, whereas **2a** exhibits dual emission and bear a peak at *ca.* 440 nm indicating the possible formation of excimers.[4d] The fluorescence intensity of **2a** and **2b** is much stronger than that of **1a** and **1b**. Similar observation that the fluorescence intensity of a naphthyl-amine-based compound is stronger than that of the corresponding naphthyl-imine-based compound has been reported.[13]

The concentration effect on the UV-Vis and fluorescence spectra of **1a**, **2a** and **2b** were studied (ESI, Fig. S1–S6†). All the UV-Vis spectra of **1a**, **2a** and **2b** in toluene ranging from 1×10^{-7} to 3×10^{-5} mol L^{-1} obey the Lambert–Beer Law well. The fluorescence spectra of **1a** ranging from 1×10^{-7} to 2.1×10^{-5} mol L^{-1} and the fluorescence spectra of **2a** and **2b** ranging from 1×10^{-7} to 5×10^{-6} mol L^{-1} follow the Lambert–Beer Law as well. However, the fluorescence intensities of **2a** and **2b** reach maxima as the concentration increasing to *ca.* 1×10^{-5} mol L^{-1}, and then decline, which suggests that the suitable concentration of sensors should preferably be below 1×10^{-5} mol L^{-1} to avoid the violation of Lambert–Beer Law.

As is evident from the CD spectra in Fig. 3, the CD curves of **1a** and **1b**, **2a** and **2b** are proximately mirror-imaged to each other, respectively, which indicates the domination of BINOL unit rather than *trans*-DACH units on the CD effect. Given that **1a** and **2b** exhibit intense positive Cotton effects at 254 and 241 nm respectively, whereas **1b** and **2a** appear opposite Cotton effects at the corresponding wavelength and on the basis of the reported CD studies on the 1,1′-binaphthyl compounds,[4d,14] it can be suggested that the binaphthyl units in **1a** or **1b** have a *transoid* conformation, *i.e.* the dihedral angle of the binaphthyl units is greater than 90°, and the **2a** and **2b** have a *cisoid* conformation *i.e.* the dihedral angle of the binaphthyl units is smaller than 90° (Fig. 4).

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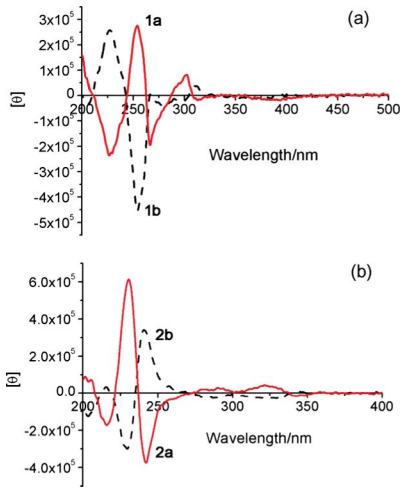


Fig. 3 CD spectra of **1a**, **1b** (a) and **2a**, **2b** (b) (5.0×10^{-6} mol L^{-1} in CH_3CN).

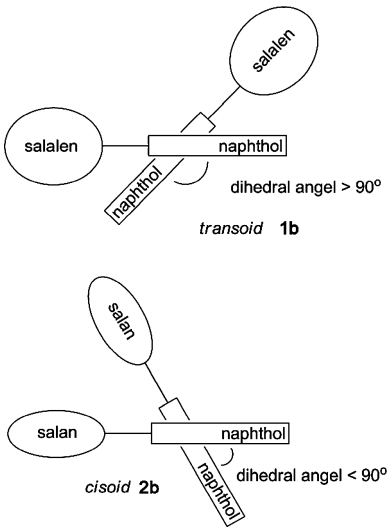


Fig. 4 Conformations of **1b** and **2b**.

3. Fluorescent recognition of mandelic acid

Fluorescence spectra obtained during the titration of **1a**, **1b**, **2a** and **2b** (1.0×10^{-6} mol L^{-1}) with (*S*)-MA or (*R*)-MA ($0 \sim 1 \times 10^{-4}$ mol L^{-1}), respectively, are shown in Fig. 5. Observed fluorescence enhancement responses indicate that the protonation of N atoms near the BINOL group by MA can suppress the PET quenching. The ratio of the fluorescence intensities *i.e.* I_R/I_S (or I_S/I_R) could be used as a criterion for the fluorescence enantioselectivity of a sensor towards guests.[4a] As shown in Fig. 5a, 5b, 5e and 5f, while **1b** is titrated with MA, the fluorescence is more enhanced by (*R*)-MA than by (*S*)-MA ($I_R/I_S = 1.45$). Whereas **1a** exhibits opposite fluorescence response ($I_S/I_R = 1.55$). Fig. 5c, 5d, 5g and 5h show that (*R*)-MA can enhance the fluorescence of **2b** or **2a** more greatly than (*S*)-MA. I_R/I_S reaches 1.42 for **2b** and 2.41 for **2a** respectively when $c_{MA} = 1 \times 10^{-4}$ mol L^{-1}. While the concentration of MA ranges from 0 to 1×10^{-4} mol L^{-1}, the maximal fluorescence enhancement ratios I_{Rmax}/I_0 reach 2.33, 1.91, 28.56 for **1b**, **2b**, **2a**, and I_{Smax}/I_0 = 2.74 for **1a**. Possessing the highest fluorescent enantioselectivity and sensitivity, **2a** is the most outstanding sensor among **1a**, **1b**, **2a** and **2b**.

When a sensor contains multiple chiral units, each chiral unit might play a different role in the recognition process. As mentioned above, the salalen-based sensors **1a** and **1b** have opposite fluorescence response towards enantiomers of MA indicating that the optically active BINOL units play a major role in the enantioselective recognition process. On the contrary, fluorescence of both salan-based sensors **2a** and **2b** were more enhanced by (*R*)-MA than by (*S*)-MA, which suggests that the chirality of *trans*-DACH units dominate the enantioselectivity.

Moreover, reported sensors bearing BINOL and *trans*-DACH units are often (*S*;*R*,*R*) or (*R*;*S*,*S*)-sensors (here, we use the *R* or *S* before and after the semicolon to represent the configuration of BINOL and DACH units respectively), and as examples **5** and **6** are listed (Scheme 2).[4d] Herein, the fluorescence enantioselectivity

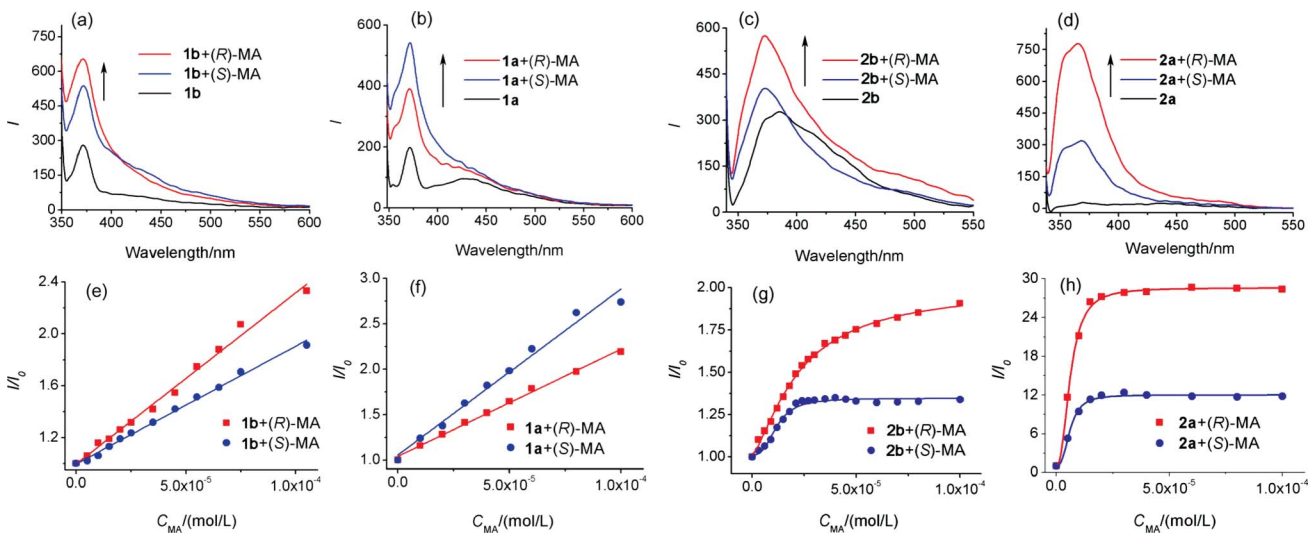
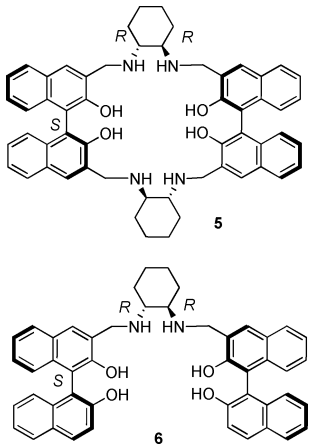


Fig. 5 Fluorescence spectra of (a) **1b**, (b) **1a**, (c) **2b** and (d) **2a** (1×10^{-6} mol L^{-1} in toluene, $\lambda_{ex} = 331$ nm) with (*S*)-MA or (*R*)-MA (1×10^{-4} mol L^{-1}) and the plots of (I/I_0) *vs.* the concentration of MA during the titration of **1b**, **1a**, **2b** and **2a** with (*S*)-MA or (*R*)-MA ($\lambda_{ex} = 331$ nm, to (e) and (f) $\lambda_{em} = 371$ nm, to (g) and (h) $\lambda_{em} = 368$ nm).



Scheme 2 Structures of **5** and **6**.

of **1a** and **2a** is obviously higher than that of **1b** and **2b**, which suggests that the (*R*;*R*,*R*)-sensors have higher fluorescence enantioselectivity than (*S*;*R*,*R*)-sensors do.

To ascertain whether the different fluorescence responses of **2a** toward two enantiomers of MA are arisen from chiral recognition, **2c**, the enantiomer of **2a**, was synthesized. The fluorescence responses of **2c** toward (*R*)- and (*S*)-MA appear the almost mirror images of that of **2a** (Fig. S7†), which confirms that the fluorescence response of **2a** toward the enantiomers of MA is indeed due to the enantioselective recognition.

The influence of the enantiomeric composition of MA on the fluorescence intensity of **2a** was also investigated. As shown in the Fig. 6, the intensity of fluorescence enhanced while adding (*R*)-MA or enantiomeric mixture of MA. With the same amount of (*R*)-MA, the enantiomeric mixture (curve a) causes a stronger fluorescence than optically pure (*R*)-MA (curve b) does, which suggests that **2a** can be applied for enantiomer composition determination of MA.

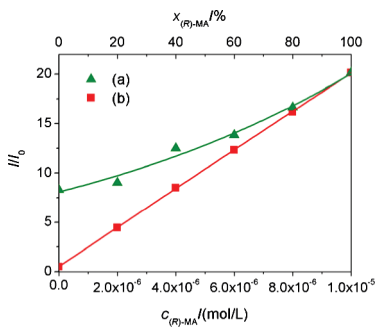


Fig. 6 Fluorescence enhancement of **2a** (1.0×10^{-6} mol L^{-1} in toluene) in the presence of the enantiomeric mixture of MA at 1×10^{-5} mol L^{-1} (curve a, top scale) and pure (*R*)-MA (curve b, bottom scale) (λ_{ex} = 331 nm, λ_{em} = 372 nm).

4. Concentration effect on the fluorescent recognition

The concentration effect on the recognition of **2a** toward the two enantiomers of MA was studied. Besides $c_{2a} = 1 \times 10^{-6}$ mol L^{-1} (Fig. 5h), the fluorescent titration of **2a** with (*S*)-MA or (*R*)-MA, when $c_{2a} = 1 \times 10^{-5}$, 1×10^{-7} mol L^{-1}, was also carried out respectively (Fig. 7). It is found that when $c_{2a} = 1 \times 10^{-5}$ mol L^{-1}, only

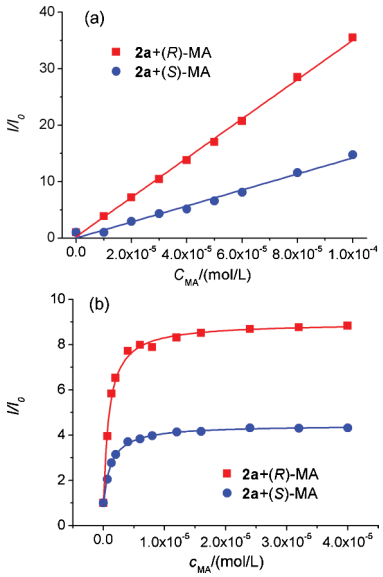


Fig. 7 Plots of (I/I_0) *vs.* the concentration of MA during the titration of **2a** with (*S*)-MA or (*R*)-MA in toluene (λ_{ex} = 331 nm, (a) $c_{2a} = 1 \times 10^{-5}$ mol L^{-1}, λ_{em} = 366.5 nm; (b) $c_{2a} = 1 \times 10^{-7}$ mol L^{-1} λ_{em} = 369 nm).

10 equiv. of (*R*)-MA (*i.e.* 1×10^{-4} mol L^{-1}) results in the fluorescence enhancement ratio I_R/I_0 coming up to 35.5 which is higher than 28.56 ($c_{2a} = 1 \times 10^{-6}$ mol L^{-1}, 100 equiv. (*R*)-MA) and 8.83 ($c_{2a} = 1 \times 10^{-7}$ mol L^{-1}, 400 equiv. (*R*)-MA). The corresponding I_R/I_S are 2.45, 2.41 and 2.04, respectively. These results demonstrate that the concentration of sensor has obvious influence upon the recognition, and the increase of the concentration of sensor can lead to the enhancement of the sensitivity and enantioselectivity.

5. Solvent effect on the fluorescent recognition

Since solvent may have influence on the recognition process even the sensitivity and enantioselectivity, the solvent effect was also studied. In this paper, besides in toluene, **2a** was titrated with (*S*)-MA or (*R*)-MA in methanol, acetonitrile and chloroform respectively (Fig. 8). In methanol, **2a** gave a major emission at 416 nm (Fig. S8). During the adding of the (*S*)-MA or (*R*)-MA, fluorescence quenching occurred. (*R*)-MA caused more obvious quenching of **2a** than (*S*)-MA did and the corresponding I_S/I_R = 1.12 ($c_{MA} = 2.0 \times 10^{-4}$ mol L^{-1}) indicating poorer fluorescence enantioselectivity in methanol than in toluene. In acetonitrile, the intensity of fluoresce was increasing while adding (*S*)-MA or (*R*)-MA. The shape of the plots is different from that in toluene and contains more than one titration flat, which suggests that there could be more than one association patterns for the host and guest and the association process might possesses several steps.[15] Poor sensitivity (I_{Rmax}/I_0 = 1.83 $c_{MA} = 2.0 \times 10^{-4}$ mol L^{-1}) and poor fluorescence enantioselectivity (I_R/I_S = 1.23) were observed. In chloroform, fluorescence responses of **2a** towards (*S*)-MA or (*R*)-MA are similar to that in toluene. Though I_R/I_0 valued 25.81 ($c_{MA} = 1 \times 10^{-4}$ mol L^{-1}) which is slightly smaller than 28.56 in toluene, it is surprising that the I_R/I_S comes up to 3.66 which is obviously larger than 2.41 in toluene indicating higher fluorescence enantioselectivity has been achieved.

It is reasonable that **2a** has higher enantioselectivity towards MA in toluene than in methanol or acetonitrile, since in chemical

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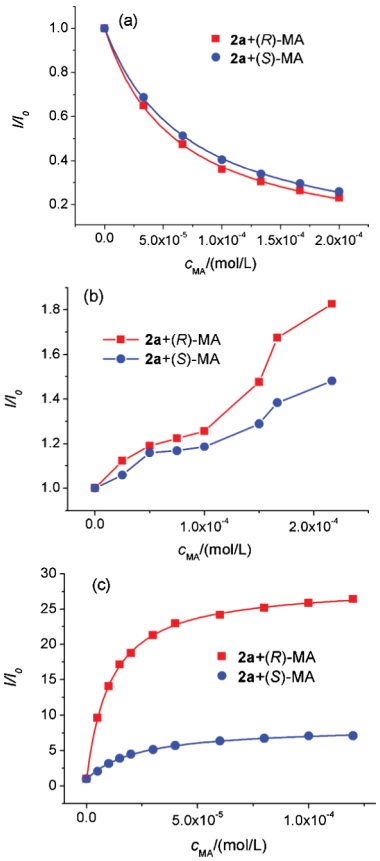

Fig. 8 Plots of (I/I_0) *vs.* the concentration of MA during the titration of **2a** (1×10^{-6} mol L^{-1}) with (*S*)-MA or (*R*)-MA ((a) in MeOH $\lambda_{ex} = 331$ nm, $\lambda_{em} = 416$ nm; (b) in CH_3CN $\lambda_{ex} = 331$ nm, $\lambda_{em} = 372$ nm; (c) in chloroform $\lambda_{ex} = 331$ nm, $\lambda_{em} = 366.5$ nm).

processes based on interactions of hydrogen bonds, the enantioselectivity and associative interactions in polar solvent are often lower than in nonpolar solvent.[1a,16]

However, why sensor **2a** can exhibit higher fluorescence enantioselectivity in chloroform a moderate polar solvent than in toluene a nonpolar solvent must be explained. Encouraged by recent brilliant achievements of Anslyn's indicator-displacement assays[17] and competitive binding assays such as Wolf's[18] and Feng's,[19] we presume that the active sites of **2a** are hydrophilic and could interact with not only MA but also solvent molecules in the recognition process, *i.e.* there exist competitions between MA and solvent molecules.

In nonpolar solvents such as toluene the solvent molecules around the active sites of **2a** are easily dispersed by both (*S*)-MA and (*R*)-MA due to their weak interactions with the active sites. While in strong polar solvents such as methanol and acetonitrile, strong intermolecular hydrogen bonds might form between the solvent molecules and the active sites or MA. Moreover, the conformational rigidity of sensors decreases as the intramolecular hydrogen bonds are broken by strong polar solvent. Thus, low associability and enantioselectivity could be observed.

Given that (*R*)-MA causes stronger fluorescence than (*S*)-MA does, we suppose that (*R*)-MA have stronger affinity for **2a** than (*S*)-MA dose. The polarity of chloroform is stronger than toluene, but weaker than methanol. Such moderate polarity might lead the chloroform molecules to form moderate hydrogen bonds with active sites and can be displaced by (*R*)-MA but harder by (*S*)-MA, thus results in higher fluorescence enantioselectivity in chloroform than in toluene. Consequently, the fluorescence enantioselectivity might be enhanced by adjusting the polarity of solvent.

To further verify the assumptions mentioned above, the solution of **2a** (1×10^{-6} mol L^{-1}) with (*S*)- or (*R*)-MA (1×10^{-4} mol L^{-1}) in toluene and in chloroform was titrated with methanol respectively. As shown in Fig. 9, while the volume percentage of methanol increases, the fluorescence intensity of **2a** with (*S*)-MA or (*R*)-MA declines indicating the MA associated with active sites of the sensor probably being dissociated and replaced by methanol molecules. When the volume percentage of methanol is 2%, the fluorescence intensity of **2a**+(*S*)-MA in toluene declines 83.5%, and **2a**+(*R*)-MA only 36.7%. Similarly, when the volume percentage of methanol is 1% in chloroform, the fluorescence intensity of **2a**+(*S*)-MA declines about 25%, and **2a**+(*R*)-MA about 22%, respectively. This result suggests that the (*S*)-MA has weaker affinity towards **2a** than (*R*)-MA does, and the adjustment of the solvent polarity by adding appropriate amount of methanol in toluene or in chloroform could lead to the enhancement of the enantioselectivity. It should be noted that, besides the disadvantages of strong polar solvents mentioned above, large amount of methanol will also lead the fluorescence intensity of **2a**+(*S*)-MA (upper curve) approach to that of **2a**+(*R*)-MA (lower curve), and the enantioselectivity will decline consequentially. These results support the solvent-guest competition mechanism mentioned above.

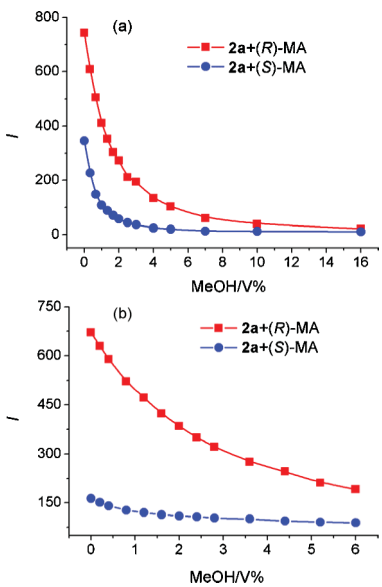

Fig. 9 Fluorescence intensity *I* of the solution of **2a** (1×10^{-6} mol L^{-1}) with (*S*)-MA or (*R*)-MA (1×10^{-4} mol L^{-1}) *vs.* the volume percentage of methanol ((a) in toluene; (b) in chloroform; $\lambda_{ex} = 331$ nm, $\lambda_{em} = 366.5$ nm.).

6. CD recognition of MA

The CD spectra of **2a**, MA, **2a**+MA in acetonitrile were recorded. Considering that the association of **2a** with (*S*)-MA or (*R*)-MA might change the CD spectrum of **2a**, a new curve **2a**~MA signifying CD spectrum of **2a** interacting with MA can be obtained

by subtracting CD curve of MA from **2a**+MA. As shown in the Fig. 10, the Cotton effects of **2a**~(*R*)-MA and **2a**~(*S*)-MA are similar to that of **2a**, indicating the conservation of *cisoid* conformation of **2a**. However, [θ] of **2a** at 230 nm decreases from 6.13×10^5 to 3.78×10^5 deg cm^2 dmol^{-1} indicating that MA has obvious interaction with **2a**. In addition, CD spectra of **2a**~(*R*)-MA and **2a**~(*S*)-MA show blue shift about 1 nm and 3 nm respectively relative to **2a**, indicating the dihedral angle of the binaphthyl unit is slightly enlarged.[4d,14] This might suggest that the MA possibly have been captured by **2a** and entered into the gaps between two salan units. Besides the difference of blue-shift values, [θ] of **2a**~(*R*)-MA also differ from that of **2a**~(*S*)-MA at 215 and 240 nm. All these reveal and corroborate the enantioselectivity of **2a** towards MA.

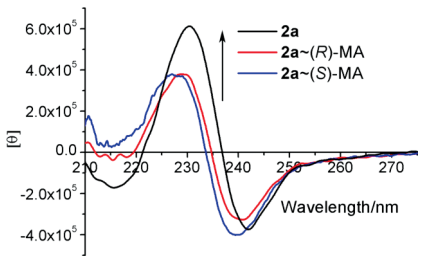

Fig. 10 CD spectra of **2a** and **2a**~MA (obtained by subtract CD curve of MA from curve of **2a**+MA) in acetonitrile ($c_{2a} = 5 \times 10^{-6}$, $c_{MA} = 2.5 \times 10^{-5}$ mol L^{-1}).

7. NMR studies on the interaction of 2a with (*R*)-MA

The interaction of **2a** with (*R*)-MA was studied using ^{1}H NMR spectroscopy while the total concentration of **2a** and (*R*)-MA was maintained at 2.0×10^{-3} mol L^{-1} in a mixed solvent of acetone-d6/DCCl$_3$ (v/v = 2.4%) (Fig. 11). The signal of a-H of (*R*)-MA at δ 5.219 was shifted upfield and δ reached minimum 4.521 while the molar ratio of (*R*)-MA/**2a** was 0.4 : 0.6; and the largest shift $\Delta\delta_{max}$ is up to 0.70. The signals of aryl A, methylene B and BINOL units (b-H is chosen as an example) of **2a** were also obviously changed. The most pronounced shift change comes from a hydrogen atom among methylene B whose δ shifted upfield from 3.805 to 3.107, and $\Delta\delta_{max}$ is also up to 0.70 at 0.5 : 0.5 molar ratio of (*R*)-MA/**2a**. These results suggest that all the hydroxyl and amino groups of **2a** are engaged in the recognition process and remarkably interact with (*R*)-MA.

The Job plot[20] of receptor **2a** with (*R*)-MA obtained by using the ^{1}H NMR signal change ($\Delta\delta = \delta - \delta_0$) of the b-H and a-H reveals that **2a** forms a 1 : 1 complex with (*R*)-MA (Fig. 12).

8. Determination of stoichiometries and association constants

The stoichiometries and stability constants of the sensor (host) with the acids (guests) can be established by use of the Benesi–Hildebrand method[21,22e] Assuming that the acids form the n : 1 inclusion complexes with the sensor, eqn (1) is applicable:

$$I = I_0 + (I_{lim} - I_0) \times \frac{KC_G^n}{1 + KC_G^n} \quad (1)$$

where K is the association constant, I represents the fluorescence intensity, and C_G is the concentration of guest. By nonlinear fitting using eqn (1), the stoichiometries and association constants can be calculated.

In the case where a 1 : 1 stoichiometry is determined, eqn (2) is applicable and more accurate for the calculation of association constant than eqn (1).[22]

$$I = I_0 + \frac{(I_{lim} - I_0)}{2C_H} \times \left[C_H + C_G + \frac{1}{K} + \sqrt{(C_H + C_G + \frac{1}{K})^2 - 4C_H C_G} \right] \quad (2)$$

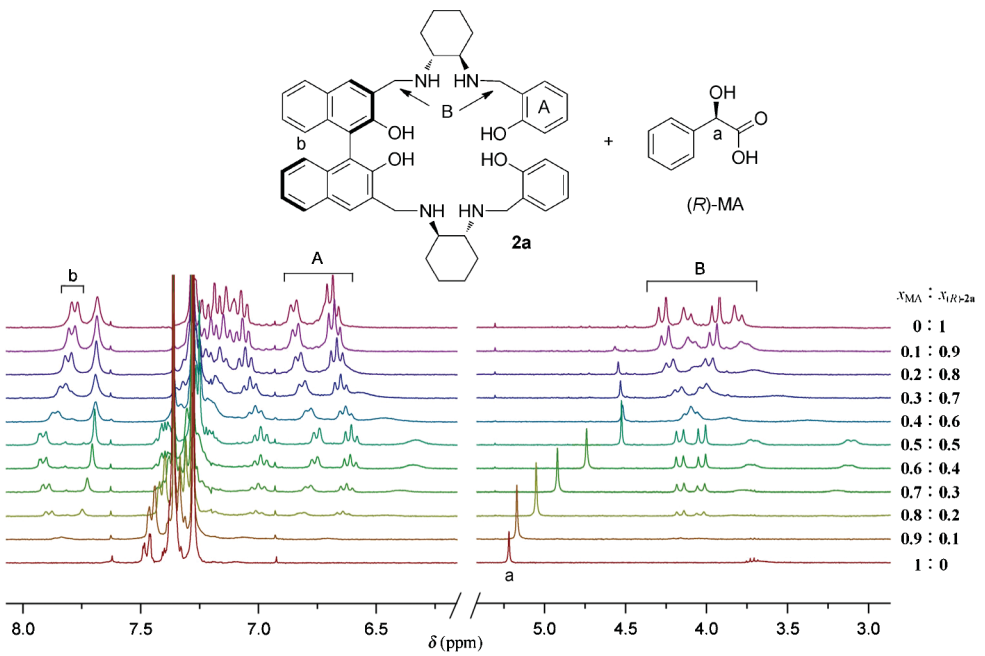

Fig. 11 Partial ^{1}H NMR (Bruck 300 MHz) spectra of **2a**+(*R*)-MA (in acetone-d6/CDCl$_3$, v/v = 2.4%). The total concentration of **2a**+(*R*)-MA was maintained at 2.0×10^{-3} mol L.

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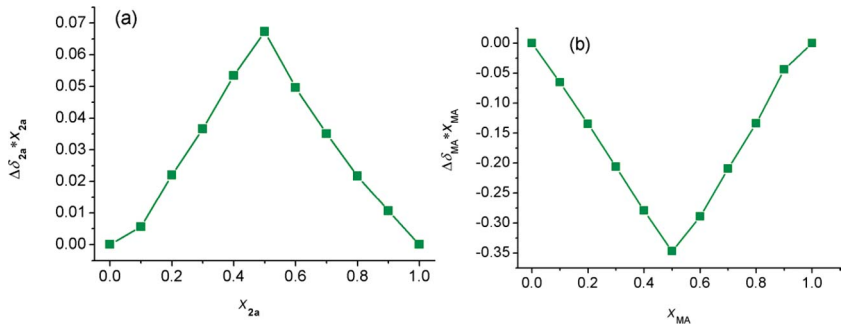


Fig. 12 Job plot of receptor **2a** with (*R*)-MA obtained by using the ^{1}H NMR signal change ($\Delta\delta = \delta - \delta_0$) of the (a) b-H of **2a** and (b) a-H of (*R*)-MA.

where C_H is the concentration of host, the other symbols have the same meaning with in eqn (1).

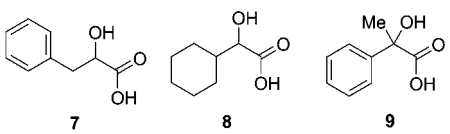
The calculation results of stoichiometries, association constants and enantioselectivity for **2a** associating with (*R*)-MA or (*S*)-MA in different solvents and different concentrations are listed in Table 1. In most cases, *n* obtained from eqn(1) is about 1 and the corresponding plots fit eqn(2) well ($r^2 > 0.98$) indicating the formation of a 1 : 1 stoichiometric complex, which is consistent with the results of ^{1}H NMR Job plot. However, when $c_{2a} = 1 \times 10^{-6}$ mol L^{-1} in toluene, the *n* values above 2, which suggests that the formed 1 : 1 complex of **2a** with MA might be able to associate with additional MA at high concentration in nonpolar solvent.

When **2a** associates with (*R*)-MA or (*S*)-MA and forms 1 : 1 complex, the association constant increases as the polarity of solvent decreases. The association constants in toluene are nearly hundred times bigger than those in methanol, and are also higher than those of many reported carboxylic acids sensors,[9g–9i,23] which indicates that **2a** is highly sensitive towards MA.

In most cases, the resulting K_R is larger than K_S, which is consistent with the previous assumption. Moreover, the enantioselectivity varies with the polarity of solvents. The most outstanding enantioselectivity in single solvent can be found in chloroform, where K_R/K_S is 2.14, and the response selectivity[24] is up to 7.27. While adjusting the polarity of chloroform with 1% (v/v) methanol, K_R/K_S increases to 2.86 *i.e.* $\Delta\Delta G$ values 2.60 kJ mol^{-1} which is comparable to that of macrocyclic ligands,[9h,25] and the response selectivity is up to 9.83 indicating that higher enantioselectivity has been achieved. In the same way, by adjusting the polarity of toluene with 1% (v/v) methanol, the response selectivity is enhanced as high as 6.02, and K_R/K_S reached 2.39. All these results reconfirm the solvent-guest competition mechanism and corroborate its validity.

9. Fluorescent recognition of other α-hydroxycarboxylic acids

Besides MA, the enantioselective fluorescent recognition of **2a** towards other three α-hydroxycarboxylic acids, 2-hydroxy-3-phenylpropanoic acid (**7**), 2-cyclohexyl-2-hydroxyacetic acid (**8**) and 2-hydroxy-2-phenylpropanoic acid (**9**) (Scheme 3) were also studied.



Scheme 3 Structures of **7**, **8** and **9**.

As shown in the Fig. 13, while **2a** was treated with enantiomers of **7**, **8** and **9** in chloroform with 1% (v/v) methanol, the fluorescence intensities enhanced. Herein, (*R*)-α-hydroxycarboxylic acid results in greater fluorescence enhancement than corresponding (*S*)-α-hydroxycarboxylic acid does at the same concentration.

Table 1 Stoichiometries, association constants and enantioselectivity for sensor **2a** towards (*R*)-MA or (*S*)-MA[a]

C_H/(mol L^{-1})	Solvent	MA	n^b	K^c/(mol L^{-1})$^{-1}$	K_R/K_S	rs^d
1×10^{-6}	methanol	*R*	1.03 ± 0.11	(1.67 ± 0.08)×10^4	1.18	1.15
		S	0.95 ± 0.13	(1.41 ± 0.06)×10^4		
	chloroform	*R*	1.01 ± 0.04	(9.64 ± 0.21)×10^4	2.14	7.27
		S	1.14 ± 0.07	(4.51 ± 0.26)×10^4		
	chloroform[e]	*R*	1.15 ± 0.11	(6.33 ± 0.40)×10^4	2.86	9.83
		S	1.12 ± 0.02	(2.21 ± 0.09)×10^4		
	toluene[f]	*R*	2.36 ± 0.70	(2.73 ± 0.26)×10^{10} M^{-2}	0.91	2.12
		S	2.70 ± 1.31	(3.00 ± 0.51)×10^{10} M^{-2}		
	toluene[g]	*R*	1.06 ± 0.03	(2.58 ± 0.14)×10^4	2.39	6.02
		S	0.93 ± 0.08	(1.08 ± 0.08)×10^4		
1×10^{-7}	toluene	*R*	1.16 ± 0.13	(1.13 ± 0.09)×10^6	1.36	2.74
		S	1.15 ± 0.08	(8.31 ± 0.05)×10^5		

[a] All data were obtained by performing nonlinear fitting according eqn (1) and (2); in most case determination coefficients $r^2 > 0.98$. [b] from eqn (1). [c] most from eqn (2); [d] response selectivity[24] $rs = (K_R F_R)/(K_S/F_S)$, $F_{R\,or\,S}$ represents maximum fluorescence enhancement by (*R*) or (*S*)-MA. [e] with 1% (v/v) methanol, titration curve and plots could be found in the ESI (Fig. S9†). [f] assuming that **2a** associated with 2 equiv. MA, the overall association constants were calculated by eqn (1) when *n* was fixed 2. [g] with 2% (v/v) methanol, titration curve and plots could be found in the ESI (Fig. S10†).

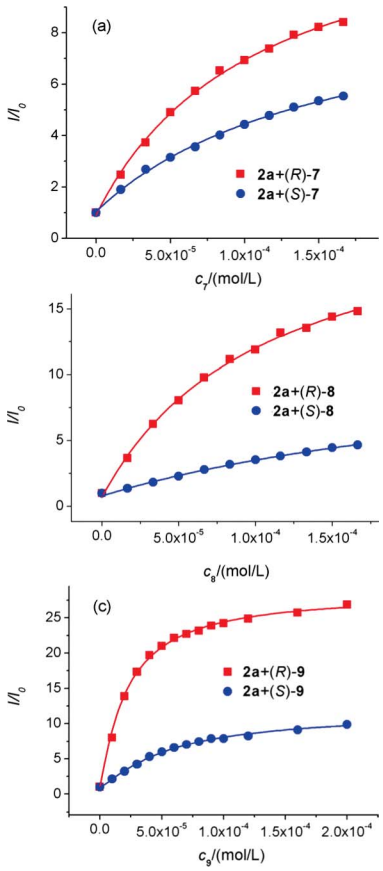


Fig. 13 The plots of (I/I_0) *vs.* the concentration of MA during the titration of **2a** (1×10^{-6} mol L^{-1}) with (a) (*R*)-**7** or (*S*)-**7**, (b) (*R*)-**8** or (*S*)-**8** and (c) (*R*)-**9** or (*S*)-**9** in chloroform with 1% (v/v) methanol (λ_{ex} = 331 nm, λ_{em} = 366.5 nm).

While concentration of α-hydroxycarboxylic acid is 1×10^{-4} mol L^{-1}, the I_R/I_0 corresponding to **7**, **8** and **9** are 7.78, 14.56 and 24.23, and the corresponding I_R/I_S are up to 1.56, 3.35 and 3.07, respectively. The sensitivity and enantioselectivity are comparable with the results of MA (I_R/I_0 = 26.9 and I_R/I_S = 4.06) obtained at the same condition (Fig. S10†).

The association constants and enantioselectivity for sensor **2a** towards the enantiomers of **7**, **8** and **9** in chloroform with 1% (v/v) methanol were calculated (Table 2). The K_R/K_S corresponding to **7** is 1.48, which is little smaller than 1.92 to MA. This decrease of enantioselectivity can be ascribed to the flexibility of the methylene unit between the benzene ring and the α position of **7**.[4a] The K_R/K_S corresponding to **8** and **9** are 2.99 and 3.25, *i.e.* $\Delta\Delta G$ values are 2.71 and 2.92 kJ mol^{-1}, and the corresponding response selectivity are up to 5.94 and 7.32, respectively, which indicates high enantioselectivity has been achieved. These results suggest that the enantioselectivity can be enhanced by the increase of the number of groups in the α position of α-hydroxycarboxylic acid or the increase of the bulk of groups. However, it can be found that the steric hindrance can also lead to the decrease of association constants as evident from the lower association constants of **2a** with **7**, **8** and **9** comparing with MA.

To ascertain whether the different fluorescence responses of **2a** towards two enantiomers of **7**, **8** and **9** are arisen from chiral recognition, **2c** was also treated with two enantiomers of **7**, **8** and **9**, respectively (Fig. S11–13†). The results show that the fluorescence responses of **2a** and **2c** toward (*R*)- or (*S*)-α-hydroxycarboxylic acids are almost mirror imaged, confirming that the fluorescence responses of **2a** toward the enantiomers of these α-hydroxycarboxylic acids are indeed arisen from the enantioselective recognition.

Table 2 Association constants and enantioselectivity for sensor **2a** towards the enantiomers of **7**, **8** and **9**

Guests	Conformation	n^a	K^b/(mol L^{-1})$^{-1}$	K_R/K_S	*rs*
7	*R*	1.18 ± 0.07	(9.26 ± 0.90)×10^3	1.48	2.03
	S	0.87 ± 0.08	(6.31 ± 0.56)×10^3		
8	*R*	1.13 ± 0.08	(9.48 ± 0.68)×10^3	2.99	5.94
	S	1.11 ± 0.07	(3.17 ± 0.30)×10^3		
9	*R*	1.14 ± 0.09	(4.52 ± 0.21)×10^4	3.25	7.32
	S	1.23 ± 0.13	(1.39 ± 0.14)×10^4		

[a] obtained from eqn (1); [b] obtained from eqn (2) and all the determination coefficients $r^2 > 0.98$.

Given above results, besides MA, **2a** can also exhibit the considerable sensitivity and the enantioselectivity toward other α-hydroxycarboxylic acids.

Conclusion

We designed and synthesized chiral salalen **1** and salan **2** composed of *trans*-DACH and BINOL units. Fluorescence recognition of MA revealed that the salan-sensors are superior to salalen-based sensors and the chirality combination (*S*;*S*,*S*) or (*R*;*R*,*R*) of BINOL and *trans*-DACH units can lead to higher sensitivity and enantioselectivity in compare with (*R*;*S*,*S*) or (*S*;*R*,*R*).

The studies on the concentration and the solvent effect on the recognition of **2a** towards MA indicate that the sensitivity and enantioselectivity could be enhanced *via* changing the concentration of sensors or altering the polarity of solvents. It is found that higher enantioselectivity can be achieved in moderate polar solvent other than in nonpolar or polar solvent. To explain this, a solvent–guest competition mechanism has been proposed and validated.

Job plot and results of nonlinear regression suggest that **2a** form the 1 : 1 complex with MA in most cases. Response selectivity and the association constant can be up to 9.83 and 10^6 L mol^{-1}, respectively, which indicates that **2a** can be used as a highly enantioselective and sensitive sensor for MA. In addition, the recognition studies of **2a** towards **7**, **8** and **9** reveal that **2a** can also enantioselectively recognize other α-hydroxycarboxylic acids with considerable sensitivity and enantioselectivity.

Experimental section

In this manuscript, all materials obtained from commercial suppliers were used without further purification unless other notification. The enantiomers of BINOL and *trans*-DACH were bought from Sigma–Aldrich and Sichuan Tiancai Fine Chemical Co. Ltd., respectively. They are high quality optically pure, puritiy≥99% and *ee*≥99% (HPLC for BINOL and GLC for *trans*-DACH). Solvents are analytical grade and further purified with standard method.[26]

NMR spectra were recorded on Bruker-300 spectrometer. Mass spectra were determined on a Thermo Finnigan LCQ ESI-MS or

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Bruker Apex Ultra FTMS 7.0 MS. The fluorescent, UV-vis, and CD spectra were recorded with Perkin–Elmer LS55, Shimadzu UV-3600, and JASCO J-720 CD spectrometers respectively. Optical rotations were measured on a Ruololph Research Analyfical Autopol III polarimeter.

Synthesis of (1*R*,2*R*)-cyclohexane-1,2-diamine monohydrochloride. This reaction was performed under nitrogen atmosphere and with exclusion of water. In a 1-L three neck flask with a mechanical stirrer, (1*R*,2*R*)-cyclohexane-1,2-diamine (10.30 g, 90.2 mmol) was dissolved in dry diethyl ether. Under vigorous stirring 1.8 M HCl in diethyl ether (50.0 mL, 90.0 mmol.) was added dropwise at 0 °C, a white solid precipitated. After stirring overnight at room temperature, the mixture was filtered and the residue was washed with diethyl ether and dried under high vacuum to afford 12.63 g white solid (yield: 92%) which was used for next step without further purification and identification.

Synthesis of (1*S*,2*S*)-cyclohexane-1,2-diamine monohydrochloride. By using the same procedure with for the preparation of (1*R*,2*R*)-cyclohexane-1,2-diamine monohydrochloride, (1*S*,2*S*)-cyclohexane-1,2-diamine monohydrochloride was obtained in 95% yield.

Synthesis and characterization of 2-((1*R*,2*R*)-2-amino-cyclohexylamino)methylphenol (4a). Under nitrogen protection, to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine monohydrochloride (1.52 g, 1.0 mmol) in 30 mL methanol and ethanol (1 : 1, v/v) salicylal (1.22 g 1.0 mmol) was added dropwise through a syringe. After that the mixture was stirred at room temperature for 10 min. Then a solution of $NaBH_4$ in methanol was added dropwise to the mixture at 0 °C until the solution became colorless and transparent. The reaction was warmed to r. t. and stirred for 30 min. After removal of most of the solvent, 30 mL H_2O was added and 2 N aqueous HCl added dropwise to the mixture keeping the pH = 5 and stirring until the solution was transparent. The mixture was neutralized with $NaHCO_3$ and then extracted with CH_2Cl_2 (30 mL×3). Combined organic phases was washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by flash column chromatography on silica gel (300–400 mesh) with CH_2Cl_2, MeOH and TEA (25 : 1 : 0.1, v/v/v) as mobile phase to afford **4a** as a white solid (1.17 g yield: 53%). m.p. 73–74 °C; $[\alpha]_D^{26} = -80.0°$(*c* = 17.2 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.19–7.10 (m, 1H), 6.99 (d, *J* = 6.8 Hz, 1H), 6.86–6.71 (m, 2H), 4.07 (d, *J* = 13.8 Hz, 1H), 3.91 (d, *J* = 13.8 Hz, 1H), 2.51–2.36 (m, 1H), 2.23–2.06 (m, 2H), 1.97–1.85 (m, 1H), 1.78–1.63 (m, 2H), 1.39–1.03 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.1, 128.2, 128.0, 123.9, 118.6, 116.1, 63.2, 54.5, 49.5, 36.4, 30.5, 25.1, 24.7. MS (ESI) M+H$^+$ 221.25; HRMS calcd for $C_{13}H_{21}N_2O$ (M+H$^+$) 221.1652; found: 221.1654.

Synthesis and characterization of 2-((1*S*,2*S*)-2-amino-cyclohexylamino)methylphenol (4b). By using the same procedure with for the preparation of **4a**, **4b** was obtained in 60% yield. m.p. 73–74 °C; $[\alpha]_D^{25} = +84.6°$(*c* = 10.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.08 (t, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.81–6.65 (m, 2H), 3.94 (d, *J* = 13.8 Hz, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 2.38–2.23 (m, 1H), 2.13–1.96 (m, 2H), 1.86–1.74 (m, 1H), 1.71–1.55 (m, 2H), 1.31–0.91 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.1, 128.3, 128.1, 123.9, 118.6, 116.2, 63.2, 54.5, 49.5, 36.4, 30.5, 25.1, 24.7; MS (ESI) M+H$^+$ 221.27; HRMS calcd for $C_{13}H_{21}N_2O$ (M+H$^+$) 221.1651; found: 221.1654.

Synthesis and characterization of (*S*)-3,3′-bis-{(1*R*,2*R*)-2-(2-hydroxybenzylamino)cyclohexyliminomethyl}1,1′binaphthalenyl-2,2′-diol (1b). The dialdehyde **3b** (193 mg, 0.56 mmol) and **4a** (250 mg, 0.113 mmol) were dissolved in CH_2Cl_2 (20 mL) and stirred for 12 h at room temperature under nitrogen. After the solvent was removed, the crude product was purified by a short silica gel column (eluted with methylene chloride) to give the macrocyclic Schiff base as a yellow solid (343 mg, yield: 82%). m.p. 143–146 °C; $[\alpha]_D^{26} = -164.9°$ (*c* = 2.42 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.91 (s, 2H), 8.69 (s, 2H), 7.98 (s, 2H), 7.93–7.84 (m, 2H), 7.36–7.26 (m, 4H), 7.23–7.14 (m, 2H), 7.08 (t, *J* = 7.4 Hz, 2H), 6.89 (d, *J* = 7.2 Hz, 2H), 6.80–6.64 (m, 4H), 3.92 (d, *J* = 14.1 Hz, 2H), 3.82 (d, *J* = 14.1 Hz, 2H), 3.24–3.08 (m, 2H), 2.76–2.58 (m, 2H), 2.17–2.01 (m, 2H), 1.85–1.49 (m, 8H), 1.46–1.12 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.9, 157.7, 154.2, 135.3, 133.8, 128.9, 128.5, 128.4, 128.0, 127.6, 124.7, 123.5, 123.2, 120.6, 119.0, 116.5, 116.2, 73.5, 61.1, 49.7, 33.7, 29.5, 24.1. MS (ESI) M –H$^-$; 745.83; HRMS calcd for $C_{48}H_{51}N_4O_4$(M+H$^+$) 747.3910; found: 747.3895.

Synthesis and characterization of (*R*)-3,3′-bis-{(1*R*,2*R*)-2-(2-hydroxybenzylamino)cyclohexyliminomethyl} - 1,1′binaphthalenyl - 2,2′-diol (1a). **1a** was prepared by using the same procedure as for the preparation of **1b**. yield 81%; m.p. 133–135 °C; $[\alpha]_D^{26}$ = –116.2°(*c* = 7.15 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 12.93 (s, 2H), 8.59 (s, 2H), 7.92 (s, 2H), 7.89–7.74 (m, 2H), 7.24 (s, 6H), 7.13–7.01 (m, 2H), 6.86 (d, *J* = 7.2 Hz, 2H), 6.78–6.61 (m, 4H), 3.94 (d, *J* = 13.8 Hz, 2H), 3.79 (d, *J* = 13.8 Hz, 2H), 3.13–2.94 (m, 2H), 2.73–2.56 (m, 2H), 2.17–1.98 (m, 2H), 1.76–1.61 (m, 6H), 1.56–1.41 (m, 2H), 1.37–1.06 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.0, 158.1, 154.4, 135.4, 133.9, 129.0, 128.6, 128.1, 127.7, 125.0, 123.6, 123.3, 120.8, 119.0, 116.6, 116.5, 73.8, 61.1, 50.0, 34.0, 30.1, 24.4, 24.2. MS (ESI) M+H$^+$; 747.33; HRMS calcd for $C_{48}H_{51}N_4O_4$(M+H$^+$) 747.3910; found: 747.3896.

Synthesis and characterization of (*S*)-3,3′-bis-{(1*R*,2*R*)-2-(2-hydroxy - benzylamino)cyclohexylamino - methyl} - 1,1′binaphthal - enyl-2,2′-diol (2b). By using the similar procedure as for the preparation of **4a**, compound **2b** was obtained as a white solid in 88% yield. m.p. 128–130 °C; $[\alpha]_D^{26} = -36.8°$ (*c* = 4.97 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.0 Hz, 2H), 7.62 (s, 2H), 7.31–7.20 (m, 2H), 7.20–6.98 (m, 6H), 6.84 (d, *J* = 7.0 Hz, 2H), 6.77–6.59 (m, 4H), 4.16 (d, *J* = 13.7 Hz, 2H), 4.02 (d, *J* = 13.6 Hz, 2H), 3.90 (d, *J* = 13.9 Hz, 2H), 3.81 (d, *J* = 13.9 Hz, 2H), 2.45–2.17 (m, 4H), 2.14–1.87 (m, 4H), 1.58 (s, 4H), 1.07 (s, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.7, 153.6, 133.8, 128.7, 128.5, 128.2, 128.0, 127.8, 126.1, 126.0, 124.9, 123.0, 119.0, 116.3, 59.8, 49.5, 49.3, 30.4, 24.2. MS (ESI) M+H$^+$ 751.50; HRMS calcd for $C_{48}H_{55}N_4O_4$(M+H$^+$) 751.4223; found: 751.4212.

Synthesis and characterization of (*R*)-3,3′-bis-{(1*R*,2*R*)-2-(2-hydroxybenzylamino)cyclohexylaminomethyl} - 1,1′binaphthalenyl - 2,2′-diol (2a). **2a** was prepared by using the same procedure as for the preparation of **2b**. yield 90%, m.p. 106–110 °C; $[\alpha]_D^{26}$ = –15.4°(*c* = 4.97 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 7.9 Hz, 2H), 7.65 (s, 2H), 7.30–7.21 (m, 2H), 7.21–7.03 (m, 6H), 6.83 (d, *J* = 7.0 Hz, 2H), 6.78–6.64 (m, 4H), 4.20 (d, *J* = 13.4 Hz, 2H), 4.04 (d, *J* = 13.4 Hz, 2H), 3.87 (d, *J* = 14.0 Hz,

2H), 3.78 (d, J = 14.0 Hz, 2H), 2.43–2.21 (m, 4H), 2.18–1.94 (m, 4H), 1.73–1.51 (m, 4H), 1.32–0.96 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.9, 153.5, 133.8, 128.6, 128.3, 127.8, 126.2, 126.0, 124.9, 123.2, 123.1, 119.0, 116.3, 60.0, 49.9, 49.7, 30.7, 30.6, 24.3; MS (ESI) M+H$^+$ 751.52; HRMS calcd for $C_{48}H_{55}N_4O_4$(M+H$^+$) 751.4223; found: 751.4215.

Synthesis and characterization of (*S*)-3,3′-bis-{(1*S*,2*S*)-2-(2-hydroxy - benzylamino) cyclohexylaminomethyl } - 1, 1′binaphthal - enyl-2,2′-diol (2c). **2c** was prepared by using the same procedure as for the preparation of **2b**. yield 87%, m.p. 105–110 °C; $[\alpha]_D^{26}$ = +17.2°(c = 2.49 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.76 (d, J = 7.9 Hz, 2H), 7.64 (s, 2H), 7.30–7.21 (m, 3H), 7.20–7.03 (m, 7H), 6.82 (d, J = 7.0 Hz, 2H), 6.78–6.63 (m, 4H), 4.15 (d, J = 13.4 Hz, 2H), 4.00 (d, J = 13.4 Hz, 2H), 3.85 (d, J = 13.9 Hz, 2H), 3.74 (d, J = 13.9 Hz, 2H), 2.40–2.18 (m, 4H), 2.15–1.93 (m, 4H), 1.60 (s, 4H), 1.09 (s, 8H); ^{13}C NMR (75 MHz, CDCl3) δ = 157.8, 153.4, 133.8, 128.7, 128.4, 128.2, 127.8, 126.3, 126.2, 124.8, 123.1, 122.9, 119.0, 116.3, 116.0, 59.7, 59.3, 48.9, 30.1, 24.3, 24.2. MS (ESI) M+H$^+$ 751.52; HRMS calcd for $C_{48}H_{55}N_4O_4$(M+H$^+$) 751.4223; found: 751.4218.

Preparation of samples for fluorescence measurement. Sensors were purified by column chromatography and then stored under the protection of nitrogen gas in a refrigerator. The enantiomers of mandelic acid were purchased from Aldrich and recrystallized from methanol. All of the solvents were freshly prepared for each measurement. A 0.001 mol L^{-1} stock solution of mandelic acid was freshly prepared in corresponding solvent. For the fluorescence enhancement study, a sensor solution was mixed with the mandelic acid solution at room temperature in a 10 mL volumetric flask and diluted to the desired concentration. The resulting solution was allowed to stand at room temperature for 2–3 h before the fluorescence measurement.

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