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Synthesis of novel chiral fluorescent sensors and their application in enantioselective discrimination of chiral carboxylic acids

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Abstract

Novel chiral fluorescent sensors are synthesized from a dibromide containing a tetraphenylethylene moiety and enantiomerically pure amino alcohols and an amine. The sensors are applied for the chiral recognition of a wide range of chiral carboxylic acids and related derivatives.

Keywords

aggregation-induced emission, carboxylic acids, chiral recognition, chiral sensors, fluorescent

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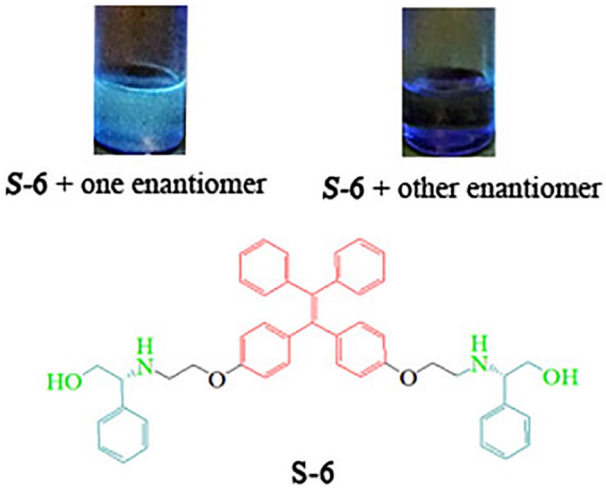
The synthesis of several novel aggregation-induced emission sensors and their application in chiral recognition are reported. The results suggest that sensors ***R*-6** and ***S*-6** are capable of recognizing various chiral carboxylic acids and their derivatives at a low concentration.



Introduction

Chiral recognition is an important process in the natural world and plays a vital role in asymmetric synthesis, chiral drug discovery, catalyst screening, and many other aspects.[1–6] However, conventional enantiomeric analyses not only usually need expensive instruments or complex chiral reagents, but they are also time-consuming in practice. Therefore, it is still important to develop simple, highly efficient, and low-cost methods for chiral recognition, such as chiral fluorescent sensors for the enantioselective discrimination of enantiomers.

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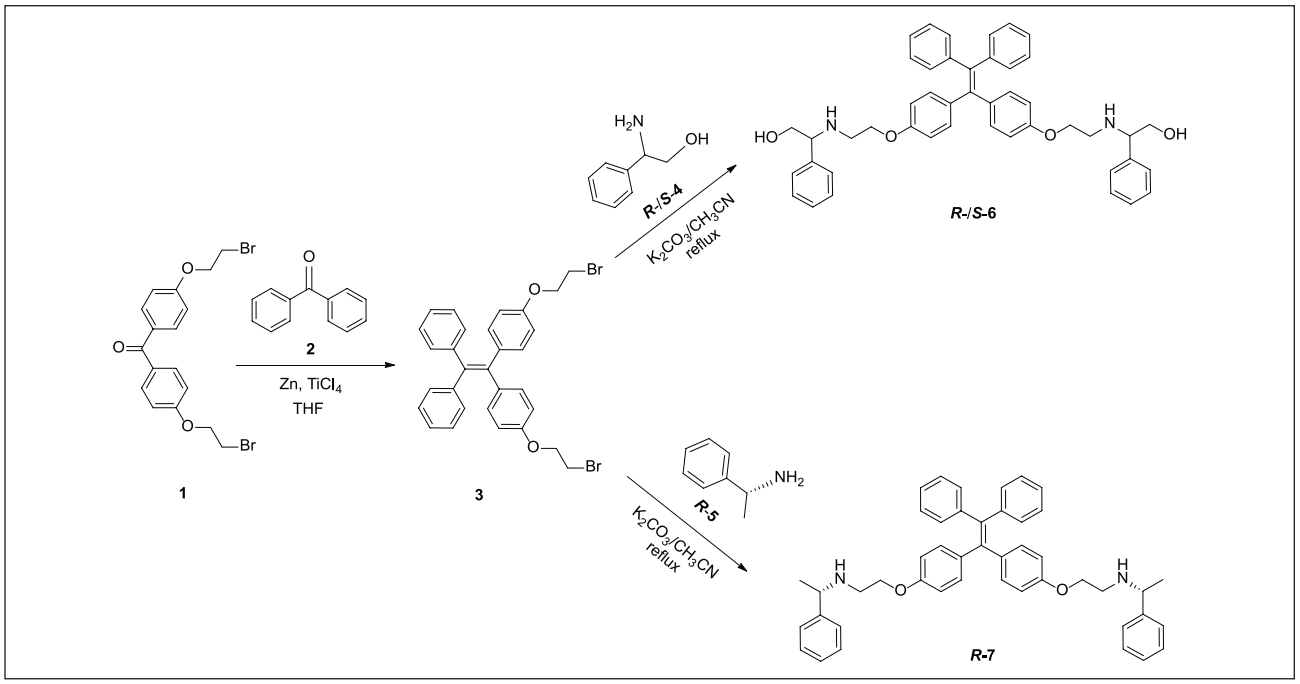


Scheme 1. Synthesis of sensors.

In 2001, Tang and co-workers observed an uncommon and unconventional phenomenon in which some compounds with unique structures are almost non-fluorescent when dissolved in an organic solvent, but which become highly emissive in the aggregate state, a process known as aggregation-induced emission (AIE) or aggregation-induced emission enhancement (AIEE).[7] It is promising that AIE compounds not only solve the aggregation-induced quenching (ACQ) problem without causing any adverse effects,[8,9] but are also stable and highly selective fluorescent sensors for proteins,[10,11] DNA,[12] sugars,[13] metal ions,[14,15] biological anions,[16] cyanide detection,[17] drug carriers,[18] cell imaging,[19,20] and explosive detection.[21,22] According to recent research achievements related to chiral recognition, the conclusion is that there is a simple and effective method to obtain excellent chiral sensors via the combination of one molecule having AIE character with another molecule having a chiral center.[23–28] Unfortunately, for chiral carboxylic acids, very few sensors have been reported, and they are required to be tested at a large concentration.[4,24,26]

Herein, in continuation of our work on enantioselective discrimination,[29–31] several new chiral sensors were designed, synthesized, and fully characterized. Their fluorescent response behaviors to various chiral substrates were analyzed by fluorescence spectroscopic methods. In addition, morphology studies for sensors were analyzed with various microscopic techniques, including transmission electron microscopy (TEM) and fluorescent inverted microscope analysis.

Results and discussion

Synthesis of the sensors

Phenylglycinol and α-methylbenzylamine are cheap and common quenchers that reduce the fluorescence intensity of fluorophores.[1] Tetraphenylethylene (TPE) and its derivatives are widely used as excellent fluorophores due to their facile synthesis and easy modification. We combined a known TPE derivative with two nitrogen-containing chiral auxiliaries in order to provide novel chiral sensors. Treatment of TPE derivative **3**,[14,16,32–34] and optically pure compounds **4** and **5** resulted in the formation of chiral sensors **6** and **7** (Scheme 1).[26] Details of the synthesis and characterization are provided in the "Experimental" section.

Photophysical studies

These chiral products were soluble in most organic solvents such as chloroform, tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), and 1,2-dichloroethane, but were insoluble in petroleum ether and water. As expected, after ***S*-6** was dissolved in THF, the solution (1.0×10^{-5} M) was not fluorescent. When an 80% fraction of water (volume ratio of water vs THF) was added to the solution, the fluorescence intensity of ***S*-6** started to increase. Next, when a 90% fraction of water was added and turbidity emerged, the solution started to emit fluorescent light. A suspension appeared when a 99% fraction of water was added, and the fluorescence intensity of the suspension increased 28.6-fold at $\lambda_{max} = 469$ nm (Figure 1). Therefore, sensor ***S*-6** was an AIE compound. With the same method, compounds ***R*-6** and ***R*-7** in a mixed solvent were also tested and were found to be AIE compounds as well (Supplemental Figure S3).

Studies of chiral recognition

The chiral recognition properties of ***S*-6** were initially tested with the interaction of ***S*-6** and several different substrates with the concentration ratio between sensor ***S*-6** and the chiral substrate being kept as 1:1 in all tests. As shown in Table 1 and Supplemental Figure S4, it was clear that ***S*-6** was capable of recognizing chiral acids and related derivatives.

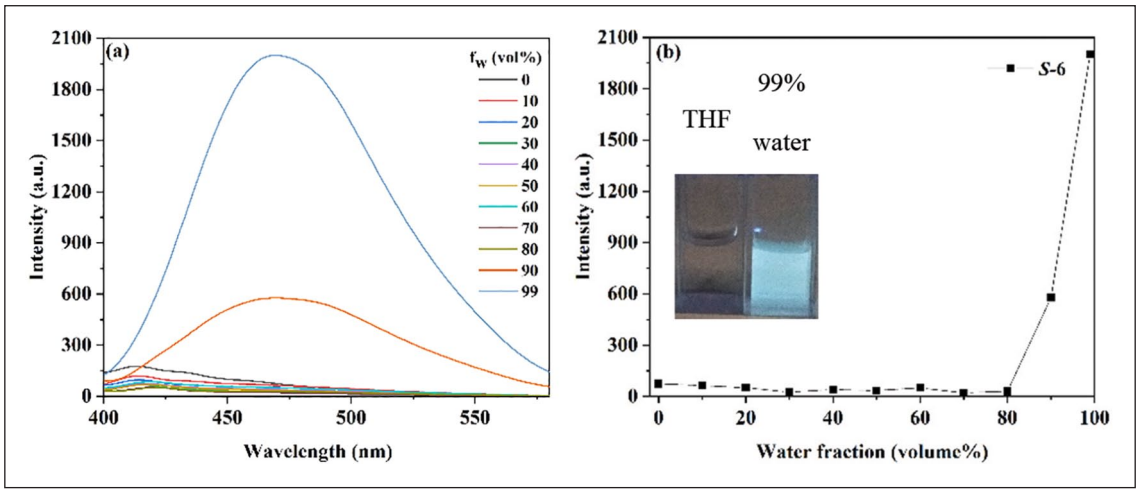
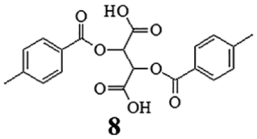
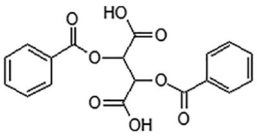
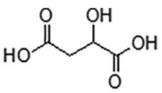
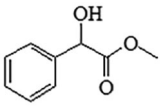
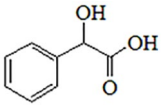
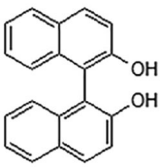


Figure 1. (a) Fluorescence emission spectra of ***S*-6** (1.0×10^{-5} M) in THF–water mixtures with different water fractions (f_w) at a fixed concentration (conditions: λ_{ex} = 320 nm, ex/em slits = 10/10 nm). (b) Curve of fluorescence intensity for ***S*-6** versus the compositions of the aqueous mixtures (λ_{max} = 469 nm). Inset: photographs taken under UV illumination (365 nm).

Table 1. Fluorescence intensity ratios of mixtures of enantiomers of analytes with ***S*-6**, ***R*-6**, and ***R*-7**.

Entry	Analyte	***S*-6** I_1/I_2[a,b]	***R*-6** I_1/I_2[a,b]	***R*-7** I_1/I_2[a,b]
1	 **8**	5.68 (*L*/*D*)	6.01 (*D*/*L*)	1.34 (*L*/*D*)
2	 **9**	2.36 (*L*/*D*)	2.71 (*D*/*L*)	1.04 (*L*/*D*)
3	 **10**	2.83 (*L*/*D*)	2.49 (*D*/*L*)	2.14 (*L*/*D*)
4	 **11**	2.63 (*S*/*R*)	2.16 (*R*/*S*)	1.01 (*S*/*R*)
5	 **12**	2.79 (*S*/*R*)	2.41 (*R*/*S*)	1.12 (*S*/*R*)
6	 **13**	2.12 (*R*/*S*)	1.78 (*S*/*R*)	1.04 (*R*/*S*)

[a]Enantiomer 1/enantiomer 2.
[b]Volume ratio of solvents, [sensor] = [analyte].

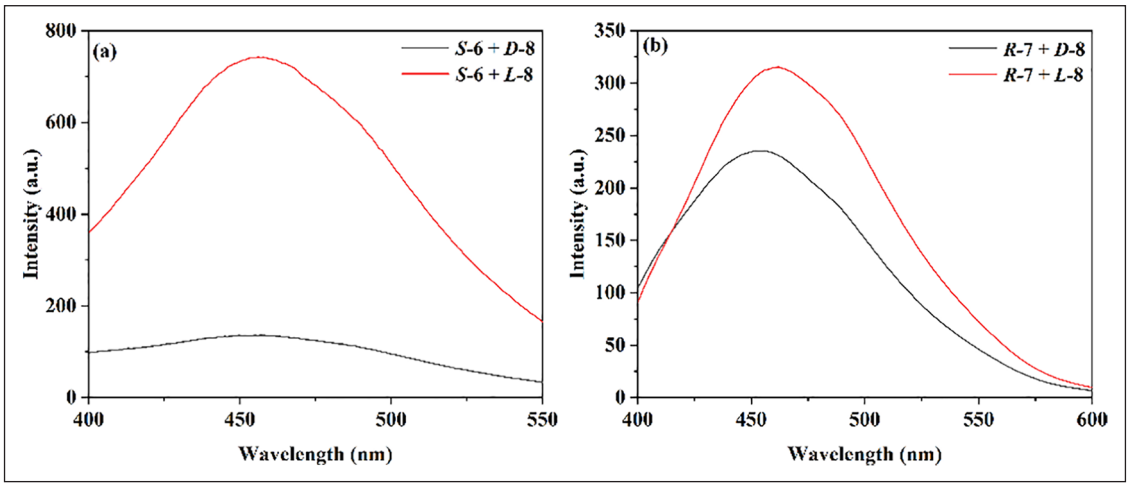


Figure 2. (a) Fluorescence spectra of a mixture of compound **8** and sensor ***S*-6** in solvent (2×10^{-4} M in 1,2-dichloroethane). (b) Fluorescence spectra of a mixture of compound **8** and sensor ***R*-7** in solvent (2×10^{-4} M in 1,2-dichloroethane). The ratio of chiral guests/chiral sensor is 1:1; conditions: λ_{ex} = 320 nm, ex/em slits = 10/10 nm.

When ***S*-6** and ***L*-8** were mixed and the mixture left to stand for 1 h at room temperature, a suspension appeared. The mixture of ***S*-6** and ***L*-8** had a fluorescence intensity of 742.4, while that of the mixture of ***S*-6** and ***D*-8** was only 130 at λ_{max} = 456 nm, showing that the fluorescence ratio of the two enantiomers was $I_{L\text{-}8}/I_{D\text{-}8}$ = 5.68 (Table 1 and Figure 2(a)). Under the same conditions, a mixture of ***L*-9** or ***D*-9** with ***S*-6** was also tested, and the fluorescence ratio of these two enantiomers was $I_{L\text{-}9}/I_{D\text{-}9}$ = 2.36 (Table 1 and Supplemental Figure S4(a)). For simple structure and low-molecular-weight chiral diacids such as malic acid (**10**), the fluorescence ratio of the two enantiomers was $I_{L\text{-}10}/I_{D\text{-}10}$ = 2.83 (Table 1 and Supplemental Figure S4(b)). In addition, a chiral monocarboxylic acid (**12**) and its esterification product (**11**) were also tested. The fluorescence ratio was 2.63 ($I_{R\text{-}11}/I_{S\text{-}11}$) and 2.79 ($I_{S\text{-}12}/I_{R\text{-}12}$) for methyl mandelate (**11**) and mandelic acid (**12**), respectively (Table 1 and Supplemental Figure S4(c) and (d)). Furthermore, for BINOL (**13**), ***S*-6** also showed a good enantioselective ability, and the fluorescence ratio was 2.12 ($I_{R\text{-}13}/I_{S\text{-}13}$) (Table 1 and Supplemental Figure S4(e)).

The analytes in Table 1 were also tested with sensors ***R*-6** and ***R*-7** in different solvent systems. The interactions of the enantiomers with ***R*-6** were tested and gave opposite results in comparison with ***S*-6** under the same conditions (Table 1). However, the test of enantioselectivity indicated that ***R*-7** was not a useful enantioselective sensor (Table 1, Figure 2(b), and Supplemental Figure S5). Structurally, the biggest difference between sensors **6** and ***R*-7** is the reduction in the number of hydrogen bonds. As there are no hydroxy groups in ***R*-7** compared with sensor **6**, it would probably be more difficult for the chiral guests to interact with the sensor ***R*-7** due to the change in the chiral environment.

In addition, the chiral response for racemic acids was also investigated. For example, when racemate **8** was added, the fluorescence ratio of ***R*-6** and ***S*-6** to the racemate was $I_{R\text{-}6}/I_{S\text{-}6}$ = 1.03 (Figure 3). In order to ascertain whether the fluorescence difference resulting from the enantioselective aggregation could be applied to determination of the enantiomeric composition, the change of fluorescence intensity with different contents of ***L*-8** in the two enantiomers of **8** was measured. As shown in Figure 4, two standard curves were drawn, and any enantiomeric composition of **8** could be obtained. Besides, the mixture of compound **8** (65% e.e. for ***L*-8**) with ***S*-6** or ***R*-6** was also tested, and the fluorescence ratio of ***R*-6** and ***S*-6** to compound **8** (65% e.e. for ***L*-8**) was $I_{S\text{-}6}/I_{R\text{-}6}$ = 3.11. Under the same conditions, when compound **8** (65% e.e. for ***D*-8**) was added, the fluorescence ratio of ***R*-6** and ***S*-6** to compound **8** (65% e.e. for ***D*-8**) was $I_{R\text{-}6}/I_{S\text{-}6}$ = 3.18. The results were similar to those listed in Figure 4. These results provided a promising entry to the high-throughput screening of chiral drugs and the rapid construction of various chiral molecules.

Microscopic studies

To understand the morphology of aggregates in mixed solvents, TEM images were examined and the formation of aggregates of ***S*-6** and ***S*-6** with **8** was revealed (Figures 5 and 6). In comparison with a solution of ***S*-6** in THF–water mixture (water fraction was 10%), numerous spherical aggregates could be observed when the water fraction was 95%. As shown in Figure 6, the morphology of aggregates of ***S*-6** with ***L*-8** was observed as spherical, but slightly different from that in the mixture of ***S*-6** and ***D*–8.** We speculate that the distinction in aggregation probably causes the differences in fluorescence intensity and mixture solubility at a macro level.

Experimental

Materials and measurements

All reagents and solvents were chemically pure (CP) or analytical reagent (AR) grade and were used as received without further purification. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AV 500 spectrometer at 303 K from sample solutions in $CDCl_3$. Mass spectra were measured on a Waters Q-TOF microspectrometer. Optical rotations were measured at 25 °C on an Anton Paar MCP 500 polarimeter with a sodium lamp as the light source (589 nm). Fluorescence emission spectra were collected on a Perkin

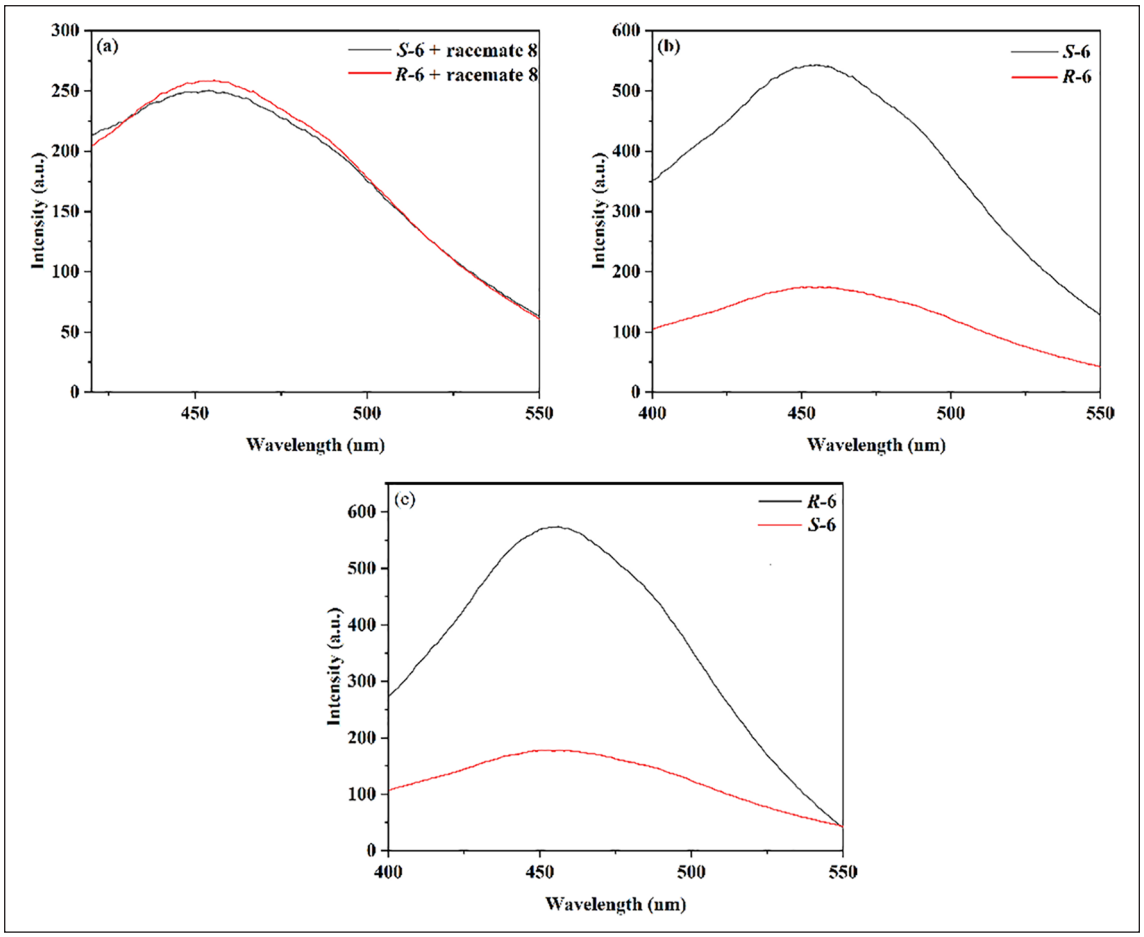


Figure 3. Fluorescence spectra of mixtures in 1,2-dichloroethane (5×10^{-4} M). Mixtures: (a) compound **8** and sensors, (b) compound **8** (65% e.e. for ***L*-8**) and sensors, and (c) compound **8** (65% e.e. for ***D*-8**) and sensors.

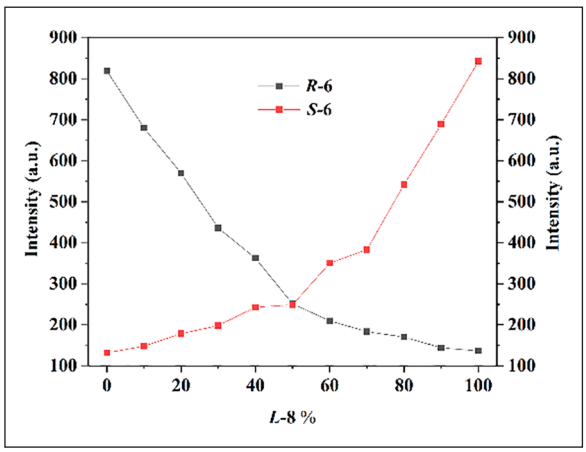


Figure 4. Change in fluorescence intensity of ***S*-6** or ***R*-6** with the enantiomeric content of compound **8** in 1,2-dichloroethane ([***S*-6**] = [***R*-6**] = [***L*-8**] + [***D*-8**] = 5×10^{-4} M).

Elmer LS 55 Fluorescence Spectrometer. The fluorescence spectra for the AIE effect were measured after preparation and leaving the mixture to stand for 2 h at 298 K. To measure changes in the fluorescence intensity in the presence of chiral guests, all mixtures of sensors ***S*-6**, ***R*-6**, and ***R*-7** and chiral guests **8**–**13** were left to stand for 2 h at 298 K before measuring their fluorescence spectra.

*Synthesis of ((S)-2-((2-(4-(1-(4-(2-(((R)-2-hydroxy-1-phenylethyl)amino)ethoxy)phenyl)-2,2-diphenylvinyl)phenoxy)ethyl)amino)-2-phenylethan-1-ol (**S*-6)*

Compound **3** was synthesized according to the reported procedure.[14,16,32–34] To a flask was added **3** (460 mg, 0.80 mmol), ***S*-4** (440 mg, 3.20 mmol), K_2CO_3 (220 mg, 1.60 mmol), and dry acetonitrile (20 mL). The mixture was refluxed overnight until **3** had disappeared (monitored by thin layer chromatography (TLC), ethyl acetate/petroleum ether, 1:5). The acetonitrile was removed by evaporation under reduced pressure, and the residue was dissolved in dichloromethane (DCM). The organic phase was washed with water twice, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, DCM/methanol, 50:1) to give ***S*-6** as a light yellow solid (282 mg, 51%); m.p. 206–208 °C; $[\alpha]^{20}_D$ +26.3 (*c* 1.1, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.34 (m, 10H), 7.12–7.10 (m, 6H), 7.05–7.03 (m, 4H), 6.94 (d, *J* = 8.5 Hz, 4H), 6.64 (d, *J* = 8.5 Hz, 4H), 3.99–3.98 (m, 4H), 3.85 (dd, *J* = 8.3, 4.2 Hz, 2H), 3.78–3.76 (m, 2H), 3.62–3.58 (m, 2H), 2.94–2.89 (m, 4H), 2.37 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 146.9, 143.1, 142.6, 141.9, 139.2, 135.2, 134.0, 131.3, 130.3, 129.8, 128.7, 116.2, 80.1,

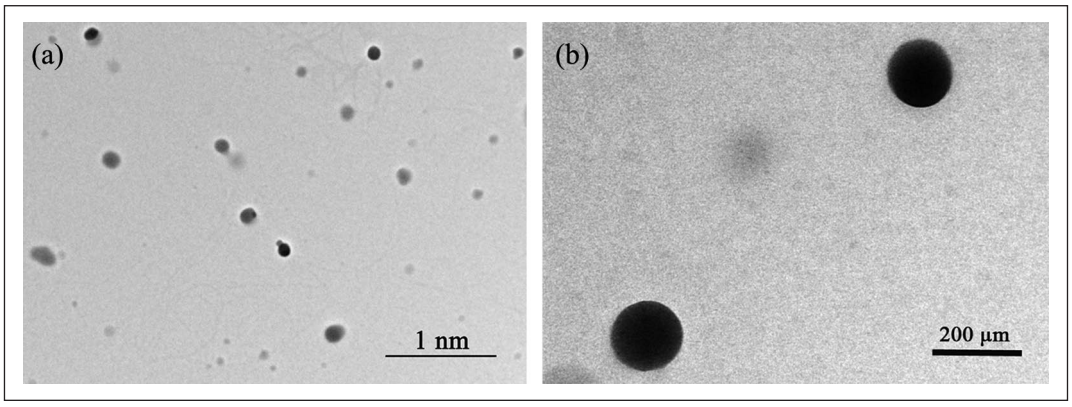


Figure 5. TEM images of a suspension of ***S*-6** in water/THF (9.5:0.5) ([***S*-6**] = 1.0 × 10^{-5} M). (a) Scale bar: 1.0 nm and (b) scale bar: 200 μm.

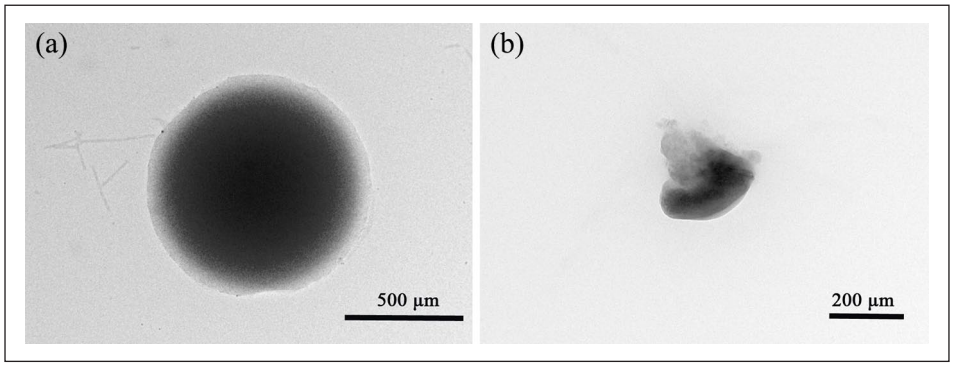


Figure 6. (a) TEM image of a suspension of ***S*-6** and ***L*-8** in 1,2-dichloroethane, scale bar: 500 μm. (b) TEM image of a solution of ***S*-6** and ***D*-8** in 1,2-dichloroethane, scale bar: 200 μm ([***S*-6**] = [***L*-8**] = [***D*-8**] = 5.0 × 10^{-4} M).

79.6, 79.2, 70.0, 69.4, 67.2, 49.0; ESI-MS: *m*/*z* calcd for $C_{46}H_{46}N_2O_4$: 690 $[M]^+$; found: 691 $[(M+v1)]^+$.

*Synthesis of ((R)-2-((2-(4-(1-(4-(2-(((S)-2-hydroxy-1-phenylethyl)amino)ethoxy)phenyl)-2,2-diphenylvinyl)phenoxy)ethyl)amino)-2-phenylethan-1-ol (**R-6**)*

The method was the same as that described for ***S*-6**. Yellow solid, 272 mg, 49%; m.p. 205–207 °C; $[\alpha]^{20}_D$ –25.9 (*c* 1.0, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.33 (m, 10H), 7.13–7.10 (m, 6H), 7.05–7.03 (m, 4H), 6.97 (d, *J* = 8.5 Hz, 4H), 6.67 (d, *J* = 8.5 Hz, 4H), 3.99–3.98 (m, 4H), 3.87 (dd, *J* = 8.2, 4.3 Hz, 2H), 3.78–3.73 (m, 2H), 3.62–3.59 (m, 2H), 2.92–2.87 (m, 4H), 2.39 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 144.2, 140.4, 139.9, 139.4, 136.6, 132.6, 131.3, 128.7, 127.7, 127.2, 126.1, 113.6, 77.3, 77.0, 76.8, 67.4, 66.8, 64.5, 46.4; ESI-MS: *m*/*z* calcd for $C_{46}H_{46}N_2O_4$: 690 $[M]^+$; found: 691 $[(M+1)]^+$.

*Synthesis of 2-(4-(2,2-diphenyl-1-(4-(2-(((R)-1-phenylethyl)amino)ethoxy)phenyl)vinyl)phenoxy)-N-((S)-1-phenylethyl)ethan-1-amine (**R-7**)*

To a flask was added **3** (460 mg, 0.80 mmol), ***R*-5** (440 mg, 3.20 mmol), K_2CO_3 (220 mg, 1.60 mmol), and dry acetonitrile (20 mL). The mixture was refluxed overnight until **3** disappeared (monitored by TLC, ethyl acetate/petroleum ether, 1:5). After the acetonitrile had been removed by evaporation under reduced pressure, the residue was dissolved in DCM. The organic phase was washed with water twice, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, DCM/methanol, 50:1) to give ***R*-7** as a light yellow solid (299 mg, 45%); m.p. 211–213 °C; $[\alpha]^{20}_D$ +21.7 (*c* 1.0, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.36 (m, 8H), 7.29–7.28 (m, 2H), 7.12–7.10 (m, 6H), 7.05–7.03 (m, 4H), 6.93 (d, *J* = 8.5 Hz, 4H), 6.64 (d, *J* = 8.6 Hz, 4H), 3.98 (m, 4H), 3.92–3.86 (m, 2H), 2.88–2.83 (m, 4H), 2.66 (s, 2H), 1.42 (d, *J* = 6.5, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 147.4, 146.9, 142.7, 141.9, 139.1, 135.1, 133.9, 132.3, 131.9, 131.1, 130.7, 130.3, 129.7, 129.3, 128.7, 128.4, 117.2, 116.8, 116.2, 80.1, 79.6, 79.2, 69.7, 60.9, 56.0, 49.2, 26.8; ESI-MS: *m*/*z* calcd for $C_{46}H_{46}N_2O_2$: 658 $[M]^+$; found: 659 $[(M+1)]^+$.

Conclusion

In summary, the combination of a TPE moiety and several optically pure molecules has provided several excellent novel chiral sensors. Sensors ***R*-6** and ***S*-6** were proven to be good chiral sensors for the chiral recognition of various carboxylic acids and their derivatives. This work has provided

an efficient methodology to synthesize new chiral fluorescent sensors and is expected to be of great value in high-throughput assays of chiral products.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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