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1,1'-Bi-2-naphthol-Fluoroacetyl Compounds in Fluorescent Recognition of Amines

*Shanshan Yu,^{a,b} Winston Plunkett,^b Michael Kim,^b Elaine Wu^b and Lin Pu^{*b}*

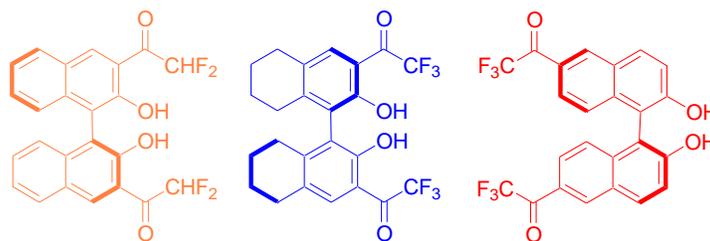
a. College of Chemistry, Sichuan University, Chengdu, China 610064

b. Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904-4319, U.S.A.

Email Address: lp6n@virginia.edu

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TOC Graphic



Fluorescent recognition of amines and diamines

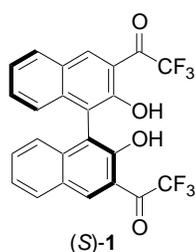
Abstract

Several 1,1'-bi-2-naphthol (BINOL) derivatives containing fluoroacetyl functions were synthesized, which included (*S*)-**4** with two difluoroacetyl groups at the 3,3'-positions of BINOL, (*R*)-**7** with two trifluoroacetyl groups at the 3,3'-positions of a partially hydrogenated BINOL, and (*S*)-**12** containing two trifluoroacetyl groups at the 6,6'-positions. Compounds (*S*)-**4** and (*R*)-**7** were nonfluorescent but (*S*)-**12** gave intense fluorescence. This indicates that intramolecular hydrogen bondings between the BINOL hydroxyl groups and the 3,3'-dicarbonyl groups of (*S*)-**4** and (*R*)-**7** could have effectively quenched their fluorescence. The fluorescence responses of these compounds towards a variety of amines were studied. It was found that (*S*)-**4** showed greatly enhanced fluorescence in the presence of diamines and also highly enantioselective fluorescent response toward a chiral diamine. However, monoamines could not turn on the fluorescence of this compound. Compound (*S*)-**12** showed greatly increased fluorescence quenching by amines in comparison with BINOL.

Introduction

The highly electrophilic property of trifluoromethyl ketones has been utilized in the development of molecular receptors for a variety of nucleophilic species.¹⁻³ Among these studies, the reactions of the trifluoroacetyl groups of these molecules with amines were observed to generate significant changes in spectroscopic signals and allow detection of these substrates.⁴⁻⁷ Recently, we reported that the 1,1'-bi-2-naphthol (BINOL)-based chiral trifluoromethyl ketone (*S*)-**1** exhibited highly enantioselective fluorescent responses toward chiral diamines.⁸ In addition, this compound also exhibited greatly enhanced fluorescence in the presence of aliphatic

diamines but had much smaller or even no fluorescence response toward aromatic diamines and various monoamines. Selective detection of amines is important in environmental, biological and clinical analyses and highly sensitive fluorescent sensors may provide practically useful tools for these areas.⁹⁻¹³ In order to gain additional understanding on the fluorescent recognition of amines by (*S*)-**1**, we have synthesized several analogs of (*S*)-**1** by modifying the carbonyl functions or the BINOL units and have compared their fluorescent responses in the presence of amines. These compounds have shown diverse fluorescent responses toward amines and are potentially useful for amine analysis. Herein, these results are reported.



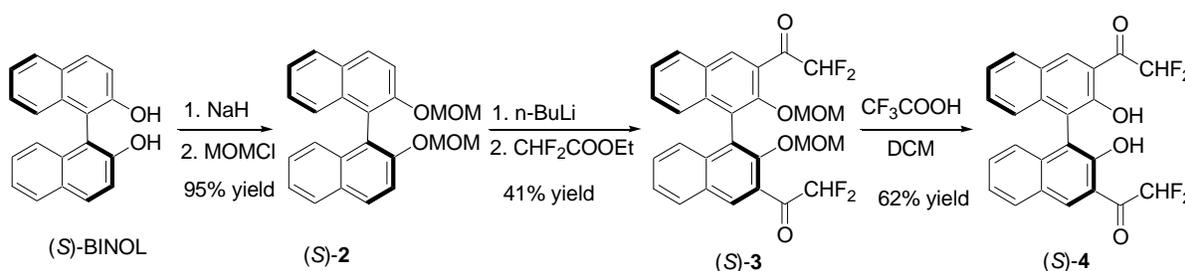
Results and Discussion

1. Synthesis and Characterization of the BINOL-Fluoroacetyl Compounds.

We prepared the 3,3'-difluoroacetyl BINOL (*S*)-**4** according to Scheme 1 in order to explore the effect of the reduced electrophilicity of the carbonyl groups on sensing. Protection of the hydroxyl groups of (*S*)-BINOL with methoxymethyl groups gave compound (*S*)-**2** in 95% yield.¹⁴ Treatment of (*S*)-**2** with ⁿBuLi followed by addition of ethyl difluoroacetate gave the 3,3'-diacetyl compound (*S*)-**3** in 41% yield. The methoxymethyl protecting groups of (*S*)-**3** was removed by reaction with trifluoroacetic acid followed by aqueous workup to give the difluoroacetyl compound (*S*)-**4** in 62% yield. The ¹H NMR spectrum of (*S*)-**4** in CDCl₃ showed a singlet at δ 10.75 for the hydroxyl group of (*S*)-**4**, consistent with an intramolecular OH...O=C

hydrogen bonding. Its ^{19}F NMR spectrum gave two signals at δ -121.31 (dd, $J = 351, 57$ Hz) and -119.82 (dd, $J = 351, 57$ Hz) for the two diastereotopic fluorine atoms in each of the two difluoroacetyl groups. The specific optical rotation of (*S*)-**4** was $[\alpha]_{\text{D}} = -153.5$ ($c = 0.21, \text{CHCl}_3$) which is similar to that of (*S*)-**1** previously reported at $[\alpha]_{\text{D}} = -167.5$ ($c = 0.355, \text{CHCl}_3$). The difluoroacetyl groups of (*S*)-**4** were expected to be less electrophilic than the trifluoroacetyl groups of (*S*)-**1**.

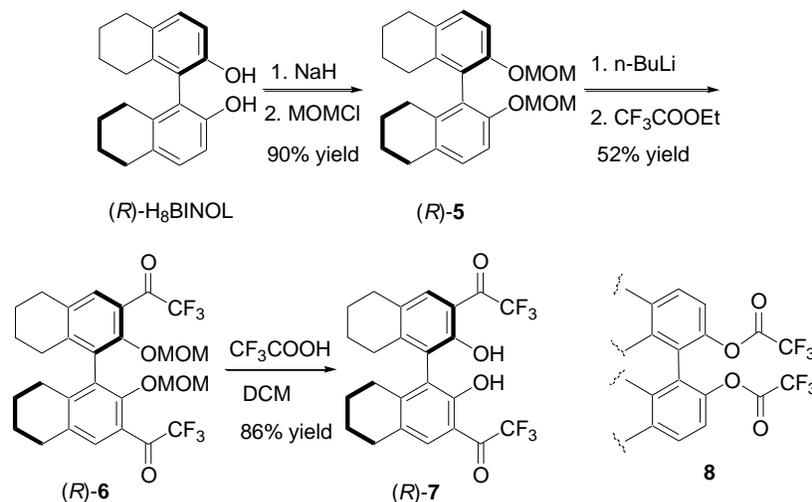
Scheme 1. Synthesis of 3,3'-Di(difluoroacetyl)-BINOL (*S*)-**4**.



The partially hydrogenated BINOL, H₈BINOL, was used to prepare an analog of (*S*)-**1** according to Scheme 2. Protection of the hydroxyl groups of (*R*)-H₈BINOL with methoxymethyl group gave (*R*)-**5** in 90% yield.¹⁵ Treatment of (*R*)-**5** with ⁿBuLi followed by addition of ethyl trifluoroacetate gave the 3,3'-diacetyl compound (*R*)-**6** in 57% yield. The methoxymethyl protecting groups of (*R*)-**6** were removed by reaction with trifluoroacetic acid and then aqueous workup to give the H₈BINOL analog (*R*)-**7** in 86% yield. The specific optical rotation of (*R*)-**7** was $[\alpha]_{\text{D}} = -38.5$ ($c = 0.36, \text{CHCl}_3$). The ^1H NMR spectrum of (*R*)-**7** in CDCl₃ gave a singlet at δ 11.14 for the hydrogen-bonded hydroxyl protons. The partially hydrogenated BINOL of (*R*)-**7** should make its hydroxyl groups less acidic and its carbonyl groups less electrophilic than those of (*S*)-**1**. In addition, the sp³ hybridized carbons in the partially hydrogenated naphthol rings of (*R*)-**7** should also provide a steric environment different from that of (*S*)-**1**. A one-step

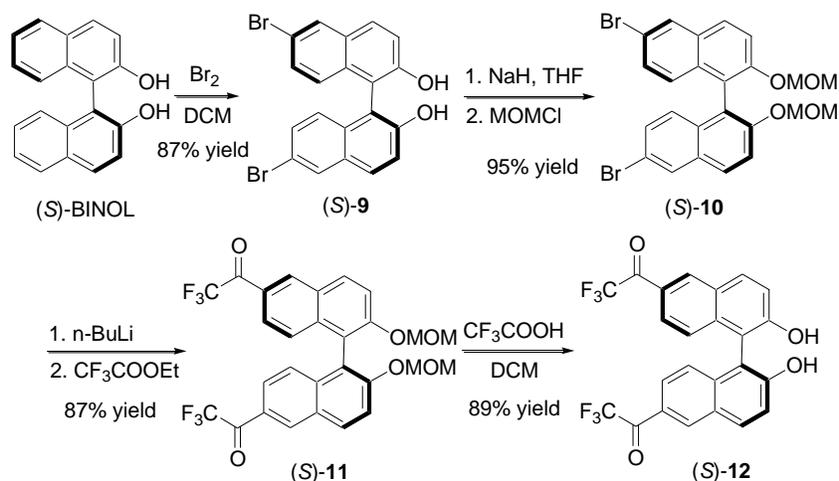
conversion of a fluoroacetate **8** to compounds like (*S*)-**1**, (*S*)-**4** or (*R*)-**7** in the presence of a Lewis acid was attempted without success.

Scheme 2. Synthesis of 3,3'-Di(trifluoroacetyl)-H₈BINOL (*R*)-**7**.



We further introduced trifluoroacetyl group to the 6,6'-positions of BINOL to make compound (*S*)-**12**. As shown in Scheme 3, bromination of (*S*)-BINOL gave the 6,6'-brominated BINOL (*S*)-**9** in 87% yield.¹⁶ After protected with the MOM group, the resulting compound (*S*)-**10** was reacted with *n*-BuLi and ethyl trifluoroacetate to produce (*S*)-**11** in 87% yield. Then trifluoroacetic acid was added to remove the MOM groups to generate (*S*)-**12** in 89% yield. The specific optical rotation of (*S*)-**12** was $[\alpha]_D = 333.6$ ($c = 0.16$, CHCl₃). The ¹H NMR spectrum of (*S*)-**12** in CDCl₃ showed a singlet at δ 5.33 for the hydroxyl group. This signal is much more upfield than those of the 3,3'-fluoroacetyl-BINOLs (*S*)-**1**, (*S*)-**4** and (*R*)-**7** described above because of the absence of the intramolecular OH \cdots O=C hydrogen bond.

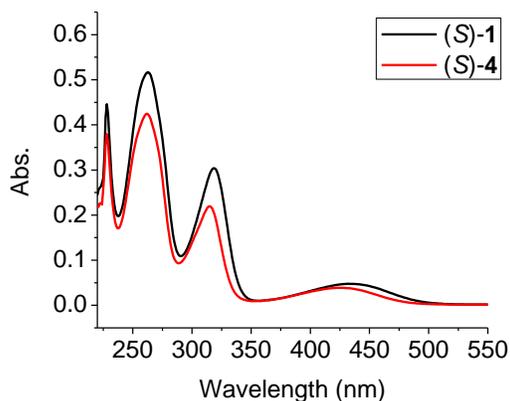
Scheme 3. Synthesis of 6,6'-Di(trifluoroacetyl)-BINOL (*S*)-**12**.



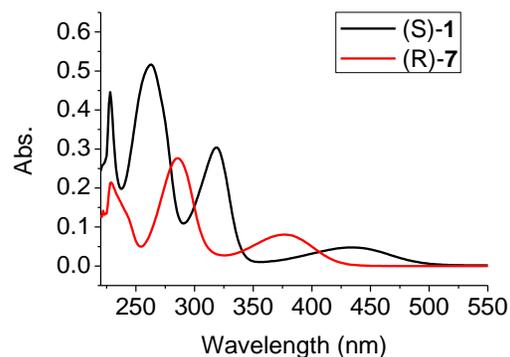
2. Comparison of the UV Spectra of (S)-4, (R)-7 and (S)-12 with That of (S)-1.

The UV spectra of (S)-4, (R)-7 and (S)-12 in methylene chloride solution were compared with that of (S)-1 in Figure 1. It shows that the longest wavelength absorption of the difluoroacetyl compound (S)-4 was slightly blue shifted to $\lambda_{\text{max}} = 425$ nm from that of (S)-1 at $\lambda_{\text{max}} = 432$ nm since the difluoroacetyl groups of (S)-4 are less efficient electron acceptors in the donor-acceptor conjugated systems of these two compounds. The H₈BINOL compound (R)-7 with less extended conjugation due to the partially hydrogenated naphthol rings showed a large blue shift of the longest wavelength absorption to $\lambda_{\text{max}} = 377$ nm. In the long wavelength absorption of the 6,6'-trifluoroacetyl compound (S)-12, a shoulder was observed at 359 nm which is greatly blue shifted from that of (S)-4. Although both (S)-1 and (S)-12 have the same electron donors and acceptors over a conjugated naphthol ring, without the intramolecular OH...O=C hydrogen bonding of (S)-1, there was a greater band gap in the absorption of (S)-12. Table 1 summarizes the UV absorption data of these compounds.

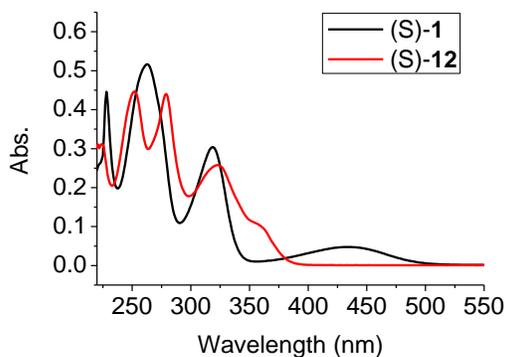
Figure 1. Comparison of the UV spectrum of (S)-1 with those of (S)-4 (a), (R)-7 (b) and (S)-12 (c) (1.0×10^{-5} M, CH₂Cl₂).



(a)



(b)



(c)

Table 1. Maximum absorption peaks and extinction coefficients of (*S*)-1, (*S*)-4, (*R*)-7 and (*S*)-12 (1.0×10^{-5} M in CH_2Cl_2).

| | $\lambda_{\text{max}}(\epsilon)$ |
|-----------------|--|
| (<i>S</i>)-1 | 228 (4.5×10^4), 263 (5.2×10^4), 319 (3.0×10^4), 432 (4.8×10^3) nm |
| (<i>S</i>)-4 | 228 (3.8×10^4), 262 (4.2×10^4), 315 (2.2×10^4), 425 (3.9×10^3) nm |
| (<i>R</i>)-7 | 229 (2.1×10^4), 285 (2.8×10^4), 377 (8.1×10^3) nm |
| (<i>S</i>)-12 | 252 (4.5×10^4), 279 (4.4×10^4), 323 (2.6×10^4), 359 (sh, 1.0×10^4) nm |

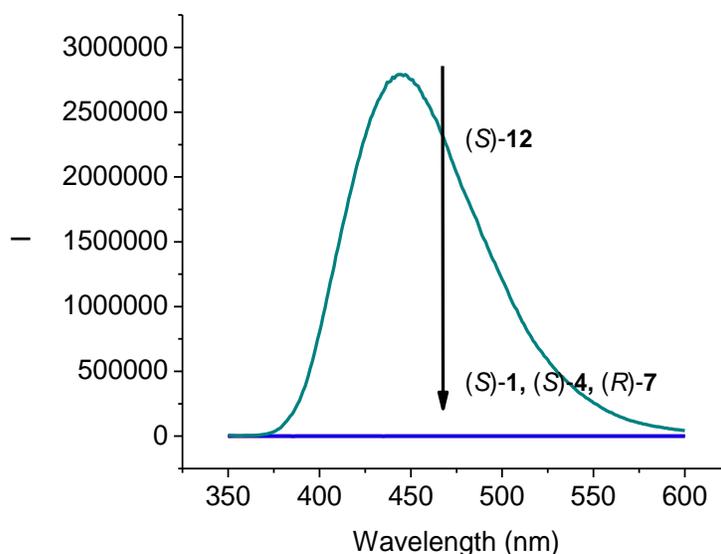
3. Comparison of the Fluorescence Spectra of (*S*)-4, (*R*)-7, and (*S*)-12 with That of (*S*)-1.

The fluorescence spectra of compounds (*S*)-4, (*R*)-7 and (*S*)-12 in CH_2Cl_2 at 1.0×10^{-5} M

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were compared with that of (*S*)-**1**. As shown in Figure 2, all the compounds (*S*)-**1**, (*S*)-**4**, and (*R*)-**7** that contain the intramolecular OH \cdots O=C hydrogen bonds were found to be nonemissive. However, the 6,6'-trifluoroacetyl compound (*S*)-**12** showed strong emission at $\lambda = 444$ nm. The emission of (*S*)-**12** was significantly red shifted from that of BINOL observed at around 360 nm,¹⁷ which could be attributed to the internal charge transfer state arisen from the incorporation of the trifluoroacetyl electron acceptor in (*S*)-**12**.

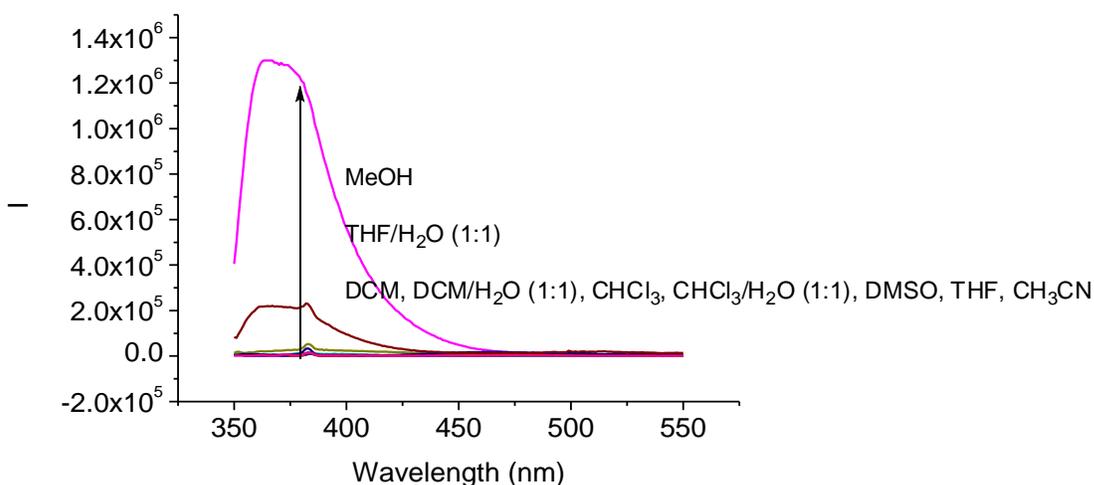
Figure 2. Fluorescence Spectra of (*S*)-**1**, (*S*)-**4**, (*R*)-**7** and (*S*)-**12** (1.0×10^{-5} M) in CH₂Cl₂. [$\lambda_{\text{exc}} = 343$ nm for (*S*)-**1**, (*S*)-**4** and (*S*)-**12**; $\lambda_{\text{exc}} = 290$ nm for (*R*)-**7**; slit = 2.0/2.0 nm].



We studied the solvent effect on the fluorescence signals of the difluoroacetyl analog (*S*)-**4**. As shown in Figure 3a, addition of water or methanol greatly enhanced the fluorescence of (*S*)-**4**. This is similar to what was observed for (*S*)-**1** except that the fluorescence intensity of (*S*)-**4** was much smaller than that of (*S*)-**1** under the same conditions.^{8b} Because of the poor solubility of water in CH₂Cl₂ and CHCl₃, addition of water to these solutions could not enhance the

fluorescence of (*S*)-**4**. We propose that the fluorescence enhancement of (*S*)-**4** in the presence of water could be attributed to the formation of hydrate upon nucleophilic addition of H₂O to the difluoroacetyl groups similar to that proposed for (*S*)-**1**.^{8b}

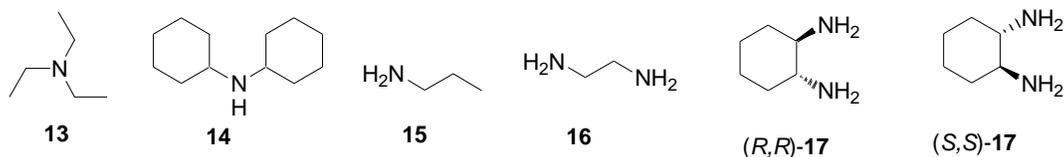
Figure 3. Fluorescence spectra of (*S*)-**4** (1.0×10^{-5} M) in various solvents. ($\lambda_{\text{exc}} = 343$ nm, slit = 2.0/2.0 nm).



5. Interaction of the BINOL-Fluoroacetyl Compounds with Amines

The interactions of the BINOL-fluoroacetyl compounds (*S*)-**4**, (*R*)-**7** and (*S*)-**12** (1×10^{-5} M) with several representative amines (Figure 4) including the tertiary amine **13**, the secondary amine **14**, the primary amine **15**, the 1,2-diamine **16**, and the chiral diamine (*R,R*)- or (*S,S*)-**17** in CH₂Cl₂ were studied.

Figure 4. Structures of Various Amines Investigated.

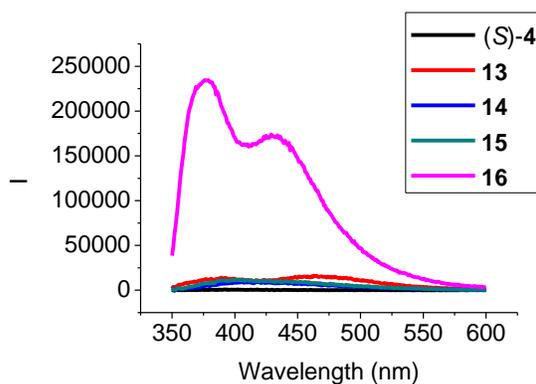


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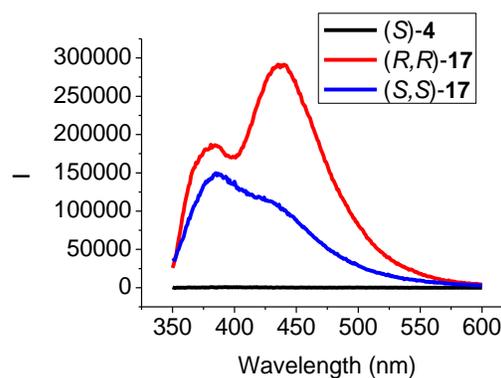
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When the difluoroacetyl compound (*S*)-**4** was treated with the monoamines **13** - **15**, only small changes in the fluorescence were observed (Figure 5a). However, when ethylenediamine **16** was used under the same conditions, large fluorescence enhancement was observed with dual emission signals at $\lambda = 377$ and 434 nm. When (*S*)-**4** was treated with the chiral diamine (*R,R*)-**17** (5.0×10^{-3} M), a large fluorescent enhancement was also observed with dual emissions at $\lambda = 385$ (λ_1) and 438 (λ_2) nm with $I_1/I_2 = 0.64$ (Figure 5b). When (*S*)-**4** was treated with (*S,S*)-**17**, a similar large fluorescence enhancement at λ_1 was also observed, but the fluorescence enhancement at λ_2 was much smaller with $I_1/I_2 = 1.47$. This demonstrates that (*S*)-**4** can serve as a highly sensitive as well as enantioselective fluorescent sensor for the recognition of the chiral diamine similar to (*S*)-**1**.⁸ It can also be used to distinguish the aliphatic 1,2-diamines from monoamines. Figure 5c gives the UV absorption responses of (*S*)-**4** toward the enantiomers of the chiral diamine. It shows that when (*S*)-**4** (1.0×10^{-5} M in CH_2Cl_2) was treated with (*R,R*)- or (*S,S*)-**17** (5.0×10^{-3} M), there were large absorption decreases at $\lambda_{\text{max}} = 262, 315$ and 425 nm and a new absorption at $\lambda_{\text{max}} = 345$ nm, but no enantioselectivity was observed.

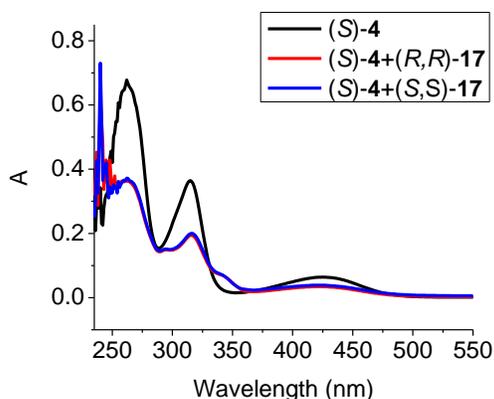
Figure 5. Fluorescence spectra of (*S*)-**4** in the presence of amines **13** - **16** (a), and (*R,R*)- or (*S,S*)-**17** (b) ($\lambda_{\text{exc}} = 343$ nm, slit = 3.0/3.0 nm). UV spectra of (*S*)-**4** in the presence of (*R,R*)- or (*S,S*)-**17** (c). [(*S*)-**4**: 1.0×10^{-5} M in CH_2Cl_2 ; amine: 5.0×10^{-3} M].



(a)



(b)



(c)

Previously, we observed that (*S*)-1 reacted with cyclohexane-1,2-diamine to form a 1:2 adduct.^{8b} On the basis of our study on the reaction of (*S*)-1 with amines, we propose the following mechanism to account for the reaction and fluorescent responses of (*S*)-4 with the diamines. As shown in Scheme 4, the intermolecular hydrogen bond between one amine group of a diamine molecule with the hydroxyl groups of (*S*)-4 in **18** should accelerate the addition of the second amine group to the difluoroacetyl group to generate the highly fluorescent hemiaminal product **19**. The fluorescent enhancement is mainly ascribed to the disruption of the original intramolecular OH \cdots O=C hydrogen bonding. The enantioselectivity in the fluorescent response of (*S*)-4 could be attributed to the different stability of the diastereomeric isomers of **19** when (*S*)-4 reacts with the two enantiomers of the diamine **17**.

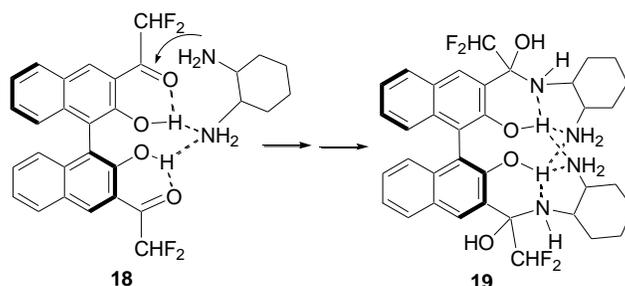
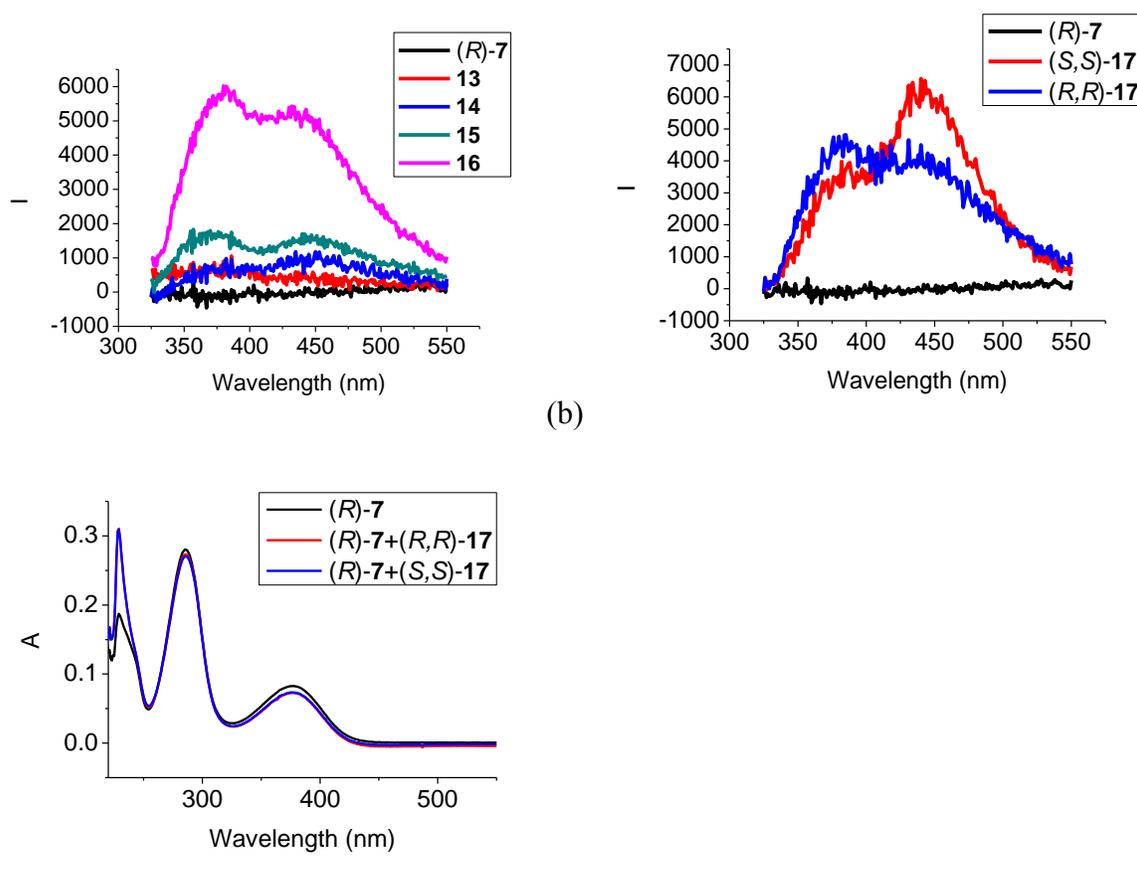
Scheme 4. Proposed Mechanism for the Reaction of (*S*)-**4** with the Chiral Diamine **17**

Figure 6 gives the fluorescence and UV responses of the H₈BINOL analogue (*R*)-**7** toward the amines. It shows that monoamines **13**, **14** and **15** caused very little change on the fluorescence of this compound (Figure 6a). Ethylenediamine **16** turned on the fluorescence of (*R*)-**7** with dual emissions at 380 and 435 nm, and the chiral diamine (*R,R*)- and (*S,S*)-**17** turned on the fluorescence of (*R*)-**7** with dual emissions at 380 nm and 443 nm (Figure 6a,b). (*R*)-**7** also showed enantioselective response toward (*R,R*)- and (*S,S*)-**17** but the fluorescent intensity was low. The UV spectrum of (*R*)-**7** in the presence of 500 equiv of the chiral diamine (*R,R*)- and (*S,S*)-**17** only gave very small changes (Figure 6c). These observations demonstrate that the less electrophilic trifluoroacetyl groups of (*R*)-**7** and its less acidic hydroxyl groups due to the partially hydrogenated naphthol rings make it less reactive with the diamines.

Figure 6. Fluorescence spectra of (*R*)-**7** in the presence of amines **13** - **16** (a), and (*R,R*)- or (*S,S*)-**17** (b) (amine: 1.0×10^{-3} M) ($\lambda_{\text{exc}} = 286$ nm, slit = 2.0/2.0 nm). UV spectra of (*R*)-**7** in the presence of (*R,R*)- and (*S,S*)-**17** (5.0×10^{-3} M) (c). [(*R*)-**7**: 1.0×10^{-5} M in CH₂Cl₂]



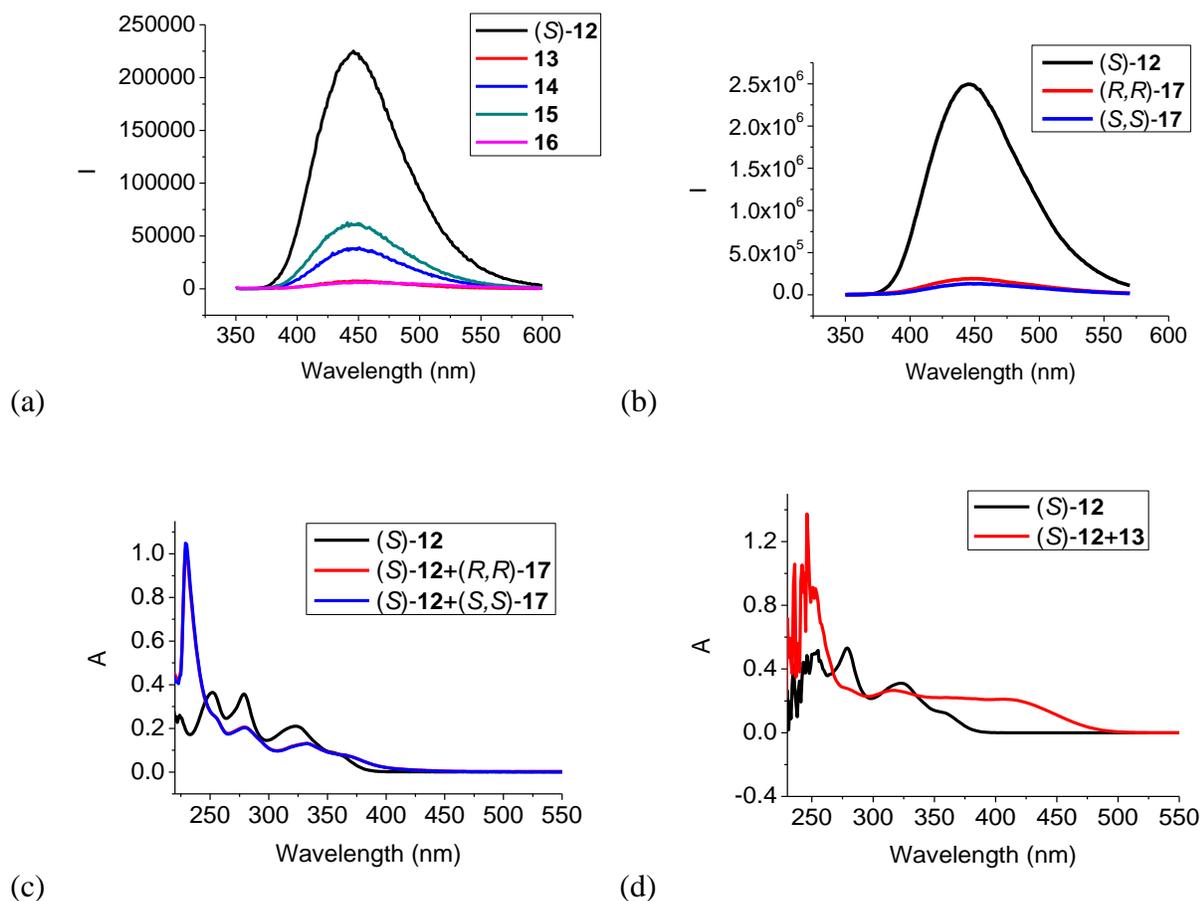
The 6,6'-trifluoroacetyl analog (*S*)-**12** exhibited significant fluorescent quenching in the presence of all of the tested amines, in which chiral diamine **17** quenched over 90% of its fluorescence with almost no enantioselectivity (Figure 7a,b). The extents of the fluorescence quenching of (*S*)-**12** by the amines in Figure 7a,b are listed below: **13** quenched 97%; **14** quenched 83%; **15** quenched 73%; **16** quenched 98%; (*S,S*)-**17** quenched 95% and (*R,R*)-**17** quenched 92%. The differences of the fluorescence quenching efficiency should be related to how strongly the amines are interacting with the fluorophore. Since (*S*)-**12** does not have the intramolecular OH...O=C hydrogen bonds of (*S*)-**1** and (*S*)-**4**, it is strongly emissive. It was reported by Iwanek and Mattay that the fluorescence of BINOL can be quenched by amines in various solvents.¹⁸ Our observed fluorescence quenching of (*S*)-**12** by the amines appears to be

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much more efficient than that of BINOL by amines. It was proposed that the fluorescence quenching of BINOL by amines could be attributed to the formation of hydrogen bonded complexes between the BINOL hydroxyl groups and the amine nitrogen as well as the corresponding excited state proton transfer complex. The increased fluorescent quenching of (*S*)-**12** by the amines could be attributed to the increased acidity of the hydroxyl groups of (*S*)-**12** caused by the two electron-withdrawing 6,6'-trifluoroacetyl groups which should increase their interaction with the amine bases. Figure 7c gives the UV responses of (*S*)-**12** when treated with (*S,S*)- and (*R,R*)-**17**. It shows an absorption increase at 228 nm, decreases at 251, 279 and 323 nm, and a new absorption at 370 nm. No enantioselectivity was observed in the UV responses. Figure 8d gives the UV responses of (*S*)-**12** when treated with the tertiary amine **13**. It shows an absorption increase at 254 nm, decreases at 278 and 323 nm, and a new broad absorption greater than 400 nm. The new long wavelength absorption of (*S*)-**12** indicates the deprotonation of (*S*)-**12** by the stronger base of triethylamine **13**.

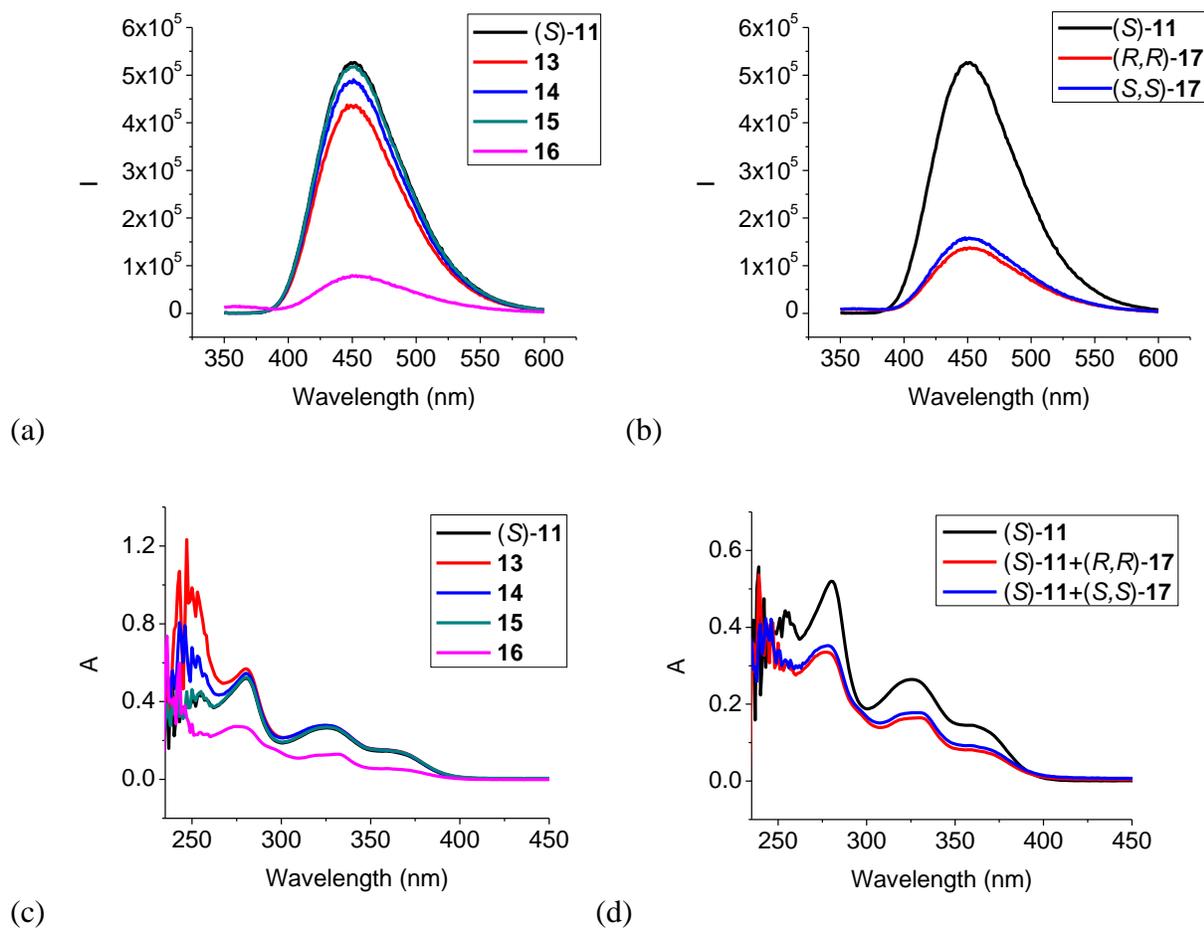
Figure 7. Fluorescence spectra of (*S*)-**12** in the presence of amines **13** - **16** (a), and (*R,R*)- or (*S,S*)-**17** (b). [$\lambda_{\text{exc}} = 343$ nm, slit = 1.0/1.0 nm for **13** - **16**, and slit = 2.0/2.0 nm for (*R,R*)- or (*S,S*)-**17**]. UV spectra of (*S*)-**12** in the presence of (*R,R*)- and (*S,S*)-**17** (c) and **13** (d). [(*S*)-**12**: 1.0×10^{-5} M in CH_2Cl_2 . amine: 5.0×10^{-3} M]



We also studied the UV and fluorescent responses of the MOM protected compound (*S*)-**11**. As Figure 8a,b show, the monoamines **13**, **14** and **15** had very little effect on the fluorescence of (*S*)-**11**, but the diamines **16** and **17** could still significantly quench the fluorescence though to a smaller extent than that of (*S*)-**12** by the diamines. The UV spectra in Figure 8c,d are consistent with the fluorescent responses, that is, the monoamines did not change the UV absorption of (*S*)-**11** but the diamines **16** and **17** significantly decreased the absorption. These observations could be attributed to a more favorable reaction for the diamines with the trifluoroacetyl groups of (*S*)-**11** than the monoamines. This study of the interaction of (*S*)-**11** with the amines also suggests that the fluorescent quenching of (*S*)-**12** by the monoamines should be mainly due to the

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 17 interaction of the acidic hydroxyl groups with the amine bases, but the diamines **16** and **17** could
 18 interact with both the hydroxyl groups and the trifluoroacetyl groups to quench the fluorescence
 19 of (*S*)-**12**. Thus, the fluorescent quenching of (*S*)-**12** by the diamines is more efficient than that
 20 of (*S*)-**11**.

21 **Figure 8.** Fluorescence spectra of (*S*)-**11** in the presence of **13** - **16** (a), and (*R,R*)- or (*S,S*)-**17** (b).
 22 ($\lambda_{\text{exc}} = 343 \text{ nm}$, slit = 1.0/1.0 nm). UV spectra of (*S*)-**11** in the presence of **13** - **16** (c), and (*R,R*)-
 23 or (*S,S*)-**17** (d). [(*S*)-**11**: $1.0 \times 10^{-5} \text{ M}$ in CH_2Cl_2 . amine: $5.0 \times 10^{-3} \text{ M}$]



56 Summary

We have synthesized and studied several BINOL-fluoroacetyl compounds for the fluorescent recognition of amines. The difluoroacetyl compound (*S*)-4 showed large fluorescence enhancement in the presence of diamines and highly enantioselective responses were observed toward a chiral diamine. However, the primary, secondary and tertiary monoamines cannot turn on the fluorescence of this compound. When the carbonyl groups are moved from the 3,3'-positions of the BINOL unit of (*S*)-1, (*S*)-4 and (*R*)-7 to the 6,6'-positions of (*S*)-12, greatly enhanced fluorescence was observed. This demonstrates that the intramolecular H...O=C hydrogen bonding in the 3,3'-dicarbonyl compounds of the BINOL derivatives should be responsible for their fluorescent quenching. (*S*)-12 showed efficient fluorescent quenching in the presence of the mono and diamines. Thus, the 6,6'-substituted analog gave the opposite fluorescent responses of the 3,3'-substituted compounds. The H₈BINOL derivative (*R*)-7 showed much weaker fluorescent responses. This work has demonstrated that the steric and electronic properties of the carbonyl groups of the BINOL-based compound can greatly influence their fluorescent responses in amine recognition.

Experimental Section

General Data

THF was distilled over sodium and benzophenone under nitrogen atmosphere. Methylene chloride and diethyl ether were dried by passing through activated alumina columns under nitrogen. Solvents were stored over 4 Å molecular sieves.

Melting points were uncorrected and obtained on a Mel-Temp II capillary melting point apparatus. Optical rotations were measured on a Jasco P-2000 digital polarimeter. NMR spectra were recorded on a Varian-300 MHz or Bruker-600 MHz spectrometer. Chemical shifts for ¹H NMR spectra were reported in parts per million relative to a singlet at 7.26 ppm for deuterated

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chloroform. Chemical shifts for ^{13}C NMR were reported relative to the centerline of a triplet at 77.16 ppm for deuterated chloroform. The ^{19}F NMR spectra were reported in units of part per million (ppm) relative to trifluoroacetic acid (δ -76.55 ppm) as an external reference. High resolution mass spectra were obtained from the University of Illinois at Urbana-Champaign (UIUC) Mass Spectrometry Facility. UV-Vis spectra were recorded on a Hewlett-Packard 8452A diode-array spectrophotometer. Steady-state fluorescence emission spectra were recorded on a Horiba FluoroMax-4 spectrofluorometer.

Preparation of Samples for Fluorescence Measurement.

Materials: The molecular receptors were purified by column chromatography followed by recrystallization and then stored in a refrigerator. All of the solvents were either HPLC or spectroscopic grade. The stock solutions of the receptors were freshly prepared for each measurement. A 0.01 M stock solution of an amine substrate in methylene chloride was freshly prepared. For the fluorescent study, a receptor solution was mixed with the amine solution at room temperature in a 5 mL volumetric flask and diluted to the desired concentration. The resulting solution was allowed to stand at room temperature for 0.5 h before the fluorescent measurement and all the fluorescence spectra were taken within 2 h.

Synthesis and Characterization of Compounds

Synthesis and Characterization of (S)-3. Under nitrogen, 2,2'-bis(methoxymethoxy)-1,1'-binaphthalene, (S)-2 (3.0 mmol, 1.12 g), was dissolved in diethyl ether (36 mL). The solution was cooled to 0 $^{\circ}\text{C}$, and n-BuLi (10.5 mmol, 2.5 M in hexane, 4.2 mL) was added dropwise. The reaction mixture was stirred for 3 h at room temperature and cooled to 0 $^{\circ}\text{C}$, and then ethyl difluoroacetate (12.0 mmol, 1.3 mL) was added slowly. The reaction mixture was allowed to

warm to room temperature and stirred for 2 h to afford a cream-like mixture. A saturated aqueous NH_4Cl solution was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine, and dried over Na_2SO_4 . After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with hexane/methylene chloride (1/2) to afford compound (*S*)-**3** as a yellow oil in 41% yield (1.23 mmol, 652 mg). ^1H NMR (300 MHz, CDCl_3) δ 2.90 (s, 6H), 4.60 (d, $J = 5.7$ Hz, 2H), 4.66 (d, $J = 5.7$ Hz, 2H), 6.69 (t, $J = 5.4$ Hz, 2H), 7.20 (d, $J = 8.4$ Hz, 2H), 7.44 (m, 2H), 7.54 (m, 2H), 8.05 (d, $J = 8.1$ Hz, 2H), 8.44 (s, 2H). ^{19}F NMR (282 MHz, CDCl_3) δ -127.93 (dd, $J = 321, 54$ Hz, 2F), -126.57 (dd, $J = 321, 54$ Hz, 2F). ^{13}C NMR (75 MHz, CDCl_3) δ 57.0, 100.2, 110.0 (t, $J = 249$ Hz), 125.4, 125.9, 126.6, 129.4, 129.7, 129.9, 130.0, 133.1, 136.0, 151.0, 190.6 (t, $J = 25.5$ Hz). HRMS Calcd for $\text{C}_{28}\text{H}_{22}\text{O}_6\text{F}_4\text{Na}$ (MNa^+): 553.1250, Found: 553.1259. $[\alpha]_{\text{D}} = 31.9$ ($c = 0.19$, CHCl_3).

Synthesis and Characterization of (*S*)-4. After compound (*S*)-**3** (0.94 mmol, 500 mg) was dissolved in a minimum amount of CH_2Cl_2 , trifluoroacetic acid (1.0 mL) was added slowly, and the mixture was stirred at room temperature for 1 h. A saturated aqueous NaHCO_3 solution was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, and dried over Na_2SO_4 . After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with hexane/methylene chloride (1/1) to afford compound (*S*)-**4** as a light yellow solid in 62% yield (0.58 mmol, 258 mg). ^1H NMR (600 MHz, CDCl_3) δ 6.53 (t, $J = 53.4$ Hz, 2H), 7.17 (d, $J = 7.8$ Hz, 2H), 7.40-7.46 (m, 4H), 8.00 (d, $J = 7.8$ Hz, 2H), 8.76 (s, 2H), 10.75 (s, 2H). ^{19}F NMR (282 MHz, CDCl_3) δ -121.31 (dd, $J = 351, 57$ Hz, 2F), -119.82 (dd, $J = 351, 57$ Hz, 2F). ^{13}C NMR (150 MHz, CDCl_3) δ 111.3 (t, $J = 252$ Hz), 116.6,

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117.6, 124.7, 124.9, 127.2, 130.8, 131.6, 135.4 (t, $J = 4.5$ Hz), 138.1, 154.8, 192.2 (t, $J = 25.5$ Hz). HRMS Calcd for $C_{24}H_{15}O_4F_4$ (MH^+): 443.0906, Found: 443.0907. m.p. 271 °C. $[\alpha]_D = -153.5$ (c = 0.21, $CHCl_3$).

Synthesis and Characterization of (R)-6. (1) Synthesis of (R)-5. Under nitrogen, (R)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl-2,2'-diol (H_8 BINOL) (25 mmol, 7.4 g) was dissolved in THF (300 mL). The solution was cooled to 0 °C, and NaH (62.8 mmol, 60% in mineral oil, 2.52 g) was added in small portions. The reaction mixture was stirred for 30 min and then chloromethyl methyl ether (62.8 mmol, 4.8 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for overnight. Water was added slowly to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine, and dried over Na_2SO_4 . After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with hexane/ethyl acetate (15/1) to afford compound (R)-5 as a white solid in 90% yield (22.5 mmol, 8.6 g). 1H NMR (300 MHz, $CDCl_3$) δ 1.65-1.76 (m, 8H), 2.07-2.17 (m, 2H), 2.27-2.37 (m, 2H), 2.78 (t, $J = 6.0$ Hz, 4H), 3.30 (s, 6H), 4.97 (d, $J = 6.6$ Hz, 2H), 5.03 (d, $J = 6.6$ Hz, 2H), 6.99 (d, $J = 8.4$ Hz, 2H), 7.05 (d, $J = 8.4$ Hz, 2H). (2) Synthesis of (R)-6. Under nitrogen, (R)-2,2'-bis(methoxymethoxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl, (R)-5 (4.4 mmol, 1.7 g), was dissolved in diethyl ether (50 mL). The solution was cooled to 0 °C, and n-BuLi (17.8 mmol, 2.5 M in hexane, 7.1 mL) was added dropwise. The reaction mixture was stirred for 4 h at room temperature and cooled to 0 °C, and then ethyl trifluoroacetate (20.0 mmol, 2.4 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 2.5 h to afford a cream-like mixture. A saturated aqueous NH_4Cl solution was added to quench the reaction. The organic layer was separated, and

the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine, and dried over Na₂SO₄. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with hexane/methylene chloride (1/3) to afford compound (*R*)-**6** as a yellow oil in 52% yield (2.3 mmol, 1.31 g). ¹H NMR (300 MHz, CDCl₃) δ 1.65-1.82 (m, 8H), 2.12-2.22 (m, 2H), 2.47-2.57 (m, 2H), 2.83-2.87 (m, 10H), 4.79 (d, *J* = 6.6 Hz, 2H), 4.83 (d, *J* = 6.6 Hz, 2H), 7.49 (s, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 22.5, 28.5, 29.6, 56.2, 100.8, 116.4 (q, *J* = 290 Hz), 123.2, 130.47, 130.51, 132.2, 133.9, 145.4, 153.5, 181.4 (q, *J* = 34.5 Hz). HRMS Calcd for C₂₈H₂₈O₆F₆Na (MNa⁺): 597.1688, Found: 197.1678. [α]_D = 43.34 (c = 0.39, CHCl₃).

Synthesis and Characterization of (*R*)-7**.** After compound (*R*)-**6** (237.8 mg, 0.41 mmol) was dissolved in a minimum amount of CH₂Cl₂, trifluoroacetic acid (1.0 mL) was added slowly, and the mixture was stirred at room temperature for 10 min. A saturated aqueous NaHCO₃ solution was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic extracts were washed with brine, and dried over Na₂SO₄. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with hexane/methylene chloride (2/1) to afford compound (*R*)-**7** as a yellow solid in 86% yield (0.35 mmol, 172 mg). ¹H NMR (300 MHz, CDCl₃) δ 1.71 - 1.88 (m, 8H), 2.25 - 2.35 (m, 2H), 2.50 - 2.60 (m, 2H), 2.88 (m, 4H), 7.67 (s, 2H), 11.1 (s, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 22.4, 22.6, 28.3, 29.4, 112.2, 116.8 (q, *J* = 288 Hz), 124.4, 129.9, 130.6 (q, *J* = 3.0 Hz), 150.0, 159.4, 184.1 (q, *J* = 34.5 Hz). HRMS Calcd for C₂₄H₂₁O₄F₆ (MH⁺): 487.1344, Found: 487.1338. m.p. 209 °C. [α]_D = -38.5 (c = 0.36, CHCl₃).

Synthesis and Characterization of (*S*)-9**.** (*S*)-BINOL (14.7 mmol, 4.2 g) was dissolved in

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CH₂Cl₂ (150 mL) and the solution was cooled to -78 °C. Br₂ (37.8 mmol, 2 mL) was added dropwise. After the reaction mixture was stirred for 2.5 h, it was warmed up to room temperature and stirred for additional 30 min. 10% NaHSO₃ solution (100 mL) was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic extracts were washed with brine, and dried over Na₂SO₄. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with hexane/ethyl acetate (4/1) to afford compound (*S*)-**9** as a white solid in 87% yield (12.8 mmol, 5.68 g). The NMR data of (*S*)-**9** matched those of the literature.¹⁹

Synthesis and Characterization of (*S*)-10. Under nitrogen, (*S*)-**9** (8.0 mmol, 3.55 g) was dissolved in THF (150 mL). The solution was cooled to 0 °C, and NaH (20 mmol, 60% in mineral oil, 0.8 g) was added in small portions. The reaction mixture was stirred for 30 min and then chloromethyl methyl ether (20 mmol, 1.5 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. Water was added slowly to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (three 30 mL aliquots). The combined organic extracts were washed with brine, and dried over Na₂SO₄. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluted with hexane/ethyl acetate (10/1) to afford compound (*S*)-**10** as a white solid in 95% yield (7.6 mmol, 4.04 g). The NMR data of (*S*)-**10** matched those reported.¹⁶

Synthesis and Characterization of (*S*)-11. Under nitrogen, (*S*)-**10** (1.0 mmol, 532 mg) was dissolved in THF (15 mL). The solution was cooled to -78 °C, and n-BuLi (4.4 mmol, 2.5 M in hexane, 1.8 mL) was added dropwise. The reaction mixture was stirred for additional 3 h at the

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4 same temperature, and then ethyl trifluoroacetate (6.6 mmol, 0.8 mL) was added slowly. The
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6 reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min and then at rt for 30 min. A saturated aqueous
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8 NH_4Cl solution was added to quench the reaction. The organic layer was separated, and the
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10 aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were
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12 washed with brine, and dried over Na_2SO_4 . After evaporation of the solvent, the residue was
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14 purified by column chromatography on silica gel eluted with hexane/methylene chloride (1/2) to
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16 afford compound (*S*)-**11** as a light yellow oil in 87% yield (0.87 mmol, 493 mg). ^1H NMR (300
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18 MHz, CDCl_3) δ 3.24 (s, 6H), 5.12 (d, $J = 7.2$ Hz, 2H), 5.21 (d, $J = 7.2$ Hz, 2H), 7.27 (d, $J = 9.0$
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20 Hz, 2H), 7.77 (d, $J = 9.0$ Hz, 2H), 7.88 (d, $J = 9.0$ Hz, 2H), 8.20 (d, $J = 9.0$ Hz, 2H), 8.72 (s, 2H).
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22 ^{19}F NMR (282 MHz, CDCl_3) δ -71.63. ^{13}C NMR (75 MHz, CDCl_3) δ 56.2, 94.5, 117.0 (t, $J =$
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24 290 Hz), 117.6, 119.8, 125.1, 125.6, 126.1, 128.4, 132.7, 133.7, 137.4, 156.2, 180.2 (t, $J = 34.5$
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26 Hz). HRMS Calcd for $\text{C}_{28}\text{H}_{20}\text{O}_6\text{F}_6\text{Na}$ (MNa^+): 589.1062, Found: 589.1063. $[\alpha]_{\text{D}} = 36.35$ ($c =$
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28 0.305, CHCl_3).
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36 **Synthesis and Characterization of (*S*)-12.** After compound (*S*)-**11** (320 mg, 0.56 mmol) was
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38 dissolved in a minimum amount of CH_2Cl_2 , trifluoroacetic acid (1 mL) was added slowly, and the
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40 mixture was stirred at room temperature for 2 h. A saturated aqueous Na_2CO_3 solution was
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42 added to quench the reaction. The organic layer was separated, and the aqueous layer was
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44 extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine, and
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46 dried over Na_2SO_4 . After evaporation of the solvent, the residue was purified by column
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48 chromatography on silica gel eluted with hexane/methylene chloride (2/1) to afford compound
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50 (*S*)-**12** as a light yellow solid in 89% yield (0.50 mmol, 238 mg). ^1H NMR (300 MHz, CDCl_3) δ
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52 5.33 (s, 2H), 7.19 (d, $J = 8.7$ Hz, 2H), 7.53 (d, $J = 9.0$ Hz, 2H), 7.92 (d, $J = 9.0$ Hz, 2H), 8.21 (d,
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54 $J = 9.0$ Hz, 2H), 8.69 (s, 2H). ^{19}F NMR (282 MHz, CDCl_3) δ -71.78. ^{13}C NMR (150 MHz,
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DMSO-*d*₆) δ 115.0, 116.8 (t, *J* = 291 Hz), 120.2, 123.3, 124.4, 125.3, 126.7, 132.5, 133.6, 137.7, 179.1 (t, *J* = 33 Hz). [α]_D = 333.6 (c = 0.16, CHCl₃). m.p. 244 °C. HRMS Calcd for C₂₄H₁₃O₄F₆ (MH⁺): 479.0718, Found: 479.0714.

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Supplementary Materials Available: NMR spectra of the new compounds and additional optical spectra.

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