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Enantioselective Fluorescent Recognition in the Fluorous Phase: Enhanced Reactivity and Expanded Chiral Recognition

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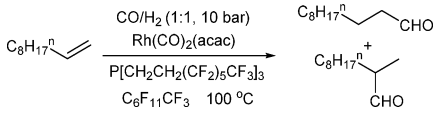
Supporting Information

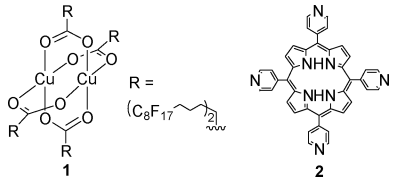
ABSTRACT: A novel perfluoroalkyl-BINOL-based chiral diketone is found to be the first highly enantioselective fluorescent sensor in the fluorous phase. One enantiomer of a chiral amino alcohol or diamine at a concentration greater than 1 mM can cause an up to 1200−2000-fold fluorescent enhancement of the sensor (0.08 mM), while the other enantiomer gives only a 10−50-fold enhancement. The fluorous-phase-based sensor is found to enhance the reactivity of the previously reported fluorous insoluble sensor with amino alcohols and expand its chiral recognition ability. Dynamic light scattering studies show the formation of aggregates of very different particle sizes when two enantiomers of a substrate interact with the sensor in perfluorohexane (FC-12). This substantial difference enables easy discrimination of the enantiomers with UV-lamps or even the naked eye. NMR, IR, and mass spectroscopic studies indicate that the fluorescent enhancement and enantioselectivity should originate from the fluorous solvent-promoted nucleophilic addition of the amino alcohols to the carbonyl groups of the sensor.

In the past two decades, a tremendous amount of research has been conducted on the use of the fluorous phase in liquid−liquid separation.[1] The unique hydrophobic and lipophobic properties of the perfluorocarbon-based fluorous solvents have exhibited important advantages in the development of new separation techniques. The initial work on the use of the fluorous phase in catalysis was reported by Horváth, and Rábai in 1994.[2] They designed a Rh catalyst containing a perfluoroalkyl substituted phosphine ligand, $P[CH_2CH_2(CF_2)_5CF_3]_3$, to catalyze the hydroformylation of 1-decene under CO and H_2 in a fluorous solvent such as a perfluorinated linear alkane or the perfluorinated methylcyclohexane ($CF_3C_6F_{11}$) to form aldehydes (Scheme 1). When the reactor was cooled to room temperature at the completion of the reaction, the perfluoroalkyl phosphine coordinated metal catalyst was soluble in the fluorous solvent but the aldehyde products were not. This allowed easy purification of the product as well as easy recovery and reuse of the catalyst.

Scheme 1. Hydroformylation in Fluorous Phase



The fluorous-phase-based phase separation technique has been extensively used in synthesis and catalysis.[1] However, very little work was conducted on applying the fluorous chemistry in sensing. There are two reports on using the fluorous-phase-based chemistry to develop molecular probes for optical detection.[3,4] In one report, Vincent described the use of the perfluoroalkyl substituted copper carboxylate complex **1** in combination with a tetrapyridylporphyrin **2** for the fluorescent detection of histamine.[3] A solution of **1** in perfluorohexane can efficiently extract the fluorophore **2** from its methylene chloride solution by coordination of the pyridyl group to the Cu(II) center to form the complex **1** + **2**. When this two-phase system was treated with histamine, coordination of histamine with the copper complex **1** can release the fluorophore **2** into the methylene chloride phase. Measuring the increase of the fluorescent intensity of **2** in the methylene chloride solution allowed the determination of the concentration of histamine. Using this fluorous-phase-based detection does not require the complex **1** + **2** and the chromophore **2** to have different optical signals because of the phase separation. In another report, selective detection of ethanol by using UV−vis absorption was observed in a similar manner.[4]



In recent years, the development of enantioselective fluorescent sensors for the recognition of chiral organic molecules has attracted significant research attention.[5−7] Among the potential applications of these sensors is their use in rapid chiral catalyst screening since fluorescence can provide real time analysis. However, direct addition of a fluorescent sensor into the product mixture of a catalyst screening experiment could cause various degrees of uncertainty in fluorescent analysis because of the possible interference from species other than the product. If the product of a screening experiment could be conveniently separated from the reaction

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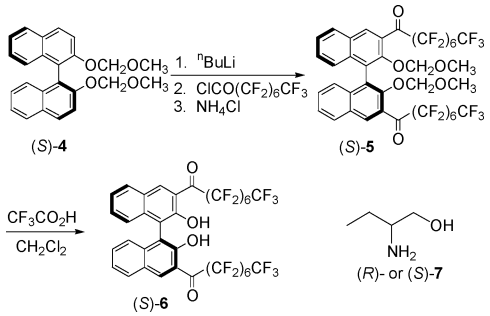
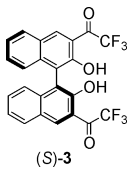
mixture, its analysis by using the enantioselective fluorescent sensor should be significantly simplified which should greatly facilitate the high throughput screening of chiral catalysts. The progress of the fluorous-phase-based separation has prompted us to propose the use of the fluorous phase for enantioselective recognition. We envision that if the enantioselective fluorescent recognition of reaction products could be conducted in the fluorous phase, it would be possible to use the fluorous-phase-based separation to minimize the interference of other species in the screening experiments, since most compounds without a highly fluorinated group are insoluble in fluorous solvents. Herein, we report the first example of enantioselective fluorescent recognition in the fluorous phase. We also show that the fluorous-phase-based sensor enhances the reactivity of the previously reported fluorous insoluble sensor with amino alcohols and expands its chiral recognition ability.

Recently, we reported that the 1,1′-bi-2-naphthol (BINOL)-based chiral trifluoromethyl ketone (*S*)-**3** exhibits highly enantioselective fluorescent recognition of chiral diamines in CH_2Cl_2.[8] However, the reaction of this compound with amino alcohols was found to be slow in CH_2Cl_2 and not easily applicable for the detection of amino alcohols. (*S*)-**3** is insoluble in fluorous solvents such as perfluorohexane (FC-72) since its two trifluoromethyl groups are too short. In order to conduct the fluorescent recognition of chiral amines in fluorous phase, we have introduced longer chain perfluorinated alkyl groups into (*S*)-**3**. As shown in Scheme 2, orthometalation

Scheme 2. Synthesis of Compound (*S*)-6



of (*S*)-**4**[9] with ^{n}BuLi followed by addition of a perfluoroalkylacyl chloride gave (*S*)-**5**. Removal of the protecting groups of (*S*)-**5** gave (*S*)-**6**. This long chain perfluoroalkyl substituted chiral ketone was found to be soluble in fluorous solvents.



We first examined the fluorescent response of (*S*)-**6** toward a chiral amino alcohol **7**, 2-amino-butanol, in a common polar organic solvent CH_2Cl_2. (*S*)-**6** gave very weak fluorescent signal in CH_2Cl_2. In the presence of either (*R*)- or (*S*)-2-aminobutanol [(*R*)-**7** or (*S*)-**7**], the fluorescent signal of (*S*)-**6** was still very weak even over a long period of time (see Figure S4 in the Supporting Information (SI)). In $CDCl_3$ solution, the ^{1}H NMR spectrum of (*S*)-**6** did not show any change with the addition of an excess amount of either (*R*)-**7** or (*S*)-**7** except for the disappearance of the OH signals of (*S*)-**6** at δ 10.58 due to the base-catalyzed proton exchange in solution (see Figures S24 and S25 in SI). Thus, no other chemical reaction was observed for (*S*)-**6** with the amino alcohol in chloroform solution within the time of the fluorescence measurement.

We then studied the fluorescent response of (*S*)-**6** toward the amino alcohol in the fluorous phase. In FC-72, (*S*)-**6** also showed no fluorescence. When (*S*)-**6** (8.0×10^{-5} M) was treated with (*S*)-**7** (0.5−5 mM) in FC-72 (containing 4% CH_2Cl_2 to dissolve the amino alcohol), very little fluorescent enhancement was observed as shown in Figure 1a. However,

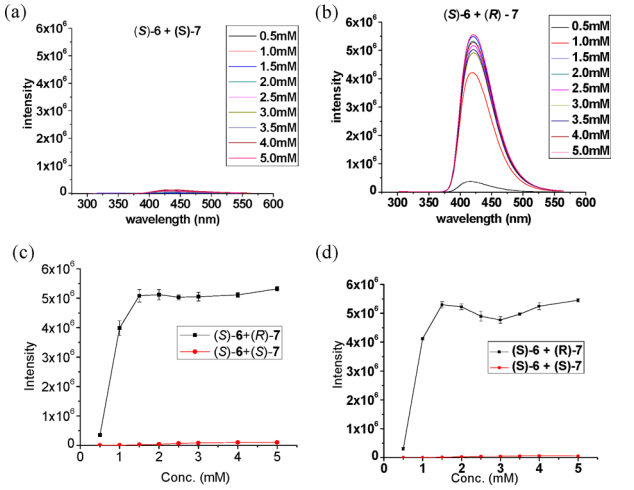


Figure 1. Fluorescent spectra of (*S*)-**6** (8.0×10^{-5} M) in the presence of (*S*)-7 (a) and (*R*)-7 (b) (Reaction time: 1 h. Solvent: 4% DCM/FC-72. λ_{ex} = 290 nm. Slit 2/2 nm). Fluorescent intensity at λ_{em} = 420 nm versus the concentration of (*R*)-7 or (*S*)-7 from four independent measurements (c) and effect of the reaction time over 1−4 h plotted with error bars (d).

when (*S*)-**6** was treated with (*R*)-**7** in FC-72 under the same conditions, large fluorescence enhancement at λ = 420 nm was observed as shown in Figure 1b. Thus, (*S*)-**6** exhibits highly enantioselective fluorescent recognition of the amino alcohol in the presence of the fluorous solvent. Figure 1c shows the fluorescent responses of (*S*)-**6** at λ = 420 nm when treated with (*R*)- and (*S*)-**7** at various concentrations. We also tested the effect of the reaction time on the fluorescent response. As shown in Figure 1d, the fluorescent responses were relatively stable over the periods of 1−4 h. Sensor (*S*)-**6** is able to detect chiral products with a concentration higher than ∼0.5 mM, which is useful for the desired applications.

We prepared the enantiomer (*R*)-**6** by starting from (*R*)-BINOL. When (*R*)-**6** was used to interact with the amino alcohol in the fluorous phase, large enhancement was observed in the presence of (*S*)-**7** with little enhancement in the presence of (*R*)-**7** (see Figure S8 in SI). That is, a mirror-image relationship was observed for the fluorescent response of (*S*)-**6** versus (*R*)-**6** toward the enantiomers of the amino alcohols. This confirms the observed enantioselective fluorescent recognition.

When (*S*)-**6** (8.0×10^{-5} M in FC-72/4% CH_2Cl_2) was treated with ≥1 mM of the amino alcohol, (*R*)-**7** changed the yellow solution to colorless with the formation of very small precipitates visible to the eye but difficult to show on a photo. The enantiomer (*S*)-**7** also changed the color of the solution but without precipitate formation. When the concentration of

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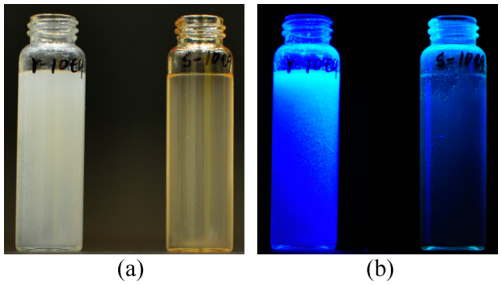
(*S*)-**6** was increased 10-fold to 8.0×10^{-4} M in FC-72 (4% CH_2Cl_2), addition of (*R*)-7 led to the formation of much more visible precipitates as shown in Figure 2a (left). Figure 2b (left)

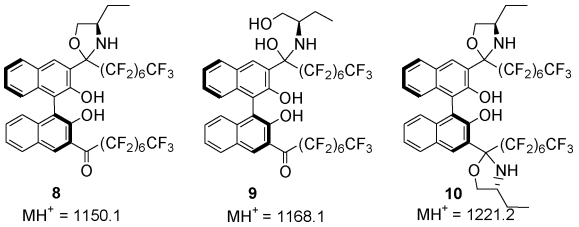


(a) (b)

Figure 2. Photos of (*S*)-**6** (8.0×10^{-4} M, FC-72/4%CH_2Cl_2) treated with (a) 10 equiv (*R*)-7 (left) and 10 equiv (*S*)-7 (right), and (b) under a UV-lamp (λ = 254 nm).

shows the strong blue emission of the precipitate formed from (*S*)-**6** + (*R*)-7 upon UV irradiation. Although the addition of (*S*)-7 also led to a cloudy solution, no solid precipitate was generated [Figure 2a (right)], and little fluorescence was observed under UV irradiation [Figure 2b (right)]. Over 12 h, the cloudy solution of (*S*)-**6** + (*S*)-7 settled to a clear solution with the formation of insoluble brown oil on the wall of the vial (see Figures S22 and S23 in SI). Therefore, using (*S*)-**6** in the fluorous solvent allows the two enantiomers of the amino alcohol to be visually distinguished.

The precipitate generated from the interaction of (*S*)-**6** with (*R*)-7 was separated by filtration through a filter paper. The IR spectrum of the precipitate shows that the two intense signals at 1661 and 1624 cm^{-1} for the carbonyl groups of (*S*)-**6** disappeared, indicating a nucleophilic addition of the amino alcohol to the carbonyl groups (see Figures S31 and S32 in SI). The electron spray mass spectrum of the precipitate displays three peaks at m/z = 1150.1, 1168.1, and 1221.2, which can be assigned to the MH^+ peaks of compounds **8**, **9**, and **10** respectively (see Figures S28–S30 in SI). However, when the precipitate was dissolved in acid-free $CDCl_3$, ^1H NMR analysis showed that the products were converted back to (*S*)-**6** and (*R*)-7 in this solution (see Figures S26 and S27 in SI). Thus, the formation of the nucleophilic addition products **8**–**10** is promoted by the fluorous solvent. We also studied the brown oily product formed from the reaction of (*S*)-**6** with the enantiomer (*S*)-7 in FC-72. The mass spectrum of the oil shows three peaks at m/z = 1150.1, 1168.1, and 1221.2, indicating the formation of products with molecular structures similar to **8**–**10**.



In order to determine the difference between the products formed from the reaction of the sensor with the two enantiomers of the chiral amino alcohol, we conducted a dynamic light scattering study on the slurry generated from the reactions of (*S*)- and (*R*)-**6** with (*R*)- and (*S*)-7. The slurry formed from the reaction of (*S*)-**6** (8.0×10^{-5} M) with (*R*)-7 (1.5 mM) in FC-72 (4% CH_2Cl_2) or (*R*)-**6** with (*S*)-7 shows the formation of much larger particles, up to 2–3 μm, than those formed from the interaction of (*S*)-**6** with (*S*)-7 or (*R*)-**6** with (*R*)-7, less than 0.5 μm, under the same conditions. Thus, although the reaction of (*S*)-**6** with (*R*)- and (*S*)-7 in the fluorous solution might give similar nucleophilic addition products, their intermolecular aggregations are very different with (*R*)-7 being able to form much larger particles than with (*S*)-7. We propose that the white precipitate generated from (*S*)-**6** + (*R*)-7 might have a much more rigid structure, giving the greatly enhanced fluorescence,[10] but the oily slurry generated from (*S*)-**6** + (*S*)-7 should have a much more flexible structure, giving little fluorescence enhancement.

We also studied the fluorescent response of (*S*)-**6** toward the amino alcohol with various enantiomeric compositions. As shown in Figure 3, a nonlinear relationship between the

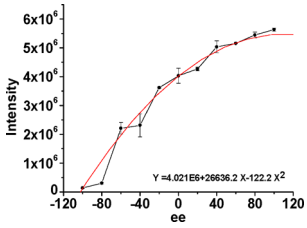
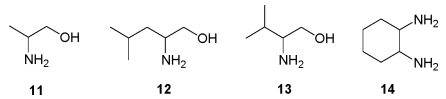


Figure 3. Fluorescent response of (*S*)-**6** (8.0×10^{-5} M) toward 7 (5 mM) at various ee [ee = (R − S)/(R + S). Reaction time = 1 h. Solvent: FC-72/4%CH_2Cl_2. λ_{em} = 420 nm. λ_{ex} = 290 nm. Slit: 2/2 nm. Red curve: second order nonlinear fitting].

fluorescent intensity of (*S*)-**6** and the enantiomeric composition of the amino alcohol is obtained. This nonlinear relationship is consistent with the proposed fluorescent enhancement from the intermolecular aggregates of the sensor–amino alcohol adducts.

We studied the fluorescent response of (*S*)-**6** toward other chiral amino alcohols and diamines in a fluorous solution. In general, highly enantioselective fluorescent responses have been observed for the chiral functional amines such as **11**–**14** (see Figures S9–S20, in SI). For the amino alcohols with concentrations higher than 1 mM, the *R* enantiomers increase the fluorescence of (*S*)-**6** by 1200–2000-fold, while the *S* enantiomers only increase it by 10–50-fold. For the chiral diamine **14**, its (*S,S*)-enantiomer increases the fluorescence of (*S*)-**6** much more than the (*R,R*)-enantiomer.



In summary, we have discovered compound (*S*)-**6** as the first enantioselective fluorescent sensor used in the fluorous phase. In perfluorohexane solution, (*S*)-**6** exhibits greatly enhanced fluorescence when treated with one enantiomer of a chiral amino alcohol and diamine such as (*R*)-7, but little fluorescent response is observed with the opposite enantiomer (*S*)-7. The fluorous solvent is found to promote the nucleophilic addition of the amino alcohols to the carbonyl groups of (*S*)-**6** as shown by IR and mass spectroscopic studies. This is quite remarkable, since such a reaction is not observed in a common polar organic solvent such as methylene chloride and chloroform. Using (*S*)-**6** in the fluorous phase also expands the chiral recognition ability of the previously reported fluorous insoluble

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sensor (*S*)-**3** which was only applicable for the recognition of chiral diamines.

Dynamic light-scattering studies demonstrate that the interaction of the two enantiomers of a chiral amino alcohol with (*S*)-**6** in the fluorous phase forms aggregates of very different sizes. The much larger particles of the (*S*)-**6** + (*R*)-**7** adducts are observed than those of (*S*)-**6** + (*S*)-**7**. Thus, the highly enantioselective fluorescent response of (*S*)-**6** toward the chiral amino alcohols could be attributed to their very different aggregation forms. The highly enantioselective fluorescent response of (*S*)-**6** in the fluorous phase is potentially useful for high throughput chiral catalyst screening. The reaction of the sensor with the chiral substrates only occurs in the fluorous phase in which most other species are not soluble and thus can be easily separated.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experiments and additional spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horváth, I. T., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

(2) Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72−75.

(3) Bakkari, M. E.; Fronton, B.; Luguya, R.; Vincent, J.-M. *J. Fluor. Chem.* **2006**, *127*, 558−564.

(4) Bakkari, M. E.; Luguya, R.; da Costa, R. C.; Vincent, J.-M. *New J. Chem.* **2008**, *32*, 193−196.

(5) Reviews on enantioselective fluorescent recognition: (a) Pu, L. *Chem. Rev.* **2004**, *104*, 1687−1716. (b) Leung, D.; Kang, S. O.; Anslyn, E. V. *Chem. Soc. Rev.* **2012**, *41*, 448−479. (c) Accetta, A.; Corradini, R.; Marchelli, R. *Top. Curr. Chem.* **2011**, *300*, 175−216. (d) Pu, L. *Acc. Chem. Res.* **2012**, *45*, 150−163. (e) Zhang, X.; Yin, J.; Yoon, J. *Chem. Rev.* **2014**, *114*, 4918−4959.

(6) (a) James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *Nature* **1995**, *374*, 345−347. (b) Lin, J.; Hu, Q.-S.; Xu, M. H.; Pu, L. *J. Am. Chem. Soc.* **2002**, *124*, 2088−2089.

(7) (a) Zhao, J.-Z.; Fyles, T. M.; James, T. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 3461−3464. (b) Zhu, L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2004**, *126*, 3676−3677. (c) Mei, X. F.; Wolf, C. *J. Am. Chem. Soc.* **2004**, *126*, 14736−14737.

(8) Yu, S. S.; Plunkett, W.; Kim, M.; Pu, L. *J. Am. Chem. Soc.* **2012**, *134*, 20282−20285.

(9) (a) Zhang, H.-C.; Huang, W.-S.; Pu, L. *J. Org. Chem.* **2001**, *66*, 481−487. (b) Cox, P.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *33*, 2253−2256.

(10) A review on aggregation induced emission: Hong, Y.; Lam, J. W. Y.; Tang, B. Z. *Chem. Soc. Rev.* **2011**, *40*, 5361−5388.

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J. Am. Chem. Soc. 2015, 137, 3747−3750