CHEMISTRY
A European Journal

A Journal of
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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201702354

Link to VoR: http://dx.doi.org/10.1002/chem.201702354

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10.1002/chem.201702354

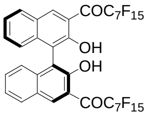
A highly fluorinated chiral aldehyde for enantioselective fluorescent recognition in a biphasic system

Chao Wang, Xuedan Wu, Lin Pu*

ABSTRACT: A 1,1'-bi-2-naphthol (BINOL)-based aldehyde (*S*)-**6** containing four perfluoroalkyl groups is designed and synthesized. It shows enantioselective fluorescence enhancement at 420 nm when treated with the enantiomers of *trans*-1,2-diaminocyclohexane in an organic/fluorous biphasic system. The enantiomeric excess of the diamine in methanol can be linearly correlated with the emission intensity of (*S*)-**6** in perfluorohexane (FC-72). This is the first example to determine the enantiomeric composition of a chiral molecule by using a fluorescent sensor in a fluorous/organic biphasic system. The mechanism of the reaction was investigated by NMR and mass spectroscopic analyses.

In the past two decades, significant progresses have been made in the field of enantioselective fluorescent sensing and a number of sensitive and enantioselective fluorescent sensors have been obtained for the recognition of a variety of chiral organic molecules.[1-3] One potential application of these sensors is to provide a fast analytical tool for high throughput screening of asymmetric reactions and catalysts. However, there is still one major challenge for this application. When an enantioselective fluorescent sensor is added to the mixture of a reaction screening experiment, other components of the reaction including the reagents, catalysts, starting materials and side products besides the desired product could also influence the fluorescence measurement and complicate the analytical results.

In order to minimize the interference of other reaction components on the product analysis, we have proposed to construct highly fluorinated molecular probes for enantioselective fluorescent recognition in fluorous phase. The highly fluorinated sensors can allow the fluorescence to be measured in the fluorous phase separated from the reaction media because of the lipophobic and hydrophobic properties of the fluorous solvents. Although there are extensive studies on the fluorous phase-based chemistry for separation and reaction developments,[4-6] no work was reported on using it for enantioselective fluorescent sensing until our recent discovery. In 2015, we found that compound **1**, prepared from 1,1'-bi-2-naphthol (BINOL, **2**), showed highly enantioselective fluorescent response in perfluorohexane (FC-72).[7] In **1**, its electrophilic perfluoroalkyl ketone groups can form adducts with the nucleophilic chiral amino alcohols in FC-12 to generate enantioselective fluorescence enhancement. This compound can be used for chiral recognition in a fluorous solvent, but it cannot be used in the fluorous/nonfluorous biphasic systems because the amino alcohol adduct has very limited solubility in the fluorous solvent and in a biphasic system the amino alcohol substrates prefer to stay in the original nonfluorous phase instead of getting into the fluorous phase to react with **1**. Chiral recognition in a biphasic system can simplify the application of such a fluorous phase-based fluorescent sensor in the reaction screening experiments since these experiments are generally conducted in nonfluorous solvents. It is therefore desirable to increase the fluorine content of the fluorescent probe in order to conduct the biphasic recognition.



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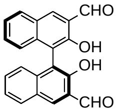
Besides the electrophilic perfluoroalkyl ketones like **1**, aldehydes have also been used to develop fluorescent sensors for amines because of their facile condensation to form imines.[8] However, when the BINOL-based dialdehyde **3** or the mono aldehyde **4** was treated with both enantiomers of *trans*-1,2-diaminocyclohexane (DACH, **5**), there was little fluorescence response unless Zn^{II} was introduced.[9] Reaction of **3** or **4** with a primary amine or diamine can generate the corresponding imine



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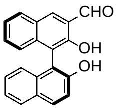

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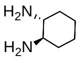

5 (DACH)

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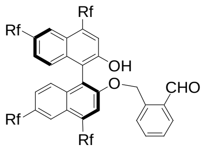
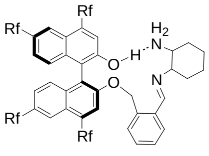
products. It was proposed that the excited state isomerization of the imine double bonds in these products could lead to fluorescence quenching. Addition of Zn^{II} can inhibit this isomerization and enhance the fluorescence of the resulting imine-Zn^{II} complex.[9,10] Introduction of additional intramolecular hydrogen bonding interaction can increase the structural rigidity of the imine compounds which can also lead to fluorescence enhancement.[8,11] In this paper, we report our design and synthesis of a novel BINOL-based aldehyde containing four perfluoroalkyl groups with the incorporation of additional intramolecular hydrogen bonding capability for the enantioselective fluorescent recognition of DACH. We have demonstrated for the first time that the enantioselective fluorescent recognition can be conducted in a fluorous/organic biphasic system.

Compound (*S*)-**6** is designed for the fluorescent recognition of DACH. In (*S*)-**6**, four perfluoroalkyl groups (Rf) will be introduced to increase its solubility in fluorous solvents. When it is treated with DACH, an imine compound like **7** should be generated. The intramolecular hydrogen bonding shown in **7** is introduced to increase the structural rigidity of this compound for fluorescence enhancement. A density functional calculation on the two diastereomers of **7** formed from the reaction of the core structure of (*S*)-**6** (without the Rf groups) with (*R*,*R*)- and (*S*,*S*)-DACH has been conducted by using the Spartan program (ωB97X-D, 6-31G*). It shows that the imine product made from (*S*)-**6** with (*R*,*R*)-DACH is more stable than that with (*S*,*S*)-DACH by 5.7 kcal/mol. This significant energy difference between the two diasteremers of **7** predicts a possible chiral discrimination. Figure 1 gives the energy minimized structure of the imine compound made from the core of (*S*)-**6** with (*R*,*R*)-DACH. In this structure, the electron rich naphthol ring is parallel with the electron deficient phenyl imine moiety with an intramolecular hydrogen bond.



(*S*)-**6**



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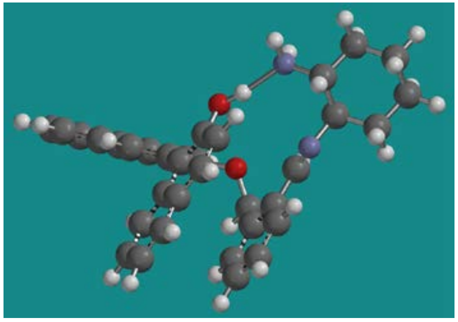
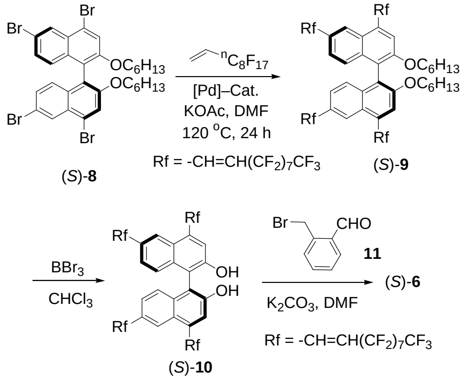


Figure 1. Energy minimized molecular modeling structure for the core of **7** made from (*S*)-**6** and (*R*,*R*)-DACH.

The distance between the two parallel aromatic rings is about 3.3 Å.

Compound (*S*)-**6** was synthesized according to the procedure in Scheme 1. Four highly fluorinated substituents were introduced by Heck coupling of (*S*)-**8**[12], with a fluorinated alkene in the presence of Herrmann΄s catalyst to give (*S*)-**9**.[13] Removal of the hexyl groups of (*S*)-**9** with BBr$_3$ gave compound (*S*)-**10**. Since in the Heck coupling step, the reaction was conducted at 120 °C for 24 h, we examined the enantiomeric purity of (*S*)-**10** by HPLC analysis of both (*S*)-**10** and its enantiomer (*R*)-**10** prepared from the corresponding (*R*)-BINOL starting material, which shows over 99% enantiomeric excess for (*S*)-**10** as well as (*R*)-**10**. Thus, there was no racemization in these reactions. Reaction of (*S*)-**10** with 1 equiv of compound **11**[14] gave (*S*)-**6**, which has a fluorine content of 59.2% (*wt*%). This compound is highly soluble in fluorous solvents such as FC-72 but only barely soluble in common organic solvents.

Scheme 1. Synthesis of (*S*)-**6**



We studied the fluorescence response of (*S*)-**6** toward DACH in a biphasic system. A solution of (*S*)-**6** (50 μM) in FC-72 was mixed with a solution of (*R*,*R*)- or (*S*,*S*)-DACH (1 – 8 equiv) in methanol (FC-72:MeOH = 4:1 v) on a shaker for 1 h to reach a 2-phase equilibrium. Then, the fluorescence spectra of the FC-72 phase were recorded. As shown in Figure 2c, mixing the FC-72 solution of (*S*)-**6** with the methanol solution of ≤ 2 equiv (*R*,*R*)-DACH gave a slight reduction of the fluorescence intensity at 420 nm. However, when more than 2 equiv of (*R*,*R*)-DACH were used, it greatly enhanced the fluorescence but (*S*,*S*)-DACH only maintained the low fluorescence of (*S*)-**6**. At 8 equiv of DACH, the enantioselective fluorescence enhancement ratio (*ef*) was found to be 4.0 [$ef = (I_{RR} - I_0) / (I_{SS} - I_0)$, where I_0 is the emission intensity of sensor blank, I_{RR} and I_{SS} are fluorescence intensities after addition of two enantiomers respectively]. Thus, (*S*)-**6** exhibits highly enantioselective fluorescent response toward the chiral diamine in the biphasic system.

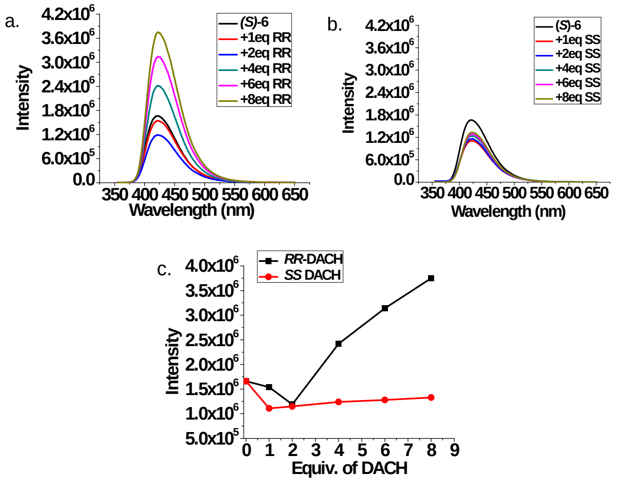


Figure 2. Fluorescence spectra of (*S*)-**6** (50 μM) in FC-72 (2 mL) treated with (a) (*R*,*R*)-DACH and (b) (*S*,*S*)-DACH in methanol (0.5 mL) at various equiv. (c) Fluorescence intensity at 420 nm was plotted against the equivalents of DACH. (λ_{ex} = 335 nm, slit 2/2 nm)

We then studied the fluorescence response of (*S*)-**6** in FC-72 toward the methanol solution of DACH at various *ee* (*ee* = [*RR*]-[*SS*]/[*RR*+*SS*] %) values with a total concentration of 8 equiv (Figure S1 in SI). As shown in Figure 3, when the *ee* of DACH increases from -100 % (*SS*) to 100 % (*RR*), the fluorescence intensity increases linearly. Thus, (*S*)-**6** can be used to determine the *ee* of this chiral diamine in the biphasic system.

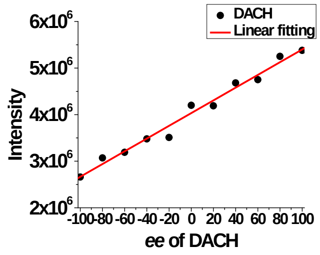


Figure 3. Emission intensities at 420 nm were plotted against *ee* when (*S*)-**6** (50 μM) was treated with DACH at various *ee* in the FC-72/methanol biphase system. (λ_{ex} = 335 nm, slit 2/2 nm).

In order to understand the origin of the fluorescence response of (*S*)-**6** toward DACH, we studied the NMR spectrum of (*S*)-**6** in FC-72 after it was treated with the methanol solution of (*R*,*R*)- and (*S*,*S*)-DACH. A capillary tube filled with acetonde-d_6 was added as an external standard. As shown in Figure 4a, the ^{1}H NMR signals of (*S*)-**6** are shifted much more upfield than those in $CDCl_3$ because of the shielding effect of the fluorine atoms in the perfluoro hydrocarbon solvent. When (*S*)-**6** was treated with more than 2 equiv of both enantiomers of DACH, the aldehyde signal of (*S*)-**6** in FC-72 completely disappeared (Figure 4b,c). The very broad ^{1}H NMR signals of the reaction mixture in FC-12 indicate possible aggregation of the highly polar amine and hydroxyl units of the products such as **7** in the fluorous phase. That is, aggregation of these units together can minimize their interaction with the fluorous solvent molecules and decrease their mobility to give the very broad ^{1}H NMR signals. The observed fluorescence enhancement of (*S*)-**6** in FC-12 can be attributed to the formation of a structurally more rigid imine product **7** as proposed. The initial decrease in fluorescence intensity when the concentration of DACH was less than 2 equiv as shown in Figure 2c may be due to an initial partial transportation of (*S*)-**6** from the fluorous phase to the methanol phase in the presence of the diamine.

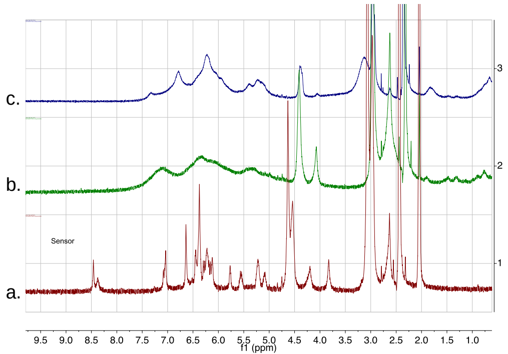


Figure 4. ^{1}H NMR spectra of (a) (*S*)-**6**; (b) with (*S*,*S*)-DACH (8 equiv); (c) with (*R*,*R*)-DACH (8 equiv) in the FC-72/methanol biphase system.

We also removed the fluorous solvent in the above NMR samples and added $CDCl_3$ to check the ^{1}H NMR spectra. It shows that in $CDCl_3$, the reaction of (*S*)-**6** with (*S*,*S*)-DACH gave complete conversion to the imine product **7** (Figure 5b) which is confirmed by mass spectroscopic analysis (MALDI) with the M$^+$ peak observed at 2317. However, the ^{1}H NMR spectrum for the reaction of (*S*)-**6** with (*R*,*R*)-DACH showed the formation of a mixture of two products (the sample also contained excess DACH) (Figure 5c). The major product is assigned to the imine product **7** and the minor product is assigned to the diimine product **8** with a ratio of 4.4:1. In the mass (MALDI) spectrum, the M+H$^+$ signal of **8**

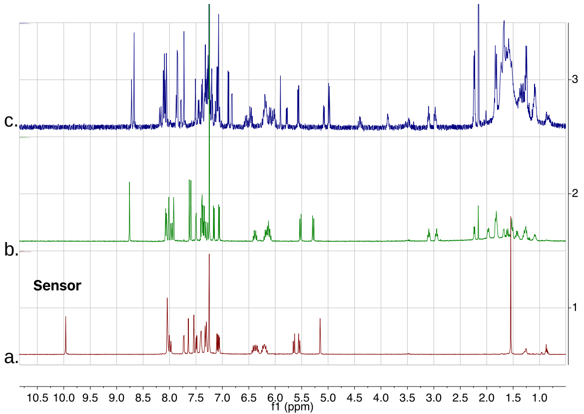
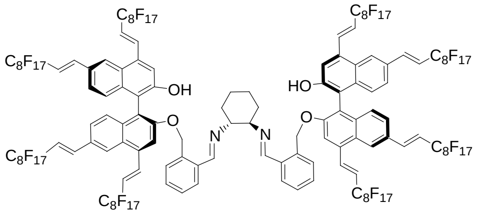


Figure 5. ^{1}H NMR spectra of (a) (*S*)-**6**; (b) with (*S*,*S*)-DACH (8 equiv); (c) with (*R*,*R*)-DACH (8 equiv) in $CDCl_3$.

was observed at 4439. Although the products formed in $CDCl_3$ might not be exactly the same as those formed in the fluorous solvent, this NMR study demonstrates that compound (*S*)-**6** reacts with the two enantiomers of DACH differently which should contribute to the observed enantioselective fluorescent response.



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In conclusion, we have demonstrated that the BINOL-based aldehyde (*S*)-**6** with four perfluoroalkyl substituents can be used to conduct highly enantioselective fluorescent recognition of a chiral diamine in a biphasic fluorous/methanol system with the *ef* value up to 4.0. This compound can be used to determine the enantiomeric composition of the chiral diamine. The fluorescent recognition in a biphasic system can simplify the analysis of the screening experiments of chemical reactions and reduce the interference of other reaction components on the fluorescence measurement.

ACKNOWLEDGMENT

We thank the support of this work by the US National Science Foundation (CHE-1565627). Partial supports of this work from the donors of the Petroleum Research Fund—administered by the American Chemical Society are also gratefully acknowledged.

Keywords: fluorous phase, enantioselective fluorescent sensing, chiral amine, BINOL, aldehyde

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