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Chiral Sensor for Enantiodiscrimination of Varied Acids

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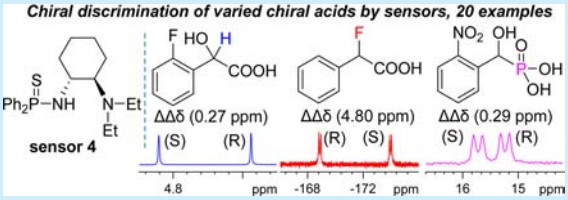
Supporting Information

ABSTRACT: A chiral thiophosphoroamide **4** derived from (1*R*,2*R*)-1,2-diaminocyclohexane is used as a highly effective chiral sensor for the chiral recognition of varied acids via ion-pairing and hydrogen-bonding interactions using ^{1}H, ^{19}F and ^{31}P NMR.



Chirality plays a significant role in biology, chemistry, and pharmacy.[1] Therefore, developing a fast and facile method for chiral recognition and determination of the enantiomeric purity of chiral compounds is very important. Many approaches have been developed for chiral analysis or enantiomeric excess measurement, such as GC,[2] HPLC,[3] IR,[4] UV,[5] fluorescence spectroscopy,[6] mass spectrometry,[7] circular dichroism,[8] electrophoresis,[9] and NMR spectroscopy.[10−12] Since the NMR sensor method[12] is easy to operate without derivatization of analyte and provides abundant information about the interactions between the chiral host and guest in solution state, the design and synthesis of novel and efficient chiral NMR sensors for chiral recognition has received significant attention. A large number of NMR chiral sensors have been developed for the enantiodiscrimination and *ee* determination of chiral compounds,[10,11] but only a few have outstanding performance. Thus, developing novel and easily synthesized sensors with high efficiency and wide application for varied chiral acids is still highly desirable.

Chiral sensors often associate with guests through non-covalent driving forces such as ion-pairing, hydrogen-bonding, $\pi-\pi$ interaction, etc. One or more of these driving forces exist in the recognition system. The coexistence of many kinds of driving forces can help to strengthen the interactions between host and guest molecules, favoring chiral recognition. Therefore, the design and synthesis of the host molecules with multiple driving forces acting with guests is an important strategy to enhance recognition ability.

In our previous studies, we designed a chiral bis-thiourea as a wonderful chiral sensor via hydrogen-bonding interaction with a carboxylic acid−base ion pair. The recognition system is a tertiary system including the bis-thiourea, a chiral acid, and an achiral base.[10y,11h,12e,g] Herein, we report a novel chiral sensor, chiral thiophosphoroamide **4** derived from (1*R*,2*R*)-1,2-diaminocyclohexane, which can be used directly for chiral recognition of chiral acids via ion-pairing and hydrogen-bonding interactions and exhibits excellent enantiomeric discrimination ability to varied chiral acids using ^{1}H, ^{19}F, and ^{31}P NMR. The corresponding recognition system is a simple binary system including only the chiral thiophosphoroamide **4** and a chiral acid.

For α-carboxylic acids, chiral sensor **4** gave large $\Delta\Delta\delta$ (chemical shift nonequivalence) values up to 0.27 ppm for α-H NMR signals. Chiral sensor **4** also gave a 0.12 ppm $\Delta\Delta\delta$ value for the β-H NMR signal of tested β-carboxylic acid.[13] ^{19}F NMR was found to be suitable for enantiodiscrimination of α-F substituted carboxylic acid and chiral carbon tetrasubstituted carboxylic acid containing an α-CF_3 group with up to 4.80 ppm $\Delta\Delta\delta$ value for the ^{19}F NMR signals of tested examples. In addition, chiral phosphonic acid, whose ee values are usually determined by a derivative method,[14] can also be recognized using chiral sensor **4** by ^{1}H and ^{31}P NMR.

Using racemic mandelic acid (MA) as the substrate, the chiral recognition ability of 1,2-diaminophosphoroamides **1a**, **2a**,[15a] and **3**,[16] having different chiral skeletons, were first investigated employing 3:1 ratio of chiral sensor:MA in $CDCl_3$ at room temperature. Compared with **1a** and **3**, which derived from (1*R*,2*R*)-diphenylethylenediamine and *L*-valine respectively, chiral sensor **2a**, which derived from (1*R*,2*R*)-1,2-diaminocyclohexane, gave the largest chemical shift nonequivalence of α-H signal of MA (0.17 ppm $\Delta\Delta\delta$ value) as shown in Table 1. Modifying the disubstituents of amino group of **2a** with different alkyl groups showed that **2c** containing diethyl groups is the best chiral sensor. Larger and smaller alkyl groups would lower the chiral recognition ability.

Further replacing the oxygen atom of the O═P bond on **2c** with a sulfur atom led to **4**, which has better chiral discriminating ability for MA as the sulfur atom increased the

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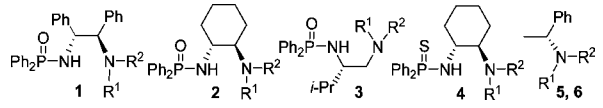
Table 1. Optimization of Chrial Phosphoraminde Structures in the Chiral Discrimination of MA (20 mM) Using Chiral Sensors by ^{1}H NMR in $CDCl_3$ at 25 °C[a]



sensor	NR^1R^2	ΔΔδ (ppm)	sensor	NR^1R^2	ΔΔδ (ppm)
1a	$N(CH_2)_4$	0.12	**2g**	$N(CH_2)_5$	0.16
1b	NH*i*-Pr	0	**3**	$N(CH_2)_4$	0.06
2a	$N(CH_2)_4$	0.17	**4**	NEt_2	0.20
2b	NMe_2	0.06	**5**	$NHP(=O)Ph_2$	<0.01
2c	NEt_2	0.18	**6**	NEt_2	0
2d	NBu_2	0.13	**4**[b]	NEt_2	0.04
2e	$N(CH_2Bu)_2$	0.13	**4**[c]	NEt_2	0.05
2f	NBn_2	0.03	**4**[d]	NEt_2	0.20

[a]MA/chiral sensor = 1:3. [b]The solvent was C_6D_6. [c]The solvent was $C_6D_5CD_3$. [d]MA/chiral sensor = 1:1.5, 10 mM of MA was used.

acidity of neighboring N−H via S═P bond for better hydrogen-bonding interaction with MA. When compound **5** without an amino group was used, the ΔΔδ value was less than 0.01 ppm. In addition, no split proton signal was obtained for MA using compound **6** containing an amino group only, indicating that both a hydrogen-bonding group and a basic group in one molecule are necessary to achieve highly efficient chiral recognition. Moreover, **1b**[15b] with a phosphoroamide group and a monosubstituted amino group also showed no recognition ability for MA, implying that the basic amino group had to be alkyl disubstituted. On the basis of the above results, we speculated that the hydrogen-bonding thiophosphoroamide group and the basic alkyl-disubstituted amino group are both essential for the chiral thiophosphoroamide to provide appropriate chiral environment for the high efficiency of enantiodifferentiation of MA. The conditions of solvent, the ratio of **4**:MA, and concentration were also optimized (see Table S1), and the best conditions were identified as 1.5:1 of **4**:MA, 10 mM of acid in $CDCl_3$.

With the optimized conditions in hand, we tested the substrate scope, and the results are listed in Table 2. The α-H signals of the tested aromatic carboxylic acids with electron-withdrawing or electron-donating groups were well resolved. The largest ΔΔδ value of 0.27 ppm was obtained when 2-fluoromandelic acid (**7e**) was used as the substrate. For 4-MeO-substituted mandelic acid (**7j**), the ΔΔδ value was 0.20 ppm. Aliphatic racemic α-hydroxyl carboxylic acids **7k** and **7l** could be well recognized with ΔΔδ value of 0.06 and 0.03 ppm, respectively. For α-OMe carboxylic acid (**7m**), the ΔΔδ value was 0.08 ppm. Chiral compounds containing fluorine atom(s) were also well enantiodiscriminated (**7b−d**). When α-F-substituted carboxylic acid (**7n**) was used as the substrate, the ΔΔδ value of ^{1}H NMR was 0.18 ppm and the ΔΔδ value of ^{19}F NMR could be as large as 4.80 ppm. ^{19}F NMR was found to be suitable for enantiodiscrimination of chiral carbon tetrasubstituted carboxylic acid containing an α-CF_3 group (**7o**). For amino group protected α-phenylglycine (**7p**) and penicillamine intermediate (**7q**), the ΔΔδ values were 0.12 and 0.06 ppm, respectively. We further applied the sensor **4** in much more challenging substrate β-carboxylic acid **7r**, obtaining a 0.12 ppm ΔΔδ value. In addition, sensor **4** also proved useful in the discrimination of chiral phosphonic acids (**7s** and **7t**)

Table 2. Determination of ^{1}H, ^{19}F, or ^{31}P NMR ΔΔδ Values of Racemic Chiral Acids (10 mM) Using Chiral Sensor 4 in $CDCl_3$ at 25 °C[a]

chiral acid and ΔΔδ (ppm)	spectra	chiral acid and ΔΔδ (ppm)	spectra
7a (0.20)	4.6 ppm	**7k** (0.06)	3.5 ppm
7b (0.19) (0.23[b])	-117 ppm	**7l** (0.03)	3.90 ppm
7c (0.24) (0.26[b])	-111 ppm	**7m** (0.08)	4.5 ppm
7d (0.21) (0.04[b])	-62.3 ppm	**7n** (0.18) (4.80[b])	-170 ppm
7e (0.27)	4.8 ppm	**7o** (0.78[b])	-71 ppm
7f (0.19)	4.6 ppm	**7p** (0.12)	5.5 ppm
7g (0.19)	4.6 ppm	**7q** (0.06)	4.6 ppm
7h (0.21)	4.6 ppm	**7r** (0.12)	4.7 ppm
7i (0.21)	5.0 ppm	**7s** (0.08) (0.19[c])	5.3 ppm / 16.4 ppm
7j (0.20)	4.6 ppm	**7t** (0.29[c])	15.5 ppm

[a]MA/sensor **4** = 1:1.5. [b]^{19}F NMR was used. [c]^{31}P NMR was used.

using ^{1}H NMR and ^{31}P NMR. However, it is noteworthy that sensor **4** has no effect on 2-phenylpropionic acid containing a CH_3 group at the chiral center. These results suggest that the strong electronegative O, F, and N atoms at the chiral center of the chiral acids facilitate the formation of the ion pair between NEt_2 group of chiral sensor **4** and chiral acids.

The Job's method was used to determine the stoichiometry. The Job plots show that the maximum of X is 0.5 (SI), which indicates that chiral sensor **4** and the chiral acid bind in a 1:1 complex. 1D NOESY experiments for the mixture of racemic MA/chiral sensor **4** were also carried out. As shown in Figure 1, the H_A on aromatic ring of chiral sensor **4** has resonances with α-Hs of both enantiomers of MA and the resonance between H_A and H_R is stronger than that between H_A and Hs indicates that the binary complex of chiral sensor **4**/(*R*)-MA is tighter than that of chiral sensor **4**/(*S*)-MA.

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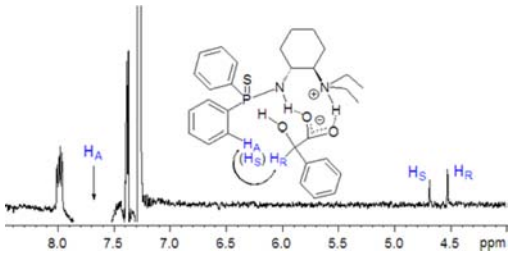

Figure 1. 1D NOESY spectrum.

Computational modeling studies[17] show that there are ion-pairing and hydrogen-bonding intermolecular interactions (Figure 2). The existence of chiral sensor **4** disturbs the microenvironment around two α-H signals of two enantiomers of MA and induces the differences of their orientations. The deshielding effect of the aromatic ring of (*R*)-MA on its α-H is less than that of (*S*)-MA, leading to the chemical shift of α-H of (*R*)-MA being more upfield with a smaller δ value (see the SI for details). We can also see from Table 3 that the trends of calculated δ values and the observed δ values are consistent.

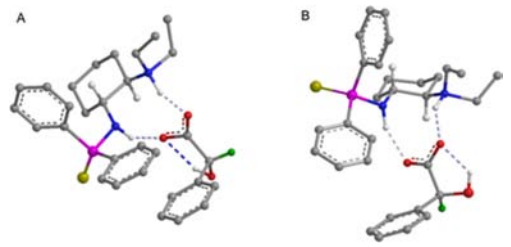

Figure 2. Space-filling representations of binary complexes: (A) sensor **4**/(*R*)-MA and (B) sensor **4**/(*S*)-MA.

Table 3. Calculated and Observed δ and $\Delta\delta^{SR}$ Values for the α-H of (*R*)- and (*S*)-MA in Binary Complexes

	$\delta^{(R)\text{-MA}}$ (ppm)	$\delta^{(S)\text{-MA}}$ (ppm)	$\Delta\delta^{SR}$ (ppm)
calcd values	4.68	4.95	0.27
obsd values	4.59	4.71	0.12

In addition, chiral sensor **4** was successfully applied in the enantiomeric determination. Several different nonracemic solutions of MA in $CDCl_3$ were prepared. As shown in Figure 3b, the experimentally measured ee by integration of *R* and *S* signals of MA in ^{1}H NMR matched very well with gravimetrically prepared samples.

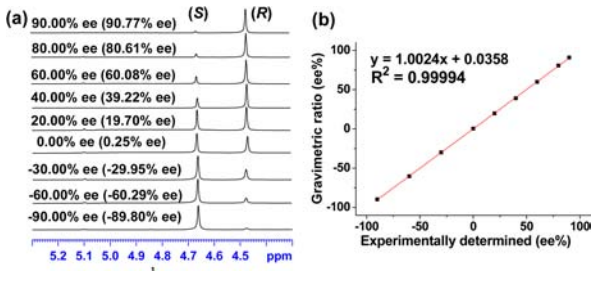

Figure 3. (a) ^{1}H NMR signals of nonracemic MA samples using sensor **4** in $CDCl_3$. (b) Linear relationship between measured ee values versus the gravimetrically determined ee values.

In conclusion, a novel chiral sensor **4** containing a thiophosphoroamide group and a disubstituted amino group was successfully applied in the chiral recognition of varied chiral acids via ion-pairing and hydrogen-bonding interactions with the use of NMR spectroscopy. Very well split NMR signals were observed with up to 0.27, 4.80, and 0.29 ppm of the $\Delta\Delta\delta$ values for proton, fluorine, and phosphorus signals, respectively.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00088.

Experimental procedures, copies of NMR spectra, and results of computational modeling (PDF)

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Author Contributions

§H.H., G.B., and H.Z. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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