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A Chiral Bisthiourea as a Chiral Solvating Agent for Carboxylic Acids in the Presence of DMAP

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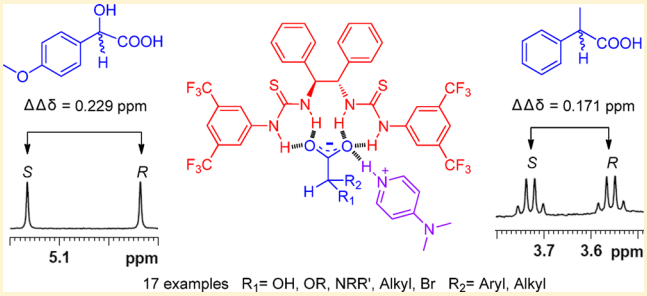
Supporting Information

ABSTRACT: A simple chiral bisthiourea has been used as a highly effective and practical chemical solvating agent (CSA) for diverse α-carboxylic acids in the presence of DMAP. Excellent enantiodiscrimination based on well-resolved α-H NMR signals of the enantiomers of carboxylic acids can be obtained without interference from the chiral bisthiourea and DMAP. To check the practicality of the chiral bisthiourea/DMAP for enantiomeric determination, the ee values of mandelic acid (MA) samples over a wide ee range were determined by integration of the α-H signal of MA in ^{1}H NMR. A discrimination mechanism is proposed, that the formation of two diasteromeric ternary complexes between the chiral bisthiourea and two in situ formed enantiomeric carboxylate-DMAPH$^+$ ion pairs discriminates the enantiomers of carboxylic acids. Computational modeling studies show that the chemical shift value of α-H of (*S*)-MA is greater than that of (*R*)-MA in ternary complexes, which is consistent with experimental observation. 1D and 2D NOESY spectra demonstrate the intermolecular noncovalent interactions between the protons on the aromatic rings of chiral bisthiourea and α-H of the enantiomers of racemic α-methoxy phenylacetic acids in the complexes.



INTRODUCTION

The increasing demand for chiral compounds in chemical, biological, and pharmaceutical fields has driven not only the development of asymmetric synthetic methodologies for obtaining chiral compounds in high yields but also the development of rapid, convenient, and accurate methodologies for measuring the optical purities of chiral compounds via multivariate analytical technologies, such as HPLC,[1] GC,[2] CE,[3] NMR,[4] etc. Among these methods, NMR spectroscopy using chiral solvating agents (CSAs) to form diastereomeric complexes with samples via noncovalent interactions might be one of the most facile methods without chiral derivatization of the analyte or using special equipment apart from the common NMR spectrometers, which has the advantages of easy performance and accessibility.[5] As soon as there is a large enough chemical shift nonequivalence to give clear baseline separation of the NMR signals of probe groups in two diastereomeric complexes formed between CSAs and samples, the enantiomeric purities of samples can be measured.

Chiral carboxylic acids are ubiquitous architectural units of natural products and drug molecules as well as versatile functional synthons.[6] In the past decades, various types of CSAs for carboxylic acid have been reported, particularly for α-carboxylic acids, such as lanthanide complexes,[7] amines,[8] amino alcohols,[9] diamines,[10] amides,[11] macrocyclic compounds,[12] and ureas(thioureas).[13] However, most of the CSAs are not practical because their ^{1}H chemical shift nonequivalences are too small to realize baseline resolution. Even for the minority that are effective,[9d,11c,12c,f,g] several synthetic steps are needed due to their structural complexities, and some are special only for carboxylic acids containing an α-oxygen atom.[9d,12f] For the few commercially available CSAs, several limitations exist, such as signal broadening for lanthanide complexes, high price for macrocyclic compounds, and limited substrate scopes for varied amines. In addition, most of those developed reagents have proton signals in the middle field region of the ^{1}H NMR chemical shift range (3.0−6.0 ppm), which may interfere with the α-H signals of some carboxylic acids. Therefore, the development of simple, highly effective, and practical CSAs for α-carboxylic acids with a broad substrate scope is still desirable.

Many reports have shown that chiral urea(thiourea) compounds are efficient organocatalysts in diverse asymmetric reactions due to the existence of multiple H-bonding interactions between ureas(thioureas) and substrates,[14] but the studies on the uses of ureas(thioureas) as CSAs are few.[13] In 1993, Rebek and co-workers[13a] first developed a neutral and asymmetric urea receptor A (Figure 1A) of carboxylate

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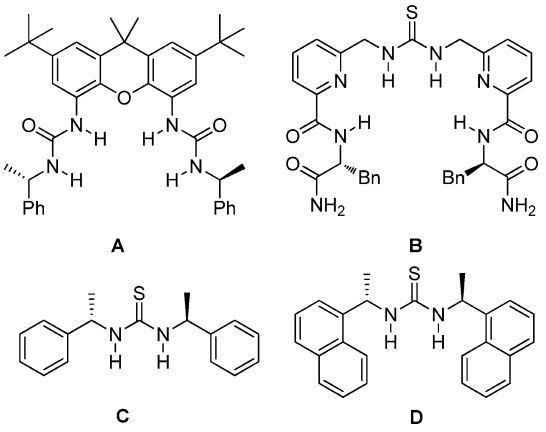

Figure 1. Chiral urea(thiourea) compounds used as CSAs.

compounds. In 2001, Kilburn and co-workers[13b] reported that a series of acyclic thioureas such as B (Figure 1B) showed good enantiodiscrimination for a range of amino acid derivatives. In 2007, Juaristi and co-workers[13c] reported that the diastereomeric complexes derived from structurally simple chiral thioureas such as C and D (Figure 1C and D) with ammonium salts of the chiral acids gave rise to separated signals of α-H. Although the above urea(thiourea) derived receptors showed discriminating abilities for carboxylate compounds, none of them was effective for carboxylic acids directly, which have relatively weak intermolecular interactions with ureas-(thioureas) compared to carboxylate compounds.

Helmchen and co-workers[15] showed that a chiral host containing strong base formed carboxylates with carboxylic acids in situ to realize the enantiodiscrimination of carboxylic acids directly with the use of pyridyl-containing diamide as a CSA. However, the synthesis of a special and suitable CSA containing strong basic groups was complicated and time-consuming. Jolly and co-workers[16] reported that adding a suitable base to form ion pairs with carboxylic acids in situ improved the resolution of α-Hs of carboxylic acids by chiral mandelonitrile. However, the discrimination was not effective enough because one chiral mandelonitrile molecule could be hydrogen bonded singly only to one ion pair of acid−base in a formed complex.

We conceived that employing a chiral bisurea(bisthiourea) as a CSA in combination with a base for enantiodifferentiation of chiral carboxylic acids should give us better resolution of α-Hs of acids due to the involvement of multiple H-bonding interactions between one chiral bisurea(bisthiourea) molecule and one ion pair of acid−base. Herein, we report the first example of a bisthiourea CSA derived from chiral 1,2-diphenylethane-1,2-diamine. With the assistance of DMAP, this easily synthesized simple *C*2-symmetrical chiral bisthiourea **1** (Figure 2A) is highly effective and practical for the enantiodiscrimination of diverse α-carboxylic acids based on well-resolved α-H signals of the enantiomers of carboxylic acids.

RESULTS AND DISCUSSION

To test the enantiomeric discriminating ability of chiral bisthiourea **1** as a CSA for carboxylic acids in combination with DMAP, we first recorded ^{1}H NMR of 10 mM racemic mandelic acids (MAs) in the presence of 1 equiv of CSA **1** in $CDCl_3$. However, the shifts of α-H signals of two enantiomers of racemic MAs were very small, resulting in unsatisfactory baseline resolution (Table 1, entry 1), indicating a very weak interaction between MA and CSA **1**. With the addition of DMAP in the above solution, these two enantiomers suffered unequal upfield shifts, and their α-H appeared as two singlets with over 10-fold increase in ^{1}H chemical shift nonequivalence ($\Delta\Delta\delta$) value. The best baseline resolution was obtained with a

Table 1. Measurements of ^{1}H Chemical Shift Nonequivalence ($\Delta\Delta\delta$) Values of Racemic MA in the Presence of CSA 1 by ^{1}H NMR (400 MHz) in $CDCl_3$ at 25 °C[a]

entry	C_{MA} (mM)	C_{DMAP} (mM)	$C_{CSA\ 1}$ (mM)	$\Delta\Delta\delta$ (ppm)[b]
1	10	0	10	0.007
2	10	5	10	0.070
3	10	10	10	0.125
4	10	20	10	0.116
5	10	10	20	0.141
6	10	10	30	0.156
7	10	10	50	0.178
8	7.5	7.5	22.5	0.163
9	**5**	**5**	**15**	**0.204**

[a]All samples were prepared by mixing the $CDCl_3$ solution of CSA **1**, DMAP, and MA in NMR tubes. [b]$\Delta\Delta\delta$ values of the α-H methine protons on the chiral centers of the acids.

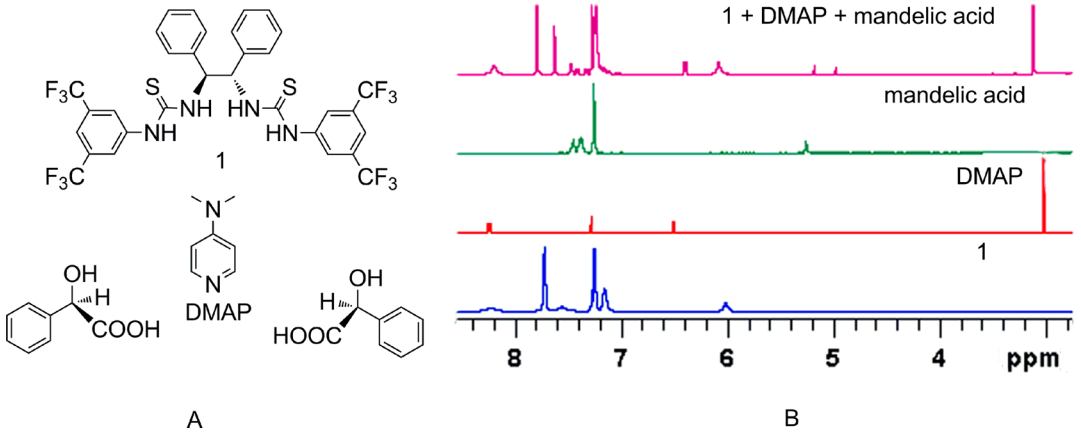

Figure 2. (A) Structures of chiral bisthiourea **1**, DMAP, and mandelic acid (MA). (B) ^{1}H NMR spectra of **1**, DMAP, MA in $CDCl_3$, and a 3:1:1 mixture of **1**/DMAP/MA.

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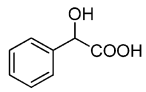
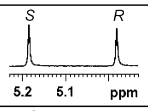
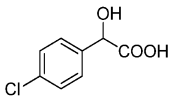
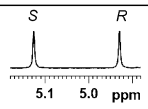
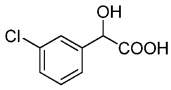
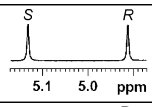
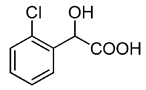
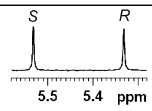
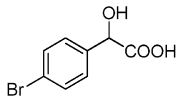
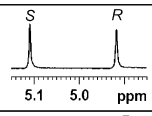
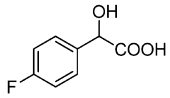
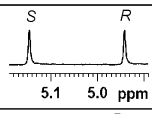
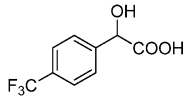
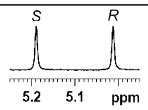
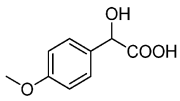
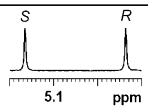
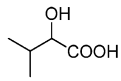
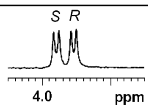
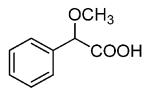
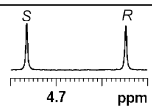
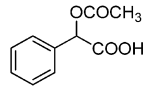
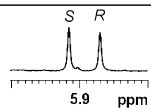
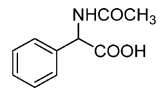
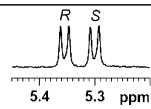
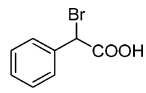
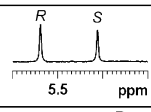
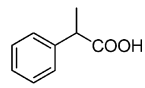
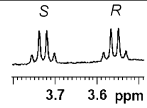
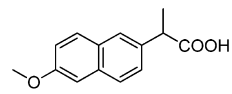
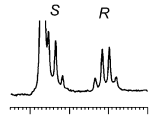
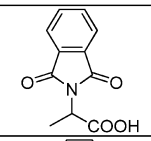
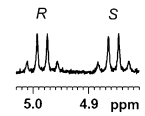
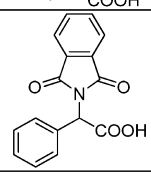
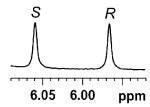
Table 2. Measurements of ^{1}H ΔΔδ values of Racemic Carboxylic Acids in the Presence of CSA 1 by ^{1}H NMR (400 MHz) in $CDCl_3$ at 25 °C[a]

Entry	carboxylic acid	ΔΔδ (ppm)[b]	Spectra[c]
1		0.204	
2		0.196	
3		0.220	
4		0.201	
5		0.192	
6		0.205	
7		0.177	
8		0.229	
9		0.025	
10		0.217	
11		0.045	
12		0.054	
13		0.127	
14		0.171	
15		0.137	
16		0.127	
17		0.094	

[a]All samples were prepared by mixing 3:1:1 of CSA **1**, DMAP, and carboxylic acids (5 mM in CDCl3) in NMR tubes except for the sample in entry 17. The ratio of CSA **1**/DMAP/carboxylic acids is 2:1:1 in entry 17. [b]ΔΔδ values of the methine protons on the chiral centers of the acids. [c]The configuration was determined by comparing with spectra of nonracemic samples of known configurations.

1:1 ratio of MA/DMAP (Table 1, entries 2−4). This result indicated that adding DMAP promoted the interaction between MA and CSA **1** to form two geometrically different diasteromeric ternary complexes so that the α-H signals of two enantiomers of racemic MAs were split. While maintaining the concentrations of MA and DMAP constant at 10 mM, further increasing the ratio of CSA **1** increased the ΔΔδ value gradually due to the right equilibrium shift of the ternary complex formation (Table 1, entries 5−7), but the resonance of the corresponding α-H of MA would decrease. Therefore, a 1:1:3 ratio of MA/DMAP/**1** should be comparatively suitable for the enantiomeric discriminating process. Moreover, concentration optimization gave 5 mM MA/5 mM DMAP/15 mM **1** as the best combination with the largest ΔΔδ value as 0.204 ppm (Table 1, entries 7−9). As shown in Figure 2B, under the optimized conditions, chiral bisthiourea **1** and DMAP gave proton signals only in the low and high field regions of the ^{1}H NMR spectral range, which did not interfere with the α-H signals of varied carboxylic acids.

The general applicability of these conditions for a variety of carboxylic acids was demonstrated by the data displayed in Table 2. The ΔΔδ values of α-H signals were large enough to give very good baseline resolution for all tested aromatic carboxylic acids on a 400 MHz NMR instrument at 25 °C. For the aromatic acids containing α-OH (Table 2, entries 1−8), 4-OCH_3-substituted aromatic acid had the largest ΔΔδ value as 0.229 ppm, and the 4-CF_3-substituted one had the lowest ΔΔδ value as 0.177 ppm. For the carboxylic acids with diverse α-substitutents (Table 2, entries 1 and 10−14), the decrease of ΔΔδ values was in the order of OCH_3, OH, CH_3, Br, $OCOCH_3$, and $NHCOCH_3$. These results indicated that an electron-donating group could enhance the enantiodifferentiation by promoting the H-bonding interaction between the two thiourea groups of CSA **1** and the carboxylate group of a carboxylic acid/DMAP ion pair and that an electron-withdrawing group had the opposite effect. As shown in the entries 12 and 17 of Table 2, a bulky group at the α-carbon contributed

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to a larger $\Delta\Delta\delta$ value. In addition, even aliphatic acids can be successfully analyzed with CSA **1** (Table 2, entries 9 and 16).

To further demonstrate the practicality of **1** as a CSA in the presence of DMAP for enantiomeric determination, the ee values of several nonracemic MA samples were determined by integration of the α-H signal of MA in ^{1}H NMR. Figure 3

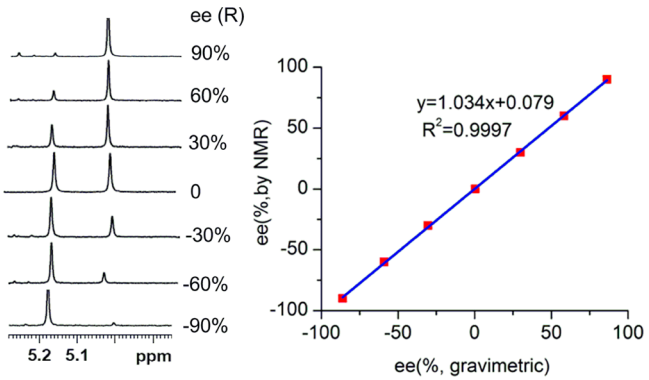

Figure 3. (Left) Selected regions of the ^{1}H NMR spectra of nonracemic MA samples (varied ee values) with CSA **1** and DMAP in $CDCl_3$. (Right) Linear correlation between ee values determined by gravimetry and NMR. ee values were defined in terms of (*R*)-MA.

shows that CSA **1** maintains analytic resolution for the MA samples over a wide range of ee values. The linear relationship between the NMR-determined values and those gravimetry-determined values is excellent with R^2 = 0.9997.

The proposed roles of DMAP and CSA **1** in chiral discrimiantion of racemic carboxylic acids are as follows: each enantiomer of racemic carboxylic acids interacts with DMAP to form a carboxylate-DMAPH$^+$ ion pair through a NH···O bond, which strengthens the interaction between the carboxylic acid and chiral CSA **1** to further form a ternary complex via multiple intermolecular H-bonding interactions between the carboxylate group of the ion pair and the two thiourea groups of CSA **1** (Figure 4).[13b,16] The two formed ternary complexes are

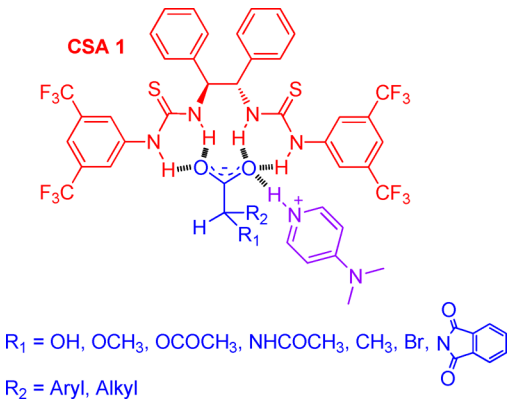

Figure 4. Proposed roles of chiral bisthiourea **1** and DMAP in chiral discrimiantion of racemic carboxylic acids.

diasteromers that place the α-H of carboxylic acid enantiomers in different chemical environments so that the α-H signals of two enantiomers of racemic carboxylic acids are split. The electron-withdrawing 3,5-bistrifluoromethyl groups in bis-thiourea **1** enhance the electrophilicity of the thiourea hydrogens, which favors the formation of a ternary complex of **1**/carboxylic acid/DMAP.

In order to verify the hypothesis of chiral discrimination mechanism, computational modeling studies were performed with the Gaussian09 program.[17] Geometries of ternary complexes of CSA **1**/(*S*)-mandelate-DMAPH$^+$ and CSA **1**/(*R*)-mandelate-DMAPH$^+$ were optimized using the molecular mechanics method initially and then the DFT method on the b3lyp/6-31+g(d,p) level. All geometry optimizations were carried out in gas phase. NMR chemical shifts were calculated on the b3lyp/6-311+g(d,p) level in chloroform solvent with the GIAO method (solvent effects were evaluated with IEFPCM model). Calculated chemical shifts for α-Hs of (*R*)- and (*S*)-MAs are reported in Table 3. The optimized space-filling

Table 3. Calculated and Experimentally Observed δ and $\Delta\delta^{RS}$ Values for the α-Hs of (*R*)- and (*S*)-MAs in Ternary Complexes

	$\delta^{(R)\text{-MA}}$ (ppm)	$\delta^{(S)\text{-MA}}$ (ppm)	$\Delta\delta^{RS}$ (ppm)
calculated values	5.57	5.64	−0.07
experimental values	4.97	5.09	−0.12

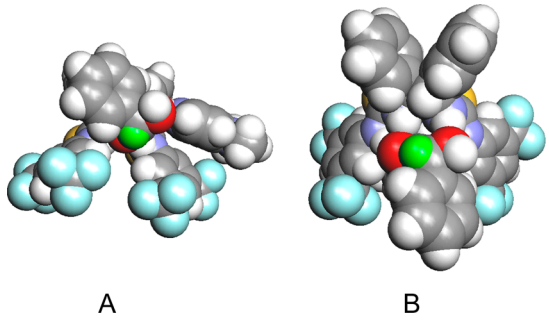

Figure 5. Space-filling representations for ternary complexes: (A) CSA **1**/(*S*)-mandelate-DMAPH$^+$ and (B) CSA **1**/(*R*)-mandelate-DMAPH$^+$. The α-Hs of (*R*)- and (*S*)-MAs are shown in green.

models presented in Figure 5 show that the α-Hs of (*R*)- and (*S*)-MAs are located in the deshielding range of the aromatic system of CSA **1** (shielding range: above/below the ring plane and inside the ring; deshielding range: around the ring plane). Whereas the α-H of (*S*)-MA is close to the aromatic rings of CSA **1** and DMAP in CSA **1**/(*S*)-mandelate-DMAPH$^+$ complex, the α-H of (*R*)-MA is relatively farther away from the aromatic ring of CSA **1** and DMAP in CSA **1**/(*R*)-mandelate-DMAPH$^+$ complex (for details, see Supporting Information). Therefore, compared with (*R*)-MA, the ^{1}H NMR signal of α-H of (*S*)-MA should be more downfield with a larger δ value because the α-H of (*S*)-MA experiences more deshielding effect than that of (*R*)-MA. As shown in Table 3, although the calculated δ values of (*R*)- and (*S*)-MAs are different from the experimental ones, the trends of calculated and experimental $\Delta\delta$ values between (*R*)- and (*S*)-MAs are consistent, as shown in Table 3.

To further confirm the formation of a ternary complex, 1D and 2D NOESY experiments for the mixture of racemic α-methoxy phenylacetic acids/DMAP/chiral bisthiourea **1** were also carried out. A solution of 30 mM racemic α-methoxy phenylacetic acids/30 mM DMAP/30 mM **1** in $CDCl_3$ gave clear 1D and 2D NOESY signals between racemic α-methoxy phenylacetic acids and **1** on 500 MHz spectrometer at 25 °C. As show in Figure 6, the α-H (H_R and H_S) resonances of both

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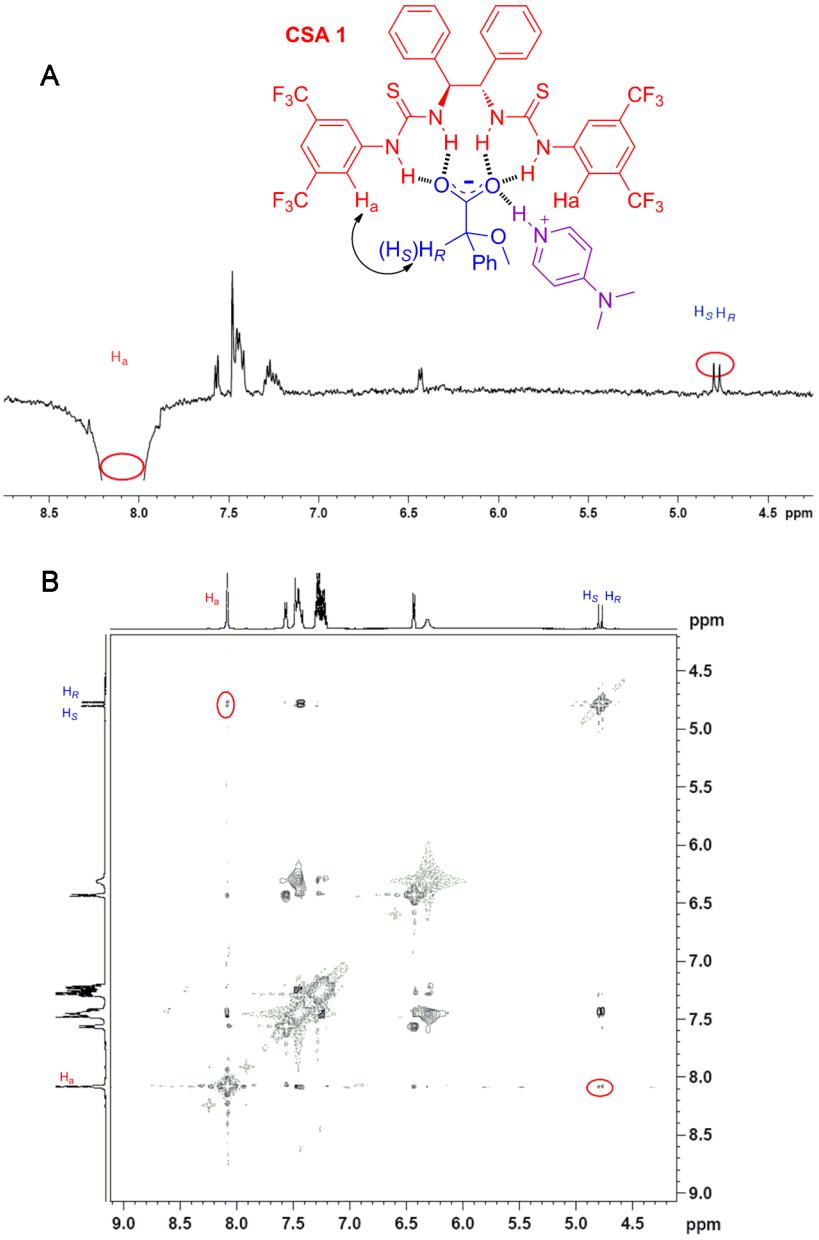

Figure 6. (A) A portion of the 500 MHz 1D NOESY spectrum of a solution of racemic α-methoxy phenylacetic acid (30 mM)/30 mM DMAP/30 mM **1** in $CDCl_3$ at 25 °C. (B) A portion of the 500 MHz 2D NOESY spectrum of a solution of racemic α-methoxy phenylacetic acid (30 mM) /30 mM DMAP/30 mM **1** in $CDCl_3$ at 25 °C. Intermolecular correlation signals of H_a to H_R and H_S are circled in red.

enantiomers of racemic α-methoxy phenylacetic acids were well correlated with the H_a signal of **1** (circled in red). These results indicated that the intermolecular noncovalent bonding interactions presented in the proposed ternary complex structure resulted in the closeness of H_a of **1** to the α-H of α-methoxy phenylacetic acid in space.

SUMMARY

We have developed a simple *C*2-symmetric chiral bisthiourea, which can be easily synthesized by only a one-step reaction from commercially available chemical reagents ((*S*,*S*)-1,2-diphenylethane-1,2-diamine and 3,5-bis(trifluoromethyl)phenyl isothiocyanate). With the addition of DAMP, this chiral bisthiourea has been shown as a highly efficient chemical solvating agent for varied α-carboxylic acids without interference with α-H signals of these carboxylic acids due to no proton signals of the chiral bisthiourea/DMAP shown in the middle field of ^{1}H NMR. The formation of geometrically different diasteromeric ternary complexes between the chiral bisthiourea and carboxylate-DMAPH$^+$ ion pair enables excellent chiral discrimination with large ^{1}H chemical shift nonequivalences of α-H signals of the enantiomers of α-carboxylic acids in ^{1}H NMR.

EXPERIMENTAL SECTION

Genenal. CSA **1** was prepared from commercial (*S*,*S*)-1,2-diphenylethane-1,2-diamine and isothiocyanate according to ref 18. Reagents were used as received from commercial suppliers. Melting point was obtained on a micro melting point apparatus. Optical rotations were measured on a automatic polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$, using TMS (δ_H or δ_C = 0) or $CDCl_3$ (δ_H = 7.26, δ_C = 77.16) as

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internal standards. NOESY spectra were recorded on a 500 MHz spectrometer at 25 °C.

Synthetic Procedure of CSA 1. To a solution of the (*S*,*S*)-1,2-diphenylethane-1,2-diamine (2 mmol) in DCM (10 mL) was added the 3,5-bis(trifluoromethyl)phenyl isothiocyanate (4.5 mmol). The solution was then stirred overnight at room temperature. After completion, the solvent was evaporated under reduced pressure. Silica gel column chromatography (eluent: petroleum ether/ethyl ether, from 10:1 to 5:1) afforded 1.28 g (85%) of CSA **1**. White solid; mp 176−177 °C; $[\alpha]^{22}_{D}$ = 81.6 (*c* 0.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (br s, 2H), 7.70 (s, 6H), 7.53 (br s, 2H), 7.23 (m, 6H), 7.14 (s, 4H), 5.99 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7, 138.5, 133.6, 133.2, 132.9, 132.6, 129.2, 128.8, 127.7, 126.8, 124.1, 121.4, 119.9, 118.7, 65.0 ppm; FTMS calcd for $C_{32}H_{22}F_{12}N_4S_2$ + H 755.1173, found 755.1167.

Chiral Solvating Agent for Carboxylic Acids. Carboxylic acid (3 μmol), DMAP (3 μmol), and CSA **1** (9 μmol) were mixed in $CDCl_3$ (0.6 mL), and ^{1}H NMR data were collected on a 400 MHz spectrometer at 25 °C. Chemical shifts (ppm) internally referenced to TMS signal (0 ppm) were obtained.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data for compounds, results of computational modeling, and ^{1}H NMR and NOESY spectra. 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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