Chemical Science

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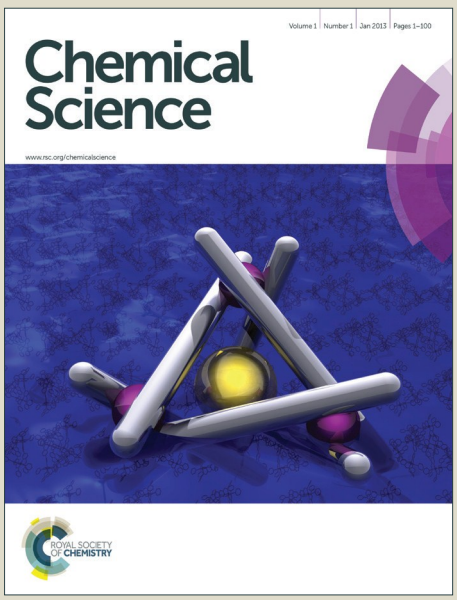

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EDGE ARTICLE

Chirality sensing of tertiary alcohols by a novel strong hydrogen-bonding donor − selenourea

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Chemical sensors are powerful for fast recognition of chiral compounds. However, the established sensing systems have shown less effective for chiral tertiary alcohol. Chiral tertiary alcohol is an important structural unit of natural products and drug molecules, and its enantioselective recognition represents a significant and challenging task. In this paper, a novel type of chiral bisselenourea sensor was first synthesized and used as a strong hydrogen-bonding donor for highly efficient chiral recognition of diverse tertiary alcohols. The obtained sharp split NMR signals are well distinguishable with large up to 0.415 ppm chemical shift nonequivalence. The NMR signal of hydroxyl hydrogen was first employed for enantiomeric excess determination of tertiary alcohol, giving accurate results with < 2% absolute errors. The studies in 2D NOESY spectra and computational mode suggest that the geometrical differentiation of formed diastereomeric complexes between sensor and tertiary alcohol enables the chiral discrimination of hydroxyl hydrogen signals of tertiary alcohol in ^{1}H NMR.

Introduction

Chirality plays a key role in modern science and technology. Therefore, the recognition of chirality and enantiomeric excess determination of chiral compounds are an intensive area of research.[1] Furthermore, the exponentially growing detection demand in modern asymmetric synthesis and drug discovery drives the development of fast, accurate and convenient systems for chiral recognition. Compared with chiral chromatograph and X-ray crystallography, sensing systems using chiral chemical sensors are appropriate for this purpose.[2] So far, a lot of chiral sensors have emerged emplying CD,[1b,3] UV-vis,[4] fluorescence[2b,5] or NMR spectroscopy[6-9] for enantiomeric excess (ee) determination of various types of guests. However, there is one kind of guest, chiral tertiary alcohol, whose enantioselective discrimination has been very challenging by now because of their large steric hindrance, weak coordination ability, and complex stereoelectronic effect.[10] Chiral tertiary alcohol group is an important substructure with fully substituted tertiary centers and can be found in many well-known compounds, for example Linalool, Bedaquiline, Camptothecin, Escitalopram, Efavirenz etc.[11] Chiral recognition of tertiary alcohol is mainly depended on using time-consuming and expensive chiral chromatograph.[12] Only very few chiral lanthanide shift reagents[13] and chiral solvating agents (CSA)[8g-8i] were reported as NMR sensors for chiral tertiary alcohols, but the resolved effects were less than satisfactory because of either inherent line broadening[6a,8a,14] or small signal split. Therefore, an accurate and highly efficient chemical sensing system for chiral tertiary alcohol is still highly desirable.

To address this problem, we targeted to achieve a chirality sensing system with NMR sensors employing the proton signal of hydroxyl group (O-H) attached on the quaternary sterogenic center of tertiary alcohol. Since the O-H involves in intermolecular interactions with CSA via hydrogen bond, the O-H signal is more easily to be split. Herein, we report a novel type of sensor, bisselenourea (*S, S*)-CSA-2 (Fig. 1, right), which could give well-resolved and sharp O-H signals for the enantio discrimination of structurally diverse tertiary alcohols by using ^{1}H NMR technology.

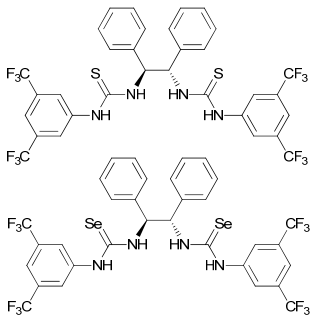

Fig. 1 Structures of bisthiourea and bisselenourea.

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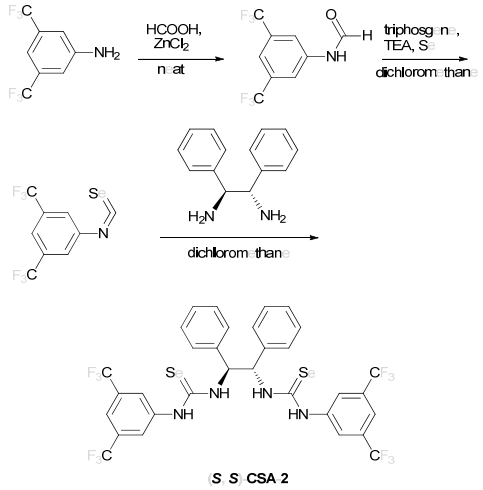
Results and discussion

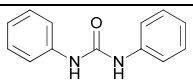
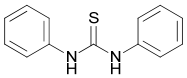
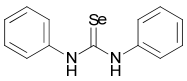
Molecular design. A large number of studies have shown that the urea (thiourea) groups of chemical molecules are important recognition sites because they are involved in intermolecular interactions with other molecules via hydrogen bond.[15] In recognition of chiral compounds, the urea (thiourea) groups primarily act as hydrogen bond donors, and their ability to provide hydrogen bond is an important factor for the success or failure of recognition. In general, a urea (thiourea) having stronger N-H acidity is a better hydrogen bond donor, which is helpful for improving chiral recognition. Accordingly, we developed a CF_3-substituted bisthiourea with strong N-H acidity (Fig. 1, left, (*S, S*)-CSA-1), which showed excellent enantiodiscrimination for a series of α-carboxylic acids based on split α-H NMR signals.[16] However, being used to discriminate several tertiary alcohols, (*S, S*)-CSA-1 gave much small splits of proton signals due to weak intermolecular interactions. To improve the chiral discrimination of chiral alcohols, we conceived that a stronger hydrogen bond donor than (*S, S*)-CSA-1 should facilitate hydrogen-bonding interactions between CSA and tertiary alcohols.

In order to achieve an outstanding performance in chiral recognition of tertiary alcohols, selenourea attracted our eyes. Selenium has similar properties to sulfur with a larger atomic radius. The larger atomic radius makes selenium to accommodate more negative charge than sulfur, which could induce a stronger N-H acidity of selenoureas.[17] Therefore, selenourea should be a stronger hydrogen-bonding donor than thiourea. However, the study of selenourea as a proton donor is few and the data of N-H acidity of selenourea is not available in literature. Using diphenyl urea, diphenyl thiourea and diphenyl selenourea as model molecules, we found that the N-H pK_a^{DMSO} values decrease in the order of diphenyl urea, diphenyl thiourea and diphenyl selenourea as shown in Table 1 by theoretical calculations, which suggests that selenourea is a stronger hydrogen-bonding donor than thiourea. This result encouraged us to employ selenourea compounds for the chiral recognition of tertiary alcohols. So, we designed and synthesized (*S, S*)-CSA-2, which is the analog of (*S, S*)-CSA-1



Scheme 1 Synthsis of bisselenourea (*S, S*)-CSA-2.

Table 1 The N-H pKa values of (thio)urea and selenourea.

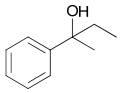
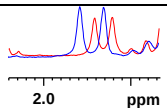
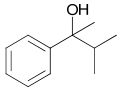
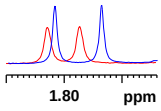
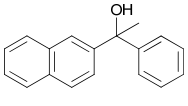
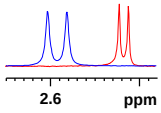
Compound	pK_a^{DMSO} (exptl)	pK_a^{DMSO} (calcd) [a]
	18.7[18]	18.5
	13.4[18]	13.8
	-	11.8
(*S, S*)-CSA-1	-	9.9 [b]
(*S, S*)-CSA-2	-	7.5 [c]

[a] Calculated pK_a^{DMSO} values with the use of the relative determination method. 4-Nitrophenol (10.8) is chosen as the reference acid. [b] N-H of 3, 5-bistrifluormethyl aniline of (*S, S*)-CSA-1. [c] N-H of 3, 5-bistrifluormethyl aniline of (*S, S*)-CSA-2.

(Scheme 1). The calculated pK_a^{DMSO} value of (*S, S*)-CSA-2 is significantly less than that of (*S, S*)-CSA-1 (Table 1). (*S, S*)-CSA-2 was expected to give better performance in chiral recognition of tertiary alcohols than (*S, S*)-CSA-1.

Test discriminating ability. With (*S, S*)-CSA-2 in hand, we first compared its enantiomeric discriminating ability with that of (*S, S*)-CSA-1 by testing several tertiary alcohols under the same experimental conditions (10 mM racemic guests and 10 mM hosts in $CDCl_3$) (Table 2). As shown in Table 2, (*S, S*)-CSA-2 does have better recognition effect than (*S, S*)-CSA-1 as our expectation. This result confirms that replacing S with Se does effectively enhance the acidity of N-H to facilitate the hydrogen bonding interaction of the alcohols with (*S, S*)-CSA-2 and improve the chiral recognition. And then, we chose guest A as a model molecule to optimize the discriminating conditions (Table 3). By changing solvent, a larger up to 0.052 ppm ΔΔδ value was obtained with deuterated benzene, implying that a tighter diastereomeric complex could be

Table 2 Comparison of discriminating ability between (*S, S*)-CSA-2 and (*S, S*)-CSA-1.[a]

Entry	Guest	Spectra[b]	ΔΔδ [c] (ppm)
1			0.027 0.020
2			0.043 0.028
3			0.022 0.012

a All samples were prepared by mixing 1:1 of CSAs and guests in NMR tubes (10mM in $CDCl_3$). b Red spectra were obtained with (*S, S*)-CSA-1, and blue spectra were obtained with (*S, S*)-CSA-2 by ^1H NMR (400 MHz) at 25 °C. c Chemical shift nonequivalences (ΔΔδ) of the O-Hs of guests, red values were obtained with (*S, S*)-CSA-1, and blue values were obtained with (*S, S*)-CSA-2.

Table 3 Optimization of the discriminating conditions for 2-phenyl-2-butanol (guest A) by (*S, S*)-CSA-2.[a]

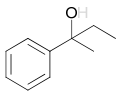
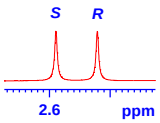
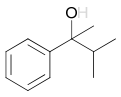
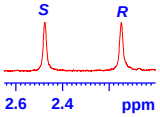
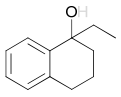
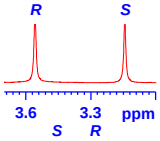
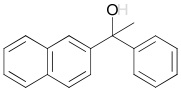
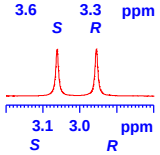
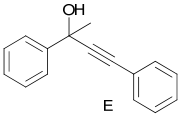
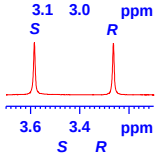
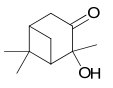
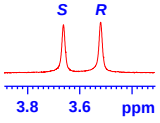
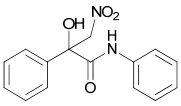
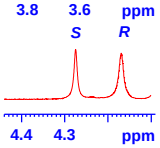
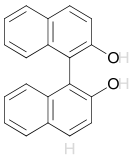
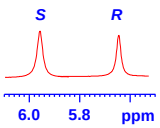
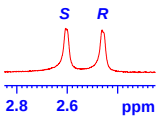
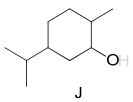
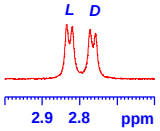
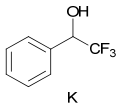
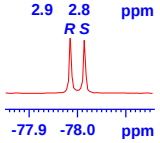
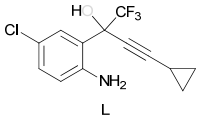
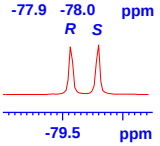
Entry	Solvent	C (mM)		ΔΔδ[b] (ppm)
		Guest A	(*S, S*)-CSA-2	
1	$CDCl_3$	10	10	0.027
2	DMSO	10	10	0
3	CD_3COCD_3	10	10	0
4	Benzene	10	10	0.052
5	Benzene	20	20	0.074
6	Benzene	30	30	0.097
7	Benzene	40	40	0.108
8	Benzene	30	60	0.125
9	**Benzene**	**30**	**90**	**0.137**

a Guest A and (*S, S*)-CSA-2 were mixed in specfied solvent (0.6 mL) and ^{1}H NMR data were collected on a Bruker Avance 400 MHz spectrometer at 25 °C. b ΔΔδ of the O-H of guest A.

formed in more nonpolar solvent resulting in a better resolution (Table 3, entries 1-4). Increasing concentrations of guest A and (*S, S*)-CSA-2, the resolution effect was significantly improved because the equilibrium of diastereomeric complex formation was driven to the right with higher concentration (Table 3, entries 4-7). The best result was obtained with 30 mM guest A and 90 mM (*S, S*)-CSA-2 (Table 3, entry 9). The corresponding ΔΔδ value is 0.137 ppm, which gave enantiodifferentiation of the enantiomers of the racemic guest A clearly. Therefore, the optimized conditions for our further investigation were chosen as follows: C_6D_6 as the solvent with 30 mM of tetiary alcohol guests and 90 mM bisselenourea (*S, S*)-CSA-2.

The applicability of these conditions for racemic alcohols with varied structures is demonstrated by the data displayed in Table 4. The ΔΔδ values of O-Hs are large enough to give baseline resolution for all tested tertiary alcohols ranging from simple to multifunctional ones on a 400 MHz NMR instrument at 25 °C (Table 4, entries 1-7). Guest C containing tetrahydronaphthyl gave well distinguishable proton signals with large up to 0.415 ppm ΔΔδ value. Racemic axially chiral BINOL (guest H), containing sp2 C-OH and being structurally similar to tertiary alcohols, could also be effectively enantiodiscriminated by (*S, S*)-CSA-2 (Table 4, entry 8). Compared with A, although secondary alcohol I lacks one electron-donating ethyl group, its smaller steric hindrance facilitates the intermolecular noncovalent interactions with (*S, S*)-CSA-2 resulting in a similar ΔΔδ value to A (Table 4, entry 9). Compared with 0.062 ppm ΔΔδ value of aliphatic secondary alcohol J, the much larger ΔΔδ value (0.144 ppm) of I indicates that pi-pi interactions between the aromatic rings of I and (*S, S*)-CSA-2 make contribution to chiral discrimination (Table 4,

Table 4 Measurements of NMR ΔΔδ of Racemic Guests in the Presence of (*S, S*)-CSA-2.[a]

Entry	Guest[19]	Spectrum[b]	ΔΔδ (ppm)
1	 A		0.137[c]
2	 B		0.328[c]
3	 C		0.415[c]
4	 D		0.105[c]
5	 E		0.320[c]
6	 F		0.144[c]
7	 G		0.111[c]
8	 H		0.315[c]
9	 I		0.144[c]
10	 J		0.062[c]
11	 K		0.029[d]
12	 L		0.046[d]

[a] All samples were prepared by mixing of (*S, S*)-CSA-2 and guests in NMR tubes (30 mM guests and 90 mM (*S, S*)-CSA-2 in 0.6 mL C_6D_6); ^{1}H NMR and ^{19}F NMR data were collected on a Bruker Avance 400 MHz spectrometer at 25 °C. [b] The O-H signals of guests A-J and fluoride signals of guests K and L; the configuration was determined by comparing with spectra of nonracemic samples of known configurations. [c] ΔΔδ of the O-H of guests A-J. [d] ΔΔδ of fluoride of guests K and L.

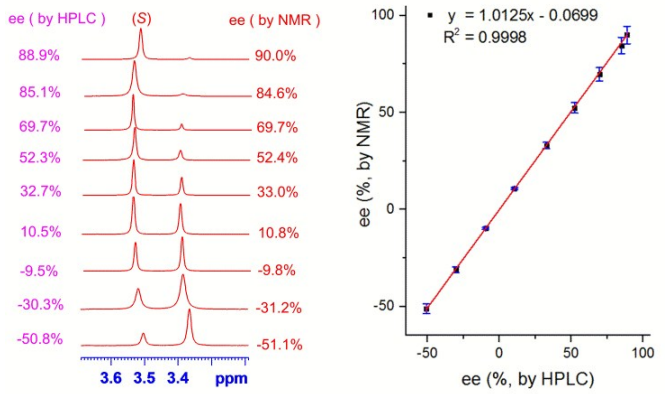


Fig. 2 Selected regions of the ^{1}H NMR spectra of nonracemic guest F (varied ee values) with (*S, S*)-CSA-2 and linear correlation between ee values determined by HPLC and NMR (ee values were defined in terms of (*S*)-F).

entries 9-10). In addition, (*S, S*)-CSA-2 has no proton signal in the middle and high fields of its ^{1}H NMR (see the ESI), so it does not interfere with O-H signals of guests. Besides ^{1}H NMR, (*S, S*)-CSA-2 could chiral discriminate tertiary alcohols by other heteronuclear NMR. For instance, guests K and L could be clearly resolved by (*S, S*)-CSA-2 by ^{19}F NMR (guest L is a precursor of Efavirenz, an important chiral drug against HIV) (Table 4, entries 11-12).

We further investigated the influences of time and temperature on the chiral discrimination of alcohols using guest I as an example. The results show that time has no influence on the chiral discrimination. Lowering the temperature increases the ΔΔδ value but has no effect on ee value (see the ESI).

To verify the accuracy of ee determination method of tertiary alcohol using (*S, S*)-CSA-2, the ee values of several nonracemic samples of guest F were determined by integration of the O-H signals of guest F. Fig. 2 shows that (*S, S*)-CSA-2 maintains analytic resolution for the samples of tertiary alcohol F over a wide range of ee values. The linear relationships between the NMR determined values (based on O-H signals) and those HPLC determined values are excellent. The absolute errors in the ee measurements by NMR and HPLC integrations are within 2%.

Molecular recognition modes. To understand the nature of chiral recognition of (*S, S*)-CSA-2 to tertiary alcohols, the recognition modes of (*S, S*)-CSA-2 to guest A were studied. We first investigated the stoichiometry of the host-guest in complex by Job plots (see the ESI). Job plots exhibit a maximum at X = 0.5 indicating 1:1 complexation of host-guest. Then, the binding constants of (*R*)-A/(*S, S*)-CSA-2 complex and (*S*)-A/(*S, S*)-CSA-2 complex were determined by nonlinear least-squares method (see the ESI). The larger binding

Table 5 Binding constants between (*S, S*)-CSA-2 and guest A.

Host	Guest	K_a (M^{-1}) [a]
(*S, S*)-CSA-2	(*R*)-A	12.4
(*S, S*)-CSA-2	(*S*)-A	26.8

[a] The K_a values were calculated by the nonlinear least-squares method.

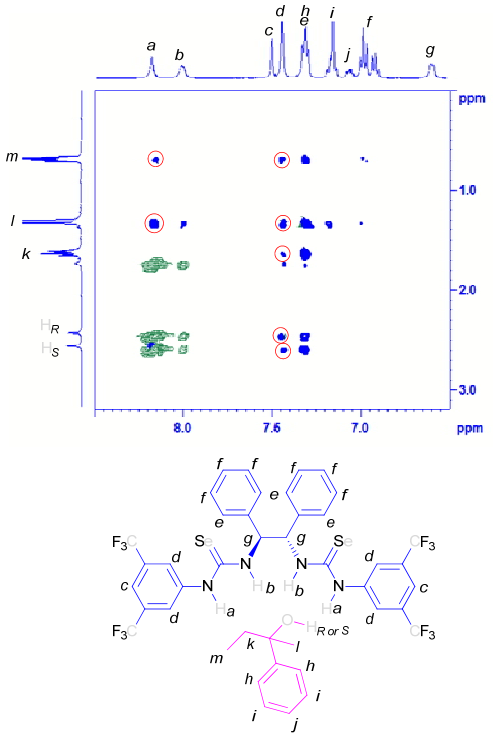


Fig. 3 A portion of the 500 MHz 2D NOESY spectrum of a solution of racemic guest A (100 mM) / (*S, S*)-CSA-2 (100 mM) in C_6D_6 at 25 °C (Intermolecular correlations of guest A to (*S, S*)-CSA-2 are circled in red).

constant of (*S*)-A/(*S, S*)-CSA-2 suggests that it is a more stable complex than (*R*)-A/(*S, S*)-CSA-2 (Table 5).

2D NOESY experiments for the mixture of racemic guest A and (*S, S*)-CSA-2 show strong correlation between guest A and (*S, S*)-CSA-2 (Fig. 3), indicating that the intermolecular noncovalent interactions presented in the complexes result in the close of multiple hydrogens (H_k, H_l, H_m, H_R or H_S) of guest A to (*S, S*)-CSA-2 (H_a and H_d) in space. Among, H_a of (*S, S*)-CSA-2 exists strong NOESY correlated signals with guest A. In addition, its chemical shift dramatically moves to downfield (see the ESI). These results suggest that H_a is more likely to be the intermolecular interaction site.

Computational modeling studies[20] show that both (*S*)-A/(*S, S*)-CSA-2 and (*R*)-A/(*S, S*)-CSA-2 complexes have hydrogen

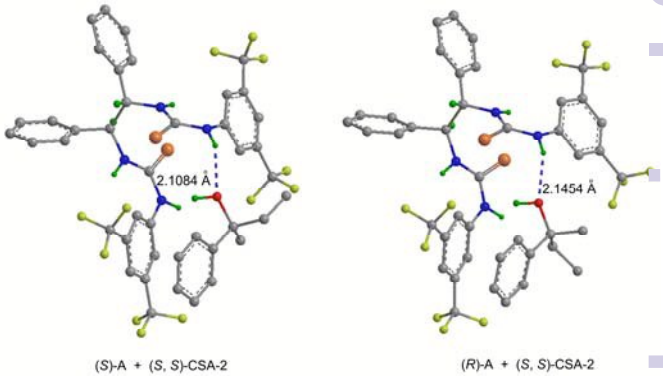


Fig. 4 Space-filling representations of complexes

Table 6 Calculated δ values of guest A and binding energies between (*S*, *S*)-CSA-2 and guest A.

Guest	δ(calcd) (ppm) [a]	-ΔG (Kcalmol^{-1})
(*R*)-A	2.17	15.8
(*S*)-A	2.54	18.0

[a] The chemical shift of O-H of guest A in guest A/ (*S, S*)-CSA-2 complex.

bonding and pi-pi interactions. As shown in Fig. 4 and Table 6, (*S*)-A/(*S*, *S*)-CSA-2 has relatively shorter hydrogen bond length, larger calculated binding energy ΔG and larger calculated chemical shift of O-H than (*R*)-A/(*S*, *S*)-CSA-2, which also indicates that (*S*)-A/(*S*, *S*)-CSA-2 is more stable. We proposed that the preference of (*S*)-A/(*S*, *S*)-CSA-2 is due to a weaker steric repulsion between (*S*)-A and (*S*, *S*)-CSA-2. As shown by the optimized structures, in (*S*)-A/(*S*, *S*)-CSA-2, the CH_3 group is situated in the bimolecular interacting region, while the larger C_2H_5 group is far away. By contrast, in (*R*)-A/(*S*, *S*)-CSA-2, the larger C_2H_5 group is situated in the bimolecular interacting region which could result in stronger steric repulsion. Therefore, (*S*)-A/(*S*, *S*)-CSA-2 is a sterically preferred complex than (*R*)-A/(*S*, *S*)-CSA-2.

On the basis of the above experimental investigations, the mechanism of chiral discrimintation of tertiary alcohol A with (*S, S*)-CSA-2 was proposed. Each enantiomer of racemic guest A interacts with chiral (*S, S*)-CSA-2 to form a 1:1 diastereomeric complex via noncovalent interactions. The spatial differentiations of two O-Hs in the formed diastereomeric complexes cause the split of the O-H signals of two enantiomers of racemic guest A. (*S*)-A combines with (*S*, *S*)-CSA-2 more tightly than (*R*)-A, which causes the chemical shift of O-H of (*S*)-A being moved more downfield with a larger δ value.

Experimental

Materials and methods. Diphenyl urea (TCI Co. Ltd.), diphenyl thiourea (TCI Co. Ltd.), BINOL (TCI Co. Ltd.), 1-phenylethanol (TCI Co. Ltd.), (1*R*, 2*R*, 5*R*)-(+)-2-hydroxy-3-pinanone (TCI Co. Ltd.), (1*S*, 2*S*, 5*S*)-(-)-2-hydroxy-3-pinanone (TCI Co. Ltd.) (1*S*, 2*R*, 5*S*)-(+)-Menthol (Adamas-beta®), (1*R*, 2*S*, 5*R*)-(-)-Menthol (Adamas-beta®), 3, 5-di(trifluoromethyl)aniline (Adamas-beta®), and (*S*, *S*)-1, 2-diphenylethane-1, 2-diamine (TCI Co. Ltd.) were used as received. Other tertiary alcohols and isoselenocyanate were synthesized by following the literature procedure.[21]

Theroretical calculation. All electronic structure calculations were performed with Gaussian09 program.[20] The pK_a^{DMSO} values were calculated with use of the relative determination method, and 4-nitrophenol (10.8) is chosen as the reference.[18] The gas-phase acidities of all compounds were calculated using the M06-2X/cc-pVTZ method, the solvent effects were evaluated with IEFPCM model, and the pK_a values of all compounds in DMSO were calculated by $\Delta pK_a = \Delta G/RT$ (ΔpK_a and ΔG are the pK_a and free energy difference between the given compound and the reference molecule). Computational modeling studies were performed with Gaussian09 program.[20] Geometries of ternary complexes were optimized using molecular mechanics method initially and then DFT method on M06-2X/cc-pVTZ level. All geometry optimizations were carried out in gas phase. Binding energies and NMR chemical shifts were calculated on M06-2X/cc-pVTZ level in benzene solvent with GIAO method (solvent effects were evaluated with IEFPCM model.

General procedure for synthesis of (*S, S*)-CSA-2. 3, 5-Bis(trifluoromethyl)aniline (10 g, 43.6 mmol) and anhydrous $ZnCl_2$ (1.186 g, 8.7 mmol) were taken in a 50 ml round bottomed flask. To the mixture, formic acid (10 ml, 267 mmol) was added drop-wise with constant stirring for 10 min. This mixture was heated at 70 °C for 5 h and the progress of the reaction was monitored by TLC. When the reaction was completed, the mixture was cooled to room temperature and diluted with ethyl acetate (40 ml). The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude product was purified by recrystallization (ethanol) to obtain the corresponding N-formyl derivative (10.66 g, 95%, mp 121-122 °C, lit.[22], 124-125 °C). To a refluxing mixture of formamide (1 g, 3.89 mmol), TEA (2.25 mL, 15.56 mmol), and 4 A molecular sieves (2 g) in dry dichloromethane (10 mL) was dropwise added a solution of triphosgene (692 mg, 2.33 mmol) in dry dichloromethane (5 mL) under Ar over a period of 1 hour. After the addition, the resulting mixture was refluxed for 4 hours and then black selenium powder (768 mg, 9.72 mmol) was added and refluxed overnight in the dark. Then, the mixture was cooled to room tempeture and filtered. The filtrate was collected and concentrated to give the residue, which was purified by column chromatography (eluting with dry hexane) afforded isoselenocyanate (0.49 g, 40%). Caution, this isoselenocyanate is best used directly after separation because it is not very stable and must be stored in the dark.

To a solution of the (*S*, *S*)-1, 2-diphenylethane-1, 2-diamine (0.21 g, 1 mmol) in dry dichloromethane (15 mL) was added the 3, 5-bis(trifluoromethyl)phenyl isoselenocyanate (0.64 g, 2 mmol). The solution was stirred overnight at room temperature in the dark. After completion, dry hexane (100 mL) was added dropwise. The solution was stirred for another 3 hours at room temperature and produce a lot of white solid which was filtered off and washed with hexane and dried under vacuum to afford (*S, S*)-CSA-2 (0.81 g, 95%). Mp 165-166 °C; $[\alpha]_{30}^{D}$ = 31.8 (c = 1.0 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.84 (br s, 2H), 7.95 (br s, 2H), 7.73-7.67 (m, 6H), 7.40-7.20 (m, 10H), 6.17 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.9, 138.1, 136.4, 133.9, 133.6, 133.2, 132.9, 129.3, 128.9, 127.8, 126.8, 124.8, 124.1, 121.4, 120.7, 118.7, 67.6 ppm; ^{77}Se NMR (95 MHz, $CDCl_3$): δ = 247; ESI-MS: calcd for $C_{32}H_{22}F_{12}N_4Se_2$+H 851.0062, found 851.0073.

General spectroscopic methods for chiral discrimination of guests. 18 μmol guests and 54 μmol (*S, S*)-CSA-2 were mixed in 0.6 mL C_6D_6, and ^{1}H NMR data were collected on a Bruker Avance 400 MHz spectrometer at 25 °C.

Conclusions

A chiral bisselenourea was rational designed and synthesized to serve as a highly efficient NMR sensor for enantiodiscrimination of varied tertiary alcohols. The method employed the sharp split NMR signals of hydroxyl hydrogens for ee determination, giving the accurate results with < 2% absolute errors. The study of chiral resolution mechanism suggests that the geometrical differentiation of formed diastereomeric complexes enables chiral discrimination of hydroxyl hydrogen signals of tertiary alcohols in ^{1}H NMR. This method can give well-resolved and sharp signals of hydroxyl hydrogens of tertiary alcohols with large chemical shift nonequivalences. Due to no proton signal of this bisselenourea in the middle and high fields of ^{1}H NMR, it does not interfere with hydroxyl hydrogen signals of tertiary alcohols. So, it is especially suitable for chiral discrimination and ee determination of tertiary alcohols.

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