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Chiral amino alcohols derived from natural amino acids as chiral solvating agents for carboxylic acids

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ABSTRACT

Several chiral amino alcohols have been synthesized conveniently and effectively. ^{1}H NMR was utilized to investigate their enantiodiscriminating abilities. Chiral amino alcohols **2** and **4** were discovered as efficient CSAs for the determination of the enantiomeric compositions of chiral carboxylic acids. In particular, for the Ts-derivatives of amino acids studied herein, **4** could be used for the assignment of the absolute configurations of the Ts-derivatives of amino acids with a neutral side chain through the chemical shift non-equivalences of their NH (Ts) protons with certain confidence.

1. Introduction

NMR spectroscopy using chiral solvating agents (CSAs) has proven to be of great utility for the determination of the enantiomeric compositions of chiral molecules, as well as for the correlation of absolute configurations.[1–4] α-Amino acids are potentially useful sources of chirality for the synthesis of chiral auxiliaries for asymmetric synthesis and chiral recognition. It is very important to check or ascertain the enantiomeric composition and absolute configuration of amino acids, as well as other carboxylic acids in scientific research. Although chiral amines[5–17] and alcohols[18–34] acting as CSAs for this purpose have been well documented in the literature, the applications of chiral amino alcohols are relatively rare in this field.[35–40] Chiral amino alcohols **1**–**3** derived from α-amino acids have been widely employed as chiral ligands in asymmetric catalysis,[41–48] but, to the best of our knowledge, there is no report on the use of this type of chiral amino alcohols as a CSA for the analysis of chiral carboxylic acids. Therefore, it is worth exploring these chiral amino alcohols in this aspect. On the basis of experimental results, we modified the structure of compound **2** further by introducing an aryl group onto its nitrogen atom and synthesized chiral amino alcohol **4** (see Fig. 1). We expected that incorporating the anisotropic group (phenyl attached by bromo as well as dimethylamino) could contribute to the modification of the differential magnetic influence of compound **2**. It is well known that increasing the number of stereogenic centres can afford an important increase in the enantiodiscriminating abilities of these two diastereoisomers.[17,49] With this in mind, we also synthesized compounds **5a** and **5b**, and explored the possibility of using these chiral amino alcohols as CSAs for the effective analysis of the enantiomeric excess of carboxylic acids. Herein, we report the facile synthesis of chiral amino alcohols from L-phenylalanine as well as their applications as CSAs for the determination of enantiomeric compositions of chiral carboxylic acids as well as for the assignment of the absolute configurations of the Ts-derivatives of some amino acids with neutral side chains.

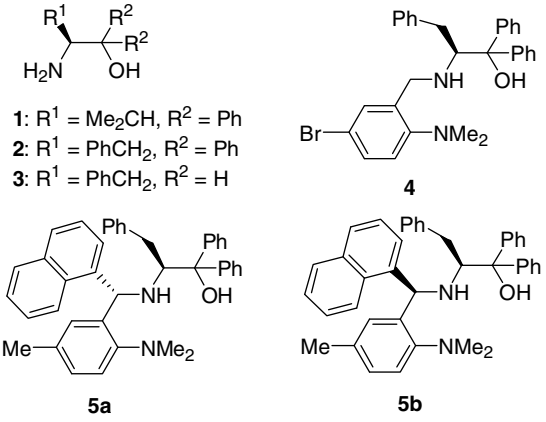

Figure 1. The structures of amino alcohols **1**–**5**.

2. Results and discussion

Chiral amino alcohols **1**–**3** were available by the literature methods[41–43] from L-valine and L-phenylalanine, respectively. Compound **2** reacted with aldehyde **6**, and then was reduced by $NaBH_4$ to give target compound **4** in good yields. The amino alcohols **5a** and **5b** were efficiently prepared by the reaction of

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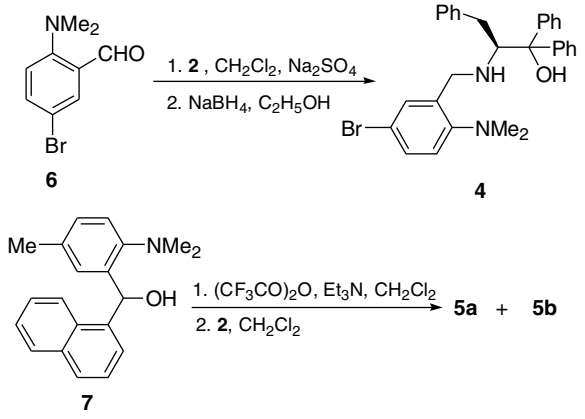
compound **7** with trifluoroacetic anhydride and then with amino alcohol **2** in the presence of triethylamine (see Scheme 1). These chiral amino alcohols were characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and EA. The crystal structure of **5b** was studied by X-ray single crystal structure analysis. The molecular structure of compound **5b** is shown in Figure 2, which indicates the newly built stereogenic centre induced by compound **2** is of an (*R*)-configuration.[50]



Scheme 1. The synthesis of chiral amino alcohols **4** and **5**.

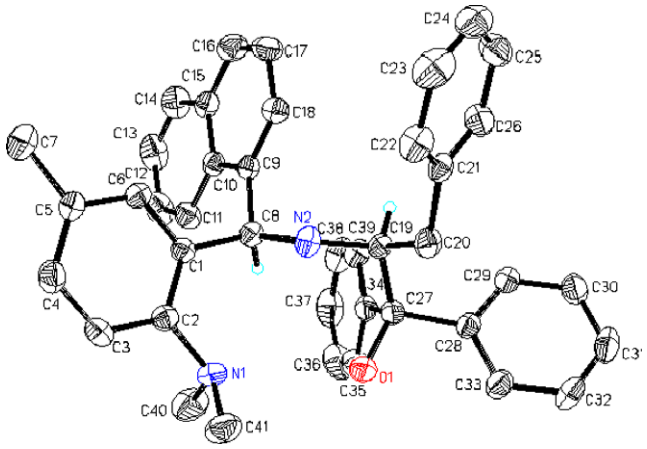


Figure 2. The molecular structure of compound **5b**.

With these desired chiral amino alcohols **1**–**5** in hand, we employed ^{1}H NMR spectroscopy to study their enantiodiscriminating abilities, and the guests included the Ts-derivatives of some α-amino acids **8**–**16**, α-hydroxyl acids **17**–**20** and dibenzoyl-tartaric acid (DBTA) **21** (see Fig. 3). At the outset, we were interested in screening chiral amino alcohols **1**–**5** as CSAs for chiral carboxylic acids to check if the structures of these amino acids and/or the introduction of aryl groups have a great influence on their enantiodiscriminating properties. Under the same experimental conditions as described in Table 1, compound **1** was capable of discriminating the enantiomers of compound **8**, obtaining appreciable non-equivalences of 15.9 Hz, 24.3 Hz and 36.6 Hz for proton signals of NH, $C_{\alpha}H$ and CH_3(Ts), respectively. Using compound **2** towards the same analyte, the chemical shift non-equivalence ($\Delta\Delta\delta$) of the NH was up to 51.1 Hz but that of the CH_3(Ts) only to 10.4 Hz (see Fig. 4). As for the $\Delta\Delta\delta$s of the CH of mandelic acid **17** and DBTA **21**, compound **2** could lead to larger $\Delta\Delta\delta$s than compound **1**. In

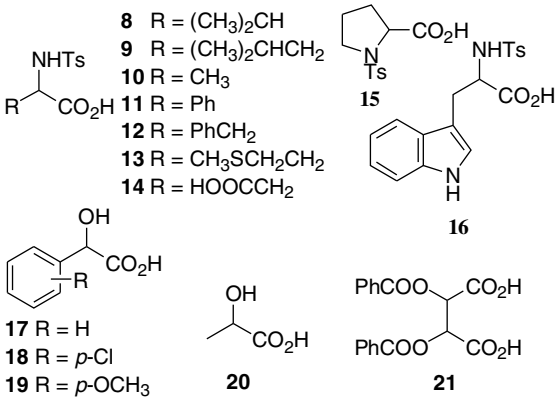


Figure 3. The structures of the guests used herein.

Table 1
Measurements of ^{1}H chemical shift non-equivalences ($\Delta\Delta\delta$, Hz, 500 MHz) of racemic guests (4 mM) in the presence of an equimolar amount of **5a** and **5b** in $CDCl_3$ at 25 °C

Guest	Signal	$\Delta\Delta\delta$ (Hz)	
		5a	**5b**
8	TsN*H*	0	40.0
	$C_{\alpha}H$	0	17.5
	CH_3(Ts)	19.0	15.0
12	TsN*H*	0	10.5
	$C_{\alpha}H$	0	22.5
	CH_3(Ts)	6.0	8.5
13	TsN*H*	0	35.5
	$C_{\alpha}H$	0	29.4
	CH_3(Ts)	21.0	27.9
17	$C_{\alpha}H$	0	2.1

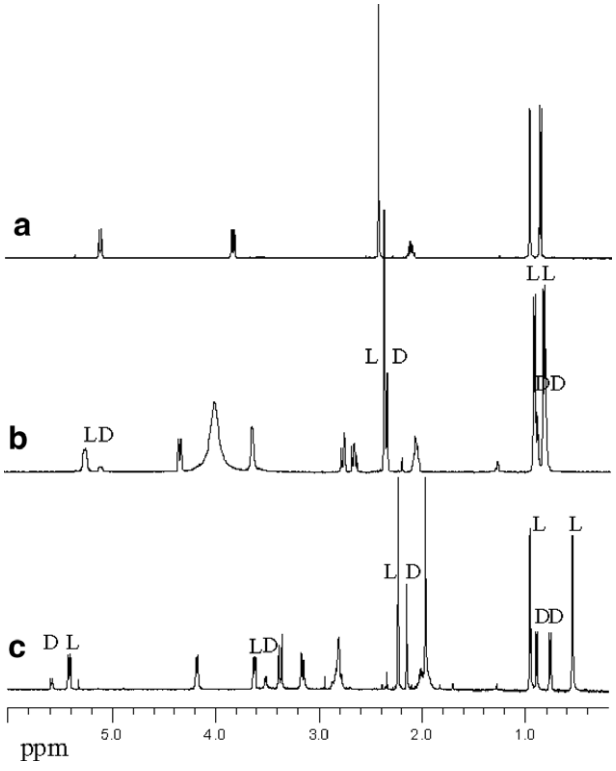


Figure 4. Partial ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) spectra of enantiomerically enriched **8** (L:D = 3:1) (a) in the presence of an equimolar amount (4 mM) of: (b) **2**; (c) **4**.

fact, the CH resonances of **17** and **21** underwent small splittings of 3.6 Hz and 7.0 Hz in the presence of compound **1**, whereas compound **2** produced large doublings of 46.0 Hz and 170.1 Hz, which were both large enough to afford baseline resolution for accurate integration. These experimental data show that compound **2** exhibits a better enantiodiscriminating ability towards these carboxylic acids than compound **1**. Comparatively, structurally simple compound **3** could only differentiate compound **8** with a difference of 2.6 Hz for the CH proton, while compound **17** merely induced a minor separation of the CH proton (6.7 Hz). These data verify that the introduction of two phenyls contribute to increasing the chiral recognition ability of compound **2**. Figure 4 shows the splitting of the signals of protons TsNH, $C_\alpha H$, CH_3(Ts) and CH_3(valine) of compound **8** after the addition of an equimolar amount of compound **2** and compound **4**. Using compound **4**, all alkyl protons signals of compound **8** exhibited appreciable enantiodiscrimination ($C_\beta H$ also see Fig. 8g); however, compound **2** could not discriminate between the $C_\alpha H$ and $C_\beta H$ proton. This result demonstrates that it is worthwhile introducing an anisotropic group on the nitrogen atom of compound **2**.

From the experimental data of the protons in Table 1, we could learn that the (*S*,*R*)-diastereoisomer **5b** represents the matched couple of the CSA towards the carboxylic acids listed, whereas the (*S*,*S*)-diastereoisomer **5a** is the 'mismatched couple'.[17,48] An inspection of these data in Tables 1 and 2 clearly shows that compounds **2** and **4** exhibit better enantiodiscriminating abilities than compounds **5a** and **5b** towards these carboxylic acids as listed in Table 1.

These good preliminary results encouraged us to further evaluate the usefulness of compound **2** and compound **4** towards other carboxylic acids. Table 2 summarizes the results of the examination of the enantiomeric discriminating abilities of compounds **2** and **4**. Some assessments could be given comparing the $\Delta\Delta\delta$s of compounds **8**–**21**. In general, using compound **4**, in almost every case, at least one resonance exhibits baseline separation, which is suitable for the determination of the enantiomeric composition of these chiral substrates. The largest $\Delta\Delta\delta$ value was up to 331.6 Hz, which was achieved on the NHTs proton after the addition of an equimolar amount of compound **2** into compound **10** in $CDCl_3$ (see Fig. 5). When polar compound **14** served as the analyte, compound **2** only could discriminate one of the CH_2 with a difference of 20.1 Hz using $CDCl_3$ (containing 4% CD_3OD) as a solvent, but compound **4** could induce this $\Delta\Delta\delta$ to 55.9 Hz. The $C_\alpha H$ and CH_3(Ts) protons of compound **14** underwent splittings of 26.8 Hz and 5.5 Hz in the presence of compound **4** under the same experimental conditions (see Fig. 6). Another example to demonstrate the efficiency of compound **4** was that the CSA could differentiate between the $C_\alpha H$ and CH_3(Ts) protons of compound **15** with the separation being 19.1 Hz and 17.4 Hz, but the two probe protons could not be resolved in the presence of compound **2**.

Table 2
Measurements of ^{1}H chemical shift non-equivalences ($\Delta\Delta\delta$, 500 MHz) of chiral or racemic guests in the presence of an equimolar amount of compounds **2** and **4** in $CDCl_3$ at 25 °C (unless indicated otherwise)

Guest	Signal	$\Delta\Delta\delta$[a] (Hz)	
		2	**4**
8[b]	TsN*H*	51.0(D)	85.2(L)
	$C_\alpha H$	0	54.3(D)
	CH_3(Ts)	10.4(D)	42.7(D)
9[b]	TsN*H*	128.2(D)	100.9(L)
	$C_\alpha H$	29.9(D)	46.5(D)
	CH_3(Ts)	4.9(D)	33.9(D)
10	TsN*H*	331.6(D)	94.6(L)
	$C_\alpha H$	35.7(D)	27.7(D)
	CH_3(Ts)	0	17.4(D)
	CH_3	77.1(D)	55.3(D)
11	TsN*H*	174.0(D)	18.8(L)
	$C_\alpha H$	76.6(D)	5.0(D)
	CH_3(Ts)	0	43.4(D)
12	TsN*H*	197.0(D)	14.5(L)
	$C_\alpha H$	38.1(D)	0
	CH_3(Ts)	0	18.0(D)
13	TsN*H*	135.6(D)	78.9(L)
	$C_\alpha H$	22.7(D)	26.0(D)
	CH_3(Ts)	3.3(D)	40.7(D)
14[c]	$C_\alpha H$	18.2(L)	26.8(D)
	CH_3(Ts)	0	5.5(D)
	CH_aH_b	20.1(D)	55.9(D)
15	$C_\alpha H$	0	19.1(L)
	CH_3(Ts)	0	17.4(L)
16	TsN*H*	150.0(D)	24.1(L)
	$C_\alpha H$	17.9(D)	15.1(D)
	CH_3(Ts)	6.4(L)	17.3(D)
17	$C_\alpha H$	46.0	14.0
18	$C_\alpha H$	19.2	10.5
19	$C_\alpha H$	48.0	12.5
	CH_3O	3.5	5.6
20	*CH*	6.0	44.3
21	*CH*	170.1	40.5

[a] In brackets: configuration of the enantiomer corresponding to the signal at higher field.
[b] The chemical shift non-equivalences of the methyl protons of $CH(CH_3)_2$ for **8** and $CH_2CH(CH_3)_2$ for **9** are large (see Fig. 4).
[c] Using $CDCl_3$ (containing 4% CD_3OD) as a solvent.

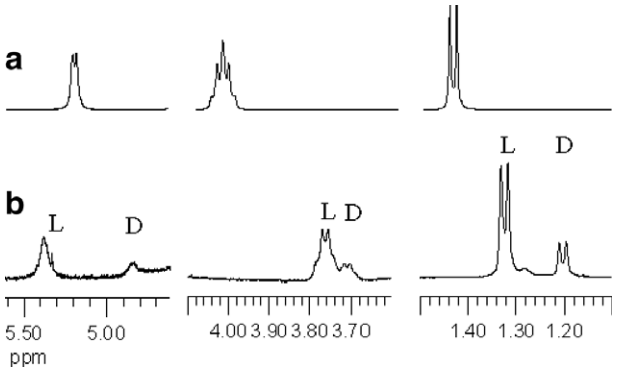


Figure 5. Partial ^{1}H NMR spectra (500 MHz) of equimolar mixtures (4 mM each) of compounds **2** and **10** at 25 °C in $CDCl_3$: (a) DL-**10**; (b) enantiomerically enriched **10** (L:D = 3:1) and compound **2**.

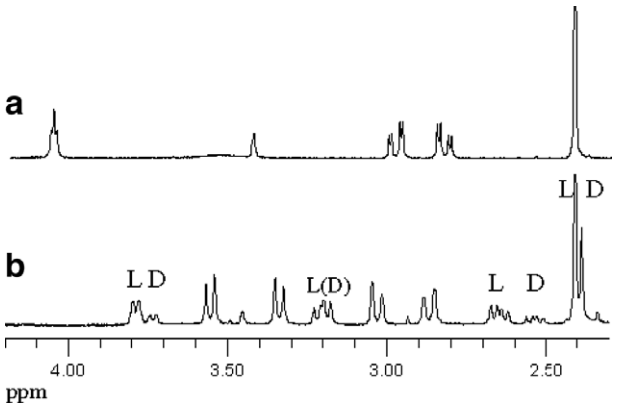


Figure 6. Partial ^{1}H NMR spectra (500 MHz) of equimolar mixtures (4 mM each) of compounds **4** and **14** at 25 °C in $CDCl_3$ (4% CD_3OD): (a) DL-**14**; (b) enantiomerically enriched **14** (L:D = 3:1) and compound **4**.

It is noteworthy that compound **2** seems to be sensitive to the TsNH protons of the Ts-derivatives of amino acids, whereas compound **4** is prone to determining the existence of the $C_\alpha H$ and CH_3(Ts) protons. Considering the effectiveness of compounds **2** and **4** in enantiodiscriminating the Ts-derivatives of amino acids, we turned our attention towards other carboxylic acids. As far as α-hydroxyl carboxylic acids are concerned, compound **2** shows better enantiomeric discrimination towards aromatic α-hydroxyl acids than compound **4** does; however, compound **4** is preferable for the analysis of alkyl hydroxyl acids such as lactic acid **20** (see Fig. 7 and Table 2). The data concerning the enantioselectivity of compounds **2** and **4** towards the derivatives of mandelic acid **18** and **19**, non-aromatic hydroxyl acid **20** and dicarboxylic acid **21** are listed in Table 2.

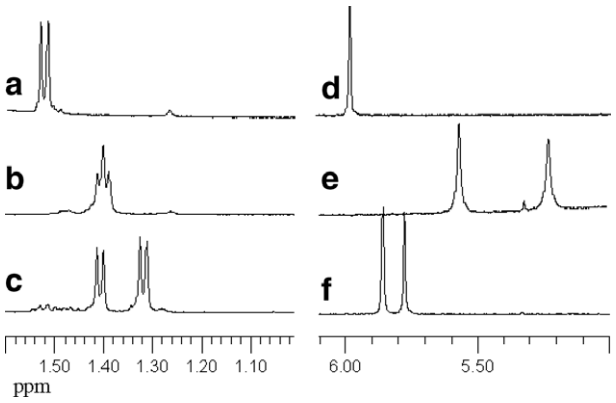


Figure 7. Partial ^{1}H NMR spectra (500 MHz) of equimolar mixtures (4 mM) CSA/racemic compound: (a) **20**; (b) **2**/**20**; (c) **4**/**20**. (d) **21**; (e) **2**/**21**; (f) **4**/ **21**.

From Table 2, we can see that all discernible proton signals in the D-enantiomers of chiral Ts-derivatives of amino acids appear consistently at a higher field relative to the same signals in the L-enantiomers in the presence of compound **2** only with two exceptions. One abnormal example appearing on the $C_\alpha H$ proton of compound **14** might be due to the existence of an additional carboxylic acid moiety of the analyte structure; another anomalous one could be observed on the CH_3(Ts) protons signal of compound **16**, which might be due to the indolyl group to participating in the host–guest interaction as well as its anisotropic influence on this probe proton. For chiral compounds **8**–**14** as well as **16**, using compound **4**, all distinguishable $C_\alpha H$ and CH_3(Ts) in the D-enantiomers of these guests consistently appear at a higher magnetic field relative to the same signals of the L-enantiomers, however, the L-enantiomers of these analytes exhibit the TsNH protons signals at a higher field. This implies that the diastereoisomeric nature of the host–guest complexes of the two enantiomers with compound **4** is more significant in causing enantiomeric discrimination than the inequivalence in association constants.[51] These results offer the possibility that compound **4** could be used for the assignment of the absolute configurations in the Ts-derivatives of chiral amino acids with neutral side chains. It could be seen that compound **4** could induce the $C_\alpha H$ and CH_3(Ts) protons signals of the L-enantiomer of compound **15** to appear at higher field. This abnormal example might be due to its rigid cyclic structure, as well as its structure devoid of the TsNH proton. In order to examine further the applicability of using compound **4** as the CSA for the assignment of the absolute configurations of the Ts-derivatives of amino acids with their chemical shift differences, we chose enantiomerically enriched Ts-serine (L:D = 3:1) as the analyte and aquired its NMR spectrum under the same experimental conditions but using $CDCl_3$ (containing 4% acetone-d_6) as a solvent. As expected, the amide proton signal of the L-enantiomer resonated at a higher field and the separation was up to 64.6 Hz. The same trend occurred with the $C_\alpha H$ and the methyl signals of the D-enantiomer, which both resonated at higher field with the separations being 21.9 Hz and 19.3 Hz, respectively.

The experimental results of the molar ratio of compound **4**/compound **8** are shown in Figure 8. The trend is consistent with studies of other CSAs, in which increasing the concentration of the reagent promotes the formation of the diastereoisomeric complexes and enhances the extent of enantiomeric discrimination in the NMR spectrum. As far as the effect of the molar ratio CSA/substrate is concerned, it is noteworthy that compound **4** also works when this ratio is lowered to 0.6.

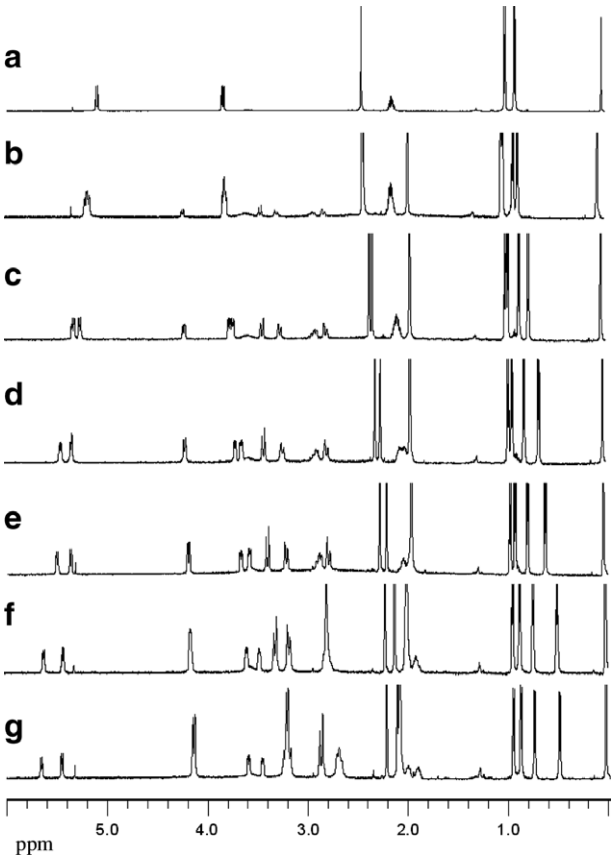


Figure 8. Evolution of partial ^{1}H NMR spectra (500 MHz) of racemate **8** (4 mM) when (a) 0 equiv, (b) 0.2 equiv, (c) 0.4 equiv, (d) 0.6 equiv, (e) 0.8 equiv, (f) 1.0 equiv, (g) 2.0 equiv of compound **4** are added. Samples dissolved in $CDCl_3$ at 25 °C.

Knowledge of the stoichiometry of the associate is important in determining the structure of the complexes. Nine samples of a constant total concentration (4 mM) were prepared containing variable ratios of compound **4** and L-**11** or D-**11**. The ^{1}H NMR spectra of these samples were recorded and chemical shift variations were observed for the CH_3(Ts) proton of L-**11** or D-**11**. The stoichiometry of the host–guest complex was determined according to Job's method of continuous variation.[52] The Job plots for the complexation of compound **4** with L-**11** or D-**11** were illustrated in Figure 9, affording a maximum of $\Delta\delta\ X$ at $X = 0.5$, which means that compound **4** forms a 1:1 instantaneous complex with L-**11** or D-**11** under these experimental conditions (see Fig. 9).

In order to evaluate further the discriminating abilities of **2** and **4**, we performed the titration curves of **2** and **4** with L-**11** or D-**11**. The association constants of **2** and **4** with L-**11** or D-**11** were determined from the titration curves by the non-linear least-squares fitting method (Table 3).[52] From Table 3, it was noticed that the D-enantiomer was more strongly bound to **2** or **4** than the L-enantiomer. In order to investigate the intrinsic chemical shift

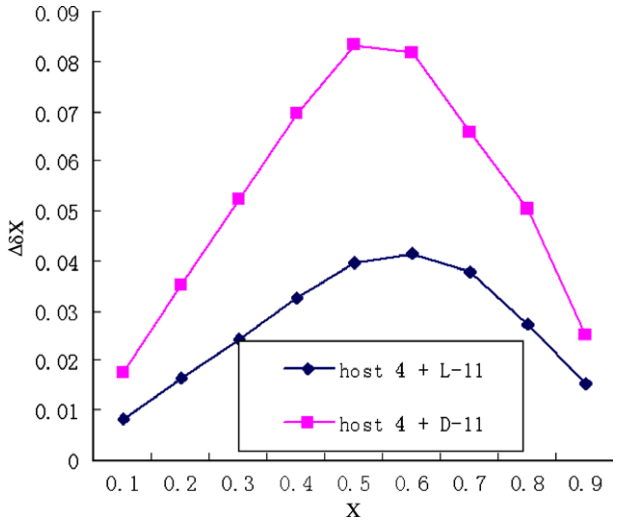


Figure 9. Job plots for the complexation of compound **4** with L-**11** and D-**11**. (X = [**4**]/([**11**] + [**4**]); $\Delta\delta$ = variation of the chemical shift of the observed proton).

Table 3
Association constants K_a $(mol/l)^{-1}$ of the host–guest complexes of hosts **2** and **4** with L-**11** or D-**11** in $CDCl_3$

Entry	CSAs	Guests	K_a $(mol/l)^{-1}$	K_a(D)/K_a(L)
1	**2**	D-**11**	$(1.9 \pm 0.6) \times 10^4$	1.58
2	**2**	L-**11**	$(1.2 \pm 0.3) \times 10^4$	
3	**4**	D-**11**	$(2.3 \pm 0.5) \times 10^4$	1.13
4	**4**	L-**11**	$(2.0 \pm 0.2) \times 10^4$	

non-equivalences of the two diastereoisomeric instantaneous complexes, we performed the NOESY spectra of the complexes formed from **4** with an equimolar amount of L-**11** or D-**11**, but no intermolecular NOE phenomena were observed. The incorporation of anisotropic group into compound **2** may play an important role for the excellent chiral recognition abilities by the combination of steric and electrical factors.

Finally, we attempted to demonstrate the accuracy of this enantiomeric excess determination method. With this aim, we prepared six samples containing different proportions of both enantiomers of **8**, and analyzed their enantiomeric compositions in the presence of compound **4** by using ^1H NMR method (see Fig. 10). The results, which were calculated based on the integrations of the corresponding CH_3(Ts) proton signals, are within ±1% of the actual enantiopurity of these samples and thus, demonstrate the high accuracy of this method.

3. Conclusion

In conclusion, several chiral amino alcohols were screened for their enantiodiscriminating abilities for carboxylic acids, and chiral amino alcohols **2** and **4** were discovered to exhibit good chiral recognition abilities towards carboxylic acids. The two new diastereoisomeric chiral amino alcohols **5a** and **5b** were also synthesized conveniently and effectively, which proved to be less effective than compound **2** and compound **4** in enantiodiscriminating chiral carboxylic acids. In particular, for the Ts-derivatives of amino acids studied herein, **4** could be used for the assignment of the absolute configurations of the Ts-derivatives of amino acids with neutral side chains through the chemical shift non-equivalences of their NH (Ts) protons with certain confidence.

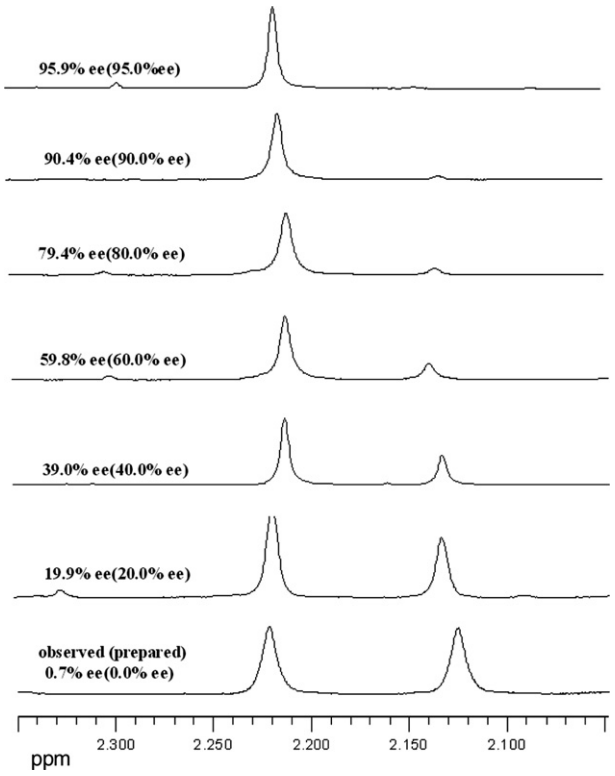


Figure 10. Partial ^1H NMR (500 MHz) spectra of **8** with various enantiomeric purities (4 mM) in the presence of an equimolar amount of compound **4**.

4. Experimental

4.1. General methods

IR spectra were obtained on a Nicolet 360 Avatar IR spectrometer as KBr pellets. NMR spectra were recorded on Avance 500 Bruker spectrometer (^1H at 500 MHz and ^{13}C at 125 MHz). Mass spectra were recorded on Trace MS 2000-Mass Spectrometer using the EI technique. The elemental analysis was performed on Vario E1 elemental analyzer. Optical rotations were measured with a Perkin–Elmer Model 343 polarimeter using the sodium D line at 589 nm.

The solvents (dichloromethane, ethanol and THF) were analytical and thoroughly dried. 2-(*N*,*N*-Dimethylamino)-5-bromo-benzaldehyde **6** (DMABB) was prepared according to the literature method.[53] Intermediate **7** [2-(dimethylamino)-5-methylphenyl]-(1-naphthyl) methanol was synthesized according to the literature method.[17]

4.2. Preparation of compounds 4 and 5

4.2.1. Preparation of (*S*)-2-(5-bromo-2-dimethylamino-benzylamino)-1,1,3-triphenyl-propan1-1-ol 4

To a mixture of chiral amino alcohol **2** (0.303 g, 1 mmol) and anhydrous sodium sulfonate (0.284 g, 2 mmol) in CH_2Cl_2 (10 mL), a solution of aldehyde **6** (0.31 g, 0.0015 mol) in dry CH_2Cl_2 (10 mL) was added at room temperature. The mixture was stirred at room temperature for 5 h. CH_2Cl_2 was evaporated, and the mixture was dissolved in anhydrous ethanol (10 mL). Then portions of $NaBH_4$ (0.076 g, 2 mmol) were added slowly at 0 °C, after 10 h, the mixture was treated with cold water and extracted with portions of CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4, evaporated and purified by flash chromatography (petroleum ether/acetyl acetate = 15:1) to give a white solid **4** (0.44 g,

85%). Compound **4**. Mp 60–61 °C; $[\alpha]_D^{20} = -41.6$ (*c* 0.44, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, ppm): δ = 7.79–6.65 (m, 18H, 18Ar*H*), 4.06 (dd, 1H, *J* = 10.7 Hz, *J* = 2.7 Hz, C*H*NH), 3.20–2.96 (m, 3H, ArCH_2NH and PhCH_A), 2.41 (dd, 1H, *J* = 10.8 Hz, *J* = 14.8 Hz, PhCH_B), 2.25 (s, 6H, 2NCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ = 151.6, 147.7, 145.1, 139.4, 136.4, 132.6, 130.5, 128.9, 128.6, 128.2, 126.6, 126.5, 126.4, 126.1, 125.7, 121.0, 115.8, 78.3, 66.2, 50.3, 44.4, 37.6; MS: *m*/*z* 515 (M^+); Anal. Calcd for $C_{30}H_{31}N_2OBr$: C, 69.90; N, 5.43; H, 6.06. Found: C, 70.38; N, 5.22; H, 6.29; IR (KBr): 3480, 3037, 2859, 2823, 2780, 1597, 1496, 1452, 1160, 776 cm^{-1}.

4.2.2. Preparation of (*S*,*S*)-2-{[(2-dimethylamino-5-methylphenyl)-naphthalen-1-yl-methyl]amino}-1,1,3-triphenyl-propan-1-ol 5a and (*S*,*R*)-2-{[(2-Dimethylamino-5-methylphenyl)-naphthalen-1-yl-methyl]amino}-1,1,3-triphenyl-propan-1-ol 5b

To a mixture of compound **7** (0.291 g, 1 mmol) and triethylamine (0.303 g, 3 mmol) in CH_2Cl_2 (10 mL), a solution of $(CF_3CO)_2O$ (0.31 g, 1.5 mmol) in dry CH_2Cl_2 (10 mL) was added at 0 °C. The mixture was stirred at 0 °C for 1 h. A solution of chiral amino alcohol **2** (0.303 g, 1 m mol) in dry CH_2Cl_2 (10 mL) was added at 0 °C. After 24 h, the mixture was treated with cold water and extracted with portions of CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4, evaporated and purified by flash chromatography (petroleum ether/acetyl acetate = 40:1) to give a white solid **5a** (0.16 g, 28 %) and a white solid **5 b** (0.26 g, 45%), respectively.

Compound **5a**. Mp 198–199 °C; $[\alpha]_D^{20} = +42.8$ (*c* 0.50, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, ppm): δ = 7.76–6.34 (m, 25H, 25Ar*H*), 5.74 (s, 1H, ArC*H*), 4.15–4.14 (m, 1H, C*H*NH), 2.69–2.67 (m, 1H, PhCH_A), 2.63 (s, 6H, 2NCH_3), 2.47 (dd, 1H, *J* = 10.0 Hz, *J* = 13.5 Hz, PhCH_B), 2.06 (s, 3H, ArCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ = 148.0, 146.4, 140.1, 137.6, 134.3, 133.7, 129.7, 129.1, 128.6, 128.5, 128.0, 126.0, 124.3, 121.6, 77.9, 61.4, 53.8, 46.8, 37.9, 21.0; MS: *m*/*z* 577 (M^++1); Anal. Calcd for $C_{41}H_{40}N_2O$: C, 85.38; N, 4.86; H, 6.99. Found: C, 85.19; N, 4.69; H, 7.32; IR (KBr): 3480, 3037, 2859, 2823, 2780, 1597, 1496, 1452, 1160, 776 cm^{-1}.

Compound **5b**. Mp 193–194 °C; $[\alpha]_D^{20} = -34.9$ (*c* 0.47, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, ppm): δ = 7.74–6.55 (m, 25H, 25Ar*H*), 6.16 (s, 1H, ArC*H*), 4.34–4.32 (m, 1H, C*H*NH), 2.96–2.93 (m, 1H, PhCH_A), 2.72–2.68 (dd, 1H, *J* = 7.9 Hz, *J* = 15.0 Hz, PhCH_B), 2.47 (s, 6H, 2NCH_3), 2.07 (s, 3H, ArCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ = 149.7, 146.8, 145.1, 139.8, 138.3, 133.7, 133.5, 128.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.1, 126.8, 126.3, 126.1, 125.7, 125.6, 125.5, 125.2, 124.9, 124.5, 121.0, 79.5, 62.3, 53.3, 46.1, 37.4, 21.1; MS: *m*/*z* 577 (M^++1); Anal. Calcd for $C_{41}H_{40}N_2O$: C, 85.38; N, 4.86; H, 6.99. Found: C, 85.30; N, 4.69; H, 6.67; IR (KBr): 3488, 3028, 2852, 2818, 2777, 1592, 1499, 1451, 1161, 784 cm^{-1}.

4.3. NMR shifts experiments

NMR shift experiments were performed on a 500 MHz NMR spectrometer at 25 °C. Samples for analysis were prepared by mixing equimolar amounts of chiral amino alcohols **1**–**5** with the guests studied herein in $CDCl_3$, making the concentrations of the hosts (or guests) normally 4 mM.

4.4. Studies of the stoichiometry of the host–guest complex (Job plots)

Compound **4**, L-**11** and D-**11** were separately dissolved in $CDCl_3$ with a concentration of 4 mM. These solutions were distributed among nine NMR tubes, with the molar fractions X of the guest in the resulting solutions increasing from 0.1 to 0.9, and the total concentration of host and guest was 4 mM. The complexation induced shifts ($\Delta\delta$) were multiplied by *X* and plotted against *X* itself to afford a 1:1 (host to guest) binding model.

4.5. NMR host–guest titrations

^1H NMR titrations were performed by adding incremental amounts of a $CDCl_3$ solution of the host to nine NMR tubes containing a solution of the corresponding L-**11** or D-**11** also in $CDCl_3$. The final concentration of L-**11** or D-**11** in all tubes was adjusted to be 2 mM while the guest concentrations varied from 0 to 8 mM. The ^1H NMR spectrum of each sample was recorded on a 500 MHz spectrometer. Assuming a 1:1 complexation, K_a was calculated by the non-linear least-squares fitting method from the observed $\Delta\delta$ values and the respective host and guest concentrations.

4.6. Evaluation of the accuracy of this determining method

To demonstrate the accuracy of our method for the determination of the enantiomeric excess of carboxylic acids, we prepared seven samples containing compound **8** with 0, 20, 40, 60, 80, 90 and 95% ee, respectively. All samples were prepared by adding 1 equiv of compound **4** into solutions of compound **8** (4 mM in $CDCl_3$) and their enantiomeric compositions were determined in the presence of compound **4** by using ^1H NMR method. The results, which were calculated based on the integrations of the CH_3Ts protons signals, are shown in Figure 10.

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