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New chiral auxiliaries derived from (*S*)-α-phenylethylamine as chiral solvating agents for carboxylic acids

Wenge Wang, Fengnian Ma, Xiumin Shen and Cong Zhang*

College of Chemistry, Beijing Normal University, Beijing 100875, China

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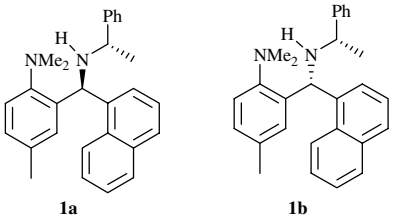
Abstract—The two new diastereoisomeric chiral auxiliaries **1a** and **1b** were synthesized conveniently and effectively. ^{1}H NMR was employed to investigate their chiral recognition ability. Compared with (*S*)-PEA, these new chiral auxiliaries exhibited better enantioselectivity towards the carboxylic acids we had chosen.

1. Introduction

In view of the importance of chiral carboxylic acids in biological and pharmaceutical chemistry,[1–4] there is a demand for the development of fast and accurate methodologies for the determination of the enantiomeric composition of these chiral compounds. Apart from chromatographic[5] and capillary electrophoretic[6] methods, NMR spectroscopy using chiral solvating agents (CSAs) is an efficient and convenient method to meet this need.[7–9] There have already been a few reports of the use of chiral amines as CSAs in this domain.[10–13] As a simple but powerful chiral adjuvant, chiral α-phenylethylamine (PEA) as well as some of its derivatives has also been applied for chiral carboxylic acid analysis but generally its ^{1}H chemical shift non-equivalences are too small to realize baseline resolution;[14–18] so further attempts to modify the structure of chiral PEA are worth studying. Recently, we reported a novel chiral macrocyclic compound with (*S*)-PEA as the chiral source, which shows excellent discriminating ability as a CSA for a broad variety of carboxylic acids by ^{1}H NMR spectroscopy.[19] In this work, some structural modifications have been made on (*S*)-PEA in order to further augment its chiral recognition ability. We designed the new chiral auxiliaries **1a** and **1b** with (*S*)-PEA as the chiral source (see Fig. 1) and expect that the incorporation of two anisotropic groups (naphthyl and phenyl attached by methyl as well as dimethylamino) can contribute to the modification of the differential magnetic influence of (*S*)-PEA. In addition, increasing the number of stereogenic centres may afford an important increase in the enantiodiscriminating abilities of these two diastereoisomers.[20] With this in mind, we envisioned the possibility of using these chiral diamines as CSAs for the effective analysis of the enantiomeric excess of carboxylic acids. Herein, we report the synthesis of chiral auxiliaries **1a** and **1b** as well as their enantiodiscriminating abilities for carboxylic acids by ^{1}H NMR spectroscopy.



1a **1b**

Figure 1. The structures of newly designed auxiliaries **1a** and **1b**.

2. Results and discussion

Chiral diamines **1a** and **1b** were efficiently synthesized by the reaction of intermediate **3** (prepared by the Grignard addition of compound **2**) with trifluoroacetic anhydride, and then with (*S*)-α-PEA (see Scheme 1). The structures of these chiral compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and EA. The crystal structure of **1b** was studied by X-ray single crystal structure analysis.[21] The molecular structure of compound **1b** is shown

* Corresponding author. Tel.: +86 13825661820; fax: +86 10 58210397; e-mail: czhang@bnu.edu.cn

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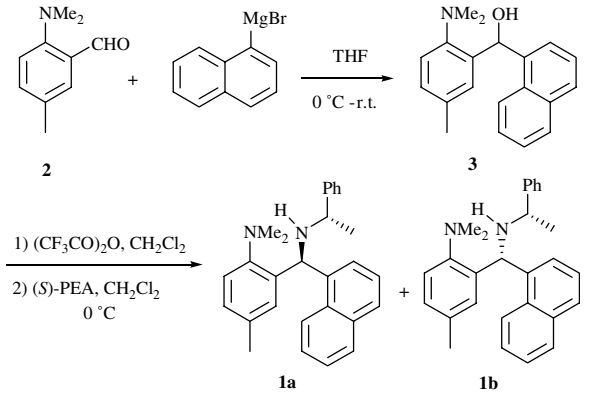

Scheme 1. The synthetic route to compounds **1a** and **1b**.

in Figure 2, which indicates the newly prepared stereogenic centre induced by (*S*)-PEA is the (*R*)-configuration.

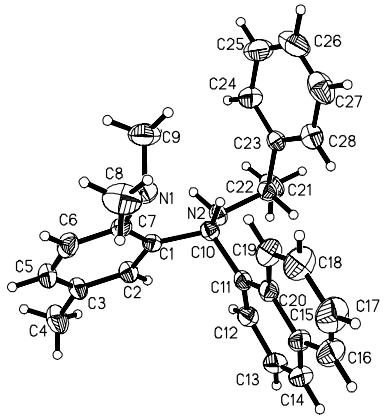

Figure 2. The molecular structure of compound **1b**.

With these desired diamines in hand, we utilized ^{1}H NMR (500 MHz) spectroscopy to study the chiral recognition abilities of compounds **1a** and **1b**, and guests (see Fig. 3) include racemic compounds of mandelic acid **4** and some of its derivatives **5**–**9**, non-aromatic lactic acid **10** and dicarboxylic acid **15**. In addition, the N-derivatives of some amino acids, including *p*-tolylsulfonyl phenylglycine (Ts-phenylglycine) **11**, *p*-tolylsulfonyl valine (Ts-valine) **12**, *p*-tolylsulfonyl leucine (Ts-leucine) **13** and *p*-tolylsulfonyl alanine (Ts-analine) **14**, were also chosen as guests to

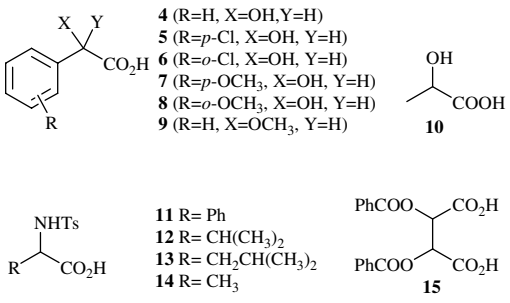

Figure 3. The structures of the guests used herein.

investigate further the enantiodiscriminating capacities of these chiral diamines. As a reference CSA, (*S*)-PEA was also utilized to recognize these carboxylic acids in order to evaluate the chiral recognition abilities of these modified chiral diamines for carboxylic acids.

Table 1 summarizes the chemical shift non-equivalences ($\Delta\Delta\delta$) of CH, CH_3 and NHTs of these guests in the presence of compounds **1a**, **1b** and (*S*)-PEA, respectively.

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

Guest	Signal	$\Delta\Delta\delta$[a] (Hz)		
		1a	**1b**	(*S*)-PEA
4	α-*H*	41.6 (*S*)	34.3 (*S*)	17.4
5	α-*H*	30.4	33.3	0
6	α-*H*	45.0	65.4	21.8
7	α-*H*	34.7	36.2	0
8	α-*H*	23.8	38.5	12.3
9	O*CH*$_3$	10.3	5.2	0
10	*CH*$_3$	12.2	53.9	0
11	α-*H*	0	32.7	15.5
	N*H*Ts	46.5	0	0
12[b]	N*H*Ts	129.8 (D)	0	0
13[b]	N*H*Ts	183.3	0	0
14	α-*CH*$_3$	37.0 (D)	46.4 (D)	0
	N*H*Ts	152.6 (D)	0	0
15[c]	*CH*	21.1	7.9	14.5

[a] In brackets: configuration of the enantiomer corresponding to the signal at higher field.
[b] The chemical shift non-equivalences of the methyl proton of $CH(CH_3)_2$ for **12** and $CH_2CH(CH_3)_2$ for **13** are large (see Fig. 5).
[c] The molar ratio of CSA and guest is 2:1.

For mandelic acid **4** and its derivatives **5**–**8**, the methine proton signals of all guests were shifted upfield in the presence of hosts **1a** and **1b**, suggesting deprotonation of the carboxylic group. Furthermore, these observed signals were all split into two peaks due to the different interactions of the two enantiomers of the substrate with the CSA. Generally, the chemical shift non-equivalences we observed were all large enough to afford baseline resolution for accurate integration. For example, the addition of hosts **1a** and **1b** to racemic **4** in $CDCl_3$ caused remarkable upfield shifts of the methine proton signal of **4** and these methine signals were split into two singlets with the separation between the two peaks being 41.6 Hz and 34.4 Hz, respectively. The chemical shift non-equivalence of the methine proton was only 17.4 Hz with (*S*)-PEA as the CSA under the same condition. We also observed the larger upfield shifts of the methine proton of chiral acid **4** towards (*S*)-**4** in the presence of compound **1a** and **1b**, which reveals that these chiral diamines have stronger chiral recognition abilities than with (*R*)-**4**.[22] The largest $\Delta\Delta\delta$ value of the methine proton was up to 65.4 Hz when acid **6** served as the guest in the presence of **1b** while under the identical conditions host **1a** and (*S*)-PEA only induced non-equivalences of 45.0 Hz and 21.8 Hz, respectively (see Fig. 4). This indicates that these new host compounds **1a** and **1b** exhibit better enantioselectivity in comparison with

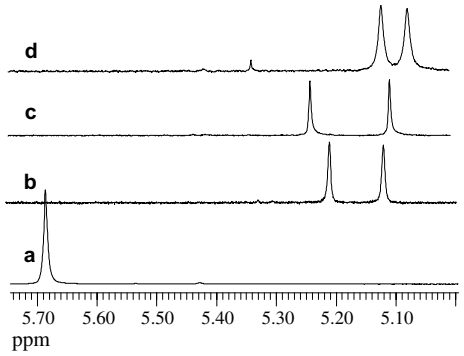

Figure 4. A portion of the ^{1}H NMR (500 MHz) spectra of (a) racemic **6**; (b) **1a** and racemic **6**; (c) **1b** and racemic **6**; (d) (*S*)-PEA and racemic **6**.

(*S*)-PEA. Although the chiral discrimination was also observed for the MeO signals of acid **9**, which are farther from the stereogenic centre, the chemical shift difference between the diastereomeric complexes was insufficient for quantitative analysis. This example also indicates that the α-hydroxyl group in the substrate play an important role for the establishment of hydrogen bonding with NH or N on host compounds. The methyl proton of aliphatic acid **10** was acquired good chiral recognition with compounds **1a** and **1b** as CSAs, which demonstrated the aromatic ring in the substrate was not necessary for chiral recognition, while no enantiomeric discrimination occurred with (*S*)-PEA as the CSA. From these analytical data, it is clear that compared with (*S*)-PEA, chiral hosts **1a** and **1b** exhibited better chiral recognition abilities towards these mentioned carboxylic acids **4**–**10**.

In Table 1, we can see that compound **1a** showed an excellent enantiodiscriminating ability towards the derivatives of amino acids as compared with compound **1b** and (*S*)-PEA. For instance, in the case of **12**, compound **1b** and (*S*)-PEA showed no enantiodiscrimination while compound **1a** induced the non-equivalence of the proton signal of NHTs up to 129.8 Hz (see Fig. 5). Here, the two diastereoisomers behave quite differently towards the same guest, demonstrating that the 'matched couple' is represented by diastereoisomer **1a** while **1b** is the 'mismatched couple'.[20] In addition, the non-equivalent two methyl protons of compound **12** also obtained good chiral recognition. The two doublets of the methyl proton signals of D-**12** were shifted upfield about 0.20 ppm and 0.34, while only about 0.12 ppm and 0.19 ppm when L-**12** served as a chosen analyte. On the contrary, we observed that all NH protons from these guests **11**–**14** resonate at lower field upon the addition of compound **1a**, which can be interpreted as the formation of a stronger intramolecular hydrogen bond with the carboxylate anion thus formed.[23] The largest $\Delta\Delta\delta$ value of the NHTs proton was up to 183.3 Hz, which was achieved upon the addition of an equimolar amount of **1a** into racemic **13** in $CDCl_3$. Dicarboxylic acid **15** also obtained good chiral recognition in the presence of compound **1a**–**1b** and (*S*)-PEA with the molar ratio of host and guest being 2:1.

A 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 **1b** and (*R*)-**4** or (*S*)-**4**. The ^{1}H NMR spectra of these samples were recorded and chemical shift variations were observed for the methine proton of the acid (*R*)-**4** or (*S*)-**4**. The stoichiometry of the host–guest complex was determined according to Job's method of continuous variation.[24] The Job plots for the complexation of compound **1b** with (*R*)-**4** and (*S*)-**4** were illustrated in Figure 6, affording a maximum of $\Delta\delta X$ at $X = 0.5$, which means that compound **1b** forms a

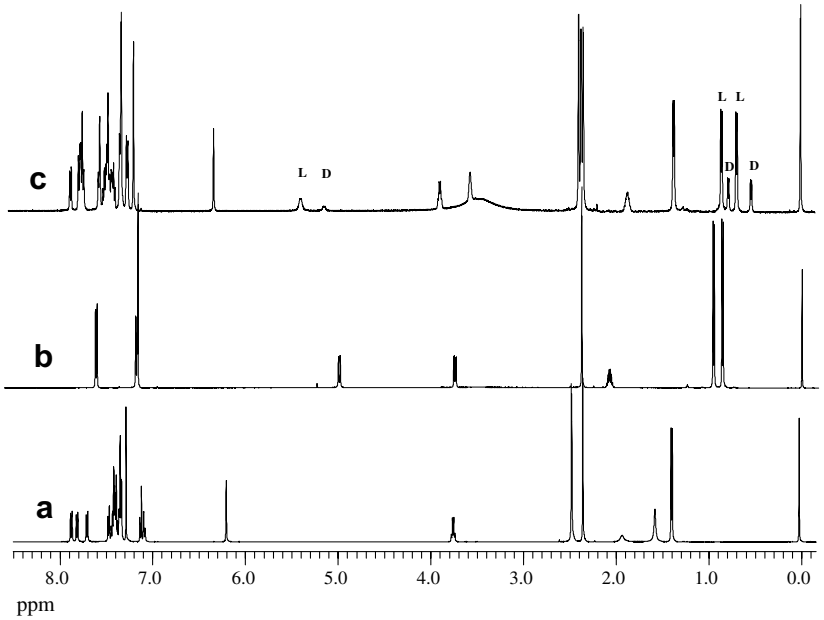

Figure 5. ^{1}H NMR spectra (500 MHz) of equimolar mixtures (4 mM each) of **12**/**1a** at 25 °C in $CDCl_3$: (a) compound **1a**; (b) free racemic **12**; (c) enantiomerically enriched **12** (L:D = 3:1) and compound **1a**.

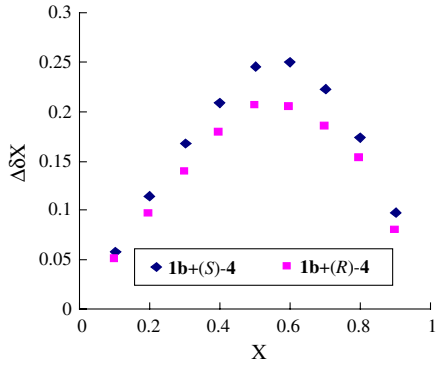

Figure 6. Job plots for the complexation of compound **1b** with (*R*)-**4** and (*S*)-**4**. ($X = [\mathbf{1b}]/([\mathbf{1b}] + [\mathbf{4}])$; $\Delta\delta$ = variation of the chemical shift of the observed proton).

1:1 instantaneous complex with (*R*)- or (*S*)-**4** under these experimental conditions. In order to further demonstrate this result, we also studied the stoichiometry of compound **1a** with L-**15** (see Fig. 7). For compound **1a**, a maximum was observed when compound **1a** versus L-**15** was 1:2 ($X = 0.67$), indicating that host **1a** formed a 1:2 instantaneous complex with L-**15**. These data further indicated that one molecule of chiral diamine **1a** or **1b** can bind with one molecule of mono-carboxylic acid to form a complex under the experimental conditions.

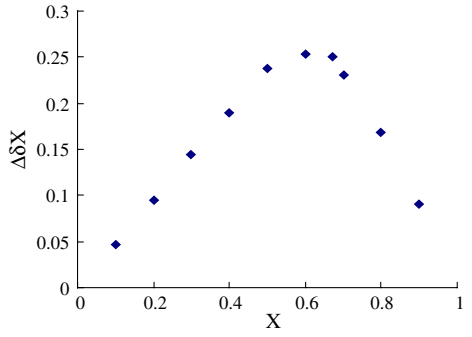

Figure 7. Job plots for the complexation of compound **1a** with L-**15**. ($X = [\mathbf{1a}]/([\mathbf{1a}] + [\mathbf{15}])$; $\Delta\delta$ = variation of the chemical shift of the observed proton).

In order to further evaluate the discriminating abilities of **1a** and **1b**, we performed the titration curves of **1a** and **1b** with chiral mandelic acid. The association constants of **1a** and **1b** with (*S*)-**4** and (*R*)-**4** were determined from the titration curves by the non-linear least-squares fitting method (Table 2).[24] From Table 2, it was seen that the (*S*)-enantiomer was more strongly bound to **1a** or **1b** than the (*R*)-enantiomer. In order to investigate the intrinsic chemical shift non-equivalence of the two diastereoisomeric instantaneous complexes, we performed the 1D GOESY spectra of the complexes formed from **1a** with an equimolar amount of (*R*)-**4** or (*S*)-**4**, but no intermolecular NOE phenomena was observed. The incorporation of two anisotropic groups into host molecules may play an important role for the excellent chiral recognition abilities by the combination of steric and electrical factors.

Table 2. Association constants K_a $(mol/l)^{-1}$ of **1a** and **1b** with (*S*)- or (*R*)-mandelic acid in $CDCl_3$

Entry	CSAs	Guests	K_a $(mol/l)^{-1}$	$K_a(S)/K_a(R)$
1	**1a**	(*S*)-**4**	$(2.2 \pm 0.6) \times 10^4$	1.8
2	**1a**	(*R*)-**4**	$(1.2 \pm 0.4) \times 10^4$	
3	**1b**	(*S*)-**4**	$(1.2 \pm 0.3) \times 10^4$	1.2
4	**1b**	(*R*)-**4**	$(9.5 \pm 1.7) \times 10^3$	

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

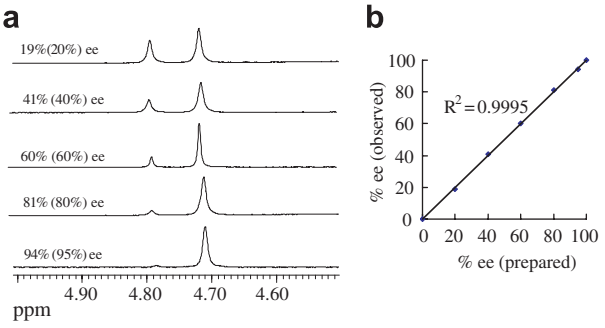

Figure 8. (a) Partial ^1H NMR (500 MHz) spectra of (*S*)-**4** with various enantiomeric purities (4 mM) in the presence of an equimolar amount of compound **1a**. (b) Correlation between the observed and prepared % ee values.

3. Conclusion

In conclusion, the two new chiral auxiliaries **1a** and **1b** derived from (*S*)-PEA have been synthesized conveniently and effectively, and have been proved to be effective chiral NMR solvating agents for chiral carboxylic acids. Compared with (*S*)-PEA, a commercially available chiral solvating agent, these host compounds exhibited better enantiodiscriminating abilities towards the chiral carboxylic acids investigated in this work with a few exceptions. In particular, compound **1a** exhibited excellent chiral recognition ability for the N-derivatives of some amino acids.

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. 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 and THF) were analytical and dried thoroughly. (*S*)-PEA is commercially available in its pure form. 2-(*N*,*N*-Dimethylamino)-5-methylbenzaldehyde **2** (DMAMB) was prepared according to the literature.[25]

4.2. Preparation of compounds 1 and 3

4.2.1. [2-(Dimethylamino)-5-methylphenyl]-(1-naphthyl)methanol 3. Under a nitrogen atmosphere, a solution of DMAMB (0.82 g, 0.005 mol) in THF (10 ml) was added dropwise in an ice-water bath to a THF solution of naphth-1-ylmagnesium bromide prepared from 1-bromonaphthalene (2.07 g, 0.01 mol) and magnesium (0.25 g, 0.0102 mol), and the mixture was stirred at room temperature for 7 h. The additive complex was treated with a solution of NH_4Cl 5% and extracted with portions of ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4, evaporated and purified by flash chromatography to give a white solid **3** (1.33 g, 91.2%). Mp 108–110 °C; ^{1}H NMR (500 MHz, $CDCl_3$, ppm): $\delta = 6.80$–8.21 (m, 10H, 10Ar*H*), 6.62 (s, 1H, C*H*OH), 2.82 (s, 6H, 2NCH_3), 2.15 (s, 3H, ArCH_3). ^{13}C NMR (125 MHz, $CDCl_3$, ppm): $\delta = 149.6$, 139.4, 137.4, 137.4, 134.8, 134.0, 131.6, 129.5, 129.1, 128.6, 128.2, 125.9, 125.5, 125.3, 125.0, 121.4, 72.7, 45.9, 20.9. MS: *m*/*z* 291 (M^+); Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; N, 4.81; H, 7.26. Found: C, 82.32; N, 4.58; H, 7.59; IR (KBr): 3158, 3051, 2861, 2829, 2777, 1508, 1493, 1455, 1165, 946, 793 cm^{-1}.

4.2.2. *N*,*N*,4-Trimethyl-2-[(*S*)-{[(*S*)-1-phenylethyl]amino}(1-naphthyl)methyl]aniline 1a and *N*,*N*,4-trimethyl-2-[(*R*)-{[(*S*)-1-phenylethyl]amino}(1-naphthyl)methyl] aniline 1b. To a mixture of **3** (1.16 g, 0.004 mol) and tri-ethylamine (0.48 g, 0.0048 mol) in CH_2Cl_2 (10 ml), a solution of $(CF_3CO)_2O$ (1.00 g, 0.0048 mol) 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 (*S*)-PEA (0.72 g, 0.006 mol) in dry CH_2Cl_2 (10 ml) was added at 0 °C. After 15 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 to give a white solid **1a** (0.61 g, 38.7%) and a white solid **1b** (0.69 g, 43.8%), respectively.

Compound **1a**: Mp 113–114 °C; $[\alpha]_D^{20} = +113.2$ (*c* 1.55, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.10–7.89 (m, 15H, 15Ar*H*), 6.21 (s, 1H, C*H*N), 3.76 (q, 1H, $J = 6.5$ Hz, PhC*H*N), 2.48 (s, 6H, 2NCH_3), 2.36 (s, 3H, ArCH_3), 1.40 (d, 3H, $J = 6.6$ Hz, PhCHCH_3); δ 7.09–7.88 (m, 15H), 6.20 (s, 1H), 3.76 (q, 1H, $J = 6.5$ Hz), 2.48 (s, 6H), 2.36 (s, 3H), 1.40 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 150.5, 145.7, 139.9, 137.9, 134.0, 133.2, 132.0, 129.4, 128.5, 127.4, 127.3, 127.1, 125.7, 125.4, 125.3, 124.8, 124.2, 120.6, 55.7, 52.9, 45.5, 23.0, 21.3; MS: *m*/*z* 295 (M^++1); Anal. Calcd for $C_{28}H_{30}N_2$: C, 85.24; N, 7.10; H, 7.66. Found: C, 84.99; N, 7.09; H, 7.93; IR (KBr): 3480, 3037, 2859, 2823, 2780, 1597, 1496, 1452, 1160, 776 cm^{-1}.

Compound **1b**: Mp 135–136 °C; $[\alpha]_D^{20} = -12.6$ (*c* 1.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 6.94–8.34 (m, 15H, 15Ar*H*), 6.04 (s, 1H, C*H*N), 3.77 (q, 1H, $J = 6.7$ Hz, PhC*H*N), 2.43 (s, 6H, 2NCH_3), 2.15 (s, 3H, ArCH_3), 1.50 (d, 3H, $J = 6.7$ Hz, PhCHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 149.3, 145.3, 140.0, 138.6, 134.0, 133.4, 132.4, 129.8, 128.4, 128.3, 128.1, 127.3, 127.1, 126.9, 125.5, 125.4, 125.2, 124.6, 124.0, 120.3, 55.8, 53.4, 45.4, 23.1, 20.9; MS: *m*/*z* 295 (M^++1); Anal. Calcd for $C_{28}H_{30}N_2$: C, 85.24; N, 7.10; H, 7.66. Found: C, 85.20; N, 7.00; H, 7.79; IR (KBr): 3488, 3028, 2852, 2818, 2777, 1592, 1499, 1451, 1161, 784 cm^{-1}.

4.3. NMR shift 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 compounds **1a**, **1b** and (*S*)-PEA 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 **1b**, (*R*)-**4** and (*S*)-**4** 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. The same procedure was performed to investigate the stoichiometry for **1a** with L-**15**.

4.5. NMR host–guest titrations

^{1}H 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 (*S*)-**4** or (*R*)-**4** also in $CDCl_3$ .The final concentration of (*S*)-**4** or (*R*)-**4** in all tubes was adjusted to be 2 mM while the guest concentration varied from 0 to 10 mM. The ^{1}H NMR spectrum of each sample was recorded on a 500 MHz spectromer. 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 **4** with 0%, 20%, 40%, 60%, 80%, 95% and 100% ee, respectively. All samples were prepared by adding 1 equiv of compound **1a** in the solutions of **4** (4 mM in $CDCl_3$) and their enantiomeric compo-

sitions were determined in the presence of compound **1a** by using the ^{1}H NMR method. The results, which were calculated based on the integrations of the methine proton signals, are shown in Figure 8a. The linear correlation between the observed and prepared % ee values was also obtained (see Fig. 8b).

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21. Crystallographic data for the structure of compound **1b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 631527. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Crystal data of **1b**: $C_{28}H_{30}N_2$, $M = 394.54$, orthorhombic, space group $P2(1)2(1)2$, $a = 8.8823(13)$ Å, $b = 15.578(2)$ Å, $c = 16.682(3)$ Å, $V = 2308.3(6)$ Å^3, $D = 1.135$ g/cm^3, $\mu = 0.066$ mm^{-1}, $F(000) = 848$, $Z = 4$, $R_1 = 0.0409$, $\omega R_2 = 0.0833$. Data collection for the crystal structure determination was carried out on a diffractometer using Mo Kα radiation ($\lambda = 0.71073$ Å) at a temperature of 294(2) K. Of the 13,141 reflections measured in the $1.79 \leqslant \theta \leqslant 26.40°$ range, 2691 reflections were unique and 1612 reflections with $I > 2\sigma(I)$ were used in structure solution and refinement, $R_{int} = 0.0534$. $w = 1/[\sigma^2(F_o^2) + (0.0371P)^2 + 0.36269P]$, where $P = (F_o^2 + 2F_c^2)/3$. The structure was solved by direct method using SHELXL-97. All of the non-hydrogen atoms were refined by full-matrix least-square methods using anisotropic displacement parameters.
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