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Amino alcohol based chiral solvating agents: synthesis and applications in the NMR enantiodiscrimination of carboxylic acids

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ABSTRACT

Four optically active amino alcohols were synthesized via the ring opening of (*R*)-*N*-(2,3-epoxypropyl)phthalimide with (*R*)-2-phenyl glycinol, (1*R*,2*S*)-*cis*-1-amino-2-indanol, (*R*)-2-amino-1-butanol and (*S*)-phenyl ethylamine in 73–93% yields. The enantioselective recognition of these receptors towards the enantiomers of racemic carboxylic acids was studied by ^{1}H NMR spectroscopy. The molar ratio and the association constants of the chiral compounds with each of the enantiomers of the guests were determined by using Job plots and a non-linear least-squares fitting method, respectively. Large non-equivalent chemical shifts (up to 30.0 Hz) can be achieved in the presence of chiral amino alcohols **2** and **5**. Amongst the chiral receptors used, compound **5** was found to be the best chiral shift reagent, and was effective in the determination of the enantiomeric excess of chiral carboxylic acids.

1. Introduction

The design and synthesis of chiral receptors for molecular recognition has gained much interest due to the role of chirality in many biological processes.[1] The specificity and efficacy of many biologically important reactions are based on chiral recognition, the process in which a chiral host molecule selectively binds one of the two enantiomers. In most countries, producers of pharmaceuticals are required to evaluate the pharmacological properties of each enantiomer and to verify the enantiomeric purity of chiral drugs, even if the final commercial product is composed of both enantiomers. Since most drug effects are due to interactions with chiral biological materials, each enantiomer may have different pharmacological properties in terms of activity, potency, toxicity, transport mechanism and metabolic route.[2]

The study of molecular recognition can provide valuable information for understanding the interactions between biological molecules, and offer new perspectives with regard to the resolution of racemic mixtures, determination of the enantiomeric composition, screening of chiral catalysts and the development of useful molecular devices in pharmaceutical studies.[3] Therefore, the design of new and efficient artificial receptors for specific target molecules remains a challenge for supramolecular chemistry and analytical techniques.[4]

Chiral carboxylic acids are the structural units of many natural products and play a key role in the design and preparation of pharmaceuticals, as they are part of the synthesis process in the production of a wide range of compounds with biological and pharmacological activities. Due to their importance in biological systems and usefulness as a source of chirality in organic synthesis, the chiral recognition of carboxylic acids by artificial receptors is of critical importance in the preparation, separation, and analysis of enantiomers. In recent years, considerable effort has been devoted to the design and synthesis of artificial receptors[5] for determination of enantiomeric purity and to understand the basis of the mechanism of host–guest complexations.

Currently, there are a variety of methods (e.g., high-performance liquid chromatography [HPLC],[6] gas chromatography [GC],[7] capillary electrophoresis [CE],[8] circular dichroism [CD],[9] absorbance spectrometry,[10] infrared transmission spectrometry,[11] X-ray anomalous scattering,[12] nuclear magnetic resonance [NMR],[13] mass spectrometry [MS])[14] available for chiral recognition and the determination of enantiomeric purity.[15]

Amongst these methods, NMR spectroscopy has been shown to be particularly useful in providing detailed information on the nature of interactions between a chiral receptor and an analyte in the solution state[16] and the structure of the diastereomeric complexes involved. The NMR spectra of the enantiomers in an achiral medium display the same chemical shifts. Enantiodifferentiation in the spectra simply requires the use of a chiral auxiliary that converts a mixture of enantiomers into a mixture of diastereoisomeric complexes.[17]

In a continuation of our work on the synthesis of chiral receptors based on the calix[4]arene platform equipped with various functionalities including azacrown ethers,[18] amines,[19] amides,[20] Schiff bases,[21] and quaternary ammonium salts[22] as well as their

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catalytic activities and enantiomeric recognition properties towards chiral amines, carboxylic acids,[23] and amino acid derivatives,[24] we herein report the synthesis of novel chiral receptors and their recognition abilities for carboxylic acids by ^{1}H NMR spectroscopy.

2. Result and discussion

Amino alcohols are versatile intermediates in the synthesis of biologically active natural and synthetic products, unnatural amino acids, and chiral auxiliaries. It was expected that chiral receptors bearing both an amino group and a hydroxyl group would be useful for the enantiomeric discrimination of carboxylic acids and could be used as chiral solvating agents (CSAs) for the fast and accurate determination of the enantiomeric excess in combination with NMR spectroscopy. Chiral amino alcohols **2**–**5** were readily synthesized by the ring opening of the (*R*)-*N*-(2,3-epoxypropyl)phthalimide with (*R*)-2-phenyl glycinol, (1*R*,2*S*)-cis-1-amino-2-indanol, (*R*)-2-amino-1-butanol and (*S*)-phenyl ethylamine (Scheme 1) in 73–93% yields.

With the chiral aminoalcohols **2**–**5** in hand, we turned our attention to the enantiodiscrimination ability of the optically active receptors as CSAs for α-chiral carboxylic acids; 2-chloropropionic acid, α-hydroxy isovaleric acid, ibuprofen, mandelic acid and 2-chloro mandelic acid (Fig. 1). In most cases, we observed that the methine and methyl proton signals of the carboxylic acids appeared as sharp singlets, doublets and quartets and did not overlap with the peaks of the other proton signals in their ^{1}H NMR spectra. The experiments were performed by mixing equimolecular amounts of the chiral receptor and the racemic acid in $CDCl_3$ (10 mM). Immediately after each addition, ^{1}H NMR spectrum was recorded in a 400 MHz spectrometer at room temperature.

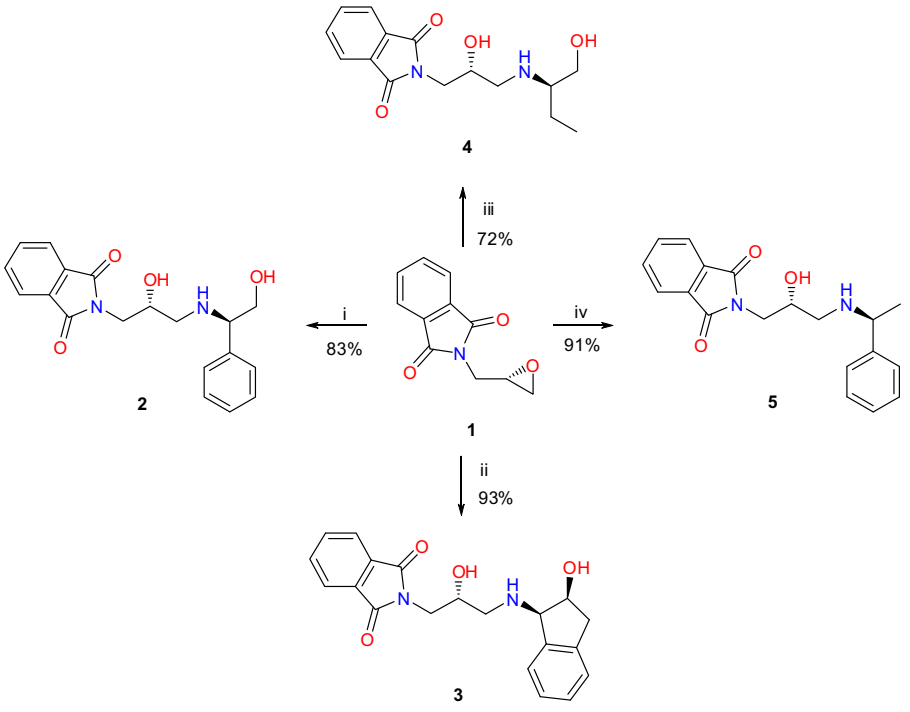
For our initial studies, the racemate of 2-chloro propionic acid was chosen as the guest and 1:1 mixtures of **2**–**5** were examined. When a solution of racemic 2-chloro propionic acid (10 mM in $CDCl_3$) was gradually added to a 10 mM solution of **2**–**5** in $CDCl_3$ until the ratio reached 1:1, the methine and methyl proton signals of 2-chloro propionic acid split into two quartets and doublets in the presence of the chiral discriminating agents **2**–**5** (Fig. 2), with an upfield chemical shift. The $\Delta\delta$, chemical shift differences relative to the original signals in the absence of chiral receptors, were in the range of 0.11–0.18 ppm.

Similarly, when a solution of racemic α-hydroxy isovaleric acid (10 mM in $CDCl_3$) was treated with an equimolar amount of receptors **2**–**5** (Fig. 3), the methine and methyl proton signals of α-hydroxy isovaleric acid were split into two sets of peaks due to the formation of two instantaneous diastereotopic complexes between the receptors and the enantiomers of α-hydroxy isovaleric acid, respectively. The largest $\Delta\Delta\delta$ value (7.2 Hz) of the methine proton was observed when receptor **5** was used as the CSA. This showed that compound **5** had the best enantiomer discriminating ability for α-hydroxy isovaleric acid when compared with the other hosts.

Enantiodifferentiation was also observed for the methine and methyl (Fig. 4) resonances of ibuprofen with each of the chiral receptors **2**–**5**. The greatest discrimination for the methyl and methine resonance was observed with **5** (Fig. 4e), whereas the methine proton signal of ibuprofen was overlapped by the signals of receptor **2**.

More significant differences occurred in the enantiomeric discrimination of the resonances of mandelic acid in mixtures with **2**–**5**. As shown in Figure 5, upon the addition of the chiral receptors **2**, **3** and **5**, the methine proton signals of mandelic acid were split into two singlets by 10.8, 8.4 and 7.6 Hz, respectively, with an upfield chemical shift due to the formation of two diastereotopic complexes between the CSAs and the enantiomers of the guest; this confirmed that chiral recognition had occurred. These results suggest a different chemical environment for the two enantiomers of mandelic acid, and that instantaneous host–guest complexes had been formed.

Table 1 shows values for the induced chemical shifts ($\Delta\delta$) on the signals of the carboxylic acids after the addition of chiral receptors **2**–**5**, as well as the splitting ($\Delta\Delta\delta$) between signals corresponding to each enantiomer of the acids. From Table 1, it can be seen that the methine protons of (*S*)-2-chloro propionic acid, D-mandelic



Scheme 1. (i)–(iv) Appropriate chiral amine or aminoalcohol, 2-propanol, reflux.

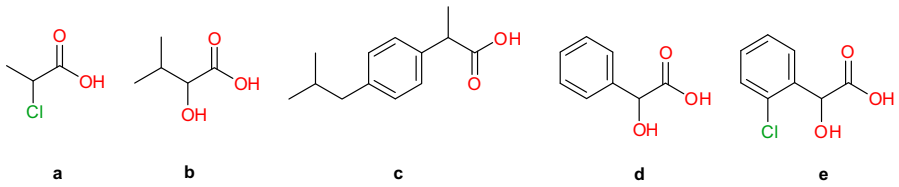


Figure 1. Chemical structures of α-chiral carboxylic acids.

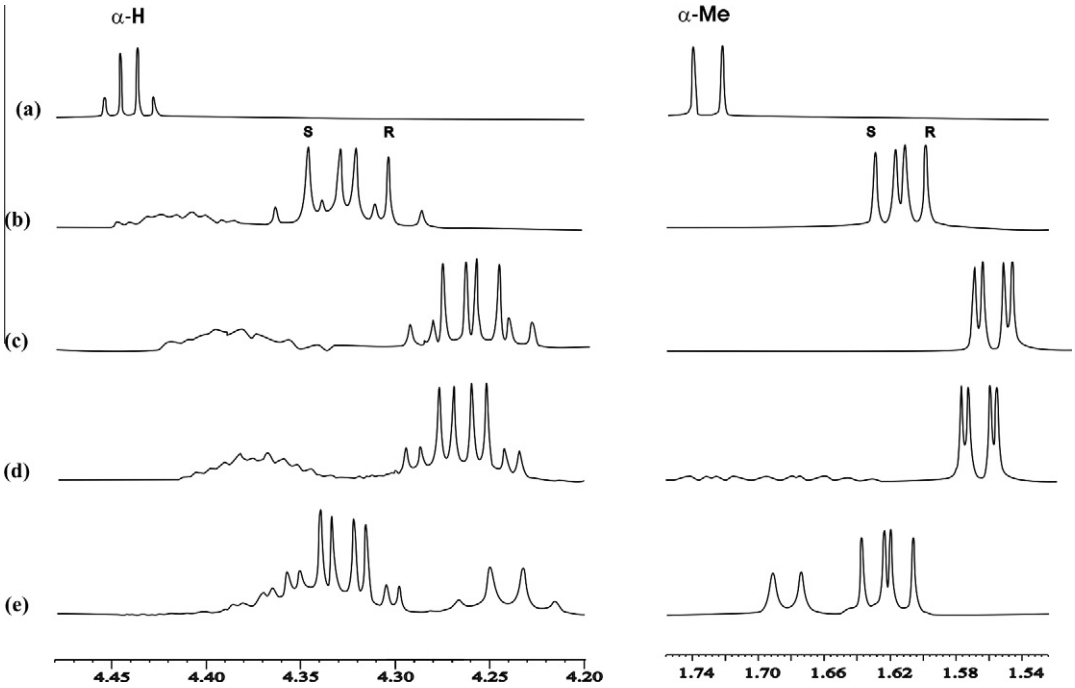


Figure 2. The 400 MHz ^{1}H NMR spectra (in $CDCl_3$ at 25 °C) of racemic 2-chloro propionic acid (10 mM) in the absence of CSA (a); and the equimolar mixtures of the chiral receptor **2** (b); **3** (c); **4** (d); **5** (e) with racemic 2-chloro propionic acid.

acid and (*S*)-α-hydroxy isovaleric acid appeared at a lower field than the corresponding (*R*)- and L-enantiomers, which were confirmed by an increase of the methine proton signal of (*S*)- and L-guests when (*S*)-2-chloro propionic acid, D-mandelic acid and (*S*)-α-hydroxy isovaleric acid were added into the complex of racemic guests with **2**–**5**. The opposite was observed for the methine proton signals of the (*S*)-enantiomer of ibuprofen. In most cases, the chemical shift non-equivalences were also observed for the methyl signals of 2-chloro propionic acid, α-hydroxy isovaleric acid and ibuprofen in the presence of chiral receptors.

A good example is the splitting of the methine proton signal of racemic 2-chloro mandelic acid in the presence of **2**–**5**. We observed the larger non-equivalence values of the methine proton in the presence of compounds **2** and **5**, which reveal that these chiral amino alcohols have better chiral recognition abilities than **3** and **4**. The largest $\Delta\Delta\delta$ value of the methine proton was up to 30.0 Hz when chiral receptor **5** was used as the host, while under the identical conditions, hosts **2**, **3** and **4** induced non-equivalences of 15.6, 5.2 and 8.4 Hz, respectively. The (*R*)-enantiomer of 2-chloro mandelic acid appeared at lower field than the corresponding (*S*)-enantiomer in the presence of the chiral hosts **2**–**5**. This indicates that the (*S*)-enantiomer binds more strongly compared to its antipode with the hosts **2**–**5**. These results were confirmed by recording the ^{1}H NMR spectra of the samples containing non-racemic guests (acids). Moreover, the signals of various protons of the hosts were shifted downfield. These shifts are due to specific host–guest complexation, and indicate that the interactions between the host and guest also occurred via multiple hydrogen bonds. As shown in Figure 6, in the presence of chiral receptors **2** and **5**, the chemical shift non-equivalences of the methine protons of 2-chloro mandelic acid are relatively large to give a baseline resolution on a 400 MHz NMR instrument at 25 °C.

Once the efficacy of chiral receptors **2** and **5** had been demonstrated, we attempted to gain a better understanding of the diastereomeric complexes formed in solution. With this aim, we focused on the complexes formed between the enantiomers of 2-chloro mandelic acid and mandelic acid and receptors **2** and **5**. The stoichiometry of the host–guest complexes was determined by ^{1}H NMR using the Job plot method.[25] The total concentration of the hosts and the guests was kept constant (10 mM) in $CDCl_3$, whilst the molar fraction of the guest {[G]/([H]+[G])} was varied continuously. The Job plots for the complexation of chiral amino alcohols **2** and **5** with the (*R*)- and (*S*)-2-chloro mandelic acid in $CDCl_3$ are shown in Figures 7 and 8, respectively. Maxima were observed when the molar ratio of the chiral receptors **2** and **5** and each enantiomer of the guests (*R*)- or (*S*)-2-chloro mandelic acid was 1:1 (X = 0.5), which indicated that hosts **2** and **5** and the guests formed instantaneous 1:1 complexes. Meanwhile, Job plots confirming the 1:1 stoichiometry were also obtained for **3** and **4** with all these enantiomerically pure guests.

In order to evaluate the enantiomeric discrimination abilities of the chiral amino alcohols, the titration curves of compounds **2** and **5** with the enantiomers of 2-chloro mandelic acid or mandelic acid were plotted, respectively (Figs. 9 and 10). The association

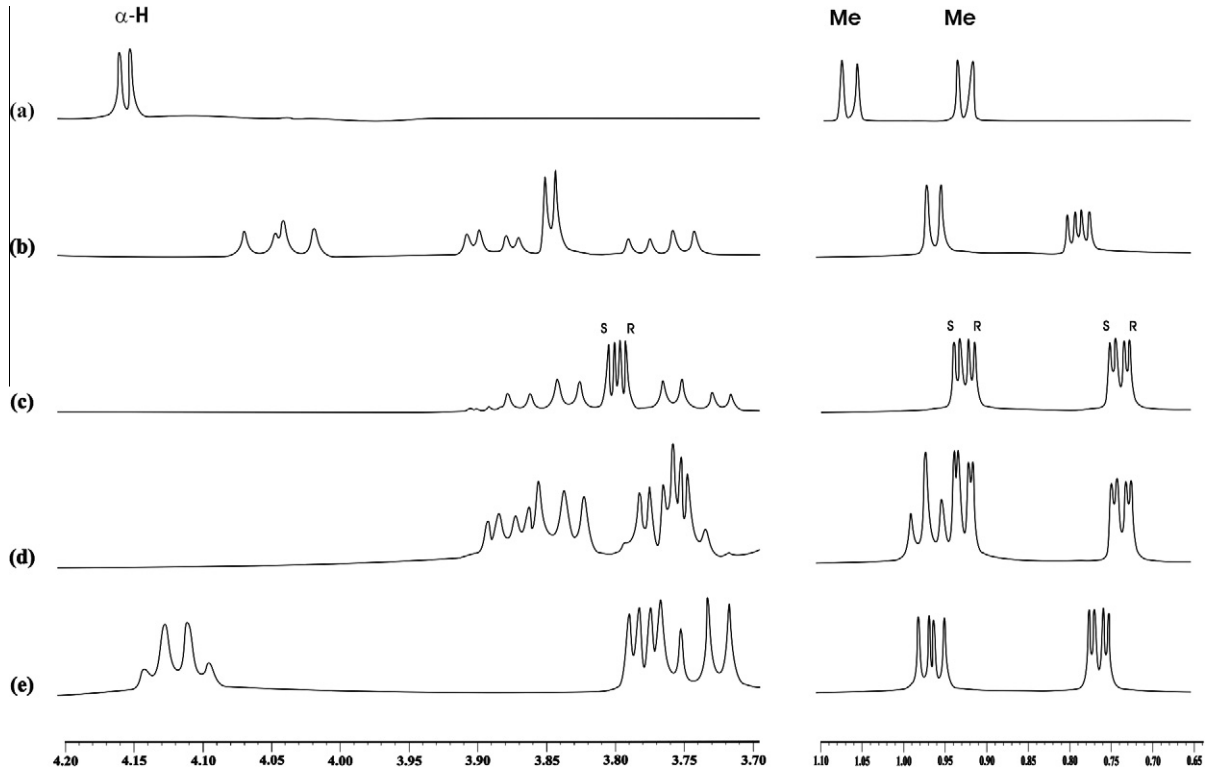


Figure 3. The 400 MHz ^{1}H NMR spectra (in $CDCl_3$ at 25 °C) of racemic α-hydroxy isovaleric acid (10 mM) in the absence of CSA (a); and the equimolar mixtures of the chiral receptor **2** (b); **3** (c); **4** (d); **5** (e) with racemic α-hydroxy isovaleric acid.

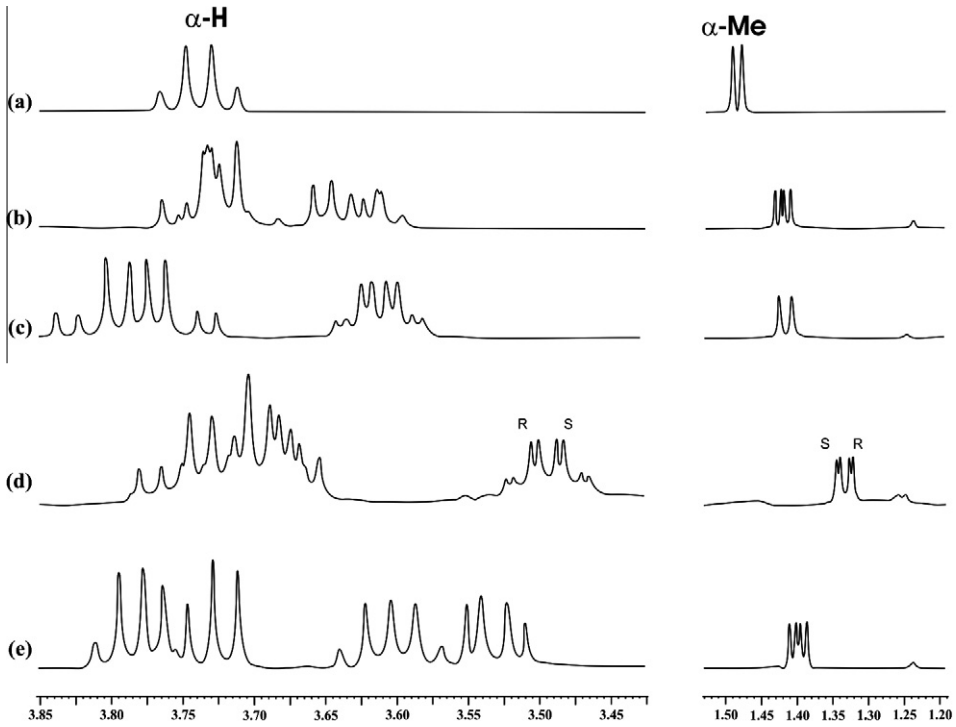


Figure 4. The 400 MHz ^{1}H NMR spectra (in $CDCl_3$ at 25 °C) of racemic ibuprofen (10 mM) in the absence of CSA (a); and the equimolar mixtures of the chiral receptor **2** (b); **3** (c); **4** (d); **5** (e) with racemic ibuprofen.

constants of **2**–**5** with enantiomerically pure guests were determined from the titration curves by a non-linear least-squares fitting method (Table 2).[26] It is evident that the chemical shift changes of (*S*)-2-chloro mandelic acid and L-mandelic acid were greater than those of the corresponding enantiomers (*R*)-2-chloro mandelic acid and D-mandelic acid in the presence of compounds **2** and **5**.

In order to investigate the intrinsic chemical shift non-equivalences of the two diastereoisomeric instantaneous complexes, we performed the 2D NOESY spectra of the complexes formed from

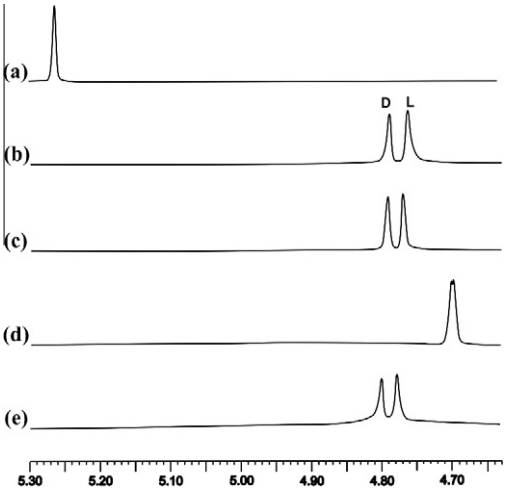


Figure 5. The 400 MHz ^{1}H NMR spectra (in $CDCl_3$ at 25 °C) of racemic mandelic acid (10 mM) in the absence of CSA (a); and the equimolar mixtures of the chiral receptor **2** (b); **3** (c); **4** (d); **5** (e) with racemic mandelic acid.

4 with an equimolar amount of 2-chloro mandelic acid (Fig. 11). Intermolecular NOEs were observed between both the methylene (next to the phthalimide and amine nitrogen) and the methyl protons in the chiral receptor and the α-methine protons in the guest.

We also investigated the influence of the molar ratio of compound **5**/2-chloro mandelic acid. As shown in Figure 12, upon the gradual addition of **5**, the ^{1}H NMR signal of the methine proton of 2-chloro mandelic acid moved upfield and the chemical shift difference between the two enantiomers gradually increased, until the addition of 1.0 equiv of **5**. However, a slight decrease in the chemical shift non-equivalences was observed in the case of more than 1.0 equiv **5** in the 2-chloro mandelic acid analyte. In view of this observation, we decided to investigate the properties of **5** as a CSA in the determination of the enantiomeric purity of chiral carboxylic acids using ^{1}H NMR spectroscopy.

To demonstrate the practical applicability of chiral receptor **5** for the determination of the ee of carboxylic acids, six samples containing 2-chloro mandelic acid with 0%, 20%, 40%, 60%, 80%, and 100% ee were prepared; the enantiomeric compositions were determined by the ^{1}H NMR method in the presence of 1.0 equiv of **5** (Fig. 13). The results, which were calculated based on the integrations of the NMR signals, were within ±1% of the actual enantiopurity of the samples. We also confirmed a linear correlation between the theoretical (y) and observed % ee values (x) (Fig. 14). The equation (for **5**, $y = 0.9957x + 0.0476$, correlation coefficient = 0.9996) demonstrates the high accuracy of this method.

The formation of the diastereomeric complexes between chiral amino alcohols **2**–**5** and α-chiral carboxylic acids possibly occurs in a two-step process. The first step is a proton transfer from the carboxylic acid to the amine nitrogen in the chiral receptors and a carboxylate anion is formed. The formation of a carboxylate anion was confirmed by the fact that the C=O stretch (1707 cm^{-1} for 2-chloro mandelic acid) disappeared in the FT-IR spectra of a 1:1 mixture of **5** and 2-chloro mandelic acid, and the observed

Table 1
Chemical shift non-equivalences ($\Delta\Delta\delta$, 400 MHz) for 1:1 diastereoisomeric complexes of **2**–**5** with racemic guests in $CDCl_3$ at 25 °C

Chiral receptor	Guest	Proton	Free	D or (*R*)	$\Delta\delta$ [D or (*R*)]	L or (*S*)	$\Delta\delta$ (L or (*S*)]	$\Delta\Delta\delta$[b] (Hz)
2	2-Chloro propionic acid	α-Me	1.73	1.608	0.122	1.619	0.111	4.4 (*R*)
		α-H	4.441	4.312	0.129	4.338	0.103	10.4 (*R*)
3				1.558	0.172	1.564	0.166	2.4 (*R*)
				4.254	0.187	4.266	0.175	4.8 (*R*)
4				1.564	0.166	1.569	0.161	2.0 (*R*)
				4.259	0.182	4.269	0.172	4.0 (*R*)
5				1.615	0.115	1.629	0.101	5.6 (*R*)
				4.324	0.117	4.331	0.11	2.8 (*R*)
2	α-Hydroxy isovaleric acid	Me	0.928	0.785	0.143	0.796	0.132	4.4 (*R*)
		Me	1.067	0.964	0.103	0.964	0.103	
		α-H	4.158	3.848	0.31	3.848	0.31	
3				0.736	0.192	0.743	0.185	2.8 (*R*)
				0.925	0.142	0.933	0.134	3.2 (*R*)
				3.797	0.361	3.801	0.357	1.6 (*R*)
4				0.733	0.195	0.741	0.187	3.2 (*R*)
				0.925[a]	0.142	0.931[a]	0.136	2.4 (*R*)
5				0.761	0.167	0.768	0.16	2.8 (*R*)
				0.959	0.108	0.977	0.09	7.2 (*R*)
				3.77	0.388	3.788	0.37	7.2 (*R*)
2	Ibuprofen	α-Me	1.482	1.426[a]	0.056	1.416[a]	0.066	4.0 (*R*)
3		α-H	3.739	1.418	0.064	1.418	0.064	0
				3.607	0.132	3.617	0.122	4.0 (*S*)
4				1.336	0.146	1.331	0.151	2.0 (*R*)
				3.497	0.242	3.492	0.247	2.0 (*S*)
5				1.408	0.074	1.39	0.092	7.2 (*R*)
				3.614	0.125	3.596	0.143	7.2 (*S*)
2	Mandelic acid	α-H	5.27	4.789	0.481	4.762	0.508	10.8 (L)
3				4.791	0.479	4.77	0.5	8.4 (L)
4				4.701	0.569	4.698	0.572	1.2 (L)
5				4.801	0.469	4.782	0.488	7.6 (L)
2	2-Chloro mandelic acid	α-H	5.67	5.3	0.37	5.261	0.409	15.6 (*S*)
3				5.261	0.409	5.248	0.422	5.2 (*S*)
4				5.15	0.52	5.129	0.541	8.4 (*S*)
5				5.242	0.428	5.167	0.503	30.0 (*S*)

[a] Overlapped with other resonances.
[b] In brackets: configuration of the enantiomer corresponding to the signal at higher field.

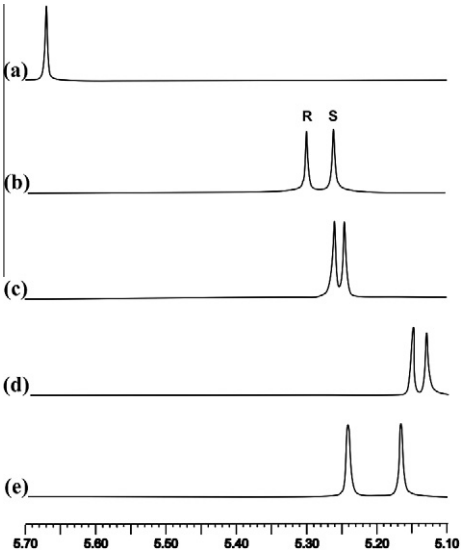


Figure 6. The 400 MHz ^{1}H NMR spectra (in $CDCl_3$ at 25 °C) of racemic 2-chloro mandelic acid (10 mM) in the absence of CSA (a); and the equimolar mixtures of the chiral receptor **2** (b); **3** (c); **4** (d); **5** (e) with racemic 2-chloro mandelic acid.

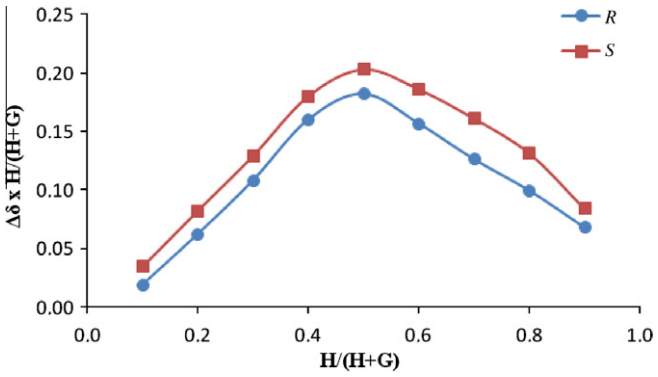


Figure 7. Job plots of **2** with (*R*)- and (*S*)-2-chloro mandelic acid [H/(H + G) = molar fraction of 2-chloro mandelic acid, Δδ = chemical shift change of the methine proton of (*R*)- and (*S*)-2-chloro mandelic acid].

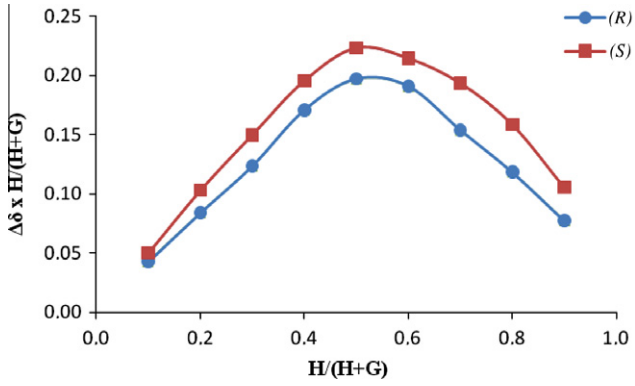


Figure 8. Job plots of **5** with (*R*)- and (*S*)-2-chloro mandelic acid [H/(H + G) = molar fraction of 2-chloro mandelic acid, Δδ = chemical shift change of the methine proton of (*R*)- and (*S*)-2-chloro mandelic acid].

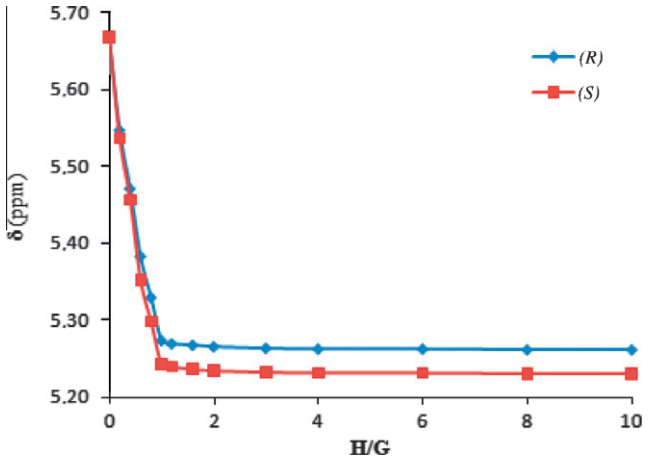


Figure 9. ^{1}H NMR titration curves of compound **2** with (*R*)- and (*S*)-2-chloro mandelic acids.

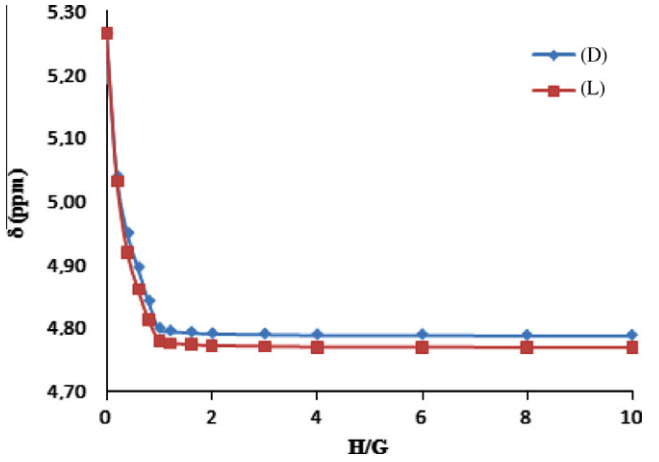


Figure 10. ^{1}H NMR titration curves of compound **5** with D- and L-mandelic acids.

Table 2
Association constants K_a $(mol/l)^{-1}$ of **2**–**5** with α-chiral carboxylic acids

Host	Guest	K ($\times 10^3$) M^{-1}	L/D or (*S*)/(*R*)
2	(*S*)-2-Chloro mandelic acid	13.85 ± 2.12	1.27
	(*R*)-2-Chloro mandelic acid	10.89 ± 1.91	
	L-Mandelic acid	14.91 ± 3.91	1.17
	D-Mandelic acid	12.73 ± 1.92	
3	(*S*)-2-Chloro mandelic acid	14.65 ± 2.13	1.01
	(*R*)-2-Chloro mandelic acid	14.49 ± 1.43	
	L-Mandelic acid	13.17 ± 2.55	1.10
	D-Mandelic acid	11.96 ± 2.03	
4	(*S*)-2-Chloro mandelic acid	29.36 ± 2.98	1.12
	(*R*)-2-Chloro mandelic acid	26.14 ± 3.14	
	L-Mandelic acid	n.d.	
	D-Mandelic acid	n.d.	
5	(*S*)-2-Chloro mandelic acid	27.06 ± 4.77	1.94
	(*R*)-2-Chloro mandelic acid	13.96 ± 2.00	
	L-Mandelic acid	13.76 ± 3.33	1.35
	D-Mandelic acid	10.14 ± 2.19	

n.d. = not determined.

intensities got stronger at 1593 cm^{-1} (the COO^- stretch). The protonated amine groups would then lead to the formation of corresponding diastereomeric salt with chiral carboxylate groups. The second step is the intermolecular non-covalent interactions between various atoms of the guest and hydrogen bonding sites defined by carbonyl oxygen, amine nitrogen, and hydroxy groups at

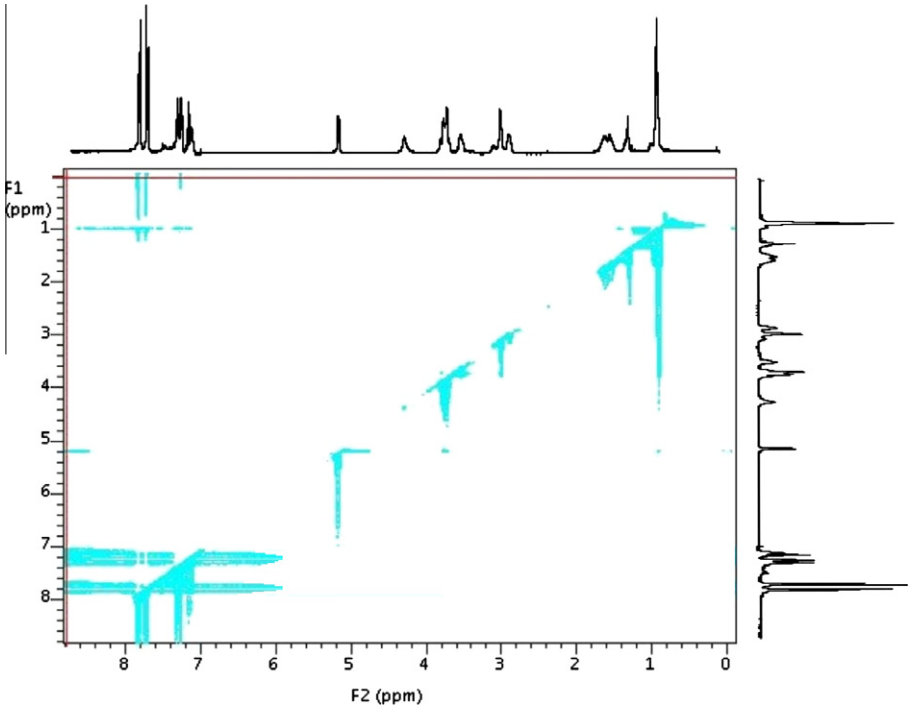


Figure 11. 2D NOESY spectra (400 MHz, 10 mM in $CDCl_3$) of a 1:1 mixture of **4** and racemic 2-chloro mandelic acid.

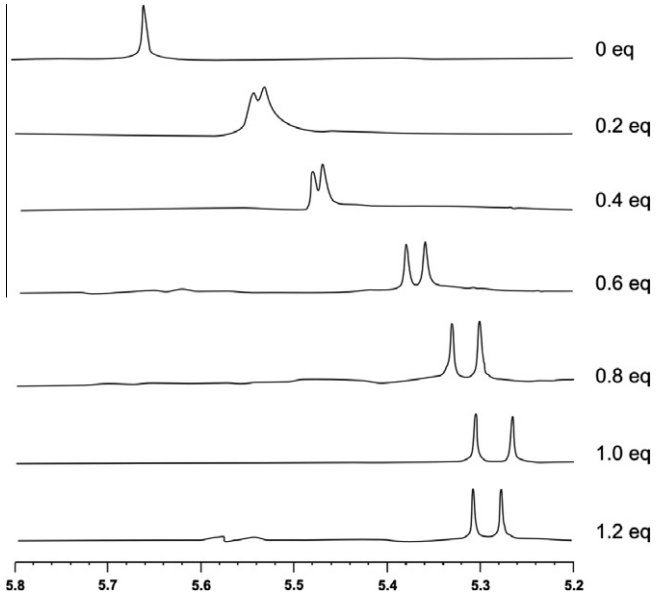


Figure 12. Variation of $\Delta\Delta\delta$ with the guest/host molar ratio for 2-chloro mandelic acid in the presence of CSA **5**. The concentration of **5** is 10 mM in $CDCl_3$.

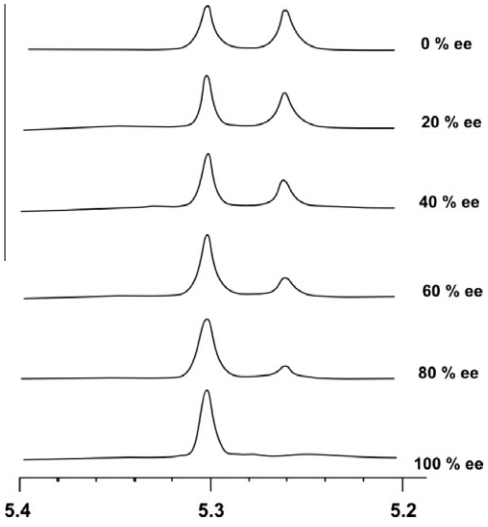


Figure 13. Selected region of the 400 MHz NMR spectra of 2-chloro mandelic acid of various enantiomeric impurities in the presence of **5**.

roughly similar positions and contribute to the stabilization of these complexes. As shown in Figure 15, the π–π interaction may also play an important role in the chiral recognition of carboxylic acids containing an aromatic moiety. The main differences between the complexes of **5** with (*R*)- and (*S*)-mandelic acid are due to the relative orientations of the phenyl groups. In the minimum energy structure for the complex formed by (*S*)-mandelic acid, the aromatic ring of the guest is located in the proximity of the aromatic ring of the phthalimide, whereas the (*R*)-mandelic acid is located far from the aromatic groups of receptor **5** for the π–π interaction. From a comparison with the chemical shift non-equivalences of α-chiral carboxylic acids, it is clear that compared with ibuprofen and 2-chloro propionic acid, guests containing a hydroxy group attached to the stereogenic centre also exhibited better results, suggesting the formation of a hydrogen bond between the α-hydroxyl and the CSAs. It should be noted that, in many cases, the protons far from the stereogenic centre, such as CH_3 in α-hydroxy isovaleric or ibuprofen, can also be completely split in the presence of chiral compounds **2**–**5**. This may be due to the fact that there is a CH_3–π interaction[27] between the aromatic groups in the hosts and the methyl protons in the guests.

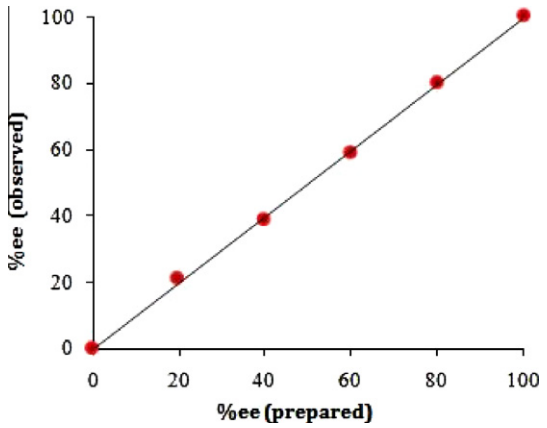


Figure 14. Correlation between prepared and observed ee values obtained by 400 MHz ^{1}H NMR titrations of enantiomerically enriched mixtures of 2-chloro mandelic acid using **5** as CSA in $CDCl_3$.

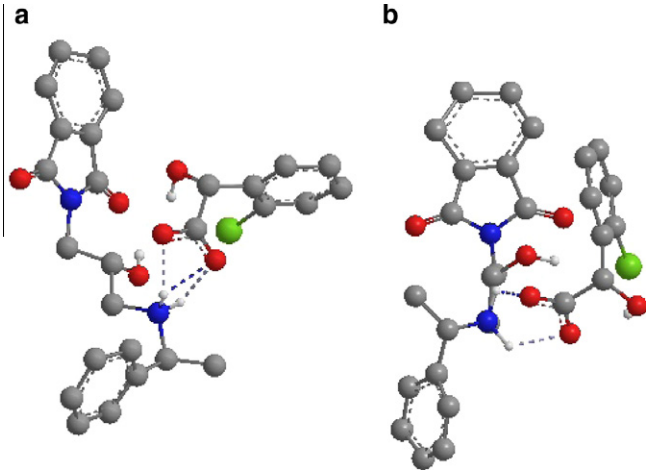


Figure 15. he minimum energy structures of **5** complexed with (a) (*R*)-2-chloro mandelic acid and (b) (*S*)-2-chloro mandelic acid.

3. Conclusion

In conclusion, chiral amino alcohols **2**–**5** have been synthesized conveniently and effectively. The ^{1}H NMR studies demonstrated that **2** and **5** were the best chiral solvating agents, and are effective in determining the enantiomeric excess of 2-chloro mandelic acid and the assignment of the absolute configuration of the corresponding carboxylic acids. Further studies of the chiral amino alcohols to allow asymmetric catalysis are currently in progress in our laboratory.

4. Experimental

4.1. General

Melting points were determined on an Electrothermal 9100 apparatus in a sealed capillary. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Varian 400 MHz spectrometer in $CDCl_3$. IR spectra were obtained on a Perkin Elmer FT-IR spectrum-100 FT-IR spectrometer using KBr pellets. Optical rotations were measured on an Atago AP-100 digital polarimeter. The HPLC measurements were carried out on Agilent 1100 equipment connected with a Zorbax RX-C18 column. Elemental analyses were performed using a Leco CHNS-932 analyzer.

Analytical TLC was performed using Merck prepared plates (Silica Gel 60 F254 on aluminium). Flash chromatography separations were performed on a Merck Silica Gel 60 (230–400 Mesh). All reactions, unless otherwise noted, were conducted under a nitrogen atmosphere. All starting materials and reagents used were of standard analytical grade from Fluka, Merck and Aldrich and used without further purification. Other commercial grade solvents were distilled, and then stored over molecular sieves. The drying agent employed was anhydrous $MgSO_4$.

4.2. Syntheses

4.2.1. General procedure for the synthesis of compounds 2–5

Compounds **2**–**5** were synthesized using a modified procedure originally reported by Roehrig et al.[28] To a cooled solution of (*R*)-(−)-*N*-(2,3-epoxypropyl)phthalimide **1** (102 mg, 0.50 mmol) in 10 mL of 2-propanol, amine or aminoalcohol (0.6 mmol, 1.2 equiv) in 10 mL of 2-propanol was added at 0 °C and stirred for 1 h. It was then refluxed for 8 h. After the completion of the reaction, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel ($CHCl_3$/MeOH 1:20 as eluent) to afford **2**–**5** as white crystals.

4.2.1.1. 2-[(2*R*)-2-Hydroxy-3-[[(1*R*)-2-hydroxy-1-phenyl-ethyl]-amino]propyl] isoindoline-1,3-dione 2. White solid, yield 83%, mp : 104–107 °C, $[\alpha]_D^{25} = +32$ (*c* 0.75, $CHCl_3$); IR (KBr): 3355, 1772, 1710, 1615 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 (dd, *J* = 3.2, 2.3 Hz, 2H, Ar*H*), 7.65 (dd, *J* = 2.9, 2.5 Hz, 2H, Ar*H*), 7.22 (m, 5H, Ar*H*), 3.94–3.91 (m, 1H, C*H*OH), 3.85–3.62 (m, 4H, NCH_2CH and ArCHCH_2), 3.53 (t, *J* = 8.6 Hz, 1H, ArC*H*CH$_2$), 2.60–2.49 (m, 5H, N*H* and O*H* and NHCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.0, 140.2, 134.4, 132.1, 128.9, 128.0, 127.4, 123.7, 69.0, 67.2, 64.9, 50.5, 42.2. Anal. Calcd for $C_{19}H_{20}N_2O_4$ (340.37): C, 67.23; H, 5.96; N, 8.24. Found: C, 67.41; H, 6.03; N, 8.19.

4.2.1.2. 2-[(2*R*)-2-Hydroxy-3-[[(1*R*,2*S*)-2-hydroxyindan-1-yl]-amino]propyl] isoindoline-1,3-dione 3. White solid; yield 93%; mp : 165–168 °C; $[\alpha]_D^{25} = +48$ (*c* 0.5, $CHCl_3$); IR (KBr): 3364, 1772, 1703, 1614 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.80 (dd, *J* = 5.5, 3.0 Hz, 2H, Ar*H*), 7.68 (dd, *J* = 5.5, 3.0 Hz, 2H, Ar*H*), 7.27–7.23 (m, 1H, Ar*H*), 7.18–7.12 (m, 3H, Ar*H*), 4.39 (td, *J* = 5.1, 2.5 Hz, 1H, NCH$_2$C*H*OH), 4.05–3.91 (m, 2H, NHC*H*CHOH and NHCHC*H*OH), 3.80 (dd, *J* = 5.6, 1.8 Hz, 2H, NCH_2CH), 2.97 (d, *J* = 5.1 Hz, 1H, CHCHCH_2CH), 2.91 (d, *J* = 2.4, 1H, CHCHCH_2CH), 2.86 (d, *J* = 5.8 Hz, 2H, CHCHCH_2NCH), 2.42–2.28 (m, 3H, N*H* and O*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.1, 142.3, 140.9, 134.5, 132.1, 128.3, 127.0, 125.8, 124.2, 123.8, 71.7, 69.9, 66.7, 52.2, 42.4, 39.9. Anal. Calcd for $C_{20}H_{20}N_2O_4$ (352.15): C, 68.24; H, 5.71; N, 7.92. Found: C, 68.31; H, 5.74; N, 7.96.

4.2.1.3. 2-[(2*R*)-2-Hydroxy-3-[[(1*R*)-1-(hydroxymethyl)propyl]-amino]propyl] isoindoline-1,3-dione 4. White solid; yield 73%; mp : 88–91 °C; $[\alpha]_D^{25} = -24$ (*c* 0.75, $CHCl_3$); IR (KBr): 3123, 1769, 1705, 1612 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.74 (dd, *J* = 2.9, 5.4 Hz, 2H, Ar*H*), 7.64 (dd, *J* = 2.9, 5.5 Hz, 2H, Ar*H*), 3.95–3.91 (m, 1H, NCH$_2$C*H*OH), 3.69 (tdd, *J* = 14.8, 10.7, 5.6 Hz, 2H, NCH_2CHOH), 3.59–3.53 (m, 4H, N*H*, O*H* and CHCH_2OH), 3.29 (dd, *J* = 6.8, 11.1 Hz, 1H, CHCH_2OH), 2.71–2.60 (m, 2H, NHCH_2CHOH), 2.49–2.46 (m, 1H, NHC*H*), 1.49–1.23 (m, 2H, CH_2CH$_3$), 0.82 (t, *J* = 7.5 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.7, 133.0, 130.9, 122.4, 67.3, 61.9, 59.7, 48.8, 40.9, 22.8, 9.3. Anal. Calcd for $C_{15}H_{20}N_2O_4$ (292.14): C, 61.62; H, 6.95; N, 9.55. Found: C, 61.69; H, 6.98; N, 9.63.

4.2.1.4. 2-[(2*R*)-2-Hydroxy-3-[[(1*S*)-1-phenylethyl]amino]propyl]-isoindoline-1,3-dione 5. White solid; yield 91%; mp : 103–106 °C; $[\alpha]_D^{25} = -16$ (*c* 1, $CHCl_3$); IR (KBr): 3348, 1767, 1708, 1615 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.77 (dd, *J* = 3.2;

2.3 Hz, 2H, Ar*H*), 7.64 (dd, *J* = 3.2; 2.3 Hz, 2H, Ar*H*), 7.25–7.12 (m, 5H, Ar*H*), 3.88–3.84 (m, 1H, NCH_2CHOH), 3.74–3.64 (m, 2H, NCH_2CH and $NCHCH_3$), 3.61 (dd, *J* = 5.1; 9.0 Hz, 1H, NCH_2CH), 2.58 (dd, *J* = 3.9; 8.6 Hz; 1H, $NHCH_2CH$), 2.37 (dd, *J* = 5.5; 7.0 Hz; 1H, $NHCH_2CH$), 2.22–2.06 (m, 2H, N*H* and O*H*), 1.29 (d, *J* = 6.6 Hz, 3H, $NHCHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.9, 145.3, 134.3, 132.2, 128.7, 127.2, 126.7, 123.6, 68.4, 58.4, 50.4, 42.1, 24.6. Anal. Calcd for $C_{19}H_{20}N_2O_3$ (324.37): C, 70.42; H, 6.23; N, 8.61. Found: C, 70.51; H, 6.25; N, 8.64.

4.3. NMR host–guest titrations

The guest compound was dissolved in an appropriate amount of solvent and the resulting solution evenly distributed between 14 NMR tubes. The first NMR tube was sealed without any host. The host compound was also dissolved in the appropriate amount of solvent and added in increasing amounts to the NMR tubes, so that solutions with the following relative amounts (equiv) of host versus guest compound (concentration was 10×10^{-3} M) were obtained: 0, 0.20, 0.40, 0.60, 0.80, 1.00, 1.20, 1.60, 2.00, 3.00, 4.00, 6.00, 8.00, 10.00 K_a were calculated by a non-linear least-squares fitting method for compounds **2**–**5** from the observed $\Delta\delta$ values and the respective host and guest concentrations.

4.4. Evaluation of the stoichiometric ratio of the host–guest complex (Job plots)

The stoichiometry of the complex between chiral hosts and enantiomers of carboxylic acids was determined by a continuous-variation plot (Job plot).[25] Equimolar amounts of host and guest compounds were dissolved in $CDCl_3$. These solutions were distributed among nine NMR tubes, with the molar fractions *X* of host and guest in the resulting solutions increasing (or decreased) from 0.1 to 0.9 (and vice versa). The complexation induced shifts ($\Delta\delta$) were multiplied by [H]/([H]+[G]) and plotted against [H]/([H]+[G]) itself.

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