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Roof shape amines: synthesis and application as NMR chiral solvating agents for discrimination of α-functionalized acids

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We wish to dedicate this paper to Professor Sukh Dev on the occasion of his 90th birthday

ABSTRACT

A series of new chiral roof shape amines have been prepared from anthracene involving simple chemical steps and enzymatic resolution of isomers. The amines were screened as chiral solvating agents for the discrimination of enantiomers of several α-functionalized acids by the ^{1}H NMR analysis. The system can also be used to accurately measure enantiomeric excess of mandelic acid by ^{1}H NMR analysis. The roof shape CSAs were capable of detecting the shift in the signals for the standard four nuclei of ^{1}H, ^{13}C, ^{19}F and ^{31}P of various optically active acids.

1. Introduction

The nature of the functionality and the shape of chiral molecules are important considerations for the design and applications of optically active compounds. These aspects play significant role in the molecular recognition and supramolecular interactions, the essential requirements for medicinal chemistry and asymmetric synthesis. Hence, it is a matter of interest for the contemporary organic chemists to design and synthesize structurally diverse novel chiral molecules. Weber introduced one such class of compounds with the concept of geometrically designed roof shape molecules.[1] The basic unit of these molecules, which resembles a roof of a house, is made up of functional groups protruding like antenna and a bulky skeleton similar to its foundation (Fig. 1). Some other compounds, such as iptycene,[2] triptycene,[3] pentiptycene[4] and molecular tweezers[5] have structural similarity and have found several useful applications, mostly as devices in material chemistry. Roof shape molecules possessing functional groups such as alcohol, amine, acid and acid derivatives have also found applications in medicinal chemistry,[6] as ligands in catalytic transformations,[7] as mediators in organocatalytic reactions[8] and in preparations of functional materials.[9] Two types of roof shape molecules are depicted as A and B in Fig. 1, which were prepared by Diels–Alder reaction of anthracene and suitable dienophile, acrylic acid or fumaric acid, respectively. Such molecules with acid as the functional group (Fg) or their reduced alcohol form, have been obtained as chirally pure isomers and studied for various applications.[10]

Importance of chiral molecules in different areas is now a well established fact and the subject of asymmetric synthesis is a universally acknowledged thrust area. Along with this growth there is increasing demand for simultaneous development of

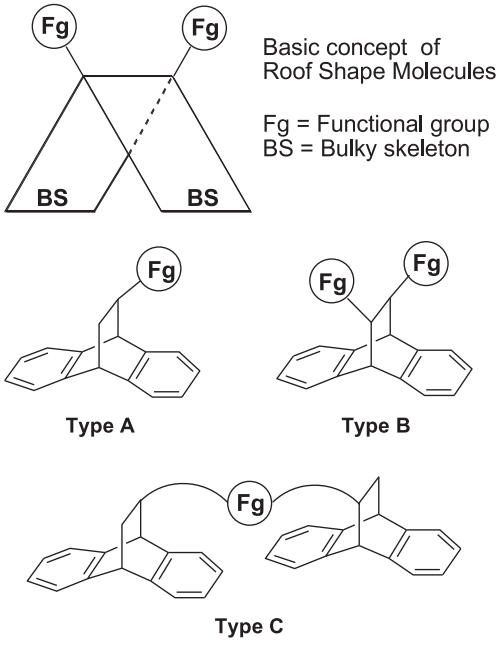

Fig. 1. Concept of roof shape molecules and proposed categories of amine derivatives.

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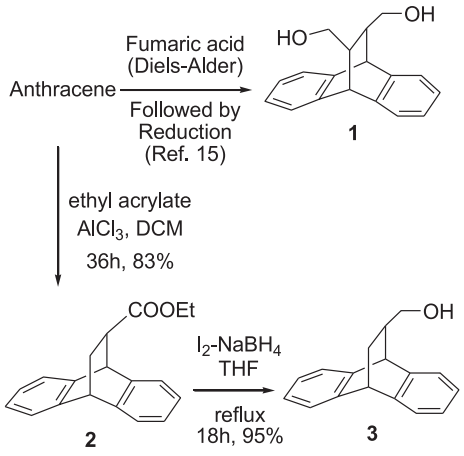
reliable and quick methods to determine optical purity of the chiral molecules. Usually the enantiomeric excess (ee) is confirmed by more than one analytical methods such as chromatography (GC or HPLC with chiral stationary phase), spectroscopy (NMR, CD), capillary electrophoresis, etc. Out of these techniques, ^{1}H NMR spectroscopy is quite effective in detail investigation of chiral purity of many molecules, particularly as the process of recording spectra is quite simple; it is non-destructive and suitable to study dynamic interactions. With the advent of NMR spectrometers most of the laboratories dealing with the chiral molecules have access to high-resolution machines for the quick analysis. The NMR spectra of the enantiomers display the same splitting pattern and chemical shifts, when recorded in achiral environment. However, the NMR active nuclei of diastereomeric compounds have slightly different environment and show significant change in the signals. Therefore, for accurate determination of the ratio of enantiomers by NMR spectroscopy, it is necessary to quantitatively convert the analyte to the diastereomers. This can be achieved by forming diastereomeric derivatives of the analyte with appropriate chiral derivatizing agents (CDAs), such as Mosher's acid,[11] involving a covalent bond. In another approach chiral solvating agents (CSAs)[12] can be mixed during the NMR analysis where they bind with the chiral analyte, temporarily creating in situ diastereomers and their ratio established by detecting signals. In the case of CSA due to the formation of diastereomers the signals split into two separate sets and can be easily measured. The latter technique has distinct advantages of simplicity, accuracy and it is non-destructive due to weak non-covalent interactions. Previously, the focus was on the use of chiral lanthanide shift reagents for determination of enantiomeric excess by NMR analysis. This technique involves the in situ formation of diastereomers of test sample (generally behaving as Lewis base) with externally added chiral lanthanide shift reagents (as Lewis acid). Besides the additional cost of these reagents, some operational difficulties such as its low solubility in NMR solvents and broadening of signals due to paramagnetic properties, the use of alternative CSAs have emerged as an attractive option. The intermolecular interactions including dipole–dipole, charge transfer, van der Waals, π–π stacking and formation of H-bonding, etc. were then exploited by many researchers in designing and preparing a series of molecules to act as CSA.[13] At the same time few chiral crown ethers have also been designed as effective CSAs where the interactions could be of different nature.[14]

2. Results and discussion

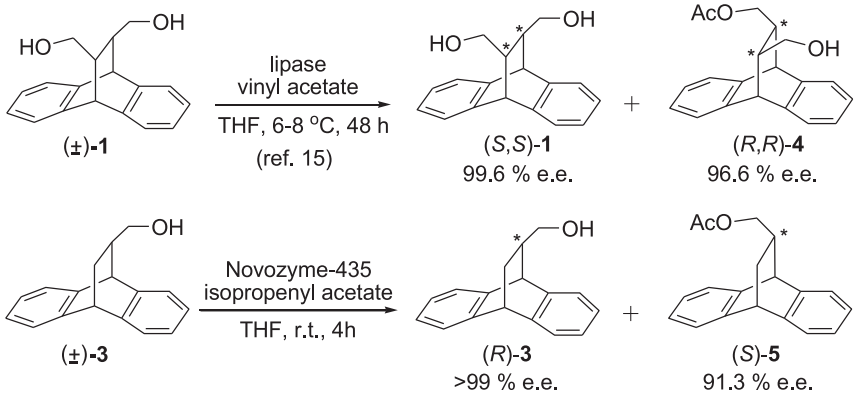
It is well established that the molecule of anthracene undergoes Diels–Alder reaction with suitable dienophile in the presence of a Lewis acid. In our ongoing work[15] we have explored this reaction to build roof shape molecules in non-racemic form and converted them to their functionalized derivatives. We have established efficient conditions for selective separation of the enantiomers of diol **1** by enzymatic transesterification, followed by their conversion to optically pure diamines. Synthesis of structurally analogous chiral roof shape molecules was also known in the literature.[16] In some cases the isomers of roof shape compounds have been resolved by fractional crystallization of their covalently bonded diastereomers.[17] In the present study we report the synthesis of chiral roof shape alcohols, their conversion to amines and their applications as chiral solvating agents (or complexing agents) for NMR discrimination.

Synthesis of the roof shape amines and diamines can be achieved via the alcohols or diols, which may intern be prepared by the Diels–Alder reaction of anthracene and unsaturated acid or ester. The cycloaddition reaction of anthracene and ethyl acrylate to furnish adduct **2**, was catalyzed by anhydrous aluminium chloride (Scheme 1). The ester was subsequently reduced with I_2–$NaBH_4$ method[18] to furnish roof shape alcohol **3**.



Scheme 1. Synthesis of roof shape diol **1** and alcohol **3**.

The diol **1** and the alcohol **3** were then resolved using enzymatic transesterification and suitable acyl donor under the appropriate conditions (Scheme 2).[15] The optimization of conditions for efficient separation of enantiomers of **3** was developed in the present work and is outlined in Table 1.



Scheme 2. Resolution of alcohol **3** and diol **1** by enzyme mediated acylation.

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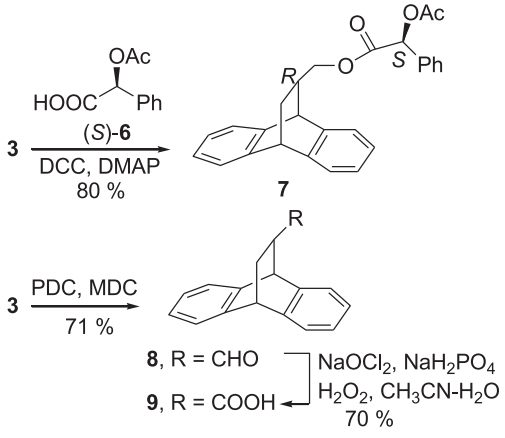
Table 1
Optimization of conditions for resolution of (±)-**3**[a]

No	Conditions	ee (%) of **3**	ee (%) of **5**	Conversion	*E* value
Steapsin lipase					
1	VA (1.5 equiv), THF 30 °C, 48 h	77	60	56	10
2	VA (1.5 equiv), THF 8–10 °C, 48 h	59	78	43	14
3	IPA (3.0 equiv), THF 30 °C, 100 h	29	61	32	6
4	VA (1.5 equiv), dioxane 30 °C, 48 h	16	80	16	11
Candida rugosa lipase					
5	VA (3.0 equiv), THF 30 °C, 96 h	4	26	13	2
Novozyme-435 lipase					
6	VA (1.0 equiv), DIPE 30 °C, 2 h	65	95	41	77
7	EA (5.0 equiv), DIPE 30 °C, 15 h	21	59	26	5
8	VA (1.0 equiv), THF 30 °C, 4 h	63	89	42	36
9	IPA (1.0 equiv), THF 30 °C, 4 h	>99	91	52	125
10	IPA (1.0 equiv), THF 8–10 °C, 6 h	85	74	53	17

VA=vinyl acetate; IPA=*iso*-propenyl acetate; EA=ethyl acetate.
[a] Ratio of (±)-**3** to enzyme: 1.0:1.3 (w/w) for entries 1 and 4; ratio of (±)-**3** to enzyme: 1.0:0.33 (w/w) for entries 5–10.

The absolute configuration of enantiomerically pure **3** was established by preparing its ester with optically pure *O*-acetyl mandelic acid.[19] The chirally pure alcohol **3** was converted to the diastereomerically pure ester **7** by its reaction with (*S*)-*O*-acetyl mandelic acid (Scheme 3). The single crystal X-ray diffraction analysis[20] of **7** clearly established the absolute configuration of the stereogenic carbon to be '*R*' (Fig. 2). The alcohol was also converted to the corresponding acid **9** of the known configuration, via the aldehyde **8** using mild oxidation reaction condition.[21] The absolute configuration was further confirmed by comparison of the sign of its specific rotation with the known data.[22]



Scheme 3. Determination of absolute configuration of (*R*)-**3**.

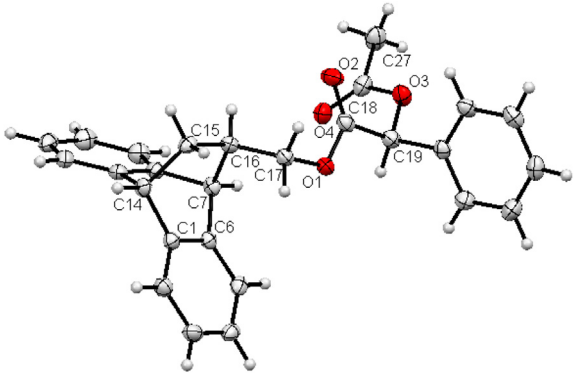


Fig. 2. ORTEP diagram of diastereomeric **7**.

The basic skeleton of the roof shape molecules offer two aromatic rings for possible π–π interaction with another system. The three dimensional bicyclic shape is also quite rigid to favour and control the intermolecular interactions and hence we have proposed to develop their amino derivatives for possible CSA applications. The optically pure diol (*S*,*S*)-**1** and alcohol (*R*)-**3** were converted to the corresponding diamines and amines[15] (Schemes 4 and 5). The chiral mono alcohol (*R*)-**3** accessed in the present work was converted to mono tosylate (*R*)-**10** and then to its mono bromo analogue (*R*)-**11** by standard conditions. The tosylate (*R*)-**10** was converted to the roof shape amines (*R*)-**13**, (*R*)-**14** and (*R*)-**15** by treatment with piperidine, piperazine and pyrrolidine, respectively.

Similar strategy was employed to prepare a set of diamines from the corresponding ditosylate (*S*,*S*)-**12** obtained from optically pure (*S*,*S*)-**1**. The three roof shape chirally pure diamines (*S*,*S*)-**16**, (*S*,*S*)-**17**, (*S*,*S*)-**18** and (*S*,*S*)-**19** were prepared by substitution with piperidine, morpholine, pyrrolidine and 1,2,3,4-tetrahydroisoquinoline, respectively (Scheme 5).

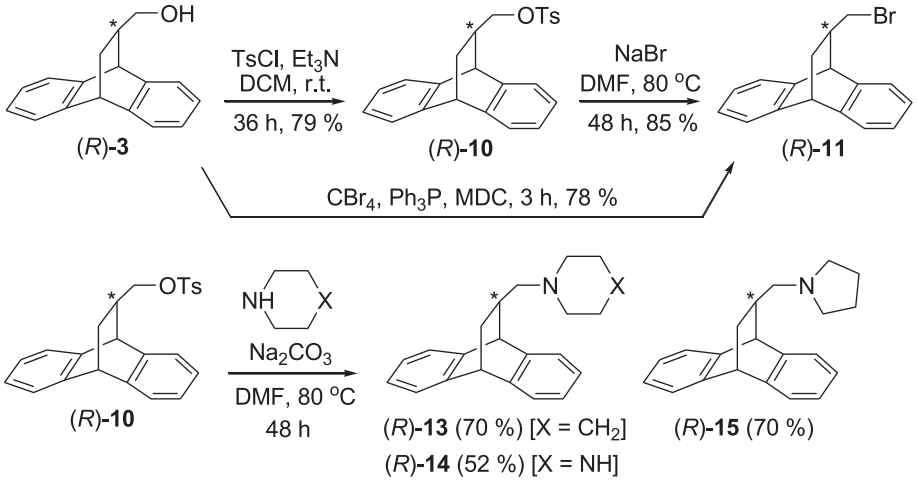
In order to study the effect of the rigid bicyclic frame with the two aromatic rings and the chiral centre, an analogous molecule was synthesized. The bromo derivative (*R*)-**11** was coupled with piperazine to obtain di-*N*-alkylated derivative (*R*,*R*)-**20**. All the roof shape chiral amines and diamines were characterized by usual spectroscopic and analytical techniques (Schemes 4–6).

The scope of the ability of optically pure roof shape amines to discriminate the chiral substrates such as α-substituted carboxylic acids was investigated by performing few NMR experiments at ambient conditions. The screening process was conducted with the racemic sample of mandelic acid **21** as the standard substrate with the amines or diamines and the results are presented schematically in Fig. 3 as well as the data is summarized in Table 2. The solution of (±)-**21** in $CDCl_3$ (20 mM) was mixed with the test amine (or diamine) whose solution is also prepared in the same solvent in the same concentration. The ^{1}H NMR of the mixture was recorded at 400 MHz at ambient conditions, the $C^{\alpha}H$ of (±)-**21** showed a slight shift towards the high field region. The induced chemical shift ($\Delta\delta$) was expressed in terms of the difference between the $C^{\alpha}H$ signal of (±)-**21** measured in $CDCl_3$ and the average of the separated signals of the two enantiomers, while the chemical shift non-equivalences ($\Delta\Delta\delta$) is the difference between the two resolved peaks.

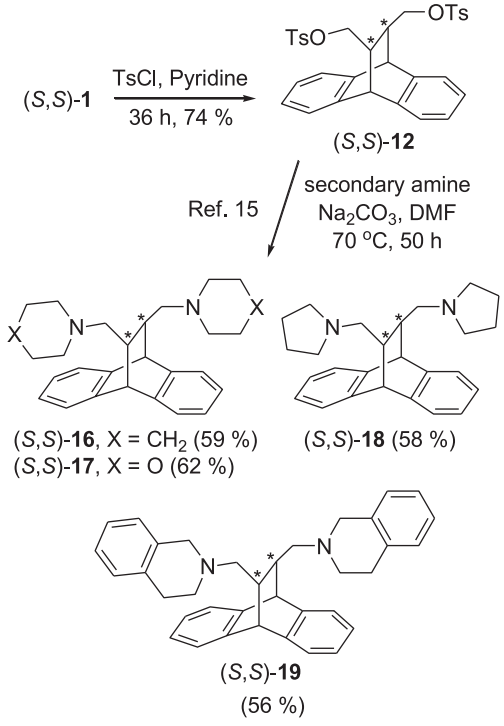
The effect of amines (*R*)-**13** to (*R*)-**15** on mandelic acid (±)-**21** was restricted mainly to the small shift of the $C^{\alpha}H$ signals to the upfield region but failed to resolve them significantly. However, addition of diamine (*S*,*S*)-**16** considerably enhanced the induced chemical shift of the $C^{\alpha}H$ signals to the upfield region but also caused a good separation of the signals. Similar but marginally lower resolution of the same signals was observed with morpholine derived diamine (*S*,*S*)-**17**. However, the pyrrolidine derived diamine (*S*,*S*)-**18** improved the separation to more extent. This may be attributed to the envelope like, slightly rigid form of the five-membered ring as against the other two six-membered chair-like conformations.

The effect of concentration on the ability of molecular recognition by the present CSAs was further investigated. The molar concentration of (*S*,*S*)-**18** and (±)-**21** was varied from 5.0 to 100.0 mM in $CDCl_3$, where the optimum values of chemical shift non-equivalences were observed at 20.0 mM, which were followed for all further experiments.

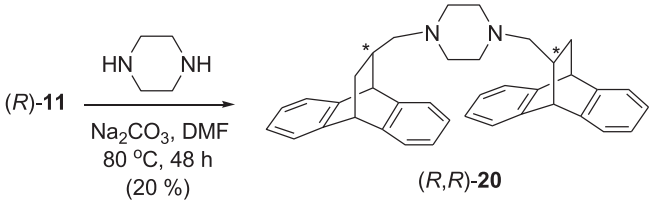
The roof shape amines, which show promise for (±)-**21** were then screened for few derivatives of mandelic acid to study the effect of substitution (Scheme 7). For most of the cases it was observed that the presence of electron withdrawing group (CF_3 or Br) showed enhanced degree of the shift of the signals as well as and the chemical shift non-equivalences compared to mandelic acid. In most of the cases of mandelic acid derivatives the diamines were more effective in causing discrimination between $C^{\alpha}H$ signals of the



Scheme 4. Conversion of optically pure alcohol **3** to amines.



Scheme 5. Synthesis of roof shape diamines from (*S*,*S*)-**1**.



Scheme 6. Synthesis of bis-amine of Type C.

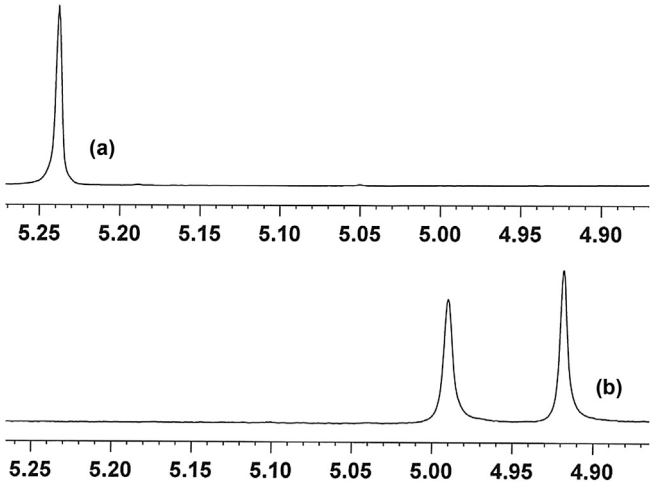


Fig. 3. Effect of the roof shape chiral amine on the $C^{\alpha}H$ of the racemic mandelic acid recorded at 20 mM, $CDCl_3$, 400 MHz, (a) pure (±)-**21**, (b) (±)-**21**+(*S*,*S*)-**18** (2:1).

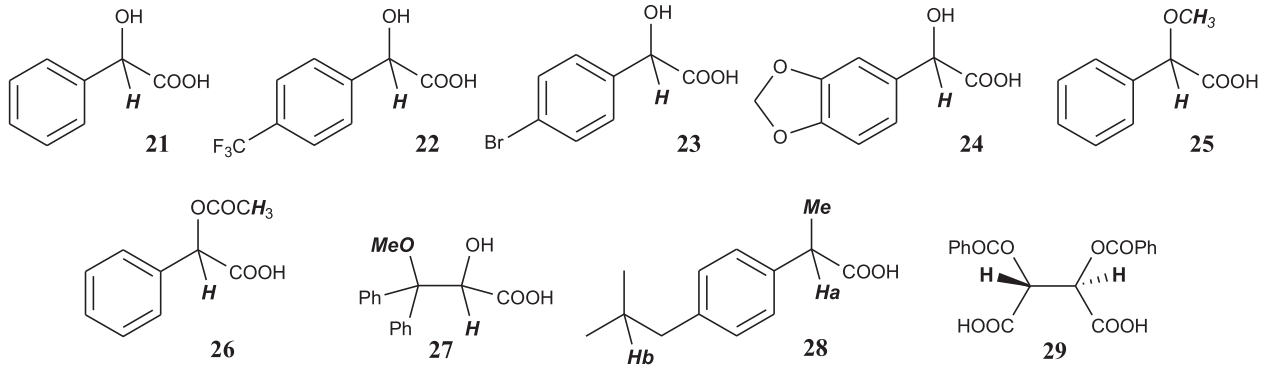
Table 2
Effect of the roof shape chiral amines and diamines on the α-proton of the racemic mandelic acid **21**. [Δδ=induced chemical shift[a]; ΔΔδ=chemical shift non-equivalences.]

No	Amine/diamine	Ratio of amine/diamine:**21**	Probe signal PhC*H*(OH)COOH	
			Δδ (ppm)	ΔΔδ (ppm)
1	(*R*)-**13**	1:1	−0.15	—[b]
2	(*R*)-**13**	2:1	−0.33	—[b]
3	(*R*)-**14**	1:1	−0.14	—[b]
4	(*R*)-**15**	1:1	−0.19	0.007
5	(*S*,*S*)-**16**	1:2	−0.26	0.056
6	(*S*,*S*)-**17**	1:2	−0.15	0.044
7	(*S*,*S*)-**18**	1:1	−0.21	0.032
8	(*S*,*S*)-**18**	1:2	−0.28	0.071
9	(*S*,*S*)-**19**	1:2	−0.21	0.024
10	(*R*,*R*)-**20**	1:1	−0.18	0.008

[a] The difference between the signals of **21** in $CDCl_3$ solution and the average of the signals of the two enantiomers after the addition of the amine or diamine.
[b] Not resolved.

two isomers, with the exception of (*R*)-**15**, (entries 1–8, Table 3). The CSA was also scanned for 2-(benzo[*d*][1,3]dioxol-6-yl)-2-hydroxyacetic acid **24**, where the amine (*S*,*S*)-**18** was found suitable (entry 4). It was noteworthy to observe the O–CH_2–O signals getting split into two sets of two doublets on complexation with (*S*,*S*)-**18** with coupling constant of 1.2 Hz.

Two derivatives of mandelic acid where the hydroxyl group is blocked by methyl ether in **25** and by acetyl ester in **26**, were scanned with CSA. Both the protons of methyl ether derivative **25**, i.e., $C^{\alpha}H$ and $C^{\alpha}OCH_3$ showed discrimination in ^{1}H NMR (entries 5



Scheme 7. List of α-functionalized acids tested with selected CSAs.

Table 3
Screening of amines and diamines as CSA for various α-substituted acids. [Δδ=induced chemical shift[a]; ΔΔδ=chemical shift non-equivalences.]

No	DL-Acid	CSA[b]	Probe signal *H* in bold (Scheme 7)	
			Δδ (ppm)	ΔΔδ (ppm)
1	**21**	(*S*,*S*)-**18**	−0.28	0.071
2	**22**	(*S*,*S*)-**18**	−0.36	0.058
3	**23**	(*S*,*S*)-**18**	−0.34	0.076
4	**24**	(*S*,*S*)-**18**	−0.28	0.040
5	**25**	(*S*,*S*)-**18**	−0.15	0.074 ($C^{\alpha}H$)
6	**25**	(*S*,*S*)-**18**	−0.07	0.063 ($C^{\alpha}OCH_3$)
7	**26**	(*S*,*S*)-**18**	−0.055	0.045 ($C^{\alpha}H$)
8	**26**	(*S*,*S*)-**18**	+0.007	0.004 ($COCH_3$)
9	**27**	(*R*)-**13**	−0.051	0.015 ($C^{\alpha}H$)
10	**27**	(*R*)-**13**	+0.043	0.008 ($C^{\beta}OCH_3$)
11	**28**	(*R*)-**13**	−0.012	0.011 ($C^{\alpha}CH_3$)
12	**28**	(*R*)-**15**	−0.015	0.007 ($C^{\alpha}CH_3$)
13	**28**	(*S*,*S*)-**16**	−0.011	0.007 (*Ha*)
14	**28**	(*R*)-**13**	−0.052	0.007 (*Ha*)
15	**28**	(*S*,*S*)-**16**	−0.062	0.007 (*Hb*)
16	**29**	(*S*,*S*)-**18**	Nil	0.043 ($C^{\alpha}H$)

[a] The difference between the signals of indicated *H* in $CDCl_3$ solution and the average of the signals of the two enantiomers after the addition of the amine or diamine.

[b] Ratio of acid/CSA was 2:1 (for entries 1–8, 13 and 15) and 1:1 (for entries 9–12, 14 and 16). All the experiments were run at 20 mM concentration.

and 6, Table 3). Similar results were observed for *O*-acetyl derivative **26** (entries 7 and 8, Table 3). This study will establish that our system detects discrimination of more than one sets of hydrogen in ^{1}H NMR analysis.

The CSA system was examined for the discrimination of signals of relatively bulky 2-hydroxy-3-methoxy-3,3-diphenyl propionic acid (±)-**27**, which is an intermediate for few pharmaceutical entities.[23] Signals of $C^{\alpha}H$ and C^{β}OMe (±)-**27** were noticed to have been affected by the complex formation between this racemic acid and the amines (entries 9 and 10, Table 3). Particularly, the two hydrogen signals of $C^{\alpha}H$ showed base line separation with (*S*,*S*)-**18**. The hydrogen from '*S*' isomer of **27** could be identified when a sample of non-racemic mixture (20% ee of '*S*-**27**') was analyzed, determining a defined control over the interactions.

The racemic sample of ibuprofen **28**, a widely used non-steroidal anti-inflammatory agent, was also analyzed for the chiral recognition with the synthesized roof shape amines. There are three hydrogens of the molecule of **28**, which showed shift on the recognition with the CSA. The $C^{\alpha}Me$ of **28** appeared as two doublets under the influence of (*R*)-**13** or (*R*)-**15** (entries 11 and 12, Table 3). The $C^{\alpha}Ha$ showed slightly more resolution with (*R*)-**13** compared with (*S*,*S*)-**18** as clearly eight lines were seen corresponding to the two separated quartets for the enantiomers (entries 13 and 14). It is significant to note that the proton present on the alkyl substituent on the aromatic ring of **28** also indicated discrimination. The methine proton (*CH*b of **28**), which should show a multiplet in ^{1}H NMR showed two sets of signals with CSA (entries 13–15). This observation is probably due to the *CH*b–π interaction between the methine proton and the aromatic ring of the CSA. We were also able to resolve the signals $C^{\alpha}H$ of tartaric acid derivative (**29**) with (*S*,*S*)-**18** (entry 16, Table 3).

The diastereomeric complex formation of the roof-shaped chiral receptor with carboxylic acid possibly occurs with a proton transfer. The formation of the carboxylate anion was confirmed when the carbonyl stretch (1716 cm^{-1} for mandelic acid) disappeared in the FTIR spectra of a mixture of (*S*,*S*-**18**)/(±)-**21** (1:1), and the observed intensities got stronger at 1615 and 1622 cm^{-1}(the COO^- stretch).[24] This may support the hypothesis that the binding of the carboxylate ion of the racemic acid with the chiral CSA may provide diastereomeric complex structure where the aromatic ring of the acid may lie over one of the aromatic rings of CSA by favouring a π–π interaction.

In continuation of our study of discrimination of signals of α-functionalized acid derivatives we further examined other nuclei, namely ^{13}C, ^{19}F and ^{31}P under the effect of CSA interactions. To the best of our knowledge not many CSAs have been effectively investigated in detecting all the four routinely targeted NMR active nuclei for such study, although individually their analysis is reported.[25]

The carbonyl carbon and $^{\alpha}$C of (±)-**22**, which are expected to show single peaks in ^{13}C NMR were observed in the presence of CSA (*S*,*S*)-**18**. The signals of carbonyl and $^{\alpha}$C appear as two well-separated peaks on treatment with CSA (Fig. 4).

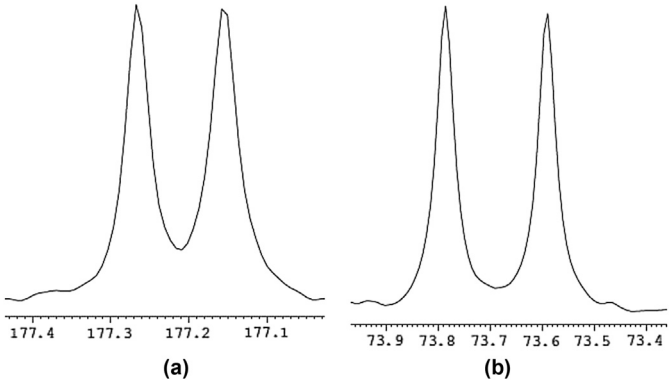


Fig. 4. (a) Carbonyl carbon of ^{13}C NMR of (±)-**22** with CSA [ΔΔδ=0.11 ppm]; (b) $^{\alpha}$C of ^{13}C NMR with CSA [ΔΔδ=0.20 ppm]; CSA=(*S*,*S*)-**18**; ratio of (±)-**22** to CSA (2:1).

The ^{19}F NMR of 4-trifluoromethyl mandelic acid (±)-**22** in presence of the CSA was then examined. Such approach was not very routinely investigated.[25a,25b] The ^{19}F NMR of (±)-**22** shows a sharp, single signal without any interference or overlap as in case of the ^{1}H NMR. The ^{19}F signal of (±)-**22** with (*S*,*S*)-**16** showed two well separated sharp signals ($\Delta\delta$=0.662 and $\Delta\Delta\delta$=0.054) corresponding to the two enantiomers of equal ratio (Fig. 5a).

biologically significant compounds and ligands for asymmetric synthesis also have phosphorous, we have extended our investigations to study ^{31}P NMR of such molecules. To assess the ability of our systems to recognize phosphorous containing acids we chose racemic sample of (±)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate **34** and studied its ^{31}P NMR (at 162 MHz in $CDCl_3$). The chiral molecule of acid **34** has recently been widely used in asym-

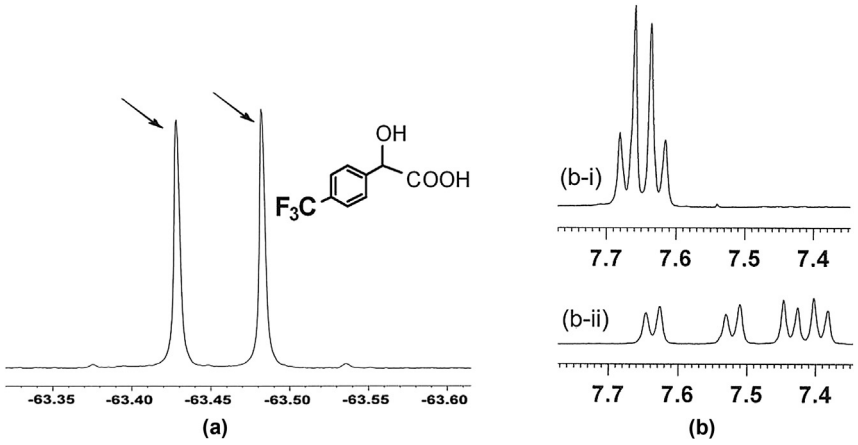


Fig. 5. (a) ^{19}F NMR spectrum (376 MHz) of (±)-**22** with (*S*,*S*)-**16** (2:1); (b) The Ar-H region of ^{1}H NMR of (±)-**22** without CSA (b-i); in presence of CSA (*S*,*S*)-**18** (2:1) (b-ii).

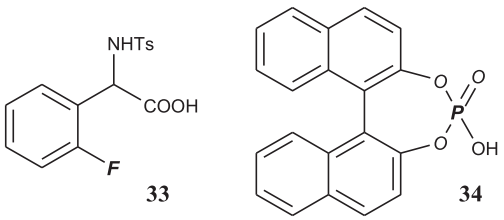
Interestingly the signals of the aromatic protons of (±)-**22** also exhibited considerable discrimination in ^{1}H NMR spectrum when recorded with the CSAs of Type-B. The three representative examples of CSA were investigated. The signals with (*S*,*S*)-**16** ($\Delta\delta$=−0.096 and $\Delta\Delta\delta$=0.197) and (*S*,*S*)-**17** ($\Delta\delta$=−0.082 and $\Delta\Delta\delta$=0.103) were slightly overlapping but with (*S*,*S*)-**18** a clear and complete separation for the two sets of signals (eight lines) were seen ($\Delta\delta$=−0.170 and $\Delta\Delta\delta$=0.202). The comparison of aromatic hydrogens without and with CSA (*S*,*S*)-**18** is presented in Fig. 5b.

Since the ^{19}F NMR is quite useful for quick and reliable analysis as the spectra have few signals, we examined our roof shape amines-based CSAs for (±)-**22**. In continuation of our observations the diamines were found to be more effective compared to the monoamine based CSA (Table 4).

Table 4
Screening of different CSAs for (±)-**22** to measure shift in ^{19}F NMR

No	CSA	$\Delta\Delta\delta$ (ppm)
1	(*S*,*S*)-**16**	0.054
2	(*S*,*S*)-**17**	0.039
3	(*S*,*S*)-**18**	0.052
4	(*R*)-**15**	0.010

We also examined the ^{19}F NMR of an amino acid derivative **33** (Scheme 8) with (*S*,*S*)-**18** where the fluorine showed two sets of signals with considerable separation. The chemical shift non-equivalence $\Delta\Delta\delta$ was recorded to be 0.017 ppm. Since many



Scheme 8. Chiral acids with other nuclei for NMR detection.

metric transformations and hence it is important to develop a reliable method to quickly determine its optical purity.[26] To the best of our information only few CSAs work efficiently[13i] for such detection because the chemical shift difference was generally not found sufficiently large for the base line separation of the signals in ^{31}P NMR.[27] Hence, we examined our most effective CSA (*S*,*S*)-**18** for the discrimination of the signal of phosphorous of the racemic sample of **34** and found very good resolution. In order to assign the configuration to the signals we scanned a non-racemic sample of **34** (2:1 for *R* isomer) with optically pure (*S*,*S*)-**16** and (*S*,*S*)-**18** and detected a good separation of signals (Fig. 6b and c), though with monoamine (*R*)-**15**, slightly less separation was observed (Fig. 6d). In both the systems the separation of isomers was very clear and can be quantitatively measured. Consistently good separation of signals for ^{31}P NMR with different CSAs was observed (Table 5) confirming the generality of our system.

Determination of the optical purity of natural and unnatural α-amino acids and their derivatives is of prime importance since they are used for the synthesis of many pharmacologically active molecules. In order to develop a facile method of determining optical purity by NMR analysis, several CSAs have been recently screened.[28] The present set of CSAs was further explored to check the discrimination of the protons located at different positions of the N-Ts derivative of α-amino acid such as phenyl glycine (Fig. 7). It is often seen that the region of ^{1}H NMR spectrum where the differentiation is observed is overlapped with the area covering the signals of CSA. The analysis will be more accurate if it is confirmed by checking the ratio of more than one protons of the sample. Hence it is more useful to examine different signals, which shift on the addition of CSA for more effective analysis of the analyte. For this study the more consistently effective diamine based CSAs (*S*,*S*)-**16**, (*S*,*S*)-**17** and (*S*,*S*)-**18** were screened to examine chiral recognition of **30** and to examine shift of its protons. In order to correlate the signals with the two enantiomers of **30** a sample of N-Ts phenyl glycine was prepared by mixing its D and L isomers in a fix ratio (2:1).

Firstly the methyl protons of the N-Ts moiety of **30** were observed with the three different CSAs in the molar ratio of 2:1 (**30**/CSA) (Fig. 8a). The single unresolved signal at δ 2.39 ppm of **30**

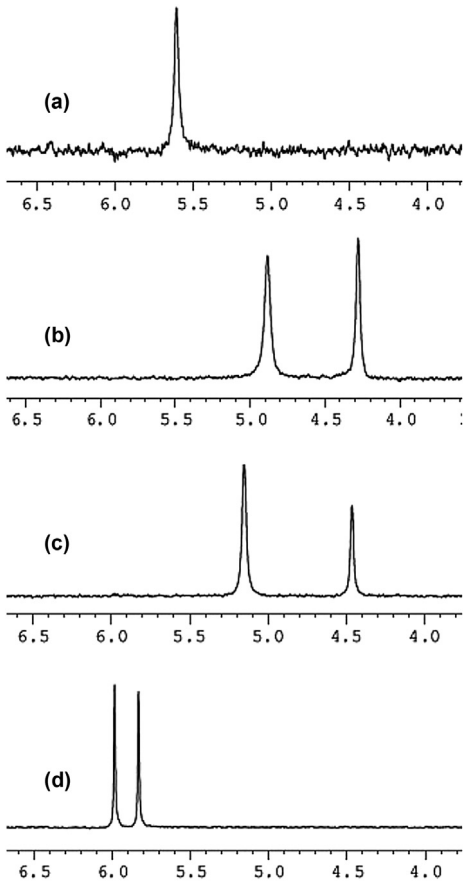


Fig. 6. ^{31}P NMR spectrum (174 MHz) of (±)-**34** with: blank (a), with (*S*,*S*)-**16** (2:1) (b), (*S*,*S*)-**18** (2:1) (c) and with (*R*)-**15** (1:1) (d).

Table 5
Screening of different CSAs for (±)-**34** to measure shift in ^{31}P NMR

No	CSA	Δδ (ppm)	ΔΔδ (ppm)
1	(*S*,*S*)-**16**	−1.01	0.60
2	(*S*,*S*)-**18**	−0.79.	0.69
3	(*R*)-**15**	+0.30	0.15

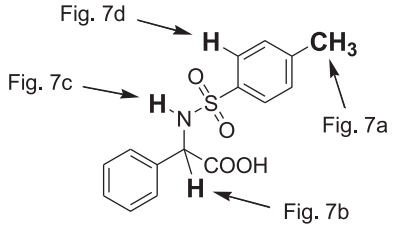


Fig. 7. Selected protons of *N*-tosyl phenyl glycine **30** resolved with CSA.

shifted upfield with all the three CSAs, but most effective separation was observed with pyrrolidine derived (*S*,*S*)-**18** (Δδ=−0.11 and ΔΔδ=0.029). It is noteworthy to observe such pronounced effect on the methyl protons, which are located far away from the chiral centre of α-amino acid.

In comparison, the $C^{\alpha}H$ directly attached to the chiral centre observed a significant shift for (*S*,*S*)-**18** (Δδ=−0.39 and ΔΔδ=0.048) and for the piperidine derived (*S*,*S*)-**16** (Δδ=−0.36 and ΔΔδ=0.036) (Fig. 8b). It is interesting to see a small shift in the pattern for morpholine derived (*S*,*S*)-**17** (Δδ=−0.24 and ΔΔδ=0.038) probably the presence of oxygen atom of the CSA is responsible for this deviation. The upfield shift of the $C^{\alpha}H$ proton in all the cases is consistent due to the deprotonation of the acid group as the shielding effect is more in case of carboxylate ion.

In the next set of study we observed the shifting of the position of the signal of N–H hydrogen on addition of CSA (Fig. 8c). These are the only signals, which move to downfield region indicating stronger intramolecular hydrogen bond with carboxylate as compared to carboxylic acid in the absence of CSA.[29] In this case all the three CSAs showed more or less same effect.

The structure of the CSA for the present study was designed in such a way as to offer a three-dimensional motif and present an aromatic plane for the effective π–π interaction with the analyte. Due to this interaction we expect some shift in the signals of the aromatic protons of (±)-**30**. Although the protons *meta* to the SO_2N group of N-Ts were merged with the aromatic signals of the CSAs, the protons *ortho* to SO_2N group appeared separately at the downfield region and were quite suitable for this study. These protons appeared as a doublet and as the most downfield, well resolved signal of the spectra. The same set of CSAs was scanned for these protons and results clearly indicate resolution of the two doublets for the two isomers of **30** (Fig. 8d). Since these protons are not attached to any electronegative atoms there was no significant shift (Δδ) but reasonable base line separation of the signal was observed for (*S*,*S*)-**16** and (*S*,*S*)-**18**, with substantial chemical shift non-equivalences (ΔΔδ=0.063 and 0.064).

Further exploration of application of CSA for other amino acids, such as N-Ts alanine **31** and N-Ts phenyl alanine **32**, revealed that the presence of a rigid π-system is required for effective interaction. Both these showed lesser degree of discrimination compared to N-Ts phenyl glycine **30** for all the four protons under study. In both the cases signals of methyl protons of Ts group showed discrimination with (*S*,*S*)-**18** similar to N-Ts phenyl glycine. While the aromatic protons of Ts moiety of **32** showed discrimination with (*S*,*S*)-**18**, the corresponding protons of **31** did not resolve, probably due to the lack of π–π interaction in alanine.

The stoichiometry of the complex formed between (*S*,*S*)-**18** and mandelic acid (*S*)-**21** was determined according to Job's method of continuous variations.[30] Equimolar solutions of (*S*,*S*)-**18** and (*S*)-**21** were prepared in $CDCl_3$ (20 mM, 5 mL) for this study. These solutions were distributed among 13 NMR tubes in such a way that the mole fractions (*X*) of (*S*,*S*)-**18** and (*S*)-**21** in the resulting solutions increased from 0·1 to 0·9. The complexation induced shifts of the methine signal (Δδ) were multiplied by the mole fraction of the acid ((*S*)-**21**) and plotted against *X* to obtain the Job's plot, which showed a maxima at 0.67 (Fig. 9). This indicates that (*S*,*S*)-**18** and the (*S*)-**21** bind in a 1:2 complex under these conditions.

Further information about the nature of the complex between CSA (*S*,*S*)-**16** and mandelic acid (±)-**21** was obtained by performing 2D NOESY experiment (Fig. 10). Analysis of the spectra clearly showed cross peak between protons of C3–C4–C3 methylenes of piperidine ring of (*S*,*S*)-**16** with $C^{\alpha}H$ of (±)-**21** and its aromatic protons. This assumption is supported by our observation when these CSAs failed to recognise α-chloro propionic acid, where there is no π–π interaction. These observations support the tightly held acid–base interaction between the roof-shaped diamines and carboxylic acid. We have also observed the role of free –OH or –NH group attached at the stereogenic centre of the α-functionalized acids for effective binding. The OAc derivative of mandelic acid, PhCH(OAc)COOH (**26**), was tested with (*S*,*S*)-**18**, and the ^{1}H NMR showed lesser degree of chemical shift non-equivalences (ΔΔδ=0.045 for **26** and 0.071 for **21**). Compared to this the α-methoxy derivative of mandelic acid **25** showed slightly better values[13q] (ΔΔδ=0.074), probably due to marginal increase in its acidity and hence electrostatic interactions.

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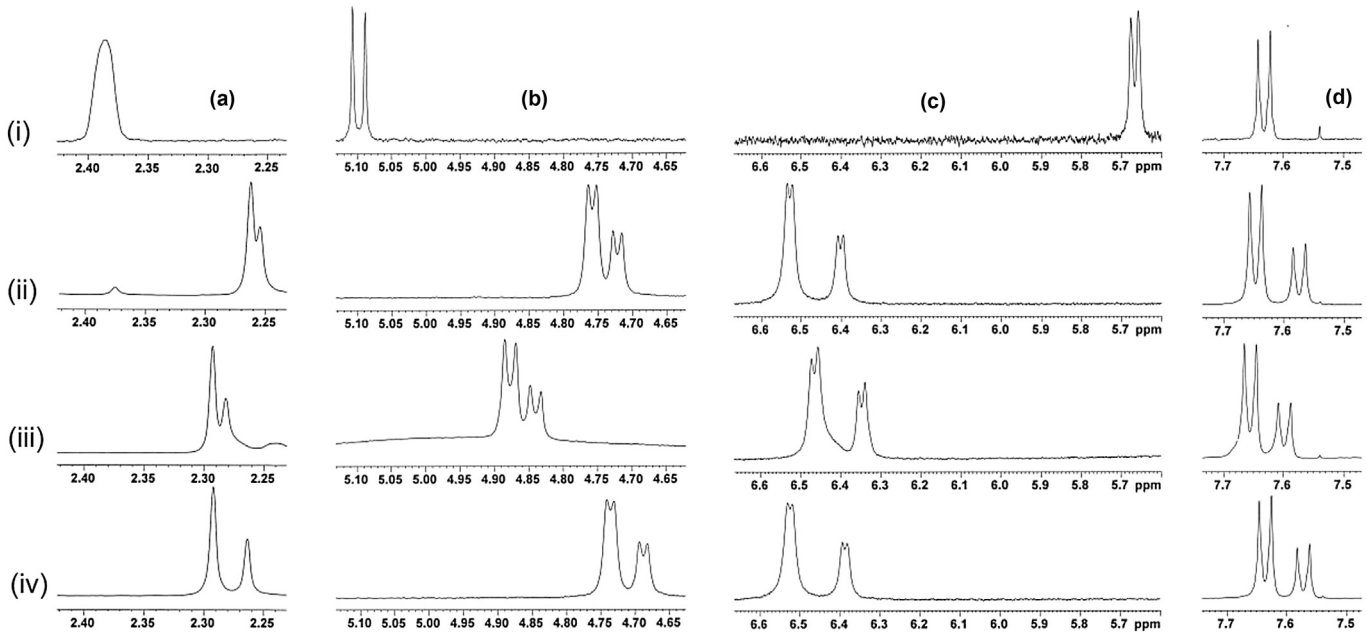

Fig. 8. ^{1}H NMR spectra of **30** with three CSAs: (7a) signal for CH_3 of **30** with (i) blank, (ii) (*S*,*S*)-**16**, (iii) (*S*,*S*)-**17** and (iv) (*S*,*S*)-**18**; (7b) signal of $C^{\alpha}H$ of **30** (D/L=2:1) with (i) blank, (ii) (*S*,*S*)-**16**, (iii) (*S*,*S*)-**17** and (iv) (*S*,*S*)-**18**; (7c) signal of N–*H* of **30** (D/L=2:1) with (i) blank, (ii) (*S*,*S*)-**16**, (iii) (*S*,*S*)-**17** and (iv) (*S*,*S*)-**18**; (7d) signal of Ar-*H* of **30** (D/L=2:1) with (i) blank, (ii) (*S*,*S*)-**16**, (iii) (*S*,*S*)-**17** and (iv) (*S*,*S*)-**18**.

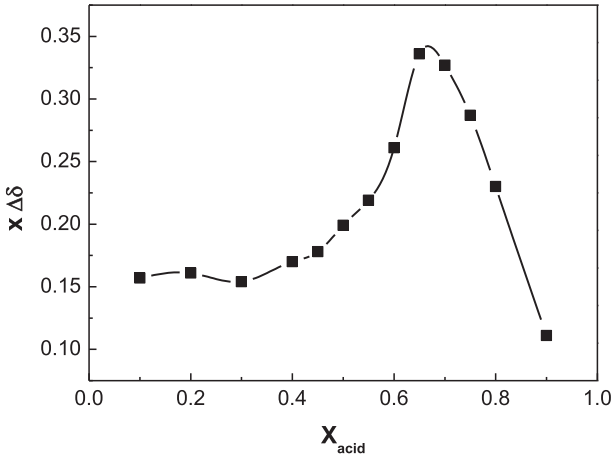

Fig. 9. Job plot for (*S*,*S*)-**18** with (*S*)-**21**.

To demonstrate practical utility of the present CSAs for the quantitative determination of enantiomeric excess (ee) of the unknown sample of mandelic acid we performed controlled experiment. A set of samples of known ee (optical purity) of mandelic acid with 0, 20, 40, 60, 80 and 95% ee, respectively, were prepared. These samples were analysed with 0.5 equiv of (*S*,*S*)-**16** by recording their ^{1}H NMR. The experimental results were in accordance with the theoretical values as can be seen from Fig. 11.

3. Conclusion

Thus in the present work we have synthesized a series of novel chiral roof shape amines and diamines and explored their utility as chiral solvating agents for discrimination of enantiomers of several α-functionalized acids. We have screened a number of different α-functionalities and studied their correlation with the ability of discrimination, in some cases we have noted four different types of hydrogen being affected in the ^{1}H NMR. We have also recorded the recognition by employing other NMR active nuclei ^{13}C, ^{19}F, ^{31}P to determine the CSA efficiency of the chiral roof shape amines. Conditions were also standardized for quantitative determination of the ratio of enantiomers in the controlled experiment, which opens up possibilities for this technique to be used for determination of ee of unknown sample.

4. Experimental section

Thin layer chromatography was performed on silica gel plates quoted on aluminium sheets. The spots were visualized under UV light or with iodine vapour. All the compounds were purified by column chromatography on silica gel (60–120 mesh) and neutral alumina. All reactions were carried out under an inert atmosphere (nitrogen) unless other conditions are specified. NMR Spectra were recorded on Bruker Avance 400 Spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, 376 MHz for ^{19}F NMR and 162 MHz for ^{31}P NMR) with $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on Thermo-Fischer DSQ II GC–MS instrument. IR spectra were recorded on a Perkin–Elmer FTIR RXI spectrometer as KBr pellets. Elemental analysis was recorded on Perkin–Elmer EA2400 series II CHNS/O analyzer. Melting points were recorded in Thiele's tube using paraffin oil and are uncorrected. Specific optical rotations were measured on JACSO P-2000 polarimeter. For the HPLC analysis Chiralcel OD-H and Chiralpak IC column were used.

For the synthesis of compounds **2**, **3** and ligands (*S*,*S*)-**16** to (*S*,*S*)-**19**, see Supplementary data.[15]

4.1. General procedure for resolution of alcohol 3

To a solution of racemic alcohol (**3**) (0.30 g, 1.27 mmol) in dry THF (5 mL), lipase (0.10 g, 33% w/w, Novozyme-435) and *iso*-propenyl acetate (0.13 mL, 1.27 mmol) were added and the reaction mixture was stirred for 4 h at 30 °C. The material was filtered and the filtrate was concentrated in vacuum. Separation was carried out by column chromatography over silica gel using ethyl acetate and petroleum ether as the eluent. The acetate was eluted with 10%

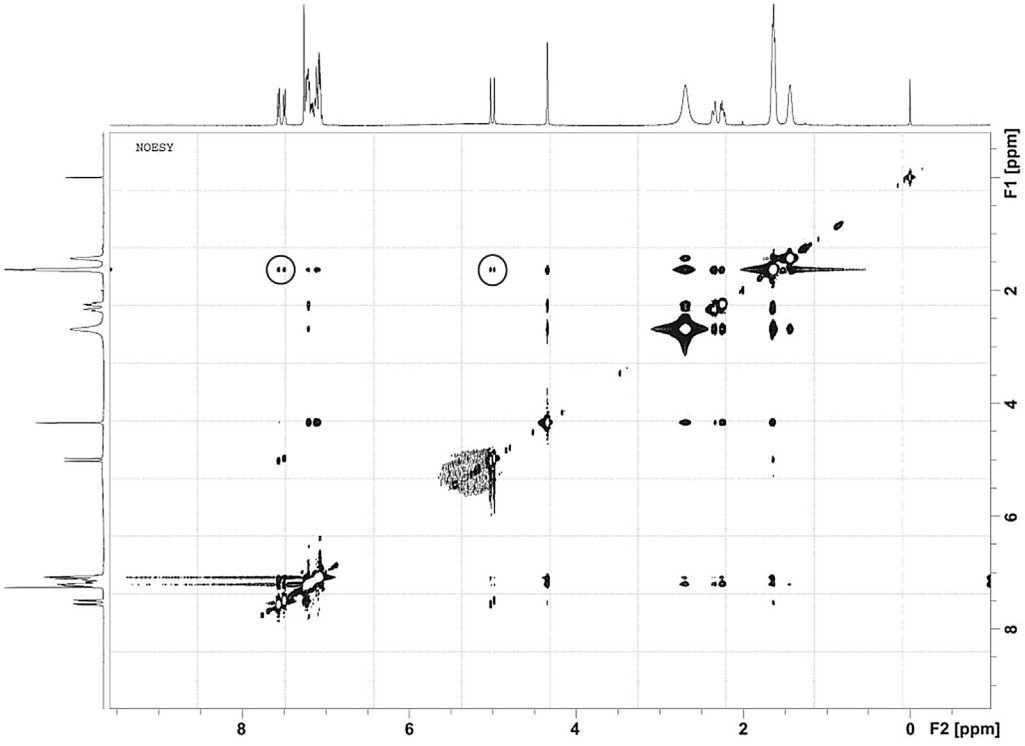

Fig. 10. 2D NOESY spectra of (*S*,*S*)-**16** with (±)-**21** (1:1 ratio at 20 mM solution in $CDCl_3$).

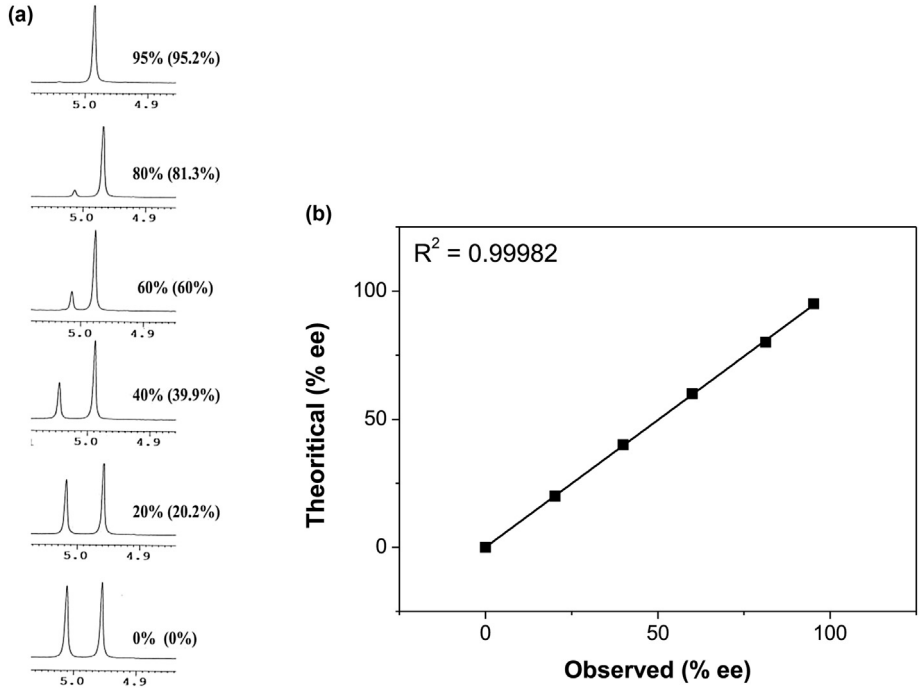

Fig. 11. (a) Select region of ^{1}H NMR spectra of (±)-**21** of various ratios of optical purity in presence of (*S*,*S*)-**16**. Values in parenthesis are observed purity. (b) Correlation between theoretical and observed ee values.

ethyl acetate/petroleum ether [R_f 0.5] (and alcohol [R_f 0.3]) with 20% ethyl acetate/petroleum ether (0.131 g, 43.5%). $[\alpha]_D^{28}$ 3.6 (*c* 0.7, methanol). HPLC condition: Chiralcel OD-H column, 10% *iso*-propanol in hexane, flow=0.7 mL/min, UV=215 nm, retention time=14.28 min for (*R*)-isomer, 17.64 min for (*S*)-isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04–1.09 (ddd, *J*=12.0, 4.8, 2.8 Hz, 1H), 1.90–1.96 (m, 1H), 2.12–2.19 (m, 1H), 2.94–2.99 (dd, *J*=10.4, 9.6 Hz, 1H), 3.32–3.36 (dd, *J*=10.4, 5.6 Hz, 1H), 4.25–4.27 (t, *J*=2.8 Hz, 1H), 4.41–4.42 (d, *J*=2.0 Hz, 1H), 7.03–7.13 (m, 4H), 7.22–7.30 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.0, 40.9, 44.0,

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45.5, 66.1, 123.2, 123.5, 123.6, 125.4, 125.6, 125.7 (2C), 126.0, 140.5, 143.8 (2C), 143.9. Mass (EI): 236 (28), 202 (26), 179 (56), 178 (100), 176(8). IR (KBr): ν 3433, 3069, 2945, 1637, 1461, 1370, 1333, 1166, 1026, 935, 750, 554 cm^{-1}.

4.2. 9,10-Dihydro-9,10-ethanoanthracene-11-acetate (*S*)-5

Yield 0.185 g, 52%, mp=119–120 °C, (lit.[31] = 119 °C) $[\alpha]_D^{28}$ 4.3 (*c* 0.7, methanol).

HPLC condition: Chiralpak IC column, 1% *iso*-propanol in hexane, flow=0.5 mL/min, UV=210 nm, retention time 19.4 min (*R*), min 20.4 min (*S*).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13–1.18 (ddd, *J*=12.4, 4.8, 2.4 Hz, 1H), 1.90–2.03 (m, 1H), 2.11 (s, 3H), 2.26–2.32 (m, 1H), 3.40–3.45 (dd, *J*=10.8, 9.8 Hz, 1H), 3.79–3.83 (dd, *J*=11.2, 6.4 Hz, 1H), 4.29–4.30 (t, *J*=2.4 Hz, 1H), 4.32–4.33 (d, *J*=2.0 Hz, 1H), 7.09–7.16 (m, 4H), 7.25–7.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.0, 31.2, 37.4, 43.8, 45.8, 67.3, 123.2, 123.5, 123.6, 125.5, 125.7, 125.8, 125.9, 126.2, 139.4, 143.4, 143.5, 143.6, 171.0. Mass (EI): 278 (1), 202 (2), 179 (15), 178 (100). IR (KBr) cm^{-1}: 3068, 3022, 2920, 1737, 1461, 1362, 1236, 1035, 951, 754. Anal.: found C 81.83, H 6.57; required $C_{19}H_{18}O_2$: C 81.99, H 6.52.

4.3. (*S*)-((11*R*)-9,10-Dihydro-9,10-ethanoanthracene-11-yl) methyl 2-acetoxy-phenylacetate 7

Alcohol (*R*)-**3** (0.40 g, 1.7 mmol), DCC (0.350 g, 1.7 mmol) and DMAP (0.020 g 0.17 mmol) were placed in two-necked flask under nitrogen atmosphere, were dissolved in dry dichloromethane (10 mL) and cooled to 0 °C. A solution of (+)-*O*-acyl mandelic acid (*S*-**6**) (0.33 g, 1.7 mmol) in dichloromethane (5 mL) was then added drop wise. The reaction mixture was stirred at 0 °C for 1 h after, which it was allowed to warm to room temperature and stirred for another 14 h. Then whole reaction mixture was passed through Celite bed, washed with dichloromethane and purified by column chromatography over silica gel [R_f 0.7] (10% ethyl acetate/petroleum ether) affording white solid (0.56 g, 80%) mp=97–98 °C $[\alpha]_D^{28}$ 63.2 (*c* 0.5, chloroform).

^{1}H NMR (400 MHz, $CDCl_3$): 1.01–1.06 (ddd, *J*=12.4, 4.8, 2.4 Hz, 1H), 1.84–1.90 (m, 1H), 2.22 (m, 4H), 3.39–3.45 (t, *J*=10.4 Hz, 1H), 3.75–3.79 (dd, *J*=6.0, 5.6 Hz, 1H), 3.95–3.96 (d, *J*=2.4 Hz, 1H), 4.19–4.21 (t, *J*=2.4 Hz, 1H), 5.96 (s, 1H), 6.73–6.75 (d, *J*=7.2 Hz, 1H), 6.95–6.99 (td, *J*=7.6, 1.2 Hz) 7.03–7.09 (m, 3H), 7.15–7.22 (m, 3H), 7.44–7.50 (m, 3H), 7.54–7.56 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 30.7, 37.2, 43.7, 45.3, 68.0, 74.4, 123.1, 123.5, 123.6, 125.3, 125.7, 125.8, 125.9, 126.1, 127.8 (2C), 128.9 (2C), 129.5, 134.1, 139.5, 143.1, 143.3, 143.5, 168.6, 170.4. Mass (EI): 412 (4), 219 (4), 203 (7), 202 (4), 179 (94) 178 (100). IR: ν 3067, 3020, 2951, 1744, 1461, 1373, 1334, 1245, 1048, 971, 746, 699 cm^{-1}. Anal.: found C 78.35, H 6.22; required $C_{27}H_{24}O_4$: C 78.62, H 5.86.

4.4. 9,10-Dihydro-9,10-ethanoanthracene-11-carbaldehyde (*R*)-8

To a solution of alcohol (*R*)-**3** (0.30 g, 1.27 mmol) in dry dichloromethane (10 mL) under nitrogen atmosphere was added PDC (2.4 g, 6.35 mmol) and mixture was stirred vigorously at room temperature (6 h). The reaction mixture was diluted with diethyl ether (30 mL) and passed through Celite. The solvent was removed under reduced pressure and the crude product was purified by short column chromatography over silica gel [R_f 0.65] (5% ethyl acetate/petroleum ether) affording white solid. Yield 0.225 g, 75%, mp=112 °C (lit.[32]=112–113 °C) $[\alpha]_D^{28}$ −13.4 (*c* 1, chloroform).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96–2.02 (m, 1H), 2.08–2.13 (m, 1H), 2.75–2.80 (m, 1H), 4.39–4.41 (t, *J*=2.4 Hz, 1H), 4.68–4.69 (d, *J*=2.4 Hz, 1H) 7.08–7.14 (m, 4H), 7.25–7.33 (m, 4H), 9.41–9.42 (d, *J*=1.6 Hz, 1H). Mass (EI): 233 (9), 202 (12), 178 (72), 177 (100). IR (KBr): ν 3069, 3021, 2949, 2813, 2710, 1714, 1457, 1390, 1234, 1023, 758 cm^{-1}.

4.5. 9,10-Dihydroethanoanthracene-11-carboxylic acid (*R*)-9

A solution of $NaClO_2$ (0.23 g, 2.05 mmol, 80% purity) in water (3 mL) was added drop wise to a stirred solution of aldehyde (*R*)-**8** (0.400 g, 1.7 mmol) in acetonitrile (3 mL), NaH_2PO_4 (0.07 g 0.59 mmol) in water (3 mL) and H_2O_2, (30%, 11.8 mmol, 0.21 mL) kept in ice bath (5–10 °C), and stirred for 3 h. A small amount of Na_2SO_3 (about 0.025 g) was added to destroy the unused HOCl and H_2O_2. Acidification with aqueous HCl (10%) afforded off white solid (0.30 g, 70%). Mp=188 °C (lit.[1a]=189 °C). $[\alpha]_D^{28}$ −7.3 (*c* 2, chloroform), lit.[22] $[\alpha]_D^{20}$ +7.2 (*c* 2, chloroform).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98–2.04 (m, 1H), 2.09–2.14 (ddd, *J*=12.8, 5.2, 2.8 Hz, 1H), 2.88–2.93 (dd, *J*=10.4, 4.8 Hz, 1H) 4.34–4.35 (t, *J*=6.4 Hz, 1H), 4.68–4.76 (d, *J*=2.4 Hz), 7.08–7.24 (m, 4H), 7.26–7.32 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.5, 43.7, 43.9, 46.5, 123.3, 123.5, 123.7, 125.0, 125.8 (2C), 126.2, 126.3, 139.6, 142.3, 143.8, 143.7, 179.0. Mass (EI): 250 (4), 202 (6), 179 (91), 178 (100). IR (KBr): ν 3311, 3024, 2972, 1706, 1459, 1403, 1230, 1124, 936, 761, 599 cm^{-1}.

4.6. 9,10-Dihydro-9,10-ethanoanthracene-11 (4-methylbenzenesulfonate) (*R*)-10

To a solution of (*R*)-**3** (1.0 g, 4.24 mmol) in dry dichloromethane (10 mL), triethyl amine (1.71 g, 16.94 mmol) was added under nitrogen atmosphere at 0 °C. Then *p*-toluenesulfonyl chloride (1.0 g, 5.29 mmol) was added in portion wise to the reaction. The solution was stirred for 24 h at room temperature. The reaction mixture was poured into cold water (50 mL) and extracted with dichloromethane (2×50 mL). The organic phase was concentrated under vacuum, which was purified by column chromatography over silica gel [R_f 0.6] (10% ethyl acetate/petroleum ether) affording white solid (1.3 g, 79%). Mp=146–147 °C (lit.[33]=148–150 °C) $[\alpha]_D^{28}$ 5.8 (*c* 1, chloroform).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94–0.99 (ddd, *J*=12.8, 4.8, 2.4 Hz, 1H), 1.90–1.97 (m, 1H), 2.30–2.33 (m, 1H), 2.49 (s, 3H), 3.22–3.27 (dd, *J*=10.4, 9.6 Hz, 1H), 3.74–3.78 (dd, *J*=9.6, 5.2 Hz, 1H), 4.23–4.24 (t, *J*=2.8 Hz, 1H), 4.32–4.33 (d, *J*=2.4 Hz, 1H), 6.96–6.97 (m, 2H), 7.10–7.12 (m, 2H), 7.19–7.28 (m, 4H), 7.37–7.37 (d, *J*=1.2 Hz, 2H), 7.79–7.98 (d, *J*=1.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 30.6, 37.5, 43.5, 44.9, 72.5, 123.1, 123.5, 123.8, 125.6, 125.7, 125.9, 126.0, 126.2, 128.0 (2C), 129.9 (2C), 132.9, 139.2, 142.9, 143.3, 143.4, 144.9. Mass (EI): 390 (1), 202 (2), 180 (1), 178 (100), 176 (4), 152 (1). IR (KBr): ν 3070, 2953, 2917, 2862, 2359, 1364, 1177, 713 cm^{-1}. Anal.: found C 73.66, H 5.62; required $C_{24}H_{22}O_3S$: C 73.82, H 5.68.

4.7. 9,10-Dihydro-9,10-ethanoanthracene-11-(bromomethyl) (*R*)-11

To a solution of alcohol (*R*)-**3** (0.40 g, 1.70 mmol) in dichloromethane (5 mL) under nitrogen atmosphere, was added CBr_4 (0.71 g, 2.13 mmol) and the mixture was stirred vigorously at room temperature for 15 min. The mixture was cooled down to 0 °C and Ph_3P (0.67 g, 2.56 mmol) was added. Then reaction mixture was stirred for 3 h at room temperature. The solvent was distilled off under reduced pressure and material was further purified by column chromatography over silica gel [R_f 0.75] (100% petroleum ether) affording white solid (0.38 g, 73%).

Mp=136 °C (lit.[34]=138 °C), $[\alpha]_D^{28}$ 27.7 (*c* 1, chloroform).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18–1.23 (ddd, *J*=12.8, 3.6, 2.8 Hz, 1H), 2.06–2.13 (m, 1H), 2.33–2.41 (m, 1H), 2.80–2.85 (t, *J*=10.0 Hz, 1H), 3.09–3.13 (dd, *J*=9.6, 6.4 Hz, 1H), 4.29–4.30 (t, *J*=2.8 Hz, 1H),

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4.50–4.51 (d, J=2.4 Hz, 1H), 7.11–7.19 (m, 4H), 7.27–7.37 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.8, 38.0, 41.0, 41.1, 47.1, 123.3, 123.4, 123.8, 125.6, 125.8, 126.0, 126.3, 139.5, 143.3, 143.5. Mass (EI): 301 (4), 299 (6), 218 (5), 178 (100). IR (KBr): ν 3036, 2938, 1456, 1286, 1228, 1022, 758, 643, 551 cm^{-1}.

4.8. 1-[(9,10-Dihydro-9,10-ethanoanthracen-11-yl)methyl]piperidine (*R*)-13

A mixture of (*R*)-**10** (0.40 g, 1.02 mmol), piperidine (0.43 g, 5.2 mmol) and Na_2CO_3 (0.54 g, 5.12 mmol) was heated at 80 °C in dry DMF (5 mL) under nitrogen atmosphere for 48 h. The reaction mixture was quenched with water and extracted with ethyl acetate (3×75 mL). The organic extract was washed with water and dried over anhydrous sodium sulfate. The crude product was purified by column chromatography over neutral alumina [R_f 0.33, 20% ethyl acetate/petroleum ether, silica gel plate] (2% ethyl acetate–petroleum ether) affording white solid. (0.22 g, 70%) mp=145 °C, $[\alpha]_D^{28}$ −3.7 (*c* 0.5, chloroform).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14–1.43 (br signal, 2H), 1.55–1.60 (m, 4H), 1.80–1.87 (m, 4H), 1.92–1.95 (m, 1H), 2.12–2.32 (br signal, 5H), 4.25–4.26 (t, J=2.4 Hz, 1H), 4.36–4.37 (d, J=2.4 Hz, 1H), 7.07–7.14 (m, 4H), 7.23–7.32 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.6, 26.1, 33.4, 35.8, 44.3, 47.2, 54.9, 64.6, 122.9, 122.9, 123.3, 123.4, 125.3, 125.5, 125.6, 125.6, 141.1, 143.9, 144.0, 145.5. Mass (EI): 304 (3), 303 (10), 203 (3), 178 (15), 98 (100). IR (KBr): ν 3066, 3020, 2932, 2800, 1454, 1377, 1330, 1214, 1154, 1125, 1095, 1005, 755 cm^{-1}. Anal.: found C 87.0, H 8.15, N 5.10; required $C_{22}H_{25}N$: C 87.08, H 8.30, N 4.62.

4.9. 1-[(9,10-Dihydro-9,10-ethanoanthracen-11-yl)methyl] piperazine (*R*)-14

Prepared by the method similar to the one described above. [R_f 0.3, 30% ethyl acetate/petroleum ether]. Off white solid: 0.162 g (52%) mp=181–182 °C, $[\alpha]_D^{28}$ 8.4 (*c* 1, chloroform).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14–1.16 (m, 1H), 1.89–2.01 (m, 3H), 2.10 (br signal, 1H), 2.56–2.72 (br signal, 4H), 3.30–3.31 (t, J=4.8 Hz, 4H), 4.27–4.28 (t, J=2.4 Hz, 1H), 4.30–4.31 (d, J=2.4 Hz, 1H), 7.10–7.26 (m, 4H), 7.27–7.29 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.7, 35.8, 44.0, 44.1, 46.5, 49.9, 123.2, 123.4, 125.3, 125.5, 125.6, 125.8, 125.9, 140.5, 143.7, 143.7, 143.8. Mass (EI): 304 (100), 261 (10), 219 (5), 202 (11), 178 (40). IR (KBr): ν 3021, 2950, 2816, 1605, 1457, 1288, 1174, 1094, 1044, 933, 753 cm^{-1}. Anal.: found C 82.65, H 7.67, N 9.45; required $C_{21}H_{24}N_2$: C 82.85, H 7.95, N, 9.20.

4.10. 1-[(9,10-Dihydro-9,10-ethanoanthracen-11-yl)methyl] pyrrolidine (*R*)-15

[R_f 0.4; 30% ethyl acetate/petroleum ether]. White solid (0.218 g, 74%): mp=121–122 °C, $[\alpha]_D^{28}$ −5.6 (*c* 1, chloroform).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22–1.26 (m, 1H), 1.76–1.79 (m, 4H), 1.92–2.04 (m, 3H), 2.11–2.17 (m, 2H), 2.40–2.47 (m, 4H), 4.26–4.28 (t, J=2.4 Hz, 1H), 4.36–4.37 (d, J=1.2 Hz, 1H), 7.10–7.14 (m, 4H), 7.25–7.32 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 33.4, 37.6, 44.3, 47.3, 54.5, 62.1, 122.9, 123.4 (2C), 125.4, 125.5, 125.6, 125.7, 140.9, 143.8, 143.9, 144.0, 144.5.

Mass (EI): 289 (27), 288 (36), 256 (22), 178 (14), 84 (100). IR (KBr): ν 3002, 2974, 2935, 2974, 2785, 1458, 1234, 758 cm^{-1}. Anal.: found C 87.18, H 8.15, N 4.82; required $C_{22}H_{25}N$: C 87.15, H 8.04, N 4.84.

4.11. 1,4-Bis (11*R*)-(9,10-dihydro-9,10-ethanoanthracene-11-yl) methyl)piperazine (*R*,*R*)-20

A mixture of (*R*)-**11** (0.25 g, 0.836 mmol), (*R*)-**14** (0.38 g, 1.25 mmol) and Na_2CO_3 (0.58 g, 4.18 mmol) was heated at 80 °C in dry DMF (5 mL) under nitrogen atmosphere for 48 h. The reaction mixture was quenched with water and extracted with ethyl acetate (3×75 mL). The organic extract was washed with water and dried over anhydrous sodium sulfate. The crude product was purified by column chromatography over neutral alumina [R_f 0.6, 20% ethyl acetate/petroleum ether, silica gel TLC] (10% ethyl acetate/petroleum ether) affording white solid (0.09 g, 20%). Mp=160–162 °C, $[\alpha]_D^{28}$ 10.8 (*c* 0.5, chloroform).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15–1.19 (ddd, J=12.4, 4.4, 2.4 Hz, 1H), 1.87–1.97 (m, 3H), 2.13 (s, 1H), 2.14–2.31 (br signal, 4H), 4.25–4.26 (t, J=2.4 Hz, 1H), 4.34–4.35 (d, J=1.2 Hz, 1H), 7.07–7.13 (m, 4H), 7.26–7.29 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.2, 35.6, 44.2, 46.2, 53.4, 63.7, 123.0, 123.3, 123.4, 125.4, 125.5, 125.5 (2C), 125.7, 140.9, 143.9 (2C), 144.4.

Mass (EI): 522 (12), 423 (10), 345 (10), 343 (43), 204 (13), 178 (100). IR (KBr): ν 3007, 3022, 2931, 1468, 1332, 1240, 1138, 1010, 819, 752 cm^{-1}. Anal.: found C 87.21, H 7.46, N 5.55; required $C_{38}H_{38}N_2$: C 87.31, H 7.33, N 5.36.

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Supplementary data

Details of the crystal structure analysis, synthesis of some ligands, the copies of spectra, HPLC charts, etc. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.05.001.

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