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PAPER

Simple and efficient methods for discrimination of chiral diacids and chiral alpha-methyl amines†

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The three-component chiral derivatization protocols have been developed for ^{1}H, ^{13}C and ^{19}F NMR spectroscopic discrimination of chiral diacids by their coordination and self-assembly with optically active (*R*)-α-methylbenzylamine and 2-formylphenylboronic acid or 3-fluoro-2-formylmethylboronic acid. These protocols yield a mixture of diastereomeric imino-boronate esters which are identified by the well-resolved diastereotopic peaks with significant chemical shift differences ranging up to 0.6 and 2.1 ppm in their corresponding ^{1}H and ^{19}F NMR spectra, without any racemization or kinetic resolution, thereby enabling the determination of enantiopurity. A protocol has also been developed for discrimination of chiral alpha-methyl amines, using optically pure *trans*-1,2-cyclohexanedicarboxylic acid in combination with 2-formylphenylboronic acid or 3-fluoro-2-fluoromethylboronic acid. The proposed strategies have been demonstrated on large number of chiral diacids and chiral alpha-methyl amines.

Introduction

The majority of bioorganic and pharmaceutical drug molecules are chiral.[1] Consequently the differentiation of enantiomers and the measurement of excess of one form over the other are important not only in pharmaceutical applications but also in chiral synthesis, catalysis, kinetics, geochronology, biochemistry and medicine.[2] Several analytical techniques are available for enantiomer discrimination, such as Nuclear Magnetic Resonance (NMR), Circular Dichroism (CD) and HPLC.[3] NMR spectroscopy, though an excellent technique, fails to discriminate the enantiomers in the commonly employed achiral NMR solvents owing to the fact that the resonances of enantiomers are isochronous. On the other hand conversion of substrates into a pair of diastereomers enables visualization of enantiomers, which is accomplished by the utilization of any one of the chiral auxiliaries, such as, chiral derivatizing agents (CDAs), chiral solvating agents (CSAs) or chiral lanthanide shift reagents (CLSRs)[4] (classical approach). The identifiable NMR peaks detected for diastereomeric species enables the determination of the enantiomeric excess of the substrates by the direct measurement of their integral areas. In the classical approach, the enantiomer resolution is achieved by the addition of chiral auxiliary to the racemic mixture. In such situations, problems are encountered when the separation of the discriminated NMR peaks is small or non-existent.

In the present study we have developed a simple three-component derivatization protocol, a combinatorial approach, which involves stirring of ternary mixture for a minute and utilization of the resulting complex for the discrimination of chiral diacids and alpha-methyl amines. These protocols are highly versatile, inexpensive, easily synthesizable and have advantages over many existing reagents. The potential utilization of these derivatization protocols is demonstrated by ^{1}H, ^{19}F and ^{13}C-NMR spectroscopy.

Experimental section

The reagents 2-formylphenylboronic acid, 3-fluoro-2-formylphenylboronic acid, *R*-α-methylbenzylamine, diacids **1–10** (Table 1), alpha-methyl amines **1–8** (Table 2), methanol-d_4 and chloroform-d of highest purity were purchased. All the reagents were taken in a round bottom flask. 100 mg of 2-formylphenylboronic acid was transferred to the round-bottom flask. To this 2 ml of methanol-d_4 was added to the reaction vessel using a glass syringe fitted with a disposable needle. The mixture was stirred using a Teflon coated magnetic stirrer. To this 80 mg of (*R*)-α-methylbenzylamine and 112 mg of chiral diacid were added and transferred to the round-bottomed flask. The mixture was stirred again for 5 min. Aliquot (0.5 ml) of the reaction mixture was transferred to the NMR tube. A similar procedure was repeated for discrimination of chiral diacids by ^{19}F NMR, where 3-fluoro-2-formylphenyl boronic acid was used instead 2-formylphenylboronic acid. The ^{13}C NMR spectra were also

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Table 1 The ^{1}H and $^{19}F\{^{1}H\}$ chemical shift differences between diasteromers measured at 400.13 MHz and 376.5 MHz respectively for racemic mixtures of **1–5** and **6–10**

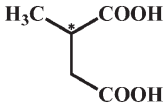
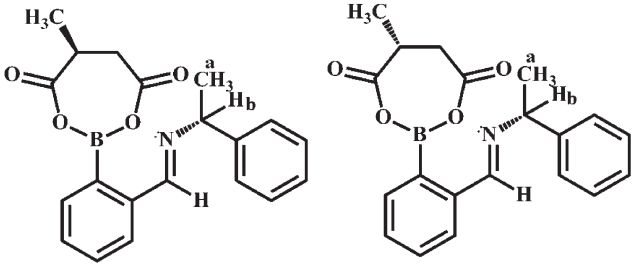
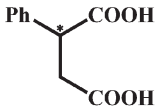
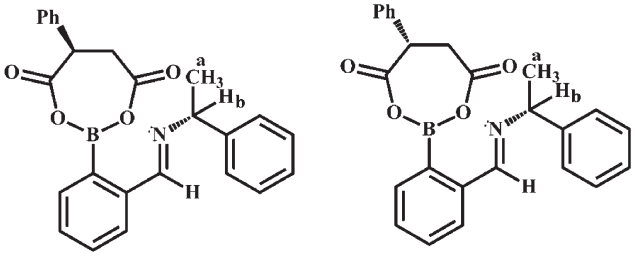
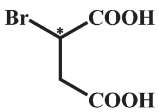
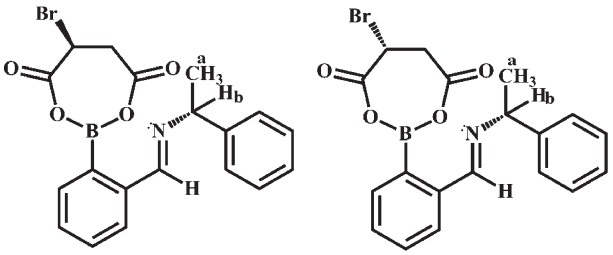
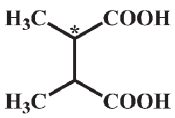
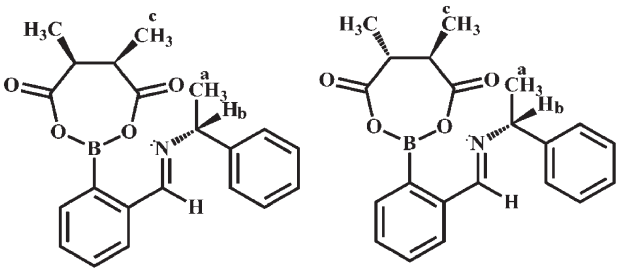
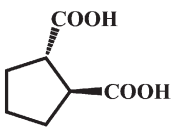
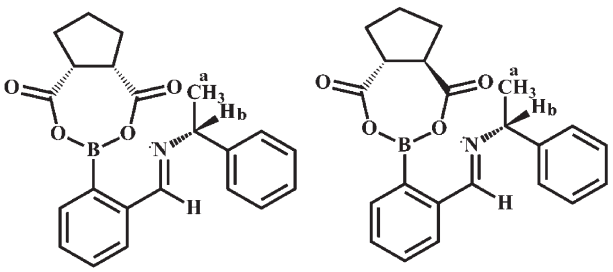
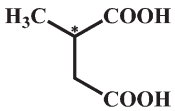
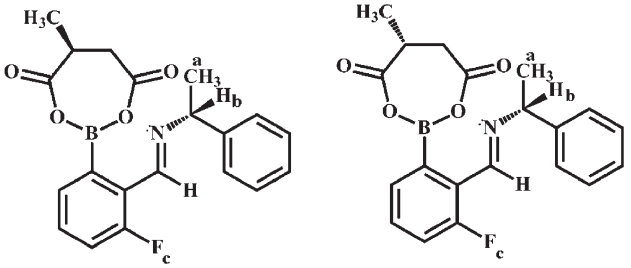
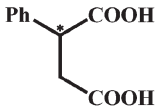
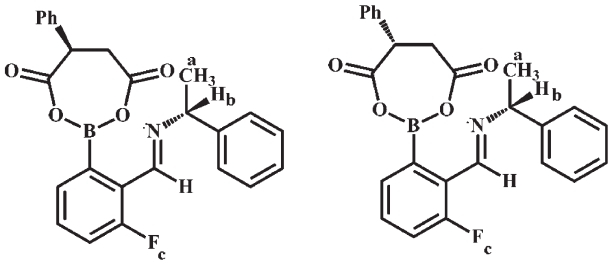
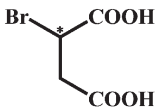
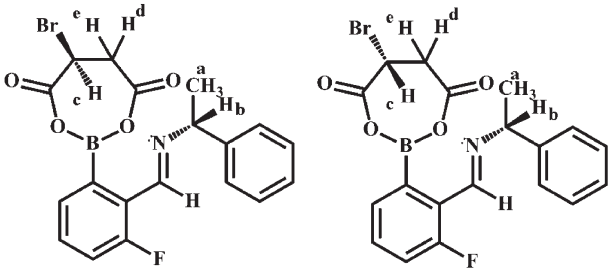
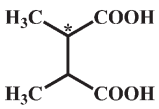
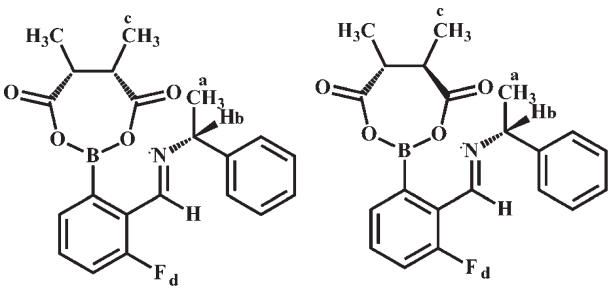
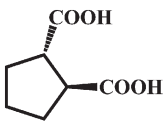
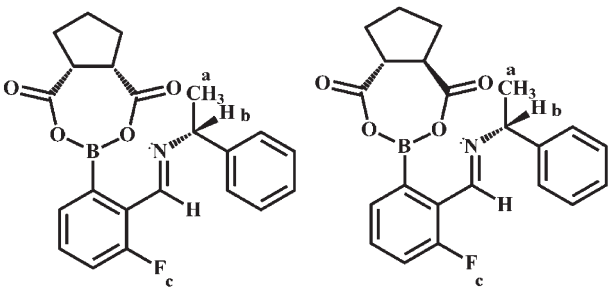
Entry	Chiral diacids	Diacid diastereoisomeric imino-boronate esters	Chemical shift difference $(\Delta\delta)^{R/S}$ in ppm
1.			0.58 (a) 0.60 (b)
2.			0.16 (a) 0.62 (b)
3.			0.15 (a) 0.60 (b)
4.			0.08 (a) 0.16 (b) 0.60 (c)
5.			0.15 (a) 0.60 (b)
6.			0.59 (a) 0.64 (b) 1.24 (c)

Table 1 *(Contd.)*

Entry	Chiral diacids	Diacid diastereoisomeric imino-boronate esters	Chemical shift difference $(\Delta\delta)^{R/S}$ in ppm
7.			0.16 (a) 0.62 (b) 1.23 (c)
8.			0.17 (a) 0.62 (b) 0.20 (c) 0.40 (d) 0.61 (e)
9.			0.09 (a) 0.16 (b) 0.60 (c) 2.40 (d)
10.			0.17 (a) 0.63 (b) 1.42 (c)

Discriminated protons and fluorine sites are marked in the respective figures.

recorded for all the molecules. As far as testing the enantiopurity of alpha-methyl amines is concerned, a similar procedure was adopted and the ^{1}H, ^{13}C and ^{19}F spectra of all the investigated molecules were employed. All the ^{1}H, $^{19}F\{^{1}H\}$ and $^{13}C\{^{1}H\}$ spectra were recorded at 400.13, 376.5 and 100.6 MHz respectively on a Bruker NMR spectrometer and the resonance peaks of ^{1}H and ^{13}C spectra were referenced with respect to TMS (0.00 ppm).

Results and discussion

Discrimination of diacids

Chiral carboxylic acid is an important functionality present in natural products, biological molecules, metabolic intermediates, and pharmaceuticals. Increase in demand for chiral carboxylic acids has resulted in the need for simple, easy to use, cheap, and reliable methods for the determination of enantiomeric purity of chiral compounds.[5] In recent years, many chiral shift reagents, such as amines, diamines, amides and macrocyclic compounds have been developed for NMR spectroscopic determination of enantiomeric excess (ee) of carboxylic acids.[6] Although the amine or amide based chiral solvating agents can give rise to comparatively large chemical shift differences between the diastereomeric species, the preparation of such reagents usually require multistep synthesis, thereby limiting their practical applicability.[6] Since it is almost impossible to have a reaction with 100% yield, the problem of kinetic resolution persists. Consequently the enantiomer separation methods utilized for the measurement of enantiomeric excess have always been

Table 2 The ^{1}H and $^{19}F\{^{1}H\}$ chemical shift differences between diasteromers measured at 400.13 and 376.5 MHz respectively for racemic mixtures of alpha-methyl amines **1–4** and **5–8**

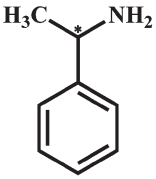
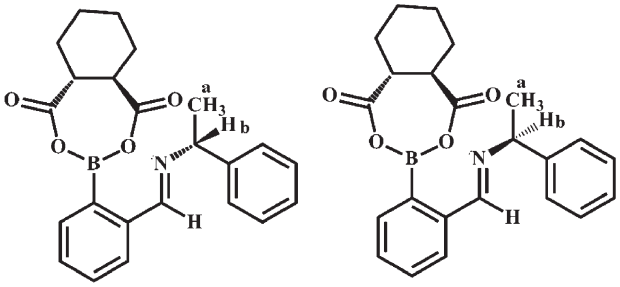
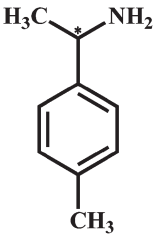
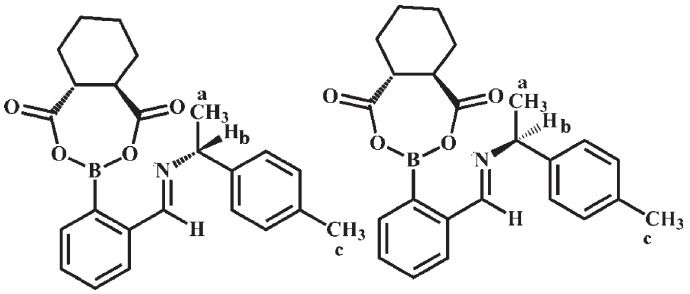
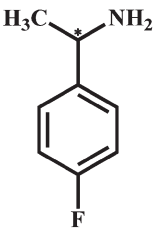
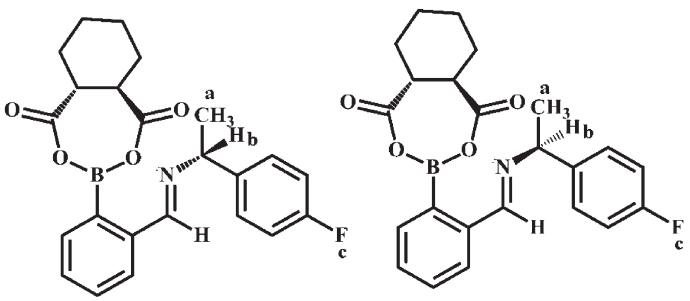
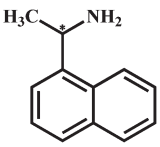
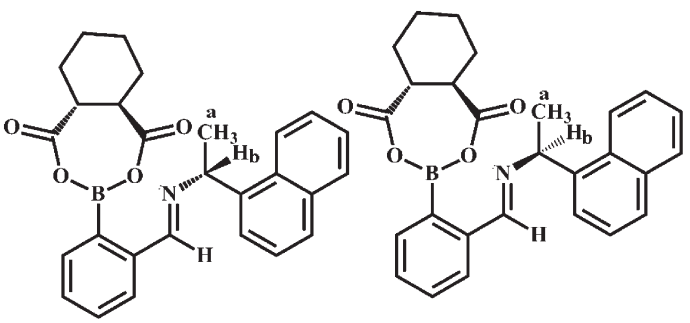
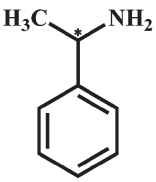
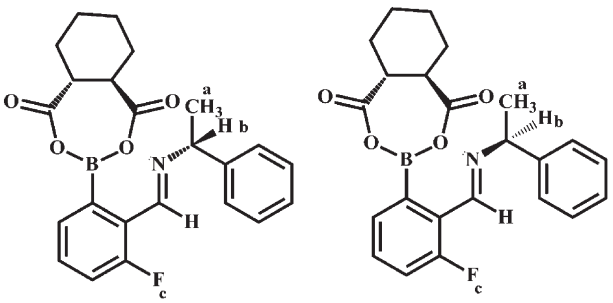
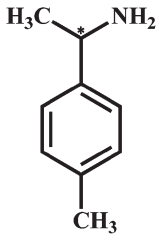
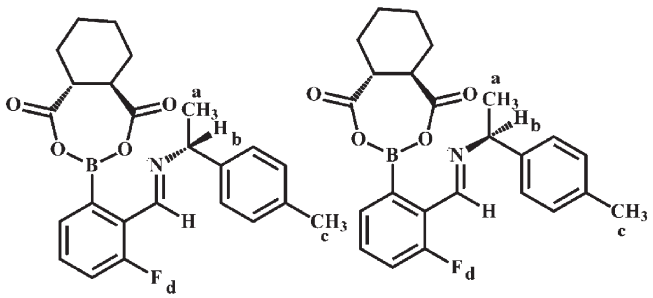
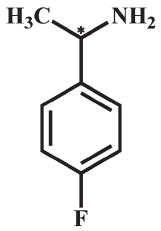
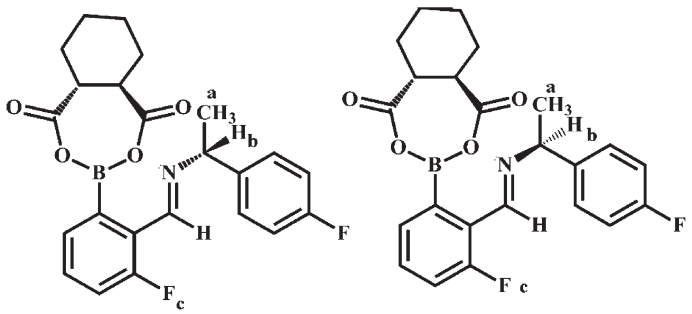
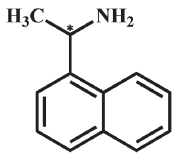
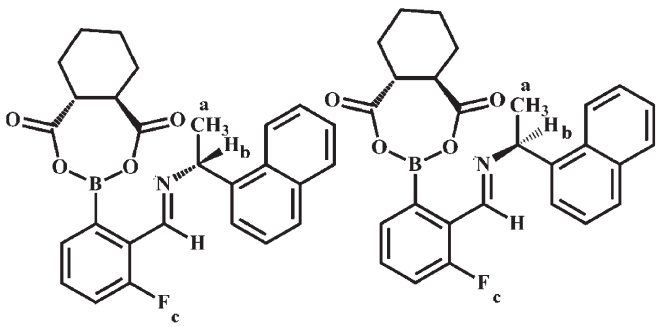
Entry	Chiral alpha methyl amines	Alpha-methyl amine diastereoisomeric imino-boronate esters	Chemical shift difference $(\Delta\delta)^{R/S}$ in ppm
1.			0.17 (a) 0.64 (b)
2.			0.15 (a) 0.61 (b) 0.02 (c)
3			0.13 (a) 0.59 (b) 1.58 (c)
4.			0.17 (a) 0.58 (b)
5.			0.17 (a) 0.64 (b) 1.70 (c)

Table 2 *(Contd.)*

Entry	Chiral alpha methyl amines	Alpha-methyl amine diastereoisomeric imino-boronate esters	Chemical shift difference $(\Delta\delta)^{R/S}$ in ppm
6.			0.17 (a) 0.64 (b) 0.02 (c) 1.93(d)
7.			0.16 (a) 0.62 (b) 1.42 (c)
8.			0.18 (a) 0.62 (b) 1.93(c)

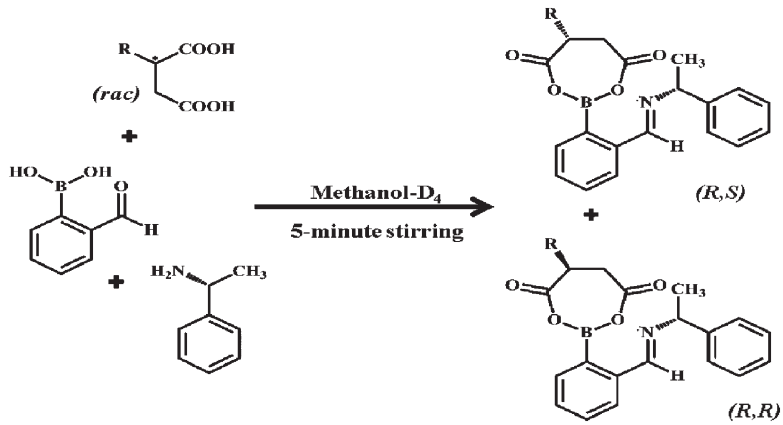
Note: the discriminated protons and fluorines are marked with letters in the respective schemes.

associated with the problem of kinetic resolution. In an earlier study James *et al.* have proposed three-component derivatization protocols for determining the enantiomeric purity of chiral primary amines, diamines and diols.[7] In the direction of their original idea, we have recently reported the three-component derivatization strategies for ^{1}H NMR spectroscopic enantio-discrimination of chiral hydroxy acids and chiral primary amines.[8] To the best of our knowledge there is no specific reagent available for the discrimination of chiral diacids. Thus in our continued efforts in this direction we have extended the idea and propose a fast, easy to prepare and cost effective three-component protocols for determination of enantiopurity of diacids.

For examining the chiral recognition ability of the proposed protocols, we have chosen chiral diacids **1–5** (please see Table 1). The general protocol involves the derivatization of diacids with 2-formylphenylboronic acid and an enantiopure (*R*)-α-methylbenzylamine in methanol-d_4. Such a three-component protocol is reported in Scheme 1.

To test this hypothesis, we have chosen racemic methyl-succinic acid (one equivalent) in the presence of one molar equiv. of (*R*)-α-methylbenzylamine and 2-formylphenylboronic acid in methanol-d_4. The reaction mixture was stirred for five minutes at room temperature. Subsequently ^{1}H-NMR spectra of aliquot were recorded to obtain the quantitative yield of diastereomers of imino-boronate esters (*R*,*S*) and (*R*,*R*) in methanol-d_4. All the ^{1}H spectra were recorded on a Bruker 400.13 MHz NMR spectrometer. The chemical shifts (ppm) are internally referenced to TMS signal (0.0 ppm). It is interesting to note that R–H of two enantiomers of racemic methylsuccinic acid gave rise to well-resolved singlets ($\Delta\Delta\delta$ = 0.64 ppm). The 400.13 MHz ^{1}H NMR spectrum of (*R*/*S*)-methylsuccinic acid is given in Fig. 1.

The discriminated CH_3 and CH groups are marked a and b respectively in Fig. 1. The chemical shift difference between each of these discriminated sites are reported in Table 1. It is clearly evident from the table that a large chemical shift difference of nearly 0.6 ppm has been observed. For the remaining carboxylic diacids **2–5** investigated, identifiable signals were observed at least for one set of diastereomeric protons in each molecule. Excellent baseline separation occurred in all the cases with $\Delta\Delta\delta$ ranging from 0.16 to 0.65 ppm for all the diacids



Scheme 1 Three-component reaction of 2-formylphenylboronic acid, (*R*)-α-methylbenzylamine and (rac) diacids (**1–5**) to yield diastereomeric imino-boronate esters (*R*,*S*)-**1–5** and (*R*,*R*)-**1–5**.

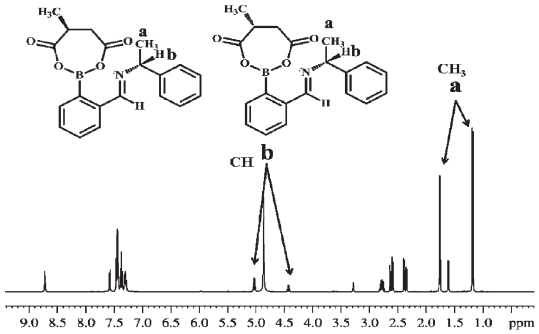


Fig. 1 400.13 MHz ^{1}H NMR spectrum of imino-boronate esters of methyl succinic acid depicting the enantiomer discrimination. The peaks a and b pertaining to CH_3 and CH groups permitted the discrimination and are marked with arrows in the figure.

investigated. The baseline separation occurred, even when the methine proton appeared as a doublet, triplet, or quartet (spectra are reported in the ESI†).

The chemical shift differences observed between the discriminated sites in ^{1}H-NMR spectra of all the molecules, **2–5**, are reported in Table 1 along with their chemical structures. The ^{1}H-NMR spectra of diacids **2–5** are given in the ESI.† There is a distinct advantage of these derivatization protocols, *viz.*, the problem of kinetic resolution does not occur when both acidic groups are reacting rapidly with a single boronic acid template and there is large chemical shift difference.

Often the NMR spectroscopic studies for chiral discrimination are restricted to ^{1}H detection, because of its ubiquity. Sometimes the severe overlap of peaks in ^{1}H NMR spectrum prevents the identification of diastereomeric peaks. Thus the utility of other NMR active nuclei such as ^{19}F, was explored using the proposed three-component protocols. There is significant advantage of employing ^{19}F NMR when compared to other less abundant nuclei. The large chemical shift dispersion compared to ^{1}H and its high natural abundance renders it also a most favourable nucleus for investigation. In spite of such benefits the use of NMR active nuclei other than ^{1}H has rarely been exploited.[9]

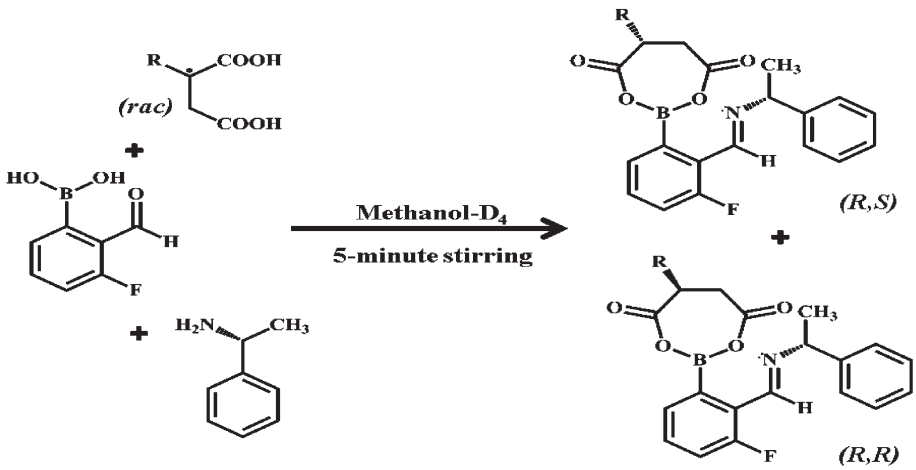
For exploring the utilization of ^{19}F NMR we have chosen the readily available 3-fluoro-2-formylphenyl boronic acid as the new bifunctional template for the purpose of derivatization instead of using 2-formylphenylboronic acid. A similar procedure to that described above was adopted for the three-component derivatization protocol. The chiral diacids were mixed with one equivalent of *R*-α-methylbenzylamine and one equivalent of 3-fluoro-2-formylphenylboronic acid in methanol-d_4 and stirred for five minutes resulting in quantitative formation of mixtures of diastereoisomeric imino-boronate esters, as reported in Scheme 2.

The acquired 376.5 MHz ^{19}F{^{1}H} NMR spectra of aliquot revealed identifiable signals for each enantiomer. The ^{19}F{^{1}H} spectrum of (*R*,*R*) and (*R*,*S*) derived from racemic mixture of methyl succinic acid and 3-fluoro-2-formylphenylboronic acid is given in Fig. 2. The imino-boronate esters of methylsuccinic acid are also given in Table 1.

The chemical shift difference between these diastereomeric peaks are given in Table 1. The marked chemical sites utilized for discrimination in other molecules and the measured chemical shift differences are also given in Table 1. It is evident from the table that consequent to the large chemical shift dispersion of ^{19}F, it is possible to observe a significant difference in the chemical shifts between many discriminated peaks. In favourable situations, the chemical shift difference as large as nearly 2.4 ppm has been observed.

For all the diacids **1–5** there is an excellent baseline separation with ^{1}H-chemical shift difference ranging from 0.16 to 0.67 ppm and in case of ^{19}F, for diacids **6–10**, the chemical shift difference range from 1.23 to 2.40 ppm. Such a large chemical shift difference depicts the versatile utility of the proposed method. In case of bromosuccinic acid almost all the protons gave rise to two anisochronous resonances with a relatively large separation.

In all the investigated diacids **1–10** the discrimination could be achieved even in the ^{13}C{^{1}H} spectra for at least one of the ^{13}C chemical sites. The ^{1}H decoupled ^{13}C NMR spectrum of iminoborate esters of methyl succinic acid is given in Fig. 3 and the discriminated ^{13}C site is identified by a circle in the chemical structure given above the spectrum. The ^{13}C{^{1}H} spectra of other investigated molecules and the measured chemical differences between discriminated sites are given in the ESI.†



Scheme 2 Three-component reaction of *R*-α-methylbenzylamine and one equivalent of 3-fluoro-2-formyl-phenylboronic acid with (rac) diacids (**6–10**) (please see Table 1) to yield diastereomeric imino-boronate esters (*R*,*S*)-**6–10** and (*R*,*R*)-**6–10**.

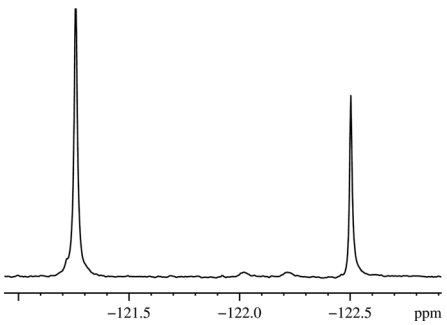


Fig. 2 The 376.5 MHz $^{19}F\{^1H\}$ NMR spectrum of (*R*,*R*) and (*R*,*S*) derived from the racemic mixture of methyl succinic acid and 3-fluoro-2-formylphenylboronic acid. The two peaks pertain to fluorine marked c of compound **6**, given in Table 1.

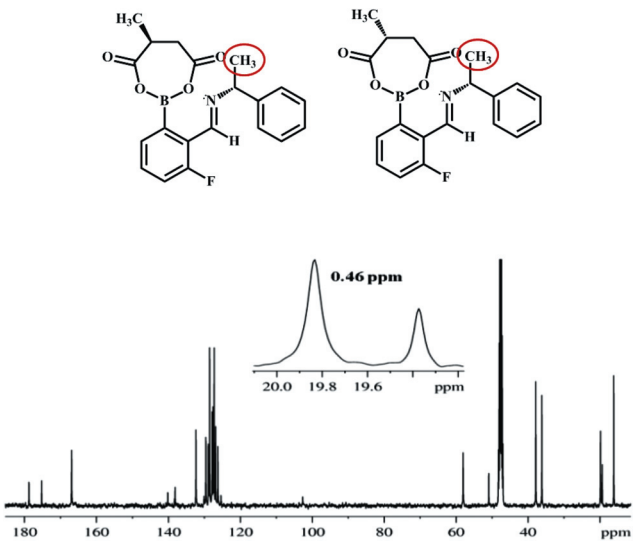


Fig. 3 100.6 MHz $^{13}C\{^1H\}$ spectrum of iminoborate esters of methyl succinic acid. The discriminated peaks pertain to CH_3 group is marked with a circle in the structure given.

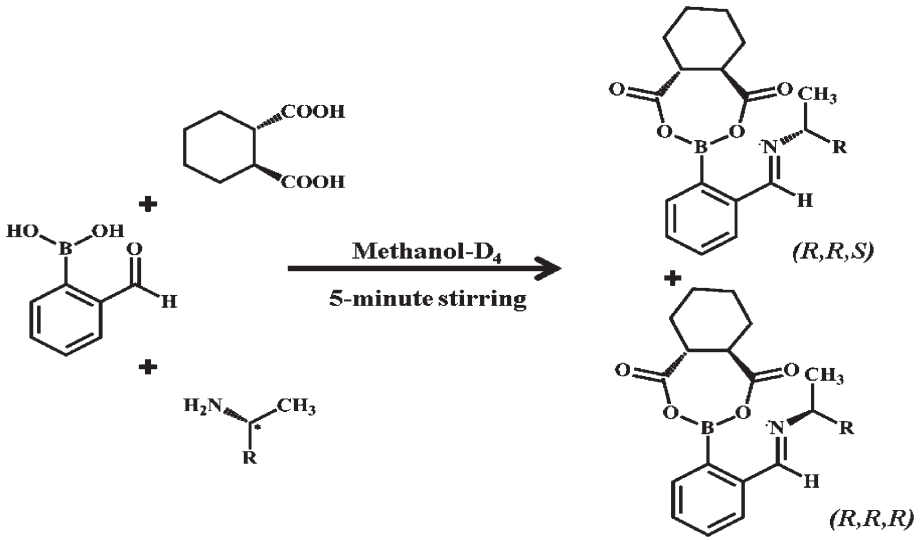
The chemical shift separation for the methyl carbon of methyl succinic acid is 0.46 ppm.

Discrimination of alpha-methyl amines

Chiral primary amines have many important chemical and pharmaceutical applications.[1,10] For the case of alpha-methyl amines, Mosher's *R*-methoxytrifluoromethyl phenylacetic acid (MTPA)[11] and Trost's *R*-methoxyphenylacetic acid (MPA)[12] are the two most widely used reagents. The diastereomeric species derived from these reagents generally exhibit negligible difference in chemical shifts.[13] The crown ethers and their derivatives[6] demand higher concentration, since it is difficult to achieve discrimination because of loss of resolution in the spectrum at lower concentration.[14] Therefore, the development of more efficient reagents giving large $\Delta\delta$ values is still an actively explored area of research. Recently we have also developed the three-component protocol for the discrimination of primary amines by using *S*-mandelic acid.[8] In the present study we have devised another protocol for derivatizing chiral alpha-methyl amines using enantiopure diacid. The protocol involves mixing of one equivalent of racemic alpha-methyl amine, optically pure *trans*-1,2-cyclohexanedicarboxylic acid and 2-formylphenylboronic acid. The general protocol reported in Scheme 3 was utilized to discriminate enantiomers using ^1H and ^{13}C NMR spectra.

The protocols for discrimination of alpha-methyl amines involve racemic α-methylbenzylamine (one equivalent) in the presence of one molar equivalent of optically pure *trans*-1,2-cyclohexanedicarboxylic acid and 2-formylphenylboronic acid in methanol-d_4. The reaction mixture was stirred for 5 min at room temperature and the spectra of aliquot were recorded.

The 400 MHz ^1H spectrum of diastereomeric imino-boronate esters (*R*,*R*,*S*) and (*R*,*R*,*R*) of α-methylbenzylamine is given in Fig. 4. Separate signals were observed for each isomer with the chemical shift difference of 0.65 ppm with baseline correction. The protocols were also tested for the series of alpha-methyl amines **2–4** and the chemical shift differences are reported in



Scheme 3 The three-component reaction of one equivalent of racemic alpha-methyl amines (**1–4**) (please see Table 2), optically pure *trans*-1,2-cyclohexanedicarboxylic acid and 2-formylphenylboronic acid to yield diastereomeric imino-boronate esters (*R*,*R*,*S*)-**1–4** and (*R*,*R*,*R*)-**1–4**.

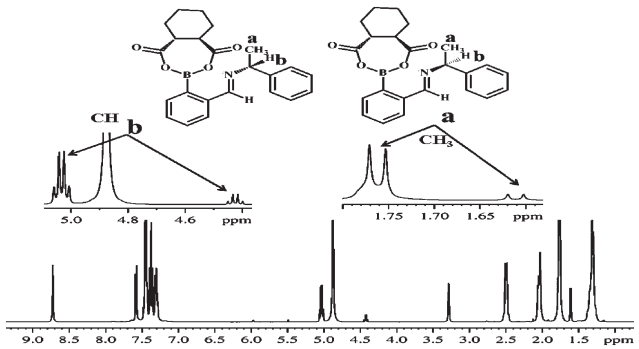
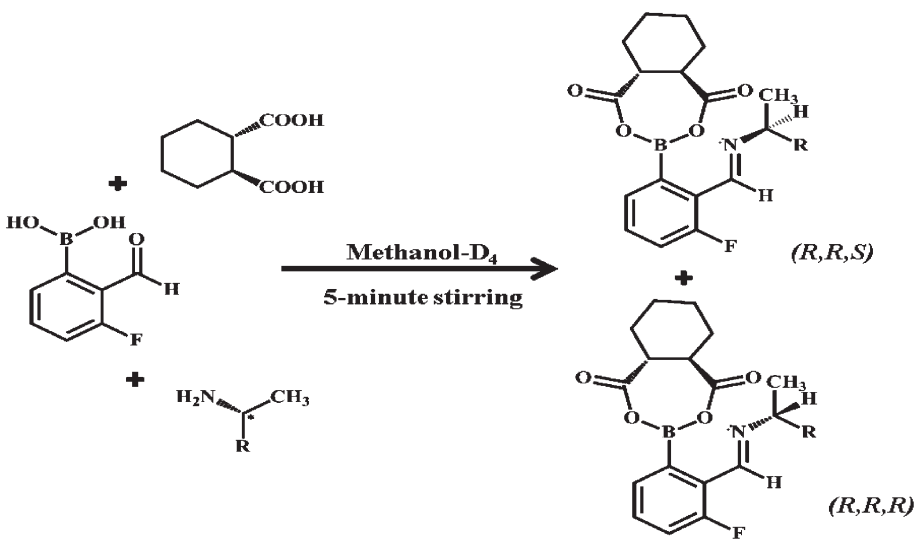


Fig. 4 400.13 MHz ^{1}H NMR spectrum of imino-boronate esters of α-methylbenzylamine depicting the enantiomer discrimination. The expanded regions of the spectrum pertaining to discriminated chemical sites marked a and b are given at the top of the spectrum.

Table 2. In all the cases we were able get enantiomer discrimination ranging from 0.15 to 0.65 ppm with baseline separation. The discrimination was also achieved in all the chosen chiral alpha-methyl amines. We have also extended the study using ^{19}F{^{1}H} with 3-fluoro-2-formylphenylboronic as bifunctional template instead of 2-formylboronic acid. This protocol is given in Scheme 4.

The ^{19}F{^{1}H} spectrum of imino-boronate esters of alpha-methylbenzylamine is given in Fig. 5. The detection of two identifiable peaks establishes the unambiguous discrimination. The discriminated protons and fluorines are marked with alphabets and the ^{1}H and ^{19}F chemical shift differences between diasterotopic peaks are summarized in Table 2. The protocols were explored for others chiral alpha-methyl amines, **6–8**. The chemical shift difference between the discriminated protons and fluorine are summarized in Table 2. All the related ^{1}H and



Scheme 4 The three-component reaction of 1 equivalent of racemic alpha-methyl amines (**5–8**) (please see Table 2), optically pure *trans*-1,2-cyclohexanedicarboxylic acid and 3-fluoro-2-formyl-phenylboronic acid to yield diastereomeric imino-boronate esters (*R*,*R*,*S*)-**5–8** and (*R*,*R*,*R*)-**5–8**.

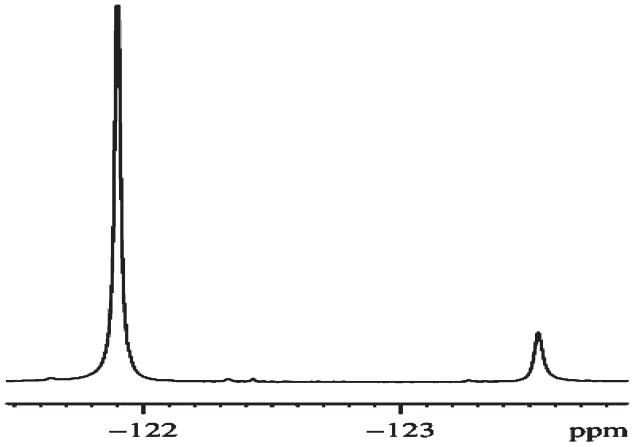


Fig. 5 376.5 MHz $^{19}F\{^{1}H\}$ spectrum of iminoborate esters of alpha-methylbenzylamine.

$^{19}F\{^{1}H\}$ and the $^{13}C\{^{1}H\}$ spectra including the derived information are given in the ESI.†

The protocols also suffer from certain limitations. The unequal intensity patterns of some of the discriminated sites of racemic mixtures prevented the precise measurement of enantiomeric excess. Thus at present these protocols are qualitative and we have not been able to quantify them.

Conclusions

In summary we have developed different three-component chiral derivatizing protocols for ^{1}H, ^{13}C and ^{19}F NMR spectroscopic evaluation of the enantiopurity of chiral diacids and chiral alpha-methyl amines. The easy preparation of these three-component protocols serve as convenient and fast derivatization methods that are ideal for routine analysis of chiral molecules. There are distinct advantages of these protocols over many other existing methods. The significant difference in the chemical shifts between diastereotopic peaks is observed both in ^{1}H and ^{19}F spectra. In favourable situations different sets of discriminated ^{1}H, ^{19}F and ^{13}C sites can be employed for unambiguously ascertaining the enantiopurity. The utilization of ^{13}C spectra when there is a severe overlap of signals in the ^{1}H spectra has also been made.

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