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Three-Component Chiral Derivatizing Protocols for NMR Spectroscopic Enantiodiscrimination of Hydroxy Acids and Primary Amines

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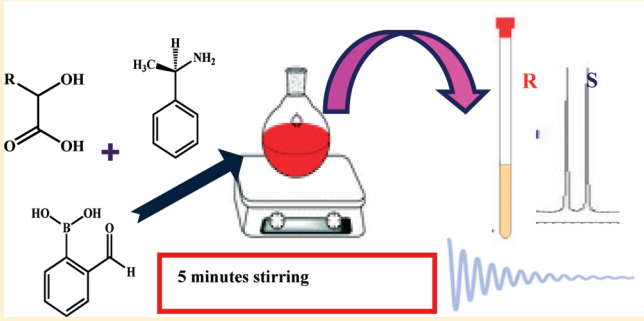
Supporting Information

ABSTRACT: The novel three-component chiral derivatization protocols have been derived for ^{1}H and ^{19}F NMR spectroscopic discrimination of a series of chiral hydroxy acids by their coordination and self-assembly with optically active α-methylbenzylamine and 2-formylphenylboronic acid. In addition, the optically pure (*S*)-mandelic acid in combination with 2-formylphenylboronic acid permits visualization of enantiomers of primary amines. These protocols have been demonstrated on enantiodiscrimination of chiral amines and hydroxy acids.



INTRODUCTION

Differentiation of enantiomers is important in diverse disciplines, such as chiral synthesis, mechanistic studies, catalysis, kinetics geochronology, biochemistry, pharmacology, and medicine.[1] Several methods have been employed to achieve enantiodiscrimination from either racemic or scalemic mixtures.[2] The determination of enantiopurity by nuclear magnetic resonance (NMR) spectroscopy is a largely explored area. Nevertheless, NMR spectroscopy is intrinsically blind to discriminate the enantiomers in the commonly utilized achiral NMR solvents. To utilize NMR as an analytical tool, the substrates must be converted to a pair of diastereomers, which is accomplished by the utilization of any of the chiral auxiliaries, such as chiral derivatizing agents (CDAs), chiral solvating agents (CSAs), or chiral lanthanide shift reagents.[3] Several reagents, such as amines, amino alcohols, diamines, amides, and macrocyclic compounds, have been reported to address the problems of determining the enantiopurity of chiral acids.[4] However, few such derivatives are utilized to determine the enantiomeric purities of carboxylic acids by ^{1}H NMR, because of negligible chemical shift differences between diastereomers. Although the amine or amide-based CSAs can afford relatively large chemical shift differences between the substrate enantiomers, the preparation of such reagents usually requires multistep syntheses, limiting their practical application. In the case of primary amines MTPA (Mosher) or MPA (Trost) amide,[5] crown ethers and their derivatives[6] are employed for their discrimination. Generally, a higher concentration of the auxiliary is required when crown ethers are employed since it is difficult to achieve discrimination because of poor resolution of the spectrum at lower concentrations. When Mosher or Trost are utilized, due to the problem of kinetic resolution, the ratio of diastereomers will be disproportional to that of two enantiomers of the original mixture, preventing the precise measurement of *ee* in such situations. To circumvent this problem, we have derived efficient and cost-effective three-component protocols for determining the enantiopurity of hydroxy acids and primary amines. In the present study, we have investigated only racemic mixtures with the main focus of differentiating enantiomers. However, the study using scalemic mixtures can be employed for the measurement of ee. The three-component derivatization protocols using 2-formylphenylboronic acid and (*S*)-BINOL for determining the enantiomeric purity of chiral primary amines, diamines, and the mixture of 2-formylphenylboronic acid and enantiopure α-methylbenzylamine to determine the enantiopurity of diols have been reported.[7] In line with the developments of James et. al,[7] we are reporting two different three-component derivatizing agents for measurement of the enantiomeric purity of chiral hydroxy acids and chiral primary amines.

RESULTS AND DISCUSSION

Chiral Discrimination of Hydroxy Acids. The chiral hydroxyl acids are a class of compounds that have never been tested to date, to the best of our knowledge, using three-component derivatizing protocols. For hydroxy acids, the protocol involves their derivatization with 2-formylphenylboronic acid and an enantiopure (*R*)-α-methylbenzylamine in $CDCl_3$. The reaction mixture was stirred for 5 min at room temperature. Subsequently, ^{1}H NMR spectra of an aliquot were recorded to obtain the quantitative yield of

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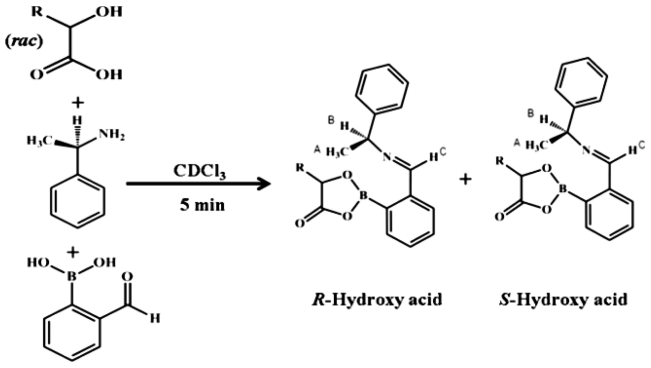
diastereomers of iminoboronate esters, (*R*,*S*) and (*R*,*R*), as shown in Scheme 1.

Scheme 1. Three-Component Reaction of 2-Formylphenylboronic Acid, (*R*)-α-Methylbenzylamine, and (rac) Hydroxy Acids (1−6) to Yield Diastereomeric Iminoboronate Esters (*R*,*S*)-1−6 and (*R*,*R*)-1−6



The analysis of ^{1}H NMR spectrum recorded at 400 MHz gave different peaks for (*R*,*S*):(*R*,*R*). As no kinetic resolution occurs in the present protocol, it is possible to obtain the accurate enantiomeric excess. The ^{1}H NMR spectrum of (*R*/*S*)-mandelic acid is given Figure 1. The discriminated peaks marked A and C in Scheme 1 and that of the proton marked D in (*R*/*S*)-mandelic acid is shown with expansion. The chemical shift difference $(\Delta\delta)^{R/S}$ measured are given in Table 1.

In the subsequent stage, the possibility of utilizing the ^{19}F NMR in fluorinated molecules was explored. The ^{19}F spectrum of (*R*/*S*)-4-trifluoromethyl mandelic acid results in two ^{19}F peaks pertaining to two enantiomers whose integral areas are approximately in the ratio of 1:1. The 376 MHz ^{19}F NMR spectrum of (*R*/*S*)-4-trifluoromethyl mandelic acid is given in Figure 2.

To investigate the scope and limitations of this chiral derivatization protocol, a range of hydroxy acids were then derivatized. The chemical shift differences observed between the enantiomers in ^{1}H NMR spectra of **1−6** are reported in Table 1, along with their chemical structures.

Discrimination of Primary Amines. We have extended the strategy for discrimination of primary amines utilizing 1 equiv of racemic primary amine, optically pure (*S*)-mandelic acid, and 2-formylphenylboronic acid. This is reported in Scheme 2.

The reaction mixture was stirred for 5 min at room temperature. The ^{1}H NMR spectra of an aliquot were recorded. The ^{1}H NMR spectrum revealed a 1:1 mixture of two diastereoisomeric complexes (*S*,*R*) and (*S*,*S*). The 400 MHz ^{1}H NMR spectrum of (*R*/*S*)-α-methylbenzylamine given in Figure 3 clearly identifies the two discriminated peaks.

The convincing results were achieved for several other primary amines using this novel three-component derivatizing protocol. The chemical shift differences between the enantiomers observed in the ^{1}H NMR spectra of **7−14** are reported in Table 2, along with their chemical structures.

CONCLUSIONS

New three-component chiral derivatizing systems for NMR spectroscopic determination of the enantiopurity of hydroxy acids and chiral amines have been developed. The easy preparation of these three-component systems acts as convenient and fast derivatization protocols that are ideal for routine analysis of chiral molecules. There are distinct advantages of these protocols over other methods. First, the different sets of integral areas of peaks can be employed for the measurement of ee. Second, the discrimination is observed at the chemical sites of both protons and fluorine that are separated by more than five bonds from the stereogenic center.

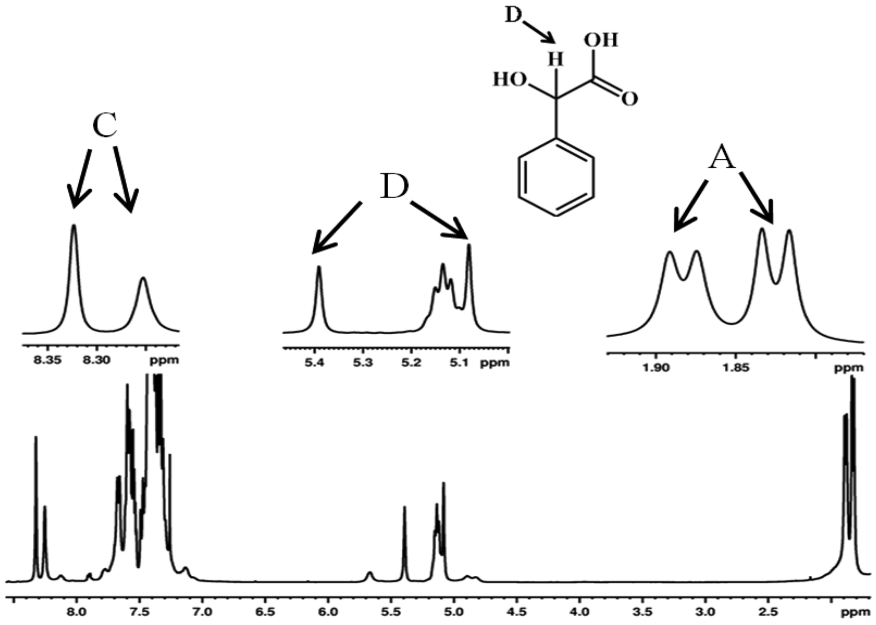


Figure 1. ^{1}H NMR spectrum (400 MHz) of (*R*/*S*)-mandelic acid exhibiting the enantiodiscrimination as given in Scheme 1.

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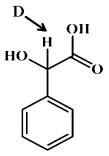
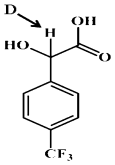
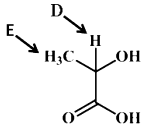
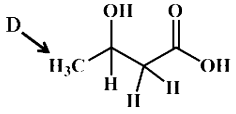
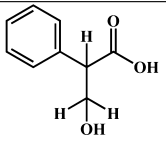
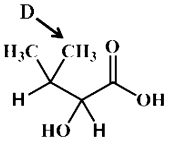
Table 1. ^{1}H Chemical Shift Differences between Diastereomers Measured at 400 MHz NMR Spectrometer for Racemic Mixtures of 1−6[a]

Entry	Chemical structure of the molecule	Chemical shift difference $(\Delta\delta)^{R/S}$ in ppm
1.		A-0.07 B-0.09 C-0.07 D-0.31
2.		A-0.07 B-0.09 C-0.07 D-0.32 ^{19}F-0.04
3.		A-0.05 B-0.07 C-0.09 D-0.52 E-0.52
4.		A-0.03 C-0.14 D-0.04
5.		A-0.17 B-0.65 C-0.03
6.		A-0.04 C-0.07 D-0.04

[a]Note: the protons A, B, and C are labeled in Scheme 1. Other protons are marked in the respective figures.

EXPERIMENTAL SECTION

2-Formylphenylboronic acid, (*S*)-mandelic acid, *R*-α-methylbenzylamine, **1**−**6** hydroxy acids (see Table 1), **7**−**14** primary amines (see Table 2), and chloroform-*d* all of high purity were purchased. All the reagents were taken in a round-bottom flask. A 100 mg portion of 2-formylphenylboronic acid was transferred to the round-bottom flask. To this transfer, 5 mL of $CDCl_3$ 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 80 mg of chiral hydroxyl acid was transferred to the round-bottom flask. The mixture was stirred for 5 min. An aliquot (0.5 mL) of the reaction mixture was transferred to the NMR tube. The ^{1}H NMR spectrum was recorded at 400 MHz and chemical shifts were referenced with respect to TMS (0.00 ppm). A similar procedure was repeated for the discrimination of chiral amines, where enantiopure (*S*)-mandelic acid was used instead of (*R*)-α-methylbenzylamine.

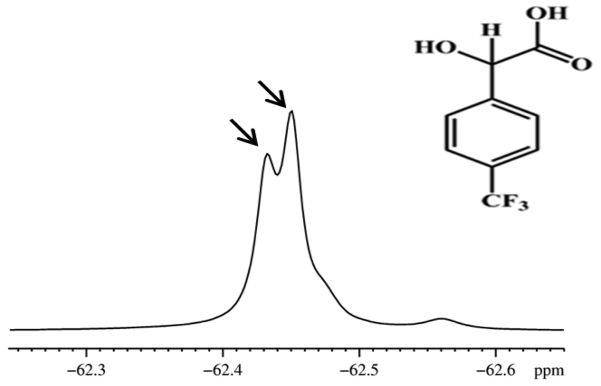
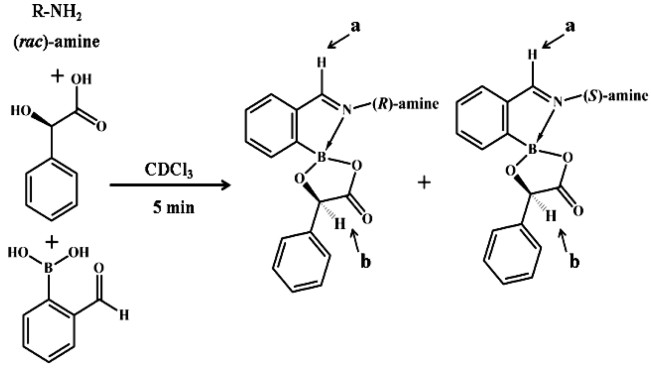


Figure 2. ^{19}F NMR spectrum (376 MHz) of (*R*/*S*)-*p*-trifluoromethyl mandelic acid.

Scheme 2. Three-Component Reaction of 2-Formylphenylboronic Acid, (*S*)-Mandelic Acid, and (rac) Primary Amines (7−14) to Yield Diastereomeric Iminoboronate Esters (*S*,*S*)-7−14 and (*S*,*R*)-7−14



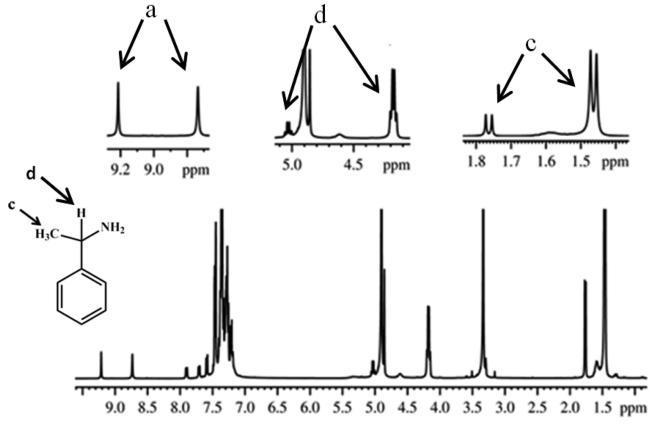


Figure 3. ^{1}H NMR spectrum (400 MHz) of (*R*/*S*)-α-methylbenzylamine exhibiting the discriminated peaks as given in Scheme 2.

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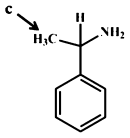
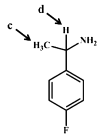
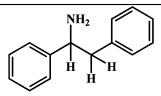
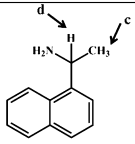
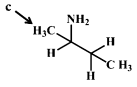
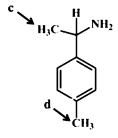
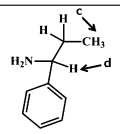
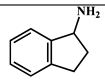
Table 2. ^{1}H Chemical Shift Differences between Diastereomers Measured at 400 MHz for Racemic Mixtures of 7−14[a]

Entry	Chemical structure of the molecule	Chemical shift difference $(\Delta\delta)^{R/S}$ in ppm
7.		a-0.06 b-0.29 c-0.06
8.		a-0.06 b-0.29 c-0.06 d-0.06 ^{19}F-0.25
9.		a-0.39 b-0.49
10.		a-0.16 b-0.04 c-0.07 d-0.04
11.		a-0.29 b-0.31 c-0.15
12.		a-0.06 b-0.25 c-0.06 d-0.01
13.		a-0.09 b-0.22 c-0.04 d-0.03
14.		a-0.17 b-0.40

[a]Note: protons a and b are marked in Scheme 2. Other protons are marked in the respective figures.

■ ASSOCIATED CONTENT

Supporting Information

The ^{1}H and ^{19}F spectra of the investigated molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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