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Simple Protocol for NMR Analysis of the Enantiomeric Purity of Diols

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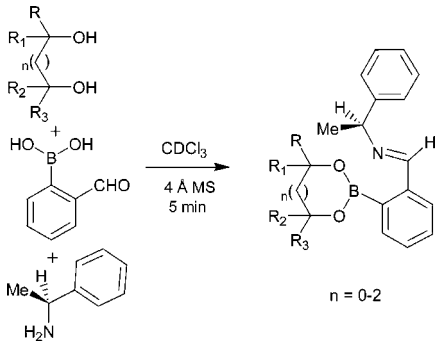
ABSTRACT



A practically simple three-component chiral derivatization protocol for determining the enantiopurity of chiral 1,2-, 1,3-, and 1,4-diols by ^{1}H NMR spectroscopic analysis is described. The method involves treatment with 2-formylphenylboronic acid and enantiopure α-methylbenzylamine to afford a mixture of diastereoisomeric iminoboronate esters whose ratio is an accurate reflection of the enantiopurity of the parent diol.

The prevalence of chiral diols as synthetic intermediates[1,2] and as fragments of biologically active compounds[3] has led to a great demand for reliable techniques to accurately determine the enantiopurity of this class of compound. Therefore, the development of an inexpensive chiral derivatization protocol that enables their enantiomeric excess to be simply determined by ^{1}H NMR spectroscopic analysis is currently of great interest to the synthetic community.

The use of chiral derivatization agents (CDAs)[4] to determine the enantiomeric excess of diols is well established,[5−8] with many having been derivatized to afford either MTPA (Mosher)[9] or MPA (Trost)[10] esters. The main drawback of using this type of approach is the need to ensure that no kinetic resolution occurs during reaction of both alcohol functionalities of the diol with 2 equiv of the CDA. Derivatization of chiral diols with CDAs that contain either a boronic acid,[11−14] dichlorophosphine,[15] dichlorophosphate,[16] or an aldehyde[17] moiety avoid such limitations since a single

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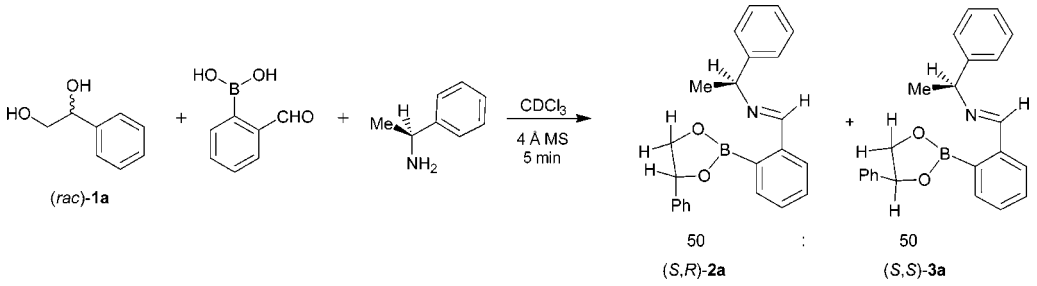
Scheme 1. Multicomponent Coupling Reaction of 2-Formylphenylboronic Acid, (*S*)-(−)-α-Methylbenzylamine, and (*rac*)-1-Phenylethane-1,2-diol **1a** to Afford Diastereoisomeric Iminoboronate Esters (*S*,*R*)-**2a** and (*S*,*S*)-**3a**



chiral derivatization agent reacts with both alcohol functionalities of the diol substrate. However, most of these enantiopure CDAs require multiple synthetic steps for their preparation and are not commercially available. The dichlorophosphate system is only suitable for determining the enantiomeric excess of C_2-symmetric diols,[16] while other CDAs of this type afford diastereoisomers that only show nonequivalence in their ^{13}C or ^{31}P NMR spectra.[11,15,18] Furthermore, while the aldehyde system (2′-methoxy-1,1′-binaphthalene-8-carboxaldehyde) has been used to determine the absolute configuration of diols using NOE experiments, the observed ^1H NMR chemical shift differences of the resultant diastereoisomeric acetonides were not reported.[17] The chemical shift differences observed by Burgess et al. for diasteroisomeric boronate esters prepared via treatment of diols with enantiopure 2-(1-methoxy-ethyl)phenylboronic acid were also low in the range of $\Delta\delta = 0.005-0.020$ ppm. Currently, diol derivatization approaches based on the use of *N*-acetylphenylglycineboronic acid[13] and derivatives[13,19] appear to be the most effective for determining the enantiopurity of chiral diols. These agents afford a resolution of $\Delta\delta = 0.060-0.360$ ppm for the resultant diastereoisomeric boronate esters.[19]

We have recently reported the development of a versatile three-component derivatization protocol for determining the enantiomeric excess of chiral primary amines.[20] This approach involved derivatization of the parent amine with 2-formylphenylboronic acid and enantiopure BINOL to afford a mixture of diastereoisomeric iminoboronate esters whose ratio may be easily determined by ^1H NMR spectroscopic analysis. We reasoned that this type of derivatization protocol would also be useful for the analysis of chiral diols, since treatment with an enantiopure amine and 2-formylphenylboronic acid would also afford diastereoisomeric iminoboronate esters that were well suited to ^1H NMR spectroscopic analysis.

To test this hypothesis, 1.0 equiv of (*rac*)-1-phenylethane-1,2-diol **1a**, 1.0 equiv of 2-formylphenylboronic acid, and 1.0 equiv of (*S*)-(α)-methylbenzylamine were dissolved in $CDCl_3$ and the ^1H NMR spectra of an aliquot acquired after 5 min. The resultant ^1H NMR spectrum revealed that a 50:50 mixture of two diastereoisomeric complexes (*S*,*R*)-**2a** and (*S*,*S*)-**3a** had been formed in quantitative yield with baseline resolution being observed for both the imine protons and the diol benzylic proton of each diastereoisomer (Scheme 1). This observation was highly promising because it meant that comparison of the relative intensities of two different sets of integrals could be used to accurately confirm the enantiopurity of a scalemic sample of this diol by ^1H NMR spectroscopy. To investigate the scope and limitation of this chiral derivatization protocol, a range of eight further racemic diols **1b**−**i** containing primary, secondary, and tertiary hydroxyl groups were then investigated. Analysis of the 400 MHz ^1H NMR spectra of the resultant 50:50 mixture of diastereoisomeric iminoboronate esters **2b**−**i** and **3b**−**i** revealed that baseline resolution had been achieved for at least one set of resonances in all cases, with up to four distinct resonances being observed in some instances. For example, analysis of the 400 MHz ^1H NMR spectra of a 50:50 mixture of iminoboronate esters (α-*S*,2*S*,3*R*)-**2e** and (α-*S*,2*R*,3*S*)-**3e** revealed that baseline resolution had been achieved for four distinct sets of signals with $\Delta\delta$ values of 0.510 ppm for the benzylic proton of the diol fragment. Importantly, in all cases splitting of the imine signal was observed (0.017−0.310 ppm) in a region of the ^1H NMR spectra that was free of any other resonances. This feature is highly desirable since the imine resonances are removed from any other resonances associated with the diol fragment, thus providing diagnostic resonances for integration that are independent of the diol being derivatized. The individual resonances corresponding to selected pairs of diastereoisomers were then assigned by comparison with the ^1H NMR spectra of authentic samples of **2a**,**c**,**f**−**i** and **3a**,**c**,**f**−**i** that were prepared independently via reaction of enantiopure diols **1a**,**c**,**f**−**i** with (*S*)-α-methylbenzylamine. Importantly, it was found that derivatization of every diol **1a**−**h** gave only two sets of diastereoisomeric iminoboronate ester resonances in their ^1H NMR spectra clearly indicating that free rotation was occurring around the aryl−boron bond on the NMR time scale. Therefore, these results clearly demonstrate that this chiral derivatization protocol is well suited for determination of the enantiopurity of a wide range of chiral 1,2-, 1,3-, or 1,4-diols.

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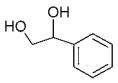
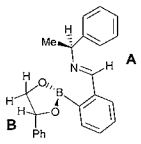
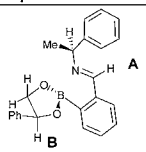
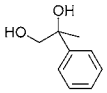
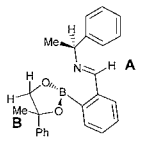
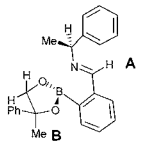
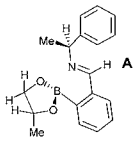
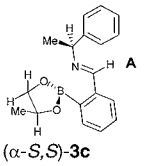
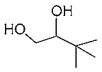
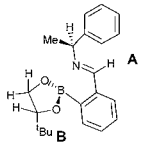
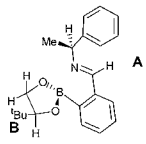
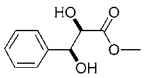
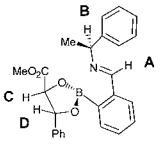
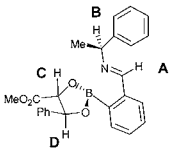
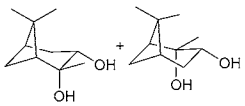
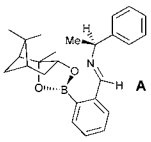
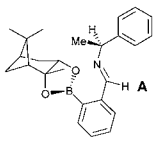
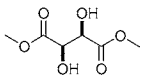
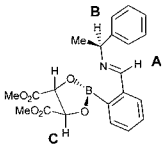
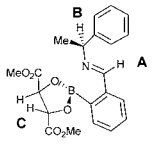
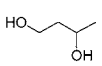
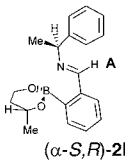
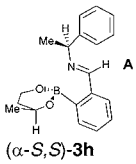
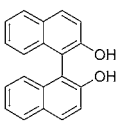
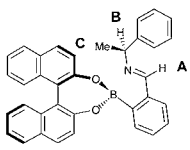
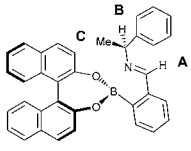
Table 1. Chemical Shift Differences ($\Delta\delta$) in the 400 MHz ^{1}H NMR Spectra of 50:50 Mixtures of **2a**−**i** and **3a**−**i** Derived from Racemic Diols **1a**−**i**

entry	(*rac*)-diol	boronate complexes		$\Delta\delta$ (δ**2**-δ**3** ppm)[a]
1				-0.066 (A)[b] -0.066 (B)[b]
	(*rac*)-**1a**	(α-*S*,*R*)-**2a**	(α-*S*,*S*)-**3a**	
2				*0.073* (A)[c] *0.040* (B)[c]
	(*rac*)-**1b**	(α-*S*,*R*)-**2b**	(α-*S*,*S*)-**3b**	
3				-0.030 (A)
	(*rac*)-**1c**	(α-*S*,*R*)-**2c**	(α-*S*,*S*)-**3c**	
4				*0.070* (A)[c] *0.044* (B)[c]
	(*rac*)-**1d**	(α-*S*,*R*)-**2d**	(α-*S*,*S*)-**3d**	
5				-0.297 (A) 0.097 (B) 0.120 (C) 0.510 (D)
	(*rac*)-**1e**	(α-*S*,2*S*,3*R*)-**2e**	(α-*S*,2*R*,3*S*)-**3e**	
6				-0.029 (A)[d]
	(*rac*)-**1f**	(α-*S*,2*S*,3*R*)-**2f**	(α-*S*,2*R*,3*S*)-**3f**	
7				-0.310 (A) 0.115 (B) 0.282 (C)
	(*rac*)-**1g**	(α-*S*,*R*,*R*)-**2g**	(α-*S*,*S*,*S*)-**3g**	
8				-0.017 (A)[b]
	(*rac*)-**1h**	(α-*S*,*R*)-**2h**	(α-*S*,*S*)-**3h**	
9				0.178 (A)[b] -0.108 (B)[b] 0.205 (C)[b]
	(*rac*)-**1i**	(α-*S*,*R*)-**2i**	(α-*S*,*S*)-**3i**	

[a] A negative value indicates that the resonance corresponding to diastereoisomer **2** was more shielded than that of diastereoisomer **3**. [b] ^{1}H NMR spectra recorded in acetone-d_6. [c] Unable to assign a sign to the $\Delta\delta$ values of these resonances because enantiopure samples of diols **1b** and **1d** were not available. [d] For simplicity only the chiral centers involved in the cyclic boronate ester are assigned.

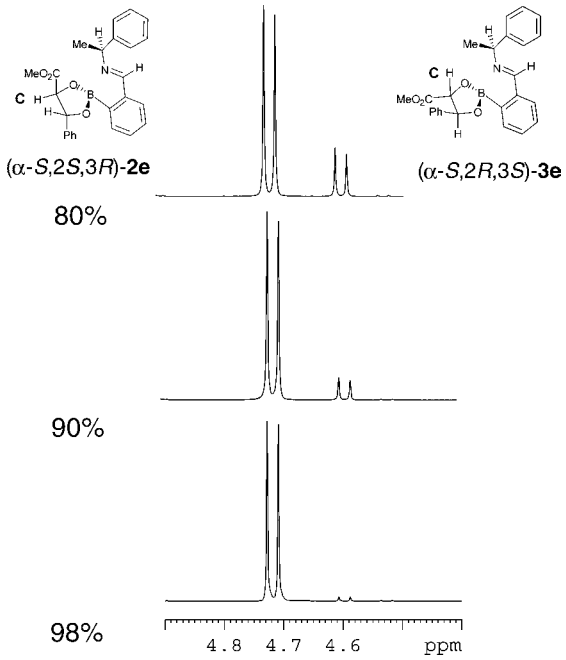


Figure 1. Expansion of the ^{1}H NMR spectra of a mixture of (α-*S*,2*S*,3*R*)-**2e** and (α-*S*,2*R*,3*S*)-**3e** prepared from (2*S*,3*R*)-**1e** of 80%, 90%, and 98% ee.

The detection limits of this new derivatization method were then determined by derivatization of three samples of (2*S*,3*R*)-**1e** of 80%, 90%, and 98% ee, respectively, using enantiopure (*S*)-α-methylbenzylamine for complex formation. Analysis of the ^{1}H NMR spectrum of each sample revealed that the calculated diastereomeric excess (de) for the resultant mixture of (α-*S*,2*S*,3*R*)-**2e** and (α-*S*,2*R*,3*S*)-**3e** was in excellent agreement with the known enantiomeric purity of the starting (2*S*,3*R*)-**1e**. Therefore, the ^{1}H NMR integrals measured for formation of (α-*S*,2*S*,3*R*)-**2e** of 81%, 89%, and 98% de correlated well with the known enantiopurity of the starting (2*S*,3*R*)-diol **1e** of 80%, 90%, and 98% ee, respectively, thus indicating that little or no kinetic resolution had occurred (Figure 1). These values are well within the accepted 5% error limit normally accepted for CDA analysis with NMR spectroscopy.[21,22] Finally, it should be noted that the derivatization protocol described herein has proven effective for determining the ee of every diol that we have investigated to date. However, in the unlikely event that α-methylbenzylamine fails to resolve a particular class of diol, we anticipate that substituting an alternative chiral amine in this three-component derivatization protocol should enable its ee to be determined.

In conclusion, we have developed a practically simple three-component chiral derivatization protocol for determining the enantiopurity of a wide range of chiral diols by ^{1}H NMR analysis. We believe that the simplicity and speed of this approach and the wide range of diols that it is capable of resolving warrants its consideration as a versatile method for determining the enantiomeric excess of diols produced in asymmetric protocols.

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Supporting Information Available: ^{1}H NMR spectra for 50:50 mixtures of **2a**−**i** and **3a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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