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Simple Chiral Derivatization Protocols for ^{1}H NMR and ^{19}F NMR Spectroscopic Analysis of the Enantiopurity of Chiral Diols

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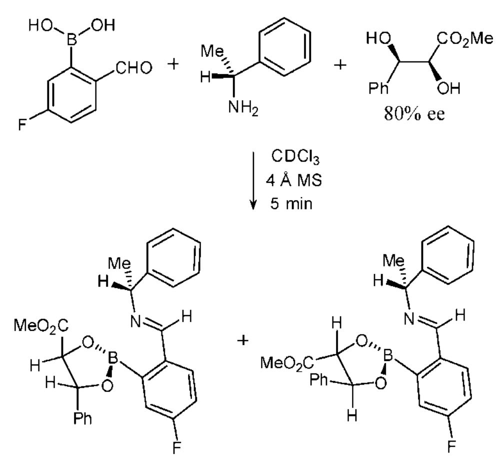

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Two practically simple chiral derivatization protocols for determining the enantiopurity of chiral diols by ^{1}H NMR and ^{19}F NMR spectroscopic analysis are described, involving treatment of the diol with 2-formylphenylboronic acid and α-methyl-4-fluorobenzylamine, or its derivatization with 4-fluoro-2-formylphenylboronic acid and α-methyl-benzylamine. Both approaches afford mixtures of imino−boronate esters whose diastereomeric ratio may be measured by ^{1}H NMR or ^{19}F NMR spectroscopy, the value of which is an accurate reflection of the enantiopurity of the parent diol.

Introduction

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 their enantiopurity. Consequently, the development of inexpensive chiral derivatization protocols that allow their enantiomeric excess to be simply determined by NMR spectroscopic analysis is currently of great interest to the synthetic community.[4] We have recently developed simple three component chiral derivatization protocols for determining the enantiopurity of chiral amines,[5] diols,[6] and diamines.[7] The enantiomeric excess of scalemic diols are determined via derivatization with 2-formylphenylboronic acid and a chiral amine to afford mixtures of diastereoisomeric imino−boronate esters whose ratios are then determined by ^{1}H NMR spectroscopic analysis. Since no kinetic resolution occurs in this derivatization process, the diastereoisomeric ratio (dr) is an accurate measure of the enantiomeric excess of the parent diol.[6]

Comparison of our three component derivatization approach with the widely used Mosher's acid derivatization protocol[8,9] reveals that it has a number of advantages. The main drawback of using Mosher's ester approach for diols is the need to employ excess chiral derivatizing agent (CDA) to ensure that no kinetic resolution occurs when both alcohol functionalities react with two equivalents of the CDA. Contrastingly, our derivatization approach results in *both* alcohol functionalities of the diol reacting rapidly with a single boronic acid template, which ensures that no kinetic resolution occurs. This means that a wide range of diols can be rapidly derivatized using moisture insensitive reagents to quantitatively afford mixtures of diastereoisomeric imino−boronate esters whose ^{1}H NMR spectra display at least one pair of baseline-resolved diastereotopic resonances that can be integrated to accurately determine diastereoisomeric excess (de). However, one potential advantage of the Mosher's acid derivatization approach for chiral diols is the ability to determine diastereomeric excess using both ^{1}H and ^{19}F NMR spectroscopy.[8,9] Consequently, we now describe herein the development of second generation three-component chiral derivatization protocols that also enable the ee of chiral diols to be accurately determined by ^{19}F NMR spectroscopic analysis.

Our first strategy was to develop a derivatization protocol employing a commercially available chiral fluorous amine as a chiral auxiliary. Therefore, six chiral diols **3a−f** were mixed

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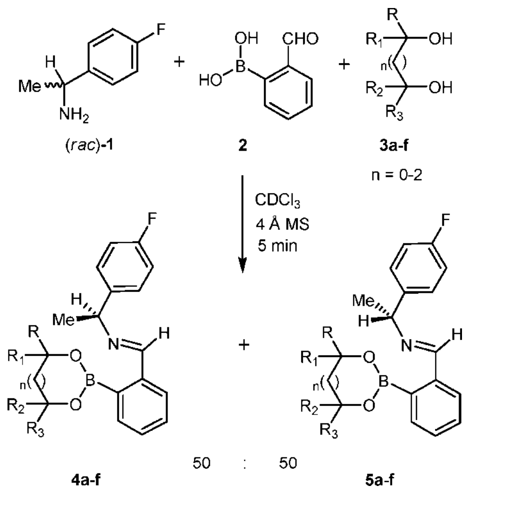
SCHEME 1. Three-Component Coupling Reaction of (*rac*)-α-Methyl-4-fluorobenzylamine 1, 2-Formylphenyl Boronic Acid 2 and Diols 3a−f to Afford Diastereomeric Imino−Boronate Esters 4a−f/5a−f



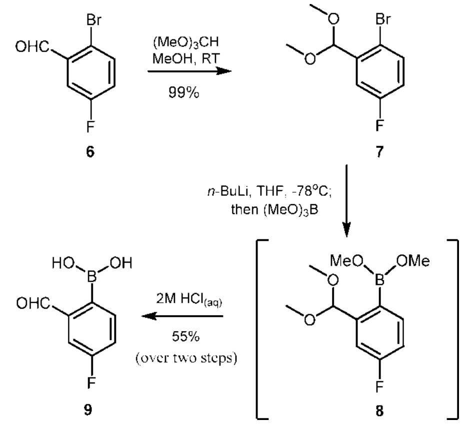
with one equivalent of (*rac*)-α-methyl-4-fluorobenzylamine **1** and one equivalent of 2-formyl-phenylboronic acid **2** in $CDCl_3$ for five minutes, resulting in quantitative formation of 50:50 mixtures of diastereomeric imino−boronate esters **4a−f/5a−f**. (Scheme 1, Supporting Information). As expected, baseline resolution of the imine resonances of each pair of diastereomeric imino−boronate esters **4a−f/5a−f** was observed in their ^{1}H NMR spectra in all cases. Moreover, nonequivalent fluorine resonances were also observed for each pair of diastereomeric imino−boronate esters **4a−f/5a−f** in their proton decoupled ^{19}F NMR spectra, with a $\Delta\delta F = 0.05-0.75$ ppm (Supporting Information). Therefore, it follows from previous precedent[6] that using enantiopure α-methyl-4-fluorobenzylamine **1**[10] as a chiral auxiliary in this derivatization protocol will enable the enantiopurity of scalemic diols to be accurately determined from their ^{1}H NMR or ^{19}F NMR spectra.

We then turned our attention to developing a more widely applicable fluorous protocol that would enable the enantiomeric purity of both diols and amines to be determined by ^{19}F NMR spectroscopy. Consequently, it was decided to prepare 4-fluoro-2-formylphenylboronic acid **9** as a new bifunctional template for carrying out our three-component derivatization protocol. This would result in formation of diastereomeric imino−boronate ester complexes containing fluorous tags within their central aryl cores, thus enabling any chiral amine (or chiral diol) to be used as a chiral auxiliary for derivatization. Therefore, commercially available 2-bromo-5-fluoro-benzaldehyde **6** was treated with trimethyl orthoformate in methanol at room temperature to afford acetal **7** in 99% yield. Treatment of acetal **7** with one equivalent of *n*-BuLi in THF at −78 °C resulted in halogen-lithiation exchange to afford an aryl anion that was quenched with trimethylborate to give boronate ester **8**, that was immediately treated with 2 M $HCl_{(aq)}$ to afford boronic acid **9** as a crystalline solid in 55% yield over two steps (Scheme 2).

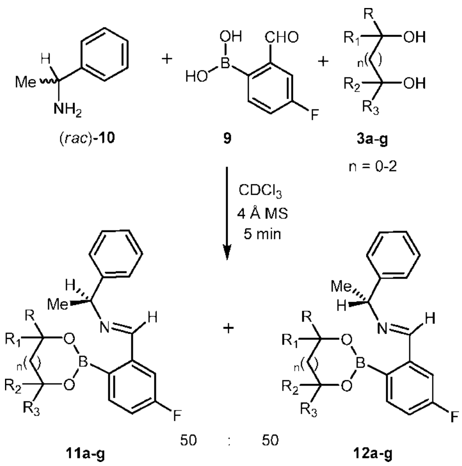
The scope and limitation of this new boronic acid template **9** was then investigated *via* treatment of a range of seven diols **3a−g** with 4-fluoro-2-formyl-phenylboronic acid **9** using (*rac*)-α-methylbenzylamine **10** as a chiral auxiliary. Analysis of the 400 MHz ^{1}H NMR spectra of the resultant 50:50 mixture of

(10) Enantiopure (*R*)- and (*S*)-α-methyl-4-fluorobenzylamine **1** are commercially available from Alfa Aesar at £34.20 per gram.

SCHEME 2. Synthesis of 4-Fluoro-2-formylphenylboronic Acid 9



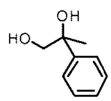
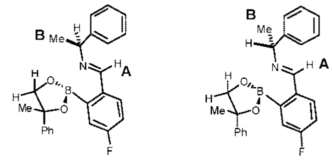
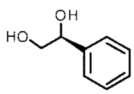
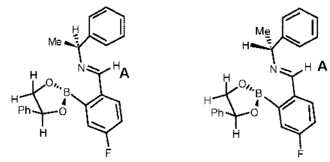
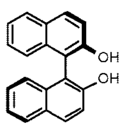
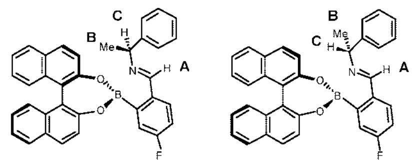
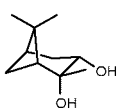
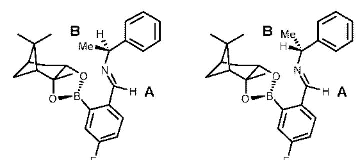
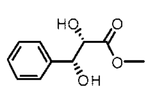
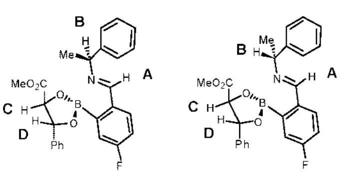
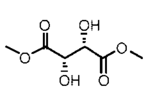
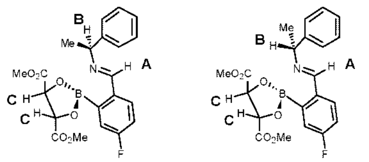
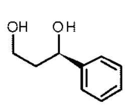
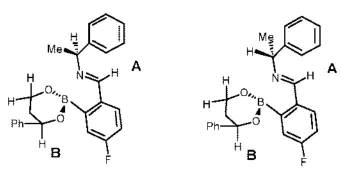
SCHEME 3. Three-Component Coupling Reaction of (*rac*)-α-Methyl-benzylamine 10, 4-Fluoro-2-formylphenyl Boronic Acid 9 and Diols 3a−g to Afford Diastereomeric Imino−Boronate Esters 11a−g/12a−g



the resultant diastereomeric iminoboronate esters **11a−g/12a−g** revealed that baseline resolution had been achieved for at least two sets of resonances in all cases (Scheme 3, Table 1). For example, analysis of the 400 MHz ^{1}H NMR spectra of a 50:50 mixture of iminoboronate esters **11e** and **12e** revealed that baseline resolution had been achieved for four distinct pairs of diastereomeric signals. Importantly, in all cases splitting of the imine signal was observed (0.05−0.35 ppm) in a region of the ^{1}H NMR spectra that was free of any other resonances. This feature is highly desirable since these imine resonances provide diagnostic resonances for integration that are independent of the diol being derivatized. Importantly, it was found that derivatization of each diol **3a−g** gave two sets of diastereomeric iminoboronate ester resonances in their ^{1}H NMR spectra, clearly indicating that free rotation around the aryl-boron bond was occurring on the NMR time scale.

We then investigated whether ^{19}F NMR spectroscopic analysis could be used to distinguish between the pairs of diastereoisomeric imino−boronate ester derivatives **11a−g/12a−g** as originally envisaged. Therefore, acquiring proton decoupled ^{19}F NMR spectra of the mixtures of diasteromeric boronate esters **11a−g/12a−g** revealed pairs of well resolved aryl-fluorine resonances in a 1:1 ratio in each case, with a $\Delta\delta$F splitting for each diastereomeric pair ranging from 0.03−0.30 ppm (Table 1).

TABLE 1. Chemical Shift Differences (δ) in the 300 MHz ^{1}H NMR and 400 MHz ^{19}F NMR Spectra of 50:50 Mixtures of Diastereomeric Imino−Boronate Esters 11a−g/12a−g Derived from 4-Fluoro-2-formylphenylboronic acid 9,(*rac*)-α-Methylbenzylamine 10 and Chiral Diols 3a−g

Diols 3a-f	Diastereoisomeric imino-boronate esters 11a-g/12a-f	Δδ ^{1}H NMR (ppm)	Δδ ^{19}F NMR (ppm)	δ^{11}B NMR (ppm)
 (*rac*)-**3a**	 (*rac*)-**11a** (*rac*)-**12a**	0.05 (A) 0.10 (B)	0.26	17.3
 (*S*)-**3b**	 (*S*,α-*S*)-**11b** (*S*,α-*R*)-**12b**	0.10 (A)	0.20	17.9
 (*R*)-**3c**	 (*R*,α-*S*)-**11c** (*R*,α-*R*)-**12c**	0.15 (A) 0.20 (B) 0.10 (C)	0.30	12.7
 (2*R*,3*S*)-**3d**	 (2*R*,3*S*,α-*S*)-**11d** (2*R*,3*S*,α-*R*)-**12d**	0.10 (A) 0.15 (B)	0.03	30.5
 (2*S*,3*R*)-**3e**	 (2*S*,3*R*,α-*S*)-**11e** (2*S*,3*R*,α-*R*)-**12e**	0.30 (A) 0.05 (B) 0.15 (C) 0.55 (D)	0.11	15.0
 (*S*,*S*)-**3f**	 (*S*,*S*,α-*S*)-**11f** (*S*,*S*,α-*R*)-**12f**	0.35 (A) 0.15 (B) 0.35 (C)	0.16	13.8
 (*R*)-**3g**	 (*R*,α-*S*)-**11g** (*R*,α-*R*)-**12g**	0.12 (A) 0.05 (B)	0.08	27.7

The detection limits of this new chiral derivatization protocol for determining the enantiopurity of scalemic samples of diol **3e** were then explored. Therefore, samples of methyl-(2*S*,3*R*)-dihydroxy-3-phenyl-propionoate **3e** of 80%, 90% and 98% ee respectively were treated with enantiopure (*R*)-α-methyl-benzylamine **10** and 2-formyl-4-fluorophenyl boronic acid **9** to afford three samples of their corresponding imino−boronate ester complexes (2*S*,3*R*,α-*R*)-**11e** and (2*R*,3*S*,α-*R*)-**12e**. Analysis of the ^{1}H NMR and ^{19}F NMR spectra of each sample revealed that the calculated diastereoisomeric excess for the resultant mixtures of (2*S*,3*R*,α-*R*)-**11e** and (2*R*,3*S*,α-*R*)-**12e** of 80%, 90%, and 98% de (^{1}H NMR) and 80%, 90% and 96% de (^{19}F NMR) were in excellent agreement with the known enantiopurity of the starting diol **3e** of 80%, 90% and 98% ee respectively (Figure 1). These values are well within the accepted 5% error limit normally accepted for CDA analysis using NMR spec-

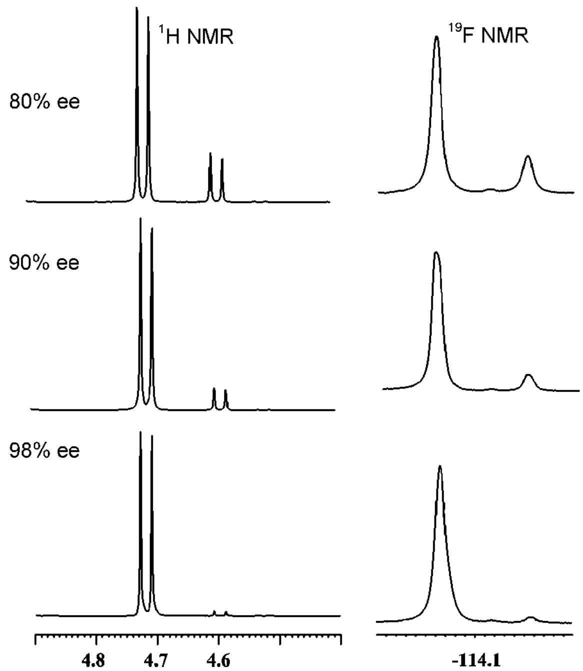


FIGURE 1. Expansion of ^{1}H NMR and ^{19}F NMR spectra of mixtures of (2*S*,3*R*,α-*R*)-**11e** and (2*R*,3*S*,α-*R*)-**12e** prepared from derivatization of diol (2*S*,3*R*)-**3e** of 80%, 90% and 98% ee.

troscopy, indicating that no kinetic resolution had occurred in the derivatization process. Therefore, these results clearly demonstrate that this new second generation CDA enables both ^{1}H and ^{19}F NMR spectroscopic analysis to be used to accurately determine the enantiomeric excess of a range of chiral diols in a highly practical manner. Furthermore, literature precedent[5,6] indicates that combining 2-formyl-4-fluorophenylboronic acid **9** with an enantiopure diol should provide an equally effective CDA for determining the ee of chiral amines via both ^{1}H and ^{19}F NMR spectroscopy.

In conclusion, we have developed a second generation derivatization protocol for determining the enantiomeric excess of a wide range of diols using ^{1}H and/or ^{19}F NMR spectroscopic analysis. We believe that the simplicity and speed of this approach and the wide range of substrates that it is capable of resolving warrants its consideration as a versatile method for determining the enantiomeric excess of chiral diols (or chiral amines) produced in asymmetric protocols.

Experimenal Section

4-Fluoro-2-formylphenylboronic Acid 9. *n*-Butyl-lithium (1.6 M in hexane, 56 mL, 89 mmol) was added dropwise via a syringe pump over a period of 1 h to a solution of 1-bromo-4-fluoro-2-dimethoxymethyl-benzene **7** (19 g, 76 mmol) in toluene/THF (4:1, 20 mL) at −78 °C under a nitrogen atmosphere. The mixture was stirred at −78 °C for an additional 30 min before being warmed to −20 °C and transferred dropwise *via* cannula to a solution of trimethylborate (9.2 g, 89 mmol) in toluene (10 mL) at −78 °C. The resulting solution was stirred at −78 °C for 1 h, warmed to −20 °C, before addition of 2 M $HCl_{(aq)}$ (74 mL) and the rapidly stirred solution allowed to warm slowly to room temperature. The organic layer was dried ($MgSO_4$), and solvent removed in vacuo to afford an oil that was recrystallized (hexane/Et_2O) to afford the title compound **9** (6.90 g, 41.00 mmol) as a white solid in 55% yield. m.p: 123−125 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.6 (2H, broad s), 7.5 (1H, dt, *J* = 8.1, 2.5 Hz), 7.7 (1H, dd, *J* = 8.8, 2.6 Hz), 8.3 (1H, dd, *J* = 7.9, 6.4 Hz), 9.8 (1H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 121.4, 121.6, 124.7, 141.6, 197.5; ^{11}B NMR (96 MHz, $CDCl_3$) δ 28.7;^{19}F NMR (400 MHz, $CDCl_3$) δ: −108.2; MS (*m*/*z*): Calcd $[M + Na]^+$; 191.0292, Found $[M + Na]^+$; 191.0286.

Supporting Information Available: General experimental procedures and synthesis of 1-bromo-4-fluoro-benzene **7**. Table of ^{1}H and ^{19}F NMR chemical shift differences of 50:50 mixtures of diastereoisomeric imino−boronate esters **4a−f/5a−f** derived from (*rac*)-α-methylbenzylamine **10** and chiral diols **3a-f**. ^{1}H and ^{19}F NMR spectra of 50:50 mixtures of diastereoisomeric imino−boronate esters **4a−f/5a−f** and **11a−g/12a−g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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