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A simple chiral derivatisation protocol for ^{1}H NMR spectroscopic analysis of the enantiopurity of *O*-silyl-1,2-amino alcohols

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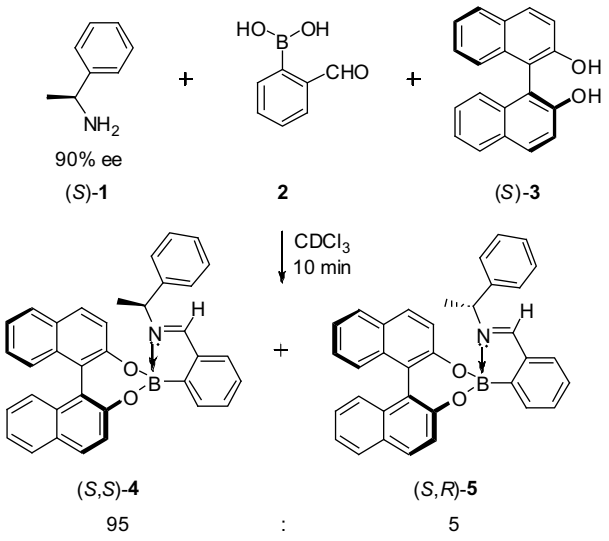
ABSTRACT

A simple chiral derivatisation protocol for determining the enantiopurity of *O*-silyl-protected-1,2-amino alcohols by ^{1}H NMR spectroscopic analysis is described, which involves their treatment with 2-formylphenylboronic acid and enantiopure (*syn*)-methyl-2,3-dihydroxy-3-phenylpropionate to afford mixtures of imino-boronate esters whose diastereoisomeric ratio is an accurate reflection of the enantiopurity of the parent amino alcohol.

Chiral 1,2-amino alcohols and their derivatives represent an important class of chiral building blocks for synthesis,[1] which have been widely used as privileged ligands for asymmetric catalysis,[2] and as chiral scaffolds for supramolecular,[3] or pharmaceutical applications.[4] Consequently, a wide range of different methodologies have been developed for their asymmetric synthesis using chiral auxiliaries, enantioselective catalysts or resolution procedures.[5] Therefore, the development of inexpensive chiral derivatisation protocols that allow their enantiomeric excesses (ee) to be rapidly determined is of great interest to the synthetic community.[6] Previous NMR-based chiral derivatisation approaches include reaction with modified Mosher's reagents to afford diastereoisomeric amides,[7] derivatisation with chiral aldehydes/ketones to afford diastereoisomeric imines[8] or conversion to oxazolidine-2-selones.[9] Their enantiomeric excess has also been determined by carrying out ^{1}H NMR spectroscopic analysis in the presence of chiral-solvating agents such as *O*-acetyl-mandelic acid[10] or *N*-Boc-phenylglycine.[11]

We had previously reported the development of versatile three-component derivatisation protocols for determining the enantiomeric excess of chiral primary amines,[12] chiral diols[13] and chiral vicinal C_2-symmetric diamines.[14] For example, derivatisation of scalemic (*S*)-α-methylbenzylamine **1** of 90% ee with 2-formylphenyl-boronic acid **2** and enantiopure BINOL (*S*)-**3** in $CDCl_3$ quantitatively affords a 95:5 mixture of diastereoisomeric imino-boronate esters (*S*,*S*)-**4** and (*S*,*R*)-**5**, whose diastereoisomeric ratio can be easily determined by ^{1}H NMR spectroscopic analysis (Scheme 1).[12] Alternatively, derivatisation of (*rac*)-1,2-diphenylethane-1,



Scheme 1. Three-component derivatisation of chiral amines to afford mixtures of diastereoisomeric imino-boronate esters, whose ratio is easily determined by ^{1}H NMR spectroscopic analysis.

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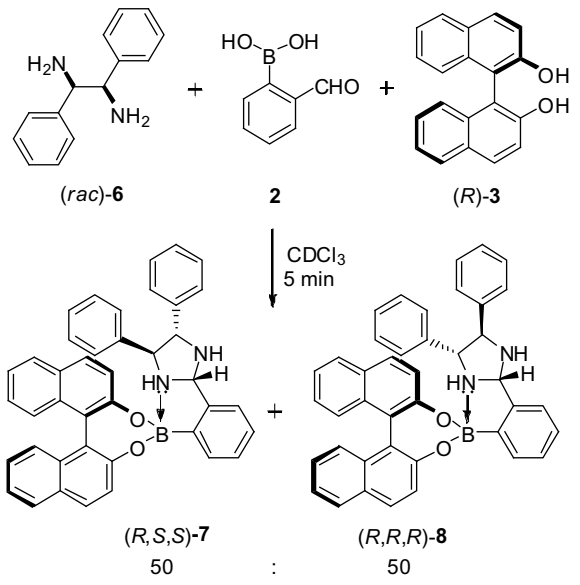
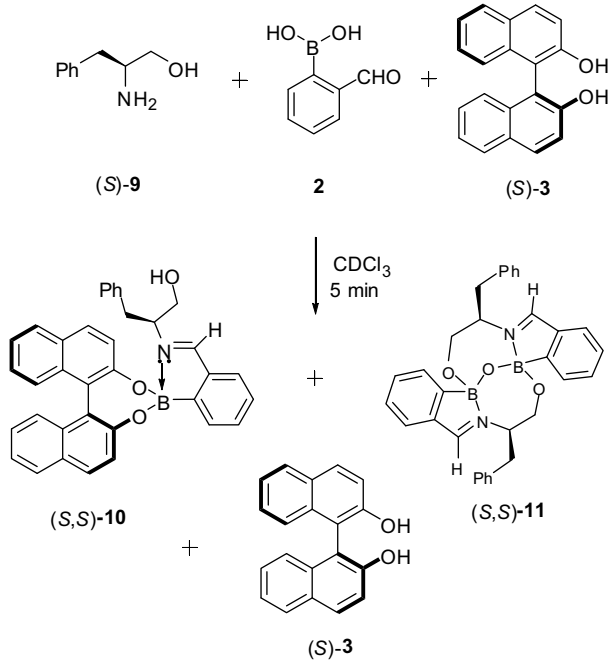
2-diamine **6** results in formation of a mixture of diastereoisomeric imidazolidine boronate esters (*R*,*S*,*S*)-**7** and (*R*,*R*,*R*)-**8**, whose diastereoisomeric excess is directly proportional to the enantiopurity of the parent diamine (Scheme 2).[14]

We proposed that this type of three-component NMR derivatisation protocol might also be useful for analysing the enantiopurity of chiral β-amino alcohols. Therefore, phenylglycinol (*S*)-**9** was treated with 1 equiv of 2-formylphenylboronic acid **2** and 1 equiv of enantiopure (*S*)-BINOL **3** in $CDCl_3$ and an ^1H NMR spectrum acquired after 5 min. This revealed that a complex mixture of species had been formed, including imino-boronate ester (*S*,*S*)-**10**, boracycle (*S*,*S*)-**11**[15] and unreacted BINOL (*S*)-**3** that was clearly unsuited for determining the enantiomeric excess of amino alcohols (Scheme 3).



Scheme 2. Three-component derivatisation of chiral diamines to afford diastereoisomeric imidazolidine-boronate esters, whose ratio can be determined by ^1H NMR spectroscopic analysis.



Scheme 3. Mixture of imine (*S*,*S*)-**10** and boracycle (*S*,*S*)-**11** formed from derivatisation of (*S*)-phenylglycinol **9** with 2-formylphenylboronic acid **2** and (*S*)-BINOL **3**.

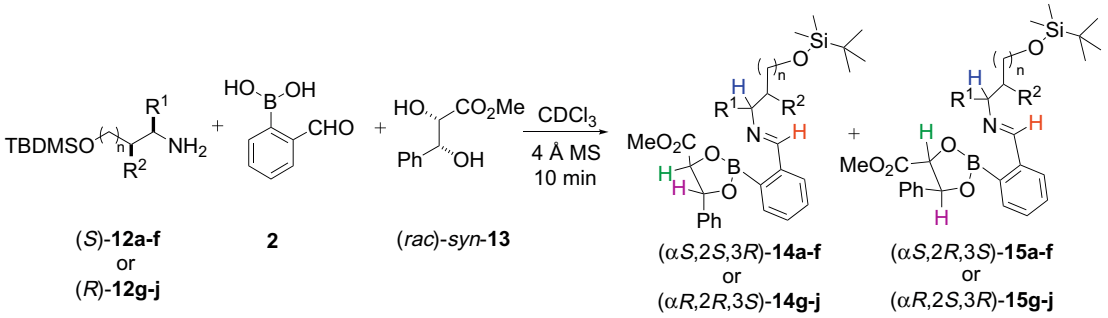
Consequently, an alternative approach was conceived, in which the hydroxyl functionality of the amino alcohol would first be *O*-silyl protected[16] prior to derivatisation (Table 1). We were aware that changing the structure of the chiral diol used for boronate ester formation had the potential to improve the performance of this three-component derivatisation protocol. Therefore, a series of 10 commercially available (*rac*)-diols were screened as chiral auxiliaries in derivatisation reactions of (*S*)-*O*-TBDMS-2-phenylglycinol **12a** with 2-formyl-phenylboronic acid **2** in $CDCl_3$.[17] This resulted in clean formation of 50:50 mixtures of their respective diastereoisomeric imino-boronate esters, whose 1H NMR spectra displayed between one and four pairs of baseline resolved diastereoisomeric resonances.

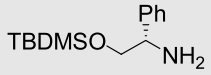
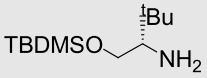
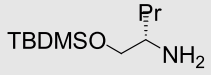
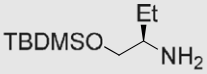
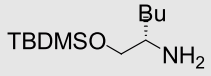
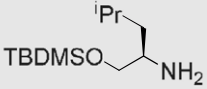
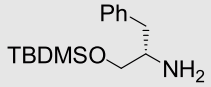
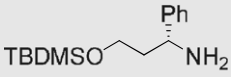
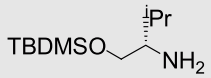
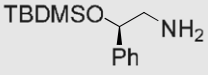
Analysis of the results from this screening study revealed that (*syn*)-methyl 2,3-dihydroxy-3-phenylpropionate **13** was a particularly efficient chiral auxiliary for resolving (*rac*)-**12a**, affording four pairs of baseline resolved diastereoisomeric resonances for its corresponding imino-boronate esters **14a/15a**. Consequently, diol **13** was chosen as a chiral auxiliary to explore the scope and limitation of this three-component derivatisation protocol for a range of ten chiral *O*-silyl-β-amino alcohols **12a–j**. Therefore, 1.0 equiv of 2-formylphenylboronic acid **2**, 1.1 equiv of (*rac*)-methyl (*syn*)-2,3-dihydroxy-3-phenylpropionate **13** and 1.0 equiv of enantiopure *O*-silyl-amino alcohols **12a–j** was dissolved in $CDCl_3$ in the presence of 4 Å molecular sieves, and the ^1H NMR spectra of an aliquot of each derivatisation reaction acquired after 10 min.[18] Analysis of the 400 MHz ^1H NMR spectra of the resultant 50:50 mixtures of diastereoisomeric imino-boronate esters **14a–j**/**15a–j** revealed that baseline resolution of at least one set of resonances had been achieved in all cases (see Table 1).[19] Importantly, in all cases, splitting of the imine signals of each pair of diastereoisomers **14a–j**/**15a–j** was observed (0.02–0.30 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, which are independent of the *O*-silyl-1,2-amino alcohol **12a–j** being derivatised.

The detection limits of this method were then determined by derivatisation of three samples of *O*-TBDMS-(*S*)-phenyl glycinol **12a** of 80% ee, 90% ee and 98% ee with enantiopure (2*S*,3*R*)-methyl 2,3-dihydroxy-3-phenylpropionate **13**, respectively. Analysis of the ^1H NMR spectrum for each sample showed that the calculated diastereomeric excess (de) for the resultant mixtures of imino-boronate esters (α*S*,2*S*,3*R*)-**14a** and (α*R*,2*S*,3*R*)-**15a** was in excellent agreement with the known enantiopurity of the starting amino alcohol **12a**. Therefore, the integrals revealed that (α*S*,2*S*,3*R*)-**14a** had been formed in 80%, 90% and 98% de, respectively, which correlated well with the known enantiopurity of the starting (*S*)-amino alcohol **12a**, thus indicating that no kinetic resolution had occurred. These values are well within the accepted 5% error limit normally accepted when using chiral derivatising agents for NMR spectroscopic analysis (Fig. 1).

In conclusion, we have developed a simple, chiral derivatisation protocol for determining the enantiopurity of chiral *O*-silyl-1,2-amino alcohols by ^1H NMR spectroscopic analysis. We believe that the simplicity and speed of this approach warrant consideration for determining the enantiopurity of many other types of primary 2-amino alcohols.

Table 1
Multicomponent coupling reactions of (*S*)-*O*-silyl-1,2-amino alcohols **12a–f** and (*R*)-*O*-silyl-1,2-amino alcohols **12g–j** with 2-formylphenylboronic acid **2** and (*rac*)-*syn*-methyl 2,3-dihydroxy-3-phenylpropionate **13** to afford 50:50 mixtures of diastereoisomeric iminoboronate esters (α*S*,2*S*,3*R*)-**14a–f**/(α*S*,2*R*,3*S*)-**14g–j** and (α*R*,2*R*,3*S*)-**15a–f**/(α*R*,2*S*,3*R*)-**15g–j**



O-silyl-β-aminoalcohol (*S*)-**12a-e**	Δδ (ppm)	*O*-silyl-β-aminoalcohol (*S*)-**12f** and (*R*)-**12g-i**	Δδ (ppm)
 (*S*)-**12a**	0.30 0.03 0.37 0.10	 (*S*)-**12f**	0.13
 (*S*)-**12b**	0.07 0.03	 (*R*)-**12g**	0.06 0.03
 (*S*)-**12c**	0.06	 (*R*)-**12h**	0.10 0.06 0.06
 (*S*)-**12d**	0.02 0.09 0.03	 (*R*)-**12i**	0.27 0.15 0.28 0.13
 (*S*)-**12e**	0.07 0.04 0.03 0.12	 (*R*)-**12j**	0.14

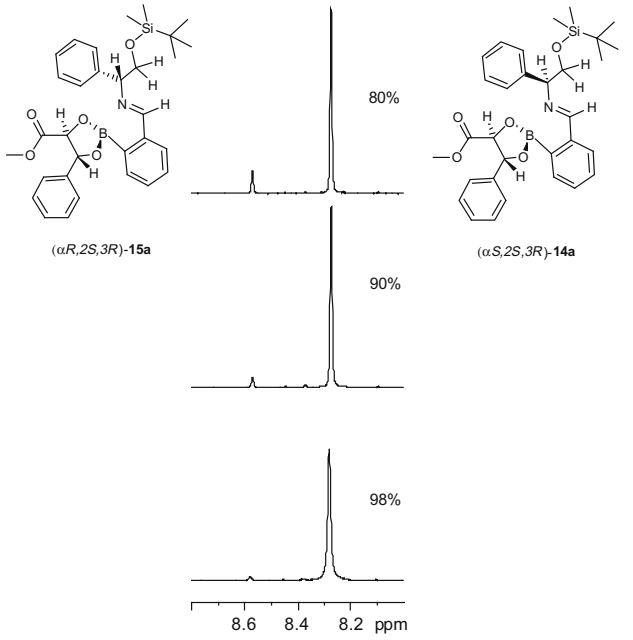


Figure 1. Expansion of the ^{1}H NMR spectra of mixtures of (α*S*,2*S*,3*R*)-**14a** and (α*R*,2*S*,3*R*)-**15a** prepared from (*S*)-phenylglycinol **14a** of 80%, 90% and 98% ee.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.013.

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16. *O*-Silyl-1,2-amino alcohols **12a–i** were prepared in 80–95% yield via silylation of their parent 1,2-amino alcohol according to the general procedure described by Novachek, K. A.; Meyers, A. I. *Tetrahedron Lett.* **1996**, *37*, 1743.
17. The (*rac*)-diols that were screened in these ^{1}H NMR derivatisation protocols were BINOL, (*syn*)-methyl 2,3-dihydroxy-3-phenylpropionate, dimethyltartrate, dibenzyltartrate, phenyl-ethane-1,2-diol, 2-phenyl-1,2-propanediol, 3,3-dimethyl-1,2-butanediol, 1,2-propanediol, 1,3-butanediol and 2,3-pinanediol.
18. Enantiopure *O*-silyl-amino alcohols **12a–j** and (*rac*)-*syn*-diol **13** were used for experimental simplicity because it enabled a single stock solution of (*rac*)-**13** to be used for derivatisation.
19. For a detailed experimental account of how to determine enantiomeric excess using this derivatisation technique see Ref. 12d.