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Simple Protocol for NMR Analysis of the Enantiomeric Purity of Primary Amines

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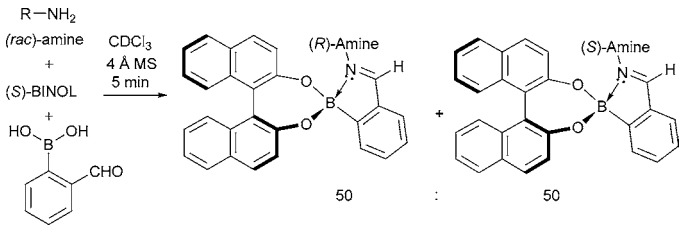
ABSTRACT



A practically simple three-component chiral derivatizing protocol for determining the enantiopurity of 13 chiral primary amines by ^{1}H NMR spectroscopic analysis is described, including analysis of those that contain remote stereocenters.

Chiral primary amines have many important chemical and pharmaceutical applications, and as a consequence, a wide range of methodologies have been developed for their asymmetric synthesis.[1] Therefore, the development of inexpensive chiral derivatization protocols that enable their enantiomeric excess (ee) to be simply determined by NMR spectroscopic analysis is currently of great interest to the synthetic community.

The most widely used chiral derivatizing agent (CDA) for determining the enantiomeric purity of chiral amines using NMR spectroscopy[2] involves derivatization to afford either MTPA (Mosher) or MPA (Trost) amides.[3,4] Despite its popularity, this methodology has its limitations, including the expense and moisture sensitivity of the acid chloride reagents, the potential for kinetic resolution with sterically demanding amines,[5] and the need to run both ^{1}H and ^{19}F NMR experiments for an accurate determination of enantiomeric purity.

As part of ongoing research programs, we required access to a robust, inexpensive protocol for rapidly determining the enantiomeric excess of a wide range of structurally diverse amines by NMR spectroscopy. In this respect, our goal was to identify inexpensive commercially available reagents that would react rapidly with a chiral amine substrate under mild conditions with no kinetic resolution occurring. Most CDAs involve covalent derivatization of a chiral substrate using a single chiral entity to afford diastereoisomers, which exhibit different chemical shifts due to the presence of different anisotropic shielding or deshielding interactions caused by aryl substituents within the CDA.[6] We envisaged an alternative "three-component" strategy, in which an achiral bifunctional aryl template would simultaneously coordinate a chiral

(1) For recent developments, see: (a) Wang, C.-J.; Sun, X.; Zhang, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 4933−4935. (b) Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549−1551. (c) Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182−7183. (d) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472−5474.

(2) For representative examples, see: (a) Rodríguez-Escrich, S.; Popa, D.; Jimeno, C.; Vidal-Ferran, A.; Pericàs, M. A. *Org. Lett.* **2005**, *7*, 3829−3832. (b) Chin, J.; Kim, D. C.; Kim, H.-J.; Panosyan, F. B.; Kim, K. M. *Org. Lett.* **2004**, *6*, 2591−2593. (c) López, B.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1999**, *121*, 9724−9725. (d) Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 4669−4675. (e) Chinchilla, R.; Falvello, L. R.; Nájera, C. *J. Org. Chem.* **1996**, *61*, 7285−7290. (f) Hoye, T. R.; Renner, M. K. *J. Org. Chem.* **1996**, *61*, 8489−8495.

(3) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143−2147.

(4) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202−4205.

(5) (a) Svatos, A.; Valterova, I.; Saman, D.; Vrkoc, J. *Collect. Czech. Chem. Commun.* **1990**, *55*, 485−490. (b) Hietaniemi, L.; Pohjala, E.; Malkonen, P.; Riekkola, M. L. *Finn. Chem. Lett.* **1989**, *16*, 67−73.

(6) For a discussion of the mode of action of commonly used CDAs and their use for predicting absolute configuration by ^{1}H NMR spectroscopy, see: Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17−117.

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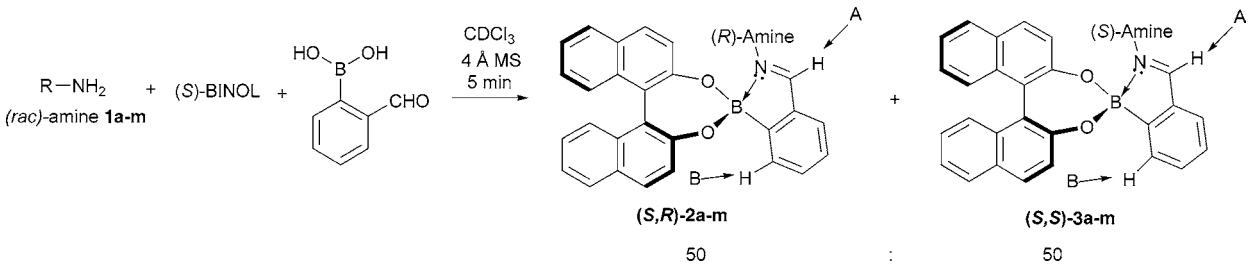
Scheme 1. Three-Component Coupling Reaction of 2-Formylphenylboronic Acid, (*S*)-BINOL, and (*rac*)-Amines **1a**−**m** to Afford Diastereoisomeric Imino-Boronate Esters (*S*,*R*)-**2a**−**m** and (*S*,*S*)-**3a**−**m**



aryl ligand and either enantiomer of a chiral amine substrate. It was proposed that this design would result in structurally rigid diastereoisomeric complexes whose amine fragments would experience significantly different anisotropic effects due to the presence of more than one aryl substituent, thus resulting in significant differences in their ^{1}H NMR spectra.

A review of the literature revealed that Dunn et al. had reported that refluxing mixtures of 2-formylphenylboronic acid, catechol, and a series of achiral primary amines in benzene had resulted in the formation of highly stable imino-boronate esters in good yield.[7] We proposed that repeating this reaction using an enantiopure diol and a primary amine as substrates might be ideally suited for the development of a three-component method for determining the enantiopurity of chiral primary amines.[8] To test this hypothesis, 1.0 equiv of 2-formylphenylboronic acid (bifunctional aryl template), 1.1 equiv of (*S*)-BINOL (chiral aryl ligand), and 1.0 equiv of (*rac*)-α-methyl-*p*-methoxybenzylamine **1a** were dissolved in $CDCl_3$ in the presence of 4 Å molecular sieves, and the ^{1}H NMR spectra of an aliquot was acquired after 5 min (Scheme 1). The resultant ^{1}H 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,[9] whose respective imine, α-methine, α-methyl, and *p*-methoxy resonances were all well resolved. This observation was highly promising because it meant that comparison of the relative intensities of four different sets of integrals could potentially be used to accurately confirm the enantiopurity of a scalemic sample of this amine by ^{1}H NMR spectroscopy.

To investigate the scope and limitation of this chiral derivatization protocol, a range of eight additional racemic amines **1b**−**i** containing stereogenic centers at their α-positions were then derivatized. The diagnostic differences in their chemical shifts are summarized in Table 1. Analysis of the 300 MHz ^{1}H NMR spectra of the resultant 50:50 mixture of diastereoisomeric imino-boronate esters (*S*,*R*)-**2a**−**i** and (*S*,*S*)-**3a**−**i** reveals that baseline resolution was achieved for at least three sets of resonances in all cases.[10] The individual resonances corresponding to each pair of diastereoisomers were then assigned by comparison with the ^{1}H NMR spectra of authentic samples of (*S*,*R*)-**2a**−**k** and (*S*,*S*)-**3a**−**k** prepared independently via reaction of enantiopure amines **1a**−**k** with either (*R*)- or (*S*)-BINOL, respectively.[11] Therefore, these results clearly demonstrate that this derivatization approach appeared to be well suited for determining the enantiopurity of a wide range of chiral primary amines, including α-arylethylamines, α-methylalkylamines, *β*-amino ethers, α-amino esters, and *β*-amino esters. Furthermore, comparison of the $\Delta\delta$ values of the diastereoisomeric complexes (*S*,*R*)-**2a**−**c** and (*S*,*S*)-**3a**−**c** (Table 1, entries 1−3) revealed the same magnitude and sign of chemical shift differences for three sets of related resonances (A, C, and D), thus indicating that this derivatization approach can be used as a technique for predicting the absolute configuration of α-arylethylamines. Similarly, examination of the ^{1}H NMR spectra of imino-boronate esters (*S*,*R*)-**2f**−**h** and (*S*,*S*)-**3f**−**h** (Table 1, entries 5−8) revealed that the *O*-methoxy (or *O*-*tert*-butyl) ester resonances of (*S*,*S*)-**3f**−**h** were significantly more deshielded than those for their corresponding (*S*,*R*)-**2f**−**h** diastereoisomers, thus demonstrating its potential for predicting the absolute configuration of α-amino esters.

We next investigated whether these types of complexes could be used to determine the enantiopurity of primary amines **1j**−**m** that contained remote stereogenic centers,[12] the results of which are described in Table 2. Therefore, it was found that treatment of racemic amines **1j**−**m** with 2-formylphenylboronic acid and (*S*)-BINOL under standard conditions afforded pairs of diastereoisomeric complexes (*S*,*R*)-**2j**−**m** and (*S*,*S*)-**3j**−**m**, whose stereogenic methyl groups were all baseline resolved in their ^{1}H NMR spectra. In the case of (*rac*)-amine **1l**, carrying out the derivatization

(7) Dunn, H. E.; Catlin, J. C.; Snyder, H. R. *J. Org. Chem.* **1968**, *33*, 4483−4486.

(8) For a previous example of an imine bond forming reaction being used to develop a CDA using 1*R*-(−)-myrtenal as a chiral auxiliary to determine the enantiomeric excess of primary amines containing α-stereocenters with small $\Delta\delta$ values, see: Dufrasne, F.; Gelbcke, M.; Nève, J. *Spectrochim. Acta, Part A* **2003**, *59*, 1239−1245.

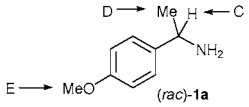
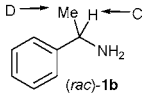
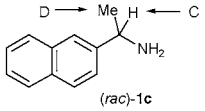
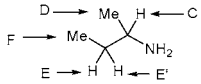
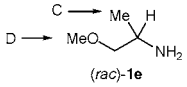
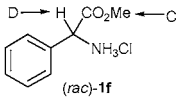
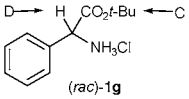
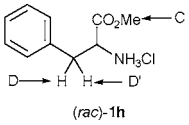
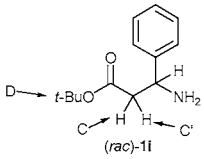
(9) For previous examples where imino-boron complexes of enantiopure BINOL have been used for asymmetric catalysis, see: (a) Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520−10524. (b) Cros, J. P.; Pérez-Fuertes, Y.; Thatcher, M. J.; Arimori, S.; Bull, S. D.; James, T. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1965−1968.

(10) Similar structures have been reported for diastereoisomeric amino-boronate ester complexes derived from enantiopure proline that were used for the resolution of (*rac*)-BINOL via fractional recrystallisation. See: Shan, Z.; Xiong, Y.; Li, W.; Zhao, D. *Tetrahedron: Asymmetry* **1998**, *9*, 3985−3989.

(11) The structures of (*S*,*R*)-**2b** and (*S*,*S*)-**3b** were confirmed by single-crystal X-ray analysis.

(12) For a previous example of CDA used to determine the enantiomeric purity of primary amines containing remote stereocenters, see: Weix, D. J.; Dreher, S. D.; Katz, T. J. *J. Am. Chem. Soc.* **2000**, *122*, 10027−10032.

Table 1. Chemical Shift Differences ($\Delta\delta$) in the 300 MHz ^{1}H NMR Spectra of 50:50 Mixtures of (*S*,*R*)-**2a**−**i** and (*S*,*S*)-**3a**−**i** Derived from Racemic Primary Amines **1a**−**i** that Contain α-Stereogenic Centers

entry	(*rac*)-amine (R-NH_2)	boronate complexes	$\Delta\delta$ (δ_{SR} - δ_{SS}) (ppm)[a]
1	 (*rac*)-**1a**	(*S*,*R*)-**2a** + (*S*,*S*)-**3a**	0.20 (A) -0.11 (C) 0.21 (D) -0.15 (E)
2	 (*rac*)-**1b**	(*S*,*R*)-**2b** + (*S*,*S*)-**3b**	0.17 (A) -0.10 (C)[b] 0.21 (D)
3	 (*rac*)-**1c**	(*S*,*R*)-**2c** + (*S*,*S*)-**3c**	0.17 (A) -0.09 (C)[c] 0.20 (D)
4	 (*rac*)-**1d**	(*S*,*R*)-**2d** + (*S*,*S*)-**3d**	0.11 (C) 0.15 (D) -0.19 (E) -0.13 (E') -0.22 (F)
5	 (*rac*)-**1e**	(*S*,*R*)-**2e** + (*S*,*S*)-**3e**	-0.09 (A) 0.09 (B) 0.14 (C) -0.20 (D)
6[d]	 (*rac*)-**1f**	(*S*,*R*)-**2f** + (*S*,*S*)-**3f**	-0.05 (B) -0.52 (C) -0.02 (D)
7[d]	 (*rac*)-**1g**	(*S*,*R*)-**2g** + (*S*,*S*)-**3g**	-0.43 (A) 0.10 (B) -0.67 (C) -0.05 (D)
8[d]	 (*rac*)-**1h**	(*S*,*R*)-**2h** + (*S*,*S*)-**3h**	0.39 (A) -0.34 (C) 0.13 (D) 0.19 (D')
9	 (*rac*)-**1i**	(*S*,*R*)-**2i** + (*S*,*S*)-**3i**	0.38 (A) -0.12 (B) -0.21 (C) 0.20 (C') 0.19 (D)

[a] A negative value indicates that the resonance corresponding to the (*S*,*S*)-diastereoisomer is more deshielded than the (*S*,*R*)-diastereoisomer. [b] The quartet corresponding to the methine proton of the (*S*,*S*)-**3b** partially overlaps with the resonance of phenolic protons of residual (*S*)-BINOL; these signals no longer overlap on addition of 5 mol % of d_6-acetone to the NMR tube. [c] The quartet corresponding to the methine proton of (*S*,*R*)-**3c** partially overlaps with the resonance of phenolic protons of residual (*S*)-BINOL. [d] 1.1 equivalents of cesium carbonate was added to liberate the free amine, with excess cesium carbonate being removed by filtration, through a small plug of celite prior to ^{1}H NMR spectrosocpic analysis.

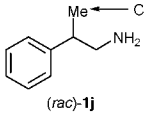
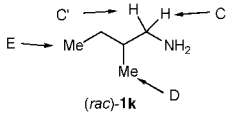
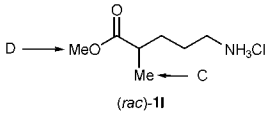
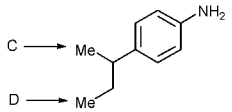
reaction in $CDCl_3$ resulted in only partial resolution of the methyl substituents of (*S*,*R*)-**2l** and (*S*,*S*)-**3l**; however, repeating this derivatization reaction in d_6-acetone resulted in baseline resolution of the two diastereoisomeric methyl groups.[13] Therefore, it is clear that this derivatization approach is also capable of distinguishing between the (*R*) and (*S*) enantiomers of amines **2j**−**m** that contain stereogenic centers at positions up to five bonds away from the amine functionality.

The detection limits of this new derivatization method were then determined by derivatizing three samples of (*R*)-α-methylbenzylamine (*R*)-**1b** of 80%, 90%, and 98% ee, respectively, using enantiopure (*S*)-BINOL as a ligand for complex formation. Analysis of the ^{1}H NMR spectrum of each sample revealed that the calculated diastereomeric excesses (de's) for the resultant mixture of (*S*,*R*)-**2b** and (*S*,*S*)-**3b** were in excellent agreement with the known enantiomeric purity of the starting α-methylbenzylamine. Thus, the ^{1}H NMR integrals measured for formation of (*S*,*R*)-**2b** of 80%, 90%, and 97% de correlated well with the known enantiopurity of the starting (*R*)-amine **1b** of 80%, 90%, and 98% ee, respectively, thus indicating that little or no kinetic resolution had occurred.

The suitability of this approach was also demonstrated for determining the diastereomeric excess of mixtures of iminoboronate esters prepared from enantiopure amines (*S*)-**1a**, (*R*)-**1d**, or (*S*)-**1e**, 2-formylphenylboronic acid, and (*S*)-BINOL of 90% ee. In each case, the de calculated from ^{1}H

(13) This derivatizing agent may be used in a wide range of NMR solvents including $CDCl_3$, CD_2Cl_2, d_6-acetone, and d_6-benzene as required.

Table 2. Chemical Shift Differences ($\Delta\delta$) in the 300 MHz ^{1}H NMR Spectra of 50:50 Mixtures of (*S*,*R*)-**2j**−**m** and (*S*,*S*)-**3j**−**m** Derived from Racemic Primary Amines **1j**−**m** that Contain Remote Stereogenic Centers

entry	amine	boronate complexes	$\Delta\delta$ (δ_{RR} - δ_{SS}) (ppm)[a]
1	 (*rac*)-**1j**	(*S*,*R*)-**2j** + (*S*,*S*)-**3j**	-0.22 (C)
2	 (*rac*)-**1k**	(*S*,*R*)-**2k** + (*S*,*S*)-**3k**	-0.08 (B) -0.31 (C) 0.30 (C') -0.11 (D) 0.40 (E)
3[c]	 (*rac*)-**1l**	(*S*,*R*)-**2l** + (*S*,*S*)-**3l**	0.04 (C)[b,c] 0.02 (D)[b,c]
4	 (*rac*)-**1m**	(*S*,*R*)-**2m** + (*S*,*S*)-**3m**	0.02 (B)[c] 0.02 (C)[c] 0.03 (D)[c]

[a] See Table 1. [b] ^{1}H NMR run in d_6-acetone. [c] Unable to assign a sign to the $\Delta\delta$ values of these resonances because an enantiopure sample of amines **1l** and **1m** were not available.

NMR integral analysis of the resultant mixture of complexes **2a**/**3a**, **2d**/**3d**, and **2e**/**3e** of 86−90% de was consistent with the 90% de values known from using (*S*)-BINOL of 90% ee for amine derivatization. This is well within the accepted 5% error limit normally accepted for CDA analysis using NMR spectroscopy.[14]

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

Acknowledgment. We wish to thank the University of Bath, the EPSRC, and the Royal Society for financial support. We would also like to thank the Mass Spectroscopic Service at Swansea, University of Wales.

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

OL052776G

(14) For examples, see: (a) Hulst, R.; Zijlstra, R. W. J.; de Vries, N. K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 1701−1710. (b) Kolodiazhyni, O. I.; Demchuk, O. M.; Gerschkovich, A. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1729−1732. (c) Caselli, E.; Danieli, C.; Morandi, S.; Bonfiglio, B.; Forni, A.; Prati, F. *Org. Lett.* **2003**, *5*, 4863−486.