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A Simple Protocol for NMR Analysis of the Enantiomeric Purity of Chiral Hydroxylamines

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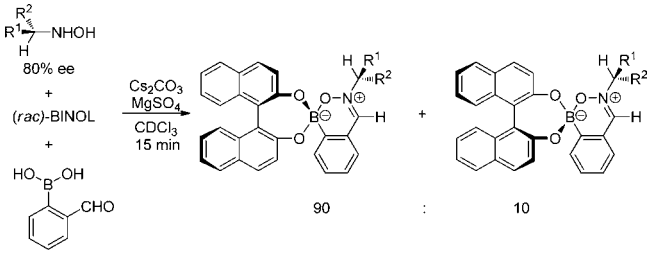
ABSTRACT



A practically simple three-component chiral derivatization protocol for determining the enantiopurity of chiral hydroxylamines by ^{1}H NMR spectroscopic analysis is described, involving their treatment with 2-formylphenylboronic acid and enantiopure BINOL to afford a mixture of diastereomeric nitrono-boronate esters whose ratio is an accurate reflection of the enantiopurity of the parent hydroxylamine.

Chiral hydroxylamines and their derivatives exhibit a wide range of biological properties[1] and have been used as substrates for a wide range of synthetic methodology. This includes reaction with α-keto-acids to afford amide bonds,[2] their use as reagents for the asymmetric α-oxyacylation of cyclic ketones,[3] as substrates for the preparation of chiral Weinreb amide derivatives,[4] and their condensation with aldehydes to afford chiral nitrones as substrates for asymmetric reactions.[5] Hydroxylamines have also been employed as versatile chiral building blocks for the preparation of chiral hydroxamic acids,[6] β-amino acids,[7] peptides,[8] and a number of natural products.[9] They are normally prepared *via* oxidation of the parent chiral amine,[10] stereoselective reduction of the corresponding oxime,[11] or amination of chiral enolates.[12] Therefore, the

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(1) (a) Vigh, L.; Literati, P. N.; Horvath, I.; Torok, A.; Balogh, G.; Glatz, A.; Kovacs, E.; Boros, I.; Ferdinandy, P.; Farkas, B.; Jaszlits, L.; Jednakovits, A.; Kornayi, L.; Maresca, B. *Nat. Med.* **1997**, *3*, 1150–1154. (b) Igarashi, N.; Moriyama, H.; Fujiwara, T.; Fukumori, Y.; Tanaka, N. *Nat. Struct. Biol.* **1997**, *4*, 276–284. (c) Hanna, P. E. *Curr. Med. Chem.* **1996**, *3*, 195–210. (d) Hogg, J. H.; Ollmann, I. R.; Haeggstrom, J. Z.; Wetterholm, A.; Samuelsson, B.; Wong, C. H. *Bioorg. Med. Chem.* **1995**, *3*, 1405–1415.

(2) (a) Bode, J. W.; Fox, R. M.; Baucom, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1248–1252. (b) Pusterla, I.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 513–516.

(3) Smithen, D. A.; Mathews, C. J.; Tomkinson, N. C. O. *Org. Biomol. Chem.* **2012**, *10*, 3756–3762.

(4) Chernega, A. N.; Davies, S. G.; Goodwin, C. J.; Hepworth, D.; Kurosawa, W.; Roberts, P. M.; Thompson, J. E. *Org. Lett.* **2009**, *11*, 3254–3257.

(5) (a) Chang, Z. Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464–3474. (b) Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron* **1985**, *41*, 3455–3462. (c) Jost, S.; Gimbert, Y.; Greene, A. E.; Fotiadu, F. *J. Org. Chem.* **1997**, *62*, 6672–6677. (d) Goti, A.; Cicchi, S.; Mannucci, V.; Cardona, F.; Guarna, F.; Merino, P.; Tejero, T. *Org. Lett.* **2003**, *5*, 4235–4238. (e) Nguyen, T. B.; Martel, A.; Dhal, R.; Dujardin, G. *Org. Lett.* **2008**, *10*, 4493–4496. (f) Fassler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M *Angew. Chem., Int. Ed.* **2002**, *41*, 3054–3056.

(6) (a) Hoshino, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 10452–10453. (b) Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 286–287.

(7) (a) Hanselmann, R.; Zhou, J. C.; Ma, P.; Confalone, P. N. *J. Org. Chem.* **2003**, *68*, 8739–8741. (b) Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E.; Toms, S. M. *Tetrahedron* **2010**, *66*, 4604–4620.

(8) Wang, L.; Phanstiel, O. *J. Org. Chem.* **2000**, *65*, 1442–1447.

(9) (a) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 4900–4901. (b) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778–7786. (c) White, J. D.; Hansen, J. D. *J. Org. Chem.* **2005**, *70*, 1963–1977. (d) Patel, S. K.; Murat, K.; Py, S.; Vallee, Y. *Org. Lett.* **2003**, *5*, 4081–4084.

(10) (a) Tokuyama, H.; Kuboyama, T.; Amano, A.; Yamashita, T.; Fukuyama, T. *Synthesis* **2000**, 1299–1304. (b) Heydari, A.; Aslanzadeh, S. *Adv. Synth. Catal.* **2005**, *347*, 1223–1225. (c) Patel, I.; Smith, N. A.; Tyler, S. N. G. *Org. Process Res. Dev.* **2009**, *13*, 49–53. (d) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 1981–1983. (e) Wang, Q. X.; King, J.; Phanstiel, O. *J. Org. Chem.* **1997**, *62*, 8104–8108.

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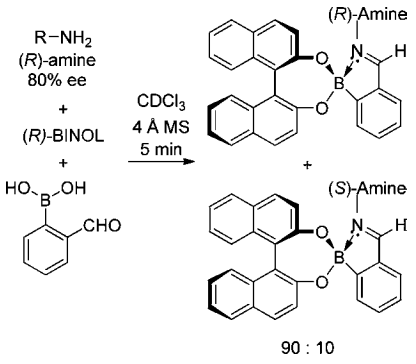
development of a simple, rapid, and inexpensive chiral derivatization protocol to enable the enantiomeric excess (*ee*) of chiral hydroxylamines to be determined by NMR spectroscopic analysis would be of great interest.

We have previously reported the development of chiral derivatization protocols for determining the *ee* of chiral primary amines, diamines, amino alcohols, and diols.[13] For the case of primary amines, the protocol involves derivatization of a chiral amine with 2-formylphenylboronic acid and enantiopure BINOL in $CDCl_3$ to quantitatively afford a mixture of diastereomeric iminoboronate esters (Scheme 1). The diastereomeric ratio (*dr*) of these complexes may then be determined by ^{1}H NMR spectroscopic analysis, and since no kinetic resolution occurs, this ratio is an accurate reflection of the *ee* of the parent amine. We now report herein that this type of three-component NMR derivatization protocol is also applicable for determining the *ee* of chiral hydroxylamines.

A series of chiral hydroxylamines **1a**–**h** were prepared from their parent chiral amines by adaptation of the literature procedure of Wovkulich and Uskoković,[14] using a two-step protocol that had been reported previously to proceed with no racemization.[15] 1.0 equiv of (*R*)-*N*-(1-phenylethyl) hydroxylamine **1a** was then treated with 1.0 equiv of 2-formylphenylboronic acid, 1.1 equiv of (*rac*)-BINOL, and 1.1 equiv of Cs_2CO_3 in $CDCl_3$ in the presence of $MgSO_4$ and stirred for 15 min (Table 1). The reaction mixture was then filtered, and a ^{1}H NMR spectrum was acquired which revealed clean formation of a 50:50 mixture of diastereomeric nitrono-boronate ester complexes (*R*,*R*)-**2a** and (*R*,*S*)-**3a** in quantitative yield, with baseline resolution observed for the benzylic (**B**) and methyl (**C**) protons of each diastereomer respectively (Table 1). This meant that the relative intensities of two different sets of diastereomeric integrals can be compared to accurately determine the enantiopurity of a scalemic sample of the parent hydroxylamine by ^{1}H NMR spectroscopy.

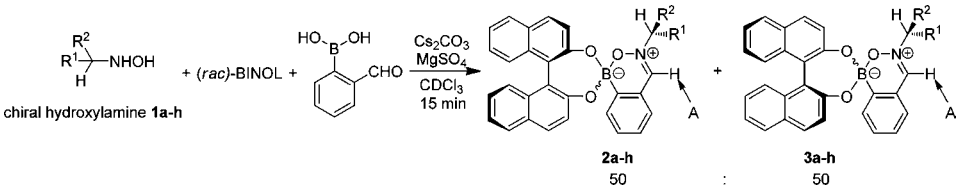
To investigate the scope and limitations of this chiral derivatization protocol further, the remaining hydroxylamines **1b**–**h** were then derivatized under the same conditions. Analysis of the 500 MHz ^{1}H NMR spectra of the resultant 50:50 mixture of diastereomeric nitrono-boronate esters **2b**–**g**/**3b**–**g** revealed a baseline resolution of at least two sets of resonances had occurred in all cases. For example, analysis of the 500 MHz ^{1}H NMR spectrum of a 50:50 mixture of nitrono-boronate esters **2e** and **3e** revealed that baseline resolution had occurred for three distinct sets of resonances with the largest $\Delta\delta$ value of 0.193 ppm being observed for their imine protons (**A**). In all cases splitting of the α-protons (**B**) and methyl protons (**C**) of the hydroxylamine fragments of **2b**–**g**/**3b**–**g** were observed.[16] The individual resonances of each pair of diastereomers were assigned by comparison with the ^{1}H NMR spectra of authentic samples of diastereomerically pure **2a**–**h** and **3a**–**h** that were prepared independently *via* a separate reaction of enantiopure hydroxylamines **1a**–**h** with (*R*)-BINOL and (*S*)-BINOL respectively. The $\Delta\delta$ differences in the chemical shifts observed for each pair of diastereomeric nitrono-boronate esters are reported in Table 1. The resonances of the α-protons (**B**) of the heterochiral diastereomers **2a**–**e** were found to be shielded relative to the resonances for their corresponding homochiral diastereomers **3a**–**e**. Conversely the resonances of the α-methyl protons (**C**) of the heterochiral diastereomers **3a**–**e** were deshielded relative to the resonances of their corresponding homochiral diastereomers **2a**–**e**. Therefore, consideration of the sign of the $\Delta\delta$ value may potentially be used to assign the unknown configuration of chiral α-methyl, α-aryl hydroxylamines formed in asymmetric protocols. The detection limit of this protocol was determined via derivatization of three samples of (*rac*)-BINOL of 98%, 80%, and 0% with enantiopure hydroxylamine **1b** and 2-formylphenyl-boronic acid.[17] Analysis of the ^{1}H NMR spectra of each sample revealed that the calculated diastereomeric ratio of the resultant mixture of (*S*,*S*)- **2b** and (*S*,*R*)-**3b** were in good agreement

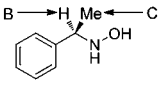
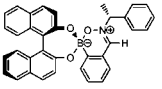
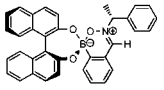
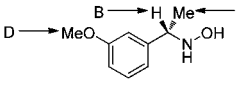
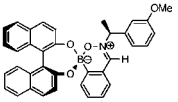
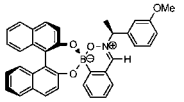
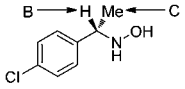
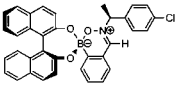
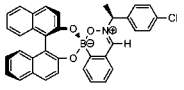
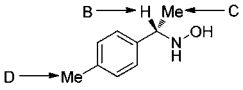
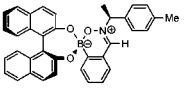
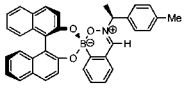
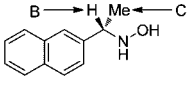
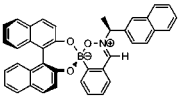
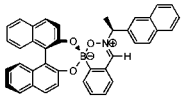
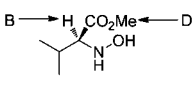
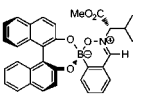
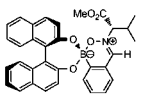
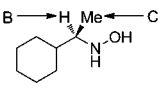
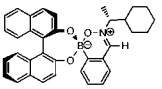
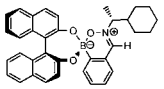
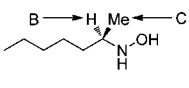
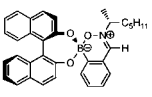
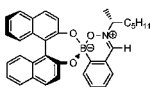
Scheme 1. Previously Reported Chiral Derivatization Protocol for Determining the Enantiopurity of Chiral Amines



(11) Feuer, H.; Vincent, B. F. *J. Am. Chem. Soc.* **1962**, *84*, 3771–3772.
(12) Oppolzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991–994.
(13) (a) Kelly, A. M.; Pérez-Fuertes, Y.; Arimori, S.; Bull, S. D.; James, T. D. *Org. Lett.* **2006**, *8*, 1971–1974. (b) Pérez-Fuertes, Y.; Kelly, A. M.; Johnson, A. L.; Arimori, S.; Bull, S. D.; James, T. D. *Org. Lett.* **2006**, *8*, 609–612. (c) Kelly, A. M.; Bull, S. D.; James, T. D. *Tetrahedron: Asymmetry* **2008**, *19*, 489–494. (d) Powell, M. E.; Kelly, A. M.; Bull, S. D.; James, T. D. *Tetrahedron Lett.* **2009**, *50*, 876–879. (e) Perez-Fuertes, Y.; Kelly, A. M.; Fossey, J. S.; Powell, M. E.; Bull, S. D.; James, T. D. *Nat. Protoc.* **2008**, *3*, 210–214. (f) Kelly, A. M.; Perez-Fuertes, Y.; Fossey, J. S.; Yeste, S. L.; Bull, S. D.; James, T. D. *Nat. Protoc.* **2008**, *3*, 215–219.
(14) Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron* **1985**, *41*, 3455–3462.
(15) Chiral hydroxylamines **1a**–**h** were prepared via treatment of their parent amines with *p*-anisaldehyde to afford imines that were reacted with mCPBA to afford their correspondng oxaziridines that were then treated with hydroxylamine hydrochloride. See Supporting Information for experimental details.
(16) Contrary to our previously reported results on iminoboronate complexes, baseline resolution of the imine protons (**A**) of complexes **2b**–**2e**/**3b**–**e** was not achieved in all cases, because they were obscured by resonances of aromatic protons, although baseline resolution of the imine protons of complexes **2a,f**–**g**/**3a,f**–**g** did occur.
(17) Scalemic samples of BINOL and enantiopure hydroxylamine were used in this study for experimental convenience; however it follows that use of enantiopure BINOL in this protocol would enable the enantiopurity of a scalemic sample of hydroxylaminea **1a**–**h** to be determined.

Table 1. Chemical Shift Differences ($\Delta\delta$) in the 500 MHz ^{1}H NMR Spectra of 50:50 Mixtures of Diastereomers **2a**–**h** and **3a**–**h** Derived from Racemic Hydroxylamines



entry	hydroxylamine **1**	nitrono-boronate esters **2**/**3**[a]	$\Delta\delta$ (δ**2** - δ**3**) (ppm)[b]
1	 (*R*)-**1a**	 (*R*,*R*)-**2a** /  (*R*,*S*)-**3a**	0.059 (B) -0.039 (C)
2	 (*S*)-**1b**	 (*S*,*S*)-**2b** /  (*S*,*R*)-**3b**	0.039 (B) -0.044 (C) -0.219 (D)
3	 (*S*)-**1c**	 (*S*,*S*)-**2c** /  (*S*,*R*)-**3c**	0.101 (B) -0.010 (C)
4	 (*S*)-**1d**	 (*S*,*S*)-**2d** /  (*S*,*R*)-**3d**	0.054 (B) -0.061 (C) -0.050 (D)
5	 (*S*)-**1e**	 (S,S)-**2e** /  (*S*,*R*)-**3e**	0.193 (A) 0.059 (B) -0.058 (C)
6	 (*S*)-**1f**	 (*S*,*S*)-**2f** /  (*S*,*R*)-**3f**	0.013 (A) 0.018 (B) 0.080 (D)
7	 (*R*)-**1g**	 (*R*,*R*)-**2g** /  (*R*,*S*)-**3g**	0.101 (B) 0.107 (C)
8	 (*R*)-**1h**	 (*R*,*R*)-**2h** /  (*R*,*S*)-**3h**	0.116 (A)[c] -0.235 (B) -0.242 (C)

[a] Diastereomer **2** corresponds to homochiral (*R*,*R*) or (*S*,*S*) complex, and diastereomer **3** corresponds to heterochiral (*R*,*S*) or (*S*,*R*) complex. [b] A negative value for $\Delta\delta$ indicates that the resonance corresponding to the heterochiral diastereomer **3** is more deshielded than that of the homochiral diastereomer **2**. [c] $\Delta\delta$ calculated for imine carbon resonaces of ^{13}C NMR spectrum of **2h**/**3h**.

with the known enantiopurity of the starting hydroxylamine **1b**. Therefore, the integrals measured from the ^{1}H NMR spectra of mixtures for the methoxy groups of (*S*,*S*)-**2b** and (*S*,*R*)-**3b** of 98%, 79%, and 0% *dr* were in excellent agreement with the known enantiopurity of the starting BINOL of 98%, 80%, and 0% *ee* respectively, indicating that no kinetic resolution had occurred during derivatization (Figure 1). These values are well within the 5% error limit normally accepted for CDA analysis using NMR spectroscopy,[18] demonstrating that our derivatization protocol is effective for determining the *ee* of hydroxylamines.

Application of this derivatization protocol to hydroxylamine **1h** proved problematic, because the α-methyl protons (**C**) of its diastereomeric nitrono-boronate esters **2h** and **3h** were not baseline resolved in its ^{1}H NMR spectrum,

(18) For examples, see: (a) Kolodiazhnyi, O. I.; Demchuk, O. M.; Gerschkovich, A. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1729–1732. (b) Caselli, E.; Danieli, C.; Morandi, S.; Bonfiglio, B.; Forni, A.; Prati, F. *Org. Lett.* **2003**, *5*, 4863–4866.

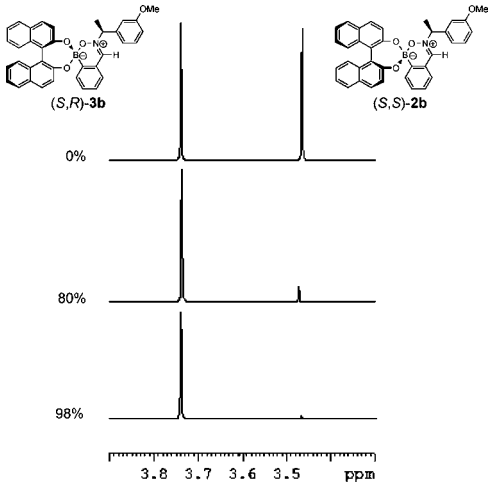


Figure 1. Expansion of the methoxy region of the ^{1}H NMR spectra of mixtures of complexes **2b** and **3b** prepared from (*S*)-**1b**, 2-formylphenylboronic acid, and samples of (*R*)-BINOL of 0%, 80%, and 98% ee.

while its α-proton (**B**) was obscured by resonances from its alkyl backbone. This meant that no pairs of diastereomeric resonances were baseline resolved, thus preventing the enantiopurity of the parent hydroxylamine **1h** from being determined. However, inspection of the ^{13}C NMR spectrum of a 50:50 mixture of nitrono-boronate esters **2h** and **3h** revealed that baseline splitting had occurred for all of the diastereomeric resonances.[19] As before, samples of BINOL of 90%, 80%, and 0% ee were derivatized using enantiopure hydroxylamine (*R*)-**1h** and 2-formylphenylboronic acid. Measurement of the integrals of the ^{13}C NMR spectrum of these mixtures of (*R*,*R*)-**2h** and (*R*,*S*)-**3h** revealed *dr*'s of 91%, 82%, and 0% which were in excellent agreement with the known enantiopurity of the starting BINOL of 90%, 80%, and 0% respectively.[20]

X-ray crystallographic analysis of diastereomer (*S*,*R*)-**3d** prepared from (*S*)-hydroxylamine **1d** and enantiopure

(19) The *dr* of fluorinated five-membered iminoboronate esters has been determined previously by ^{19}F NMR spectroscopic analysis; see: Yeste, S. L.; Powell, M. E.; Bull, S. D.; James, T. D. *J. Org. Chem.* **2009**, *74*, 427–430.

(20) These ^{13}C NMR experiments were carried out using a T1 relaxation time of 120 s to enable accurate integration of the peak areas of pairs of diasteromeric resonances of nitrono-boronates **2h/3h**.

(21) For a previous report describing the synthesis of achiral nitrono-boronate esters of 2-formylphenyl boronic acid, see: Kliegel, W.; Nanninga, D. *J. Organomet. Chem.* **1983**, *243*, 247–252.

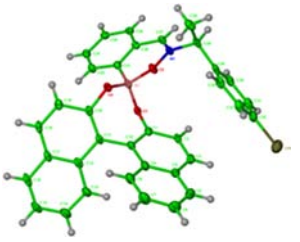


Figure 2. Crystal structure of nitrono-boronate ester (*S*,*R*)-**3d**.

(*R*)-BINOL showed that its nitrono-boronate structure[21] was clearly different from the five-membered iminoboronate esters reported previously for derivatization of amines using this protocol (cf. Scheme 1).[12] Nitrono-boronate ester (*S*,*R*)-**3d** has a tetrahedral boron atom whose presence in solution was confirmed by ^{11}B NMR spectroscopic analysis which revealed a single resonance visible at δ12.0 ppm. However, in contrast to the iminoboronate structures reported previously, its six-membered ring contains an unusual zwitterionic $N^{+}-O-B^{-}$ arrangement (Figure 2). Further inspection of the crystal structure reveals that its six-membered ring is comprised of coplanar carbon, nitrogen, and oxygen atoms with its spirocyclic boron atom occupying the bow position of a half-chair conformer.

In conclusion, we have reported the first chiral derivatization protocol for determining the enantiopurity of chiral hydroxylamines by NMR spectroscopy.[22] We believe that the simplicity of this approach, and the range of hydroxylamines that it can resolve, means that it will prove to be a versatile method for determining the *ee*'s of chiral hydroxylamines produced in asymmetric reactions.

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Supporting Information Available. Experimental details, spectroscopic data, details of mechanistic experiments, and crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

(22) Powell, M. E.; Evans, C. D.; Bull, S. D.; James, T. D. Diastereomeric derivitisation for spectroscopy. *Comprehensive Chirality*; Elsevier: 2012.

The authors declare no competing financial interest.