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(*S*)-(+)-*N*-Acetylphenylglycineboronic Acid: A Chiral Derivatizing Agent for Ee Determination of 1,2-Diols

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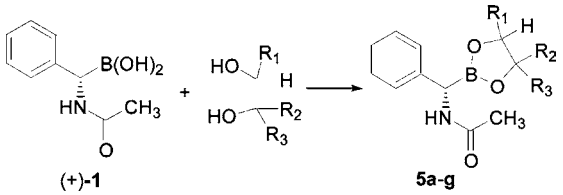
ABSTRACT



A new chiral derivatizing agent for ee determination of 1,2-diols via ^{1}H NMR is described. (*S*)-(+)-*N*-Acetylphenylglycineboronic acid (1) is synthesized in enantiomerically pure form; its reaction with chiral diols quantitatively yields cyclic boronic esters 5a–g. The latter show a remarkably high diastereodifferentiation of proton NMR signals useful for de determination.

1,2-Diols are important molecules both as synthetic intermediates[1] and as biologically active molecules.[2] The fact that chiral diols can be easily obtained through enantioselective bishydroxylation[3] highlights the importance of finding reliable methods for ee determination. For this purpose NMR analysis is a general approach that requires conversion of enantiomers into diastereomeric derivatives through chiral auxiliaries. Whereas the use of chiral derivatizing agents (CDAs) for alcohols is well established, and compounds such as mandelic acid[4] or α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid)[5] are widely available, there are no examples of commercially available CDAs specific for diols. Certain precautions are necessary when a diol is analyzed: particular care has to be taken in order to derivatize both functionalities, possible kinetic resolution has to be avoided, and nearly enantiomerically pure CDA is necessary in order to avoid formation of other diastereoisomers. Therefore, an ideal CDA for diols should have a single functional group capable of quantitatively reacting with both the hydroxy functionalities and should be easily available in enantiomerically pure form. Accordingly, previous studies have proposed compounds bearing either a boronic acid or a dichlorophosphate functional group and have identified three molecules (Figure 1, compounds **I**−**III**) that react with a diol to form a cyclic boronate or phosphate ester. In all three cases, the resulting diastereomeric esters were analyzed by NMR, a generally useful technique for determining de. In the first example, the signal nonequivalences induced by the camphanylboronic acid **I**[6] were observed only in the ^{13}C NMR spectra, a low-sensitivity technique not well suited to quantitation. In a second case, diastereomeric phophates formed between menthyldichlorophosphate **II**[7] and 1,2-diols displayed useful nonequivalence only for C2 symmetry molecules in the ^{31}P NMR spectra, which moreover is not a routinely monitored nucleus to be observed.

(1) *Chiral Intermediates*; Challenger, A. C., Ed.; Ashgate Publishing Limited: Hampshire, England, 2001.
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(4) Trost, B. M.; Belletire, J. L.; Godleski S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.
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(6) Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1988**, *29*, 6063.
(7) Garner, C. M.; McWorther, C.; Goerke, A. R. *Tetrahedron Lett.* **1997**, *38*, 7717.

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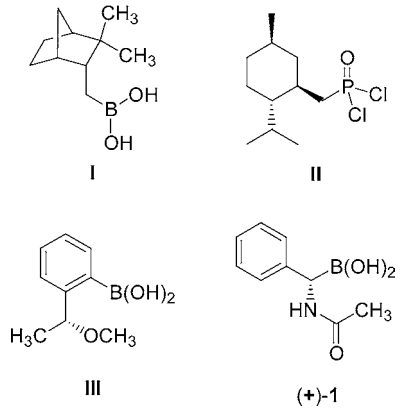
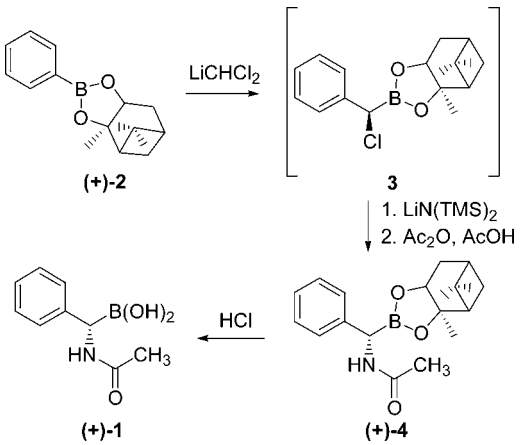


Figure 1. Structures of reported CDA for diols (**I**−**III**) and of (*S*)-(+)-*N*-acetylphenylglycineboronic acid (**1**).

In the last example, nonequivalence suitable for integration was displayed in the easily accessible ^{1}H NMR spectra, but the $\Delta\delta$ values of the boronic esters formed with the arylboronic acid **III**[8] were low (5−20 ppb). This letter reports the use of optically active *N*-acetylphenylglycineboronic acid (+)-**1** (Figure 1) as a chiral derivatizing agent for diols: both enantiomers of this compound are easily accessible in enantiomerically pure form, derivatization with diols is quantitative, and the ^{1}H NMR spectra of the corresponding boronic esters show a remarkably high separation ($\Delta\delta$ = 70−220 ppb) of signals useful for diastereomeric excess determination.

Synthesis of (+)-**1** was accomplished through Matteson homologation[9] reaction of pinanediol phenylboronate[10] (+)-**2** (Scheme 1). This reaction inserts a halogenated carbon atom

Scheme 1. Diastereoselective Synthesis of (+)-**1**



in the α-position to the boron, and the stereochemical outcome of the reaction is highly controlled (de > 98%) by the boronic acid protective group pinanediol, which is commercially available in both enantiomeric forms. In particular, (−)-pinanediol is known[9a] to induce (*R*)-stereochemistry.

The (*R*)-α-chloro-α-phenylmethaneboronic ester **3** was not isolated; displacement of the chlorine by a nitrogen nucleophile (lithium bistrimethylsilylamide) occurs by means of the S_N2 mechanism, and subsequent deprotection and acylation, using a mixture of acetic acid and acetic anhydride, furnished diastereomerically pure (de > 98%) pinanediyl (*S*)-*N*-acetylphenylglycineboronic ester (+)-**4**[11] in 77% overall yield. The de of this compound can be unambiguously assigned on the basis of its ^{1}H NMR resonances according to literature.[12] Pinanediol ester hydrolysis was accomplished in refluxing HCl to give (*S*)-(+)-**1**[13] as a white solid.[14]

To explore diastereomeric differentiation of racemic diols, seven 1,2-diols (**a**−**g**, Scheme 2) were chosen bearing primary, secondary, and tertiary hydroxy functionalities as well as diols with *C*2 symmetry.

Derivatization of diols (Scheme 2) was performed in THF for 1 h: a slight excess (5−10%) of boronic acid (+)-**1** was

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(9) (a) Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294. (b) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535. (c) Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51.

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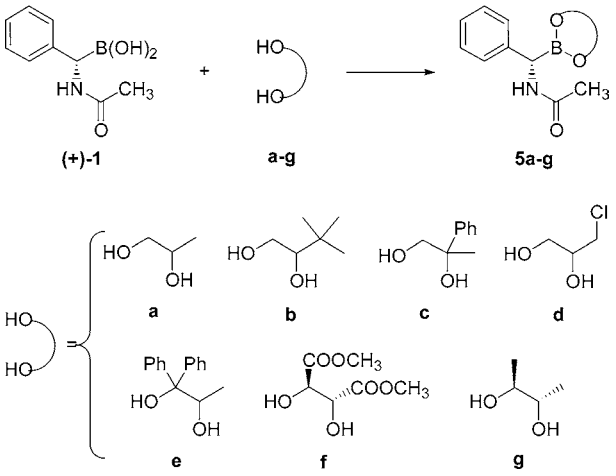
(11) (−)-**Pinanediol (*S*)-α-Acetamido-α-phenylmethaneboronate ((+)-4).** *n*-BuLi (2.8 mL of a 2.5 M solution in hexane, 7.0 mmol) was added dropwise to a solution of CH_2Cl_2 (0.55 mL, 8.6 mmol) in THF (13 mL) while stirring at −100 °C under argon: dichloromethyllithium precipitated as a white microcrystalline solid towards the end of the BuLi additions. After 30 min, the mixture was treated with pinanediolphenylboronate (+)-**2**[10] (1.3 g, 5.3 mmol) and allowed to reach room temperature with stirring. The tetrahedral boronate adduct precipitated as an abundant white solid at −80 °C and redissolved upon warming. After 1 h at 0 °C, the reaction mixture was recooled to −78 °C; $LiN(TMS)_2$ (5.3 mL of a 1 M solution in THF, 5.3 mmol) was added, and the resulting solution was allowed to warm gradually to room temperature and stirred overnight. The mixture was then recooled to −78 °C and treated with a solution of Ac_2O (2.0 mL, 21.2 mmol) and AcOH (0.4 mL, 6.5 mmol) in THF (4 mL), allowed to warm to room temperature, and stirred overnight. The solution was diluted in EtOAc (250 mL) and H_2O (50 mL); the organic phase was washed ($NaHCO_3$ to basic pH, 40 mL H_2O, 50 mL of brine), dried on $MgSO_4$, filtrated, and concentrated in vacuo to yield a brownish oil that was purified by gradient chromatography (Et_2O/MeOH 9:1 to 1:1), affording (+)-**4** as a white solid (1.3 g, 77%), which was recrystallized from MeOH, mp 210−213 °C, $[\alpha]_D$ = +73.8 (*c* 0.93, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.78 (3H, s, pinanyl CH_3), 1.20 (1H, d, J = 10.5, pinanyl H_{endo}), 1.20 (3H, s, pinanyl CH_3), 1.28 (3H, s, pinanyl CH_3), 1.33−2.25 (5H, m, pinanyl protons), 2.14 (3H, s, COOCH_3), 3.91 (1H, s, C*H*B), 4.10 (1H, dd, J = 8.6, 2.3, pinanyl C*H*OB), 7.08−7.37 (5H, m, *Ph*), 7.69 (1H, bs, N*H*CO). ^{13}C NMR ($CDCl_3$): δ 20.2, 25.5, 27.8, 28.6, 30.3, 37.7, 39.4, 41.3, 50.4 (br, *C*HB), 53.7, 78.1, 85.2, 127.3, 127.6, 129.6, 142.1, 176.2. EIMS: *m*/*z* 327 (71%, M^+), 284 (7), 229 (11), 212 (11), 192 (29), 176 (43), 175 (63), 150 (66), 148 (52), 131 (100), 130 (53), 117 (37), 106 (65), 93 (82), 91 (43), 79 (24), 77 (22), 67 (11), 55 (12). Anal. Calcd for $C_{19}H_{26}BNO_3$: N = 4.28; C = 69.74; H = 8.01. Found: N = 4.45; C = 69.57; H = 7.91.

(12) (a) Tsai, D. J. S.; Jesthi, P. K.; Matteson, D. S. *Organometallics* **1983**, *2*, 1543. (b) Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810.

(13) **(*S*)-(+)-*N*-Acetylphenylglycineboronic Acid (1).** The boronic ester (+)-**4** (65 mg, 0.2 mmol) was refluxed for 1 h in 3 N HCl (4.3 mL, 13.0 mmol, prepared with degassed H_2O) under Ar. The resulting reaction mixture was washed twice with EtOAc (10 and 6 mL) and the aqueous phase concentrated in vacuo, affording the free boronic acid as a white amorphous solid. Yield 95%, $[\alpha]_D$ = +250.5 (*c* 0.42, CH_3OH). ^{1}H NMR (200 MHz, CD_3OD): δ 2.34 (3 H, s, −COCH_3); 3.85 (1 H, s, H_α); 7.11−7.33 (5 H, m, Ph). ^{13}C NMR (200 MHz, CD_3OD): δ 15.5 (CO*C*H_3); 53.1 (*C*HB); 125.9; 128.3; 140.7; 178.3 (*C* = O). EI-MS: 194 (3%, M^+ + 1); 149 (41); 106 (52); 105 (100); 91 (28); 77 (32); 51 (7).

(14) To verify the stability of (+)-**1** and to assess that no racemization occurred under the relatively harsh conditions of the hydrolysis, a sample of (+)-**1** was stored under argon for 15 days at room temperature and then converted to (+)-**4** by reaction with a slight excess of (+)-pinanediol: (+)-**4** was recovered in 97% yield and de > 98%.

Scheme 2. Derivatization of Racemic Diols **a**−**g** with (+)-**1**



used in order to avoid kinetic resolutions, and complete conversion of the diols (20−30 mg) to boronic esters **5a**−**g** was always observed within 30 min, even for highly sterically hindered diols such as **c** and **e**. Subsequent removal of the solvent in vacuo and desiccation over P_2O_5 at 2 mmHg for 12 h furnished the diastereoisomeric couples of the boronic esters **5a**−**g**, which did not require further purification. The structure of compounds **5a**−**g** was confirmed by mass spectrometry and ^{1}H NMR and ^{13}C NMR spectroscopy. A careful study was conducted in order to assign all the proton resonances correctly (see Supporting Information), and ^{1}H−^{1}H COSY, ^{1}H−^{13}C HMQC, DEPT 135, and NOESY spectra were recorded when necessary. To our satisfaction, NMR (200 MHz) spectra of *N*-acetylphenylglycineboronic esters **5a**−**g** always clearly revealed the presence of the two diastereoisomers; differences in the chemical shift of signals of diastereotopic groups were significant, with $\Delta\delta$ values ranging from 20 to 220 ppb for the proton (Figure 2) and from 120 to 890 ppb for the carbon.

Baseline resolved peaks useful for de determination ($\Delta\delta$ from 70 to 220 ppb) were always observed except for compound **5c**. Even though the splitting of the signals originated from the CDA is an attractive feature, in our spectra the proton resonances derived from the diols are better separated than those from the boronic acid. In particular, neither the proton α to the boron nor the acetamido methyl singlet generally split as hoped. Our results are nevertheless significant if compared with those last published[8] since the $\Delta\delta$ values are increased by 1 order of magnitude, probably due to the proximity of the CDA chiral center to the diol. Furthermore, NOESY experiments conducted on compounds **5a** and **5d** point to a proximity between the proton H_b of the diol and the phenyl ortho hydrogens of the CDA: this suggests that the insertion of a methoxy group in this position of the phenyl ring could probably lead to a useful CDA signal for de determination.

To verify that reliable ee values of a chiral diol are obtainable from diastereotopic proton signals, samples of 1,2-propanediol **a** in different ee (96, 77.4, 58.2, and 5%) were prepared using the commercially available (*R*)-**a** (98% ee) and (±)-**a**, and derivatizations with (*S*)-(+)-**1** were performed as described. ^{1}H NMR spectra of the samples were recorded and de values calculated on the diol methyl signals (Figure 3) on the basis of the height of the peaks;[15] values of 96, 78, 55, and 7% ee were obtained.

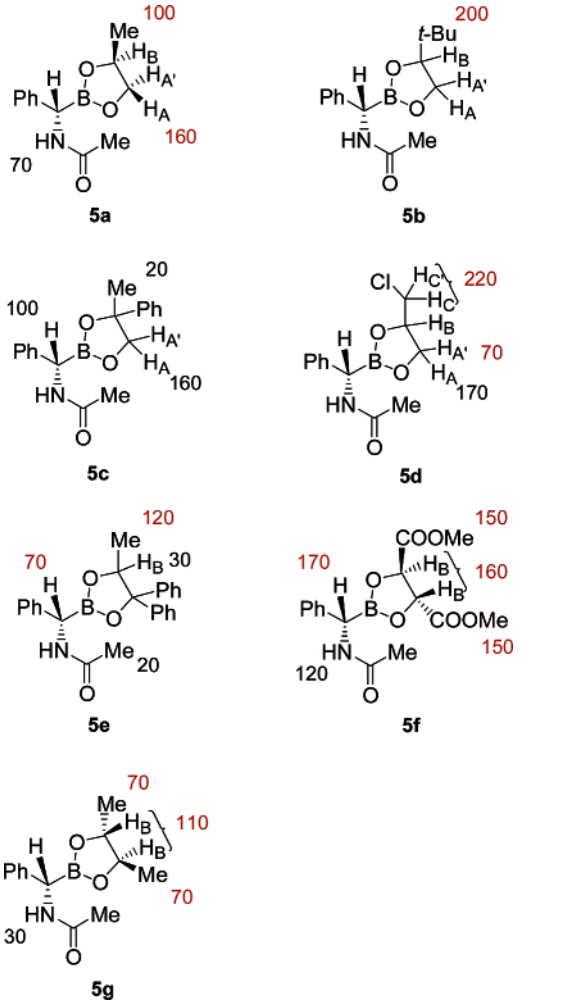


Figure 2. Nonequivalence ^{1}H NMR ($\Delta\delta$ values in ppb) observed in diastereoisomeric couples of boronic esters **5a**−**g**. Useful nonequivalences for de determination are in red.

These results show that the de values are always in good agreement with the expected ee of the diol, and even traces of one diastereoisomer are detectable by this technique.

To summarize, this work explores the advantages of using chiral α-acetamido-α-phenylglycineboronic acid (*S*)-(+)-**1** as CDA for 1,2-diols. This compound is obtainable in enantiomerically pure form; its reaction with diols is quantitative, and the resulting diastereoisomers are easily analyzed by ^{1}H NMR in standard conditions ($CDCl_3$ as a

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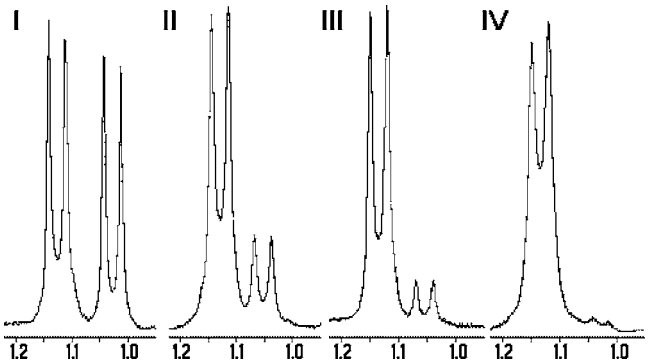

Figure 3. ^{1}H NMR spectra relative to the signals of the diastereotopic methyl group of boronic ester **5a**: I−IV refer to samples obtained from diol **a** in 5, 58.2, 77.4, and 96% ee, respectively.

solvent, 200 MHz). Remarkably high $\Delta\delta$ values (70−220 ppb) of diastereomeric proton signals are obtained (Figure 2), and the determined de values are in good agreement with the known ee of the diol. Modifications of the structure of (+)-**1** are in progress in our lab in order to obtain diagnostic signals on the resonances of the CDA.

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Supporting Information Available: Spectroscopic characterization (^{1}H NMR, ^{13}C NMR, and mass spectra) for compounds **5a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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