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Enantiomeric excess of 1,2-diols by formation of cyclic boronates: an improved method

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Abstract—A reliable method for determining the enantiomeric composition of 1,2-diols by the formation of diastereomeric cyclic esters with boronic acid is described. Starting from a previously reported structure of boronic chiral derivatizing agent (CDA), seven structurally related racemic CDAs were synthesized and their discriminating ability towards diols measured. The most promising amongst these was synthesized in its enantiomerically pure form according to Matteson's protocol for the stereoselective homologation of pinanediol boronates; this CDA quantitatively and rapidly reacts with 1,2-diols in very mild conditions affording a couple of diastereoisomers, whose composition can be determined via ^{1}H NMR analysis. In particular, an attractive feature is that the resonance used for the analysis originated from the CDA as a couple of baseline-separated singlets ($\Delta\delta$ up to 0.3 ppm) is useful for integration.

1. Introduction

Boronic acids and boronates play an important role in many fields of chemical research and technology because of their application in synthetic organic chemistry[1,2] (including stereoselective synthesis),[3–5] enzyme inhibition,[6,7] carbohydrate recognition,[8] transmembrane transport[9] and separation of glycoproteins.[10] Several of these diverse fields of application are due to the ability of boronic acids to bind hydroxyl groups, and in particular to form reversible cyclic esters[11] with diols. The ubiquitous presence of a stereodefined diol moiety in biomolecules, drugs[12] and synthetic intermediates,[13,14] highlights the potential of boronic acids for the isolation and characterization[15–18] of this class of compounds.

In this respect, enantiomerically pure boronic acids could be reliable chiral derivatizing agents (CDAs) for the determination of the enantiomeric composition of optically active diols via ^{1}H NMR analysis.[15,16,19] In fact, the point has been well made[16,20] that none of the widely diffused methods for the NMR determination of ee of alcohols (formation of methoxyphenyltrifluoromethyl acetates, mandelates, 2-phenylpropanoates) are particularly suitable for diols: syntheses of bis-Mosher's esters, for instance, are especially susceptible to kinetic resolutions, while substrate diols with inequivalent OH functionalities give two sets of NMR marker peaks in narrow regions of the ^{1}H and ^{19}F NMR spectra.

Chiral boronic acids, bearing a single functional group capable of reacting with both hydroxyl groups of several diols avoid both of these problems, giving rise to a diastereomeric mixture of cyclic esters whose composition can be assessed by NMR techniques. The first report on such a use of chiral boronic acids belongs to Tokles and Snyder,[15] who measured the anisochronies of the ^{13}C nucleus,[13] while later Burgess[16] reported useful, even though very low, anisochronies in the ^{1}H NMR spectrum. Typically, a $\Delta\delta$ of 10 ppb at 400 MHz was detected. More recently,[19] we have shown that (*S*)-(+)-*N*-acetylphenylglycineboronic acid **1** (Scheme 1), when reacted with racemic diols, gave rise to a diastereomeric couple showing baseline resolved peaks with remarkably high $\Delta\delta$ values (70–220 ppb) under routine conditions (200 MHz, $CDCl_3$), thus allowing the ee determination of the starting diol. Unfortunately, we observed such a separation only for the signals originating from the diol, while very poor or no separation at all were detected for

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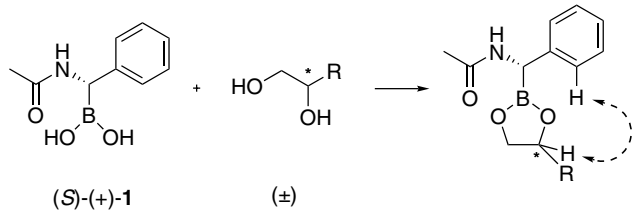


Scheme 1. Formation of cyclic boronate by reaction of (*S*)-(+)-**1** with racemic 1,2-diols; the molar composition of the diastereomeric pair can be determined by ^{1}H NMR analysis.

those from the CDA. Since, for general application of the proposed method, a marker peak on the CDA is an attractive feature, we were prompted to develop new boronic CDAs structures related to (*S*)-(+)-**1**. Herein, we report the results of our efforts to improve (*S*)-(+)-**1**, allowing the identification of a reliable derivatizing agent for 1,2-diols.

2. Results and discussion

A rational design of new structures derived from **1** suggested retaining its key features, that is, a stereocentre adjacent to the boron atom bearing an aromatic ring and an electron-withdrawing group, namely an amide. This latter is known to stabilize the boronate by intramolecular coordination of the carbonyl oxygen to the electrophilic boron atom,[21] thus favouring its esterification with the diol.[11] Aiming to obtain a marker peak (possibly as narrow singlet) on our CDA, we reasoned that a methyl or methoxy group could be conveniently introduced onto the phenyl ring. Structures **2** and **3** were therefore selected as first choice (Fig. 1). This idea was corroborated by NOESY experiments performed on diastereomeric mixtures derived from the reaction of (*S*)-(+)-**1** with diols.[19] The observed proximity of the *ortho*-phenyl hydrogen with the diol C*H*O proton

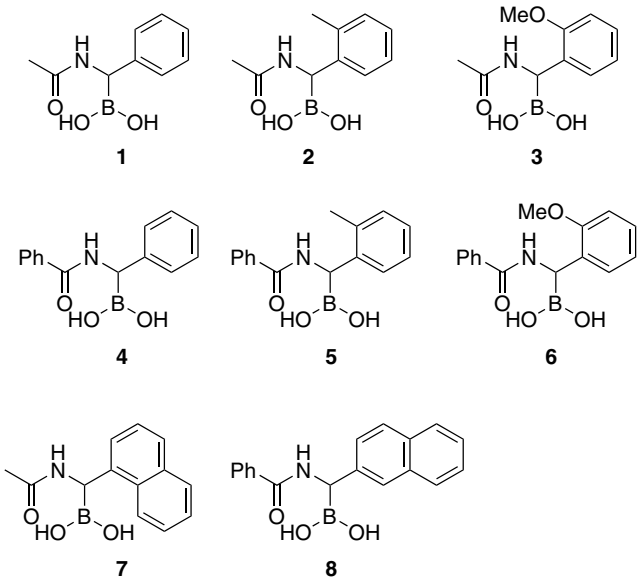


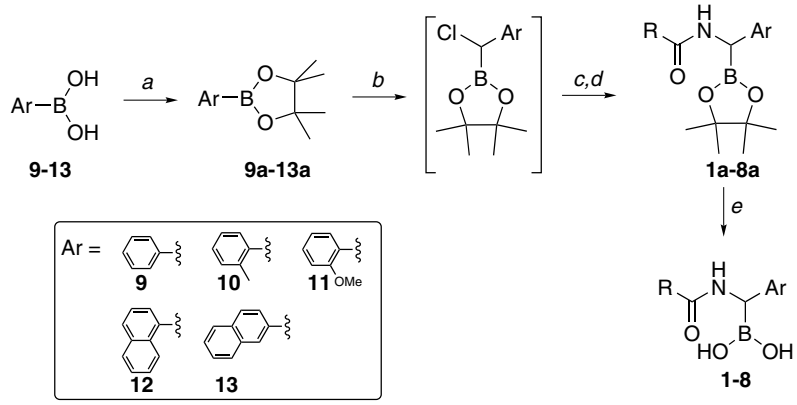
Figure 1. Structures of the designed CDA.

(Scheme 1) suggested that the resonance of a group in this aromatic position should be sensitive to the stereochemical arrangement of the diol, possibly affording the splitting of its signals. Furthermore, since the methyl group of (*S*)-(+)-**1** never displayed the desired separation (only a broadening of the signal was generally recorded),[19] we also planned to evaluate the properties of benzamides **4**–**6**, aiming to enhance the magnetic anisotropy of the CDA. Finally, according to a common way of improving the discrimination of diastereoisomeric derivatives,[22] we included compounds **7** and **8**, where the more sterically demanding α- or β-naphthyl groups were introduced, respectively.

The next step in this study was the synthesis of the selected structures **1**–**8**. The first screening of their discriminating ability towards chiral diols was easily evaluated on racemic compounds, which were synthesized according to Scheme 2, starting from commercially available arylboronic acids **9**–**13**, which were first protected as pinacol esters. These cyclic boronates **9a**–**13a** were obtained in nearly quantitative yields by simple exposure to an equimolar amount of pinacol (**a**) in dry THF, once more confirming the high affinity of boronic acids for 1,2-diols.

These esters are characterized by a moderate stability, allowing chromatographic purification of the intermediates and removal of the protecting group at the end of the synthetic sequence. The well-known homologation of boronates[3–5] was selected as the reaction of choice to install the stereogenic carbon atom. The addition of in situ-generated (dichloromethyl)lithium to boronate at −100 °C in anhydrous THF resulted in a chain extension to the α-chloro derivative, which was not isolated, but in situ treated with lithium bis-trimethylsilylamide followed by addition of the selected acylating agent (acetic anhydride/acetic acid or benzoylchloride/benzoic acid). Chromatographic purification of the crude reaction mixture allowed the isolation of the expected pinacol boronates **1a**–**8a** as white solids, stable on the laboratory shelf for months, in 24–78% overall yield from arylboronates. All physical and spectroscopic characterizations of compounds **1a**–**8a** confirmed the expected structure; in particular, ^{13}C NMR spectra (H-decoupled) displayed a typical signal at 45–66 ppm with high multiplicity, which can be accounted for the newly inserted stereogenic centre, broadened by the coupling with the adjacent boron atom. A correlation with a singlet at 3.6–4.7 ppm in ^{1}H NMR spectra (COSY experiments) confirmed this attribution. Interestingly, these latter spectra exhibited high nonequivalences of the pinacol methyl signals (ranging from $\Delta\delta$ 60 ppb observed for **3a**, up to 210 ppb for **7a**), thus indicating a marked magnetic anisotropy of the two faces of the [1,3,2]oxaborolidine.

Removal of the protecting pinacol was first performed in aqueous 3 M HCl at 100 °C for 1 h, following a procedure already described.[23] This method provided good yields (68–89%) only in the recovery of acetamides **1**–**3**, whilst disappointing yields (22–45%) or even complete degradation was observed for benzamido

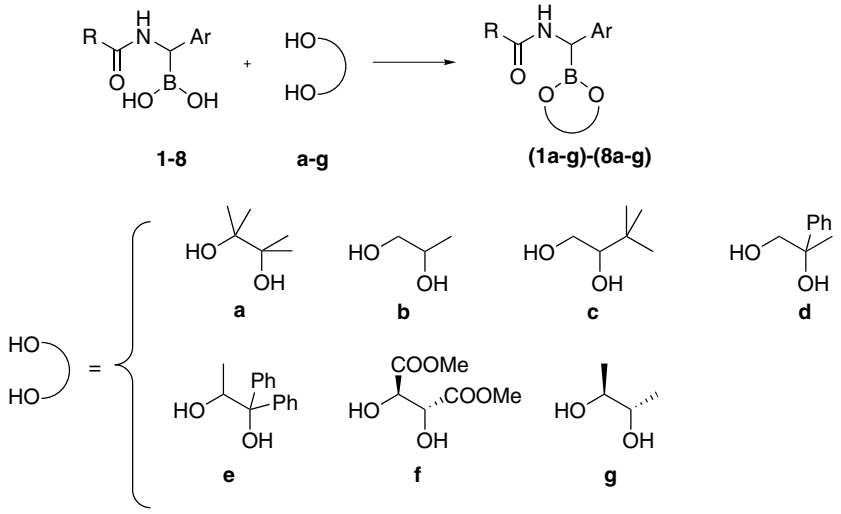


Scheme 2. Reagents and conditions: (a) Pinacol, THF, rt; (b) (dichloromethyl)lithium, THF, −100 °C → rt; (c) lithium bis(trimethylsilyl)amide, THF, −78 °C → rt; (d) Ac_2O/AcOH or PhCOCl/PhCOOH, THF, −78 °C → rt; (e) aqueous HCl 10%, 1 h, 100 °C or HCl 4 M in MeOH, 1 h, rt.

derivatives **4**–**6** and naphthyl derivatives **7** and **8**, respectively. Several other methods proposed in the literature[3–7,24] for boronate hydrolysis were therefore tried, and we experienced that the best results, combined with the mild conditions, were obtained performing an alcoholysis in methanolic 4 M HCl for 1 h at room temperature, followed by treatment with water. Compounds **4**–**8** were recovered in 82–87% yield. ^{1}H NMR and ^{13}C NMR of compounds **1**–**8** were consistent with the structures, even though elemental analyses and mass spectra were unsatisfactory.[25] This fact was likely due to the known easy formation of polymeric anhydride (often as cyclic trimer), typical of boronic acids. In fact, simple exposure of these acids to a stoichiometric amount of pinacol **a** in dry THF always afforded the expected boronates **1a**–**8a** in quantitative yields (Scheme 3).

We were therefore ready to evaluate the discriminating ability of the synthesized boronic acids towards racemic 1,2-diols. Since our specific aim was to obtain a CDA with a marker peak, for the first screening, we selected two very simple molecules, namely (±)-1,2-propanediol **b** (Scheme 3) and (±)-3,3-dimethyl-1,2-butanediol **c**: the absence of any π system on the diol, and consequently the very low induced magnetic anisotropy, makes them ideal probes to test our CDAs. In fact, if a separation of the CDA marker peak was detected for their diastereoisomeric derivatives, higher separations were likely to be expected for more complex diols, bearing for instance a phenyl or a carbonyl group, such as in **d**–**f** (Scheme 3).

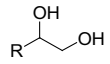
Derivatization of (±)-**b**,**c** with (±)-**1**–**8** was simple. The diol (20–30 mg) was added to a solution of a slight excess (5%) of a freshly prepared CDA sample in anhydrous THF and the resulting solution allowed to react for 1 h at room temperature. After solvent removal and desiccation over P_2O_5 at 2 mmHg for 12 h, the residue was dissolved in $CDCl_3$ and the ^{1}H NMR spectrum recorded (200 MHz). In most cases, the excess of the boronic acid was not a problem. When occasionally an overlap of the signal related to the marker peak of the unreacted CDA with those of the diastereoisomeric esters was observed, unreacted CDA was easily separated loading the crude mixture on a short silica gel column and eluting with dichloromethane. The most representative inequivalences (Δδ, ppb) measured for



Scheme 3. Derivatization of racemic diols **a**–**g** with CDA **1**–**8**.

corresponding nuclei of each diastereomeric couple **1b**–**8b** and **1c**–**8c** are summarized in Table 1.

Table 1. Inequivalences ($\Delta\delta$ in ppb) measured in the ^{1}H NMR spectra recorded at 200 MHz in $CDCl_3$ for the diastereoisomeric pairs **1b**–**8b** and **1c**–**8c**

Diol 	Entry	CDA	Compound	Nonequivalences (ppb)		
				On diol		On CDA
				R	CH_2O	
b (R = Me)	1	**1**	**1b**	100	160	—
	2	**2**	**2b**	60	100	10 (Me)
	3	**3**	**3b**	80	—	—
	4	**4**	**4b**	70	180	—
	5	**5**	**5b**	60	110	50 (Me)
	6	**6**	**6b**	70	100	30 (OMe)
	7	**7**	**7b**	230	320	30 (Ac)
	8	**8**	**8b**	100	160	10 (Ac)
c (R = ^{t}Bu)	9	**1**	**1c**	200	—	—
	10	**2**	**2c**	160	200	—
	11	**3**	**3c**	150	—	10 (OMe)
	12	**4**	**4c**	150	—	—
	13	**5**	**5c**	150	200	50 (Me)
	14	**6**	**6c**	160	130	10 (OMe)
	15	**7**	**7c**	300	360	50 (Ac)
	16	**8**	**8c**	190	—	—

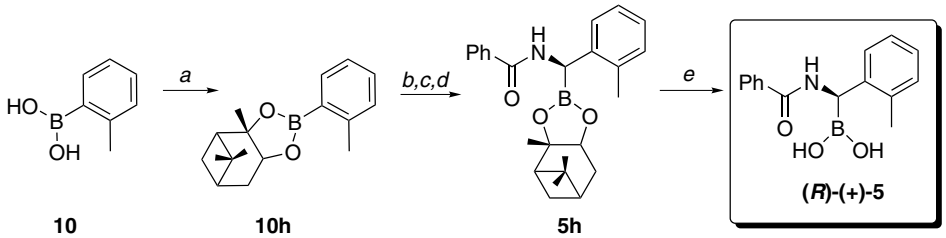
As already reported for CDA **1**,[19] high inequivalences ($\Delta\delta$ 60–360 ppb) and baseline resolved peaks were generally observed for the diol signals for all derivatives. In this respect, comparing the performances of CDAs **2**–**8** with **1**, the insertion of the methyl or methoxyl group on the phenyl ring of **1**, leading to CDAs **2** and **3**, respectively, resulted in slightly worse separations (entries 2 and 3 vs 1; entries 10 and 11 vs 9), while the substitution of the acetyl moiety of **1**–**3** with the benzoyl (CDAs **4**–**6**) did not significantly affect the inequivalences (entries 4–6 vs 1–3; entries 12–14 vs 9–11). Conversely, CDA **7** showed a marked increase of stereoisomer-differentiation (entry 7 vs 1; entry 15 vs 9), due to the strong magnetic anisotropy induced by the sterically demanding α-naphthyl group; it is worth noting that the β-naphthyl group of CDA **8** did not affect the separations (entry 8 vs 1; entry 16 vs 9) at all.

Most importantly, inequivalencies were also displayed in some instances for reagent-derived resonances: even though lower ($\Delta\delta_{max}$ 50 ppb) with respect to those from the diol, useful separations were in fact measured for the methyl, methoxy and acetyl groups of CDAs **5**–**7**, respectively (entries 5–7; 13–15). Unfortunately, a non-baseline resolution of these peaks for **6** (methoxy group) and **7** (acetyl group) was observed, as a consequence of a marked broadening of the signals. This feature was also retained in different solvents, such as C_6D_6 or d_6-DMSO and forced us to abandon these structures for further developments. CDA **5** showed baseline resolved peaks in both derivatives **5b** and **5c**, with a satisfactory shape of the signals (a line width <2 Hz was recorded), suitable for integration; hence, asymmetric synthesis of enantiomerically pure **5** was performed.

The synthetic strategy relied again on Matteson's homologation of boronates, but this time pinanediol **h** was selected as the esterifying alcohol (Scheme 4). In fact, it is well known[3–5,26] that the stereochemical course of the homologation reaction is strictly controlled by the (+)- or (−)-pinanediol, which selectively induces the (*S*)- or (*R*)-absolute configuration, respectively, at the newly inserted chlorine-bearing carbon atom.

Therefore, 2-methylphenylboronic acid **10** was treated in anhydrous THF with an equimolar amount of (+)-pinanediol and the resulting ester (−)-**10h** subjected to the same reaction sequence described for the synthesis of racemic **5a**: (+)-**5h** (de >98%) was isolated in 44% overall yield. The diastereoselectivity of the homologation was determined by using the H_{endo} proton[26] of the pinanyl moiety (1.17 ppm, doublet) as a diagnostic marker. Since (+)-pinanediol stereoselectively induces the formation of (*S*)-α-chloroboronic esters,[3,26] and nucleophilic displacement occurs with clean inversion of configuration, the (*R*)-absolute configuration could be assigned to (+)-**5h**. Final hydrolysis with 3 M HCl afforded (*R*)-(+)-**5** in 54% yield as a white solid, which could be stored for an indefinite time at room temperature under argon. It is worth noting that, even though harsh conditions were required for the removal of the pinanediol, no racemization occurred during the hydrolysis: in fact, a sample of (*R*)-(+)-**5** exposed to a small excess of (+)-pinanediol, afforded (+)-**5d** in quantitative yield and de >98%. Moreover, since pinanediol is also commercially available in the laevorotatory form, both enantiomers of **5** can be synthesized.

With enantiomerically pure (+)-**5** in hand, we analyzed several racemic diols **b**–**g**, including sterically hindered **e** and C_2-symmetry **f**, **g** compounds. Following the procedure already described for racemic CDA, cyclic boronates were obtained and the spectra recorded at 200



Scheme 4. Reagents and conditions: (a) (1*S*,2*S*,3*R*,5*S*)-(+)-Pinanediol, THF, rt; (b) (dichloromethyl)-lithium, THF, −100 °C → rt; (c) lithium bis(trimethylsilyl)amide, THF, −78 °C → rt; (d) PhCOCl/PhCOOH, THF, −78 °C → rt; (e) aqueous HCl 10%, 1 h, 100 °C.

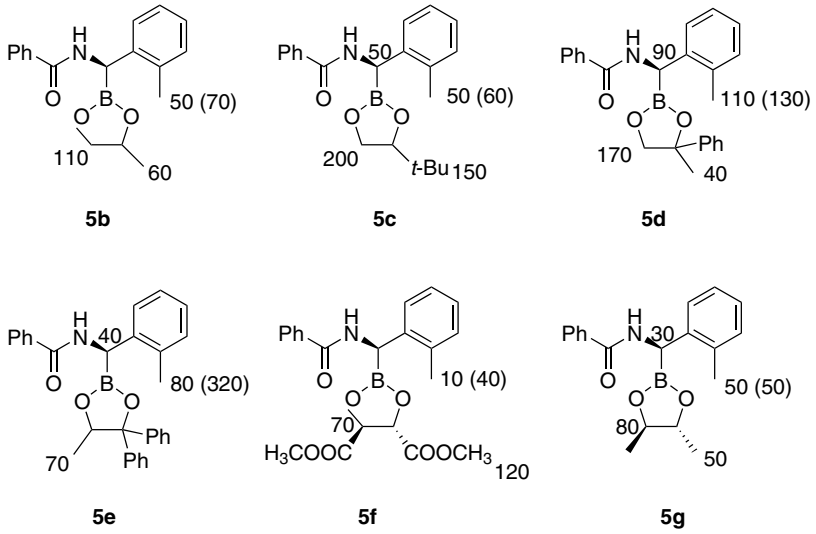


Figure 2. Inequivalencies (in ppb) useful for de determinations observed for racemic diols derivatized with (*R*)-(+)-**5**. The reported values are measured in the ^{1}H NMR spectra in $CDCl_3$ (in brackets the values in C_6D_6) at 200 MHz.

and 400 MHz, $CDCl_3$ and C_6D_6 as solvents. Baseline resolved peaks useful for ee determination were generally displayed by diol signals at the lowest magnetic field in chloroform, without sensitive improvement for spectra recorded in C_6D_6. The most significant $\Delta\delta$ values are shown in Figure 2. Useful separations were also observed for signals generated from the CDA, as shown in Figure 3, where expanded regions of the ^{1}H NMR spectrum (400 MHz) of the diastereomeric pair **5e** are considered.

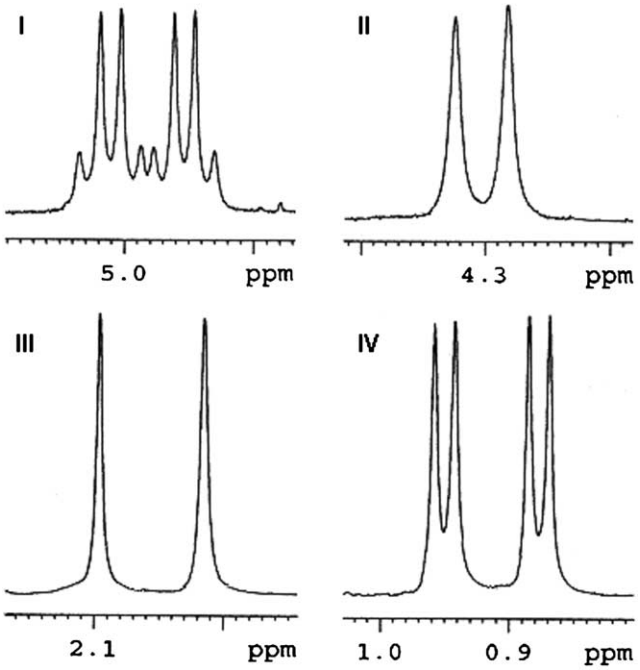


Figure 3. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the diastereoisomeric pair **5e**. Spectral regions relative to the resonances of C*H*–CH_3 (I), C*H*B (II), CH_3Ph (III) and CH_3–CH (IV).

The inequivalencies measured for the reference signal (CH_3Ph) were $\Delta\delta$ 10–110 ppb in chloroform and increased to 40–320 ppb in C_6D_6, thus indicating that this group can be conveniently used as a probe signal for the de determination of the diastereoisomeric pair.

These values, when compared with those already reported in the literature,[16] represent a significant improvement in the separation of the reagent-derived signals and further demonstrate the usefulness of this technique for the ee determination of 1,2-diols. In fact, even if direct chromatographic analyses by enantioselective GC or HPLC are ideal, a chemical derivatization of the diol sample has generally has to be carried out,[14] due to the low vapour pressure (GC) or weak absorption in UV–vis region (HPLC). The proposed ^{1}H NMR method combines efficient derivatization in very mild conditions with remarkable stereoisomer discrimination.

3. Conclusion

In summary, we have shown that the enantiomeric composition of 1,2-diols can be conveniently assessed by ^{1}H NMR analysis of their cyclic boronates, easily and quantitatively obtained by simple exposure of the diol to the boronic acid (*R*)-(+)-**5**. This latter is obtainable in both enantiomerically pure forms by stereoselective homologation of commercially available 2-methylphenylboronic acid. The crude product can be conveniently analyzed by ^{1}H NMR: high inequivalencies are observed not only for the diol signals, but most importantly, resonance used for the analysis originated from the CDA as a couple of baseline-separated singlets.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-200 or Avance 400 spectrometer; chemical shifts

(δ) are reported in ppm downfield from TMS as internal standard (s singlet, d doublet, t triplet, q quartet, m multiplet, br broad signal); coupling constants (J) are given in hertz. Two-dimensional NMR techniques (COSY, HMBC and HSQC) were utilized to aid in the assignment of signals in ^{1}H and ^{13}C spectra, in particular for CDA (+)-**5**. Mass spectra were determined on a Finnigan MAT SSQ A mass spectrometer (EI, 70 eV). Melting points were obtained on a Gallenkamp apparatus. Optical rotations were recorded at +20 °C on a Perkin–Elmer 241 polarimeter and specific rotations are in 10^{-1} deg cm^2 g^{-1}.

All reactions requiring anhydrous conditions were performed under argon using oven-dried glassware. Solvents (THF and diethyl ether) were dried according to classical procedures and distilled from Na and benzophenone before use. Temperature of −100 °C was reached by addition of liquid nitrogen to a pre-cooled (−78 °C) bath containing an 1:1 EtOH–MeOH mixture.

Chromatographic purification of the compounds was accomplished on silica gel (0.05–0.20 mm). Arylboronic acids **9**–**13** were purchased from Sigma–Aldrich.

4.2. General procedure for the synthesis of pinacol arylboronates 9a–13a

A selected boronic acid **9**–**13** (3.4 mmol) and pinacol (3.4 mmol) were dissolved in anhydrous Et_2O; the mixture was stirred for 1 h at rt and concentrated under reduced pressure. The crude product was purified by distillation or by chromatography (3:7 EtOAc–EtPet), yielding the ester in the form of white crystalline solid.

4.2.1. Pinacol phenylboronate 9a. Yield: 95%, mp 27–28 °C, bp 100–102 °C/8 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.38 (12H, s, CH_3), 7.33–7.53 (3H, m, arom), 7.84 (2H, dd, $J = 8.0$, 2.0 Hz, arom). ^{13}C NMR ($CDCl_3$): δ 25.2, 84.1, 128.0, 131.6, 135.1 (*C*–B not seen). EI-MS: m/z 204 (17%, M$^+$), 198 (55%), 118 (62%), 105 (100%), 77 (15%), 43 (48%). Anal. Calcd for $C_{12}H_{17}BO_2$: C, 70.63; H, 8.40. Found: C, 70.77; H, 8.61.

4.2.2. Pinacol 2-methylphenylboronate 10a. Yield: 93%, colourless viscous liquid which slowly solidified in the refrigerator. ^{1}H NMR ($CDCl_3$): δ 1.39 (12H, s, CH_3), 2.60 (3H, s, PhCH_3), 7.15–7.28 (2H, m, arom), 7.31–7.43 (1H, m, arom), 7.78–7.88 (1H, m, arom). ^{13}C NMR ($CDCl_3$): δ 22.2, 24.9, 83.4, 124.7, 129.8, 130.8, 135.9, 144.8 (*C*–B not seen). EI-MS: m/z 218 (7%, M$^+$), 203 (7%), 119 (100%), 161 (37%), 132 (10%), 91 (23%), 65 (27%), 43 (96%). Anal. Calcd. for $C_{13}H_{19}BO_2$: C, 71.59; H, 7.78. Found: C, 71.41; H, 7.73.

4.2.3. Pinacol 2-methoxyphenylboronate 11a. Yield: 97%, mp 80–81 °C. ^{1}H NMR ($CDCl_3$): δ 1.37 (12H, s, CH_3), 3.84 (3H, s, OCH_3), 6.87 (1H, d, $J = 8.3$ Hz, H_3 arom), 6.97 (1H, t, $J = 7.2$ Hz, H_5 arom), 7.40 (1H, dt, $J = 8.3$, 1.8 Hz, H_4 arom), 7.69 (1H, dd, $J = 7.2$, 1.8 Hz, H_6 arom). ^{13}C NMR ($CDCl_3$): δ 24.8, 55.8, 83.4, 110.5, 120.2, 132.4, 136.7, 164.2 (*C*–B not seen). EI-MS: m/z 234 (55%, M$^+$), 219 (23%), 203 (10%), 176 (8%), 161 (28%), 134 (100%), 118 (12%), 105 (48%), 91 (65%), 77 (13%). Anal. Calcd for $C_{13}H_{19}BO_3$: C, 66.70; H, 8.18. Found: C, 66.52; H, 8.11.

4.2.4. Pinacol 1-naphthylboronate 12a. Yield: 99%, mp 51–52 °C. ^{1}H NMR ($CDCl_3$): δ 1.44 (12H, s, CH_3), 7.43–7.60 (3H, m, arom), 7.84 (1H, dd, $J = 8.3$, 1.9 Hz, arom), 7.94 (1H, d, $J = 8.3$ Hz, arom), 8.09 (1H, dd, $J = 6.8$, 1.4 Hz, arom), 8.77 (1H, d, $J = 8.0$ Hz, arom). ^{13}C NMR ($CDCl_3$): δ 26.3, 85.1, 126.3, 126.8, 127.7, 129.7, 129.8, 132.9, 134.6, 137.0, 138.3 (*C*–B not seen). EI-MS: m/z 254 (69%, M$^+$), 239 (12%), 210 (15%), 196 (12%), 181 (19%), 168 (38%), 154 (100%), 127 (12%), 85 (6%), 57 (5%). Anal. Calcd for $C_{16}H_{19}BO_2$: C, 75.62; H, 7.54. Found: C, 75.79; H, 7.50.

4.2.5. Pinacol 2-naphthylboronate 13a. Yield: 96%, mp 62–65 °C. ^{1}H NMR ($CDCl_3$): δ 1.42 (12H, s, CH_3), 7.45–7.59 (2H, m, arom), 7.80–7.97 (4H, m, arom), 8.41 (1H, s, H_1 arom). ^{13}C NMR ($CDCl_3$): δ 24.9, 83.9, 125.8, 126.9, 127.7, 127.9, 128.6, 130.4, 132.9, 135.1, 136.2 (*C*–B not seen). EI-MS: m/z 254 (58%, M$^+$), 239 (12%), 168 (88%), 154 (100%), 128 (10%), 120 (12%), 85 (16%). Anal. Calcd for $C_{16}H_{19}BO_2$: C, 75.62; H, 7.54. Found: C, 75.73; H, 7.63.

4.3. General procedure for the synthesis of (±)-pinacol methaneboronates 1a–8a

n-BuLi (2.5 M solution in hexane, 3.3 mmol) was added dropwise to a solution of CH_2Cl_2 (4.1 mmol) in THF (3 mL) while being stirred at −100 °C under argon: $LiCHCl_2$ precipitated as a white microcrystalline solid. After 30 min, the mixture was treated with the selected pinacol arylboronate **9a**–**13a** (2.6 mmol) and allowed to reach rt overnight. $LiN(TMS)_2$ (1 M solution in THF, 2.6 mmol) was added at −78 °C, and the reaction mixture then allowed to warm gradually. After 16 h at rt, the mixture was re-cooled at −78 °C and treated with the proper acylating agent, allowed to reach rt and stirred overnight. In the case of acetamido derivatives **1a**–**3a**, **7a** and **8a**, the acylating mixture was a solution of Ac_2O/AcOH (8.5/3.1 mmol) in THF (2 mL), whilst a solution of benzoylchloride/benzoic acid (6.2/3.1 mmol) in THF (3 mL) was used for benzamido derivatives **4a**–**6a**. The resulting solution was partitioned between EtOAc (45 mL) and H_2O (20 mL), the organic phase dried over $MgSO_4$ concentrated in vacuo affording the crude product, which was purified by chromatography (Et_2O–MeOH 95:5 or 9:1 for acetamido derivatives; EtOAc–EtPet 7:3 or 1:1 for benzamido derivatives).

4.3.1. Pinacol (±)-1-acetamido-1-phenylmethaneboronate 1a. After chromatography (Et_2O–MeOH 9:1), **1a** was obtained as a white solid, mp 184–187 °C, in 60% yield. ^{1}H NMR ($CDCl_3$): δ 0.85 (6H, s, CH_3), 0.98 (6H, s, CH_3), 2.05 (3H, s, COCH_3), 3.62 (1H, s, C*H*B), 7.02 (2H, d, $J = 6.8$ Hz, H_2 arom), 7.09–7.26 (3H, m, $H_{3,4}$ arom), 9.59 (1H, br s, N*H*). ^{13}C NMR ($CDCl_3$): δ 17.5, 24.8, 25.2, 52.9 (br, *C*B), 80.9, 126.0, 127.0, 128.2, 141.1, 176.8. EI-MS: m/z 275 (56%, M$^+$), 260 (13%), 217 (19%), 175 (48%), 150 (60%), 131 (100%),

118 (69%), 106 (51%), 91 (28%), 84 (29%), 77 (26%), 55 (21%), 43 (90%). Anal. Calcd for $C_{15}H_{22}BNO_3$: C, 65.48; H, 8.06; N, 5.09. Found: C, 65.66; H, 8.31; N, 5.01.

4.3.2. Pinacol (±)-1-acetamido-1-(2-methylphenyl)methane-boronate 2a. Column chromatography (Et_2O–MeOH 95:5) afforded **2a** in the form of a white solid, mp 138–140 °C, in 78% yield. ^1H NMR ($CDCl_3$): δ 0.94 (6H, s, CH_3), 1.07 (6H, s, CH_3), 2.14 (3H, s, COCH_3), 2.32 (3H, s, PhCH_3), 4.06 (1H, s, C*H*B), 6.97–7.18 (4H, m, arom), 7.97 (1H, br s, N*H*). ^{13}C NMR ($CDCl_3$): δ 18.0, 19.8, 24.5, 24.9, 47.5 (br, *C*B), 80.8, 125.5, 125.8, 126.3, 129.9, 134.7, 138.8, 176.0. EI-MS: *m*/*z* 289 (50%, M^+), 274 (12%), 231 (23%), 189 (15%), 164 (36%), 145 (100%), 120 (31%), 104 (58%), 93 (12%), 91 (19%). Anal. Calcd for $C_{16}H_{24}BNO_3$: C, 66.45; H, 8.37; N, 4.84. Found: C, 66.28; H, 8.46; N, 4.94.

4.3.3. Pinacol (±)-1-acetamido-1-(2-methoxyphenyl)-methane-boronate 3a. Chromatography (Et_2O–MeOH 95:5) afforded **3a** as a white solid, mp 136–137 °C, in 25% yield. ^1H NMR ($CDCl_3$): δ 1.11 (6H, s, CH_3), 1.17 (6H, s, CH_3), 2.13 (3H, s, COCH_3), 3.81 (3H, s, OCH_3), 4.38 (1H, d, $J = 3.4$ Hz, C*H*B), 6.79 (1H, br s, N*H*), 6.83 (1H, dt, $J = 8.1$, 1.0 Hz, H_3 arom), 6.91 (1H, dd, $J = 7.5$, 1.0 Hz, H_5 arom), 7.18 (1H, dt, $J = 8.1$, 1.7 Hz, H_4 arom), 7.31 (1H, dd, $J = 7.5$, 1.7 Hz, H_6 arom). ^{13}C NMR ($CDCl_3$): δ 19.0, 25.8, 26.1, 46.0 (br, *C*B), 56.2, 82.1, 111.1, 121.7, 127.8, 128.6, 130.9, 157.1, 177.1. EI-MS: *m*/*z* 305 (88%, M^+), 290 (12%), 262 (8%), 247 (23%), 205 (12%), 190 (12%), 178 (27%), 161 (17%), 148 (100%), 133 (62%), 117 (23%), 91 (30%), 77 (19%), 55 (18%). Anal. Calcd for $C_{16}H_{24}BNO_4$: C, 62.97; H, 7.93; N, 4.59. Found: C, 63.15; H, 7.81; N, 4.79.

4.3.4. Pinacol (±)-1-benzamido-1-phenylmethaneboronate 4a. After chromatography (light petroleum–ethylacetate 3:7), **4a** was isolated in 37% yield as a white solid, mp 190–193 °C. ^1H NMR ($CDCl_3$): δ 0.91 (6H, s, CH_3), 0.99 (6H, s, CH_3), 3.89 (1H, s, C*H*B), 7.06–7.55 (8H, m, arom), 7.87–8.00 (2H, m, arom), 9.84 (1H, br s, N*H*). ^{13}C NMR ($CDCl_3$): δ 25.6, 25.9, 54.3 (br, *C*B), 82.2, 127.1, 128.4, 129.3, 129.9, 130.1, 135.0, 142.3, 173.5. EI-MS: *m*/*z* 337 (44%, M^+), 336 (30%), 322 (5%), 279 (10%), 254 (10%), 237 (19%), 221 (11%), 211 (35%), 210 (30%), 193 (29%), 161 (10%), 132 (8%), 117 (9%), 106 (171%), 105 (100%), 104 (30%), 91 (8%), 77 (43%), 55 (7%). Anal. Calcd for $C_{20}H_{24}BNO_3$: C, 71.23; H, 7.17; N, 4.15. Found: C, 71.38; H, 7.02; N, 4.39.

4.3.5. Pinacol (±)-1-benzamido-1-(2-methylphenyl)methane-boronate 5a. Column chromatography (light petroleum–ethylacetate 1:1) afforded **5a** as a white solid, mp 171–172 °C, 24% yield. ^1H NMR ($CDCl_3$): δ 1.02 (6H, s, CH_3), 1.11 (6H, s, CH_3), 2.37 (3H, s, PhCH_3), 4.27 (1H, d, $J = 1.6$ Hz, C*H*B), 7.02–7.18 (4H, m, H_3–H_6 disubstituted Ph), 7.38–7.64 (3H, m, H_3,H_4 monosubstituted Ph), 7.83–7.93 (2H, m, H_2 monosubstituted Ph), 8.18 (1H, br s, N*H*). ^{13}C NMR ($CDCl_3$): δ 19.9, 24.6, 24.9, 55.4 (br, *C*B), 81.0, 125.6, 125.8, 126.6, 127.5, 128.2 (2C), 128.7 (2C), 130.0, 133.4, 134.9, 139.1, 171.6. EI-MS: *m*/*z* 351 (61%, M^+), 336 (6%), 293 (22%), 251 (13%), 224 (16%), 207 (43%), 145 (13%), 105 (100%), 77 (46%). Anal. Calcd for $C_{21}H_{26}BNO_3$: C, 71.81; H, 7.46; N, 3.99. Found: C, 72.03; H, 7.69; N, 4.13.

4.3.6. Pinacol (±)-1-benzamido-1-(2-methoxyphenyl)-methane-boronate 6a. Chromatography (light petroleum–ethyl acetate 3:7) afforded the title compound **6a** as a pale yellow viscous oil, 26% yield. ^1H NMR ($CDCl_3$): δ 1.02 (6H, s, CH_3), 1.08 (6H, s, CH_3), 3.69 (3H, s, OCH_3), 4.42 (1H, d, $J = 1.9$ Hz, C*H*B), 6.73–6.88 (2H, m, H_2 disubstituted Ph), 7.05–7.17 (2H, m, H_3,H_5 disubstituted Ph), 7.32–7.57 (3H, m, H_4, H_6 disubstituted Ph, H_4 monosubstituted Ph), 7.88–7.97 (2H, m, H_2 monosubstituted Ph), 9.01 (1H, br s, N*H*). ^{13}C NMR ($CDCl_3$): δ 24.5, 24.8, 45.0 (br, *C*B), 55.0, 82.7, 109.9, 120.3, 126.6, 127.1, 127.5, 127.88, 127.9, 128.5, 129.7, 131.7, 133.0, 156.6, 171.4. EI-MS: *m*/*z* 367 (63%, M^+), 352 (18%), 309 (31%), 267 (27%), 161 (20%), 148 (75%), 133 (53%), 105 (100%), 91 (41%), 77 (31%), 55 (23%). Anal. Calcd for $C_{21}H_{26}BNO_4$: C, 68.68; H, 7.14; N, 3.81. Found: C, 68.51; H, 7.04; N, 4.00.

4.3.7. Pinacol (±)-1-acetamido-1-(naphth-1-yl)methane-boronate 7a. Purification by column chromatography (diethyl ether–methanol 95:5) of the crude residue afforded **7a** as a white solid, mp 217–218 °C, 38% yield. ^1H NMR ($CDCl_3$): δ 0.86 (6H, s, CH_3), 1.07 (6H, s, CH_3), 2.23 (3H, s, COCH_3), 4.73 (1H, s, C*H*B), 7.24–7.52 (5H, m, N*H* and arom), 7.68 (1H, d, $J = 7.7$ Hz, arom), 7.83 (1H, d, $J = 8.3$, 1.2 Hz, arom), 8.08 (1H, d, $J = 8.3$ Hz, arom). ^{13}C NMR ($CDCl_3$): δ 18.6, 26.2, 26.4, 49.5 (br, *C*B), 82.4, 123.3, 125.4, 126.67, 127.70, 127.3, 129.7, 132.3, 134.9, 138.1, 178.0. EI-MS: *m*/*z* 325 (45%, M^+), 310 (32%), 267 (6%), 225 (8%), 199 (48%), 181 (66%), 167 (36%), 156 (100%), 141 (39%), 129 (48%), 115 (24%), 91 (16%), 84 (81%), 49 (69%). Anal. Calcd for $C_{19}H_{24}BNO_4$: C, 70.17; H, 7.44; N, 4.31. Found: C, 69.95; H, 7.56; N, 4.17.

4.3.8. Pinacol (±)-1-acetamido-1-(naphth-2-yl)methane-boronate 8a. Chromatographic purification (diethyl ether–methanol 95:5) afforded **8a** as a whitish solid, mp 229–231 °C, 38% yield. ^1H NMR ($CDCl_3$): δ 0.89 (6H, s, CH_3), 1.04 (6H, s, CH_3), 2.09 (3H, s, COCH_3), 3.89 (1H, s, C*H*B), 7.24 (1H, dd, $J = 8.6$, 1.7 Hz, arom), 7.38–7.50 (3H, m, arom), 7.65–7.84 (3H, m, arom), 8.54 (1H, br s, N*H*). ^{13}C NMR ($CDCl_3$): δ 19.1, 25.9, 26.3, 53.2 (br, *C*B), 82.1, 125.7, 126.4, 127.2, 127.3, 128.88, 128.94, 133.5, 134.8, 139.8, 177.6. EI-MS: *m*/*z* 325 (54%, M^+), 310 (4%), 267 (12%), 225 (19%), 200 (35%), 181 (100%), 167 (54%), 156 (42%), 141 (23%), 91 (12%), 84 (23%). Anal. Calcd for $C_{19}H_{24}BNO_4$: C, 70.17; H, 7.44; N, 4.31. Found: C, 69.90; H, 7.63; N, 4.13.

4.4. General procedures for the hydrolysis of pinacol methylboronates to free boronic acids 1–8

Method A: Pinacol methaneboronates (0.2 mmol) were treated with degassed HCl 3 M (4 mL) at 100 °C for 1 h under argon. The reaction mixture was extracted

with EtOAc (10 mL) and the aqueous phase concentrated in vacuo to afford the boronic acids as vitreous solids, which were dried over P_2O_5 until a constant weight.

Method B: Pinacol methaneboronates (0.2 mmol) were stirred for 1 h in 4 M HCl in anhydrous MeOH (2.5 mL) at rt. The solvent was evaporated in vacuo and the residue partitioned between Et_2O (5 mL) and H_2O (3 mL); the aqueous phase was concentrated under reduced pressure, yielding the free boronic acids as vitreous solids, which were dried over P_2O_5 until constant weight.

MS fragmentation and elemental analyses of boronic acids **1**–**8** were not obtainable, because of the formation of dehydration products. Nevertheless, exposure of a solution of these acids in THF to an equimolar amount of pinacol always afforded the expected esters **1a**–**8a** in quantitative yield with satisfactory MS fragmentation and elemental compositions.

4.4.1. (±)-1-Acetamido-1-phenylmethaneboronic acid 1. Method A: 89% yield. ^{1}H NMR (CD_3OD): δ 2.34 (3H, s, COCH_3), 3.85 (1H, s, C*H*B), 7.11–7.33 (5H, m, arom). ^{13}C NMR (CD_3OD): δ 15.5, 53.1 (br, *C*B), 125.9, 128.3, 140.7, 178.3.

4.4.2. (±)-1-Acetamido-1-(2-methylphenyl)methaneboronic acid 2. Method A: 70%. ^{1}H NMR (CD_3OD): δ 2.30 (3H, s, COCH_3), 2.40 (3H, s, PhCH_3), 4.13 (1H, s, C*H*B), 6.90–7.40 (4H, m, arom). ^{13}C NMR (CD_3OD): δ 15.1, 18.4, 51.1 (br, *C*B), 123.4, 125.4, 125.5, 129.7, 134.4, 138.0, 177.8.

4.4.3. (±)-1-Acetamido-1-(2-methoxyphenyl)methaneboronic acid 3. Method A: 68%. ^{1}H NMR (CD_3OD): δ 2.35 (3H, d, $J = 1.3$ Hz, COCH_3), 3.83 (3H, s, OCH_3), 4.23 (1H, s, C*H*B), 6.82–7.26 (4H, m, arom). ^{13}C NMR (CD_3OD): δ 15.0, 40.0 (br, *C*B), 54.5, 110.0, 120.1, 125.2, 126.7, 128.1, 156.4, 178.1.

4.4.4. (±)-1-Benzamido-1-phenylmethaneboronic acid 4. Method A: 45%; method B 86%. ^{1}H NMR (CD_3OD): δ 4.05 (1H, s, C*H*B), 7.10–7.36 (5H, m, arom), 7.58–7.83 (3H, m, arom), 8.08–8.18 (2H, m, arom). ^{13}C NMR (CD_3OD): δ 56.7 (br, *C*B), 126.9, 127.2, 129.3, 129.9, 130.4, 135.9 (C=O not seen).

4.4.5. (±)-1-Benzamido-1-(2-methylphenyl)methaneboronic acid 5. Method A: 22%; method B: 87%. ^{1}H NMR (CD_3OD): δ 2.38 (3H, s, PhCH_3); 4.24 (1H, s, C*H*B); 7.02–7.21 (4H, m, H_3–H_6 disubstituted Ph), 7.66 (2H, t, $J = 7.6$ Hz, H_3 monosubstituted Ph), 7.79 (1H, t, $J = 7.6$ Hz, H_4 monosubstituted Ph), 8.15 (2H, t, $J = 7.6$ Hz, H_2 monosubstituted Ph). ^{13}C NMR (CD_3OD): δ 18.5, 50.7 (br, *C*B), 124.0, 125.1, 125.4, 128.4, 129.0, 134.42, 134.44, 139.1, 172.8.

4.4.6. (±)-1-Benzamido-1-(2-methoxyphenyl)methaneboronic acid 6. Method A: 43%; method B: 82%. ^{1}H NMR (CD_3OD): δ 3.79 (3H, s, OCH_3), 4.26 (1H, s, C*H*B), 6.91–7.14 (3H, m, H_3 disubstituted Ph and H_3 monosubstituted Ph), 7.25 (1H, dt, $J = 6.8$, 2.1 Hz, H_5 disubstituted Ph), 7.53–7.67 (2H, m, H_4 disubstituted Ph, H_4 monosubstituted Ph), 7.69–7.81 (1H, m, H_6 disubstituted Ph), 7.95–8.50 (2H, m, H_2 monosubstituted Ph). ^{13}C NMR (CD_3OD): δ 41.4 (br, *C*B), 55.0, 111.4, 121.1, 126.1, 127.5, 128.3, 129.1, 129.8, 158.7, 172.9.

4.4.7. (±)-1-Acetamido-1-(naphth-1-yl)methaneboronic acid 7. Method B: 82%. ^{1}H NMR (CD_3OD): δ 2.43 (3H, d, $J = 0.9$ Hz, COCH_3), 4.63 (1H, s, C*H*B), 7.22 (1H, dt, $J = 7.2$, 1.0 Hz, H_2 disubstituted Ph), 7.37–7.55 (4H, m, arom), 7.71 (1H, d, $J = 8.2$ Hz, arom), 7.79–7.91 (1H, m, arom), 8.00–8.13 (1H, m, arom). ^{13}C NMR (CD_3OD): δ 16.5, 52.0 (br, *C*B), 121.4, 124.2, 124.8, 126.4, 126.7, 127.1, 129.5, 132.2, 135.2, 179.7.

4.4.8. (±)-1-Acetamido-1-(naphth-2-yl)methaneboronic acid 8. Method B: 87%. ^{1}H NMR (CD_3OD): δ 2.36 (3H, d, $J = 1.1$ Hz, COCH_3), 3.98 (1H, s, C*H*B), 7.28 (1H, dd, $J = 8.5$, 1.7 Hz, arom), 7.33–7.50 (2H, m, arom), 7.56 (1H, s, arom), 7.72–7.85 (3H, m, arom). ^{13}C NMR (CD_3OD): δ 15.0, 53.6 (br, *C*B), 122.9, 124.7, 124.8, 125.6, 127.0, 127.2, 127.3, 132.5, 133.6, 138.4, 177.8.

4.5. Asymmetric synthesis of (*R*)-(+)-5

4.5.1. (+)-Pinanediol (2-methylphenyl)methaneboronate (−)-10h. Boronic acid **10** (1.00 g, 7.4 mmol) and (+)-pinanediol (1.26 g, 7.4 mmol) were dissolved in anhydrous THF (8 mL). The mixture was stirred for 1 h at rt and concentrated in vacuo. The crude product was purified by chromatography (EtOAc–EtPet 2:8), yielding the ester (1.95 g, 98%) as colourless viscous oil, $[\alpha]_D = -3.5$ (*c* 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, s, pinanyl CH_3), 1.29 (1H, d, $J = 10.7$ Hz, pinanyl H_{endo}), 1.35 (3H, s, pinanyl CH_3), 1.52 (3H, s, pinanyl CH_3), 1.90–2.53 (5H, m, pinanyl protons), 2.59 (3H, s, PhCH_3), 4.48 (1H, dd, $J = 8.5$, 1.9 Hz, pinanyl C*H*OB), 7.14–7.43 (3H, m, H_3–H_5 arom), 7.82 (1H, dd, $J = 6.7$, 1.9 Hz, arom). ^{13}C NMR ($CDCl_3$): δ 22.3, 24.1, 26.6, 27.1, 28.8, 35.8, 38.5, 39.6, 51.5, 78.0, 85.8, 124.8, 129.8, 130.8, 136.0, 144.8 (*C*–B not seen). EI-MS: *m*/*z* 270 (54%, M^+), 255 (30%), 229 (17%), 214 (16%), 201 (100%), 187 (25%), 174 (92%), 134 (50%), 119 (42%), 91 (27%), 83 (58%), 67 (46%), 55 (25%). Anal. Calcd for $C_{17}H_{23}BO_2$: C, 75.57; H, 8.58. Found: C, 75.39; H, 8.69.

4.5.2. (+)-Pinanediol (1*R*)-1-benzamido-1-(2-methylphenyl)-methaneboronate (+)-5h. A solution of methylene chloride (230 μL, 3.6 mmol) in THF (3 mL) was cooled at −100 °C and treated with a 2.5 M solution of butyllithium in hexanes (1.1 mL, 2.6 mmol) under an argon flow and magnetic stirring: $LiCHCl_2$ precipitated as a white microcrystalline solid. After 30 min, a solution of the above pinanediol arylboronate (−)-**10h** (600 mg, 2.2 mmol) in anhydrous THF (2 mL) was added dropwise at −100 °C over a 20 min period. The mixture was gradually allowed to reach 0 °C over 6 h and stirred at this temperature for one additional hour.

Thereafter, the solution was cooled at −78 °C and $LiN(TMS)_2$ (1 M solution in THF, 2.6 mL, 2.6 mmol) added and the reaction mixture allowed to warm gradually. After 16 h at rt, the mixture was cooled again at −78 °C, treated with a solution of freshly distilled benzoylchloride (620 μL, 5.3 mmol) and benzoic acid (320 mg, 2.7 mmol) in THF (3 mL) allowed to reach rt and stirred overnight. The resulting brownish solution was partitioned between Et_2O (60 mL) and H_2O (20 mL) and the aqueous phase extracted repeatedly with Et_2O (60, 40 and 20 mL). The collected organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure affording the crude product as a viscous brown oil which was purified by gradient chromatography (EtPet–EtOAc from 7:3 to 3:7). The pure product **5h** was isolated as a white amorphous solid, mp 75 °C, 45% overall yield from **10h**. $[\alpha]_D = +6.1$ (*c* 1.8, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.80 (3H, s, pinanyl CH_3), 1.21 (3H, s, pinanyl CH_3), 1.31 (1H, d, $J = 10.3$ Hz, pinanyl H_{endo}), 1.33 (3H, s, pinanyl CH_3), 1.51–2.30 (5H, m, pinanyl protons), 2.39 (3H, s, PhCH_3), 4.19 (1H, dd, $J = 8.0$, 1.8 Hz, pinanyl C*H*OB), 4.41 (1H, d, $J = 1.9$ Hz, C*H*B), 7.01–7.20 (4H, m, H_3–H_6 disubstituted Ph), 7.36–7.61 (3H, m, H_3 and H_4 monosubstituted Ph), 7.70–7.92 (3H, m, H_2 monosubstituted Ph and N*H*). ^{13}C NMR ($CDCl_3$): δ 21.3, 25.5, 27.7, 28.6, 30.3, 37.7, 39.5, 41.3, 46.6 (br, *C*B), 53.5, 78.2, 85.6, 127.0, 127.2, 127.4, 129.3, 130.1 (2C), 131.6, 134.4, 136.2, 140.4, 172.2. EI-MS: *m*/*z* 403 (39%, M^+), 251 (14%), 224 (17%), 207 (33%), 126 (29%), 105 (100%), 93 (42%), 77 (35%), 71 (21%), 55 (14%). Anal. Calcd for $C_{25}H_{30}BNO_3$: C, 74.45; H, 7.50; N, 3.47. Found: C, 74.32; H, 7.68; N, 3.39.

4.5.3. (1*R*)-1-Benzamido-1-(2-methylphenyl)methaneboronic acid (+)-5). Compound (+)-**5h** (400 mg, 0.99 mmol) was treated with degassed HCl 3 M (22 mL) at 100 °C for 1 h under argon. The reaction mixture was extracted with Et_2O (40, 20 mL) and the aqueous phase concentrated under reduced pressure to afford a white solid which was dried over P_2O_5 until constant weight, yielding 136 mg (54% yield) of (+)-**5**. Mp 56–57 °C; $[\alpha]_D = +26.6$ (*c* 0.7, CH_3OH). ^1H NMR and ^{13}C NMR were identical to those shown by (±)-**5**. To assess that no racemization occurred during the hydrolysis, a sample of (+)-**5** was converted to (+)-**5h** by reaction with a slight excess of (+)-pinanediol; this latter was recovered in a quantitative yield and de >98%.

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