

Amination-reduction reaction as simple protocol for potential boronic molecular receptors. Insight in supramolecular structure directed by weak interactions

Invited Paper

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Abstract: The synthesis of the potential molecular receptors in the amination-reduction reaction has been investigated within the model system comprising (2-formylphenyl)boronic acid and morpholine. The 3-amine substituted benzoxaborole was identified to be the intermediate of the synthesis and the unsubstituted benzoxaborole as the by-product resulting from reduction of the starting material. The insight into the reactivity of the starting materials as well as the intermediate benzoxaborole enabled significant rise in the yield of 2-(aminomethyl)phenylboronic acids synthesis. The solid state structure of 2-(piperidylmethyl)phenylboronic acid has been re-determined, and the description of the molecule and the crystal is given. The supramolecular layer structure directed by the weak C-H...O and C-H... π interactions was identified and scrutinized based on the geometry and Hirshfeld surface analyses

Keywords: Boronic acids • Benzoxaboroles • X-ray structure • Hirshfeld surface • Supramolecular structure

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1. Introduction

2-(Aminomethyl)phenylboronic acids are known as potent saccharide molecular receptors active at the physiological pH level [1]. The continuous demand for new and selective receptors, not only for sugars but also for other hydroxyl compounds, makes their effective and economical synthesis of crucial importance. Several synthetic methods for 2-(aminomethyl)phenylboronic acids have been reported up to now [2]. Unfortunately, many of them are multi-step processes or suffer from low selectivity and yields [3]. Some specific problems with boronic acid purification e.g. irreversible binding with silica-gel or formation of boroxins at elevated temperatures make the issue of selectivity of their synthesis even more important [4].

The amination-reduction reaction of commercially available (2-formylphenyl)boronic acid (1) with secondary amines seems to be the most reasonable synthetic strategy. According to the previously published reports on the chemistry of boronic compounds, however, various products could be expected under the amination-reduction reaction conditions of (2-formylphenyl)boronic acid with secondary amines [5-7]. Therefore, careful investigation of the system was undertaken to assess the real potential of the synthetic method and to optimize reaction conditions.

Recent reports by Davis [8] imply that the receptor properties of boron compounds result not only from the boron-containing groups, but also from weak interactions with other parts of the receptor. Hence, the investigations of the supramolecular structure of substituted boronic acids may be of significance.

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2. Experimental Procedure

2.1. General

^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer operating at frequency 400 and 100.1 MHz, respectively. ^{11}B NMR spectra were recorded on a Varian Unity Plus 200 operating at 64 MHz, chemical shifts were determined using inserts with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in benzene ($\delta = 0.0$ ppm). Elemental analyses for C, H and N were obtained using Perkin Elmer CHNS/O II Model 240 analyzer.

(2-Formylphenyl)boronic acid was obtained according to a known procedure, and its purity was confirmed on the basis of ^1H NMR; morpholine and piperidine were purchased from Sigma-Aldrich and solvents from POCH.

2.2. General synthetic procedure for 2-(morpholin-4-ylmethyl)phenyl] boronic acid (3)

Morpholine and (2-formylphenyl)boronic acid were dissolved in methanol in 1 : 1 ratio at the appropriate temperature (Table 1). NaBH_4 (1 molar ratio) was added to the resulting clear solution while intense stirring. After 20 minutes, 10 mL of 3 M HCl solution was added (pH ca. 1) and **4** was extracted with diethyl ether (4×20 mL). After separation of phases, the aqueous phase was neutralized with $\text{NH}_{3\text{aq}}$ until pH ca. 7. Product **3** was isolated upon extraction of the neutral aqueous phase with diethyl ether (4×20 mL).

3. Cream crystals, yield 51-84%, the identity and purity of the products was confirmed on the basis of ^1H NMR spectrum that were analogous to the previously reported [10].

2.3. Reduction of (2-formylphenyl) boronic acid, synthesis of 2,1-benzoxaborol-1 (3H)-ol (4)

1 (0.147 g, 0.1 mmol) was dissolved in methanol (5 mL). NaBH_4 (0.040 g, 0.105 mmol) was added to the resulting clear solution and stirring was continued for the next 20 minutes at room temperature. HCl_{aq} (3 M, 10 mL) was added to the resulting mixture. The aqueous phase was extracted with Et_2O (3×20 mL), the solution dried over anhydrous Na_2SO_4 and solvent evaporated under reduced pressure. Analogous reduction with NaBH_3CN resulted in 98% yield of pure **4**.

4. White crystals, yield 97%, 0.128 g, mp 96-99°C (lit. 94-98°C) [22]. ^1H NMR analogous to the one previously reported [6].

2.4. Reduction of 3-morpholin-4-yl-2,1-benzoxaborol-1(3H)-ol (5)

To solution of **5** (0.150 g, 0.7 mmol) in methanol (5 mL) at 25°C NaBH_4 (0.038 g, 1 mmol) was added and the mixture was stirred for 20 min. After this time 3 M HCl (10 mL) was added and left to stir for 10 min. The resulting reaction mixture was extracted with diethyl ether (3×20 mL), and the organic layer was evaporated to afford **4** (0.030 g, 22% yield). The remaining aqueous layer was neutralized to pH ca. 7-8 by adding 25% aqueous ammonia solution. The reaction mixture was extracted with diethyl ether (3×20 mL), and the organic layer was evaporated to afford 0.124 g of the oily residue containing **3** as the sole aromatic product contaminated with small amounts of morpholine.

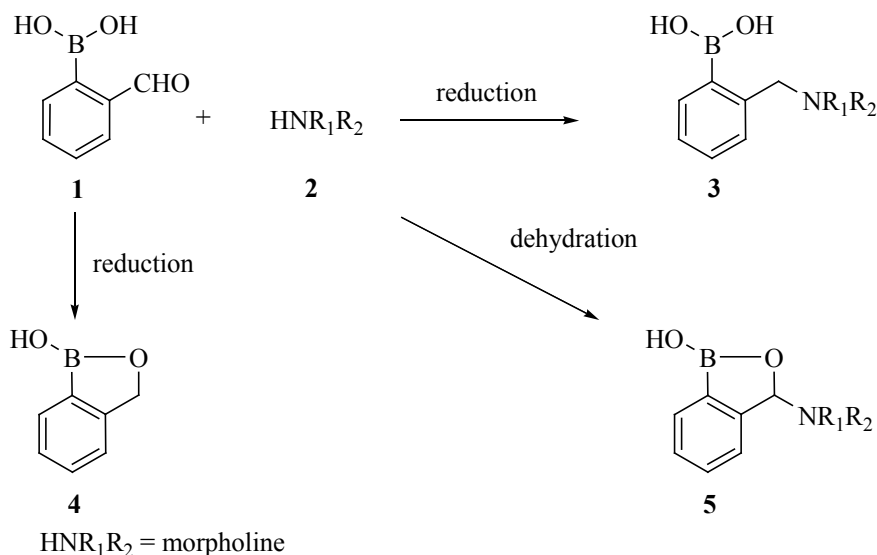
2.5. Synthesis of [2-(piperidin-1-ylmethyl)phenyl]boronic acid (3a)

A solution of piperidine (0.568 g, 6.7 mmol) in methanol (30 mL) was prepared at -10°C. **1** (1 g, 6.7 mmol) was added, followed by addition of NaBH_4 (0.57 g, 6.7 mmol) with vigorous stirring. After 20 min, HCl_{aq} (3 M, 10 mL) was added (pH ca. 1) and mixed for another 10 min. Et_2O (40 mL) was added to the post-reaction mixture resulting in precipitation of the solid, which dissolved by addition of water. The aqueous phase was extracted with Et_2O (2×30 mL) and then neutralized with $\text{NH}_{3\text{aq}}$ (pH ca. 7). **3a** was extracted with Et_2O (3×40 mL) from the resulting neutral aqueous phase. The combined organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure.

3a. White crystals, yield 59%, 0.869 g, mp 192-193°C, ^1H NMR (400 MHz, CDCl_3) δ_{H} 2.91-1.25 (10H, m, br, 5CH_2), 3.58 [2H, s, CH_2], 7.16-7.14 [1H, m, Ar], 7.32 [2H, m, Ar], 7.92 [m, 1H, Ar], 9.06 [s, br, $\text{B}(\text{OH})_2$ lower intensity due to the exchange]. ^1H NMR (400 MHz, CD_3OD) δ_{H} 1.64 (2H, m, CH_2), 1.78 (4H, br, 2CH_2), 2.89 (4H, br, 2CH_2), 4.13 (2H, s, CH_2), 7.16-7.10 (2H, m, Ar), 7.24 (1H, m, Ar), 7.65 (1H, d, $^3J_{\text{HH}} = 7.6$ Hz, Ar). ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 23.8, 25.1, 53.1, 64.5, 127.3, 129.8, 130.4, 136.2, 141.4. ^{11}B NMR (64 MHz, CDCl_3) δ_{B} 30.9. ^{11}B NMR (64 MHz, CD_3OD) δ_{B} 5.8, 18.5. Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{BNO}_2$ (219.14): C, 65.79; H, 8.28; N, 6.39%, Found: C, 65.69; H, 8.21; N, 6.31%.

2.6. Hirshfeld surface analysis

Molecular Hirshfeld surface in the crystal structure is constructed basing on the electron distribution calculated as the sum of spherical atom electron densities [18,19]. The surface enclosing a molecule is defined by points



Scheme 1. Reactivity of **1** under amination-reduction conditions.

where the contribution to the electron density from the molecule of interest is equal to the contribution from all the other molecules. For each point on that isosurface two distances are defined: d_e , the distance from the point to the nearest nucleus external to the surface, and d_i the distance to the nearest nucleus internal to the surface. These distances can be normalized (d_{norm}) using atomic vdW radii [20]. The value of d_{norm} is negative/positive when intermolecular contacts are shorter/longer than vdW separations. Because of the symmetry between d_e and d_i in the expression for d_{norm} , where two Hirshfeld surfaces touch, both will display a red spot identical in color intensity as well as size and shape. Graphical plots of the molecular Hirshfeld surfaces mapped with d_{norm} are displayed using a red–white–blue color scheme, where red highlights shorter contacts, white is used for contacts around the vdW separation, and blue is for longer contacts. Fig. 1 was generated using Crystal Explorer 2.1 program [23].

3. Results and Discussion

The reactivity of (2-formylphenyl)boronic acid (**1**) in the amination-reduction reaction with morpholine has been investigated. According to our previously reported results, simple reduction of **1** and subsequent cyclization result in 2,1-benzoxaborol-1(3H)-ol (**4**) [6]. The other possibility is the reaction of (2-formylphenyl)boronic acid (**1**) with morpholine (**2**) resulting in 3-morpholin-4-yl-2,1-benzoxaborol-1(3H)-ol (**5**) [7,9]. The desired 2-aminomethyl product (**3**) has previously been obtained at amination-reduction conditions yet with moderate

yield (Scheme 1) [10]. In order to improve the synthetic strategy for new potential boronic receptors, the reaction was investigated within the presented model system comprising (2-formylphenyl)boronic acid (**1**) and morpholine (**2**).

Reduction of **1** with both NaBH_4 and NaBH_3CN in methanol at room temperature resulted in **4** almost quantitatively. Extraction of the product with Et_2O from the acidic aqueous phase results in much better yields of **4** in comparison with the previously reported methodology (rise from 45% [6] to 97% in the present study).

The ^1H NMR spectrum of **1** and **2** mixture in CD_3OD revealed exclusively signals corresponding to **5** immediately after preparation at room temperature. No traces of the previously postulated imine intermediate [11] have been detected.

Due to the above mentioned facts, formation of **4** and **5** under the amination-reduction reaction conditions was expected. Several amination-reduction reactions were carried out in methanol. Identification of the structure and purity of the products was done by ^1H NMR of the post-reaction mixtures in CDCl_3 . The signals at 3.65 ppm (2H) in **3** and 5.10 ppm (2H) in **4** have been taken into account. Formation of **5** was verified with the 5.87 ppm (1H) signal, and conversion of **1** with the presence of the formyl group signal at ca. 10 ppm (1H).

Surprisingly, none of the post-reaction mixtures contained any traces of the expected benzoxaborole **5**. The reason of that lies in the reactivity of **5**, which has not been investigated so far. To explore the problem, compound **5** was obtained according to the previously described procedure [7,9], dissolved in MeOH and

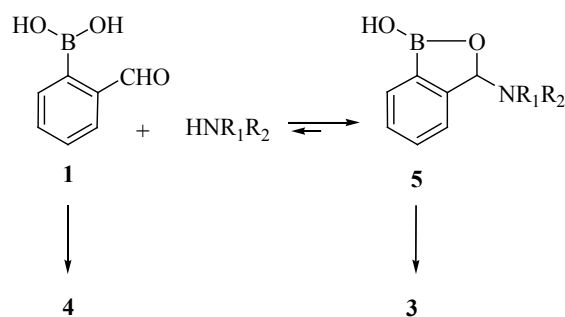
treated with NaBH_4 , resulting in **3** (56% yield). The result clearly indicates that **5**, formed instantly after mixing of **1** and **2** in the amination reaction, gives the desired product (**3**) upon reduction, so **5** can be treated as an intermediate for the synthesis of **3**. Unexpectedly, the other isolated product of the reaction was **4** (22% yield). The most probable explanation of this observation is a fast equilibrium in solution (Scheme 2).

The equilibrium must be strongly right-shifted, as the solution of **5** in CD_3OD displays no traces of the signal corresponding to the CHO group. The fast reduction of **1**, however, shifts the equilibrium to the left resulting in **4** in a reasonable yield. Due to instant and quantitative formation of **5** in the reaction of **1** and morpholine, the limiting factor of the synthesis is not the expected [11] low reactivity of the amine, rather a fast rate of the reduction of **1** resulting in a stable **4**. Therefore, limiting the reduction rate of **1** should result in higher yields of **3**.

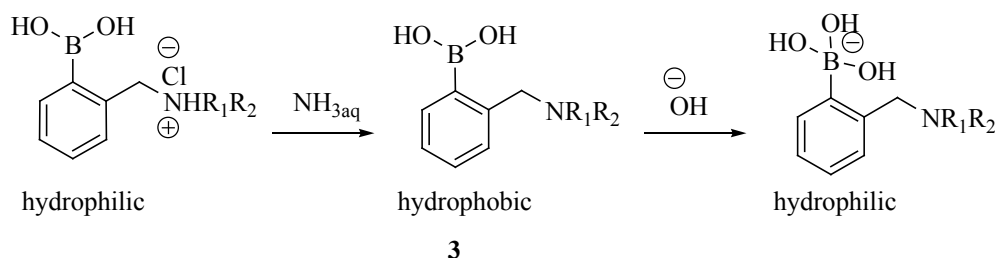
The influence of temperature on yields of **3** and **4** has been investigated within the model system according to

Table 1. Isolated yields of **3** and **4** depending on temperature of the reaction.

Temp. (°C)	Yield of 3 (%)	Yield of 4 (%)
65	51	35
25	67	22
0	74	20
-10	84	11



Scheme 2. Formation of **3** and **4** under the amination-reduction reaction conditions.



Scheme 3. Various forms of **3** depending on pH.

the general procedure. Decreasing reaction temperature resulted in an increase of the yield of **3** and simultaneous drop in the amount of **4** formed (Table 1), which strongly supports the hypothesis.

In the case of many investigated amination-reduction reactions of **1** with morpholine, mixtures of **3** and **4** have been obtained. Due to this fact, it was important to develop an efficient purification method. The separation of the products was possible due to the hydrophilic character of **3** hydrochloride formed after the acidification of the reaction with HCl_{aq} . The selective extraction of **4** with diethyl ether was possible under these conditions. The extraction of hydrophobic **3** with diethyl ether was possible at neutral pH after addition of $\text{NH}_{3\text{aq}}$. The basification should be carried out carefully, as both **3** and **4** transform into hydrophilic species at basic pH (Scheme 3).

Following the developed procedure, [2-(piperidin-1-ylmethyl)phenyl]boronic acid (**3a**, HNR_1R_2 = piperidine) has been obtained in reasonable yield (59%) and fully characterized. The cyclic anhydride of **3a** has been previously obtained by Wulff and co-workers [12] by the amination of the anhydride of the corresponding bromide. The characteristic signals of the benzyl protons in the ^1H NMR spectra of **3a** and its boroxin in CDCl_3 are 3.58 and 3.90 ppm [12], respectively. **3a** has been previously investigated as potential receptor of hydroxyacids and diols [13]. Following the contribution of Collins and co-workers [14], the structure of **3a** in methanol solution was investigated by ^{11}B NMR spectroscopy. The presence of the methyl ester with the N-B dative bond (major signal at 18 ppm) and the fully solvated form with proton transfer (minor signal at ca. 6 ppm) was identified. Surprisingly, crystallization of the sample from methanol solution resulted in the crystals of **3a**, containing free $\text{B}(\text{OH})_2$ group and no built up methanol molecules. Its X-ray structure has been previously determined [15], yet only the formation of a molecular dimer was indicated. Hence, we present here a detailed molecular and crystal structure of **3a**.

Molecules of **3a** crystallize in the $P2_1/n$ space group symmetry of the monoclinic system. The crystal data are summarized in Supplemental Table 1 of the

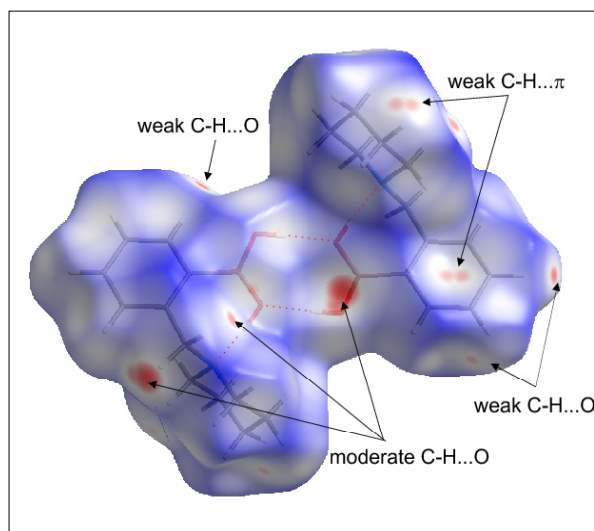


Figure 1. Hirshfeld surface of O–H...O bonded **3a** dimer mapped with d_{norm} . The O–H...O and O–H...N hydrogen bonds within the surface are shown as a dashed lined. The red spots on the surface indicate the presence of weaker intermolecular interactions.

Supplementary materials. Supplemental Tables 2 and 3 list the selected geometrical parameters and the geometry of hydrogen bonds, respectively. The B(OH)_2 fragment in **3a** is twisted with respect to the phenyl ring by $27.9(6)^\circ$. The similar twist was observed in the previously described morpholine and thiomorpholine analogs [10]. The piperidyl substituent in **3a** has a chair conformation and is oriented in a way that enables the formation of an intramolecular O–H...N hydrogen bond. It should be noted that these are the only interactions that involve the nitrogen atom. Both the intramolecular O–H...N and the intermolecular O–H...O hydrogen bonds that form a centrosymmetric dimer in **3a** are also found in the above-mentioned analogs. The dimer is described by the $R_2^2(8)$ graph set [16,17] and it can be regarded as a primary supramolecular motif.

To rate the weaker interactions that are present in the crystals of **3a** we used the Hirshfeld surface analysis [18] that is a useful tool for depicting types and directionality of weak intermolecular interactions [19]. The graphical plot of the molecular Hirshfeld surface of

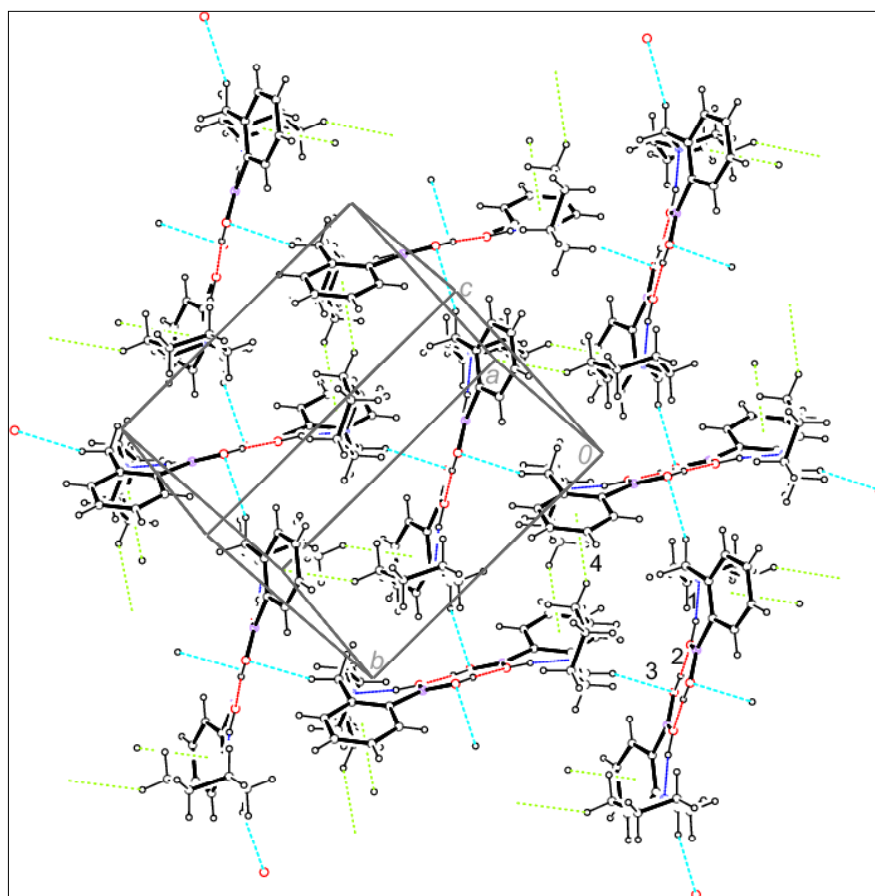


Figure 2. The square-grid layer structure of **3a** directed by C–H...O hydrogen bonds and enhanced by weak C–H... π interactions. View towards the (-101) plane. H-bonds are presented as dashed lines and labeled from 1 to 4 in order: N–H...O (intramolecular), O–H...O, C–H...O and C–H... π (intermolecular).

3a dimer mapped with d_{norm} [20] is presented in Fig. 1. The red depressions on the surface (distances shorter than sum of the vdW radii) indicate the regions of significant interactions, highlighting both acceptors and donors. The most intense spots occur above the oxygen atom and the methylene group hydrogen atoms. They correspond to two C–H...O interactions of which the shortest has a C...O bond distance equal to 3.585(1) Å (labeled 3 in Fig. 2). These H-bonds join the dimers of **3a** into a square grid layer structure on the (–101) plane (Fig. 2).

Each mesh of the grid is additionally enhanced by weak C–H... π interactions (labeled 4 in Fig. 2). They appear on the Hirshfeld surface as small spots above the phenyl ring, which is acting as a π -acceptor. The donors are the protons from the piperidyl substituent. Therefore, the second level of molecular arrangement in **3a** is a 2-D assembly with the symmetry of $p2_1/b$ layer group [21]. These layers are further zipped into a 3-D structure by rather weak C–H...O interactions between H-donors from the phenyl ring and the oxygen atom (small red spots in Fig. 1).

4. Conclusions

The amination-reduction reaction can act as simple and efficacious protocol for 2-(aminomethyl)phenylboronic acids. In case of the investigated amines, the amination reaction resulting in amine substituted benzoxaborole intermediate turned out to be fast and efficient, yet reversible. The reversibility of its formation together with the fast reduction of the starting aldehyde were the main obstacles that were circumvented by lowering the reaction

temperature and use of an appropriate purification method. The role of weak intermolecular interactions in the crystals of 2-(aminomethyl)phenylboronic acids was shown, and the resulting supramolecular structure was described.

Supplementary materials

Crystal data for **3a**, details of solution and refinement are given in supplementary file and summarized in Supplemental Table 1. Supplemental Figure 1 presents a dimer of **3a** with thermal ellipsoids and atoms numbering scheme. Supplemental Tables 2 and 3 list the selected geometrical parameters and geometry of the hydrogen bonds, respectively. CCDC 784187 contains the crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; e-mail: deposit@ccdc.cam.ac.uk. Copies of ^1H , ^{13}C and ^{11}B spectra of **3a** are also provided.

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References

- [1] T.D. James, M.D. Phillips, S. Shinkai, *Boronic Acids in Saccharide Recognition* (RSC Publishing, Cambridge, 2006) 48, 54–55
- [2] A. Sporzyński, A. Żubrowska, A. Adamczyk-Woźniak, In: V.I. Rybachenko (Ed.), *Synthetic receptors in molecular recognition* (Schidnyj wydawnyczyj dim, Donetsk, Ukraine, 2007) 51–87
- [3] W. Tan, D. Zhang, D. Zhu, *Bioorg. Med. Chem. Lett.* 17, 2629 (2007)
- [4] D.G. Hall. (Ed.), *Boronic Acids. Preparation, applications in organic synthesis and medicine* (VCH, Weinheim, 2005)
- [5] A. Adamczyk-Woźniak, M.K. Cyrański, A. Żubrowska, A. Sporzyński, *J. Organomet. Chem.* 694, 3533 (2009)
- [6] A. Adamczyk-Woźniak, M.K. Cyrański, M. Jakubczyk, P. Klimientowska, A. Koll, J. Kołodziejczak, G. Pojma, A. Żubrowska, G.Z. Żukowska, A. Sporzyński, *J. Phys. Chem. A* 114, 2324 (2010)
- [7] A. Adamczyk-Woźniak, I. Madura, A.H. Velders, A. Sporzyński, *Tetrahedron Lett.* 51, 6181 (2010)
- [8] A.P. Davis, *Nature* 464, 169 (2010)
- [9] A. Sporzyński, M. Lewandowski, P. Rogowska, M.K. Cyrański, *Appl. Organometal. Chem.* 19, 1202 (2005)
- [10] A. Adamczyk-Woźniak, Z. Brzózka, M.K. Cyrański, A. Filipowicz-Szymańska, P. Klimientowska, A. Żubrowska, K. Żukowski, A. Sporzyński, *Appl. Organometal. Chem.* 22, 427 (2008)
- [11] P.J. Duggan, T.A. Houston, M.J. Kiefel, S.M. Levonis, B.D. Smith, M.L. Szydzik, *Tetrahedron* 64, 7122 (2008)
- [12] M. Lauer, H. Böhnke, R. Grotstollen, M. Salehnia,

- G. Wulff, *Chem. Ber.* 118, 246 (1985)
- [13] L. Zhu, Z. Zhong, E.V.J. Anslyn, *J. Am. Chem. Soc.* 127, 4260 (2005)
- [14] B.E. Collins, S. Sorey, A.E. Hargrove, S.H. Shabbir, V.M. Lynch, E.V.J. Anslyn, *J. Org. Chem.* 74, 4055 (2009)
- [15] L. Zhu, S.H. Shabbir, M. Gray, V.M. Lynch, S. Sorey, E.V.J. Anslyn, *J. Am. Chem. Soc.* 128, 1222 (2006)
- [16] M.C. Etter, *Acc. Chem. Res.* 23, 120 (1990)
- [17] M.C. Etter, J.C. MacDonald, J. Bernstein, *Acta Crystallogr. B* 46, 256 (1990)
- [18] M.A. Spackman, P.G. Byrom, *Chem. Phys. Lett.* 267, 215 (1997)
- [19] M.A. Spackman, D. Jayatilaka, *CrystEngComm.* 11, 19 (2009)
- [20] J.J. McKinnon, D. Jayatilaka, M.A. Spackman, *Chem. Commun.* 3814 (2007)
- [21] V. Kopsky, D.B. Litvin, (Eds.), *International Tables for Crystallography, Subperiodic groups* (Kluwer Academic Publishers, Dordrecht, 2002) Vol. E
- [22] R.R. Haynes, H.R. Snyder, *J. Org. Chem.* 29, 3229 (1964)
- [23] S.K. Wolff, D.J. Grimwood, J.J. McKinnon, D. Jayatilaka, M.A. Spackman, *CrystalExplorer 2.1* (University of Western Australia, Perth, 2007) <http://hirshfeldsurface.net/CrystalExplorer>