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# Reactivity of 2-formylphenylboronic acid toward secondary aromatic amines in amination–reduction reactions

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ABSTRACT

The synthesis of 2-(arylaminomethyl)phenylboronic acid via an amination–reduction reaction has been investigated within a model system comprising 2-formylphenylboronic acid acid and *N*-ethylaniline. Adoption of the appropriate reaction conditions influences the reactivity of 2-formylphenylboronic acid, enabling efficient synthesis of so-far unobtainable 2-(arylaminomethyl)phenylboronic compounds. The first crystal structure of the aromatic amine derivative has been determined and described.



There has been much interest over the past decade in 2-(arylaminomethyl)phenylboronic acids, mostly due to their applications in sensor research.[1–7] Derivatives of secondary aromatic amines are important due to their possible fluorescence and resulting analytical utility in sensing. The amination–reduction reaction of 2-formylphenylboronic acid would appear to be the cheapest and most straightforward preparative strategy for these types of receptors, especially since some of the synthetic obstacles have recently been circumvented.[8] The success of the amination–reduction reaction depends mainly on the reactivity of both the carbonyl and amine groups as well as the selectivity of the reducing agent employed.[9] The so-far reported yields of 2-(arylaminomethyl)phenylboronic acids via amination–reduction reaction are very low,[10] probably because of the poor nucleophilic character of secondary aromatic amines.[11] There are many reports on increasing the nucleophilicity of amines in amination–reduction reactions,[9] however none of these consider the specific reactivity of the boronic unit in such a system.[8] Here we present an extensive study providing appropriate conditions for the formation of 2-(arylaminomethyl)phenylboronic acids.

The differences in reactivity between the aliphatic and aromatic amines toward 2-formylphenylboronic acid result from the lower nucleophilic character of the nitrogen atom in the latter.[11] Another substantial difference is a consequence of the C-nucleophilic character of the *ortho* and *para* positions of the aminal phenyl ring manifested in the formation of 3-phenyl-substituted benzoxaborole.[12] In order to optimize the reaction conditions for selectivity and yield in 2-(arylaminomethyl)phenylboronic acid synthesis, several parameters including reaction temperature, reducing agent, solvent, the use of dehydrating agents, and an acidic catalyst were investigated within the model reaction using 2-formylphenylboronic acid and *N*-ethylaniline as a secondary aromatic amine. According to our previous studies, the possible formation of several products has been taken into account (Scheme 1, **3**–**7**).[8,12] The unsubstituted benzoxaborole by-product **4** has been removed successfully from the post-reaction mixture by adoption of the previously developed procedure,[8] that is, acidification of the post-reaction mixture followed by selective extraction of **4** with diethyl ether. Neutralization of the aqueous phase and subsequent extraction resulted in pure **3**. The presence of compounds **3**–**5** in the resulting oily mixtures was monitored by $^1$H NMR spectroscopy on the basis of the appropriate analytical signals, that is, the 2-(arylaminomethyl)phenylboronic acid **3** (4.5 ppm), benzoxaborole **4** (5.0 ppm) and the phenyl-substituted benzoxaborole **5** (6.1 ppm) in $(CD_3)_2CO$.

The signal corresponding to the substituted benzoxaborole **6** was expected to appear at around 6 ppm[11]; however, the only signal detected in this region was that corresponding to **5**. The identification of compound **5** as a constituent of the post-reaction mixtures was confirmed by the addition of a standard sample,[12] resulting in an increase of the considered signal intensity. In

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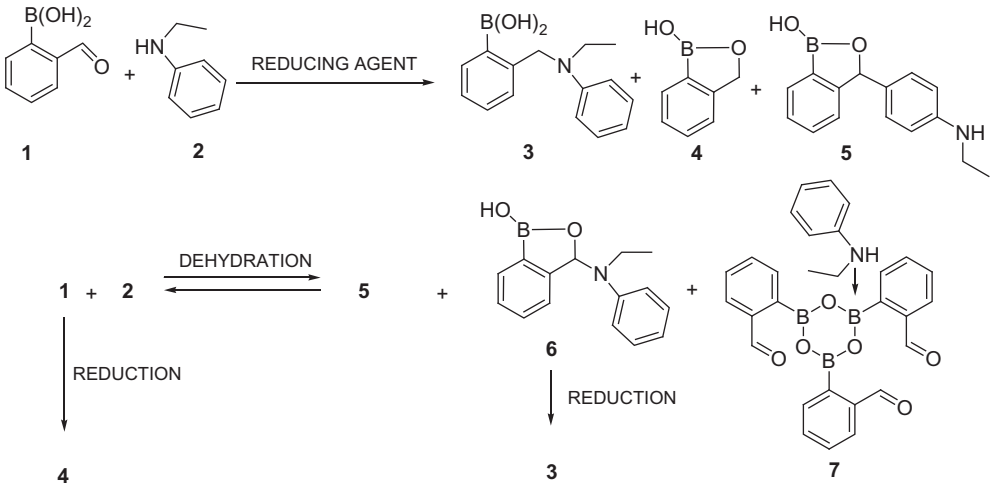


**Scheme 1.** The reactivity of 2-formylphenylboronic acid (**1**) with *N*-ethylaniline.

contrast to **6**, which can easily be reduced to yield the desired product **3**, formation of benzoxaborole **5** results in a lower yield of **3**; therefore, avoiding its formation in the amination reaction is highly desirable.

An extensive study was conducted in order to find appropriate conditions for the formation of 2-(arylaminomethyl)phenylboronic acids (Table S1, Supplementary data). The crude products **3** were often contaminated with unreacted amine, therefore the spectroscopic yield was used for the optimization experiments. The use of $NaBH_4$ as a reducing agent and methanol as the solvent, successful in the case of aliphatic amines,[8] failed to result in **3**. The use of acetonitrile resulted in the formation of **3** in 4% yield, therefore, further research was carried out using acetonitrile as a solvent. One of the easiest ways to increase the yield of the amination reaction was to shift the equilibrium toward the formation of the product by removing water formed during the reaction.[9] In the case of boronic acids however, the formation of complexed boroxin **7,** which can influence considerably the reactivity, must be taken into account.[11,13] The use of $MgSO_4$ or molecular sieves as dehydrating agents did not result in satisfactory yields of **3**. The yield of **3** increased to 20% upon lowering the reaction temperature to 15 °C, but this was still unsatisfactory. The positive influence of the reaction temperature probably results from a decrease of the rate of reduction of the starting material. Replacement of $NaBH_4$ by a milder reducing agent such as $NaBH(OAc)_3$ resulted in a reasonable rise in the yield of **3**. Interestingly, lowering the temperature of the reaction to 0 °C totally eliminated the formation of **5** with the yield of **3** remaining satisfactory. Application of *p*-toluenesulfonic acid as the catalyst improved slightly the yield of **3**. The use of 2 equiv of acetic acid afforded the desired product **3** in 46% yield, and by using a twofold molar excess of 2-formylphenylboronic acid the yield increased to 56%. Accordingly, the yield of **4** obtained as a by-product by reduction of the starting material decreased. This result implies that the amination–reduction reaction of 2-formylphenylboronic acid is not as simple as it first appears and that the acid-boroxin equilibrium may play an important role. A further increase in the yield of **3** to 66% was achieved by the application of both excess of 2-formylphenylboronic acid and acetic acid catalysts. The use of a milder reducing agent and lower reaction temperature limited the reduction of the starting 2-formylphenylboronic acid. At the same time, lowering the reaction temperature limited the irreversible formation of **5**. Application of a drying agent shifted the equilibrium toward *N*-substituted benzoxaborole product **6** enabling subsequent formation of **3**. Having optimized the various reaction parameters, 2-(arylaminomethyl)phenylboronic acids (**3**, **3a,** and **3b)**, Fig. 1)

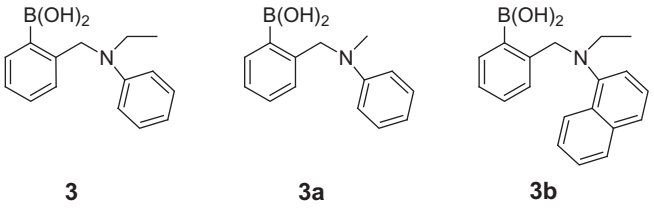


**Figure 1.** Structures of the synthesized 2-(arylaminomethyl)phenylboronic acids.

were obtained in satisfactory isolated yields, that is, more than 43%. Compound **3b** gave crystals suitable for X-ray measurements enabling determination of the first example of an aromatic amine derivative of phenylboronic acid.[14]

Molecules of **3b** were crystallized in the $p\bar{1}$ space group of the triclinic system. The crystal data are summarized in Table S2 while Table S3 (Supplementary data) lists selected geometrical parameters. The boron atom in molecules of **3b** showed trigonal coordination with two equidistant B–O bonds (within error margins) (Table S3). The $-B(OH)_2$ moiety adopts a *syn–anti* conformation and is twisted with respect to the phenyl ring by 27.5(1)° (Fig. 2). This may be attributed to the formation of an intramolecular O–H···N hydrogen bond. In **3b** the *anti*-oriented OH donor interacts with the naphthylamine nitrogen forming a seven-membered ring with a relatively linear O–H···N hydrogen bond. The O···N distance of 2.671(1) Å, (H···N distance = 1.78(2) Å) as well as the O–H···N angle of 168(2)° indicate a very strong interaction.[15] The graph set[16] related to this bond is given as *S*(7). It is worth noting that in the *syn–anti* conformation, a twist of the $-B(OH)_2$ versus the phenyl ring and the O–H···N intramolecular hydrogen bond are observed in all structurally characterized aliphatic amine analogs.[7,8,15,17–20] In all cases, slight pyramidalization of the nitrogen atom from the plane defined by the surrounding carbon atoms was apparent, ranging from 0.40 to 0.48 Å. In **3b** the distance of the nitrogen atom from this plane is found to be 0.422(1) Å. Further, the naphthyl ring and the phenylboronic unit are perpendicular to each other with the dihedral angle being equal to 89.96(5)° (Fig. 2b). This edge-to-face orientation enables formation of a weak intramolecular interaction of C–H···π type (H···C distance = 2.79 Å) between the naphthyl first ring, acting as a C–H donor, and the phenylboronic ring being the π-acceptor. According to examples collected recently by Nishio,[21] this interaction in cooperation with the strong O–H···N hydrogen bond may stabilize the geometry of molecules of **3b**. Moreover, the two molecules of **3b** related by an inversion

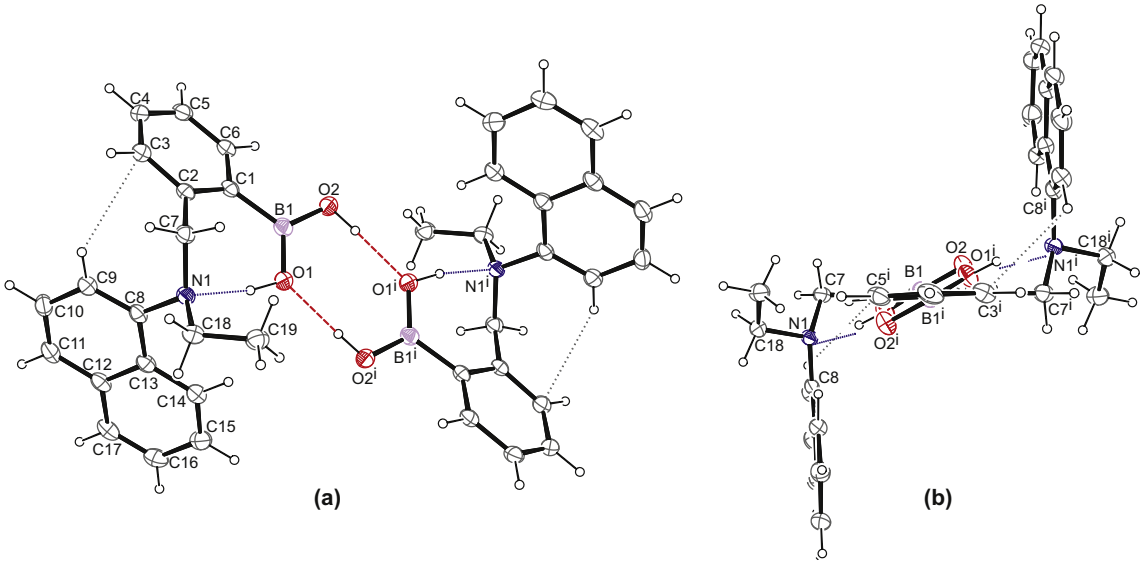


**Figure 2.** (a) Hydrogen bonded dimer of **3b** with the atom numbering scheme. Intramolecular O–H···N and C–H···π interactions are presented as dotted lines, while intermolecular O–H···O bonds appear as dashed lines. Thermal ellipsoids are drawn with 50% probability; (b) Side view of the centrosymmetric dimer showing the twist of the $-B(OH)_2$ moiety and the perpendicular orientation of the phenylboronic and naphthyl rings.

center form a dimer via two strong O–H···O hydrogen bonds between the *syn*-oriented OH donor groups and oxygen atoms from the *anti* OH groups acting as acceptors (Fig. 2). The O···O distance is 2.734(1) Å [H···O distance = 1.85(2) Å] while the O–H···O angle reaches a value of 177(1)°. This centrosymmetric dimer is described by the $R_2^2(8)$ graph set[16] and together with the intramolecular hydrogen bond motif constitute the first level graph set $N_1 = S(7)R_2^2(8)$.[22] Such a graph set is also present in all aliphatic analogs and can be treated as the first order supramolecular object present in the crystal state of phenylboronic acids with *ortho*-aminomethyl substituents.

The amination–reduction reaction conditions strongly influence the reactivity of 2-formylphenylboronic acid toward secondary aromatic amines. Application of excess of the carbonyl reagent, acetic acid as the protonating agent, MeCN as the solvent, molecular sieves as the dehydrating agent, and $NaBH(OAc)_3$ as the reducing agent enables the synthesis of 2-(arylaminomethyl)phenylboronic acids in reasonable yields. The first example of the crystal structure of 2-(arylaminomethyl)phenylboronic acid displaying intramolecular C–H···π interactions has been reported.

### Synthesis of (2-{[ethyl(phenyl)amino]methyl}phenyl)boronic acid (3)

To a 50 ml flask equipped with a stir bar, MeCN (10 ml), molecular sieves (3 Å, 1 g), 2-formylphenylboronic acid (**1**) (0.200 g, 1.334 mmol), *N*-ethylaniline (**2**) (0.0808 g, 0.667 mmol), and AcOH (0.0801 g, 1.334 mmol) were added. The flask was placed in an ice bath and the mixture was stirred for 3 h at 0 °C after which $NaBH(OAc)_3$ (0.283 g, 1.334 mmol) was added. Stirring was continued for another 10 min, and the molecular sieves were removed by filtration. The filtrate was concentrated under reduced pressure and the residue was dissolved in 3 M HCl (4 ml) and $H_2O$ (10 ml) and stirred for 5 min. Extraction was carried out with $Et_2O$ (4 × 15 ml). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure to afford product **4**. The pH of the aqueous phase was adjusted to 7 with 25% aq $NH_3$ and extraction was carried out with $Et_2O$ (4 × 15 ml). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure to afford product **3** (highest yield was 66%). The product was isolated in the form of the anhydride contaminated with **3**, which was confirmed on the basis of elemental analysis as well as the $^1H$ NMR spectrum. The spectrum of the pure acid was obtained after the addition of one drop of $D_2O$.

Yellow crystals (mp = 84–89 °C for the anhydride contaminated with **3**).

Elemental analysis calculated for the anhydride: $C_{45}H_{48}B_3N_3O_3$ (711.4) C, 75.98; H, 6.80; N, 5.91; and for **3**: $C_{15}H_{18}BNO_2$ (255.14): C, 70.62; H, 7.11; N, 5.49; found: C, 74.03; H, 6.84; N, 5.71. $^1H$ NMR [$(CD_3)_2CO$ with one drop of $D_2O$, 400 MHz]: 7.72 (m, 1H, Ar); 7.26–7.13 (m, 5H, Ar); 6.91 (m, 2H, Ar); 6.75 (m, 1H, Ar); 4.52 (s, 2H, $CH_2$); 3.30 (q, $J$ = 7.2 Hz, 2H, $CH_2$); 1.03 (t, $J$ = 7.2 Hz 3H, $CH_3$).

$^{13}C$ NMR [$(CD_3)_2CO$ with one drop of $D_2O$, 100 MHz]: 149.3, 143.6, 135.9, 130.1, 129.6, 128.6, 126.8, 120.0, 117.5, 56,7, 46.6, 11.5. $^{11}B$ NMR [$(CD_3)_2CO$ with one drop of $D_2O$, 64 MHz]: 29.6, 20.0 (100:14).

### Synthesis of (2-{[methyl(phenyl)amino]methyl}phenyl)boronic acid (3a)

To a 250 ml flask equipped with a stir bar, MeCN (185 ml), molecular sieves (3 Å, 18 g), 2-formylphenylboronic acid (**1**) (5.600 g; 37.371 mmol), *N*-methylaniline (2.000 g, 18.665 mmol), and $Ac_2O$ (3.815 g, 37.371 mmol) were added. The flask was placed in an ice bath and the mixture was stirred for 3 h at 0 °C after which $NaBH(OAc)_3$ (7.900 g, 37.371 mmol) was added. Stirring was continued for another 10 min, and the molecular sieves were removed by filtration. The filtrate was concentrated under reduced pressure and the residue was dissolved in 3 M HCl (8 ml) and $H_2O$ (150 ml) and stirred for 5 min. Extraction was carried out with $Et_2O$ (4 × 25 ml). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure to afford product **4**. The pH of the aqueous phase was adjusted to 7 with 25% aq $NH_3$ and the resulting white precipitate was filtered to afford **3a** (1.953 g, 43% yield).

White powder (mp = 89–95 °C). Elemental analysis calculated for the acid: $C_{14}H_{16}BNO_2$ (241.10): C, 69.75; H, 6.69; N, 5.81; found: C, 69.52; H, 6.62; N, 5.85.

The $^1H$ NMR spectrum in $CDCl_3$ revealed signals corresponding to the acid as well as to boroxin. Addition of one drop of $D_2O$ resulted in the spectrum of pure boronic acid.

$^1$H NMR ($CDCl_3$, 400 MHz): 7.93 (1H, Ar); 7.82 (d, $J$ = 6.9 Hz, 1H, Ar); 7.36–7.33 (m, 6H, Ar); 7.26–7.20 (m, 7H, Ar); 6.93–6.83 (m, 2H, Ar); 4.68 (s, 6H, $3 \times CH_2$); 4.22 (s, 2H, $CH_2$); 2.96 (s, 9H, $3 \times CH_3$); 2.66 (s, 3H, $CH_3$).

$^1$H NMR ($CDCl_3$ with one drop of $D_2O$, 400 MHz): 7.95–7.93 (m, 1H, Ar); 7.36–7.31 (m, 4H, Ar); 7.22–7.18 (m, 3H, Ar); 7.08 (t, $J$ = 7.2 Hz, 1H, Ar); 4.22(s, 2H, $CH_2$); 2.66 (s, 3H, $CH_3$).

$^{13}$C NMR ($CDCl_3$ with one drop of $D_2O$, 100 MHz): 150.5, 141.4, 136.3, 131.0, 130.4, 129.3, 127.6, 123.7, 120.3, 62.4, 40.4. $^{11}$B NMR ($CDCl_3$ with one drop of $D_2O$, 64 MHz) 29.0 (br s), 20.0 (minor intensity).

### Synthesis of (2-{[ethyl(1-naphthyl)amino]methyl}phenyl) boronic acid (3b)

To a 100 ml flask equipped with a stir bar, MeCN (24 ml), molecular sieves (3 Å, 2.4 g), 2-formylphenylboronic acid (**1**) (0.788 g, 5.259 mmol), and *N*-ethyl-1-naphthylamine (0.300 g, 1.752 mmol) were added. The flask was placed in an ice bath and the mixture was stirred for 3 h at 0 °C after which the reducing agent, $NaBH(OAc)_3$, (1.112 g, 5.259 mmol) was added. Stirring was continued for another 10 min, and the molecular sieves were removed by filtration. The filtrate was concentrated under reduced pressure and the residue was dissolved in 3 M HCl (4 ml) and $H_2O$ (10 ml) and stirred for 10 min. Extraction was carried out with $Et_2O$ ($4 \times 15$ ml). The organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure to afford **4**. The pH of the aqueous phase was adjusted to 7 with 25% aq $NH_3$ and the resulting pink precipitate was filtered to afford **3b** (0.207 g, 38% yield). An analogous reaction carried out in the presence of an equimolar amount of AcOH resulted in 0.303 g (56% yield) of the desired product.

Pink powder (mp = 119–130 °C). Crystallization from $CDCl_3$ afforded colorless crystals suitable for X-ray measurements.

Elemental analysis calculated for the acid: $C_{19}H_{20}BNO_2$ (305.18): C, 74.78; H, 6.61; N, 4.59; found: C, 74.66; H, 6.66; N, 4.60.

$^1$H NMR ($CDCl_3$ with one drop of $D_2O$, 400 MHz): 8.13 (d, $J$ = 8.3 Hz, 1H, Ar); 7.86 (d, $J$ = 6.8 Hz, 1H, Ar); 7.81 (d, $J$ = 8.0 Hz, 1H, Ar); 7.65–7.63 (m, 1H, Ar); 7.53–7.50 (m, 1H, Ar); 7.48–7.40 (m, 3H, Ar); 7.33–7.27 (m, 3H, Ar); 4.44 (s, 2H, $CH_2$); 3.28 (q, $J$ = 7.2 Hz, 2H, $CH_2$); 0.97 (t, $J$ = 7.2 Hz, 3H, $CH_3$).

$^{13}$C NMR ($CDCl_3$ with one drop of $D_2O$, 100 MHz): 144.1, 141.2, 136.2, 134.8, 131.5, 130.2, 129.5, 128.7, 127.4, 126.1, 125.9, 125. 8, 125.0, 122.8, 119.7, 57.5, 49.3, 9.3. $^{11}$B NMR ($CDCl_3$ with one drop of $D_2O$, 64 MHz): 29.3, 20.0 (minor intensity).

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### Supplementary data

Supplementary data (a table describing the optimization experiments. Details of X-ray measurements. Crystal data for **3b**, Selected geometrical parameters of crystals of **3b**. Copies of $^1$H, $^{13}$C and $^{11}$B NMR spectra of **3**, **3a** and **3b**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.008.

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