Synthesis and structure of bifunctional *N*-alkylbenzimidazole phenylboronate derivatives

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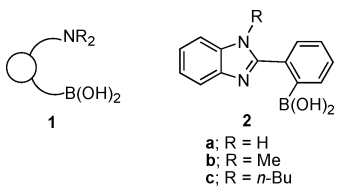
N-Methyl and *N*-*n*-butyl-2-(2-boronophenyl)benzimidazoles are accessed from the corresponding mono-*N*-alkyl-*ortho*-phenylenediamines, either using a polyphosphoric acid-mediated cyclisation with *ortho*-bromobenzoic acid, or preferably using an Oxone™-mediated cyclisation of the corresponding aldehyde, followed by a lithium-exchange and borylation sequence. The resulting boronic acids show unusual physical and chemical properties, as shown by ^{11}B NMR and X-ray crystallography.

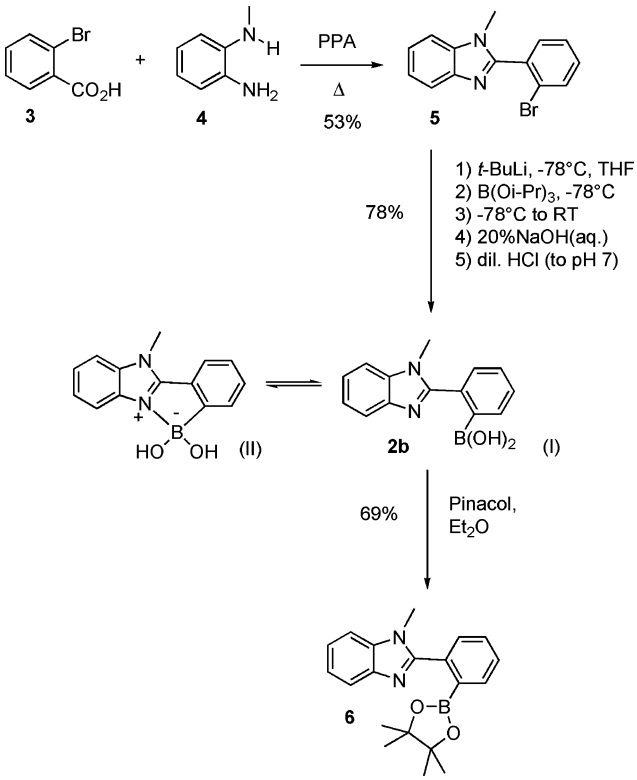
Introduction

There are many examples of polyfunctional catalysts which do not contain transition or lanthanide metals,[1] including organocatalysts.[2] Some of the earliest reported examples of non-transition metal containing systems are based on organoboron bifunctional systems, reported as early as the 1950s, and are effective catalysts for the hydrolysis of chloroalcohols.[3] It was suggested that such systems promoted the hydrolysis of chloroalcohols through the cooperative interaction of both the amine and boronic acid functionalities,[3] hence amino boronate-containing systems of general structure **1** are of general interest as bifunctional catalysts, which are perhaps closely related to organic catalysts if they are chemically stable organoboronate derivatives. In addition, there is increasing interest in the use of bifunctional aminoboronate analogues as selective binding agents and sensors for polyfunctional molecules, such as carbohydrates, and hydroxy acids.[4] As part of a programme aimed at investigating the potential of such systems, we have examined the synthesis, structure and physical properties of several classes of such aminoboronates and recently applied certain systems in direct amide formation,[5] and herein report our recent studies on *N*-alkylbenzimidazole boronate derivatives of type **2**.



Results and discussion

Benzimidazole phenylboronic acid **2a** has been reported by Letsinger[3] as an effective catalyst for chlorohydrin hydrolysis, however, its low solubility in organic solvents led us to investigate the preparation of *N*-alkyl derivatives. Initially, we examined the synthesis of *N*-methyl analogue **2b**, as outlined in Scheme 1.



Scheme 1 Synthesis of *N*-methylbenzimidazolephenylboronic acid (**2b**) and pinacol ester **6**.

Hence, condensation of *N*-methyl-1,2-phenylenediamine **4** and 2-bromobenzoic acid **3** in polyphosphoric[6] acid gave 2-(2-bromophenyl)-*N*-methylbenzimidazole **5** in 53% yield. Attempts to improve this conversion using either P_2O_5 or microwave techniques failed to improve this reaction. Lithium–halogen exchange, followed by *trans*-metallation and aqueous work-up produced a compound which was assigned the overall formula of boronic acid derivative **2b** in 78% yield, due to its similarity to data reported by Letsinger.[7] However, the ^{11}B NMR spectrum of this compound

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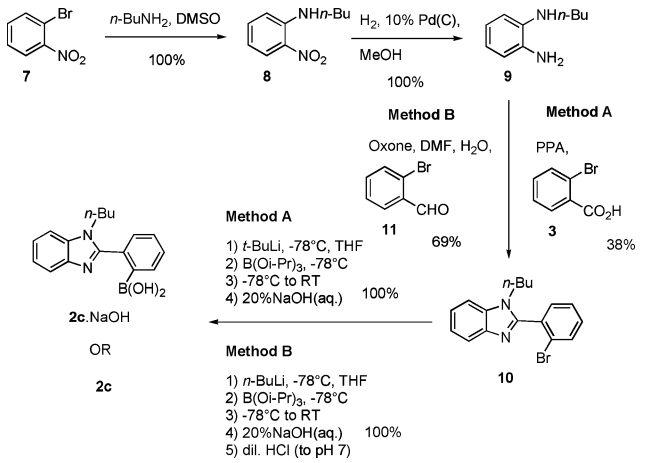
was not as expected for a free boronic acid (*vide infra*), appearing as a very broad signal δ 15.5, *i.e.* as drawn in structure (**I**) (Scheme 1). Confirmation of the formation of a compound which behaved as boronic acid **2b** was readily obtained by formation of the pinacol ester as a crystalline solid in 69% yield. This compound exhibited an ^{11}B NMR shift at δ 29.7, showing that it exists as shown in diagram **6**, *i.e.* without N–B interaction (*vide infra*). The poor solubility of what appeared to be boronic acid **2b** in organic solvents led us to attempt to prepare a derivative which would be expected to have improved solubility in organic solvents, *i.e.* the *N*-butyl analogue **2c**. Hence, this synthesis of this compound was attempted, initially using a similar approach to that outlined in Scheme 1, *i.e.* as outlined in Scheme 2.

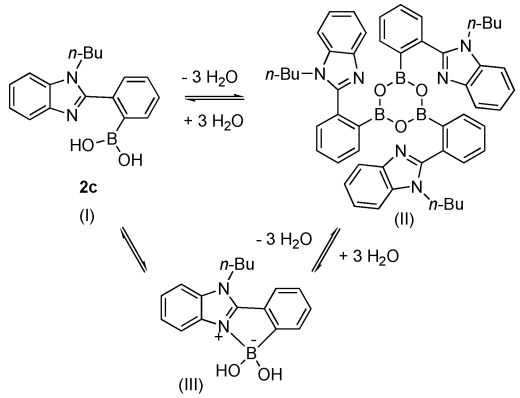


Scheme 2 Synthesis of *N*-*n*-butylbenzimidazolephenylboronic acid (**2c**) and derivatives.

The synthesis of boronic acid derivative **2c** started with preparation of *N*-*n*-butyl-1,2-phenylenediamine **9**, which was prepared over two steps in essentially quantitative yield (Scheme 2). This was followed by exposure to the polyphosphoric acid-mediated cyclisation with *ortho*-bromobenzoic acid **3**. This was an exceptionally capricious reaction, which after a lengthy work up and purification procedure could provide the required benzimidazole **10** in up to 38% yield. All attempts to find an improved method of preparing the benzimidazole **10** from diamine **9** using polyphosphoric acid failed. Hence, further alternatives were sought.

There are many alternative approaches for the formation of benzimidazoles from diamines,[8] with perhaps the simplest involving the coupling of 1,2-phenylenediamines with aldehydes, rather than carboxylic acids, but carried out under oxidising conditions. Initial attempted reactions of the phenylenediamine **9** with benzaldehyde **11** in refluxing NMP or DMF in air[9] failed to provide any of the desired benzimidazole **10**, however, addition of 0.6 equivalents of Oxone™ to this type of reaction was more successful,[10] especially when carried out in DMF–water mixture, which resulted in the clean formation of benzimidazole **10** in 69% yield (Scheme 2).

The preparation of the boronate **2c** was then performed according to Scheme 2, *via* lithium–halogen exchange of bromide **10**, followed by quenching with triisopropyl borate. After quenching with aqueous sodium hydroxide (method A), boronate **2c** was isolated in quantitative yield as a white precipitate as the sodium hydroxide complex, as evidenced by a ^{11}B NMR shift of δ 2.9, which is typical of a boronate 'ate'-complex.[11] Since method A (Scheme 2) resulted in the formation of the 'ate'-complex of **2c**, the preparation of the free boronic acid **2c** was examined in a similar way to that of the 'ate'-complex, but using a final acidification step of the reaction mixture to pH 7 (method B). The material recovered by this method showed a ^{11}B NMR (CD_3CN–D_2O) spectrum which contained peaks at δ 12.5, 19.7 and 32.8 for the intramolecular N–B chelate (**III**), boroxine (**II**) and free amino boronic (**I**) acid, respectively,[11] as shown in Scheme 3. Mass spectrometric data (ES+) obtained for this material confirmed the boronic acid **2a** due to signals observed at *m*/*z* 295.2 (MH^+) and 317.2 (MNa^+), but also revealed the existence of a dimer at *m*/*z* 553.4 (2M–2OH) which may either be due to fragmentation of the boroxine trimer (**II**) during analysis, or it may also be due to the presence of a dimer which is implicated as the intermediate in the formation of boroxine (**II**) from free boronate (**I**) (Scheme 3). The corresponding *N*-methyl derivative **2b** behaves similarly in terms of mass spectrometric analysis, however, its ^{11}B NMR spectrum (*vide supra*) was quite different, showing a single broad peak at δ 15.5. This suggests that interconversion between each of the different possible forms is relatively fast on the NMR timescale, however, the intramolecular chelate version, *i.e.* form (**II**) Scheme 1, predominates, explaining the observed chemical shift. Hence, the *N*-*n*-butyl group *versus* *N*-methyl group in **2b** *versus* **2c** has the effect of seemingly slowing interconversion between each of the different possible species present in solution, *i.e.* between species (**I**), (**II**) and (**III**) (Scheme 3) in the case of the *N*-*n*-butyl system **2c**.



Scheme 3 Equilibrium between the various forms of the *N*-*n*-butylbenzimidazolephenylboronic acid **2c**.

The interesting behaviour exhibited by boronates **2b** and **2c** is consistent with other amino boronate complexes which are capable of intramolecular N–B bonding.[12] Since the ^{11}B NMR signal for the free boronate of **2c**, *i.e.* form (**I**), appears at δ 32.8, and yet it is in equilibrium with signals at δ 12.5 and 19.7 indicates that pH 7 is slightly below the isoelectric point for *N*-*n*-butylbenzimidazolephenylboronic acid system **2c**.[13] In an attempt to further probe the structural behaviour of **2c**, crystallisation was attempted, but this proved extremely difficult. This was largely due to (a) its poor solubility in most solvents and (b) presumably the fact that in solution, it exists in several possible equilibrium species (see Scheme 3). However, of the numerous solvent systems tested, the most successful was found to be a mixture of DMF and chloroform, recrystallisation from which was encouraged by

temperature cycling. In addition, this crystallisation had to be performed on a sample of boronate **2c** which had first been acidified to pH <5 with dilute HCl and then re-precipitated from neutral solution. This method yielded, concomitantly, single crystals of four very different habits, which could represent different forms of the boronate **2c** (Scheme 3). Unfortunately, only one crystal was suitable for single crystal X-ray diffraction analysis, which revealed the structure of the boroxine trimer (**II**) (Fig. 1) and hence, also confirmed the chemical connectivity of the monomeric form of boronic acid **2c**. The molecule **2c** (**II**) contains a puckered 1,3,5-boroxine (B_3O_3) ring, in which the B(1), B(2) and B(3) atoms deviate from the O_3 plane by 0.04, 0.36 and −0.34 Å, respectively. The B(1) atom has planar–trigonal geometry, its plane is inclined by 14° to the adjacent benzene ring. The B(2) and B(3) atoms are 4-coordinate through additional intramolecular N → B donations. These require planarisation of the ligands, wherein the dihedral angle between the benzimidazole and benzene planes is reduced to 7°, against 81° in the monodentate ligand bonded to B(1). In the latter ligand, the "unsupported" benzimidazole moiety is intensely librating (or statically disordered) within its own plane, and besides the *n*-butyl side-chain is conformationally disordered.

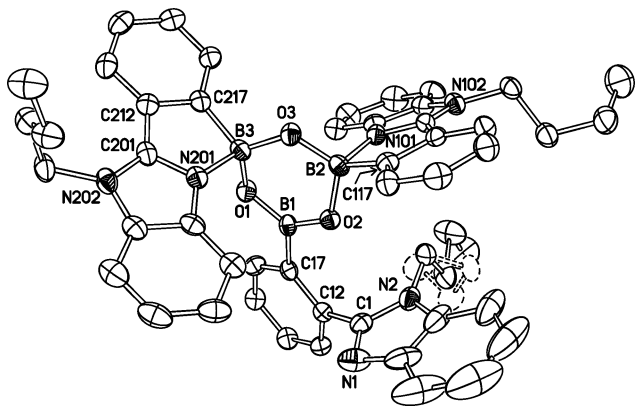


Fig. 1 Molecular structure of **2c** (**II**) (Scheme 3) (50% thermal ellipsoids, H atoms are omitted for clarity).

A survey of the November 2005 release of the Cambridge Structural Database,[14] revealed 29 neutral (rather than anionic) boroxines $(RBO)_3$ where R = alkyl or aryl. Of these, 12 contain only planar–trigonal boron atoms and 13 combine one 4-coordinate atom with two 3-coordinate, but only two compounds have two out of three borons 4-coordinate, namely $(Me_2NXC_6H_4BO)_3$, where X = CH_2[15a] or CH=N.[15b] These compounds resemble **2c** (**II**) in having two of the ligands C–N-chelating, while the third one remains C-monodentate. This indicates that tetrahedrisation of boron atoms becomes progressively more difficult, obviously due to steric overcrowding. Nevertheless, the difficulty is not unsurmountable, since two boroxines are known to have all boron atoms 4-coordinate.[5a,15a]

The strength of the N: → B donor–acceptor interaction is highly variable. In 218 known adducts of the N: → $B(OR)_2R$ type (R = organic group), the B–N distances range from 1.56 to 1.98 Å;[14] those in **2c** (**II**) (see Table 1) are *ca.* 0.1 Å from the lower limit. Toyota *et al.*[15c] suggested a method to quantify 'tetrahedral character' (TCH), of a boron atom by the average angle θ between the covalent bonds, as θ can vary from 120° for planar–trigonal coordination to 109.5° for the tetrahedral; hence TCH = $(120° - \theta)/(120°–109.5°)$. TCH shows better correlation with the stability of adducts than the B–N distance.[15c] By this estimate, B(2) and B(3) have TCH of 48 and 53%, respectively, showing the relative lability of the N → B bonds. Indeed, in solution, this compound shows a single ^{11}B NMR resonance at δ = 19, which indicates fluxional behaviour (on the NMR timescale) with all three nitrogen ligands, which rapidly switch between boron chelation and decomplexation.

Summary and conclusions

The requirements for cooperative bifunctional binding of substrates using aminoboronate systems are essentially similar to the requirements for catalytic effects.[3–5] It is becoming clear that seemingly minor changes in the structure of the aminoboronate system can have profound effects on the physical, and subsequently, the chemical properties of such compounds. In the present case, a seemingly minor substitution (methyl *versus n*-butyl in **2b** and **2c**, respectively) results in subtle changes in the dynamics of the B–N chelation, as evidenced by ^{11}B NMR. Both these benzimidazoles also show very different physical and chemical behaviour to, for example, *ortho*-benzylaminoboronic acid derivatives, where B–N chelation can be switched on and off by using simple steric effects,[5d] which results in the latter systems being efficient direct amide formation catalysts, whereas the present systems are unreactive. However, the aminoboronate systems **2** discussed herein are active catalysts for chloroalcohol hydrolysis,[3] and are therefore likely to have other catalytic applications which directly correlate with their unique chemical and structural properties. Further reports on the application of these systems for novel catalytic applications will be reported in due course.

Table 1 Selected bond distances (Å) and angles (°) in **2c** (**II**) (Scheme 3)

Bond	Distance (angle)	Bond	Distance (angle)
B(3)–O(1)	1.480(4)	B(2)–O(2)	1.458(4)
B(2)–O(3)	1.417(4)	B(3)–O(3)	1.416(4)
B(2)–C(117)	1.634(4)	B(3)–C(217)	1.630(5)
B(2)–N(101)	1.666(4)	B(3)–N(201)	1.641(4)
B(1)–O(1)	1.358(4)	B(1)–O(2)	1.358(4)
B(1)–C(17)	1.586(4)	O(1)B(1)O(2)	122.1(3)
O(1)B(1)C(17)	118.2(2)	O(2)B(1)C(17)	119.5(3)
O(2)B(2)O(3)	115.2(2)	O(1)B(3)O(3)	114.3(2)
O(2)B(2)C(117)	113.8(3)	O(3)B(3)C(217)	116.3(3)
O(3)B(2)C(117)	115.9(3)	O(1)B(3)C(217)	112.7(2)
N(101)B(2)C(117)	94.1(2)	N(201)B(3)C(217)	94.6(2)

Experimental

All starting materials were obtained commercially from Aldrich, Lancaster or Fluka and were used as received or prepared by known methods, unless otherwise stated. Solvents were also used as received or dried by known methods, unless otherwise stated. In the case of DCM and toluene this involved refluxing over calcium hydride under argon and in the case of ether and THF involved refluxing over sodium and benzophenone under argon. Purification by column chromatography was performed using Lancaster silica gel with pore size 60 Å. TLC was carried out using Merck aluminium-backed or plastic-backed pre-coated plates. TLC plates were analysed by UV at 254 and 365 nm, and visualisation was performed using standard solutions of 4-anisaldehyde, vanillin or phosphomolybdic acid. NMR spectra were recorded at 200, 300 or 400 MHz using a Varian Mercury 200 MHz spectrometer, Varian Unity 300 MHz spectrometer or a Brucker 400 MHz spectrometer, respectively, unless otherwise stated. Electrospray (ES) mass spectra were recorded using a Micromass LCT spectrometer. Infrared spectra were obtained using FT1600 series spectrometer. Ultra-violet spectra were measured using a Unicam UV-Vis UV2 spectrometer. Melting points were measured with an Electrothermal apparatus and were uncorrected. Evaporations were carried out at 20 mm Hg using a Büchi rotary evaporator and water bath, followed by evaporation to dryness under vacuum (<2 mm Hg). Chloroform used in the preparation of the phosphoryl compounds was Aldrich HPLC grade 99.9% stabilised with amylenes.

N-Methyl-2-(2-bromophenyl)benzimidazole (5)

N-Methylphenylene-1,2-diamine **4** (12.0 g, 0.10 mmol), 2-bromobenzoic acid **3** (19.9 g, 0.01 mmol) and polyphosphoric acid (60.0 g) were mixed into a paste and heated to 175 °C under argon for 4 h. The reaction solution was then poured into ice-water (400 ml) and the pH adjusted to 10–11 with ammonium hydroxide. The resulting sticky solid was then dissolved in ethanol (50 ml) and reprecipitated with dilute ammonium hydroxide at pH 10–11 to yield pale purple needles (23.7 g). The needles were then removed by filtration and purified by dissolving in ethyl acetate passing through a short dry silica gel column (toluene–ethyl acetate, 9 : 1, as eluent), to give *N*-methyl-2-(2-bromophenyl)benzimidazole **5** as a pale cream solid (15.2 g, 53%); mp 116 °C; ν_{max}(nujol)/cm^{-1} *inter alia* 752, 782, 1023, 1240, 1281, 1327, 1434, 1523, 1560, 1598, 1612 cm^{-1}; λ_{max}(EtOH)/nm 206.0 (ε/dm^{3}mol^{-1}cm^{-1} 59180), 256.0 (9470), 278.0 (12370), 284.0 (11940); δ_H(400 MHz, $CDCl_3$) 3.66 (3H, s, C*H*$_3$N), 7.30–7.43 (4H, m, ArH), 7.46 (1H, td, *J* 7.4 and 1.4, ArH), 7.54 (dd, 1H, *J* 7.6 and 1.6, ArH), 7.71 (dd, 1H, *J* 8.0 and 0.8, ArH), 7.84 (dd, 1H, *J* 7.1 and 1.6, ArH); δ_C(100 MHz, $CDCl_3$) 31.1, 109.9, 120.4, 122.7, 123.2, 124.1, 127.8, 131.7, 132.4, 132.7, 133.1, 135.7, 143.0, 152.8; *m*/*z* (EI+) *inter alia* 288 (94%, M$^{+\bullet}$ ^{81}Br), 286 (96, M$^{+\bullet}$ ^{79}Br), 207 (100), 206 (75); found C, 59.04; H, 3.87; N, 9.78; $C_{14}H_{11}N_2Br$ requires C, 58.56; H, 3.86; N 9.76%.

N-Methyl-2-(2-boronophenyl)benzimidazole (2b)

t-Butyllithium (29 ml, 1.69 M in hexanes, 48.8 mmol) and dry diethyl ether (162 ml) were placed in a flask and cooled to −78 °C. A solution of *N*-methyl-2-(2-bromophenyl)benzimidazole **5** (7.0 g, 24.4 mmol in 315 ml of dry diethyl ether) was then added dropwise over 1.5 h. The resulting suspension was then stirred for a further 2 h at −72 °C. A solution of triisopropylborate (23.5 ml in 250 ml of dry diethyl ether) was then added dropwise over 0.5 h. After stirring at −78 °C for further 0.5 h the solution was allowed to warm to room temperature overnight. 5% Aqueous sodium hydroxide (300 ml) was then added and the layers separated. The pH of the aqueous phase was then adjusted to pH 1–2 with concentrated HCl. The aqueous phase was then washed with diethyl ether (3 × 50 ml). The aqueous phase was then adjusted to pH 7–8 with 5% sodium hydroxide, saturated with salt and extracted with chloroform (3 × 100 ml). Evaporation gave *N*-methyl-2-(2-boronophenyl)benzimidazole **2b** as a cream solid (4.8 g, 78%); mp. 218 dec °C; ν_{max}(nujol)/cm^{-1} 1734, 1596, 1532, 1491, 1433, 1370, 1325, 1296, 1279, 1256, 1239, 1174, 1135, 1118, 1063, 749; λ_{max}(MeCN)/nm 208.0 (ε/dm^{3}mol^{-1}cm^{-1} 49610), 244.0 (15620); δ_H (400 MHz, $CDCl_3$) 3.16 (3H, s, C*H*$_3$N), 7.00–7.08 (1H, m, Ar–H), 7.18–7.24 (2H, m, Ar–H), 7.26–7.32 (2H, m, Ar–H), 7.38–7.48 (2H, m, Ar–H), 7.55–7.60 (1H, m, Ar–H); δ_C (100 MHz, $CDCl_3$) 30.8, 109.5, 117.2, 122.2, 122.7, 124.0, 125.0, 127.9, 130.1, 131.4, 132.4, 132.6, 136.0, 137.0, 155.6; δ_B (96 MHz, $CDCl_3$) 15.5 (br s); *m*/*z* (ES+) *inter alia* 253 (100%, M + H), 469 (65%, 2M + H–2OH); HRMS (ES+) found (M + H) 253.1172, $C_{14}H_{14}N_2O_2B$ requires 253.1148.

N-Methyl-2-(2-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)phenyl)benzimidazole (6)

N-Methyl-2-(2-boronophenyl)benzimidazole **2b** (1.0 g; 3.97 mmol) was added to a solution of pinacol (0.45 g; 3.97 mmol in 25 ml of diethyl ether) and the resulting suspension stirred at room temperature overnight. The desired boronic acid ester **6** was then isolated by filtration as white solid (0.92 g; 69%); mp. 169 °C; ν_{max}(nujol)/cm^{-1} 1603, 1523, 1353, 1143, 1090, 1045, 859, 749, 658; λ_{max}(MeCN)/nm 208.0 (ε/dm^{3}mol^{-1}cm^{-1} 79890), 244.0 (18140); δ_H(400 MHz, $CDCl_3$) 1.12 (12H, s, 4 × C*H*$_3$C), 3.67 (3H, s, C*H*$_3$N), 7.27–7.40 (3H, m, Ar*H*), 7.44–7.56 (3H, m, ArH), 7.76–7.79 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) 24.9, 31.3, 83.8, 109.5, 119.7, 122.1, 122.5, 129.2, 130.3, 134.9, 135.7, 136.2, 142.8, 155.2; δ_B (96 MHz, $(CD_3)_2SO$) 29.7 (br s); *m*/*z* (EI+) *inter alia* 333 (M–H, 100), 334 (M$^+$, 44); found C, 71.65; H, 6.95; N, 8.22; $C_{20}H_{23}BN_2O_2$ requires C, 71.87; H, 6.94; N, 8.38%.

1-Butylamino-2-nitrobenzene (8)[16]

2-Bromonitrobenzene **7** (20.0 g; 0.099 mol) and *n*-butylamine (36 ml; 0.366 mol) were dissolved in DMSO (100 ml) and heated to 80 °C and stirred overnight. The reaction solution was then allowed to cool to room temperature before the addition of water (300 ml). The resulting solution was then extracted with DCM (3 × 150 ml). The combined extracts were then washed with brine (3 × 100 ml) and dried over $MgSO_4$. Filtration and evaporation gave nitrophenylamine **8**[16] as a yellow oil in quantitative yield, which was used for the following step without further purification; ν_{max}(neat)/cm^{-1} *inter alia* 3381, 3084, 1618, 1572, 1510, 1419, 1354, 1263, 2333, 1159, 1038, 861, 742; λ_{max}(EtOH)/nm 208.3 (ε/dm^{3}mol^{-1}cm^{-1} 9550), 230.0 (21990), 260.8 (5580), 283.9 (7660); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, t, *J* 7.2, CH_2CH_3), 1.47 (2H, sextet, *J* 7.4, $CH_2CH_2CH_3$), 1.71 (2H, quintet, *J* 7.3, $CH_2CH_2CH_2$), 3.28 (2H, m,CH_2NH), 6.60 (1H, ddd, *J* 8.5, 6.8, 1.3, Ar–H), 6.83

(1H, ddd, *J* 8.8, 0.8 and 0.4, Ar–H), 7.41 (1H, dddd, *J* 8.8, 6.8, 1.6 and 0.8), 8.04 (1H, br s, N–H), 8.14 (1H, ddd, *J* 8.4, 1.6 and 0.4); δ_C (100 MHz, $CDCl_3$) 14.0, 20.5, 31.2, 42.9, 114.0, 115.2, 127.1, 131.9, 136.4, 145.9. *m/z* (ES+) *inter alia* 217 (100, M + Na), 195 (M + H); HRMS (ES+) found: (M + Na) 217.0962, $C_{10}H_{14}N_2O_2$ requires 217.0953.

N-*n*-Butyl-1,2-phenylenediamine (9)[16]

1-*n*-Butylamino-2-nitrobenzene **8** (20 g; 0.10 mol) and Pd/C catalyst (2 g 10% Pd/C; 1.88 mmol) were placed in methanol and stirred under hydrogen for 3 h. The reaction was maintained at room temperature by the use of an ice-water bath. The resulting solution was the filtered through a short silica gel column to remove the catalyst, to give a clear colourless solution which turned brown upon standing. Evaporation gave the diamine **9**[16] as a viscous brown liquid, which was used for the following step without further purification; δ_H (400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.4, CH_3CH_2), 1.48 (2H, hextet, *J* 7.4, $CH_2CH_2CH_3$), 1.68 (2H, quintet, *J* 7.3, $CH_2CH_2CH_2$), 3.12, (2H, t, *J* 7, CH_2N), 3.37 (3H, br s, N–H), 6.66–6.76 (3H, m, Ar–H), 6.85 (1H, td, *J* 7.4 and 1.8, Ar–H); δ_C (100 MHz, $CDCl_3$) 14.3, 20.7, 32.0, 44.3, 112.0, 116.7, 118.7, 121.0, 134.3, 138.2.

2-(2-Bromophenyl)-*N*-butylbenzimidazole (10)[17]

N-Butyl-1,2-phenylenediamine **9** (20 g; 0.122 mol) and 2-bromobenzoic acid **3** (26.8 g; 0.133 mol) were mixed into PPA (80 g), placed under an atmosphere of argon and heated to 180 °C for 6 h. This resulted in the formation of a black solution which was poured into ice-water (*ca.* 500 ml) whilst hot. The resulting water–tar mixture solution was then adjusted to alkaline pH by the addition of dilute ammonium hydroxide and further ice. The aqueous phase was then extracted with DCM (1 × 300 ml). Sodium chloride was then added to the remaining aqueous phase and the solution was further extracted with DCM (2 × 200 ml). The combined extracts were then washed with ammonium hydroxide (10% *v*/*v*) containing a trace of ethanol and dried over $MgSO_4$. Evaporation gave a viscous black oil (28.7 g) which was purified by passing through a short dry silica gel column (diethyl ether as eluant) to give 2-(2-bromophenyl)-*N*-*n*-butylbenzimidazole **10**[17] as a viscous brown oil (14.2 g; 35%); ν_{max}/cm^{-1} *inter alia* 3661 (amine), 3391 (amine), 3059 (Ar), 2958 (CH), 2931 (CH), 2871 (CH), 1613 (Ar), 1599 (Ar), 1453, 1393 (CH), 1281 (benzimidazole), 1243 (benzimidazole), 1026 (benzimidazole) and 706 (ArBr); δ_H (400 MHz, $CDCl_3$) 0.71 (t, *J* 7.4 Hz, 3 H, CH_3), 1.11 (hextet, *J* 7.5 Hz, 2 H, $CH_3CH_2CH_2$), 1.61 (quintet, *J* 7.5 Hz, 2 H, $CH_2CH_2CH_2$), 3.98 (t, *J* 7.2 Hz, 2 H, NCH_2CH_2), 7.25–7.46 (m, 6 H, ArH), 7.64–7.66 (m, 1 H, ArH) and 7.76–7.80 (m, 1 H, ArH); δ_C (100 MHz, $CDCl_3$) 13.5 (CH_3), 20.0 (CH_2), 31.5 (CH_2), 44.4 (CH_2), 110.2 (Ar), 120.2 (Ar), 122.4 (Ar), 123.0 (Ar), 124.0 (Ar), 127.4 (Ar), 131.4 (Ar), 132.4 (Ar), 132.9 (Ar), 134.4 (Ar), 145.6 (Ar) and 152.3 (Ar); *m/z* EI (+) *inter alia* 206.0 (M–CH_2CHCH_2Br, 91%), 284.7 (M–CH_2CHCH_2, 56%), 286.7 (M–CH_2CHCH_2, 56%), 327.8 (MH, 100%) and 329.8 (MH, 99%); *m/z* EI (+) 327.8 (M–H, 95.57%) 329.8 (M–H, 89.07%); HRMS (ES+) $C_{17}H_{17}N_2Br$ requires 328.2487 and 330.2467.

Synthesis of the 2-(2-bromophenyl)-*N*-*n*-butyl-benzimidazole (10)[18]

A solution of **9** (4.977 g, 30.40 mmol) in DMF (50 ml) and H_2O (1.6 ml), was treated with 2-bromobenzaldehyde **11** (3.52 ml, 30.4 mmol) and Oxone™ (11.008 g, 18.2 mmol). After stirring at room temperature for 12 h, the reaction was carefully quenched by the addition of an aqueous solution of K_2CO_3 (0.04 M, 310 ml). The resulting suspension was extracted with ethyl acetate (3 × 150 ml) and the combined organic extracts dried ($MgSO_4$) and evaporated. The resulting residue was purified by silica gel chromatography (hexane–ethyl acetate, gradient elution) to provide **10**[18] as a viscous pale brown oil (6.936 g, 69%), which was identical to that prepared in the previous experiment.

Synthesis of the 2-(2-boronophenyl)-*N*-*n*-butyl-benzimidazole sodium hydroxide salt of 2c

A solution of benzimidazole **10** (0.223 g, 0.677 mmol) in ether (7 ml) at −78 °C under argon was treated with *t*-BuLi (1.69 ml, 0.52 M in pentane, 0.879 mmol) over a period of 15 min. The resultant solution was stirred at −78 °C for 1 h, treated with $B(O^iPr)_3$ (0.355 ml, 1.54 mmol) and the solution stirred for 48 h during which it was allowed to warm slowly from −78 °C to room temperature. NaOH (20% *w*/*v*, 7 ml) was then added, and the mixture was stirred at room temperature for 1 h. The yellow precipitate that formed, was filtered, washed with ether and dried to give **2c**·NaOH as a white solid (0.161 g, 100%); mp 147.7–148.9 °C; λ_{max} (EtOH)/nm 225sh, 245sh, 252sh, 297sh and 316 ($\varepsilon/dm^3\ mol^{-1}\ cm^{-1}$ 15 015, 9 610, 8 408, 10 811 and 13 513); ν_{max} (KBr)/cm^{-1} *inter alia* 3418 (amine), 3044 (Ar), 2959 (CH), 2931 (CH), 2873 (CH), 1455, 1397 (CH), 1284 (benzimidazole), 1204, 1173, 1059 (benzimidazole), 959, 897, 866 and 745; δ_H (400 MHz, CD_3CN–D_2O, 3 : 1) 0.71 (t, *J* 7.4 Hz, 3 H, CH_3), 1.14 (hextet, *J* 7.5 Hz, 2 H, $CH_3CH_2CH_2$), 1.64 (quintet, *J* 7.5 Hz, 2 H, $NCH_2CH_2CH_2$), 3.99 (m, 2 H, NCH_2CH_2), 7.25–7.32 (m, 4 H, ArH), 7.39–7.43 (m, 1 H, ArH), 7.54–7.57 (m, 1 H, ArH), 7.64–7.66 (m, 1 H, ArH) and 7.70 (d, *J* 7.2 Hz, 1 H, ArH); δ_C (400 MHz, CD_3CN–D_2O, 3 : 1) 10.2, 16.7, 28.3, 41.6, 108.5, 115.3, 119.9, 120.0, 122.7, 126.2, 126.5, 129.0, 129.7, 131.9 and 159.0; δ_B (128 MHz, D_2O) 2.9; *m/z* ES (−) 309.5 (M–Na, 22%), 293.5 (M–NaOH, 100%); *m/z* ES (+) 611.4 (2M–Na–2OH, 35%), 317.2 (M–OH, 100%); HMRS ES (+) found 295.1627, $C_{17}H_{20}O_2N_2B$ requires 295.1630.

Synthesis of the 2-(2-boronophenyl)-*N*-*n*-butyl-benzimidazole (2c)

A solution of **10** (0.369 g, 1.12 mmol) in diethyl ether (3 ml) at −78 °C under argon, was treated with *n*-BuLi (0.896 ml, 2.5 M in pentane, 2.24 mmol) over 30 min, and the resultant solution stirred for 1 h. $B(O^iPr)_3$ (0.52 ml, 2 × 1.12 mmol) was added and the solution stirred for 4 h at −78 °C and allowed to warm to room temperature. The solution was quenched with aqueous NaOH (10% *w*/*v*, 2 ml), and stirred at room temperature for 15 min. The pH of the solution was adjusted to pH 7 with aqueous HCl (10% *w*/*v*) and the resulting precipitate was filtered, washed (diethyl ether) and dried to give **2c** as a white solid (0.261 g, 79%); mp 235.6–239.9 °C; ν_{max} (KBr)/cm^{-1} *inter alia* 3439 (amine), 3049 (Ar), 2957 (CH), 2930 (CH), 2872 (CH), 1636, 1616 (Ar), 1524, 1461, 1360, 1300 ($ArB(OH)_2$), 1171, 1007 (boroxine) and 953; δ_H (400 MHz, CD_3CN–D_2O, 3 : 1) 0.90 (t, *J* 7 Hz, 3 H, CH_3), 1.40 (hextet, *J* 7.5 Hz, 2 H, CH_2), 1.90 (quintet, *J* 8 Hz, 2 H, CH_2), 4.55

(t, J 7 Hz, 2 H, NCH_2), 7.41–7.51 (m, 4 H, Ar), 7.64–7.67 (m, 2 H, Ar) and 7.79–7.83 (m, 2 H, Ar); δ_C (400 MHz, CD_3CN–D_2O, 3 : 1) 12.7, 19.3, 31.0, 44.3, 111.3, 114.4, 116.4, 123.0, 123.5, 124.4, 127.5, 129.3, 130.16, 131.0, 133.1, 136.1 and 159; δ_B (128 MHz, CD_3CN–D_2O, 3 : 1) 12.5, 19.7 and 32.8; m/z ES (+) 553.4 (2M–2OH, 100%), 317.2 (47) and 295.2 (25); HRMS (ES+) found m/z 295.1627 [M + H], $C_{17}H_{20}N_2O_2B$ requires m/z 295.1618.

X-Ray crystallography†

The diffraction experiment for (**II**) (Scheme 3) was carried out on a 3-circle Bruker diffractometer with a SMART 6 K CCD area detector, using graphite-monochromated Mo Kα radiation ($\bar{\lambda}$ = 0.71073 Å) and a Cryostream (Oxford Cryosystems) open-flow N_2 cryostat. The structure was solved by direct methods and refined by full-matrix least squares against F^2 of all reflections, using SHELXTL software.[18] Refining high-ADP atoms of the uncoordinated benzimidazole group in two split positions gave no improvement. Crystal data: $C_{51}H_{51}B_3N_6O_3$, M = 828.41, T = 120 K, triclinic, space group P1 (No. 2), a = 11.223(2), b = 13.252(3), c = 16.734(3) Å, α = 75.48(3), β = 73.58(3), γ = 70.65(3)°, U = 2218.3(8) Å^3, Z = 2, D_c = 1.240 g cm^{-3}, μ = 0.08 mm^{-1}, 14759 reflections with $2\theta \leq 50°$, R_{int} = 0.070, w$R(F^2)$ = 0.130 (7766 unique data), $R(F)$ = 0.058 [3854 data with $I \geq 2\sigma(I)$].

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References

1 (*a*) C. Mocquet and S. Warriner, *SYNLETT*, 2004, **2**, 356; (*b*) B. M. Nugent, R. A. Yoder and J. N. Johnston, *J. Am. Chem. Soc.*, 2004, **126**, 3418.

2 (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726; (*b*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138.

3 (*a*) R. L. Letsinger, S. Dandegaonker, W. J. Vullo and J. D. Morrison, *J. Am. Chem. Soc.*, 1963, **85**, 2223; (*b*) R. L. Letsinger and J. D. Morrison, *J. Am. Chem. Soc.*, 1963, **85**, 2227; (*c*) R. L. Letsinger and A. J. Wysocki, *J. Org. Chem.*, 1963, **28**, 3199; (*d*) R. L. Letsinger and S. Dandegaonker, *J. Am. Chem. Soc.*, 1959, **81**, 498.

4 (*a*) C. W. Gray and T. A. Houston, *J. Org. Chem.*, 2002, **67**, 5426; (*b*) M. Yamamoto, M. Takeuchi, S. Shinkai, F. T. Tani and Y. Naruta, *J. Chem. Soc., Perkin Trans. 2*, 2000, 9; (*c*) M. Bielecki, H. Eggert and J. C. Norrild, *J. Chem. Soc., Perkin Trans. 2*, 1999, 449; (*d*) B. Appleton and T. D. Gibson, *Sens. Actuators, B*, 2000, **65**, 302.

5 (*a*) R. L. Giles, J. A. K. Howard, L. G. F. Patrick, M. R. Probert, G. E. Smith and A. Whiting, *J. Organomet. Chem.*, 2003, **680**, 257; (*b*) S. W. Coghlan, R. L. Giles, J. A. K. Howard, M. R. Probert, G. E. Smith and A. Whiting, *J. Organomet. Chem.*, 2005, **690**, 4784; (*c*) A. S. Batsanov, R. L. Giles, M. R. Probert, G. E. Smith and A. Whiting, *Acta Crystallogr., Sect. E*, 2006, **62**, o466; (*d*) K. Arnold, B. Davies, R. L. Giles, C. Grosjean, G. E. Smith and A. Whiting, *Adv. Synth. Catal.*, 2006, **348**, 813.

6 (*a*) J. C. Craig, N. N. Ekwuribe, C. C. Fu and K. A. M. Walker, *Synth. Commun.*, 1981, 303; (*b*) E. Alcade, I. Dinares, L. Perez-Garcia and T. Roca, *Synthesis*, 1992, 395.

7 R. L. Letsinger and D. B. MacLean, *J. Am. Chem. Soc.*, 1963, **85**, 2230.

8 (*a*) M. R. Grimmet, in *Comprehensive Organic Chemistry: The Synthesis and Reactions of Organic Compounds, vol. 4*, ed. D. Barton, W. D. Ollis and P. G. Sammes, Pergamon Press, Oxford, 1979, p. 395; (*b*) M. R. Grimmet, in *Comprehensive Heterocyclic Chemistry, vol. 5*, ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, p. 457.

9 (*a*) A. Harizi and H. Zantour, *Synth. Commun.*, 2002, **32**, 387; (*b*) M. T. Bilodeau and A. M. Cunningham, *J. Org. Chem.*, 1998, **63**, 2800; (*c*) H. Akamatsu, K. Fukase and S. Kusumoto, *J. Comb. Chem.*, 2002, **4**, 475; (*d*) K. Nagata, T. Itoh, H. Ishikawa and A. Ohsawa, *Heterocycles*, 2003, **61**, 93; (*e*) D. Yang, D. Fokas, J. Li, L. Yu and C. M. Baldino, *Synthesis*, 2005, **1**, 47.

10 P. L. Beaulieu, B. Haché and E. von Moos, *Synthesis*, 2003, **11**, 1683.

11 H. Nöth and B. Wrackmeyer, *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*, Springer-Verlag, Berlin, 1978, p. 14.

12 (*a*) L. I. Bosch, T. M. Fyles and T. D. James, *Tetrahedron*, 2004, **60**, 11175; (*b*) M. Yamamoto, M. Takeuchi and S. Shinkai, *Tetrahedron*, 1998, **54**, 3125; (*c*) S. Shinkai and M. Takeuchi, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 40; (*d*) L. Zhu, S. H. Shabbir, M. Gray, V. M. Lynch, S. Sorey and E. V. Anslyn, *J. Am. Chem. Soc.*, 2006, **128**, 1222.

13 D. Voet and J. G. Voet, *Biochemistry, 2nd edn*, John Wiley and Sons, 1997, p. 56.

14 F. H. Allen and R. Taylor, *Chem. Soc. Rev.*, 2004, 463.

15 (*a*) J. C. Norrid and I. Sotofte, *J. Chem. Soc., Perkin Trans. 2*, 2002, 303; (*b*) P. D. Robinson, M. P. Grozniak and L. Yi, *Acta Crystallogr., Sect. C*, 1996, **52**, 2826; (*c*) S. Toyota and M. Ōki, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 1832.

16 (*a*) J. Beger, G. Wagner, E. Uhlig and U. Dinjus, *J. Prakt. Chem.*, 1983, **325**, 708; (*b*) S. M. Chiacchiera, J. O. Singh, J. D. Anunziata and J. J. Silber, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1585; (*c*) B. W. Ashton and H. Suschitzky, *J. Chem. Soc.*, 1957, 4559; (*d*) J. T. Ralph, *Synth. Commun.*, 1989, **19**, 1381.

17 K. R. Reddy and G. G. Krishna, *Tetrahedron Lett.*, 2005, **46**, 661.

18 *SHELXTL, version 6.12*, Bruker AXS, Madison, Wisconsin, USA.

† CCDC reference number 608045. For crystallographic data in CIF format see DOI: 10.1039/b607127a

