The Synthesis and Applications of Heterocyclic Boronic Acids

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Abstract: Boronic acids are valued by organic chemists for their important role in the synthesis of biphenyls via a palladium(0) catalysed cross-coupling reaction with aryl halides (Suzuki reaction). Despite their synthetic utility and known biological activities heterocyclic boronic acids feature less frequently often due to difficulties in their synthesis. This paper provides an overview of the synthesis and applications of a range of heterocyclic boronic acids.

1 Introduction

Boronic acids have become established as an important reagent for the synthesis of biphenyls via a cross-coupling reaction with aryl halides typically catalysed by palladium. The Suzuki coupling reaction has since found considerable utility in the synthesis of unsymmetrical biphenyls and related compounds. The advantage that their use have over organolithium, organomagnesium and other organometallic reagents in related coupling reactions are their tolerance to a wide variety of functional groups, their air stability and their relatively low toxicity.

The antineoplastic, protease inhibitory as well as a range of other significant medicinal roles involving boronic acids have been highlighted, consequently their use in the synthesis of novel analogues for high throughput screening has intensified. The novel use of boronic acids as solid support linkers as well as the translation of metal catalysed cross-coupling reactions to solid support synthesis has now been accomplished.

In contrast to the many examples of Suzuki coupling reactions between heterocyclic halides and phenyl boronic acids that have appeared in the literature over the past two decades the corresponding reactions involving heterocyclic boronic acids are noticeably fewer. Frequently the examples that are cited in the literature involve magnesium, zinc or tin reagents. Nevertheless interest in heterocyclic boronic acids continues to grow and it is the intention of this report to review the developments and optimisations in their syntheses.

2 Nitrogen Heterocycles

2.1 Pyridinylboronic Acids

Examples whereby pyridinyl derivatives act as the nucleophilic source in Suzuki coupling reactions e.g. pyridinylboronic acid are few and far between and the corresponding number of publications are equally limited in number.

2.1.1 2-Pyridinylboronic Acid

The synthesis of 2-pyridinylboronic acid has remained elusive, however the successful isolation of the corresponding lithium borate salt has been achieved. Exposure of the acid to protic solvents however leads to its rapid decomposition to pyridine and boric acid. In contrast to the instability of the acid the complex and the corresponding borate exist as stable compounds (Scheme 1). The stability of both the borate and the corresponding dimer have been explained in terms of the intermolecular B–N bond length and the tetrahedral character of the boron atom itself.

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From a synthetic point of view the diethyl borates have proved as reactive as boronic acids for use in Suzuki coupling reactions.36,37

2.1.2 3- and 4-Pyridinylboronic Acids

One of the earliest syntheses of both 3- and 4-pyridinylboronic acids were revealed in 1965.38 The authors were interested in their chemical and physical characteristics and later described both the thermal and photoinduced deboronation of these compounds.39

In these first recorded syntheses 3-pyridinylboronic acid (4), was obtained in low yield (28%) from the treatment of 3-pyridinylmagnesium bromide with either methyl or butyl borate (Scheme 2). For the corresponding 4-pyridinylboronic acid (5) the authors found that the coupling of 4-pyridinyllithium with methyl borate was effective but again low yielding (20%). The low yields reported by the authors in these early syntheses of pyridinylboronic acids reflect the difficulty in their isolation attributed to the amphoteric nature of 3-pyridinylboronic acid (4) at a pH of

Biographical Sketches

Elizabeth Tyrrell was born, too long ago to remember, in London. She was awarded a First Class Honours degree from the Open University (UK) in 1985 and continued her postgraduate studies at Southampton University in 1986. At Southampton she studied ‘Approaches to the Synthesis of Histrionocotoxin’ with Professor Phil Parsons and was awarded her PhD in 1989. The same year she accepted a position at Brighton Polytechnic as Lecturer in Organic and Polymer Chemistry. Since 1992 she has been at Kingston University where she is a Principal Lecturer in Organic and Medicinal Chemistry. Her research interests include tandem cyclisation reactions involving organo-cobalt clusters, asymmetric synthesis, cycloaddition reactions, natural product synthesis and synthesis on solid (polymer as well as silica) supports.

Phillip Brookes was born in 1973 in Leamington Spa (UK). He received his BSc in Chemistry from the University of Leeds in 1995 and continued his studies at Loughborough University. He received an MSc in 1996 and a PhD in 2000 under the supervision of Professor W. R. Bowman for his studies on the radical cycloaddition and rearrangement reactions of nitriles. He became a research chemist at Maybridge plc (Cornwall), in collaboration with Kingston University through a Teaching Company Scheme (TCS). His work at Maybridge plc was directed to the synthesis and applications boronic acids. At the present time he is employed as a postdoctoral researcher by Aavecita Ltd in Huddersfield in the development of novel asymmetric catalysts.
Suzuki modification is the avoidance of water during the isolation of the pinacol.

A common problem associated with the Suzuki reaction involving bromopyridines is the lithium–halogen exchange step when conducted in THF. The acidic nature of bromopyridines often leads to a competing deprotonation reaction however this effect may be minimised by conducting the reaction at very low temperatures (−100 °C).

In a recent development Cai reported a clean procedure for effecting lithium-halogen exchange using toluene as the solvent. Thus exposure of 3-pyridyllithium to triisoborate led to an efficient synthesis of 4 in 98–99% yield.

The author had previously attempted a magnesium-halogen exchange with 3-bromopyridine. This, however, gave unsatisfactory results due to (i) the poor solubility of the 3-pyridinylmagnesium chloride, which precipitated from solution, and (ii) unsatisfactory conversion to the corresponding boronic acid due to low reactivity.

Most recently the formation of libraries of halopyridinylboronic acids and esters for use in combinatorial syntheses have been carried out.

In the first of these papers the synthesis of 6-halopyridin-3-yl-boronic esters and acids were accomplished (Scheme 4). By exploiting the well-known reactivity differences between the two halogens in 10 lithium–halogen exchange was followed with reaction with triisopropylborate [B(i-PrO)₃]. In an adaptation to the usual work-up and recovery techniques the authors isolated both the boronic ester derivative in 78% (X = Br) and the acid 75% (X = Br). A range of dihalopyridines were synthesised and challenged to the same reaction conditions. Apart from 2,5-diiodopyridine and 5-bromo-2-iodopyridine all produced the boronic acids and esters however the best results were obtained from substrates containing a C-5 bromine atom.

The same authors recently reported the synthesis of an array of the 2-halopyridinyl-3-yl-boronic acids and esters (Scheme 5), as well as the 4- and 5-halopyridinyl-3-yl-boronic acids and esters using similar chemistry. The difference, however, was that as the expected boronic acid moiety was ortho to a halogen they could compare metal–halogen exchange with a directed ortho-metallation process.
one of two routes (Scheme 7). Thus regioselective nitration of the N-oxide derivative 27, derived from 26a–c gave 28 which was reduced and converted to the desired compounds 30a (36% overall yield) and 30b (32%) using a Sandmeyer bromination reaction. Compound 30c, derived from 2-fluoropyridine 26c, as well as 30b, were obtained in good yield via a homotransmetalation of compound 31. This phenomena, whereby the bromine atom is observed to ‘dance’ to another position on the ring, has been observed during metalation studies of 3-bromo-2-halopyridines.54 The key C(4) bromine-lithium exchange was effected using the Marsais55 methodology involving exposure of the halopyridine with an BuLi/TMEDA chelate at –60 °C. These were then exposed to trisoborate56 and isolated as the boronic acids (64–68%) as well as the pinacol esters (60–66%).

In the synthesis of the corresponding 3-halopyridin-4-yl boronic acid arrays the authors were able to exploit the ortho position of the expected boronic acid in 32a–c, with relation to the position in the ring of the halogen (Scheme 8). This process is known to proceed especially well with the lithiation of 3-fluoropyridine57,58 32c. Thus regioselective51 lithiation to afford 33 and subsequent quenching, at –60 °C, provided 34 which following classical work-up aimed at avoiding the formation of pyridinium salts, provided both the pinacol 35a–c and the acids 36a–c in acceptable overall yields.

2.2 Pyrrolylboronic Acids

Until as recent as 199159 there were no reports of pyrrole containing boronic acids and even up to the present time there have been relatively few articles published. Although pyrrole may be lithiated directly or undergo a halogen exchange reaction protection of the nitrogen atom must initially be undertaken. The protecting groups that have currently been used include:

(i) tert-butoxycarbonyl (Boc) group59
(ii) triisopropylsilyl (TIPS) group60
(iii) phenylsulfonyl group61

2.2.1 Pyrrole-2-boronic Acid

In the earliest synthesis of a pyrrole-2-boronic acid Schluter59 reported the synthesis \( \text{N-(Boc)-pyrrol-2-ylboronic acid} \) (38) in a modest yield from 37 (Scheme 9). Compound 37 became available in multi-gram quantities using a modification to an earlier syntheses.62,63 The N-Boc protected pyrrole 37 was added to a –78 °C solution of BuLi with a slight excess of 2,2,6,6-tetramethylpiperidine (TMP) whereupon trimethyl borate was added. The corresponding boronate, which was initially formed, was hydrolysed in situ to afford 38 in a yield of 40%. The major disadvantage in the use of 38 is its reported susceptibility to deboronation when heated under the appropriate Suzuki coupling reaction conditions.64 Compound 38 was also obtained using an analogous procedure in a recent synthesis of 2,5-disubstituted pyroles for use as selective dopamine \( D_3 \) receptor antagonists.65
The authors reported that in addition to deboronation another complication was the production of the homodimer 39.

The first synthesis of nonylprodigiosin 40, a potent cytotoxic prodigiosin alkaloid, was published recently.66 It was envisaged that the pivotal macrocyclisation step would involve the ring-closing metathesis reaction (RCM) of diene 41. The diene 41, would itself, be obtained by a Suzuki coupling reaction between the triflate 42 and the pyrrole-2-boronic acid 43, as indicated, (Scheme 10). The coupling reaction between 42 and 43 proved to be quite troublesome due to the inherent lability of the boronic acid 43. The authors reported that 43 was best prepared by an ortho-metalation reaction of N-Boc protected 2-(pent-4-enyl) pyrrole using lithium tetramethylpiperidininide, as base, and quenching the lithiated pyrrole derivative with an excess of dimethyl borate followed by acid hydrolysis.

This procedure provided the boronic acid 43 as an unstable solid in a yield of 58%. Again the authors observed significant proto-deboronation during attempts at the Pd(0) coupling reaction with 42.

In an effort to reduce the problems associated with both deboronation and dimerisation during Suzuki coupling reactions involving pyrrole-2-boronic acid 38, Ketcha61 investigated the use of the N-phenylsulfonyl moiety as an alternative protecting group (Scheme 11). A major limitation to this approach is the known tendency of 1-(phenylsulfonyl)pyrrole (44) to undergo competitive desulfonylation when attempting to effect a C-2 lithiation reaction.67,68 The authors were unable to avoid this serious side reaction and were only able to obtain the corresponding acid 45 in very low yield. They did report, however, that the corresponding Suzuki coupling reaction took place efficiently in yields ranging from 39–91% without the concomitant deboronation reaction highlighted above. The highest yields were obtained with aryl halides containing electron-withdrawing groups.

2.2.2 Pyrrole-3-boronic Acid

The only recorded synthesis of a pyrrol-3-ylboronic acid was that revealed by Muchowski60 who formed 1-(triisopropylsilyl)pyrrol-3-ylboronic acid (48) in 43% yield (Scheme 12). This was synthesised in two steps from the known TIPS-protected pyrrole 46 Selective C-3 iodination, using N-iodosuccinimide (NIS), provided 47 which was lithiated with t-BuLi and reacted with trimethyl borate to form the boronic acid 48 as a crystalline solid upon hydrolysis with aqueous methanol.

2.3 Indolylboronic Acids

The indole motif is an integral component found in a wide variety of natural products. Despite this, and the fact that indolylboronic acids themselves are known to possess sugar binding properties, it is perhaps somewhat surprising that examples of indole boronic acids for use in the synthesis of novel indole nuclei, are so few. The first reported synthesis of an indolylboronic acid was as relatively late as 1990.71

As with pyroles the nitrogen atom requires protection before attempting the reaction and the following protecting groups have been used:

(i) N-tosylation72
(ii) N-Boc65
(iii) N–Me, N–OMe, N–SO \(_2\) Ph73,74
(iv) N–TBS75
(v) N-potassium salt76,77

2.3.1 Indol-2-ylboronic Acid

One of the very few publications describing the synthesis of indol-2-ylboronic acids was that revealed by Johnson65 in 1998. In his synthesis, (Scheme 13), the N-(Boc)indole 49 was deprotonated, using 1-lithio-2,2,6,6-tetramethylpiperidine (LiTMP) in THF, and then exposed to trisopropyl borate whereupon an acidic workup provided the indole boronic acid 50 in 65% overall yield. The authors reported that the subsequent Suzuki coupling reaction of 50 with a range of aryl halides occurred in a lower yield compared to similar coupling reactions with the pyrrole...
analogue 38. This was attributed to steric hindrance between the N-Boc group and the hydrogen atom at C-7 position of the indole ring. Again significant dimerisation to afford the 2,2’-dimer 51 was observed during the coupling step.

Scheme 13

Complementary to these studies the Ishikura group recently reported the successful synthesis of a range of N-substituted indol-2-ylborates 53 which underwent subsequent Suzuki coupling reactions with both bromides and triflates (R–X) derivatives (Scheme 14). The generation of the indolylborates 53 was effected by the in situ treatment of 52 with BuLi in THF, under an argon atmosphere, followed by exposure with triethylborane. The borates were then successfully coupled to a range of aryl, 2- and 3-pyridyl and 3-thienyl electrophiles under palladium catalysis. This provided the indolyl derivatives 54 in yields that critically depended upon the nature of the N-protecting group e.g. 15% (Z = SO2 Ph) to 80% (Z = Me).

Scheme 14

Interestingly the 1-methoxymethylindoleborate 55 proved resistant to all attempts at the Suzuki coupling reaction. Treatment with methanol, however, produced an unexpected boryl migration to afford the corresponding 2-alkyl-1-methylindole 56 upon protonolysis (Scheme 15).

Scheme 15

A variety of natural products that show anti-tumour activity as well as protein kinase C inhibitory properties contain an indolecarbazole motif in their structure. In their 1997 studies Merlic and his group prepared the unsymmetrical 2,2’-biindole 59, as substrates for a pivotal benzannulation reaction, via the Suzuki coupling of the boronic ester 58 and 2-iodoindole (Scheme 16). The authors studied the effects of a range of different nitrogen protecting groups upon the subsequent coupling reaction. They found that whereas the N-protection of 2-iodoindole occurred almost quantitatively to provide 57 the coupling reaction with 2-iodoindole proved inefficient with the N-allyl protected boronic acid and failed completely for the corresponding N-phenylsulfonyl derivative. No explanation was offered for this failure.

Scheme 16

2.3.2 Indol-3-ylboronic Acid

A precautionary measure, when employing lithium–halogen exchange chemistry for the synthesis of 3-indoleboronic acids, is the need to maintain the temperature of the reaction flask below –100 °C. The authors reported that above this temperature complete rearrangement of the previously unknown 3-lithio-1-(phenylsulphonyl)indole (61) to the more stable 2-lithio species 62 took place (Scheme 17).

Scheme 17

In his studies into the synthesis and resolution of the atropisomerically chiral ligand 2-diphenylphosphino-1-(1’-isoquinoyl)naphthalene (QUINAP), for use in catalytic asymmetric allylation studies, Brown extended the range of ligand structures to include the corresponding indoyl analogue 67. His synthesis involved the Suzuki cou-
pling between boronic acid 65 with 1-chloroisouquinoline to afford the biaryl 3-(1'-isoquinoyl)-1-phenylsulfonyl-
lindole 66 (Scheme 18).

This was then readily converted to 67 via an N-deprotection/N-methylation reaction followed by phosphinylation
using Schlosser base.82 Although the synthesis of the boronic acid 65 occurred in a modest 41% yield the subse-
cquent coupling reaction proved straightforward yielding 66 in 84% yield.

In contrast to this synthesis, where the need to maintain a temperature below –100 °C during the metal–halogen ex-
change is of paramount importance in order to prevent isomerisation to the 2-lithiated species, the reaction in-
volving 68, featuring an alternative N-protecting group, was considerably less temperature sensitive. Thus in his
synthesis of the anti-viral/anti-tumour bis(indoyl)imidazole topsentin (71) Ohta75 carried out a lithium–halogen
exchange upon the N-TBS protected indole 68, at –78 °C, without observing any C-3 to C-2 isomerisation of lithium
(Scheme 19). The authors reported the synthesis of boronic acid 69, from 68, which was used without further puri-
fication in the subsequent coupling reaction with 5-bromo-2-phenylthio-1-[2-(trimethylsilyl)-ethoxy]methyl-1H-imidazole to afford the cross-coupled product 70 in an excellent 79% yield overall.

Further confirmation of the stabilising influence of the N-
protecting group, during lithium-halogen exchange reac-
tions, is seen in the Hoerrner synthesis of boronic acid

Clearly the choice of the N-protecting group is crucial to the outcomes in these reactions. Silicon based protecting
groups appear to facilitate the selective lithium–halogen exchange at milder temperatures to afford the boronic acid with enhanced yields compared to other N-protecting moieties.

Others have investigated methods for improving both the selectivity and the efficiency in the synthesis of indol-3-
ylboronic acids via metal–halogen exchange reactions.

In his vinylation studies at the 3-position of the indole ring77 Martin72,84 reported the synthesis of 1-tosyl-3-indole-
boronic acid 76 in 50% yield using standard metal–halo-
gen exchange conditions (Scheme 21). He was, however, able to improve the yield considerably by using a mercu-
ration-boronation techniques.85

Compared to metal–halogen exchange procedures these authors reported a greater tolerance of the mercuration technique to potentially sensitive functional groups, the absence of isomerisation, the ease of the procedure and an enhancement in yields.

2.3.3 5/6/7-Indolylboronic Acid

The application of an N-potassio-salt76,77 of 5-bromoindole 79 was used by Martin86 as a form of protection of the indole nitrogen atom. Furthermore he was able to establish that lithium–halogen exchange took place without
metallation at C-2 position of the indole role. Using standard boronation techniques he was able to effect the synthesis of indol-5-ylboronic acid (80) in a moderate yield (Scheme 22). The novel 5-substituted indoles originating from his studies were designed as potential serotonin agonists and antagonists.

![Scheme 22](image)

A similar methodology, to that detailed above, was used by Roussi and his team in their synthetic approach to the macropolypeptides chloropeptin I, II and Kistamycin. They reported the successful synthesis of 5-, 6- and 7-indolylboronic acids from the corresponding bromoindoles via the N-1 potassio salt described by Rapoport.

### 2.4 Imidazoylboronic Acids

Despite the wide variety of natural products that contain an imidazole motif in their framework Suzuki cross-coupling reactions involving this moiety as the nucleophilic coupling partner are, at the present time, limited to just one example.

In his synthesis of topsentin (71) Ohta investigated two palladium catalysed routes for the introduction of the indolyl group to the 5-position of the imidazole. The first was the condensation of an imidazoyl halide with indolylboronic acid (Scheme 19) the second route involved the condensation of the indolyl halide with the imidazoylboronic acid (Scheme 23). Imidazoylboronic acid was in turn synthesised from the 1,2-protected imidazole via lithiation and treatment of the lithiated species with trimethyl borate followed by aqueous hydrolysis. Although the yield of the boronic acid was not quoted, as it was used crude directly for the in situ coupling reaction, it appears to have been formed in an acceptable yield. The corresponding Suzuki coupling with however, was less successful and 70 was reported to be formed in only 7% yield. The authors did not discuss this outcome to any extent other than to suggest that the low yield may be due to the instability of rather than failure of the coupling reaction to take place efficiently.

### 2.5 Quinolinylboronic Acids

Quinolin-8-ylboronic acid (85) (Scheme 24) was first synthesised as long ago as 1959 where its use as selective catalysts for certain base catalysed reactions was under scrutiny. Although the authors were successful in obtaining this particular acid attempts at the synthesis of iso-meric boronic acids failed. The authors suggested that the metal–halogen exchange was facilitated, in the case of 8-bromoquinoline (84), by coordination of butyllithium with the ring nitrogen atom.

More recently however Queguiner reported the synthesis of 2-chloroquinolin-3-ylboronic acid (87) in good yield from 2-chloroquinoline (86). In this example chlorine appears to function as an ortho-directing metallating group (DMG).

### 2.6 Pyrimidinylboronic Acids

The role of localised organoboron reagents as potential anti-tumour reagents precipitated the earliest syntheses of the pyrimidinylboronic acids by Liao in 1964 (Scheme 25). The pyrimidinyl ethers were formed, using a standard protocol, lithiated, using Langley’s procedure and reacted in situ with either trimethyl borate or tributyl borate. As proved to be rather unstable it was converted to the more stable 5-uracilboronic acid by a catalytic hydrogenation process.

![Scheme 24](image)

![Scheme 25](image)
In connection with his work on novel antiviral compounds Gronowitz\textsuperscript{96,97} investigated the synthesis of uracils bearing a range of heterocyclic moieties for conversion to nucleosides.

The initial approach involved the Pd(0) catalysed coupling of halogenated uracils with appropriate boronic acids, they found, however, that the couplings were unsuccessful. In contrast to these results they found that coupling of the corresponding pyrimidinylboronic acid\textsuperscript{95} with \(\pi\)-electron deficient heterocyclic halides took place in good to excellent yields (Scheme 26).

The acid\textsuperscript{95} was efficiently prepared in a two step process from 5-bromouracil (\textsuperscript{92}) using a similar procedure to that used by Liao.\textsuperscript{93} This involved the initial treatment of \textsuperscript{92} with phosphorus oxychloride, to effect dehydroxyhalogeneration, to afford \textsuperscript{93} followed by chloride displacement with sodium tert-butoxide. Extensive studies from these laboratories have confirmed the general suitability of \textsuperscript{95} as a nucleophilic partner in a variety of Pd(0) catalysed cross-coupling reactions.\textsuperscript{97–99}

Pyrimidin-5-ylboronic acid (\textsuperscript{97}) is not a trivial compound to make, due to competing reactions during formation, however Gronowitz has accomplished its synthesis, in 52\% yield from \textsuperscript{96}, by maintaining very low temperatures during the lithium exchange reaction.\textsuperscript{96}

In a recent study into the syntheses of novel potent inositol monophosphatase (IMPase) inhibitors Piettre was successful in the coupling of the same acid, pyrimidin-5-ylboronic acid (\textsuperscript{97}), to the tropolone derivatives \textsuperscript{98} and \textsuperscript{100} in modest yields to afford \textsuperscript{99} and \textsuperscript{101} (Scheme 27).\textsuperscript{100}

These coupled compounds formed part of a library of functionalised mono-and disubstituted tropolone screens. The authors have subsequently discovered that some couplings may be adapted to solid phase syntheses.\textsuperscript{20}

### 3 Sulfur Heterocycles

#### 3.1 Thiienylboronic Acids

The thiophene moiety is not only found in a wide range of natural products and chemotherapeutics but polythiophenes are highly conducting polymers that possess good processing qualities.\textsuperscript{101} These industrially important applications made the synthesis of thiophenylboronic acids one of the first heterocyclic boronic acids to be undertaken.

**3.1.1 2-Thienylboronic Acid**

2-Thienylboronic acid may be readily formed by exposure of either the thienyllithium (\textsuperscript{102})\textsuperscript{102} or the thienyl Grignard reagent \textsuperscript{103}\textsuperscript{103} with a trialkylborate followed by acid hydrolysis (Scheme 28).

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#### 3 Sulfur Heterocycles

**Scheme 26**

**Scheme 27**

**Scheme 28**

**Scheme 29**
In his syntheses of various 5-substituted uracils Gronowitz recently coupled 3-methyl-2-thienylboronic acid (108) with the with the pyrimidine derivative 94 to afford the thienylpyrimidine 109 in an acceptable yield (Scheme 30). This compound was then further hydrolysed to the uracil 110 for screening as a potential antiviral agent.

Scheme 30

The commercial availability of 2-thienylboronic acid 104 has led to a wide variety of coupling reactions to afford examples such as the thienyl indolecarboxylate 111, ketone 112, the ninhydrin analogue 113, terheterocycles 114, unsymmetrical bithienyls 115 and the thienyl benzoate 116 generated via a resin bound Suzuki coupling reaction (Scheme 31).

Scheme 31

3.1.2 3-Thienylboronic Acids

The formation of 3-thienylboronic acid proved to be far from straightforward and the synthesis of 3-thioliophene (118) was first reported by Gronowitz as recently as 1974. The 3-isomer was observed to readily equilibrate to the 2-isomer 119 as the temperature was raised to 0 °C to afford a product mixture (Scheme 32). The procedure consisted of a metal–halogen exchange reaction between 3-bromothiophene 117 and butyllithium in a polar solvent, such as diethyl ether, at –70 °C. However this methodology lacked generality as many electrophiles proved to be too unreactive towards the organolithium species at these low temperatures.

Scheme 32

In his studies, aimed at addressing this problem, Rieke was the first to establish a dependency of the isomerisation reaction to the solvent. From these studies the synthesis of 3-thioliophene (118) was achieved selectively, at ambient temperatures, using a solvent couple consisting of hexane–THF (10:1).

Lawsess synthesised thien-3-ylboronic acid (120) by exposing the organolithium species 118 to a suitable trialkylborate at –60 °C. The coupling of 3-thienylboronic acid 120 with 3-bromothiophene provided the symmetrical bithiophene (121) in good yield (Scheme 33).

Scheme 33

The ready availability of thien-3-ylboronic acid (120) and its various derivatives has created great interest, particularly from the laboratories of Gronowitz, and led to their use in the formation of a variety of molecular types.

The bisthienopyridine (124) was synthesised in one-pot by the Pd(0) catalysed coupling of 2-formylthien-3-ylboronic acid (122) with the carbamate (Scheme 34). The authors reported the synthesis of six out of the possible nine isomeric bisthienopyridines, each containing the same phenanthrene annelation pattern, using these procedures.
Terheterocycles, such as 125, are not only interesting as monomers for conducting polymers but have also been recorded as showing light induced anti-fungal, anti-algal, plant inhibitory and herbicidal activities. The authors were successful in the synthesis of the 3,2′:5′:3′-terthiophene (125) (Scheme 35). They reported the need for an excess of boronic acid 120 during the coupling reaction, due to spontaneous deboronation that is frequently observed with π-excessive heterocycles even under these weak alkaline conditions.

The synthesis of the pyridinylthiophene 127 (and its isomers) was reported, by Gronowitz, via a Pd(0) catalysed coupling of 120 with an appropriate bromopyridine (Scheme 36). Bromination, to give 128, followed by a selective debromination, using a halogen-metal exchange reaction, gave 2-bromo(2-pyridin-4-yl)thiophene (129). This was then converted to the corresponding pyridin-4-ylthien-2-ylboronic ester 130 using a standard Suzuki coupling protocol. These, as well as the 3-and 4-pyridinyl derivatives, were then oxidised, using hydrogen peroxide, to afford the corresponding 4-pyridyl-2-hydroxothiophene systems.

The successful Suzuki coupling reactions between 2-formylthien-3-ylboronic acid (122) and 3-amino-4iodopyridine (131) as well as between 4-formylthienyl-3-boronic acid (132) and 3-amino-4-iodopyridine (131) provided a useful one-pot synthesis of the thieno[2,3-c]1.7-naphthyridine (133) and thieno[3,4-c]1.7-naphthyridine (134) respectively in acceptable yields (Scheme 37).

### 3.2 Benzothienylboronic Acids

Benzothien-2-ylboronic acid (135) has been shown to act as a potent inhibitor of the β-lactamase enzyme AmpC in E. Coli bacteria, thus providing an alternative treatment against microbial resistance to antibiotics. Iddon reported its synthesis in 1970 however he found that the cyclotriboroxane 136 was formed in a 95% yield as a result of the dehydration of the acid 135 during the work up procedure (Scheme 38).

### 4 Oxygen Heterocycles

#### 4.1 Furanylboronic Acids

The furanyl motif is found as a component in a wide variety of natural products of both marine and terrestrial origin, furthermore 3,4-disubstituted furans feature as key intermediates in organic syntheses. From electronegativity considerations, electrophilic substitution and metallation reactions occur most readily at the α-position. The reactivity differences between α- and β-furanylboronic acids have been the subject of previous reports.

#### 4.1.1 2-Furanyl Boronic Acids

Although this is commercially available as a reagent the synthesis of 2-furanylboronic acid (137) was in fact accomplished as long ago as 1975 via the direct metallation of furan with ethyllithium (Scheme 39).
The authors of this first synthesis reported upon the physicochemical differences that existed between the array of 2-furylboronic acid derivatives 138a–d.126

4.1.2 3-Furylboronic Acid

Roques125 was also one of the earliest to report the synthesis of 3-furylboronic acid. Due to reactivity differences between the α- and β-positions in furan the synthesis was achieved via a halogen-metal exchange reaction of 3-bromofuran and ethyllithium.

In their studies into the synthetic applications of 3,4-bis(trimethylsilyl)furan (139) in synthesis Wong and his co-workers127 were able to successfully achieve a Suzuki cross-coupling reaction with the trimeric anhydride boroxine 140 to afford 141.

The synthetically useful furan 139 was conveniently obtained through a Diels–Alder reaction between 4-phenyloxazole and bis(trimethylsilyl)acetylene (Scheme 40).

The authors reported that 139 underwent a regioselective ipso substitution reaction, with an excess of boron trichloride, to afford the boroxine 140 in a quantitative yield. This then underwent Suzuki type couplings with a variety of aromatic and heterocyclic halides to afford a library of derivatives 141 (Scheme 41). They observed that the coupling reaction of boroxine 140 took place highly efficiently irrespective of the diverse electronic and steric nature of the electrophile used during these studies. The one limitation in the choice of the electrophile was the need for Lewis acid insensitive substituents. They further reported that boron trichloride was a more effective Lewis acid, compared to boron trifluoride, for the displacement of the silyl group in 139. The initially formed dichloroborane, from the reaction of 139 with boron trichloride, was readily hydrolysed to 140 and then used extensively throughout these studies. This synthetic cycle was then repeated, using the same conditions, to effect the synthesis of boroxine 142 which underwent a second Suzuki coupling reaction to afford a range of 3,4-disubstituted furans.

Continuing his studies, into the synthesis of various terheterocyclic compounds, Gronowitz109 achieved the synthesis of 2,6-di-(3-furyl)pyridine (145) and 2,5-di-(3-furyl)thiophene (147) in about 50% yield. These were formed from a Suzuki coupling reaction between furylboronic acid and 2,6-dibromopyridine (144) and 2,5-dibromothiophene (146) respectively (Scheme 42).

4.2 Benzofuranylboronic Acids

Snieckus recently highlighted the inroads that his team had made into the use of polymer supported Suzuki coupling reactions19,128 using the Merrifield resin bound bromobenzene-acetal Leznoff linker129,130 148.

Furostifoline 155, a furo[3,2-a]carbazole alkaloid, was only isolated from Murraya euchrestifolia as recently as 1990.131 It structural similarity to current indolo-isoquinoline antiretroviral reagents has aroused some interest and
the first synthesis was recently reported. Timari recently disclosed his total synthesis using boronic acid chemistry (Scheme 44). Benzofuran 152 was synthesised in good yield via a known procedure and converted to the boronic acid 153 using a conventional lithium–halogen exchange reaction. Coupling of 153 with 2-bromotrobenzene gave the biaryl 154 in 72% yield. Nitrene formation from 154, using triethylphosphite to effect deoxygenation of the nitro moiety, resulted exclusively in the formation of furostifoline 155 in an acceptable 42% yield.

![Scheme 44](image)

5 Conclusions

In this paper we have attempted to provide an up to date overview into the synthesis and utility of various heterocyclic boronic acids. The fact that some classes are absent from this review is not an omission on the part of the authors but a reflection upon the state of the art. Thus, derivatives can act as the electrophilic coupling partner in the Suzuki coupling reaction or alternatively the use of other metal-palladium couplings may be used. Nevertheless the advantages in the use of boron derived coupling reactions should ensure that these unknown heterocyclic boronic acids should soon become a reality.

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