

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.

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Key words: Suzuki reaction, heterocyclic boronic acids, palladium(0) catalysed cross-coupling, trialkylboranes, lithium-halogen exchange

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 reaction¹ has since found considerable utility in the synthesis of unsymmetrical biphenyls and related compounds.^{2–4} 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,^{5–10} their air stability and their relatively low toxicity.

The antineoplastic,¹¹ protease inhibitory¹² as well as a range of other significant medicinal roles involving boronic acids have been highlighted,^{13–15} consequently their use in the synthesis of novel analogues for high throughput screening has intensified¹⁶. The novel use of boronic acids as solid support linkers¹⁷ as well as the translation of metal catalysed cross-coupling reactions to solid support synthesis has now been accomplished.^{18–22}

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^{3,4} the corresponding reactions involving heterocyclic boronic acids are noticeably fewer. Frequently the examples that are cited in the literature involve magnesium,^{3,22,23} zinc^{3,24} or tin^{3,25} 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

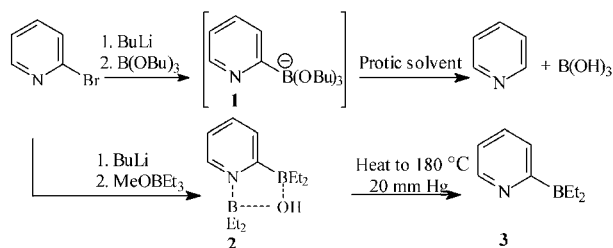
2.1 Pyridinylboronic Acids

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.^{26–30}

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 **1** has been achieved.³¹ Exposure of **1** to protic solvents however leads to its rapid decomposition to pyridine and boric acid.

In contrast to the instability of the acid **1** the complex **2** and the corresponding borate **3**, formed upon heat treatment of **2**, exist as stable compounds³² (Scheme 1). The stability of both the borate **3** and the corresponding dimer have been explained in terms of the intermolecular B–N bond length^{33,34} and the tetrahedral character of the boron atom itself.³⁵



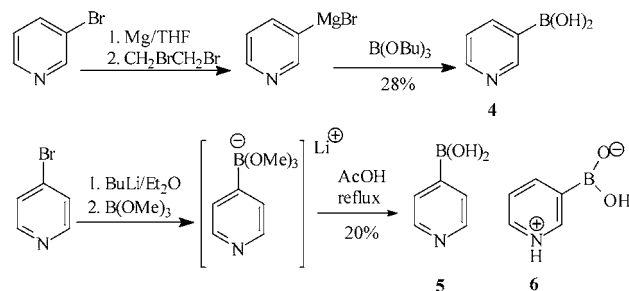
Scheme 1

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 deboration 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-pyridinylmagnesium bromide 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



Scheme 2

7. At this pH **4** exists predominantly as the zwitterionic pyridinium boronate **6**.

The resulting hydrophilic nature of both the 3- and 4-isomers makes their isolation from aqueous media difficult.⁴⁰ The recognition of these isolation problems has led to improved procedures for their synthesis. Most notably by Halazy whose synthesis of **5** was accomplished in 65% yield using triisopropyl borate (Scheme 3).⁴¹ The authors were able to generate 4-bromopyridine and store it for a limited time by base treatment of the corresponding pyridinium salt **7**.

In a modification, aimed at dispensing with the use of the reportedly⁴² unstable 4-bromopyridine, Coudret developed an alternative approach involving a new synthesis of 4-iodopyridine⁴³ (**8**). This was then converted to the corresponding boronic acid **5** and immediately protected as the novel air-stable pinacol boronate **9** using Suzuki's one-pot procedure⁴⁴ in 74% from **8**. The advantage of the

Biographical Sketches



Elizabeth Tyrell 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 Histriocotoxin' 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 Or-

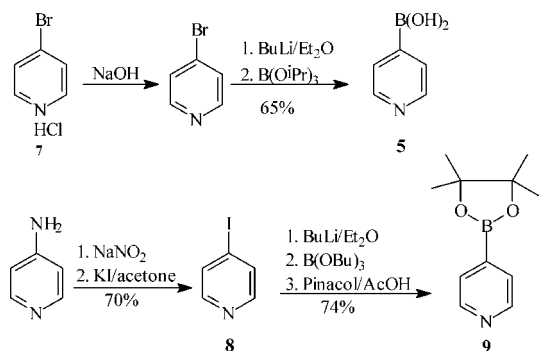
ganic and Medicinal Chemistry. Her research interests include tandem cyclisation reactions involving organocobalt clusters, asymmetric synthesis, cycloaddition reactions, natural product synthesis and synthesis on solid (polymer as well as silica) supports.



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 May-

bridge plc was directed to the synthesis and applications boronic acids. At the present time he is employed as a postdoctoral researcher by Avecia Ltd in Huddersfield in the development of novel asymmetric catalysts.



Scheme 3

Suzuki modification is the avoidance of water during the isolation of the pinacol.

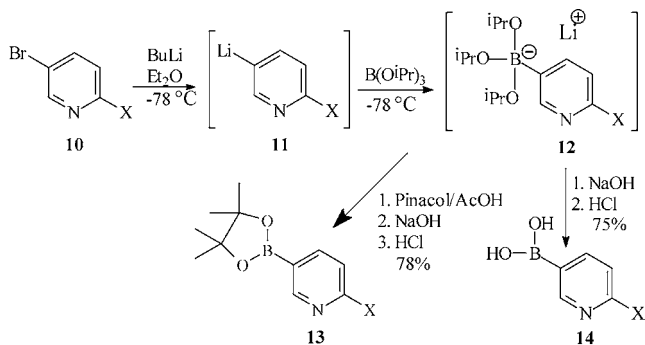
A common problem associated with the Suzuki reaction involving bromopyridines is the lithium-halogen exchange step when conducted in THF. The acidic nature of bromopyridines often leads to a competing deprotonation reaction⁴⁵ however this effect may be minimised by conducting the reaction at very low temperatures (−100 °C).

In a recent development Cai²⁸ 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 exchange⁴⁶ 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 halopyridinyl-boronic acids and esters for use in combinatorial syntheses have been carried out.

In the first of these papers²⁹ the synthesis of 6-halopyridin-3-yl-boronic esters **13** and acids **14** were accomplished (Scheme 4). By exploiting the well-known reactivity differences between the two halogens in **10**⁴⁷ lithium-halogen exchange was followed by 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 **13** in 78% (X = Br) and the acid **14** 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 esters⁴⁸ 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*-metalation process.



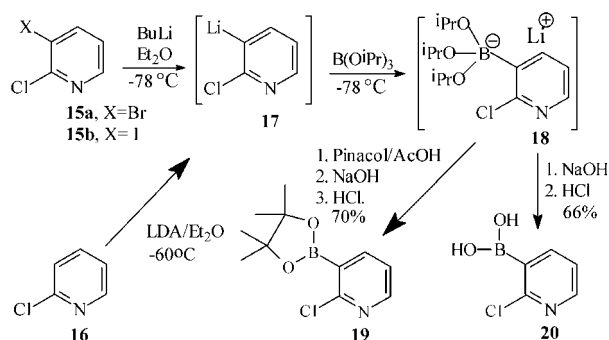
Scheme 4

Using a procedure described by Achab⁴⁹ the metalation of 2-chloropyridine **16** with LDA occurred regioselectively to afford **17**.

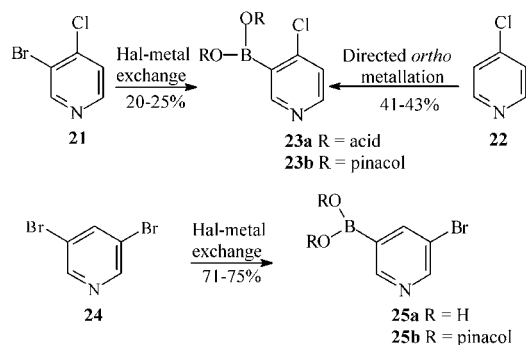
This was quenched at low temperature, by the addition of triisopropylborate, to afford **18**, which again, could be selectively transformed to either the pinacol ester **19** in 70% yield or the acid **20** in 66% yield. The yields of **19** and **20** obtained were all acceptable, (62–70%), regardless of whether a halogen-metal exchange, X = Br (**15a**) or X = I (**15b**), or directed *ortho*-metalation, X = H, reaction was employed.

A directed *ortho*-metalation reaction was the method of choice for the synthesis of 4-halopyridin-3-yl-boronic acid **23a** and the ester **23b** from the known dihalopyridine **21**⁵⁰ (Scheme 6). Using a halogen-metal exchange technique with **21** and quenching the metalated compound with triisopropylborate produced the boronic acid **23a** and the ester **23b** in low yields after the usual work-up. In contrast, prompted by the successful applications of analogous directed *ortho*-metalation reactions reported elsewhere,^{51,52} the authors were able to access the desired compounds with an increased efficiency. Using a lithium-halogen exchange technique the synthesis of the 5-halopyridin-3-yl-boronic acid **25a** and the ester **25b** were accomplished, highly efficiently.

In the third paper of this series the syntheses of 2- or 3-halopyridin-4-yl-boronic acids and esters were revealed.⁵³ The substrates required for the syntheses of 2-halopyridin-4-yl-boronic acids and esters were the 2,4-dihalopyridines **30a–c** which were conveniently synthesised by

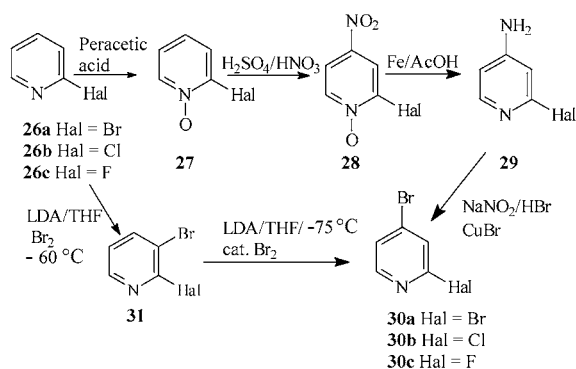


Scheme 5



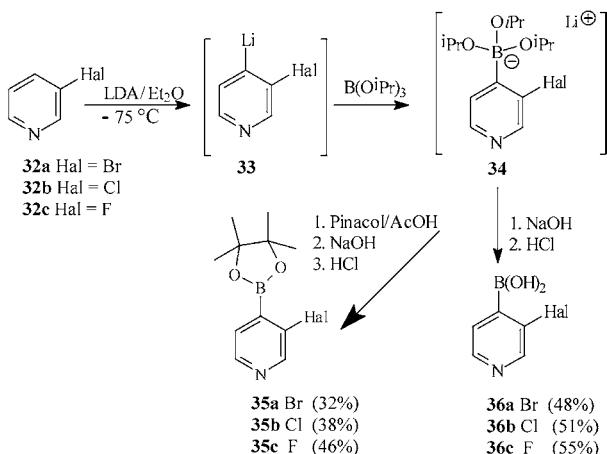
Scheme 6

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 triisoborate⁵⁶ and isolated as the boronic acids (64–68%) as well as the pinacol esters (60–66%).



Scheme 7

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-fluoropyridine^{57,58} **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.



Scheme 8

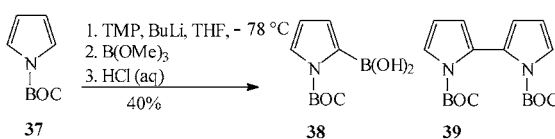
2.2 Pyrrolylboronic Acids

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

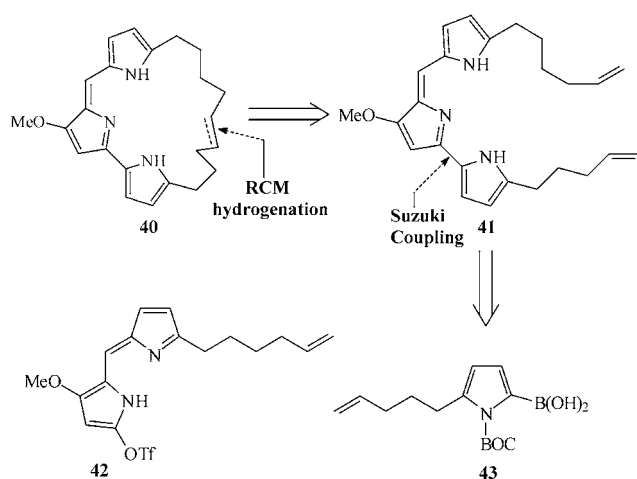
In the earliest synthesis of a pyrrole-2-boronic acid Schluter⁵⁹ reported the synthesis *N*-(Boc)-pyrrol-2-ylboronic acid (**38**) in a modest yield from **37** (Scheme 9). Compound **37** became available in multi-gram quantities using a modification to an earlier syntheses.^{62,63} The *N*-Boc protected 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 pyrroles for use as selective dopamine D₃ receptor antagonists.⁶⁵



Scheme 9

The authors reported that in addition to deboronation another complication was the production of the homodimer **39**.

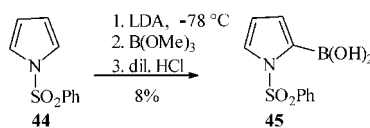
The first synthesis of nonylprodigiosin **40**, a potent cytotoxic prodigiosin alkaloid, was published recently.⁶⁶ It was envisaged that the pivotal macrocyclisation step would involve the ring-closing metathesis reaction (RCM) of diene **41**. The diene **41**, would itself, be obtained by a Suzuki 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 tetramethylpiperidinide, as base, and quenching the lithiated pyrrole derivative with an excess of dimethyl borate followed by acid hydrolysis.



Scheme 10

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**.

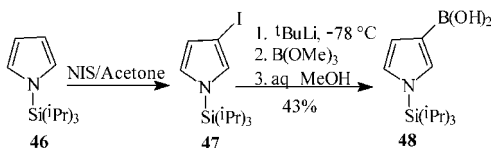
In an effort to reduce the problems associated with both deboronation and dimerisation during Suzuki coupling reactions involving pyrrole-2-boronic acid **38**, Ketcha⁶¹ investigated the use of the N-phenylsulfonyl moiety as an alternative protecting group (Scheme 11). A major limitation to this approach 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.



Scheme 11

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**.⁶⁹ 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.



Scheme 12

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,⁷⁰ 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

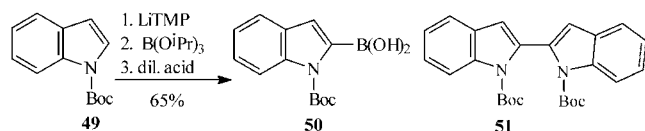
As with pyrroles the nitrogen atom requires protection before attempting the reaction and the following protecting groups have been used:

- (i) N-tosylation⁷²
- (ii) N-Boc⁶⁵
- (iii) N-Me,⁷³ N-OMe,⁷³ N-SO₂Ph^{73,74}
- (iv) N-TBS⁷⁵
- (v) N-potassio salt^{76,77}

2.3.1 Indol-2-ylboronic Acid

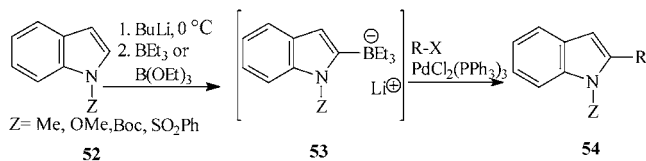
One of the very few publications describing the synthesis of indol-2-ylboronic acids was that revealed by Johnson⁶⁵ in 1998. In his synthesis, (Scheme 13), the *N*-(Boc)indole **49** was deprotonated, using 1-lithio-2,2,6,6-tetramethylpyridine (LiTMP) in THF, and then exposed to triisopropyl borate whereupon 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 arylhalides 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.



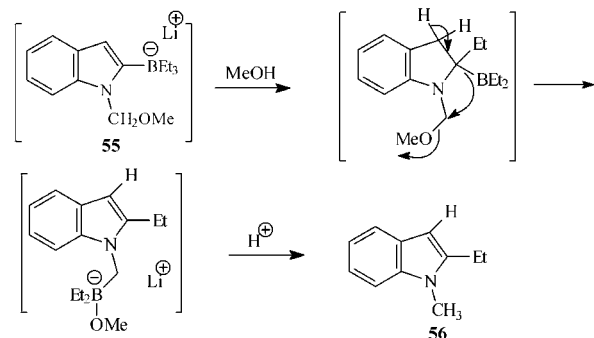
Scheme 13

Complementary to these studies the Ishikura⁷³ 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 = SO₂Ph) to 80% (Z = Me).



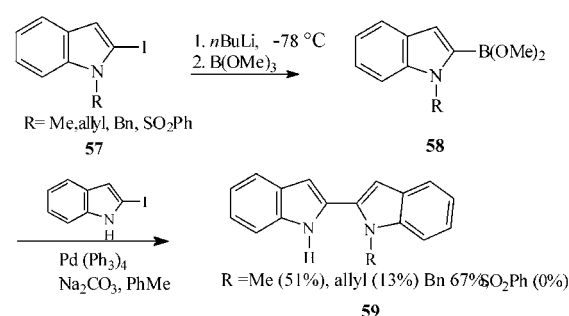
Scheme 14

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). The authors have most recently⁷⁸ extended their investigations by the conversion of borate **53** (Z = Boc) into a pyrido[4,3,b]carbazole moiety characteristic of the anti-tumour alkaloid ellipticine.



Scheme 15

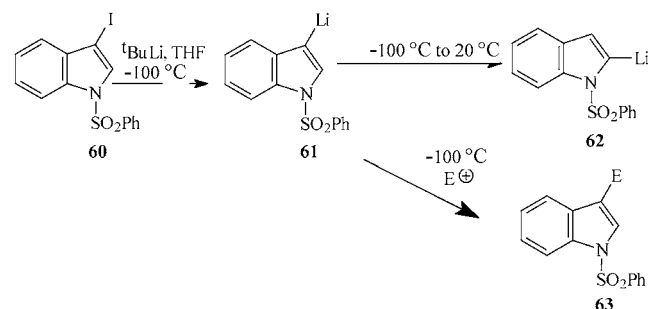
A variety of natural products that show anti-tumour activity as well as protein kinase C inhibitory properties contain an indolecarbazole motif in their structure. In their 1997 studies Merlic and his group^{79,80} prepared the unsymmetrical 2,2'-biindole **59**, as substrates for a pivotal benzannulation 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

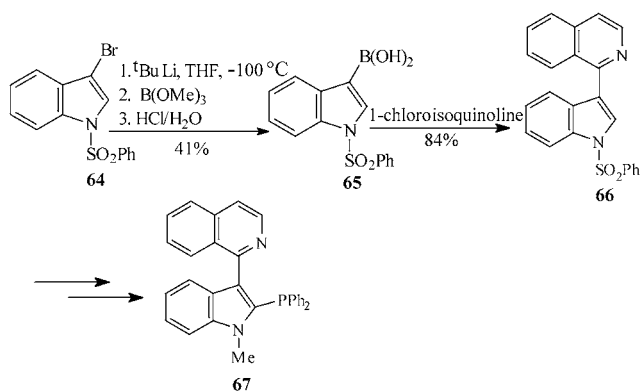
2.3.2 Indol-3-ylboronic Acid

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.⁷⁴ The authors reported that above this temperature complete rearrangement of the previously unknown 3-lithio-1-(phenylsulfonyl)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, Brown⁸¹ extended the range of ligand structures to include the corresponding indolyl analogue **67**. His synthesis involved the Suzuki cou-



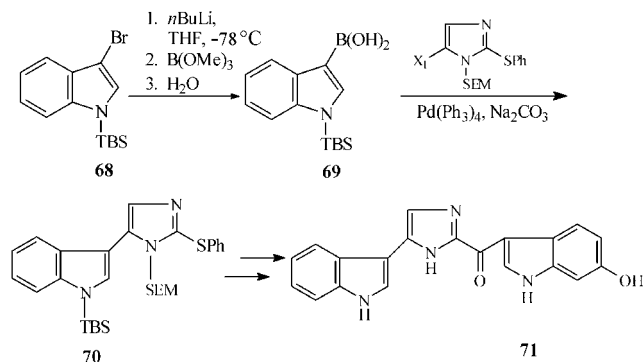
Scheme 18

pling between boronic acid **65** with 1-chloroisoquinoline to afford the biaryl 3-(1'-isoquinoyl)-1-phenylsulfonyl-indole **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 subsequent coupling reaction proved straightforward yielding **66** in 84% yield.

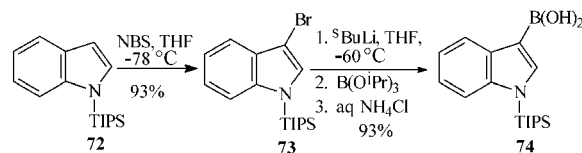
In contrast to this synthesis, where the need to maintain a temperature below $-100\text{ }^{\circ}\text{C}$ during the metal-halogen exchange is of paramount importance in order to prevent isomerisation to the 2-lithiated species, the reaction involving **68**, featuring an alternative N-protecting group, was considerably less temperature sensitive. Thus in his synthesis of the anti-viral/anti-tumour bis(indolyl)imidazole topsentin (**71**) Ohta⁷⁵ carried out a lithium-halogen exchange upon the N-TBS protected indole **68**, at $-78\text{ }^{\circ}\text{C}$, 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 purification in the subsequent coupling reaction with 5-bromo-2-phenylthio-1-[2-(trimethylsilyl)-ethoxy]methyl-1*H*-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 reactions, is seen in the Hoerrner synthesis of boronic acid



Scheme 19

74⁸³ (Scheme 20). This was then coupled to a (*Z*)-vinyl bromide and this adduct subjected to asymmetric hydrogenation in an effort to establish a flexible and novel route to β -methyltryptophans. *N*-TIPS-3-bromoindole (**73**), efficiently formed by the NBS bromination of indole **72**, was then converted to the boronic acid **74** in a 93% yield using standard conditions at $-60\text{ }^{\circ}\text{C}$.

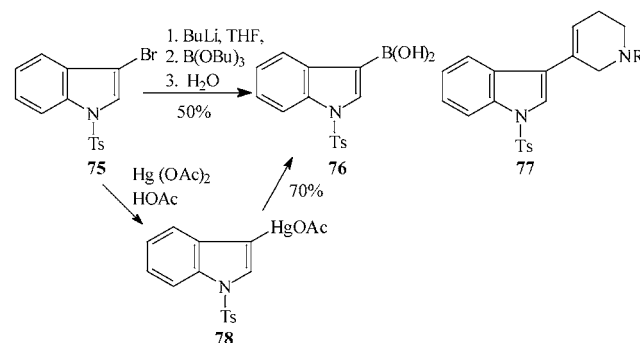


Scheme 20

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 ring **77** Martin^{72,84} reported the synthesis of 1-tosyl-3-indoleboronic acid **76** in 50% yield using standard metal-halogen exchange conditions (Scheme 21). He was, however, able to improve the yield considerably by using a mercuration-boronation techniques.⁸⁵



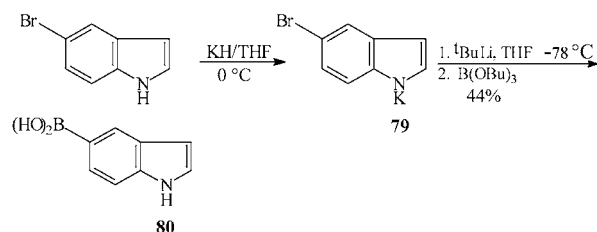
Scheme 21

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-salt^{76,77} 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 studies⁸⁷ were designed as potential serotonin agonists and antagonists.



Scheme 22

A similar methodology, to that detailed above, was used by Roussi and his team⁷⁶ 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 potassium salt described by Rapoport.⁷⁷

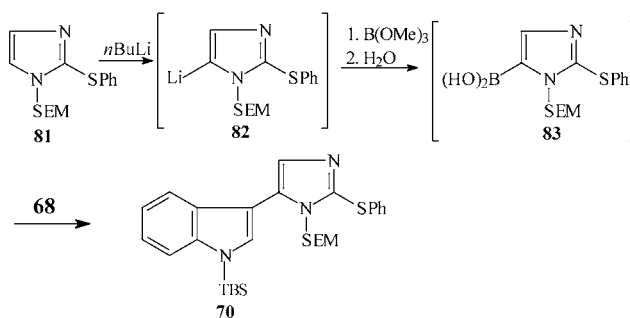
2.4 Imidazolylboronic Acids

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**) Ohta⁷⁵ 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 imidazolyl halide with indolylboronic acid **69** (Scheme 19) the second route involved the condensation of the indolyl halide **68** with the imidazolylboronic acid **83** (Scheme 23). Imidazolylboronic acid **83** was in turn synthesised from the 1,2-protected imidazole **81**^{88,89} via lithiation and treatment of the lithiated species **82** with trimethyl borate followed by aqueous hydrolysis. Although the yield of the boronic acid **83** 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 **68**, 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 **68** rather than failure of the coupling reaction to take place efficiently.

2.5 Quinolinyboronic Acids

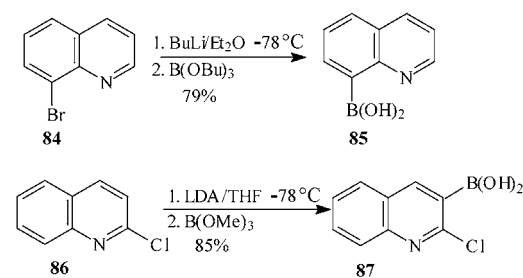
Quinol-8-ylboronic acid **85** (Scheme 24) was first synthesised as long ago as 1959 where its use as selective catalysts for certain base catalysed reactions was under scrutiny.⁹⁰ Although the authors were successful in obtaining this particular acid attempts at the synthesis of iso-



Scheme 23

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.

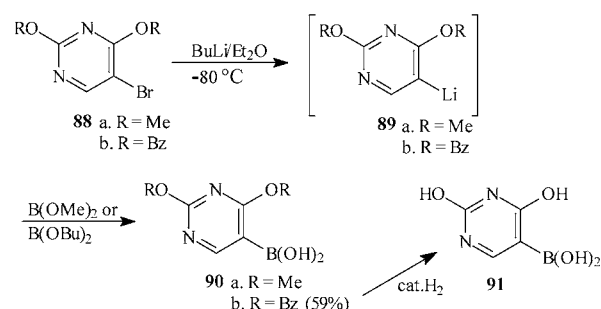
More recently however Queguiner reported the synthesis of 2-chloroquinolin-3-ylboronic acid (**87**) in good yield from 2-chloroquinoline (**86**).⁹¹ In this example chlorine appears to function as an *ortho*-directing metallating group (DMG).⁹²



Scheme 24

2.6 Pyrimidinylboronic Acids

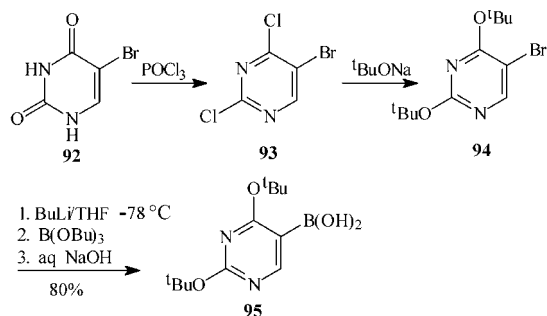
The role of localised organoboron reagents as potential anti-tumour reagents precipitated the earliest syntheses of the pyrimidinylboronic acids **90a**, **90b** and **91** by Liao⁹³ in 1964 (Scheme 25). The pyrimidinyl ethers **88a,b** were formed, using a standard protocol,⁹⁴ lithiated, using Langley's procedure⁹⁵ and reacted in situ with either trimethyl borate or tributyl borate. As **90b** proved to be rather unstable it was converted to the more stable 5-uracilboronic acid **91** by a catalytic hydrogenation process.



Scheme 25

In connection with his work on novel antiviral compounds Gronowitz^{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 **95** with π -electron deficient heterocyclic halides took place in good to excellent yields (Scheme 26).



Scheme 26

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

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

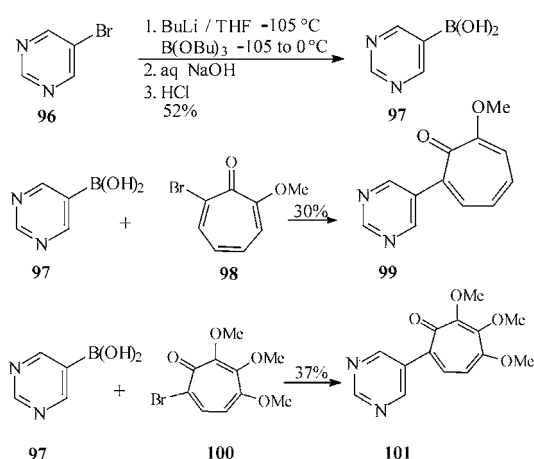
In a recent study into the syntheses of novel potent inositol monophosphatase (IMPase) inhibitors Pietre was successful in the coupling of the same acid, pyrimidin-5-ylboronic acid (**97**), to the tropolone derivatives **98** and **100** in modest yields to afford **99** and **101** (Scheme 27).¹⁰⁰

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.²⁰

3 Sulfur Heterocycles

3.1 Thienylboronic 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

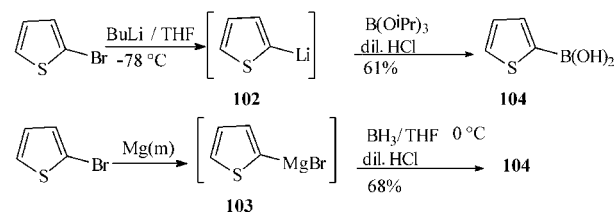


Scheme 27

good processing qualities.¹⁰¹ These industrially important applications made the synthesis of thiophenylboronic acids one of the first heterocyclic boronic acids to be undertaken.

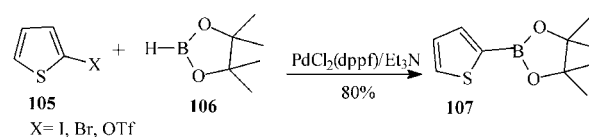
3.1.1 2-Thienylboronic Acid

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



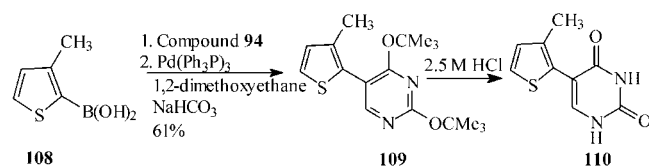
Scheme 28

More recently, Masuda has revealed the utility of pinacolborane **106** for the convenient synthesis of arylboronates.^{104,105} As both **106** and the pinacolboronates are air and moisture insensitive as well as tolerant to a variety of functional groups they represent a useful addition to this repertoire of methodologies (Scheme 29). The palladium catalysed coupling reaction between the dialkoxyhydroborane **106** with a wide range of aryl halides and triflates derivatives provided the corresponding arylboronates in good yield. In their studies the authors were able to secure the thienylboronate **107** in a yield of 80% from the coupling of **106** with the thienyl derivatives **105**.



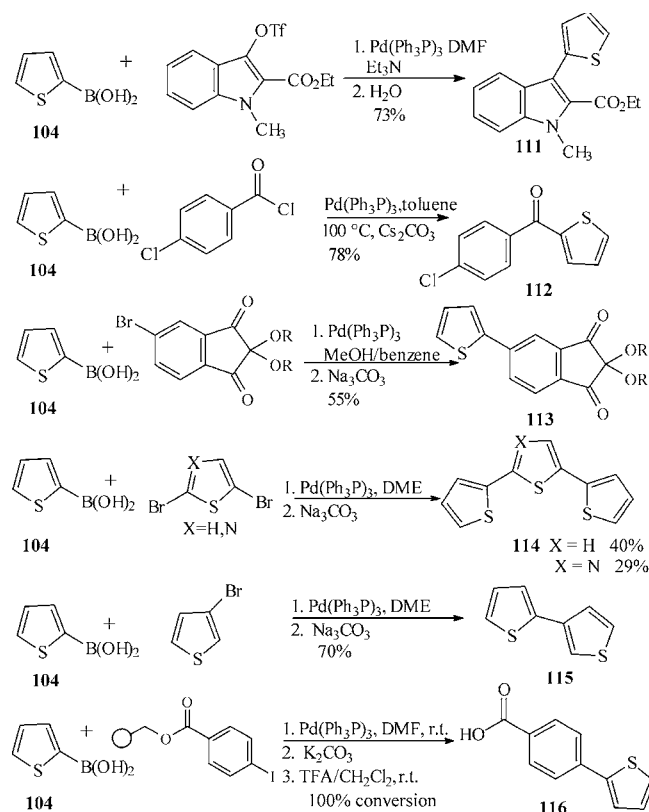
Scheme 29

In his syntheses of various 5-substituted uracils Gronowitz^{96,97} successfully coupled 3-methyl-2-thienylboronic acid (**108**) 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 anti-viral 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**,¹⁰⁶ ketone **112**,¹⁰⁷ the ninhydrin analogue **113**,¹⁰⁸ terheterocycles **114**,¹⁰⁹ unsymmetrical bithienyls **115**¹¹⁰ and the thienyl benzoate **116**³⁷ generated via a resin bound Suzuki coupling reaction (Scheme 31).

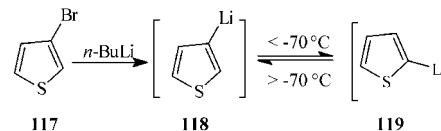


Scheme 31

3.1.2 3-Thienylboronic Acids

The formation of 3-thienylboronic acid proved to be far from straightforward and the synthesis of 3-lithiothiophene (**118**) was first reported by Gronowitz as re-

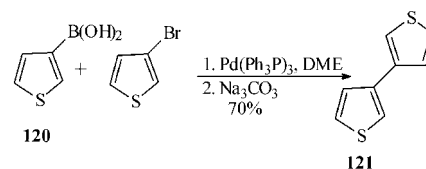
cently as 1974.¹¹¹ The 3-isomer was observed to readily equilibrate to the 2-isomer **119** as the temperature was raised to 0 °C^{112,113} to afford a product mixture (Scheme 32). The procedure consisted of a metal-halogen exchange reaction between 3-bromothiophene **117** and butyllithium in a polar 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.¹¹⁴ From these studies the synthesis of 3-lithiothiophene (**118**) was achieved selectively, at ambient temperatures, using a solvent couple consisting of hexane-THF (10:1).

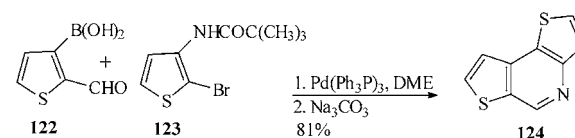
Lawesson¹¹⁵ synthesised thien-3-ylboronic acid (**120**) by exposing the organolithium species **118** to a suitable trialkylborate at -60 °C. The coupling of 3-thienylboronic acid **120** with 3-bromothiophene provided the symmetrical bithiophene (**121**) in good yield¹¹⁰ (Scheme 33).



Scheme 33

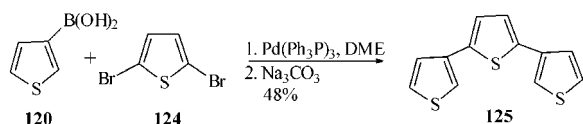
The ready availability of thien-3-ylboronic acid (**120**) and its various derivatives **122** and **127** has created great interest, particularly from the laboratories of Gronowitz, and led to their use in the formation of a variety of molecular types.

The bisthienopyridine (**124**) was synthesised in one-pot by the Pd(0) catalysed coupling of 2-formylthien-3-ylboronic acid (**122**) with the carbamate **123** (Scheme 34).¹¹⁶ The authors reported the synthesis of six out of the possible nine isomeric bisthienopyridines, each containing the same phenanthrene annelation pattern, using these procedures.



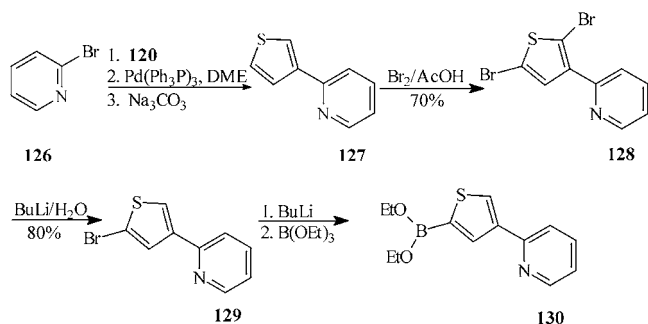
Scheme 34

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.¹¹⁷ 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.¹⁰⁹



Scheme 35

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).¹¹⁸ 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-hydroxythiophene systems.

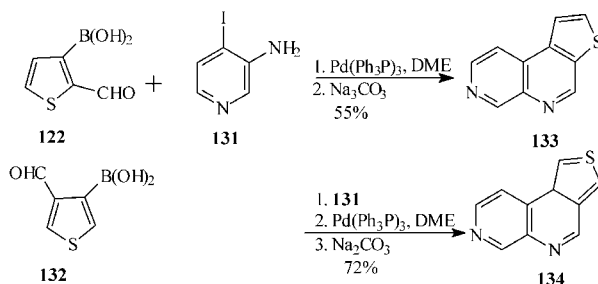


Scheme 36

The successful Suzuki coupling reactions between 2-formylthien-3-ylboronic acid (**122**) and 3-amino-4-iodopyridine (**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).¹¹⁹

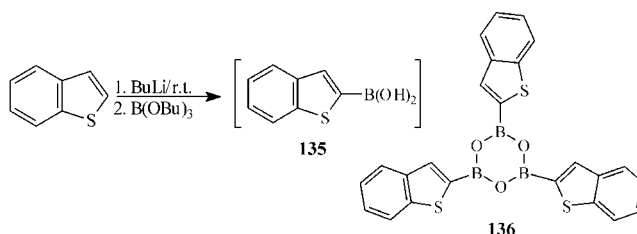
3.2 Benzothienylboronic Acids

Benzothien-2-ylboronic acid (**135**) has been shown to act as a potent inhibitor of the β -lactamase enzyme AmpC in *E. Coli* bacteria^{14,120} thus providing an alternative treat-



Scheme 37

ment against microbial resistance to antibiotics. Iddon¹²¹ 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).



Scheme 38

4 Oxygen Heterocycles

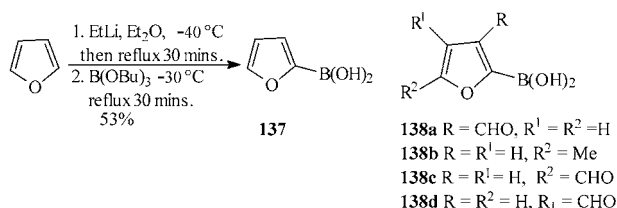
4.1 Furylboronic Acids

The furanyl motif is found as a component in a wide variety of natural products of both marine and terrestrial origin^{122,123} furthermore 3,4-disubstituted furans feature as key intermediates in organic syntheses.¹²⁴

From electronegativity considerations, electrophilic substitution and metallation reactions occur most readily at the α -position. The reactivity differences between α - and β -furylboronic acids have been the subject of previous reports.^{125,126}

4.1.1 2-Furylboronic Acids

Although this is commercially available as a reagent the synthesis of 2-furylboronic acid (**137**) was in fact accomplished as long ago as 1975 via the direct metallation of furan with ethyllithium (Scheme 39).¹²⁵



Scheme 39

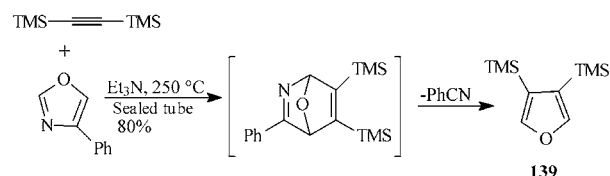
The authors of this first synthesis reported upon the physicochemical differences that existed between the array of 2-furylboronic acid derivatives **138a–d**.¹²⁶

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**.

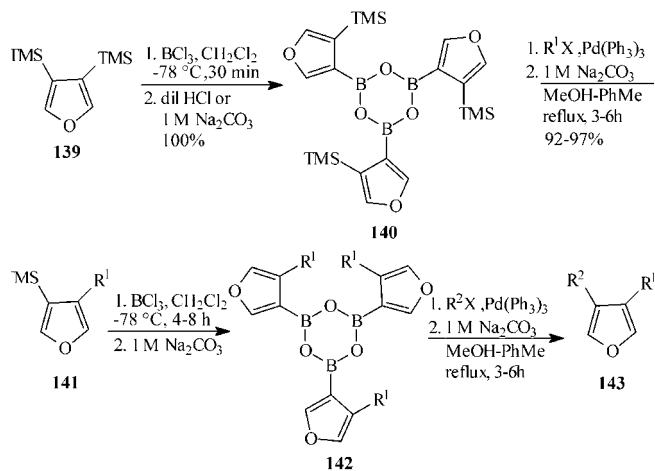
The synthetically useful furan **139** was conveniently obtained through a Diels–Alder reaction between 4-phenyl-oxazole and bis(trimethylsilyl)acetylene (Scheme 40).



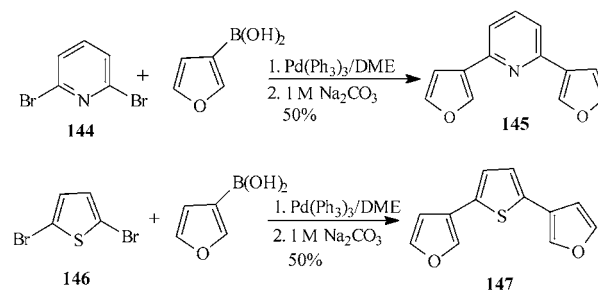
Scheme 40

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).



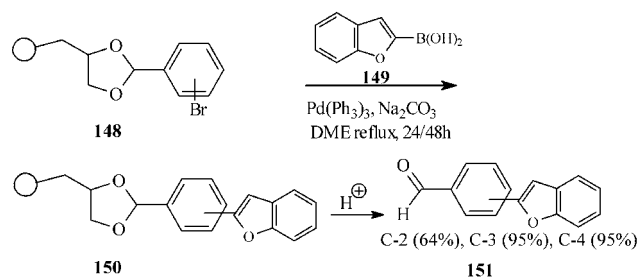
Scheme 41



Scheme 42

4.2 Benzofuranylboronic Acids

Snieckus recently highlighted the inroads that his team had made into the use of polymer supported Suzuki coupling reactions^{19,128} using the Merrifield resin bound bromobenzene-acetal Leznoff linker^{129,130} **148**.

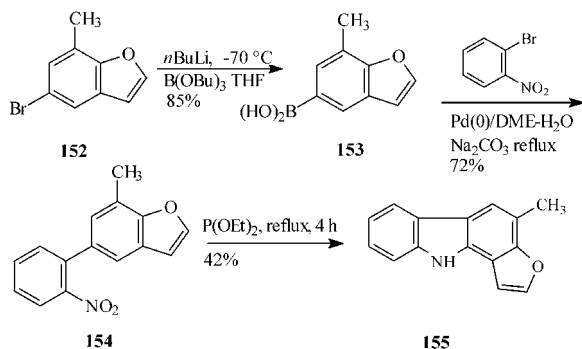


Scheme 43

The polymer supported cross-coupling reaction was accomplished with benzofuran-2-ylboronic acid (**149**). This provided the heteroaromatics **150**, which upon acetal hydrolysis, and liberation from the support medium, delivered the heterobiaryls **151** in excellent yields (Scheme 43).

Furostifoline **155**, a furo[3,2-*a*]carbazole alkaloid, was only isolated from *Murraya euchrestifolia* as recently as 1990.¹³¹ Its structural similarity to current indolo-isoquinoline antiretroviral reagents has aroused some interest and

the first synthesis was recently reported.¹³² Timari¹³³ recently disclosed his total synthesis using boronic acid chemistry (Scheme 44). Benzofuran **152** was synthesised in good yield via a known procedure¹³⁴ and converted to the boronic acid **153** using a conventional lithium–halogen exchange reaction. Coupling of **153** with 2-bromonitrobenzene 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

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, despite attempts at their synthesis from a number of different laboratories the synthesis of thiazole, oxazolyl, imidazolyl, pyrazinyl and other boronic acids remain elusive. Fortunately in most cases the corresponding haloderivative 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.

Acknowledgment

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References

- (1) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513.
- (2) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
- (3) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.
- (4) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.
- (5) Darses, S.; Jeffery, T.; Genet, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1996**, *37*, 3857.

- (6) Willis, D. M.; Strongin, R. M. *Tetrahedron Lett.* **2000**, *41*, 6271.
- (7) Manickam, G.; Schluter, A. D. *Synthesis* **2000**, 442.
- (8) Goodby, J. W.; Hird, M.; Lewis, R. A.; Toyne, K. J. *J. Chem. Soc., Chem. Commun.* **1996**, 2719.
- (9) Maes, B. U.; Lemiere, G. L. F.; Dommissie, R.; Augustyns, K.; Haemers, A. *Tetrahedron* **2000**, *56*, 1777.
- (10) Ren, D.; McClelland, R. A. *Can. J. Chem.* **1998**, *76*, 78.
- (11) Adams, J.; Elliott, P. *J. Oncogene* **2000**, *19*, 6687.
- (12) Groviak, M. P. *Am. J. of Therapeutics* **2001**, *8*, 321.
- (13) Westmark, P. R.; Smith, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 9343.
- (14) Weston, G. S.; Blazquez, F.; Baquero, F.; Shoichet, B. K. *J. Med. Chem.* **1998**, *41*, 4577.
- (15) James, T. D.; Sandanayake, K.; Iguchi, R.; Shinkai, S. *J. Am. Chem. Soc.* **1995**, *117*, 8982.
- (16) Products for Suzuki Coupling *Aldrich ChemFiles* **2001**, 1
- (17) Carboni, B.; Pourbaix, C.; Carreaux, F.; Deleuze, H.; Maillard, B. *Tetrahedron Lett.* **1999**, *40*, 7979.
- (18) Tois, J.; Franzen, R.; Aitio, O.; Laakso, I.; Huuskonen, J.; Taskinen, J. *Comb. Chem. High Throughput Screening* **2001**, *4*, 521.
- (19) Chamoin, S.; Houldsworth, S.; Kruse, C. G.; Bakker, I.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4179.
- (20) Piettre, S. R.; Baltzer, S. *Tetrahedron Lett.* **1997**, *38*, 1197.
- (21) Arimori, S.; Hartley, J. H.; Bell, M. L.; Oh, C. S.; James, T. D. *Tetrahedron Lett.* **2000**, *41*, 10291.
- (22) Minato, A.; Tamao, K.; Hayashi, T.; Suzuki, K.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 5319.
- (23) Morris, G. A.; Nguyen, S. T. *Tetrahedron Lett.* **2001**, *42*, 2093.
- (24) Filippini, L.; Gusmeroli, M.; Riva, R. *Tetrahedron Lett.* **1992**, *33*, 1755.
- (25) Alvarez, A.; Guzman, A.; Ruiz, A.; Velarde, E. *J. Org. Chem.* **1992**, *57*, 1653.
- (26) Lohse, O.; Thevenin, P.; Waldvogel, E. *Synlett* **1999**, 45.
- (27) Stavenuiter, J.; Hamzink, M.; Van der Hulst, R.; Zomer, G.; Westra, G.; Kriek, E. *Heterocycles* **1987**, *26*, 2711.
- (28) Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 4285.
- (29) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885.
- (30) Yang, Y.; Martin, A. R. *Heterocycles* **1992**, *34*, 1395.
- (31) Mikhailov, B. M.; Kozminskaya, T. K. *Izv. Akad. Nauk. USSR* **1959**, 76.
- (32) Ishikura, M.; Mano, T.; Oda, I.; Terashima, M. *Heterocycles* **1984**, *22*, 2471.
- (33) Wakabayashi, S.; Sugihara, Y.; Takakura, K.; Murata, S.; Tomoika, H.; Ohnishi, S.; Tatsumi, K. *J. Org. Chem.* **1999**, *64*, 6999.
- (34) Murafuji, T.; Mouri, R.; Sugihara, Y.; Takakura, K.; Mikata, Y.; Tano, S. *Tetrahedron* **1996**, *52*, 13933.
- (35) Toyota, S.; Oki, M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1832.
- (36) Ishikura, M.; Kamada, M.; Ohta, T.; Terashima, M. *Heterocycles* **1984**, *22*, 2475.
- (37) Guiles, J. W.; Johnson, S. G.; Murray, W. V. *J. Org. Chem.* **1996**, *61*, 5169.
- (38) Fischer, F. C.; Havinga, E. *Recueil* **1965**, *84*, 439.
- (39) Fischer, F. C.; Havinga, E. *Recueil* **1974**, *93*, 21.
- (40) Mohler, L. K.; Czarnik, A. W. *J. Am. Chem. Soc.* **1993**, *115*, 2998.
- (41) Lamothe, M.; Pauwels, P. J.; Belliard, K.; Schambel, P.; Halazy, S. *J. Med. Chem.* **1997**, *40*, 3542.
- (42) Albers, W. A.; Canters, G. W.; Reedijk, J. *Tetrahedron* **1995**, *51*, 3895.
- (43) Coudret, C. *Synth. Commun.* **1996**, *26*, 3543.

- (44) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.
- (45) Cai, D.; Hughes, D. L.; Verhoeven, T. R. *Tetrahedron Lett.* **1996**, *37*, 2537.
- (46) Trecourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Queguiner, G. *Tetrahedron* **2000**, *56*, 1349.
- (47) Pandey, G.; Bagul, T. D.; Trusar, D.; Sahoo, A. K. *J. Org. Chem.* **1998**, 760.
- (48) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323.
- (49) Ahab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1993**, *34*, 2127.
- (50) Trecourt, F.; Queguiner, G. *J. Chem. Res., Miniprint* **1982**, *3*, 912.
- (51) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151.
- (52) Radinov, R.; Haimova, M.; Simova, E. *Synthesis* **1986**, 886.
- (53) Bouillon, A.; Lancelot, J. C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369.
- (54) Mallet, M.; Marsais, F.; Branger, G.; Queguiner, G. *J. Organomet. Chem.* **1990**, *382*, 319.
- (55) Marsais, F.; Pineau, P.; Nivolliers, F.; Turck, A.; Godard, A.; Queguiner, G. *J. Org. Chem.* **1992**, *52*, 565.
- (56) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859.
- (57) Mongin, F.; Queguiner, G. *Tetrahedron* **2001**, *57*, 4059.
- (58) Queguiner, G. *J. Heterocycl. Chem.* **2000**, *37*, 615.
- (59) Martina, S.; Enkelmann, V.; Wegner, G.; Schluter, A.-D. *Synthesis* **1991**, 613.
- (60) Alvarez, A.; Guzman, A.; Ruiz, A.; Velande, E.; Muchowski, J. M. *J. Org. Chem.* **1992**, *57*, 1653.
- (61) Greib, J. G.; Ketcha, D. M. *Synth. Commun.* **1995**, *25*, 2145.
- (62) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 296; *Angew. Chem.* **1984**, *96*, 291.
- (63) Rawal, V. H.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6141.
- (64) Martina, S.; Schluter, A.-D. *Macromolecules* **1992**, *25*, 3607.
- (65) Johnson, C. N.; Stemp, G.; Anand, N.; Stephen, S. C.; Gallagher, T. *Synlett* **1998**, 1025.
- (66) Furstner, A.; Grabowski, J.; Lehmann, C. W. *J. Org. Chem.* **1999**, *64*, 8275.
- (67) Gharepure, M.; Stoller, A.; Bellamy, F.; Firna, G.; Snieckus, V. *Synthesis* **1991**, 1079.
- (68) Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.
- (69) Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317.
- (70) Nagai, Y.; Kobayashi, K.; Toi, H.; Aoyama, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2965.
- (71) Conway, S. C.; Gribble, G. W. *Heterocycles* **1990**, *30*, 627.
- (72) Zheng, Q.; Yang, Y.; Martin, A. R. *Heterocycles* **1994**, *37*, 1761.
- (73) Ishikura, M.; Agata, I.; Katagiri, N. *J. Heterocycl. Chem.* **1999**, *36*, 873.
- (74) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757.
- (75) Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887.
- (76) Carbonnelle, A.-C.; Zamora, E. G.; Beugelmans, R.; Roussi, G. *Tetrahedron Lett.* **1998**, *39*, 4467.
- (77) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106.
- (78) Ishikura, M.; Hino, A.; Yaginuma, T.; Agata, I.; Katagiri, N. *Tetrahedron* **2000**, *56*, 193.
- (79) Merlic, C. A.; McInnes, D. M.; You, Y. *Tetrahedron Lett.* **1997**, *38*, 6787.
- (80) Merlic, C. A.; McInnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 7661.
- (81) Claridge, T. D. W.; Long, J. M.; Brown, J. M.; Hibbs, D.; Hursthouse, M. B. *Tetrahedron* **1997**, *53*, 4035.
- (82) Schlosser, M. J. *Organometal. Chem.* **1967**, *8*, 9.
- (83) Hoerner, R. S.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 3455.
- (84) Zheng, Q.; Yang, Y.; Martin, A. R. *Tetrahedron Lett.* **1993**, *34*, 2235.
- (85) Breuer, S. W.; Thorpe, F. G. *Tetrahedron Lett.* **1974**, 371.
- (86) Yang, Y.; Martin, A. R.; Nelson, D. L.; Regan, J. *Heterocycles* **1992**, *34*, 1169.
- (87) Yang, Y.; Martin, A. R. *Heterocycles* **1992**, *34*, 1395.
- (88) Horenstein, B. A.; Zabinski, R. F.; Schramm, V. L. *Tetrahedron Lett.* **1993**, *34*, 7213.
- (89) Evans, G. B.; Furneaux, R. H.; Gainsford, G. J.; Schramm, V. L.; Tyler, P. C. *Tetrahedron* **2000**, *56*, 3053.
- (90) Letsinger, R. L.; Dandagaonker, S. H. *J. Am. Chem. Soc.* **1959**, *81*, 498.
- (91) Marsais, F.; Godard, A.; Queguiner, G. *J. Heterocycl. Chem.* **1989**, *26*, 1589.
- (92) Green, L.; Chauder, B.; Snieckus, V. *J. Heterocycl. Chem.* **1999**, *36*, 1453.
- (93) Liao, T. K.; Podrebarac, E. G.; Cheng, C. C. *J. Am. Chem. Soc.* **1964**, *86*, 1869.
- (94) Hilbert, G. E.; Jansen, E. F. *J. Am. Chem. Soc.* **1934**, *56*, 134.
- (95) Langley, B. W. *J. Am. Chem. Soc.* **1956**, *78*, 2136.
- (96) Gronowitz, S.; Hornfeldt, A.-B.; Kristjansson, V.; Musil, T. *Chem. Scr.* **1986**, *26*, 305.
- (97) Peters, D.; Hornfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1990**, *27*, 2165.
- (98) Wellmar, U.; Hornfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, *32*, 1159.
- (99) Wellmar, U.; Hornfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1996**, *33*, 409.
- (100) Piettre, S. R.; Andre, C.; Chanal, M.-C.; Ducep, J.-B.; Lesur, B.; Piriou, F.; Raboisson, P.; Rondeau, J.-M.; Schelcher, C.; Zimmerman, P.; Ganzhorn, A. J. *J. Med. Chem.* **1997**, *40*, 4208.
- (101) *Handbook of Conducting Polymers*; Skotheim, T. A., Ed.; Marcel Dekker: New York, **1986**.
- (102) Cullen, K. E.; Sharp, J. T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2565.
- (103) Kabalka, G. W.; Sastry, U.; Sastry, K. A. R.; Knapp, F. K. Jr.; Srivastava, P. C. *J. Organomet. Chem.* **1983**, *259*, 269.
- (104) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458.
- (105) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164.
- (106) Andrieu-Malapel, B.; Merour, J.-Y. *Tetrahedron* **1998**, *54*, 11079.
- (107) Haddach, M.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 3109.
- (108) Hark, R. R.; Hauze, D. B.; Petrovskaja, O.; Joullie, M. M. *Tetrahedron Lett.* **1994**, *43*, 7719.
- (109) Gronowitz, S.; Peters, D. *Heterocycles* **1990**, *30*, 645.
- (110) Gronowitz, S.; Bobosik, V.; Lawitz, K. *Chem. Scr.* **1984**, *23*, 120.
- (111) Gronowitz, S.; Cederlund, B.; Hornfeldt, A.-B. *Chem. Scr.* **1974**, *5*, 217.
- (112) Ritter, S. K.; Nofle, R. E. *Chem. Mater.* **1992**, *58*, 7026.
- (113) Moses, P.; Gronowitz, S. *Arkiv. Kemi* **1961**, *18*, 119.
- (114) Wu, X.; Chen, T.-A.; Zhu, L.; Rieke, R. D. *Tetrahedron Lett.* **1994**, *35*, 3673.
- (115) Lawesson, S.-O. *Arkiv Kemi* **1957**, *11*, 387.
- (116) Yang, Y.; Hornfeldt, A.-B.; Gronowitz, S. *Chem. Scr.* **1988**, *28*, 275.
- (117) Carpita, A.; Rossi, R. *Gazz. Chim. Ital.* **1985**, *115*, 575.

- (118) Zhang, Y.; Hornfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, 32, 435.
- (119) Malm, J.; Rehn, B.; Hornfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1994**, 31, 11.
- (120) Courvalin, P. *J. Antimicrob. Chemother.* **1996**, 37, 855.
- (121) Dickenson, R. P.; Iddon, B. *J. Chem. Soc. (C)* **1970**, 1926.
- (122) Cambie, R. C.; Craw, P. A.; Stone, M. J. *J. Nat. Prod.* **1988**, 51, 293.
- (123) Hirsch, S.; Kashman, Y. *J. Nat. Prod.* **1988**, 51, 1243.
- (124) Eberbach, W.; Laber, N.; Bussenius, J.; Fritz, H.; Rihs, G. *Chem. Ber.* **1993**, 126, 975; and references cited therein.
- (125) Roques, B. P.; Florentin, D.; Callanquin, M. *J. Heterocycl. Chem.* **1975**, 12, 195.
- (126) Florentin, D.; Fournie-Zaluski, M. C.; Callanquin, M.; Roques, B. P. *J. Heterocycl. Chem.* **1976**, 13, 1265.
- (127) Song, Z. Z.; Ho, M. S.; Wong, H. N. C. *J. Org. Chem.* **1994**, 59, 3917.
- (128) Green, L.; Chauder, B.; Snieckus, V. *J. Heterocycl. Chem.* **1999**, 36, 1453.
- (129) Leznoff, C. C.; Wong, J. Y. *Can. J. Chem.* **1973**, 51, 3756.
- (130) Leznoff, C. C.; Sywanyk, W. *J. Org. Chem.* **1977**, 42, 3203.
- (131) Ito, C.; Furukawa, H. *Chem. Pharm. Bull.* **1990**, 38, 1548.
- (132) Knolker, H.-J.; Frohner, W. *Tetrahedron Lett.* **1996**, 37, 9183.
- (133) Soos, T.; Timari, G.; Hajos, G. *Tetrahedron Lett.* **1999**, 40, 8607.
- (134) Rohrkasten, R.; Konrad, M. *Methoden der Organischen Chemie, Houben-Weyl*, E6b; Kreher, R. P., Ed.; Thieme: Stuttgart, **1994**, 94.