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Intramolecular (directed) electrophilic C–H borylation

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The intramolecular C–H borylation of (hetero)arenes and alkenes using electrophilic boranes is a powerful transition metal free methodology for forming C–B bonds. These C–H borylation reactions are preceded by intermolecular bond (both dative and covalent) formation, with examples proceeding *via* initial C–B and N–B bond formation dominating this field thus both are discussed in depth herein. Less prevalent intramolecular electrophilic C–H borylation reactions that proceed by intermolecular O–B, S–B and P–B bond formation are also summarised. Mechanistic studies are presented that reveal two mechanisms for C–H borylation, (i) electrophilic aromatic substitution (prevalent with B–X electrophiles); (ii) σ-bond metathesis mediated (prevalent with B–H and B–R electrophiles). To date, intramolecular electrophilic C–H borylation is utilised mainly for accessing boron containing conjugated organic materials, however recent developments, summarized herein alongside early studies, have highlighted the applicability of this methodology for forming synthetically versatile organo-boronate esters and boron containing bioactives. The multitude of synthetic procedures reported for intramolecular electrophilic C–H borylation contain many common features and this enables key requirements for successful C–H borylation and the factors effecting regioselectivity and substrate scope to be identified, discussed and summarized.

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1. Introduction

The formation of (sp^2)C–B bonds is of significant import across many fields. Historically, this is due to the power of organoboranes in functional group transformations coupled with their low toxicity and ease of handling (relative to other organometallic reagents).[1]

The past twenty years in particular have seen the utility of organoboranes expand with the incorporation of (sp^2)C–B units now established as a useful function imparting tool in sensors[2] and organic materials (Fig. 1).[3] Concomitantly, there has been a number of boracycles containing (sp^2)C–B units identified as bioactive molecules, such as diazaborines and benzoxaboroles including commercialised drugs such as tavaborole (Fig. 1).[4]

This broad importance has led to the development of many methods to form (sp^2)C–B bonds. While the most prevalent synthetic route proceeds *via* metalation of an organohalide and

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Jürgen Pahl obtained both his BSc and MSc in chemistry at the Friedrich-Alexander Universität Erlangen-Nürnberg. At the same university he focused his studies on group 2 coordination chemistry where he received his PhD degree 2019 under the supervision of Professor Sjoerd Harder. In 2019 he joined the Ingleson Group at the University of Edinburgh where he is investigating new methods for directed electrophilic borylation.

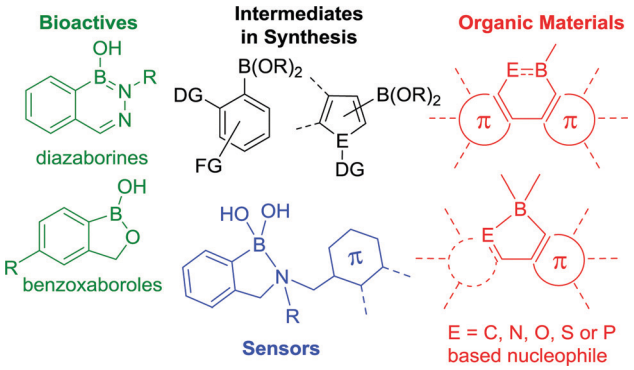
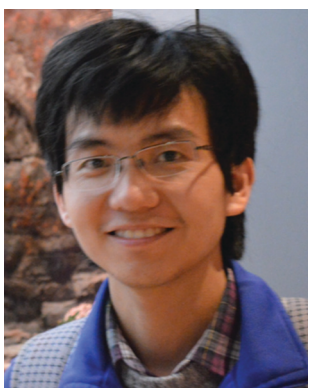


Fig. 1 Applications of (sp^2)C–B containing molecules focusing on general structures accessed (or potentially accessible) by intramolecular electrophilic C–H borylation. DG = directing group, FG = functional group.

trapping the organometallic product with $B(OR)_3$, a more efficient approach is the conversion of C–H to C–B. This has been achieved predominantly through (sp^2)C–M intermediates *via*: (i) C–H deprotonation (*e.g.* with an organolithium) then *in situ* trapping with a $B(OR)_3$ electrophile and (ii) transition metal catalysed C–H borylation, with iridium catalysis being the most powerful example of the latter.[5] C–H acidity and steric factors dominate selectivity *via* metal mediated C–H borylation routes (i) and (ii). An alternative route that avoids C–M containing intermediates is electrophilic C–H borylation. This affords borylated products often under combined steric and electronic control and *via* an S_EAr mechanism.[6] Notably, these three C–H borylation routes generally do not lead to the formation of *ortho* substituted arylboranes. Instead substrates containing directing groups (DGs) are required, *e.g.* to enable *ortho* C–H metalation with subsequent C–M to C–B conversion forming *ortho* borylated products. For more on metal mediated directed C–H borylation the reader is directed to recent reviews.[7]

An alternative approach to access *ortho*-borylated compounds is directed electrophilic C–H borylation. This transformation proceeds *via* an initial intermolecular step that forms an E–B bond (E = C, N, O, S, P), followed by intramolecular electrophilic C–H borylation. Since its discovery in the 1950s this transformation has been most widely used to make boron containing organic materials containing three and four coordinate boron centres.[8] While its use is well established in the organic materials field, intramolecular electrophilic C–H borylation is much more rarely utilised to access organoboranes for use in functional group transformations or for accessing the boracycles found in sensors and bioactive molecules. This is in part due to the misconception that C–H borylation always requires forcing conditions and reactive catalysts (*e.g.* $AlCl_3$). In fact, the conditions required to effect C–H borylation depend on multiple factors and there are many facile (*e.g.* proceeding within 1 h at room temperature without catalyst) intramolecular electrophilic C–H borylation reactions reported. Key variables effecting the reaction conditions required for intramolecular electrophilic C–H borylation include: the type of directing group, the nucleophilicity of the (hetero)arene being functionalised, the nature (*e.g.* ring size) of the boracycle being formed, the electrophilicity of the borane Lewis acid, the presence of an exogenous Brønsted base *etc.* This review focuses on identifying, discussing and summarizing the key factors required for intramolecular electrophilic (sp^2)C–H borylation. It aims to increase the understanding of this topic and thereby facilitate the wider utilisation of directed electrophilic C–H borylation. To maintain focus on these principle objectives this review omits a number of other directed borylation reactions, such as hydroboration[9] and (sp^3)C–H borylation.[10] Throughout the major focus is on discussing the conditions required (and the underlying reasons) for successful directed electrophilic C–H borylation and highlighting key structure–reactivity relationships. When multiple examples are reported proceeding *via* effectively identical synthetic procedures to access closely related borylated products this review focuses only on the key synthetic observations and does not provide an exhaustive list of products



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M. J. Ingleson

Mike Ingleson received his PhD. in organometallic chemistry in 2004 working with Prof. Andrew S. Weller. He then pursued post-doctoral studies with Prof. Kenneth G. Caulton at Indiana University and with Professor Matthew J. Rosseinsky at the University of Liverpool. He started his independent career at the University of Manchester in 2008 with a Royal Society University Research Fellowship. At Manchester, he was promoted to Reader in 2012 and Full Professor in 2018. He joined the University of Edinburgh in 2019. His research focuses on main group chemistry, and he has a particular fondness for all things boron.

accessed *via* intramolecular electrophilic C–H borylation. Due to a number of commonalities in mechanism and C–H borylation conditions, this review covers the formation of borylated products that are 3 and 4 coordinate at boron.

2. Intramolecular electrophilic C–H borylation: the early years

The pioneering work on N-directed electrophilic C–H borylation comes from the group of Dewar and was developed concomitantly to intermolecular electrophilic C–H borylation.[11] From 1958 onwards Dewar and co-workers published a series of N-directed C–H borylation studies utilising BCl_3 and $PhBCl_2$ with $AlCl_3$ as catalyst to form BN analogues of polycyclic aromatic hydrocarbons (PAHs).[12] For example, compounds **1–3** (Fig. 2) amongst others, were made by combining aniline derivatives with BCl_3 to initially form $ArylN(H)BCl_2$ intermediates post heating (*e.g.* inset Fig. 2).[12,13] The significant B=N multiple bond character in these intermediates considerably reduces the Lewis acidity at boron and thus an additional Lewis acid (*e.g.* $AlCl_3$) was required as a catalyst to generate a more reactive boron electrophile able to effect C–H borylation. In these reports using $AlCl_3$ as a catalyst intramolecular electrophilic C–H borylation was performed under forcing conditions (140–175 °C). However, this temperature is principally required to access the melt phase and it is important to note that subsequently **1** (Y = Cl) was accessed using $BCl_3/AlCl_3$ at a lower temperature by performing the reaction in refluxing benzene.[14] The exact origin of the high barrier for C–B bond formation in these examples is unclear, although it should be noted that in concurrent studies Dewar and co-workers showed that 2-vinyl-anilines undergo C–H borylation, *e.g.* to form **4**, under milder conditions (using $PhBCl_2$ or BCl_3 without $AlCl_3$ C–H borylation proceeded at 80 °C).[15]

The active boron electrophile in these arene-borylation examples will be derived from $AlCl_3$ interacting with either N or Cl in the amido-borane (*e.g.* inset Fig. 2), with species related to the latter proposed as the key electrophiles in intermolecular C–H borylation by Olah and co-workers.[16] Compounds containing $R_2N{=}B(Cl){-}(\mu\text{-}Cl){-}AlCl_3$ and $R_2(AlCl_3)N{-}BCl_2$ units can be viewed as containing borenium cation (three coordinate at boron cationic compounds) type sub-units (though formally they are zwitterionic). For discussions on the role of borenium cations (and their functional equivalents) in intermolecular C–H borylation see recent reviews.[6c,17]

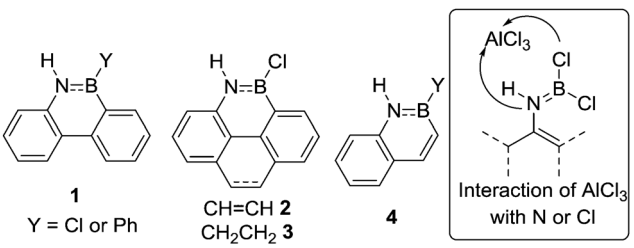


Fig. 2 Select products from Dewar's N-directed electrophilic C–H borylation studies. Inset, the reactivity of $AlCl_3$ with $R(H)NBCl_2$ can be at Cl or N.

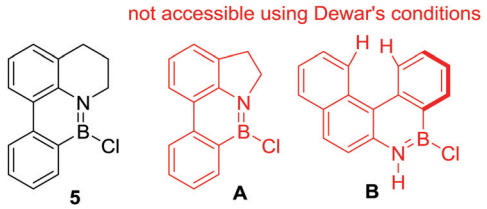
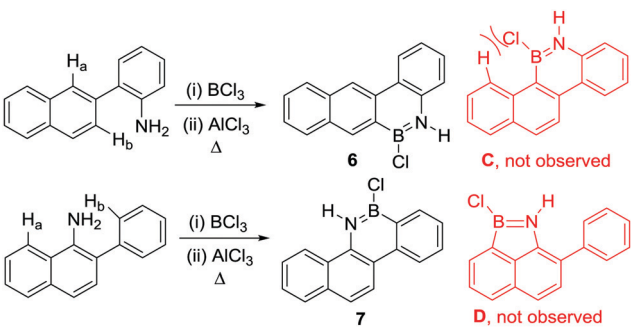


Fig. 3 The sensitivity of Dewar's electrophilic C–H borylation conditions to modifications in ring size and increased dihedral angles.

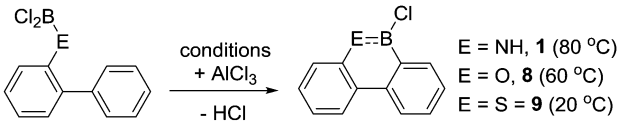
Irrespective of the identity of the active boron electrophile, Dewar's studies highlighted some key considerations controlling the feasibility of R_2N-directed electrophilic C–H borylation. For example, while compound **5** (Fig. 3) is accessible from 8-phenyl-tetrahydroquinoline on reaction with BCl_3 in the presence of $AlCl_3$ at high temperature, its five membered ring analogue, **A**, was not formed under identical conditions.[18] This can be attributed to the smaller bond angles in the five membered N-heterocyclic analogue creating a less favourable geometry for C–H borylation and thus higher reaction barriers. A related rationale can be applied to the fact that compound **B** is not accessible from the parent aniline using Dewar's forcing C–H borylation conditions. In this case steric clash in the fjord region will enforce non-planarity and presumably result in high barriers for C–H borylation to form **B**.

Other notable observations from these early studies include the formation of a single BN containing borylated product when commencing from aniline derivatives containing multiple proximal sites that could feasibly undergo directed electrophilic C–H borylation (Scheme 1, H_a and H_b can both be substituted).[13] For example, compound **6** is formed exclusively with no compound **C** observed. This indicates that steric effects are important in controlling the overall outcome from R_2N-directed intramolecular C–H borylation under these conditions, with no products from C–H borylation of the more hindered peri position (H_a) observed despite this position generally being more reactive in S_EAr reactions. This suggests that these high temperature reaction conditions are leading to the thermodynamic borylated products. Furthermore, the six membered boracycle containing compound **7** is formed exclusively with no compound **D** observed.

Dewar and co-workers also reported the propensity of an isoelectronic biphenyl series containing 2-NH_2, 2-OH and 2-SH directing groups to undergo electrophilic C–H borylation.[19]



Scheme 1 Highly selective directed electrophilic C–H borylation.

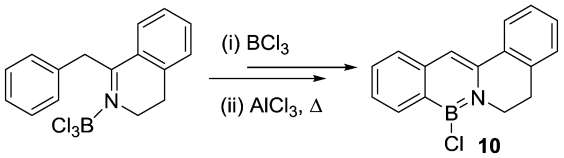


Scheme 2 Varying C–H borylation conditions reported for an isoelectronic 2-($EBCl_2$)-biphenyl series.

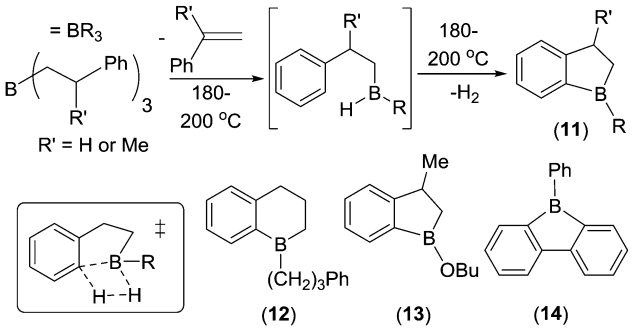
In each case combination with BCl_3 resulted in loss of HCl (which occurred more readily for the O and S derivatives relative to N) and formation of (biphenylyl)E–BCl_2 intermediates (E = NH, O, S). Notably, the subsequent intramolecular C–H borylation step proceeded under drastically different conditions in each case (Scheme 2). While requiring catalysis by $AlCl_3$ in all three reactions, the C–H borylation conditions correlated to the π donor ability of the heteroatom bonded to boron. Hence the sulfur congener underwent C–H borylation most readily presumably as poorer π donation to the boron centre (relative to O and N congeners) generates the most reactive boron electrophile of the series. Related effects were subsequently seen in intermolecular electrophilic C–H borylation and were correlated to relative LUMO energies by calculations.[20] The formation of **9** at 20 °C confirms that intramolecular electrophilic C–H borylation can occur at room temperature provided a sufficiently electrophilic borane is generated and the higher temperature conditions required for borylation in RN(H)BCl_2/$AlCl_3$ systems (R = aromatic containing hydrocarbyl group) is principally due to the presence of weaker boron electrophiles.

Dewar and co-workers also reported the reaction of an imine with BCl_3/$AlCl_3$ that ultimately led to intramolecular C–H borylation (Scheme 3).[18] This is potentially the earliest example of a dative bonded species (N→BCl_3) leading to intramolecular electrophilic C–H borylation. However, the identity of the initial product from C–H borylation is unknown and the species isolated post heating, **10**, contained an enamine unit (Scheme 3). Thus, in this case intramolecular C–H borylation may occur pre- or post-transformation of the imine into an enamine. The latter would contain a R_2N=BCl_2 unit and not a datively bonded borane unit.

In parallel to Dewar's work, from 1959 onwards Köster and co-workers reported another series of intramolecular C–H borylation reactions. These proceeded *via* B–H electrophiles generated from organoboranes at high temperatures.[21] On heating, a range of triorganoboranes underwent retro-hydroboration to produce compounds such as (ArylCH_2)B(R)H that then reacted *via* intramolecular C–H borylation evolving H_2. This electrophilic borylation reaction is comparable to Hurd's earlier work on borylating benzene with B_2H_6 (where H_2 is also the only by-product).[22]



Scheme 3 The formation of **10** by N-directed C–H borylation *via* a Lewis adduct.



Scheme 4 Select examples of Köster and co-workers' intramolecular C–H borylation studies. Inset bottom left, the proposed transition state for C–H borylation mediated by B–H containing electrophiles.

These transformations have also been termed dehydrogenative electrophilic borylation. Köster's work included the formation of 1-boraindanes (**11**) and 1-boratetralins (**12**, Scheme 4). A mechanism proceeding through a four membered σ-bond metathesis transition state for C–H borylation was proposed (inset bottom left, Scheme 4). This mechanism was supported by subsequent calculations, which also found that the barrier to aryl-C–H borylation correlated well with Hammett σ_p values, with electron donating substituents having lower barriers.[23] Köster's reports showed that multiple compounds with one aryl containing substituent and one substituent that can undergo retro-hydroboration are amenable to intramolecular C–H borylation. Even an alkoxy group on boron was tolerated, with **13** formed from a R_2BOR species *via* initial retro-hydroboration (albeit at 190 °C).

During these studies it was observed that the loss of RH (R = hydrocarbyl) as the by-product from boracycle formation (*via* a transition state related to that shown in inset Scheme 4 where B–H is replaced with B–R) had a much higher barrier than the respective borylation involving loss of H_2. For example, 2-biphenyldiphenyl borane evolves benzene and forms 9-phenylborafluorene, **14**, only at temperatures >280 °C. Whereas Köster and co-workers[24] found that the formation of 9-borafluorenes *via* electrophilic borylation using B–H containing intermediates and evolving H_2 proceeded at 120 °C. In most cases the major factor controlling reaction temperature in these studies is accessing the R_2BH/RBH_2 electrophile that effects C–H borylation. These are generally formed by retro-hydroboration which generally requires high temperature. Lower temperatures can be utilised for C–H borylation by accessing the key HBR_2 species *via* alternative routes; *e.g.* substituent redistribution between BR_3 and H_3B–NEt_3 or by alkene hydroboration (indeed intramolecular C–H borylation to form 1-boratetralins can occur at only 50 °C, *vide infra*).[25]

These early reports from the groups of Dewar and Köster demonstrate that both B–X and B–H electrophiles can effect intramolecular C–H borylation to give single products in good yield. However, after these reports intramolecular electrophilic C–H borylation was only infrequently utilised until the last decade. This review next discusses the developments post Dewar's and Köster's seminal studies and is organised by the type of interaction between

the boron electrophile and the directing group (covalent E–BCl_2 *versus* dative $[E \rightarrow BCl_2]^+$) and the identity of E in the directing group. It should be noted that there are significant commonalities in the factors controlling the reaction conditions and selectivity across these classes, and these are highlighted where appropriate.

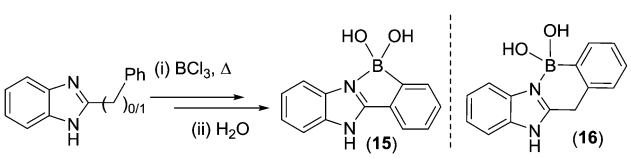
3. Intramolecular C–H borylation preceded *via* covalent (E–BY_2) bond formation

This section discusses reports where intramolecular C–H borylation is preceded by formation of E–BY_2 (containing a conventional covalent bond, Y = halide or hydride most commonly). In some cases, the E–BY_2 intermediate is observed, in others its presence is assumed based on literature precedence. The two major classes are where E is an amido (R_2N) or a hydrocarbyl group, and these are discussed first in separate sections followed by the limited examples involving other heteroatom based directing groups.

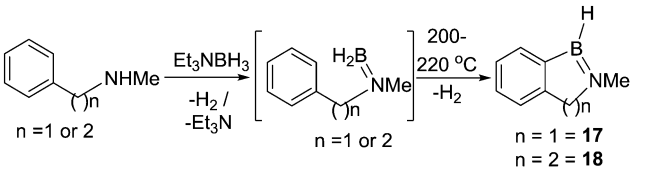
3.1 *Via* R_2N–BY_2 intermediates

To our knowledge, post Dewar's work the next report of N-directed electrophilic C–H borylation is from Letsinger and MacLean.[26] The combination of 2-substituted benzimidazoles with BCl_3 under forcing conditions (passing a stream of BCl_3 through the substrate in the melt phase (>260 °C)) was proposed to form $R_2N{=}BCl_2$ species that then led to C–H borylation and, post work up isolation of **15** and **16** (Scheme 5). However, an alternative scenario involving $N \rightarrow BCl_3$ formation and borylation without $R_2N{=}BCl_2$ formation cannot be precluded (*vide infra* for discussion of the calculations on this system). This is also the case for a related system from Hatakeyama and co-workers where a 2-substituted benzimidazole undergoes double C–H borylation (using each N as a directing group) with BBr_3 at 200 °C.[27] In Letsinger's and MacLean's work it is also unclear if the high temperatures were essential for C–H borylation in the absence of $AlCl_3$ as no lower temperature reactions were reported.

In 1968, Köster and co-workers reported the first N-directed electrophilic C–H borylation reaction using B–H electrophiles (Scheme 6).[28] The reaction of triethylamine-borane with *N*-methylbenzylamine was followed by H_2 loss to produce the amino-borane. Under forcing conditions this formed **17** by dehydrogenative C–H borylation along with substituent redistribution products. Compounds containing six membered boracycles, *e.g.* **18**, were also accessible under similar conditions. The forcing conditions (>200 °C) required to access **17** and **18** are consistent with N=B multiple bond character reducing the electrophilicity of the key



Scheme 5 C2-Substituted benzimidazoles undergoing directed C–H borylation.

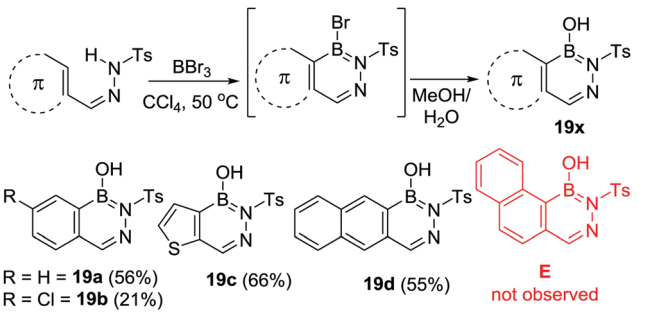


Scheme 6 N-Directed electrophilic borylation *via* a B–H electrophile.

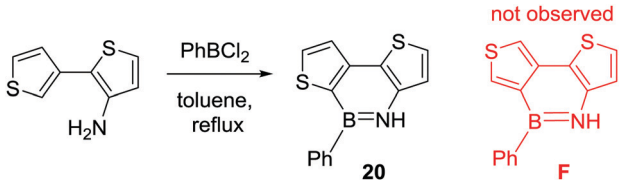
boron species (presumably $R_2N{=}BH_2$), as discussed subsequently carbon analogues (RBH_2) undergo C–H borylation at temperatures as low as 50 °C.[25,28]

Subsequent to this work, Müller and Grassberger utilised R_2N directed electrophilic C–H borylation for the formation of a range of 2,3,1-diazaborines (**19x**, Scheme 7).[29] In these independent reports arylsulfonyl-hydrazones were borylated using excess BX_3 (X = Cl or Br), with work up affording **19x**. The reaction conditions were relatively mild, proceeding at 60 °C and without requiring $AlCl_3$ as catalyst. Other notable points include BBr_3 outperforming BCl_3 in terms of the isolated yield of borylated products. This is presumably due to bromoborane species being more electrophilic than the chloro analogues. Steric effects were found to be important with a single isomer (**19d**) formed for the naphthalene congener with the more hindered isomer, **E** (Scheme 7), from borylation at the peri position not observed. The yield of **19b** is lower than **19a**, **c** and **d** under comparable conditions consistent with electron withdrawing groups (positive σ_{para} values) leading to a higher barrier in the S_EAr reaction. The milder borylation conditions in this study relative to Dewar's work can be attributed to the electron withdrawing sulfonyl group which presumably enhances the Lewis acidity of the key R_2N-substituted boron electrophile that effects C–H borylation.

The concomitant study by Grassberger and co-workers also noted that a catalyst was not necessary for C–H borylation, although they obtained higher yields when using BX_3 in combination with $FeCl_3$ as catalyst. This report contained a comprehensive substrate scope study with Me, F, Cl, Br, NH_2, NMe_2, NO_2 functional groups tolerated. This study revealed, again, that electron withdrawing substituents on the aromatic group being borylated led to much lower yields. Furthermore, attempts to borylate deactivated (towards S_EAr) heteroaromatics led to no conversion, this included pyridines, imidazoles and isothiazoles. Intramolecular C–H borylation to form 2,3,1-diazaborines also was shown to be applicable to other sulfonylamides.



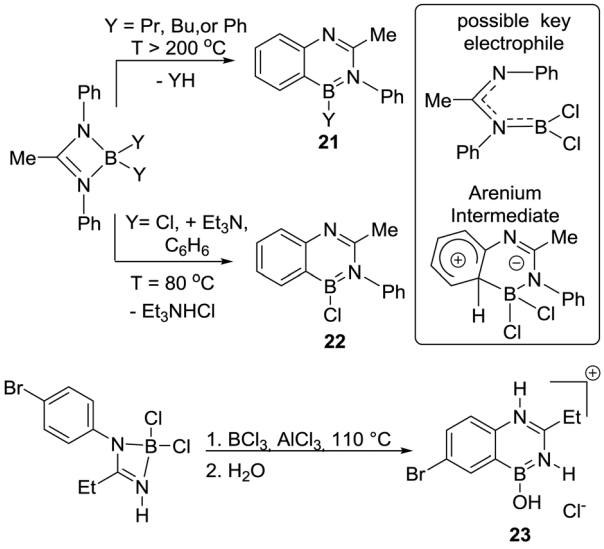
Scheme 7 C–H borylation of sulfonyl-hydrazones with BBr_3 (isolated yields in parentheses).



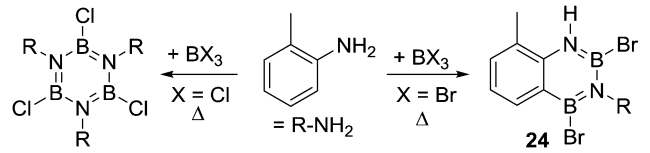
Scheme 8 N-Directed C–H borylation of bithiophenes using $PhBCl_2$.

Consistent with C–H borylation being dependent on the nucleophilicity of the (hetero)aromatic, Gronowitz and co-workers reported the facile intramolecular C–H borylation of bithiophenes. Amino bithiophenes were borylated using the less electrophilic borane $PhBCl_2$ (compared to BCl_3) in refluxing toluene without any Lewis acid activator (Scheme 8).[30] The disparity to the biphenyl analogues (*e.g.* **1**) studied by Dewar highlights the milder borylation conditions (specifically no requirement for $AlCl_3$ as a catalyst) permitted by moving to more nucleophilic (hetero)aromatics. The preference for thienyl alpha borylation over beta borylation (**20** is formed selectively with no **F** observed, Scheme 8) is consistent with the S_EAr of thiophenes.

Isoelectronic analogues of **19** were formed by Mikhailov and co-workers, with intramolecular electrophilic C–H borylation providing 4-boraquinazolines **21** and **22**.[31] Forcing conditions were required to access **21** due to the mechanism proceeding *via* evolution of R–H during the electrophilic C–H borylation step (analogous to Köster's work). In contrast, the use of chloroborane electrophiles and a Brønsted base led to milder C–H borylation conditions (enabling formation of **22** at 80 °C Scheme 9). Notably, this is an early example of an exogenous Brønsted base being added in an electrophilic C–H borylation reaction. The base may enable directed C–H borylation of a phenyl ring to proceed at a lower temperature (80 °C) in the absence of $AlCl_3$ by facilitating a deprotonation step, *e.g.* of an arenium cation intermediate (in weakly basic media the deprotonation of arenium cations can be rate limiting in S_EAr, *vide infra*).[6c] Subsequent work from



Scheme 9 N-Directed C–H borylation of amidines.



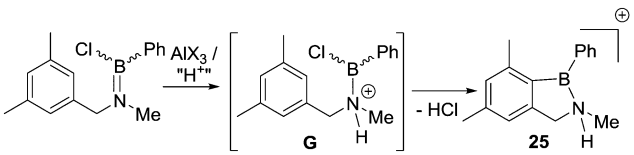
Scheme 10 BX_3 disparity in the formation of borazine (X = Cl) or **24** (X = Br).

Prasad and co-workers reported the closely related compound **23** (post work-up), albeit under more forcing conditions. However, no exploration of lower temperatures or the use of an exogenous base was reported.[32]

Another closely related compound, **24**, was produced in good yield during attempts to form a bromo substituted borazine (Scheme 10). Compound **24** was formed on combining 1 : 1 ratios of *o*-toluidine and BBr_3 (at 130 °C). In contrast, a borazine product was produced using BCl_3 under identical conditions.[33] This again indicates that the use of bromo-boranes enables access to more reactive electrophiles and/or generates a more effective base (*e.g.* possible bases maybe $[BBr_4]^-$ and $[BCl_4]^-$, respectively, with the former a better Brønsted base, *vide infra*). These factors, individually or combined, enable the intramolecular S_EAr reaction starting from BBr_3 in contrast to the chloro congener for this system.

A notable study targeting analogues of **17** using B–Cl electrophiles (instead of B–H) was reported by Nagy and co-workers.[34] In this report the addition of AlX_3 (X = Cl or Br) to an aminoborane led to C–H borylation occurring at only 0 °C to form **25** (Scheme 11). An *in situ* NMR spectroscopy study was performed and the authors suggested a borenium cation (**G**),[35] formed by protonation at N, as the key electrophile enabling the low temperature S_EAr reaction. The proton source was attributed to adventitious moisture/impure AlX_3. The contrast between these borylation conditions and Dewar's conditions, which both use $R_2NBCl(Ph)/AlCl_3$ is notable. While the flexibility of the sp^3C centre present in **G** may be a factor facilitating C–H borylation (relative to Dewar's more rigid systems), the formation of a borenium cation and the enhanced electrophilicity (relative to neutral boranes) provided by the unit positive charge may also be vital. The *in situ* conversion of an aminoborane into an amine-stabilised borenium cation (**G**) blurs the distinction between directed C–H borylation proceeding *via* a $R_2N{=}BX_2$ unit containing a covalent N–B bond, or $[R_2(E)N{-}BX_2]^+$ (E = H for example) species containing a dative N→B bond.

Later more detailed studies (see Section 4) confirmed that using borenium cations can lead to low barriers for intramolecular electrophilic C–H borylation. Thus, protonating nitrogen



Scheme 11 The formation of **25** proposed to proceed *via* a borenium cation intermediate (**G**).

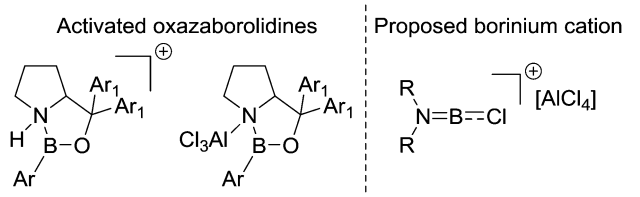


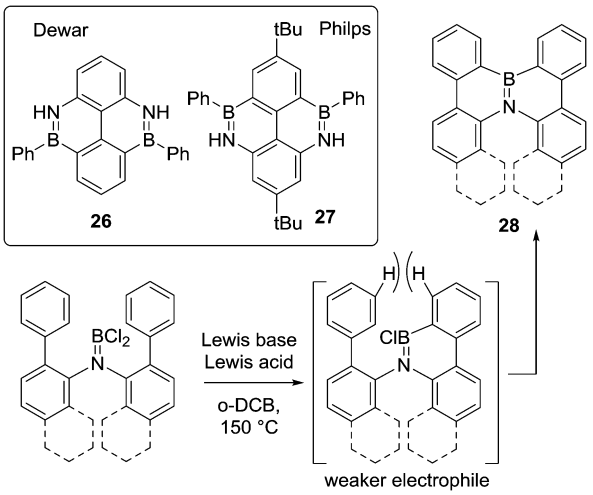
Fig. 4 Left, oxazaborolidines activated by a Lewis acid or a Brønsted acid. Right, Dewar's proposed key electrophile for intramolecular electrophilic borylation.

in a $R_2N{=}BX_2$ species appears to be an overlooked route to facilitate low barrier intramolecular electrophilic C–H borylation reactions starting from $R_2N{=}BX_2$ species. Furthermore, it suggests that $AlCl_3$ is a less effective activator than "H^+" with respect to forming strong boron electrophiles derived from R_2NBY_2 species. This is consistent with Corey and co-workers' studies developing Lewis acidic borane catalysts by activating oxazaborolidines by binding electrophiles at N (Fig. 4). In these studies, the addition of $AlCl_3$ led to a significantly less active (less Lewis acidic) boron based catalyst than the use of strong Brønsted acids (*e.g.* HOTf) to protonate at N.[36]

Dewar suggested that the role of $AlCl_3$ in these borylation reactions was to abstract halide from $R_2N{=}BCl_2$ to form $[R_2NBCl][AlCl_4]$ borinium (two coordinate at boron) cations, (Fig. 4, right) which then effect the intramolecular S_EAr reaction.[37] However, subsequent work has shown that related borinium cations are extremely challenging to access in the condensed phase even using very strong halophilic Lewis acids.[38] Indeed, weakly stabilised two and three coordinate (at boron) borocations have very high Lewis acidity towards chloride (often greater than $AlCl_3$) and a propensity to oligomerise.[39] While $[R_2NBCl]^+$ borinium cations are unlikely to be accessible in these reactions they cannot be precluded. However, it is more likely that these reactions proceed *via* species such as $R_2NB(Cl)$–(μ-Cl)–$AlCl_3$ or $R_2(AlCl_3)N$–BCl_2.

Regardless of the active electrophile, there are now many reports on the borylation of 2-aminobiphenyls (and derivatives) using Dewar's conditions (or minor modifications thereof). It is worth noting here that amino-borane mediated C–H borylation reactions often require prolonged heating, however the time can be significantly reduced by using microwave irradiation. For example, using the same reagents and solvents compound **1** could be isolated in moderate yield (42%) after only 15 min under microwave irradiation (115 W).[40]

The current interest in exploring larger BN-doped polycyclic aromatic hydrocarbons (PAHs) for organic materials applications has led to a growth in the utilisation of amine directed electrophilic C–H borylation. In this context the early work of Dewar in forming **26**,[41] and that from the group of Philp is noteworthy. The latter performed N-directed diborylation by reacting a *t*-butyl-(2,6-diamino)biphenyl with $PhBCl_2$ and $AlCl_3$ as catalyst in refluxing xylene to form **27** (Scheme 12, inset).[42] The formation of **26** and **27** initially both proceeds by evolution of two equivalents of HCl on heating to form the respective aminoboranes, Ph(Cl)B═N(H)aryl, to which $AlCl_3$ is added. Compound **27**

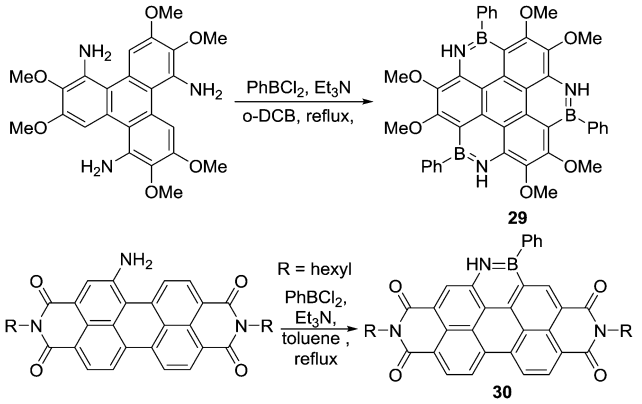


Scheme 12 Formation of NB embedded PAHs by directed electrophilic borylation.

is then accessible from this combination at lower temperature than **26**, possibly due to the inductive effect of the ^{t}Bu groups generating a more nucleophilic arene.

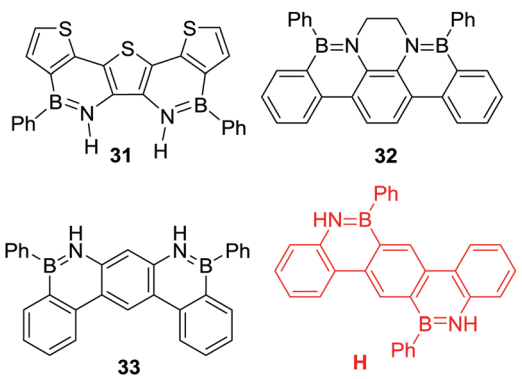
Other notable work in this area is the use of a single boron centre in double C–H borylation. In this case of bis(biphenylyl)-amines to form **28** (and derivatives, Scheme 12). This was achieved using a Lewis acid activator and a bulky base at 150 °C.[43] The requirement for forcing conditions was ascribed to the lower Lewis acidity at boron in the intermediate formed from the first C–H borylation reaction (*e.g.* bottom right Scheme 12, due to π donation from the aromatic group) and the twisted conformation due to the steric demand of the hydrogens *ortho* to the borylated carbon atoms. Screening of different Lewis acids and bases as well as different reagent stoichiometry revealed dramatic variations in yield. The optimal reaction conditions utilised 4 eq. of $AlCl_3$ and 1.5 eq. of 2,2,6,6-tetramethylpiperidine (TMP) as a non-nucleophilic Brønsted base. When either the amount of Lewis acid or amine were changed, even by only 0.5 eq., the yield was lowered significantly. It is currently unclear precisely what is leading to these changes in yield, however, the requirement for at least four equivalents of $AlCl_3$ to obtain acceptable yields suggests the higher chloride affinity associated with Al_2Cl_6 (relative to $AlCl_3$) maybe essential to access the key boron electrophile.[44]

Subsequently, Pei and co-workers and Zhang and co-workers reported the synthesis of BN–PAHs such as heterocoronene, **29**, (Scheme 13).[45] The electron rich nature of the aromatic being borylated and the use of a base made it possible to use $PhBCl_2$ without any Lewis acid catalyst (the absence of which was essential to minimise ether cleavage) to achieve C–H borylation. The use of exogenous base even enabled Zhang and co-workers to synthesise a BN-fused perylenediimide (**30**) by amine directed C–H borylation. This is notable due to the electron deficient nature of perylenediimides (thus they have low energy HOMO) and indicates that directed electrophilic C–H borylation can be extended to deactivated (towards S_EAr) aromatics using the appropriate conditions (such as using an exogenous base potentially facilitating deprotonation of an arenium cation).[46]

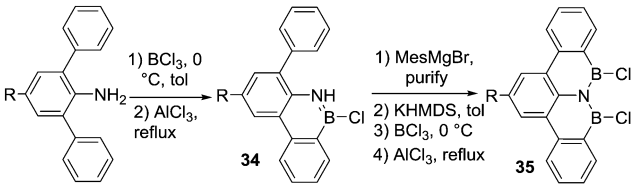


Scheme 13 Top, functional group tolerant triple N-directed C–H borylation and bottom, N-directed C–H borylation of a perylene diimide.

Multiple N-directed C–H borylation reactions have been reported of terphenyl derivatives. While the more nucleophilic thienyl congener **31** was accessible in good yield (89% using $PhBCl_2/Et_3N$ reflux in PhCl) it is noteworthy that out of the three other BN-terphenyl compounds in Scheme 14, only **32** was accessible from the parent amino-terphenyl under catalyst free conditions (using $PhBCl_2$, 3 eq. NEt_3, 130 °C, 24 h).[47] More forcing conditions were required to access **33**, which could be obtained only after heating the precursor in the presence of $PhBCl_2$ and $FeCl_3$ at 260 °C for 7 h.[48] While the origin of this disparity is not clear it may be due to the relative basicity of the respective anilines, with the parent aniline of **32** containing more basic nitrogen centres, which will favour dative bond formation with $PhBCl_2$. This is the first step in directed electrophilic borylation, and without initial dative bond formation no C–H borylation will proceed. It is also notable that compound **H** was not accessible by heating the parent amino-terphenyl with $PhBCl_2/Et_3N$ at 180 °C. This was attributed to the challenge of doubly borylating the central 1,4-phenylene ring with the first borylation installing a mesomerically deactivating boron moiety.[49] Consistent with previous reports, directed C–H borylation was more readily achieved when the unit being borylated was a more nucleophilic congener of **H**, *e.g.* with a thienyl derivative as the central aromatic unit being borylated.



Scheme 14 Select accessible (and inaccessible) products derived from amino-terphenyl directed C–H borylation.

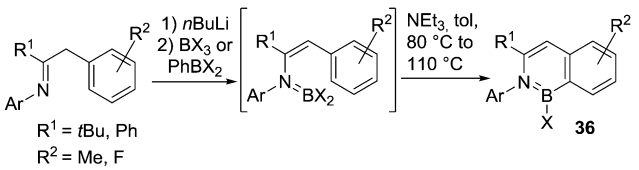


Scheme 15 Metalation assisted N-directed electrophilic C–H borylation.

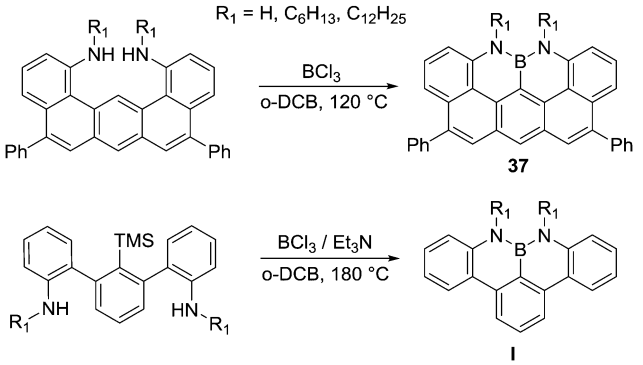
Bettinger and co-workers attempted to access a BNB-benzo-tetracene, **35**, *via* double N-directed C–H borylation of an amino-terphenyl. However, using BCl_3 and $AlCl_3$ in refluxing toluene led only to the borylation of one phenyl ring and formation of **34** (Scheme 15).[50] This can be attributed to a significant reduction in the basicity of the N centre in **34** by N to B π-donation preventing further BCl_3 coordination to this nitrogen (and thus precluding the second C–H borylation). The Lewis basicity of the N-directing group is an important consideration for enabling C–H borylation, as a minimum basicity is required to access $R_2N(H)–BY_3$ intermediates. If low Lewis basicity precludes adduct formation (as in **34**), then metalation of N–H and a subsequent salt metathesis, *e.g.* by addition of BCl_3, provides a solution and can afford the desired species (*e.g.* R_2NBCl_2). Thus, treatment of the B-mesityl derivative of **34** with potassium bis(trimethylsilyl)amide and subsequent reaction with BCl_3 followed by $AlCl_3$ addition and heating to 110 °C led to the desired BNB-benzo-tetracene **35** (C–H borylation occurs along with B-Mes to B-Cl conversion).

Deprotonation of a N–H substrate with a strong base followed by a *trans*-metalation reaction (using BX_3) is essential in many cases where dative bond formation (*e.g.* forming $R_2(H)N–BX_3$) or where loss of HX post adduct formation to form R_2NBX_2 is not favoured. In this context, the metalation/BX_3 transmetalation approach has been applied by Cui and co-workers for the functionalisation of benzyl imines to form borazanaphthalenes, **36** (Scheme 16).[51] Borylation proceeded with no added Lewis acid catalyst and at temperatures <110 °C due to the presence of an exogenous base. Notably, no C–H borylation is observed in the absence of Et_3N under these conditions. This suggests that a deprotonation step during S_EAr is rate limiting in this example. As expected, the use of more electrophilic borylating agents led to faster borylation reactions that also proceeded at lower reaction temperatures.

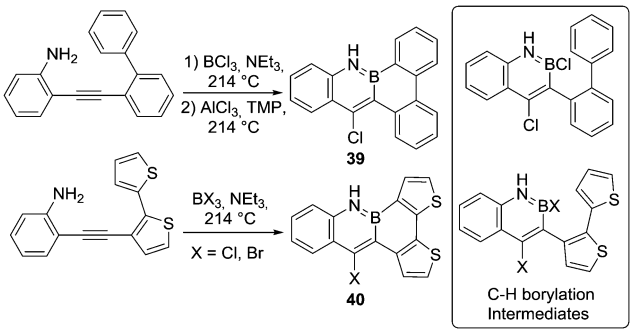
The formation of NBN–PAHs also can be achieved by intramolecular electrophilic C–H borylation. Milder reaction conditions (no $AlCl_3$ required, in contrast to Dewar's conditions) were used to access compound **37**, and this was attributed to the extended



Scheme 16 Imine conversion to an enamine for use in subsequent N-directed electrophilic C–H borylation.



Scheme 17 Formation of NBN PAHs *via* N-directed electrophilic borylation.



Scheme 19 Sequential *trans*-haloboration and directed C–H borylation reactions.

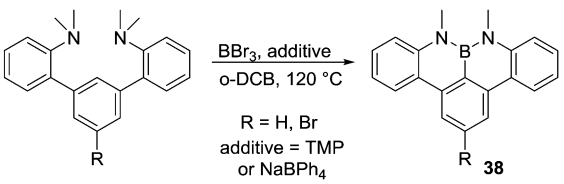
π-conjugated backbone generating a more nucleophilic aromatic facilitating electrophilic attack (Scheme 17).[52] Indeed, a related compound without an extended PAH required installation of trimethylsilyl group to enable subsequent formation of the C–B bond in **I**, with no electrophilic C–H borylation observed when using a non-silylated precursor.

A method to access NBN containing PAHs was reported by Hatakeyama and co-workers.[53] This accompanied directed C–H borylation with demethylation of *N*,*N*-dimethylaniline groups in the presence of basic additives (Scheme 18), although it is not currently known if C–H borylation occurs pre or post demethylation. The presence of $NaBPh_4$ as an additive produced higher yields (*ca.* 70%), and it was proposed that the borate anion acts as a non-coordinating (towards BY_3) Brønsted base. Consistent with the importance of base in this reaction 2,2,6,6-tetramethylpiperidine (TMP) also successfully enabled formation of **38** (albeit in lower yield). In the absence of any base conversion was extremely low, again highlighting the importance of exogenous base in enabling certain electrophilic C–H borylation reactions. This work also emphasises the importance of using Brønsted bases that do not strongly coordinate to boron Lewis acids.

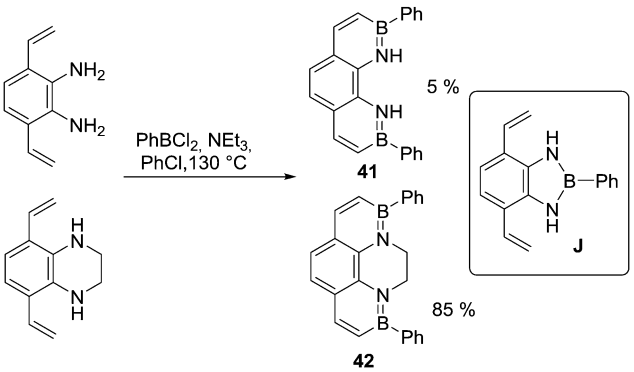
Other reactions can be utilised to access the key boron species for N-directed C–H borylation, as exemplified by the synthesis of **39** and **40** (Scheme 19). In these reactions N-directed alkyne *trans*-haloboration is followed by intramolecular C–H borylation.[54] The low yields and the harsh reaction conditions (using $AlCl_3$ along with a sterically encumbered base in refluxing 1,2,4-trichlorobenzene (boiling point 214 °C)) are presumably required in part due to the low electrophilicity of the boron species performing electrophilic borylation (*e.g.* inset right Scheme 19). As expected, the reaction proceeds under more facile conditions (without $AlCl_3$ and a hindered base) when a more nucleophilic thiophene unit is borylated. The relative ease of thiophenes to undergo electrophilic C–H borylation has been widely exploited in the synthesis of BN-containing PAHs. Similar borylation conditions ($PhBCl_2$ or BX_3, NR_3, aromatic solvent, reflux) have been found to produce good outcomes (yields >60%) for many N-directed C–H borylation reactions of thiophene containing systems. However, in the interest of brevity we do not discuss these transformations individually herein.[55]

In addition to activated heteroarenes such as thiophene, non-aromatic π systems (*e.g.* alkenes) also undergo N-directed C–H borylation reliably under milder (compared to analogous aromatic systems) reaction conditions (*e.g.* without $AlCl_3$, at temperatures <130 °C) using a variety of boron electrophiles.[56] Provided the amine is sufficiently Lewis basic to form the initial N→B dative bond N-directed alkene C–H borylation has been used to synthesise many extended BN containing PAHs.[57] Again in cases where amine Lewis basicity is low deprotonation/*trans*-metalation can be used to access the R_2N–BCl_2 intermediate. Another consideration is highlighted by the observation that **41** is much less accessible than an *N*-alkylated analogue **42** (Scheme 20). This emphasises the importance of precluding unwanted side reactions, as formation of a diazaborole (*e.g.* **J**) is presumably competing with directed C–H borylation to form **41** but not to form **42**.[58] This is in contrast to the formation of **32**, potentially due to the relatively facile C–H borylation of thienyls and the greater strain in fusing two all sp^2 five membered rings through beta positions.

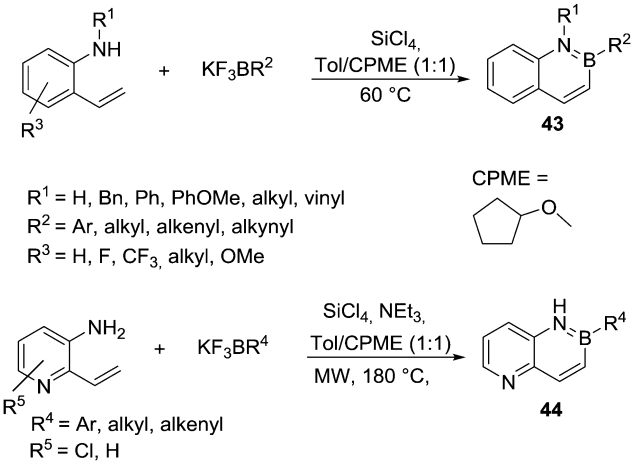
In the area of N-directed alkene C–H borylation the work of Molander and co-workers is notable. They accessed a large



Scheme 18 Demethylative N-directed C–H borylation.



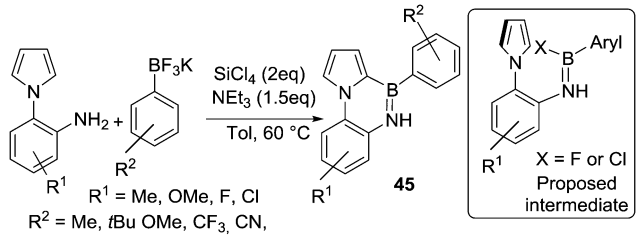
Scheme 20 The *N*-substituent dependent formation of BN-phenanthrenes.



Scheme 21 C–H borylation using potassium organo-trifluoroborates/$SiCl_4$.

variety of 2,1 borazanaphthalenes, **43** (Scheme 21), using combinations of potassium organo-trifluoroborate salts and $SiCl_4$.[59] This allowed for the *in situ* generation of the electrophilic boron reagent (*e.g.* organoBCl_2) by halide exchange between boron and silicon centres. Alkene borylation then proceeded effectively without $AlCl_3$ and at temperatures <60 °C consistent with other reports on intramolecular alkene C–H borylation being facile relative to that of aromatics. An impressive range of functional groups (on B and N substituents) are tolerated under the reaction conditions. However, borylation of deactivated N-heterocycles (*e.g.* pyridines) was not reported in this work. Rombouts and co-workers adapted Molander's conditions to extend this methodology to borylate 2-vinyl-3-amino-pyridines (Scheme 21, bottom) to access **44**.[60] The reaction was carried out using microwave assisted heating at 180 °C in the presence of $SiCl_4$ and NEt_3. The higher temperature was proposed to be required to enable S_EAr of the deactivated π system, while NEt_3 may also be essential to facilitate a deprotonation step during C–H borylation. However, Molander and co-workers subsequently suggested that pyridyl (and other Lewis basic N-heterocycles) coordination to main group Lewis acids was preventing N-directed borylation in their previous work.[61] Therefore they increased the amount of Lewis acid ($SiCl_4$) to two equivalents (with respect to the N-heterocycle) and included Et_3N as a relatively hindered base. Combined this enabled N-directed alkene C–H borylation at only 80 °C including of vinyl-amino-pyridines. This method was used subsequently by Vaquero and co-workers to synthesize an intermediate on the way to a BN-embedded chrysene.[62]

The group of Yan and co-workers also utilised this synthetic approach to borylate 1-(2-aminophenyl)pyrroles to form **45**. In this case C–H borylation is occurring on a heteroarene not an alkene (Scheme 22),[63] but borylation conditions are still relatively mild due to the highly nucleophilic nature of pyrroles. Unsurprisingly, the reaction does not proceed in coordinating solvents such as DMF, which will sequester the main group Lewis acids required for electrophilic borylation. BCl_3 can be used in place of $SiCl_4$ to access the key electrophile (*e.g.* ArylBCl_2) and more notably BF_3–OEt_2 also worked as the Lewis acid activator.



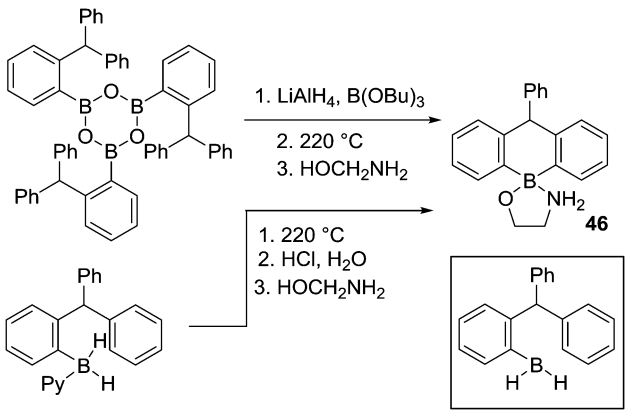
Scheme 22 N-Directed C–H borylation of pyrroles using potassium organo-trifluoroborates/$SiCl_4$ to generate boron electrophiles. Inset the proposed intermediate, note that X = F is from replacing $SiCl_4$ with BF_3.

This suggests that ArylBF_2 species are effective for directed C–H borylation under these conditions, at least of highly activated heteroaromatics, *via* the possible intermediate shown (inset Scheme 22).

As the above demonstrates, N-directed electrophilic C–H borylation is a powerful tool for the functionalisation of arenes, heteroarenes and alkenes. This reaction proceeds selectively to give six membered boracycles in most cases (especially for boracycles containing all sp^2 main group atoms) and can proceed under mild conditions with broad functional group tolerance, particularly when borylating more nucleophilic aromatic systems or alkenes. These points indicate it will continue to be a highly useful methodology.

3.2 Borylation *via* C–BY_2 intermediates (Y = H, R or halide)

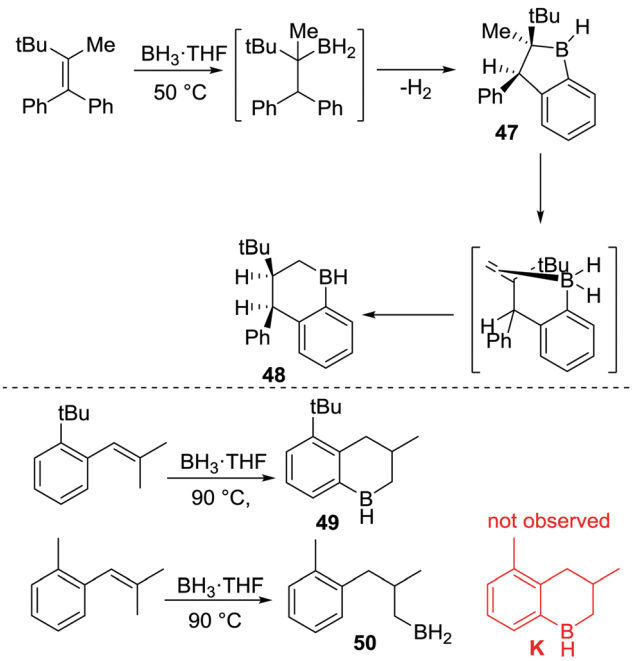
After N-directed C–H borylation the next most reported is borylation proceeding *via* initial intermolecular C–B bond formation. While pioneered by Köster and co-workers, their borylation procedures are not practical due to the high temperature conditions required. Shortly after Köster's work Bickelhaupt and co-worker performed pyrolysis on a mixture of tris(2-benzhydylphenyl)boroxine, lithium aluminium hydride and tributoxyborane at 220 °C leading to C–H borylation product **46** (Scheme 23). The reaction may proceed *via* a primary borane (RBH_2, insert Scheme 23) or other derivatives (*e.g.* RB(H)(OBu)).[64a] The same product could also be accessed by the pyrolysis of the borane-pyridine adduct at 220 °C.[64b]



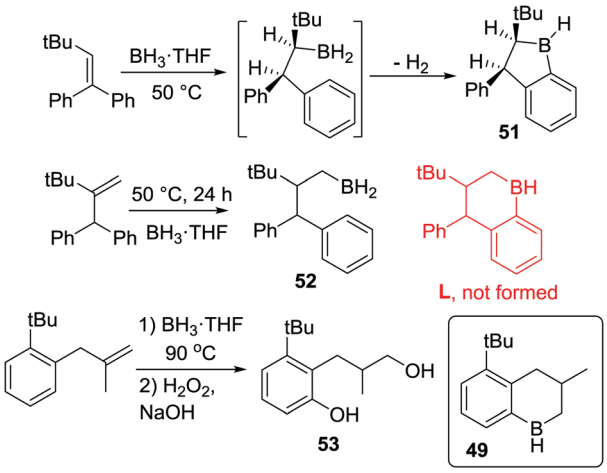
Scheme 23 Alternative routes to access B–H species effective for intramolecular C–H borylation.

This early work on C–BY_2 mediated C–H borylation required extremely high temperatures, though the high barrier in many cases in Köster's work arises from the retro-hydroboration step required to generate the key boron electrophiles. Thus, lower temperature intramolecular C–H borylation processes using C–B(R)–H based electrophiles are feasible by using more facile routes to access the key electrophile. To our knowledge this was first demonstrated in 1999 when Knochel and co-workers reported the synthesis of cyclic boranes by intramolecular C–H borylation using a B–H electrophile under relatively mild conditions.[25] By heating a mixture of a tetra-substituted olefin with a borane at 50 °C both five- and six-membered boracycles, **47** and **48**, were obtained after one hour indicating a lower barrier process compared to Köster's systems.[25c] Notably, only **48** was observed after 24 h at 50 °C (Scheme 24),[25a] with the formation of specific boracycles confirmed by oxidative workup. While **47** was formed through sequential hydroboration/intramolecular C–H borylation reactions, mechanistic studies indicated that compound **48** was generated from **47** *via* a retro-hydroboration/hydroboration sequence. Calculations showed that **48** was thermodynamically favored over **47** by 5 kcal mol^{-1}, indicating that **47** is the kinetic product but **48** is the thermodynamic product.

This methodology also could be applied to several tri-substituted alkenes, *e.g.* to form **49**, under similar conditions (Scheme 24, bottom). Notably, proximal bulky groups were found to be essential for C–H borylation at these lower temperatures. For example, replacement of a *tert*-butyl group with a methyl group led to no C–H borylation (**K** is not formed) and only **50** was produced. The *tert*-butyl group is proposed to orientate the initial hydroboration product into a productive conformation for C–H borylation, thus enabling low temperature C–H borylation.



Scheme 24 Relatively low temperature intramolecular C–H borylation *via* B–H intermediates.

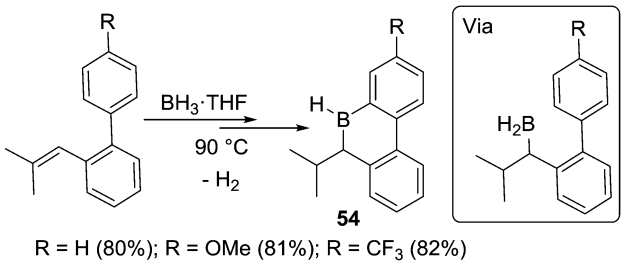


Scheme 25 Disparities in C–H borylation reactions proceeding initially to form five or six membered boracycles.

The importance of bulk proximal to the C–BH_2 unit for C–H borylation to proceed was also observed in other related examples, as was the finding that five membered boracycles are the kinetic products derived from the C(sp^3)–BH_2 intermediates, while six membered boracycles were often the thermodynamic products.[25c]

In further studies, Knochel and co-workers obtained the five-membered boracycle **51** (Scheme 25) exclusively as an analogous rearrangement to a six-membered boracycle (as per formation of **48**) is not possible. In contrast, only hydroboration product **52** was formed, with no six-membered boracycle, **L**, generated under these lower temperature (50 °C) reaction conditions.[25c] This is consistent with the slower formation of six membered boracycles in these systems. Hence longer reaction times and higher temperatures are required to form six membered boracycles directly *via* sp^3C–BH_2 electrophiles. This is emphasized by only 16% of diol **53** being formed after the C–H borylation step had been heated for 9 days at 90 °C (**53** is formed from boracycle **49**). This is in contrast to the outcome using an isomeric alkene where initial C–H borylation can proceed *via* a five membered boracycle (*e.g.* formation of **49** is high yielding in Scheme 24, bottom). In the formation of five membered boracycles it is unclear if the energetic barrier requiring heating to 50 °C comes from dissociation of THF to form free RBH_2 or the C–H borylation step.

This methodology could also be extended to form boracycles derived from biphenyl substrates (and related molecules), again provided sufficiently bulky tri-substituted alkenes are used.[25c] The six-membered boracycles **54** are prepared *via* sequential hydroboration/C–H borylation reactions (Scheme 26). Notably, the borylation reaction was found to be insensitive to the electronic nature of substituents on the *meta* position (relative to the borylation site) of the phenyl group. Similar yields were obtained for substrates containing H, methoxy or trifluoromethyl at this position under the same reaction conditions. The authors used this to conclude that the C–H borylation step was proceeding *via* a four membered metathesis type transition state (analogous to Köster's proposal) and not an S_EAr mechanism.



Scheme 26 Hydroboration/C–H borylation of biphenyl derivatives.

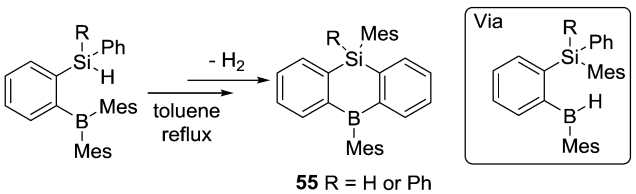
Subsequent to Knochel's work on directed C–H borylation, Kawachi and co-workers found that *o*-(hydrosilyl)-(dimesitylboryl)benzene compounds undergo intramolecular H/mesityl exchange in refluxing toluene to afford hydroborane intermediates.[65] The rigid skeleton of the intermediate forces the B–H moiety to be in close proximity to the Si-phenyl group and dehydrogenative C–H borylation proceeds under these conditions to form **55**. This is an alternative route to alkene hydroboration or alkyl borane retro-hydroboration to form an active (for C–H borylation) B–H intermediate (Scheme 27). Other intramolecular C–H borylation reactions have been reported using B–H containing electrophiles, but as these proceed *via* NHC–borenium cations they are discussed in Section 4.3 post the detailed discussion on amine-ligated borenium cations in intramolecular C–H borylation.

To our knowledge, Kaufmann and co-workers reported the first intramolecular C–H borylation reactions mediated by a C–BX_2 species instead of a hydroborane, albeit at very high temperatures.[66] At 780 °C, the five membered boracycle **56** was produced *via* intramolecular electrophilic C–H borylation along with products from substituent redistribution (*e.g.* inset top right, Scheme 28). Interestingly, a four-membered boracycle, **57**, could be generated despite the ring strain. The formation of **57** was confirmed by a trapping reaction with an alkyne to form **58**. The high temperatures required was attributed to the lower electrophilicity of chloroboranes (relative to B–Br), and the lack of both an exogenous base and a catalyst (such as $AlCl_3$).

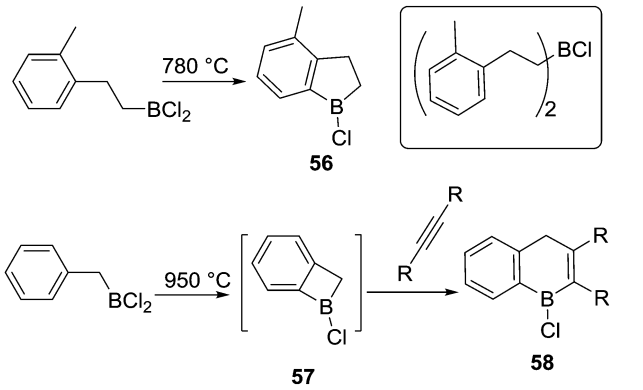
In contrast to this earlier work, in 2015 Hatakeyama and co-workers reported a carbon-directed intramolecular C–H borylation reaction that proceeded under much milder conditions (Scheme 29).[67] Directed lithiation of 1,3-diphenoxybenzene followed by *trans*-metalation to boron afforded an arylBBr_2 species that in the presence of *N*,*N*-diisopropylethylamine led to high yielding double intramolecular C–H borylation at 120 °C to afford compound **59**. Notably, the base was crucial for the borylation reaction with only 16% yield obtained without the base. The authors also found that both 1,2,2,6,6-pentamethylpiperidine and *N*,*N*-dimethyl-*p*-toluidine are effective at enabling formation of **59**, while **59** was formed in only 13% yield when triethylamine was used. This again emphasizes the need for weakly nucleophilic (towards boranes) Brønsted bases for enabling C–H borylation. It is notable that this reaction proceeds without requiring a Lewis acid activator (*e.g.* AlX_3) and this can be attributed to the presence of an exogenous base, the electronically activating effect of the *ortho*-OR group, and the fact that ArylBBr_2 species are more Lewis acidic than R_2NBX_2 and $RBCl_2$ species.

Interestingly, for the borylation of 1,3-bis(naphthalen-2-yloxy)-benzene, the more hindered product **60** was obtained as the major product while the less congested isomer **61** was only obtained in 2% yield (Scheme 30). This suggests the kinetic product (derived from functionalization of the two alpha-naphthalene positions) is formed under these conditions, possibly due to the presence of a base enabling rapid and irreversible deprotonation (and thus irreversible borylation).

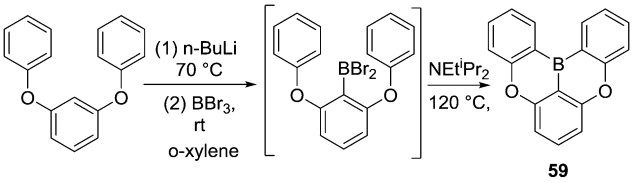
The lithiation/*trans*-metalation to BX_3/electrophilic C–H borylation strategy has been applied to a variety of substrates using similar reaction conditions. While this has generated



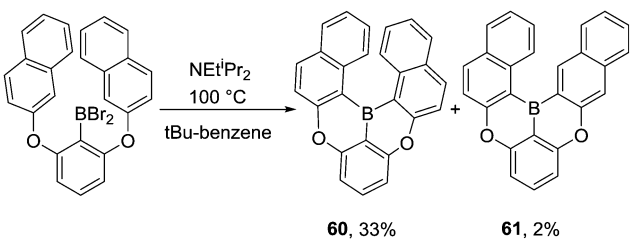
Scheme 27 Si/B substituent exchange enabling C–H borylation.



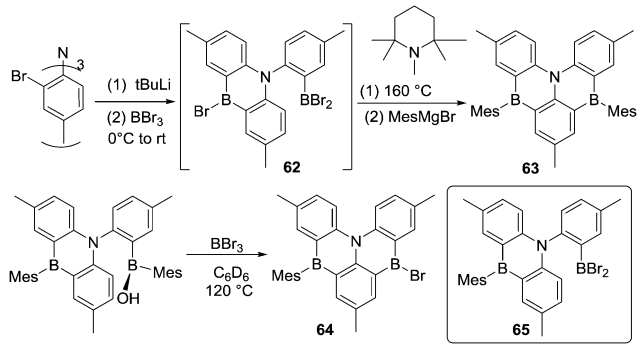
Scheme 28 Intramolecular C–H borylation mediated by organoBCl_2 species.



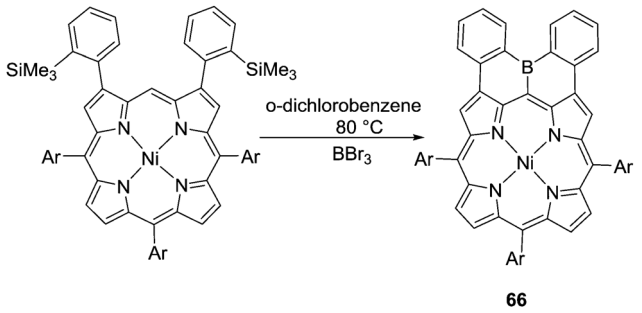
Scheme 29 Lithiation/*trans*-metalation/intramolecular C–H borylation.



Scheme 30 Isomer distribution from C–BBr_2 mediated intramolecular electrophilic C–H borylation of a bisnaphthyl derivative.



Scheme 31 C-Directed borylation of triphenylamine derivatives.



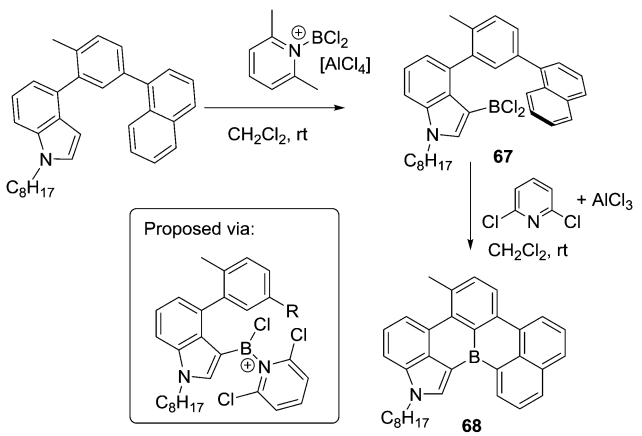
Scheme 32 Borodesilylation enabling intramolecular C–H borylation.

many molecules with intriguing properties a comprehensive listing of these is not the focus of this review.[68] However, it is noteworthy from a synthetic perspective that this approach also can be used to introduce more than one boron moiety into a PAH. For example, a triple lithiation followed by addition of two equivalents of BBr_3 likely affords intermediate **62**, which in the presence of 1,2,2,6,6-pentamethylpiperidine, undergoes electrophilic borylation at 160 °C to give **63** (Scheme 31).[69] Interestingly, Wang and co-workers prepared closely related compounds *via* a different method. By heating a mixture of a borinic acid and BBr_3 at 120 °C for 1 hour, a substituent exchange reaction occurred (to generate intermediate **65**) along with an intramolecular electrophilic C–H borylation. This proceeded in the absence of an exogenous base to afford compound **64** as the major product (Scheme 31, bottom).[70] It should be noted that the formation of **64** from the borinic acid also occurred at room temperature (using 5 eq. of BBr_3) albeit requiring *ca.* 20 h for full consumption of the starting material. The addition of Hünig's base did not alter the outcome of this reaction or accelerate the formation of **64**, suggesting an alternative Brønsted base is involved in the deprotonation step in this S_EAr reaction. The disparity to the conditions required to form **61** is notable and it is feasible that a borate base derived from B-OH/B-Mes/B-Br substituent redistribution reactions is playing a role in the formation of **62** as observed in C–H borylation reactions using $[BPh_4]^-$ as a Brønsted base (which in some reports is more effective at enabling C–H borylation than hindered amines).[53] Regardless of the identity of the base this report confirms that intramolecular electrophilic C–H borylation proceeding *via* $C–BBr_2$ intermediates can proceed at room temperature.

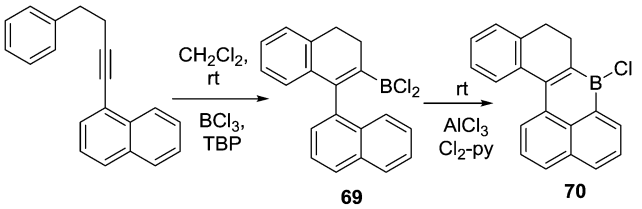
Instead of using organolithium reagents to enable formation of the $C–BX_2$ intermediates, Osuka and co-workers prepared diphenylborane-fused porphyrin **66** *via* boron–silicon exchange using BBr_3 and then electrophilic C–H borylation (Scheme 32).[71] Presumably, due to the high nucleophilicity of the *meso* position in these compounds, the C–H borylation reaction occurs at relatively mild conditions without using any exogenous base.

Other routes to generate $C–BX_2$ units for subsequent use in intramolecular C–H borylation reactions have been reported. For example, Ingleson and co-workers developed a sequential inter-/intra-molecular electrophilic C–H borylation of an indole substrate using an amine, BCl_3 and $AlCl_3$.[72] The propensity of the indole C3 position to undergo electrophilic substitution enables facile intermolecular C–H borylation with a borenium cation to give **67**. A double intramolecular C–H borylation to form **68** then was achieved by addition of 2,6-dichloropyridine (Cl_2-py) and $AlCl_3$ to **67** (proposed to form a reactive borenium cation *in situ* that is effective for electrophilic borylation at room temperature, inset Scheme 33). There are a number of other reports of intermolecular electrophilic C–H borylation being followed by intramolecular C–H borylation to form boron containing PAHs. These reactions are presumably also proceeding *via* $ArylBX_2$ species, however, due to the fact that these intermediates are either not observed or that the synthetic conditions used for intramolecular C–H borylation are similar to those already discussed in this section these reports are not discussed individually herein.[73]

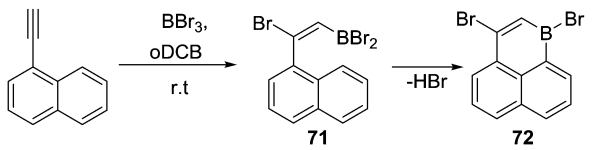
Another alternative route to install the $C–BX_2$ unit for subsequent intramolecular borylation is borylative cyclisation of 1-(4-phenylbut-1-yn-1-yl)-naphthalene (and derivatives) to give **69** using BCl_3/2,4,6-tri-*tert*-butyl pyridine (TBP).[74] Addition of stoichiometric $AlCl_3$ and 2,6-dichloropyridine to **69** enabled intramolecular C–H borylation within 20 minutes at room temperature to afford compound **70** in good yield (Scheme 34). Again, the results clearly demonstrate the key role of $AlCl_3$/amine base in promoting intramolecular electrophilic C–H borylation at room temperature. This is presumably due to borenium cation formation, although these intermediates are not observed in this case.



Scheme 33 Intermolecular and intramolecular electrophilic C–H borylation.



Scheme 34 Borylative cyclisation preceding intramolecular C–H borylation.



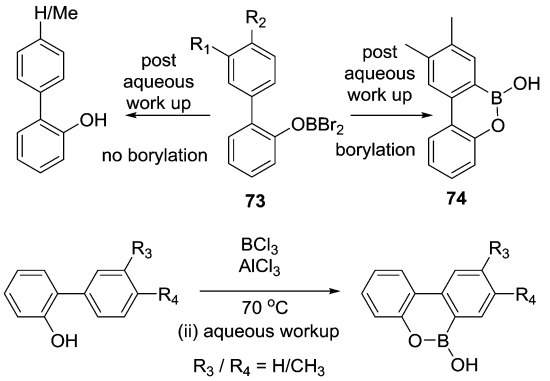
Scheme 35 *trans*-Haloboration followed by intramolecular C–H borylation.

Other alkyne transformations can be used to install the C–BX_2 unit for subsequent intramolecular C–H borylation, including haloboration, both *trans*-1,2-haloboration and 1,1-haloboration.[75] For example, when 1-ethynylnaphthalene was treated with BBr_3, a bromoboration/intramolecular C–H borylation reaction sequence proceeded (Scheme 35). The intermediate **71** was formed upon addition of BBr_3 *via* alkyne *trans*-bromoboration, the subsequent intramolecular C–H borylation from the vinylBBr_2 species then occurred at room temperature to generate **72** without additional Lewis acid or base. This is in contrast to the reactivity of vinylBCl_2 units (*e.g.* **69**) which required Lewis acid/base additives (to enable borenium formation). Presumably, this is due to the enhanced Lewis acidity of vinylBBr_2 relative to vinylBCl_2 combined with the absence of H···H steric clash (which is present in the fjord region of **69**). However, the identity of the base deprotonating the arenium cation in these reactions is unclear, it is potentially a $[BBr_4]^-$ species generated *in situ*. As noted for other C–BX_2 containing systems double C–BX_2 installation by borylative cyclisation and haloboration can be followed by twofold intramolecular C–H borylation to form B_2-containing PAHs.[75b]

The development of multiple routes to generate C–BX_2 intermediates using simple precursors, coupled with the observation of subsequent high yielding, intramolecular C–H borylation clearly indicates the significant utility of the approaches outlined above, particularly in forming PAHs containing C_3B units. The preference for forming six membered boracycles in systems containing all sp^2 hybridised centres is pronounced. This is presumably due to a combination of more favourable bond angles in six membered all sp^2 boracycles and the higher energy of anti-aromatic borole units present in structures when five membered C_4B boracycles are formed.

3.3 Other heteroatom–BX_2 directed borylations

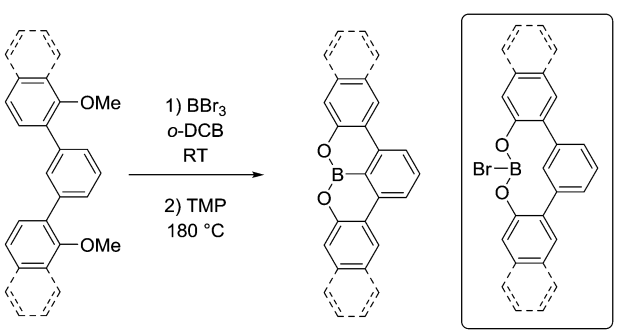
Dewar's studies into O directed C–H borylation (to form **8** and **9**, respectively) were extended by Zhou and co-workers using anisole derivatives in-place of hydroxyl precursors. The reaction of a 2-phenylanisole derivative with BBr_3 led to ether cleavage (with evolution of bromomethane) and then room temperature



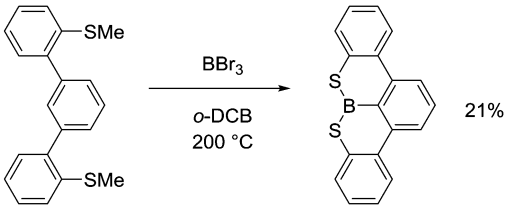
Scheme 36 O directed C–H borylation using BBr_3 and $BCl_3/AlCl_3$.

C–H borylation.[14] This work also demonstrated a disparity between BBr_3 *versus* BCl_3. Borylation proceeded rapidly at room temperature with O–BBr_2 derivatives **73** to form **74**, whereas with the chloro analogues (**73-Cl**) an additional Lewis acid ($AlCl_3$) was required. It is likely that $AlCl_3$ coordinates at O or Cl in **73-Cl** enhancing the electrophilicity at boron. With both systems, there is a dependence on the nucleophilicity of the arene being borylated. For example, using BBr_3 only the dimethyl substrate (R_1 and R_2 = Me, Scheme 36) produced the C–H borylation product **74**. While with the $BCl_3/AlCl_3$ system the presence of two electron-withdrawing fluorine substituents (R_3 and R_4 = F) produced no borylated product, but when R_3 = Me (located *para* to the borylation site) C–H borylation occurred even with R_4 = F.

O and S directed C–H borylation has been employed in the synthesis of larger B-doped PAHs. In this area the cleavage of ArylO-Me with BBr_3 to form Aryl$OBBr_2$ units that then effect intramolecular C–H borylation is most common, for example, in the synthesis of **75** and **76** (Scheme 37).[53] Demethylation proceeded at room temperature to afford the demethylated intermediate (inset Scheme 37) with subsequent heating in the presence of an amine producing **75** in moderate to good yield (without a base **75** is formed in much lower yield). The high temperature required may be in part due to the lower Lewis acidity of the diaryloxy-borane electrophile (*e.g.* inset) relative to $RBBr_2$ for which borylation proceeds at room temperature.



Scheme 37 Demethylative borylation using BBr_3 to form BO-containing PAHs.

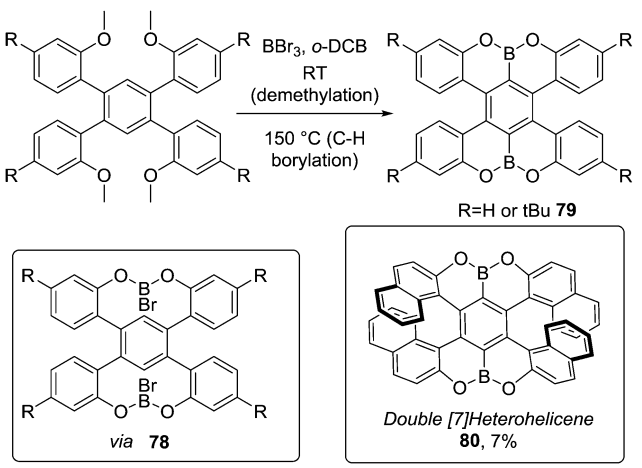


Scheme 38 Demethylative thioanisole directed intramolecular C–H borylation.

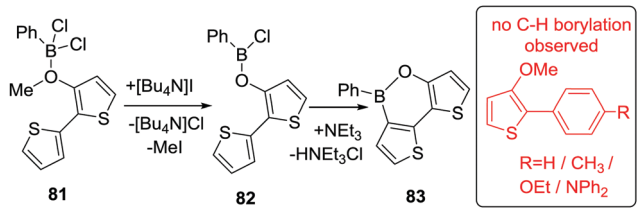
Thioether congeners required more forcing conditions for an analogous demethylative S-directed C–H borylation, in part due to the lower reactivity of thioanisoles towards demethylation with boron electrophiles.[76] For example, heating at 200 °C resulted in only a 21% yield of **77** (Scheme 38). Interestingly, the addition of bases to this S directed C–H borylation reaction did not improve the conversion (using either a hindered amine or $NaBPh_4$), suggesting the deprotonation step is not the limiting factor leading to low yields in this case.

Demethylative directed C–H borylation of anisole derivatives also has been extended to form B_2-PAHs (Scheme 39).[77] Addition of BBr_3 at room temperature forms the demethylated O–B–O intermediate **78**, which then undergoes high yielding C–H borylation at 150 °C to form **79**. This methodology also was applied to pyrene derivatives and as double demethylation occurs rapidly (relative to C–H borylation) the selectivity is high in the subsequent C–H borylation step in these systems.[78] Müllen and co-workers also prepared the double helicene **80** (using BBr_3 at 180 °C) albeit in low yield (Scheme 39) *via* directed C–H borylation.[79] The low yield relative to **79** was attributed to the significant strain during the borylative ring closure.

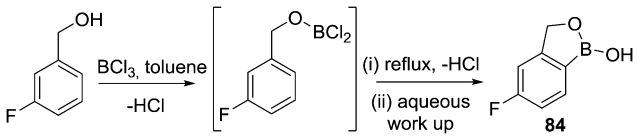
Subsequently, Suga, Mitsudo and co-workers demonstrated a demethylative borylation to yield thiophene-fused 1,2-oxaborine derivatives.[80] Notably, the use of $PhBCl_2$ as the borylating electrophile required an iodide salt to facilitate demethylation. Iodide was proposed to be acting as the nucleophile to demethylate the less activated ArO(Me)–borane adduct (less activated due to



Scheme 39 Demethylative double O-directed C–H borylation to produce OBO–PAHs *via* O–B–O intermediates.



Scheme 40 Dithieno-oxaborine synthesis using $PhBCl_2$ and iodide mediated demethylation followed by O-directed C–H borylation.



Scheme 41 Intramolecular electrophilic C–H borylation to form tavaborole.

coordination of Ar(O)Me to a less Lewis acidic borane). Iodide demethylation of **81** initially produced MeI and **82**, the latter then underwent C–H borylation at 135 °C in the presence of triethylamine to form **83**. This methodology was applicable to a range of other substituted thiophenes and extended to BCl_3 as the borane source. As expected, in substrates where multiple six membered boracycles could be formed, the reaction proceeded selectively at the more nucleophilic site. Furthermore, the reaction did not proceed under the same reaction conditions with less nucleophilic aromatics (inset Scheme 40).

Finally in this section, in recent patent literature an O-directed electrophilic C–H borylation route to access benzoxaboroles has been reported.[81] In this report a benzyl alcohol was reacted with BCl_3 at low temperature, proposed to form an RO–BCl_2 species (Scheme 41), which on refluxing in toluene led to C–H borylation. Notably, aqueous work up then led to benzoxaboroles, including the commercialised tavaborole, **84**, in moderate yields (*ca.* 40%). The ability of this transformation to proceed in the absence of $AlCl_3$ is, again, consistent with the formation of five membered boracycles having lower reaction barriers for systems containing at least one sp^3 centre.

While O directed electrophilic C–H borylation has lagged behind N– and C–BX_2 mediated intramolecular electrophilic C–H borylation the recent successes in forming BO-containing PAHs and tavaborole (**84**) confirms the considerable potential that this methodology has. It is also clear that RS–BX_2 mediated intramolecular C–H borylation requires further development before it is a reliable, high yielding methodology with broad applicability.

4. Intramolecular C–H borylation *via* E–BY_3 dative bond containing intermediates

This section discusses systems where intramolecular C–H borylation is preceded by formation of a E→BY_3 unit (Y = halide or hydride most commonly) and where the dative bond

is unlikely to be transformed into a covalent bond (*e.g.* cannot form a neutral E–BY_2 unit by loss of HY). In this section the major class is when E is a nitrogen Lewis base, and this area is discussed first followed by the more limited examples involving other heteroatom centred Lewis bases (*e.g.* carbonyls).

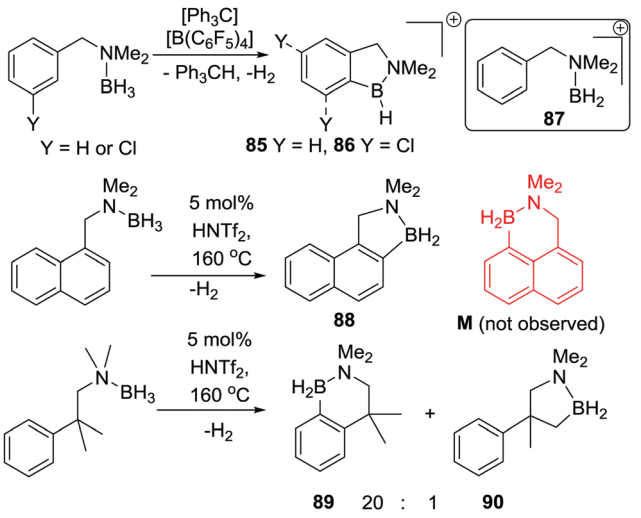
4.1 *Via* N→BY_3 intermediates

An important study into N→B dative bond directed electrophilic C–H borylation was from Vedejs and co-workers in 2009.[82] The trityl salt of the robust weakly coordinating anion $[B(C_6F_5)_4]^-$ (essential to avoid anion decomposition when combined with borocations) was used to abstract hydride from *N*,*N*-dimethylbenzylamine borane. At room temperature this led to the C–H borylation product, **85**, with the reaction proposed to proceed *via* a borenium cation (**87**, Scheme 42). A limited selection of functionalised benzyl derivatives was utilised successfully in this C–H borylation reaction, *e.g.* containing halide or Me groups, with halide substituents, again, leading to slower C–H borylation. Borylation could be extended to form 6-membered boracycle analogues in good yield, however, low yields were observed for seven membered boracycle analogues. It is notable that compound **85** could be hydrolysed readily to the boronic acid derivative that contains the core-structure of the glucose sensor shown in Fig. 1.

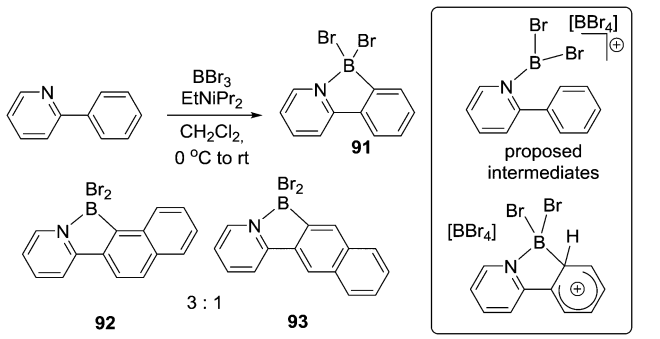
The use of forcing conditions (160 °C) enabled the borylation to form **85** (and derivatives) to be carried out with only 5 mol% of the hydride abstractor, $[Ph_3C][B(C_6F_5)_4]$ or $HNTf_2$. Hydride transfer from $BnMe_2NBH_3$ to **85** was proposed as turnover enabling. With catalytic C–H borylation proceeding under kinetic control (*i.e.* it was shown to be irreversible under the reaction conditions) it is notable that **88** is formed exclusively, with no compound **M** observed. From these studies in flexible systems (containing multiple sp^3 centres) the formation of five membered boracycles is preferred, at least kinetically, over six membered (consistent with observations on covalently bonded C–BH_2 directed borylation systems discussed above). Notably, in the formation of **86** the isomer distribution in the catalytic (with $HNTf_2$ at 160 °C) and stoichiometric (with $[Ph_3C][B(C_6F_5)_4]$ at ambient temperature) borylation reactions was dramatically different. The purified isomers of **86** did not equilibrate on heating under the borylation conditions thus the isomer ratio is fixed during C–B bond formation/C–H cleavage (*i.e.* the products are formed under kinetic control). The difference in selectivity was attributed in these reports to different borylating electrophiles generated using NTf_2 and $[B(C_6F_5)_4]$, with borylation at 160 °C potentially not proceeding *via* simple borenium cations such as **87**.[83,84]

Considering the mechanism for the ambient temperature borylation with $[B(C_6F_5)_4]^-$ as the counterion, a four membered B–H/C–H metathesis transition state for forming **85** from **87** was calculated. As **85** is isoelectronic to 1-boraindenes (*e.g.* **11**) it is notable that the calculated mechanism for these two types of borylation reactions are closely related. In both, post formation of the key electrophile (R–BH_2 or isoelectronic $[R_3N→BH_2]^+$), subsequent C–H borylation can actually be a facile process forming five membered boracycles as the kinetic products. The calculation of a metathesis type transition state leading to **85** also was consistent with the observation of a kinetic isotope effect (KIE) of 2.8 using an *ortho*-mono-deuterated analogue of $BnMe_2NBH_3$. This indicated that the C–H bond at which boron substitution occurs is broken during or before the regioselectivity-determining step. This is in contrast to Friedel–Crafts reactions, in these there is negligible or inverse KIEs.[85] This highlights a mechanistic distinction that can occur between C–H borylation with B–X (S_EAr mechanism, *vide infra*) and B–H (σ-bond metathesis type transition state) electrophiles. Related systems to **87** were subsequently shown to lead to intramolecular sp^3C–H borylation under forcing conditions (albeit with a different key electrophile proposed).[10] These studies also revealed that borylation of sp^2C–H sites is preferred over sp^3C–H (Scheme 42, bottom **89** *vs.* **90**).

Shortly after Vedejs' seminal work Murakami reported a method to borylate 2-aryl-pyridines and derivatives using BBr_3 and a bulky tertiary amine (Scheme 43) *e.g.* to form **91**.[86] This work was notable as it proceeded in high yield at ambient temperature using simple precursors. The authors proposed



Scheme 42 Hydride abstraction leading to: top, room temperature stoichiometric (in activator) borylation; middle, catalytic in activator C–H borylation at raised temperatures; bottom, sp^2C–H borylation dominating over sp^3C–H borylation.



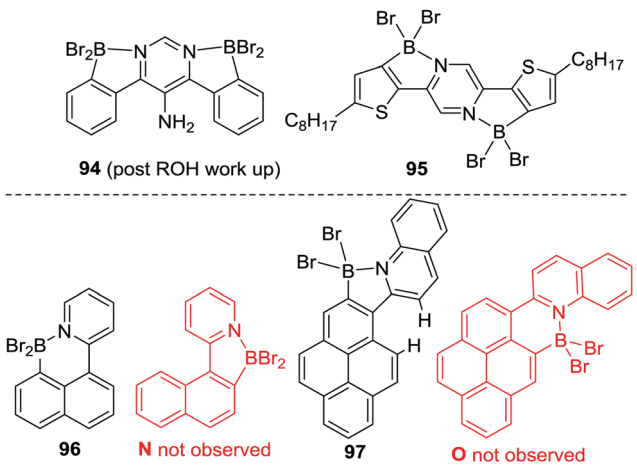
Scheme 43 Select examples from Murakami's pyridine directed C–H borylation.

borenium cation intermediates and an S_EAr mechanism (inset right Scheme 43). During the borylation of a naphthyl substituted pyridine two isomers, **92** and **93**, were formed, with the product from borylation at the more nucleophilic peri C–H position dominating. This is in contrast to Dewar's work on borylating naphthyl substituted anilines (Scheme 1) where no peri C–H borylation was observed. This disparity can be attributed to rapid and irreversible borylation (possibly due to rapid deprotonation of the arenium cation either by amine or $[BBr_4]^-$) in Murakami's system. This leads to product formation under kinetic control as previously observed in intermolecular C–H borylation reactions proceeding in the presence of an effective Brønsted base.[87] In Dewar's system the more forcing conditions and the absence of exogenous base presumably led to slow deprotonation (enabling isomerisation potentially at the arenium cation stage), ultimately forming the thermodynamic product (which is from borylation at the less hindered naphthyl beta position).[67]

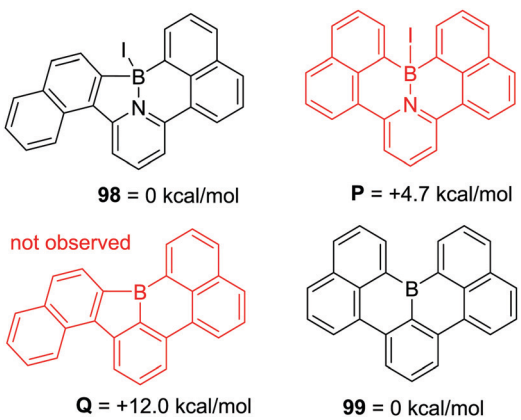
Since this original report Murakami's C–H borylation conditions have been used extensively, and extended to other N-directing groups including: 2-phenoxy-pyridines, imidazolones, pyrazines, pyrimidines, pyrazoles, imidazoles and quinolines.[88] It worth noting that with certain ditopic Lewis basic heteroarene directing groups, *e.g.* pyrazines and pyrimidines, double directed C–H borylation has also been achieved using BBr_3 and base, *e.g.* to form **94** and **95** (Scheme 44, top). Additional points of note from these reports include further evidence of kinetic control; *i.e.* the selective formation of **96** from borylation at the more nucleophilic naphthyl peri position (Scheme 44, bottom).[89,90] In contrast, applying comparable borylation conditions to related systems five membered boracycles are formed exclusively, *e.g.* **97**, with no compound O observed (**97** forms despite the presence of strain arising from close H···H contacts causing non-planarity in the polycyclic aromatic). Indeed, the formation of five membered boracycles using pyridyl directing groups is the most common outcome. Calculations performed on **96** and its isomer **N** at the M06-2X/6-311G(d,p) PCM (DCM) level and the B3LYP/6-31G(d)/LANL2DZ level (both commonly used in the literature for calculating boracycle structures and their relative energies) found them to be effectively isoenergetic (ΔE < 1.2 kcal mol^{-1}) at both levels. This supports the conclusion that pyridyl directed electrophilic C–H borylation reactions using BBr_3/base are proceeding under kinetic control (as only **96** is observed). In summary, these reports indicate that while five membered boracycles are often the kinetically preferred products from pyridyl directed C–H borylation minor changes in the compound being borylated can switch this selectivity from five to six membered boracycle formation.

A pyridyl directed C–H borylation reaction using a related borylation reagent mixture to Murakami's, BI_3 and *N*,*N*-dimethyl-*p*-toluidine, led to the formation of a five and a six membered boracycle in a single compound, **98** (Scheme 45) albeit at high temperature (140 °C). This report compared this outcome to the fact that only six membered boracycle formation was observed for the related C–BX_2 mediated intramolecular C–H borylation, with compound **99** (Scheme 45, bottom) being the thermodynamic product. This further emphasises the fact that when forming all sp^2-containing boracycles six membered rings are the generally observed products. In contrast, due to the presence of a tetrahedral boron centre (preferring bond angles around boron ≪120°) compound **P** was found to be 4.7 kcal mol^{-1} higher in energy than **98** and was not observed during borylation.[91]

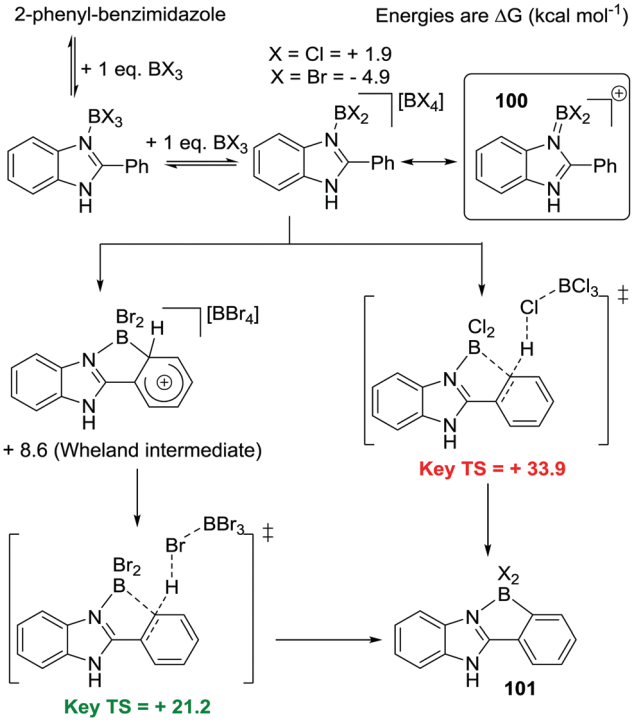
The mechanism of N→BX_3 mediated intramolecular C–H borylation was explored computationally by Uchiyama and Wang using 2-phenylbenzimidazole.[92] Starting from BBr_3 and BCl_3 borenium cations, **100**, were found to be key intermediates on the C–H borylation pathway (boreniums may be more readily accessible in this case due to a B=N containing resonance form stabilising the borocation to a greater extent than possible with $[pyridylBX_2]^+$,[93] Scheme 46, inset top right). From the borenium cations a C–H insertion mechanism proceeding *via* a four membered σ-bond metathesis transition state (related to that calculated for B–H electrophiles) was found to be a high barrier process. Instead Friedel–Crafts type mechanisms had lower energy barriers leading to **101**. With the B–Br congener a Wheland intermediate was found, which underwent subsequent



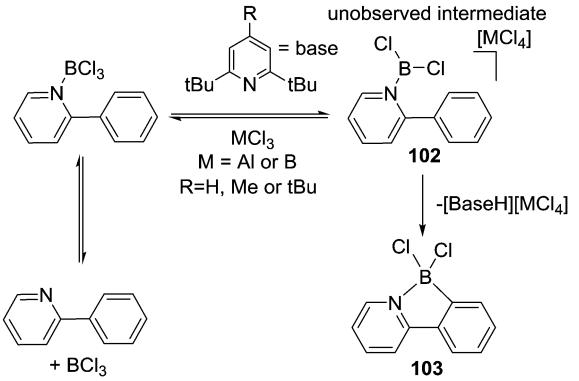
Scheme 44 Double directed borylation using Murakami's borylation conditions. Bottom, evidence for kinetic control in borylation using Murakami's conditions.



Scheme 45 Calculated energies on products from related N and C directed C–H borylation reactions at the B3LYP level of theory with a LANL2DZ basis set for iodine and 6-31G(d) basis set for the other atoms.



Scheme 46 Calculated mechanism for intramolecular C–H borylation of 2-phenyl-benzimidazole highlighting the disparity between the halide congeners.



Scheme 47 BCl_3/hindered base/MCl_3 directed borylation.

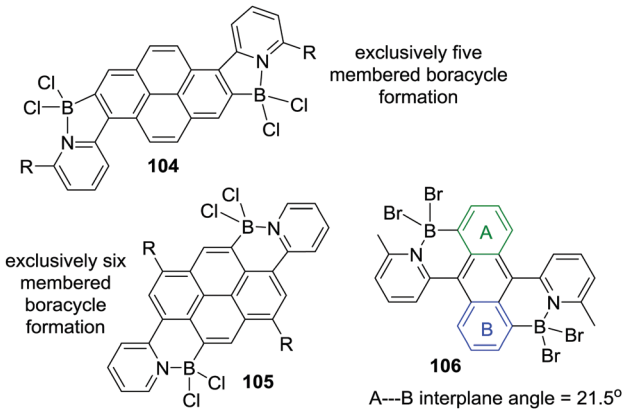
deprotonation with $[BBr_4]^-$, while for the B–Cl analogue a concerted process was calculated involving formation of the B–C bond concomitantly with deprotonation by $[BCl_4]^-$ (Scheme 46). The key differences between BCl_3/BBr_3 thus appears to be that forming the borenium cation **100** is more thermodynamically favoured with the bromo congener and that the $[BBr_4]^-$ anion enables more facile deprotonation than $[BCl_4]^-$. From these observations C–H borylation will be facilitated by: (i) increasing the solution concentration of the borenium cation by using more halophilic Lewis acids (*e.g.* $AlCl_3$) and (ii) adding exogenous bases to facilitate deprotonation.

Notably, 2-aryl pyridines do undergo borylation on addition of excess BCl_3 (or $PhBCl_2$)[94] even in the absence of an additional base. However, in studies with 2-phenyl pyridine the absence of additional base led to 0.5 eq. of protonated 2-phenyl-pyridine and 0.5 eq. of borylated 2-aryl pyridine. This indicates that some free 2-phenyl-pyridine is present in solution (due to the equilibrium between the pyridyl→BCl_3 Lewis adduct and free pyridyl/BCl_3) which is then enabling directed C–H borylation by fulfilling the role of Brønsted base (presumably with a lower barrier than if $[BCl_4]^-$ is the base based on Uchiyama's calculations). On addition of a hindered base (a 2,6-ditertbutyl substituted pyridine to preclude dative bond formation with Lewis acids) 2-phenyl pyridine borylation with BCl_3 proceeds slowly at ambient temperature and more rapidly on heating, and forms the C–H borylated product (**103**) quantitatively. Therefore, pyridyl-directed C–H borylation is feasible with just BCl_3 provided there is a suitable Brønsted base present. The combination of a hindered base and equimolar BCl_3/$AlCl_3$ also led to borylation to form **103** in this case borylation is rapid at room temperature.[93] Borylation is presumably proceeding *via* the borenium cation (**102**) expected from adding $AlCl_3$ to py-BCl_3 adducts (Scheme 47).[95] It should be noted that **103** can transfer chloride to **102**, resulting in additional Lewis acid being required to ensure high yielding borylation occurs. The more rapid borylation to form **103** observed in the presence of BCl_3/$AlCl_3$/hindered base (*vs.* with just BCl_3/hindered base) is presumably due to a higher solution concentration of the borenium cation than that using BCl_3 as halide abstractor (consistent with related borenium cation formation using BCl_3 being calculated to be endergonic – Scheme 44).

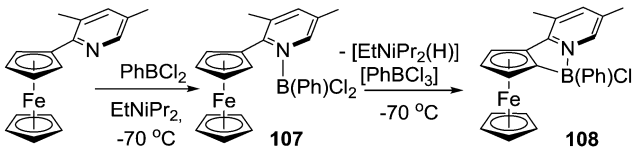
From these studies a number of key considerations for borenium cation mediated borylation can be defined: (a) ensuring a sufficient concentration of the borenium cation is present in solution; (b) that a competent Brønsted base is present otherwise the deprotonation step can have a high barrier. Thus, the addition of exogenous bases can be key to facilitate borylation *via* N→B dative bonded species, particularly with BCl_3 derived electrophiles due to the less basic nature of $[BCl_4]^-$ (relative to $[BBr_4]^-$). This is also consistent with earlier observations on E–BX_2 systems where many borylation reactions were facilitated by exogenous base.

The selectivity in borylation using BCl_3/$AlCl_3$/hindered base appears comparable to Murakami's conditions thus is presumably also proceeding under kinetic control, with both five and six membered boracycles accessible depending on the specific aromatic being borylated (*e.g.* **104** and **105** have both been reported, Scheme 48). Again, five membered boracycle formation is generally favoured over six, suggesting that their formation has a lower barrier in the absence of other factors (*e.g.* steric crowding/ring strain *etc.* Scheme 48).[96] Notably, these borylation conditions can be used to access borylated systems containing considerable strain (*e.g.* **106** in Scheme 48 which has significant distortion in the fused anthracene moiety).

It should also be noted that N→B directed electrophilic C–H borylation also can be performed with electrophiles other than BX_3, including with Ph_2BCl[97] and $PhBCl_2$ in the presence of a base. With $PhBCl_2$ borenium cations, again, are postulated but are not observed even at −70 °C,[94] with only the py-$BPhCl_2$ adduct, **107**, and the ferrocene borylation product, **108**, observable by NMR spectroscopy (Scheme 49). This suggests that the rate limiting step in this example involving borylation with $PhBCl_2$ may well be



Scheme 48 Five and six membered boracycle formation and right, a significantly strained system generated by electrophilic C–H borylation.

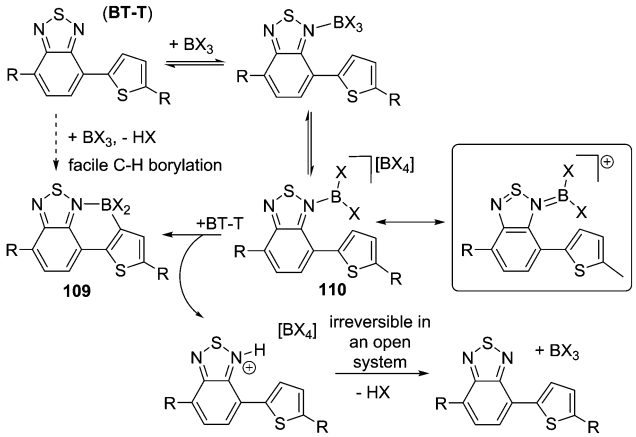


Scheme 49 Low temperature pyridyl directed borylation of ferrocene.

borenium cation formation, with subsequent C–B bond formation/deprotonation rapid in the presence of the exogenous base. It is notable that this N-directed borylation occurs at very low temperature, which in this case can be attributed to a combination of: (a) the highly nucleophilic nature of ferrocene and (b) the presence of an exogenous base.

Alongside pyridyl, another well studied Lewis basic moiety used in directed electrophilic C–H borylation is 2,1,3-benzothiadiazole (BT). It is notable that in contrast to pyridyl, benzothiadiazole directed C–H borylation reactions are rapid at room temperature with BBr_3 and with BCl_3 even in the absence of an exogenous base.[98] In an open system (where HX is removed with a flow of N_2) or on addition of a hindered base, borylation proceeds facilely and rapidly to form **109** (Scheme 50). This occurs when the π system being borylated is thiophene, but also with less nucleophilic aromatics (*e.g.* fluorene, phenyl). The more rapid borylation (relative to pyridyl analogues) is attributed to benzothiadiazole more effectively facilitating deprotonation (possibly due to the equilibrium for Lewis adduct formation favouring free benzothiadiazole significantly more than free pyridine due to the lower Lewis basicity of BT relative to pyridine). In addition, the borenium cation **110** will be more thermodynamically accessible than borenium **102**. This is due to a greater stabilisation of the boron centre by enhanced N=BCl_2 multiple bond character (see inset) with BT, supported by calculations on borenium cations ligated by both pyridine and BT.[93]

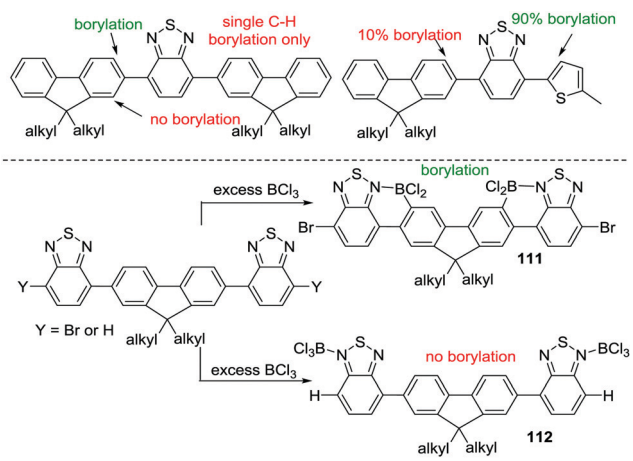
In benzothiadiazole directed electrophilic borylation steric effects again are significant, with steric hinderance disfavouring borylation (see Scheme 51 top). As expected, C–H borylation is more rapid with increasing arene nucleophilicity, which can be used to provide reasonable selectivity during borylation of



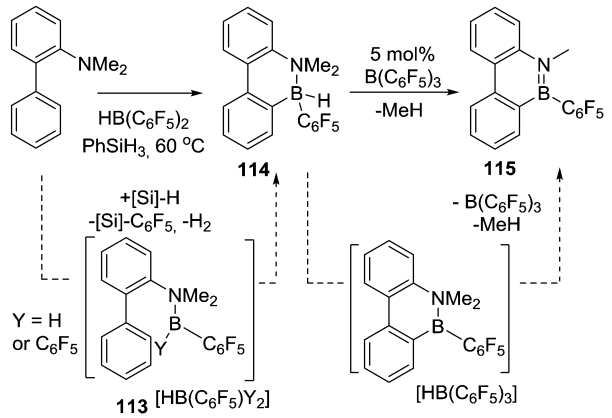
Scheme 50 Proposed mechanism for C–H borylation directed by benzothiadiazole (BT).

unsymmetrically substituted derivatives (Scheme 51, top right). Benzothiadiazole directed C–H borylation could be achieved using $PhBCl_2$ and also can be applied to borylate BT containing conjugated polymers using BCl_3.[99] Directed borylation also could be extended to the Se and N–R analogues of benzothiadiazole (2,1,3-benzoselenodiazole and benzotriazole).[100] Notably, while benzothiadiazole contains two nitrogen Lewis basic sites it only directs a single electrophilic C–H borylation. Presumably this is due to the lower Lewis basicity of BT (*e.g.* relative to pyrimidine where double borylation does proceed *e.g.* to form **94**), which will be further reduced on binding a Lewis acid to one N thereby precluding coordination of a second boron Lewis acid at the remaining nitrogen of BT. Molecules containing two BT groups can undergo double borylation with just BCl_3, *e.g.* to form **111**, provided a substituent disfavours BCl_3 coordination to the external nitrogen site, which otherwise forms more stable Lewis adducts such as **112** (see Scheme 51, bottom).

Recently, Chang, Park and co-workers have reported the directed C–H borylation of *N*,*N*-dimethyl-biphenyl-2-amines using a combination of $HB(C_6F_5)_2$ and $PhSiH_3$.[101] The exact electrophile performing C–H borylation is not known, but it is



Scheme 51 Selectivity/steric effects in BT directed C–H borylation.



Scheme 52 N-Directed borylation using an electrophile derived from $HB(C_6F_5)_2$.

feasible that borenium salts such as **113** (Scheme 52) generated by hydride abstraction (by a neutral borane) are intermediates consistent with the mechanistic work discussed early in this section. At some point Si–H/C_6F_5–B exchange occurs, with Si–C_6F_5 products observed, however, this may occur before or after the C–H borylation step. A functional group tolerance study revealed that while alkyl and halide groups were tolerated the presence of strong boron (and silicon) electrophiles led to decomposition of groups such as OMe and CF_3 as expected. Finally, the addition of $B(C_6F_5)_3$ to **114** enables demethylation, in a process again potentially mediated by a borenium cation, to generate **115** and methane as the by-product.

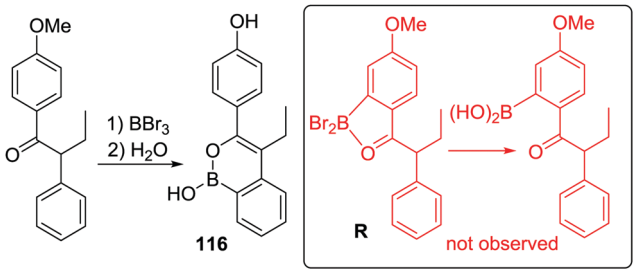
Directed electrophilic C–H borylation *via* N→B dative bond formation and borenium cations is the most well studied and understood system in Section 4. As well as providing access to many interesting borylated materials the increased understanding provided by breakthroughs in this area have enabled the expansion of E→BX_3 mediated directed C–H borylation to a wider selection of directing groups, including non-nitrogen based systems and these are discussed next.

4.2 *Via* BY_3 coordination to oxygen centred Lewis bases

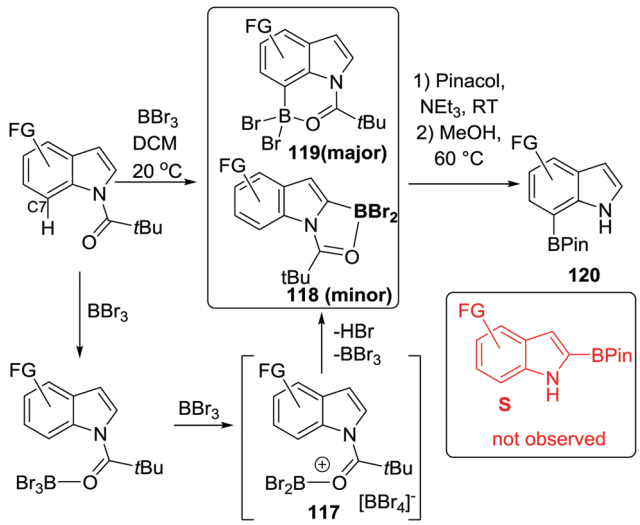
Nicholson and co-workers reported what is potentially the first example of a carbonyl directed electrophilic C–H borylation reaction.[102] Addition of excess BBr_3 enabled C–H borylation at room temperature to form **116** (isolated post treatment with H_2O, Scheme 53). Notably, C–H borylation was selective for six membered boracycles formation, with no products derived from a five membered boracycle observed (*e.g.* **R**). This may indicate boron-enolate formation prior to C–H borylation (as this would lead to an all sp^2 system which would now favour six membered boracycles formation), however the sensitivity of electrophilic C–H borylation to substituent effects (such as a deactivating OR group *meta* to the C–H borylation position, R maybe Me or BBr_2 formed through ether cleavage) may also preclude five membered boracycle formation *via* a carbonyl-BBr_3 adduct (and the borenium derived therefrom).

An expansion of carbonyl-directed C–H borylation to selective indole C7–H borylation was reported in 2019 independently by Ingleson and co-workers,[103] and Shi and co-workers (Scheme 54).[104] Steric interactions between the ^{t}Bu group with the C7–H of indole orients the directing group with the oxygen positioned proximal to the C7 position.[105] Mechanistic studies indicated that two eq. of BBr_3 are involved in C–H borylation, one coordinating to the acyl group, with the second then abstracting bromide to form borenium salt **117**. This is comparable to calculations on N→BX_3 mediated directed borylation reactions from Uchiyama and Wang. This intermediate then forms the borylated compounds **118** and **119** by S_EAr. These studies also calculated that for these substrates the six membered boracycle is the thermodynamic product. However, the reaction again appears to be proceeding under kinetic control with minor C2-borylation products (*e.g.* **118**, containing five membered boracycles) observed with some substrates. Notably, certain substrates that produced a mixture of **118** and **119** reacted further on addition of pinacol/NEt_3 to convert **118** to the C7-pinacol boronate-ester product, **120**, with the C2 isomer, **S**, not observed. It is unclear how this reaction proceeds as mixtures of **118** and **119** are stable under the borylation reaction conditions and on heating, thus pinacol appears essential to trigger C2–B cleavage/C7–B bond formation. This highlights the importance of observing primary products during C–H borylation for determining selectivity.

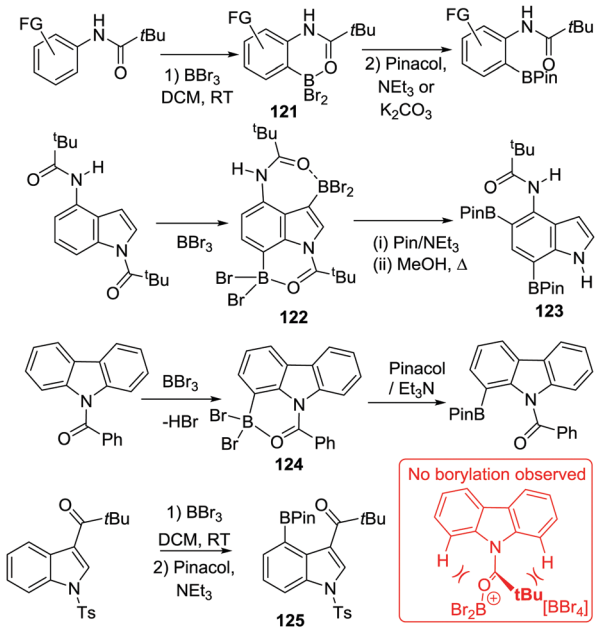
Both teams independently extended this methodology to selectively borylate anilines at the *ortho* position (Scheme 55 top)



Scheme 53 Carbonyl directed borylation for six membered boracycle formation.



Scheme 54 N-Pivaloyl directed C–H borylation of indoles.



Scheme 55 Extending acyl directed electrophilic C–H borylation to anilines, carbazoles and the C4 and C5 borylation of indoles.

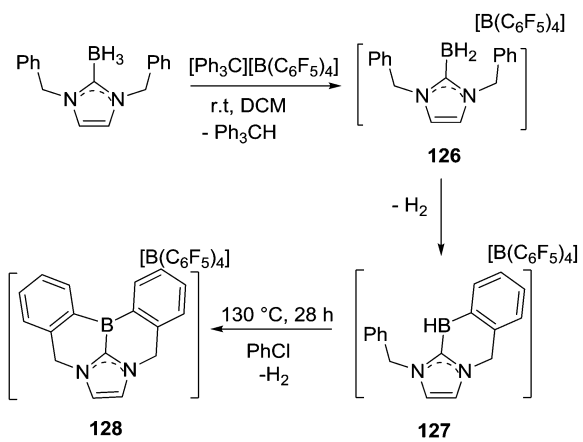
to form **121**. Calculations by Shi, Houk and co-workers on an aniline substrate indicated a borenium cation mediated directed C–H borylation mechanism. One significant difference between the calculations on the directed electrophilic C–H borylation of aniline and indole is the relative barriers of each step. For indole C7 borylation the barrier to arenium cation formation and subsequent deprotonation (by $[BBr_4]^-$) are effectively isoenergetic ($\delta\Delta G$ = 0.2 kcal mol^{-1}). However, for aniline C–H borylation the deprotonation step has a significantly larger barrier ($\delta\Delta G$ 8.1 kcal mol^{-1}) compared to arenium cation formation, indicating deprotonation is rate limiting in this case (nevertheless the barrier is still relatively low and reactions proceed within 1 h).

Regarding the scope of directed electrophilic borylation of anilines both benzoyl and pivaloyl directing groups were effective and a range of functional groups at the *ortho*, *meta* and *para* positions were tolerated. Notably, directed borylation of anilines could be combined with directed C7-indole borylation to enable a double carbonyl directed C–H borylation of a single substrate using BBr_3 to afford **122**. Again, the intermediate underwent a C–B cleavage/C–B bond formation process during protection with pinacol to afford **123**. Notably, pivaloyl directed borylation of carbazole was not successful, however, a benzoyl directing group enabled carbazole C–H borylation to form **124** (Scheme 55, middle). This can be attributed to the larger steric impact of the pivaloyl group relative to benzoyl that presumably results in the required orientation for C–H borylation having a much higher energy barrier (inset bottom right for a schematic highlighting these steric interactions, Scheme 55). Finally, Shi and co-workers extended this approach to the acyl directed C4 borylation of indoles, again, using just BBr_3 (Scheme 55, bottom) to form **125** (post pinacol protection), with a range of functional groups again tolerated. These studies clearly demonstrate that carbonyl directed electrophilic C–H borylation mediated by borenium cations is an underexplored route to access synthetically useful organoboranes.

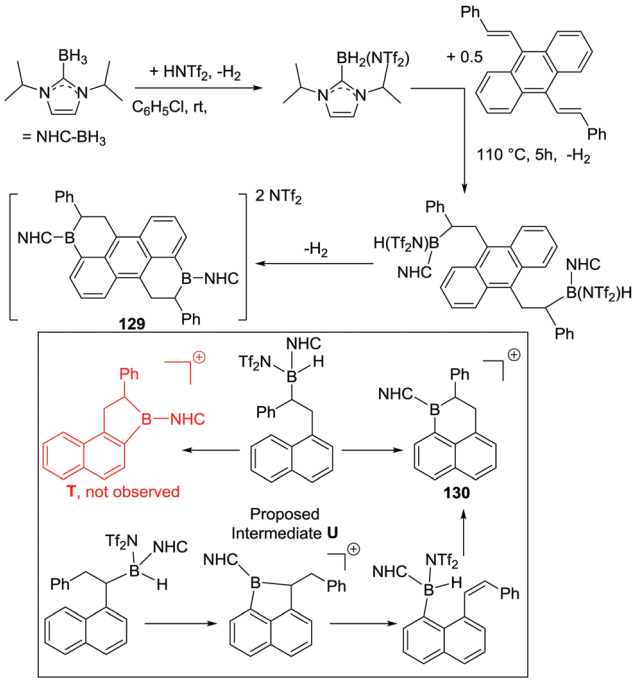
4.3 Other Lewis base directed borylation

Outside of the use of N and O Lewis bases as directing groups there are a limited number of examples using other Lewis bases to direct electrophilic C–H borylation. One notable exception is the report from Stephan and co-workers on intramolecular electrophilic C–H borylation using an NHC–borenium cation (NHC = N-heterocyclic carbene, Scheme 56). Hydride abstraction from an NHC–borane affords **126** (or a functional equivalent), which subsequently undergoes a dehydrogenative borylation to form **127** at room temperature.[106] The mild conditions required for this transformation is consistent with weakly stabilized borenium cations being able to rapidly perform intramolecular C–H borylation reactions. Further dehydrogenative borylation of **127** was achieved, albeit at 130 °C (24 h), affording borenium salt **128**. The reduced borylating reactivity of **127** compared with **126** is attributed to the reduced Lewis acidity of the boron center in **127** as a result of enforced planarity (increasing π delocalization) and strain in the transition state due to the fused nature of borenium **127**.

Extending this approach, Würthner and co-workers developed a sequential hydroboration-electrophilic C–H borylation of arylalkenes using NHC–borenium equivalents. This enabled access to a wide range of boron containing PAHs.[107] The initial borenium cation equivalent (NTf_2 is bound to boron in these species) was generated by treating the NHC–borane adduct with $HNTf_2$ at room temperature (evolving H_2).[108] By heating the mixture of the borenium functional equivalent and an appropriate alkene, *e.g.* 9,10-distyrylanthracene, at 110 °C a six-membered boracycle containing compound, **129**, was obtained *via* sequential alkene hydroboration – intramolecular electrophilic C–H borylation (Scheme 57). Hydroboration is presumed to precede C–H borylation as in previous work hydroboration using related boron electrophiles proceeded at room temperature.[108] The requirement for higher temperatures for C–H borylation to occur than when



Scheme 56 Intramolecular borylation directed by NHC→B dative bond.

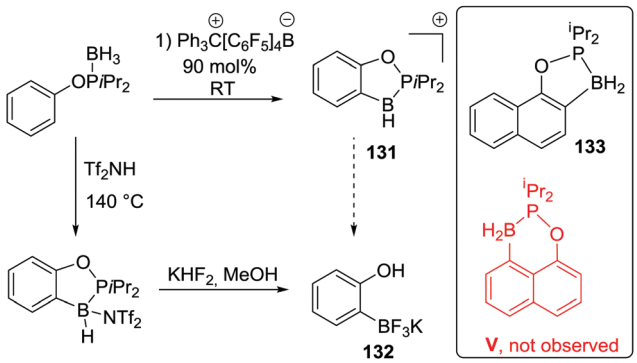


Scheme 57 Sequential hydroboration, intramolecular C–H borylation to form B_2-doped PAHs. Inset bottom, selectivity observed during the intramolecular C–H borylation and a plausible mechanism *via* a five membered boracycles.

using $[B(C_6F_5)_4]^-$ (*e.g.* to access **127**) may be attributed to the requirement to displace the NTf_2 anion in this case to generate the active boron electrophile, $[(NHC)B(R)–H]^+$, which then undergoes C–H borylation. In the formation of **127–129** H_2 is the observed by-product, thus, a four membered σ-bond metathesis transition state related to that proposed for C–H borylation using RBH_2 and $[R_3N–BH_2]^+$ electrophiles is presumably key in this C–B bond forming process.

Notably, in substrates where 5 or 6 membered boracycles are feasible final products (*e.g.* naphthyl derivatives) only six membered boracycles are observed (*e.g.* **130** is formed in good yield, with compound **T** not observed). Several related borylation reactions proceeding *via* borenium cations were shown to be irreversible and proceed under kinetic control. Thus, the formation of **130** directly from the alkene hydroboration product is unlikely (based on Knochel's work identifying the relatively slow kinetics of six membered boracycle formation in systems with multiple sp^3-centres). An alternative mechanism is more probable proceeding *via* the alternative alkene hydroboration isomer, then formation of a five membered boracycle (**U**) and finally isomerization *via* a retrohydroboration/hydroboration sequence in line with Knochel's studies (Scheme 57, bottom).

Phosphorous centred Lewis bases also have been used to direct electrophilic C–H borylation, albeit to our knowledge in only one report.[109] Phosphinite boranes were activated to form borenium cations (or functional equivalents) using trityl salts or strong Brønsted acids. When the anion was $[B(C_6F_5)_4]^-$ this led to rapid room temperature borylation to form **131** (Scheme 58). Notably, when the anion was Tf_2N^- instead of $[B(C_6F_5)_4]^-$

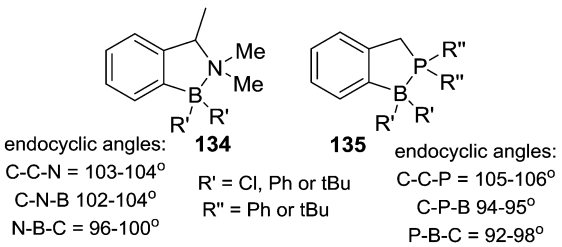


Scheme 58 Phosphorous directed *ortho*-C–H borylation of phenols.

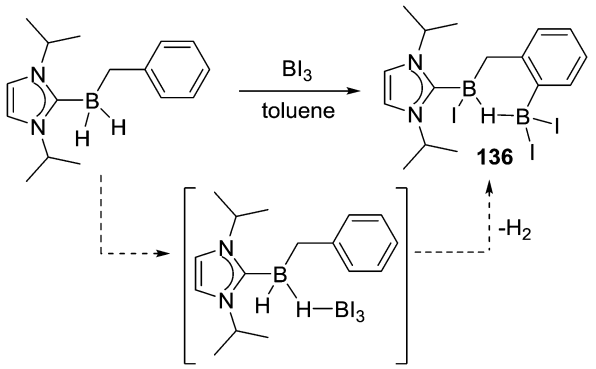
prolonged heating was required for C–H borylation to proceed, while with $^-$OTf only traces of the borylated product was observed even after prolonged heating. This, again, confirms the importance of accessing a highly electrophilic borenium type intermediate for C–H borylation to proceed, something facilitated by more weakly coordinating anions.

The primary products (*e.g.* **131**) could be reduced to the neutral BH_2 analogues by addition of a borohydride salt or converted into the respective *ortho*-phenol-trifluoro-organoborates, **132.** The latter conversion can be viewed as a traceless *ortho*-C–H borylation of phenols. However, the intermediacy of highly reactive borenium type species limited functional group tolerance while regioselectivity in *meta* substituted derivatives also was low. As expected, the borylation of a naphthyl derivative led to the selective formation of **133** (post addition of $[BH_4]^-$) with no six membered boracycle product, **V**, observed. This is consistent with the outcome for the isoelectronic amine analogues (compound **88**) and further confirms that five membered boracycles are the kinetic products (when containing multiple sp^3 centres). While the observation of comparable outcomes for nitrogen and phosphorous derivatives is notable, there are significant differences in the metrics for PB and NB boracycles. Analysis of solid state structures for the related series of compounds **134** and **135** reveal that BP containing systems have smaller bond angles presumably due to the longer B–P and P–C bond distances (Scheme 59).[110] Thus, there may be different outcomes in forming PB-boracycles *via* C–H borylation and further work is required to firmly identify reactivity and selectivity trends with P directing groups.

Finally, a B–H bond can also act as a directing group to enable C–H borylation using BI_3 to form **136**, albeit in low yield (12%, Scheme 60).[111] In this unusual example the more Lewis



Scheme 59 Comparison of boracycle metrics in N and P analogues.



Scheme 60 B–H directed intramolecular C–H borylation using BI_3.

acidic borane BI_3 is essential with BBr_3 and BCl_3 not leading to C–H borylation, possibly as these boranes do not form the initial hydride bridged complex (bottom, Scheme 60). The mechanism of borylation and the precise boron electrophile are unknown in this system, but HI evolution occurs, indicating either iodide or $[BI_4]^-$ (with $H[BI_4]$ then evolving HI) are acting as the base. Post C–H borylation the reaction of HI with a B–H species would then give the observed species (**136**), but HI was also reported to lead to decomposition of **136** and thus may also result in the low yield of **136**.

5. Conclusions

To facilitate summarizing important points this section is split into three covering key considerations regarding: (i) mechanism, (ii) reaction conditions and (iii) scope/selectivity. It should be noted that directed C–H borylation involving third period elements (*e.g.* S and P based directing groups) is under developed, therefore the discussion below applies only to C, N and O based directing groups.

5.1 Mechanistic considerations

There are two mechanisms reported to operate in intramolecular electrophilic C–H borylation, with the lowest energy pathway dependent principally on the identity of the boron electrophile. With B–X (X = halide) containing electrophiles directed C–H borylation generally proceeds *via* an S_EAr mechanism, with borenium cations proposed or calculated as intermediates in multiple cases. However, in other cases the active electrophile is unidentified, and some neutral electrophiles, such as C–BX_2 (X = Br or I) species, are also sufficiently reactive to effect intramolecular C–H borylation (even at ambient temperature and below). In some cases, the mechanism proceeds *via* an arenium cation intermediate, in other cases the C–B bond forming step and deprotonation step are concerted. Furthermore, in a number of cases the rate-determining step has been shown to be the deprotonation of an arenium cation. This is presumably due to the low basicity nature of the borylating medium. Thus, the electrophilicity of the borane and the identity (particularly the basicity) of the Brønsted base are often both important in enabling facile C–H borylation *via* this mechanism.

The second mechanism, sometimes termed dehydrogenative electrophilic borylation, involves intramolecular C–H borylation proceeding *via* B–H (and to a lesser extent B–R) containing electrophiles. This process proceeds *via* a four membered σ bond metathesis transition state and evolves H_2 (from B–H electrophiles) concomitant with C–B bond formation. It has been found to be the lowest barrier mechanism for C–H borylation mediated by both neutral and cationic B–H containing species and can also proceed rapidly at room temperature.

5.2 Reaction conditions

In many of the cases discussed the key requirement to enable C–H borylation is accessing a sufficiently electrophilic boron centre. Indeed, the greater the electrophilicity at boron the more facile the C–H borylation step generally is. Hence weakly stabilised borenium (*e.g.* $[R_3N\rightarrow BH_2]^+$) cations are particularly effective borylating species. A number of neutral boron electrophiles also are effective for borylation, particularly examples that do not contain good π donors that reduce the Lewis acidity at boron. Thus, intramolecular C–H borylation often proceeds readily with C–BX_2 and C–BH_2 electrophiles without the addition of Lewis acidic activators. In contrast, in systems containing amide groups, which are good π donors, additional Lewis acids are generally essential to convert the R_2NBX_2 species into a more electrophilic borane to enable C–H borylation. This can proceed *via* addition of an electrophile to N, converting the amido borane into a borenium cation or a functional equivalent thereof (*e.g.* $R_2(E)NBX_2$, E = electrophile, and when E = H^+ this is a borenium cation). Indeed, intramolecular C–H borylation reactions proceeding through bona-fide borenium cations are amongst the more facile conversions. Therefore, the major consideration in many systems is identifying an appropriate reagent to access the borenium cation.

With enhancing of electrophilicity at boron an enabling factor for intramolecular C–H borylation, it is no surprise that bromo-boranes are more effective at C–H borylation than chloro analogues. This is due in part to enhanced electrophilicity *e.g.* of C–BBr_2 *vs.* C–BCl_2 species, but also due to borenium cations being more readily accessible through bromide abstraction from Lewis adducts of BBr_3 (*e.g.* by another equivalent of BBr_3) compared to Lewis adducts of BCl_3 (where chloride abstraction from $L\rightarrow BCl_3$ with BCl_3 is more energetically uphill). It should be noted that accessing borenium cations from $L\rightarrow BH_3$ species invariably requires stoichiometric quantities of strong hydridophiles that are relatively expensive (*e.g.* $[Ph_3C][B(C_6F_5)_4]$), thus making these routes less attractive for large scale synthetic applications unless they can be made to turnover (and therefore use sub-stoichiometric amounts of the hydridophile activator).

The Lewis basicity of the directing group, be it involved in a dative bond or a covalent bond to boron, is also crucial. A number of factors need to be considered: (i) the Lewis base has to be sufficiently basic to form a dative bond to the borane reagent, if not this problem can be circumvented *e.g.* in N–H containing system by using deprotonation and subsequent transmetalation to BX_3; (ii) a less basic (be it as a dative bond or π donor to boron) nucleophile leads to a more reactive boron electrophile and thus more facile C–H borylation.

Finally, the role of a basic additive often proves vital in many C–H borylation reactions, particularly those proceeding *via* an S_EAr mechanism (the base is not involved in the rate determining step in the σ-bond metathesis mediated borylation, thus exogenous bases do not facilitate borylation *via* this mechanism). The repeated observation that bases (both bulky amines and borate anions) dramatically improve C–H borylation outcomes is consistent with calculations on intramolecular C–H borylation reactions that proceed *via* an S_EAr mechanism. In these arenium cation deprotonation is often rate limiting, thus an appropriate base (that does not quench the boron electrophile by adduct formation) that has sufficient Brønsted basicity can result in lower barriers for C–H borylation. In the absence of an exogenous base *in situ* formed borate anions, such as $[BBr_4]^-$, can fulfil this role (and then subsequently release HBr to form BBr_3 for further C–H borylation). Therefore, the identity of the by-product from borenium cation formation can also be important in determining if intramolecular C–H borylation reactions proceed.

5.3 Factors controlling substrate scope and selectivity

In both borylation mechanisms the nucleophilicity of the π system has been found to be important. Unactivated and deactivated (towards reaction with an electrophile) (hetero)arenes are challenging to borylate using any directing group. Activated heteroarenes, such as thiophenes, are much more amenable to directed electrophilic C–H borylation, as are alkenes, with both readily borylated even using weaker boron electrophiles (including a fluoroborane electrophile in one case). Functional group tolerance is clearly dependent on the electrophilicity of the borane, thus less Lewis acidic boranes will have greater functional group tolerance but be restricted to borylating only the most nucleophilic π systems. However, with the optimal conditions, directed C–H borylation can occur facilely at room temperature and tolerate a broad range of functional groups. This is particularly the case in the borylation of nucleophilic arenes where borylation is rapid, and thus occur in preference to undesired side reactions. For example, in a very recent report directed electrophilic C–H borylation of aniline derivatives tolerated Me, ^{t}Bu, F, Cl, Br, I, CF_3, esters, CN, $OSiR_3$, SMe, OR, N=NPh and heteroaryl functional groups.[112]

In systems where multiple boracycles are potentially accessible through intramolecular electrophilic C–H borylation the boracycle ring size formed is dependent on the boron electrophile and the unit linking the π system to the directing group. For example, for all sp^2 based systems six membered boracycles are the observed products. This is partly due to the more favourable bond angles present in six membered all sp^2-boracycles, but also due to the higher energy of five membered all sp^2 C_4B boracycle units that are formally anti-aromatic. Notably, the introduction of one or more tetrahedral centres into the boracycle forming through the C–H borylation step leads to more complex outcomes. In general, in systems with one or more tetrahedral centres five membered boracycles are the kinetic products from intramolecular C–H borylation, but in some cases these can convert to six membered boracycles (*e.g.* by retrohydroboration–hydroboration) and these can be the thermodynamic products. The occurrence of this isomerisation depends not only on the relative energy of the five and six membered boracycle but there being a viable isomerisation pathway. In many borylation systems where there is an exogenous base present (for S_EAr mechanisms) or if H_2 is lost (*via* dehydrogenative borylation), C–H borylation is irreversible and thus the kinetic product is formed exclusively. Which in most cases is a five membered boracycle (provided at least one sp^3 centre is present).

Other factors that can affect the outcome from C–H borylation include ring strain and torsional twisting in PAHs (*e.g.* to reduce steric effects in fjord regions). Both can lead to C–H borylation being precluded or less common C–H borylation selectivity (*e.g.* switching from five to six membered boracycles as the kinetic products in pyridyl directed borylation). Finally, most C–H borylation reactions discussed herein show a significant preference to borylate the less sterically hindered C–H position when there are multiple feasible borylation sites present in a molecule. Although in cases where the kinetic and thermodynamic products are different the borylation conditions again will control the outcome. For example, alpha borylation of naphthalenes (the kinetic product) is observed in room temperature irreversible borylation reactions despite this site being more hindered. In contrast, in other cases the thermodynamic product from beta naphthalene C–H borylation is the only product observed *e.g.* under Dewar's more forcing borylation conditions which appear to be operating under thermodynamic control. However, these are among the exceptions, and in the majority of cases C–H borylation proceeds under combined steric (least hindered) and electronic (most nucleophilic) control enabling there to be high confidence in predicting the borylation reaction outcome *a priori*.

The future of intramolecular electrophilic C–H borylation will hopefully see many more impressive advances as there remains much scope for applying this methodology in synthetic endeavours, particularly outside of the organic materials field. In addition, the utilisation of directing groups that are not based on nitrogen is still relatively undeveloped. Therefore, further investigations utilising other directing groups, particularly based on the third period (and below) elements, are overdue.

Conflicts of interest

There are no conflicts to declare.

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