Chemoselective Suzuki-Miyaura Cross-coupling Enabled by Speciation Control

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By

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3. "*Strategies Towards Chemoselective Suzuki-Miyaura Cross-Coupling*": J. W. B. Fyfe and A. J. B. Watson, *Synlett,* 2015, **26**, 1139–1144.
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5. "*Tandem One-pot Chemoselective Suzuki-Miyaura Cross-Coupling Enabled by Nucleophile Speciation Control*": C. P. Seath, J. W. B. Fyfe, J. J. Molloy and A. J. B. Watson, *Angew. Chem., Int. Ed.,* 2015*,* **54***,* 9976–9979.
6. "*When Two Reactions Become One"*: J. W. B. Fyfe and A. J. B. Watson, *Science*, 2016, **351**, 26–27.
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8. "*Synthesis of Oxindoles and Benzofuranones via Oxidation of 2-Heterocyclic BMIDAs"*: C. P. Seath, J. W. B. Fyfe, J. J. Molloy and A. J. B. Watson, *Synthesis,* 2017, **49**, 891–898.
9. "*Chemoselective Suzuki-Miyaura Cross-coupling via Kinetic Transmetallation"*: J. W. B. Fyfe, N. J. Fazakerley and A. J. B. Watson, *Angew. Chem., Int. Ed.,* 2017*,* **56***,* 1249 –1253.

Abstract

Boronic acids and esters are one of the most widely used compound classes in organic chemistry. Recently, diboron systems have emerged as a powerful approach towards complex molecule synthesis. Selectivity in these systems is typically achieved through the use of protecting group strategies in which one boron residue is rendered unreactive under the prevailing reaction conditions, allowing selective manipulation of an unprotected unit. However, while these methods offer excellent selectivity, they do have the drawback of requiring additional synthetic manipulations, *i.e.*, removal of the protecting group to allow subsequent functionalisation, limiting the overall efficiency of these processes.

Boronic acids and esters undergo complex equilibria in solution. We have shown that control of these equilibria has been leveraged during the Suzuki-Miyaura reaction to enable the formation of a new, reactive BPin ester without the need for additional protecting group manipulations. Extensive optimisation identified that the nature of the base and quantity of water in the reaction were key in controlling the speciation events in the reaction. This allowed the generation of a broad substrate scope of formally homologated BPin esters. These newly generated reactive boron species were then reacted *in situ* in an iterative process, forming either terminal triaryl or contolled homologation products. The reaction was also found to have a temperature dependence, where under identical controlled basic conditions either the homologated BPin or the cross-coupled BMIDA species could be obtained based purely upon the temperature of the reaction. A series of control reactions aided in identifying the key processes in the reaction and, more importantly, the order in which these processes must occur in order to achieve the desired reaction.

This work led to the development of methods to enable chemoselective reactions within non-protected diboron systems. This demonstrated how chemoselective Suzuki-Miyaura cross-coupling can be achieved within boronic acid/BPin ester diboron systems by exploiting kinetic control of transmetallation while maintaining control of solution speciation events. This allows the selective reaction of boronic acids in the presence of BPin esters again without the need for protecting group manipulations, as either additional synthetic steps or *in situ*.

Chemoselective transmetallation was then combined with chemoselective oxidative addition in order to establish the first complete chemoselective control over two of the three key mechanistic processes of the Suzuki-Miyaura reaction. This enables a one-pot sequential chemoselective Suzuki-Miyaura reaction without the requirement for any *in situ* modification of the reaction conditions (temperature change, sequential addition) or reactants (protecting group removal, boron species interconversion).

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Lastly I would like to thank my supervisor Dr Allan Watson, whose enthusiasm and support have made me the seasoned chemist I am today. Your tendancy to ask the impossible has shown me just how much can be accomplished if you work hard enough and also – the invaluable lesson that the senior academic is not always right. It has been both a pleasure and a priviledge to work with you for the past 3 years.

Abbreviations

Ac – Acyl

Bn – Benzyl

BOC – *t*-Butoxycarbonyl

BINOL – 1,1'-Bi-2-naphthol

BrettPhos – 2-(Dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-tri*iso*propyl-1,1′-biphenyl

Cat – Catalyst

Cbz – Carboxybenzyl

CFL – Compact fluorescent lamp

Cy – Cyclohexyl

DAN – Diaminonapthalene

DavePhos – 2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl

Dba – Dibenzylideneacetone

DCE - Dichloroethane

DCM – Dichloromethane

DMP – Dess-Martin periodinane

DMSO – Dimethyl sulfoxide

Dppe – 1,2-Bis(diphenylphosphino)ethane

Dppp - 1,3-Bis(diphenylphosphino)propane

Dppf – 1,1'-Bis(diphenylphosphino)ferrocene

Dtbbpy – 4,4'-Di-*tert*-butylbipyridyl

EDG – Electron donating group

EWG – Electron withdrawing group

Equiv – Equivalents

HPLC – High performance liquid chromatography

HTMP – 2,2,6,6-Tetramethylpiperidine

JohnPhos – (2-Biphenyl)di-*tert*-butylphosphine

MIDA – *N*-Methyliminodiacetic acid

NMR – Nuclear magnetic resonance

nOe – Nuclear Overhauser effect

OTf – Triflate

Pin – Pinacol

RuPhos – 2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl

R.t. – Room temperature

SM – Suzuki-Miyaura

SPhos – 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl

TES – Triethylsilane

THF – Tetrahydrofuran

XantPhos – 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

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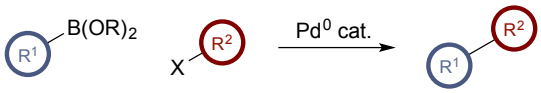
1 Introduction

1.1 The Suzuki-Miyaura reaction

Since its inception in 1979, the Suzuki-Miyaura (SM) cross-coupling has become one of the most widely implemented methods of carbon-carbon bond formation in synthetic organic chemistry. Originally reported by Akira Suzuki and Norio Miyaura,[1] the reaction to which they lend their names involves the palladium catalysed cross-coupling of an organoboron species with an organohalide or pseudo-halide (Scheme 1).



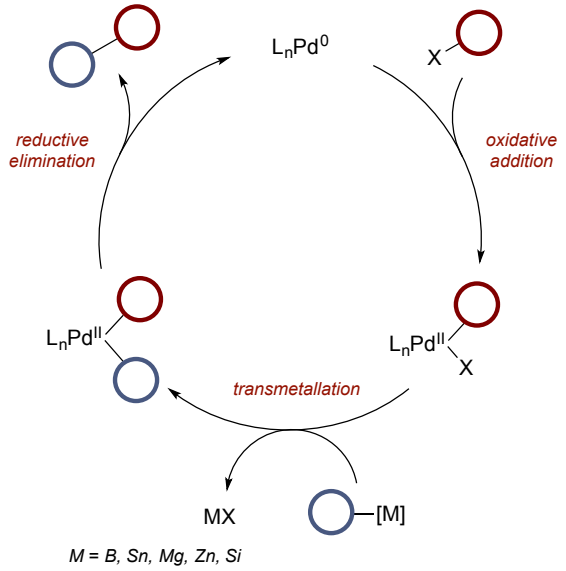
Scheme 1: Suzuki-Miyaura cross-coupling

The SM reaction has found favour among both academic and industrial chemists due to its mild conditions and excellent functional group tolerance. In addition to this, and in contrast to other palladium-catalysed cross-couplings developed around the same time, the SM reaction utilises relatively inert organoboron reagents and produces relatively benign byproducts. This makes it ideal for use in pharmaceutical and agrochemical synthesis in which downstream toxicity is a major concern. Indeed, a study in 2011 showed that over 40% of all C-C bond formations in industry were accomplished using the SM reaction.[2] Other palladium-catalysed cross-coupling reactions such as the Kumada (organomagnesium),[3] Negishi (organozinc),[4] or Stille (organostannane)[5] utilise highly reactive or toxic organometallic reagents, thus limiting their reaction scope and prohibiting their use on scale. In contrast, the organoboron reagents employed in SM cross-coupling are relatively benign and, as a result of this, a large selection is commercially available.

In addition to its popularity in an industrial setting, the SM reaction has also received a great deal of attention from academia over the past few decades. A large number of studies have been carried out focussing on expanding the scope of Suzuki and Miyaura's seminal paper, in order to tolerate a much more diverse range of both organoboron nucleophiles and organohalide electrophiles.

1.2 Mechanism of the Suzuki-Miyaura reaction

As with other palladium-catalysed cross-couplings, the Suzuki-Miyaura reaction proceeds through a three-step catalytic cycle involving: oxidative addition, transmetallation, and reductive elimination (Scheme 2).



Scheme 2: General catalytic cycle for palladium-catalysed cross-coupling

Research into the various phases of this mechanistic pathway have led to a much greater understanding of the SM reaction and as a result of this, a series of new catalysts, ligands, and even organoboron reagents have been developed in order to facilitate more general and efficient cross-coupling.[6,7] The various aspects of the mechanism of the SM reaction and the advances associated with them will be discussed in the following sections, with a focus on transmetallation.

1.2.1 Oxidative addition

The first step of the SM catalytic cycle involves the oxidative addition of the Pd^0 catalyst into the carbon-halogen bond of the organohalide. This forms a Pd^{II} intermediate. This step of the catalytic cycle is often rate-determining.[8–10] The relative rates at which oxidative addition occurs to various organohalides was outlined by Suzuki and generally follows the trend where I > OTf > Br >> Cl.[8] This order of reactivity tracks with the bond dissociation energy (BDE) of the parent halide (Figure 1).[11] Due to their high BDE, it is more difficult to achieve oxidative

addition into aryl chlorides and very difficult in the case of aryl fluorides. This makes them typically inert with respect to SM cross-coupling, however this can be overcome in the case of aryl chlorides by utilising tailored catalyst and ligand systems (*vide infra)*.

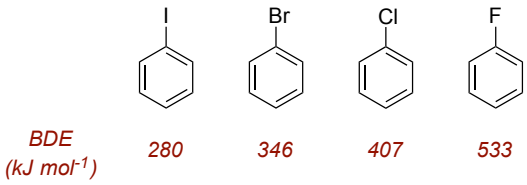


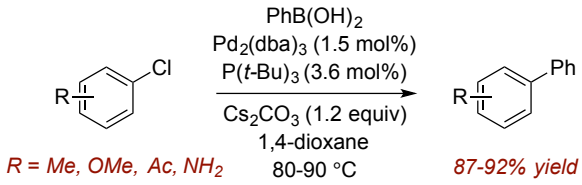
Figure 1: Bond dissociation energies of aryl halides

Despite not being the most activated towards oxidative addition, bromides are the most commonly employed halide electrophiles in SM cross-coupling. This is most likely due to their high commercial availability in comparison to iodides and triflates, in addition to being much more reactive than the equivalent chlorides.[12]

The rate of oxidative addition can be influenced by the nature of the other substituents on the aryl ring.[8] For example, the introduction of electron withdrawing groups (EWG) can enhance the rate of oxidative addition by drawing electron density away from the ring and serving to weaken the carbon-halogen bond. This electronic tuning can allow less reactive aryl chlorides to be successfully cross-coupled. Conversely the addition of electron donating groups (EDG) will serve to deactivate halide electrophiles, resulting in slower oxidative addition and precluding the use of less reactive chloride electrophiles in SM cross-coupling.

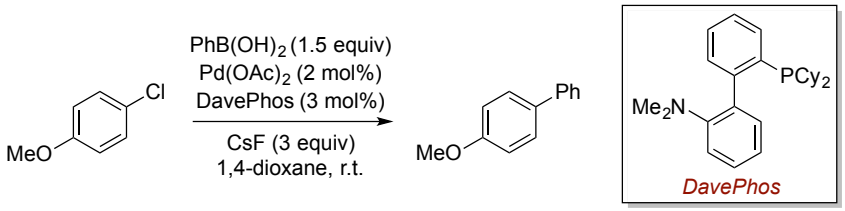
In order to combat this limitation in the electrophile scope, in the late 90's a series of electron rich phosphine ligands were developed which could promote the oxidative addition of less reactive organohalides and pseudohalides. Fu and co-workers demonstrated the use of bulky trialkyl phosphine ligands to facilitate the cross-coupling of electron rich aryl chlorides in high yield.[13] It was proposed that, when bound to palladium, the electron rich phosphine increases the nucleophilicity of the metal, thus promoting oxidative addition. The steric bulk of the ligand was also attributed with increasing the rate of reductive elimination. The group found that P(*t*-Bu)$_3$ in combination with $Pd_2(dba)_3$ was effective in cross-coupling aryl chlorides

bearing a range of substituents, including deactivating electron donating groups (Scheme 3). This catalyst/ligand system was also effective in cross-coupling substrates bearing *ortho* substituents, enabling the reaction of the sterically hindered 2-chloro toluene with 2-methylphenylboronic acid in good yield (87%).



Scheme 3: Use of trialkyl phosphines to cross-couple unactivated chlorides

In the same year that Fu demonstrated the use of trialkyl phosphines as ligands for SM cross-coupling, Buchwald and co-workers reported the development of a range of dialkylbiaryl phosphine ligands. While investigating the use of this class of ligand for C-N bond formation, the group found that their ligand DavePhos was particularly effective in SM reactions, enabling the efficient cross-coupling of unactivated aryl chlorides at room temperature (Scheme 4).[14]



Scheme 4: Room temperature coupling of unactivated chlorides with dialkylbiaryl phosphines

These dialkylbiaryl phosphines were found to be competent in a range of cross-coupling reactions, by varying the aryl substituents as well as the sterics of the alkyl groups in order to tune reactivity (Figure 2).[6,15] In general the bulky and electron donating character of these ligands helps to stabilise the monoligated [L_1Pd^0] species, which is thought to be the active species in the catalytic cycle, prior to oxidative addition.[16] It has been shown that oxidative addition occurs much faster from the monoligated species in comparison to the equivalent bisligated [L_2Pd^0] species.[9] It is believed this is simply based on sterics, with the smaller [L_1Pd^0] able to achieve closer proximity to the organohalide electrophile and therefore undergo faster oxidative addition. The addition of substituents in the *ortho* position of the lower ring

(R_1 and R_2) aids in avoiding the formation of [L_2Pd^0] and thus increasing the concentration of the active [L_1Pd^0] species. Substituents in these positions also avoid the formation of palladacycles, again ensuring a high quantity of [L_1Pd^0] remains available. The alkyl substituents on phosphorus increase the rate of oxidative addition by increasing the electron density on phosphorus. The steric bulk of these substituents also influences the rate of reductive elimination, with bulky *t*Bu groups offering the greatest increase. Lastly the introduction of substituents in the *ortho* position of the top aryl ring ensures the PR_2 is conformationally fixed over the lower ring, which in turn stabilises the [L_1Pd^0] species and promotes reductive elimination.

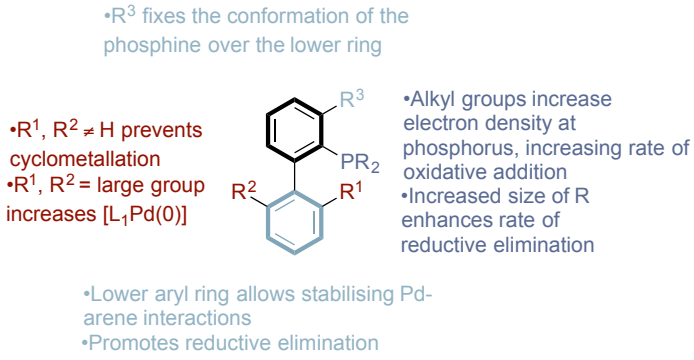


Figure 2: Structural features of dialkylbiaryl phosphines and their effect on reactivity

Through the modification of these parameters, the Buchwald group were able to rationally design a wide range of dialkylbiaryl phosphines to promote a number of cross-coupling reactions which were previously impossible (Figure 3).[17–19] For example, using SPhos as a ligand enabled the cross-coupling of very hindered coupling partners in excellent yield,[18] whereas the BrettPhos ligand enabled the efficient cross-coupling of aryl tosylate and mesylate electrophiles with a range of boronic acids and esters (Scheme 5).[19]

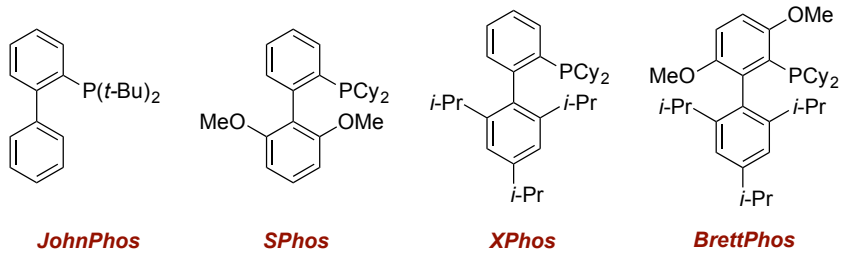
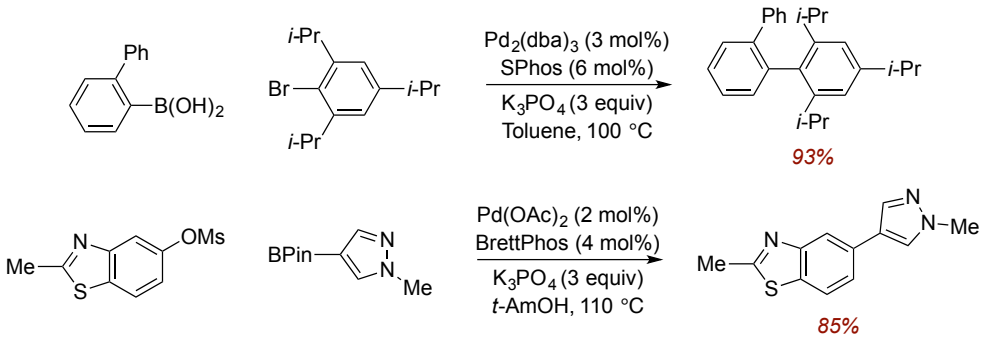
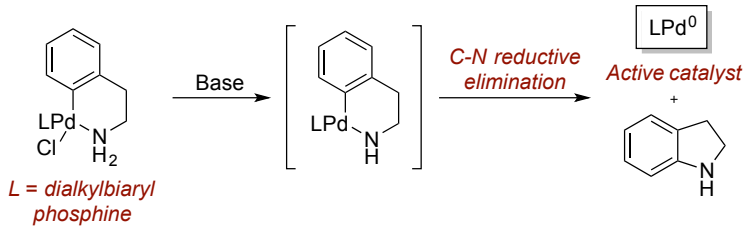


Figure 3: Selection of dialkylbiaryl phosphines developed by Buchwald and coworkers



Scheme 5: Cross-coupling of challenging electrophiles with Buchwald ligands

Having demonstrated that monoligated [L_1Pd^0] species constitute the active catalytic component in terms of oxidative addition, Buchwald and co-workers then sought to develop more efficient methods for the generation of this active catalytic species *in situ*. Classical sources of Pd^0, such as $Pd_2(dba)_3$, utilise coordinating ligands which can hinder the formation of the active [L_1Pd^0] species[20] or even deactivate the catalyst[21] whereas Pd^{II} salts such as $Pd(OAc)_2$ require an *in situ* reduction.[22] To circumvent this, Buchwald developed a palladacycle precatalyst containing palladium bound to a dialkylbiaryl phosphine ligand which, upon treatment with a base, could undergo C-N reductive elimination to form the active [L_1Pd^0] species (Scheme 6).[23]



Scheme 6: Active catalyst generation from palladacycle precatalyst

Since the introduction of this class of palladacycle precatalyst, the group have worked on increasing the efficiency of the generation of the active catalytic species (Figure 4). As such, these have evolved to undergo reductive elimination under even milder conditions. This is a result of the higher acidity of the aromatic amine in comparison to the aliphatic amine, allow a more facile deprotonation (Figure 4, 1st Gen *vs*. 2nd Gen).[24] In order to further increase the stability of these precatalysts and allow the generation of complexes bearing bulkier phosphine ligands such as

BrettPhos (see Figure 3 above), the group developed precatalysts based on a 2-aminobiphenylmesylate palladacycle (Figure 4, 3rd Gen).[25] The latest generation addresses one of the drawbacks resulting from the incorporation of the 2-aminobiphenyl backbone.[26] With these precatalysts, upon C-N reductive elimination to generate the active catalyst, a carbazole byproduct is also formed. This can potentially undergo *N*-arylation, consuming valuable starting material and reducing overall reaction efficiency. To overcome this potential issue, the 4th generation features an *N*-methylaminobiphenyl backbone. This produces *N*-methylcarbazole as a byproduct and therefore eliminated the possibility of undergoing *N*-arylation.

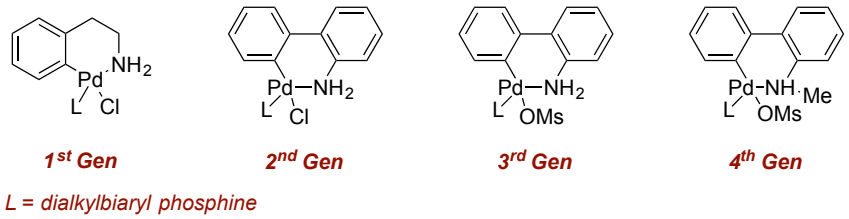
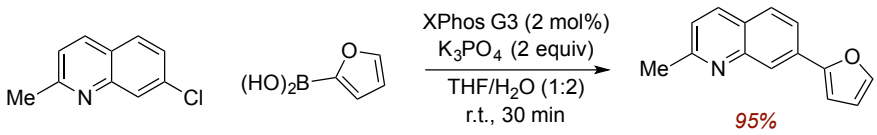


Figure 4: Buchwald palladacycle precatalysts

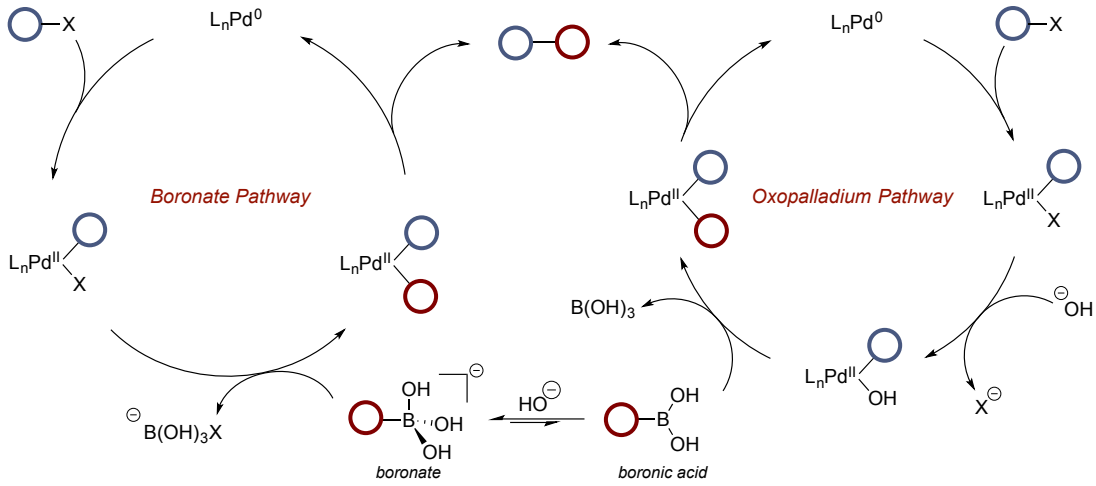
These precatalysts mark a significant advance in the field of cross-coupling, enabling the rapid generation of active monoligated Pd^0 under mild conditions. This allowed the cross-coupling of particularly sensitive substrates, such as 2-heteroaryl boronic acids, species which are prone to protodeboronation under typical SM conditions (Scheme 7). Due to the rapid generation of the highly active [L_1Pd^0] species, oxidative addition can occur at an enhanced rate, without the requirement for forcing reaction conditions such as high temperature. The mild reaction conditions also ensure that unstable boronic acids undergo protodeboronation less readily, and therefore transmetallation with the oxidative addition complex [$L_2Pd^{II}Ar(X)$] becomes the favoured pathway, allowing unstable heteroaryl boronic acids to be coupled efficiently in excellent yield.



Scheme 7: Use of palladacycle precatalyst to cross-coupling sensitive heteroaryl boronic acids

1.2.2 Transmetallation

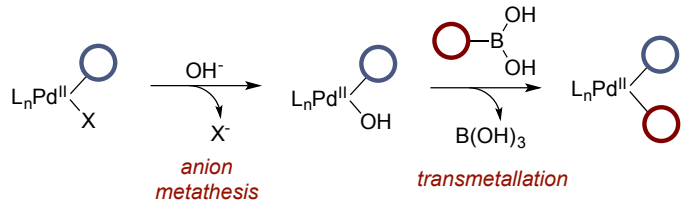
While oxidative addition is relatively well understood, the second step of the SM catalytic cycle, transmetallation, has been the subject of much debate. Two pathways have been proposed in the literature, the originally favoured boronate pathway and the more recently discovered oxo-palladium pathway (Scheme 8).[27]



Scheme 8: Proposed catalytic cycles for the SM reaction

The boronate pathway was originally proposed by Suzuki and co-workers in 1979,[1] and for many years was the accepted mechanism for transmetallation. In this pathway, following oxidative addition of the Pd^0 catalyst the organohalide, a charged boronate undergoes transmetallation with the Pd-halide complex. This tetrahedral boronate is formed from the parent boronic acid under the basic reaction conditions, and it was thought that the more nucleophilic charged species was necessary for transmetallation to occur. However, in recent years a number of studies have suggested that transmetallation takes place from the neutral boronic acid, and not the charged boronate.[27] Here, following oxidative addition, the Pd-halide complex undergoes anion metathesis with the hydroxide anion formed under the, usually, aqueous basic reaction conditions. This oxo-palladium species can then undergo transmetallation with the neutral sp^2 hybridised boronic acid and, releasing boric acid (Scheme 9). Suzuki and Miyaura originally proposed this as a possible mechanism for transmetallation in 1985 when, following a study on the cross-coupling of alkenyl

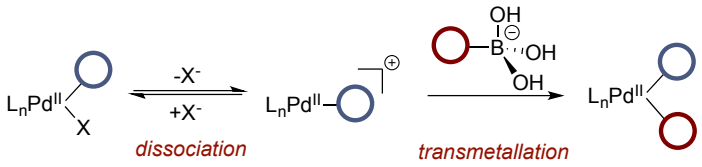
boron reagents with alkenyl halides, they made several observations that seemed to contradict the boronate pathway.[28]



Scheme 9: Anion metathesis and oxo-palladium transmetallation

Firstly, the authors noted that when using Lewis bases such as trimethylamine in place of hydroxide or alkoxide, no transmetallation occurred. Secondly, when using a preformed lithium boronate in the absence of base only a small amount of product was formed (9% yield). Lastly, trace quantities of reduction products were observed. These were attributed to the formation of an alkoxopalladium(II) species followed by PdH formation which leads to reduction. These observations suggested that the reaction was proceeding through an oxo-palladium species. However, based on this evidence alone a boronate pathway could not be ruled out as, for example in the case of the Lewis base experiment, the absence of hydroxide would have precluded the formation of any boronate and therefore prevent transmetallation *via* that pathway.

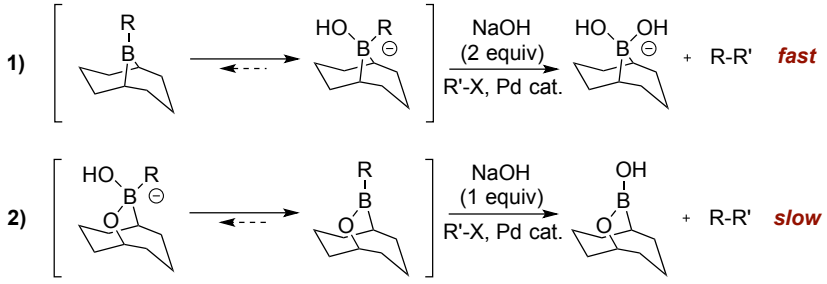
One of the earliest kinetic investigations into the SM catalytic cycle was carried out by Smith *et al* in 1994.[29] Their kinetic data revealed that when using an aryl bromide, oxidative addition was indeed the rate-determining step (see section 1.2.1 above). However, they found that when using an aryl iodide the rate-determining step switched to transmetallation. Further analysis suggested that both [$L_2Pd^{II}Ar(X)$] complexes (where X = I, Br) had similar reactivity towards transmetallation, therefore ruling out a mechanism involving halide dissociation pre-transmetallation to form a cationic palladium species (Scheme 10).



Scheme 10: Ligand dissociation to form cationic Pd

This, in combination with the reliance on H_2O and bases of a certain pK_a, led the authors to believe transmetallation was occurring through the boronate pathway.

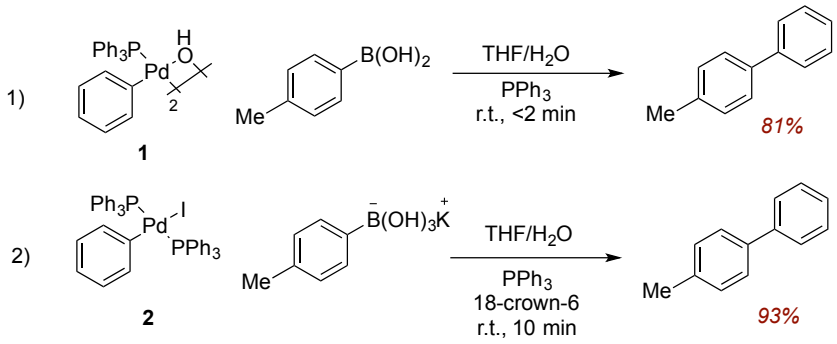
Shortly after this, in 1998, Soderquist and co-workers performed mechanistic studies on a series of alkylboranes,[30] and came to the conclusion that the pathway for transmetallation was dependant on the nature of the boron species. More Lewis acidic alkylboranes formed boronates more readily, and therefore required 2 equivalents of hydroxide base for the reaction to proceed (Scheme 11, Eq 1). Less Lewis acidic alkylborinates on the other underwent hydroxide association much less readily (Scheme 11, Eq 2).



Scheme 11: Varying rates of boronate formation for different boron species

It was therefore proposed that for alkylboranes transmetallation proceeded through the boronate pathway, with oxidative addition serving as the rate-determining step. For alkylborinates however, it was proposed transmetallation occurred *via* the neutral oxo-palladium pathway, with the rate-determining step in this case being the hydrolysis of $[L_2Pd^{II}Ar(X)]$ to $[L_2Pd^{II}Ar(OH)]$. This of course presented the possibility that both pathways could be at work, and the authors therefore noted that the kinetics of individual steps in the catalytic cycle could vary depending on the reaction conditions (*i.e.*, quantity of H_2O, nature of the base, etc.).

In attempts to further elucidate the mechanism of the SM reaction, Hartwig,[31] Amatore and Jutand,[32] and Schmidt[33] recently undertook independent investigations into the mechanism of transmetallation. Hartwig probed the possible pathways by measuring the relative rates of transmetallation of isolated arylpalladium hydroxo (**1**) and arylpalladium halide complexes (**2**) with aryl boronic acids and aryl trihydroxyborates respectively (Scheme 12).



Scheme 12: Measurement of the relative rates of transmetallation from isolated Pd complexes

A control reaction using PhI and *p*-tolylboronic acid with $Pd(PPh_3)_4$ as a catalyst afforded the desired 4-methylbiphenyl in 96% yield after 3 h at 80 °C, significantly slower than both stoichiometric reactions, suggesting either could potentially be the pathway for transmetallation. At room temperature, the neutral boronic acid was found to transmetallate over four times faster than the boronate (Scheme 12, Eq 1 vs. Eq 2). It was also found that the nature of the neutral boron species could affect the rate of transmetallation, with a series of boronic esters (catechol, neopentyl, and pinacol) found to transmetallate with the isolated oxo-Pd species **1** (Figure 5). Interestingly, the pinacol ester was found to transmetallate forty-five times slower under these conditions than the other neutral species, although still significantly faster than the equivalent Pd-halide complex and trihydroxyborate.

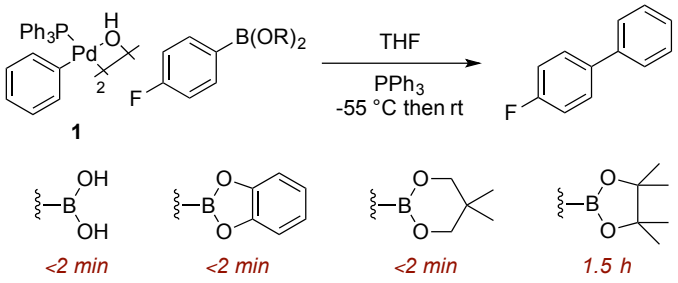
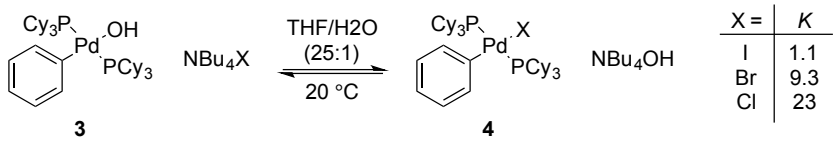


Figure 5: Rates of transmetallation of different neutral boron species

The authors reasoned that the prominent pathway would be dictated by the relative concentrations of complex **1** and **2**, along with their respective boron species, and the relative rate constants for the two stoichiometric reactions depicted in Scheme 12. Transmetallation would occur *via* the pathway with the largest product of the rate constant, concentration of palladium complex, and concentration of boron species. In

order to calculate this, Hartwig *et al* studied the equilibria between palladium hydroxo and halide complexes along with the equilibria between boronic acids and trihydroxyborates under typical SM conditions. It was found that the equilibrium constant for the formation of the palladium halide complex **4** from the oxo-Pd complex **3** with tetrabutylammonium iodide was 1.1 (Scheme 13). Other halide salts formed more stable Pd-halide complexes but their equilibrium constants were still relatively small (K = 9.3 for Br and 23 for Cl).

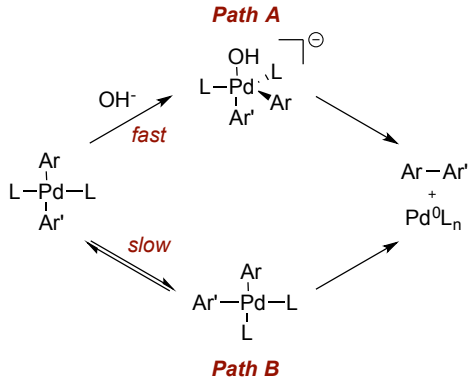


Scheme 13: Equilibria between palladium hydroxo and palladium halide complexes in solution

This led to the conclusion that both oxo-Pd and Pd-halide complexes are present in solution under aqueous SM conditions, with palladium halide having a higher concentration albeit by less than an order of magnitude. Interestingly, the authors did note that in systems containing a lower concentration of H_2O, the concentration of oxo-palladium complex increased, presumably due to a decreased hydration of the hydroxide ions in solution.

In the same year Amatore and Jutand published their study on transmetallation, which elaborates on the role of the hydroxide anion in the SM reaction.[32] By utilising electrochemical techniques, the authors were able to determine the concentrations of various species in the catalytic cycle and therefore extrapolate rate constants for the transmetallation from both oxo-Pd and Pd-halide species. This led to the conclusion that hydroxide ions serve three key roles in the SM catalytic cyclic. Firstly, the concentration of hydroxide ions directly influences the concentration of the active oxo-Pd species. However, the presence of hydroxide also leads to the formation of the less reactive trihydroxyborate. This means that the concentration of hydroxide is responsible for counter-productive reaction pathways. At low concentrations of hydroxide, lower quantities of active oxo-Pd will be formed, resulting in a slower reaction. However, at high concentrations, formation of the less reactive trihydroxyborate becomes more competitive, again leading to a slower reaction due to the decreased population of reactive boronic acid. The third and final role of the

hydroxide ion was unexpected, promoting reductive elimination from stable *trans*-bis-(aryl)palladium complexes. It was thought that following transmetallation, under the basic reaction conditions, hydroxide could coordinate as a fifth ligand to form a pentacoordinated anionic palladium complex (Scheme 14, Path A). This would force a more *cis*-like relationship between the aryl substituents, which is required for reductive elimination, while bypassing the thermodynamically unfavourable isomerisation (Scheme 14, Path B). These data support the conclusions drawn by Hartwig,[31] in that transmetallation occurs faster from an oxo-Pd complex with a neutral boronic acid than from a Pd-halide complex in combination with a charged trihydroxyborate; however, the relative concentrations of these species are dependant on the reaction conditions (*i.e.*, type of inorganic base used, quantity of H_2O).

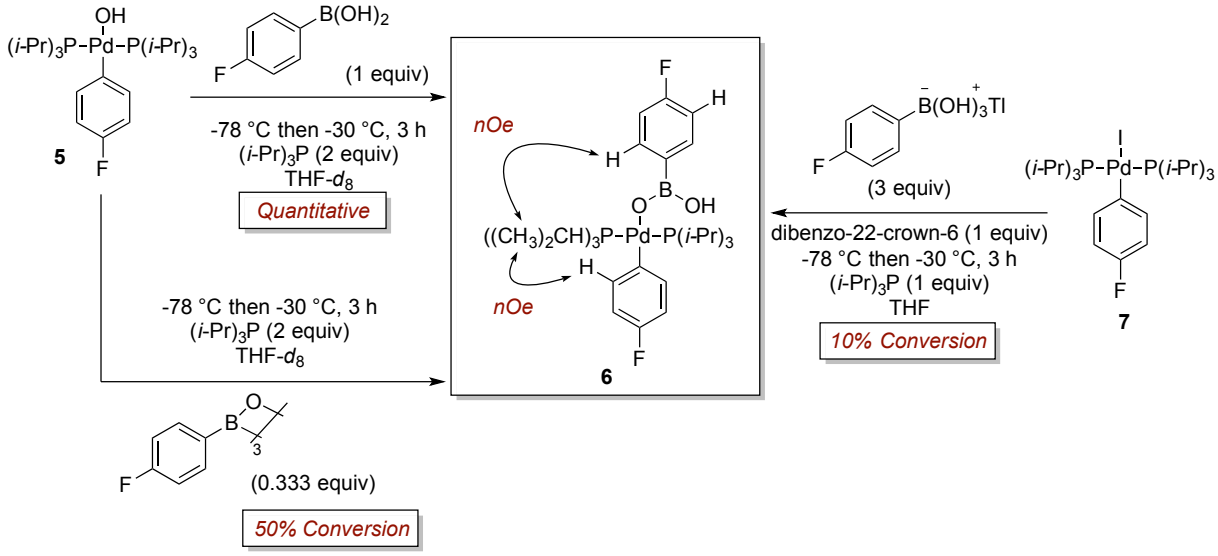


Scheme 14: Third role of hydroxide in SM reaction

Using UV-vis experiments in combination with ^{11}B NMR spectroscopy, Schmidt has reported further kinetic data supporting these conclusions, that transmetallation is favoured from the oxo-Pd and neutral boronic acid but that the presence of basic anions in solution can also drive the formation of the undesired borate.[33]

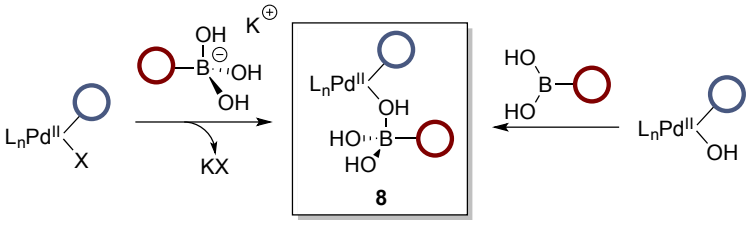
While all of these groundbreaking studies indicate that transmetallation through an oxo-Pd pathway is indeed the favoured mechanism for SM, none had ever observed the pre-transmetallation intermediates. Denmark and Thomas recently utilised new rapid injection low temperature NMR technology to monitor the formation of these intermediates and thus identify the "missing link" in the mechanistic pathway.[34] Using this technique, the authors were able to identify and characterise the pre-transmetallation intermediate formed through the combination of various aryl-Pd

complexes with different boron species (Scheme 15). Through the reaction of preformed oxo-Pd complex **5** with neutral 4-fluorophenylboronic acid, Denmark and Thomas observed the quantitative formation of a new species **6**, which was characterised to contain a Pd-O-B bond linkage. Nuclear Overhauser effects (nOe), in combination with ^{11}B NMR, confirmed the tricoordinate geometry of the boron atom, whose signal appeared as a broad singlet at 29 ppm, consistent with other 6-B-3 complexes of this type.[35] To further confirm the structure of **6**, the authors independently synthesised it *via* two further routes, firstly from the Pd-halide complex **7** and its requisite boronate, as well as from the oxo-Pd complex **5** along with a boron trimer.



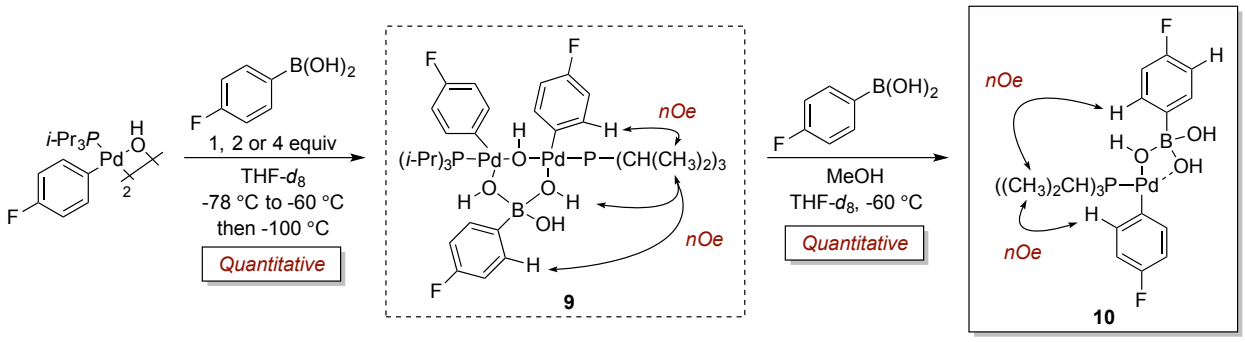
Scheme 15: Synthesis of pre-transmetallation complex containing a Pd-O-B bond linkage

Both routes produced the desired complex **6** although in reduced yield. This demonstrated that the pre-transmetallation complex **6** could be accessed without going through an oxo-Pd species such as **5**. The authors reasoned that the formation of **6** must proceed through an 8-B-4 complex such as **8** (Scheme 16); however attempts to drive the equilibria through the addition of hydroxide bases to form such a complex were unsuccessful, resulting in no change by ^{11}B, ^{19}F, or ^{31}P NMR.



Scheme 16: Proposed formation of 8-B-4 complex as precursor to 6

This led to the use of dimeric, monoligated oxo-Pd complexes more akin to those generated from $Pd(OAc)_2$, which allowed the generation of the proposed 8-B-4 complex **10** *via* a bridged bis-arylpalladium arylboronate complex **9** (Scheme 17). Complex **9** was also synthesised from the equivalent dimeric monoligated Pd-halide complex; however, as with the synthesis of complex **6**, this was found to proceed less efficiently than from the oxo-Pd species (~50 % conversion *vs*. quantitative). With these complexes in hand the authors were able to demonstrate that both complexes **6** and **9** were competent transmetallation precursors, with both delivering the desired cross-coupled product upon heating. As shown in Scheme 17, complex **9** first underwent fragmentation to form **10** which could then deliver the cross-coupled product. Complex **6** was found to first undergo dissociation of one phosphine ligand to form a monoligated complex similar to **10** which could then afford the cross-coupled product; however, as this complex was only present in very low-equilibrium concentration, the coordination state of boron in the Pd-O-B complex could not be definitively established. This study nevertheless unambiguously identifies the previously unreported pre-transmetallation complexes present in the SM catalytic cycle. It also provides further evidence that while transmetallation can occur from the Pd-halide and trihydroxyborate, this pathway is kinetically disfavoured in comparison to the oxo-palladium pathway.



Scheme 17: Synthesis of 8-B-4 complexes from dimeric oxo-Pd species

1.3 Boron reagents in the Suzuki-Miyaura reaction

While a large body of research has been dedicated to expanding the scope of organohalides tolerated in the SM reaction through the development of new catalysts, (see section 1.2.1 above), there has also been some focus on expanding the range of organoboron coupling partners which can be employed.[7] This section aims to highlight some of these classes of boron reagents, looking at the various advantages and disadvantages of each along with selected examples of their application.

1.3.1 Organoboranes

Organoboranes were the first class of boron reagent to be utilised in the SM reaction.[1] These species contain an sp^2 hybridised boron atom bonded to three carbon atoms (Figure 6). The use of these highly reactive species in the early stages of cross-coupling development stemmed from their ease of preparation through the hydroboration of alkenes and alkynes.[36]

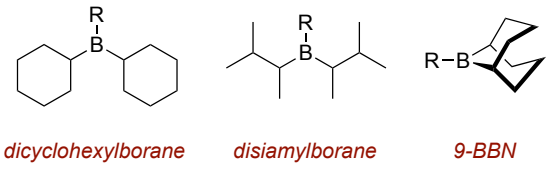
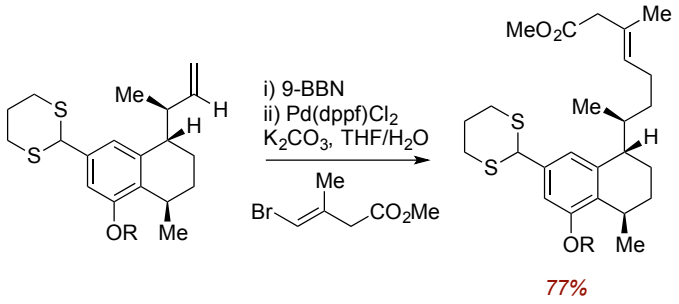


Figure 6: Examples of common organoboranes

However the reactivity of these species can cause problems in SM cross-coupling, with poor selectivity arising during transmetallation between the three alkyl substituents which can be transferred to Pd. Alkylboranes can also suffer from a number of degradation processes such as aerobic oxidation, dehydroboration, and

protodeboronation, resulting in reduced yields. Of the organoborane reagents shown in Figure 6, 9-borabicyclo[3,3,1]-nonane (9-BBN) has found the most use in cross-coupling. Its rigid structure aids in increasing selectivity during transmetallation, while its steric bulk results in anti-Markovnikov selectivity during hydroboration. This, in combination with its high reactivity, had led to 9-BBN being used as a coupling-partner in a wide range of sp^3 cross-couplings which would typically be problematic using less stable alkylboronic acids or esters. There have been many examples of this type of tandem hydroboration/cross-coupling throughout natural product synthesis, with one example being Uemura and co-workers synthesis of (±)-dihydroxyserrulatic acid (Scheme 18).[37] Here, Uemura was able to perform an anti-Markovnikov hydroboration of a terminal alkene and then react the alkylborane adduct *in situ* to perform an sp^2-sp^3 SM cross-coupling in high yield. A further four synthetic transformations then furnished the desired natural product.

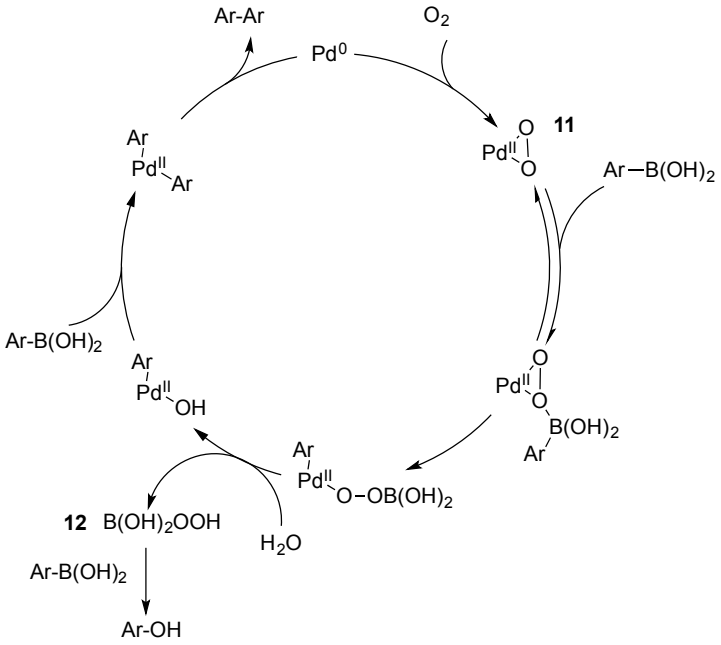


Scheme 18: Hydroboration/SM cross-coupling in synthesis of (±)-dihydroxyserrulatic acid

1.3.2 Boronic acids

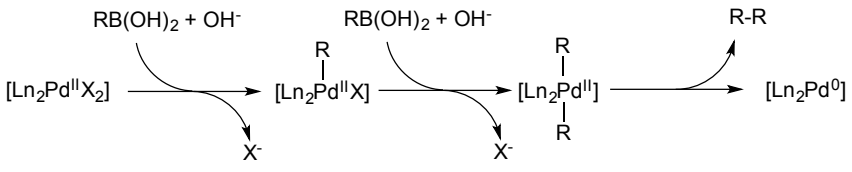
Since they were first introduced as coupling partners in 1981, boronic acids have become one of the most widely used reagents for SM cross-coupling.[38] This stems from their wide commercial availability, in addition to their high solubility in organic solvents typically employed in SM reactions.[39] Boronic acids are more reactive towards transmetallation than their ester counterparts (*vide supra*) and this greater activity has resulted in boronic acids being used as coupling partners in other metal catalysed cross-couplings outside the SM, such as Hayashi (rhodium)[40] and Chan-Evans-Lam (copper).[41–43] Unfortunately this reactivity also leads to boronic acids undertaking a number of detrimental side reactions, such as oxidation, homocoupling, and protodeboronation.

Oxidation of boronic acids results from the presence of oxygen in the reaction mixture, and leads to the formation of Pd^{II} peroxo species **11** (Scheme 19).[44] Once formed, peroxo species **11** can then react with two equivalents of boronic acid to form the homocoupled product. This peroxo species can also lead to the formation of the corresponding alcohol products *via* perboric acid **12**. It is for this reason SM reactions are nearly always conducted under an inert atmosphere.



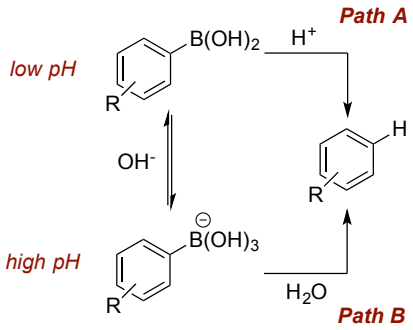
Scheme 19: Mechanism of oxidation of boronic acids

Homocoupled products can also be formed through the reductive activation of a Pd^{II} catalyst to the active Pd^0 species (Scheme 20).[7,22] Similar to oxidative homocoupling, this involves the reaction of two equivalents of boronic acid with the Pd^{II} catalyst. Each boronic acid transfers its aryl unit the metal catalyst and reductive elimination then furnishes the homocoupled product in addition to the active Pd^0 species.



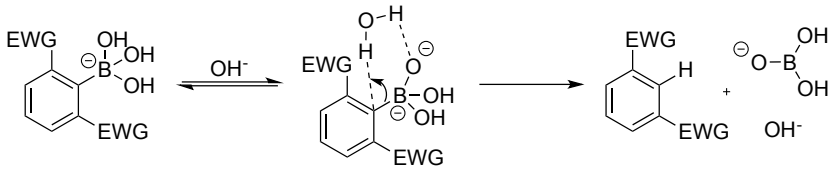
Scheme 20: Homocoupling from reduction activation of Pd^{II}

Perhaps the most common and detrimental side reaction which boronic acids undergo is protodeboronation.[39] This reaction can occur under acidic, basic, and even neutral media and is exacerbated by high temperatures and variation in pH. Interestingly, the first detailed study on the mechanism of protodeboronation was carried out by Kuivila in the early 1960's, two decades before boronic acids were ever used in cross-coupling.[45,46] Kuivila reported investigations into protodeboronation under aqueous organic media by measuring pH rate profiles. From these studies he proposed two mechanistic pathways for protodeboronation: acid-mediated from the neutral boronic acid; and base-mediated *via* hydrolysis of the boronate anion (Scheme 21, Path A and B, respectively). Kuivila's study also showed that electron withdrawing groups at the *para*- or *meta*-position can temper protodeboronation under both pathways.



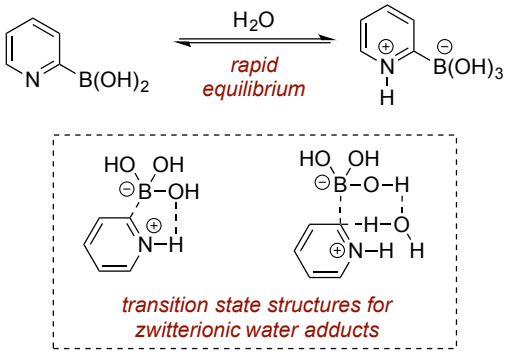
Scheme 21: Proposed pathways of protodeboronation

While Kuivila's study was ahead of its time and served as the basis for our understanding of the mechanism of protodeboronation, there was a drawback to this. The kinetics were measure using UV-Vis spectroscopy and, as a result, the pH could only be measured up to 6.7. Above this pH, boronic acid oxidation was observed which interfered with the UV measurements. With the advent of the SM reaction and its propensity to be carried out in aqueous basic media, there has since become a greater need for understanding of the mechanism of protodeboronation at high pH. A number of studies have since been carried out, primarily on substituted aryl boronic acids.[24,47,48] In 2014, Perrin proposed a third pathway of protodeboronation, in which 2,6-disubstituted arylboronic acids underwent base-mediated protolysis of the boronate anion (Scheme 22).[49] Interestingly the same compounds exhibited no protodeboronation under acidic conditions.



Scheme 22: Perrin's proposed mechanism for base-mediated protodeboronation

As previously mentioned, the majority of studies on protodeboronation have been conducted on substituted arylboronic acids, although Noonan and Leach have recently modelled the energy of protodeboronation of phenylboronic acid.[50] However, heteroarylboronic acids are known to be some of the worst offenders in terms of protodeboronation, with many undergoing degradation rapidly under SM reaction conditions and even upon storage.[39,50] As heterocycles are important structural motifs in the pharmaceutical, agrochemical and materials industries, the ability to understand the mechanism by which these capricious reagents undergo protodeboronation, and therefore be able to guard against it, is highly desirable. To this end, Lloyd-Jones has recently disclosed an in-depth study into the mechanism by which known unstable classes of boronic acid undergo protodeboronation.[51] It was proposed that heterocyclic boronic acids undergo degradation *via* a zwitterionic water adduct which serves to stabilise the boric acid leaving group, resulting in rapid protodeboronation at neutral pH (Scheme 23).



Scheme 23: Transition states for water assisted 2-pyridyl protodeboronation

This rapid process could be tempered through the addition of Lewis acids such as $CuCl_2$ and $ZnCl_2$ which can bind to the basic nitrogen and prevent the formation of the zwitterionic intermediate. Lloyd-Jones also proposed that in other heterocycles, for example 5-thiazole and 5-pyrazole, the adjacent antibonding orbital can also

serve to stabilise the carbanion generating during C-B bond cleavage (Figure 7). However, in contrast to the 2-pyridyl system, the addition of Lewis acids in this case increased the rate of protodeboronation (3-fold increase in rate with $ZnCl_2$).

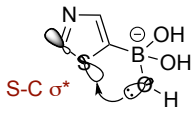
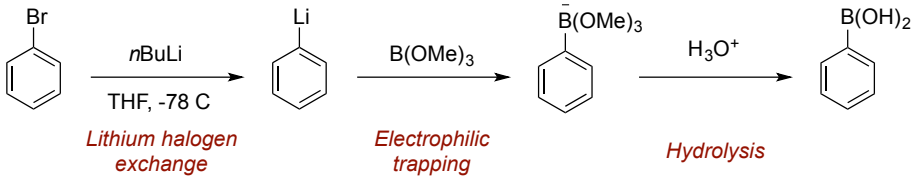


Figure 7: Adjacent antibonding orbital stabilisation in 5-thiazole

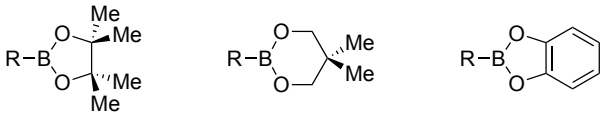
Boronic acids can be readily prepared from the corresponding aryl halide *via* a metallation (lithium halogen exchange or Grignard formation) followed by trapping with an electrophilic boron species (Scheme 24).[39] This forms a boronic ester which, upon acidic hydrolysis, affords the desired boronic acid. One of the drawbacks of this method of synthesising boronic acids, in addition to the need for cryogenic reaction conditions, is the limited functional group tolerance of the metallation step.



Scheme 24: Lithium halogen exchange strategy for synthesis of aryl boronic acids

1.3.3 Boronic esters

Boronic esters offer a more stable alternative to their acid counterparts, and as such have seen much greater application in cross-coupling in the last 20 years. Most commonly employed are the pinacol, neopentylglycol, and catechol derivatives (Figure 8). In these esters, with the exception of catechol, the σ-donating ability of the carbon backbone renders the lone pairs on oxygen more available. This results in greater donation into the empty p-orbital on boron, thus rendering the boronic ester less Lewis acidic, and hence less reactive and more stabilised than its acid counterpart.

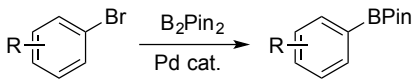


Boronic acid pinacol ester (BPin) | *Boronic acid neopentylglycol ester (BNep)* | *Boronic acid catechol ester (BCat)*

Figure 8: Boronic esters commonly employed in cross-coupling

While investigations into the mechanism of transmetallation have been more numerous in recent years, they have primarily focussed upon the use of boronic acids as nucleophiles and, as such, the nature of boronic ester transmetallation remains unclear. With some boronic esters which are readily hydrolysed, such as catechol, it is thought that transmetallation occurs from the parent boronic acid *via in situ* hydrolysis.[7] However, in the case of boronic acid pinacol esters, which are typically only hydrolysed under strongly acidic or basic conditions,[52] it is thought that transmetallation may occur directly from the boronic ester through either the oxo-palladium or boronate pathways previously discussed.

The increased use of boronic esters in SM cross-coupling in recent years is a result of not only their increased stability relative to boronic acids, but also their ease of preparation. In a seminal report in 1995,[53] Miyaura disclosed the Pd-catalyzed borylation of aryl halides with bis(pinacolato)diboron (B_2Pin_2), which enabled the facile synthesis of aryl BPin units without the need for stoichiometric metallation (Scheme 25). In a mechanism similar to that of the SM reaction, aryl halides undergo oxidative addition with a Pd^0 catalyst. This complex then undergoes transmetallation with B_2Pin_2, and reductive elimination furnishes the desired boronic ester. This important advance in the area greatly increased the scope of aryl BPin esters which could be easily synthesized and thus applied in further synthetic transformations.

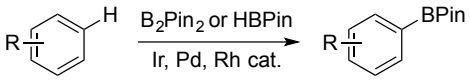


Scheme 25: Miyaura borylation of aryl halides

Since this initial report by Miyaura, there have been a number of developments in sp^2 borylation of aryl halides. Metal catalyzed borylation of aryl halides is no longer

limited to palladium catalysts – a range of inexpensive, abundant and less toxic transition metals including Cu, Ni, Zn, and Fe can now be utilized as catalysts.[54,55]

The borylation of aryl halides (and pseudohalides) is not the only area to receive significant attention in recent years. Originally reported shortly after the Miyaura process, the transition metal-catalysed borylation of seemingly inactive aryl C-H bonds represented a significant step forward in aromatic functionalization (Scheme 26).[56] Recent advances have succeeded in tempering reaction conditions, increasing the scope of both functional group tolerance and classes of aromatic and heteroaromatic compounds, as well as vastly increasing the regioselectivity of the process.



Scheme 26: Metal catalysed C-H borylation

1.3.4 Protected boronic acids

The use of protecting groups in organic synthesis is well practiced, allowing reactive functional groups to be taken through a variety of synthetic transformation unaffected, before deprotection reveals the reactive moiety.[57] This strategy has been applied to boron reagents in recent years, with protecting groups being utilised in order to carry reactive boronic acids through numerous synthetic transformations for later functionalisation.[57] Examples of such protected boronic acids commonly employed in synthesis are: potassium organotrifluoroborates (BF_3K); *N*-coordinated boronates derived from *N*-methyliminodiacetic acid (BMIDA); and 1,8 diaminonaphthyl boranes (BDAN) (Figure 9).

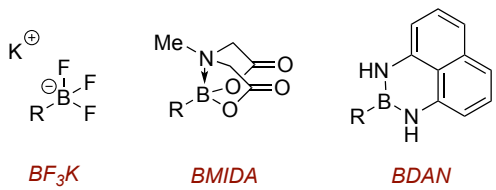
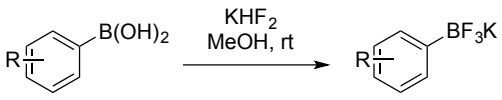


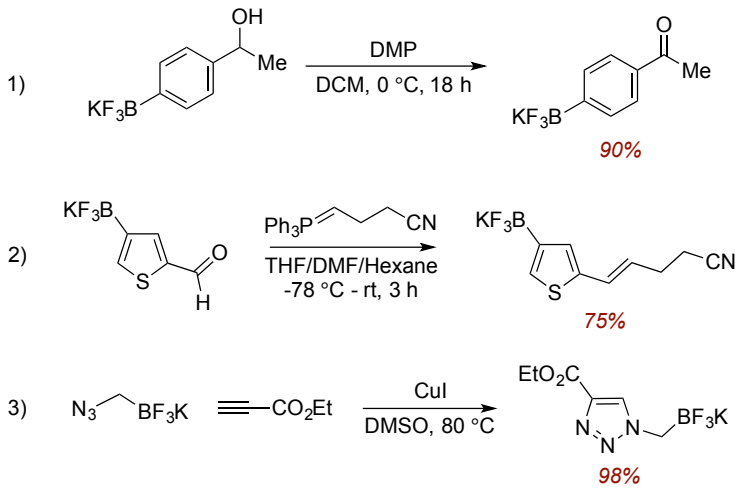
Figure 9: Selection of protected boronic acids

Potassium organotrifluoroborate salts were first reported by Chambers in 1960,[58] but did not find wide use in organic synthesis until the mid 1990's when they were extensively developed by Molander.[59] Unlike their acid and ester counterparts, organotrifluoroborates are tetrahedral in geometry, and the boron atom is non-Lewis acidic as a result of ligand coordination. Consequently, these salts are often free-flowing crystalline solids which are stable to air and moisture, meaning they can be easily stored and handled without any degradation. Organotrifluoroborate salts are easily prepared from the parent boronic acid by simply stirring with aqueous KHF_2 in methanol (Scheme 26). The desired salt can then be precipitated from solution, avoiding the need for any purification.



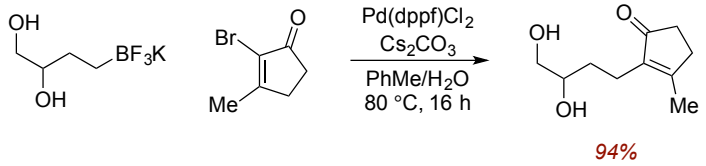
Scheme 26: Synthesis of BF_3K from the corresponding boronic acid

These protected boronic acids are stable under anhydrous conditions, and as such can tolerate a variety of organic transformations under such media. For example, Molander has shown organotrifluoroborates to be able to withstand a range of oxidising conditions, including Swern, Ley, and Dess-Martin (Scheme 27, Eq 1).[60] In addition, reductive processes are also tolerated, such as reductive amination.[61] More complex carbon-carbon bond forming synthetic manipulations could also be carried out on organotrifluoroborates. Wittig/Horner-Wadsworth-Edmonds olefinations[62] and Huigsen type 1,3-dipolar cycloadditions[63] could also tolerate the presence of a BF_3K moiety (Scheme 27, Eq 2 and 3). This allows the rapid construction of carbon frameworks while still maintaining a protected boron species for further functionalisation.

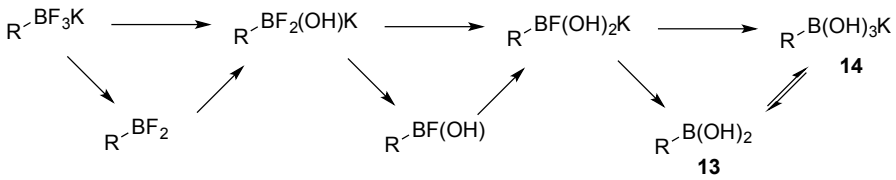


Scheme 27: Examples of synthetic transformations on BF_3K

Potassium organotrifluoroborates have also been utilised in a series of cross-couplings which are difficult to accomplish with boronic acids or esters.[64] One example is the use of alkyl trifluoroborates in sp^3-sp^2 cross-coupling (Scheme 28).[65] While sp^3 boronic acids are notoriously unstable,[39] organotrifluoroborates are slowly hydrolysed under the reaction conditions, ensuring a low concentration of the reactive boronic acid is maintained throughout the reaction.[65] Hydrolysis of the BF_3K salt proceeds through a complex series of boron species, resulting in an equilibrium between boronic acid **13** and boronate **14** (Scheme 29).[66]



Scheme 28: Use of alkyl trifluoroborate in SM cross-coupling

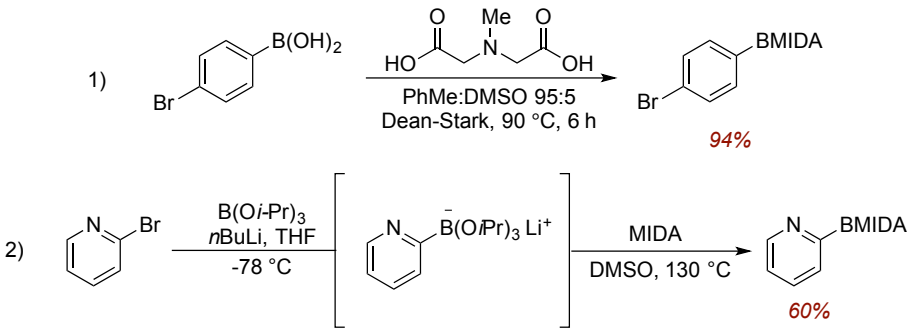


Scheme 29: Slow release of boronic acid from BF_3K through hydrolysis cascade

While Molander and co-workers have demonstrated the stability of organotrifluoroborates to a variety of organic transformations, they do experience some drawbacks. The reagents hydrolyse under basic or acidic conditions, and can

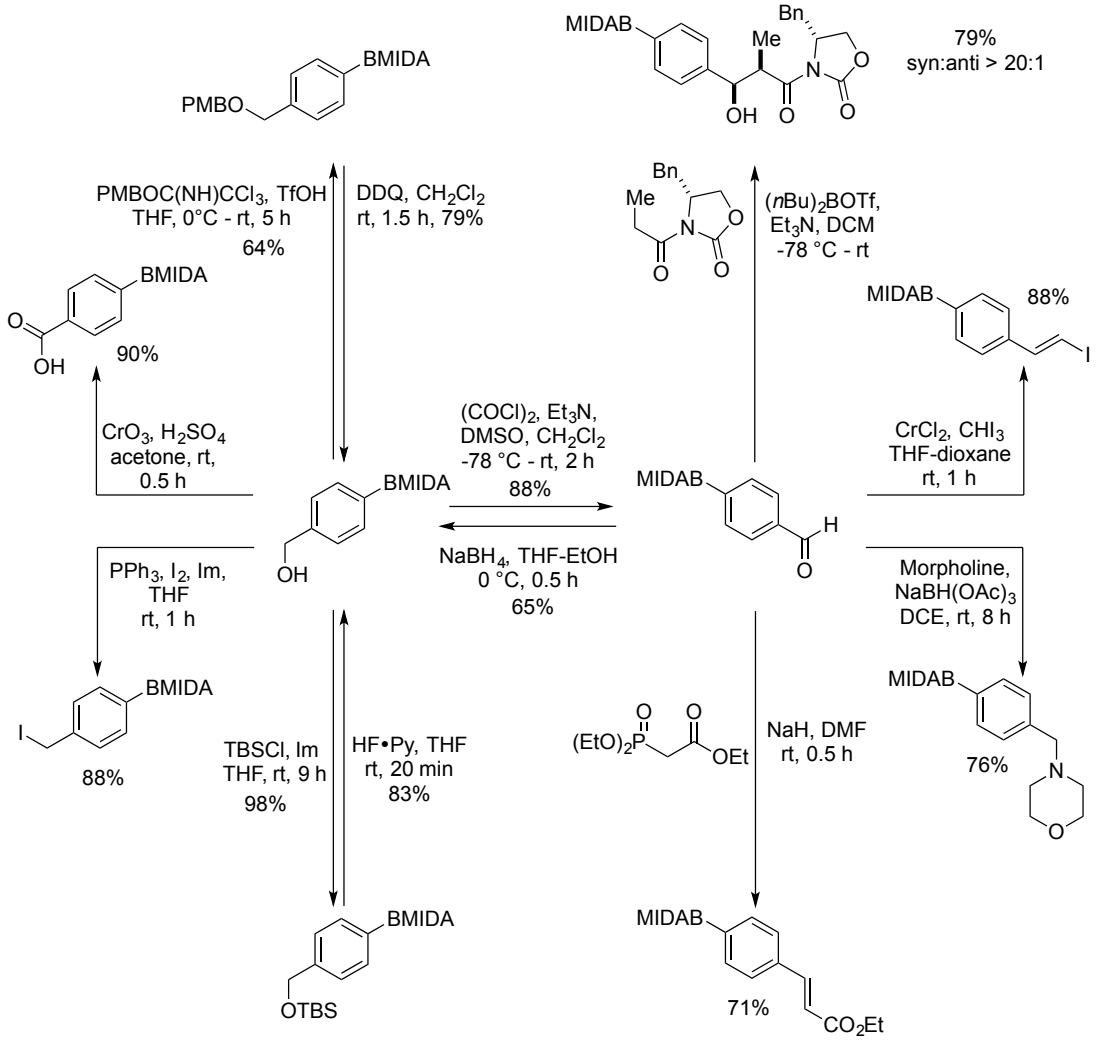
decompose upon exposure to silica and some protic solvents, prohibiting the use of chromatography for purification.[7] In addition to this, some of the processes reported by Molander require a KHF_2 workup, presumably to regenerate any BF_3K which has hydrolysed under the reaction conditions.[61,67] The necessity for this can limit the potential scope of functional groups, *e.g.*, silyl protecting groups which are cleaved by fluoride anions.

Similar to organotrifluoroborates, MIDA boronates have a tetrahedral geometry and are stable to a range of organic transformations, including transmetallation.[68] This stems from the donation of the lone pair on nitrogen into the empty p-orbital on boron. MIDA boronates were originally reported by Mancilla in the 1980's[69] and in the past decade the pioneering work of Burke has brought BMIDA reagents to the forefront of boron chemistry.[68,70] BMIDA reagents can be hydrolysed to the corresponding boronic acid under aqueous basic conditions. A recent study from Burke in collaboration with Lloyd-Jones has shown that the mechanism of hydrolysis varies depending on the conditions used.[71] Under proposed "fast hydrolysis" conditions with NaOH, the reaction proceeds through a standard base mediated ester mechanism. However, under "slow hydrolysis" conditions with K_3PO_4, the reaction proceeds *via* a neutral mechanism involving coordination of H_2O to boron. BMIDAs can be readily prepared from the corresponding boronic acid through condensation with *N*-methyliminodiacetic acid (Scheme 30, Eq 1).[72] The resulting BMIDA can be precipitated or recrystallised as an air stable solid. If the boronic acid is unavailable or unstable, as is the case with some heterocycles, direct lithiation/borylation followed by *in situ* trapping can be used to access the BMIDA species (Scheme 30, Eq 2).[73]



Scheme 30: Preparation of BMIDA reagents

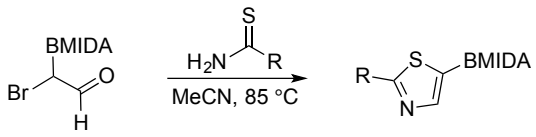
Early use of these reagents focussed on iterative cross-coupling, carrying a protected boronic acid through a SM reaction under anhydrous conditions before a basic hydrolysis revealed the parent boronic acid for subsequent cross-coupling.[70] This use of BMIDAs will be discussed in more detail in Section 1.4.2. Along with stability towards cross-coupling, Burke and co-workers have also demonstrated the BMIDA reagents can tolerate a range of functional group manipulations.[74] As shown below in Scheme 31, a range of oxidation, reduction, olefination, Aldol, protection and deprotection processes could all be carried out on BMIDA species with no undesired reaction or degradation of the protected boron species.[74]



Scheme 31: Functional group interconversion of BMIDA containing building blocks

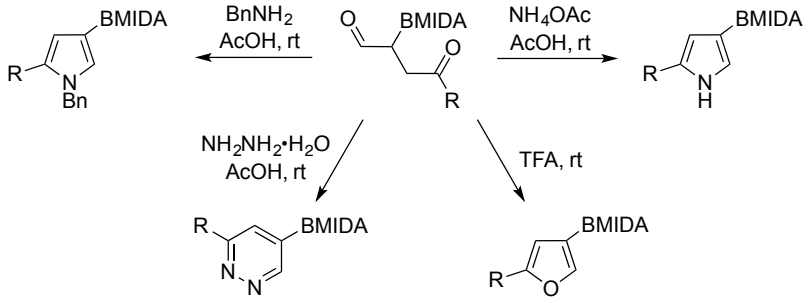
Yudin and co-workers have also adopted the BMIDA functionality, and have demonstrated its use in α-boryl aldehydes to enable the synthesis of a variety of

borylated heterocycles.[75] This methodology is complementary to traditional synthesis (*i.e.*, lithiation/borylation) or even newly developed C-H borylation methods,[56] both of which typically deliver C2 borylated heterocycles. In contrast, through condensation with a variety of reagents, α-boryl aldehydes can deliver borylated heterocycles which would be difficult to access using conventional methodology. Reaction of α-bromo boryl aldehydes with thioamides enables the facile synthesis of the corresponding 2,5-disubstituted borylated thiazoles (Scheme 32).[76]



Scheme 32: Synthesis of borylated thiazoles from α-bromo boryl aldehydes

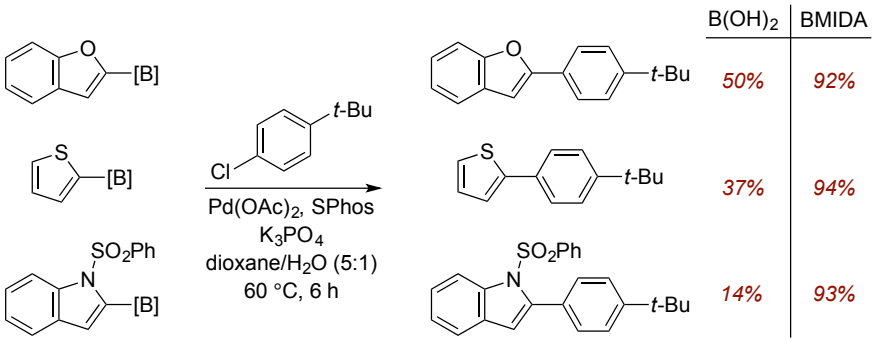
Alternately, by utilising 1,4-dicarbonyl boronates, the authors demonstrate the expedient synthesis of substituted pyrroles, furans, and pyridazines (Scheme 33).[77]



Scheme 33: Synthesis of borylated heterocycles from 1,4-dicarbonyl boronates

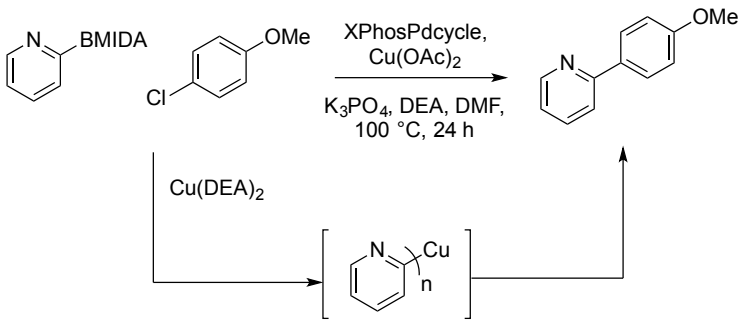
The ability to efficiently synthesise borylated heterocycles has obvious advantages in terms of easily incorporating these valuable motifs into pharmaceutical, agrochemical and material scaffolds *via* cross-coupling. However, a number of borylated heterocycles are notoriously unstable and therefore difficult to cross-couple effectively.[51] The ability to synthesise heterocycles substituted with a BMIDA group is therefore even more desirable, as they offer a stable reagent for cross-coupling. Burke and co-workers have shown that under appropriate aqueous basic conditions, BMIDA reagents can be hydrolysed and act as a slow release of active boronic acid in solution.[78] This ensures that the concentration of the unstable species is kept to a minimum, allowing efficient cross-coupling with minimal degradation. The authors

effectively demonstrated this slow release mechanism by comparing the isolated yields of cross-coupled product across a range of heterocyclic boron species (Scheme 34). In all cases the BMIDA offered greater yields than the equivalent boronic acid, demonstrating the first general solution to the cross-coupling of unstable boronic acids.



Scheme 34: Cross-coupling of unstable boronic acids *via* slow release mechanism

Perhaps the most widely recognised example of this use of BMIDAs is Burke's solution to the 2-pyridyl problem.[79] Pyridyl units bearing a boryl substituent in the 2-position are known to be especially unstable,[51] making cross-coupling of these valuable motifs extremely challenging. Indeed, even under their slow release conditions which had proved so effective for other sensitive heterocyclic residues, Burke and co-workers found efficient cross-coupling of 2-pyridyl motifs remained elusive. It was found that use of a stoichiometric Cu additive significantly increased the yields of cross-coupled product. The authors proposed the combination of $Cu(OAc)_2$ and diethylamine (DEA) formed a $Cu(DEA)_n$ complex which could transmetallate with the boron species to form a 2-pyridyl Cu complex (Scheme 35). This would then undergo transmetallation with Pd to form the cross-coupled product. Recent work from Lloyd-Jones, however, suggests that Cu acts as a Lewis acid to stabilise the 2-pyridyl boronic acid and inhibit protodeboronation (see section 1.3.2 above).[51]



Scheme 35: Cu-mediated cross-coupling of 2-pyridyl BMIDA

BDAN reagents, originally reported by Suginome,[80] exhibit properties similar to those of BMIDA and BF_3K. In this case, the boron atom is stabilised by the lone pairs of the adjacent nitrogen atoms, however, unlike BMIDA and BF_3K reagents, BDAN's remain in an sp^2 hybridised trigonal geometry. In a further departure from other protected boronic acids, BDAN reagents are base stable and acid labile, making them compatible with the aqueous basic conditions typically employed in SM reactions. This allows BDAN reagents to be utilised in both iterative and chemoselective cross-coupling reactions.[81] This will be discussed in more detail in Section 1.4.2.

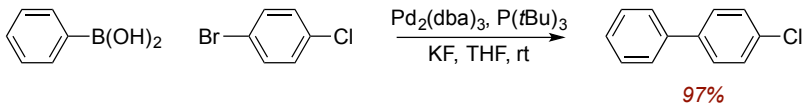
1.4 Chemoselectivity in Suzuki-Miyaura cross-coupling

The Suzuki-Miyaura cross-coupling represents the most common method of C-C bond formation in industry.[82,83] It is therefore hardly surprising that methods which enable multiple selective cross-couplings have emerged as powerful tools for the rapid and efficient construction of molecular scaffolds.[57] Chemoselectivity in the SM reaction can be divided into two main categories based upon the reaction mechanism: control over the oxidative addition event, or electrophile chemoselectivity; and control over the transmetallation event, or nucleophile selectivity. This section will discuss the current state of the art of both these methods of achieving chemoselectivity.

1.4.1 Chemoselectivity *via* oxidative addition

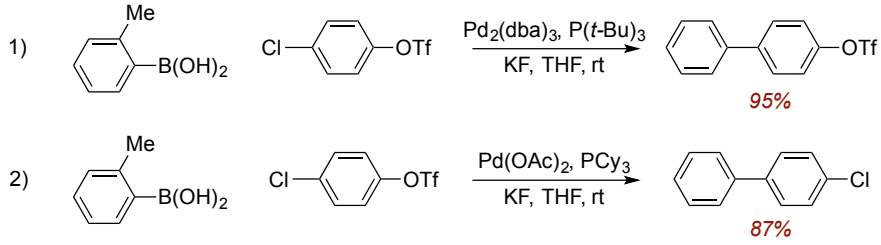
Electrophile chemoselectivity has been achieved by exploiting the different rates of oxidative addition of various halides and pseudohalides (see section 1.2.1 above).[8]

This allows the selective monofunctionalisation of one halide in the presence of another based on their different reactivity. The first comprehensive demonstration of this electrophile chemoselectivity in the context of SM was reported by Fu in 2000, with the selective monocoupling of a boronic acid to a dihaloarene (Scheme 36).[84]



Scheme 36: Chemoselective monocoupling of 1-bromo-4-chlorobenzene

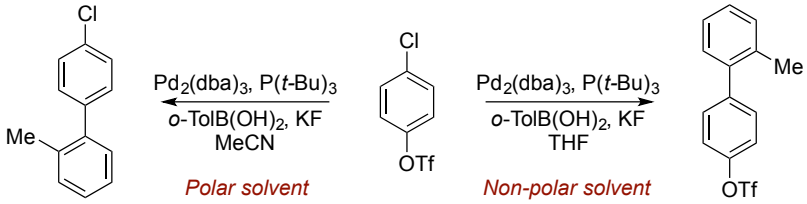
Of particular note was the ability to tailor the chemoselectivity of certain halides and pseudohalides based on judicious selection of catalyst and ligand (Scheme 37). When $Pd_2(dba)_3$ was used as a catalyst in combination with P(*t*-Bu)$_3$ as a ligand, an aryl chloride could be selectively cross-coupled over an aryl triflate (Scheme 37, Eq 1). However, when using $Pd(OAc)_2$ and PCy_3, reaction of the triflate was favoured (Scheme 37, Eq 2). This was the first example of a seemingly less reactive chloride being coupled selectively in the presence of a more reactive triflate, inverting traditional reactivity profiles.



Scheme 37: Inversion of chemoselectivity based on catalyst/ligand system

In depth computational studies by Schoenebeck and Houk have shown that the origin of this remarkable shift in chemoselectivity stems from the different ligation states of palladium.[85] When using PCy_3 as a ligand, it can form either mono- or bisligated complexes with Pd. The bisligated $Pd(PCy_3)_2$ species is more nucleophilic and has a higher HOMO than the monoligated equivalent. This causes it to undergo insertion into the C-OTf bond, the site of the lowest LUMO energy, more readily. The steric bulk of P(*t*-Bu)$_3$ on the other hand precludes the formation of bisligated species. This results in addition into the C-Cl bond to be more favoured. The C-Cl bonding orbital can form an interaction with the vacent site of the monoligated Pd, thus stabilising

the transition state.[85] Interestingly, Schoenebeck has also shown that selectivity between chlorides and triflates can be leveraged using the same catalyst/ligand system by varying the solvent (Scheme 38).[86] When using a non-polar solvent, such as THF, Schoenebeck *et al* observed the same chloride selectivity as Fu. However, using a polar solvent such as MeCN, reaction at the C-OTf bond was favoured. Schoenebeck proposed this was due to the formation of an anionic Pd species in polar solvents which can coordinate more strongly with the C-OTf bond and therefore react preferentially at that site.



Scheme 38: Electrophile chemoselectivity based on solvent effects

While Fu and Schoenebeck achieve chemoselectivity through manipulation of the reaction conditions, another method for realising selective cross-coupling is by exploiting the natural reactivity of the substrate. This has been demonstrated most widely in the case of dihaloheterocycles, where two equivalent electrophiles can be differentiated *via* either electronics (where the most electron deficient halide will react first) or by directing group effects. In an excellent review, Fairlamb describes the various site-selectivities of a range of dihaloheterocycles.[87] This approach has been key in both the pharmaceutical and agrochemical industries for the efficient synthesis of multi-substituted heterocycles from readily available starting materials.[88] At the centre of this approach is Zhang's method for predicting the site of preferred reaction *via* the ^{1}H NMR shifts of the non-halogenated parent heterocycle. Here, the most deshielded proton (highest chemical shift) indicates the site of highest reactivity toward cross-coupling in the halogenated compound (Figure 10).

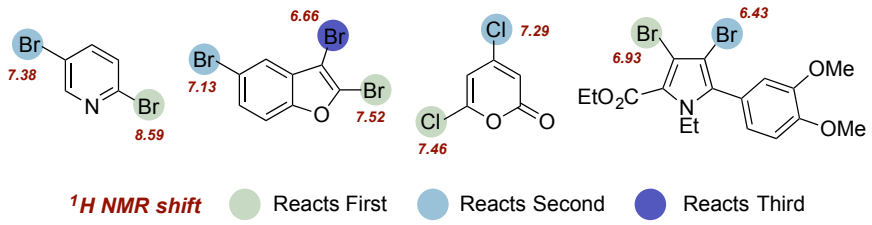
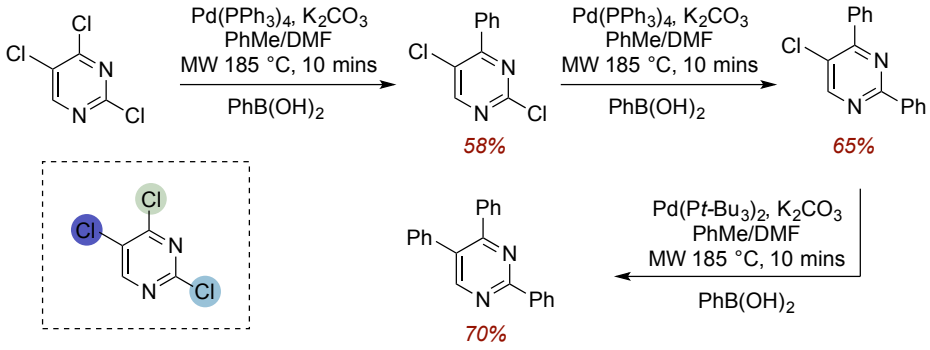


Figure 10: Electronic discrimination in dihaloheterocycles

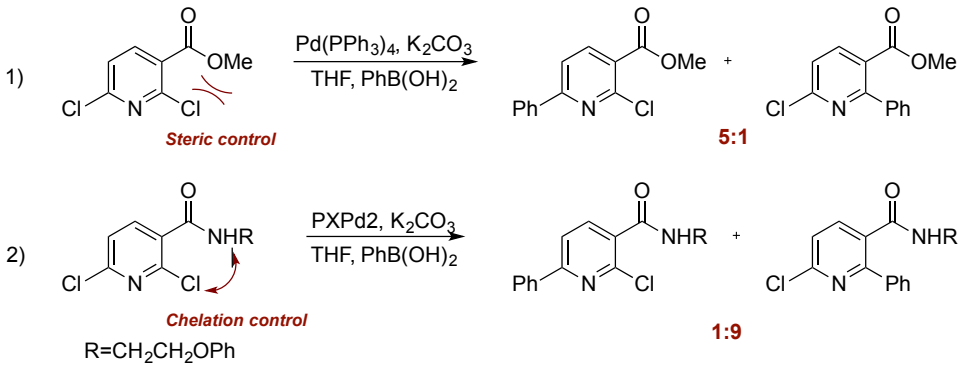
One particularly elegant example of chemoselectivity in multi-halogenated heterocycles comes from Ceide and Montalban, who were able to differentiate between three chloro substituents on a pyrimidine core (Scheme 39).[89] Under microwave irradiation, reaction occurred preferentially at the 4-position. Under the same conditions, coupling then occurred at the less active 2-position, before switching to a more active catalyst system enabled a final coupling at the 5-position. It should be noted that while selectivity was generally good for the 4-position in the first coupling, trace amounts of the 2-substituted- and 2,4-disubstituted product were observed. This demonstrates that while coupling may be favoured at one position, this method is not unequivocally selective.



Scheme 39: Sequential chemoselective coupling of 2,4,5-trichloropyrimidine

An alternate method for achieving chemoselectivity of equivalent dihalides is through the directing group effects of neighbouring Lewis bases. An example of this from Yang and co-workers used different substituents in the 3-position of 2,6-dichloropyridines to attain chemoselectivity (Scheme 40).[90] When employing a poorly directing ester in the 3-position, steric effects take hold and oxidative addition occurs at the less sterically demanding 6-postion (Scheme 40, Eq 1). The selectivity could be driven towards the 2-position through use of a [di-*tert*-

butyl(chloro)phosphine] palladium(II) dichloride dimer (PXPd2), however, selectivity was moderate (2.7:1 2-position:6-position). In contrast, when utilising a more chelating amide at the 3-position, selectivity for the 2-chloro markedly increases (Scheme 40, Eq 2).



Scheme 40: Chemeoselectivity *via* directing group effects

This occurs due to the greater propensity of nitrogen to chelate Pd,[91] in addition to the ether tether, offering two-point chelation and thus bringing it into closer proximity to the 2-chloro and therefore favouring oxidative addition at that position.

1.4.2 Chemoselectivity *via* transmetallation

In recent years, chemoselective reactions of multi-boron containing systems have emerged as a powerful tool in synthetic chemistry, allowing the rapid construction of complex carbon frameworks while leaving a reactive boron residue in place for further functionalisation.[92,93] Chemoselectivity within these systems is achieved through control of the transmetallation step of the SM catalytic cycle. Specifically, one boron moiety is rendered inert to transmetallation under the prevailing reaction conditions. In some cases, this involves simultaneous activation of the second boron moiety (*vide infra*). There are three main methods currently employed in the literature for achieving chemoselective transmetallation, these are: the use of additives to enable aryl/benzyl chemoselectivity; neighbouring group activation; and protecting group strategies (Figure 11).

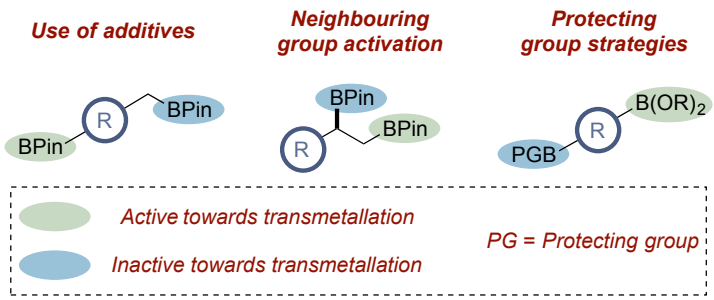


Figure 11: Methods of achieving chemoselective transmetallation

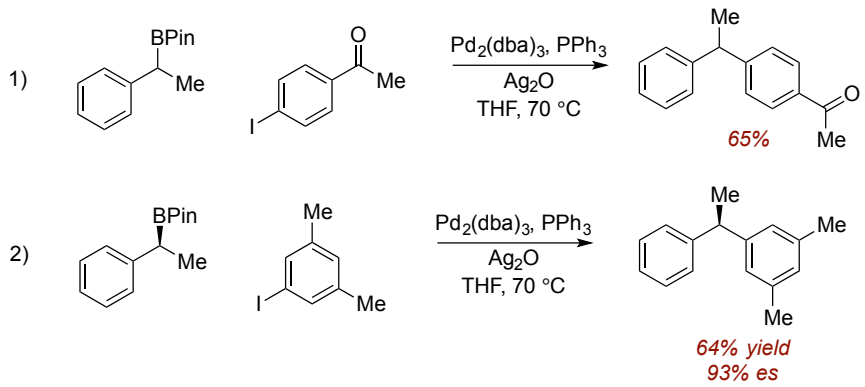
Each of these will be discussed in detail in the following section.

Use of additives

The use of additives to enhance the rate of cross-coupling in SM was first reported by Kishi in 1987 while working towards the synthesis of palytoxin.[94] The authors proposed that in the case of high molecular weight substrates, the rate-determining step was not oxidative addition, but in fact transmetallation. Working from the mechanism proposed by Suzuki and Miyaura,[1] with particular onus being placed on the role of hydroxide, Kishi and co-workers investigated the use of other bases in the hope of forming more water-soluble salts. It was found that employing Ag_2O as a base offered a 30-fold increase in reaction rate, while use of TlOH offered a staggering 1000-fold increase.

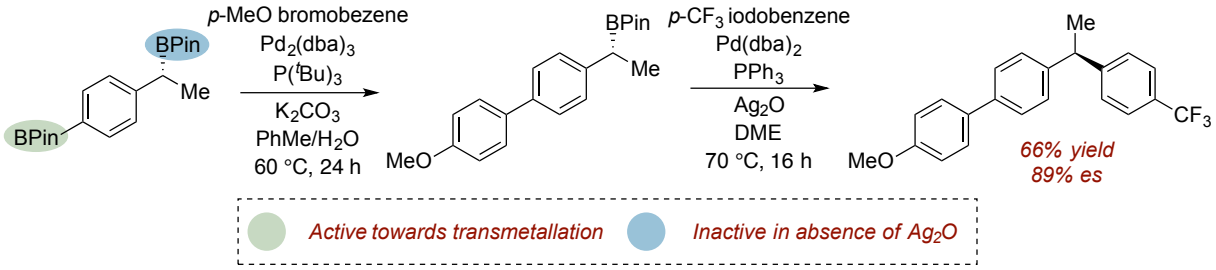
Some years later, in 2009, Crudden and co-workers reported the use of Ag_2O as a base to enable the cross-coupling of benzylic BPin reagents (Scheme 41, Eq 1).[95] No cross-coupling was observed under standard SM conditions (*i.e.*, using K_3PO_4 or Cs_2CO_3 as a base). Other silver salts did show some activity but none were comparable to Ag_2O: Ag_2CO_3 gave 38% conversion while $AgBF_4$ afforded only 3%, suggesting it was not merely the effect of the silver counter-ion that was responsible for the rate increase. Despite its success in Kishi's system, thallium hydroxide was not screened, presumably due to the toxicity of Tl salts in solution. Crudden *et al* were able to apply their Ag_2O system to enable the stereoretentive cross-coupling of enantioenriched benzylic BPins (Scheme 41, Eq 2). When the authors applied their Ag_2O conditions to non-benzylic systems, *i.e.*, primary alkyl BPins, no reaction was observed. Interestingly, while other secondary alkyl BPins showed no reactivity,

allylic BPins were found to undergo cross-coupling under Ag_2O mediated conditions, suggesting the need for an adjacent π system in order to achieve reactivity.[96]



Scheme 41: Use of Ag_2O to enable benzylic BPin cross-coupling

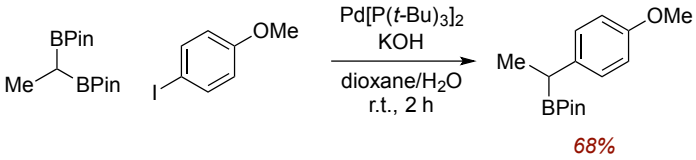
Having demonstrated that benzylic BPins undergo no reaction in the absence of Ag_2O, Crudden and co-workers sought to leverage this to enable the chemoselective cross-coupling of diborylated molecules.[97] The authors demonstrated that under standard SM conditions, using K_2CO_3 as a base, an aryl BPin unit could be cross-coupled exclusively in the presence a benzylic BPin on the same molecule (Scheme 42). The benzylic BPin moiety could then undergo subsequent cross-coupling under the developed Ag_2O conditions. This enables the rapid construction of multi-arylated skeletons bearing a chiral centre, something that is highly desirable in the pharmaceutical, agrochemical, and materials industries, and serves as an excellent example of chemoselective cross-coupling of multi-boron containing systems as a powerful synthetic technique.



Scheme 42: Chemoselective sequential cross-coupling through use of additives

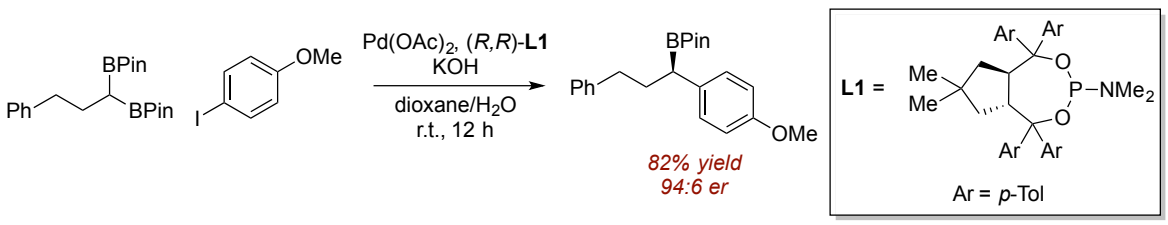
Neighbouring group activation

The first example of neighbouring group activation in terms of cross-coupling was reported by Endo and Shibata in 2010.[98] The authors utilised 1,1-diborylalkanes, or geminal BPin, to enable mono-selective sp^3-sp^2 cross-coupling under mild conditions (Scheme 43). It was proposed that the geminal BPin activation occurs *via* an increased Lewis acidity of one of the boron atoms. This enables the selective formation of a single boronate under the basic reaction conditions, which can then undergo transmetallation with Pd *via* the boronate pathway (see section 1.2.2 above).



Scheme 43: Selective mono-coupling of geminal BPins

Endo and Shibata offered a number of compelling arguments for their proposed theory: 1) formation of an alkyl BPin boronate is typically achieved only under forcing conditions; 2) the formation of a boronate was observed by NMR at room temperature upon treatment of the geminal BPin with KOH; 3) no boronate formation was observed upon treatment of the equivalent 1,1-borylsilylalkane or alkyl-BPin with KOH. The authors therefore proposed that the second boryl unit acts to stabilise the α-B–Pd^{II} intermediate. More recently, Morken has developed this selective cross-coupling and rendered it enantioselective through the use of a chiral phosphonite ligand to discriminate between the enantiotopic geminal BPins (Scheme 44).[99] While the authors did not comment on the hybridisation of the active boron species, a large excess of KOH was required for selectivity, suggesting that the reaction proceeds through the formation of BPin boronate as proposed by Endo and Shibata.



Scheme 44: Enantioselective mono-coupling of geminal BPins

In 2011, Hall reported an alternate method for the selective cross-coupling of 1,1-diborylalkanes.[100] Here, in place of a geminal BPin unit, Hall and co-workers employed a BPin/BDAN diboron system. Reports from Suginome[101] and Molander[102] had shown how a coordinating β-amide could aid in transmetallation to enable the stereoinvertive cross-coupling of alkyl boron species (Figure 12). Hall hypothesised that the enantioenriched BPin unit could be cross-coupled selectively through activation from an ester group in the β-position (Figure 12). This selectivity would be aided by the inert nature of BDAN moieties to cross-coupling under basic conditions.

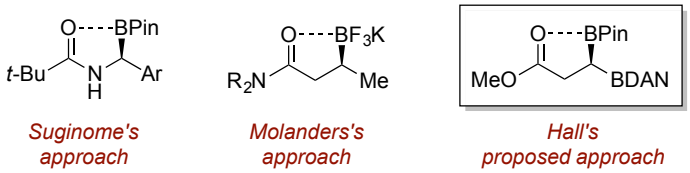
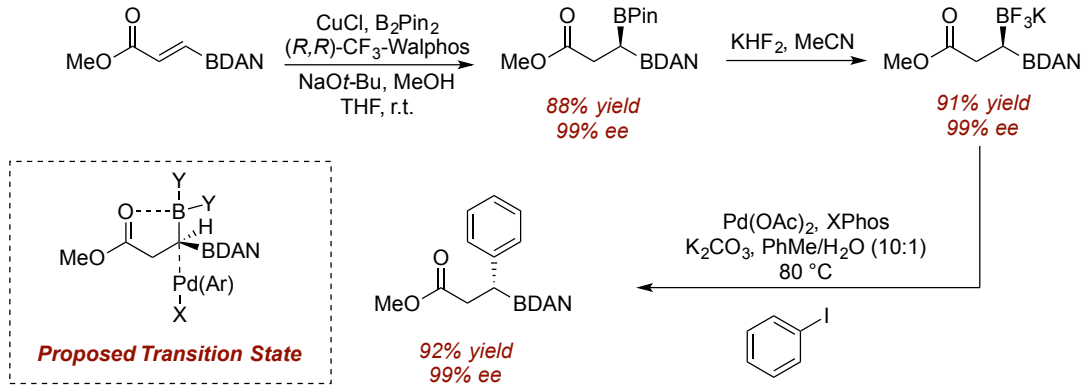


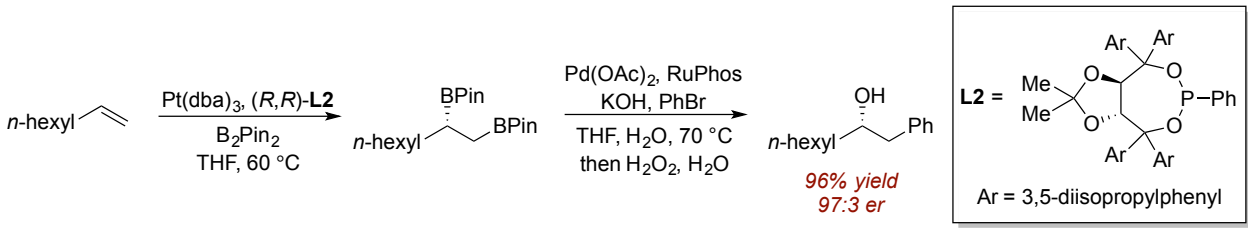
Figure 12: Approaches for intramolecular activation towards transmetallation

The BPin was installed through enantioselective cuproboration of an β-boryl unsaturated ester (Scheme 45). Unfortunately the authors found that while the β-carbonyl of the ester was sufficient in activating the BPin unit towards cross-coupling, it did so with no retention of stereochemistry, affording the cross-coupled products as racemates. The BPin was therefore converted into the corresponding BF_3K and it was found that the reaction proceeded with complete inversion of stereochemistry, akin to Molander's process (Scheme 45).[102] Hall proposed the inversion is a result of backside attack of the palladium complex on the boron bearing carbon, similar to that proposed by Suginome and Molander.[101,102] It was also suggested that activation of the BF_3K towards cross-coupling comes from a combination of the intramolecular donation of the oxygen lone pair and the stabilising effect of the BDAN unit on the α-B–Pd^{II} intermediate, as proposed by Endo and Shibata.[98]



Scheme 45: Enantioinvertive SM cross-coupling of 1,1-diboryl compounds

In addition to his work with geminal BPins, Morken has also demonstrated the selective cross-coupling of vicinal BPin units. Building on Miyaura and Suzuki's original process,[103] Morken and co-workers employed another chiral phosphonite ligand in combination with a Pt catalyst to affect enantioselective diboration of terminal alkenes.[104] The authors were then able to employ these enantioenriched vicinal diboron species in chemoselective SM cross-coupling (Scheme 46).[105] An oxidative workup was then applied to convert the remaining BPin unit to the corresponding alcohol to aid purification.



Scheme 46: Enantioselective diboration and subsequent chemoselective cross-coupling

In contrast to the mechanism put forward by Endo and Shibata,[98] Morken proposes an intramolecular Lewis acid-Lewis base interaction (Figure 13) between the empty p-orbital of the proximal BPin unit (**a**) and the oxygen of the terminal BPin unit (**b**). This neighbouring group activation renders the latter activated towards transmetallation while subsequently deactivating the former, enabling selective cross-coupling.

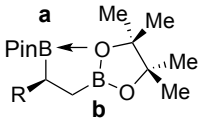
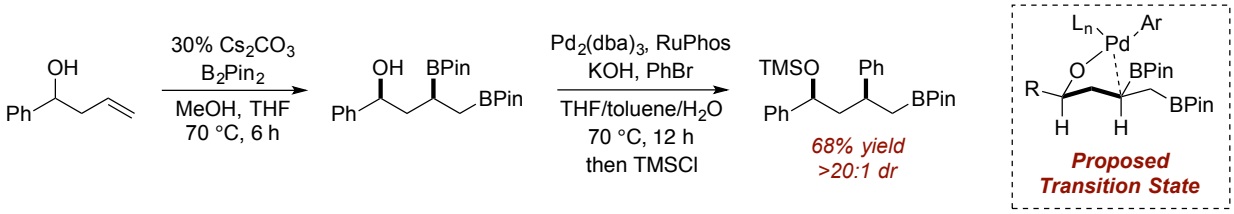


Figure 13: Neighbouring group activation in vicinal diboron systems

Shortly afterwards, the same group reported a complementary procedure which enabled a selectivity switch in the cross-coupling of these vicinal diboron systems.[106] Here, Morken employs a base mediated diboration of alkenes bearing a β-hydroxyl,[107] which then serves to direct the subsequent coupling, this time *via* hydroxyl-mediated neighbouring group activation (Scheme 47), inverting the selectivity of their previously reported process and thus demonstrating the potential of these diboron systems for divergent synthesis.



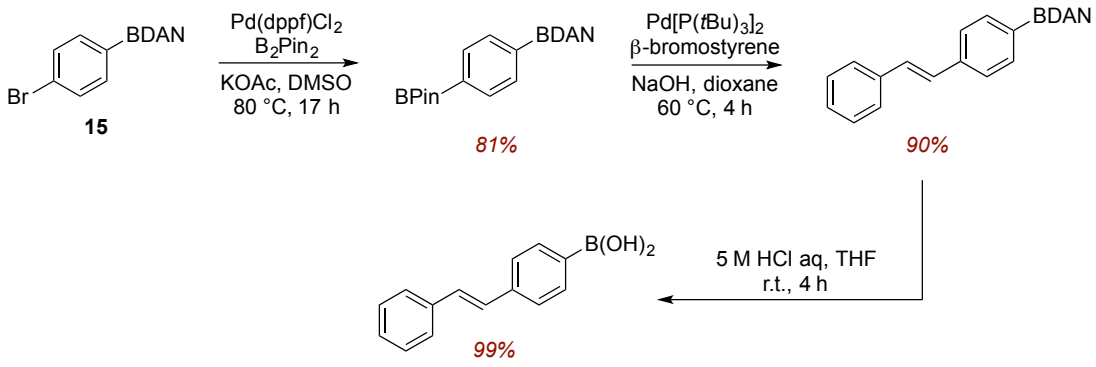
Scheme 47: Hydroxyl mediated chemoselective cross-coupling of vicinal BPins

Protecting group strategies

The use of protecting group strategies as a means for chemoselective SM cross-coupling has increased exponentially in the past 10 years thanks mainly to the work of Suginome, Molander, and Burke in their development and application of BDAN, BF_3K, and BMIDA reagents, respectively.[92,93] These protected boronic acids are effectively inert to transmetallation under specific reaction conditions, allowing a reactive boronic acid or ester to be selectively coupled in their presence. The protecting group can then be removed to reveal the parent boronic acid, which can then be used in subsequent cross-couplings, allowing molecules to be built up in an iterative fashion.

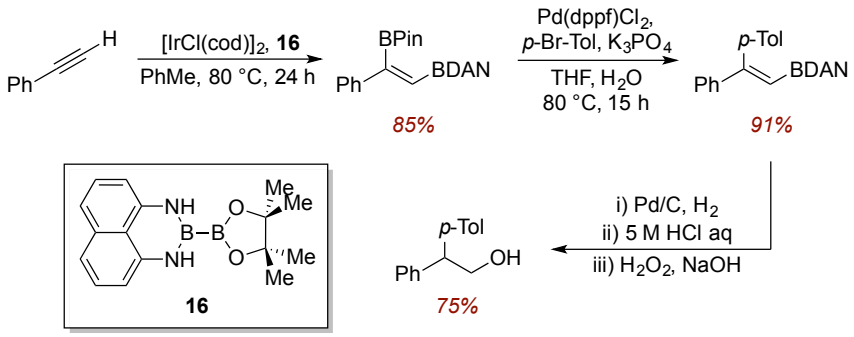
As previously mentioned, the 1,8 diaminonaphthyl boranes developed by Suginome are acid labile, meaning these protected boronic acids are stable under the aqueous basic conditions typically employed within SM cross-coupling.[80] Suginome has

demonstrated the use of BDAN reagents in the preparation and subsequent chemoselective cross-coupling of diboron species (Scheme 48).[81] Miyaura borylation of haloaryl BDAN **15** affords a diboron species, containing a reactive boron moiety in BPin and a protected boronic acid in BDAN. This can then be selectively cross-coupled at the BPin position under aqueous basic conditions, leaving the acid labile BDAN intact. Subsequent acid-mediated hydrolysis then reveals the parent boronic acid for further functionalisation.



Scheme 48: Synthesis and chemoselective cross-coupling of BPin/BDAN reagents

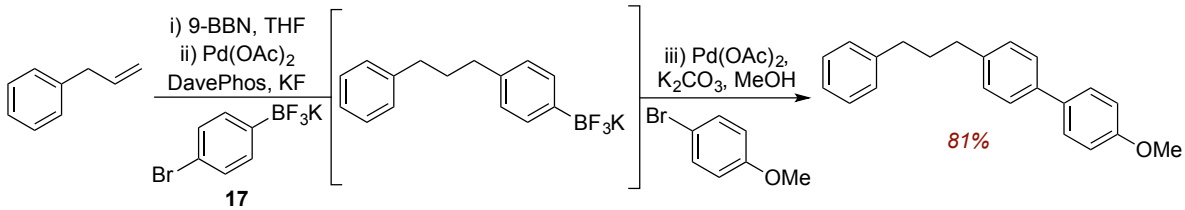
Another property of BDAN reagents which has been exploited in synthesis is their steric bulk. Using unsymmetrical diboron reagent **16**, diboration across a terminal alkyne affords the BDAN moiety at the least hindered position (Scheme 49).[108] This then allows the BPin reagent to be selectively cross-coupling under conventional SM conditions as before. Reduction of the double bond followed by acid hydrolysis and oxidation then affords the terminal alcohol. This innovative use of BDANs steric bulk to invert traditional selectivity is an excellent example of the synthetic utility, allowing selective cross-coupling at the more hindered site of a functionalised alkene.



Scheme 49: Diboration and subsequent chemoselective functionalisation of BPin/BDAN

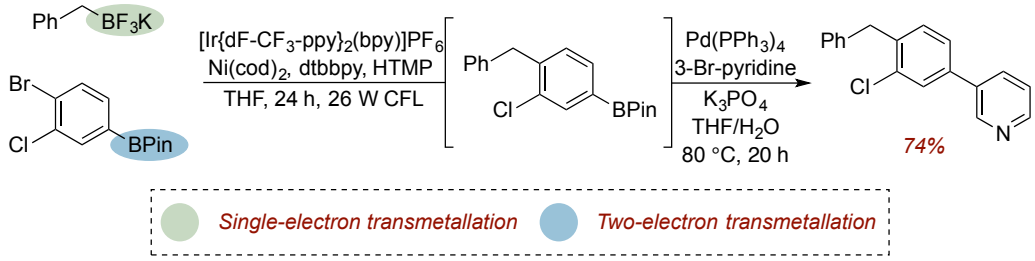
Despite this valuable ability to invert traditional chemoselectivity, as well as their tolerance for traditional cross-coupling conditions, BDANs have seen a much lower uptake in synthesis than other protecting groups, particularly BMIDAs. This is perhaps due to the relatively forcing acidic conditions required for their hydrolysis, limiting functional group tolerance and boronic acid substrate scope – once revealed, unstable boronic acids such as heterocyclic motifs are unlikely to survive under exposure to concentrated acid. Despite this, however, BDAN reagents remain a valuable tool in terms of manipulation of chemoselectivity.

Molander's organotrifluoroborate reagents have also seen use in diboron systems, allowing chemoselective transmetallation of a reactive boron species while preserving the integrity of the protected BF_3K, allowing iterative cross-coupling.[109] In one example, Molander generated a reactive alkyl borane *in situ*, which was then cross-coupled to the haloaryl boron species **17**, generating a new BF_3K species (Scheme 50). This could then be subsequently cross-coupled to an aryl halide under conventional SM conditions. Important to note is the use of KF as a base in the first cross-coupling, presumably to ensure the integrity of the BF_3K species.



Scheme 50: Use of BF_3K in iterative cross-coupling

In addition to this, Molander was able to invert the traditional chemoselectivity of organotrifluoroborates through the use of Ir/Ni photoredox catalysis.[110] This allowed the selective cross-coupling of an alkyltrifluoroborate under the single-electron transmetallation manifold while maintaining a second reactive boron species, in this case a BPin moiety, intact for further functionalisation through traditional two-electron SM cross-coupling (Scheme 51).[111] This offers an alternative to conventional protecting group strategies for sequential cross-coupling, enabling efficient elaboration of functionalized building blocks without the need for intermediate purification or modification through deprotection.

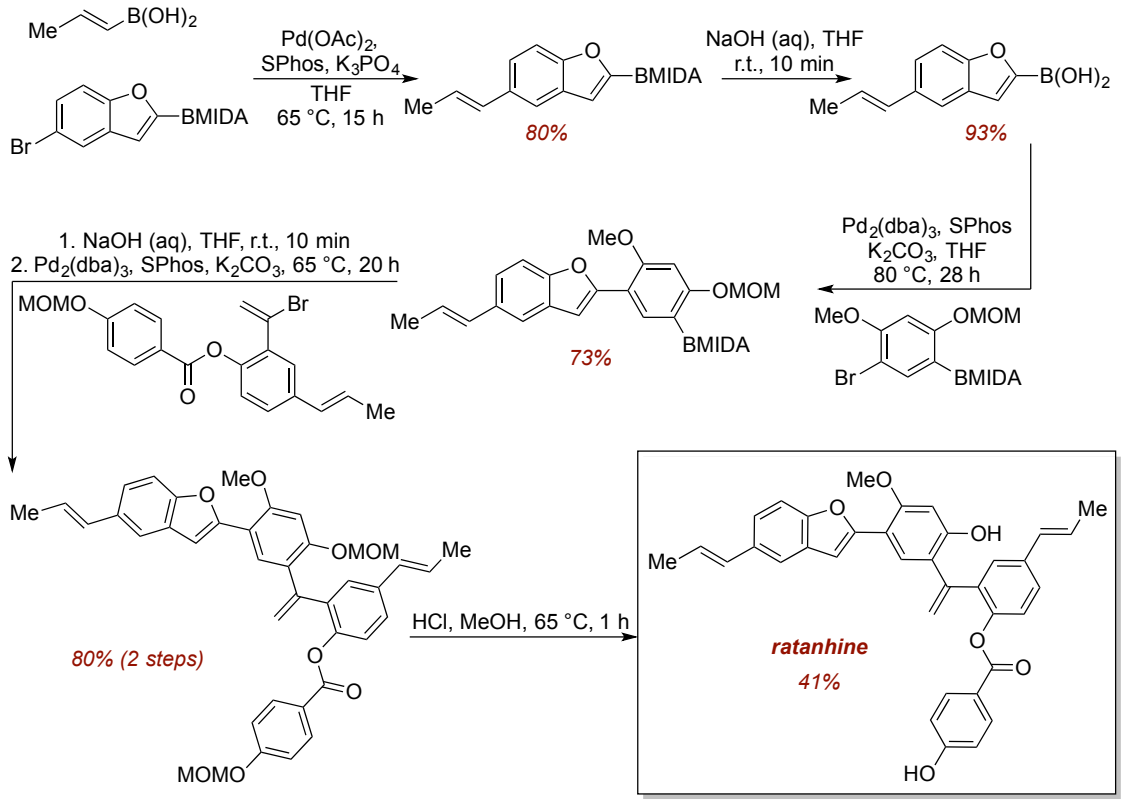


Scheme 51: Orthogonal reactivity of BF_3K *via* photoredox catalysis

This development of a new mechanism for transmetallation of potassium organotrifluoroborates further demonstrates the continued diversity and importance of protected organoboron reagents in chemoselective cross-coupling.

Perhaps the most widely developed protected boron reagents in terms of chemoselective transmetallation are the MIDA boronates. While it would be easy to think that their base lability would preclude them from selective cross-coupling, Burke has developed an extensive programme showcasing the power of these reagents in iterative cross-coupling.[70] Using a sequential cross-coupling/deprotection strategy, Burke and co-workers have been able to synthesise a range of natural products, such as ratanhine,[112] from a very small number of building blocks (Scheme 52).[113] Here the haloaryl BMIDA building blocks were chemoselectively cross-coupled under anhydrous conditions to maintain the integrity of the protecting group. The BMIDA could then be efficiently hydrolysed by reaction with aqueous base to reveal the parent boronic acid for subsequent cross-coupling. This allowed the complex scaffold of ratanhine to be constructed in just six simple steps and served as

an early demonstration of the power of protected boron reagents in iterative synthesis.



Scheme 52: Synthesis of ratanhine through iterative cross-coupling of BMIDA building blocks

This type of iterative synthesis using BMIDA building blocks is not limited to aromatic systems. Indeed, Burke's development of BMIDA reagents for iterative synthesis stemmed from his interest in polyene natural products, such as amphotericin B – an antifungal heptaene macrolide (Figure 14), and a desire to enable the efficient synthesis of this class of biologically important natural products.[114]

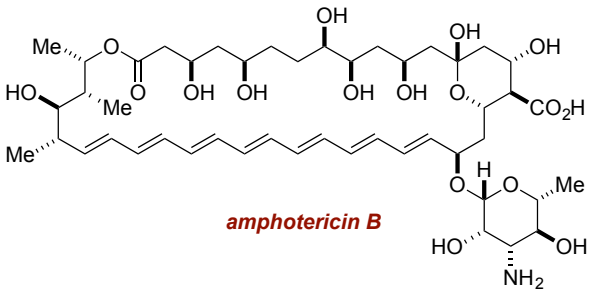
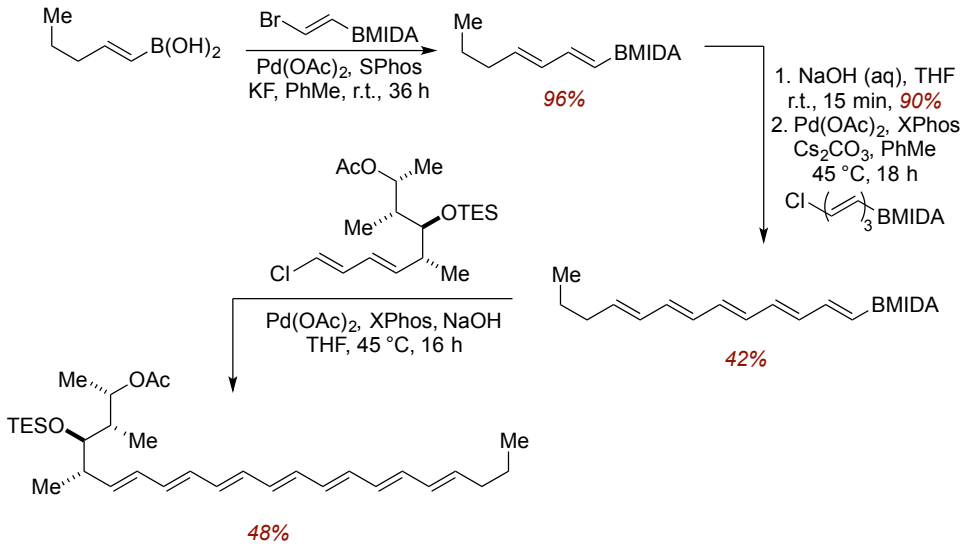


Figure 14: Polyene natural product amphotericin B

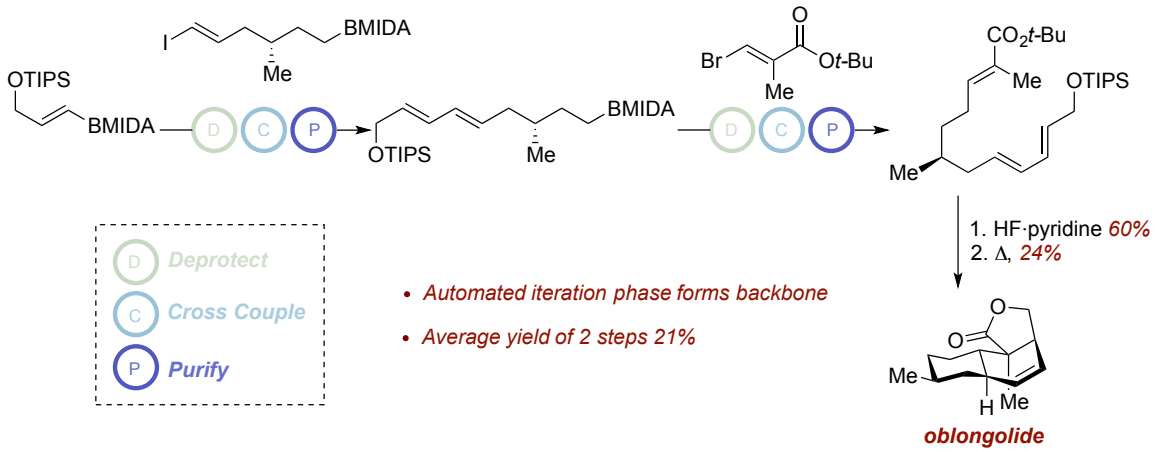
It was proposed that this type of polyene natural product could be rapidly constructed using an iterative cross-coupling approach, however, vinyl boronic acids – particularly those derived from polyenes – are notoriously unstable.[115] BMIDA reagents therefore offered the perfect platform to enable the iterative synthesis of these valuable biological materials, ensuring that each intermediate could be isolated as an air stable compound and that the potentially any unstable boronic acids could be taken directly into the next cross-coupling. Using this method, Burke and co-workers were able to synthesise a range of polyene natural products, including the polyene backbone of amphotericin B (Scheme 53).[114]



Scheme 53: Synthesis of amphotericin backbone *via* iterative cross-coupling

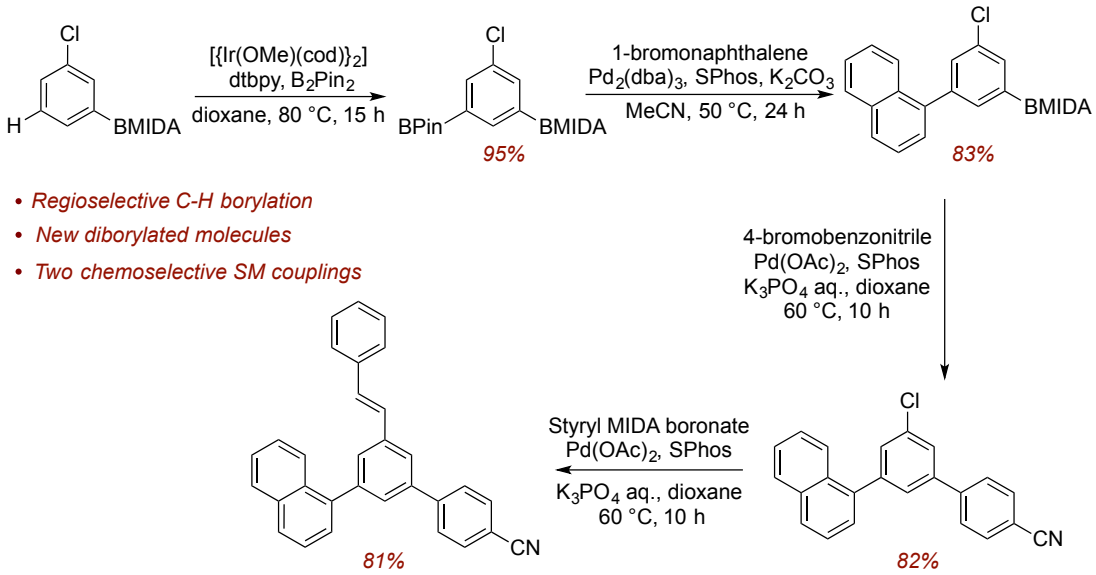
Burke and co-workers were also responsible for one of the most impressive advances in iterative cross-coupling with the development of their "synthesis machine".[116] This machine allows the group to perform iterative cross-coupling in an automated fashion, akin to that of peptide synthesis,[117] using a sequential deprotection/cross-coupling manifold in combination with a "catch and release" type purification method.[116] This involves exploiting the polarity of the BMIDA protecting group, which can bind to a silica column and allow any impurities to be washed away with a mixture of MeOH and Et_2O. The desired BMIDA product can then be flushed from the column with THF, ready for the next deprotection and cross-coupling reaction. This automated process has allowed Burke *et al* to rapidly synthesise an incredibly diverse range of compounds from commercial starting materials, including 20

unnatural analogues of the natural product ratanhine, substituting various aspects of the core structure with pharmaceutically-relevant functional groups and motifs. The group also demonstrated the ability of their "synthesis machine" to generate more complex macro- and polycyclic natural products and natural product–like cores, such as oblongolide (Scheme 54).[116]



Scheme 54: Automated synthesis of the natural product oblongolide *via* iterative SM cross-coupling

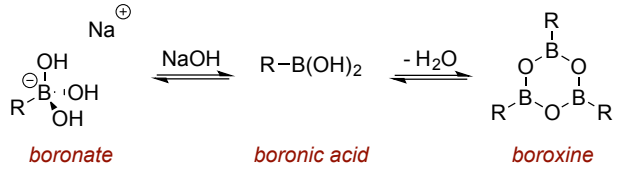
Although his contributions to the area have been numerous, Burke is not the only person to have utilised BMIDA reagents in iterative cross-coupling. Li and co-workers utilised aryl BMIDA building blocks in an Ir catalysed C-H borylation protocol to furnish diborylated arenes which could then be chemoselectively cross-coupled in an iterative fashion (Scheme 55).[118] This methodology offers a complementary approach to Suginome's method for the synthesis of diborylated arenes, in this case afforded compounds bearing a base labile BMIDA group in place of Suginome's acid labile BDAN.



Scheme 55: Synthesis and chemoselective cross-coupling of diborylated arenes

1.5 Boron speciation

The concept of boron speciation pertains to the behaviour of boron species in solution, specifically how they can undergo changes in ligand association and oxidation state through influence of the reaction media. An example of this has already been discussed in the context of the SM reaction, wherein neutral planar boronic acids exist in an equilibrium with their charged tetrahedral counterparts, boronates, under basic conditions (Scheme 56). Boronic acids can also form trimeric anhydrides, known as boroxines, under anhydrous conditions.[7] Formation of these species liberates three equivalents of H_2O and is entropically favoured. Boroxines are also stabilised by their partial aromatic character. This serves as an example of the equilibria which boron species can undergo in solution.



Scheme 56: Boronic acid speciation in solution

In relation to SM, this can affect the efficiency of a reaction. For example, if a boronic acid sits exclusively as its boronate under the reaction conditions, transmetallation *via* the oxo-palladium pathway is precluded.[27] This change in

speciation can also effect the physical location of the boron species in the reaction – in biphasic systems, neutral boronic acids tend to reside in the bulk organic phase, while the more water soluble boronate can be sequestered into the aqueous phase.[27]

This problem of boron speciation is further complicated when boronic esters are introduced. These species can undergo transesterification with free diols, leading to a mixture of esters in solution (Scheme 57).[119] This idea of transesterification was explored in the late 1980's by Brown[120] in order to recover the costly pinanediol auxiliary used in Matteson's asymmetric homologation process.[121]

Scheme 57: General scheme for transesterification of boronic esters

However, it was found that the pinanediol was incredibly difficult to displace *via* transesterification. This led to a comprehensive investigation by Roy and Brown into the stability and relative rates of transesterification of various boronic esters.[119] The authors highlighted a number key points relating to the effect of structure on both the stability of the ester and the propensity of the diol to undergo transesterification. From this they were able to establish an order of stability of various boronic esters (Figure 15).

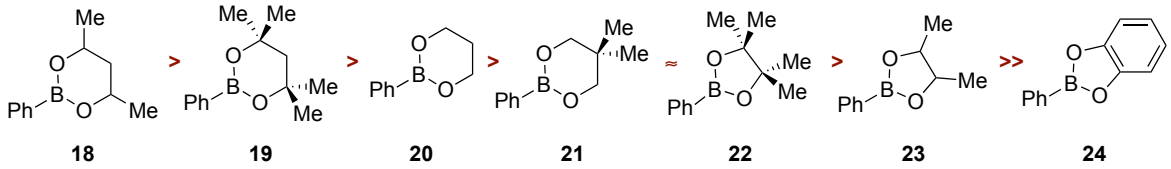


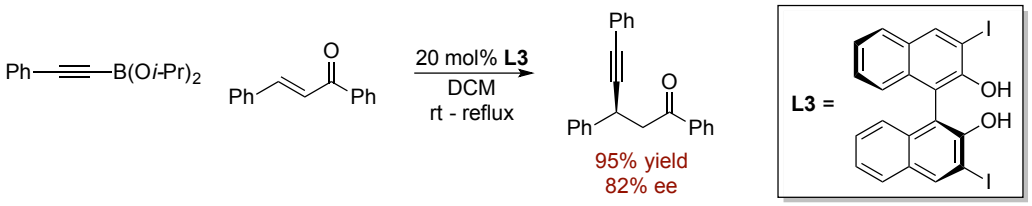
Figure 15: Order of stability of selected boronic esters

It was found that 6-membered cyclic boronic esters were more stable than the equivalent 5-membered systems, likely as a result of improved orbital overlap between the B and O allowing for better donation of the O lone pair.[7,119] In the case of cyclic diols, a *cis*-configuration was required for transesterification to occur – *trans* diols were found to be completely inert. With respect to ring substitution, an interesting distinction was observed when it came to ring size. With 6-membered boronic esters, mono-substitution at the α-position increased stability (Figure 15, **18**

vs. **20**), however di-substitution in this position was less stabilised (**18** *vs.* **19**). The opposite was true in 5-membered systems, here greater substitution in the α-position directly correlated with greater stability. In terms of boronic esters commonly employed in SM cross-coupling, neopentyl- and pinacolboronic esters, **21** and **22,** respectively, were found to be of comparable stability, with boronic esters derived from catechol (**24**) significantly less stable.

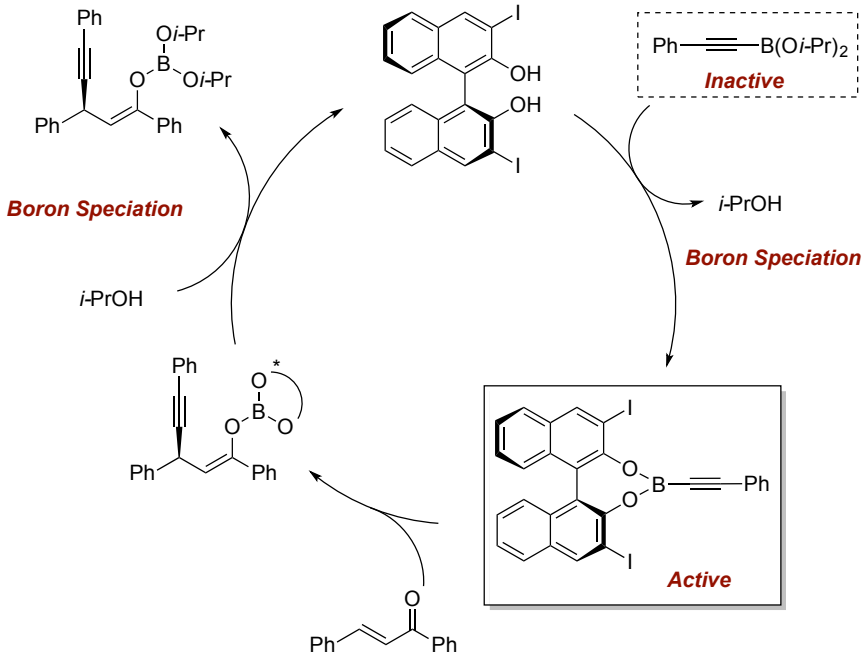
A detailed study into the effects of reaction media was carried out in 2004 by Springsteen and Wang.[122] Specifically, the authors sought to determine the optimum conditions for diol conjugation and therefore measured the binding affinities of a variety of diols with a range of arylboronic acids at varying pH. The pK_a of boronic acids is known to vary extensively based on the electronics of the aromatic ring. Electron withdrawing groups exhibit a much greater effect on pK_a than electron donating. A range of 25 boronic acids of varying pK_as were examined, from the electron deficient *N*-benzyl-3-pyridineboronic acid (pK_a = 4.2) to the electron rich *o*-methoxyphenyl boronic acid (pK_a = 9.0). The authors concluded that the optimum pH for diol conjugation lay between the pK_a of the boronic acid and the diol. Although the pK_a of the boronic acid could vary from 4-9, the pK_a of the diol was typically >10. For this reason, it was found that basic conditions between pH 8-10 were optimal for diol conjugation.

While these groundbreaking studies focussed on the understanding of boron speciation, there are also a number of examples which elegantly exploit boron speciation for synthetic gain. Hutton employed polymer bound boronic acid as a means to deprotect pinacol esters to afford the corresponding boronic acid, a process which typically requires much more forcing conditions.[52] In 2005, Chong utilised a chiral diol to facilitate the conjugate addition of alkynylboronic esters to enones (Scheme 58).[123]



Scheme 58: Asymmetric conjugate addition enabled by diol transesterification

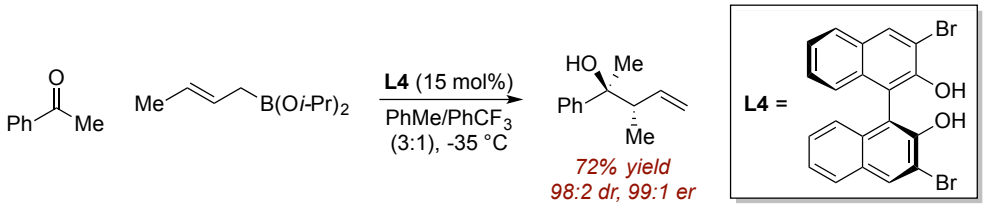
Chong's process relied upon the starting achiral boronic ester being less reactive than the chiral ester formed following transesterification. It also required the chiral diol to be released following conjugate addition in order for the reaction to be catalytic in chiral diol (Scheme 59). It was found that 1,1'-bi-2-naphthol (BINOL) type ligands were singularly effective in this process; most standard achiral diols, such as pinacol and ethylene glycol did not catalyse the reaction, while diisopropyl tartarate, another commonly used ligand in asymmetric boron chemistry, delivered only racemic product. Chong was later able to expand upon this process to enable asymmetric alkenylation of enones under the same manifold.[124]



Scheme 59: Proposed catalytic cycle for asymmetric conjugate addition

Shortly after the initial report by Chong, Schaus and co-workers reported an asymmetric allylboration process which proceeded *via* a similar transesterification mechanism.[125] Schaus' process also used a BINOL derived ligand to enable the

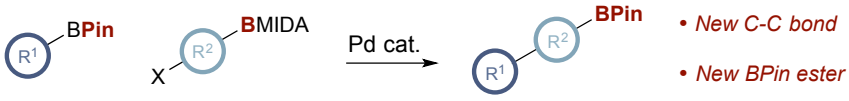
asymmetric addition of achiral allylboronic esters to a variety of ketones (Scheme 60). While enantioselective allylboration is well known, it is typically less effective on ketones, and requires the prior synthesis of a chiral boron reagent.[126] The work of Schaus and Chong demonstrates the benefits of harnessing boron speciation in order to generate new reactive boron species *in situ*.



Scheme 60: Asymmetric allylboration enabled by diol transesterification

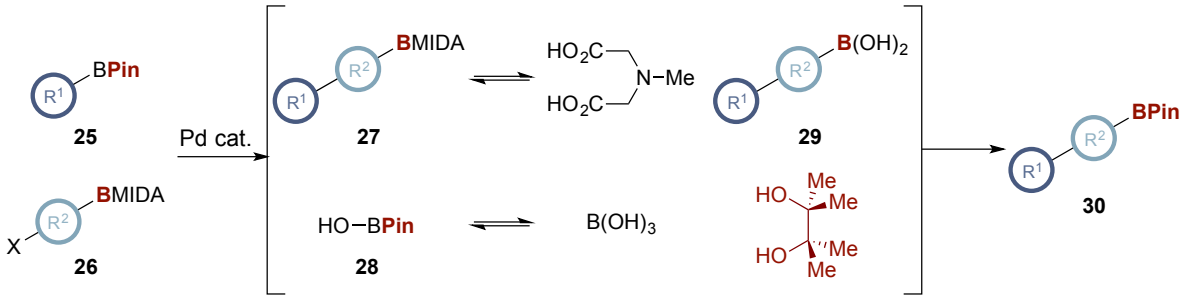
2. Project aims

While numerous advances have been made with regards to SM cross-coupling in diboron systems, of the current methods for achieving chemoselectivity within such systems, only protecting group strategies pertain to systems containing two arylboron species. Although the chemistries developed by Molander, Suginome, and Burke exhibit excellent selectivity for the reactive boronic acid or ester over the protected species, they do have the drawback of requiring an additional protection and deprotection step, in addition to necessitating careful control of the reaction conditions to avoid premature hydrolysis. With modern synthetic chemistry striving towards more "ideal" synthesis,[127] methods for the efficient interconversion of reagents without the need for superfluous protecting group manipulations are highly sought after. It was therefore proposed that combining Burke's ground-breaking work on the iterative cross-coupling of haloaryl BMIDA species with the power of boron speciation could provide a method for the chemoselective cross-coupling of two arylboron species to generate a new reactive boronic ester (Scheme 61).[128,129] This would preclude the need for any additional deprotection steps, furnishing a reactive boron species for further functionalisation from a single reaction, thus increasing overall efficiency.



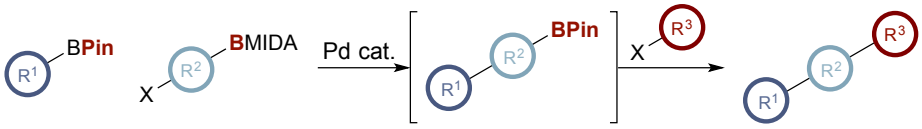
Scheme 61: Chemoselective boronic ester synthesis enabled by speciation control

It was anticipated that the overall transformation would proceed through three fundamental steps (Scheme 62): i) the initial cross-coupling between BPin **25** and haloaryl BMIDA **26** to yield the cross-coupled product **27**, along with the HO-BPin byproduct **28**; ii) hydrolysis of both these species to afford the parent boronic acid **29** in addition to the free pinacol ligand; and iii) conjugation of the free pinacol with **29** to furnish the new formally homologated boronic ester **30**.



Scheme 62: Proposed mechanism of formal homologation of BPin *via* speciation control

If suitable conditions could be developed for the formal homologation of BPin esters, this would in turn enable the development of sequential cross-coupling procedures. The newly formed reactive BPin could be reacted *in situ* with a second electrophile, forming two selective C-C bonds in a single operation, without the need for intermediate isolation, purification, or protection/deprotection (Scheme 63). This process of nucleophile control could then potentially be combined with electrophile control: exploiting different rates of oxidative addition of various aryl halides to enable of truly one-pot process with no need for sequential addition.



Scheme 63: Potential for sequential cross-coupling *via* speciation control

Based upon the work of Hartwig, which demonstrated the difference in rates of transmetallation of boronic acids and BPins,[31] it was also proposed that chemoselectivity betweent these two species could be achieved directly, without the need for protecting groups. This would demonstrate the first example of chemoselectivity between two obstensibly equivalently reactive aryl boron species within SM cross-coupling, and would represent another important advance in terms of both chemoselective control and overall reaction efficiency.

3. Results and discussion

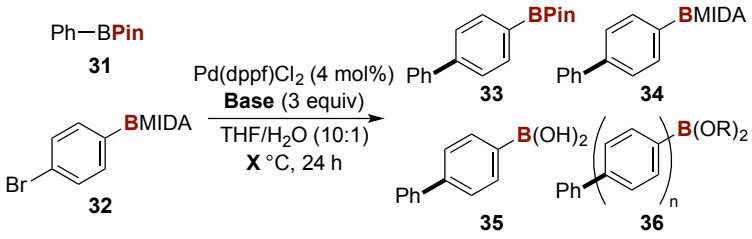
3.1 Chemoselective Suzuki-Miyaura cross-coupling enabled by speciation control

This section is based upon the following publications: *Angew. Chem., Int. Ed.*, 2014, **53**, 12077–12080[128] and *Chem.– Eur. J.*, 2015, **21**, 8951–8964.[129]

Although each of the steps proposed in Scheme 62 are well precedented in the literature,[113,122] it was foreseen that combining them could prove problematic. To ensure selective cross-coupling between **25** and **26** would require the reaction to be run in the absence of aqueous base to avoid premature hydrolysis of BMIDA **26**. However, the hydrolysis of **27** and **28** along with the conjugation of pinacol with boronic acid **29** to form **30** are all processes which are promoted by basic conditions. In addition to this, there was also a potential reactivity issue if **29** was formed before **26** was fully consumed as Hartwig has shown boronic acids to transmetallate faster than BPins under Pd catalysis.[31] This in turn would again require control over the quantity of aqueous base present in reaction to ensure BMIDA **27** was not hydrolysed too rapidly.

Investigation into the formal homogation of boronic esters therefore began with a benchmark reaction involving phenylboronic acid pinacol ester **31** and 4-bromophenyl BMIDA **32** under conventional SM conditions – Pd(dppf)Cl_2 was selected as a catalyst along with two common inorganic bases, K_3PO_4 and Cs_2CO_3 (Table 1). The reaction was performed in THF using a relatively limited quantity of H_2O (10:1 solvent:H_2O). SM reactions are often run using large quantities of H_2O (4:1 – 7:1),[7] however, as control of the BMIDA hydrolysis required a slow release of aqueous base, it was thought that limiting the quantity of H_2O in the reaction would be key. The reactions were analysed by HPLC and conversions calculated by addition of a known standard.

Table 1: Initial screening with K_3PO_4 and Cs_2CO_3 and 10:1 THF/H_2O

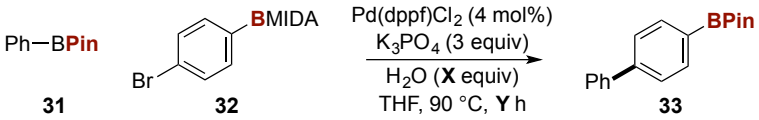


Entry	Base	Temperature (°C)	33:34:35:36 (%)[a]
1	K_3PO_4	50	57:13:7:0
2	Cs_2CO_3	50	52:6:7:0
3	K_3PO_4	90	30:0:0:70
4	Cs_2CO_3	90	27:0:0:73

[a] Determined by HPLC analysis.

The results of these initial reactions were quite promising. Good conversion to product **33** was seen with both bases at 50 °C (Table 1, Entries 1 and 2). Small quantities of the intermediate boron species **34** and **35** were also observed (between 13 and 20%), however, no oligomeric products were seen. Unfortunately, the reaction did not go to completion under these milder conditions, affording only ~70% conversion. Under more forcing conditions at 90 °C (Entries 4 and 5), lower conversion to **33** was observed (~30%) with the mass balance consisting of oligomeric materials (**36**). Although the conversion to the desired product **33** was lower than the reactions at 50 °C, confidence was taken from the fact that full consumption of the starting materials was achieved under these conditions. It was thought that the large degree of oligomerisation observed was a result of premature hydrolysis of the starting BMIDA **32** and/or intermediate BMIDA **34** under the more forcing conditions and that this could be tempered by further limiting the quantity of H_2O in the system. It was for this reason that optimisation was continued at 90 °C. As both bases surveyed exhibited similar conversions K_3PO_4 was elected to be carried forward purely for cost purposes (£123.12/mol compared to £1055.66/mol for Cs_2CO_3).

K_3PO_4 is known to be hygroscopic and able to form stable tetrahydrates.[130] It was therefore thought that the base could act as an internal desiccant and sequester H_2O, limiting HO^- formation. Equally, Lloyd-Jones has discussed the concept of a basic biphase, in the context of SM, acting as an internal reservoir of HO^-.[27,66] It was thought in this case that an internal reservoir of HO^- would allow slow release of hydroxide ions into the bulk organic phase and in turn facilitate slow hydrolysis of the BMIDA species. A systematic evaluation of the effect of varying quantities of H_2O on the reaction over time was therefore undertaken (Scheme 64 and Chart 1).



Scheme 64: Evaluation of effect of H_2O on conversion to 33 over time

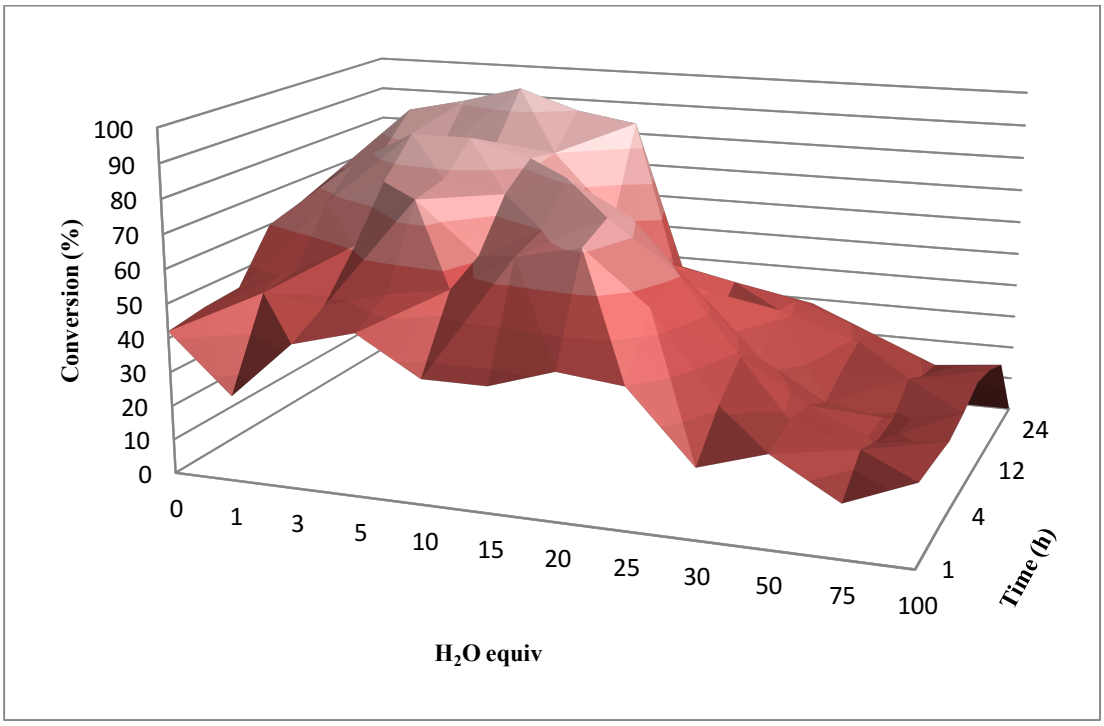


Chart 1: Effect of H_2O on conversion to 33 over time

As predicted the quantity of H_2O present in the system had a dramatic effect on the conversion to the desired product **33**. Four main regions were observed in the response surface shown above in Chart 1:

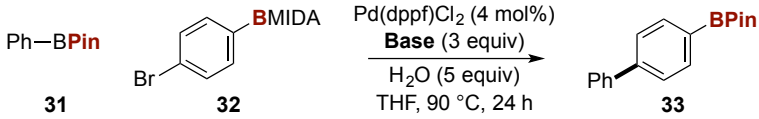
1) 0 equivalents of H_2O: this resulted in moderate conversion to **33** (40 – 60%), with even extended reaction times failing to push the reaction to completion. However, the moderate conversion to **33** is interesting as theoretically neither the cross-coupling nor hydrolysis/conjugation should proceed in the complete absence of OH^-, suggesting there is enough advanticious H_2O in the system to allow both reactions to proceed to some extent.
2) 5 – 15 equivalents H_2O: this was found to be the optimum region for the reaction, with conversion to **33** increasing steadily to excellent levels over 24 h (92% with 5 equiv H_2O). Shorter reaction times afforded varying level of intermediate boron species **34** and **35**, indicating a rapid initial cross-coupling following by slower transesterification.
3) 15 – 25 equivalents H_2O: under these conditions conversions were found to be unpredictable, with shorter reaction times offering good conversion to **33** but longer reaction times producing higher levels of oligomerisation. It was thought a possible reason for this unpredictably stemmed from the formation of a more pronounced basic biphase, with reactions beginning to become more noticeably biphasic as H_2O increased.
4) > 25 equivalent H_2O: conversion to **33** was consistently poor (20 – 30%) with high levels of oligomeric material observed. This suggested, as predicted, that higher quantities of H_2O resulted in poor control of BMIDA hydrolysis.

Based on these observations and the excellent conversion to **33**, 5 equivalents of H_2O along with 24 h reaction times were selected as the optimum conditions to proceed.

Having established the effect of H_2O on the reaction, the role of the base was then evaluated. Although K_3PO_4 had been shown to be effective in affording high conversion to **33**, it was unclear if other bases would be equally effective. Amatore and Jutand have have described the triple role of hydroxide in the SM cross-coupling,[32] along with the role of the counterion.[131] As hydroxide is also known to play a role in the hydrolysis of BMIDA,[71] it was thought that different sources of hydroxide, along with their physical properties, may have a marked effect on the reaction.

Firstly, a survey of different potassium bases was undertaken to assess the effect of the anion, specifically the pK_a of the conjugate acid (Table 2).

Table 2: Survey of potassium bases



Entry	Base	Approx. pK_a[132]	Conversion to 33(%)[a]
1	KTFA	0	0
2	KH_2PO_4	2	0
3	KOAc	5	37
4	K_2HPO_4	7	0
5	K_2CO_3	10	51
6	K_3PO_4	12	92
7	KOH	16	22
8	KO*t*-Bu	18	23

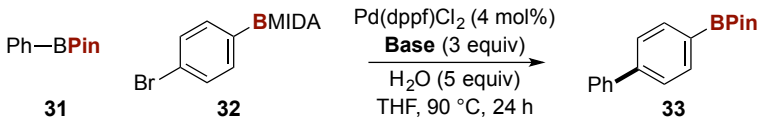
[a] Determined by HPLC analysis.

Bases with low pK_a were found to give no conversion to the product **33** (Entries 1 and 2). This is unsurprising as the initial cross-coupling, BMIDA hydrolysis, and subsequent diol conjugation are all processes known to be favoured under basic conditions, *i.e.*, pH > 7. Upon increasing the pK_a, conversion to **33** was seen to increase (Etnries 3 – 6), with the exception of K_2HPO_4, which gave no conversion despite being of higher pK_a than KOAc, which afforded **33** in 37% (Entry 3 vs. 4). This suggested that while pK_a, and therefore the resultant solution pH, was important in controlling the reaction, it was not the only factor at work. Interesting to note was the distribution of products in reactions with KOAc and K_2CO_3 (Entries 3 and 5). In each case, intermediate boron species **34** and **35** were not detected, signifying that the overall efficiency of the reaction was entirely

dependent on the efficiency of the initial cross-coupling. As before, K_3PO_4 was found to be optimum in both providing efficient cross-coupling and controlling speciation (Entry 6). When the pK_a of the base was further increased with the use of KOH and KO*t*-Bu, poor conversion to product was observed (Entries 7 and 8). Extensive oligomerisation was observed with these bases, presumably as a result of rapid BMIDA hydrolysis. This is in line with the recently published study from Burke and Lloyd-Jones who demonstrated rapid BMIDA hydrolysis with KOH vs. slow hydrolysis with K_3PO_4.[71]

The stark difference in conversion when using KOAc and K_2HPO_4 suggested that the relationship between pK_a and reaction efficiency was non-linear. To further investigate this, a series of phosphate bases with different metal counterions were examined (Table 3). As tribasic phosphate appeared to be optimum for the reaction, it was expected that other phosphate bases of similar pK_a would afford similar conversion. However, the effect of the counterion was found to be surprisingly pronounced, with tribasic potassium phosphate being singularly effective (Entry 3).

Table 3: Survey of tribasic phosphates with different metal counterions



Entry	Base	pH of aq. metal ion[130]	Conversion to 33 (%)[a]
1	Li_3PO_4	13.6	0
2	Na_3PO_4	13.9	0
3	K_3PO_4	14.0	92
4	Cs_3PO_4	-	0
5	$Mg_3(PO_4)_2$	11.2	0

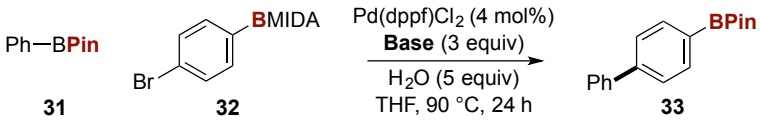
6	$Ca_3(PO_4)_2$	12.7	0

[a] Determined by HPLC analysis.

As previously mentioned, Amatore and Jutand have discussed the effect of the counterion on transmetallation in SM cross-coupling.[131] The metal cation can coordinate to the active oxo-palladium species and serve to decelerate transmetallation, with Na^+ and Cs^+ having a greater effect than K^+. This may contribute to the marked difference in reactivity across different tribasic phosphates (Entry 1 – 3). Alkali earth metals have a more acidic counterion than the alkali metals (Entries 5 and 6 vs. 1 – 3).[130] It is possible that in the cases of $Mg_3(PO_4)_2$ and $Ca_3(PO_4)_2$ (Entries 5 and 6), this may buffer the pH of the solution, therefore moving away from the optimum pH required for speciation control. However, this was unsatisfactory in qualifying the failure of these bases in the reaction. Bases with a more acidic counteranion, such as KOAc (Table 2, Entry 3), would deliver a significantly lower solution pH and were still successful in providing moderate conversion to product.

To further understand the effect of the choice of base on conversion, the physical properties of the bases examined, particularly solubility, were taken into account (Table 4).

Table 4: Evaluation of physical properties of different bases screened



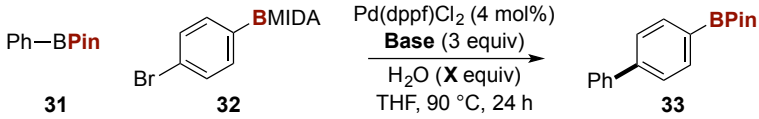
Entry	Base	pK_a[132]	Solubility at r.t. (g/100 mL H_2O)[130]	Conversion to 33 (%)[a]
1	Li_3PO_4	12.7	0.027	0
2	Na_3PO_4	12.7	14.25	0
3	K_3PO_4	12.7	106	92

4	Cs_3PO_4	12.7	-	0
5	Cs_2CO_3	10.3	261	48
6	$Mg_3(PO_4)_2$	12.7	0.0009	0
7	$Ca_3(PO_4)_2$	12.7	0.00012	0
8	KTFA	- 0.25	-	0
9	KOAc	4.8	269	37
10	K_2CO_3	10.3	111	51
11	KOH	14.2	121	22
12	KO*t*-Bu	17.0	-	23
13	KH_2PO_4	2.1	25	0
14	K_2HPO_4	7.2	168	0

[a] Determined by HPLC analysis.

This data shows a clear relationship between solubility, pK_a, and conversion. As solubility increases, conversion increases (Entry 1 – 3). If solubility is removed as a factor, *i.e.*, bases with solubility > 1 g/mL, then pK_a dictates the reaction efficiency. For example, both Cs_2CO_3 and K_2CO_3 exhibit good solubility and, with a pK_a of 10.3, both afford very similar conversion to product at ~50%. KOAc also demonstrates good solubility, however, with its lower pK_a, conversion is less efficient under the more acidic reaction media. KOH, which demonstrates good solubility and higher pK_a, is likely less efficient due to an increased concentration of hydroxide ions in solution, resulting in poor speciation control, *i.e.*, rapid BMIDA hydrolysis. It was proposed that in the case of bases with lower solubility but within the optimum pK_a range, such as the phosphate salts, conversion could be improved by addition of a greater quantity of H_2O. Subsequently, reaction of these bases was evaluated with 22 and 50 equivalents H_2O (Table 5).

Table 5: Evaluation of phosphate bases with increased H_2O



Entry	Base	H_2O (equiv)	Conversion to 33 (%)[a]
1	Li_3PO_4	22	0
2	Li_3PO_4	50	8
3	Na_3PO_4	22	16
4	Na_3PO_4	50	20
5	K_3PO_4	22	30
6	K_3PO_4	50	26
7	Cs_3PO_4	22	8
8	Cs_3PO_4	50	6

[a] Determined by HPLC analysis.

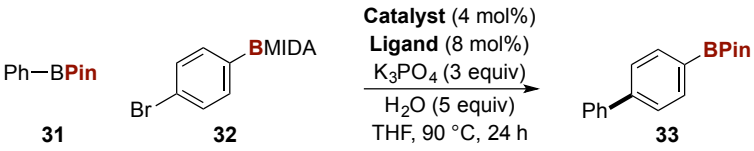
It was found that increasing the quantity of H_2O did indeed increase conversion. With Li_3PO_4, which exhibited very low aqueous solubility, conversion to product could begin to be recovered with addition of 50 equivalents H_2O (Entry 2). Similarly, conversion with Na_3PO_4 increased to 20% with 50 equivalents H_2O, a marked improvement over reaction with 5 equivalents H_2O (0%) (Table 5, Entry 4 vs. Table 3, Entry 2). Interestingly, conversion rapidly decreased in reactions with K_3PO_4 upon addition of greater quantities of H_2O (Table 5, Entries 5 and 6 vs. Table 3, Entry 3), leading to uncontrolled oligomerisation. Some reactivity was recovered with Cs_3PO_4, although conversion remained minimal (Entries 7 and 8).

It was therefore established that the key factors affecting conversion were both the solubility and pK_a of the base, with K_3PO_4 offering the optimum properties of

both. With less soluble bases in the correct pH range conversion could be partially recovered through the addition of greater quantities of H_2O; however, this resulted in poor speciation control and therefore led to low yield of desired product **33**.

Having found the optimum conditions in terms of base and H_2O content, the nature of the Pd catalyst was then examined. It was clear that the nature of the base and the quantity of H_2O were key in affording control over the hydrolysis and subsequent pinacol conjugation steps. The catalyst would primarily control the efficiency of C-C bond formation. A comprehensive catalyst and ligand screen was therefore carried out (Table 6), and a number of key observations were made.

Table 6: Catalyst and ligand screen



Entry	Catalyst	Ligand	Conversion to 33 (%)[a]
1	$PdCl_2$	-	0
2	$Pd(OAc)_2$	-	5
3	$Pd_2(dba)_3$	-	7
4	$Pd(PPh_3)_4$	-	36
5	$Pd(PPh_3)_2Cl_2$	-	63
6	$Pd(dppf)Cl_2$	-	92
7	$PdCl_2$	PPh_3	56
8	$Pd(OAc)_2$	PPh_3	70

9	$PdCl_2$	P(*t*-Bu)$_3$[b]	41
10	$Pd(OAc)_2$	P(*t*-Bu)$_3$[b]	55
11	$PdCl_2$	dppe	4
12	$Pd(OAc)_2$	dppe	0
13	$PdCl_2$	dppp	0
14	$Pd(OAc)_2$	dppp	55
15	$PdCl_2$	dppf	1
16	$Pd(OAc)_2$	dppf	24
17	$PdCl_2$	BINAP	13
18	$Pd(OAc)_2$	BINAP	67
19	$PdCl_2$	XantPhos	0
20	$Pd(OAc)_2$	XantPhos	10
21	$PdCl_2$	SPhos	14
22	$Pd(OAc)_2$	SPhos	77
23	$PdCl_2$	XPhos	20
24	$Pd(OAc)_2$	XPhos	67
25	$PdCl_2$	CyJohnPhos	4
26	$Pd(OAc)_2$	CyJohnPhos	72
27	$PdCl_2$	DavePhos	23
28	$Pd(OAc)_2$	DavePhos	71

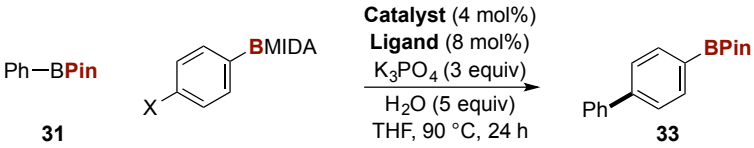
[a] Determined by HPLC analysis. [b] As HBF_4 salt.

In general, Pd^{II} precatalysts performed better than the equilvalent Pd^{0} species (for example, Entry 4 vs. 5). In addition, the reaction required the presence of a phosphine ligand to ensure efficient coupling, with reactions performed in the absence of a phosphine ligand offering very little conversion to product (Entries 1 – 3). In systems where a preformed catalyst was not used, *i.e.*, a Pd^{II} salt and ligand were added individually, $Pd(OAc)_2$ consistently performed better than $PdCl_2$ (for example, Entry 7 vs. 8). Both mono- and bidentate ligands could be used to effectively catalyse the reaction although, interestingly, in the case of 1,1'-bis(diphenylphosphino)ferrocene (dppf), the combination of the ligand with a Pd^{II} salt was significantly less effective that the preformed catalyst (Entry 6 vs. Entries 15 and 16). This was not the case with simpler monodentate ligands such as PPh_3, in which the precatalyst performed comparably to the combination of ligand and Pd^{II} salt (Entry 5 vs. Entries 7 and 8). In general, the dialkylbiaryl phosphines developed by Buchwald offered good conversion when combined with $Pd(OAc)_2$ however, they were less effective than $Pd(dppf)Cl_2$ (Entry 6 vs. Entries 21 – 28).

Having demonstrated that $Pd(dppf)Cl_2$ was indeed the optimum catalyst for the transformation with bromoaryl BMIDA, the scope of the electrophile was then examined with this catalyst, along with the most promising of the dialkylbiaryl phosphines tested (Table 7). $Pd(dppf)Cl_2$ was found to be consistently effective in catalysing the reaction of iodides, bromides, and triflates (Entries 1, 3, and 5). Interestingly, the conversion using iodoaryl BMIDA was significantly less than the equivalent bromide (60% vs. 92%, Entry 1 vs. Entry 3). As previously discussed, aryl iodides have a lower BDE than bromides and therefore generally undergo oxidative addition with Pd catalyst much faster.[8,11] However, Amatore and Jutand have reported that oxidative addition of aryl iodides can be hindered by bidentate ligands, with BINAP showing the greatest effect.[20] Equally, Buchwald has shown that aryl iodides can form Pd dimers when used in conjuction with bulky phosphine ligands, which can hinder reactivity.[133,134] This may explain the poor conversion observed with $Pd(OAc)_2$/SPhos (Entry 2). Unfortunately, when the reaction with chloroaryl BMIDA was attempted, $Pd(dppf)Cl_2$ was found to be ineffective (Entry 7). However, excellent

conversion of these less reactive coupling partners could be achieved through the use of electron rich dialkylbiaryl phosphines, with SPhos being particularly effective (Entries 8 and 9).

Table 7: Catalyst screening for various aryl electrophiles

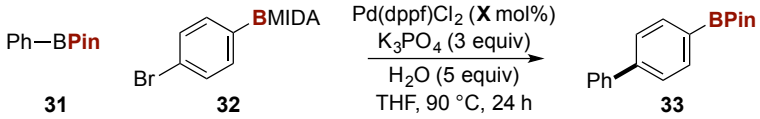


Entry	Catalyst	Ligand	X	Conversion to 33(%)[a]
1	$Pd(dppf)Cl_2$	-	I	60
2	$Pd(OAc)_2$	SPhos	I	34
3	$Pd(dppf)Cl_2$	-	Br	92
4	$Pd(OAc)_2$	SPhos	Br	77
5	$Pd(dppf)Cl_2$	-	OTf	61
6	$Pd(OAc)_2$	SPhos	OTf	48
7	$Pd(dppf)Cl_2$	-	Cl	0
8	$Pd(OAc)_2$	CyJohnPhos	Cl	68
9	$Pd(OAc)_2$	SPhos	Cl	82

[a] Determined by HPLC analysis.

Having identified conditions which afforded excellent conversion to product **33**, a number of other screens were undertaken in attempts to further increase reaction efficiency. Firstly, the loading of the optimum $Pd(dppf)Cl_2$ catalyst was investigated (Table 8). It was found that reasonable conversion could still be achieved with as little as 1 mol% loading (67%, Entry 1); however, optimum conversion was achieved with 4 mol% (Entry 3).

Table 8: Variation of catalyst loading

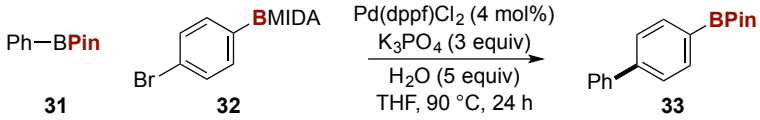


Entry	Catalyst loading	Conversion to 33(%)[a]
1	1 mol%	67
2	2 mol%	84
3	4 mol%	92

[a] Determined by HPLC analysis.

The stoichiometry of BPin **31** was also investigated. Throughout, bromoaryl BMIDA **32** had been used as the limiting reagent, with an excess of 1.5 equiv **31**. In an attempt to increase the efficiency of the process, reaction with lower equivalents of **31** were examined. It was quickly found that using any less than 1.5 equivalents of PhBPin results in a loss of yield, although the difference between 1 and 1.4 equivalents was negligible and still afforded the desired product in good yield (Table 9, Entries 1 – 5). This is reassuring as it demonstrates that in the case of more precious BPin reagents, such as expensive or those that require a number of steps to synthesise, 1 equivalent can be used with only a small loss of yield.

Table 9: Variation of BPin equiv



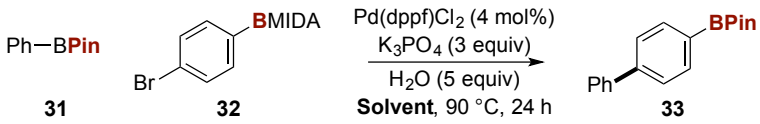
Entry	Equivalents of PhBPin **31**	Conversion to 33(%)[a]
1	1.0	74
2	1.1	77

3	1.2	78
4	1.3	78
5	1.4	78
6	1.5	92

[a] Determined by HPLC analysis.

Evaluation of the reaction solvent was also undertaken. This identified that MeCN and 1,4-dioxane were also effective in providing the desired product, though in slightly reduced yield (Table 10, Entry 2 and 3). Conversely, toluene, although commonly employed in SM cross-coupling, was found to be ineffective in this transformation (Entry 4), presumably as a result of its poor miscibility with H_2O,[130] resulting in the formation of a more pronounced basic biphase which can act as a reservoir for hydroxide ions.[27] Polar protic solvents such as EtOH were also ineffective (Entry 6).

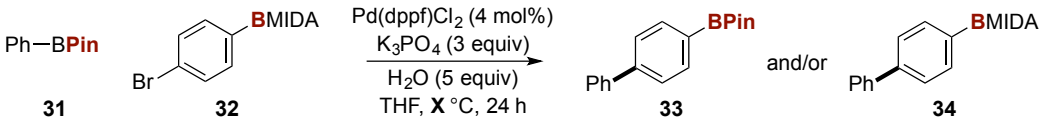
Table 10: Variation of solvent



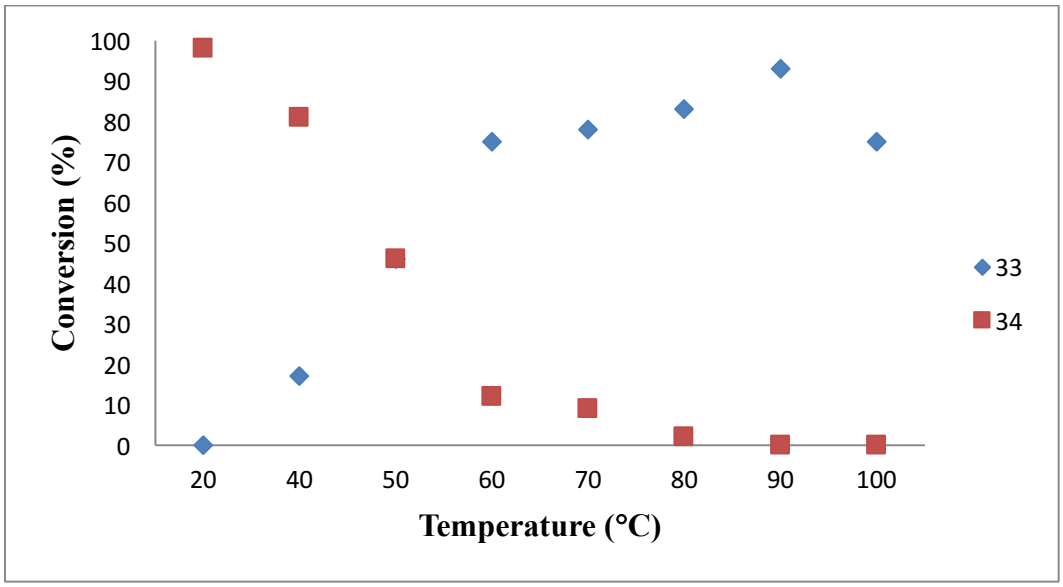
Entry	Solvent	Conversion to 33(%)[a]
1	THF	92
2	MeCN	70
3	1,4-dioxane	76
4	PhMe	10
5	DCE	60
6	EtOH	25

[a] Determined by HPLC analysis.

Upon investigation of the temperature of the reaction, an interesting correlation was observed (Scheme 65 and Graph 1). While optimum conversion to **33** was achieved at 90 °C, it was found that that at lower temperatures (r.t. – 70 °C) the decreased yield resulted from incomplete transesterification and not incomplete cross-coupling. Indeed, at 50 °C, the product distribution was almost exactly 1:1 of **33**:**34** and at room temperature the sole product of the reaction was **34**. This demonstrated that the reaction required a thermal driving force in order to hydrolyse **34**, even in the presence of aqueous base.



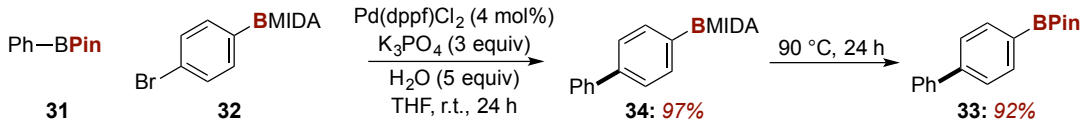
Scheme 65: Effect of temperature variation on product distribution



Graph 1: Temperature-dependant control of boron speciation

This theory was tested through a simple control reaction, in which the reaction was run at room temperature and analysed before heating to 90 °C (Scheme 66). After 24 h at room temperature the BMIDA product **34** was formed in 97% yield. Upon heating to 90 °C for a further 24 h, this was then converted into ArBPin **33** in excellent yield. This clearly showed that under the developed reaction conditions, the BMIDA component is stable to aqueous base in the absence of a thermal driving force. Upon heating, the BMIDA is hydrolysed to the boronic acid which can then

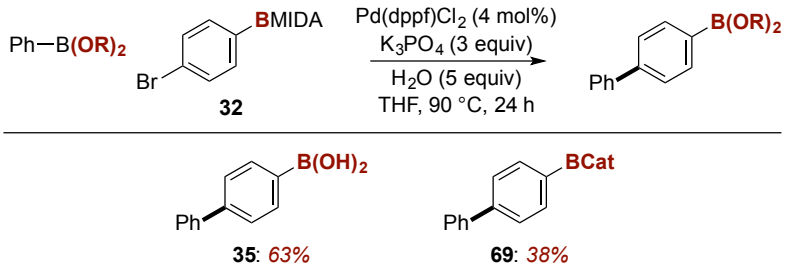
undergo diol conjugation. As BPin esters are not readily hydrolysed under the basic reaction conditions[52] (*vide infra*), this product is then thermodynamically stable.



Scheme 66: Temperature control of boron species

This meant it was possible to synthesise either the kinetic BMIDA product **34** or the thermodynamic BPin product **33** under the same reactions conditions based purely on temperature control, opening up a number of synthetic possibilities.

The homologation of other boron species was also explored. Under the optimised conditions, boronic acids and catechol esters could also be formally homologated in moderate to good yield (Scheme 67). This demonstrates a generality to the process which may be synthetically useful – boronic acids can undergo transformations in which the equivalent pinacol esters are typically ineffective, such as rhodium-catalysed conjugate addition.[135] It should be noted that these are unoptimised conditions – further optimisation on the boronic acid process enabled the homologation of this class of boron species in >90% yield.[136] In the case of the catechol esters, the low yield was due to the stability of the product, which readily hydrolysed to the boronic acid under the reaction conditions, in line with Roy and Brown's study.[119] For this reason the homologation of catechol esters was not pursued.



Scheme 67: Homologation of different boron species under optimised conditions

Having established the optimum conditions for the speciation controlled cross-coupling reaction, the scope was then investigated. It was quickly found that

purification using standard silica chromatography was ineffective at delivering pure products. Due to the non-polar nature of the aryl BPin starting materials and products, under normal-phase chromatography separation between the desired product and any unreacted BPin starting material was problematic. In addition to this, problems were encountered with grease-like hydrocarbon impurities, again due the non-polar nature of the products. Pleasingly however, it was found that upon switching to reverse phase C18 chromatography, using a solvent system of $MeCN/H_2O$, the desired products could be isolated cleanly in excellent yield.

A wide range of synthetically useful functional groups were tolerated, including electron rich and electron deficient BPin starting materials (Figure 16). Amides (**38**), esters (**41**, **50**), ethers (**44**), and nitriles (**43**) all delivered the desired products in good to excellent yield. A range of heterocyclic BPins were also effective coupling partners, including thiophene, pyrazole, pyran, and furan (**40**, **45**, **48** and **49**). This was particularly promising as these types of motif are regularly employed in the agrochemical and pharmaceutical industries,[82] demonstrating the potential applicability of this method. In relation to the bromoaryl BMIDA component, *ortho*, *meta*, and *para*-substitution patterns were tolerated, although in the case of *o*-bromoaryl BMIDA, BPins of a less sterically demanding nature were typically more effective (**42**, **45**). Under the optimised conditions, fluoro substituted bromoaryl BMIDA cores could also be effectively cross-coupled in moderate to good yield. This could potentially provide multiple avenues for downstream functionalisation: in addition to the newly formed boronic ester, which can be further cross-coupling under conventional Pd catalysis, new methods have emerged for the Ni catalysed cross-coupling of aryl fluorides,[137] providing a further opportunity for late stage derivatisation.

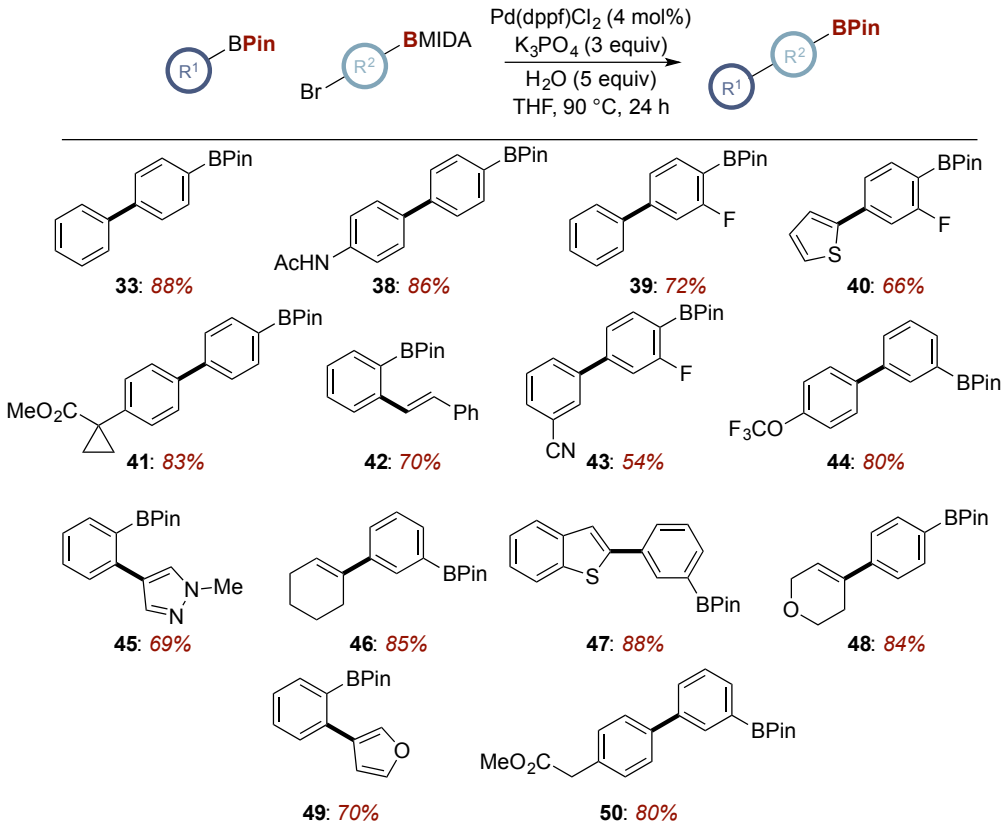
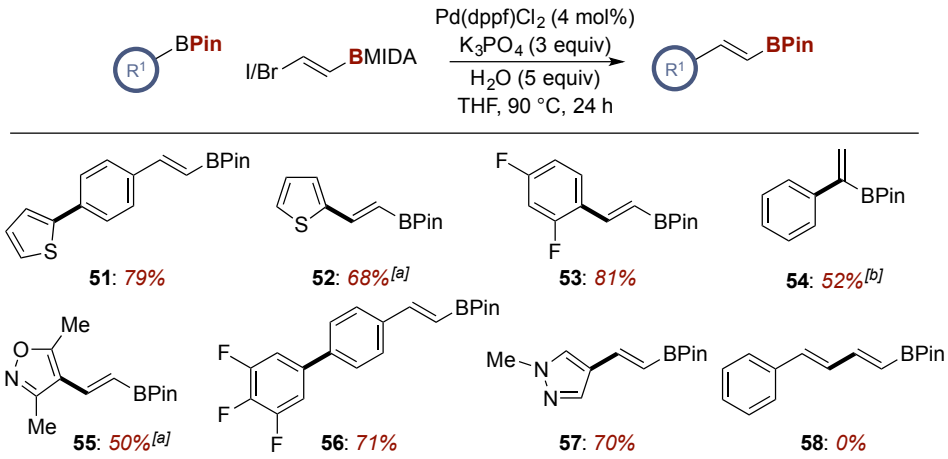


Figure 16: Scope of formal homologation using bromoaryl BMIDA

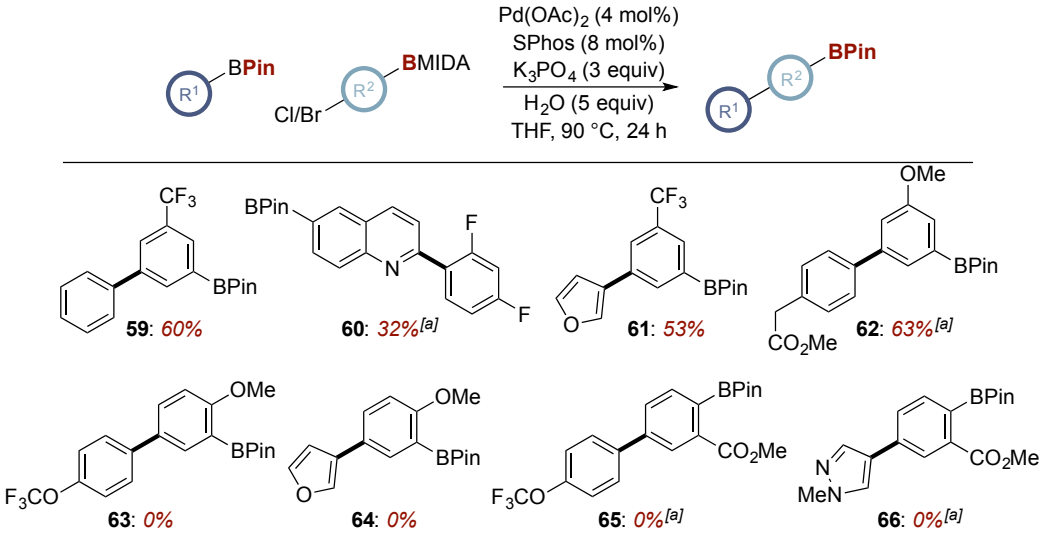
The developed conditions could also be readily applied to the cross-coupling of haloalkenyl BMIDA reagents, enabling the synthesis of a range of functionalised vinyl BPin species in good to excellent yield (Figure 17). This was particularly pleasing as this process would proceed *via* a vinyl boronic acid intermediate, which are known to be unstable.[39] While 1,2-haloalkenyl BMIDAs could be effectively utilised, it was found that the use of the equivalent 1,1-haloalkenyl BMIDA led to the formation of a mixture of regioisomers (**54**). This was perhaps not unsurprising, as Burke had previously reported this isomerisation problem with these reagents.[138] Burke was able to overcome this issue through use of Ag_2CO_3 as a base; however, due to the previously discussed capricious nature of this reaction with regards to base, it was thought that use of Ag_2CO_3 would require substantial re-optimisation, and was therefore not investigated further. Unfortunately, the synthesis of dienyl BPins (**58**) was also ineffective under these conditions, presumably due to the increased instability of the intermediate boronic acid.[39,114]



[a] Using iodovinyl BMIDA. [b] As a mixture of olefin regioisomers.

Figure 17: Scope of formal homologation using haloalkenyl BMIDA

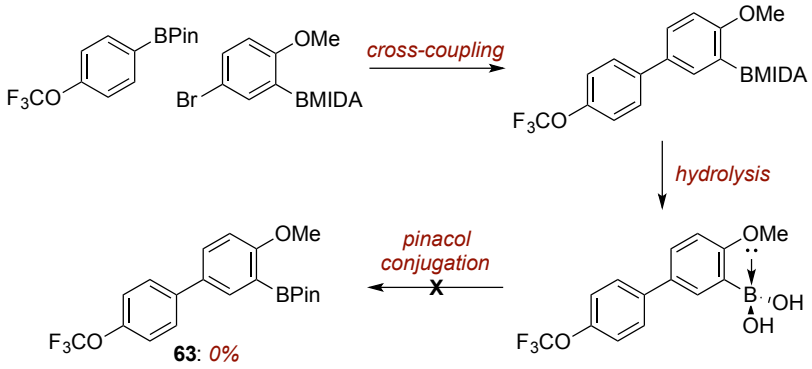
In order to further enhance the scope of this formal homologation process, a series of substituted haloaryl BMIDA were employed (Figure 18). It was quickly identified that cross-coupling of these substituted cores was ineffective under the optimised conditions. While this was expected for chloroaryl BMIDA reagents (*vide supra*) this lack of reactivity was surprising for bromoaryl BMIDAs, particularly those bearing electron withdrawing substituents, as this should have resulted in a faster oxidative addition.[8] Fortunately, upon switching to a $Pd(OAc)_2$/SPhos catalyst systems, substituted haloaryl BMIDAs could be effectively cross-coupled in moderate to good yield.[6]



[a] Using chloroaryl BMIDA.

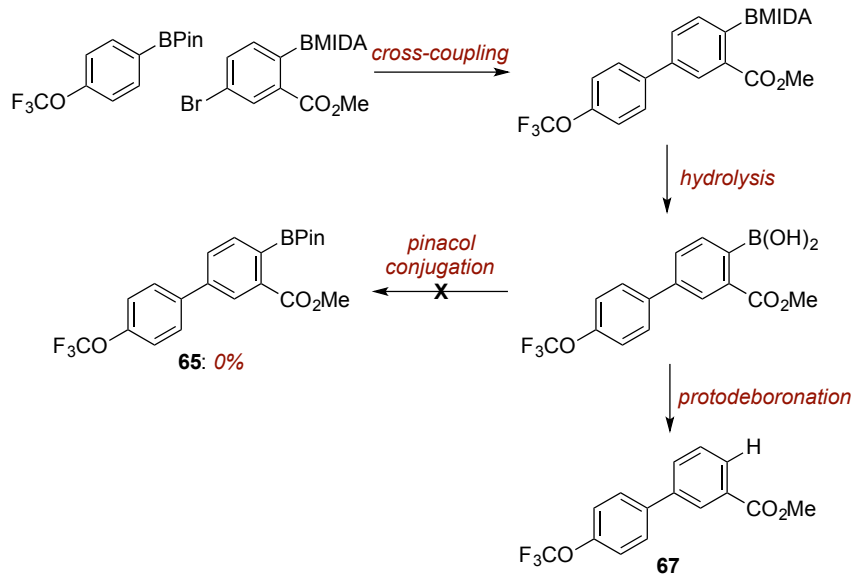
Figure 18: Scope of formal homologation using substituted haloaryl BMIDA

Both electron deficient (**59**) and electron rich substituents (**62**) were tolerated although the substitution pattern was found to be important for certain functional groups (**63** – **66**). When methoxy and methyl ester substituents were placed *ortho* to the BMIDA functionality, no conversion to the desired BPin product was observed (**63** and **64**). Upon further analysis of the reaction, it was found that both the cross-coupling and BMIDA hydrolysis were proceeding as normal under the reaction conditions, and that the failure to produce the product was seemingly the result of a sluggish pinacol conjugation. It was hypothesised that in the case of the methoxy substituent, following cross-coupling and BMIDA hydrolysis, the oxygen lone-pair could donate into the empty p-orbital on boron in a frustrated Lewis pair type interaction,[139,140] thereby stabilising the boronic acid intermediate and preventing diol conjugation (Scheme 68).



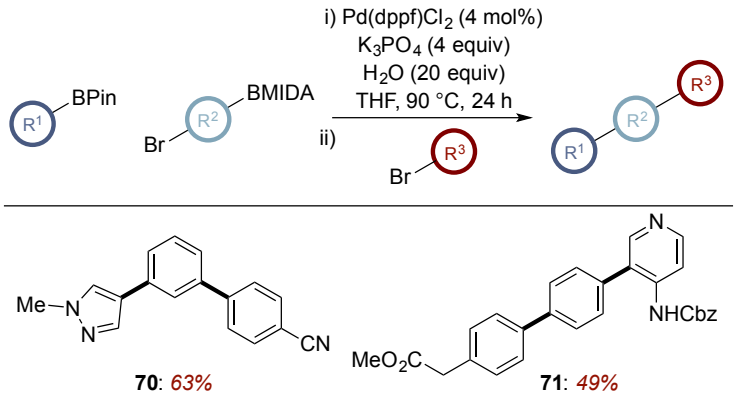
Scheme 68: Possible Lewis pair inhibition of pinacol conjugation

Although NMR analysis did not confirm the presence of any boronate type species, the fact that methoxy substituents were tolerated *meta* to the boron substituent (**62**, Figure 5) lends credence to this theory of a frustrated Lewis pair interaction. In the case of *ortho* ester substituted haloaryl BMIDAs, a large amount of the protodeboronated product was observed (**67**, Scheme 69). It was thought that the electron withdrawing nature of the *ortho* ester could be in inhibiting diol conjugation, again possibly through formation of a stabilised boronate. This could in turn lead to rapid protodeboronation under the basic reaction conditions based in accordance with the work of Perrin, (see section 1.3.2 above).[49]



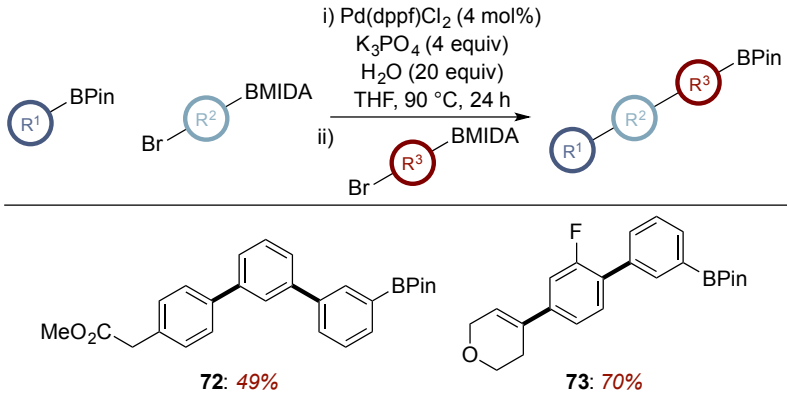
Scheme 69: Protodeboronation of *ortho* ester substrates

Having demonstrated the scope of the formal homologation process, the utility of the newly generated BPin products was then explored. The first question to be answered was if the catalyst was still active following the initial cross-coupling and transesterification. This would allow a second cross-coupling to be performed *in situ* without the need for catalyst renewal. To probe this, a second aryl bromide was added to the reaction mixture following the initial 24 hour reaction time. It was quickly found that while the catalyst was still active the second coupling was sluggish. It was thought this may be due to the lack of available base for the second cross-coupling reaction – reactions were noted to be heterogeneous mixtures following prolonged heating. For this reason, the equivalents of both H_2O and K_3PO_4 were increased and pleasingly, this allowed the second coupling to proceed in good yield (Scheme 70).



Scheme 70: One-pot double SM cross-coupling enabled *via* formal homologation

This one-pot double SM protocol demonstrated that the catalyst was sufficiently active to perform a second cross-coupling *in situ*. This in turn set the scene for the development of an iterative process, in which the formal homologation procedure could be repeated through the addition of a second equivalent of haloaryl BMIDA (Scheme 71). This reaction marks a significant advance in terms of efficiency, with a large number of bond-breaking and bond-making events taking place in one-reaction. Firstly, the initial cross-coupling event forms a new C-C bond. Speciation control then hydrolyses the newly formed biaryl BMIDA and allows conjugation of the diol to form the new reactive BPin ester. This can then undergo cross-coupling with a second equivalent of haloaryl BMIDA, forming another C-C bond before controlled speciation processes again deliver the boronic acid pinacol ester. All this proceeds without the need for catalyst renewal, intermediate isolation or purification, and demonstrates a highly efficient process for the iterative homologation of aryl boronic esters. This idea of controlled homologation has subsequently been adopted by other research groups in the synthesis of polythiophenes.[141,142]



Scheme 71: Iterative homologation of aryl boronic esters enabled by speciation control

With the utility of the newly formed BPin products demonstrated, attention then turned to the room temperature process for the synthesis of biaryl BMIDA compounds under aqueous basic conditions, and the scope of this transformation was subsequently explored. The process turned out to be very general, offering high yields of the BMIDA products across a range of functional groups (Figure 19). Particularly pleasing was the tolerance of the procedure for a range of temperature sensitive functionalities, such as heterocyclic BMIDAs (**74**, **76**, **80**) and protecting groups (**77**, **86**), which were found to decompose or hydrolyse, respectively, under the more forcing conditions of the BPin homologation procedure.

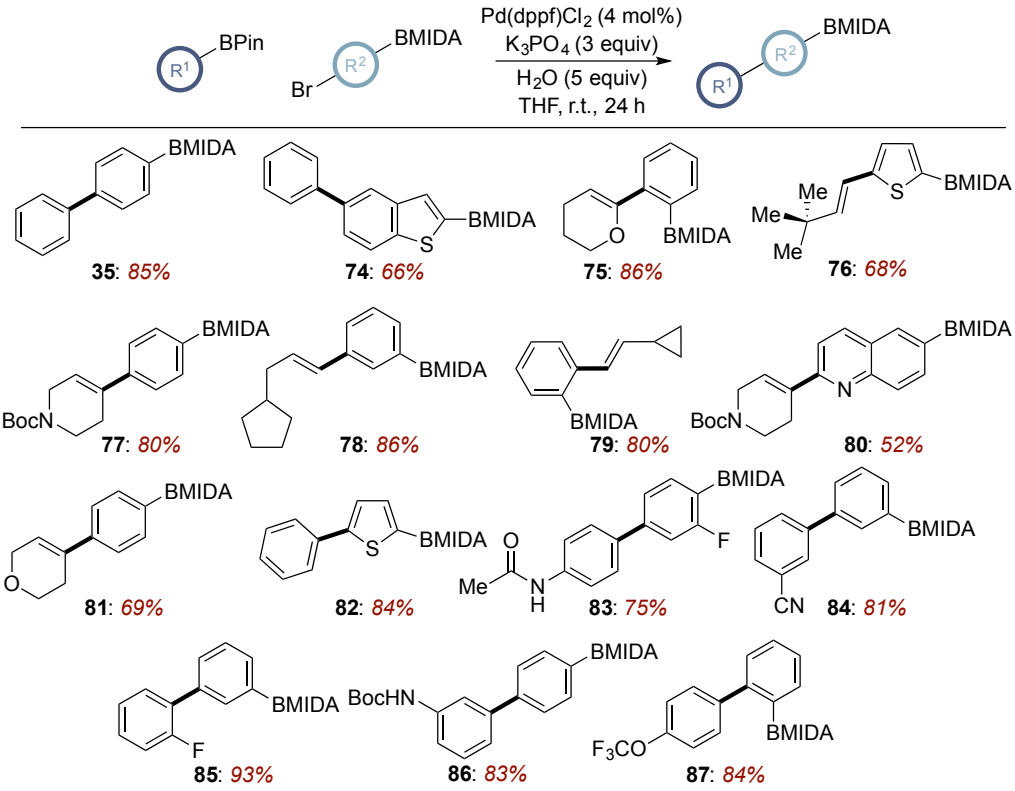
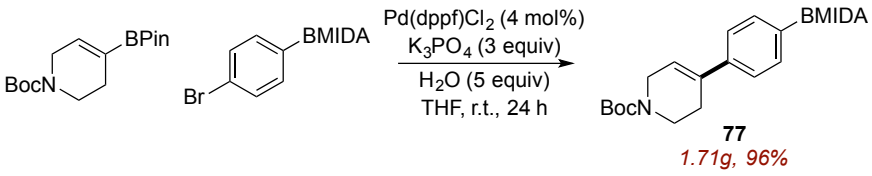


Figure 19: Room temperature cross-coupling of haloaryl BMIDA in the presence of aqueous base

Of particular note with this procedure was that while BMIDA compounds are known to be stable to silica chromatography,[68] this was typically not required in the isolation of these compounds. The pure BMIDA products could be isolated as crystalline solids following an aqueous wash and precipitation with Et_2O, again demonstrating the efficiency of the process by eliminating the need for column chromatography. This was particularly useful for scale up purposes, allowing the reaction to be carried out on gram scale in excellent yield without the need for any chromatographic purification (Scheme 72).



Scheme 72: Room temperature cross-coupling of haloaryl BMIDA in the presence of aqueous base on gram scale

Unfortunately, it was found that in cases where the reaction did not go to completion, separation of the two aryl BMIDA compounds (starting material and product) by both recrystallization and/or chromatography proved challenging. Haloalkenyl BMIDAs were also tolerated under the developed conditions which, in contrast to the BPin homologation procedure, enabled the synthesis of borylated dienes (Figure 20, **92**, **93**).

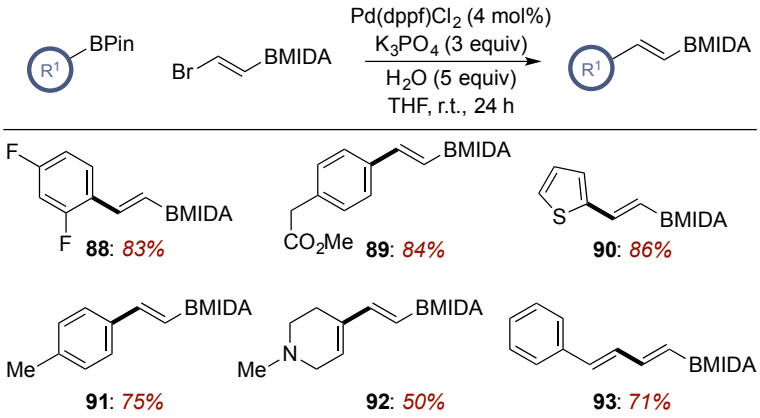


Figure 20: Room temperature cross-coupling of haloalkenyl BMIDA in the presence of aqueous base

While Burke has reported extensive work on the cross-coupling of haloaryl BMIDAs with the retention of the BMIDA functionality, these processes are typically carried out under strictly anhydrous conditions, often employing excess base or solvents such as DMSO, presumably to aid solubility.[68,143] The developed method is therefore potentially beneficial as it avoids the need for these stringent reaction parameters. To offer a direct comparison to other methods, five substrates of varying functionality were synthesised used both the developed room temperature process and conditions previously reported by Burke *et al* (Table 11).[143] The developed room temperature procedure (Table 11, Conditions A) consistently provided high yields of the desired products. The previously reported conditions (Conditions B) on the other hand were more variable. In some cases, the yields were comparable (Entries 1 and 2), however in other cases these conditions delivered no product or reduced yield (Entries 3 – 5). Interestingly in both examples using *ortho*-bromophenyl BMIDA (Entries 3 and 4), no coupling was observed and the starting BMIDA was returned intact, despite the more forcing conditions and use of the same catalyst. In the case of 2-pyran BPin (Entry 3) this was due to decomposition of the starting BPin at the elevated

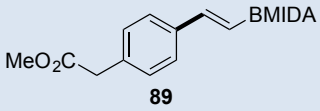
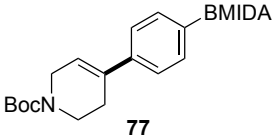
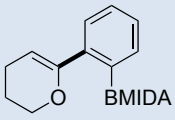
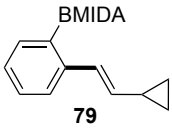
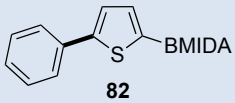
temperature – this species had previously been observed to decompose under the elevated temperature of the formal homologation procedure. The lower yield observed in Entry 5 was a result of protodeboronation of the product even under the mildly elevated temperature.

Table 11: Comparison of procedures for retaining BMIDA during SM cross-coupling

Reactions conditions

A: $Pd(dppf)Cl_2$ (4 mol%), K_3PO_4 (3 equiv), H_2O (5 equiv), THF, r.t.

B: $Pd(dppf)Cl_2$ (5 mol%), K_3PO_4 (6 equiv), DMSO, 45 °C

Entry	Product	Conditions	Yield (%)
1	 **89**	A B	84 64
2	 **77**	A B	80 87
3	 **75**	A B	86 -
4	 **79**	A B	80 -
5	 **82**	A B	84 39

Throughout the course of the substrate investigation (Figure 19) there appeared to be a correlation between reactivity and the substitution pattern of the haloaryl BMIDA. Specifically, it was noted that reactions of *meta*-bromophenyl BMIDA substrates frequently did not go to completion, even over extended time periods (Figure 21). It was thought that this was not a result of the BPin coupling partner, as some of the BPins tested proved competent coupling partners in other reactions – indeed, with

simple phenyl BPin, 88% isolated yield was achieved in the reaction with *para*-bromophenyl BMIDA (Figure 16), whereas with the *meta* regioisomer the reaction was incomplete even after 72 hours.

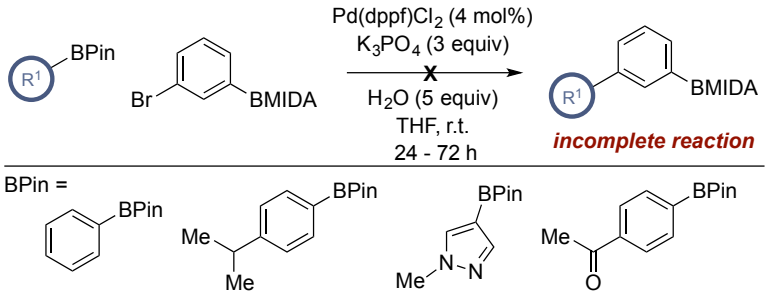


Figure 21: Examples of reactivity disparity with *meta*-regioisomers

The properties of all three regioisomers of bromophenyl BMIDA were therefore considered. Burke and co-workers have reported that the BMIDA moiety is neither electron donating nor withdrawing based on ^{13}C NMR analysis.[143] This suggested that the disparity in the reactivity of the regioisomers was not based on an electronic component. To confirm this, ^{13}C NMR analysis of the three regioisomers was undertaken (Figure 22). Interesting, upon analysis of the chemical shift of the bromo-bearing carbons, it was found that the *para*- and *meta*-substituted bromophenyl BMIDAs were very similar, whereas the shift for the *ortho*-substituted bromophenyl BMIDA was significantly more downfield. This suggests that the *ortho*-isomer should be the most the most electron deficient and therefore the most predisposed to oxidative addition, with the *para*- and *meta*-isomers roughly equivalent.

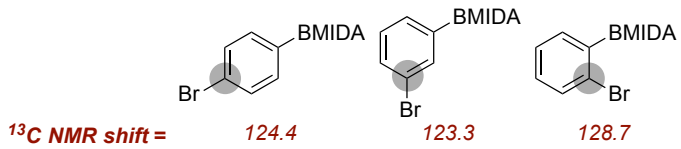


Figure 22: ^{13}C NMR shifts of bromo-bearing carbon in bromophenyl BMIDA regioisomers

The three regioisomers were also analysed by X-ray crystallography. Again, it was the *ortho*-isomer which displayed outlying properties. The C-C-B bond angle in this substrate was observed to be distorted as a result of the proximity of the sterically demanding BMIDA group to the bromine atom - ≈ 128° in comparison to ≈ 122° for the *para*- and *meta*-isomers (Figure 23).

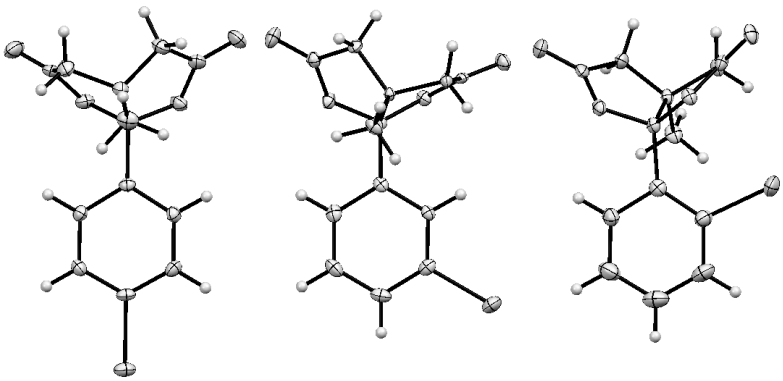
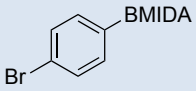
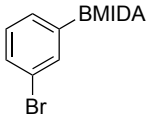
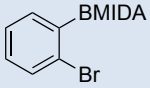


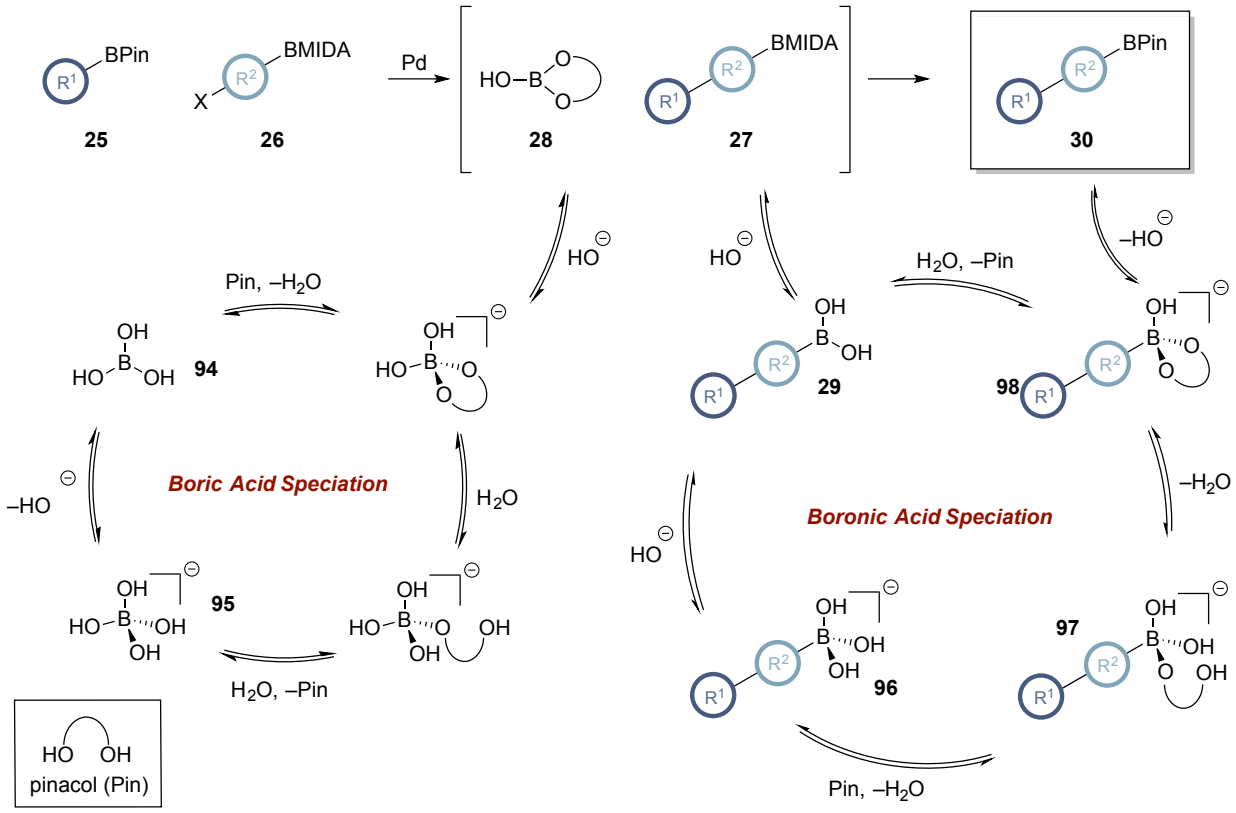
Figure 23: X-ray crystal structures of bromophenyl BMIDA regioisomers

Analysis of the stereoelectronics of the three regioisomers suggests that it should be the *ortho*-isomer which is the consistent outlier in terms of reactivity. However, this was not the case, as this isomer was found to react well under the standard conditions provided the steric requirements were met. It was therefore hypothesised that the physical properties of the reagents may be responsible for the disparity in reactivity. It had been noted during the investigation of the reaction scope that the *meta*-isomer was seemingly less soluble under the reaction conditions than its *para* and *ortho* counterparts. While BMIDA reagents generally display a low solubility in organic solvents, a fact which aids in their purification, it was thought that the additional lack of solubility for the *meta*-bromophenyl BMIDA may be responsible for its reduced reactivity. Analysis of the solubility of the three regioisomers in THF revealed that the *meta*-isomer was indeed less soluble (Table 12, Entry 2). It was therefore believed that the difficulty in driving these reactions to completion even over extended time periods was a result of the poor solubility of the *meta*-bromophenyl BMIDA. Unfortunately, conventional methods for increasing solubility, such as heating and/or addition of a co-solvent, were unsuccessful as they upset the delicate equilibrium and resulted in speciation events (*i.e.* hydrolysis of the BMIDA and diol conjugation).

Table 12: Solubility of bromophenyl BMIDA regioisomers

Entry	Regioisomer	Solubility in THF (mg/mL)
1		56
2		19
3		27

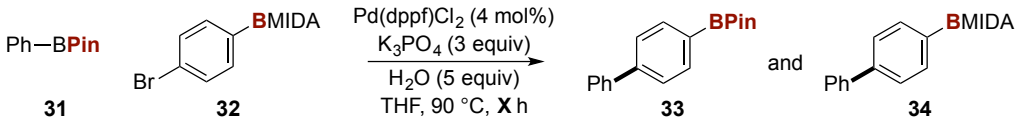
Having demonstrated the utility of the speciation controlled cross-coupling processes, the mechanism of the formal homologation procedure was then considered in more detail. The process requires control over a complex series of boron solution equilibria (Scheme 73). Following the initial cross-coupling of BPin **25** and haloaryl BMIDA **26**, both the expected biaryl product **27** and the HOBPin byproduct **28** can undergo hydrolysis under the basic reaction conditions. Hydrolysis of **28** affords boric acid **94**, along with its conjugate boronate **95**, both of which will be sequestered to the basic aqueous phase.[66] Pinacol is also liberated from this hydrolysis. BMIDA **27** is hydrolysed to boronic acid **29** under the basic reaction conditions,[71] which can undergo a series of equilibria including the formation of its boronate, **96**. Diol conjugation is favoured at high pH,[122] and therefore esterification of pinacol, liberated from the hydrolysis of **28**, proceeds *via* boronate **97** to form the thermodynamically stable **98** which afford the desired product **30** upon completion of the reaction. While all these processes are equilibria driven and therefore reversible, it was believed that diol conjugation acts as a thermodynamic sink, trapping the liberated pinacol and thus driving the reaction towards completion.



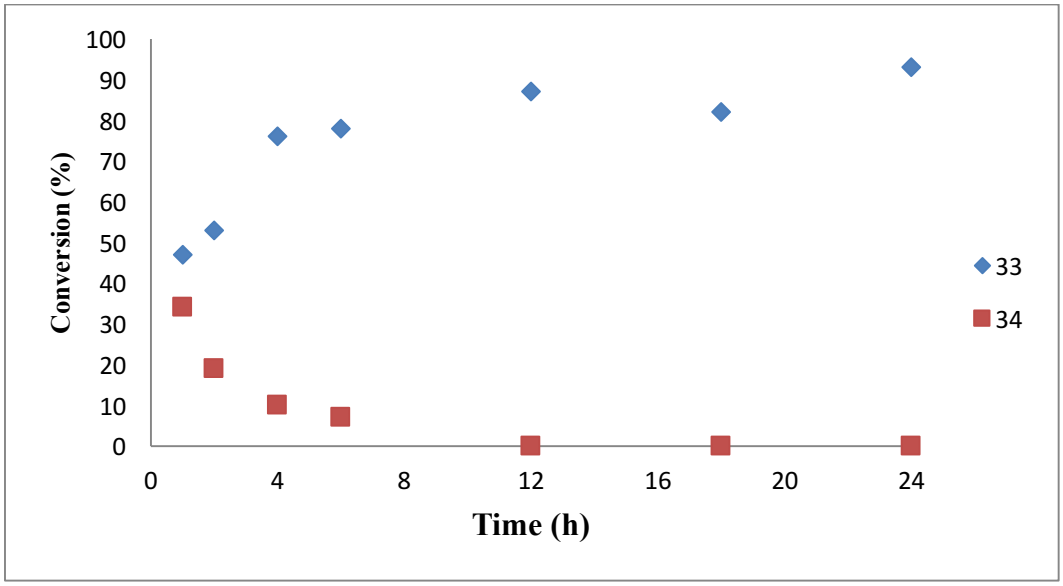
Scheme 73: Proposed speciation equilibria associated with formal homologation process

In order for the reaction to proceed as proposed, the execution of individual events was crucial. For example, the initial cross-coupling between **25** and **26** must be complete before hydrolysis of **27** (and by extension **26**) begins. If this is not the case, competition would arise between the BPin ester **25** and boronic acid **29**. Similarly, if any of **26** remains following the formation of **30**, competition would again arise.

HPLC analysis of the reaction showed the product distribution over time (Scheme 74 and Graph 2). It was found that the cross-coupling was indeed rapid, with complete consumption of starting material within 1 hour. Hydrolysis of **34** was mostly complete in the following 4 hours. Throughout the process no boronic acid **35** was observed, suggesting that following hydrolysis of **34**, diol conjugation occurs rapidly under the basic reaction conditions in accordance with the findings of Springsteen and Wang.[122]

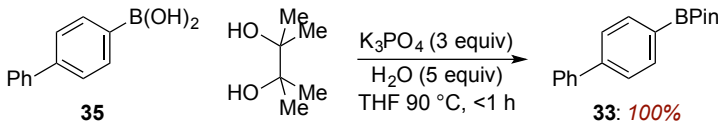


Scheme 74: Effect of time on product distribution for optimised formal homologation process

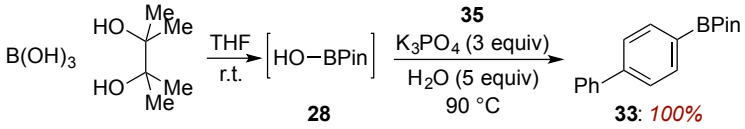


Graph 2: HPLC analysis of product distribution over time

This was confirmed through the independent reaction of boronic acid **35** with pinacol under the optimised reaction conditions (in the absence of Pd) (Scheme 75). Diol conjugation occurred rapidly, affording quantitative conversion to **33** in < 1 hour. Conjugation was similarly efficient from the SM byproduct, **28**, demonstrating the thermodynamic preference for the formation of **33** (Scheme 76).

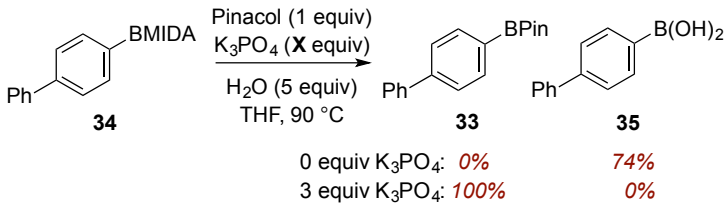


Scheme 75: Diol conjugation under representative reaction conditions



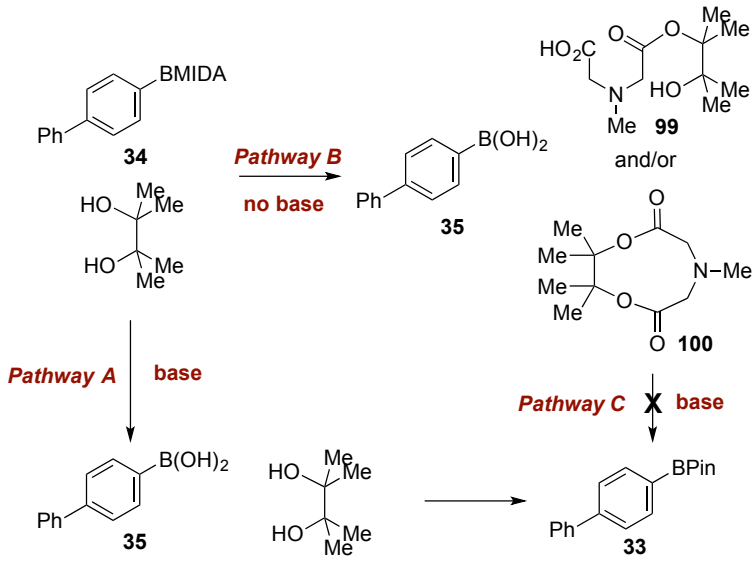
Scheme 76: Formation of 33 from 28 under representative reaction conditions

In order to rule out any other possible esterification pathways, control experiments were conducted using BMIDA **34** and pinacol in the presence and absence of base (Scheme 77). As expected, in the presence of base **34** is converted quantitatively into BPin **33**, supporting a mechanism in which **34** undergoes basic hydrolysis followed by esterification (Scheme 78, Pathway A).[71,122] Interestingly, however, in the absence of any base only boronic acid **35** was formed. This could possibly occur *via* a mechanism in which pinacol reacts directly with the BMIDA to induce hydrolysis (Scheme 78, Pathway B).



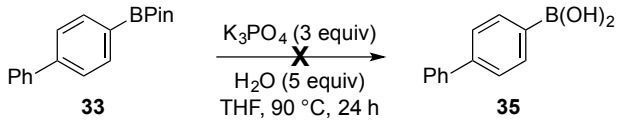
Scheme 77: Reaction of 34 with pinacol in the presence and absence of base

This would result in the formation **99**/**100**, effectively tying up the pinacol ligand and preventing the formation of **33**. It was thought that following the base free hydrolysis, addition of base could hydrolyse **99**/**100**, liberating pinacol and esterification could occur (Scheme 78, Pathways B and C). However, this was found to not produce product **33**, again supporting the sequence of events depicted in Pathway A.



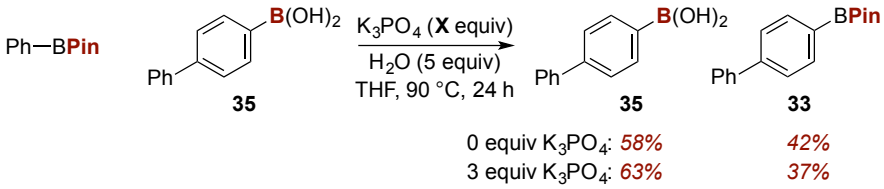
Scheme 78: Proposed mechanism of the reaction of 34 with pinacol in the presence and absence of base

As demonstrated in Scheme 75, formation of **33** from **35** under basic conditions is rapid, suggesting that the reverse process, *i.e.*, BPin hydrolysis, is disfavoured under these conditions. This was confirmed when no hydrolysis was observed even under prolonged exposure of **33** to the reaction conditions (Scheme 79). This again gives support to the theory that formation of **98** is the thermodynamic end-point of the reaction, and that transesterification of BPin esters does not proceed *via* hydrolysis to the boronic acid.



Scheme 79: Attempted hydrolysis of 33 to 35 under representative reaction conditions

As has been demonstrated by Hutton,[52] hydrolysis of BPins proceeds much more readily in the presence of a second boron species to facilitate equilibration. This was confirmed to be true for the system in question when phenyl BPin was treated with **35** in both the presence and absence of base (Scheme 80). A mixture of **33** and **35** were observed under both conditions.



Scheme 80: Equilibration of boron species in the presence and absence of base

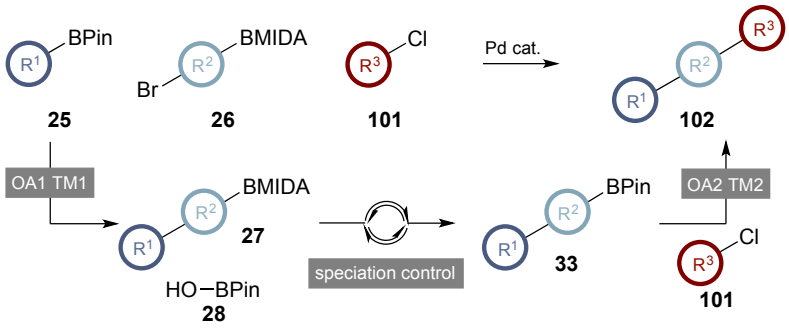
This further supports the proposed series of events, in that cross-coupling of **25** and **26** must be complete prior to any BMIDA hydrolysis. If this was not the case, and **27** began to hydrolyse prior to the consumption of **25**, a mixture of boron species would be produced from the resulting equilibria. This would cause selectivity issues with regards to the cross-coupling with **26**, as boronic acids are known to transmetallate faster than BPins.[31,144]

These observations support the proposed mechanism for the formal homologation of BPin esters *via* speciation control. A rapid cross-coupling occurs between BPin **25** and haloaryl BMIDA **26**, followed by slow hydrolysis of the resulting biaryl BMIDA

27 under the carefully controlled aqueous basic conditions. Diol conjugation with pinacol liberated from hydrolysis of the SM byproduct **28** then proceeds rapidly to afford the formally homologated product **33**. Control of the reaction media was key in this process, with both the choice of base and quantity of H_2O being paramount to the reactions success.

3.1.1 Tandem chemoselective Suzuki-Miyaura cross-coupling enabled by speciation control

This process of speciation control in cross-coupling was further developed to incorporate electrophile chemoselectivity. By exploiting the different rates of oxidative addition of aryl halides in combination with speciation control of multiple boron species, a one-pot tandem process was developed, enabling the chemoselective formation of two C-C bonds in a single reaction without the need for intermediate isolation or purification or any sequential addition of reagents.[145] In this tandem process, cross-coupling between BPin **25** and haloaryl BMIDA **26** proceeds as before, forming **27** and **28** (Scheme 81). The chemoselectivity in this step is a result of the higher rate of oxidative addition of bromides over chlorides, allowing the aryl chloride **101** to be present in the reaction from the start without interfering with the initial cross-coupling. Speciation control then affords BPin **33** which, with the more reactive bromide already consumed, can now react with aryl chloride **101** in a second SM cross-coupling to afford triaryl product **102**.



Scheme 81: Tandem chemoselective SM cross-coupling enabled by speciation control

As with the sequential triarylation procedure (see Scheme 70 above), an increase in base and H_2O equivalents was required to affect the second the cross-coupling. A switch to a more active catalyst/ligand system was also required to engage the less

reactive chloride. This process could also be inverted to expand the scope – a bromoaryl chloride could be used in combination with an aryl BPin and aryl BMIDA, enabling a much wider range of commercial starting materials to be employed.

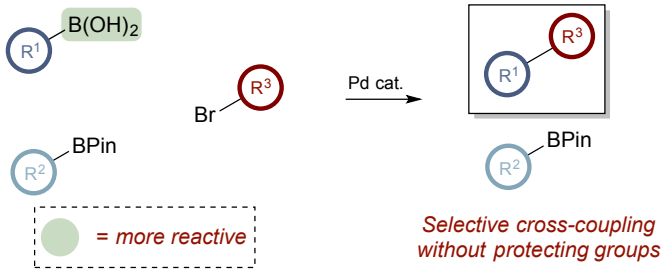
The development of this process marked an important step forward in speciation control research, combining nucleophile chemoselectivity with electrophile chemoselectivity to afford control over two of the three steps of a SM catalytic cycle, namely oxidative addition and transmetallation.

3.2 Chemoselective Suzuki-Miyaura cross-coupling enabled by kinetic transmetallation

This section is based upon the following publication: *Angew. Chem. Int. Ed.* **2017***, 56,* 1249 –1253.[144]

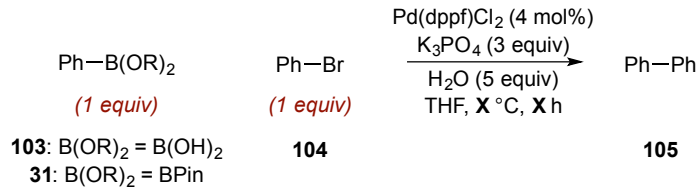
Throughout the course of the mechanistic investigations into the formal homologation process, it became clear that the rate of BMIDA hydrolysis was critical in achieving chemoselectivity for several reasons. Firstly, premature hydrolysis could lead to oligomerisation issues. Equally, hydrolysis of the BMIDA functionality to reveal the boronic acid could result in diol equilibration between the BPin and boronic acid.[119,129] As boronic acids are known to transmetallate faster than BPins,[31] this would result in selectivity issues within the cross-coupling. This demonstrates one of the greatest strengths of protecting group strategies within SM cross-coupling – not only do these protected boron species offer exquisite chemoselectivity, they also preclude any boron species equilibration. However, as previously mentioned, these protecting groups do require additional synthetic manipulations, namely deprotection steps, decreasing the efficiency of their application in synthesis. With Hartwig's data showing that boronic acids can transmetallate faster than BPins under manufactured conditions (see Figure 5 above),[31] and the results of the previous study showing that boron speciation equilibria can be controlled through modification of the reaction media, it was proposed that chemoselective cross-coupling of two reactive boron species, namely boronic acids and pinacol esters, could be achieved without the need for protecting group strategies (Scheme 82). This would represent the first example of chemoselective control within cross-coupling of aryl boron

species without the use of protecting groups and would represent a step forward in terms of reaction (and atom) efficiency.

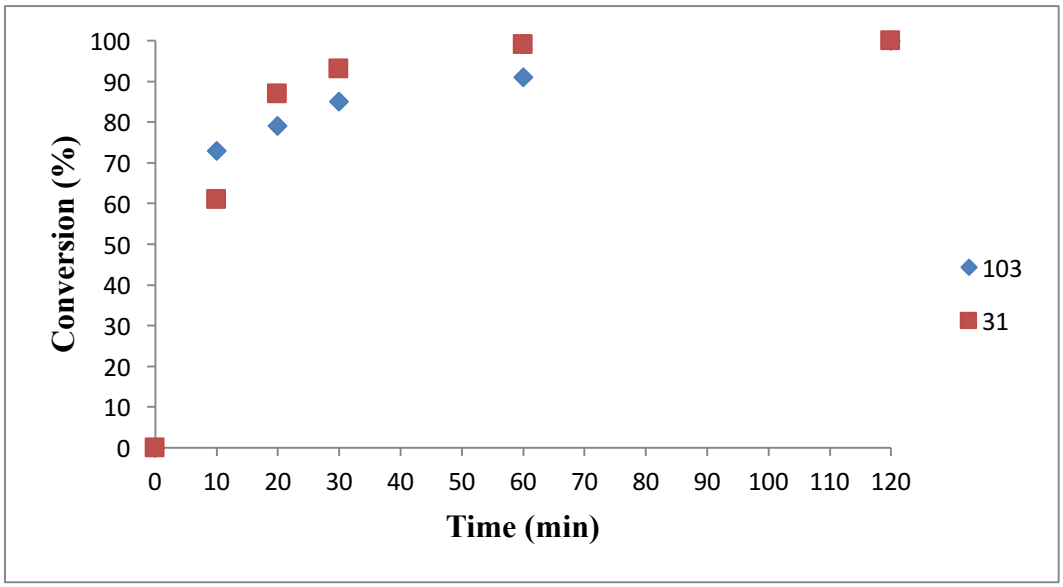


Scheme 82: Chemoselective cross-coupling enabled by kinetic transmetallation

To probe the feasibility of kinetically controlled transmetallation, the rates of cross-coupling of both boronic acid and BPin ester were independently assessed under conditions which had been shown to be effective at controlling boron speciation (Scheme 83). Initial screening at 50 °C suggested that the two boron species had comparable reactivity, as both reacted at approximately the same rate and afforded complete conversion to product **105** over 2 hours (Graph 3).

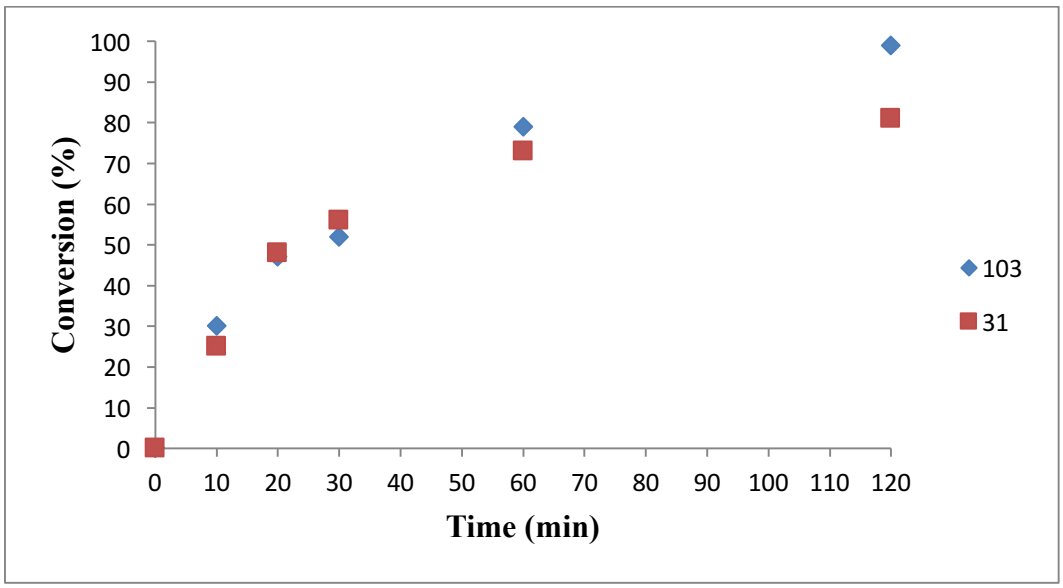


Scheme 83: Independent cross-coupling of boronic acid 103 and BPin 31 with bromide 104

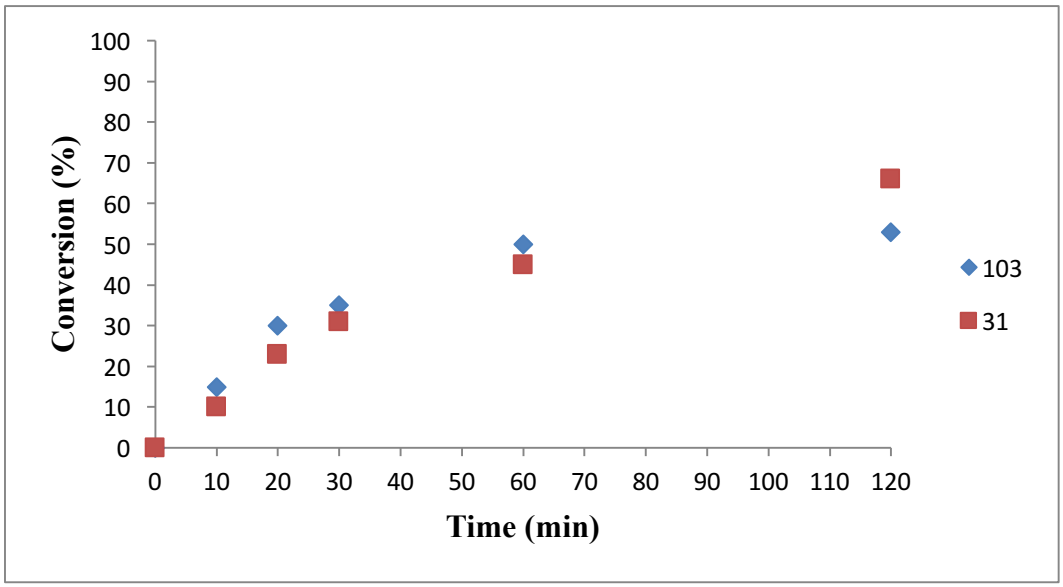


Graph 3: Rates of cross-coupling of boronic acid 103 and BPin 31 at 50 °C

In an attempt to leverage some chemoselectivity, the reaction was investigated at lower temperature (30 °C and room temperature, Graphs 4 and 5, respectively). However, these milder conditions only served to decrease the rate of cross-coupling, affording lower conversion but no chemoselectivity, with the initial rates of both boron species reduced equally.

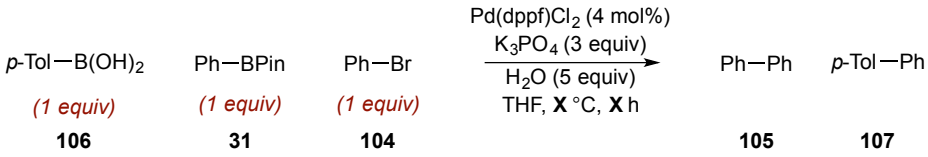


Graph 4: Rates of cross-coupling of boronic acid 103 and BPin 31 at 30 °C



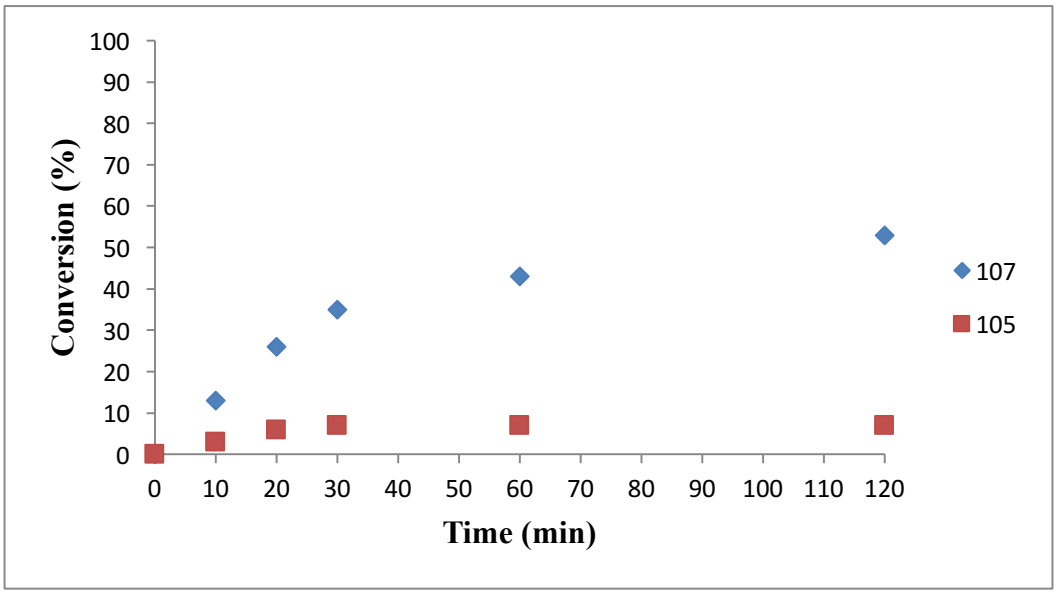
Graph 5: Rates of cross-coupling of boronic acid 103 and BPin 31 at room temperature

While discouraging, these results were perhaps not surprising, as boronic acids and BPin esters are both known to be competent coupling partners in SM reactions,[7] with BPins often used for preference due to their enhanced stability.[7] It was therefore thought that in order to exploit any potential kinetic window of transmetallation and therefore leverage any chemoselectivity would require the two boron species to be in a directly competitive system (Scheme 84).

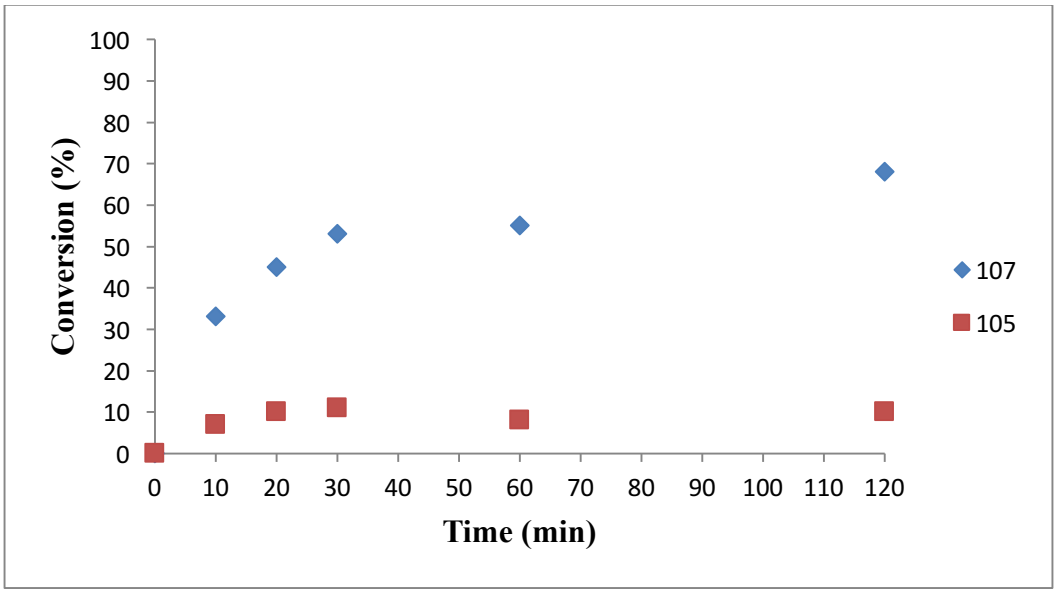


Scheme 84: Competitive cross-coupling of boronic acid 106 and BPin 31 with bromide 104

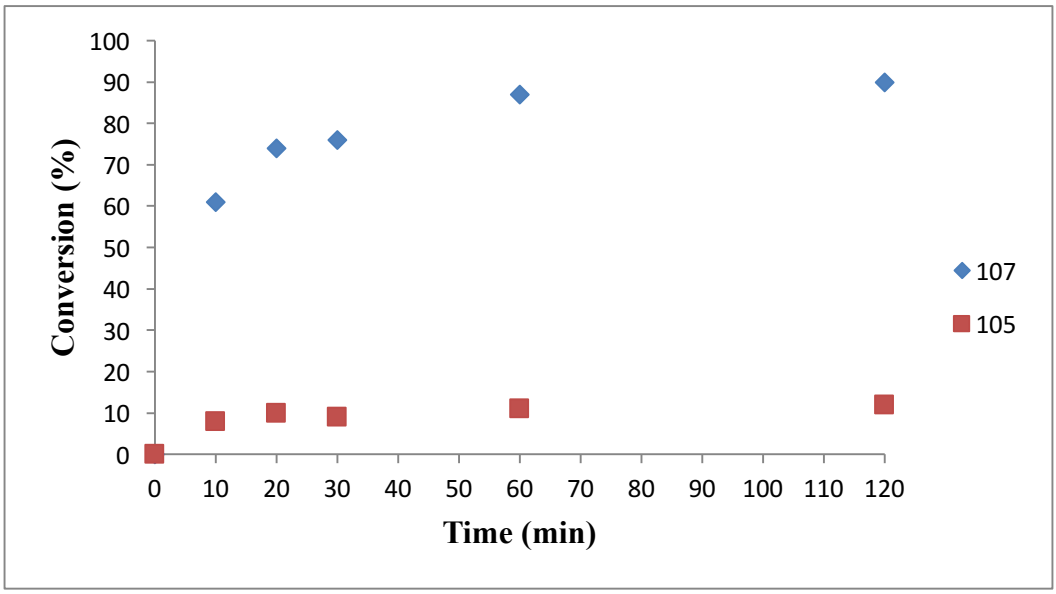
Remarkably, under identical reaction conditions, a kinetic window of transmetallation was observed in the competitive system, affording good selectivity for the boronic acid (Graphs 6 – 8). Although good selectivity was observed at all three temperatures, conversion was significantly lower at room temperature and 30 °C, affording < 70% conversion to **107** over 2 hours (Graphs 6 and 7). Reaction at 50 °C on the other hand afforded ~ 90% conversion to **107** after just 1 hour (Graph 8).



Graph 6: Competitive cross-coupling of boronic acid 106 and BPin 31 at room temperature



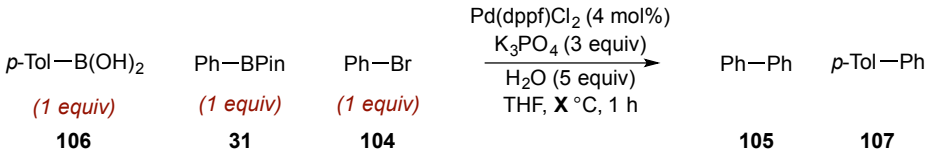
Graph 7: Competitive cross-coupling of boronic acid 106 and BPin 31 at 30 °C



Graph 8: Competitive cross-coupling of boronic acid 106 and BPin 31 at 50 °C

Increasing the temperature of the reaction had little effect of conversion or selectivity over 1 hour (Table 13). Optimisation was therefore continued at 70 °C as it was predicted to offer the best balance of reactivity and selectivity going forward.

Table 13: Effect of temperature on conversion and selectivity



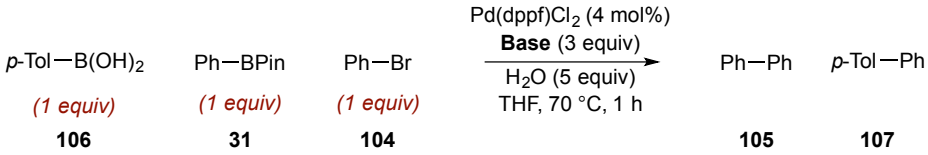
Entry	Temperature (°C)	Conversion 105:107 (%)[a]
1	r.t.	7:43
2	30	8:55
3	50	11:87
4	70	14:86
5	90	10:87

[a] Determined by HPLC analysis.

Similarly, a screen of other inorganic bases was found to have little effect on both the efficiency and selectivity of the cross-coupling (Table 14). Both K_2CO_3 and Cs_2CO_3

offered similar selectivity with marginally lower conversion (Entries 2 and 3). K_3PO_4 was therefore selected as the optimum base for the kinetic transmetallation process.

Table 14: Effect of base on conversion and selectivity

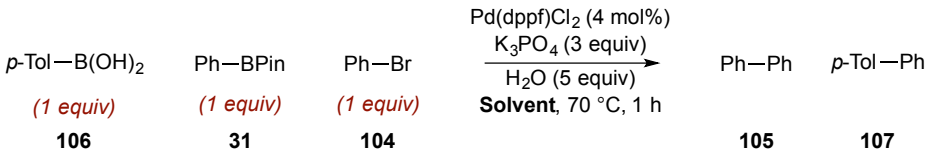


Entry	Base	Conversion 105:107 (%)[a]
1	K_3PO_4	14:86
2	K_2CO_3	6:76
3	Cs_2CO_3	7:80

[a] Determined by HPLC analysis.

A short solvent screen highlighted 1,4-dioxane as the optimum solvent for the process, affording excellent selectivity for the desired cross-coupled product **107** (Table 15, Entry 2).

Table 15: Effect of solvent on conversion and selectivity

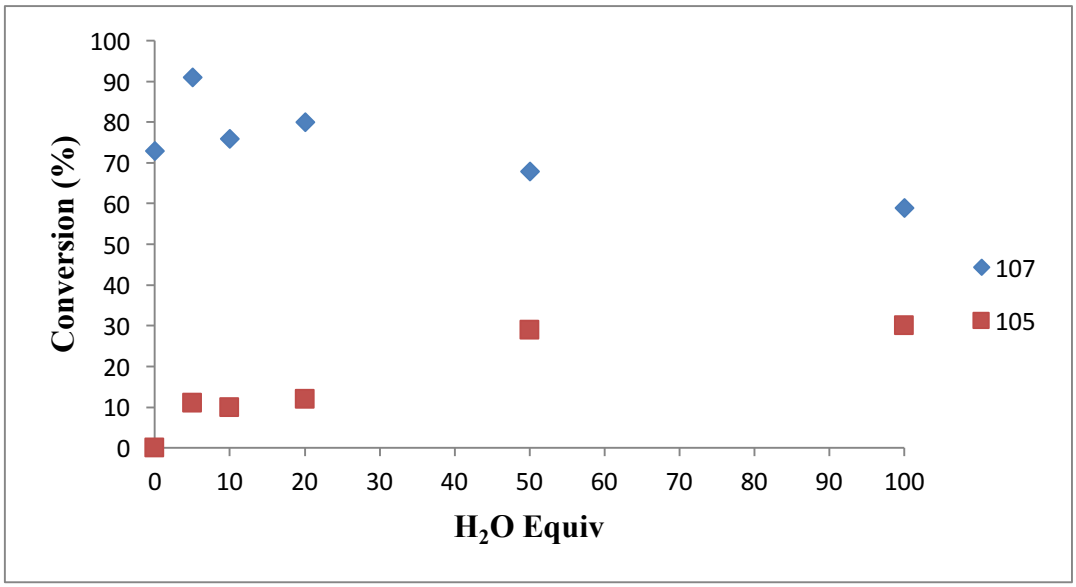


Entry	Solvent	Conversion 105:107 (%)[a]
1	THF	14:86
2	1,4-dioxane	0:100
3	MeCN	9:77

[a] Determined by HPLC analysis.

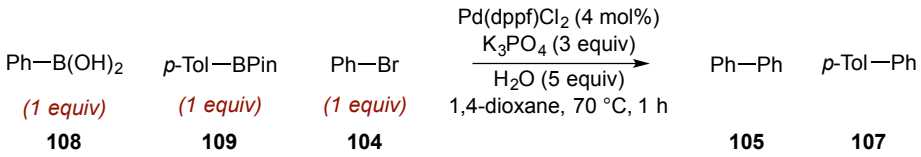
In light of the profound effect it had on speciation control in the formal homologation studies,[128,129] the effect of H_2O content was also considered (Graph 9). As expected, selectivity rapidly decreased as H_2O content increased. Interestingly,

conversion to products **105** and **107** was found to be directly proportional, with the undesired BPin coupling increasing as the desired boronic acid coupling decreased.



Graph 9: Effect of H_2O content on conversion and selectivity

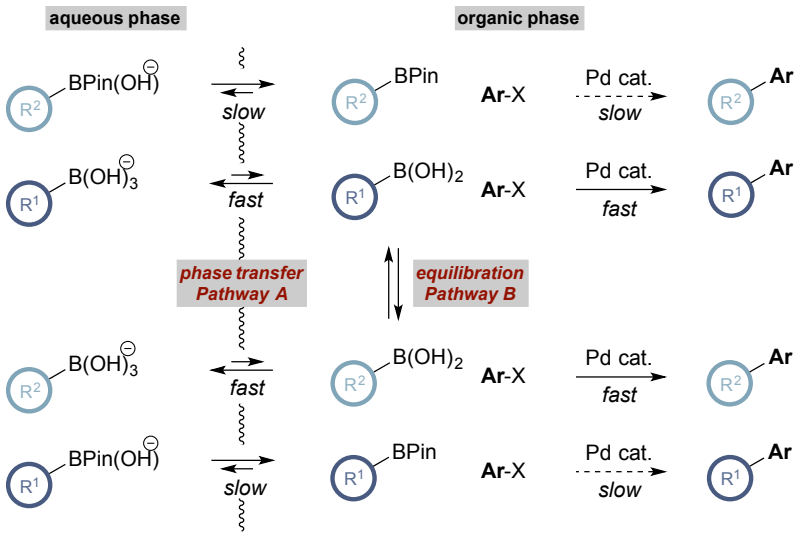
In order to confirm that the observed selectivity was indeed a result of a kinetic transmetallation and not influenced by electronics of the substituents, *i.e.*, the *p*-Me, the inverse reaction was carried out (Scheme 85). Pleasingly this afforded comparable results (95:5 **105**:**107**), confirming that the selectivity of the process was indeed derived from the nature of the boron species.



Scheme 85: Inverse reaction to confirm kinetic transmetallation

The nature of the effect of H_2O on the selectivity of the system was then investigated in more detail. Previous work within the Watson group had demonstrated the preference of boronic acids to form the corresponding boronate under biphasic reaction conditions.[146] Once formed, these boronates readily undergo phase transfer to reside predominantly in the aqueous phase. BPins, on the other hand, do not form boronates as readily, presumably as a result of the less Lewis acidic boron, and therefore are not as prone to phase-crossing. It was thought that this phenomenon

may also be responsible for the reduced selectivity when more H_2O was present in the system under investigation. This would result in a reduced concentration of the boronic acid in the bulk organic phase, leading to less efficient coupling, assuming the catalyst and halide remained predominately in the organic phase (Scheme 86, Pathway A). Similarly, poor control of the diol equilibration between the two boron species would result in reduced selectivity (Pathway B).

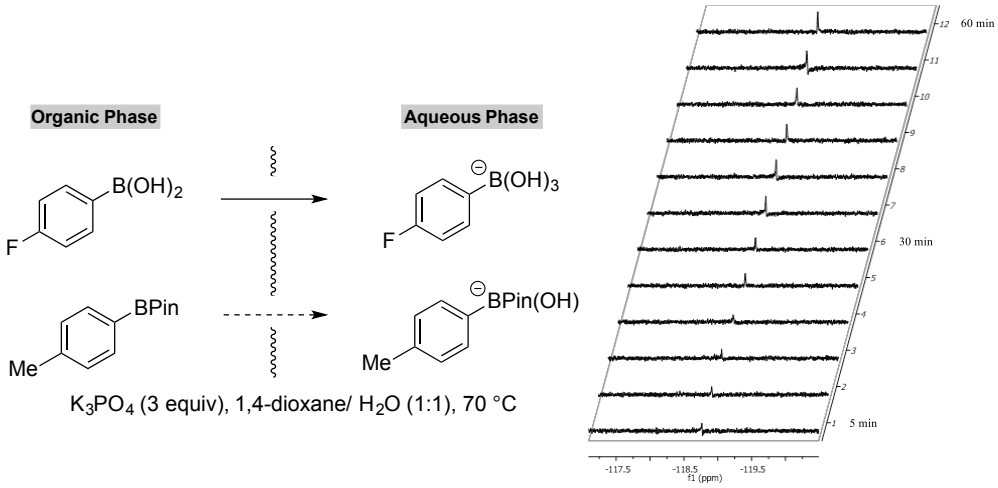


Scheme 86: Potential pathways effecting chemoselectivity

This would result in the formation of second, competitive boronic acid, along with a less reactive BPin, thereby affording more of the undesired cross-coupling product. To confirm these suspicions, a series of spectroscopic investigations was undertaken, analysing the system under representative optimum (limited H_2O) and biphasic conditions. These experiments were carried out in the absence of Pd and halide in order to solely analyse the behaviour of the boron species prior to cross-coupling.

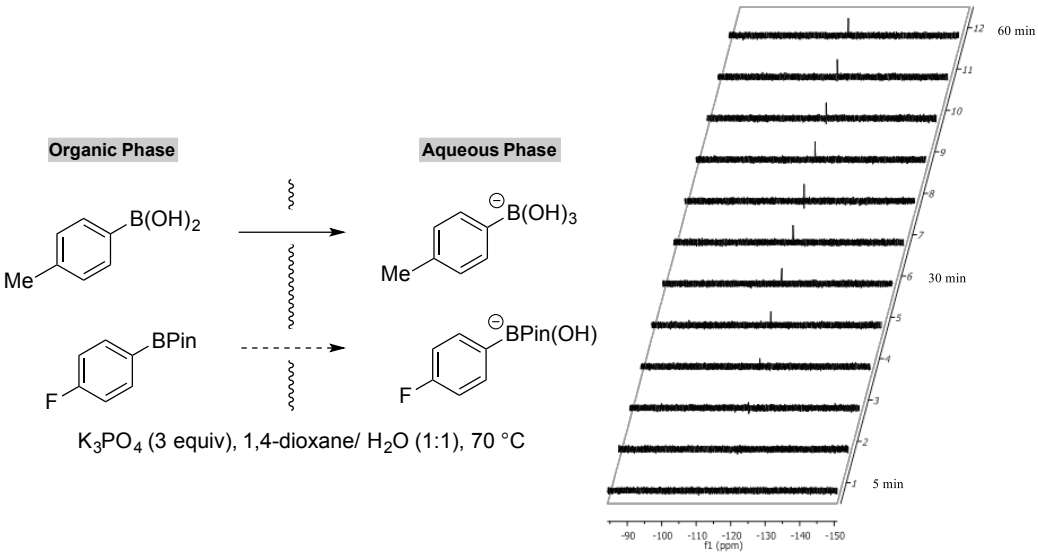
Firstly, the possibility of phase transfer of the active boron species (as its corresponding boronate) was considered. Under optimum reactions conditions with a restricted quantity of H_2O (98:2, 1,4-dioxane:H_2O), the formation of a bulk aqueous phase is precluded and, as such, any phase transfer of boron species is also precluded. Under biphasic conditions, *i.e.*, using a 1:1 mixture of 1,4-dioxane:H_2O, a bulk basic aqueous phase is created. Using *p*-fluorophenylboronic acid to provide an NMR handle, a ^{19}F NMR of the aqueous phase was recorded every 5 minutes to track the ingress of the boronic acid into the aqueous phase as its corresponding boronate

(Scheme 87). Boronate acid boronate formation and subsequent phase transfer was found to occur immediately under the biphasic reaction conditions.



Scheme 87: Boronic acid boronate formation and phase transfer

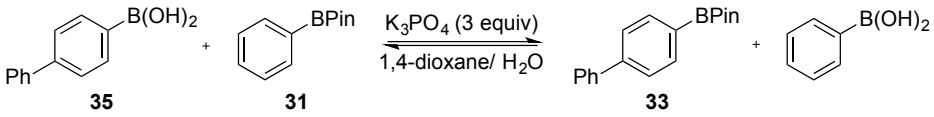
The same reaction was performed with the corresponding *p*-fluorophenyl BPin (Scheme 88). Unlike the boronic acid no phase transfer occurred immediately. Interesting, however, phase transfer was observed after ~ 20 minutes. It was thought this may be the result of diol equilibration over time as no BPin boronate formation was seen under similar conditions in the absence of a boronic acid.[146] This experiment was also performed with *p*-fluorobromobenzene and no phase transfer was observed, confirming the halide remains in the organic phase.



Scheme 88: BPin boronate formation and phase transfer

To confirm that diol equilibration was responsible for the phase transfer of the BPin species, and to also compare the extent to which diol equilibration occurred under the two conditions, HPLC analysis was carried out. 4-Biphenylboronic acid (**35**) was mixed with phenyl BPin (**31**) and K_3PO_4 under optimum (98:2) and biphasic (1:1) conditions, and the quantity of **35** and **33** (formed from diol equilibration) were measured after 10 minutes at 70 °C (Table 16).

Table 16: Effect of H_2O content on diol equilibration



Entry	1,4-dioxane/H_2O ratio	35:33[a]
1	98:2	16.4:1
2	1:1	2:1

[a] Determined by HPLC analysis.

Although a small amount of diol equilibration was observed in the optimum system (Entry 1), the system maintained ~95% integrity of the initial species. As cross-coupling under these conditions is rapid (see Graph 7 above), it was thought that in the presence of catalyst and halide, cross-coupling could effectively outcompete diol

equilibration under these limited H_2O conditions. Under biphasic conditions however, rapid diol equilibration was observed, forming a large quantity of the undesired BPin after just 10 minutes (Entry 2).

Based on the results of these control experiments, it was confirmed that the reduced selectivity of the cross-coupling process was a result of two main factors: 1) increased boronic acid boronate formation and subsequent phase transfer reduces the concentration of the boronic acid in the organic phase, allowing more competitive BPin cross-coupling, which does not phase transfer under these conditions; 2) increased diol equilibration under the biphasic reaction conditions leads to the formation of more undesired $ArB(OH)_2$ and converts the desired $ArB(OH)_2$ into the less reactive ArBPin species, again reducing the concentration of the desired boronic acid in the reaction mixture while also introducing a second competitive boron species.

With optimum conditions for the selective boronic acid cross-coupling identified, and the reasons behind the chemoselectivity confirmed, the substrate scope was then investigated. To fully probe the generality of the process, the boronic acid, BPin, and bromide components were all varied systematically (Figure 24). In all cases, high selectivity for the boronic acid cross-coupling was observed. As previously confirmed with the tolyl system (see Scheme 85 above), selectivity was not affected by the nature of the substituents on the boron species. For example, high levels of boronic acid selectivity were achieved in cases where the same aryl derivative was applied as both the boronic acid and BPin component (**110** – **112** vs. **118** – **120**), further demonstrating that the source of chemoselectivity was indeed the nature of the boron species and not a factor of electronics. A diverse range of bromides were also well tolerated in the selective cross-coupling procedure. In order to effectively separate the desired boronic acid cross-coupled products from the unreacted BPin, reactions were submitted to an oxidative workup. Treatment with H_2O_2 under previously developed conditions[147] efficiently converted the unreacted BPin into the corresponding phenol, which could be easily separated from the cross-coupled product. In some cases, reduced yields of boronic acid cross-coupling were observed when sensitive heterocyclic boronic acids were employed (**113** and **114**). Although

the boronic acid cross-coupling was still the major reaction product, a small amount of the competitive BPin cross-coupling was observed. This was attributed to some protodeboronation of the boronic acid, leaving an excess of aryl bromide which could then react with the BPin.

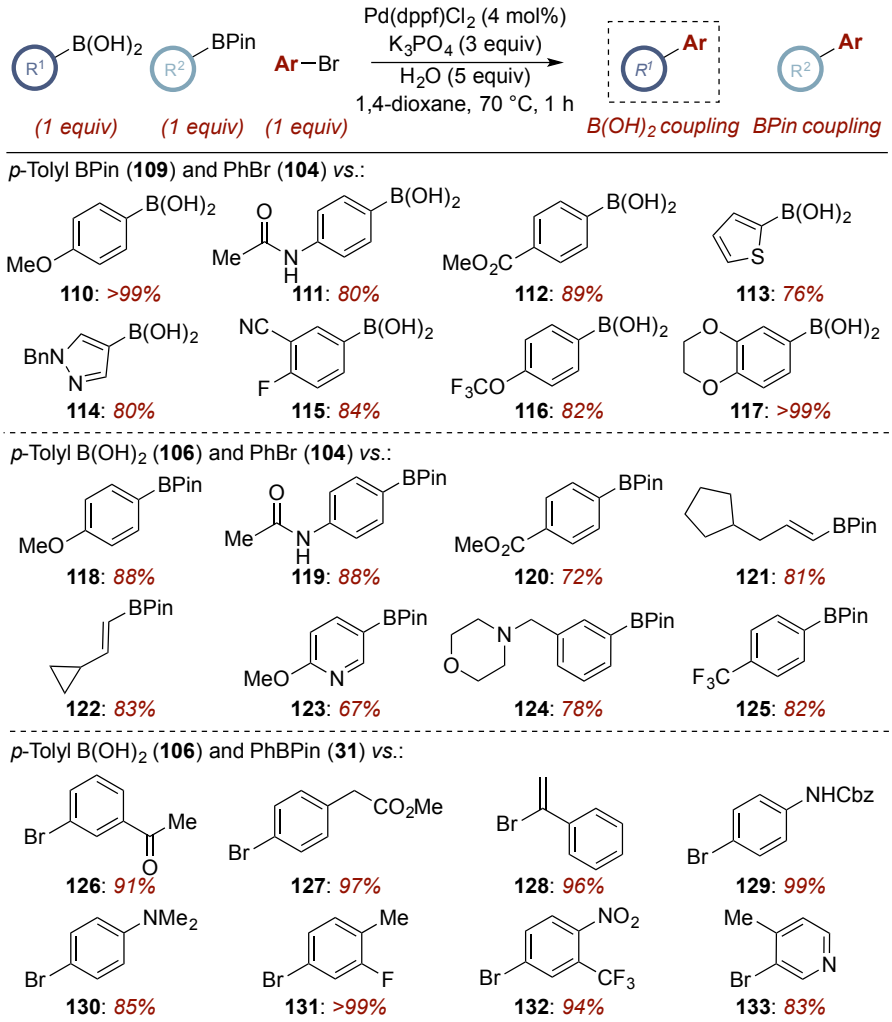
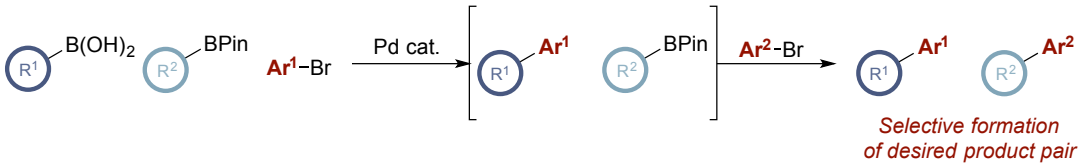


Figure 24: Scope of chemoselective cross-coupling of boronic acid vs. BPin

As with the previous formal homologation process, the validity of the catalyst following the initial cross-coupling was then investigated (see Scheme 70, Section 3.1 above). It was proposed that if the catalyst remained active, which was deemed likely given the short reaction time, addition of a second aryl bromide following the initial cross-coupling could utilise the unreacted BPin component to form a second selective cross-coupled product (Scheme 89).



Scheme 89: Sequential one-pot selective cross-coupling

Based on previous experience, it was predicted more H_2O would be required to facilitate the second cross-coupling. Therefore, in addition to adding a second bromide to the reaction following the completion of the initial cross-coupling, an additional 15 equivalents of H_2O were also added. The reaction was then heated to 90 °C for a further 24 hours to selectively afford the desired pair of cross-coupled products. A small substrate scope was investigated to demonstrate that the process was general, and that desired product pairs could be selectively isolated in good yield without the need for intermediate isolation or catalyst renewal (Figure 25).

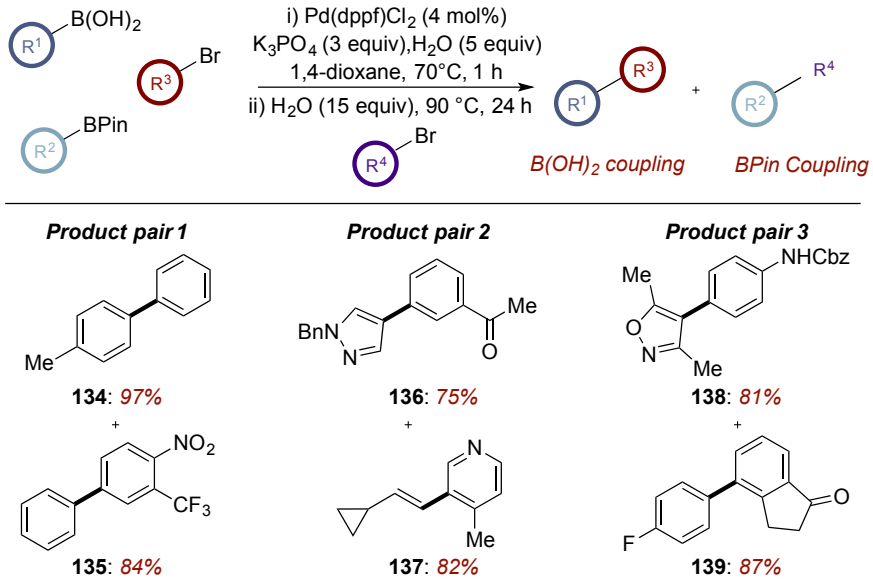
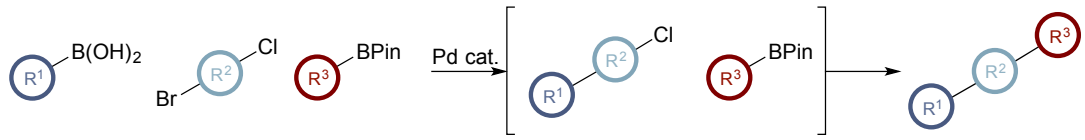


Figure 25: Scope of sequential one-pot selective cross-coupling

Having demonstrated that the catalyst remained sufficiently active to facilitate a second cross-coupling, attention then turned to performing a tandem chemoselective cross-coupling *in situ*, without the need for sequential addition of reagents. Based on previous work, it was proposed this could be accomplished by simultaneously controlling the oxidative addition and transmetallation steps of the SM catalytic cycle. This would be achieved through selective engagement of an aryl bromide over

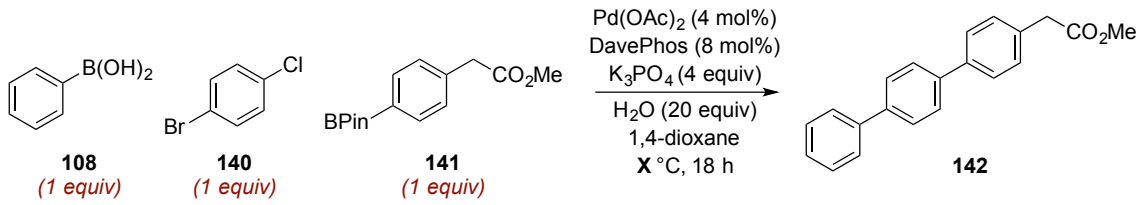
the less reactive chloride. This Pd^{II} complex can then transmetallation with the more reactive boronic acid. Following completion of the initial cross-coupling, the catalyst can then engage the less reactive chloride and undergo transmetallation with the unreacted BPin (Scheme 90).



Scheme 90: Chemoselective tandem cross-coupling without protecting groups

Previous optimisation of tandem cross-coupling had shown that a greater quantity of base and H_2O was typically required to facilitate the second cross-coupling. For this reason, it was elected to begin screening on a model reaction with the previously optimised system of 4 equivalents K_3PO_4 and 20 equivalents H_2O. A catalyst/ligand system of $Pd(OAc)_2$/DavePhos was selected based upon its previously demonstrated ability to effectively control the rates of oxidative additions of aryl halides.[145] An initial temperature screen over an 18 hour reaction time was informative (Table 17). Running the reaction at 70 °C provided the highest conversion (Entry 3), with lower temperatures giving reduced conversion (Entry 1 – 2). Interestingly, increasing the temperature to 90 °C offered no increase in conversion, presumably due to increased protodeboronation (Entry 4). It was therefore elected to continue optimisation at 70 °C for efficiency reasons.

Table 17: Effect of temperature on conversion



108 *(1 equiv)* **140** *(1 equiv)* **141** *(1 equiv)* **142**

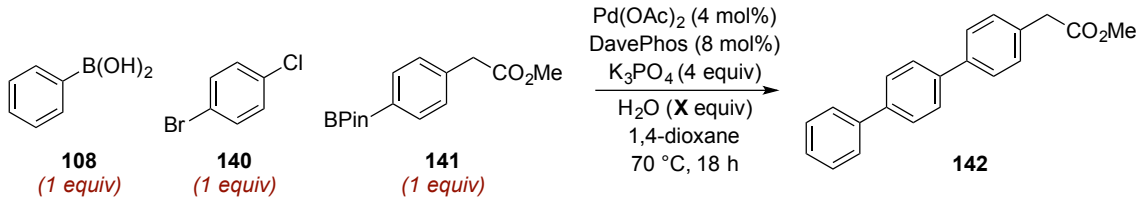
Entry	Temperature (°C)	Conversion to 142 (%)[a]
1	30	25
2	50	41
3	70	56

4	90	53

[a] Determined by HPLC analysis.

As H_2O content had been shown to be key in both phase transfer and diol equilibration, an H_2O study was carried out (Table 18). The results indicated that in this instance, 15 equivalents provided optimal conversion (Entry 4).

Table 18: Effect of H_2O content on conversion



108 *(1 equiv)* **140** *(1 equiv)* **141** *(1 equiv)* **142**

Entry	H_2O Equivalents	Conversion to 142 (%)[a]
1	5	48
2	10	48
3	15	72
4	20	56
5	25	61
6	30	55

[a] Determined by HPLC analysis.

It was predicted that increasing the quantity of **108** (to an excess) would result in more competitive $B(OH)_2$/Cl coupling following the completion of the initial $B(OH)_2$/Br coupling. This increase in $B(OH)_2$ could also result in increased diol equilibration and therefore result in reduced selectivity. In order to mitigate against these factors, a slight excess of **140** and **141** were employed in the reaction. This afforded **142** in excellent selectivity and isolated yield. This allowed a small compound library to be generated (Figure 26). A range of common functionalities were tolerated, including substituted Br/Cl cores (**148**, **150**, **152**). Isolated yields indicated the reaction typically proceeded with ~80% efficiency per C-C bond formation.

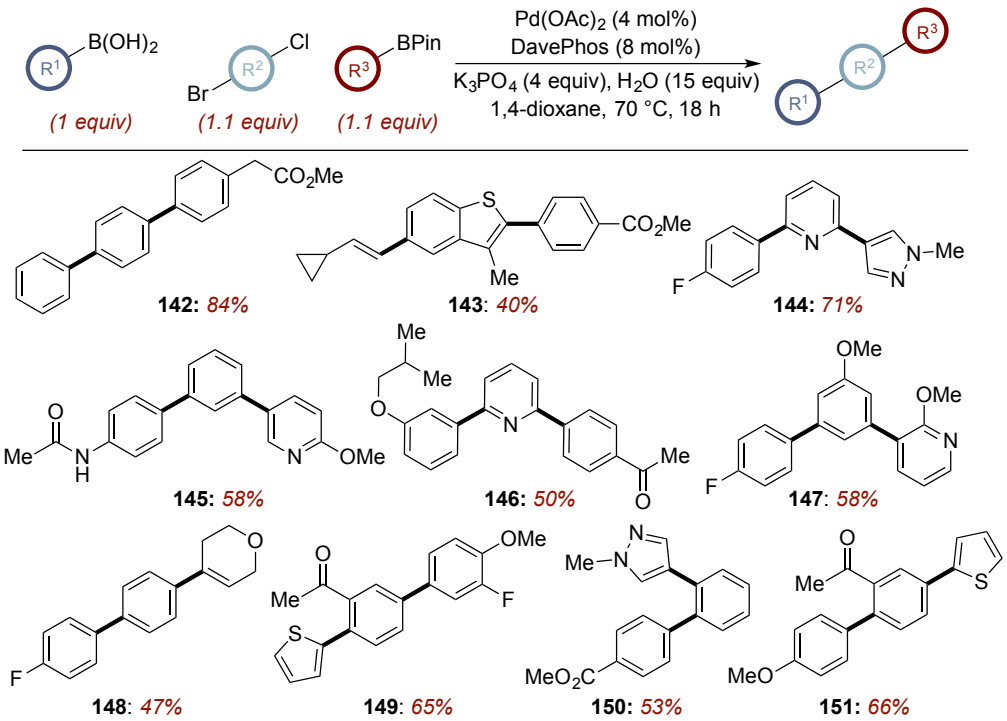


Figure 26: Scope of chemoselective tandem cross-coupling

In examples where the yield was lower (*e.g.*, **143**, **148**) the mass balance was typically identified as the biaryl chloride product of mono-boronic acid selective cross-coupling, indicating a problematic second cross-coupling. The unreacted BPin was typically not recovered in these cases, possibly due to protodeboronation, either directly from the BPin or possibly following diol equilibration reveal the less stable boronic acid. Another case where reduced selectivity was observed was in the case of olefinic BPin reagents (**144**). Results with these compounds would suggest the kinetic window of transmetallation between vinyl BPin and aryl $B(OH)_2$ is smaller, *i.e.*, vinyl BPin reagents transmetallate faster than the equivalent aryl compounds. This would agree with previous results which demonstrated that olefinic bromides would outcompete aryl bromides in oxidative addition – possibly through pre-coordination of the Pd catalyst as a π acid. In any case, this methodology still marks an advance in terms of efficient tandem cross-coupling. The reaction proceeds in a one-pot fashion with no intermediate isolation or purification, requirement for additional catalyst or additives, and without the need for any protecting group manipulations, either as sequential reactions or *in situ*.

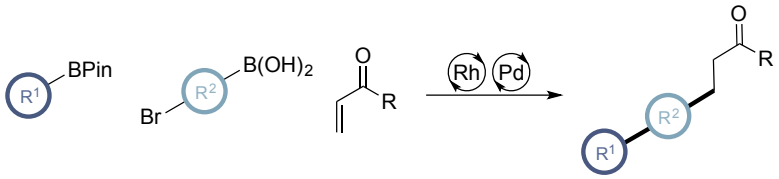
4. Conclusions

Through careful control of reaction media, the solution speciation event of various organoboron species can be controlled to enable chemoselective Suzuk-Miyaura cross-coupling. The physical properties of inorganic bases in combination with the quantity of H_2O in the reaction mixture was found to be key in enabling speciation control, with the base acting as an internal dessicant in order to prevent premature hydrolysis and oligomerisation while simultaneously promoting diol conjugation to form the thermodynamic BPin products. Interesting the product distribution was found to be temperature dependant, with reaction run at high temperature forming the thermodynamic BPin products and reaction run at room temperature forming the kinetic cross-coupled BMIDA even under aqueous basic conditions. This enabled the synthesis of a range of functionally diverse BPin and BMIDA adducts. The synthetic utility of the homologated BPin products was demonstrated through the sequential one-pot cross-coupling with a further aryl bromide, as well as the controlled iterative homologation. Control experiments were informative in establishing both the key events in the reaction an addition to the order in which they must occur for speciation control to be achieved. A rapid initial cross-coupling is followed by controlled hydrolysis of the BMIDA unit and subsequent diol conjugation promoted by the basic conditions.

This understanding of the behaviour of boron species under controlled basic conditions has enabled the development of a chemoselective Suzuk-Miyaura cross-coupling without the use of protecting groups. Under suitably controlled aqueous basic conditions, a kinetic window of transmetallation between boronic acids and their corresponding pinacol esters can be leveredged to enable chemoselectivity. Spectroscopic experiments have shed light on the effect of H_2O on chemoselectivity, with more biphasic systems reducing selectivity due to competing phase transfer and diol equilibration. This in turn has enabled the development of a chemoselective tandem cross-coupling in one-pot without the need for any protecting group manipulations, catalyst renewal, or intermediate purification.

5. Future work

That chemoselectivity can be leveraged between two reactive boron species in Pd catalysed cross-coupling through speciation control has interesting implications for other metal mediated reactions. A number of metal-mediated processes are known to proceed readily with boronic acid while the corresponding BPin are less effective (*e.g.*, Rh catalysed conjugate addition[40] and Chan-Lam amination[148]). Having demonstrated chemoselectivity of multiple boron nucleophiles within Pd-catalysed processes, it would be interesting to explore whether this could be expanded to dual catalyst systems. For example, by controlling the speciation events in solution, could two distinct catalytic cycles be combined in a one-pot process (Scheme 91).



Scheme 91: Proposed chemoselective dual catalysis

In perhaps a more general sense, the effect of H_2O on selectivity could also have wider ramifications. Increasingly biphasic reaction conditions were seen to decrease boronic acid coupling through boronate formation and subsequent phase transfer. In standard Suzuki-Miyaura cross-coupling (*i.e.*, using only a boronic acid) the use of a biphasic media could result in boronate formation and phase transfer, thus limiting the efficiency of the cross-coupling. In addition to protodeboronation, this could explain why boronic acids are typically used in excess in SM cross-couplings.[7] A systematic evaluation of reaction efficiency in biphasic systems vs. limited H_2O could afford interesting results in terms of increasing the efficiency of one of the widest practiced reactions in modern synthetic chemistry.

6. Experimental

General

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[90]

Purification of Solvents

Dry solvents for reactions were either obtained from a PureSolv SPS-400-5 solvent purification system (THF). These solvents were transferred to and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves and purged with and stored under nitrogen. CH_2Cl_2, Et_2O, EtOAc, MeCN, and petroleum ether 40-60° for purification purposes were used as obtained from suppliers without further purification.

Drying of Inorganic Bases

Inorganic bases were dried in a Heraeus Vacutherm oven at 60 °C under vacuum for a minimum of 24 hours before use.

Experimental Details

Reactions were carried out using conventional glassware or in capped 5 mL microwave vials. Glassware was oven-dried (150 °C) and purged with N_2 before use. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature was generally 20 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

Purification of Products

Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light or developed using potassium permanganate solution. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel. Reverse phase flash chromatography was carried out using IST Isolute C18 cartridges.

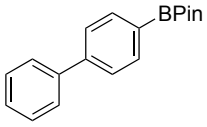
Analysis of Products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{19}F NMR spectra were obtained on a Bruker AV 400 spectrometer at 376 MHz. ^{11}B NMR spectra were obtained on a Bruker AV 400 spectrometer at 128 MHz. ^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AV 400 at 400 MHz and 125 MHz, respectively, or Bruker DRX 500 at 500 MHz and 126 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 ppm (^{1}H) and 77.0 ppm (^{13}C) and DMSO-d_6 referenced at 2.50 ppm (^{1}H) and 39.5 ppm (^{13}C). Unless stated otherwise the carbon bearing boron was not observed. In cases where ^{13}C NMR count is low one or more coincident signals were observed. High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University. Reverse phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column. Analysis was performed using a gradient method, eluting with 5 – 80% MeCN/H_2O over 16 minutes at a flow rate of 2 mL/min. Samples for HPLC analysis were prepared through the addition of 2 mL of caffeine standard to the completed reaction mixture, the resulting solution was then stirred before the removal of a 200 μL aliquot. The aliquot was diluted to 1 mL with MeCN, a 200 μL aliquot of the diluted solution was then filtered and further diluted with 800 μL MeCN and 500 μL H_2O for HPLC analysis against established conversion factors.

6.1 General procedures

General Procedure A: General procedure for formal homologation optimisation (Table 1)

For example, synthesis of 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **33**

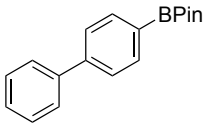


To an oven-dried 5 mL microwave vial was added 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (76 mg,

0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The vial was then capped and purged with N_2 before addition of THF/H_2O (10:1, 1 mL, 0.25 M) The reaction mixture was then heated to 50 °C for 24 h in a sand bath. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration (57% conversion).

General Procedure B: Optimised conditions for formal homologation process with Pd(dppf)Cl_2·DCM (Figure 16)

For example, synthesis of 2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **33**



To an oven-dried 5 mL microwave vial was added 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (76 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The vial was then capped and purged with N_2 before addition of THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was then heated to 90 °C for 24 h in a sand bath. The mixture was allowed to cool to room temperature and diluted with H_2O (4 mL) before loading directly onto a C18 column. The crude mixture was then purified by reverse phase chromatography (20 – 75% MeCN in H_2O). Fractions containing product were collected and the volatile organics were removed under vacuum. The resulting aqueous mixture was then extracted with EtOAc (2×100 mL). The combined organics were dried (Na_2SO_4) and concentrated under vacuum to give the desired product as an off-white solid (56 mg, 88%).

υ_{max} (film): 2978, 1396, 1359, 1143, 1091 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.66 – 7.63 (m, 4H), 7.45-7.49 (m, 2H), 7.38, (tt, *J* = 7.4, 1.2 Hz, 1H), 1.39 (s, 12H).

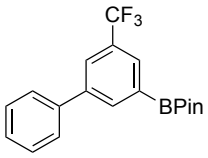
^{13}C NMR ($CDCl_3$, 126 MHz): δ 143.4, 140.6, 134.8, 128.3, 127.0, 126.7, 126.0, 83.3, 24.4.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{22}BO_2$) requires *m/z* 281.1707, found *m/z* 281.1709.

General Procedure C: Optimised conditions for formal homologation process with $Pd(OAc)_2$/SPhos (Figure 18)

For example, synthesis of 2-(3-bromo-5-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **59**



To an oven-dried 5 mL microwave vial was added 3-bromo-5-(trifluoromethyl)phenylboronic acid MIDA ester (88 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (76 mg, 0.375 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The vial was then capped and purged with N_2 before addition of THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was then heated to 90 °C for 24 h. The mixture was allowed to cool to room temperature and diluted with H_2O (4 mL) before loading directly onto a C18 column. The crude mixture was then purified by reverse phase chromatography (20-75% MeCN in H_2O). Fractions containing product were collected and the volatile organics were removed under vacuum. The resulting aqueous mixture was then extracted with EtOAc (2×100 mL). The combined organics were dried (Na_2SO_4) and concentrated under vacuum to give the desired product as a yellow gum (53 mg, 60%).

υ_{max} (film): 2980, 2929, 1600, 1471 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (s, 1H), 8.06 (s, 1H), 7.93 (s, 1H), 7.69 – 7.62 (m, 2H), 7.53 – 7.46 (m, 2H), 7.42 (d, *J* = 7.3 Hz, 1H), 1.40 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 141.3, 139.7, 136.7, 130.1 (d, $^3J_{C\text{-}F}$ = 3.4 Hz), 128.9, 127.9, 127.3, 126.4 (d, $^3J_{C\text{-}F}$ = 3.4 Hz), 84.4, 24.9. CF_3 carbon and carbon bearing CF_3 not observed.

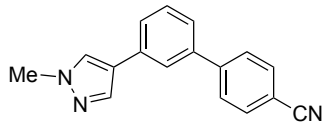
^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.0.

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 62.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{21}BF_3O_2$) requires *m/z* 349.1581, found *m/z* 349.1581.

General Procedure D: One-pot iterative SM cross-coupling enabled via controlled speciation (Scheme 70)

For example, synthesis of 3'-(1-Methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-4-carbonitrile, **70**



To an oven-dried 5 mL microwave vial was added 3-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), (1-methyl-1*H*-pyrazol-4-yl)boronic acid pinacol ester (78 mg, 0.375 mmol, 1.5 equiv), $Pd(dppf)Cl_2$·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv). The vial was then capped and purged with N_2 before addition of THF (1 mL, 0.25 M) and H_2O (90 μL, 5 mmol, 20 equiv). The reaction mixture was then heated to 90 °C for 24 h. The reaction mixture was allowed to cool to room temperature before adding 4-bromobenzonitrile (68 mg, 0.375 mmol, 1.5 equiv). The vial was then recapped and purged again with nitrogen before being heated to 90 °C for a further 24 h. The reaction mixture was then cooled to room temperature before being quenched with H_2O (20 mL) and extracted with EtOAc (2×20 mL). The combined organics were collected, dried (Na_2SO_4), filtered, and concentrated under vacuum to a residue that was purified by reverse phase preparative HPLC (20 – 95% MeCN in H_2O) to afford the desired product as a white solid (40 mg, 63%).

υ_{max} (film): 2226, 1452, 1369, 1174, 1143, 1107, 844, 783, 700 cm^{-1}.

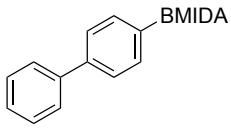
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (dd, *J* = 22.8, 8.4 Hz, 4H), 7.69 – 7.49 (m, 5H), 6.43 (s, 1H), 3.98 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.7, 140.0, 132.8, 131.1, 129.6, 128.9, 127.8, 127.7, 127.6, 118.7, 111.6, 106.6, 37.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{14}N_3$) requires *m/z* 260.1182, found *m/z* 260.1183.

General Procedure E: Room temperature cross-coupling of haloaryl BMIDA in the presence of aqueous base (Figure 19)

For example, synthesis of [1,1'-Biphenyl]-4-ylboronic acid MIDA ester, **35**



To an oven-dried 5 mL microwave vial was added 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (76 mg, 0.375 mmol, 1.5 equiv), $Pd(dppf)Cl_2$·DCM (8.2 mg, 0.01 mmol, 4 mol%), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The vial was then capped and purged with N_2 before addition of THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was then stirred at room temperature for 24 h. The reaction mixture was then diluted with MeCN (5 mL) and filtered through a pad of Celite® and washed with MeCN (10 mL). The filtrate was then concentrated under vacuum before adding Et_2O (10 mL) to form a precipitate. The precipitate was then dissolved in DCM (5 mL) and washed with H_2O (2 × 5 mL). The organics were then passed through a hydrophobic frit before being concentrated under vacuum to afford the title compound as a beige solid (65 mg, 85%).

υ_{max} (film): 2957, 2922, 1755, 1743, 1460, 1209, 1041, 983, 829, 761 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 – 7.65 (m, 4H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.47 (t, *J* = 7.9 Hz, 2H), 7.39 – 7.35 (m, 1H), 4.65 (d, *J* = 17.6 Hz, 2H), 4.14 (d, *J* = 17.8 Hz, 2H), 2.55 (s, 3H).

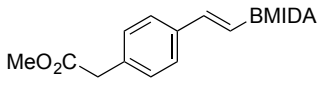
^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.4, 140.5, 140.1, 133.1, 128.9, 127.5, 126.6, 125.9, 61.8, 47.6.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 12.30.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{17}BNO_4$) requires m/z 310.1245, found m/z 310.1245.

General Procedure F: Previously published procedure for cross-coupling of haloaryl BMIDA (Table 11)[143]

For example, synthesis of *trans*-(4-(2-methoxy-2-oxoethyl)styryl)boronic acid MIDA ester, **89**



To an oven-dried 5 mL microwave vial was added *trans*-2-bromovinylboronic acid MIDA ester (65 mg, 0.25 mmol, 1 equiv), (4-(2-methoxy-2-oxoethyl)phenyl)boronic acid pinacol ester (100 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (10.3 mg, 0.013 mmol, 5 mol%) and K_3PO_4 (318 mg, 1.5 mmol, 6 equiv). The vial was then capped and purged with N_2 before addition of DMSO (3.5 mL, 0.07 M). The reaction mixture was then heated to 55 °C for 24 h. The reaction mixture was then cooled to room temperature and diluted with EtOAc (20 mL) before being washed with brine (2 × 40 mL) and H_2O (2 × 40 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure before being purified by flash chromatography (30 – 90% EtOAc/petroleum ether) to afford the desired compound as a brown solid (53 mg, 64%).

υ_{max} (film): 2991, 2949, 1762, 1726, 1224, 1024, 1004 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.44 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.81 (d, *J* = 18.2 Hz, 1H), 6.25 (d, *J* = 18.2 Hz, 1H), 4.25 (d, *J* = 17.1 Hz, 2H), 4.04 (d, *J* = 17.1 Hz, 2H), 3.66 (s, 2H), 3.60 (s, 3H), 2.79 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 171.5, 169.2, 140.6, 136.5, 134.0, 129.5, 126.4, 61.4, 51.6, 46.7, 24.6.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 12.49.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}BNO_6$) requires m/z 332.1300, found m/z 332.1299.

General Procedure G: Independent cross-coupling of boronic acid and BPin (Scheme 83)

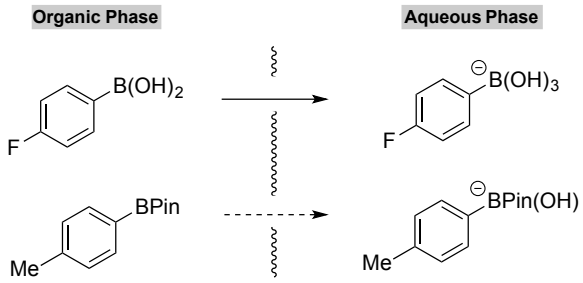
To an oven-dried 5 mL microwave vial was added either phenylboronic acid (31 mg, 0.25 mmol, 1 equiv) or phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), bromobenzene (26 μL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%) and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The microwave vial was then capped and purged with N_2 before adding THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was then heated to 50 °C for 1 h. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration.

General Procedure H: Competitive cross-coupling of boronic acid and BPin (Scheme 84)

To an oven-dried 5 mL microwave vial was added 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), bromobenzene (26 μL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%) and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The microwave vial was then capped and purged with N2 before adding THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was then heated to 50 °C for 1 h. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration.

General Procedure I: Effect of H_2O on selectivity – NMR analysis (Scheme 87)

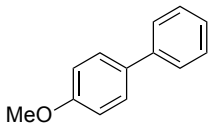
For example, boronic acid boronate formation and phase transfer



4-Fluorophenylboronic acid (28 mg, 0.20 mmol, 1 equiv) and 4-tolylboronic acid pinacol ester (44 mg, 0.20 mmol, 1 equiv) were dissolved in 1,4-dioxane (0.8 mL, 0.25 M) and transferred to a quartz NMR tube (Tube A). K_3PO_4 (127 mg, 0.60 mmol, 3 equiv) was weighed out into a vial (Vial A) and dissolved in D_2O (0.8 mL) for later use. A D_2O blank (0.8 mL) NMR sample tube (Tube B) was prepared and used as a lock on the NMR machine. After locking (Tube B) was complete, Vial A containing inorganics was transferred slowly *via* syringe and long needle (needle must reach the bottom of the NMR tube) to Tube A to generate an aqueous biphasic system. The biphasic NMR sample (Tube A) was placed in the magnet and after shimming a data set of the aqueous phase was recorded every 5 min for 1 h at 343 K (16 scans per data set recording. No spinning was used in this NMR study). This reaction was performed in the absence of an internal standard and serves as a qualitative analysis of the species present in the aqueous phase. Boronic acid boronate formation and subsequent phase transfer was observed immediately.

General Procedure J: Chemoselective cross-coupling of boronic acid vs. BPin (Figure 24)

For example, synthesis of 4-methoxy-1,1'-biphenyl, **110**



To an oven-dried 5 mL microwave vial was added 4-methoxyphenylboronic acid (38 mg, 0.25 mmol, 1 equiv), 4-tolylboronic acid pinacol ester (55 mg, 0.25 mmol, 1 equiv), bromobenzene (26 μL, 0.25 mmol, 1 equiv), $Pd(dppf)Cl_2 \cdot DCM$ (8.2 mg, 0.01 mmol, 4 mol%) and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The microwave vial was then capped and purged with N_2 before adding 1,4-dioxane (1 mL, 0.25 M) and H_2O

(22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was then heated to 70 °C for 1 h before being decapped and cooled to 0 °C. H_2O_2 (30 wt. % in H_2O, 200 µL) was then added in order to oxidise the unreacted boronic acid pinacol ester. The reaction mixture was then warmed to r.t. and stirred for 1 h before being quenched with sodium metabisulfite (190 mg, 1 mmol, 4 equiv). The reaction mixture was then diluted with EtOAc (30 mL) and washed with sat. NH_4Cl (30 mL) and brine (30 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure before being purified by flash chromatography (silica gel, 0 – 2% Et_2O/petroleum ether) to afford the desired compound as a white solid (46 mg, quant.).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 – 7.50 (m, 4H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.34 – 7.27 (m, 1H), 7.02 – 6.94 (m, 2H), 3.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 159.6, 141.3, 134.2, 129.2, 128.6, 127.2, 114.7, 55.8.

The spectral data were consistent with those previously reported in the literature.[149]

General Procedure K: Sequential one-pot selective cross-coupling (Figure 25)

For example, synthesis of 4-methyl-1,1'-biphenyl **134** and 4-nitro-3-(trifluoromethyl)-1,1'-biphenyl **135**

To an oven-dried 5 mL microwave vial was added 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%) and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The microwave vial was then capped and purged with N_2 before adding 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was then heated to 70 °C for 1 h before being allowed to cool to r.t. and decapped. 4-Bromo-1-nitro-2-(trifluoromethyl)benzene (68 mg, 0.25 mmol, 1 equiv) was then added and vial was

recapped and purged with N_2 before adding H_2O (67.5 μL, 3.75 mmol, 15 equiv). The reaction mixture was then heated to 90 °C for 24 h. The reaction mixture was then diluted with EtOAc (30 mL) and washed with brine (30 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure before being purified by flash chromatography (silica gel, 2 – 10% Et_2O/petroleum ether) to afford 4-methyl-1,1'-biphenyl **134** as a white solid (41 mg, 97%) and 4-nitro-3-(trifluoromethyl)-1,1'-biphenyl **135** as a colourless liquid (56 mg, 84%).

Data for 4-methyl-1,1'-biphenyl **134**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 – 7.57 (m, 2H), 7.53 – 7.48 (m, 2H), 7.47 – 7.40 (m, 2H), 7.36 – 7.29 (m, 1H), 7.29 – 7.23 (m, 2H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.3, 138.5, 137.2, 129.6, 128.9, 127.1, 21.2.

The spectral data were consistent with those previously reported in the literature.[14]

Data for 4-nitro-3-(trifluoromethyl)-1,1'-biphenyl **135**

υ_{max} (film): 1537, 1361, 1323, 1264, 1139, 1048, 756 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 – 7.99 (m, 2H), 7.90 (dd, J = 8.4, 1.6 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.56 – 7.46 (m, 3H).

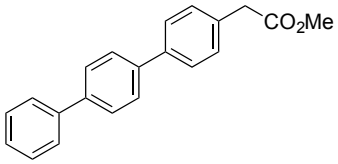
^{19}F NMR ($CDCl_3$, 376 MHz): δ – 59.91 (s, 3F).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 146.3, 137.6, 131.2, 129.6, 129.5, 127.5, 126.6 (q, $^{3}J_{C\text{-}F}$ = 5.1 Hz), 126.0, 124.5 (q, $^{2}J_{C\text{-}F}$ = 34.0 Hz), 122.2 (q, $^{1}J_{C\text{-}F}$ = 273.4 Hz). Carbon bearing NO_2 not observed.

HRMS: exact mass calculated for $[M]^+$ ($C_{13}H_8F_3NO_2$) requires m/z 267.0507, found m/z 267.0505.

General Procedure L: Chemoselective tandem cross-coupling without protecting groups optimisation (Table 17)

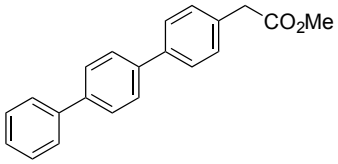
For example, synthesis of methyl 2-([1,1':4',1''-terphenyl]-4-yl)acetate, **142**



To an oven-dried 5 mL microwave vial was added phenylboronic acid (31 mg, 0.25 mmol, 1 equiv), (4-(2-methoxy-2-oxoethyl)phenyl)boronic acid pinacol ester (76 mg, 0.275 mmol, 1.1 equiv), 1-bromo-4-chlorobenzene (53 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), DavePhos (7.8 mg, 0.02 mmol, 8 mol%) and K_3PO_4 (212 mg, 1 mmol, 4 equiv). The microwave vial was then capped and purged with N_2 before adding 1,4-dioxane (1 mL, 0.25 M) and H_2O (90 μL, 20 equiv). The reaction mixture was then heated to 70 °C for 18 h. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration.

General Procedure M: Chemoselective tandem cross-coupling (Figure 26)

For example, synthesis of methyl 2-([1,1':4',1''-terphenyl]-4-yl)acetate, **142**



To an oven-dried 5 mL microwave vial was added phenylboronic acid (31 mg, 0.25 mmol, 1 equiv), (4-(2-methoxy-2-oxoethyl)phenyl)boronic acid pinacol ester (76 mg, 0.275 mmol, 1.1 equiv), 1-bromo-4-chlorobenzene (53 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), DavePhos (7.8 mg, 0.02 mmol, 8 mol%) and K_3PO_4 (212 mg, 1 mmol, 4 equiv). The microwave vial was then capped and purged with N_2 before adding 1,4-dioxane (0.83 mL, 0.3 M) and H_2O (67.5 μL, 15 equiv). The reaction mixture was then heated to 70 °C for 18 h before being allowed to cool to r.t. and decapped. The reaction mixture was then diluted with EtOAc (30 mL) and washed with brine (30 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure before being purified by flash chromatography (silica gel, 2 – 10% Et_2O/petroleum ether) to afford the desired compound as an off-white solid (64 mg, 84%).

υ_{max} (solid): 3036, 2956, 2922, 1735, 1485, 1437, 1146, 815, 761 cm^{-1}.

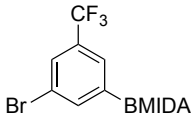
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (s, 4H), 7.64 (d, J = 7.3 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.40 – 7.34 (m, 3H), 3.73 (s, 3H), 3.69 (s, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.0, 140.7, 140.2, 139.7, 139.6, 133.1, 129.8, 128.8, 127.5, 127.42, 127.35, 127.2, 127.1, 52.1, 40.9.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_{21}H_{22}NO_2$) requires m/z 320.1645, found m/z 320.1645.

General Procedure N: Synthesis of MIDA Esters from Boronic Acids

For example, for the preparation of 3-bromo-5-(trifluoromethyl)phenylboronic acid MIDA ester, **S1**



A mixture of 3-bromo-5-(trifluoromethyl)phenylboronic acid (2.0 g, 7.6 mmol, 1 equiv), *N*-methyliminodiacetic acid (1.17 g, 8 mmol, 1.05 equiv) in DMF (100 mL) was heated to 90 °C for 18 h under air. The reaction mixture was allowed to cool to room temperature and concentrated under vacuum to give an off-white slurry. EtOAc (100 mL) was added and the resulting precipitate was collected by filtration. The precipitate was washed with H_2O (2×50 mL) and Et_2O (2×50 mL) before being dried under vacuum to give the desired product as a white crystalline solid (1.63 g, 57%).

υ_{max} (film): 3344, 3014, 2978, 1760, 1323, 1286, 1201, 1159, 1103, 1035, 864 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.96 (s, 1H), 7.92 (s, 1H), 7.79 (s, 1H), 4.38 (d, J = 17.2 Hz, 2H), 4.21 (d, J = 17.2 Hz, 2H), 2.62 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.2, 139.4, 130.4 (d, $^{2}J_{C\text{-}F}$ = 31.9 Hz), 128.2 (dd, $J_{C\text{-}F}$ = 32.7, 3.4 Hz), 123.4 (d, $^{1}J_{C\text{-}F}$ = 272.8 Hz), 122.2, 62.4, 48.0.

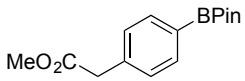
^{11}B NMR (DMSO-d_6, 128 MHz) δ 10.0.

^{19}F NMR (DMSO-d_6, 376 MHz): δ – 61.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{11}BBrF_3NO_4$) requires *m/z* 379.9911, found *m/z* 379.9911.

General Procedure O: Miyaura Borylation of Aryl Bromides

For example, for the preparation of (4-(2-methoxy-2-oxoethyl)phenyl)boronic acid pinacol ester, **S2**



A mixture of methyl 2-(4-bromophenyl)acetate (3.0 g, 13.2 mmol, 1 equiv), bis(pinacolato)diboron (3.38 g, 13.3 mmol, 1.01 equiv), and KOAc (3.87 g, 39.5 mmol, 3 equiv) in 1,4-dioxane (65 mL), was degassed for 30 min by bubbling N_2 through the mixture. Pd(dppf)Cl_2·DCM (323 mg, 0.4 mmol, 3 mol%), was then added and the vessel was purged with N_2 before being heated to 100°C for 18 h. The reaction mixture was allowed to cool to room temperature and filtered through celite, washing with Et_2O. The filtrate was concentrated under vacuum to a residue that was dissolved in Et_2O (100 mL) and washed with H_2O (3 × 100 mL) and brine (4 × 50 mL). The organic extract was dried (Na_2SO_4), filtered, and concentrated under vacuum to a residue that was purified by column chromatography on silica (3 – 7% Et_2O in petroleum ether) to afford the desired product as an off-white solid (2.74 g, 75%).

υ_{max} (film): 2978, 1737, 1616, 1519, 1479 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, *J* = 7.8 Hz, 2 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 3.71 (s, 3 H), 3.67 (s, 2 H), 1.37 (s, 12 H).

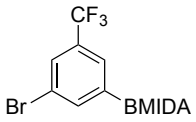
^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.7, 137.1, 135.1, 128.6, 83.8, 52.0, 41.4, 24.8.

^{1}B NMR ($CDCl_3$, 128 MHz): δ 31.2.

HRMS: exact mass calculated for $[M+Na]^+$ (($C_{15}H_{21}BO_4Na$) requires *m/z* 299.1425, found *m/z* 299.1423.

6.2 Synthesis of intermediates

3-Bromo-5-(trifluoromethyl)phenylboronic acid MIDA ester, **S1**



Reaction carried out according to General Procedure N using 3-bromo-5-(trifluoromethyl)phenylboronic acid (2.0 g, 7.6 mmol, 1 equiv), *N*-methyliminodiacetic acid (1.17 g, 8 mmol, 1.05 equiv) in DMF (100 mL) to afford the desired product as a white crystalline solid (1.63 g, 57%).

υ_{max} (film): 3344, 3014, 2978, 1760, 1323, 1286, 1201, 1159, 1103, 1035, 864 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.96 (s, 1H), 7.92 (s, 1H), 7.79 (s, 1H), 4.38 (d, J = 17.2 Hz, 2H), 4.21 (d, J = 17.2 Hz, 2H), 2.62 (s, 3H).

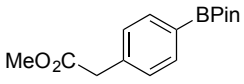
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.2, 139.4, 130.4 (d, $^{2}J_{C\text{-}F}$ = 31.9 Hz), 128.2 (dd, $J_{C\text{-}F}$ = 32.7, 3.4 Hz), 123.4 (d, $^{1}J_{C\text{-}F}$ = 272.8 Hz), 122.2, 62.4, 48.0.

^{11}B NMR (DMSO-d_6, 128 MHz) δ 10.0.

^{19}F NMR (DMSO-d_6, 376 MHz): δ – 61.0 (s, 3F).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{11}BBrF_3NO_4$) requires *m/z* 379.9911, found *m/z* 379.9911.

Methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate, **S2**



Reaction carried out according to General Procedure O using methyl 2-(4-bromophenyl)acetate (3.0 g, 13.2 mmol, 1 equiv), bis(pinacolato)diboron (3.38 g, 13.3 mmol, 1.01 equiv), KOAc (3.87 g, 39.5 mmol, 3 equiv), Pd(dppf)Cl_2·DCM (323 mg, 0.4 mmol, 3 mol%), and 1,4-dioxane (65 mL). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 3 – 7% Et_2O in petroleum ether) to afford the desired product as an off-white solid (2.74 g, 75%).

υ_{max} (film): 2978, 1737, 1616, 1519, 1479 cm^{-1}.

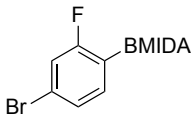
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, *J* = 7.8 Hz, 2 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 3.71 (s, 3 H), 3.67 (s, 2 H), 1.37 (s, 12 H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.7, 137.1, 135.1, 128.6, 83.8, 52.0, 41.4, 24.8.

^{1}B NMR ($CDCl_3$, 128 MHz): δ 31.2.

HRMS: exact mass calculated for $[M+Na]^+$ ($(C_{15}H_{21}BO_4Na)$ requires *m/z* 299.1425, found *m/z* 299.1423.

4-Bromo-2-fluorophenylboronic acid MIDA ester, **S3**



Reaction carried out according to General Procedure N using 4-bromo-2-fluorophenylboronic acid (875 mg, 4 mmol, 1 equiv), *N*-methyliminodiacetic acid (618 mg, 4.2 mmol, 1.05 equiv), and DMF (50 mL) to afford the desired product as a white crystalline solid (994 mg, 75%).

υ_{max} (film): 3014, 2978, 1761, 1575, 1340, 1292, 1255, 1193, 1033, 999, 871, 815 cm^{-1}.

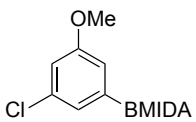
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.48 – 7.40 (m, 3H), 4.42 (d, *J* = 17.3 Hz, 2H), 4.10 (d, *J* = 17.3 Hz, 2H), 2.63 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 168.8, 165.3 (d, $^{1}J_{C\text{-}F}$ = 246.1), 136.4 (d, $^{3}J_{C\text{-}F}$ = 10.0 Hz), 127.4, 123.3 (d, $^{3}J_{C\text{-}F}$ = 10.0 Hz), 118.3 (d, $^{2}J_{C\text{-}F}$ = 28.8 Hz), 62.4, 47.5.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.7; ^{19}F NMR (DMSO-d_6, 376 MHz): δ –102.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{11}H_{11}BBrFNO_4$) requires *m/z* 329.9943, found *m/z* 329.9944.

3-Chloro-5-methoxyphenylboronic acid MIDA ester, **S4**



Reaction carried out according to General Procedure N using 3-chloro-5-methoxyphenylboronic acid (1.82 g, 9.8 mmol, 1 equiv), *N*-methyliminodiacetic acid (1.58 g, 10.7 mmol, 1.05 equiv), and DMF (50 mL) to afford the desired product as a white crystalline solid (2.8 g, 96%).

υ_{max} (film): 1747, 1332, 1292, 1271, 1238, 1193, 1178, 1031, 1002, 835 cm^{-1}.

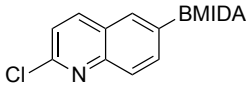
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.02 – 6.98 (m, 2H), 6.93 – 6.89 (m, 1H), 4.33 (d, *J* = 17.2 Hz, 2H), 4.14 (d, *J* = 17.2 Hz, 2H), 3.78 (s, 3H), 2.56 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.2, 159.8, 133.5, 124.1, 116.9, 114.2, 62.0, 55.4, 47.6.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 11.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{14}BClNO_5$) requires *m/z* 298.0648, found *m/z*298.0651.

(2-Chloroquinolin-6-yl)boronic acid MIDA ester, **S5**



Reaction carried out according to General Procedure N using (2-chloroquinolin-6-yl)boronic acid (300 mg, 1.45 mmol, 1 equiv), *N*-methyliminodiacetic acid (234 mg, 1.6 mmol, 1.05 equiv), and DMF (10 mL) to afford the desired product as a white solid (420 mg, 91%).

υ_{max} (film): 1768, 1743, 1446, 1178, 1141, 1029, 1001, 835 cm^{-1}.

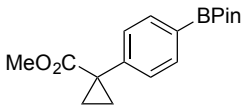
^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.49 (d, *J* = 8.5 Hz, 1H), 8.13 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.88 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 4.41 (d, *J* = 17.3 Hz, 2H), 4.20 (d, *J* = 17.3 Hz, 2H), 2.55 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.3, 150.0, 147.7, 140.3, 134.5, 132.9, 126.7, 126.2, 122.3, 62.0, 47.7.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{13}BClN_2O_4$) requires *m/z* 319.0651, found *m/z* 319.0652.

(4-(1-(Methoxycarbonyl)cyclopropyl)phenyl)boronic acid pinacol ester, **S6**



Reaction carried out according to General Procedure O using methyl 1-(4-bromophenyl)cyclopropanecarboxylate (2.50 g, 9.8 mmol, 1 equiv), bis(pinacolato)diboron (2.51 g, 9.9 mmol, 1.01 equiv), KOAc (2.88 g, 29.4 mmol, 3 equiv), Pd(dppf)Cl_2·DCM (240 mg, 0.29 mmol, 3 mol%), and 1,4-dioxane (49 mL, 0.2 M). After 18 h, the reaction mixture was subjected to the purification outlined in the General Procedure (silica gel, 3 – 8% Et_2O in petroleum ether) to afford the desired product as a white solid (1.2 g, 40%).

υ_{max} (film): 2978, 1708, 1614, 1372, 1298, 1168, 1101, 858 cm^{-1}.

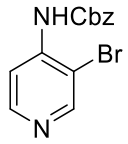
^1H NMR (CD_3CN, 400 MHz): δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 3.64 (s, 3H), 1.63 (q, *J* = 4.0 Hz, 2H), 1.36 (s, 12H), 1.22 (q, *J* = 4.0 Hz, 2H).

^{13}C NMR (CD_3CN, 126 MHz): δ 174.4, 142.1, 134.2, 129.4, 83.3, 51.9, 28.6, 24.3, 16.2.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{24}BO_4$) requires m/z 303.1762, found m/z 313.1767.

Benzyl (3-bromopyridin-4-yl)carbamate, **S7**



4-Amino-3-bromopyrdine (3.0 g, 17.3 mmol, 1 equiv) taken up in dry DCM (90 mL), purged with N_2 and cooled to 0 °C. Triethylamine (6.05 mL, 43.3 mmol, 2.5 equiv) was then added followed by the dropwise addition of benzyl chloroformate (2.7 mL, 19.1 mmol, 1.1 equiv). The reaction was stirred for 30 minutes before being allowed to warm to room temperature and was stirred for a further 16 h. The reaction mixture was quenched with aqueous sodium bicarbonate (20 mL) and then diluted with DCM (100 mL). The solution was washed with sat. aq. $NaHCO_3$ solution (200 mL). The aqueous extract was re-extracted with DCM (100 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated to yield crude product which was dry-loaded onto silica and purified by flash chromatography (10 – 30% EtOAc in petroleum ether) to afford the desired compound as a white solid. (5.1 g, 80%).

υ_{max} (solid): 3391, 3262, 1742, 1662, 1582, 1506 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.62 (s, 1 H), 8.43 (d, J = 5.5 Hz, 1 H), 8.20 (d, J = 5.5 Hz, 1 H), 7.47 – 7.39 (m, 6 H), 5.27 (s, 2 H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 151.8, 151.2, 149.1, 142.2, 134.6, 128.3, 128.2, 128.1, 112.8, 109.3, 67.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{12}BrN_2O_2$) requires *m/z* 307.0077, found *m/z* 307.0077.

6.3 Experimental procedures and characterisation data for Section 3.1

Results from Table 1

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (76 mg, 0.375 mmol, 1.5 equiv), $Pd(dppf)Cl_2 \cdot DCM$ (8.2 mg, 0.01 mmol, 4 mol%), **Base** (0.75 mmol, 3 equiv), and THF/H_2O (10:1, 1 mL) at **X** °C for 24 h.

Entry	Base (Mass)	Temperature (°C)	33:34:35:36 (%)

1	K_3PO_4 (159 mg)	50	57:13:7:0
2	Cs_2CO_3 (244 mg)	50	52:6:7:0
3	K_3PO_4 (159 mg)	90	30:0:0:70
4	Cs_2CO_3 (244 mg)	90	27:0:0:73

Results from Scheme 64/Chart 1

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), phenylboronic acid pinacol ester (69 mg, 0.339 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (7.4 mg, 0.01 mmol, 4 mol%), K_3PO_4 (144 mg, 0.678 mmol, 3 equiv), THF (0.9 mL, 0.25 M), and H_2O (**X** equiv) at 90 °C for **X** h.

0 equiv H_2O (0 mL)

Entry	Time (h)	Conversion (%)
1	1	42%
2	2	44%
3	4	45%
4	6	60%
5	12	63%
6	18	67%
7	24	61%

1 equiv H_2O (4.1 µL)

Entry	Time (h)	Conversion (%)
1	1	25%

2	2	50%
3	4	52%
4	6	68%
5	12	77%
6	18	77%
7	24	87%

3 equiv H_2O (12.2 µL)

Entry	Time (h)	Conversion (%)
1	1	42%
2	2	48%
3	4	61%
4	6	76%
5	12	87%
6	18	78%
7	24	91%

5 equiv H_2O (20.4 µL)

Entry	Time (h)	Conversion (%)
1	1	47%
2	2	53%
3	4	76%
4	6	78%

5	12	87%
6	18	82%
7	24	92%

10 equiv H_2O (40.7 µL)

Entry	Time (h)	Conversion (%)
1	1	36%
2	2	56%
3	4	61%
4	6	75%
5	12	82%
6	18	80%
7	24	90%

15 equiv H_2O (61.1 µL)

Entry	Time (h)	Conversion (%)
1	1	36%
2	2	67%
3	4	70%
4	6	81%
5	12	49%
6	18	61%
7	24	87%

20 equiv H_2O (81.4 µL)

Entry	Time (h)	Conversion (%)
1	1	42%
2	2	71%
3	4	75%
4	6	71%
5	12	54%
6	18	48%
7	24	32%

25 equiv H_2O (0.102 mL)

Entry	Time (h)	Conversion (%)
1	1	40%
2	2	56%
3	4	62%
4	6	52%
5	12	36%
6	18	44%
7	24	25%

30 equiv H_2O (0.122 mL)

Entry	Time (h)	Conversion (%)
1	1	20%

2	2	31%
3	4	39%
4	6	33%
5	12	42%
6	18	40%
7	24	34%

50 equiv H_2O (0.203 mL)

Entry	Time (h)	Conversion (%)
1	1	26%
2	2	29%
3	4	27%
4	6	22%
5	12	26%
6	18	29%
7	24	26%

75 equiv H_2O (0.305 mL)

Entry	Time (h)	Conversion (%)
1	1	15%
2	2	23%
3	4	19%
4	6	19%

5	12	25%
6	18	20%
7	24	18%

100 equiv H_2O (0.407 mL)

Entry	Time (h)	Conversion (%)
1	1	23%
2	2	22%
3	4	21%
4	6	23%
5	12	26%
6	18	24%
7	24	19%

Results from Table 2

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), phenylboronic acid pinacol ester (69 mg, 0.339 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (7.4 mg, 0.01 mmol, 4 mol%), **Base** (0.678 mmol, 3 equiv), THF (0.9 mL, 0.25 M), and H_2O (20.4 µL, 1.13 mmol, 5 equiv) at 90 °C for 24 h.

Entry	Base (Mass)	Conversion (%)
1	KTFA (114 mg)	0
2	KH_2PO_4 (102 mg)	0
3	KOAc (74 mg)	37

4	K_2HPO_4 (131 mg)	0
5	K_2CO_3 (104 mg)	51
6	K_3PO_4 (144 mg)	92
7	KOH (42 mg)	22
8	KO*t*-Bu (84mg)	23

Results from Table 3

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), phenylboronic acid pinacol ester (69 mg, 0.339 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (7.4 mg, 0.01 mmol, 4 mol%), **Base** (0.678 mmol, 3 equiv), THF (0.9 mL, 0.25 M), and H_2O (20.4 µL, 1.13 mmol, 5 equiv) at 90 °C for 24 h.

Entry	Base (Mass)	Conversion (%)
1	Li_3PO_4 (87 mg)	0
2	Na_3PO_4 (123 mg)	0
3	K_3PO_4 (144 mg)	92
4	Cs_3PO_4 (370 mg)	0
5	$Mg_3(PO_4)_2$ (305 mg)	0
6	$Ca_3(PO_4)_2$ (233mg)	0

Results from Table 5

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), phenylboronic acid pinacol ester (69 mg, 0.339 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (7.4 mg, 0.01 mmol, 4 mol%), **Base** (0.678 mmol, 3 equiv), THF (0.9 mL, 0.25M), and H_2O (20.4 µL, 1.13 mmol, 5 equiv) at 90 °C for 24 h.

Entry	Base (Mass)	H_2O equiv	Conversion (%)
1	Li_3PO_4 (87 mg)	22	0
2	Li_3PO_4 (87 mg)	50	8
3	Na_3PO_4 (123 mg)	22	16
4	Na_3PO_4 (123 mg)	50	20
5	K_3PO_4 (144 mg)	22	30
6	K_3PO_4 (144 mg)	50	26
7	Cs_3PO_4 (370 mg)	22	8
8	Cs_3PO_4 (370 mg)	50	6

Results from Table 6

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), phenylboronic acid pinacol ester (69 mg, 0.339 mmol, 1.5 equiv), **Catalyst** (0.01 mmol, 4 mol%), **Ligand** (0.02 mmol, 8 mol%), K_3PO_4 (144 mg, 0.678 mmol, 3 equiv), THF (0.9 mL, 0.25 M), and H_2O (20.4 µL, 1.13 mmol, 5 equiv) at 90 °C for 24 h.

Entry	Catalyst (Mass)	Ligand (Mass)	Conversion (%)
1	$PdCl_2$ (1.6 mg)	-	0
2	$Pd(OAc)_2$ (2.0 mg)	-	5
3	$Pd_2(dba)_3$ (8.3 mg)	-	7
4	$Pd(PPh_3)_4$ (10.4 mg)	-	36
5	$Pd(PPh_3)_2Cl_2$ (6.4 mg)	-	63
6	$Pd(dppf)Cl_2$·DCM (7.4 mg)	-	92

7	$PdCl_2$ (1.6 mg)	PPh_3 (4.7 mg)	56
8	$Pd(OAc)_2$ (2.0 mg)	PPh_3 (4.7 mg)	70
9	$PdCl_2$ (1.6 mg)	P(*t*-Bu)$_3$* (5.2 mg)	41
10	$Pd(OAc)_2$ (2.0 mg)	P(*t*-Bu)$_3$* (5.2 mg)	55
11	$PdCl_2$ (1.6 mg)	dppe (7.2 mg)	4
12	$Pd(OAc)_2$ (2.0 mg)	dppe (7.2 mg)	0
13	$PdCl_2$ (1.6 mg)	dppp (7.5 mg)	0
14	$Pd(OAc)_2$ (2.0 mg)	dppp (7.5 mg)	55
15	$PdCl_2$ (1.6 mg)	dppf (10.0 mg)	1
16	$Pd(OAc)_2$ (2.0 mg)	dppf (10.0 mg)	24
17	$PdCl_2$ (1.6 mg)	BINAP (11.3 mg)	13
18	$Pd(OAc)_2$ (2.0 mg)	BINAP (11.3 mg)	67
19	$PdCl_2$ (1.6 mg)	XantPhos (10.5 mg)	0
20	$Pd(OAc)_2$ (2.0 mg)	XantPhos (10.5 mg)	10
21	$PdCl_2$ (1.6 mg)	SPhos (7.4 mg)	14
22	$Pd(OAc)_2$ (2.0 mg)	SPhos (7.4 mg)	77
23	$PdCl_2$ (1.6 mg)	XPhos (8.6 mg)	20
24	$Pd(OAc)_2$ (2.0 mg)	XPhos (8.6 mg)	67
25	$PdCl_2$ (1.6 mg)	CyJohnPhos (6.3 mg)	4

26	$Pd(OAc)_2$ (2.0 mg)	CyJohnPhos (6.3 mg)	72
27	$PdCl_2$ (1.6 mg)	DavePhos (7.1 mg)	23
28	$Pd(OAc)_2$ (2.0 mg)	DavePhos (7.1 mg)	71

Results from Table 7

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), phenylboronic acid pinacol ester (69 mg, 0.339 mmol, 1.5 equiv), **Catalyst** (0.01 mmol, 4 mol%), **Ligand** (0.02 mmol, 8 mol%), K_3PO_4 (144 mg, 0.678 mmol, 3 equiv), THF (0.9 mL, 0.25 M), and H_2O (20.4 µL, 1.13 mmol, 5 equiv) at 90 °C for 24 h.

Entry	Catalyst	Ligand	X	Conversion (%)
1	$Pd(dppf)Cl_2$·DCM (7.4 mg)	-	I	60
2	$Pd(OAc)_2$ (2.0 mg)	SPhos (7.4 mg)	I	34
3	$Pd(dppf)Cl_2$·DCM (7.4 mg)	-	Br	92
4	$Pd(OAc)_2$ (2.0 mg)	SPhos (7.4 mg)	Br	77
5	$Pd(dppf)Cl_2$·DCM (7.4 mg)	-	OTf	61
6	$Pd(OAc)_2$ (2.0 mg)	SPhos (7.4 mg)	OTf	48
7	$Pd(dppf)Cl_2$·DCM (7.4 mg)	-	Cl	0

8	$Pd(OAc)_2$ (2.0 mg)	CyJohnPhos (6.3 mg)	Cl	68
9	$Pd(OAc)_2$ (2.0 mg)	SPhos (7.4 mg)	Cl	82

Results from Table 8

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), phenylboronic acid pinacol ester (69 mg, 0.339 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (**X** mol%), K_3PO_4 (144 mg, 0.678 mmol, 3 equiv), THF (0.9 mL, 0.25 M), and H_2O (20.4 µL, 1.13 mmol, 5 equiv) at 90 °C for 24 h.

Entry	Catalyst loading (Mass)	Conversion (%)
1	1 mol% (1.9 mg)	67
2	2 mol% (3.7 mg)	84
3	4 mol% (7.4 mg)	92

Results from Table 9

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), phenylboronic acid pinacol ester (**X** equiv), Pd(dppf)Cl_2·DCM (7.4 mg, 0.01 mmol, 4 mol%), K_3PO_4 (144 mg, 0.678 mmol, 3 equiv), THF (0.9 mL, 0.25 M), and H_2O (20.4 µL, 1.13 mmol, 5 equiv) at 90 °C for 24 h.

Entry	Equivalents of BPin (Mass)	Conversion (%)
1	1 (46 mg)	74
2	1.1 (51 mg)	77

3	1.2 (55 mg)	78
4	1.3 (60 mg)	78
5	1.4 (64 mg)	78
6	1.5 (69 mg)	92

Results from Table 10

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), phenylboronic acid pinacol ester (69 mg, 0.339 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (7.4 mg, 0.01 mmol, 4 mol%), K_3PO_4 (144 mg, 0.678 mmol, 3 equiv), **Solvent** (0.9 mL, 0.25 M), and H_2O (20.4 µL, 1.13 mmol, 5 equiv) at 90 °C for 24 h.

Entry	Solvent	Conversion (%)
1	THF	92
2	MeCN	70
3	1,4-dioxane	76
4	PhMe	10
5	DCE	60
6	EtOH	25

Results from Scheme 65/Graph 1

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), phenylboronic acid pinacol ester (69 mg, 0.339 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (7.4 mg, 0.01 mmol, 4 mol%), K_3PO_4 (144 mg, 0.678 mmol, 3 equiv), THF (0.9 mL, 0.25 M), and H_2O (20.4 µL, 1.13 mmol, 5 equiv) at **X** °C for 24 h.

Entry	Temperature (°C)	Conversion to 33 (%)	Conversion to 34 (%)
1	20	0	98
2	40	17	81
3	50	46	46
4	60	75	12
5	70	78	9
6	80	83	2
7	90	93	0
8	100	75	0

Results from Scheme 66

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), phenylboronic acid pinacol ester (69 mg, 0.339 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (7.4 mg, 0.01 mmol, 4 mol%), K_3PO_4 (144 mg, 0.678 mmol, 3 equiv), THF (0.9 mL, 0.25 M), and H_2O (20.4 µL, 1.13 mmol, 5 equiv) at r.t. for 24 h. The reaction was carried out in duplicate. After 24 h one reaction was analysed by HPLC against a caffeine standard of known concentration (97% conversion to **34**). The second reaction was heated to 90 °C for a further 24 h then analysed HPLC against a caffeine standard of known concentration (92% conversion to **33**).

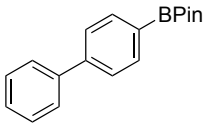
Results from Scheme 67

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), **phenyl $B(OR)_2$** (0.339 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (7.4 mg, 0.01 mmol, 4 mol%), K_3PO_4 (144 mg, 0.678 mmol, 3 equiv), THF (0.9 mL, 0.25 M), and H_2O (20.4 µL, 1.13 mmol, 5 equiv) at 90 °C for 24 h.

Entry	Phenyl $B(OR)_2$ (Mass)	Conversion (%)
1	$B(OH)_2$ (41 mg)	63
2	BCat (66 mg)	38

Characterisation of products from Figure 16

2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **33**



Prepared according to General Procedure B using 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (76 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 75% MeCN in H_2O) to afford the desired product as a beige solid (56 mg, 88%).

υ_{max} (film): 2978, 1396, 1359, 1143, 1091 cm^{-1}.

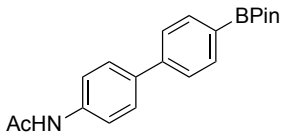
^1H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.66 – 7.63 (m, 4H), 7.45-7.49 (m, 2H), 7.38, (tt, *J* = 7.4, 1.2 Hz, 1H), 1.39 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 143.4, 140.6, 134.8, 128.3, 127.0, 126.7, 126.0, 83.3, 24.4.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{22}BO_2$) requires *m/z* 281.1707, found *m/z* 281.1709.

N-(4'-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)acetamide, **38**



Prepared according to General Procedure B using 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), *N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (98 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the general procedure (C18 silica gel, 20 – 50% MeCN in H_2O) to afford the desired product as a beige solid (72 mg, 86%).

υ_{max} (film): 3317, 2978, 2926, 1662, 1529, 1396, 1357, 1321, 1143, 1091, 819 cm^{-1}.

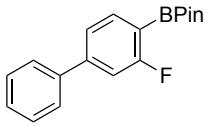
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.61 – 7.59 (m, 6H), 2.23 (s, 3H), 1.39 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.7, 142.6, 136.9, 134.8, 127.2, 125.6, 119.5, 83.3, 29.2, 24.4.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 32.0.

HRMS: exact mass calculated for $[M]^+$ ($C_{20}H_{24}BNO_3$) requires *m/z* 337.1958, found *m/z* 337.1962.

2-(3-Fluoro-[1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **39**



Prepared according to General Procedure B using 4-bromo-2-fluorophenylboronic acid MIDA ester (82 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (76 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to

the purification outlined in the General Procedure (C18 silica gel, 20 – 80% MeCN in H_2O) to afford the desired product as a brown solid (53 mg, 72%).

υ_{max} (film): 2978, 1620, 1404, 1384, 1354, 1325, 1136, 1078 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.84 (t, *J* = 7.0 Hz, 1H), 7.63 (d, *J* = 7.3 Hz, 2H), 7.41 – 7.50 (m, 5H), 7.33 – 7.30 (m, 1H), 1.42 (s, 12H).

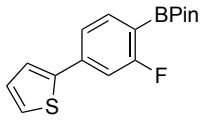
^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.7 (d, $^1J_{C\text{-}F}$ = 250.6 Hz), 146.6 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 139.6, 137.2 (d, $^3J_{C\text{-}F}$ = 8.6 Hz), 128.9, 128.2, 127.1, 122.2, 113.7 (d, $^2J_{C\text{-}F}$ = 25.0 Hz), 83.9, 24.8.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 29.9.

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 102.6 (s, 1F).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{21}BFO_2$) requires *m/z* 299.1616, found *m/z* 299.1613.

2-(2-Fluoro-4-(thiophen-2-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **40**



Prepared according to General Procedure B using 4-bromo-2-fluorophenylboronic acid MIDA ester (82 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-(thiophen-2-yl)-1,3,2-dioxaborolane (79 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 70% MeCN in H_2O) to afford the desired product as a brown solid (50 mg, 66%).

υ_{max} (film): 2978, 1618, 1413, 1386, 1354, 1325, 1134, 1070 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.76 (dd, *J* = 7.7, 6.4 Hz, 1H), 7.42 – 7.38 (m, 2H), 7.37 – 7.29 (m, 2H), 7.12 (dd, *J* = 5.1, 3.6 Hz, 1H), 1.40 (s, 12H).

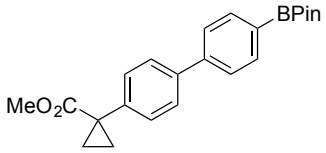
^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.6 (d, $^{1}J_{C\text{-}F}$ = 250.8 Hz), 142.8, 139.4 (d, $^{3}J_{C\text{-}F}$ = 9.4 Hz), 137.4 (d, $^{3}J_{C\text{-}F}$ = 9.4 Hz), 128.2, 126.0, 124.3, 120.9, 112.3 (d, $^{2}J_{C\text{-}F}$ = 25.9 Hz), 83.9, 24.8.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.2.

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 102.6 (s, 1F).

HRMS: exact mass calculated for $[M]^+$ ($C_{16}H_{18}BFO_2S$) requires *m/z* 303.1138, found *m/z* 303.1138.

Methyl 1-(4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylate, **41**



Prepared according to General Procedure B using 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), methyl 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)cyclopropane-1-carboxylate (113 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 60% MeCN in H_2O) to afford the desired product as a beige solid (79 mg, 83%).

υ_{max} (film): 1724, 1359, 1298, 1166, 1143, 1093 cm^{-1}.

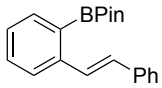
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.61 (dd, *J* = 13.8, 8.2 Hz, 4H), 7.44 (d, *J* = 8.2 Hz, 2H), 3.68 (s, 3H), 1.66 (q, *J* = 3.9 Hz, 2H), 1.39 (s, 12H), 1.25 (q, *J* = 3.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 175.0, 143.4, 139.9, 138.9, 135.2, 130.9, 127.0, 126.4, 83.8, 52.4, 29.7, 28.7, 24.9, 16.8.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{23}H_{28}BO_4$) requires *m/z* 379.2075, found *m/z* 379.2074.

trans-4,4,5,5-Tetramethyl-2-(2-styrylphenyl)-1,3,2-dioxaborolane, **42**



Prepared according to General Procedure B using 2-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), *trans*-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (86 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 75% MeCN in H_2O) to afford the desired product as a brown solid (54 mg, 70%).

υ_{max} (film): 2978, 2360, 1373, 1346, 1313, 1143, 763 cm^{-1}.

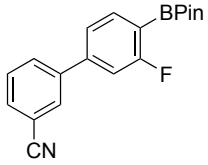
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (d, *J* = 16.3 Hz, 1H), 7.85 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.58 – 7.56 (m, 2H), 7.48 – 7.44 (m, 1H), 7.41 – 7.37 (m, 2H), 7.30 – 7.26 (m, 2H), 7.06 (d, *J* = 16.3 Hz, 1H), 1.42 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 143.5, 138.1, 136.2, 131.1, 129.9, 129.3, 128.7, 127.3, 126.6, 124.5, 83.8, 25.0.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{24}BO_2$) requires *m/z* 307.1864, found *m/z* 307.1863.

3'-Fluoro-4'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-3-carbonitrile, **43**



Prepared according to general procedure B using 4-bromo-2-fluorophenylboronic acid MIDA ester (82 mg, 0.25 mmol, 1 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (86 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 75% MeCN in H_2O) to afford the desired product as a brown solid (43 mg, 54%).

υ_{max} (film): 2980, 2927, 2229, 1622, 1390, 1354, 1330, 1138, 1080 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.88 – 7.81 (m, 3H), 7.68 – 7.66 (m, 1H), 7.57 (t, J = 7.8 Hz, 1H), 7.36 (dd, J = 7.8, 1.6 Hz, 1H), 7.27 – 7.25 (m, 1H), 1.39 (s, 12H).

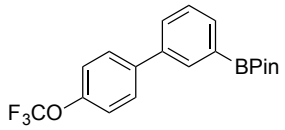
^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.6 (d, $^1J_{C\text{-}F}$ = 251.8 Hz), 143.9 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 140.9, 137.7 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 131.5, 131.4, 130.7, 129.8, 122.2, 118.5, 113.9, 113.5 (d, $^2J_{C\text{-}F}$ = 47.8 Hz), 84.1, 24.8.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.9.

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 101.8 (s, 1F).

HRMS: exact mass calculated for $[M]^+$ ($C_{19}H_{19}BFNO_2$) requires *m/z* 322.1520, found *m/z* 322.1524.

4,4,5,5-Tetramethyl-2-(4'-(trifluoromethoxy)-[1,1'-biphenyl]-3-yl)-1,3,2-dioxaborolane, **44**



Prepared according to General Procedure B using 3-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-(4-(trifluoromethoxy)phenyl)-1,3,2-dioxaborolane (108 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the

reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 60% MeCN in H_2O) to afford the desired product as a brown solid (73 mg, 80%).

υ_{max} (film): 1359, 1255, 1213, 1165, 1143 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.84 (dt, *J* = 7.3, 1.1 Hz, 1H), 7.69 – 7.65 (m, 3H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.31 – 7.28 (m, 3H), 1.39 (s, 12H).

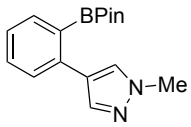
^{13}C NMR ($CDCl_3$, 126 MHz): δ 140.0, 139.2, 136.5, 134.0, 133.5, 129.9, 128.6, 128.3, 121.1, 119.3, 84.0, 24.9.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.3.

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 57.8 (s, 3F).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{21}BF_3O_3$) requires *m/z* 365.1530, found *m/z* 365.1530.

1-Methyl-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole, **45**



Prepared according to General Procedure B using 2-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (78 mg, 0.375 mmol, 1.5 equiv), $Pd(dppf)Cl_2$·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 10 – 40% MeCN in H_2O) to afford the desired product as a colourless oil (48 mg, 69%).

υ_{max} (film): 2978, 2926, 1381, 1350, 1317, 1143, 858 cm^{-1}.

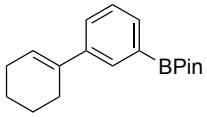
^1H NMR ($CDCl_3$, 400 MHz): δ 7.81 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.49 – 7.41 (m, 3H), 7.28 (dd, *J* = 7.3, 1.2 Hz, 1H), 6.19 (s, 1H), 3.67 (s, 3H), 1.19 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 137.4, 134.8, 130.4, 130.0, 128.1, 106.7, 83.8, 36.7, 24.6.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{22}BN_2O_2$) requires *m/z* 285.1769, found *m/z* 285.1768.

4,4,5,5-Tetramethyl-2-(2',3',4',5'-tetrahydro-[1,1'-biphenyl]-3-yl)-1,3,2-dioxaborolane, **46**



Prepared according to General Procedure B using 3-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 2-(cyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (108 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 90% MeCN in H_2O) to afford the desired product as a beige solid (60 mg, 85%).

υ_{max} (film): 2976, 2927, 1356, 1311, 1271, 1143 cm^{-1}.

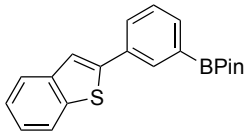
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (br. s, 1H), 7.69 – 7.67 (m, 1H), 7.50 – 7.47 (m, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 6.16 – 6.13 (m, 1H), 2.48 – 2.43 (m, 2H), 2.25 – 2.20 (m, 2H), 1.77-1.83 (m, 2H), 1.71 – 1.65 (m, 2H), 1.37 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 142.1, 136.7, 132.9, 131.4, 128.0, 127.6, 124.9, 83.7, 27.5, 25.8, 24.9, 23.1, 22.2.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{26}BO_2$) requires *m/z* 285.2020, found *m/z* 285.2020.

2-(3-(Benzo[b]thiophen-2-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **47**



Prepared according to General Procedure B using 3-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 2-(benzo[b]thiophen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (98 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 80% MeCN in H_2O) to afford the desired product as a brown solid (74 mg, 88%).

υ_{max} (film): 2976, 1355, 1317, 1141 cm^{-1}.

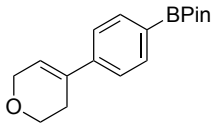
^1H NMR ($CDCl_3$, 400 MHz): δ 8.20 (br. s, 1H), 7.87 – 7.79 (m, 4H), 7.64 (s, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.40 – 7.31 (m, 2H), 1.40 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.3, 140.7, 139.6, 134.6, 133.7, 132.7, 129.3, 128.3, 124.4, 124.2, 123.5, 122.3, 119.6, 84.0, 24.9.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{22}BO_2S$) requires *m/z* 337.1428, found *m/z* 337.1427.

2-(4-(3,6-Dihydro-2H-pyran-4-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **48**



Prepared according to General Procedure B using 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 2-(3,6-dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (79 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture

was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 60% MeCN in H_2O) to afford the desired product as a brown solid (60 mg, 84%).

υ_{max} (film): 2976, 2926, 1606, 1398, 1357, 1323, 1143, 1091 cm^{-1}.

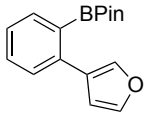
^1H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H), 6.22 (tt, *J* = 2.8, 1.5 Hz, 1H), 4.36 (q, *J* = 2.8 Hz, 2H), 3.96 (t, *J* = 5.5 Hz, 2H), 2.54-2.58 (m, 2H), 1.37 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 142.9, 134.9, 134.2, 124.0, 123.3, 83.8, 65.9, 64.4, 27.1, 24.9.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{24}BO_3$) requires *m/z* 287.1813, found *m/z* 287.1810.

2-(2-(Furan-3-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **49**



Prepared according to General Procedure B using 2-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 2-(furan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (73 mg, 0.375 mmol, 1.5 equiv), $Pd(dppf)Cl_2$·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 60% MeCN in H_2O) to afford the desired product as a brown liquid (47 mg, 70%).

υ_{max} (film): 2978, 1483, 1438, 1348, 1311, 1143, 873, 759 cm^{-1}.

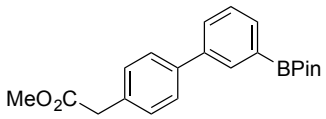
^1H NMR ($CDCl_3$, 400 MHz): δ 7.71 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.60 (dd, *J* = 1.5, 0.9 Hz, 1H), 7.44 (t, *J* = 1.7 Hz, 1H), 7.42 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.36 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.30 (td, *J* = 7.4, 1.3 Hz, 1H), 6.60 (dd, *J* = 1.8, 0.8 Hz, 1H), 1.31 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 142.1, 140.0, 137.7, 134.8, 130.3, 128.9, 127.4, 126.3, 112.1, 83.8, 24.7.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{20}BO_3$) requires *m/z* 271.1500, found *m/z* 271.1498.

Methyl 2-(3'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)acetate, **50**



Prepared according to General Procedure B using 3-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (104 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 50% MeCN in H_2O) to afford the desired product as an orange/brown oil (71 mg, 80%).

υ_{max} (film): 2978, 1737, 1431, 1355, 1317, 1257, 1143 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (br. s, 1H), 7.81 (dt, *J* = 7.3, 1.1 Hz, 1H), 7.70 (ddd, *J* = 7.8, 2.0, 1.3 Hz, 1H), 7.63 – 7.60 (m, 2H), 7.49 – 7.45 (m, 1H), 7.38 – 7.36 (m, 2H), 3.74 (s, 3H), 3.70 (s, 2H), 1.39 (s, 12H).

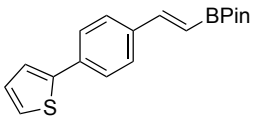
^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.0, 140.1, 135.1, 133.7, 133.5, 132.9, 129.9, 129.6, 128.7, 128.2, 127.5, 83.9, 52.1, 40.9, 24.9.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{26}BO_4$) requires *m/z* 353.1919, found *m/z* 353.1924.

Characterisation of product from Figure 17

trans-4,4,5,5-Tetramethyl-2-(4-(thiophen-2-yl)styryl)-1,3,2-dioxaborolane, **51**



Prepared according to General Procedure B using *trans*-2-(4-bromophenyl)vinylboronic acid MIDA ester (85 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-(thiophen-2-yl)-1,3,2-dioxaborolane (79 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 75% MeCN in H_2O) to afford the desired product as a beige solid (62 mg, 79%).

υ_{max} (film): 2978, 2358, 1622, 1357, 1323, 1213, 1143, 808 cm^{-1}.

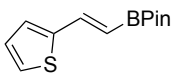
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.63 – 7.51 (m, 4H), 7.42 (d, *J* = 18.4 Hz, 1H), 7.36 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.31 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.11 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.20 (d, *J* = 18.4 Hz, 1H), 1.35 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 148.8, 144.0, 136.6, 134.8, 128.1, 127.6, 126.0, 125.1, 123.3, 83.4, 24.8.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{21}BF_3O_2$) requires *m/z* 361.1581, found *m/z* 361.1577.

trans-4,4,5,5-Tetramethyl-2-(2-(thiophen-2-yl)vinyl)-1,3,2-dioxaborolane, **52**



Prepared according to General Procedure B using *trans*-2-iodovinylboronic acid MIDA ester (77 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-(thiophen-2-yl)-1,3,2-dioxaborolane (79 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg,

0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to purification *via* reverse phase preparative HPLC (20 – 95% MeCN in H_2O) to afford the desired product as a colourless liquid (40 mg, 68%).

υ_{max} (film): 2978, 2926, 2854, 1616, 1371, 1325, 1143, 848 cm^{-1}.

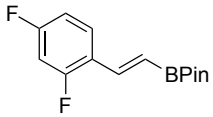
^1H NMR ($CDCl_3$, 400 MHz): δ 7.48 (d, J = 18.1 Hz, 1H), 7.25 (d, *J* = 5.0 Hz, 1H), 7.09 (d, *J* = 3.1 Hz, 1H), 6.99 (dd, *J* = 5.0 Hz, 1H), 5.92 (d, *J* = 18.1 Hz, 1H), 1.31 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 143.9, 141.8, 127.7, 127.6, 126.3, 83.4, 24.8.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{17}BO_2S$) requires *m/z* 237.1115, found *m/z* 237.1114.

trans-2-(2,4-Difluorostyryl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **53**



Prepared according to General Procedure B using *trans*-2-bromovinylboronic acid MIDA ester (65 mg, 0.25 mmol, 1 equiv), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (90 mg, 0.375 mmol, 1.5 equiv), $Pd(dppf)Cl_2 \cdot DCM$ (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to purification *via* reverse phase preparative HPLC (20 – 95% MeCN in H_2O) to afford the desired product as a yellow oil (54 mg, 81%).

υ_{max} (film): 2980, 1627, 1500, 1350, 1328, 1141, 968, 850 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.57 – 7.48 (m, 2H), 6.89 – 6.84 (m, 1H), 6.83 – 6.77 (m, 1H), 6.17 (d, *J* = 18.6 Hz, 1H), 1.32 (s, 12H).

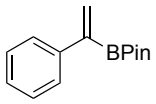
^{13}C NMR ($CDCl_3$, 126 MHz): δ 163.2 (dd, $^{1}J_{C\text{-}F}$ = 230.6, $^{3}J_{C\text{-}F}$ = 12.0 Hz), 160.7 (dd, $^{1}J_{C\text{-}F}$ = 260.6, $^{3}J_{C\text{-}F}$ = 12.0 Hz), 140.3 (d, $^{3}J_{C\text{-}F}$ = 2.6 Hz), 128.4 (dd, $^{2}J_{C\text{-}F}$ = 9.6, $^{3}J_{C\text{-}F}$ = 4.9 Hz), 121.9 (dd, $^{2}J_{C\text{-}F}$ = 11.9, $^{3}J_{C\text{-}F}$ = 3.8 Hz), 111.6 (dd, $^{2}J_{C\text{-}F}$ = 21.6, $^{3}J_{C\text{-}F}$ = 3.4 Hz), 104.1 (t, $^{3}J_{C\text{-}F}$ = 25.6 Hz), 83.5, 24.8.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.2.

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 111.3 (d, $J_{F\text{-}F}$ = 7.5 Hz, 1F), – 113.2 (d, $J_{F\text{-}F}$ = 7.5 Hz, 1F).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{18}BF_2O_2$) requires *m/z* 267.1362, found *m/z* 267.1363.

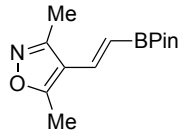
4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane, **54**



Prepared according to General Procedure B using (1-bromovinyl)boronic acid MIDA ester (65 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (76 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to purification *via* reverse phase preparative HPLC (20 – 95% MeCN in H_2O) to afford the desired product as a mixture of regioisomers cloudy gum (30 mg, 52%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 – 7.83 (m, 2H), 7.53 – 7.47 (m, 2H), 7.41 – 7.33 (m, 3H), 6.22 – 6.08 (m, 1H), 1.38 (s, 12H), 1.35 (s, 5H).

trans-3,5-Dimethyl-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2 yl)vinyl)isoxazole, **55**



Prepared according to General Procedure B using *trans*-2-iodovinylboronic acid MIDA ester (65 mg, 0.25 mmol, 1 equiv), 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (84 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to purification *via* column chromatography on silica (10 – 20% EtOAc in petroleum ether) to afford the desired product as a beige solid (31 mg, 50%).

υ_{max} (film): 2978, 1641, 1344, 1325, 1269, 1141, 968, 850 cm^{-1}.

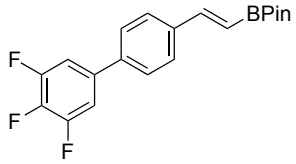
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11 (d, *J* = 18.8 Hz, 1H), 5.83 (d, *J* = 18.8 Hz, 1H), 2.47 (s, 3H), 2.37 (s, 3H), 1.32 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.5, 158.5, 137.3, 113.9, 83.5, 24.8, 11.8, 11.6.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 29.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{21}BNO_3$) requires *m/z* 250.1609, found *m/z* 250.1605.

trans-4,4,5,5-Tetramethyl-2-(2-(3',4',5'-trifluoro-[1,1'-biphenyl]-4-yl)vinyl)-1,3,2-dioxaborolane, **56**



Prepared according to General Procedure B using *trans*-2-(4-bromophenyl)vinylboronic acid MIDA ester (85 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-(3,4,5-trifluorophenyl)-1,3,2-dioxaborolane (97 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 70% MeCN in H_2O) to afford the desired product as a brown liquid (64 mg, 71%).

υ_{max} (film): 2981, 1618, 1537, 1508, 1381, 1358, 1323, 1247, 1141, 1043, 806 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 – 7.48 (m, 4H), 7.44 (d, *J* = 18.4 Hz, 1H), 7.22 (dd, *J* = 8.9, 6.5 Hz, 2H), 6.25 (d, *J* = 18.4 Hz, 1H), 1.35 (s, 12H).

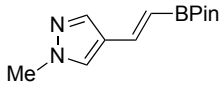
^{13}C NMR ($CDCl_3$, 126 MHz): δ 151.5 (ddd, $^{1}J_{C\text{-}F}$ = 249.4, $^{2}J_{C\text{-}F}$ = 10.0, $^{3}J_{C\text{-}F}$ = 3.9 Hz,), 148.3, 139.3 (dt, $^{1}J_{C\text{-}F}$ = 252.3, $^{2}J_{C\text{-}F}$ = 15.1 Hz,), 138.4, 137.6, 136.7 (dd, $^{2}J_{C\text{-}F}$ = 12.3, $^{3}J_{C\text{-}F}$ = 7.7 Hz,), 127.7, 127.0, 110.9 (dd, $^{2}J_{C\text{-}F}$ = 15.9, $^{3}J_{C\text{-}F}$ = 5.9 Hz), 83.5, 24.8.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 30.7.

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 134.1 (d, $J_{F\text{-}F}$ = 20.5 Hz, 2F), – 162.4 (t, $J_{F\text{-}F}$ = 20.5 Hz, 1F).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{21}BF_3O_2$) requires *m/z* 361.1581, found *m/z* 361.1577.

trans-1-Methyl-4-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1*H*-pyrazole, **57**



Prepared according to General Procedure B using *trans*-2-bromovinylboronic acid MIDA ester (65 mg, 0.25 mmol, 1 equiv), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (78 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to purification *via* column chromatography on silica (10 – 40% EtOAc in petroleum ether) to afford the desired product as a beige solid (41 mg, 70%).

υ_{max} (film): 2978, 2927, 1626, 1373, 1344, 1325, 1143, 850 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, *J* = 1.9 Hz, 1H), 7.25 (d, *J* = 18.3 Hz, 1H), 6.50 (d, *J* = 1.9 Hz, 1H), 6.07 (d, *J* = 18.3 Hz, 1H), 3.94 (s, 3H), 1.33 (s, 12H).

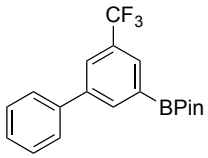
^{13}C NMR ($CDCl_3$, 126 MHz): δ 141.3, 138.4, 134.5, 104.4, 83.6, 36.8, 24.8.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 29.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{20}BN_2O_2$) requires *m/z* 235.1612, found *m/z* 235.1610.

Characterisation of products from Figure 18

2-(3-Bromo-5-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **59**



Prepared according to General Procedure C using 3-bromo-5-(trifluoromethyl)phenylboronic acid MIDA ester (88 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (76 mg, 0.375 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the general procedure (20 – 75% MeCN in H_2O) to afford the desired product as a yellow gum (53 mg, 60%).

υ_{max} (film): 2980, 2929, 1600, 1471 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.22 (s, 1H), 8.06 (s, 1H), 7.93 (s, 1H), 7.69 – 7.62 (m, 2H), 7.53 – 7.46 (m, 2H), 7.42 (d, J = 7.3 Hz, 1H), 1.40 (s, 12H).

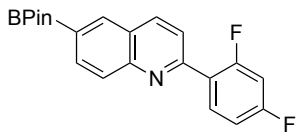
^{13}C NMR ($CDCl_3$, 126 MHz): δ 141.3, 139.7, 136.7, 130.1 (d, $^3J_{C\text{-}F}$ = 3.4 Hz), 128.9, 127.9, 127.3, 126.4 (d, $^3J_{C\text{-}F}$ = 3.4 Hz), 84.4, 24.9. CF_3 carbon and carbon bearing CF_3 not observed.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.0.

^{19}F NMR ($CDCl_3$, 376 MHz): δ –62.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{21}BF_3O_2$) requires *m/z* 349.1581, found *m/z* 349.1581.

2-(2,4-Difluorophenyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolone, **60**



Prepared according to General Procedure C using (2-chloroquinolin-6-yl)boronic acid MIDA ester (80 mg, 0.25 mmol, 1 equiv), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (90 mg, 0.375 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 10 – 60% MeCN in H_2O) to afford the desired product as an off-white solid (29 mg, 32%).

υ_{max} (film): 2978, 2358, 1600, 1471, 1357, 1300, 1261, 1141, 1103, 850 cm^{-1}.

^1H NMR (CD_3CN, 400 MHz): δ 8.41 (d, J = 8.7 Hz, 1H), 8.36 (s, 1H), 8.20 – 8.02 (m, 3H), 7.91 (dd, J = 8.7, 2.7 Hz, 1H), 7.19 – 7.10 (m, 2H), 1.40 (s, 12H).

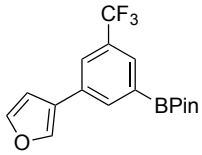
^{13}C NMR (CD_3CN, 126 MHz): δ 170.1 (d, $^2J_{C\text{-}F}$ = 12.0 Hz), 167.6 (t, $^2J_{C\text{-}F}$ = 11.8 Hz), 165.0 (d, $^2J_{C\text{-}F}$ = 12.8 Hz), 159.2, 154.8, 142.5, 140.9, 139.5, 138.2, 133.9, 133.4, 131.9, 129.5 (dd, $^2J_{C\text{-}F}$ = 12.2, $^3J_{C\text{-}F}$ = 3.7 Hz), 127.4, 117.3 (dd, $^2J_{C\text{-}F}$ = 21.3, $^3J_{C\text{-}F}$ = 3.3 Hz), 109.7 (t, $^2J_{C\text{-}F}$ = 26.7 Hz), 89.5, 29.6.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 36.5.

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 104.9 (d, $J_{F\text{-}F}$ = 8.7 Hz, 1F), – 108.4 (d, $J_{F\text{-}F}$ = 8.7 Hz, 1F).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{21}BF_2NO_2$) requires *m/z* 368.1628, found *m/z* 368.1629.

2-(3-(Furan-3-yl)-5-(trifluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **61**



Prepared according to General Procedure C using 3-bromo-5-(trifluoromethyl)phenylboronic acid MIDA ester (88 mg, 0.25 mmol, 1 equiv), 2-(furan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (73 mg, 0.375 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 10 – 75% MeCN in H_2O) to afford the desired product as a brown gum (45 mg, 53%).

υ_{max} (film): 2980, 2932, 1304, 1279, 1166, 1125, 871 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.09 (s, 1H), 7.97 (s, 1H), 7.85 – 7.84 (m, 1H), 7.81 (br. s, 1H), 7.52 (t, J = 1.7 Hz, 1H), 6.79 (dd, J = 1.7, 0.9 Hz, 1H), 1.40 (s, 12H).

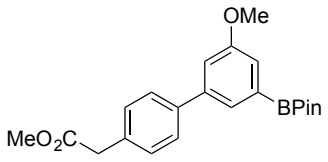
^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.0, 139.1, 135.2, 132.6, 129.8 (d, $^3J_{C\text{-}F}$ = 4.0 Hz), 125.3, 125.0 (d, $^3J_{C\text{-}F}$ = 4.0 Hz), 108.7, 103.6, 84.4, 24.9. CF_3 carbon and carbon bearing CF_3 not observed.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.2.

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 62.7 (s, 3F).

HRMS: exact mass calculated for $[M]^+$ ($C_{17}H_{18}BF_3O_3$) requires *m/z* 337.1334, found *m/z* 337.1332.

Methyl 2-(3'-methoxy-5'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1'-biphenyl]-4-yl)acetate, **62**



Prepared according to General Procedure C using (3-chloro-5-methoxyphenyl)boronic acid MIDA ester (74 mg, 0.25 mmol, 1 equiv), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (104 mg, 0.375 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M), and H_2O (22.5

μL, 1.25 mmol, 5 equiv). After 24 h, the reaction mixture was subjected to the purification outlined in the General Procedure (C18 silica gel, 20 – 60% MeCN in H_2O) to afford the desired product as an off-white solid (60 mg, 63%).

υ_{max} (film): 2978, 2358, 1373, 1575, 1452, 1369 cm^{-1}.

^1H NMR (CD_3CN, 400 MHz): δ 7.66 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.33 (dd, *J* = 2.6, 0.7 Hz, 1H), 7.24 (dd, *J* = 2.6, 1.7 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 3H), 3.69 (s, 2H), 1.38 (s, 12H).

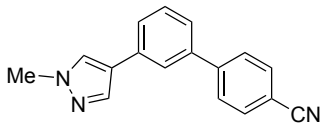
^{13}C NMR (CD_3CN, 126 MHz): δ 172.0, 159.5, 141.7, 139.8, 133.1, 129.5, 127.5, 126.1, 117.5, 116.6,83.9, 55.4, 52.1, 40.9, 24.9.

^{11}B NMR (CD_3CN, 128 MHz): δ 31.7.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{22}H_{27}BO_5Na$) requires *m/z* 405.1844, found *m/z* 405.1846.

Characterisation of products from Scheme 70

3'-(1-Methyl-1*H*-pyrazol-4-yl)-[1,1'-biphenyl]-4-carbonitrile, **70**



Prepared according to General Procedure D using 3-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (78 mg, 0.375 mmol, 1.5 equiv), $Pd(dppf)Cl_2 \cdot DCM$ (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), THF (1 mL, 0.25 M), H_2O (90 μL, 5 mmol, 20 equiv), and 4-bromobenzonitrile (68 mg, 0.375 mmol, 1.5 equiv). After 48 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a white solid (40 mg, 63%).

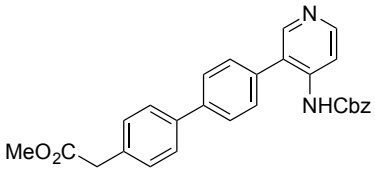
υ_{max} (film): 2226, 1452, 1369, 1174, 1143, 1107, 844, 783, 700 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.76 (dd, *J* =22.8, 8.4 Hz, 4H), 7.69 – 7.49 (m, 5H), 6.43 (s, 1H), 3.98 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.7, 140.0, 132.8, 131.1, 129.6, 128.9, 127.8, 127.7, 127.6, 118.7, 111.6, 106.6, 37.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{14}N_3$) requires *m/z* 260.1182, found *m/z* 260.1183.

Methyl 2-(4'-(4-(((benzyloxy)carbonyl)amino)pyridin-3-yl)-[1,1'-biphenyl]-4-yl)acetate, **71**



Prepared according to General Procedure D using 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (104 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), THF (1 mL, 0.25 M), H_2O (90 μL, 5 mmol, 20 equiv), and benzyl (3-bromopyridin-4-yl)carbamate (115 mg, 0.375 mmol, 1.5 equiv). After 48 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as a white solid (55 mg, 49%).

υ_{max} (film): 1732, 1498, 1193, 1155, 1139, 1049 cm^{-1}.

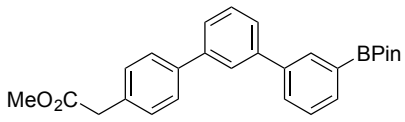
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.85 (d, *J* = 6.8 Hz, 1H), 8.68 (d, *J* = 6.8 Hz, 1H), 8.64 (s, 1H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.54 (s, 1H), 7.46 – 7.39 (m, 8H), 5.26 (s, 2H), 3.75 (s, 3H), 3.72 (s, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.9, 161.5, 161.1, 151.6, 150.2, 143.4, 141.5, 138.2, 134.3, 134.1, 130.1, 129.4, 129.2, 129.1, 129.0, 128.9, 128.4, 127.6, 127.4, 113.3,69.1, 52.2, 40.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{28}H_{25}N_2O_4$) requires *m/z* 453.1809, found *m/z* 453.1804.

Characterisation of products from Scheme 71

Methyl 2-(3"-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1':3',1"-terphenyl]-4-yl)acetate, **72**



Prepared according to General Procedure D using 3-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (104 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), THF (1 mL, 0.25 M), H_2O (90 µL, 5 mmol, 20 equiv), and 3-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), After 48 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as an off-white solid (52 mg, 49%).

υ_{max} (film): 2924, 1735, 1431, 1357, 1257, 1143, 707 cm^{-1}.

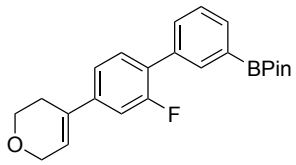
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (s, 1H), 7.81 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.71 – 7.68 (m, 2H), 7.62 (d, *J* = 8.3 Hz, 3H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.39 – 7.36 (m, 3H), 3.74 (s, 3H), 3.70 (s, 2H), 1.39 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.0, 140.1, 133.7, 133.4, 132.9, 132.4, 129.9, 129.8, 129.7, 129.6, 128.8, 127.5, 127.4, 127.2, 126.0, 83.9, 52.1, 40.9, 24.9.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{27}H_{30}BO_4$) requires *m/z* 429.2232, found *m/z* 429.2227.

2-(4'-(3,6-Dihydro-2*H*-pyran-4-yl)-2'-fluoro-[1,1'-biphenyl]-3-yl)-4,4,5,5-tetramethyl-1,3,2- dioxaborolane, **73**



Prepared according to General Procedure D using 4-bromo-2-fluorophenylboronic acid MIDA ester (82 mg, 0.25 mmol, 1 equiv), 2-(3,6-dihydro-2*H*-pyran-4-yl)-4,4,5,5- tetramethyl-1,3,2-dioxaborolane (79 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), THF (1 mL, 0.25 M), H_2O (90 μL, 5 mmol, 20 equiv), and 3-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), After 48 h, the reaction mixture was subjected to the purification outlined in the General Procedure to afford the desired product as an brown oil (67 mg, 70%).

υ_{max} (film): 2978, 2927, 1355, 1141, 1130, 906, 729, 705, 677 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (d, *J* = 1.0 Hz, 1H), 7.82 (dt, *J* = 7.3, 1.1 Hz, 1H), 7.67 (ddd, *J* = 7.7, 3.2, 1.8 Hz, 1H), 7.45 (td, *J* = 7.9, 3.0 Hz, 2H), 7.24 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.17 (dd, *J* = 12.3, 1.7 Hz, 1H), 6.23 – 6.19 (m, 1H), 4.38 (dd, *J* = 5.5, 2.7 Hz, 2H), 3.99 (t, *J* = 5.5 Hz, 2H), 2.57 – 2.52 (m, 1H), 1.36 (s, 12H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.9 (d, $^1J_{C\text{-}F}$ = 247.4 Hz), 141.2 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 135.1, 134.9, 134.1, 132.9, 131.9 (d, $^3J_{C\text{-}F}$ = 3.3 Hz), 130.7, 127.8, 127.7 (d, $^2J_{C\text{-}F}$ = 13.8 Hz), 123.1, 120.4 (d, $^3J_{C\text{-}F}$ = 3.3 Hz), 112.2 (d, $^2J_{C\text{-}F}$ = 24.1 Hz), 84.0, 65.7, 64.4, 27.0, 24.9.

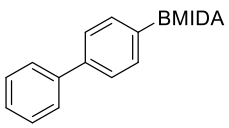
^{11}B NMR ($CDCl_3$, 128 MHz): δ 31.9.

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 118.24 (s, 1F).

HRMS: exact mass calculated for [M+NH_4]+ ($C_{23}H_{29}BFNO_3$) requires *m/z* 398.2298, found *m/z* 398.2298.

Characterisation of products from Figure 19

[1,1'-Biphenyl]-4-ylboronic acid MIDA ester, **35**



Prepared according to General Procedure E using 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane

(76 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a beige solid (65 mg, 85%).

υ_{max} (film): 2957, 2922, 1755, 1743, 1460, 1209, 1041, 983, 829, 761 cm^{-1}.

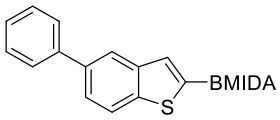
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 – 7.65 (m, 4H), 7.53 (d, 2H, *J* = 8.1 Hz), 7.47 (t, 2H, *J* = 7.9 Hz), 7.39 – 7.35 (m, 1H), 4.65 (d, 2H, *J* = 17.6 Hz), 4.14 (d, 2H, *J* = 17.8 Hz), 2.55 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.4, 140.5, 140.1, 133.1, 128.9, 127.5, 126.6, 125.9, 61.8, 47.6.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 12.30.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{17}BNO_4$) requires *m/z* 310.1245, found *m/z* 310.1245.

(5-Phenylbenzo[b]thiophen-2-yl)boronic acid MIDA ester, **74**



Prepared according to General Procedure E using (5-bromobenzo[b]thiophen-2-yl)boronic acid MIDA ester (92 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (76 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a brown solid (60 mg, 66%).

υ_{max} (film): 1766, 1276, 1031, 808, 758, 698 cm^{-1}.

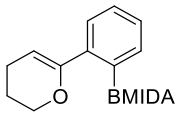
^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.15 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.66 – 7.61 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 1H), 4.43 (d, *J* = 17.2 Hz, 2H), 4.21 (d, *J* = 17.2 Hz, 2H), 2.70 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 168.9, 141.5, 141.1, 140.3, 136.5, 130.3, 128.9, 127.2, 126.9, 123.5, 122.8, 121.6, 61.6, 47.5.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 9.99.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{17}BNO_4S$) requires *m/z* 366.0966, found *m/z* 366.0965.

(2-(3,4-Dihydro-2H-pyran-6-yl)phenyl)boronic acid MIDA ester, **75**



Prepared according to General Procedure E using 2-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 2-(3,4-dihydro-2H-pyran-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (79 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a brown solid (68 mg, 86%).

υ_{max} (film): 1759, 1741, 1454, 1303, 1201, 1072, 1028, 1002, 860, 750 cm^{-1}.

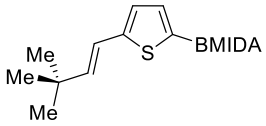
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.42 – 7.40 (m, 1H), 7.33 – 7.31 (m, 2H), 7.25 – 7.23 (m, 1H), 4.76 (t, *J* = 3.8 Hz, 1H), 4.35 (d, *J* = 17.4 Hz, 2H), 4.11 (d, *J* = 17.3 Hz, 2H), 4.01 – 3.99 (m, 2H), 2.61 (s, 3H), 2.09 – 2.05 (m, 2H), 1.83 – 1.77 (m, 2H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.5, 155.4, 142.0, 134.0, 129.9, 128.7, 127.2, 98.9, 65.9, 63.5, 49.3, 20.8, 20.2.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 12.09.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}BNO_5$) requires *m/z* 316.1351, found *m/z* 316.1353.

Trans-(5-(3,3-dimethylbut-1-en-1-yl)thiophen-2-yl)boronic acid MIDA ester, **76**



Prepared according to General Procedure E using 5-bromo-2-thiophenylboronic acid MIDA ester (80 mg, 0.25 mmol, 1 equiv), *trans*-2-(3,3-dimethylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (79 mg, 0.375 mmol, 1.5 equiv), $Pd(dppf)Cl_2 \cdot DCM$ (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a beige solid (55 mg, 68%).

υ_{max} (film): 2956, 1770, 1454, 1274, 1165, 1029, 958 cm^{-1}.

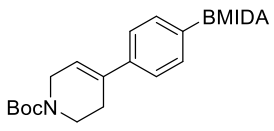
^1H NMR (DMSO-d_6, 400 MHz): δ 7.04 (dd, *J* = 15.3, 3.3 Hz, 2H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.09 (d, *J* = 16.1 Hz, 1H), 4.33 (d, *J* = 17.2 Hz, 2H), 4.10 (d, *J* = 17.2 Hz, 2H), 2.60 (s, 3H), 1.07 (s, 9H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 168.8, 146.3, 141.5, 133.3, 126.4, 118.3, 61.3, 47.3, 33.1, 29.3.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 9.83.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}BNO_4S$) requires *m/z* 322.1279, found *m/z* 322.1281.

(4-(1-(*tert*-Butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)boronic acid MIDA ester, **77**



Prepared according to General Procedure E using 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (116 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as an off white solid (82 mg, 80%).

υ_{max} (film): 1766, 1693, 1283, 1035, 989 cm^{-1}.

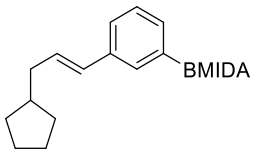
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.44 – 7.39 (m, 4H), 6.18 (br. s, 1H), 4.32 (d, *J* = 17.2 Hz, 2H), 4.10 (d, *J* = 17.1 Hz, 2H), 4.00 (br.s, 2H), 3.54 (t, *J* = 5.6 Hz, 2H), 1.43 (s, 9H). CH_2 signal obscured by solvent signal.

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.3, 153.9, 140.3, 134.4, 132.5, 123.9, 121.0, 78.8, 61.7, 47.5, 28.1, 26.5.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.66.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{21}H_{26}BN_2O_6$) requires *m/z* 413.1879, found *m/z* 413.1873.

Trans-(3-(3-cyclopentylprop-1-en-1-yl)phenyl)boronic acid MIDA ester, **78**



Prepared according to General Procedure E using 3-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), *trans*-2-(3-cyclopentylprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (89 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a beige solid (73 mg, 86%).

υ_{max} (film): 2947, 2864, 1764, 1745, 1298, 1247, 1026, 1006, 964 cm^{-1}.

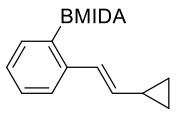
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.40 – 7.39 (m, 2H), 7.29 – 7.27 (m, 2H), 6.40 (d, *J* = 15.9 Hz, 1H), 6.30 – 6.23 (m, 1H), 4.32 (d, *J* = 17.2 Hz, 2H), 4.12 (d, *J* = 17.2 Hz, 2H), 2.19 (t, *J* = 6.7 Hz, 2H), 1.94 (dt, *J* = 14.9, 7.4 Hz, 1H), 1.76 – 1.70 (m, 2H), 1.61 – 1.49 (m, 4H), 1.21 – 1.16 (m, 2H). MIDA CH_3 signal obscured by solvent signal.

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.3, 136.4, 130.9, 130.3, 130.0, 129.7, 127.8, 126.1, 61.8, 47.5, 38.8, 31.8, 24.6. CH signal obscured by solvent signal.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 13.13.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{25}BNO_4$) requires *m/z* 342.1871, found *m/z* 342.1870.

Trans-(2-(2-cyclopropylvinyl)phenyl)boronic acid MIDA ester, **79**



Prepared according to General Procedure E using 2-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), *trans*-2-(2-cyclopropylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (73 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a yellow solid (61 mg, 82%).

υ_{max} (film): 3005, 1759, 1280, 1197, 1028, 989, 854, 754 cm^{-1}.

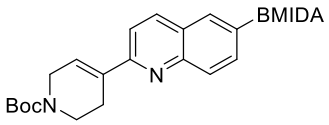
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.41 – 7.33 (m, 2H), 7.30 (td, *J* = 7.5, 1.4 Hz, 1H), 7.20 (td, *J* = 7.5, 1.3 Hz, 1H), 6.80 (d, *J* = 15.6 Hz, 1H), 5.61 (dd, *J* = 15.6, 8.7 Hz, 1H), 4.36 (d, *J* = 17.3 Hz, 2H), 4.04 (d, *J* = 17.3 Hz, 2H), 2.46 (s, 3H), 1.47 (ddd, *J* = 12.3, 8.3, 3.6 Hz, 1H), 0.81 – 0.71 (m, 2H), 0.52 – 0.44 (m, 2H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.1, 142.7, 136.4, 133.5, 129.1, 127.5, 126.1, 125.8, 62.2, 47.4, 14.4, 6.9.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 12.02.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}BNO_4$) requires *m/z* 300.1402, found *m/z* 300.1400.

2-(1-(*tert*-Butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)quinolin-6-yl)boronic acid MIDA ester, **80**



Prepared according to General Procedure E using (2-chloroquinolin-6-yl)boronic acid MIDA ester (80 mg, 0.25 mmol, 1 equiv), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (116 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a beige solid (60 mg, 52%).

υ_{max} (film): 1766, 1681, 1286, 1238, 1170, 1039, 1002, 825 cm^{-1}.

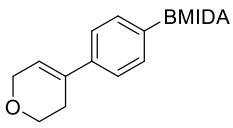
^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.32 (d, *J* = 8.7 Hz, 1H), 8.01 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.80 (dd, *J* = 20.1, 8.5 Hz, 2H), 6.85 (s, 1H), 4.40 (d, *J* = 17.2 Hz, 2H), 4.19 (d, *J* = 17.2 Hz, 2H), 4.12 (s, 2H), 3.58 (t, *J* = 5.3 Hz, 2H), 2.76 (s, 2H), 2.54 (s, 3H), 1.44 (s, 9H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.3, 156.6, 153.9, 147.5, 136.6, 135.5, 133.2, 132.5, 127.9, 126.2, 117.6, 78.9, 61.9, 47.7, 28.1.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 11.57.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{24}H_{29}BN_3O_6$) requires *m/z* 466.2144, found *m/z* 466.2149.

(4-(3,6-Dihydro-2H-pyran-4-yl)phenyl)boronic acid MIDA ester, **81**



Prepared according to General Procedure E using 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (79 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M)) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a white solid (54 mg, 69%).

υ_{max} (film): 1747, 1266, 1219, 1124, 1033, 987, 854, 806 cm^{-1}.

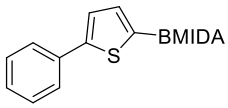
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.46 – 7.39 (m, 4H), 6.31 – 6.26 (m, 1H), 4.32 (d, *J* = 17.2 Hz, 2H), 4.23 (q, *J* = 2.7 Hz, 2H), 4.10 (d, *J* = 17.2 Hz, 2H), 3.82 (t, *J* = 5.5 Hz, 2H), 2.48 – 2.43 (m, 2H). MIDA CH_3 signal obscured by solvent signal.

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.4, 140.0, 133.2, 132.5, 123.7, 122.8, 65.1, 63.6, 61.7, 47.5, 26.4.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.35.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}BNO_5$) requires *m/z* 316.1351, found *m/z* 316.1353.

(5-Phenylthiophen-2-yl)boronic acid MIDA ester, **82**



Prepared according to General Procedure E using 5-bromo-2-thiophenylboronic acid MIDA ester (80 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (76 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to

the purification outlined in the General Procedure to afford the title compound as a brown solid (67 mg, 84%).

υ_{max} (film): 1759, 1454, 1278, 1249, 1166, 1026, 979, 810 cm^{-1}.

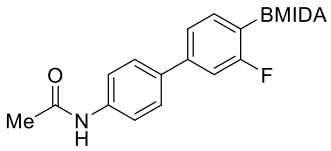
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.71 – 7.63 (m, 2H), 7.54 (t, *J* = 5.8 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 3.5 Hz, 1H), 4.37 (d, *J* = 17.2 Hz, 2H), 4.15 (d, *J* = 17.2 Hz, 2H), 2.67 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 168.8, 147.0, 134.2, 133.8, 129.1, 127.5, 125.4, 124.9, 61.4, 47.4.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 12.26.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{15}BNO_4S$) requires *m/z* 316.0809, found *m/z* 316.0810.

(4'-Acetamido-3-fluoro-[1,1'-biphenyl]-4-yl)boronic acid MIDA ester, **83**



Prepared according to General Procedure E using 2-fluoro-4-bromophenylboronic acid MIDA ester (83 mg, 0.25 mmol, 1 equiv), *N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (98 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as an off-white solid (72 mg, 75%).

υ_{max} (film): 1769, 1526, 1313, 1259, 1036, 816 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.05 (s, 1H), 7.68 (s, 4H), 7.57 – 7.48 (m, 2H), 7.42 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 17.3 Hz, 2H), 4.11 (d, *J* = 17.2 Hz, 2H), 2.66 (s, 3H), 2.07 (s, 3H).

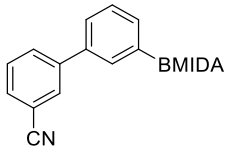
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.0, 168.4, 166.1 (d, $^{1}J_{C\text{-}F}$ = 241.1 Hz), 143.3 (d, $^{3}J_{C\text{-}F}$ = 8.8 Hz), 139.4, 135.3 (d, $^{3}J_{C\text{-}F}$ = 10.0 Hz), 132.9, 127.0, 121.7, 119.3, 112.3 (d, $^{2}J_{C\text{-}F}$ = 26.0 Hz), 62.4, 47.5, 24.0.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 11.47.

^{19}F NMR (DMSO-d_6, 376 MHz): δ – 105.39 (s, 1F).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{19}BFN_2O_5$) requires *m/z* 385.1366, found *m/z* 385.1362.

(3'-Cyano-[1,1'-biphenyl]-3-yl)boronic acid MIDA ester, **84**



Prepared according to General Procedure E using 3-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (86 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a brown solid (58 mg, 81%).

υ_{max} (film): 2227, 1764, 1745, 1288, 1211, 1035, 995, 788 cm^{-1}.

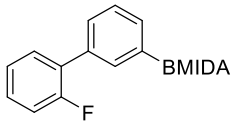
^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.19 (t, *J* = 1.5 Hz, 1H), 8.06 – 8.02 (m, 1H), 7.85 – 7.80 (m, 1H), 7.73 (dd, *J* = 4.4, 3.3 Hz, 2H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.52 – 7.47 (m, 2H), 4.36 (d, *J* = 17.2 Hz, 2H), 4.17 (d, *J* = 17.1 Hz, 2H), 2.58 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.4, 141.8, 137.4, 132.4, 131.7, 131.0, 130.9, 130.3, 130.0, 128.4, 127.6, 118.8, 112.0, 62.0, 47.8.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.07.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{16}BN_2O_4$) requires *m/z* 335.1198, found *m/z* 335.1199.

(2'-Fluoro-[1,1'-biphenyl]-3-yl)boronic acid MIDA ester, **85**



Prepared according to General Procedure E using 3-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 2-(2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (83 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a brown solid (76 mg, 93%).

υ_{max} (film): 1747, 1288, 1217, 1029, 1010, 862, 756 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.62 – 7.52 (m, 3H), 7.50 – 7.43 (m, 2H), 7.44 – 7.37 (m, 1H), 7.35 – 7.26 (m, 2H), 4.35 (d, *J* = 17.2 Hz, 2H), 4.15 (d, *J* = 17.2 Hz, 2H), 2.55 (s, 3H).

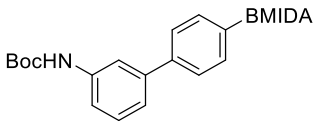
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.4, 159.1 (d, $^1J_{C\text{-}F}$ = 245.7 Hz), 134.2, 132.8, 131.9, 130.9 (d, $J_{C\text{-}F}$ = 2.9 Hz), 129.3, 128.6 (d, $^3J_{C\text{-}F}$ = 13.3 Hz), 127.8, 124.8 (d, $J_{C\text{-}F}$ = 2.9 Hz), 116.0 (d, $^2J_{C\text{-}F}$ = 22.6 Hz), 61.9, 47.7.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 13.02.

^{19}F NMR (DMSO-d_6, 376 MHz): δ – 118.37 (s, 1F).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{16}BFNO_4$) requires *m/z* 328.1151, found *m/z* 328.1149.

(3'-((*tert*-Butoxycarbonyl)amino)-[1,1'-biphenyl]-4-yl)boronic acid MIDA ester, **86**



Prepared according to General Procedure E using 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), *tert*-butyl (3-(4,4,5,5-tetramethyl-1,3,2-

dioxaborolan-2-yl)phenyl)carbamate (120 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as an off-white solid (88 mg, 83%).

υ_{max} (film): 1764, 1712, 1284, 1230, 1155, 1035, 989, 827 cm^{-1}.

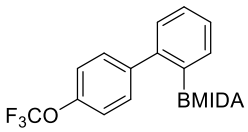
^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.41 (s, 1H), 7.80 (s, 1H), 7.55 (dd, *J* = 20.6, 8.1 Hz, 4H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 4.35 (d, *J* = 17.2 Hz, 2H), 4.14 (d, *J* = 17.2 Hz, 2H), 2.55 (s, 3H), 1.49 (s, 9H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.3, 152.8, 140.7, 140.1, 133.0, 129.2, 125.9, 120.4, 117.2, 116.3, 79.1, 61.7, 47.6, 28.1.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.77.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{26}BN_2O_6$) requires *m/z* 425.1878, found *m/z* 425.1875.

(4'-(Trifluoromethoxy)-[1,1'-biphenyl]-2-yl)boronic acid MIDA ester, **87**



Prepared according to General Procedure E using 2-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-(4-(trifluoromethoxy)phenyl)-1,3,2-dioxaborolane (108 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a beige solid (83 mg, 84%).

υ_{max} (film): 1766, 1251, 1228, 1197, 1165, 1031, 1004 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.64 – 7.56 (m, 1H), 7.43 – 7.38 (m, 2H), 7.31 (dd, *J* = 31.7, 8.2 Hz, 4H), 7.13 – 7.06 (m, 1H), 4.13 (d, *J* = 17.2 Hz, 2H), 3.65 (d, *J* = 17.2 Hz, 2H), 2.46 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 168.3, 147.1, 146.0, 142.7, 134.0, 130.8, 130.4, 128.6, 126.8, 120.1 (d, $^{1}J_{C\text{-}F}$ = 255.7 Hz), 120.0, 62.2, 48.0.

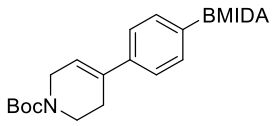
^{11}B NMR (DMSO-d_6, 128 MHz): δ 11.06.

^{19}F NMR (DMSO-d_6, 376 MHz): δ – 56.65 (s, 3F).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{16}BF_3NO_5$) requires *m/z* 394.1068, found *m/z* 394.1067.

Characterisation of products from Scheme 72

(4-(1-(*tert*-Butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)boronic acid MIDA ester, **77**



Prepared according to General Procedure E in a 50 mL round bottomed flask using 4-bromophenylboronic acid MIDA ester (1.34 g, 4.31 mmol, 1 equiv), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2 g, 6.47 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (140 mg, 1.72 mmol, 4 mol%), K_3PO_4 (2.74 g, 12.9 mmol, 3 equiv), THF (17 mL, 0.25 M) and H_2O (0.39 mL, 21.6 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as an off white solid (82 mg, 80%).

υ_{max} (film): 1766, 1693, 1283, 1035, 989 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.44 – 7.39 (m, 4H), 6.18 (br. s, 1H), 4.32 (d, *J* = 17.2 Hz, 2H), 4.10 (d, *J* = 17.1 Hz, 2H), 4.00 (br.s, 2H), 3.54 (t, *J* = 5.6 Hz, 2H), 1.43 (s, 9H). CH_2 signal obscured by solvent signal.

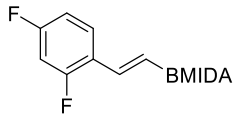
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.3, 153.9, 140.3, 134.4, 132.5, 123.9, 121.0, 78.8, 61.7, 47.5, 28.1, 26.5.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.66.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{21}H_{26}BN_2O_6$) requires *m/z* 413.1879, found *m/z* 413.1873.

Characterisation of products from Figure 20

Trans-(2,4-difluorostyryl)boronic acid MIDA ester, **88**



Prepared according to General Procedure E using *trans*-2-bromovinylboronic acid MIDA ester (65 mg, 0.25 mmol, 1 equiv), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (90 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a yellow solid (61 mg, 83%).

υ_{max} (film): 1755, 1498, 1274, 989, 964, 839 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.74 (dd, *J* = 15.7, 8.4 Hz, 1H), 7.23 (t, *J* = 10.2 Hz, 1H), 7.10 (t, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 18.3 Hz, 1H), 6.34 (d, *J* = 18.4 Hz, 1H), 4.27 (d, *J* = 17.1 Hz, 2H), 4.05 (d, *J* = 17.1 Hz, 2H), 2.81 (s, 3H).

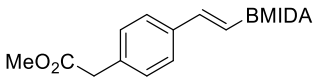
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.1, 161.9 (dd, $^1J_{C\text{-}F}$ = 222.9, $^3J_{C\text{-}F}$ = 12.2 Hz), 159.4 (dd, $^1J_{C\text{-}F}$ = 225.6, $^3J_{C\text{-}F}$ = 12.1 Hz), 131.3, 128.5 (dd, $^3J_{C\text{-}F}$ = 9.7, $J_{C\text{-}F}$ = 5.1 Hz), 122.1 (dd, $^3J_{C\text{-}F}$ = 11.6, $J_{C\text{-}F}$ = 3.7 Hz), 111.9 (dd, $^2J_{C\text{-}F}$ = 21.7, $J_{C\text{-}F}$ = 2.9 Hz), 104.0 (t, $^2J_{C\text{-}F}$ = 26.2 Hz), 61.4, 46.8.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.45.

^{19}F NMR (DMSO-d_6, 376 MHz): δ – 110.58 (d, $J_{F\text{-}F}$ = 7.2 Hz, 1F), – 115.51 (d, $J_{F\text{-}F}$ = 7.3 Hz, 1F).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{13}BF_2NO_4$) requires *m/z* 296.0900, found *m/z* 296.0899.

Trans-(4-(2-Methoxy-2-oxoethyl)styryl)boronic acid MIDA ester, **89**



Prepared according to General Procedure E using *trans*-2-bromovinylboronic acid MIDA ester (65 mg, 0.25 mmol, 1 equiv), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (103 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a brown solid (69 mg, 84%).

υ_{max} (film): 2991, 2949, 1762, 1726, 1224, 1024, 1004 cm^{-1}.

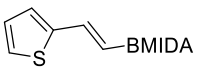
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.44 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.81 (d, *J* = 18.2 Hz, 1H), 6.25 (d, *J* = 18.2 Hz, 1H), 4.25 (d, *J* = 17.1 Hz, 2H), 4.04 (d, *J* = 17.1 Hz, 2H), 3.66 (s, 2H), 3.60 (s, 3H), 2.79 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 171.5, 169.2, 140.6, 136.5, 134.0, 129.5, 126.4, 61.4, 51.6, 46.7, 24.6.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 12.49.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}BNO_6$) requires *m/z* 332.1300, found *m/z* 332.1299.

Trans-(2-(thiophen-2-yl)vinyl)boronic acid MIDA ester, **90**



Prepared according to General Procedure E using *trans*-2-bromovinylboronic acid MIDA ester (65 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-(thiophen-2-yl)-1,3,2-dioxaborolane (79 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and

H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a brown solid (57 mg, 86%).

υ_{max} (film): 1747, 1616, 1282, 1109 1024, 987, 700 cm^{-1}.

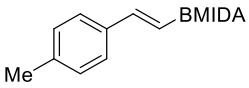
^1H NMR (DMSO-d_6, 400 MHz): δ 7.43 (d, *J* = 5.1 Hz, 1H), 7.12 (d, *J* = 3.3 Hz, 1H), 7.02 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.95 (d, *J* = 17.9 Hz, 1H), 5.94 (d, *J* = 17.9 Hz, 1H), 4.24 (d, *J* = 17.0 Hz, 2H), 4.05 (d, *J* = 17.0 Hz, 2H), 2.80 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.0, 144.0, 134.0, 127.7, 126.4, 125.4, 61.4, 46.7.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.86.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{11}H_{13}BNO_4S$) requires *m/z* 266.0653, found *m/z* 266.0652.

Trans-(4-methylstyryl)boronic acid MIDA ester, **91**



Prepared according to General Procedure E using *trans*-2-bromovinylboronic acid MIDA ester (65 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane (82 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a beige solid (51 mg, 75%).

υ_{max} (film): 1755, 1292, 1112, 1018, 989, 950, 833 cm^{-1}.

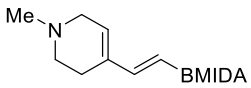
^1H NMR (DMSO-d_6, 400 MHz): δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.78 (d, *J* = 18.2 Hz, 1H), 6.20 (d, *J* = 18.2 Hz, 1H), 4.24 (d, *J* = 17.1 Hz, 2H), 4.03 (d, *J* = 17.1 Hz, 2H), 2.79 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.1, 140.8, 137.2, 135.0, 129.0, 126.3, 61.3, 46.6, 20.7.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 12.73.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}BNO_4$) requires *m/z* 274.1245, found *m/z* 274.1247.

Trans-(2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)vinyl)boronic acid MIDA ester, **92**



Prepared according to General Procedure E using *trans*-2-bromovinylboronic acid MIDA ester (65 mg, 0.25 mmol, 1 equiv), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine (84 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a brown solid (35 mg, 50%).

υ_{max} (film): 1743, 1610, 1307, 1130, 989, 962 cm^{-1}.

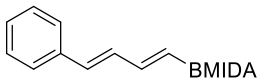
^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.46 (d, *J* = 18.0 Hz, 1H), 5.75 (s, 1H), 5.47 (d, *J* = 18.0 Hz, 1H), 4.20 (d, *J* = 17.0 Hz, 2H), 3.98 (d, *J* = 17.0 Hz, 2H), 3.44 – 3.27 (m, 2H), 2.93 (s, 2H), 2.73 (s, 3H), 2.47 (t, *J* = 5.6 Hz, 2H), 2.23 (s, 3H).

^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.1, 143.1, 134.4, 127.3, 61.2, 54.4, 51.7, 46.6, 45.4, 24.9.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 10.89.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{20}BN_2O_4$) requires *m/z* 279.1511, found *m/z* 279.1508.

Trans-(4-Phenylbuta-1,3-dien-1-yl)boronic acid MIDA ester, **93**



Prepared according to General Procedure E using *trans*-2-bromovinylboronic acid MIDA ester (65 mg, 0.25 mmol, 1 equiv), *trans*-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (86 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a yellow solid (50 mg, 71%).

υ_{max} (film): 1743, 1340, 1303, 1111, 1012, 866, 750, 694 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.48 (d, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 6.92 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.70 – 6.57 (m, 2H), 5.77 (d, *J* = 19.2 Hz, 1H), 4.23 (d, *J* = 17.1 Hz, 2H), 4.02 (d, *J* = 17.1 Hz, 2H), 2.78 (s, 3H).

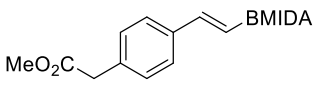
^{13}C NMR (DMSO-d_6, 126 MHz): δ 169.1, 141.8, 136.8, 132.8, 130.8, 128.6, 127.6, 126.4, 61.3, 46.7.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 9.62.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{17}BNO_4$) requires *m/z* 286.1245, found *m/z* 286.1248.

Experimental procedures from Table 11 – Conditions B. For Conditions A and product characterisation, see above

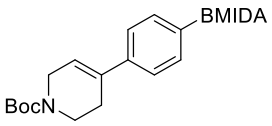
Trans-(4-(2-Methoxy-2-oxoethyl)styryl)boronic acid MIDA ester, **89**



Prepared according to General Procedure F using *trans*-2-bromovinylboronic acid MIDA ester (65 mg, 0.25 mmol, 1 equiv), (4-(2-methoxy-2-oxoethyl)phenyl)boronic acid pinacol ester (100 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (10.3 mg, 0.013 mmol, 5 mol%), K_3PO_4 (318 mg, 1.5 mmol, 6 equiv) and DMSO (3.5 mL,

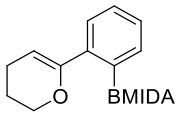
0.07 M). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as a brown solid (53 mg, 64%).

(4-(1-(*tert*-Butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)boronic acid MIDA ester, **77**



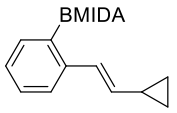
Prepared according to General Procedure F using 4-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (116 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (10.3 mg, 0.013 mmol, 5 mol%), K_3PO_4 (318 mg, 1.5 mmol, 6 equiv) and DMSO (3.5 mL, 0.07 M). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as an off white solid (90 mg, 87%).

(2-(3,4-Dihydro-2H-pyran-6-yl)phenyl)boronic acid MIDA ester, **75**



Prepared according to General Procedure F using 2-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), 2-(3,4-dihydro-2H-pyran-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (79 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (10.3 mg, 0.013 mmol, 5 mol%), K_3PO_4 (318 mg, 1.5 mmol, 6 equiv) and DMSO (3.5 mL, 0.07 M). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure however no product was isolated.

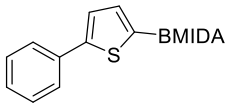
Trans-(2-(2-Cyclopropylvinyl)phenyl)boronic acid MIDA ester, **79**



Prepared according to General Procedure F using 2-bromophenylboronic acid MIDA ester (78 mg, 0.25 mmol, 1 equiv), *trans*-2-(2-cyclopropylvinyl)-4,4,5,5-tetramethyl-

1,3,2-dioxaborolane (73 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (10.3 mg, 0.013 mmol, 5 mol%), K_3PO_4 (318 mg, 1.5 mmol, 6 equiv) and DMSO (3.5 mL, 0.07 M). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure however no product was isolated.

(5-Phenylthiophen-2-yl)boronic acid MIDA ester, **82**



Prepared according to General Procedure F using 5-bromo-2-thiophenylboronic acid MIDA ester (80 mg, 0.25 mmol, 1 equiv), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (76 mg, 0.375 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (10.3 mg, 0.013 mmol, 5 mol%), K_3PO_4 (318 mg, 1.5 mmol, 6 equiv) and DMSO (3.5 mL, 0.07 M). After 24 h the reaction mixture was subjected to the purification outlined in the General Procedure to afford the title compound as an off white solid (31 mg, 39%).

Results from Table 12

To an oven-dried 5 mL microwave vial was added 4-bromophenylboronic acid MIDA ester (200 mg, 0.64 mmol) and THF (2 mL) to give a saturated solution. The vial was then sealed with a rubber septum and stirred at room temperature for 2 h. The slurry was then left to stand for 30 minutes before extracting 1 mL of solution. This was then passed through a syringe filter into a weighed vial and the solvent evaporated. The vial was then weighed and the quantity of substrate (mg per mL) of the saturated solution was established. This process was repeated for both the 3- and 2-bromophenylboronic acid MIDA ester isomers.

Results from Scheme 74/Graph 2

Reactions carried out according to General Procedure A using 4-bromophenylboronic acid MIDA ester (71 mg, 0.226 mmol, 1 equiv), phenylboronic acid pinacol ester (69 mg, 0.339 mmol, 1.5 equiv), Pd(dppf)Cl_2·DCM (7.4 mg, 0.01 mmol, 4 mol%), K_3PO_4 (144 mg, 0.678 mmol, 3 equiv), THF (0.9 mL, 0.25 M), and H_2O (20.4 µL, 1.13 mmol, 5 equiv) at 90 °C for **X** h.

Entry	Time (h)	Conversion to 33 (%)	Conversion to 34 (%)
1	1	47	34
2	2	53	19
3	4	76	10
4	6	78	7
5	12	87	0
6	18	82	0
7	24	93	0

Results from Scheme 75

To an oven-dried 5 mL microwave vial was added 4-biphenylboronic acid (50 mg, 0.25 mmol, 1 equiv), pinacol (30 mg, 0.25 mmol, 1 equiv), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The vial was then capped and purged with N_2 before addition of THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was then heated to 90 °C for 1 h in a sand bath. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration (100% conversion).

Results from Scheme 76

To an oven-dried 5 mL microwave vial was added boric acid (23 mg, 0.375 mmol, 1.5 equiv) and pinacol (44 mg, 0.375 mmol, 1.5 equiv). The vial was then capped and purged with N_2 before addition of THF (1 mL, 0.25 M). The reaction mixture was then stirred at room temperature for 1 hour before being decapped and added 4-biphenylboronic acid (50 mg, 0.25 mmol, 1 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The vial was then recapped and purged with N_2 before being heated to 90 °C for 24 h in a sand bath. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration (100% conversion).

Results from Scheme 77

To an oven-dried 5 mL microwave vial was added 4-biphenylboronic acid MIDA ester (77 mg, 0.25 mmol, 1 equiv), pinacol (30 mg, 0.25 mmol, 1 equiv), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv or 0 equiv in the absence of base). The vial was then capped and purged with N_2 before addition of THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was then heated to 90 °C for 1 h in a sand bath. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration.

Entry	K_3PO_4 Equiv	Conversion to 33 (%)	Conversion to 35 (%)
1	0	0	74
2	3	100	0

Results from Scheme 79

To an oven-dried 5 mL microwave vial was added 4-biphenylboronic acid pinacol ester (70 mg, 0.25 mmol, 1 equiv) and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The vial was then capped and purged with N_2 before addition of THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was then heated to 90 °C for 1 h in a sand bath. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration (0% conversion to **35**).

Results from Scheme 80

To an oven-dried 5 mL microwave vial was added 4-biphenylboronic acid (50 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv or 0 equiv in the absence of base). The vial was then capped and purged with N_2 before addition of THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was then heated to 90 °C for 1 h in a sand bath. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration.

Entry	K_3PO_4 Equiv	Conversion to 33 (%)	Conversion to 35 (%)

1	0	42	58
2	3	37	63

6.4 Experimental procedures and characterisation data for Section 3.2

Results from Graph 3

Prepared according to General Procedure G using **phenyl B(OR)$_2$** (0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl$_2$·DCM (8.2 mg, 0.01 mmol, 4 mol%) and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv) at 50 °C for **X** min.

Entry	B(OR)$_2$ (Mass)	Time (min)	Conversion (%)
1	B(OH)$_2$ (31 mg)	10	73
2	B(OH)$_2$ (31 mg)	20	79
3	B(OH)$_2$ (31 mg)	30	85
4	B(OH)$_2$ (31 mg)	60	91
5	B(OH)$_2$ (31 mg)	120	100
6	BPin (51 mg)	10	61
7	BPin (51 mg)	20	87
8	BPin (51 mg)	30	93
9	BPin (51 mg)	60	99
10	BPin (51 mg)	120	100

Results from Graph 4

Prepared according to General Procedure G using **phenyl B(OR)$_2$** (0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl$_2$·DCM (8.2 mg, 0.01 mmol, 4 mol%) and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv) at 30 °C for **X** min.

Entry	$B(OR)_2$ (Mass)	Time (min)	Conversion (%)
1	$B(OH)_2$ (31 mg)	10	30
2	$B(OH)_2$ (31 mg)	20	47
3	$B(OH)_2$ (31 mg)	30	52
4	$B(OH)_2$ (31 mg)	60	79
5	$B(OH)_2$ (31 mg)	120	99
6	BPin (51 mg)	10	25
7	BPin (51 mg)	20	48
8	BPin (51 mg)	30	56
9	BPin (51 mg)	60	73
10	BPin (51 mg)	120	81

Results from Graph 5

Prepared according to General Procedure G using **phenyl $B(OR)_2$** (0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), $Pd(dppf)Cl_2 \cdot DCM$ (8.2 mg, 0.01 mmol, 4 mol%) and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv) at r.t. for **X** min.

Entry	$B(OR)_2$ (Mass)	Time (min)	Conversion (%)
1	$B(OH)_2$ (31 mg)	10	15
2	$B(OH)_2$ (31 mg)	20	30
3	$B(OH)_2$ (31 mg)	30	35
4	$B(OH)_2$ (31 mg)	60	50
5	$B(OH)_2$ (31 mg)	120	53

6	BPin (51 mg)	10	10
7	BPin (51 mg)	20	23
8	BPin (51 mg)	30	31
9	BPin (51 mg)	60	45
10	BPin (51 mg)	120	66

Results from Graph 6

Prepared according to General Procedure H using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv) at r.t. for **X** h.

Entry	Time (min)	Conversion to 105 (%)	Conversion to 107 (%)
1	10	3	13
2	20	6	26
3	30	7	35
4	60	7	43
5	120	7	53

Results from Graph 7

Prepared according to General Procedure H using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv) at 30 °C for **X** h.

Entry	Time (min)	Conversion to 105 (%)	Conversion to 107 (%)
1	10	7	33
2	20	10	45
3	30	11	53
4	60	8	55
5	120	10	68

Results from Graph 8

Prepared according to General Procedure H using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv) at 50 °C for **X** h.

Entry	Time (min)	Conversion to 105 (%)	Conversion to 107 (%)
1	10	8	61
2	20	10	74
3	30	9	76
4	60	11	87
5	120	12	90

Results from Table 13

Prepared according to General Procedure H using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv) at **X** °C for 1 h.

Entry	Temperature (°C)	Conversion 105:107 (%)
1	r.t.	7:43
2	30	8:55
3	50	11:87
4	70	14:86
5	90	10:87

Results from Table 14

Prepared according to General Procedure H using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), **Base** (0.75 mmol, 3 equiv), THF (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv) at 70 °C for 1 h.

Entry	Base (Mass)	Conversion 105:107 (%)
1	K_3PO_4 (159 mg)	14:86
2	K_2CO_3 (104 mg)	6:76
3	Cs_2CO_3 (244 mg)	7:80

Results from Table 15

Prepared according to General Procedure H using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), **Solvent** (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv) at 70 °C for 1 h.

Entry	Solvent	Conversion 105:107 (%)
1	THF	14:86
2	1,4-dioxane	0:100

3	MeCN	9:77

Results from Graph 9

Prepared according to General Procedure H using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (**X** equiv) at 70 °C for 1 h.

Entry	H2O equiv (volume)	Conversion to 105 (%)	Conversion to 107 (%)
1	0	0	73
2	5	11	91
3	10	10	76
4	20	12	80
5	50	29	68
6	100	30	59

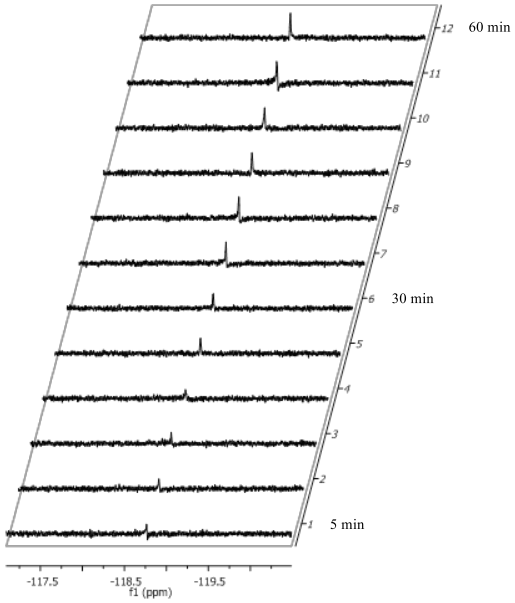
Results from Scheme 85

Prepared according to General Procedure H using phenylboronic acid (31 mg, 0.25 mmol, 1 equiv), 4-tolylboronic acid pinacol ester (54 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv),1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv) at 70 °C for 1 h before analysis by HPLC against a caffeine standard of known concentration (95:5% **105**:**107**).

Results from Scheme 87

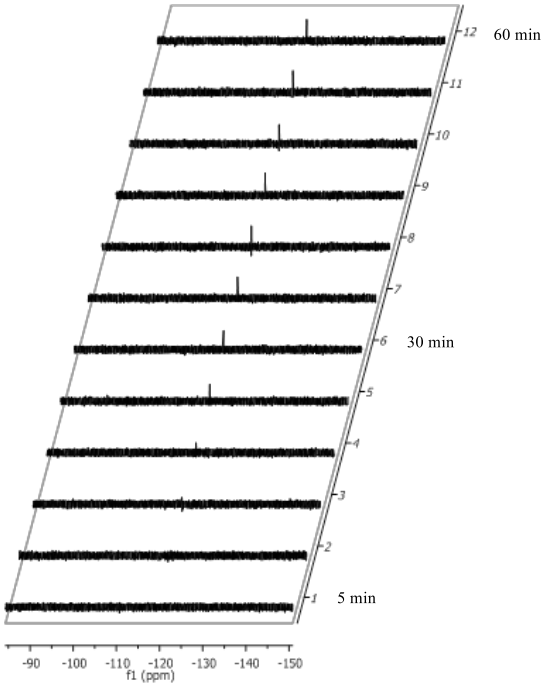
The NMR experiment was carried out according to General Procedure I using 4-fluorophenylboronic acid (28 mg, 0.20 mmol, 1 equiv), 4-tolylboronic acid pinacol

ester (44 mg, 0.20 mmol, 1 equiv), K_3PO_4 (127 mg, 0.60 mmol, 3 equiv), 1,4-dioxane (0.8 mL, 0.25 M) and D_2O blank (0.8 mL). A ^{19}F NMR was recorded of the aqueous phase every 5 minutes according to General Procedure I. Boronic acid boronate formation and subsequent phase transfer was observed immediately.



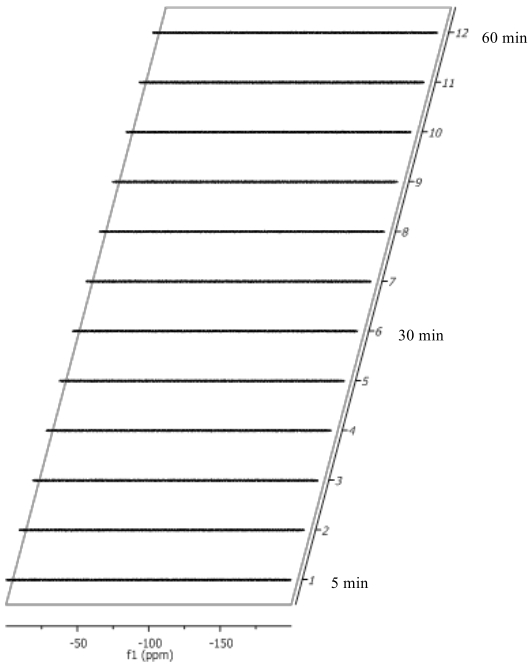
Results from Scheme 88

The NMR experiment was carried out according to General Procedure I using 4-tolylboronic acid (27 mg, 0.20 mmol, 1 equiv), 4-fluorophenylboronic acid pinacol ester (45 mg, 0.20 mmol, 1 equiv), K_3PO_4 (127 mg, 0.60 mmol, 3 equiv), 1,4-dioxane (0.8 mL, 0.25 M) and D_2O blank (0.8 mL). A ^{19}F NMR was recorded of the aqueous phase every 5 minutes according to General Procedure I. Phase transfer was observed after 25 minutes, presumably as a result of diol equilibration and subsequent boronic acid boronate formation and phase transfer.



Results from *p*-fluorobromobenzene phase transfer control

The NMR experiment was carried out according to General Procedure I using 1-bromo-4-fluorobenzene (22 μL, 0.20 mmol, 1 equiv), K_3PO_4 (127 mg, 0.60 mmol, 3 equiv), 1,4-dioxane (0.8 mL, 0.25 M) and D_2O blank (0.8 mL). A ^{19}F NMR was recorded of the aqueous phase every 5 minutes according to General Procedure I. No phase transfer of the aryl halide was observed.



Results from Table 16

Optimum conditions

An oven dried 5 mL microwave vial was charged with biphenylboronic acid (50 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv) and caffeine (49 mg, 0.25 mmol, 1 equiv) before adding 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was then heated to 70 °C for 10 minutes before taking a 10 µL aliquot. This was then diluted with 0.5 mL MeCN and 0.5 mL H_2O and analysed by HPLC to calculate the quantity of biphenylboronic acid (82%) and biphenylboronic acid pinacol ester (5%).

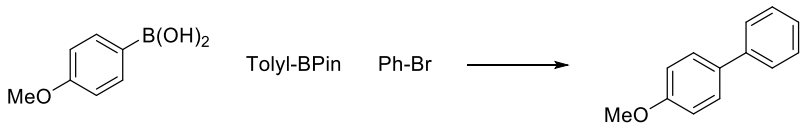
Biphasic Conditions

An oven dried 5 mL microwave vial was charged with biphenylboronic acid (50 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv) and caffeine (49 mg, 0.25 mmol, 1 equiv) before adding 1,4-dioxane (1 mL, 0.25 M) and H_2O (1 mL, 0.25 M). The reaction mixture was then heated to 70 °C for 10 minutes before taking a 10 µL aliquot. This was then diluted with 0.5 mL MeCN and 0.5 mL H_2O and analysed by HPLC to

calculate the quantity of biphenylboronic acid (59%) and biphenylboronic acid pinacol ester (31%).

Characterisation of products from Figure 24

4-Methoxyphenylboronic acid vs. 4-tolylboronic acid pinacol ester to give 4-methoxy-1,1'-biphenyl, **110**



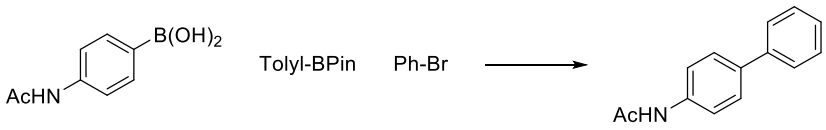
Prepared according to General Procedure J using 4-methoxyphenylboronic acid (38 mg, 0.25 mmol, 1 equiv), 4-tolylboronic acid pinacol ester (55 mg, 0.25 mmol, 1 equiv), bromobenzene (26 μL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol,5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 0 – 2% Et_2O/petroleum ether) to afford the desired product as a white solid (46 mg, quant.).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 – 7.50 (m, 4H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.34 – 7.27 (m, 1H), 7.02 – 6.94 (m, 2H), 3.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 159.6, 141.3, 134.2, 129.2, 128.6, 127.2, 114.7, 55.8.

The spectral data were consistent with those previously reported in the literature.[149]

(4-(Acetamido)phenyl)boronic acid vs. 4-tolylboronic acid pinacol ester to give *N*-([1,1'-biphenyl]-4-yl)acetamide, **111**



Prepared according to General Procedure J using (4-(acetamido)phenyl)boronic acid (45 mg, 0.25 mmol, 1 equiv), 4-tolylboronic acid pinacol ester (55 mg, 0.25 mmol, 1 equiv), bromobenzene (26 μL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M)

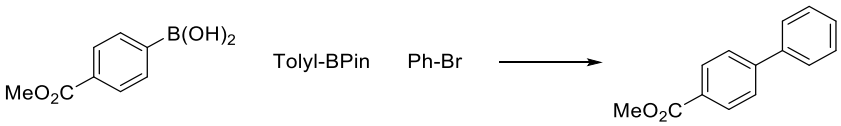
and H_2O (22.5 µL, 1.25 mmol,5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 5 – 50% EtOAc/petroleum ether) to afford the desired product as a white solid (42 mg, 80%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 – 7.54 (m, 6H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.19 (br. s, 1H), 2.21 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.9, 140.6, 137.4, 137.3, 128.9, 127.7, 127.2, 126.9, 120.5, 24.6.

The spectral data were consistent with those previously reported in the literature.[150]

(4-(Methoxycarbonyl)phenyl)boronic acid vs. 4-tolylboronic acid pinacol ester to give methyl [1,1'-biphenyl]-4-carboxylate, **112**



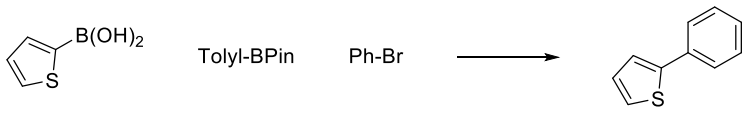
Prepared according to General Procedure J using (4-(methoxycarbonyl)phenyl)boronic acid (45 mg, 0.25 mmol, 1 equiv), 4-tolylboronic acid pinacol ester (55 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol,5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 0 – 10% Et_2O/petroleum ether) to afford the desired product as a white solid (47 mg, 89%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 – 8.09 (m, 2H), 7.68 – 7.65 (m, 2H), 7.65 – 7.61 (m, 2H), 7.50 – 7.44 (m, 2H), 7.42 – 7.36 (m, 1H), 3.95 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 167.0, 145.7, 140.0, 130.1, 128.9, 128.1, 127.3, 127.1, 52.1.

One carbon signal not observed. The spectral data were consistent with those previously reported in the literature.[151]

Thiophen-2-ylboronic acid vs. 4-tolylboronic acid pinacol ester to give 2-phenylthiophene, **113**



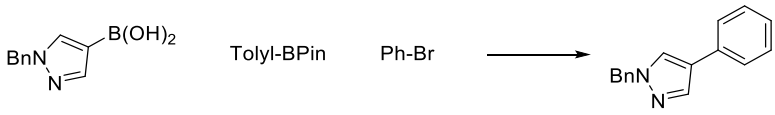
Prepared according to General Procedure J using thiophen-2-ylboronic acid (32 mg, 0.25 mmol, 1 equiv), 4-tolylboronic acid pinacol ester (55 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 0 – 5% Et_2O/petroleum ether) to afford the desired product as a white solid (30 mg, 76%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 – 7.60 (m, 2H), 7.42 – 7.36 (m, 2H), 7.34 – 7.26 (m, 3H), 7.09 (dd, *J* = 5.1, 3.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 144.6, 134.6, 129.0, 128.1, 127.6, 126.1, 124.9, 123.2.

The spectral data were consistent with those previously reported in the literature.[150]

(1-Benzyl-1H-pyrazol-4-yl)boronic acid vs. 4-tolylboronic acid pinacol ester to give 1-benzyl-4-phenyl-1H-pyrazole, **114**



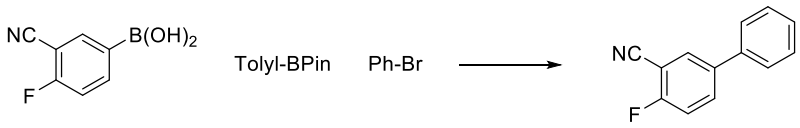
Prepared according to General Procedure J using (1-benzyl-1H-pyrazol-4-yl)boronic acid (51 mg, 0.25 mmol, 1 equiv), 4-tolylboronic acid pinacol ester (55 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 10 – 30% Et_2O/petroleum ether) to afford the desired product as a white solid (47 mg, 80%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, *J* = 0.6 Hz, 1H), 7.62 (d, *J* = 0.6 Hz, 1H), 7.48 – 7.43 (m, 2H), 7.40 – 7.31 (m, 5H), 7.29 – 7.25 (m, 2H), 7.24 – 7.18 (m, 1H), 5.34 (s, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 137.2, 136.6, 132.7, 129.1, 129.0, 128.3, 127.9, 126.6, 126.3, 125.7, 123.7, 56.4.

The spectral data were consistent with those previously reported in the literature.[152]

(3-Cyano-4-fluorophenyl)boronic acid vs. 4-tolylboronic acid pinacol ester to give 4-fluoro-[1,1'-biphenyl]-3-carbonitrile, **115**



Prepared according to General Procedure J using (3-cyano-4-fluorophenyl)boronic acid (41 mg, 0.25 mmol, 1 equiv), 4-tolylboronic acid pinacol ester (55 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), $Pd(dppf)Cl_2 \cdot DCM$ (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 5 – 10% Et_2O/petroleum ether) to afford the desired product as a white solid (41 mg, 84%).

υ_{max} (solid): 3058, 2236, 1515, 1487, 1279, 1247, 1124, 841, 769 cm^{-1}.

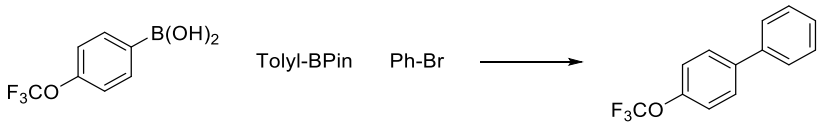
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.83 – 7.77 (m, 2H), 7.53 – 7.45 (m, 4H), 7.44 – 7.39 (m, 1H), 7.29 (t, *J* = 8.6 Hz, 1H).

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 109.46 (dt, *J* = 8.6, 5.6 Hz, 1F).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 162.5 (d, $^{1}J_{C\text{-}F}$ = 259.5 Hz), 138.6 (d, $J_{C\text{-}F}$ = 3.7 Hz), 138.0, 133.7 (d, $^{3}J_{C\text{-}F}$ = 8.4 Hz), 131.8, 129.2, 128.4, 127.0, 116.8 (d, $^{2}J_{C\text{-}F}$ = 20.0 Hz), 114.0, 101.9 (d, $^{2}J_{C\text{-}F}$ = 15.8 Hz).

HRMS: exact mass calculated for $[M]^+$ ($C_{13}H_8FN$) requires m/z 197.0641, found m/z 197.0645.

(4-(Trifluoromethoxy)phenyl)boronic acid vs. 4-tolylboronic acid pinacol ester to give 4-(trifluoromethoxy)-1,1'-biphenyl, **116**



Prepared according to General Procedure J using (4-(trifluoromethoxy)phenyl)boronic acid (52 mg, 0.25 mmol, 1 equiv), 4-tolylboronic acid pinacol ester (55 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 0 – 5% Et_2O/petroleum ether) to afford the desired product as a white solid (49 mg, 82%).

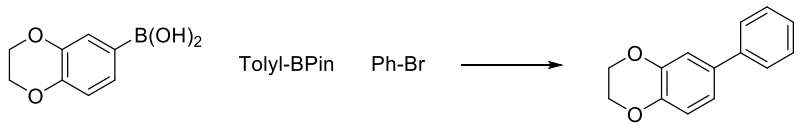
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 – 7.59 (m, 2H), 7.59 – 7.55 (m, 2H), 7.50 – 7.44 (m, 2H), 7.42 – 7.35 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H).

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 57.81 (s, 3F).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.1 (app. d, $^3J_{C\text{-}F}$ = 13.3 Hz), 129.6, 129.1, 128.9, 128.6, 127.8, 127.3, 127.1, 121.4. CF_3 carbon not observed.

The spectral data were consistent with those previously reported in the literature.[153]

(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid vs. 4-tolylboronic acid pinacol ester to give 6-phenyl-2,3-dihydrobenzo[*b*][1,4]dioxine, **117**



Prepared according to General Procedure J using (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid (45 mg, 0.25 mmol, 1 equiv), 4-tolylboronic acid pinacol ester (55 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1

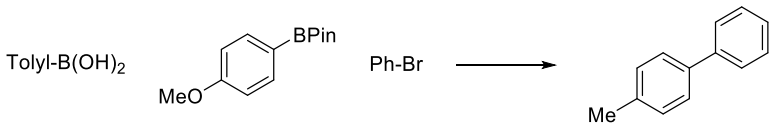
h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 0 – 5% Et_2O/petroleum ether) to afford the desired product as a cloudy oil (55 mg, quant.).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 – 7.50 (m, 2H), 7.43 – 7.37 (m, 2H), 7.33 – 7.27 (m, 1H), 7.12 (d, *J* = 2.2 Hz, 1H), 7.09 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 4.30 (s, 4H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 143.2, 142.7, 140.1, 134.3, 128.2, 126.4, 126.3, 119.7, 117.1, 115.4, 64.0.

The spectral data were consistent with those previously reported in the literature.[154]

4-Tolylboronic acid vs. 4-methoxyphenylboronic acid pinacol ester to give 4-methyl-1,1'-biphenyl, **118**



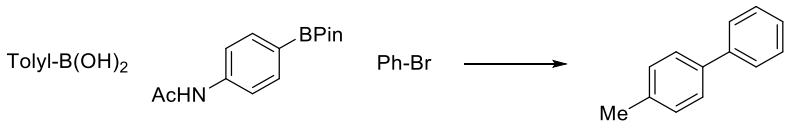
Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), 4-methoxyphenylboronic acid pinacol ester (59 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 5% Et_2O/petroleum ether) to afford the desired product as a white solid (37 mg, 88%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 – 7.57 (m, 2H), 7.53 – 7.48 (m, 2H), 7.47 – 7.40 (m, 2H), 7.36 – 7.29 (m, 1H), 7.29 – 7.23 (m, 2H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.3, 138.5, 137.2, 129.6, 128.9, 127.1, 21.2.

The spectral data were consistent with those previously reported in the literature.[14]

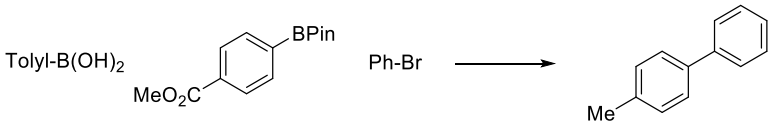
4-Tolylboronic acid vs. (4-(acetamido)phenyl)boronic acid pinacol ester to give 4-methyl-1,1'-biphenyl, **119**



Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), (4-(acetamido)phenyl)boronic acid pinacol ester (65 mg, 0.25 mmol, 1 equiv), bromobenzene (26 μL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 5% Et_2O/petroleum ether) to afford the desired product as a white solid (37 mg, 88%).

For spectral data for, see **118** above.

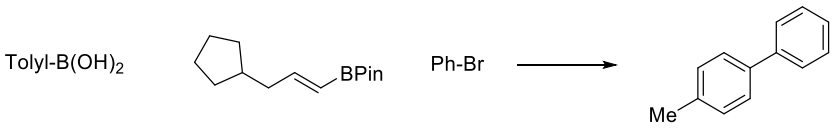
4-Tolylboronic acid vs. (4-(methoxycarbonyl)phenyl)boronic acid pinacol ester to give 4-methyl-1,1'-biphenyl, **120**



Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), (4-(methoxycarbonyl)phenyl)boronic acid pinacol ester (66 mg, 0.25 mmol, 1 equiv), bromobenzene (26 μL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 5% Et_2O/petroleum ether) to afford the desired product as a white solid (30 mg, 72%).

For spectral data for, see **118** above.

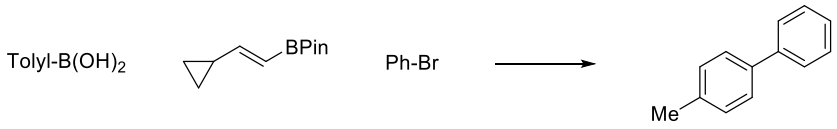
4-Tolylboronic acid vs. *trans*-(3-cyclopentylprop-1-en-1-yl)boronic acid pinacol ester to give 4-methyl-1,1'-biphenyl, **121**



Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), *trans*-(3-cyclopentylprop-1-en-1-yl)boronic acid pinacol ester (59 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 5% Et_2O/petroleum ether) to afford the desired product as a white solid (34 mg, 81%).

For spectral data for, see **118** above.

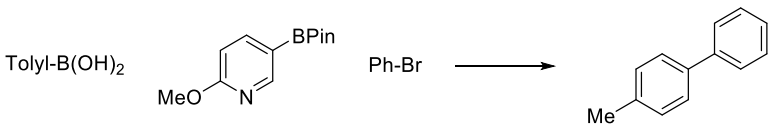
4-Tolylboronic acid vs. *trans*-(2-cyclopropylvinyl)boronic acid pinacol ester to give 4-methyl-1,1'-biphenyl, **122**



Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), *trans*-(2-cyclopropylvinyl)boronic acid pinacol ester (49 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 5% Et_2O/petroleum ether) to afford the desired product as a white solid (35 mg, 83%).

For spectral data for, see **118** above.

4-Tolylboronic acid vs. (6-methoxypyridin-3-yl)boronic acid pinacol ester to give 4-methyl-1,1'-biphenyl, **123**

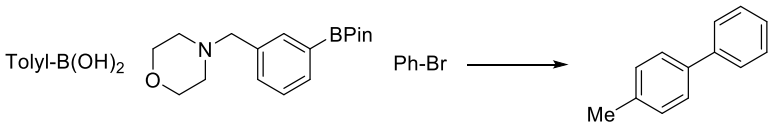


Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), (6-methoxypyridin-3-yl)boronic acid pinacol ester (59 mg, 0.25

mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 5% Et_2O/petroleum ether) to afford the desired product as a white solid (28 mg, 67%).

For spectral data for, see **118** above.

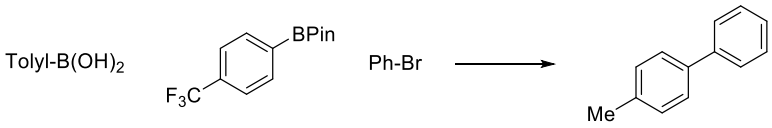
4-Tolylboronic acid vs. (3-(morpholinomethyl)phenyl)boronic acid pinacol ester to give 4-methyl-1,1'-biphenyl, **124**



Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), (3-(morpholinomethyl)phenyl)boronic acid pinacol ester (76 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 5% Et_2O/petroleum ether) to afford the desired product as a white solid (33 mg, 78%).

For spectral data for, see **118** above.

4-Tolylboronic acid vs. (4-(trifluoromethyl)phenyl)boronic acid pinacol ester to give 4-methyl-1,1'-biphenyl, **125**

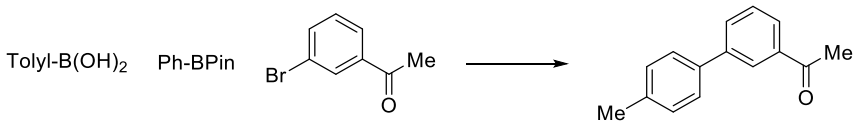


Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), (4-(trifluoromethyl)phenyl)boronic acid pinacol ester (68 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was

subjected to the purification outlined in General Procedure J (silica gel, 5% Et_2O/petroleum ether) to afford the desired product as a white solid (34 mg, 82%).

For spectral data for, see **118** above.

4-Tolylboronic acid vs. phenylboronic acid pinacol ester with 1-(3-bromophenyl)ethan-1-one to give 1-(4'-methyl-[1,1'-biphenyl]-3-yl)ethan-1-one, **126**



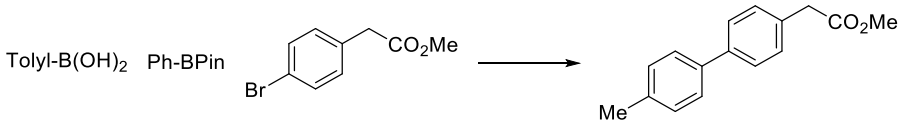
Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), 1-(3-bromophenyl)ethan-1-one (50 mg, 0.25 mmol, 1 equiv), $Pd(dppf)Cl_2 \cdot DCM$ (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 0 – 10% Et_2O/petroleum ether) to afford the desired product as a colourless oil (48 mg, 91%).

^1H NMR ($CDCl_3$, 400 MHz): δ 8.17 (t, J = 1.7 Hz, 1H), 7.91 (ddd, J = 7.7, 1.7, 1.2 Hz, 1H), 7.78 (ddd, J = 7.7, 1.7, 1.2 Hz, 1H), 7.55 – 7.50 (m, 3H), 7.28 (d, J = 7.8 Hz, 2H), 2.66 (s, 3H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 198.2, 141.7, 137.8, 137.7, 137.4, 131.6, 129.7, 129.1, 127.1, 127.0, 126.8, 26.8, 21.2.

The spectral data were consistent with those previously reported in the literature.[155]

4-Tolylboronic acid vs. phenylboronic acid pinacol ester with methyl 2-(4-bromophenyl)acetate to give methyl 2-(4'-methyl-[1,1'-biphenyl]-4-yl)acetate, **127**



Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv),

methyl 2-(4-bromophenyl)acetate (57 mg, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 0 – 20% Et_2O/petroleum ether) to afford the desired product as a colourless liquid (58 mg, 97%).

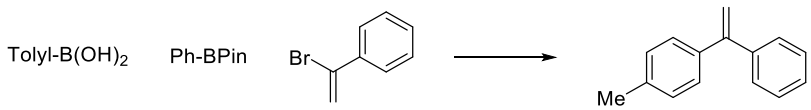
υ_{max} (solid): 3029, 2954, 1735, 1519, 1353, 1247, 1135, 810 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.28 – 7.25 (m, 2H), 3.74 (s, 3H), 3.70 (s, 2H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.6, 139.5, 137.4, 136.6, 132.2, 129.1, 129.0, 126.7, 126.4, 51.6, 40.3, 20.6.

HRMS: exact mass calculated for $[M]^+$ ($C_{16}H_{16}O_2$) requires m/z 240.1150, found m/z 240.1159.

4-Tolylboronic acid vs. phenylboronic acid pinacol ester with (1-bromovinyl)benzene to give 1-methyl-4-(1-phenylvinyl)benzene, **128**



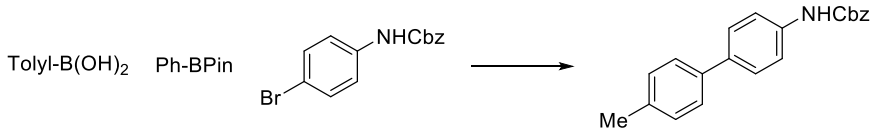
Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), (1-bromovinyl)benzene (32 μL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 5% Et_2O/petroleum ether) to afford the desired product as a pale yellow liquid (46 mg, 96%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36 – 7.30 (m, 5H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.42 (dd, *J* = 13.9, 1.0 Hz, 2H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 150.1, 141.9, 138.8, 137.7, 134.9, 129.0, 128.4, 128.30, 128.27, 127.8, 113.8, 21.3.

The spectral data were consistent with those previously reported in the literature.[156]

4-Tolylboronic acid vs. phenylboronic acid pinacol ester with benzyl (4-bromophenyl)carbamate to give benzyl (4'-methyl-[1,1'-biphenyl]-4-yl)carbamate, **129**



Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), benzyl (4-bromophenyl)carbamate (77 mg, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 0 – 10% Et_2O/petroleum ether) to afford the desired product as a colourless liquid (78 mg, 99%).

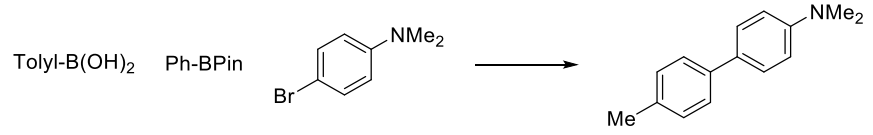
υ_{max} (solid): 3315, 3032, 2921, 1705, 1523, 1506, 1238, 1227, 1068, 808 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56 – 7.50 (m, 2H), 7.48 – 7.33 (m, 9H), 7.23 (d, J = 7.9 Hz, 2H), 6.70 (br. s, 1H), 5.23 (s, 2H), 2.39 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.3, 137.7, 136.8, 136.5, 136.1, 129.5, 128.7, 128.40, 128.36, 127.5, 126.6, 119.0, 67.1, 21.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{20}NO_2$) requires m/z 318.1489, found m/z 318.1489.

4-Tolylboronic acid vs. phenylboronic acid pinacol ester with 4-bromo-*N*,*N*-dimethylaniline to give *N*,*N*,4'-trimethyl-[1,1'-biphenyl]-4-amine, **130**



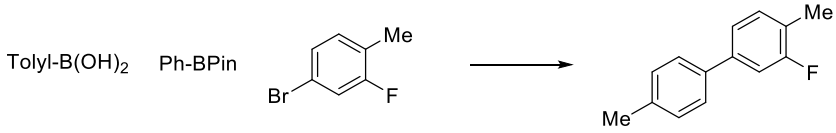
Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), 4-bromo-*N*,*N*-dimethylaniline (50 mg, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 0 – 10% Et_2O/petroleum ether) to afford the desired product as a white solid (45 mg, 85%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 – 7.47 (m, 2H), 7.47 – 7.43 (m, 2H), 7.20 (dd, *J* = 8.4, 0.5 Hz, 2H), 6.84 – 6.78 (m, 2H), 2.99 (s, 6H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 149.9, 138.5, 135.8, 129.5, 127.7, 126.3, 113.0, 40.8, 21.2.

The spectral data were consistent with those previously reported in the literature.[157]

4-Tolylboronic acid vs. phenylboronic acid pinacol ester with 4-bromo-2-fluoro-1-methylbenzene to give 3-fluoro-4,4'-dimethyl-1,1'-biphenyl, **131**



Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), 4-bromo-2-fluoro-1-methylbenzene (32 μL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 2% Et_2O/petroleum ether) to afford the desired product as a white solid (50 mg, quant.).

υ_{max} (solid): 3029, 2921, 2859, 1565, 1502, 1491, 1398, 1133, 808 cm^{-1}.

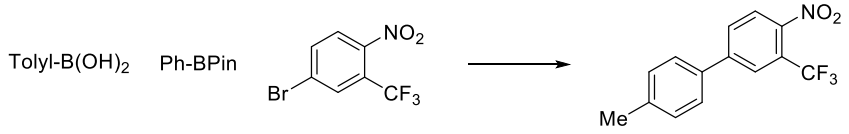
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 – 7.44 (m, 2H), 7.29 – 7.18 (m, 5H), 2.40 (s, 3H), 2.32 (d, *J* = 1.8 Hz, 3H).

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 117.60 (s, 1F).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.1 (d, $^1J_{C\text{-}F}$ = 244.5 Hz), 140.2 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 136.9, 136.6, 131.1 (d, $^3J_{C\text{-}F}$ = 6.1 Hz), 129.1, 126.2, 122.8 (d, $^2J_{C\text{-}F}$ = 17.4 Hz), 121.6 (d, $J_{C\text{-}F}$ = 2.9 Hz), 112.8 (d, $^2J_{C\text{-}F}$ = 22.8 Hz), 20.6, 13.8 (d, $^3J_{C\text{-}F}$ = 3.6 Hz).

HRMS: exact mass calculated for $[M]^+$ ($C_{14}H_{13}F$) requires m/z 200.1001, found m/z 200.1005.

4-Tolylboronic acid vs. phenylboronic acid pinacol ester with 4-bromo-1-nitro-2-(trifluoromethyl)benzene to give 4'-methyl-4-nitro-3-(trifluoromethyl)-1,1'-biphenyl, **132**



Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), 4-bromo-1-nitro-2-(trifluoromethyl)benzene (68 mg, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 0 – 10% Et_2O/petroleum ether) to afford the desired product as a yellow gum (66 mg, 94%).

υ_{max} (solid): 1597, 1532, 1353, 1333, 1323, 1267, 1139, 1046, 815 cm^{-1}.

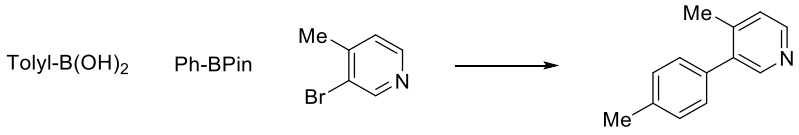
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.99 (d, J = 8.3 Hz, 2H), 7.87 (dd, J = 8.4, 1.7 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 2.43 (s, 3H).

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 59.91 (s, 3F).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 146.3, 139.9, 134.7, 130.8, 130.2, 127.3, 126.3 (q, $^3J_{C\text{-}F}$ = 5.3 Hz), 126.0, 124.5 (q, $^2J_{C\text{-}F}$ = 33.7 Hz), 122.2 (q, $^1J_{C\text{-}F}$ = 273.6 Hz), 21.3. Carbon bearing NO_2 not observed.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{11}F_3NO_2$) requires m/z 282.0742, found m/z 282.0740.

4-Tolylboronic acid vs. phenylboronic acid pinacol ester with 3-bromo-4-methylpyridine to give 4-methyl-3-(*p*-tolyl)pyridine, **133**



Prepared according to General Procedure J using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), 3-bromo-4-methylpyridine (43 mg, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h the reaction mixture was subjected to the purification outlined in General Procedure J (silica gel, 10 – 20% EtOAc/petroleum ether) to afford the desired product as an off-white solid (38 mg, 83%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.42 (app. t, *J* = 2.4 Hz, 2H), 7.23 (dd, *J* = 20.1, 7.9 Hz, 4H), 7.17 (d, *J* = 5.0 Hz, 1H), 2.41 (s, 3H), 2.28 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 150.1, 148.2, 144.6, 137.8, 137.5, 135.1, 129.3, 129.2, 125.3, 21.3, 19.9.

The spectral data were consistent with those previously reported in the literature.[158]

Products from Figure 25

Product Pair 1: 4-Methyl-1,1'-biphenyl **134** and 4-nitro-3-(trifluoromethyl)-1,1'-biphenyl **135**

Prepared according to General Procedure K using 4-tolylboronic acid (34 mg, 0.25 mmol, 1 equiv), phenylboronic acid pinacol ester (51 mg, 0.25 mmol, 1 equiv), bromobenzene (26 µL, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h 4-bromo-1-nitro-2-(trifluoromethyl)benzene

(68 mg, 0.25 mmol, 1 equiv) and H_2O (67.5 µL, 3.75 mmol, 15 equiv) were added. After 24 h the reaction mixture was subjected to the purification outlined in General Procedure K (silica gel, 2 – 10% Et_2O/petroleum ether) to afford 4-methyl-1,1'-biphenyl **134** as a white solid (41 mg, 97%) and 4-nitro-3-(trifluoromethyl)-1,1'-biphenyl **135** as a colourless liquid (56 mg, 84%).

Data 4-methyl-1,1'-biphenyl **134**

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 – 7.57 (m, 2H), 7.53 – 7.48 (m, 2H), 7.47 – 7.40 (m, 2H), 7.36 – 7.29 (m, 1H), 7.29 – 7.23 (m, 2H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 141.3, 138.5, 137.2, 129.6, 128.9, 127.1, 21.2.

The spectral data were consistent with those previously reported in the literature.[14]

Data for 4-nitro-3-(trifluoromethyl)-1,1'-biphenyl **135**

υ_{max} (film): 1537, 1361, 1323, 1264, 1139, 1048, 756 cm^{-1}.

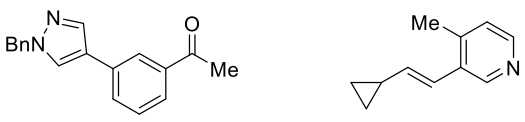
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01 – 7.99 (m, 2H), 7.90 (dd, J = 8.4, 1.6 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.56 – 7.46 (m, 3H).

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 59.91 (s, 3F).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 146.3, 137.6, 131.2, 129.6, 129.5, 127.5, 126.6 (q, $^3J_{C\text{-}F}$ = 5.1 Hz), 126.0, 124.5 (q, $^2J_{C\text{-}F}$ = 34.0 Hz), 122.2 (q, $^1J_{C\text{-}F}$ = 273.4 Hz). Carbon bearing NO_2 not observed.

HRMS: exact mass calculated for $[M]^+$ ($C_{13}H_8F_3NO_2$) requires m/z 267.0507, found m/z 267.0505.

Product Pair 2: 1-(3-(1-benzyl-1H-pyrazol-4-yl)phenyl)ethan-1-one **136** and *trans*-3-(2-cyclopropylvinyl)-4-methylpyridine **137**



Prepared according to General Procedure K using (1-benzyl-1H-pyrazol-4-yl)boronic acid (41 mg, 0.2 mmol, 1 equiv), *trans*-(2-cyclopropylvinyl)boronic acid pinacol

ester (39 mg, 0.20 mmol, 1 equiv), 1-(3-bromophenyl)ethan-1-one (40 mg, 0.20 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (6.6 mg, 0.01 mmol, 4 mol%), K_3PO_4 (127 mg, 0.60 mmol, 3 equiv), 1,4-dioxane (0.8 mL, 0.25 M) and H_2O (18 μL, 1 mmol, 5 equiv). After 1 h 3-bromo-4-methylpyridine (34 mg, 0.20 mmol, 1 equiv) and H_2O (54 μL, 3 mmol, 15 equiv) were added. After 24 h the reaction mixture was subjected to the purification outlined in General Procedure K (silica gel, 35% EtOAc/petroleum ether) to afford 1-(3-(1-benzyl-1H-pyrazol-4-yl)phenyl)ethan-1-one **136** as a yellow gum (41 mg, 75%) and *trans*-3-(2-cyclopropylvinyl)-4-methylpyridine **137** as a colourless oil (26 mg, 82%).

Data for 1-(3-(1-benzyl-1H-pyrazol-4-yl)phenyl)ethan-1-one **136**

υ_{max} (film): 1681, 1608, 1359, 1258, 793 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 8.03 (s, 1H), 7.87 (s, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.69 (s, 1H), 7.65 (dd, *J* = 7.7, 0.5 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.40 – 7.31 (m, 3H), 7.30 – 7.25 (m, 2H), 5.35 (s, 2H), 2.62 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 198.3, 137.8, 137.2, 136.3, 133.3, 130.1, 129.2, 129.1, 128.4, 128.0, 126.60, 126.56, 125.1, 122.8, 56.5, 26.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}N_2O$) requires m/z 277.1335, found m/z 277.1334.

Data for *trans*-3-(2-cyclopropylvinyl)-4-methylpyridine **137**

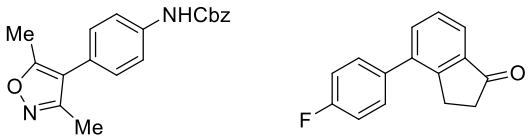
υ_{max} (film): 3008, 1649, 1591, 1411, 957 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.50 (s, 1H), 8.25 (d, *J* = 5.0 Hz, 1H), 7.00 (d, *J* = 5.0 Hz, 1H), 6.54 (d, *J* = 15.7 Hz, 1H), 5.64 (dd, *J* = 15.7, 9.0 Hz, 1H), 2.31 (s, 3H), 1.67 – 1.51 (m, 1H), 0.88 – 0.81 (m, 2H), 0.56 – 0.49 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 147.2, 146.7, 143.3, 138.5, 133.2, 125.0, 122.0, 19.4, 15.1, 7.6.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{11}H_{12}N$) requires m/z 158.0970, found m/z 158.0972.

Product Pair 3: Benzyl (4-(3,5-dimethylisoxazol-4-yl)phenyl)carbamate **138** and 4-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-one **139**



Prepared according to General Procedure K using (3,5-dimethylisoxazol-4-yl)boronic acid (35 mg, 0.25 mmol, 1 equiv), 4-fluorophenylboronic acid pinacol ester (56 mg, 0.25 mmol, 1 equiv), benzyl (4-bromophenyl)carbamate (77 mg, 0.25 mmol, 1 equiv), Pd(dppf)Cl_2·DCM (8.2 mg, 0.01 mmol, 4 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After 1 h 4-bromo-2,3-dihydro-1H-inden-1-one (53 mg, 0.25 mmol, 1 equiv) and H_2O (67.5 µL, 3.75 mmol, 15 equiv) were added. After 24 h the reaction mixture was subjected to the purification outlined in General Procedure K (silica gel, 10% EtOAc/petroleum ether) to afford benzyl (4-(3,5-dimethylisoxazol-4-yl)phenyl)carbamate **138** as an off-white solid (65 mg, 81%) and 4-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-one **139** as an off-white solid (49 mg, 87%).

Data for benzyl (4-(3,5-dimethylisoxazol-4-yl)phenyl)carbamate **138**

υ_{max} (solid): 3274, 1718, 1601, 1539, 1409, 1323, 1219, 1057, 852 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, J = 8.5 Hz, 2H), 7.44 – 7.34 (m, 5H), 7.22 – 7.17 (m, 2H), 6.78 (br. s, 1H), 5.23 (s, 2H), 2.38 (s, 3H), 2.25 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 165.2, 158.9, 153.4, 137.4, 136.1, 130.0, 128.8, 128.6, 128.5, 125.7, 119.1, 116.3, 67.3, 11.7, 10.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{19}N_2O_3$) requires m/z 323.1390, found m/z 323.1387.

Data for 4-(4-fluorophenyl)-2,3-dihydro-1H-inden-1-one **139**

υ_{max} (solid): 2926, 1698, 1517, 1474, 1230, 783 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.56 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.20 – 7.14 (m, 2H), 3.18 – 3.08 (m, 2H), 2.74 – 2.66 (m, 2H).

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 114.42 (m, 1F).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 206.4, 161.9 (d, $^{1}J_{C\text{-}F}$ = 247.6 Hz), 152.0, 139.0, 137.2, 134.7, 134.2 129.6 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 127.5, 122.4, 115.1 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz), 35.8, 25.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{12}FO$) requires m/z 227.0872, found m/z 227.0873.

Results from Table 17

Prepared according to General Procedure L using phenylboronic acid (31 mg, 0.25 mmol, 1 equiv), (4-(2-methoxy-2-oxoethyl)phenyl)boronic acid pinacol ester (76 mg, 0.275 mmol, 1.1 equiv), 1-bromo-4-chlorobenzene (53 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), DavePhos (7.8 mg, 0.02 mmol, 8 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (90 µL, 20 equiv) at **X** °C for 18 h.

Entry	Temperature (°C)	Conversion (%)
1	30	25
2	50	41
3	70	56
4	90	53

Results from Table 18

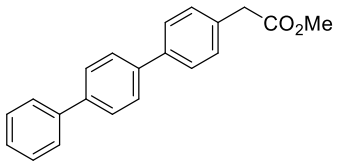
Prepared according to General Procedure L using phenylboronic acid (31 mg, 0.25 mmol, 1 equiv), (4-(2-methoxy-2-oxoethyl)phenyl)boronic acid pinacol ester (76 mg, 0.275 mmol, 1.1 equiv), 1-bromo-4-chlorobenzene (53 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), DavePhos (7.8 mg, 0.02 mmol, 8 mol%),

K_3PO_4 (212 mg, 1 mmol, 4 equiv), 1,4-dioxane (1 mL, 0.25 M) and H_2O (**X** equiv) at 70 °C for 18 h.

Entry	H_2O Equiv (Volume)	Conversion (%)
1	5 (22.5 µL)	48
2	10 (45 µL)	48
3	15 (67.5 µL)	72
4	20 (90 µL)	56
5	25 (112.5 µL)	61
6	30 (135 µL)	55

Characterisation of products from Figure 26

Methyl 2-([1,1':4',1''-terphenyl]-4-yl)acetate, **143**



Prepared according to General Procedure M using phenylboronic acid (31 mg, 0.25 mmol, 1 equiv), (4-(2-methoxy-2-oxoethyl)phenyl)boronic acid pinacol ester (76 mg, 0.275 mmol, 1.1 equiv), 1-bromo-4-chlorobenzene (53 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), DavePhos (7.8 mg, 0.02 mmol, 8 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), 1,4-dioxane (0.83 mL, 0.3 M) and H_2O (67.5 µL, 15 equiv). After 18 h the reaction mixture was subjected to the purification outlined in General Procedure M (silica gel, 2 – 10% Et_2O/petroleum ether) to afford the desired compound as an off-white solid (64 mg, 84%).

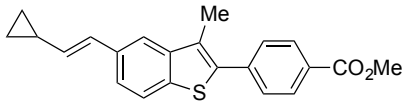
υ_{max} (solid): 3036, 2956, 2922, 1735, 1485, 1437, 1146, 815, 761 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.67 (s, 4H), 7.64 (d, J = 7.3 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.40 – 7.34 (m, 3H), 3.73 (s, 3H), 3.69 (s, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.0, 140.7, 140.2, 139.7, 139.6, 133.1, 129.8, 128.8, 127.5, 127.42, 127.35, 127.2, 127.1, 52.1, 40.9.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_{21}H_{22}NO_2$) requires m/z 320.1645, found m/z 320.1645.

Methyl *trans*-4-(5-(2-cyclopropylvinyl)-3-methylbenzo[*b*]thiophen-2-yl)benzoate, **144**



Prepared according to General Prodedure M using (4-(methoxycarbonyl)phenyl)boronic acid (45 mg, 0.25 mmol, 1 equiv), 2-bromo-5-chloro-3-methylbenzo[*b*]thiophene (72 mg, 0.275 mmol, 1.1 equiv), *trans*-(2-cyclopropylvinyl)boronic acid pinacol ester (53 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), DavePhos (7.8 mg, 0.02 mmol, 8 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), 1,4-dioxane (0.83 mL, 0.3 M) and H_2O (67.5 µL, 15 equiv). After 18 h the reaction mixture was subjected to the purification outlined in General Procedure M (silica gel, 2 – 10% Et_2O/petroleum ether) to afford the desired compound as a white solid (35 mg, 40%).

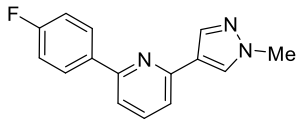
υ_{max} (solid): 2992, 2946, 1713, 1603, 1432, 1274, 1183, 1106, 957, 859, 771 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 8.12 (d, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.66 – 7.58 (m, 3H), 7.38 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.62 (d, *J* = 15.7 Hz, 1H), 5.83 (dd, *J* = 15.7, 8.9 Hz, 1H), 3.95 (s, 3H), 2.48 (s, 3H), 1.65 – 1.58 (m, 1H), 0.90 – 0.82 (m, 1H), 0.60 – 0.53 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.8, 141.6, 139.5, 137.3, 137.2, 134.6, 134.5, 129.8, 129.5, 129.2, 128.7, 127.5, 122.6, 122.1, 119.4, 52.2, 14.6, 12.8, 7.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{21}O_2S$) requires m/z 349.1262, found m/z 349.1266.

2-(4-Fluorophenyl)-6-(1-methyl-1H-pyrazol-4-yl)pyridine, **145**



Prepared according to General Procedure M using 4-fluorophenylboronic acid (35 mg, 0.25 mmol, 1 equiv), (1-methyl-1H-pyrazol-4-yl)boronic acid pinacol ester (57 mg, 0.275 mmol, 1.1 equiv), 2-bromo-6-chloropyridine (53 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), DavePhos (7.8 mg, 0.02 mmol, 8 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), 1,4-dioxane (0.83 mL, 0.3 M) and H_2O (67.5 µL, 15 equiv). After 18 h the reaction mixture was subjected to the purification outlined in General Procedure M (silica gel, 10 – 50% EtOAc/petroleum ether) to afford the desired compound as a yellow gum (45 mg, 71%).

υ_{max} (solid): 1603, 1593, 1571, 1558, 1511, 1457, 1439, 1221, 1171, 975, 798 cm^{-1}.

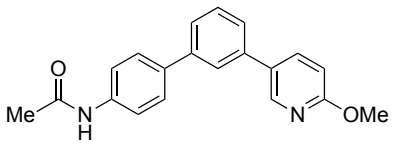
^1H NMR ($CDCl_3$, 400 MHz): δ 8.09 – 8.04 (m, 2H), 8.01 (d, *J* = 3.1 Hz, 2H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.50 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.38 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.16 (app. t, *J* = 8.7 Hz, 2H), 3.98 (s, 3H).

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 113.32 (s, 1F).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.5 (d, $^1J_{C\text{-}F}$ = 248.2 Hz), 155.9, 151.7, 137.6, 137.4, 135.6 (d, $J_{C\text{-}F}$ = 3.4 Hz), 129.0, 128.7 (d, $^3J_{C\text{-}F}$ = 8.5 Hz), 123.9, 117.6, 117.3, 115.5 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 39.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{13}FN_3$) requires m/z 254.1088, found m/z 254.1088.

N-(3'-(6-methoxypyridin-3-yl)-[1,1'-biphenyl]-4-yl)acetamide, **146**



Prepared according to General Procedure M using (4-acetamidophenyl)boronic acid (45 mg, 0.25 mmol, 1 equiv), 1-bromo-3-chlorobenzene (53 mg, 0.275 mmol, 1.1 equiv), 2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (65 mg, 0.275, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), DavePhos (7.8 mg, 0.02 mmol, 8 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), 1,4-dioxane (0.83 mL, 0.3 M) and H_2O (67.5 µL, 15 equiv). After 18 h the reaction mixture was subjected to the

purification outlined in General Procedure M (silica gel, 10 – 50% EtOAc/petroleum ether) to afford the desired compound as a white solid (46 mg, 58%).

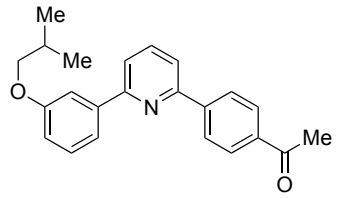
υ_{max} (solid): 3286, 2946, 2920, 2847, 1657, 1595, 1538, 1499, 1474, 1289, 1021, 835, 792 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 8.44 (d, *J* = 2.3 Hz, 1H), 7.84 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.70 (s, 1H), 7.60 (s, 4H), 7.58 – 7.54 (m, 1H), 7.53 – 7.47 (m, 2H), 6.84 (d, *J* = 8.6 Hz, 1H), 4.00 (s, 3H), 2.21 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.9, 164.2, 145.5, 141.7, 138.9, 137.3, 130.5, 129.9, 128.1, 126.3, 125.9, 125.7, 120.7, 111.3, 54.0, 30.1, 25.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{19}N_2O_2$) requires m/z 319.1442, found 319.1441.

1-(4-(6-(3-Isobutoxyphenyl)pyridin-2-yl)phenyl)ethan-1-one, **147**



Prepared according to General Procedure M using (3-isobutoxyphenyl)boronic acid (49 mg, 0.25 mmol, 1 equiv), 2-bromo-6-chloropyridine (53 mg, 0.275 mmol, 1.1 equiv), 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-one (68 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), DavePhos (7.8 mg, 0.02 mmol, 8 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), 1,4-dioxane (0.83 mL, 0.3 M) and H_2O (67.5 μL, 15 equiv). After 18 h the reaction mixture was subjected to the purification outlined in General Procedure M (silica gel, 5 – 15% EtOAc/petroleum ether) to afford the desired compound as a yellow liquid (43 mg, 50%).

υ_{max} (solid): 2951, 2921, 2866, 1679, 1564, 1456, 1268, 1216, 1034, 805, 779.

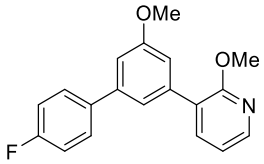
^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.4 Hz, 2H), 8.09 (d, *J* = 8.4 Hz, 2H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.79 – 7.71 (m, 3H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.9

Hz, 1H), 6.99 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.84 (d, *J* = 6.5 Hz, 2H), 2.67 (s, 3H), 2.19 – 2.12 (m, 1H), 1.07 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 197.9, 159.8, 158.1, 155.4, 143.7, 140.6, 137.6, 137.2, 129.7, 128.8, 127.1, 119.7, 119.2, 115.3, 113.4, 74.6, 28.4, 26.8, 19.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{23}H_{24}NO_2$) requires m/z 346.1801, found 346.1802.

3-(4'-Fluoro-5-methoxy-[1,1'-biphenyl]-3-yl)-2-methoxypyridine, **148**



Prepared according to General Procedure M using 4-fluorophenylboronic acid (35 mg, 0.25 mmol, 1 equiv), (2-methoxypyridin-3-yl)boronic acid pinacol ester (65 mg, 0.275 mmol, 1.1 equiv), 1-bromo-3-chloro-5-methoxybenzene (61 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), 1,4-dioxane (0.83 mL, 0.3 M) and H_2O (67.5 μL, 15 equiv). After 18 h the reaction mixture was subjected to the purification outlined in General Procedure M (silica gel, 1 – 4% EtOAc/petroleum ether) to afford the desired compound as a colourless gum (45 mg, 58%).

υ_{max} (film): 2950, 1578, 1513, 1388, 1217, 1204, 1016, 832 cm^{-1}.

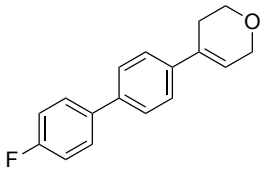
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.66 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.30 (t, *J* = 1.5 Hz, 1H), 7.17 – 7.09 (m, 3H), 7.08 – 7.06 (m, 1H), 6.99 (dd, *J* = 7.3, 5.0 Hz, 1H), 4.00 (s, 3H), 3.90 (s, 3H).

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 115.35 (s, 1F).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 163.03 (d, $^1J_{C\text{-}F}$ = 246.4 Hz), 161.3, 160.3, 146.5, 142.1, 139.1, 137.6 (d, $J_{C\text{-}F}$ = 2.9 Hz), 129.3 (d, $^3J_{C\text{-}F}$ = 7.8 Hz), 124.8, 121.1, 117.5, 116.2, 116.1 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 114.3, 112.5, 55.9, 54.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{17}FNO_2$) requires m/z 310.1238, found m/z 310.1238.

4-(4'-Fluoro-[1,1'-biphenyl]-4-yl)-3,6-dihydro-2*H*-pyran, **149**



Prepared according to General Procedure M using (4-fluorophenyl)boronic acid (35 mg, 0.25 mmol, 1 equiv), 1-bromo-4-chlorobenzene (53 mg, 0.275 mmol, 1.1 equiv), 2-(3,6-dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (58 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), 1,4-dioxane (0.83 mL, 0.3 M) and H_2O (67.5 µL, 15 equiv). After 18 h the reaction mixture was subjected to the purification outlined in General Procedure M (silica gel, 5 – 20% Et_2O/petroleum ether) to afford the desired compound as a white solid (30 mg, 47%).

υ_{max} (solid): 2923, 2853, 1595, 1495, 1238, 1207, 1130, 809.

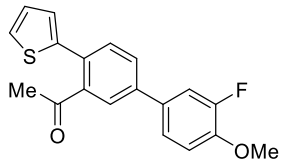
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.54 (m, 2H), 7.54 – 7.44 (m, 4H), 7.17 – 7.06 (m, 2H), 6.22 – 6.16 (m, 1H), 4.35 (q, *J* = 2.8 Hz, 2H), 3.96 (t, *J* = 5.5 Hz, 2H), 2.59 – 2.54 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0 (d, $^1J_{C\text{-}F}$ = 246.6 Hz), 138.7, 138.6, 136.3 (d, $J_{C\text{-}F}$ = 3.4 Hz), 133.1, 128.0 (d, $^3J_{C\text{-}F}$ = 8.1 Hz), 126.5, 124.6, 122.1, 115.16 (d, $^2J_{C\text{-}F}$ = 21.5 Hz), 65.4, 64.0, 26.7.

^{19}F NMR ($CDCl_3$, 376 MHz): δ – 115.72 (s, 1F).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{16}FO$) requires m/z 255.1185, found 255.1184.

1-(3'-Fluoro-4'-methoxy-4-(thiophen-2-yl)-[1,1'-biphenyl]-3-yl)ethan-1-one, **150**



Prepared according to General Procedure M using thiophen-2-ylboronic acid (32 mg, 0.25 mmol, 1 equiv), (3-fluoro-4-methoxyphenyl)boronic acid pinacol ester (69 mg, 0.275 mmol, 1.1 equiv), 1-(2-bromo-5-chlorophenyl)ethan-1-one (64 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), DavePhos (7.8 mg, 0.02 mmol, 8 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), 1,4-dioxane (0.83 mL, 0.3 M) and H_2O (67.5 μL, 15 equiv). After 18 h the reaction mixture was subjected to the purification outlined in General Procedure M (silica gel, 15 – 20% EtOAc/petroleum ether) to afford the desired compound as a colourless gum (53 mg, 65%).

υ_{max} (solid): 3107, 3071, 3004, 2967, 2941, 2917, 2844, 1692, 1519, 1483, 1439, 1271, 1245, 1230, 1176, 1139, 817, 711 cm^{-1}.

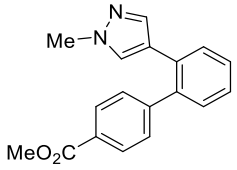
^1H NMR ($CDCl_3$, 400 MHz): δ 7.65 – 7.61 (m, 2H), 7.53 (dd, *J* = 7.1, 1.5 Hz, 1H), 7.41 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.10 (dd, *J* = 5.1, 3.5 Hz, 1H), 7.07 – 7.02 (m, 2H), 3.94 (s, 3H), 2.18 (s, 3H).

^{19}F NMR ($CDCl_3$, 376 MHz): δ –134.50 (dd, *J* = 11.8, 8.9 Hz, 1F).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 205.1, 152.8 (d, $^1J_{C\text{-}F}$ = 246.4 Hz), 147.7 (d, $^3J_{C\text{-}F}$ = 10.7 Hz), 142.1, 141.3, 139.6, 132.8 (d, $^3J_{C\text{-}F}$ = 6.7 Hz), 131.3, 131.2, 128.6, 128.1, 127.9, 127.0, 125.8, 122.8 (d, $J_{C\text{-}F}$ = 3.7 Hz), 114.8 (d, $^2J_{C\text{-}F}$ = 19.0 Hz), 113.9, 56.5, 30.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{16}FO_2S$) requires m/z 327.0850, found m/z 327.0850.

Methyl 2'-(1-methyl-1H-pyrazol-4-yl)-[1,1'-biphenyl]-4-carboxylate, **151**



Prepared according to General Procedure M using (4-(methoxycarbonyl)phenyl)boronic acid (45 mg, 0.25 mmol, 1 equiv), (1-methyl-1H-pyrazol-4-yl)boronic acid pinacol ester (57 mg, 0.275 mmol, 1.1 equiv), 1-bromo-2-chlorobenzene (53 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), 1,4-dioxane (0.83 mL, 0.3 M) and H_2O (67.5 µL, 15 equiv). After 18 h the reaction mixture was subjected to the purification outlined in General Procedure M (silica gel, 2 – 30% EtOAc/petroleum ether) to afford the desired compound as a yellow gum (45 mg, 62%).

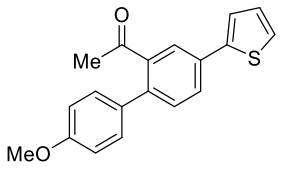
υ_{max} (film): 2950, 2928, 1718, 1610, 1437, 1279, 1115, 1104, 759, 711 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.39 (td, *J* = 7.4, 1.8 Hz, 1H), 7.35 – 7.28 (m, 4H), 7.22 (s, 1H), 6.87 (s, 1H), 3.93 (s, 3H), 3.77 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 167.0, 146.9, 139.1, 138.8, 131.1, 130.4, 129.7, 129.5, 129.3, 128.9, 128.7, 128.2, 126.8, 121.7, 52.1, 38.9.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{17}N_2O_2$) requires m/z 293.1285, found m/z 293.1284.

1-(4'-Methoxy-4-(thiophen-2-yl)-[1,1'-biphenyl]-2-yl)ethan-1-one, **152**



Prepared according to General Procedure M using 4-methoxyphenylboronic acid (38 mg, 0.25 mmol, 1 equiv), thiophen-2-ylboronic acid pinacol ester (58 mg, 0.275 mmol, 1.1 equiv), 1-(2-bromo-5-chlorophenyl)ethan-1-one (64 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), DavePhos (7.8 mg, 0.02 mmol, 8 mol%), K_3PO_4 (212 mg, 1 mmol, 4 equiv), 1,4-dioxane (0.83 mL, 0.3 M) and H_2O (67.5 µL, 15 equiv). After 18 h the reaction mixture was subjected to the purification outlined in General Procedure M (silica gel, 10 – 15% Et_2O/petroleum ether) to afford the desired compound as a cloudy gum (51 mg, 66%).

υ_{max} (solid): 1675, 1517, 1482, 1247, 703 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68 – 7.63 (m, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 5.1 Hz, 1H), 7.10 (dd, *J* = 5.0, 3.6 Hz, 1H), 7.03 (d, *J* = 3.5 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H), 2.19 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 205.2, 159.8, 141.9, 141.5, 140.7, 132.1, 131.1, 130.6, 128.6, 128.2, 128.1, 127.7, 126.8, 125.7, 114.5, 55.5, 30.4.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{17}O_2S$) requires m/z 309.0944, found m/z 309.0943.

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