Design and Development of Halodeboronation Methods for Organic Synthesis

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Thesis submitted to the University of Strathclyde in fulfilment of the requirements for the degree of Doctor of Philosophy

By

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Abstract

Boronic acids and derivatives are one of the most useful classes of compounds in organic synthesis. Methodologies involving diboron systems have emerged recently as a rapid and powerful approach to synthesize complex molecules. Selectivity in these systems is a key aspect and is typically achieved through protecting group strategies. In this approach one boron species is rendered inert under reaction conditions, while the unprotected boron residue can be selectively manipulated. Nonetheless those methods have the drawback of requiring additional actions to allow subsequent functionalisation (such as removal of the protecting group), which limits overall efficiency. However, unprotected diboron systems can undergo a series of equilibria while in solution, which can lead to side reactions and therefore by-products or mixture of products. For instance, inorganic base in reaction mixtures can trigger speciation between the boron compounds, leading to a complex scramble of starting materials and therefore products.

The work described in this manuscript investigated the possibility of conducting a chemoselective chlorination, implementing non-protected diboron systems. This would allow the discriminatory functionalisation of boronic acids in the presence of BPin esters, selectively generating an electrophile species *in situ*. By successfully performing the selective halogenation, the development of the first selective di-nucleophile Suzuki-Miyaura cross-coupling reaction employing two distinct boron species was endeavoured and accomplished.

The chemoselectivity in this case could be achieved by a selective activation of boronic acid species over boronic ester in the reaction mixture. The activation of boronic acids approach was then applied to synthesise SPECT imaging agents. The developed technique would provide a metal-free alternative towards the usual metal-catalysed iododeboronation processes.

Acknowledgements

First of all, I have to thank my supervisor Dr. Allan J. B. Watson, for guidance and help through my PhD. Secondly I must pay a special thanks to Prof. Dr. Graham, Dr. Davidson, Isabel Scott and Lesley Liggat, for all the support through the difficult days. I also want to thank my second supervisor Prof. Billy Kerr and Harry Kelly for giving me the opportunity to pursue my PhD in Scotland.

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Great appreciation goes to the late Edson Nobrega and Prof. Dr. Luiz Fernando da Silva Jr, whose passion for organic chemistry inspired me to pursue a degree in the field.

Abbreviations

Ac – acyl

Acac – acetylacetonato

BDE – bond dissociation energy

BINAP – 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

BINOL – 1,1’-bi-2-naphthol

Bn – benzyl

Boc – *tert*-butoxycarbonyl

BQ – 1,4-benzoquinone

BrettPhos – 2-(dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl

B_2Pin_2 – bis(pinacolato)diboron

Bpy – bipyridyl

Cat – catalyst

CEL reaction – Chan-Evans-Lam reaction

COD – 1,5-cyclooctadiene

CPME – cyclopentyl methyl ether

Cy – cyclohexyl

CyJohnPhos – (2-biphenyl)dicyclohexylphosphine

DAN – 1,8-diaminonaphthalene

DavePhos – 2-dicyclohexylphosphino-2’-(*N,N*-dimethylamino)biphenyl

DBDMH – 1,3-dibromo-5,5-dimethylhydantoin

DCDMH – 1,3-dichloro-5,5-dimethylhydantoin

DCE – dichloroethane

DCM – dichloromethane

DFT – density functional theory

DIAD – diisopropyl azodicarboxylate

DMAP – dimethylamino pyridine

DMC – dimethyl carbonate

DMF – *N*,*N*-dimethyl formamide

DMSO – dimethyl sulfoxide

Dppb – 1,4-bis(diphenylphosphino)butane

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

Dtbbpy – 4,4’-di-*tert*-butylbipyridyl

DTBP – di-*tert*-butyl peroxide

EBT – electrophilic borate trapping

EDG – electron donating group

ENG – electron neutral group

EWG – electron withdrawing group

Equiv. – equivalent(s)

Et – ethyl

FXa inhibitor – factor Xa (‘xabans’) inhibitor

HPLC – high performance liquid chromatography

*i*Pr – *iso*-propyl

Me – methyl

MIDA – methyliminodiacetic acid

MS – molecular sieves

NIMI – *N*-iodo-morpholinium iodide

NIS – *N*-iodo succinimide

NCS – *N*-chloro succinimide

NMP – *N*-methyl-2-pyrrolidone

NMR – nuclear magnetic resonance

OTf – Triflate

Dba - dibenzylideneacetonato

PE – petroleum ether bp 40°-60°

Pin – pinacolato

Rt – room temperature

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

SAR – structure-activity relationship

SMCC – Suzuki-Miyaura cross-coupling

SPECT - single-photon emission computed tomography

SPhos – 2-dicyclohexylphosphino-2'-6'-dimethoxybiphenyl

TBAF – tetra-*n*-butylammonium fluoride

*t*Bu – *tert*-butyl

TCICA – trichloro isocianuric acid

THF – tetrahydrofuran

TM – transition-metal

TMS – trimethyl silyl

TS – transition state

XPhos – 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

(*R*,*R*)-CF_3-WalPhos – (R)-1-{(R_P)-2-[2-(diphenylphosphino)phenyl]ferrocenyl}ethylbis[3,5-bis-(trifluoromethyl)phenyl]phosphine

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1 Introduction

1.1 Boronic acids and derivatives

1.1.1 General aspects

Although the first isolation of a boronic acid was reported in 1860 by Frankland,[1] it was not until the late 1980s that the field of boron chemistry ascended, pioneered by the ground-breaking works from Brown,[2] Matteson,[3] and Suzuki and Miyaura.[4] The applicability of organoboron compounds in organic synthesis is vast, acting not only as a versatile tool for derivatisation but also as a Lewis acid for several types of reactions,[5] or even as sensors for biomolecular recognition in chemical biology.[6] Through the past few years, remarkable advances have been conquered in the area which has led to more reliable methodologies and milder reaction conditions, as well as better understanding of mechanisms and reactivity.[1]

Boron has two naturally occurring and stable isotopes, ^{11}B and ^{10}B, the first one being the most abundant. With six valence electrons, neutral boron species appears predominantly in its sp^2-hybridised form, with a trigonal planar molecular geometry that holds a perpendicular vacant p-orbital (Figure 1).

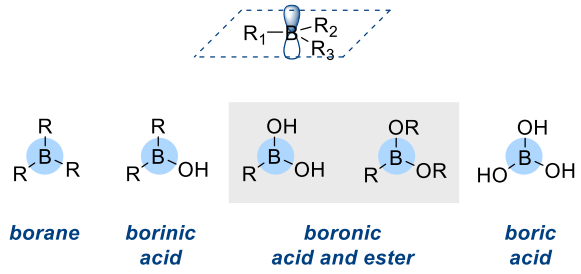


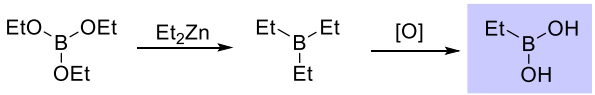
Figure 1 - Boron centre hybridisation and oxygen-containing boron species

The resulting product of onefold oxidation of boranes is borinic acid, a species significantly more unstable than boranes.[1] Products of second oxidation of boranes, boronic acids are structurally a trivalent boron-containing compound with one carbon-based substituent and two hydroxy groups (or alkoxy groups in the case of boronic ester). Different from carboxylic acids, boronic acids are not found in nature

and require to be synthesized from a primary source of boron, such as boric acid and borates (boron-containing oxyanions). The third oxidation product of boranes is boric acid, which is a very stable and environmental friendly compound. The most common boron species employed in catalysis are shown above in Figure 1, however only the highlighted boronic acids and esters will be covered in this work.

1.1.2 Synthesis of boronic acids and derivatives

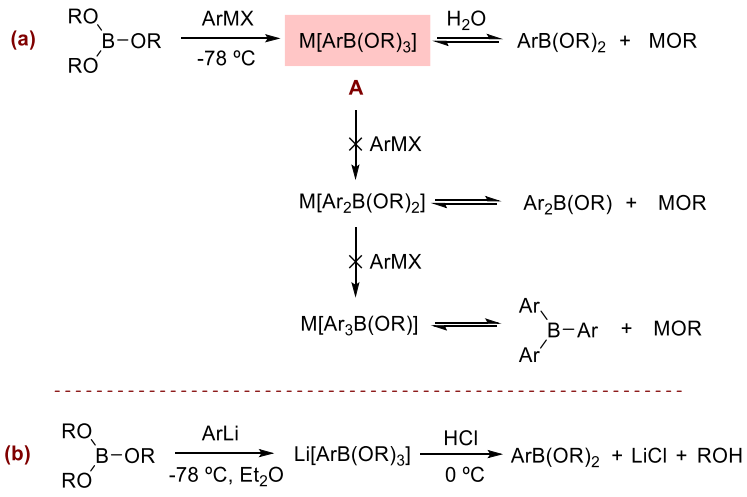
As mentioned previously, the first isolation of an organoboron compound occurred in the 19th century when diethylzinc was treated with $B(OEt)_3$ to form the air-sensitive triethylborane, which was slowly oxidised under ambient conditions, affording ethylboronic acid (Scheme 1).[7,8] As an alternative to zinc reactants, organolithium and magnesium reagents could also be employed in the synthesis of boronic acids.[2,9,10]



Scheme 1 - Frankland's procedure for the synthesis of ethylboronic acid

Whilst the electrophilic borate trapping (EBT) approach, first described by Frankland, remains one of the most common methods towards the synthesis of boronic acids and derivatives,[1] the development of more efficient conditions and stable starting materials to install the carbon-boron bond have been investigated over the past few decades. In the early 1930s, Johnson's group provided a solution for the low yielding protocols to prepare phenylboronic acids by the addition of methylborate (or boron trifluoride) into a solution of phenylmagnesium bromide.[9] The Grignard reactant was gradually added to a solution of trialkylborate at low temperatures in order to prevent intermediate **A** from forming the undesired analogous borane or borinic acid through an additional Grignard reagent displacement (Scheme 2a). The intermediate could then be hydrolysed to the free boronic acid by aqueous workup, albeit in reduced yields due to the solubility of

products in aqueous medium, an issue particularly prominent with more polar substrates.[10]

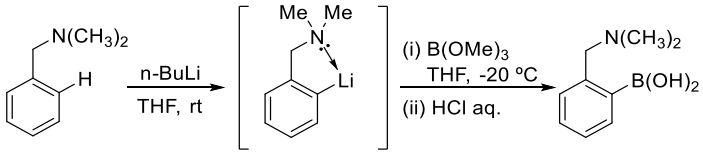


Scheme 2 - Series of equilibria involved in the EBT methodology

In order to overcome isolation issues, Brown and co-workers reported the reaction of triisopropylborate with organolithium reagents at -78 °C (Scheme 2b). The reaction would deliver a similar intermediate as shown previously which, upon treating with hydrochloric acid at 0 °C, afforded the desired boronic ester. The method afforded the product with a higher purity and easier purification than the previously described procedure due to the formation of lithium chloride and isopropanol during workup.[2] The methodology involving the *in situ* generation of an organolithium reagent was first described in the late 1990s, and could be achieved by treating an aryl halide with *n*-butyllithium which would rapidly react with isopropylborate, delivering the desired boronic acid in good yields, *via* subsequent acidic quench.[11,12] The analogous pinacol boronic ester could also be synthesized through a crystallisation to provide the boroxine, followed by a treatment with pinacol in toluene.[11] The process is amenable to a wide range of temperatures, being optimum at -40 °C, providing comparable yields even at 0 °C. The success of this protocol rests in the lithium-halogen exchange process, which has been proven to be faster than the reaction between *n*-BuLi and isopropyl borate while minimising the side-reactions.[2] Li and Nelson conducted studies towards this

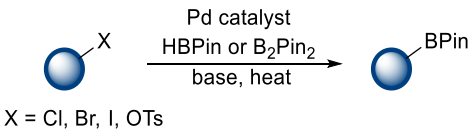
method in 2002 and demonstrated its broad scope, delivering products such as functionalised aryl, heteroaryl and even α-haloaryl boron species.[12]

Another possible approach using the electrophilic borate trapping methodology is the direct *ortho*-metalation assisted by organolithium reagents (Scheme 3).[13,14] In this case, the presence of a coordinating group such as amines, esters and carbamates can direct an *ortho*-lithiation, giving the metallated intermediate, which can be trapped by boric esters and provide the desired product. The process allows access to a variety of interesting motifs such as heteroaryl and alkenylboron species and hence is a reliable approach to synthesise valuable intermediates.[15,16]



Scheme 3 - *Ortho*-directed borylation

Although the metal-halogen exchange process is still applied on large-scale synthesis,[1] the search for more air- and moisture-stable procedures remains a promising field of research. Perhaps the most common process to access organoboron building blocks in both industry and academia is *via* transition metal catalysis, which enables the conversion of a C-H or a C-X (where X = Cl, Br, I or OTs) bond to a C-B bond (Scheme 4).[17–20]

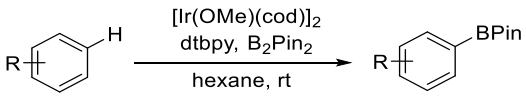


Scheme 4 - General reaction scheme for transition metal-catalysed borylations

Miyaura published a ground-breaking work in the 1990s which introduced bis(pinacolato)diboron (B_2Pin_2) as a nucleophilic borylating agent for Pd-catalysed reaction with organohalides or pseudohalides.[17] Notwithstanding its importance as a prime example of C-B bond formation, a more atom-economical approach was developed by Masuda and co-workers who used H-BPin for borylation of halides

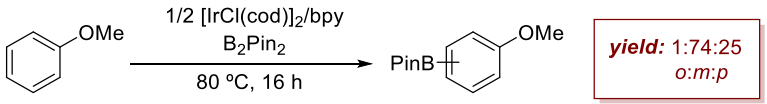
and triflates.[21] Subsequent efforts towards the design of new borane and diboron compounds have been foregathered to improve aspects including functional group tolerance, stability through purification and sensitivity towards hydrolysis.[22–24]

Following a seminal report by Smith and Maleczka,[25] Ir-catalysed C-H borylation was efficiently developed by Hartwig and co-workers (Scheme 5).[26,27] Hartwig's group described both sp^2 and sp^3 C-H borylation methods in the late 90s, employing rhenium as well as rhodium, and succeeded in meliorating the efficiency and stability of the process. The group not only accomplished the synthesis of various boronic esters, but also demonstrated that a subsequent derivatisation to the corresponding boronic acids and trifluoroborates could be achieved.[28,29]



Scheme 5 - General reaction conditions for Hartwig's borylations

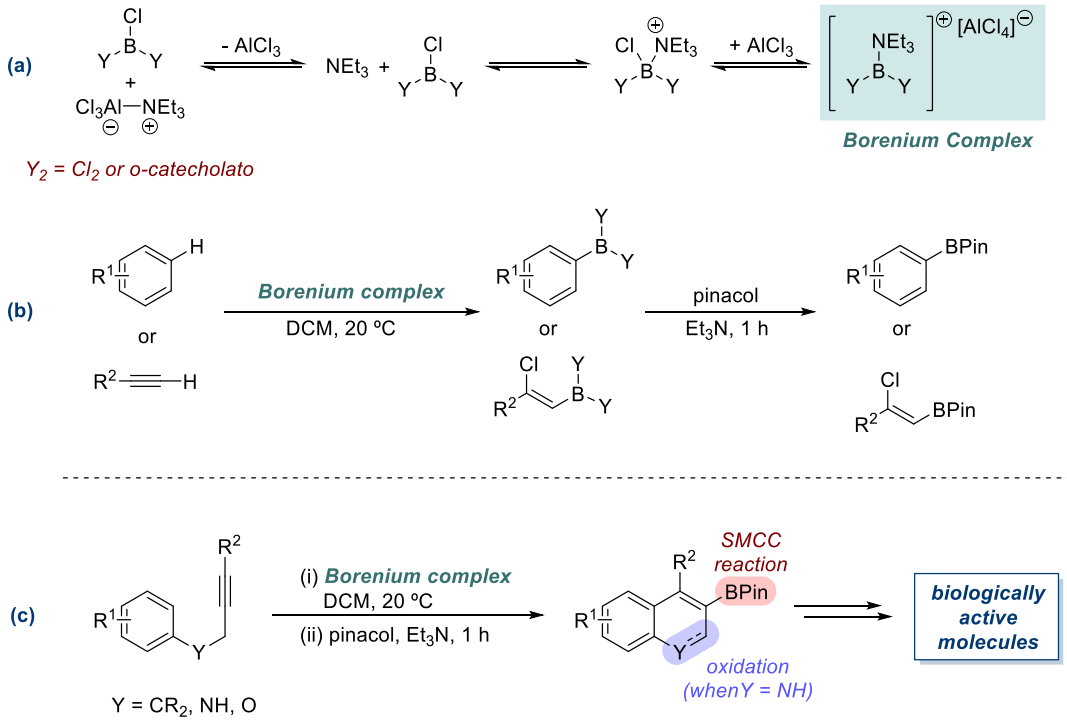
Despite initial difficulties encountered mainly regarding regioselectivity of borylation (Scheme 6), issues related to reaction efficiency and catalyst deactivation were overcome, which translate directly into functional group tolerance. After extensive studies around the subject, the regioselective borylation of arenes was conducted basing its reliance on steric effects.[26] In contrast to the rationale to access regioselective products from arenes, the site-selectivity for the borylation of heteroarenes is largely controlled by electronic effects.[30]



Scheme 6 - Example of regioselectivity issue observed from Hartwig's work

More recently, Ingleson and co-workers examined the use of inexpensive boron sources, Lewis acid species and mild conditions for borylations. The entire process relies on a series of equilibria to form the key intermediate descrived in Scheme 7a,[31] which are driven by halide transfer and affinity between the boron centre and the activating amine. To achieve the formation of the desired borenium cation, the

presence of an amine was required as an activating agent for *B*-chlorocatecholborane (Cl-BCat) or BCl_3 to promote the halide abstraction.[32–34] Since the halide transfer from boron to aluminium is a series of equilibria, the formed complex $[Y_2B(amine)]^+[AlCl_4]^-$ can disproportionate back to a mixture of Lewis acid species and $Y_2B(amine)Cl$, and the latter on the free amine and Y_2BCl.

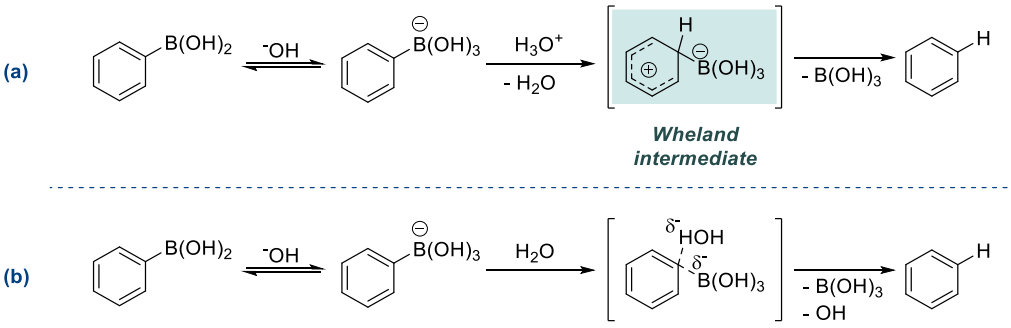


Scheme 7 - (a) Equilibria for the formation of borenium complex; (b) Formation of desired boronic pinacol esters; (c) Application of methodology to prepare active molecules

An appealing feature of employing borenium cations is illustrated in Scheme 7b. In this example, the bench stable boronic ester could be accessed *via* a direct borylation of an arene followed by speciation with pinacol, delivering important compounds for further derivatisation. By enabling access to both aryl and polysubstituted vinyl boronic esters, this methodology could be employed in conjunction with other subsequent transformations, such as the cascade borylative cyclisation depicted in Scheme 7c, which could then be followed by Suzuki-Miyaura cross-coupling and oxidation to afford biologically relevant molecules.[34]

1.1.3 Protodeboronation

Boron species are known to withstand different reaction conditions, but protodeboronation can be a drawback while scoping a methodology.[35] Kuivila tried to solve this in the 1960s through detailed kinetic work that investigated not only the stability of arylboronic acids in water, but also identified protodeboronation mechanisms under acidic and basic pH buffers[36] and metal salts,[37] addressing potential issues for a range of relevant reactions, including oxidation and homocoupling by-products. Protodeboronation studies employing metal salts (such as Cu and Zn) are important since the presence of them can significantly affect, for instance, the Chan-Evans-Lam reaction (a cross-coupling reaction between an aryl boronic acid and an alcohol or an amine to form the corresponding secondary aryl amines or aryl ethers), in addition to the oxidised by-products which the coupling is notorious for generating. The studies under a basic pH buffer would be pertinent to the Suzuki-Miyaura cross-coupling (SMCC) conditions, since super-stoichiometric amounts of inorganic bases are employed in the transformation.[35] The results of Hammett analysis conducted by the Lloyd-Jones group suggest a slightly positive-charged aryl ring. It corroborates with the direct protonolysis mechanism instead of cleavage *via* a Wheland intermediate (Scheme 8), where there is a positive charge in resonance through the aromatic ring, forming a benzenium ion. The electronic nature of the substituents on the aromatic ring also plays an important role, since both boronate equilibria and the rate of carbon-boron bond cleavage (which leads to protodeboronation) conflict in electronic demands.



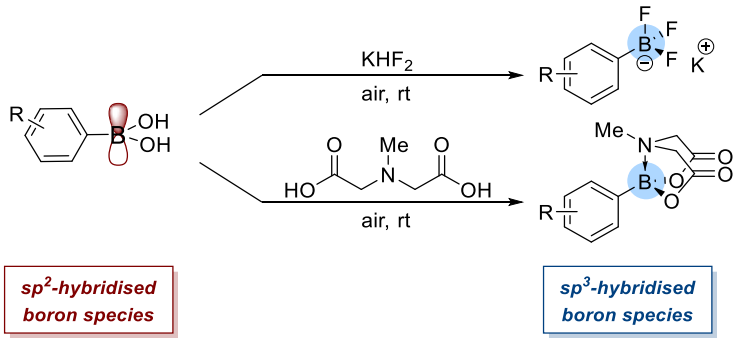
Scheme 8 - Cleavage of C-B bond *via* (a) a Wheland intermediate and (b) a base-catalysed direct protonolysis

Lloyd-Jones and co-workers described through elaborate DFT and NMR studies, that the tendency to protodeboronate surpasses the nature of the boron substituents, showing the electronic effects of the aromatic ring play an extremely important role in the correlation between the aqueous pH-rates and its propensity to protodeboronation.[38,39] Protodeboronation under classic Suzuki–Miyaura coupling conditions can become more prominent than anticipated when base concentration and solvation are coupled with the multivariable cross-coupling sequence.

Equally problematic is the protodeboronation mechanism iniciated by metal-ions.[37] Metals such as silver, cadmium and zinc are examples in the list of metals that can undergo electrophilic displacement with areneboronic acids. Copper catalysts are notorious for producing significant amounts of those by-products, as it is seen in the Chan-Evans-Lam coupling reaction, althought its mechanism remains unclear. To overcome the features described, protecting groups and activation strategies were developed together with catalysts to accelerate the cross-coupling and therefore supress the side reaction.[35]

1.1.4 Protected boron species

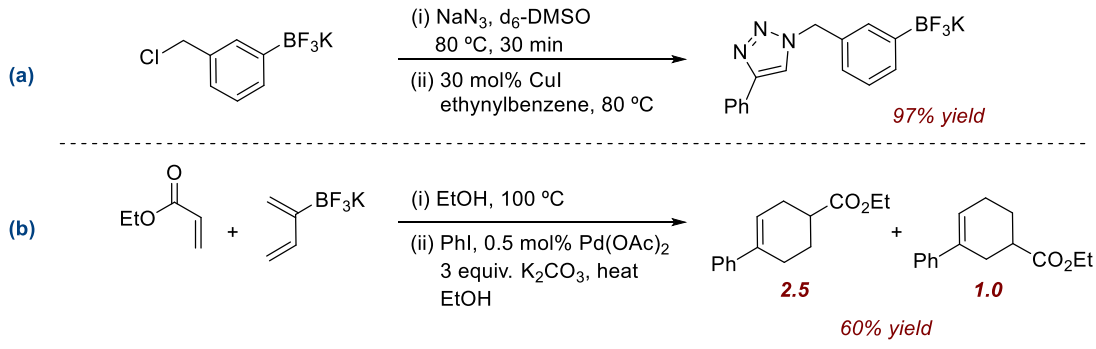
Once the carbon-boron bond is formed, the resulting boronic acid can be converted to various distinct borates, which can be conveniently accessed *via* simple and mild conditions procedures (Scheme 9).[35,40] To modulate the reactivity of the boron centre during the subsequential synthetic steps, different protecting groups were developed in order to prevent side reactions and undesired by-products.



Scheme 9 - General procedure for the introduction of protecting groups

The synthesis of organotrifluoroborates (Ar-BF_3K) emerged as a method to access highly stable boron compounds through a rapid procedure that essentially does not require any chromatographic purification, making them very attractive species.[41–43] Although the first isolation of a BF_3K salt species was reported in 1960, it was not until the mid-1990s that its implementation as a protected boron species was reported.

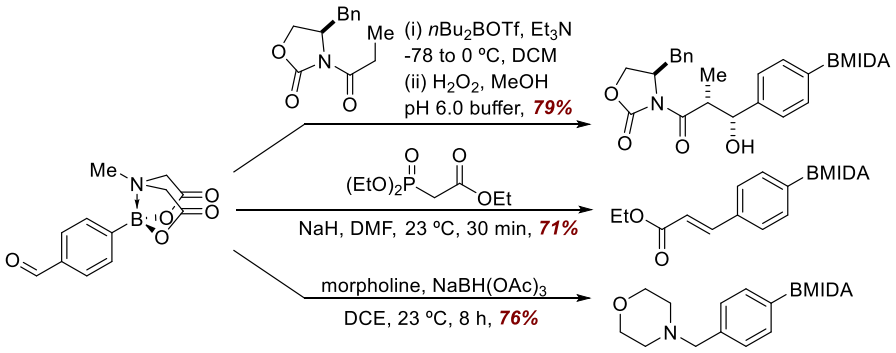
The pioneering work of Molander and co-workers promoted investigation of the physical properties and broadened the applicability of these sp^3-hybridised organoboron species. These borates have the advantage to tolerate a wide range of common transformations in organic synthesis as illustrated in Scheme 10.[40,42,43] The BF_3K species can be used in a wide range of transformations typically conducted in organic synthesis, from alkylation and various oxidative processes to click chemistry and Diels-Alder reactions.[42,43] The high stability of BF_3K species can be derived from their tetrahedral coordinated geometry as well as the strength of the B-F bond.



Scheme 10 - Examples (a) click chemistry; (b) Diels-Alder reaction followed by Suzuki-Miyaura cross-coupling

Methyliminodiacetic-acid (MIDA) was originally reported in the 1980s by Contreras and Mancella as a boron-protecting group,[44] then *N*-coordinated boronates derived from MIDA were extensive explored by Burke as a tool in the synthesis of natural products.[45,46] Their re-hybridisation from a sp^2 to a sp^3 boron centre has shown to increase the stability of the species and inertness towards different transformations. For instance, BMIDAs are inert to the transmetallation step of SMCC and, therefore, *in situ* hydrolysis to the boronic acid is required for the reaction to occur. In addition to the practical aspects derived from its inherent stability, such as storage and handling, MIDA boronate emerged as an alternative as robust and efficient as potassium trifluoroborates, being amenable to reaction conditions employed in various pharmaceutically and industrially relevant processes.

Paterson aldol, Horner-Wadsworth-Emmons olefination and reductive amination, for instance, are only a few of the examples among the many that were successfully performed and delivered the desired boronic MIDA ester (Scheme 11).[40,47] Moreover, the protected boron species can survive a series of transition metal-catalysed transformations, such as olefin metathesis, Heck and SMCC reactions, leaving the carbon-boron bond intact for further functionalisation.[47]



Scheme 11 - Examples of reactions demonstrating the stability of boronic MIDA esters

In addition to their outstanding applicability in a variety of transformations, these species have the additional advantages of simple installation and removal. The hydrolysis of potassium trifluoroborates and boronic MIDA esters can be easily

accomplished under aqueous basic conditions,[41,48,49] generating the free boronic acids *in situ*, which can be employed in subsequent manipulation.

Together with the role of classic protecting groups in organic chemistry, these boronates were developed to ensure selectivity when more than one presumably equivalent functional group is present in the reaction mixture.[40] In the past few years, researchers have extensively explored the potential utility of those species in one-pot chemoselective processes.

1.2 Reactions using boronic acids and derivatives

Boronic acids and esters are useful building blocks to access a diversity of functionalised compounds and can be applied in a substantial range of reactions as shown in Figure 2. The applications of organoboron reagents in organic synthesis are numerous and offer extensive advantages including ease of handling, stability and readily reactivity compared to other nucleophilic species.

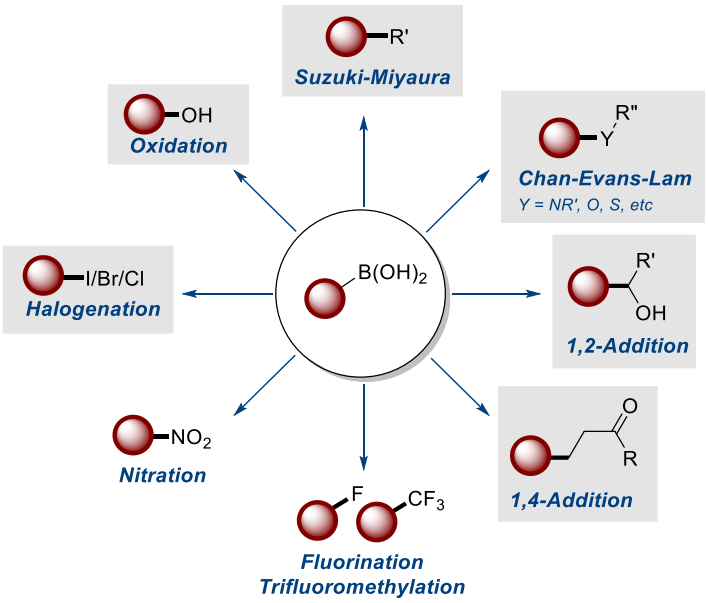


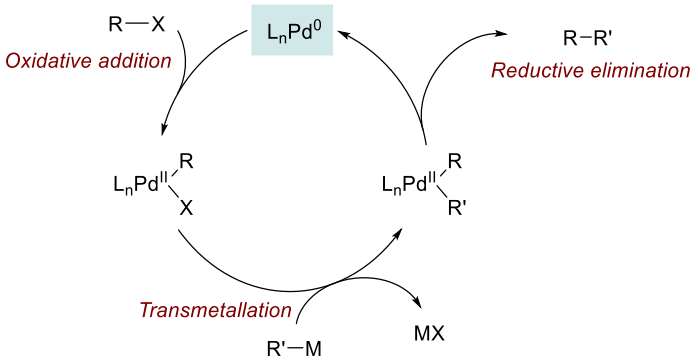
Figure 2 - Examples of reactions using boronic acids

Despitetheir importance for organic synthesis, not all reactions shown above will be covered in this thesis. The relevant transformations highlighted in Figure 2 will be discussed in the following sections.

1.2.1 **Suzuki-Miyaura cross-coupling reaction (SMCC)**

As a powerful technique towards a wide range of C-C bond formation, palladium-catalysed reactions have been well-known for the past decades.[50,51] Suzuki first published in 1979 a palladium-catalysed cross-coupling between an organoboronic acid and an organohalide.[52] It emerged as the most popular method to form sp^2-sp^2 C-C bonds, being widely applied both in industry and academia due to its efficiency and functional group tolerance.[4,35,53] Moreover, the mild conditions used and substantial functional group tolerance are attractive aspects of this reaction.

Similarly to other palladium-catalysed cross-coupling reactions,[54–56] the Suzuki-Miyaura reaction was firstly thought to proceed through a three-step catalytic cycle (Scheme 12), which begins with the oxidative addition of the organohalide into the Pd^0 complex, forming a Pd^{II} species. In the case of the Pd-catalysed SMCC, this step is generally the rate-determining step of the cycle. The oxidative addition relative rates that occur commonly follow the trend where I > Br ≈ OTf >> Cl.



Scheme 12 - General Pd-catalysed reaction catalytic cycle

The reactivity of an organo or pseudo-organo halide is inversely proportional to its bond dissociation energy (BDE) shown in Figure 3.[57] Thus, due to a lower BDE, aryl

bromides would react faster when compared to aryl chlorides, which can translate directly into milder conditions and shorter reaction time.

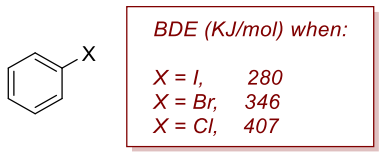
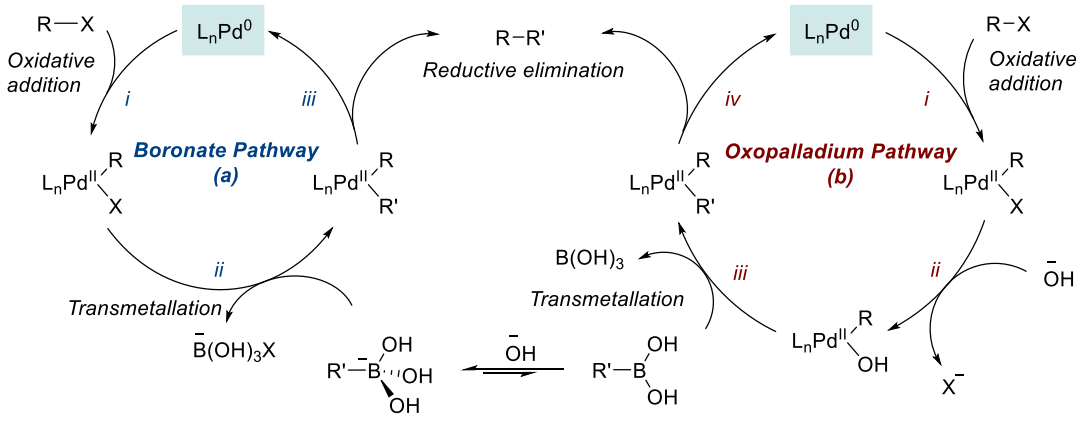


Figure 3 - BDE of various phenyl halides

The substituents on the aryl ring can significantly influence the oxidative addition step. The presence of electron-withdrawing (EW) groups in the ring generally weakens the carbon-halogen bond, enabling the cross-coupling of even less reactive species such as aryl chlorides. Contrarily to substrates bearing EW groups, electron-donating (ED) groups tend to inhibit the step, limiting the variety of electrophiles and requiring harsher conditions for the reaction to successfully proceed. Studies carried out since the first report of the SMCC indicate the possibility of more than one catalytic pathway for the reaction, which differ in one aspect along the cycle.[58]

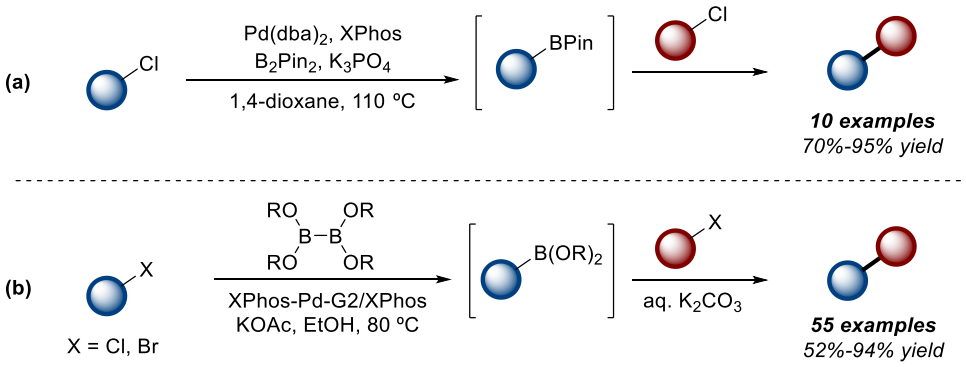
After undergoing the oxidative addition, equal for both pathways, the following step is the transmetallation of the organoboron species into the complex, where the debate resides. Under the *Boronate pathway* proposed by Suzuki in 1979 (Scheme 13, **pathway (a)**), the transmetallation occurs from the boronate species, generated due to the presence of base and water in the mixture.



Scheme 13 - SMCC accepted (a) boronate and (b) oxopalladium pathway

Finally, from the complex with *cis* configuration, the reductive elimination (Scheme 13, **pathway (a)**, step *iii*) takes place, delivering the desired product and reducing the complex back to Pd(0), completing the cycle and enabling it to begin once again.[59] The *Oxopalladium pathway* (Scheme 13, **pathway (b)**) proposes a slight change to the previous cycle.[52,60–62] After the oxidative addition (step *i*) has occurred, forming the $L_nRPd^{II}X$ species, a displacement of the halide for a hydroxyl group occurs and delivers the oxopalladium complex (Scheme 13, **pathway (b)**, step *ii*). The $L_nRPd^{II}OH$ species would then undergo transmetallation (Scheme 13, **pathway (b)**, step *iii*) with the boronic acid species instead of the boronate. The reductive elimination (Scheme 13, **pathway (b)**, step *iv*) similarly to what has been shown in **pathway (a)**, completing the cycle and affording the C-C coupled product. With the work of Hartwig, Schmidt, Amatore and Jutand, coercive evidences indicated the catalytic transit may follow the oxopalladium pathway.[62,63] Even though few studies afforded compelling results corroborating the boronate pathway, it cannot be discarded.

It is not novel that palladium chemistry can provide easy access to aryl motifs through a C-C bond formation. Examples in the literature, however, have recently demonstrated that the same catalyst employed for a Miyaura borylation can successfully perform a further SMCC, indicating that the isolation of the boron species is not necessary.[59] Buchwald *et al*. applied the methodology to arylchlorides in 2007, using simple and commercially available Pd catalysts and phosphine ligands.[64] The reaction produced both symmetrical and unsymmetrical biaryl compounds in excellent yields, with particularly interesting functionalities along the substrate scope (Scheme 14a). Wang's group reported in 2012 the one-pot borylation/SMCC reaction using cyclopalladated ferrocenylimine as catalyst to afford unsymmetrical biaryls, with no need of a second catalyst addition.[65] The same year, Molander and co-workers reported the transformation in milder conditions while forming a different boron species (Scheme 14b).[23,66,67]



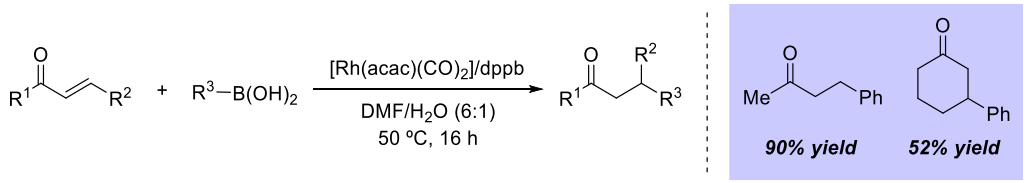
Scheme 14 - (a) Buchwald's and (b) Molander's one-pot borylation/SMCC procedure

Although requiring a preformed catalyst for this methodology, the arylboronic acid can be generated *in situ* and subsequently functionalized in fairly high yields, with no need of another Pd catalyst. Yu[68] and co-workers later introduced additional examples of phosphine ligands, synthesized within the group, that can conduct a one-pot borylation/SMCC procedure, obtaining excellent results for both symmetric and asymmetric biaryl motifs.

1.2.2 Conjugate addition of boron species

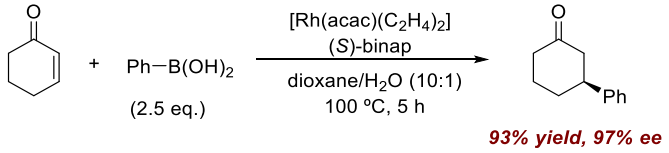
Since the seminal work reported by Umera[69] using palladium and by Miyaura[70] using rhodium, the transition metal-catalysed conjugate addition of boronic acids to enones has emerged as one of the most reliable and functional group tolerant methods to form carbon-carbon bonds, which could further be applied to large-scale synthesis and used for new ligand development.[71–73]

In his first report, Miyaura observed lower yields for β–substituted enones in comparison to unsubstituted ones (Scheme 15).[70] The improvement of performance using β-substituted enones is highly desirable, since it would enable the creation of a stereogenic carbon centre. Nevertheless, the reaction offered several advantages over other 1,4-addition reactions, such as functional group tolerance and potential to be performed in an enantioselective manner.



Scheme 15 - Rhodium-catalysed conjugate addition of boronic acids to enones

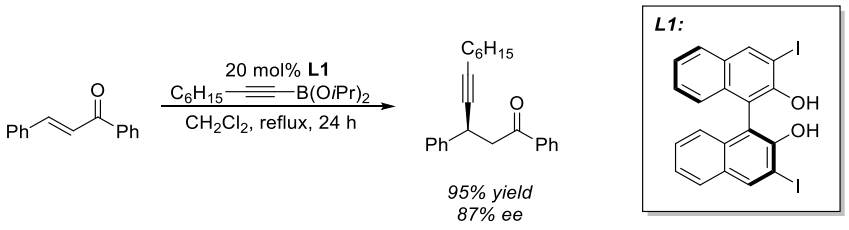
Hayashi and Miyaura reported in 1998 the first asymmetric conjugate addition using boronic acids as nucleophiles (Scheme 16).[74] Changing the chiral catalyst precursor to [Rh(acac)(C_2H_4)$_2$] was key to improve the enantioselectivity, as shown in the NMR studies conducted by the group, since it can form [Rh(acac)(binap)] more rapidly than [Rh(acac)(CO)$_2$]. The weaker coordination of ethylene compared to carbon monoxide accounts for the higher enantioselectivity. The conditions developed not only tolerate cyclic enones in various ring-sizes, but also work for alkenyl boronic acids, maintaining excellent enantioselectivity in all cases.



Scheme 16 - Asymmetric conjugate addition of boronic acids

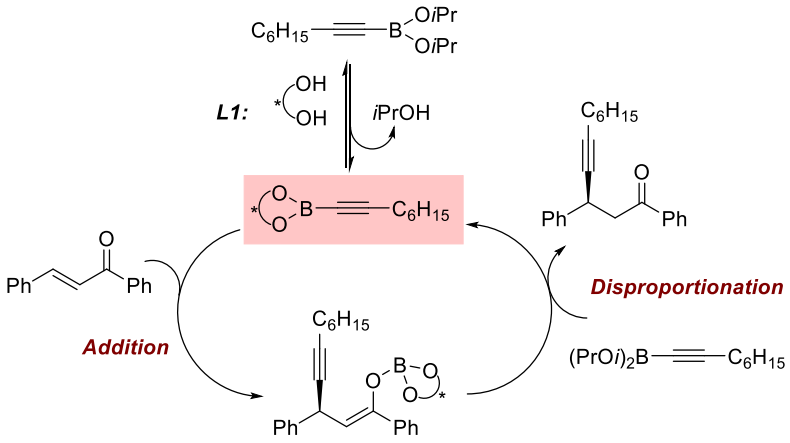
Based on Miyaura and Hayashi's pioneering work in the field, researchers expanded the application of the asymmetric methodology to unsaturated esters,[75] amides,[76] phosphonates,[77] and nitroalkenes,[78] as well as to different boron species such as BCat[79] and BF_3K[80] species. Furthermore, the boronic ester could be generated *in situ* from the aryl bromide in an one-pot manner without affecting the reaction's performance.[81]

The work reported by Chong in 2005 demonstrated the usefulness of chiral 1,1'-bi-2-naphthol (BINOL) type catalysts to assist the conjugate addition of alkynylboronic esters to α,β-unsaturated ketones (Scheme 17).[82]



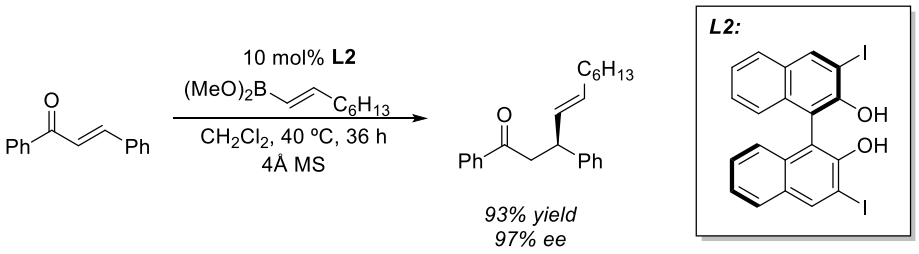
Scheme 17 - Chong's conjugate addition of alkynylboronic esters to enones

This work not only proposed a catalytic cycle for the methodologies developed but also identified, through control experiments, the formation of a more reactive boronate intermediate in the catalytic cycle (Scheme 18).



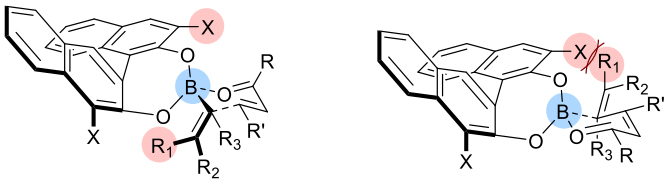
Scheme 18 - Catalytic cycle of Chong's conjugate addition of alkynylboronic esters to α,β-unsaturated ketones

Results from the study demonstrated that the rate of reaction between *B*-1-octynyldiisopropylboronate and the enone is significantly slower that the rate of reaction of the highlighted chiral BINOL species with the enone, suggesting it is a ligand-accelerated process. NMR studies have shown equilibrium between achiral boronic ester and chiral active intermediate, which is established rapidly at room temperature, indicating that either the addition or disproportionation step must be the rate-determining step of this process.[82] Two years later, Chong extended the methodology to alkenylboronates (Scheme 19).[83]



Scheme 19 - Chong's conjugate addition of alkenylboronic esters to enones

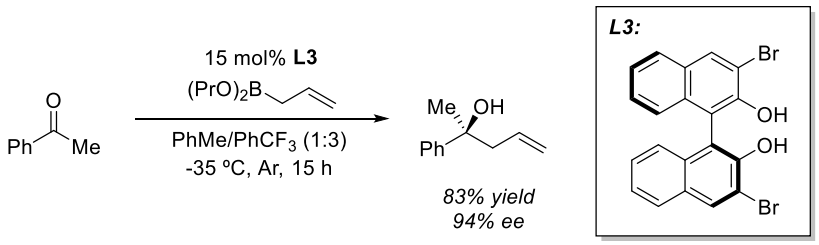
Relying on work discussed previously, the Chong group proposed possible transition states, rationalising the stereochemical outcome of the product (Figure 4). The chair-like transition state **(B)** is disfavoured due to the clash between the bulky iodine substituents in the BINOL ligand and the functional groups present in the alkenylboronate. The active intermediate is forced to sit in transition state **(A)** conformation, with a more accessible face for the carbonyl to approach, since the interaction between the substituents highlighted are minimised.



Favoured *TS (A)* **Disfavoured *TS (B)***

Figure 4 - Comparison between transition states (disfavoured clash of substituents shown in red)

Through a similar boronate-type transition state described by Chong and co-workers, Schaus and co-workers reported in 2005 the first asymmetric allylboration of ketones catalysed by chiral diols as an alternative from the known Cu(I) and Ag(I)-catalysed processes previously reported in the literature (Scheme 20).[84] The study conducted effectively facilitates the access a wide range of chiral allylic alcohols, in high yields and *ees*.



Scheme 20 - Schaus' work on asymmetric allylboration of ketones

Although the scope only included a variation of functional groups in the ketone component, Schaus demonstrated that optimal conditions can successfully perform an stereoselective crotylboration of acetophenone, affording the *anti*-isomer from the (*E*)-crotyl boronate in high dr and er, and the *syn* product from the (*Z*)-crotyl boronate, also in good yields with high selectivity.

Mechanistic investigations suggested a rapid catalyst and boronate association and NMR studies also indicated a fast exchange of one of the isopropoxy ligands. Based on empirical observations from the study, the group modelled and proposed a chair-like transition state (Figure 5), demonstrating the origin of selectivity in which the catalyst-boronate complex transfers selectivity by the activation of the alkoxy ligand *via* hydrogen bonding, which leads to a Si facial attack on the ketone. More recently, Goodman and co-workers expanded the work on allylboration of carbonyl compounds catalysed by chiral BINOL phosphoric acids.[85–87]

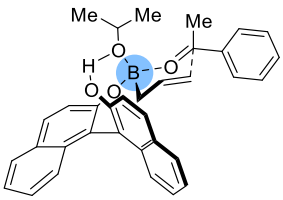


Figure 5 - Model of transition state proposed by Schaus

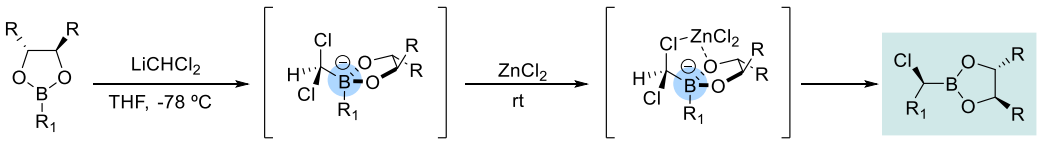
The main difference from the two works described, although they share the same boronate-type transition state, relies in the interaction between the catalyst and the boronic ester. While the chiral BINOL catalyst binds directly to the boron species forming a more active intermediate, in Schaus' proposed TS the catalyst displace an alkoxy group and activates the remaining isopropoxy ligand. Those examples were

the first reports demonstrating a chiral BINOL-activation of boron species towards asymmetric synthesis.

1.2.3 Homologation of organoboronic acid pinacol esters

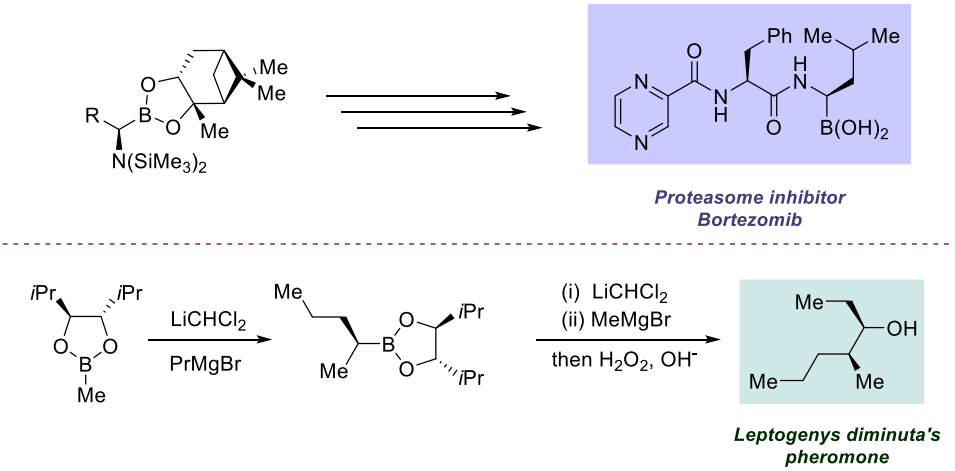
The analogous esters are known to be a less reactive and more stable alternative to boronic acids in a range of transformations. However, harsh conditions are often required to obtain similar results.[35] The work by Matteson in the early 1980s on the homologation of boronic esters opened a door to a new area of research in the field of organoboron chemistry.[3,88–90]

The methodology showed that high diastereoselectivity could be achieved in reactions of (dichloromethyl)lithium with boronic esters and Grignard reaction with the formed (α-haloalkyl)boronic esters (Scheme 21).



Scheme 21 - Matteson's homologation towards α-haloalkyl boronic esters

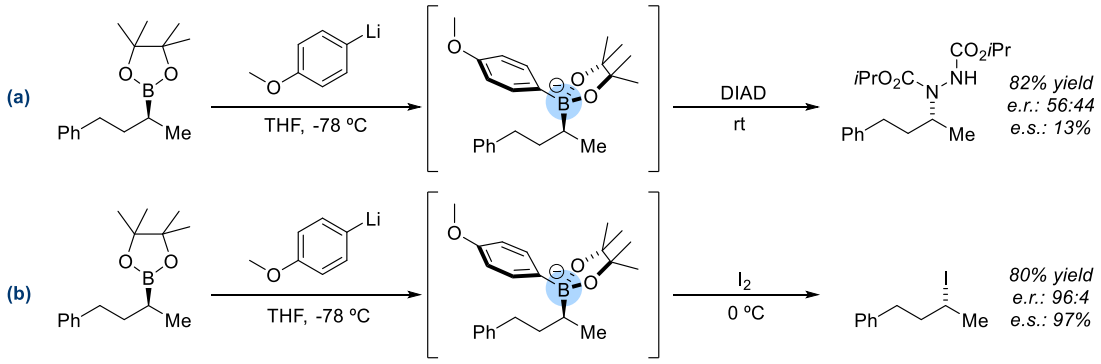
Matteson's pioneer work allowed preparation of enantioenriched compounds *via* sequential installation of a series of stereocenters, with tolerance to a wide variety of suitably protected functional substituents. The developed method enabled the synthesis of (α-amidoalkyl)boronic acids, including the proteasome inhibitor Bortezomib, used for treatment of multiple myeloma and mantle cell lymphoma, and other interesting natural product such as the trial pheromone of the ant *Leptogenys diminuta*, both shown in Scheme 22.[3,90–92]



Scheme 22 – Matteson's key intermediate to the synthesis of Bortezomib and the synthetic route to ant *Leptogenys diminuta* pheromone

However, in Matteson's approach chirality is incorporated in the diol moiety of the boronic ester and the subsequent reactions are controlled by its stereochemistry. Aggarwal's group extensively studied asymmetric homologation methodology using enantioenriched boronic acid pinacol esters assisted by organolithium species.[93,94] In this case, in contrast with Matteson's initial report, the chirality was not embedded in the diol.

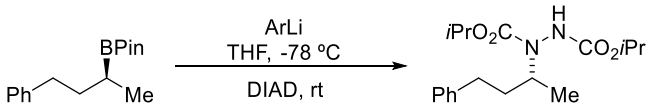
The transformation can proceed through a radical-based mechanism, which would lead to a racemic product, or an S_E2 reaction, where the inversion of stereochemistry would be achieved. However, the stereocontrol of the process was not observed from the beginning of the investigations.[93] The reaction of the boronic ester and DIAD afforded the hydrazine product in good yields however with basically no stereocontrol (Scheme 23a), whereas the enantioenriched product was observed when I_2 was used (Scheme 23b).



Scheme 23 - Aggarwal's homologation of boronic pinacol esters

Observations collected from Aggarwal's study suggested that the aryllithium species and its electronic properties are crucial aspects to be considered in order to enhance the S_E2 reaction and therefore the inversion of stereochemistry in the product (Table 1).

Table 1 - Effect of EW and ED groups in enantioselectivity

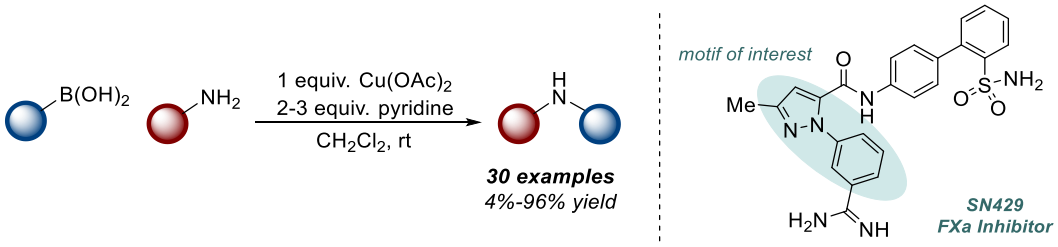


Ar	Yield	e.r.
4-MeOC$_6$H$_4$	82%	56:44
Ph	90%	63:37
3,5-(CF$_3$)$_2$C$_6$H$_3$	74%	80:20

1.2.4 Chan-Evans-Lam (CEL) reaction

Reported in the late 1990s, the discovery of the CEL reaction turned into a great advance in the field of transition metal-catalysed carbon-heteroatom bond formation.[95–98] Even though the CEL methodology uses two nucleophilic species, whereas the alternative Buchwald-Hartwig coupling employes an electrophile component to couple with a nucleophile, it offered the advantage of being conducted under mild conditions and ambient atmosphere.

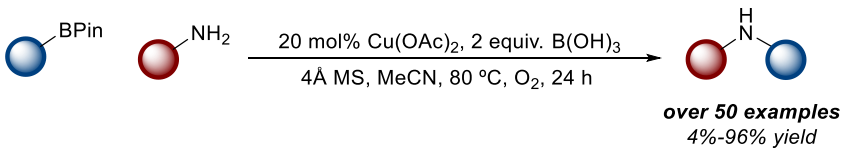
As reported in Chan's work, the reaction demonstrated, with stoichiometric amounts of copper catalyst, to tolerate a wide range of substrates including imides, carbamates, sulphonamides, and ureas.[96] The scope could be further extended to heterocyclic anilines, even though chelating nitrogen atoms of the anilines could potentially interfere in the reaction's performance. Since *N*-arylated heterocycles had remained under-explored, Lam's group had to work towards a robust methodology to access the desired motifs shown in Scheme 24.[95] The lack of analogous natural products containing the mentioned motif during that time could perhaps be a reason to why there were not many methods to access *N*-arylated heterocyclic compounds.



Scheme 24 - Report on C-N bond formation and Lam's template of interest for FXa inhibitor SAR

Even though extensive reports demonstrated the CEL reaction is applicable to a vast range of amines and boronic acids, boronic esters were still not tolerated as starting materials and the problem remained, until recently, a challenge to be overcome. The use of other boron species such as boronic pinacol esters was highly desired, since that would increase both stability and range of the substrates available for the reaction.

The insightful work reported by the Watson group identified a simple and general procedure that could efficiently promote the cross-coupling between aryl BPins and both alkyl and aryl amines (Scheme 25).[99,100]

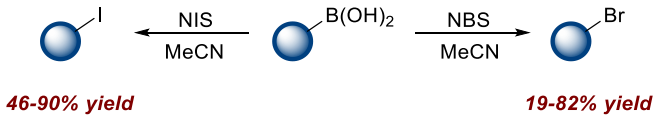


Scheme 25 - Watson's conditions for CEL reaction using aryl BPins

1.2.5 Halogenation of boron species

Methodologies to access carbon-halogen bonds are extremely valued,[101] as aryl halides are ubiquitous and have been extensively employed as versatile synthetic precursors. Haloarenes also emerged in the last decade as essential components of many pharmaceutical compounds.[102,103] The introduction of aryl-halogen bonds into complex polyfunctional molecules is highly desirable.[104,105] The boron-halogen exchange came then as an alternative to the direct electrophilic substitution and the Sandmeyer reaction,[106] as well as the use of hazard reagents, such as bromine.

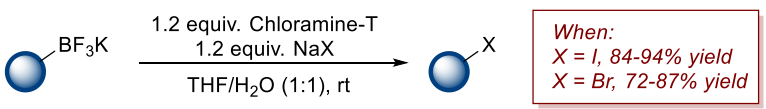
Olah reported in 1998 a general halodeboronation procedure to access aryl bromides and iodides.[107] In the presence of NIS, aryl iodides could be accessed in high yields, while demonstrating its generality, robustness, and functional groups tolerance (Scheme 26).



Scheme 26 - Olah's mild preparation of aryl bromides and iodides

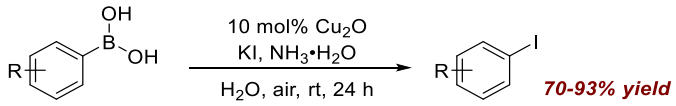
Later, an efficient *ipso*-halogenation of arylboronic acids was disclosed.[108] The halogenating reagents of choice in the case were 1,3-dibromo and 1,3-dichloro-5,5-dimethylhydantoin (DBDMH and DCDMH, respectively), converting arylboronic acids to its analogous bromides and chlorides in excellent yields.

The work reported by Kabalka and Mereddy[109,110] extended the scope of boron species to potassium aryl trifluoroboronates, where a halogenating agent was generated *in situ* from a mixture of chloramine-T and NaI or NaBr (Scheme 27). In this case, chloramine-T reacts with the halide salt to form BrCl or ICl, which reacts with the aryl boronic acid to deliver the corresponding aryl halide.



Scheme 27 - Kabalka and Mereddy halodeboronation procedure

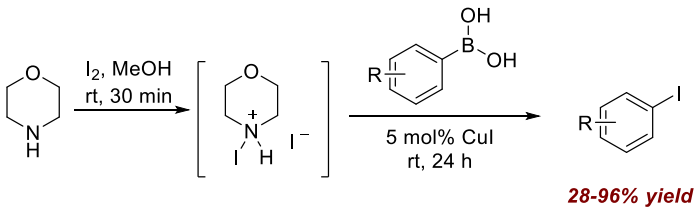
Fu and co-workers[111] developed a general copper(I)-catalysed iodination of arylboronic acids in 2011. The attractive methodology can be conducted effectively in water at room temperature, using oxygen present in the air as oxidant and ammonia to activate the copper catalyst. Under these particularly mild conditions, electron-rich and electron-deficient aryl iodides were prepared in high yields (Scheme 28).



Scheme 28 - Fu's copper-catalysed iododeboronation

In the past few years, researchers sought new methodologies especially towards C-I bond formation to provide an alternative to access radiolabelled aryl iodides for SPECT imaging. To be applicable for radiolabelling techniques, though, a few aspects have to be considered such as short reaction times (due to the half-life of ^{123}I) and suppression of formation of possible radioactive by-products.[112,113]

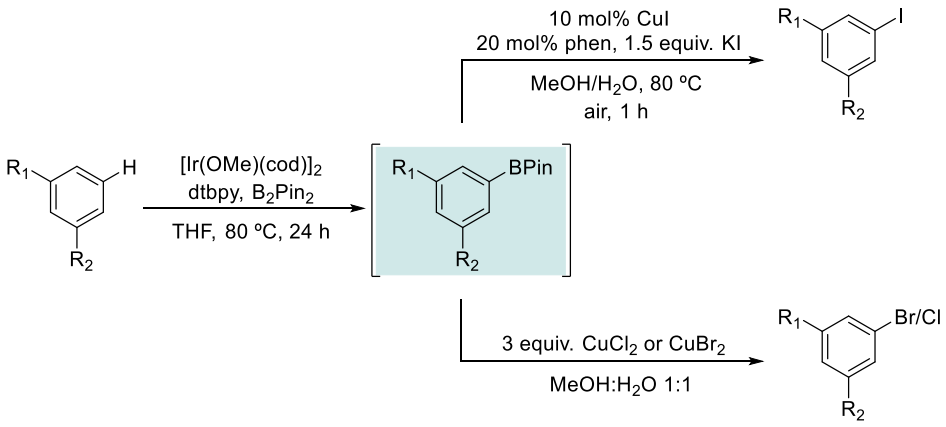
Tale's group reported a variation of this reaction, demonstrating the use of *N*-iodo-morpholinium iodide (NIMI) as iodinating agents on a copper(I)-catalysed procedure (Scheme 29).[114] The use of NIMI enabled the reaction to be conducted under milder conditions and lower catalyst loading, with excellent functional group tolerance. Apart from the classical *ipso*-iodination pathway, a NIMI-assisted copper-catalysed iodination pathway was proposed for this transformation.



Scheme 29 - Iodination of aryl boronic acids using NIMI

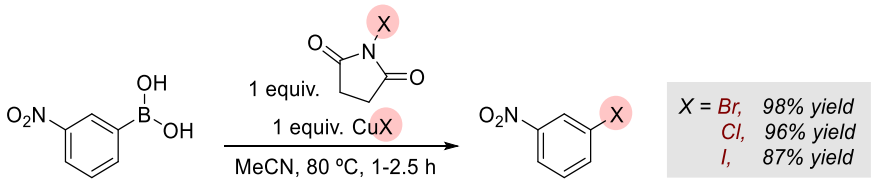
Hartwig reported a sterically controlled iodination of arenes through a Ir-catalysed C-H borylation.[115] The technique is an extension from previous reports from the group, where the aryl chlorides and bromides could be accessed *via* a similar

procedure, although super stoichiometric amounts of copper catalysts were employed (Scheme 30).[116]



Scheme 30 - Buchwald's Ir-cat borylation followed by Cu-cat halogenation of arylBPins

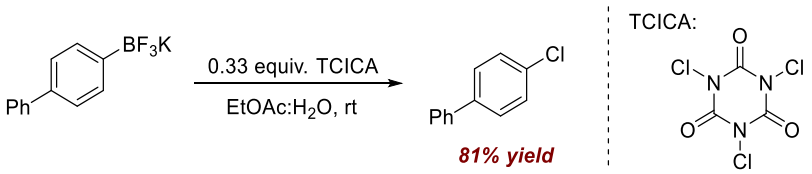
A mild, efficient, Cu(I)-catalysed method to access aryl halides from arylboronic acids was reported by Wu and Hynes.[117] The described method works optimally when the copper(I) catalyst and electrophilic halogen source bear the same halogen (for example, using NCS with CuCl) are employed, as shown in Scheme 31.



Scheme 31 - Wu and Hynes methodology

It performs equally well under both sub- and stoichiometric amounts of Cu(I) catalyst, only requiring a longer reaction time when catalytic quantities are employed. The group suggested that the reaction undergoes the same mechanism proposed by Liebeskind in the cross-coupling of arylboronic acids and *N*-thioimides, which will be described and discussed later in this section.[118] Perhaps the most intriguing observation reported by Wu and Hynes was the ability of $CuCl_2$ to also catalyse the chlorodeboronation as well as the best Cu(I) source. However, no further investigations around the subject were conducted by the group.

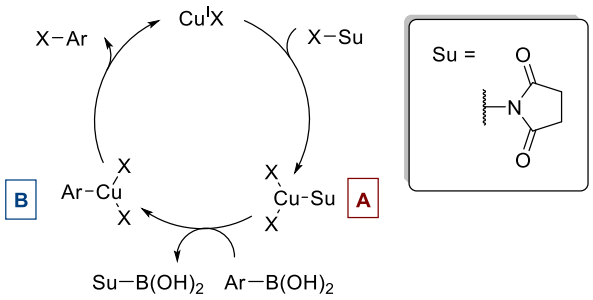
Molander extended the methodology to potassium trifluoroborate species, delivering the desired products in excellent yields under mild and metal-free conditions (Scheme 32).[119] A range of different electrophilic chlorinating agents including NCS, DCDMH (1,3-dichloro-5,5-dimethylhydantoin), *N*-chloro tosylamide, sodium hypochlorite, and TCICA (trichloroisocyanuric acid) were assessed, and TCICA found to be the most appropriate for the transformation. Interestingly, the reaction using 0.16 equiv. of TCICA and 1.5 equiv. of NaCl showed comparable performance against the conditions where only TCICA was employed. Under these conditions the *in situ* formation of chlorine gas was hypothesized, which would explain how sub-stoichiometric amount of the electrophile could successfully be employed. The second reaction conditions demonstrated to be as efficient as the previous one. The scope involved aryl, alkyl, alkenyl, and alkynyl trifluoroborates, affording the corresponding chlorinated products in good yields.



Scheme 32 - Molander's chlorodeboronation of potassium trifluoroboronate

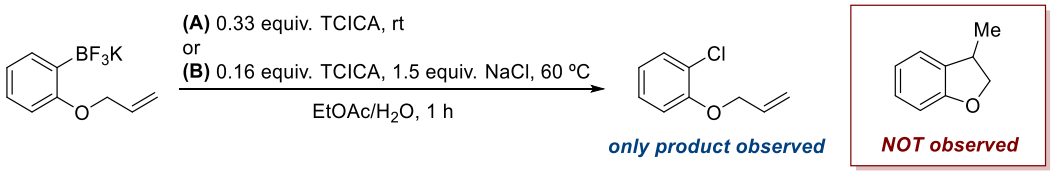
When it comes to carbon-halogen bond formation, the mechanism is more challenging to be determined. As some literature examples discussed earlier revealed, the procedure does not entirely depend on a catalyst to occur, although it can be copper-assisted.

Wu and Hynes proposed the following catalytic cycle (Scheme 33).[119–121] The formation of the Cu^{III} complex **A** starts with the oxidative addition of the *N*-chlorosuccinimide on the Cu(I) halide. This step is followed by the transmetallation with the boron species to generate the copper-aryl species **B**, which undergoes reductive elimination to give the desired aryl halide. Although the mechanism seems plausible, the group does not discard alternative pathways due to the complex nature of copper chemistry.



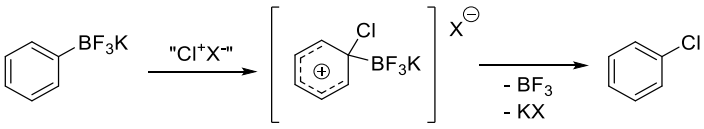
Scheme 33 - Proposed mechanism for Wu and Hyne's copper(I) catalysed chlorination

Molander's work investigated the mechanism in more details, and the possibility of going *via* a radical mechanism was considered. The group conducted experiments with potassium [2-(allyloxy)phenyl]trifluoroborate, as shown in Scheme 34, under both reaction conditions developed. If the procedure would go through a radical pathway, the mentioned substrate would be expected to undergo a radical cyclisation, forming the 5-membered cyclic ester by-product.[119] However, the corresponding chlorinated product was the only product observed in the mixture under both set of conditions.



Scheme 34 - Mechanistic investigations from Molander's work

The transformation was predicted not to involve radical species, mainly due to the observation of delivering the desired product even under sub-stoichiometric amounts of electrophilic chlorine. Based on entry shown in Scheme 34, it was advocated the electrophilic substitution through an *ipso* attack is more likely happen, similar to what had been reported in Olah's work (Scheme 35).[122,123]



Scheme 35 - Electrophilic aromatic *ipso*-substitution suggested by Molander

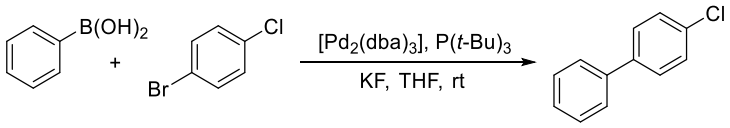
Although some mechanistic evaluations were conducted to identify and validate the correct pathway for the transformation, it seems to require more in-depth studies for the transformation to be fully understood. Researchers in the field are likely to be confronting more than one possible mechanism, which makes it exceptionally challenging to determine how the reaction proceeds.

1.3 Chemoselectivity in organoboron reactions

1.3.1 Suzuki-Miyaura cross-coupling (SMCC) reaction

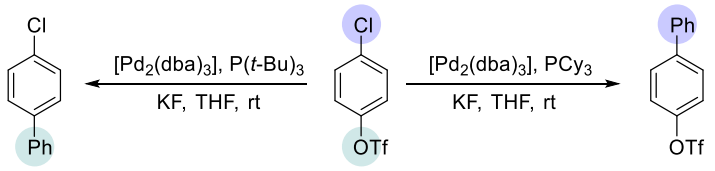
As the most popular C-C bond formation method in industry, it is not surprising that approaches enabling selective Suzuki-Miyaura cross-coupling reactions have emerged to efficiently construct complex scaffolds. Chemoselectivity in SMCC reaction can be achieved mainly through either controlling the oxidative addition or the transmetallation steps.

By exploiting the relative rates of oxidative addition (see section 1.2.1), Fu and co-workers were able to demonstrate in 2000 a selective monocoupling of boronic acids and aryldihalides (Scheme 36).[124]



Scheme 36 - Selective monocoupling of phenylboronic acid and 1-bromo-4-chlorobenzene

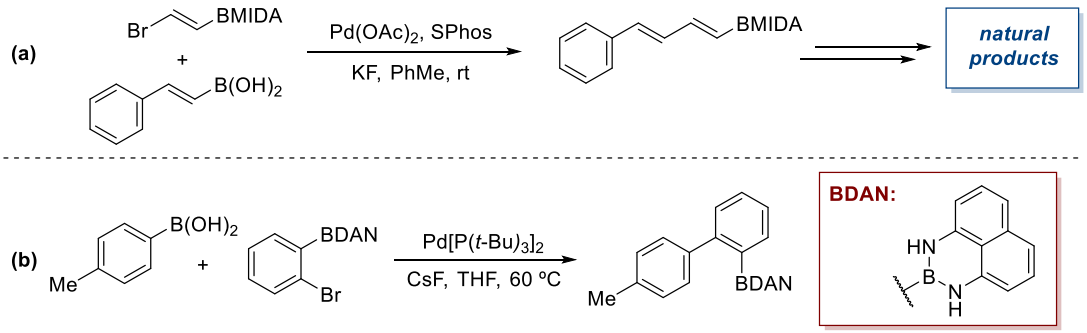
Based on judicious catalyst and ligand combination the group was able to adjust the chemoselectivity of certain halides and pseudohalides (Scheme 37). When $Pd_2(dba)_3$ and P(*t*-Bu)$_3$ were used, aryl triflates could be coupled over aryl chlorides. However, by changing the ligand of choice to PCy_3, the coupling of the aryl chloride was favoured, demonstrating the first inversion of an usual reactivity profile.



Scheme 37 - Selective coupling based on catalyst/ligand system

Schoenebeck *et al.* reported an in-depth study of the origin of this shift in reactivity.[125] When PCy_3 is used as a ligand, it can form both the mono- and bisligated Pd complexes. The $Pd(PCy_3)_2$ complex is more nucleophilic and can undergo oxidative insertion into the C-OTf bond more readily. The $P(t\text{-}Bu)_3$ on the other hand, due to its large substituents, prevents the formation of $Pd[P(t\text{-}Bu_3)]_2$ complex. Thus, the monoligated Pd species makes the addition into the C-Cl bond more favoured in this case.

Another approach to perform chemoselective SMCC reactions is controlling the transmetallation step. The most common strategies are by either neighbouring effect or use of protecting groups.[126] The protecting groups BMIDA and BDAN (DAN = 1,8-diaminonaphthalene) have extensively been reported by Burke[45,48,127,128] and Suginome[129–132] respectively as powerful tools to enable selective SMCC reactions (Scheme 38).

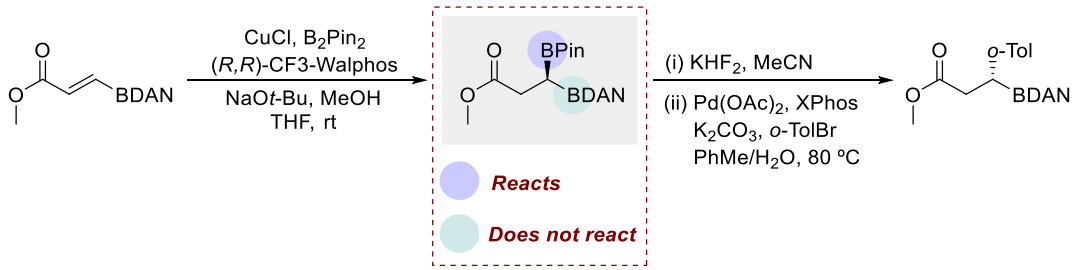


Scheme 38 - Use of protecting groups in selective SMCC

As described in section 1.1.2, BMIDAs are sp^3-hybridized species which are easily hydrolysed to the corresponding boronic acid under basic conditions. BDANs behave similarly to the MIDA boronate, with stabilization by the adjacent nitrogen lone pairs, precluding the transmetallation step. However, BDANs still have sp^2

hybridization and offer the advantage of being acid labile, which make them inert to basic SMCC conditions and at the same time easy to be removed for further functionalisation.

In the second main strategy, chemoselectivity can be obtained through activation of one species over its vicinal or geminal neighbour. The pioneer contribution of Shibata in the synthesis and application of 1,1-organodiboronates was fundamental for the field.[133–135] Those species have been used in the formation of alkenylboronates as well as chemoselective and regiospecific Suzuki-Miyaura cross-coupling reactions, to enable high functionalised moeits. Later, Hall and co-workers described in 2011 the use of geminal diboron BPin/BDAN compounds in selective cross-coupling reactions. The diboron systems could be accessed through an asymmetric hydroboration of the alkenyl BDAN species leading to geminal BPin/BDAN derivative (Scheme 39).[136] The species could be cross-coupled with a complete inversion of stereochemistry ensuing from ligand/protecting group manipulation.



Scheme 39 - Hall's asymmetric hydroboration and selective cross-coupling procedure

Through this process the BPin moiety is the most reactive site, due to the nature of the 1,8-diaminonaphthalene substituent. As mentioned previously, unlike BMIDAs, BDANs are sp^2-hybridized species and stable to basic SMCC conditions. Moreover, Hall's group proposes that the coordination of the carbonyl group forms a stabilized transition-state as shown in Figure 6, which would deliver the coupled product with the opposite stereochemistry, corroborating the transition state with empiric observations.[136]

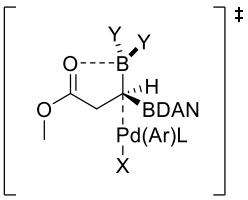
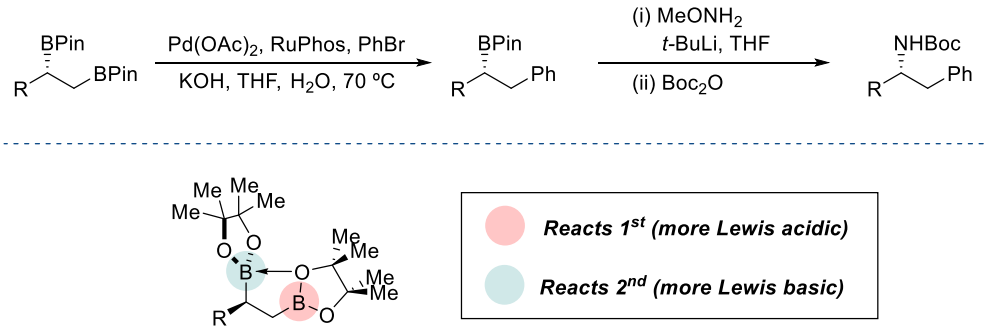


Figure 6 - Hall's proposed stabilized TS to give inversion of stereochemistry

Morken reported in 2013 a cascade asymmetric diboration/selective cross-coupling protocol.[137,138] The method would enable the formation of chiral vicinal diBpin species which would allow rapid access to enantioenriched organic compounds (Scheme 40).



Scheme 40 - Synthesis of *N*-Boc-(*S*)-amphetamine via Morken methodology, and description of Lewis acid/base interaction between boron species

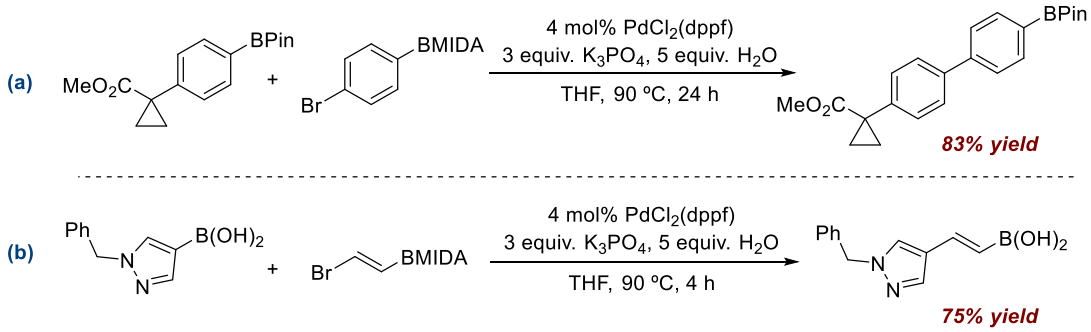
Chemoselectivity in this case can be explained by the neighbouring activation/protection described above which arises from a Lewis acid/Lewis base interaction.[137] The lone pair for the pinacol oxygen donates into the boron empty *p*-orbital, making the terminal BPin more Lewis acidic and consequently more prone to transmetallation. The proximal BPin is simultaneously rendered, more Lewis basic and therefore less reactive.

A drawback from most methodologies outlined is the requirement of protecting group manipulation, which increases the number of steps in the synthesis. Ideally, chemoselective methods to access stable and reactive boron species in a one-pot manner are highly desired, mainly to avoid wasting material and time.

1.4 Previous work within the group in chemoselectivity in diboron systems

1.4.1 Chemoselectivity in SMCC reaction

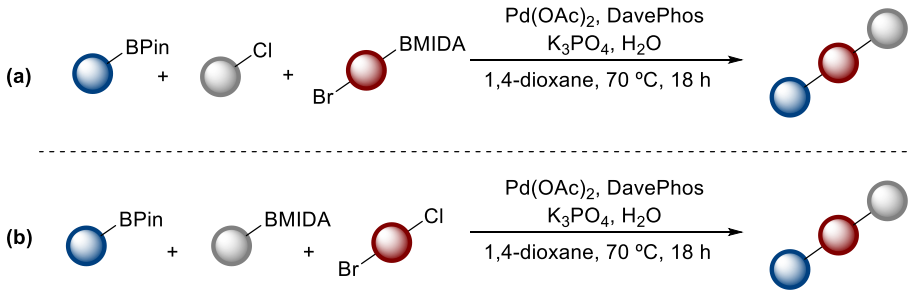
Our group recently demonstrated that controlled conditions are key to perform successfully chemoselective cross-coupling using BMIDAs esters.[139] The methodology enabled a formal homologation procedure with BPin species and BMIDA-arylhalides, affording a unique and more functionalised boronic pinacol ester (Scheme 41a). Under the similar conditions, the methodology has also proven to react with either the aryl BPin or $B(OH)_2$, tuning kinetic and thermodynamic aspects. Later, the methodology was efficiently extended to boronic acids (Scheme 41b).[140]



Scheme 41 - Formal homologation of (a) boronic pinacol esters and (b) boronic acids

The group then later reported a tandem cross-coupling between dihaloarenes, boronic pinacol and MIDA esters, providing remarkably selective and quick access to triaryl moieties.[141] By establishing electrophile and nucleophile selectivity simultaneously, successive cross-couplings could be performed in a single operation.

Taking advantage of the nucleophile speciation, the work explored different combinations of boron species and organohalides (Scheme 42). As for the other procedures mentioned previously, the balance between water and base in the mixture was crucial to access selectivity, which relies on the completion of the first cross-coupling between the boronic pinacol esters and the bromide prior to the MIDA hydrolysis.



Scheme 42 - Tandem SMCC cascade protocol

After investigating selectivity *via* controlled speciation, it was investigated whether chemoselectivity could be achieved also by exploring the natural reactivity of the electrophile. This has been demonstrated with more evidence in cases of dihaloheteroarenes, where the electrophiles can be differentiated mainly due to electronics effects. In the case of dichloropyrimidine, the most electron deficient halide will react first.[142,143] The liability of alkenyl against aryl electrophiles (explored by the use of 1-bromo-2-(4-bromophenyl)ethylene) would also allow selectivity to be achieved (Figure 7).

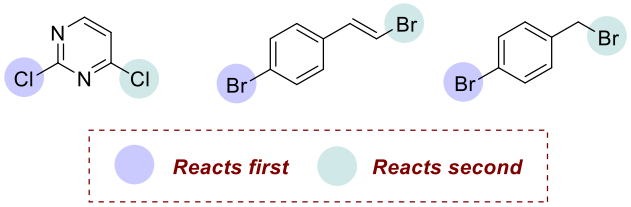
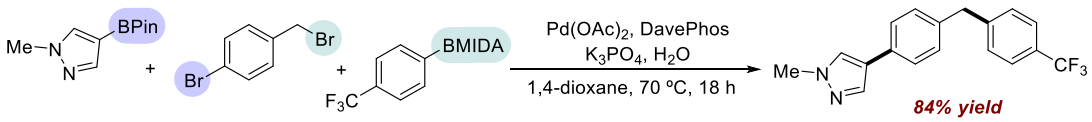


Figure 7 - Sites that would react first for SMCC reaction

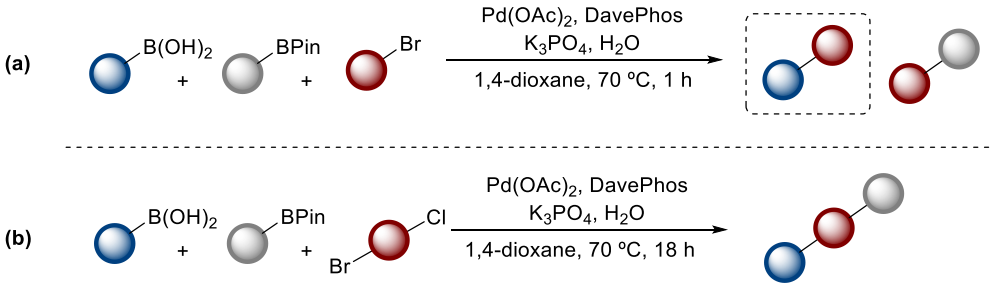
In a similar manner, distinctions between sp^2 *vs.* sp^3 electrophiles were investigated employing 4-bromobenzyl bromide, realizing the selective triaryl in 84% yield as shown in Scheme 43.



Scheme 43 - Tandem SMCC cascade reaction

The Watson group improved their developed methodology, demonstrating the dispensability of the protecting group while maintaining excellent selectivity, which

could be achieved *via* kinetic transmetallation (Scheme 44a).[144] The method overcame potential issues, such as the base-promoted pinacol exchange and the boronate equilibria, negatively enhanced under uncontrolled amounts of water in the reaction mixture. In this report, even it both boronic acids and BPins species exhibit similar reactivity when reacted independently, temperature was a key aspect to be evaluated in order to obtain selectivity for the competitive cross-coupling. Speciation is another potential issue, which could lead to undesired by-products. Inorganic bases are known to minimize the diol exchange between the species and, therefore, supress the side reactions. Additionally, excess H_2O was detrimental to the selectivity. Gathering pertinent information from the investigations, optimal conditions were obtained which allowed to selectively access one cross-coupled product. It was also possible to perform a one-pot tandem chemoselective SMCC cascade reaction to access triaryl motifs (Scheme 44b).



Scheme 44 - Chemoselective SMCC *via* kinetic transmetallation

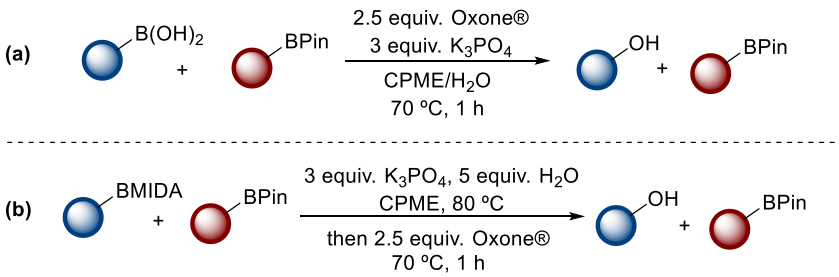
The examples above demonstrated that chemoselectivity can be achieved through both manipulation of the reaction conditions[139–141] or *via* kinetic transmetallation.[144]

1.4.2 **Chemoselective oxidation of boron species**

The examples found in literature around oxidation of boronic acids and derivatives are known robust methodologies and can be conducted using a variety of different oxidants, mainly peroxides and inorganic bases.[145–147] Methodologies available cover a wide range of conditions, enabling the access of the oxidised product under water-based media in extremely short reaction times and mild temperatures.

Furthermore, the scope includes a variety of organoboron compounds such as BPin[145,147,148] and BF_3K[149] species.

Molloy *et al.*[150] recently explored diboron systems and described a chemoselective Brown-type oxidation (Scheme 45a). The chemoselectivity between the species could be predicted based on clog P calculations, which indicated greater aqueous solubility for boronic acids (also found for the corresponding boronate adducts) compared to BPins. Observed in this work, an inversion of conventional selectivity could be achieved, enabling a chemoselective oxidation of BMIDA species over BPins, which are typically more reactive substrates (Scheme 45b). The work extends its application to a chemoselective Chan-Evans-Lam etherification, forming the coupled product in high yields and a one-pot manner.



Scheme 45 - Oxidation of (a) arylboronic acids and (b) BMIDAs over BPins

The work not only found general conditions which tolerate a wide range of arylboron species but also demonstrated, by ^{19}F and ^{11}B NMR and HPLC investigations, the origin of the chemoselectivity (Figure 8).

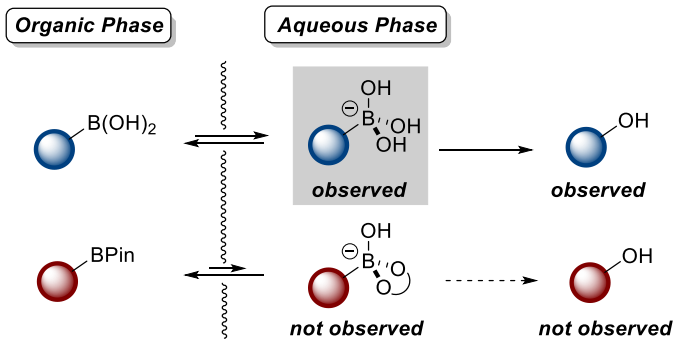


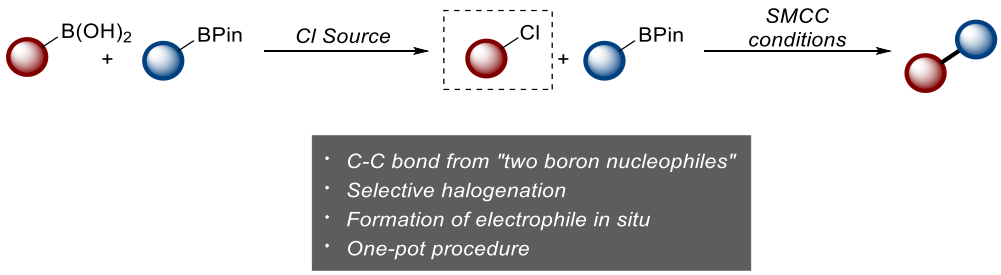
Figure 8 - Base-promoted phase-selective discrimination of arylboronic acids over BPins

The discrimination of the species occurs through a base-promoted phase-transfer, where boronic acids can access the aqueous phase due to their ability as they easily form a boronate. The oxidant employed in the methodology is stable in the aqueous phase, so the site of reaction can only be approached by the species which is able to access the aqueous phase of the reaction media. The boronic acid species could be identified both by NMR and HPLC analysis and the oxidation can occur, demonstrating the origin of chemoselectivity since both boronic acid and oxidant are present in the same phase. In the case of aryl BPins, as it is less prone to form the analogous boronate, it cannot access the aqueous phase and therefore not be oxidized.

2 Project aims

2.1 Di-nucleophile SMCC

A variety of chemoselective procedures in the presence of more than one boron species were enabled,[124,125] taking advantage of both kinetic window between species,[135] as well as using controlled conditions.[45,129] Within the group, the approach was explored using different methodologies, demonstrating to be efficient and applicable to a range of transformations, including C-O[150] and C-C[141,144,151] bond formation.



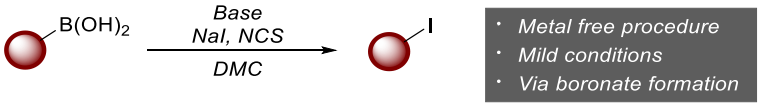
Scheme 46 - General scheme of the one-pot di-nucleophile SMCC procedure developed via a chemoselective chlorination

In this work, we aimed to develop the first one-pot di-nucleophile SMCC reaction using two boron species *via* chemoselective chlorination. To do so, conditions reported in literature for chlorodeboronation procedures will be investigated.[117,119] Control experiments will be conducted to verify how suitable the chemoselective chlorination conditions are *prior* to applying those in the one-pot process. Should it be successful, the di-nucleophile SMCC will be optimized and analysed against a range of functionalised boron species.

2.2 Base-catalysed iododeboronation for SPECT imaging

Aryl iodides are versatile intermediates employed in organic total synthesis and medicinal chemistry.[152,153] Their importance can be demonstrated by the employment of radioactive iodoarenes in single photon emission computed

tomography (SPECT) imaging, a technique which is used in the clinical diagnosis of diseases and also in drug development.[113,154] The synthesis of those compounds currently relies on the use of metal catalysts,[111,112,114,117] hence the development of new methodologies is highly desired.



Scheme 47 - General scheme of the iododeboronation for SPECT imaging

Herein, using the methodology developed and described in the first chapter, we aimed to report a metal-free iododeboronation method to apply in SPECT imaging agents' development. For the optimization, a selection of bases will be explored and their performance evaluated. With relatively mild conditions, the process would enable an inexpensive and more environmental-friendly alternative for the methods available in the literature.

3 Results and discussion

3.1 Di-nucleophile SMCC *via* copper-catalysed chemoselective chlorination

3.1.1 Introduction to numbering method

In order to make it easier to follow the work in this chapter, a small introduction to the numbering system employed in this manuscript will be endeavoured. Each compound, apart from biaryl moeits synthesized and displayed in Sections 3.1 to 3.3, will be represented by a number followed by a letter as shown in Figure 9. The number varies according to the compound´s structure (e.g. 4-biphenyl will be number **1**, naphthalen-1-yl will be number **2**, and so on). The letter component of the numbering system refers to the correpondent species (e.g. boronic acids are represented by the letter **a**, chlorides by the letter **c**, BMIDAs by the letter **d**, and so on).

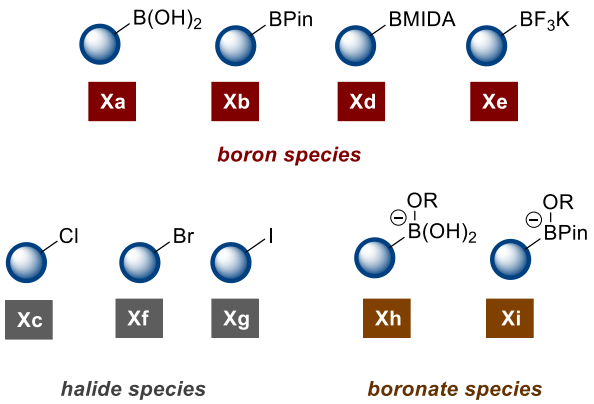
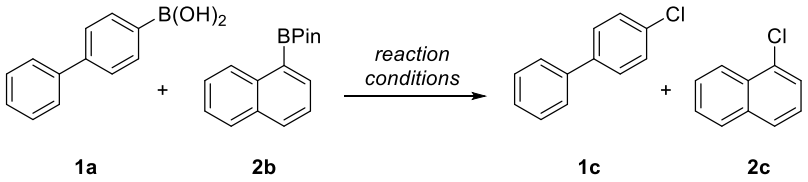


Figure 9 - Numbering method used throughout the thesis

Pairing those two components, the compound´s representation is complete. An example of how the aforementioned system works can be found below (Scheme 48). There we exhibit [1,1'-biphenyl]-4-ylboronic acid **1a**, in which the number represents the 4-biphenyl structure and the letter represents the boronic acid species. It yields the product 4-chlorobiphenyl **1c**, which bears the same number due to its structure (4-biphenyl) but a different letter since it is the corresponding chloride. In the case of compound **2b**, the structure 1-naphthyl is represented by the number **2** and the species, since it is a boronic acid pinacol esters, is

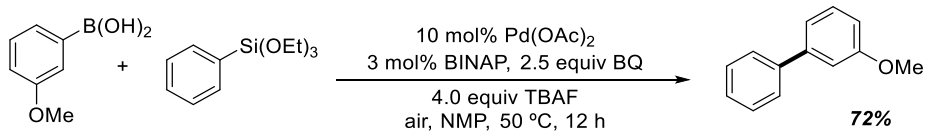
represented by the letter **b**. Its corresponding product is **2c**, as the chloride species are represented by the letter **c** paired, with its structure 1-naphthyl.



Scheme 48 – An example of the numbering system

3.1.2 **Chemoselective Chlorination**

Transition-metal-catalysed reactions to form C-C bonds are among the most widely used transformations in industry,[50] proving to be versatile and reliable tools in organic synthesis.[155] A range of such reactions has been developed including Suzuki-Miyaura, Stille, Kumada, Negishi, and Hiyama cross-coupling reactions. Aside from the traditional approach, between an organometallic nucleophile and an electrophile (halides or pseudo-halides), the reductive coupling of two electrophiles and the oxidative coupling of two nucleophiles represent alternative reaction manifolds through which cross-coupling can be achieved. The vast majority of research in the field has focused on traditional cross-coupling processes, whereas the latter two reaction types remain comparatively underexplored. Main developments in both areas emerged in 2015, when Weix and co-workers enabled a reductive cross coupling of aryl bromide and triflates as a Ullmann-type reaction catalysed by nickel and palladium[156] and, contrastingly, the first oxidative cross-coupling using nucleophile species was reported by Zhang's group (Scheme 49).[157]



Scheme 49 - Zhang's conditions for the oxidative cross-coupling of arylboronic acids and arylsilanes

Inspired by the work conducted by Zhang and co-workers, we envisaged a cross-coupling reaction performed between two boron species *via* a selective

manipulation of one of the functional groups to form the electrophile *in situ* (page 38, Scheme 46). To do so it was postulated that the difference of reactivity between a boronic acid and BPin would be appropriate for the proposed approach. A validation of the project was sought, in order to demonstrate that the gap of reactivity between boronic acids and its analogous esters could be explored. Inspired by Molander's and Hynes' work, the first trails were designed for both boronic acids and BPins species separately, and to out delight the chlorination of boronic acids gave excellent isolated yields (Figure 10).

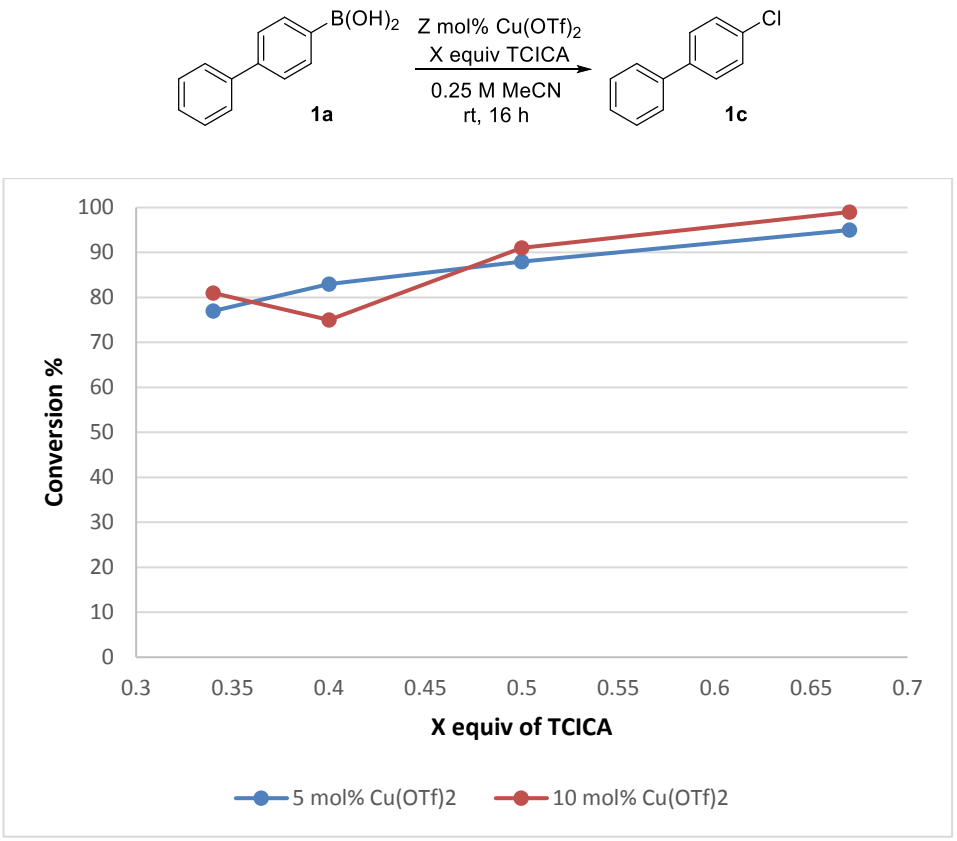
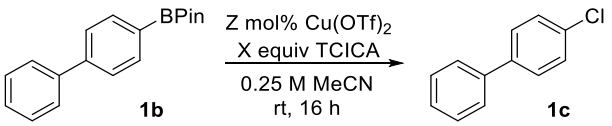


Figure 10 - Chlorination of boronic acids

Known to be inert against a range of transformations, the same reaction with boronic esters barely afforded the desired chlorinated product (Figure 11). Overall, poor yields only were obtained when the reaction was submitted to heat and excess of chlorinating agents.



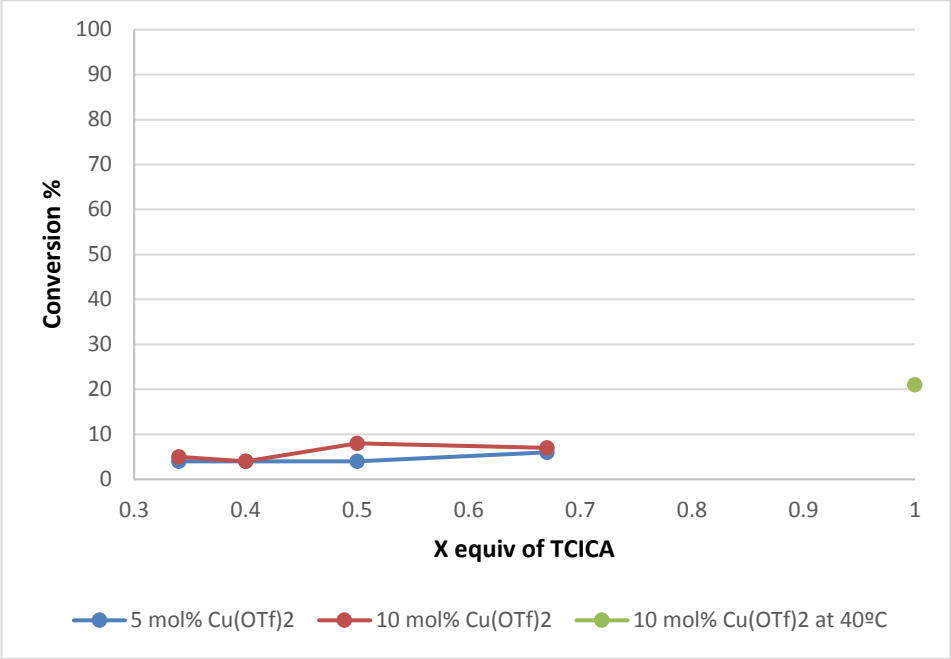
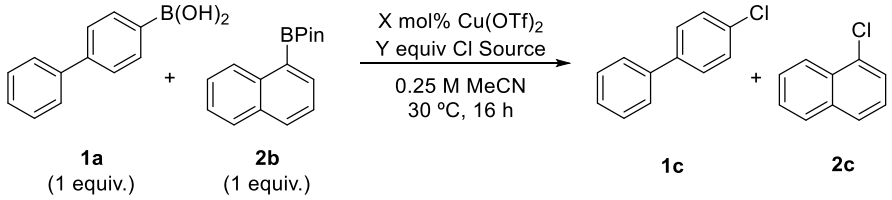


Figure 11 - Chlorination of boronic pinacol esters

With this information in hand, the aim was to perform a chemoselective chlorination of a boronic acid in the presence of a BPin. Taking inspiration from previous publications in the literature[117,119] and the initial investigations, the optimization of this process was conducted using [1,1'-biphenyl]-4-ylboronic acid **1a** and naphthalen-1-ylboronic acid pinacol ester **2a** due to their electronic similarity. As proof of concept, different chlorinating agents (both nucleophilic and electrophilic) were tested to identify the best agent for the reaction (Table 2). Moreover, control reactions only in the presence of CuCl and $CuCl_2$ showed the chlorine does not come from the catalyst. When NCS was employed, only poor conversions were achieved to desired product. However, to our delight, the reaction using TCICA afforded product **1b** in good conversion.

Table 2 - Screen of chlorinating agents for prove of concept



1a (1 equiv.) **2b** (1 equiv.) **1c** **2c**

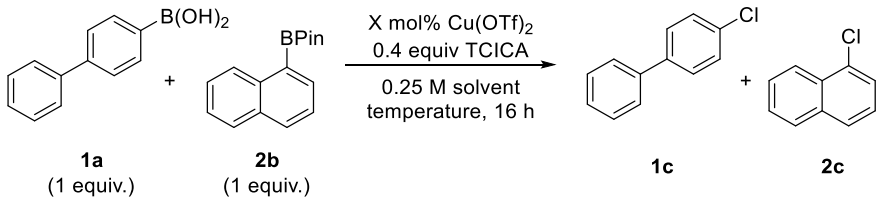
Entry	Source of Chlorine	Copper Catalyst	Equiv Cl Agent	Conversion to 1c (%)[a]	Selectivity 1c:2c[a]
1	KCl	5 mol% $Cu(OTf)_2$	1.5	-	-
2	NaCl	5 mol% $Cu(OTf)_2$	1.5	-	-
3	LiCl	5 mol% $Cu(OTf)_2$	1.5	-	-
4	$CuCl_2$	-	1.5	-	-
5	CuCl	-	1.5	-	-
6	NCS	10 mol% $Cu(OTf)_2$	2.0	20	-
7	TCICA	-	0.4	42	4.7:1

[a] Determined by HPLC analysis.

With the results above, a differentiation of reactivity between the two boron species could be observed, which could be further explored in order to access the desired chemoselectivity in the reaction. Next step was evaluating the most suitable solvent to be used in the process (Table 3). A range of solvents with distinct polarities were evaluated and, corroborating with previous literature examples, MeCN was the only solvent to deliver the chlorinated product in moderate conversion. Poor conversion was observed when using EtOAc at 50 °C and THF 90 °C

in the presence of $Cu(OTf)_2$. Only traces of 4-chlorobiphenyl product were observed in the other cases stated.

Table 3 - Solvent screening

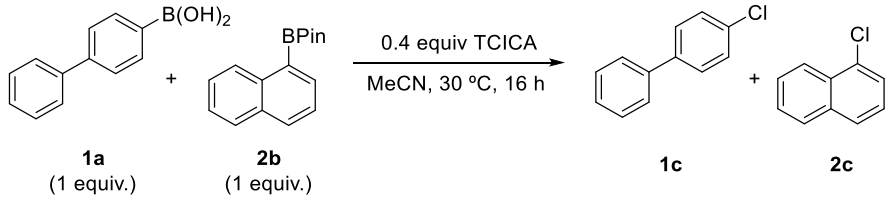


Entry	Copper Catalyst	Temp. (°C)	Solvent	Conversion to 1c (%)[a]	Selectivity 1c:2c[a]
1	-	30	MeCN	42	4.7:1
2	-	50	EtOAc	27	3:1
3	-	50	THF	4	-
4	10 mol% $Cu(OTf)_2$	90	THF	15	-
5	-	50	PhMe	<1	-
6	-	50	DCM	<1	-

[a] Determined by HPLC analysis.

The concentration study did not show improvement neither regarding conversion nor selectivity as displayed in Table 4. Increasing the concentration was detrimental to conversion and selectivity reducing both by almost fifty percent, whereas, at lower concentrations, the decrease is less significant.

Table 4 - Concentration study



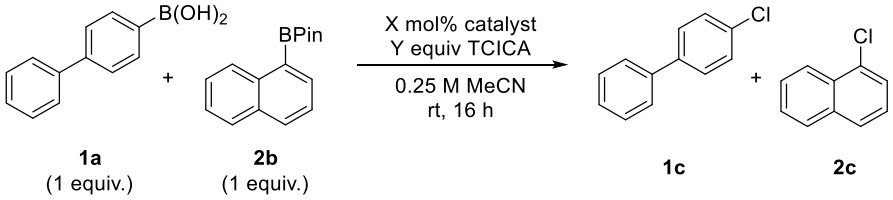
Entry	Conc. (M)	Conversion to 1c (%)[a]	Selectivity 1c:2c[a]
1	0.1	37	3:1
2	0.25	42	4.7:1
3	0.5	26	2:1
4	1.0	24	1.9:1

[a] Determined by HPLC analysis.

Copper catalysts are known to catalyse the chlorination of arylboronic acids.[117] When the best conditions found so far (Table 4, entry 2) were employed with 10 mol% $Cu(OTf)_2$, an increase in of both selectivity ratio and conversion could be observed. With this information, and after assembling a few parameters in the preliminary study, an investigation of the amount of chlorinating reagent and loading of $Cu(OTf)_2$ was necessary (Tables 5 and 6). This appraisal was conducted at room temperature and 30 °C to observe possible trends and help the reaction to go to completion.

Overall the conversion to 4-chlorobiphenyl **1c** increased with the addition of more chlorinating agent either with 10 or 5 mol% catalyst loading, whereas entry 3 in Table 5 did not followed the stated trend. Selectivity, on the other hand, deviated significantly using 10 mol% of $Cu(OTf)_2$ while the experiments using 5 mol% of catalyst loading demonstrated to increase with the loading of TCICA.

Table 5 - Screening loading of chlorinating agent and catalyst at rt



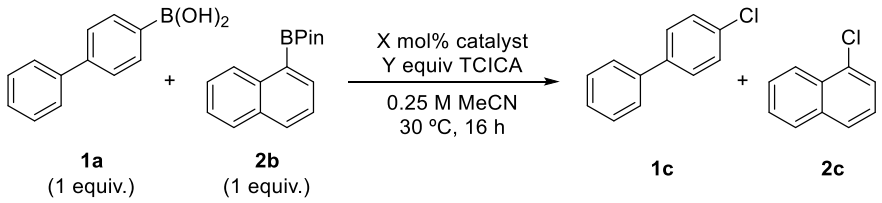
Entry	X mol% Copper Catalyst	Y equiv. TCICA	Conversion to 1c (%)[a]	Selectivity 1c:2c[a]
1	10 mol% $Cu(OTf)_2$	0.34	31	5.4:1
2	10 mol% $Cu(OTf)_2$	0.4	51	8:1
3	10 mol% $Cu(OTf)_2$	0.5	52	3:1
4	10 mol% $Cu(OTf)_2$	0.67	80	4.4:1
5	10 mol% $Cu(OTf)_2$	1.0	82	5:1
6	5 mol% $Cu(OTf)_2$	0.34	36	3.3:1
7	5 mol% $Cu(OTf)_2$	0.4	38	4:1
8	5 mol% $Cu(OTf)_2$	0.5	72	4:1
9	5 mol% $Cu(OTf)_2$	0.67	80	5:1
10	5 mol% $Cu(OTf)_2$	1.0	70	10:1

[a] Determined by HPLC analysis.

Remarkably, a slight increase in temperature had a dramatic effect in both conversion and selectivity (Table 6). Generally, conversions to 1c are higher for the reaction conducted at 30 °C. However, selectivity ratios of the reactions at 30 °C (Table 6, entries 4, 5, 9 and 10) are better the room temperature reactions (Table 5, entries 4, 5, 9 and 10) when 0.67 or 1.0 equiv of TCICA are used. Regardless of the

catalyst loading, the reaction achieves full conversion to desired product **1c** with 1.0 equiv of TCICA, however excellent selectivity is obtained at 10 mol% of $Cu(OTf)_2$ (Table 6, entry 5).

Table 6 - Screening loading of chlorinating agent and catalyst at 30 °C

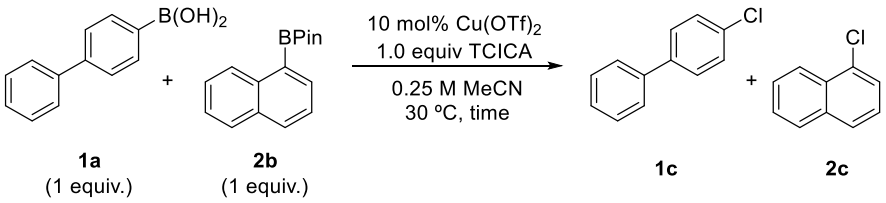


Entry	X mol% Catalyst	Y equiv. TCICA	Conversion to 1c (%)[a]	Selectivity 1c:2c[a]
1	10 mol% $Cu(OTf)_2$	0.34	30	2:1
2	10 mol% $Cu(OTf)_2$	0.4	36	6:1
3	10 mol% $Cu(OTf)_2$	0.5	57	8:1
4	10 mol% $Cu(OTf)_2$	0.67	78	11:1
5	10 mol% $Cu(OTf)_2$	1.0	92	30:1
6	5 mol% $Cu(OTf)_2$	0.34	33	5.6:1
7	5 mol% $Cu(OTf)_2$	0.4	43	6.5:1
8	5 mol% $Cu(OTf)_2$	0.5	49	7:1
9	5 mol% $Cu(OTf)_2$	0.67	70	7:1
10	5 mol% $Cu(OTf)_2$	1.0	94	16:1

[a] Determined by HPLC analysis.

Regarding time of reaction, excellent conversion were observed after 6 h, with no significant difference afterwards (Table 7). Excellent selectivity was observed throughout, achieving ratio **1c**:**2c** of 30:1 after 6 h (Table 7, entry 3).

Table 7 - Reaction time study

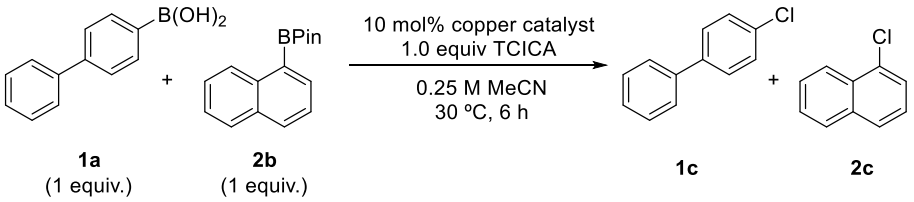


Entry	Time (h)	Conversion to 1c (%)[a]	Selectivity 1c:2c[a]
1	2	61	8:1
2	4	72	12:1
3	6	89	30:1
4	16	92	34:1

[a] Determined by HPLC analysis.

Having found the optimum conditions in terms of chlorinating agent, concentration and temperature components, the nature of the copper species was examined next (Table 8). Copper(I) bromide afforded the product **1c** in excellent conversion although with decreased selectivity. Moreover, a by-product could be observed in the HLPC spectrum in a retention time close to 4-chlorobiphenyl which was later identified by GCMS as 4-bromobiphenyl. The origin of this by-product formation was investigated and reported in the Section 3.2 of this manuscript. In the case of copper(II) bromide, reduced selectivity was also observed together with the same by-product. Surprinsingly, both copper chloride catalysts delivered the chlorinated product in poor conversion. Copper iodide formed the major 4-chlorobiphenyl **1c** in good conversion, however considerably low selectivity.

Table 8 - Copper catalyst study



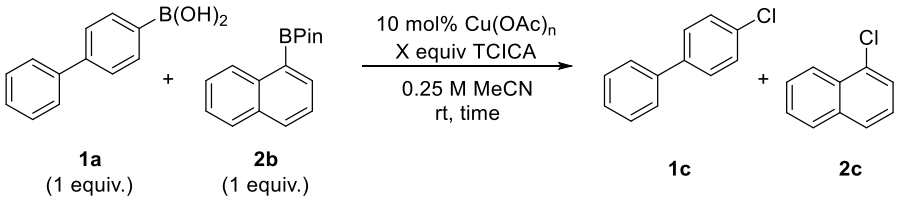
Entry	Copper Catalyst	Conversion to 1c (%)[a]	Selectivity 1c:2c[a]	Conversion to by-product (%)[a]
1	10 mol% $Cu(OTf)_2$	92	30:1	-
2	10 mol% CuBr	91	5:1	8
3	10 mol% $CuBr_2$	75	4:1	15
4	10 mol% $CuCl_2$	20	-	-
5	10 mol% CuCl	13	-	-
6	10 mol% CuI	70	2.1:1	-
7	10 mol% $Cu(OAc)_2$	96	28:1	-
8	10 mol% CuOAc	98	30:1	-

[a] Determined by HPLC analysis.

Notably, both CuOAc and $Cu(OAc)_2$ had the best performance in both conversion and selectivity aspects and therefore a final optimization was designed (Table 9). Both catalysts required a reaction time of 4 h to consume the boronic acid starting material with excellent selectivity towards the formation of **1c**. A comparable results were observed under 30 °C (Table 8, entry 8) and at room temperature (Table 9, entry 1). The shortening in reaction time to 4 h was detrimental to its performance (Table 9, entry 3). It was observed that, although had similar **1c**:**2c** ratios, the conversions were lower under $Cu(OAc)_2$ conditions when compared to CuOAc. The reaction not only tolerated a TCICA loading reduction from 1.0 equiv to

0.67 equiv keeping the same conversion, but also almost doubled the selectivity ratio (Table 9, entry 7). Any further reduction of the equiv of chlorinating reactant was adverse for the reaction's peformance. Since the initial proposal was to conduct the chemoselective chlorination and the SMCC in a tandem one-pot procedure, low temperatures were required to avoid homocoupling by-products, hence the decision to use room temperature as the most suitable.

Table 9 - Final optimization using copper(I) acetate and copper(II) acetate



Entry	$Cu(OAc)_n$	X equiv TCICA	Time (h)	Conversion to 1c (%)[a]	Selectivity 1c:2c[a]
1	CuOAc	1.00	6	95	26:1
2	CuOAc	1.00	4	93	25:1
3	CuOAc	1.00	2	80	11:1
4	$Cu(OAc)_2$	1.00	6	92	22:1
5	$Cu(OAc)_2$	1.00	4	92	18:1
6	$Cu(OAc)_2$	1.00	2	79	13:1
7	CuOAc	0.67	4	96	50:1

[a] Determined by HPLC analysis.

With optimal conditions in hand, the substrate scope was investigated. As described in Figure 12, 4-chlorobiphenyl **1c** was invariably the major product accessed, with good to excellent ratio of selectivity against a range of BPins species. ED and EN groups in the BPin partner at the *para*-position (**3b** and **5b**) showed slight decrease

in yield, whereas more EW substituents (**4b** and **8b**) showed full conversion to **1c** with complete selectivity. The 4-chlorobiphenyl **1c** was accessed with excellent conversion against the fluorinated BPins **6b** and **7b**, although in slightly lower selectivity ratio compared to previous substrates.

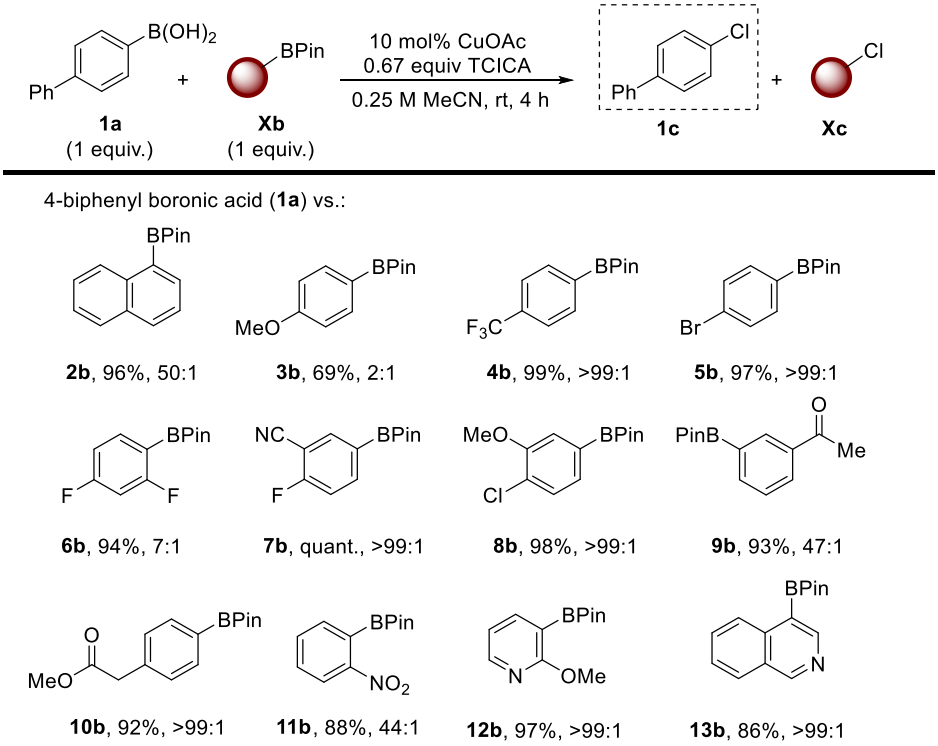


Figure 12 - Substrate scope varying the arylBPin content

Notably, when against arylBpins bearing ketones (**9b**) and methyl esters (**10b**) groups, the 4-chlorobiphenyl **1c** product was afforded with excellent conversion and selectivity ratio in both cases. Even large EW-subtituents at the *ortho*-position such as nitro group (**11b**) were tolerated, displaying excellent selectivity ratio. Heterocycles such as 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine **12b** and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline **13b** showed to be tolerated in this methodology, affording exclusevily the 4-chlorobiphenyl **1c** product.

While varying the boronic acid, a similar trend could be observed. Arylboronic acids bearing ED groups (**3a**) showed better conversions and selectivity, whereas EW functionalities, such as trifluoromethyl group, (**4a**) had a decrease in conversion,

and selectivity ratio. The 4-fluoro-3-cyanophenylboronic acid **7a** displayed a similar decrease in conversion, although with remarkable selectivity. The presence of ketone functionality at the *meta*-position (**9a**) had a noteworthy impact in the reaction's performance delivering the product **9c** in moderate conversion and with virtually no selectivity.

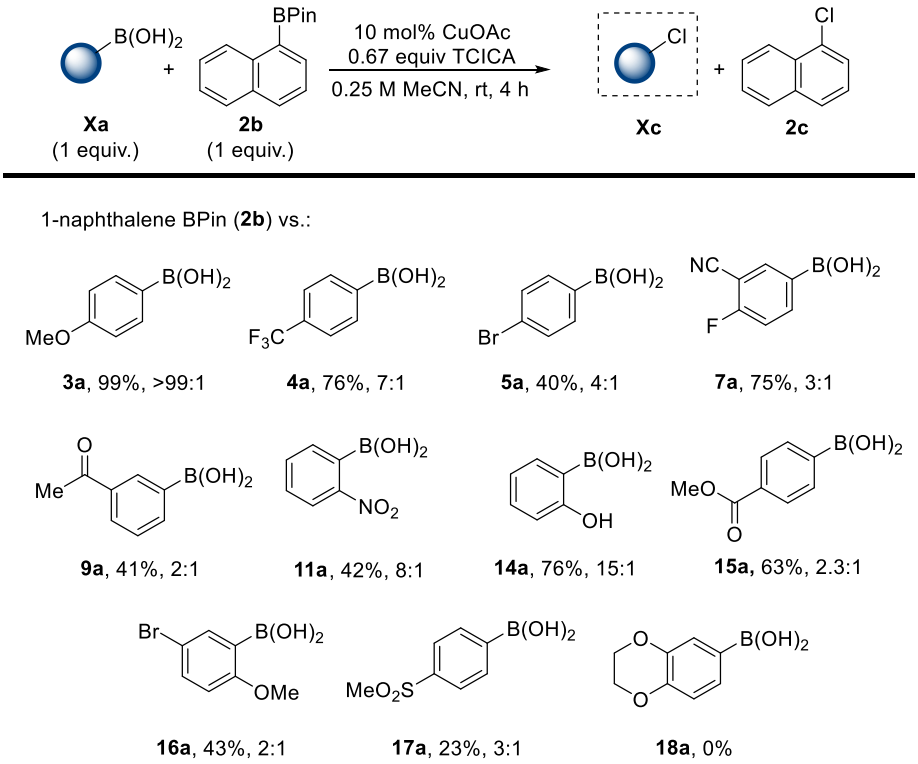
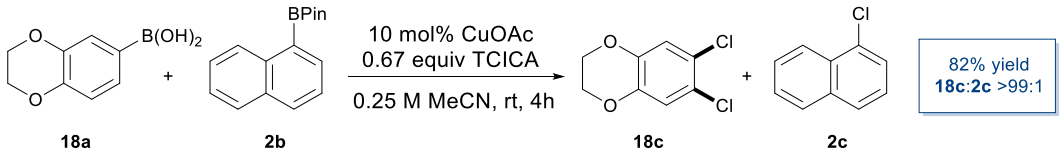


Figure 13 - Substrate scope varying the arylboronic acid content

The 2-hydroxyphenylboronic acid **14a** was converted to the correspondent chlorinated product both with good conversion and excellent selectivity ratio. Esters (**15a**) were tolerated significantly better than methylsulfonyl (**17a**) groups under the set of conditions developed, affording selectivily the correspondent chlorinated product **15c** and **17c** in good and poor conversions, respectively. The reaction has reduced performance when bearing EDG at the *ortho*-position, yielding the product 4-bromo-2-chloro-1-methoxybenzene **16c** with moderate conversion and poor ratio of selectivity. In the case of (2,3-dihydrobenzo[b][1,4]dioxin-6-yl)boronic acid **18a**, no 6-chloro-2,3-dihydrobenzo[b][1,4]dioxine product was isolated from the reaction mixture.

In the entry highlighted in Scheme 50, only the di-chlorinated product 6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxine **18c** could be observed, with complete selectivity over the competing 1-chloronaphthalene **2c** product. In this case the products were isolated due to product **18c** being untraceable by the HPLC method developed.



Scheme 50 - Entry 2b *vs*. 18a in Figure 13

The donating effect of the dioxane substituents helps activating, together with the chlorine, the C7 position in the ring through a *para*-direction from the ether substituent and *ortho*-direction by the halogen. The entry was re-attempted using 0.34 equiv of TCICA as an effort to access the mono-chlorinated product, however, any attempt to synthetize 6-chloro-2,3-dihydrobenzo[b][1,4]dioxine was unsuccessful. Instead, the only di-chlorinated product was obtained in reduced yield. The observation suggests that, once formed, the mono-chlorinated product is more reactive to an aromatic substitution than the boronic acid starting material **18a** itself.

Along the substrate scope, incompatibility with a range of functionalitites was encountered as described in Figure 14. Although still keeping a significant selectivity towards the boronic acid partner, the 2-thiophene boronic acid **19a** showed a pronounced decrease in reactivity when compared to the previously evaluated substrates.

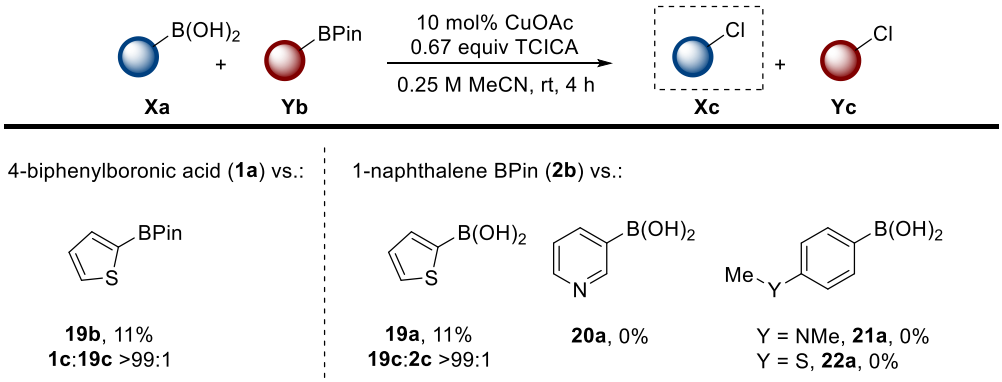


Figure 14 - Unsuitable substrates for the chemoselective chlorination

As demonstrated possible for the BPin partner, the possibility of incorporating *N*-containing functionalities in the boronic acid partner was sought. Neither amino-substituted boronic acids (**23a**) nor *N*-containing heteroarylboronic acids (**22a**) afforded the desired chlorinated product, even though full consumption of the boronic acid species was observed. Notorious for their predisposition to protodeboronate,[38] especially in the case of heteroarylboronic acids such as the thiophen-2-ylboronic acid **21a** and pyrid-3-ylboronic acid **22a**, substrates such as the above mentioned can be challenging obstacles to overcome while scoping a methodology.

In order to investigate the scope, other boron partners for this methodology were investigated (Figure 15). Even though 4-chlorobiphenyl **1c** was the major product encountered, both conversion and selectivity had a drastic decline when naphthalen-1-ylboronic acid MIDA ester **2d** was used. On the other hand, **2e** was preferably chlorinated over the [1,1'-biphenyl]-4-ylboronic acid **1a**. Notably, a significant selectivity ratio **1c**:**2c** of 1:9 was observed when 1-naphthylboronic acid **2a** was used aganist [1,1'-biphenyl]-4-ylboronic acid **1a**. According to the last result displayed, it was postulated that **2a** is a more reactive substrate than **1a** due to the steric interaction present in **2a** between the boron substituent and the proton of the adjacent ring, which accelerates the aromatic substitution.

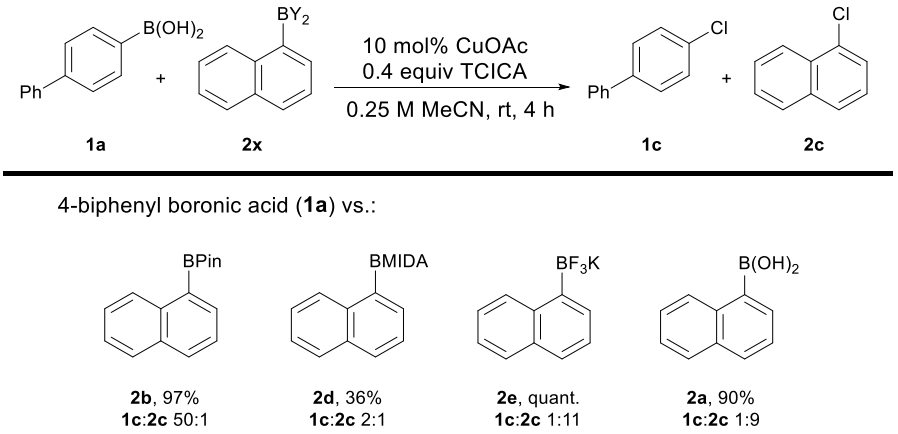


Figure 15 - Scope of boron partners *vs*. 1a

In order to understand if the selectivity obtained previously relies on substrate specificity rather than a trend of reactivity, the 1-naphthyl boronic acid **2a** was tested against different 4-biphenyl boron species (Figure 16).

Corroborating with the last results in the previous table where the 1-naphthyl boronic acid **2a** showed to be more reactive, 1-chloronaphthalene **2c** was the major product against [1,1'-biphenyl]-4-ylboronic acid pinacol ester **1b** and [1,1'-biphenyl]-4-ylboronic acid MIDA ester **1d**. Notably, opposite trend was observed for the pair **2a** and potassium 4-biphenyltrifluoroborates **1e**, where 1-chloronaphthalene **2c** was the major product obtained.

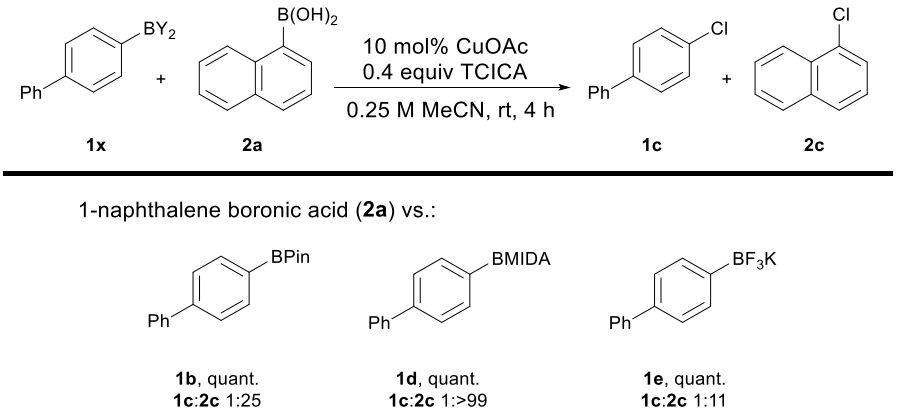


Figure 16 - Scope of boron partners *vs*. 2a

3.1.3 One-pot di-nucleophile SMCC

After investigating cthe chlorination step, the initial idea of the di-nucleophile SMCC was endeavoured. The overall process would consist in performing a chemoselective chlorination followed by a Suzuki-Miyaura reaction to couple the generated halide and the remaining boron species. However, before attempting the one-pot procedure, a few controls experiments were necessary to identify any potential issues that could be encountered during the tandem process. To do so, we selected entry **10b** in Figure 12 as a suitable pair of boron species to investigate the one-pot SMCC. Not only for providing easy track by HPLC analysis but also clearly identifiable peaks through ^{1}H NMR spectrum. Since the investigation would only be relevant for the SMCC step, the entry **10b** was used for the control conditions.

To explore if by-products from the first step would be detrimental to the cross-coupling step, standard conditions developed within the group[151] were subjected to all possible by-products and their combinations, in order to mimic the reaction mixture. After the chlorination is finished, under the optimized conditions, there would still be excess of TCICA remaining in the mixture for the Suzuki step. Moreover, ICA (**23**) is the direct by-product of complete dehalogenation of TCICA. The incomplete consumption of the chlorinating agent could be either or both DCICA (**25**) and CICA (**24**) as shown in Figure 17. To simplify the experiments, it was hypothesized that both **24** and **25** would provide the same reaction outcome as the chlorinating agent TCICA itself.

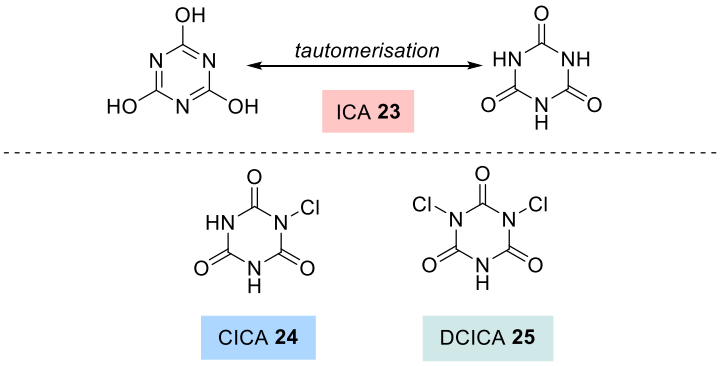
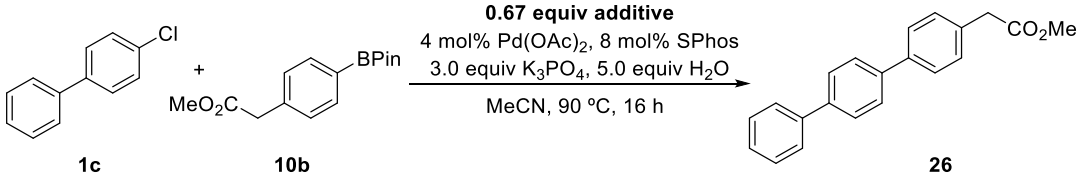


Figure 17 - By-products from consumption of TCICA

Results and discussion

Firstly, the conditions employed performed as expected, delivering the coupled triaryl in high conversion (Table 10, entry 1). Unfortunately, TCICA completely inhibited the SMCC, yielding only the starting materials (Table 10, entry 2). It was hypothesized that the agent irreversibly poisons the palladium catalyst and therefore prevent the reaction from proceeding. Notwithstanding, **23** did not entirely interrupted the cross-coupling step, yielding the coupled product only in moderate conversion (Table 10, entry 3). Also, no protodeboronation of the boronic ester was observed. The triaryl was only observed in good conversion when CuOAc was added to the mixture (Table 10, entry 4). Not surprisingly, the combined addition of TCICA and CuOAc to the reaction mixture also inhibited the SMCC reaction (Table 10, entry 5). The simultaneous presence of ICA and CuOAc provided the Suzuki-Miyuara coupling product in moderate conversion (Table 10, entry 6).

Table 10 - Control experiments



1c **10b** **26**

Entry	Additive	Conversion (%)[a]
1	None	92
2	TCICA	0
3	**23**	56
4	CuOAc	68
5	TCICA + CuOAc	0
6	**23** + CuOAc	49

[a] Determined by HPLC analysis.

As a result, from the information gathered in this control study, few drawbacks from the process could be identified and addressed. First of all, and most importantly, no excess of TCICA can remain in the mixture, otherwise the Suzuki-Miyaura coupling will not proceed and, since both TCICA and $Pd(OAc)_2$ can not coexist in the reaction mixture, late-addition of the catalyst is required in this case. Although this valuable information prevented us from encountering several issues during optimization, the initial aim of having all reactants present from the start has proved unfortunately to be impracticable.

Thus an evaluation of the procedure and all possible side products that could emerge was overseen before describing the optimization (Figure 18). The CEL coupling is notorious for presenting oxidation and protodeboronation (therefore homocoupling too) of boron species as its main side reactions.[100] As it was identified by Chu[158] and Vantourout *et. al.*,[99,100] the presence of CuOAc (derived from the reductive elimination step of the CEL catalytic cycle) in the mixture triggers the production of oxidation and protodeboronation by-products, regardless the boron species in use. Although stoichiometric amounts of CuOAc are not employed, likewise several examples for the CEL coupling, the oxidation/protodeboronation can still impact the one-pot process in different aspects:

1) Consuming starting material: obviously, the formation of by-products is detrimental for its performance and affects directly the overall yield.

2) Not complete use of the chlorinating agent: as the control experiments demonstrated, the issue of not full consumption of TCICA would result in partially or entirely poison of the palladium catalyst, supressing the Suzuki-Miyaura coupling step.

3) Loss of selectivity: boronic acids are more prone to protodeboronation and oxidation than BPins and, once all boronic acid in the reaction mixture is consumed, only the boronic ester will be available to be chlorinated, decreasing the selectivity ratio as well as the overall yield.

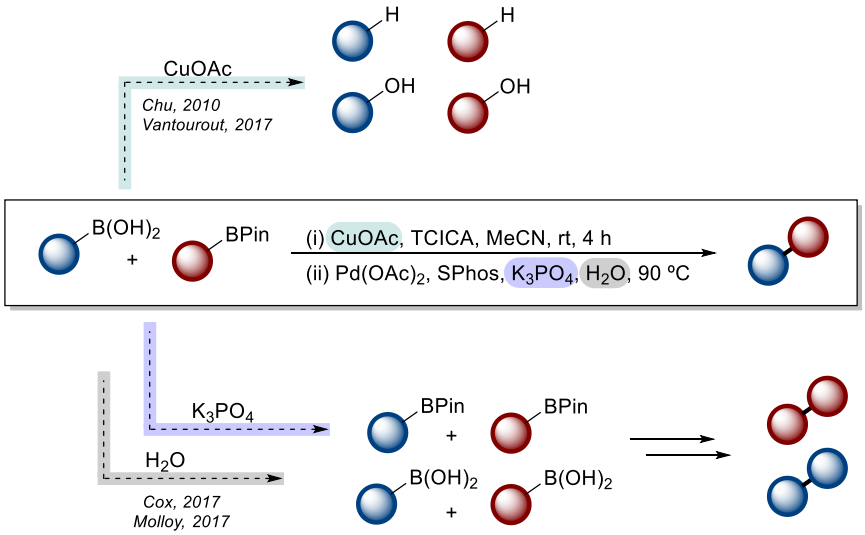


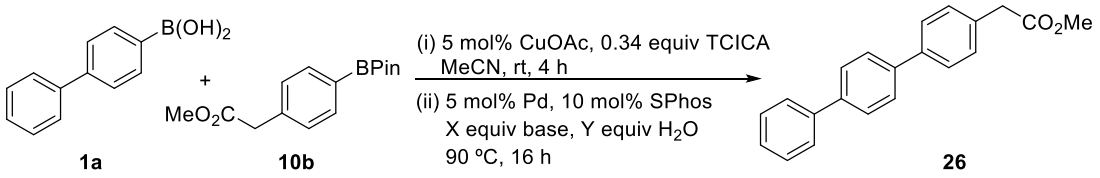
Figure 18 - Evaluation of side reactions and possible by-products

Even though rising significantly less damaging issues to the reaction, the presence of base and water in the reaction mixture can still be problematic. Boronic acid pinacol esters can be hydrolysed delivering the respective free boronic acid in the mixture, which can undergo a base catalysed protodeboronation mechanism described by Lloyd-Jones.[35,38,39] If the reaction is not selective and a significant amount of boronic acid remains unreacted in the mixture, pinacol exchange demonstrated by Molloy *et. al*.[150] could yield a complex mixture of boron species that could culminate in homocoupled products as shown in Figure 18. With several potential issues to be overcome, the one-pot procedure has proven to be an ambitious however feasible project once a very careful and detailed study of its variables were accomplished.

As previously outlined the use of the pair **1a** *vs* **10b** of boron species in Figure 12, the initial optimization study was conducted. From previous projects within the group,[139–141,144] the amount of base and water in the reaction mixture has demonstrated to play a crucial role in the reaction outcome, hence we focused on these aspects initialy. The inorganic base K_3PO_4 was found to be the most suitable base for SMCC. K_3PO_4 is known to be hygroscopic and able to form stable tetra-hydrate species.[151] It was thought that the base could sequester H_2O, limiting hydroxide formation and consequently pinacol deprotection and protodeboronation. The concept of a basic biphase in the context of SMCC has been

previously discussed by Lloyd-Jones,[159] where the basic aqueous phase would act as a reservoir of hydroxide ions. In this case, a slow release of HO^- into the organic phase would enable the SMCC catalytic cycle to progress and minimize any of the by-products highlighted above.

Interestingly the combination of water and K_3PO_4 has proven to be crucial for the overall yield of the process (Figure 19). Moderate to excellent yields were observed in the range of 5 to 7 equiv of H_2O. The use of 3 equiv of K_3PO_4 or less demonstrated to have reduction in performance. For this methodology 4 equiv of K_3PO_4 were the most competent load of base to catalyse the SMCC. A significant decrease in the overall conversion was identified when using 10 equiv of H_2O, regardless of the amount of base in the reaction media. This effect was observed in other projects related to the topic within the group.[139,141,151] The ultimate combination of 4 equiv of K_3PO_4 and 7 equiv of H_2O in the mixture helped affording the desired coupled product in 91% conversion and 90% isolated yields.



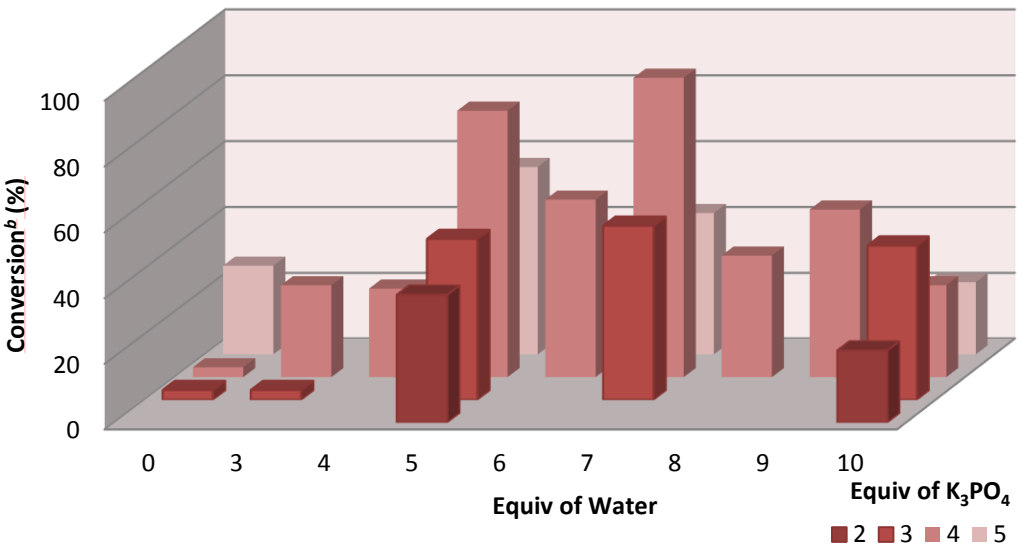
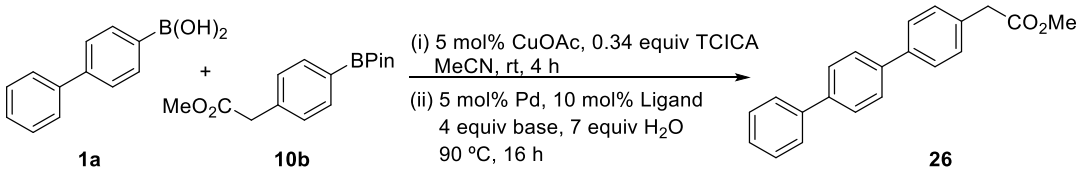


Figure 19 - Graphic screening K_3PO_4 vs. H_2O equivalents

Results and discussion

Table 11 shows that no other inorganic base could outperform K_3PO_4, even though both K_2CO_3 and Cs_2CO_3 are commonly used bases for Suzuki-Miyaura cross-couling reactions. Likewise, was the case of ligands catalysts screened for the one-pot process. Notably, DavePhos and CyJohnPhos did not equate the performance of SPhos, poorly yielding the desired product **26**. The replacement of $Pd(OAc)_2$ by $PdCl_2$ was detrimental to the overall yield. As predicted to be inefficient to catalyse the reaction due to the electron-defficiency of its ligand, $PdCl_2$(dppf) DCM and $[Pd(PPh_3)_4]$ did not form significant ammounts of the coupled product.

Table 11 - Catalyst and base final optimization



Entry	Pd Catalyst	Ligand	Base	Conversion (%)[a]
1	$Pd(OAc)_2$	SPhos	K_3PO_4	91
2	$Pd(OAc)_2$	SPhos	Cs_2CO_3	28
3	$Pd(OAc)_2$	SPhos	K_2CO_3	24
4	$Pd(OAc)_2$	DavePhos	K_3PO_4	19
5	$Pd(OAc)_2$	CyJohnPhos	K_3PO_4	19
6	$PdCl_2$	SPhos	K_3PO_4	11
7	$PdCl_2$(dppf) DCM	-	K_3PO_4	16
8	$Pd(PPh_3)_4$	-	K_3PO_4	13

[a] Determined by HPLC analysis.

With optimal conditions in hands, the substrate scope was composed (Figure 19). The work shown in Figure 20 had been done in collaboration with Joseph E. Dixon, who synthesized the compounds **29**-**32**, **35** and **36**.

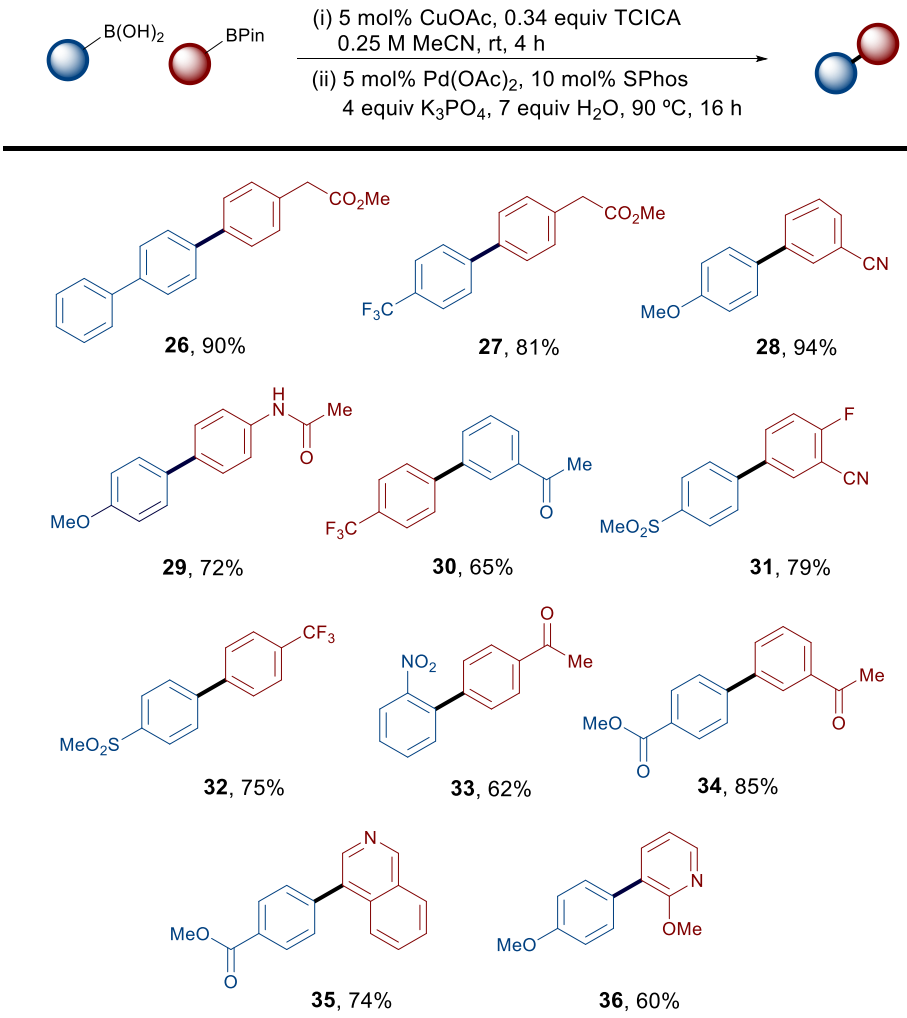


Figure 20 - Substrate scope for the one-pot di-nucleophile SMCC procedure

The optimized pair (**26**) was isolated in excellent yield. Although with a small decrease when the boronic acid partner bears a more EW subtituent, compound **27** could be isolated in good yield. The method tolerates boronic pinacol esters bearing nitriles (**28**) and amides (**29**) groups, delivering the coupled product, using 4-methoxyphenylboronic acid as its partner, in excellent and good yields, respectively. Ketones (**30**) and sulfones (**31** and **32**) are also tolerated substituents. 1-(2'-Nitro-[1,1'-biphenyl]-4-yl)ethan-1-one **33** demonstrates the reaction performs well when using EWG at the *ortho*-position of the aryl boronic acid, affording the desired final

product in moderate yield. Under the optimized conditions arylboronic acids with esters functionalities (**34** and **35**) were found to be suitable partners. Also heteroaryl BPins, such as isoquinolin-4-ylboronic acid pinacol ester and (2-methoxypyridin-3-yl)boronic acid pinacol ester, were tolerated and delivered compounds **35** and **36** in moderate yields.

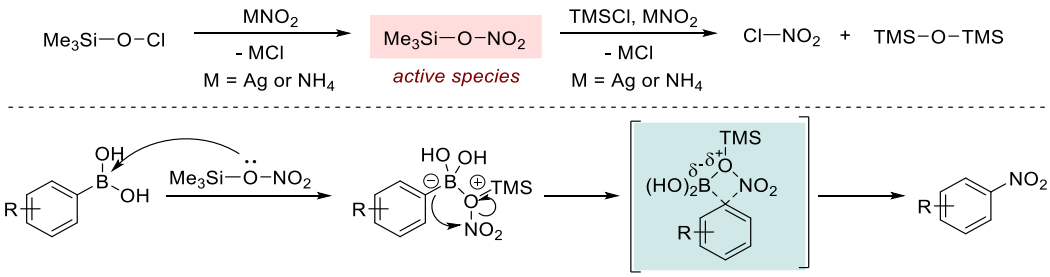
3.2 Mechanistic Investigations

Although examples reported in the literature proposed mechanisms for the transformation, these studies were often minimal or superficial. Moreover, none of them properly addressed nor rationalised the reason as to why the reaction can be catalysed by both Cu(I) and Cu(II) species, as previously seen by Hynes and also verified during the optimisation for the process described in the last section.[117]

At first our initial studies investigated the possibility of the chlorination to proceed through radical pathway, which was considered by Molander[119] and discussed previously in this manuscript under Section 1.2.5. In the possession of this information, Molander then proposed that the transformation proceeds *via* an *ipso*-substitution, as also suggested by Olah's group study on nitration of boronic acids.[123,160]

Perhaps the most interesting aspect to highlight from Olah's work is the mechanistic investigation conducted (Scheme 51).[123] Since the group reported only mono-nitration of the boron species, without regioselectivity issues, it could be postulated that the electrophilic aromatic substitution would occur at the *ipso*-position. It is well-known that TMSCl (Me_3Si-O-Cl) reacts with nitrate salts to generate the active TMS-O-NO_2 species.[123] After formation of the active pecies, the boronate intermediate is generated through attack of the oxygen present in the siloxyl group to the boron due to the high oxophilicity of the boron centre. The formation of the C-N bond is suggested to go through a concerted mechanism, diverging from a classic electrophilic aromatic substitution which normally goes through a Wheland

intermediate (see page 7, Scheme 8). In the Wheland intermediate pathway, the attack into the nitro group would occur from a double bond of the aromatic ring, with concomitant cleavage of the C-B bond. Additionally, the excess of TMS present in the mixture can react with the active species to generate Cl-NO_2, which can also act as an active species in this transformation.[161] The main drawback is that the latter can deliver either the nitrated or the chlorinated product,[123,161] even though the chlorinated by-product has not been observed in Olah's substrate scope.

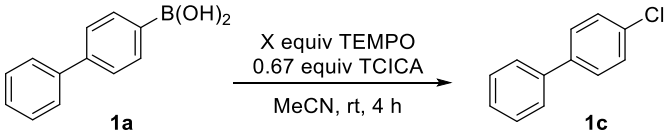


Scheme 51 - Formation of active species and mechanism presented for the *ipso*-nitration of boronic acids

Since the mentioned activation of nitrate salts by TMSCl is well-known,[161,162] Olah's group ceased investigating to eliminate other possible pathways and proposed the mechanism described above. The oxygen lone pair of the active species generated *in situ* attacks the boron empty *p* orbital, forming a boronate-type intermediate as shown, which is claimed to assist the nitration at the *ipso*-position. Olah *et. al.* proposed a concerted mechanism that forms a 4-membered transition state, highlighted in Scheme 52, which is supported by the first order dependence of TMSCl available in solution to form the active species.[122,123]

Even though previous work reported in literature suggests the reaction is unlikely to undergo a radical mechanism, experiments were designed to help understanding aspects of the reaction. As it is widely employed, the radical scavenger TEMPO was used to investigate whether the reaction would be affected. As the process is not strictly mediated by this metal, the investigation was conducted under those three different set of conditions shown in Table 12.

Table 12 - Experiments with radical scavenger

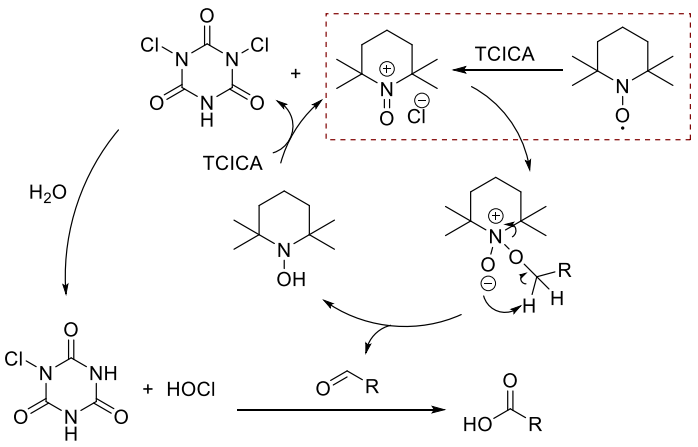


Entry	TEMPO	Conversion with CuOAc (%)[a]	Conversion with $Cu(OAc)_2$ (%)[a]	Conversion without catalyst (%)[a]
1	-	98%	96%	92%
2	1.0 equiv	92%	90%	94%
3	2.0 equiv	53%	64%	60%
4	3.0 equiv	25%	48%	56%
5	5.0 equiv	20%	40%	38%
6	10.0 equiv	4%	12%	13%

[a] Determined by HPLC analysis.

Notably, the reaction yields diminished significantly with the addition of 2 or more equivalents of TEMPO, almost completely inhibiting the reaction when employing 10 equivalents of the scavenger (Table 12). Although the data strongly indicates the reaction could involve radical species, it is crucial to acknowledge that, the latter entry for instance required 0.5 g of TEMPO to be added in a 1 mL MeCN solution. This implies that the scavenger is more prone to interfere in other aspects of the reaction, such as stirring and material dispersion, due to the large amount of material in the vessel.

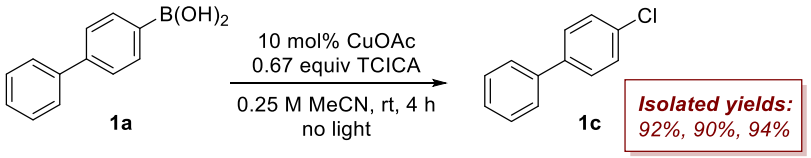
A study conducted by Giacomelli employs TCICA and catalytic amounts of TEMPO to oxidize alcohols to the corresponding carboxylic acid (Scheme 52).[163] Giacomelli's group developed experiments to clarify some mechanistic aspects.



Scheme 52 - Mechanism proposed for the TCICA/TEMPO oxidation of alcohols

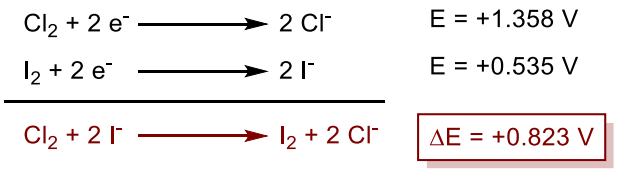
The reaction slowed significantly when NCS was used instead of TCICA. A catalytic amount of NaBr was used in the reaction (which also tolerates other salts such as NaI and LiF), however, its role in the mechanistic pathway was not mentioned. The hydrolysis of TCICA seems to be catalysed by the presence of halide ions. In the absence of it, no oxidation to carboxylic acids occured. The study also pointed out that TEMPO was not required to access the final product from its intermediate. In fact, the aldehyde was rapidly oxidized to the corresponding carboxylic acid by treatment with one equivalent of TCICA in a mixture of Acetone/H_2O, without adding TEMPO. The Giocomelli's work helped elucidating the dramatic decrease in yield observed in the table above, as TEMPO showed to consume TCICA and therefore preventing the chlorination to occur.

Our observations and the work reported by Giacomelli cannot completely disprove that the reaction goes *via* a radical mechanism while further experiments to analyse the formation of the radical species were conducted. One of the principal initiators for radical-based reactions is the use of UV light.[164] Therefore, to obtain more information to validate the possibility of a radical-based reaction, the optimum conditions described in General Procedure G were applied in the complete absence of light (Scheme 53). Interestingly, the reaction performed effectively and consistently under these conditions. In conclusion, no concrete evidence was obtained to assume that the reaction proceeds *via* a radical pathway.



Scheme 53 - Experiments in the absence of light

Simultaneous to the studies shown previously, the possibility of generating of chlorine gas *in situ* was considered. To verify the formation of Cl_2, it was considered that a redox reaction, where the gas could be readily reduced by, for instance, iodine anion, would be a rapid and simple indicator for the purpose. The standard reduction potentials[165] are reported in Scheme 54 with its overall positive ΔE, which means that the oxidation of iodide to iodine by chlorine gas is spontaneous and readily detectable since the solution would go from colourless (aqueous solution of NaI) to dark brown or purple (due to the formation of molecular iodine in the mixture). The solvation of iodine by water in the solution described above did not produce a coloured solution, which helps a more accure and rapid identification of I_2 formation.



Scheme 54 - Standard reduction potentials in aqueous solutions at 25 °C and the potential of the proposed experiment

The designed experiment described in Figure 21 would reproduce the reaction medium and, by saturating the solution with N_2, the Cl_2 generated would be forced into the second vessel, containing a saturated solution of sodium iodide. This simple technique would allow a qualitative analysis of Cl_2 formation.

All the different reaction environments were assembled (with and without the presence of copper catalyst), as well as a control experiment, where only the solvent would be present to reassure no false positive will be detected, leading to misinterpretation. An iodine paper indicator was also used in the study.

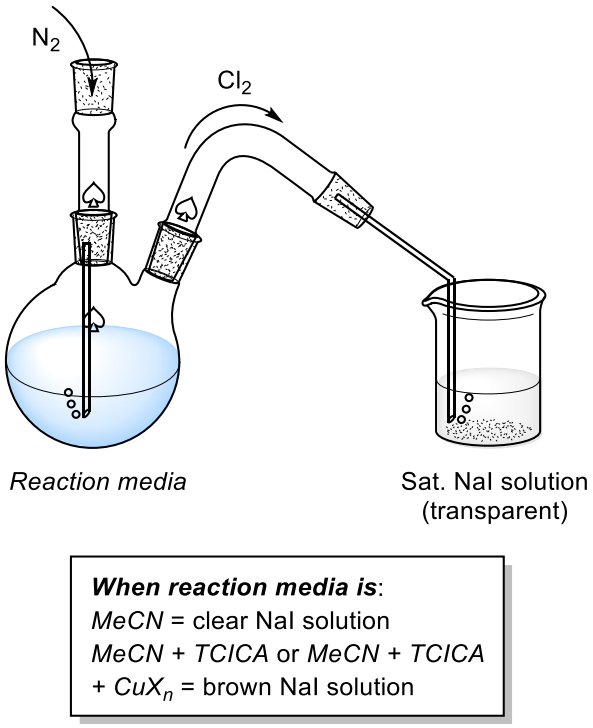
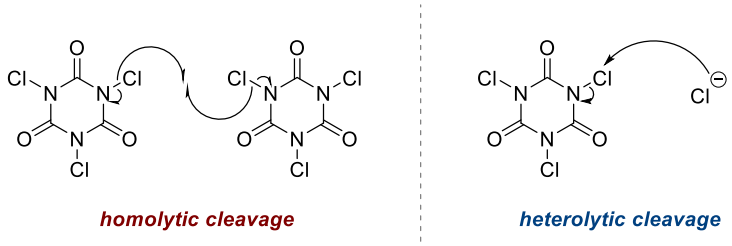


Figure 21 - Equipment used in the study

As expected in the blank sample, where the reaction media is only MeCN, no change in colour was observed either in the NaI solution or the paper indicator and, therefore, no formation of Cl_2 gas happened. When TCICA was present in the mixture, invariably, the solution went from transparent to dark brown indicating the presence of I_2 from the redox reaction.

The observations suggest the formation of Cl_2 *in situ*, which indicates a homolytic cleavage of the N-Cl bond, corroborating with the proposed formation of radicals in the reaction mixture (Scheme 55).



Scheme 55 - Possible pathways according to reaction conditions

When only TCICA is present in the reaction mixture, the Cl_2 gas must be produced from two N-Cl homolytic cleavages (either intermolecular or intramolecular). The other approach reported by Molander (Scheme 51, reaction conditions **(B)**),[119] where substoichiometric quantities of the electrophilic chlorinating agent were used in combination with NaCl without affecting the overall yield of the process, goes through a heterolytic bond cleavage. In this case, the chlorine anion attacks the electrophilic chlorine to form Cl_2. Since the studies conducted only used TCICA, the developed chlorination pathway must go through a homolytic cleavage.

Previous investigations elucidated few aspects of the transformation and helped understanding reactivity, however they did not elucidate how chemoselectivity could be achieved. Experiments to observe the potential interactions between reaction components were then sought. From observations collected during our optimisation, it is known that the reaction proceeds in the absence of either Cu(I) or Cu(II) catalysts, although with reduced yield and consequently poor selectivity (page 43, Table 2). Through this data, it was anticipated that an interaction between copper and TCICA which could enhance its reactivity. We envisioned that infrared (IR) experiments could be an interesting technique to verify whether a significant interaction between chlorinating agent and copper catalyst.

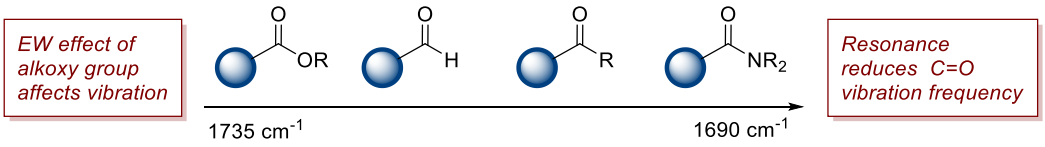


Figure 22 - Infrared scale for carbonyl vibration frequency for different functional groups

The carbonyl vibration lies within the range of 1750-1600 cm^{-1} in the IR spectrum,[166] which is extensive enough to enable recognition of different functional groups (Figure 22). If an interaction between catalyst and the carbonyl moieties of TCICA exists, a possible shift in the C=O stretching frequency could be observed. The procedure used in this analysis is described in General Procedure E. To avoid misinterpretation, both $Cu(OAc)_n$ and $CuCl_n$ were investigated. Moreover, the TCICA ν_{CO} is 1731 cm^{-1}, as evidenced in Figure 23.

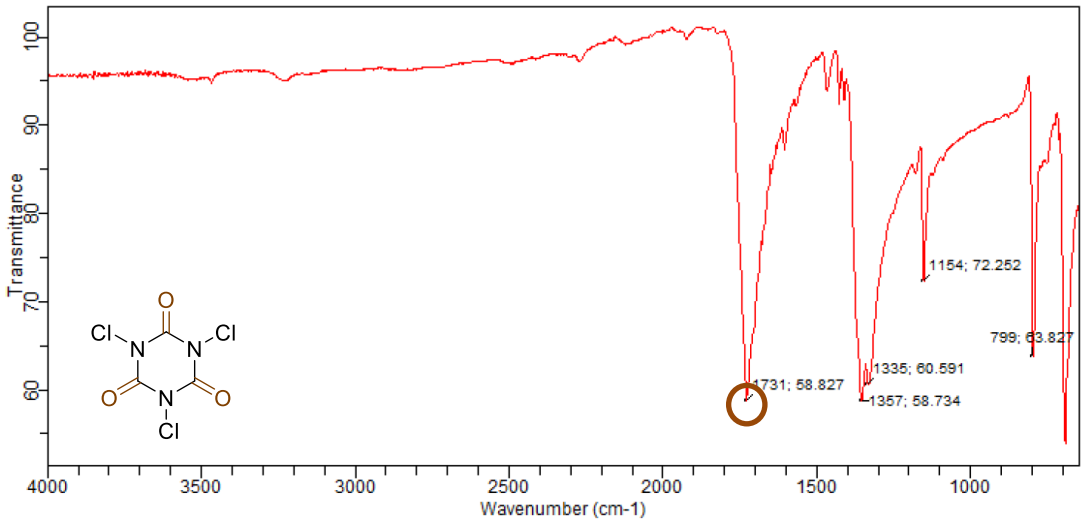


Figure 23 - IR spectrum of TCICA

When the mixture of TCICA and CuOAc was analysed, no difference from the previous IR spectrum was observed, with the same occurring for the mixture using CuCl. Interestingly, for both $Cu(OAc)_2$ and $CuCl_2$ experiments, an extra peak could be observed in the spectrum in the region of 1597 cm^{-1}, eliminating any possible interference that could emerge from the acetate ligand (Figure 24). This new band was observed in a typical region for amides. The observation perhaps can result from interaction between the copper catalyst and TCICA. The results obtained, showing a different reactivity between copper(I) and copper(II) catalysts, could perhaps suggest that the reaction may undergo a different mechanism depending on the catalyst of choice.

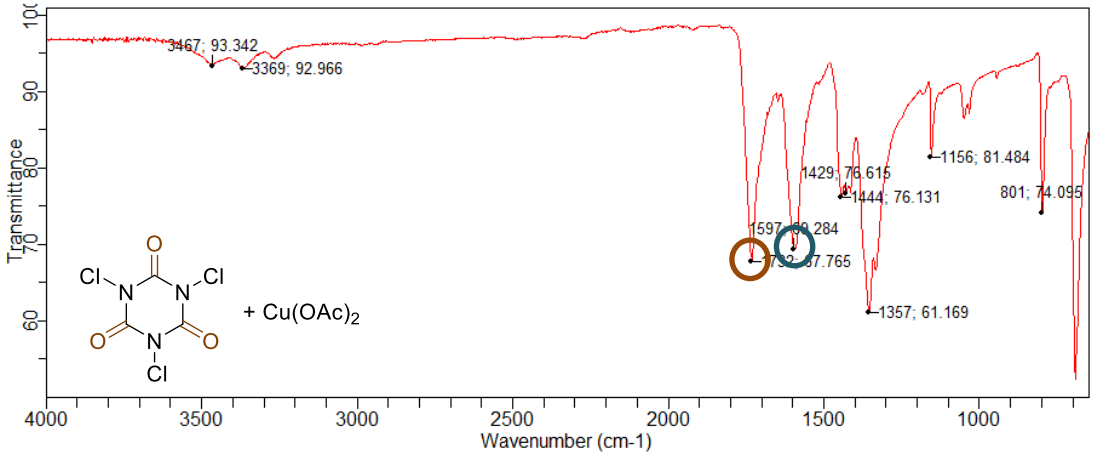
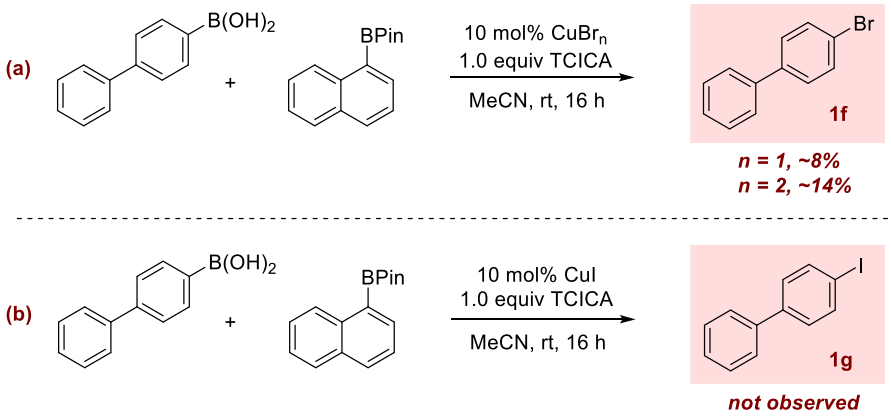


Figure 24 - IR spectrum of the TCICA + $Cu(OAc)_2$ mixture

Another aspect worth investigating that may provide evidences of multiple possible mechanisms is the by-product obtained in one reaction during the copper catalyst screening shown in Table 8. When CuBr and $CuBr_2$ were used, significant amounts of a by-product were observed by HPLC, which later was found to be 4-bromobiphenyl (Scheme 56a). Interestingly, the analogous 4-iodobiphenyl by-product was not observed when using CuI (Scheme 56b).

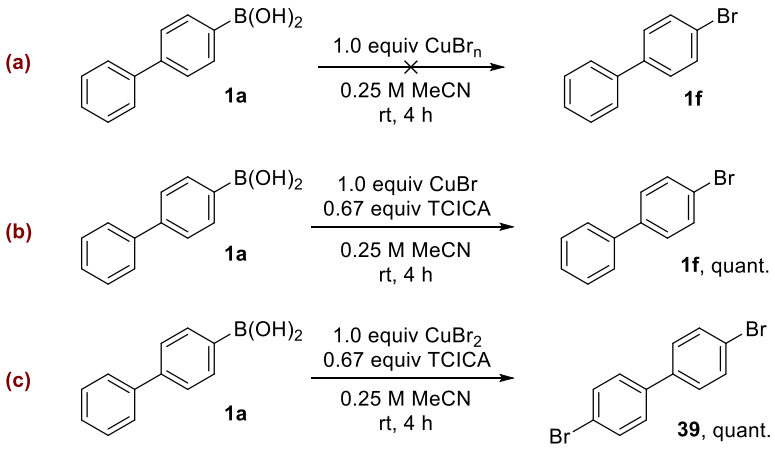


Scheme 56 - By-products observed in entries from Table 8

The first aspect of the by-product is that it comes only from boronic acid species and not the arylBPin component. It is important to notice that, either using CuBr or $CuBr_2$, nearly all the bromine available in the mixture is incorporated in the by-product. Based on those initial observations, the question of a competing

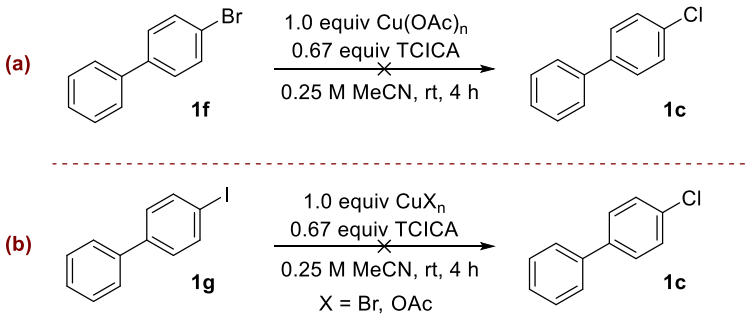
bromination process arose, as well as if there is a requirement of TCICA for by-product formation.

No by-product was observed when only 1.0 equivalent of CuBr or $CuBr_2$ was present in the reaction media (Scheme 57a). Notably, TCICA in the presence of 1.0 equiv of CuBr only afforded 4-bromobiphenyl as the product, with no traces of the chlorinated biaryl (Scheme 57b). The use of 1.0 equiv of $CuBr_2$ and TCICA delivered exclusively the di-brominated product **39** (Scheme 57c). The information collected from the above experiments suggests that TCICA, perhaps acting as an oxidant, is crucial for the formation of brominated by-products. It also indicates that copper might not be essential for the bromination to occur.



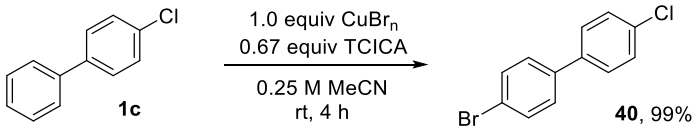
Scheme 57 - Investigations of by-product formation

It was also hypothesised that the copper catalyst would not be able to reinsert into the C-Br bond and therefore 4-bromobiphenyl would be observed as a by-product. However, when using CuI, once starting material was consumed giving a mixture of chlorinated and iodinated products, the copper catalyst could reinsert into the C-I bond and deliver the chlorinated product. Although unlikely, this possibility had to be discarded. We then submitted both 4-iodobiphenyl and 4-bromobiphenyl, separately, to the optimum conditions to verify if there is formation of the chlorinated product (Scheme 58).



Scheme 58 - Investigations of the formation of 1c from by-product

Both sets of conditions used in the tests failed to deliver 4-chlorobiphenyl. This information suggests the formation of by-product is irreversible. The by-product could however come from the 4-chlorobiphenyl instead of the boronic acid starting material. In order to verify thIs hypothesis, 4-chlorobiphenyl **1c** was subjected to the reaction conditions in which the by-product **1f** was observed (Scheme 59). Notably, the reaction did not afford 4-bromobiphenyl **1f** but unexpectedly produced the 4-bromo-4'-chloro-1,1'-biphenyl product **40**.



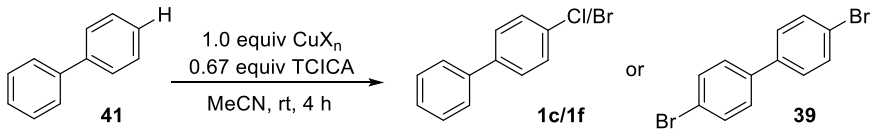
Scheme 59 - Investigations of the formation of by-product

The bromination occurred opposite to the chlorine position which, through inductive effect of the chlorine,[167] is the most electron-negative position in the molecule.

Hitherto what could be concluded from the observation gathered is that: 1) the by-product **1f** observed does not come from the chlorinated product but from the arylboronic acid starting material, 2) the reaction likely requires a source of "Br^+" in the mixture and 3) the chlorinated product **1c** can also suffer halogenation (as shown in Scheme 60). However, in all previous examples, a substituent was already in place and therefore could electronically affect its reactivity. An aspect worth exploring is if the same kind of reactivity would be noticed for the unfunctionalised

biphenyl **41**. Therefore, **41** was submitted to similar conditions and the results obtained are displayed in Table 13.

Table 13 - Formation of halogenated products from biphenyl



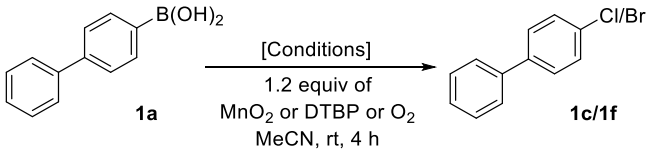
Entry	CuX_n	Conversion (%)[a]
1	CuBr	>99% of **1f**
2	$CuBr_2$	>99% of **39**
3	CuCl	28% of **1c**
4	$CuCl_2$	80% of **1c**
5	CuOAc or $Cu(OAc)_2$	traces of **1c**

[a] Determined by HPLC analysis.

Using copper(I) bromide, the reaction delivered quantitatively the mono-brominated product **1f** whereas, when employing copper(II) bromide, only the di-brominated product was afforded. In the case of CuCl and $CuCl_2$, both produced the 4-chlorobiphenyl **1c** as its only product in poor and good yields, respectively. Remarkably, the optimal conditions only afforded traces of 4-chlorobiphenyl **1c**, and no desired product was observed when $Cu(OAc)_2$ was used instead. These results show that, for the copper catalysts bearing halide counter ions, the equivalent halogenated biaryl products have been formed. Under the optimal conditions developed the reaction failed to deliver the product **1c**. The following results suggest that the by-product **1f** initially observed could derive from either the

boronic acid or the protodeboronated by-product. Although these studies clarifies the origin of the side reaction, it still does not solve the question regarding the necessity or role of copper in the reaction or by-product formation. It was then contemplated whether an oxidant other than TCICA could promote the formation of brominated by-products. For this study, the oxidants chosen were MnO_2, di*tert*-butyl peroxide (DTBP) and a balloon of O_2. The studies were conducted employing individually each of the oxidants listed above under the set of conditions described in Table 14.

Table 14 - Screening of oxidants for halodeboronation



Entry	Conditions	Conversion (%)[a]
1	10 mol% CuOAc and 2.0 equiv TBAC	No reaction
2	1.0 equiv CuCl	30% of **1c** (MnO_2), 64% of **1c** (DTBP), 52% of **1c** (O_2 atm)
3	1.0 equiv NaBr	No reaction
4	1.0 equiv CuBr	45% of **1f** (MnO_2), 72% of **1f** (DTBP), 17% of **1f** (O_2 atm)

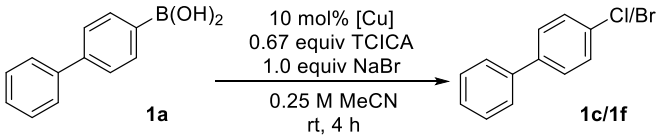
[a] Determined by HPLC analysis.

The use of TBAC as a nucleophilic source of chlorine in the presence of CuOAc failed to form the desired product **1c** regardless of the oxidant employed. In contrast, the chlorinated product was observed in all cases when CuCl was the chlorine source. Neither of the chosen oxidants was competent to promote the bromination using solely sodium bromide. Likewise, it was noticed when CuCl and CuBr were used as the halogenating agent, accompanied by any of the oxidants attempted, yielded

significant amounts of the product **1f**. According to results displayed, the most competent oxidant was DTBP despite of being invariably worse than TCICA.

It is known that product **1f** is exclusively formed in the presence of CuBr and TCICA. In order to understand what is necessary for the formation of the electrophilic bromine, the competing bromination was studied, under the optimal conditions, using NaBr as the source of bromine instead of the previously used $CuBr_n$ (Table 16).

Table 15 - Observation on competing bromination in the presence and absence of copper catalysts

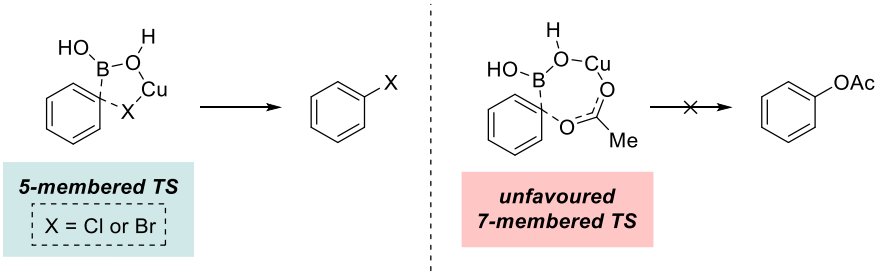


Entry	Copper Source	Conversion (%)[a]
1	10 mol% CuOAc	72% **1c**, 27% **1f**
2	10 mol% $Cu(OAc)_2$	70% **1c**, 28% **1f**
3	-	90% **1c**, 10% **1f**

[a] Determined by HPLC analysis.

Comparable results could be observed when CuOAc or $Cu(OAc)_2$ were used, affording 4-chlorobiphenyl **1c** as its major product, with a ratio **1c**:**1f** of approximately 2.5:1. Curiously, in the absence of any copper catalyst the ratio **1c**:**1f** was greater than what was previously observed. This indicates that the chlorination of the boronic acid occurs more rapidly, in the absence of copper, than the by-product formation. The evidences gathered so far cannot exclude the possibility of other processes, which do not require oxidation of Br^- to Br^+, to participate. For instance, a concerted transmetallation involving the R-$B(OH)_2$ and the Cu-X system, implicating a 5-membered transition state to deliver the product, cannot be

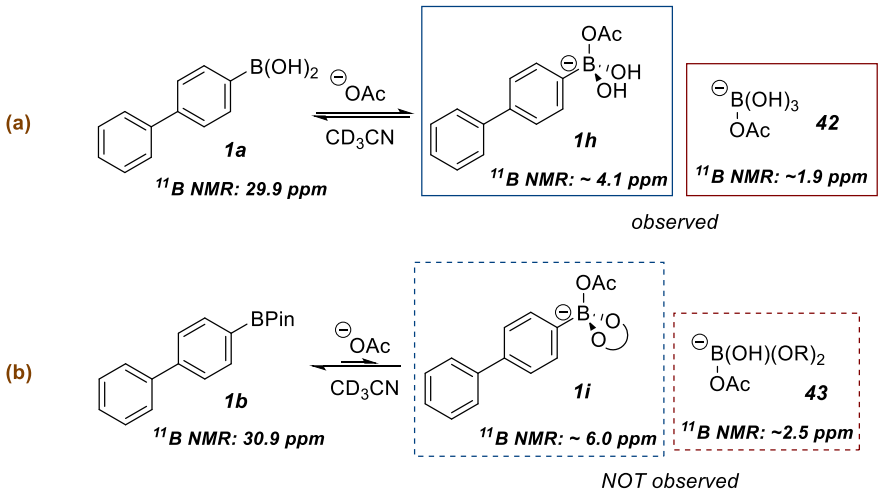
discarded (Scheme 60). Moreover, the above proposal is also consistent with the observation of the $Cu(OAc)_n$ failing to afford the acetylated product, as it would require a less-favoured 7-membered TS.



Scheme 60 - 5-membered TS for CuX and unfavoured 7-membered TS when employing CuOAc

Although insightful, the collected observations did not help clarifying the original question: if it is not entirely necessary, how does the catalyst assist this process and enhance chemoselectivity?

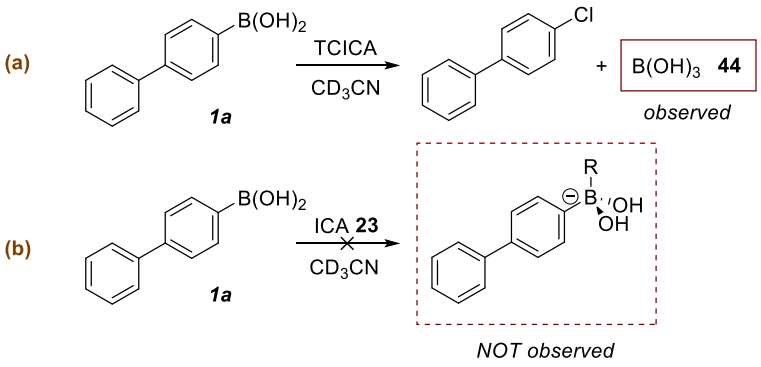
Based on what was observed previously, the best catalysts for this methodology were CuOAc and $Cu(OAc)_2$. In order to identify potential interactions between the boron species and the copper catalyst, ^{11}B NMR studies were conducted. The studies were performed using both boronic acid and corresponding pinacol ester separately, to avoid overlapping of peaks and therefore misinterpretation of spectrum. When 4-biphenyl boronic acid **1a** was stirred with CuOAc, two additional peaks appeared at the 4.1 and 1.9 ppm region in the spectrum shown in Scheme 61, which corresponded to a boronate species and the borate by-product, respectively, according to similar examples previously reported in the literature.[100,150]



Scheme 61 - Boronate formation investigated by 11B NMR for (a) boronic acid and (b) boronic acid pinacol ester

For the study conducted using [1,1'-biphenyl]-4-ylboronic acid pinacol ester, the boronate adduct was not observed in either of the cases. Based on those observations it was hypothesized, that the copper catalyst would most likely behave as a source of anion for the boronate formation, the latter being a significantly more reactive species hence chemoselectivity could be obtained in the process.

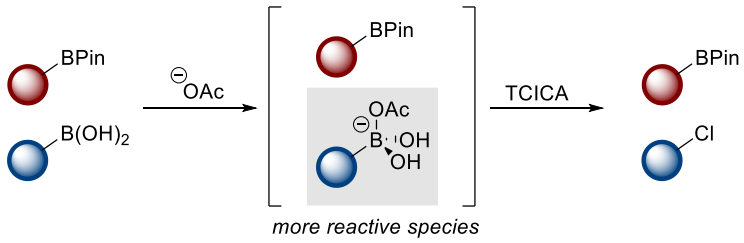
In order to probe other potential interactions that could also enhance selectivity in this process, the same ^{11}B NMR experiment was conducted in the presence only of TCICA and ICA **23**, separately (Scheme 62).



Scheme 62 - Potential interactions examined by 11B NMR using (a) TCICA and (b) ICA

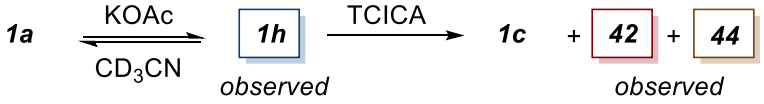
The chlorinating agent, as well as its by-product, are *N*-containing molecules, which can donate electron density to the boron empty *p*-orbital, forming a boronate and thus catalysing the reaction. In both cases, no interactions were observed that could

lead to the formation of a boronate species, which proves that the chemoselectivity is accessed through the copper species, more specifically *via* its acetate counter ion. So if the hypothesis postulated in Scheme 63 is correct, then any source of acetate or other additive able to enhance the proposed boronate formation, could satisfactorily catalyse the chlorination with comparable selectivity.



Scheme 63 - Hypothesis of chemoselectivity origin

As a proof of concept, the reaction conditions were submitted to the previously described NMR study procedure, only using KOAc as the activator in this occasion (Scheme 64). The same behaviour previously observed for CuOAc was also noticed in this case by ^{11}B NMR, demonstrating the formation of boronate intermediate **1h** and its by-products $B(OH)_3$ **44** and $[(OR)B(OH)_3]^-$ **42**. Experiments to screen acetate salts and bases were designed under the previously optimal conditions developed to investigate if it supports the hypothesis proposed.



Scheme 64 - The observations from ^{11}B NMR of reaction mixture using KOAc

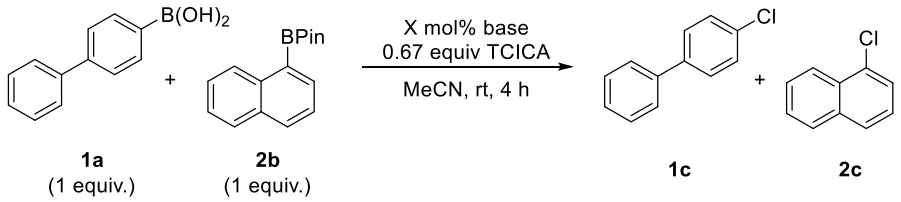
3.3 Di-nucleophile SMCC *via* base-promoted chemoselective chlorination

3.3.1 Base-promoted chemoselective chlorination

Based on the evidences gathered base-catalysed chemoselective chlorination in the NMR study, we postulated the chemoselective halogenation could be base-promoted since the same behaviour was observed when compared both CuOAc and $Cu(OAc)_2$ spectra against the KOAc spectrum. To validate the hypothesis, our

developed system was subjected to the optimal conditions, substituting the copper catalysts for acetate salts available in lab (Table 16).

Table 16 - Base screen



Entry	Base	X	Conversion to 1c (%)[a]	Selectivity 1c:2c[a]
1	NaOAc	10	90	10:1
2	KOAc	10	94	14:1
3	CsOAc	10	92	11:1
4	KOAc	20	96	15:1
5	KOAc	50	95	14:1
6	KOAc	100	96	10:1

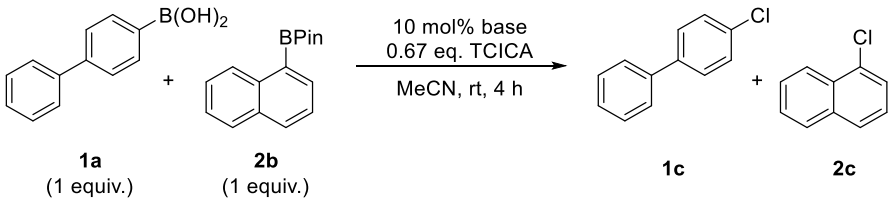
[a] Determined by HPLC analysis.

Encouragingly, the selected acetate salts exhibited comparable results to the copper-promoted optimal conditions, demonstrating excellent conversion and selectivity. Interestingly, KOAc had the best performance. It could be noticed no improvement in neither conversion nor selectivity with the addition of more than 20 mol% of KOAc. To prevent potential future issues with speciation and protodeboronation side-products, the loading was kept to its minimum of 10 mol%.

Relying on the boronate formation hypothesis, not only acetate salts would be suitable to catalyse this process but any inorganic base able to generate hydroxide *in situ*. Other bases were examined, showing ideal performance when using Cs_2CO_3

(Table 17). The implement of Cs_2CO_3 has shortened the reaction time to 3 h, keeping excellent conversion and complete selectivity towards the 4-chlorobiphenyl product.

Table 17 - Final optimization



Entry	Base	Time (h)	Conversion to 1c (%)[a]	Selectivity 1c:2c[a]
1	KOAc	4	94	13:1
2	Cs_2CO_3	4	96	>99:1
3	K_2CO_3	4	75	12:1
4	K_3PO_4	4	83	4:1
5	Cs_2CO_3	2	90	>99:1
6	Cs_2CO_3	3	97	>99:1

[a] Determined by HPLC analysis.

With a new set of conditions elected, the substrate scope was investigated firstly by evaluating the performance of 4-biphenylboronic acid **1a** against a range of differente BPins (Figure 25).

The conditions developed demonstrated excellent conversion and selectivity against a range of arylBPins. As noticed previously, 4-biphenylboronic acid **1a** performs slightly better against BPins bearing EW groups (**4b**, **6b**, **7b**, **9b** and **11b**) than BPins with ED and EN groups (**3b**, **5b** and **10b**). The scope demonstrated good selectivity

across different substituents present in the arylboronic ester, regardless the position of the ring.

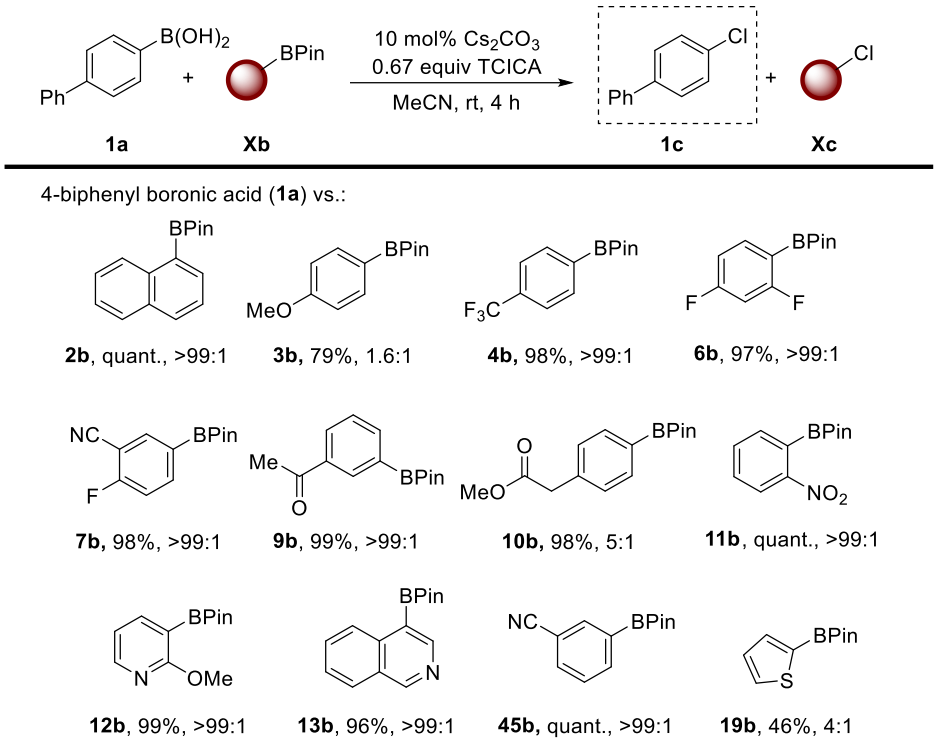


Figure 25 - Substrate scope varying boronic acid pinacol ester content

The process was found to tolerate *N*-containing heteroarylBpins (**12b** and **13b**), affording exclusively 4-chlorobiphenyl **1c**, and almost quantitatively. The reaction also performed effectively when using the 3-cyanophenylboronic acid pinacol ester **45b**. Unfortunately, thiophen-2-ylboronic acid pinacol ester **19b** displayed the same issues previously encountered, which suggests an incompatibility of TCICA, rather than the copper species, with *S*-containing heteroarylBpins.

When the conditions were used against different arylboronic acids, a similar trend could be observed. Electron-rich boronic acids (**3a**) performed better in terms of both conversion and selectivity than electron-defficient ones (**4a**). Both arylboronic acids bearing ENG like bromine at the *para*-position (**5a**) were converted to their corresponding chlorinated product with moderate selectivity and conversion. The arylboronic acid **7a** displayed moderate reactivity and selectivity. Notably, the new

set of conditions demonstrated to not tolerate substituents at the *para*-position such as a large nitro group (**11a**), bearly affording the **11c** product.

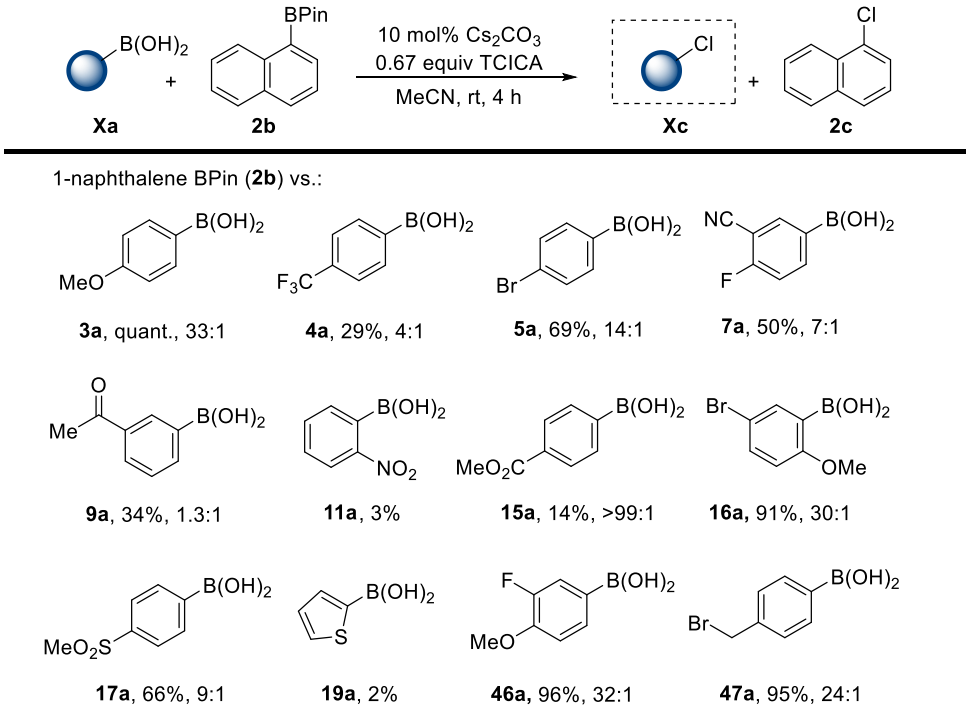


Figure 26 - Substrate scope varying boronic acid content

Esters (**15a**) and ketones (**9a**) displayed poor reactivity under the optimal conditions. Methylsulfonyl group in the boronic acid partner (**17a**) showed to be tolerated, delivering the correspondent chlorinated product in good conversion and selectivity. 4-Bromo-2-chloro-1-methoxybenzene **16c** was formed in good conversion and excellent selectivity against the benchmark arylBPin **2b**. The presence of a fluorine adjacent to the methoxy group the electron-defficient 3-fluoro-4-methoxyphenylboronic acid **46a** did not supress its reactivity, delivering its product **14c** in excellent conversion and selectivity. 4-Bromobenzylboronic acid **47a** also afforded the correspondent chlorinated product **47c** in high conversion and selectivity. Similar to what was previously noticed, thiophen-2-ylboronic acid **19a** performed poorly under the optimum conditions, corroborating with the hypothesis of an incompatibility with the chlorinating agent.

Envisioning the expansion of the scope, the possibility of using other boron partners for this methodology was investigated (Figure 27). Even though 4-chlorobiphenyl **1c**

was the major product obtained, with moderate conversion, against naphthalen-1-ylboronic acid MIDA ester **2d**, the selectivity has diminished to a ratio of 1.5:1. The unexpected result for **1a** *vs* **2d** could be imputed to the basic reaction conditions, which catalyse the hydrolysis of BMIDA species. An evidence to support the suggestion is the observation of the BMIDA hydrolysed product (**2a**). On the other hand, the potassium naphthalen-1-yltrifluoroborate **2e** was chlorinated quantitatively over the [1,1'-biphenyl]-4-ylboronic acid **1a**, with good selectivity. Notably, an incredible selectivity ratio **1c**:**2c** of 1:27 was observed for the pair 1-naphthylboronic acid **2a** and [1,1'-biphenyl]-4-ylboronic acid **1a**, being the ratio perceived three times more selective than the same entry using CuOAc.

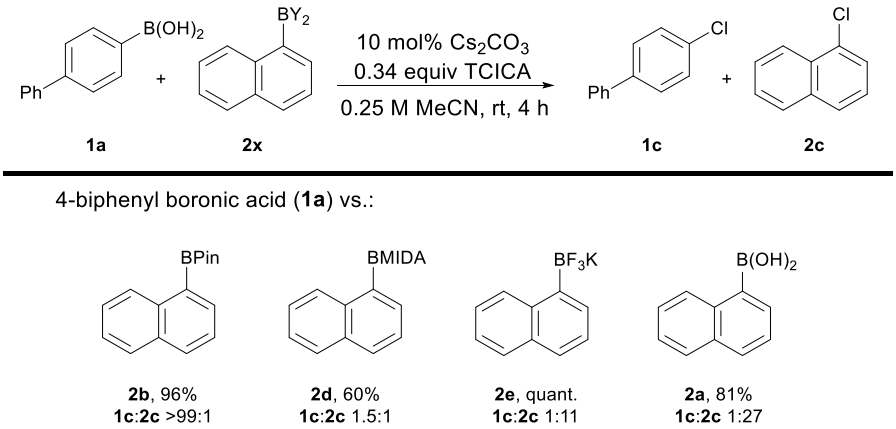


Figure 27 - Scope of 1a *vs* different boron partners

As done previously, the naphthalen-1-ylboronic acid **2a** was examined against different 4-biphenyl boron species (Figure 28). Corroborating with the results seen previously and supporting the tendency in performance observed in Section 3.1, 1-chloronaphthalene **2c** was the major product against both [1,1'-biphenyl]-4-ylboronic acid pinacol ester **1b** and [1,1'-biphenyl]-4-ylboronic acid MIDA ester **1d**, with good selectivity in both cases. Notably, the opposite behaviour was observed for the pair naphthalen-1-ylboronic acid **2a** and potassium [1,1'-biphenyl]-4-yltrifluoroborates **1e**, where 1-chloronaphthalene **2c** was found to be the major product.

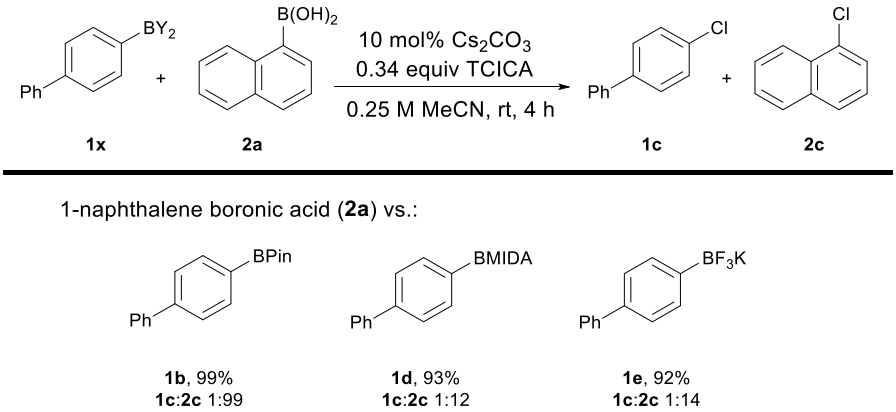
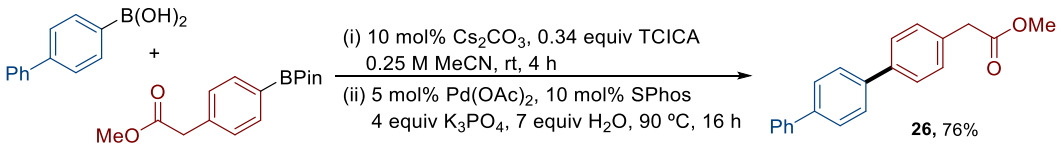


Figure 28 - Scope of 2a *vs* different boron partners

3.3.2 **One-pot base-promoted di-nucleophile SMCC**

As highlighted in Table 10 and Figure 16 of Section 3.1, the one-pot protocol endeavoured have potential by-products, such as boron speciation, oxidation and protodeboronation, and specific requirements regarding reaction set up, such as later addition of palladium catalyst and ligand due to catalyst poisoning by the chlorinating agent. These specific requirements have proven to make the process extremely challenging. The replacement of CuOAc for Cs_2CO_3 helped minimizing the oxidation side-reaction, however, the protodeboronation pathway can also by catalysed by basic conditions as described by Lloyd-Jones and coworkers.[39] The potential disadvantage of using a base to promote the first step is that the base present in reaction medium can initiate boron speciation and yield a complex mixture of starting materials, and therefore, products. So, to minimize side-product formation the loading of Cs_2CO_3 was kept to its necessary minimum.

The previously optimized conditions were employed using the benchmark pair 4-biphenylboronic acid **1a** and 4-(phenylacetate)boronic acid pinacol ester **10b** nonetheless the compound **26** was obtained in only 76% isolated yield, significantly lower when contrasted against to the antecedent protocol developed for the Cu-assisted chlorination (Scheme 65).



Scheme 65 - Benchmark pair 1a and 10b for the di-nucleophile SMCC

Changes in the set of conditions, such as type of base, equiv of water and equiv of base, to improve the overall yield did not succeed, however the substrate scope was attempted in order to investigate and compare the performance of the new optimum conditions (Figure 29).

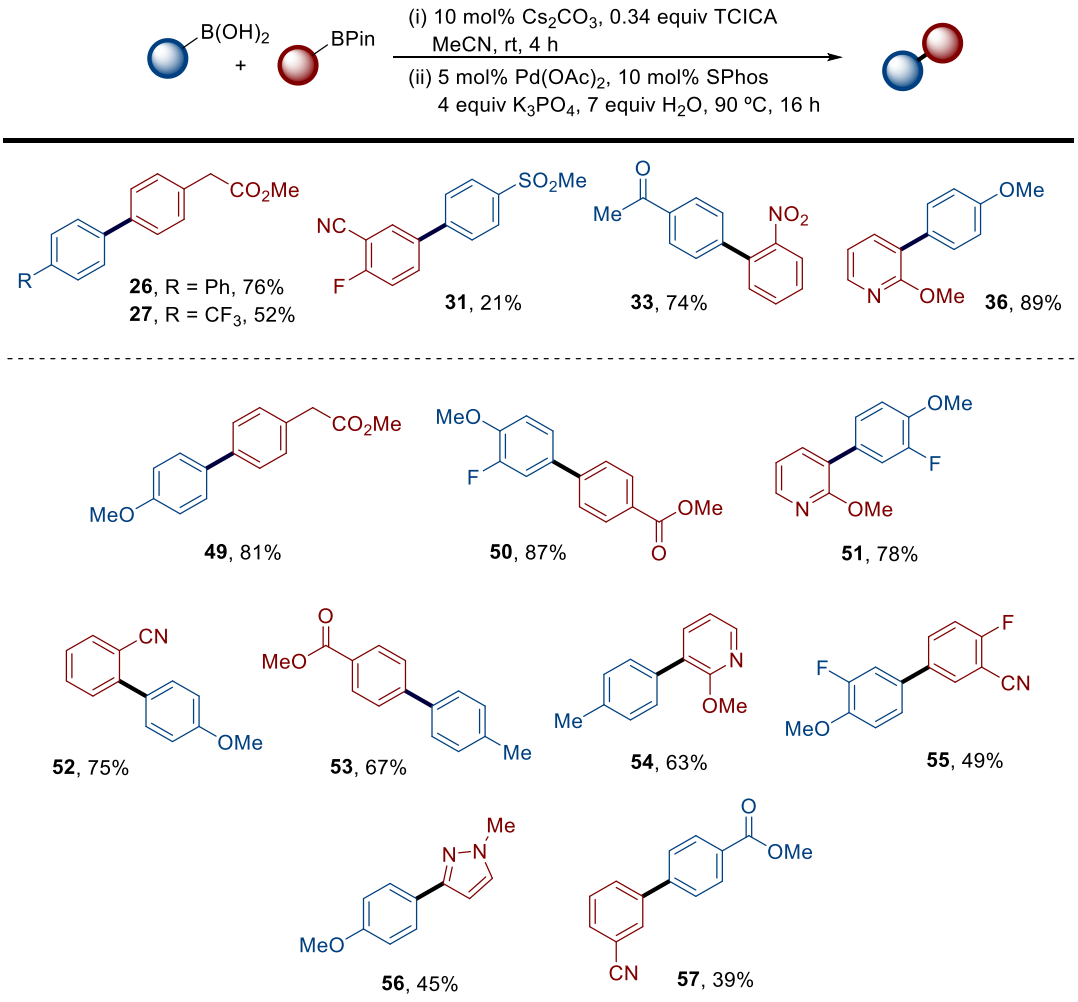


Figure 29 - Substrate scope for the base-catalysed di-nucleophile SMCC procedure

Firstly we used the 4-(phenylacetate)boronic acid pinacol ester **10b** and varied the substitution of the boronic acid content. When 4-methoxyphenylboronic acid **2a** was used, methyl 2-[(4'-(methoxy)-(1,1'-biphenyl)-4-yl]acetate **49** could be isolated

in good yields, performing slightly better than the benchmark pair used in the optimization which yielded compound **26**. A more EWG in the arylboronic acid partner such as in 4-trifluoromethylphenylboronic acid only delivered the desired product **27** in moderate yield. The presence of fluorine adjacent to the methoxy group did not significantly affect the overall selectivity, forming the coupled product methyl 3'-fluoro-4'-methoxy-[1,1'-biphenyl]-4-carboxylate **50** in excellent overall isolated yield. Substitution at the *ortho*-position of the arylBpin partner demonstrated to perform well under those conditions and afford the coupled product **52** in good yield. Notably, the reaction performs well using heteroaryl Pins such as (2-methoxypyridin-3-yl)boronic acid pinacol ester, delivering the coupled products **36**, **51** and **54** in 89%, 78% and 63% isolated yields, respectively. Distinctively from what was observed using the previous conditions, 4-tolylboronic acid endured under these developed copper-free conditions, yielding methyl 4'-methyl-[1,1'-biphenyl]-4-carboxylate **53**. The reaction also tolerated (1-methyl-1H-pyrazol-3-yl)boronic acid pinacol ester, affording product **56** in moderate yields.

Even though the reaction exhibits a slight decrease in performance when using electron-deficient arylboronic acids and esters, the products **55** and **57** could be isolated both in moderate yields. The methodology demonstrated low tolerance against methylsulphonyl substituents in the boronic acid component, isolating 4-fluoro-4'-(methylsulfonyl)-[1,1'-biphenyl]-3-carbonitrile **31** in poor yields compared to the copper-catalysed set of reaction conditions.

The utility of the protocol developed to provide access to valuable biaryl moieties was demonstrated in the synthesis of industrial relevant scaffolds and intermediates (Figure 30). One of the selected targets was 4’-methyl-2-biphenylcarbonitrile **58**, since it is a key intermediate in the preparation of sartans (angiotensin II receptor antagonists).[168]

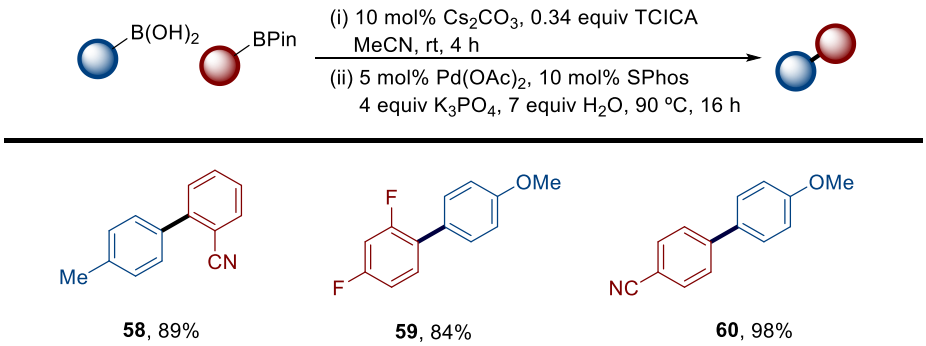


Figure 30 - Substrate scope of industrial relevant biaryls for the base-catalysed di-nucleophile SMCC procedure

Compound **58** was successfully isolated in excellent overall yield using the methodology developed. Another interesting scaffold prepared was 2,4-difluoro-4'-methoxy-1,1'-biphenyl **59**, an important intermediate in the route patented by Giordiano *et. al.* to synthesize Diflunisal®.[169] Diflunisal® is a salicylic acid derivative developed by Merck Sharp & Dohme in 1971, presenting both analgesic and anti-inflammatory activity. Intermediate 2,4-difluoro-4'-methoxy-1,1'-biphenyl **59** was prepared, using our developed methodology, in 84% overall isolated yield.[169,170] Additionally, 4-methoxy-4'-cyanobiphenyl **60**, a component encountered in liquid crystals blend,[171] was isolated in 98% isolated yield using our optimized one-pot set of conditions. The mentioned compound was key in a study conducted to understand structure and orientational distribution ordering in the nematic mesophase.[172]

3.4 Base-assisted iododeboronation for SPECT imaging

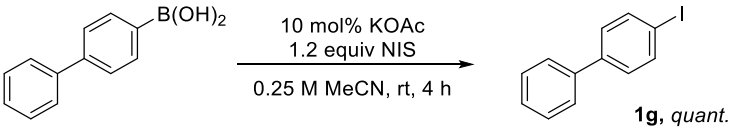
Single-photon emission computed tomography (SPECT) is a nuclear tomographic imaging scan technique that integrates two technologies to view the target in the body: computed tomography (CT) and a radioactive material (tracer). The tracer, or imaging agent, whose properties bind it to certain types of tissues, is what allows gamma cameras to collect information of a place of interest in the body. The technique requires delivery of a gamma-emitting radioisotope into the

patient, which can be either through injection into the bloodstream or, on occasions, using a simple soluble dissolved ion.

The radioisotopes typically used in SPECT to label tracers are iodine-123, technetium-99m, xenon-133, thallium-201, and fluorine-18. These radioactive forms of natural elements will pass safely through your body and be detected by the scanner. Various drugs and other chemicals can be labelled with these isotopes. Other radioactive isotopes of iodine commonly used in medicine as imaging agents are ^{124}I, ^{125}I and ^{131}I however, due to their half-lives (4 d, 59 d and 8 d respectively), the radioactive isotope ^{123}I (half-life of 13 h) is the most suitable for SPECT imaging as it neither accumulates in the body for long period of time nor cause tissue damage. Moreover, the energy of photon produced by the ^{123}I decay is ideal for detectors of gamma ray cameras used in the diagnostic study of thyroid diseases.

As mentioned previously in Section 1.2.5, the synthesis of radioactive aryl iodides currently relies on the use of metal catalysts hence the development of new radio-iodination methodologies of aryl-containing agents for SPECT imaging is highly desired.[154] Based on the evidences gathered in the conducted NMR studies to identify the boronate formation in the chemoselective chlorinating procedure, we postulated the boronate-mediated halogenation could also be a cheap viable metal-free alternative to enhance reactivity in the iododeboronation reaction. The relatively mild conditions can directly translate into functional group tolerance and suppression of by-products formation. This work was conducted in collaboration with the Sutherland group at the University of Glasgow.

The optimization of this process started using the benchmark 4-biphenyl boronic acid as the boron species and *N*-iodosuccinimide as the iodinating agent of choice. Auspiciously, the reaction went to completion according to HPLC analysis within 4 h, at room temperature (Scheme 66).

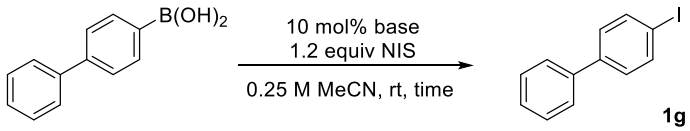


Scheme 66 - Initial trials for the base-catalysed iododeboronation

Even though the time frame in this case is appropriately applicable for radioactive labelling systems (considering ^{123}I half-life decay of 13 h), problems may arise if other substrates require longer reaction time. Another aspect amenable to improvement is the amounts of iodinating agent used. As ^{123}I is extremely harmful and expensive, the surfeit of the reactant should be avoided if possible. To overcome those potential issues, a fast and efficient set of conditions were sought during the aforementioned optimization.

Since preliminary trials were successful, initial investigations were conducted to identify when the reaction was complete, and if any other type of base would have a superior performance.

Table 18 - Optimization reactions on type of base



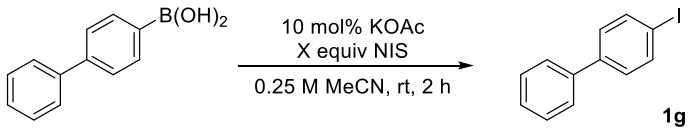
Entry	Base	Time (h)	Conversion (%)[a]
1	NaOAc	4	90
2	CsOAc	4	95
3	Cs_2CO_3	4	91
4	KOAc	4	99
5	KOAc	2	98
6	KOAc	1	94

[a] Determined by HPLC analysis.

As shown in Table 18, KOAc was the most suitable and efficient base to catalyse the reaction, completing the reaction faster than the other acetate salts NaOAc and CsOAc. Curiously it did also perform better than Cs_2CO_3, which is the base employed in the chemoselective chlorination optimized conditions. As it is known that neither acetates nor carbonates can readily form a boronate species from the starting material **1a**, the difference in reactivity in this case could perhaps be attributed to its basicity, which could trigger an accelerated decomposition of the iodinating agent.

Although considerably low, the next stage would be trying to reduce the equivalents of NIS used in the mixture. This is due to cost and safety issues when applying the methodology to the radioactive synthesis. As demonstrated in Table 20, the conversion to desired product was excellent until 1.05 equivalents of NIS, then dropping significantly with lower loadings of the reactant.

Table 19 - Optimization reactions equivalents of NIS



Entry	X equiv NIS	Conversion (%)[a]
1	1.2	98
2	1.1	89
3	1.05	90
4	1.02	79

[a] Determined by HPLC analysis.

In order to overcome the slight decrease in yield observed previously, the loading of KOAc for the reaction was investigated to verify if any improvement to its performance could be achieved. As the graphic in Figure 31 demonstrates, the

reaction seems to have a linear progression until it reaches a saturation point at approximately 10 mol%, showing no furtherance in conversion with higher loadings.

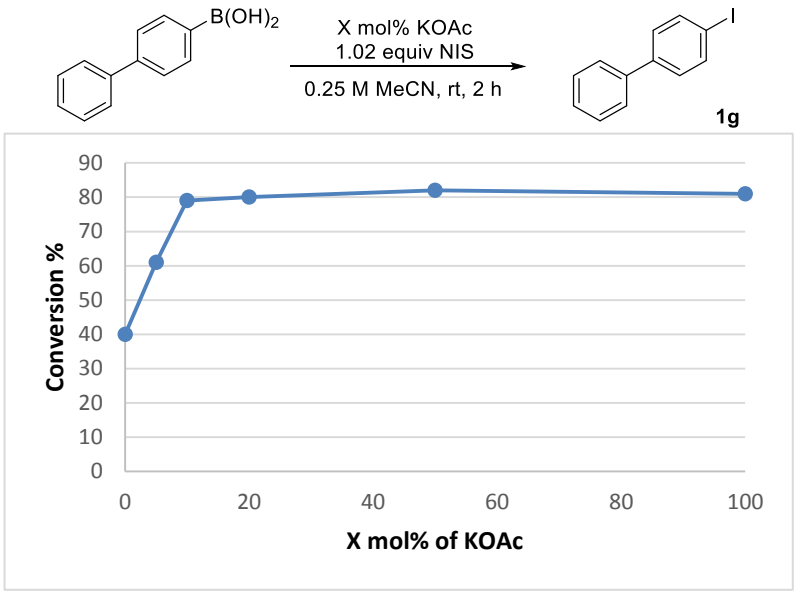
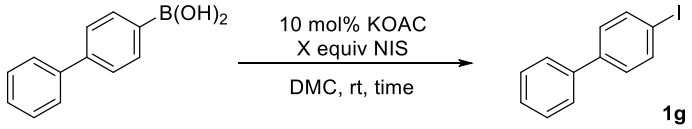


Figure 31 - Graphic of conversion *vs*. KOAc loading in MeCN

The change of solvent from MeCN to DMC, a more environmental friendly solvent used in recently published radioactive work from the Sutherland group,[173] showed a slight improvement in conversions to desired product. A re-evaluation screening in the conditions showed an optimum reaction time of 2 h, which helped increase the conversion to desired product, and no difference between when adding more than 1.05 equivalents of NIS in this case (Table 20).

Table 20 - Final optimization



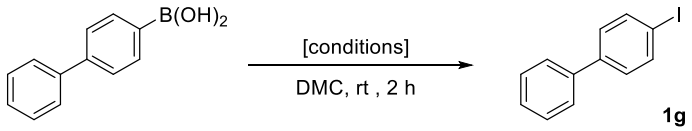
Entry	X equiv NIS	Time (h)	Conversion (%)[a]
1	1.05	0.5	73
2	1.05	1	83
3	1.05	1.5	85
4	1.05	2	93
5	1.1	0.5	80
6	1.1	1	83
7	1.1	1.5	84
8	1.1	2	90

[a] Determined by HPLC analysis.

Through control experiments, it could be seen that the presence of base in the reaction enhanced its performance (Table 21), more than doubling the yield of desired product. To synthesize radioactive iodoarenes, the usual methodologies are done by mixing NCS to a commercially available solution of NaI[123] prior to the addition of other reactants,[112,173] hence the optimal system was tested under that guidance.

The developed conditions behaved similarly when NIS was employed or the iodination agent was prepared *in situ*, affording the desired product quantitatively. Notably, the control experiments in the absence of base showed significantly increase in conversion under the *in situ* preparation conditions.

Table 21 - Control experiments using different preparation procedures



Base	Preparation of iodination agent	Conversion (%)[a]
10 mol% KOAc	NIS	93
10 mol% KOAc	*in situ* (NCS + NaI)	98
-	NIS	40
-	*in situ* (NCS + NaI)	67

[a] Determined by HPLC analysis.

This empirical observation demonstrate the formation of a more reactive species *in situ*, when mixing NaI and NCS, that cannot be formed as readily only by using NIS itself (Figure 32).[119,123]

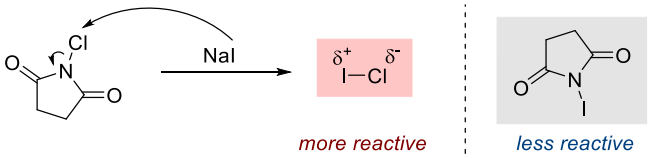


Figure 32 - Reactive iodinating species in the reaction mixture

The strong nucleophilicity of iodine is enough to attack the chlorine and generate ICl in the reaction mixture which is an active species towards electrophilic aromatic substitution.[165] Nevertheless, when only using NIS, the formation of a similar species, that in this case would be I_2, occurs considerably slower than the first case due to the absence of a strong nucleophile to displace the electrophilic halogen. This observation corroborates Molander's work[119] as well as the experiments previously described for the *in situ* generation of Cl_2 (see Section 3.2).

Raising the temperature of reaction to 50 °C allowed shortening the time to 1 h without compromising its efficiency and isolated yield. So with optimized conditions in hands, the substrate scope of the methodology developed was studied, employing a range of electronically and sterically distinct boronic acids in the process (Figure 33).

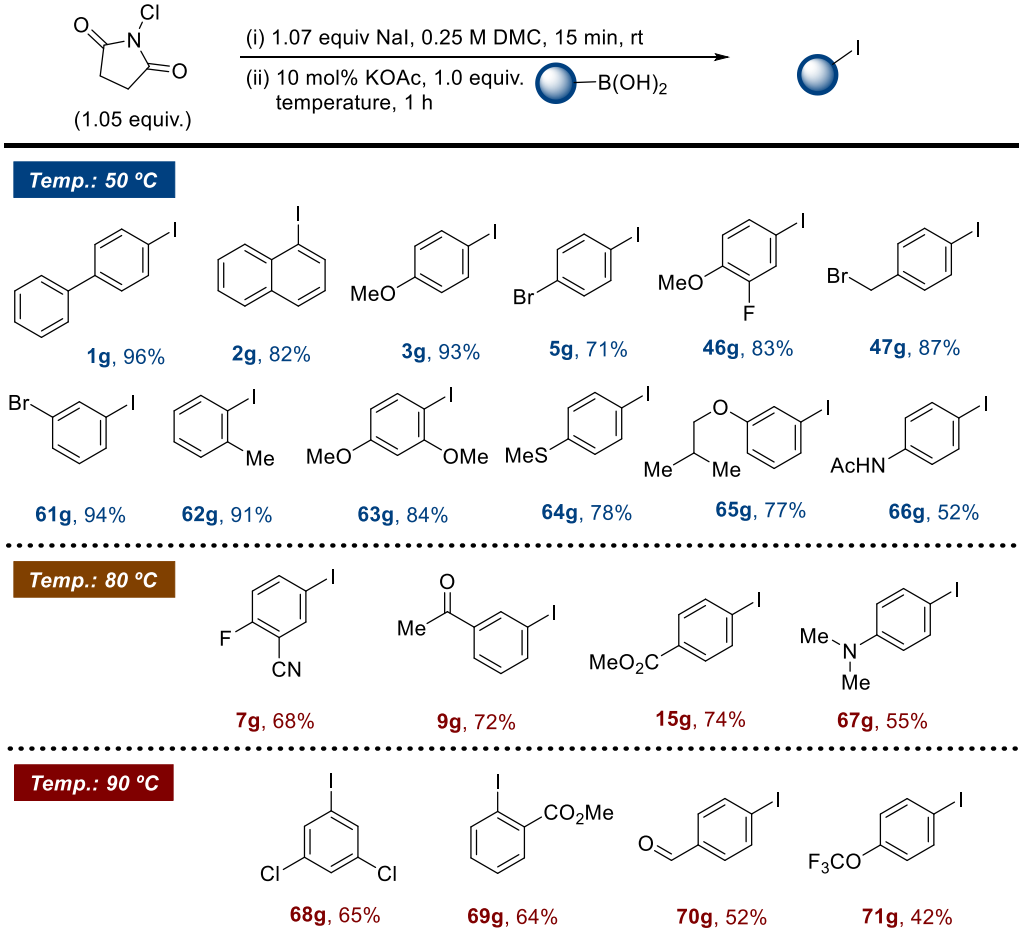


Figure 33 - Substrate scope non-radioactive iododeboronation

The process demonstrated the same behaviour as observed in the chemoselective chlorination. Under the optimized conditions were observed that aryl boronic acids bearing ED and EN groups (compounds **1g**, **2g**, **3g**, **5g**, **47g**, and **61g** to **65g**) were converted to its corresponding iodoarene product in good to excellent yields. One the other hand, more EW substituents (compounds **15g**, **68g** to **71g**) required a slight increase in temperature to afford the desired product in moderate to good yields. Regardless of the nature of the substituent, the conditions developed

tolerate functionalities in all *ortho*-, *meta*- and *para*-positions of the ring, not showing reduced reactivity due to steric hindrance of the substrates.

A few entries are interesting to highlight in this protocol. Isolated in excellent yield, 2-fluoro-4-iodo-1-methoxybenzene **46g** did not require increase either in temperature or reaction time, even if its starting material is a more electron deficient boronic acid when compared to non-fluorinated 4-methoxyphenylboronic acid **3a**. The reason to why, although having a methoxy group at the *para*-position, is due to the presence of a fluorine next to the –OMe substituent, which supresses the donating resonance contribution and evidences its withdrawing effect.

In the case of the *N*-containing substrates, the 4-iodo-*N*,*N*-dimethylaniline **67g** demanded more forcing conditions to be isolated in moderate yields. *N*-(4-iodophenyl)acetamide **66g** was also synthesized in moderate yield without needing to increase the reaction temperature. The methodology enabled the synthesis of compounds **66g** and **67g**, showing complementarity between functional groups since other methods available failed to synthesis those products.[173]

Even though (3-cyano-4-fluorophenyl)boronic acid is significantly acidic which thus is readily prone to protodeboronate,[39] the product 2-fluoro-5-iodobenzonitrile **7g** was afforded in moderate yields. Methyl 4-iodobenzoate **15g** performed significantly better when comparing to 4-iodobenzaldehyde **70g**, delivering the product in good and moderate yields, respectively. Perhaps another interesting entry to be considered is methyl 2-iodobenzoate **69g** could be isolated in moderate yields, whose its corresponding starting material is also prone to accelerate protodeboronation due to the proximity of the EW ester functionality.[151,174] Extending the reaction time in those cases did not improve the yield.

The methodology has a few drawbacks regarding functional group tolerance (Figure 34). The electron-withdrawing 3,5-di(trifluoromethyl)phenyl boronic acid **72a** and 4-(methylsulfonyl)phenylboronic acid **17a**, only afforded the desired product in poor yields. Similarly to what was reported in Section 3.1.2, these conditions were incompatible with *N*- and *S*-containing heteroarenes (2-thiophene boronic acid **19a**

and 3-pyridyl boronic acid **20a**) as well as aryl boronic acids bearing alkenes (4-vinylphenylboronic acid). Fluorinated compounds such as 2,4-difluorophenylboronic acid **6a**, which are readily prone to protodeboronation as shown by Lloyd-Jones and co-workers recently,[39] did not afford any iodinated product either.

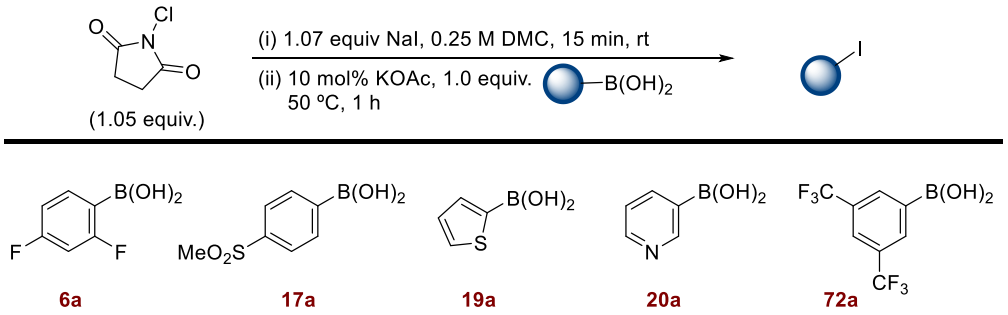


Figure 34 - Unsuitable substrates for the iodination of boronic acids

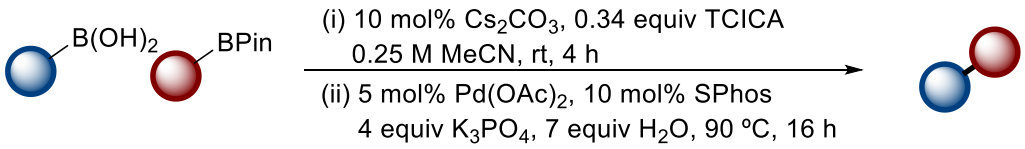
The reaction developed represents a clean method to access iodoarenes, yielding no iodinated by-products, which becomes particularly relevant when applying the methodology to SPECT imaging agent development. Since the radioactive agents are used straight away without flash chromatography purification, radioactive by-products can potentially be harmful to patients.[154,173]

After investigating the non-radioactive iodoarene scope, enough evidence was gathered to expect a similar performance for the radioactive part of this approach. Initial trials using the developed conditions showed comparable conversions to the desired radioactive products **1g**, **2g** and **3g**. Those results were considered promising and further work in ongoing at the University of Glasgow under the supervision of Dr. Andrew Sutherland.[175]

4 Conclusion

4.1 Di-nucleophile SMCC *via* chemoselective chlorination

This project aimed to develop a one-pot di-nucleophile coupling, with two boron species *via* chemoselective chlorination. Initial studies demonstrated that CuOAc and $Cu(OAc)_2$ were the most suitable catalysts for the reaction, however, after mechanistic studies, the reaction showed comparable results when copper was replaced by Cs_2CO_3. The use of catalytic amounts of Cs_2CO_3 helped promoting the chlorination of boronic acid over BPin, as well as enhancing selectivity. Chemoselectivity was crucial to the chlorination step, as it diminished the formation of by-products, which would later affect the one-pot process.

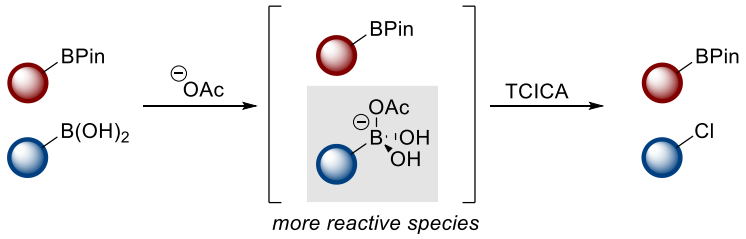


Scheme 67 - One-pot di-nucleophile SMCC conditions

Despite issues and limitations that arose from the procedure, such as a later addition of reactants and functional group tolerance, we successfully applied the technique to the synthesis of a vast range of interesting and industrial relevant biaryl moieties.

4.2 Mechanistic aspects

Motivated by the reactivity of the chlorination step, we designed a series of experiments to understand the formation of by-products and, perhaps, identify the origin of the chemoselectivity of the process. The use of analysis techniques allowed us to identify important key-intermediates in the reaction. The copper anion present in the mixture promotes the formation of a boronate intermediate from the boronic acid, which, since it is more reactive under the reaction conditions, undergoes chlorination faster than the BPin species (Scheme 68).

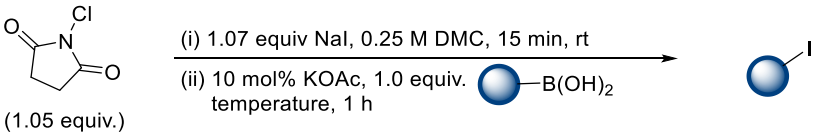


Scheme 68 - Proposed base-promoted boronate formation

Based on the observations resulting from the mechanistic experiments, the proposed boronate formation did not required copper and therefore could ultimately be accessed by a simple anion in the reaction mixture. The same intermediate was observed when the boron species were exposed to a series of different inorganic bases, such as KOAc, K_3PO_4 and Cs_2CO_3.

4.3 Iododeboronation protocol

Using the base-mediated halogenation methodology developed, an iododeboronation protocol for radioactive labelling in SPECT imaging has been successfully performed. Experiments conducted had proved that the boronate intermediate, firstly identified during mechanistic studies of the chemoselective chlorination, indeed enhances the reactivity of the species, facilitating the reaction to occur.



Scheme 69 - Base-promoted iodination of boronic acids for the synthesis SPECT imaging agents

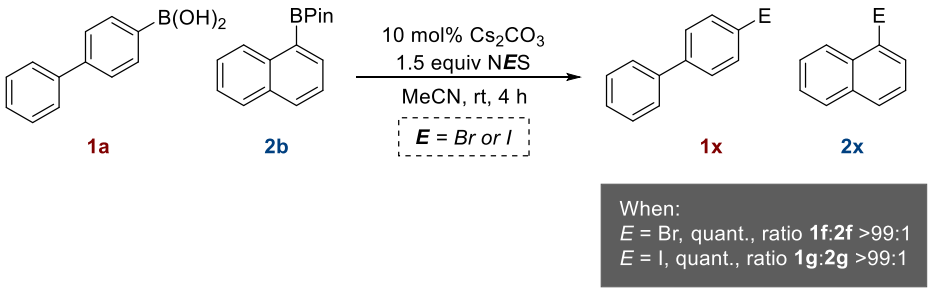
Under these conditions, the substrate scope demonstrated tolerance to an excellent variety of functional groups in different positions around the ring, delivering the desired iodinated product in good to excellent yield. Promising results were obtained in the first trials when a radioactive solution of $Na^{123}I$ was used in the procedure. Further work to investigate the performance and formation of

radioactive iodoarenes is currently ongoing in a collaborative project with the Sutherland group at the University of Glasgow.

5 Future work

In this work a chemoselective chlorination reaction was explored under the base-promoted boronate formation proposal – with indicatives that the methodology can also enhance, for instance, the iododeboronation reaction.

As a proof of concept, investigations towards the use of other halogen electrophiles to react the formed boronate were conducted and demonstrated that the process is not limited to chlorinating agents as electrophiles. The base-promoted chemoselective functionalisation has proven to be a viable approach toward selective manipulate boronic acids under mild conditions with excellent conversion and selectivity (Scheme 70).



Scheme 70 - General scheme for chemoselective functionalisation of boron species

For future work, we aim to extend the methodology to a range of electrophiles, including disulfides and diselenides compounds, exploring their applicability in total synthesis and formation important intermediates in route of pharmaceutical scaffolds.[102,103] Furthermore, the methodology would benefit from an extensive and more in-depth study using different boron species, so the scope could be extended to species that are unstable in the form of boronic acids.

6 Experimental

6.1 General techniques

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.[176]

6.1.1 Purification of solvents

i) Solvents used for dry reactions (THF, PhMe, Et_2O, DCM) were obtained from a PureSolv SPS-400-5 solvent purification system. 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.

ii) Acetonitrile, which could not be obtained from a PureSolv SPS-400-5 solvent purification system, was distilled under CaH_2, stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves and purged with and stored under nitrogen.

iii) Dichloromethane, diethyl ether, ethyl acetate, methanol, and petroleum ether (40-60° boiling point) for purification purposes were used as obtained from suppliers without further purification.

6.1.2 Experimental details

i) Reactions were carried out using conventional glassware or in capped 5 mL microwave vials. Glassware was oven-dried (150 °C), cooled to room temperature under vaccum and purged before use. Air-sensitive reactions were carried out using conventional glassware.

ii) Purging refers to a vacuum/nitrogen-refilling procedure.

iii) Reactions were carried out at 0 °C using ice/water baths.

iv) Room temperature average was 18 °C.

v) Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

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

6.1.3 **Purification of products**

i) Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analysed under 254 nm UV light or developed using potassium permanganate solution.

ii) Flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel or IST Isolute Flash silica cartridges.

6.1.4 **Analysis of products**

i) Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine.

ii) ^{19}F NMR spectra were obtained on a Bruker AV 400 spectrometer (Oxford magnet) at 376 MHz. ^{11}B NMR spectra were obtained on a Bruker AV 400 spectrometer (Oxford magnet) at 128 MHz. ^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AV 400 (Oxford magnet) at 400 MHz and 125 MHz, respectively, or a Bruker Ascend AV(III) HD 500 at 500 MHz and 126 MHz, respectively. ^{11}B NMR spectra for the NMR studies were obtained in Norell® natural quartz 5 mm NMR tube (500 MHz limit). Chemical shifts are reported in ppm and coupling constants are reported in Hz with $CDCl_3$ referenced at 7.26 ppm (^{1}H) and 77.4 ppm (^{13}C), DMSO-d_6 referenced at 2.54 ppm (^{1}H) and 40.5 ppm (^{13}C).[177]

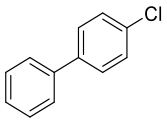
iii) High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

iv) 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. Conversion factors were established as a 1:1 ratio caffeine/analyte. Reaction HPLC samples were run with a 1:4 ratio caffeine/analyte unless stated otherwise.

6.2 General experimental procedures

General Procedure A – Independent chlorination of boronic acid and boronic acid pinacol ester

For example, results for Figures 10 and 11

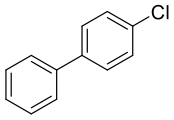


To an oven-dried 5 mL microwave vial was added either [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg) **1a** or [1,1'-biphenyl]-4-ylboronic acid pinacol ester **1b** (1 equiv, 0.25 mmol, 70 mg), trichloroisocyanuric acid (1 equiv, 0.25 mmol, 56 mg), $Cu(OTf)_2$ (10 mol%, 0.025 mmol, 9 mg) and MeCN (0.25 M, 1 mL). The reaction mixture was then allowed to react for 16 h at room temperature. The resulting mixture was then cooled to 0 ˚C and quenched with sodium metabisulphite (190 mg, 1 mmol, 4 equiv) before being extracted in EtOAc (20 mL) and washed with saturated NH_4Cl solution (20 mL) and brine (20 mL). The organic layer was then

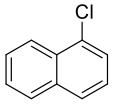
passed through a hydrophobic frit and concentrated under vacuum to afford the crude product, which was then purified by flash chromatography, with a gradient from 1% EtOAc in petroleum ether, to give the desired product 4-chlorobiphenyl **1c** as an amorphous white solid.

General Procedure B – Copper chemoselective chlorination of boron species

For example, [1,1'-biphenyl]-4-ylboronic acid **1a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



1c

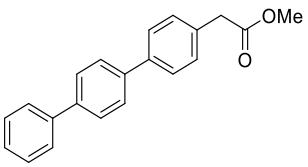


2c

An oven-dried vial fitted with a stirrer bar, was added copper(I) acetate (10 mol%, 0.025 mmol, 3 mg), [1,1'-biphenyl]-4-ylboronic acid **1a** (1 equiv, 0.25 mmol, 45 mg), naphthalen-1-ylboronic acid pinacol ester **2b** (1 equiv, 0.25 mmol, 64 mg), trichloroisocyanuric acid (0.67 equiv, 0.1675 mmol, 39 mg) and MeCN (0.25 M, 1 mL) were added and the reaction was allowed to proceed for 4 h at room temperature. After 4 h, an internal standard solution was added to reaction mixture, agitated for 10 min, the mixture was then aliquoted and analysed *via* HPLC method described above.

General Procedure C – General procedure for one-pot procedure for di-nucleophile Suzuki-Miyaura cross-coupling optimisation

For example, for the synthesis of methyl 2-([1,1':4',1''-terphenyl]-4-yl)acetate **26**[141]

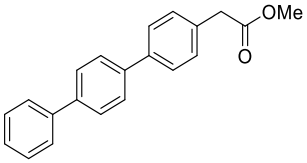


Experimental

An oven-dried microwave vial fitted with a stirrer bar, was added copper(I) acetate (5 mol%, 0.0125 mmol, 2 mg), [1,1'-biphenyl]-4-ylboronic acid **1a** (1.1 equiv, 0.275 mmol, 54 mg), methyl 4-(phenylacetate)boronic acid, pinacol ester **10b** (1 equiv, 0.25 mmol, 69 mg) and trichloroisocyanuric acid (0.34 equiv, 0.084 mmol, 20 mg). The vial was then caped and nitrogen was purged three times. After that, MeCN (0.25 M, 1 mL) was added and the reaction was allowed to proceed for 4 hours. In an oven-dried vial, palladium(II) acetate (5 mol%, 0.0125 mmol, 3 mg), SPhos (10 mol%, 0.025 mmol, 10 mg) and dry K_3PO_4 (4.0 equiv, 1.00 mmol, 213 mg) were pre-weighted before being added to the mixture. The vial was sealed and nitrogen was purged twice. To the reaction mixture the pre-weighted solids were rapidly added and the microwave vial was rapidly capped, purging nitrogen into the mixture five times. The resulting mixture was heated to 90 °C and left to react overnight. The reaction mixture was allowed to cool to room temperature before analysis *via* HPLC against a caffeine standard of known concentration.

General Procedure D – Optimised conditions for the one-pot procedure for di-nucleophile Suzuki-Miyaura cross coupling *via* copper-catalysed chemoselective chlorination

For example, for the synthesis of methyl 2-([1,1':4',1''-terphenyl]-4-yl)acetate **26**[141]



An oven-dried microwave vial fitted with a stirrer bar, was added copper(I) acetate (5 mol%, 0.0125 mmol, 2 mg), [1,1'-biphenyl]-4-ylboronic acid **1a** (1.1 equiv, 0.275 mmol, 54 mg), methyl 4-(phenylacetate)boronic acid, pinacol ester **10b** (1 equiv, 0.25 mmol, 69 mg) and trichloroisocyanuric acid (0.34 equiv, 0.084 mmol, 20 mg). The vial was then caped and nitrogen was purged three times. After that, MeCN (0.25 M, 1 mL) was added and the reaction was allowed to proceed for 4 hours. In

an oven-dried vial, palladium(II) acetate (5 mol%, 0.0125 mmol, 3 mg), SPhos (10 mol%, 0.025 mmol, 10 mg) and dry K_3PO_4 (4.0 equiv, 1.00 mmol, 213 mg) were pre-weighted before being added to the mixture. The vial was sealed and nitrogen was purged twice. To the reaction mixture the pre-weighted solids were rapidly added and the microwave vial was rapidly capped, purging nitrogen into the mixture five times. The resulting mixture was heated to 90 °C and left to react overnight. The reaction mixture was allowed to cool to room temperature, then decapped before being submitted to an oxidative workup in order to simplify purification. The reaction mixture was cooled to 0 °C, and 30% wt. aq. H_2O_2 (10 equiv, 2.5 mmol, 195 µL) was added dropwise. The reaction mixture was then stirred at room temperature for 1 h. The reaction mixture was then cooled to 0 ˚C and quenched with sodium metabisulphite (190 mg, 1 mmol, 4 equiv) before being extracted in EtOAc (20 mL) and washed with saturated NH_4Cl solution (20 mL) and brine (20 mL). The organic layer was then passed through a hydrophobic frit and concentrated under vacuum to afford the crude product, which was then purified by flash chromatography, with a gradient from 5 to 15% EtOAc in petroleum ether, to give the desired product as an amorphous white solid (69 mg, 91% yield).

ν_{max} (neat): 3030, 2953, 2845, 1734 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.59 (m, 8H), 7.49 – 7.43 (m, 2H), 7.40 – 7.34 (m, 3H), 3.73 (s, 3H), 3.69 (s, 2H).

^{13}C NMR (126 Hz, $CDCl_3$): δ 172.2, 140.8, 104.3, 139.8, 133.3, 129.9, 129.0, 127.7, 127.6, 127.5, 127.4, 127.2, 52.3, 41.0, 31.1.

HRMS ($C_{21}H_{18}O_2$): exact calculated mass for [$M+NH_4^+$] requires 320.1645 (100%), 321.1679 (10%); found [$M+NH_4^+$] 320.1646 (100%), 321.1676 (10%).

General Procedure E – Iodine experiment

For example, Cl_2 gas generation

A dry two-necked round bottom flask fitted with a stirrer bar, MeCN (0.25 M, 5 mL) was added and degassed prior to the addition of TCICA by purging N_2 through the solution for 5 min. In one of the necks, a tube was connected with the opening bubbling through a saturated solution of sodium iodide for further 5 min to rule out any potential false positive. Then, trichloroisocyanuric acid (1 equiv, 0.25 mmol, 39 mg) was added, the flask sealed and, with the solution under N_2, the solution was stirred for 10 min and the colour of the solution of NaI observed visually and confirmed using iodine paper indicator.

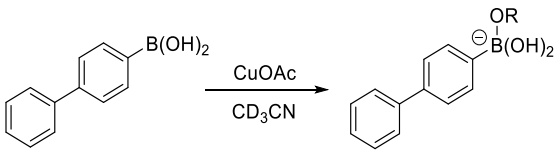
General Procedure F – IR studies

For example, catalyst-reactant interaction

In a dry round bottom flask fitted with a stirrer bar, copper(I) acetate (1 equiv, 0.25 mmol, 31 mg), trichloroisocyanuric acid (1 equiv, 0.25 mmol, 39 mg) and MeCN (0.25 M, 1 mL) were added. The mixture was stirred for 10 min, until homogeneous, then to be concentrated under vaccum. The resulting solid was analysed using a Shimadzu IRAffinity-1 machine.

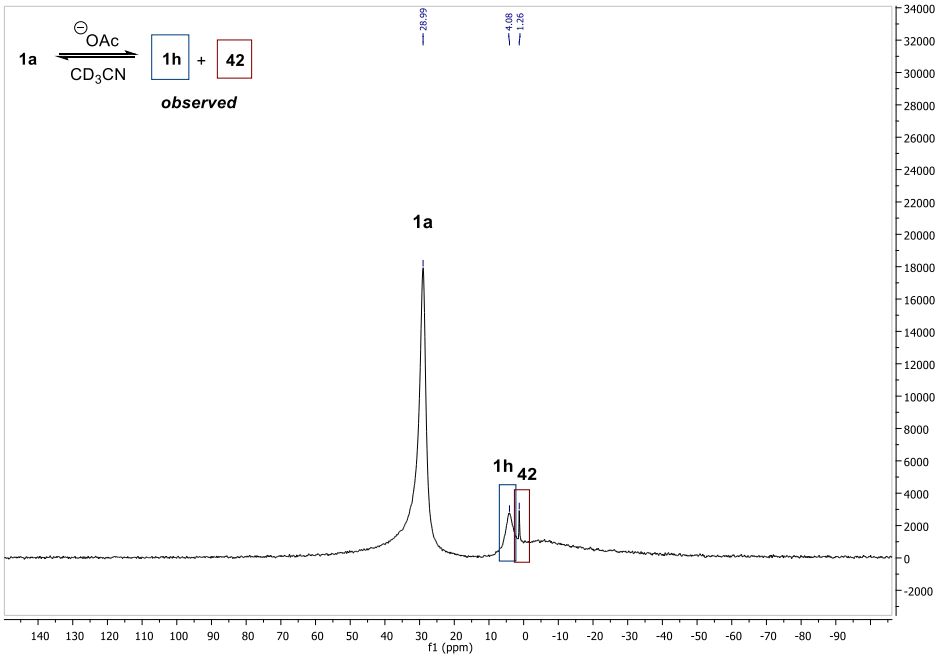
General Procedure G – ^{11}B NMR studies

For example, boronic acid boronate formation



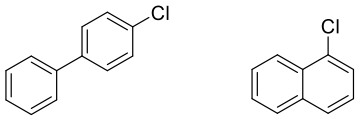
Experimental

In an oven-dried vial, [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.125 mmol, 25 mg) and CuOAc (20 mol%, 0.025 mmol, 3 mg) were dissolved in CD_3CN (0.25 M, 0.5 mL), stirred for 15 min and transferred to a quartz NMR tube and analysed *via* ^{11}B NMR. This reaction serves as a qualitative analysis of the boronate formation, since it was performed in the absence of an internal standard. Boronic acid boronate **1h** could be observed immediately, together with its by-product $[(RO)B(OH)_3]^-$ **42**.



General Procedure H – Base-catalysed chemoselective chlorination

For example, [1,1'-biphenyl]-4-ylboronic acid **1a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



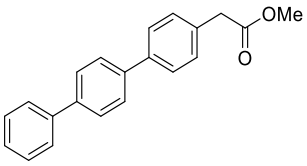
1c **2c**

An oven-dried vial fitted with a stirrer bar, was added caesium carbonate (10 mol%, 0.025 mmol, 8 mg), [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 45 mg), 2-naphthanyl boronic acid pinacol ester (1 equiv, 0.25 mmol, 6 mg),

trichloroisocyanuric acid (0.67 equiv, 0.17 mmol, 39 mg) and MeCN (0.25 M, 1 mL) were added and the reaction was allowed to proceed for 3 h at room temperature. An internal standard solution was added to reaction mixture after, agitated for 10 min, the mixture was then aliquoted and analysed *via* HPLC method described above.

General Procedure I – One-pot procedure for di-nucleophile Suzuki-Miyaura cross coupling *via* base-catalysed chemoselective chlorination

For example, for the synthesis of methyl 2-([1,1':4',1''-terphenyl]-4-yl)acetate **26**[141]



An oven-dried microwave vial fitted with a stirrer bar, was added caesium carbonate (10 mol%, 0.025 mmol, 8 mg), [1,1'-biphenyl]-4-ylboronic acid (1.1 equiv, 0.275 mmol, 54 mg), methyl 4-(phenylacetate)boronic acid, pinacol ester (1 equiv, 0.25 mmol, 69 mg) and trichloroisocyanuric acid (0.34 equiv, 0.084 mmol, 19 mg). The vial was then caped, purged nitrogen three times and MeCN (0.25 M, 1 mL) was added and the reaction was allowed to proceed for 4 hours at room temperature. In an oven-dried vial, palladium(II) acetate (5 mol%, 0.0125 mmol, 3 mg), SPhos (10 mol%, 0.025 mmol, 10 mg) and oven-dried K_3PO_4 (4.0 equiv, 1.00 mmol, 213 mg) were pre-weighted in a vial. The vial was sealed and nitrogen was purged three times. To the reaction mixture the pre-weighted solids were rapidly added and the microwave vial was rapidly capped, and nitrogen was purged into the mixture five times. The resulting mixture was heated to 90 °C and left to react overnight. The reaction mixture was cooled to 0 °C, and 30% wt. aq. H_2O_2 (10 equiv, 2.5 mmol, 195 µL) was added dropwise. The reaction mixture was then stirred at room temperature for 1 h. The reaction mixture was then cooled to 0 °C and quenched with sodium metabisulphite (4 equiv, 1 mmol, 190 mg) before being extracted in

EtOAc (10 mL) and washed with saturated NH_4Cl solution (10 mL) and brine (10 mL). The organic layer was then passed through a phase separator and concentrated under vacuum to afford the crude product, which was then purified by flash silica chromatography (5%-15% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (57 mg, 76% yield).

ν_{max} (neat): 3030, 2953, 2845, 1734 cm^{-1}.

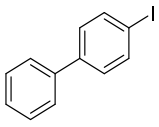
^1H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.59 (m, 8H), 7.49 – 7.43 (m, 2H), 7.40 – 7.34 (m, 3H), 3.73 (s, 3H), 3.69 (s, 2H).

^{13}C NMR (126 Hz, $CDCl_3$): δ 172.2, 140.8, 104.3, 139.8, 133.3, 129.9, 129.0, 127.7, 127.6, 127.5, 127.4, 127.2, 52.3, 41.0, 31.1.

HRMS ($C_{21}H_{18}O_2$): exact calculated mass for [$M+NH_4^+$] requires 320.1645 (100%), 321.1679 (10%); found [$M+NH_4^+$] 320.1646 (100%), 321.1676 (10%).

General Procedure J – General procedure for the base-assisted iododeboronation optimization

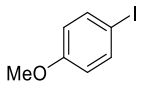
For example, for the synthesis of 4-iodobiphenyl **1g**[178]



An oven-dried microwave vial fitted with a stirrer bar, NCS (1.05 equiv, 0.2625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL) were added and allowed to stir for 15 min. Then, [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg) and potassium acetate (10 mol%, 0.025 mmol, 3 mg) were added, the mixture was heated to 50 °C for 1 h. The reaction mixture was allowed to cool to room temperature before analysis *via* HPLC method described previously against a caffeine standard of known concentration.

General Procedure K – Optimized conditions for the base-assisted iododeboronation

For example, for the synthesis of 4-iodoanisole **3g**



An oven-dried microwave vial fitted with a stirrer bar, NCS (1.05 equiv, 0.2625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL) were added and allowed to stir for 15 min. Then, 4-methoxyphenyl boronic acid (1.0 equiv, 0.25 mmol, 38 mg) and potassium acetate (10 mol%, 0.025 mmol, 3 mg) were added, the mixture was heated to 50 °C and allowed to proceed for 1 h. The reaction was quenched with a solution of sodium metabisulphite before being extracted in EtOAc (10 mL) and washed with saturated NH_4Cl solution (10 mL) and brine (10 mL). The organic layer was then passed through a phase separator and concentrated under vacuum to afford the crude product, which was then purified by flash silica chromatography (2% Et_2O in petroleum ether), to give the desired product as light yellow liquid (55 mg, 93% yield).

υ_{max} (film): 2837, 1865, 1485, 1240, 1028, 808 cm^{-1}.

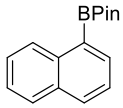
^1H NMR (500 MHz, $CDCl_3$): δ 7.58-7.54 (m, 2H), 6.70-6.66 (m, 2H), 3.78 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.6, 138.4, 116.5, 82.8, 55.5.

Spectroscopic data were in agreement with literature values.[179]

General Procedure L – Synthesis of boronic acid pinacol esters substrates

For example, for the synthesis of naphthalen-1-ylboronic acid, pinacol ester **2b**



In a dried vial fitted with a stirrer bar, naphthalen-1-ylboronic acid (1.0 equiv, 29.1 mmol, 5.0 g) and pinacol (1.5 equiv, 43.6 mmol, 5.15 g) and diethyl ether (0.1 M, 200 mL) were added. Once homogeneous, trifluoroacetic acid (10 mol%, 2.91 mol, 0.22 mL) was added to the mixture and it was allowed to proceed for 2h at room temperature. The reaction mixture was washed extensively with water to remove excess of pinacol. The organic layer was concentrated under vaccum to afford the desired product as a creamy solid, with no further purification being required (7.40 g, quant. yield).

υ_{max} (film): 2971, 1508, 1335, 1134, 782 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.77 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.09 (dd, *J* = 6.8, 1.4 Hz, 1H), 7.94 (dt, *J* = 8.2, 1.4 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.48 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 2H), 1.43 (s, 12H).

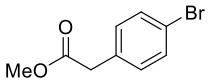
^{13}C NMR (101 MHz, $CDCl_3$): δ 137.1, 135.8, 133.4, 131.8, 128.6, 128.5, 126.5, 125.6, 125.1, 83.9, 25.1.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.6.

Spectroscopic data were in agreement with literature values.[180]

General Procedure M – Esterification procedure

For example, for the synthesis of 4-bromo phenylacetate **S1**



An oven-dried round-bottom flask, fitted with a stirrer bar, 4-bromo phenylacetic acid (1 equiv., 17.46 mmol, 4.0 g) and methanol (5 equiv, 87.31 mmol, 4 mL) were added. The mixture was put under a cold water bath and concentrated sulfuric acid (1 equiv, 17.46 mmol, 1.01 mL) was added dropwise while stirring. The reaction was then taken from the cold bath, heated to 80 °C and allowed to proceed for 4 h. The organic layer was extracted with EtOAc and washed twice with distilled water and twice with brine. The solvent was evaporated, with no further purification being required, to deliver the desired product as a light yellow oil (4.56 g, 96% yield).

υ_{max} (film): 2847, 1731, 1488, 1158, 803 cm^{-1}.

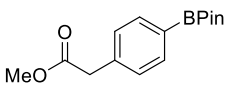
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 3.69 (s, 3H), 3.58 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.6, 133.0, 131.8, 131.2, 121.3, 52.3, 40.7.

Spectroscopic data were in agreement with literature values.[181]

General Procedure N – Miyaura-borylation procedure

For example, for the synthesis of methyl 4-(phenylacetate)boronic acid, pinacol ester **10b**[141]



An oven-dried round-bottom flask, fitted with a stirrer bar, 4-bromo phenylacetate (1 equiv., 17.5 mmol, 4.00 g), bispinacol diboron (1.01 equiv, 17.6 mmol, 2.08 g),

potassium acetate (3 equiv, 52.5 mmol, 5.16 g) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with DCM (3 mol%, 0.53 mmol, 429 mg) were added. The flask was then sealed with a septum and parafilm tape. After that, N_2 was purged three times and 1,4-dioxane (150 mL) was added. The reaction was allowed to proceed at 100 °C for 24 h and monitored by TLC. After completion of reaction, the reaction mixture was evaporated under vacuum and the crude was purified by flash column chromatography eluted with gradient of 5% to 20% EtOAc in petroleum ether, affording the desired product as an off-white solid (3.68 g, 76% yield).

υ_{max} (film): 2975, 1739, 1616, 1361, 1140, 859 cm^{-1}.

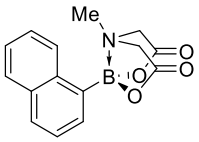
^1H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 3.68 (s, 3H), 3.64 (s, 2H), 1.34 (s, 12H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.9, 137.2, 135.2, 128.8, 83.9, 52.2, 41.6, 25.0.

^{11}B NMR (160 Hz, $CDCl_3$): δ 31.1.

General Procedure O – Boronic MIDA ester formation to access naphthalen-1-ylboronic MIDA ester

For example, for the synthesis of methyl 2-([1,1':4',1''-terphenyl]-4-yl)acetate **2d**[151]



In an oven-dried round-bottom flask, fitted with a stirrer bar, naphthalen-1-ylboronic acid (1.0 equiv, 11.63 mmol, 2.0 g), *N*-methyliminodiacetic acid (1.05 equiv, 12.21 mmol, 1.78 g) and DMF (110 mL, 0.1 M) were added. The reaction was heated to 90 °C and allowed to proceed for 18 h. The mixture was allowed to cool down, concentrated under vaccum and, to the resulting slurry, EtOAc was added

and the formed precipitate was collected by filtration. The precipitate was washed with H_2O and Et_2O, dried under vaccum to give the desired product as an amorphous off-white solid (2.37 g, 72% yield).

υ_{max} (film): 3004, 1738, 1309, 959, 779 cm^{-1}.

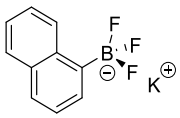
^1H NMR (400 MHz, DMSO-d_6): δ 8.22 – 8.15 (m, 1H), 7.98 – 7.89 (m, 2H), 7.59 (dd, *J* = 7.0, 1.4 Hz, 1H), 7.54 – 7.46 (m, 3H), 4.41 (d, *J* = 17.3 Hz, 2H), 4.21 (d, *J* = 17.3 Hz, 2H), 2.49 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 169.5, 133.4, 133.0, 130.0, 128.9, 127.2, 125.9, 125.2, 62.0, 47.2.

^{11}B NMR (128 MHz, DMSO-d_6): δ 12.3.

General Procedure P – Potassium trifluoroborate formation to access potassium naphthalen-1-yl-trifluoroborate

For example, for the synthesis of potassium naphthalen-1-yl-trifluoroborate **2e**[182]



An oven-dried round-bottom flask, fitted with a stirrer bar, naphthalen-1-ylboronic acid (1 equiv., 5.81 mmol, 1.0 g), KHF_2 (3 equiv., 17.44 mmol, 1.36 g) and MeOH (0.1 M, 60 mL) were added. The mixture was allowed to proceed at room temperature for 2h. The resulting reaction mixture was concentrated under vaccum, dissolved in acetone and left still for 5 min, to decant the remaining excess of KHF_2. The solution was filtered and concentrated under vaccum. The same process was repeated twice, to deliver the desired product as amorphous white solid (1.39 g, 98% yield).

υ_{max} (film): 3040, 1608, 1232, 1082, 931, 803 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.4 Hz, 1H), 7.56 (dd, *J* = 13.5, 7.4 Hz, 2H), 7.34 – 7.22 (m, 3H).

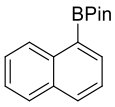
^{13}C NMR (101 MHz, DMSO-d_6): δ 136.6, 133.0, 130.3, 128.5, 127.4, 125.2, 124.9, 123.9, 123.4.

^{19}F NMR (376 MHz, DMSO-d_6): δ -135.2.

^{11}B NMR (128 MHz, DMSO-d_6): δ 3.2.

6.3 Synthesis of intermediates and starting materials

Naphthalen-1-ylboronic acid pinacol ester **2b**



The reaction was carried out according to General Procedure L described in the previous section, using naphthalen-1-ylboronic acid (1.0 equiv, 29.1 mmol, 5.0 g) and pinacol (1.5 equiv, 43.6 mmol, 5.15 g) and diethyl ether (200 mL, 0.1 M). The reaction mixture was subjected to the workup procedure outlined previously to give the desired product naphthalen-1-ylboronic acid pinacol ester as an amorphous off-white solid (7.40 g, quant. yield). No flash chromatography purification was conducted.

υ_{max} (film): 2971, 1508, 1335, 1134, 782 cm^{-1}.

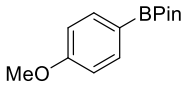
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.77 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.09 (dd, *J* = 6.8, 1.4 Hz, 1H), 7.94 (dt, *J* = 8.2, 1.4 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.48 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 2H), 1.43 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 137.1, 135.8, 133.4, 131.8, 128.6, 128.5, 126.5, 125.6, 125.1, 83.9, 25.1.

^{11}B NMR (128 MHz, $CDCl_3$): δ 31.6.

Spectroscopic data were in agreement with literature values.[180]

4-Methoxyphenylboronic acid, pinacol ester **3b**



The reaction was carried out according to General Procedure L described in the previous section, using (4-methoxy)phenylboronic acid (1.0 equiv, 1.0 mmol, 152 mg) and pinacol (1.5 equiv, 1.5 mmol, 177 mg) in Et_2O (200 mL, 0.1 M). The reaction mixture was subjected to the workup procedure outlined previously to give the desired product 3-cyano-4-iodobiphenyl as an amorphous yellow solid (210 mg, 91% yield). No flash chromatography purification was conducted.

υ_{max} (film): 2973, 1603, 1357, 1246, 1142, 831 cm^{-1}.

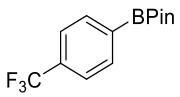
^1H NMR (400 MHz, $CDCl_3$): δ 7.79 – 7.71 (m, 2H), 6.92 – 6.87 (m, 2H), 3.83 (s, 3H), 1.33 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.3, 136.7, 113.5, 83.7, 55.2, 25.0.

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

Spectroscopic data were in agreement with literature values.[180]

4-Trifluoromethylphenylboronic acid, pinacol ester **4b**



The reaction was carried out according to General Procedure L described in the previous section, using (4-trifluoromethyl)phenylboronic acid (1.0 equiv, 2.5 mmol, 0.5 g) and pinacol (1.5 equiv, 3.75 mmol, 0.48 g) in Et_2O (25 mL, 0.1 M). The reaction mixture was subjected to the workup procedure outlined previously to give the

desired product (4-trifluoromethyl)phenylboronic acid pinacol ester **4b** as an amorphous yellow solid (730 mg, quant). No flash chromatography purification was conducted.

υ_{max} (film): 2978, 1403, 1322, 1098, 844 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.7 Hz, 2H), 7.61 (d, *J* = 7.7 Hz, 2H), 1.36 (s, 12H).

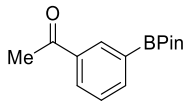
^{13}C NMR (101 MHz, $CDCl_3$): δ 135.8, 131.7, 128,5 (d, $^{3}J_{C\text{-}F}$ = 4.5 Hz), 127.5 (d, $^{1}J_{C\text{-}F}$ = 202.4 Hz), 125.4 (d, $^{2}J_{C\text{-}F}$ = 51.4 Hz), 83.9, 25.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.1.

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

Spectroscopic data were in agreement with literature values.[180]

3-Acetylphenylboronic acid, pinacol ester **9b**



The reaction was carried out according to General Procedure L described in the previous section, using (3-acetyl)phenylboronic acid (1.0 equiv, 1.24 mmol, 204 mg) and pinacol (1.5 equiv, 1.86 mmol, 220 mg) in Et_2O (15 mL, 0.1 M). The reaction mixture was subjected to the workup procedure outlined previously to give the desired product (3-acetyl)phenylboronic acid pinacol ester **9b** as an amorphous yellow solid (249 mg, 80% yield). No flash chromatography purification was conducted.

υ_{max} (film): 2975, 1681, 1329, 1248, 844 cm^{-1}.

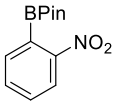
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.10 – 8.03 (m, 1H), 7.99 (d, *J* = 7.3 Hz, 1H), 7.50 – 7.44 (m, 1H), 2.64 (s, 3H), 1.36 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.6, 135.0, 130.9, 128.2, 84.3, 26.9, 25.0.

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

Spectroscopic data were in agreement with literature values.[183]

2-Nitrophenylboronic acid, pinacol ester **11b**



The reaction was carried out according to General Procedure L described in the previous section, using (2-nitro)phenylboronic acid (1.0 equiv, 1.1 mmol, 184 mg) and pinacol (1.5 equiv, 1.2 mmol, 142 mg) in Et_2O (4 mL, 0.1 M). The reaction mixture was subjected to the workup procedure outlined previously to give the desired product (2-nitro)phenylboronic acid pinacol ester **11b** as an amorphous yellow solid (274 mg, quant). No flash chromatography purification was conducted.

υ_{max} (film): 2975, 1519, 1339, 1143, 853 cm^{-1}.

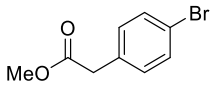
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.1 Hz, 1H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.58 – 7.50 (m, 2H), 1.43 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 133.9, 133.0, 130.2, 123.2, 84.8, 24.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ 30.8.

Spectroscopic data were in agreement with literature values.[184]

4-Bromo phenylacetate **S1**



Experimental

The reaction was carried out according to General Procedure M described in the previous section, using 4-bromo phenylacetic acid (1 equiv., 17.46 mmol, 4.0 g) and MeOH (10 equiv, 174.6 mmol, 7 mL). The reaction mixture was subjected to the workup procedure outlined previously to give the desired product 4-bromo phenylacetate as light yellow oil (4.56 g, 96% yield). No flash chromatography purification was conducted.

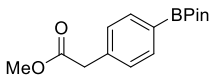
υ_{max} (film): 2847, 1731, 1488, 1158, 803 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 3.69 (s, 3H), 3.58 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.6, 133.0, 131.8, 131.2, 121.3, 52.3, 40.7.

Spectroscopic data were in agreement with literature values.[185]

Methyl 4-(phenylacetate)boronic acid, pinacol ester **10b**



The reaction was carried out according to General Procedure N described in the previous section, using 4-bromo phenylacetate (1 equiv., 17.5 mmol, 4.00 g), bispinacol diboron (1.01 equiv, 17.6 mmol, 2.08 g), potassium acetate (3 equiv, 52.5 mmol, 5.16 g) and 1,4-dioxane (0.2 M, 150 mL). The reaction mixture was subjected to the workup procedure outlined previously. The crude was purified by flash column chromatography eluted with gradient of 5% to 20% EtOAc in petroleum ether, affording the desired product as an amorphous off-white solid (3.68 g, 76% yield).

υ_{max} (film): 2975, 1739, 1616, 1361, 1140, 859 cm^{-1}.

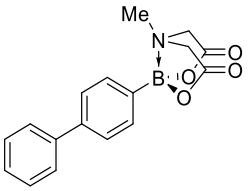
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 2H), 3.68 (s, 3H), 3.64 (s, 2H), 1.34 (s, 12H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 171.9, 137.2, 135.2, 128.8, 83.9, 52.2, 41.6, 25.0.

^{11}B NMR (160 Hz, $CDCl_3$): δ 31.1.

Spectroscopic data were in agreement with literature values.[181]

[1,1'-biphenyl]-4-ylboronic acid MIDA ester **1d**



The reaction was carried out according to General Procedure O described in the previous section, using 4-biphenyl boronic acid (1 equiv., 2.53 mmol, 0.5 g), N-methyliminodiacetic acid (1.05 equiv., 2.65 mmol, 0.39 g) and DMF (25 mL, 0.1 M). The reaction mixture was subjected to the workup procedure outlined previously to give the desired product 4-biphenyl boronic MIDA ester as an amorphous beige solid (660 mg, 85% yield). No flash chromatography purification was conducted.

υ_{max} (film): 3006, 1742, 1210, 985, 764 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.72 – 7.63 (m, 4H), 7.55 – 7.51 (m, 2H), 7.49 – 7.45 (m, 2H), 7.40 – 7.35 (m, 1H), 4.35 (d, *J* = 17.2 Hz, 2H), 4.14 (d, *J* = 17.2 Hz, 2H), 2.55 (s, 3H).

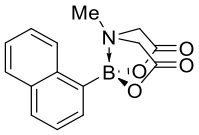
^{13}C NMR (126 MHz, DMSO-d_6): δ 169.4, 140.5, 140.1, 133.1, 128.9, 127.5, 126.6, 125.9, 61.8, 47.6.

^{11}B NMR (128 MHz, DMSO-d_6): δ 11.8.

Spectroscopic data were in agreement with literature values.[151]

Experimental

Naphthalen-1-yl boronic MIDA ester **2d**



The reaction was carried out according to General Procedure O described in the previous section, using naphthalen-1-ylboronic acid (1.0 equiv, 11.63 mmol, 2.0 g), N-methyliminodiacetic acid (1.05 equiv, 12.21 mmol, 1.78 g) and DMF (110 mL, 0.1 M). The reaction mixture was subjected to the workup procedure outlined previously to give the desired product 1-naphthalenyl boronic MIDA ester as an amorphous yellow solid (2.37 g, 72% yield). No flash chromatography purification was conducted.

υ_{max} (film): 3004, 1738, 1309, 959, 779 cm^{-1}.

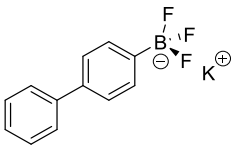
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 – 8.15 (m, 1H), 7.98 – 7.89 (m, 2H), 7.59 (dd, *J* = 7.0, 1.4 Hz, 1H), 7.54 – 7.46 (m, 3H), 4.41 (d, *J* = 17.3 Hz, 2H), 4.21 (d, *J* = 17.3 Hz, 2H), 2.49 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 169.5, 133.4, 133.0, 130.0, 128.9, 127.2, 125.9, 125.2, 62.0, 47.2.

^{11}B NMR (128 MHz, DMSO-d_6): δ 12.3.

Spectroscopic data were in agreement with literature values.[151]

Potassium biphen-4-yl-trifluoroborate **1e**



The reaction was carried out according to General Procedure P described in the previous section, using 4-biphenylboronic acid (1 equiv., 5.03 mmol, 1.0 g), KHF_2 (1

equiv., 15.08 mmol, 1.18 g) and MeOH (0.1 M, 50 mL). The reaction mixture was subjected to the workup procedure outlined previously to give the desired product potassium biphen-4-yl-trifluoroborate **1e** as an amorphous white solid (1.20 g, 92% yield). No flash chromatography purification was conducted.

υ_{max} (film): 3030, 1606, 1392, 1223, 918 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62 – 7.58 (m, 2H), 7.44 – 7.36 (m, 6H), 7.31 – 7.26 (m, 1H).

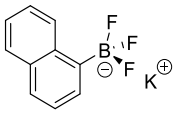
^{13}C NMR (101 MHz, DMSO-d_6): δ 141.5, 136.8, 132.0, 128.7, 126.5, 126.3, 124.7.

^{19}F NMR (376 MHz, DMSO-d_6): δ -139.1.

^{11}B NMR (128 MHz, DMSO-d_6): δ 3.0.

Spectroscopic data were in agreement with literature values.[186]

Potassium naphthalen-1-yl-trifluoroborate **2e**



The reaction was carried out according to General Procedure P described in the previous section, using naphthalen-1-ylboronic acid (1 equiv., 5.81 mmol, 1.0 g), KHF_2 (3 equiv., 17.44 mmol, 1.36 g) and MeOH (0.1 M, 60 mL). The reaction mixture was subjected to the workup procedure outlined previously to give the desired product potassium naphthalen-1-yl-trifluoroborate as an amorphous white solid (1.33 g, 98% yield). No flash chromatography purification was conducted.

υ_{max} (film): 3040, 1608, 1232, 1082, 931, 803 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.39 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.4 Hz, 1H), 7.56 (dd, *J* = 13.5, 7.4 Hz, 2H), 7.34 – 7.22 (m, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 136.6, 133.0, 130.3, 128.5, 127.4, 125.2, 124.9, 123.9, 123.4.

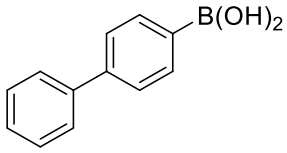
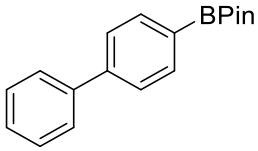
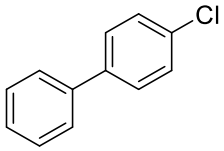
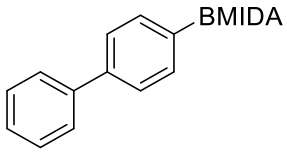
^{19}F NMR (376 MHz, DMSO-d_6): δ -135.2.

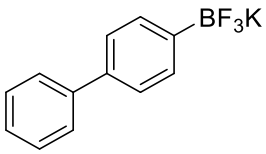
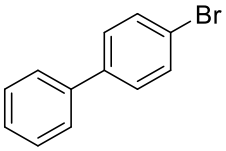
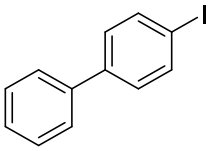
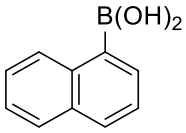
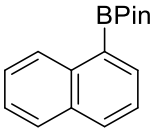
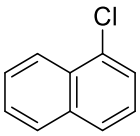
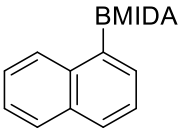
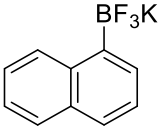
^{11}B NMR (128 MHz, DMSO-d_6): δ 3.2.

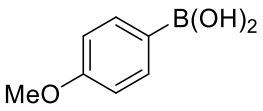
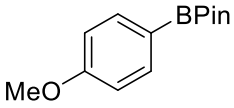
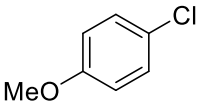
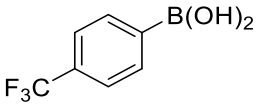
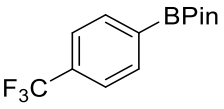
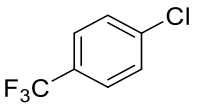
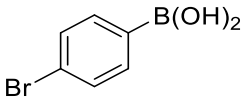
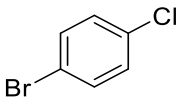
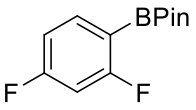
Spectroscopic data were in agreement with literature values.[182]

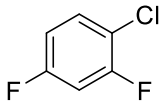
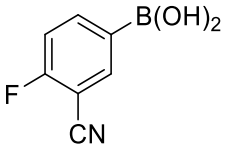
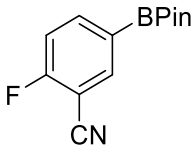
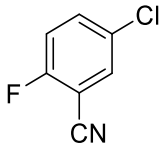
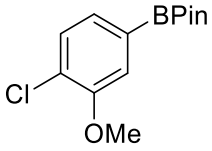
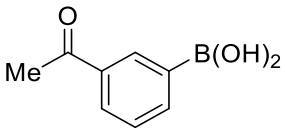
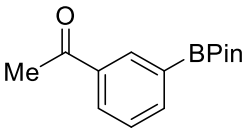
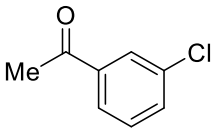
6.4 Retention time, response factor and characterisation of compounds for HPLC assay

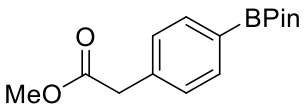
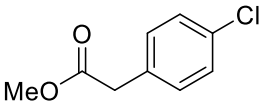
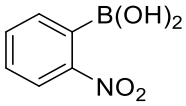
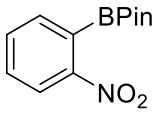
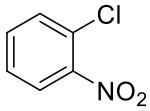
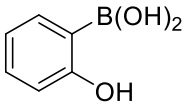
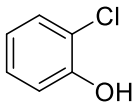
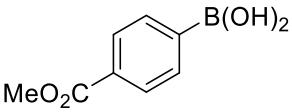
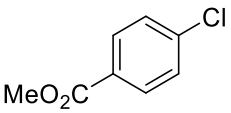
6.4.1 Table of HPLC Assay

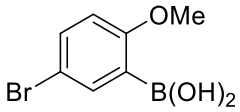
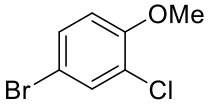
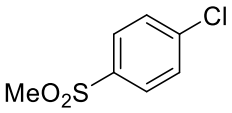
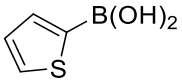
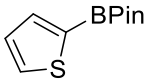
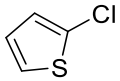
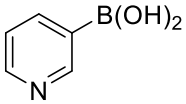
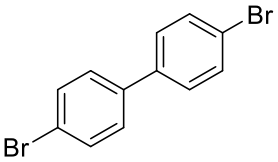
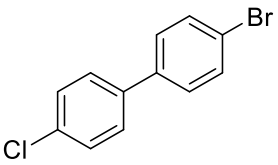
Compound	Structure	Retention Time (min)	Response Factor
1a		6.6	5.35
1b		10.9	5.68
1c		10.1	6.07
1d		7.1	5.66

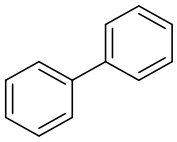
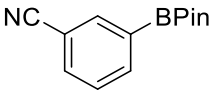
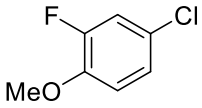
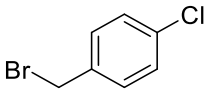
1e		6.7	5.52
1f		10.3	5.93
1g		10.4	6.21
2a		5.2	0.43
2b		10.6	0.35
2c		9.6	0.44
2d		6.0	0.43
2e		5.2	0.38

3a		3.3	1.08
3b		9.8	1.04
3c		7.9	0.07
4a		6.1	0.06
4b		10.5	0.04
4c		9.1	0.05
5a		5.4	0.1
5c		8.6	0.07
6b		3.8	0.06

6c		8.1	0.10
7a		4.3	0.04
7b		4.4	0.04
7c		7.0	0.05
8b		4.9	0.55
9a		3.2	3.14
9b		8.5	1.60
9c		6.7	3.10

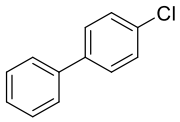
10b		8.7	0.07
10c		7.4	0.04
11a		1.8	1.15
11b		8.5	1.10
11c		7.0	1.06
14a		3.2	0.03
14c		5.2	0.10
15c		3.9	6.30
15c		7.7	2.78

16a		5.9	1.01
16c		9.0	0.86
17c		6.1	0.29
19a		2.5	1.99
19b		8.7	2.14
19c		7.5	1.22
20a		0.4	1.19
39		11.1	3.69
40		10.8	3.84

41		9.3	5.15
45b		7.5	0.09
46c		7.9	0.09
47c		8.8	0.95

6.4.2 **Characterisation data for assay compounds**

4-Chlorobiphenyl, **1c**



Appearance: white solid

υ_{max} (neat): 3062, 3032, 1593, 1476, 1097, 833 cm^{-1}.

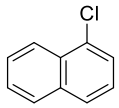
^{1}H NMR (500 MHz, DMSO-d_6): δ 7.39 (m, 1H), 7.48 (m, 4H), 7.68 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.1, 139.8, 133.5, 129.0, 128.5, 127.7, 127.1.

Spectroscopic data were in agreement with literature values.[119]

Experimental

1-Chloronaphthalene, **2c**



Appearance: slightly yellow liquid

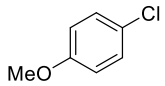
υ_{max} (neat): 3051, 1379, 1251, 968, 790 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (dd, *J* = 8.4, 0.7 Hz, 1H), 8.02 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.72 – 7.60 (m, 3H), 7.50 (dd, *J* = 8.1, 7.6 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 134.2, 130.5, 129.9, 128.5, 127.6, 127.6, 127.0, 126.4, 126.2, 123.5.

Spectroscopic data were in agreement with literature values.[119]

4-Methoxy-chlorobenzene, **3c**



Appearance: colourless liquid

υ_{max} (neat): 3004, 2939, 1582, 1491, 1169, 1033, 821 cm^{-1}.

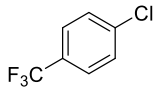
^{1}H NMR (500 MHz, DMSO-d_6): δ 7.35 – 7.29 (m, 2H), 6.98 – 6.92 (m, 2H), 3.75 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 158.1, 129.2, 124.2, 115.6, 55.4.

Spectroscopic data were in agreement with literature values.[119]

Experimental

4-Chlorobenzotrifluoride, **4c**



Appearance: colourless liquid

υ_{max} (neat): 3106, 1517, 1413, 1223, 1052, 844 cm^{-1}.

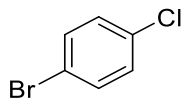
^{1}H NMR (500 MHz, DMSO-d_6): δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.6 Hz, 2H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 137.5, 129.5, 128.0 (q, $^{2}J_{C-F}$ = 31.4 Hz), 127.2 (q, $^{3}J_{C-F}$ = 7.3 Hz), 124.8 (d, $^{1}J_{C-F}$ = 272.0 Hz).

^{19}F NMR (376 MHz, DMSO-d_6): δ -61.2.

Spectroscopic data were in agreement with literature values.[117]

4-Bromochlorobenzene, **5c**



Appearance: white solid

υ_{max} (neat): 3082, 1472, 1390, 1085, 1007, 810 cm^{-1}.

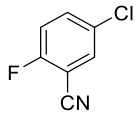
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.65 – 7.55 (m, 1H), 7.45 – 7.38 (m, 1H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 133.1, 132.4, 130.5, 120.0.

Spectroscopic data were in agreement with literature values.[119]

Experimental

4-Fluoro-3-cyano-chlorobenzene, **7c**



Appearance: white solid

υ_{max} (neat): 2974, 2234, 1489, 1314, 1145, 827 cm^{-1}.

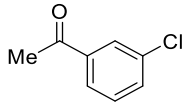
^{1}H NMR (500 MHz, DMSO-d_6): δ 7.59 (t, *J* = 9.0 Hz, 1H), 7.88 (ddd, *J* = 8.9, 4.7, 2.7 Hz, 1H), 7.52 (dd, *J* = 5.6, 2.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.9 (d, $^{1}J_{C\text{-}F}$ = 259.7 Hz), 135.3 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 133.0, 130.3 (d, $^{3}J_{C\text{-}F}$ = 3.5 Hz), 118.1 (d, $^{2}J_{C\text{-}F}$ = 21.0 Hz), 112.8, 103.2 (d, $^{2}J_{C\text{-}F}$ = 17.1 Hz).

^{19}F NMR (471 MHz, $CDCl_3$): δ -108.8.

Spectroscopic data were in agreement with literature values.[187]

3-Chloroacetophenone, **9c**



Appearance: colourless liquid

υ_{max} (neat): 3064, 1686, 1422, 1247, 1074, 786 cm^{-1}.

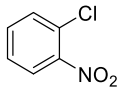
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (t, *J* = 1.7 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 2.59 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 196.8, 138.8, 135.1, 133.2, 130.1, 128.5, 126.5, 26.8.

Spectroscopic data were in agreement with literature values.[119]

Experimental

2-Nitrochlorobenzene, **11c**



Appearance: dark yellow solid

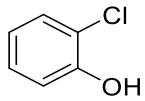
υ_{max} (neat): 3092, 1530, 1472, 1349, 1089, 855 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.54 (dtd, *J* = 9.5, 8.1, 1.4 Hz, 2H), 7.44 – 7.39 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 133.3, 132.1, 127.7, 127.3, 125.7.

Spectroscopic data were in agreement with literature values.[117]

2-Chlorophenol, **14c**



Appearance: light red liquid

υ_{max} (neat): 3508, 3073, 1584, 1290, 1028, 833, 745 cm^{-1}.

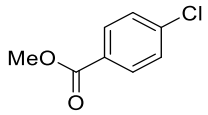
^{1}H NMR (500 MHz, DMSO-d_6): δ 6.78 (td, *J* = 7.9, 1.4 Hz, 1H), 6.96 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.13 (td, *J* = 8.1, 1.5 Hz, 1H), 7.30 (dd, *J* = 7.9, 1.5 Hz, 1H), 10.08 (s, 1H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 116.7, 119.6, 120.0, 128.0, 129.8, 153.1.

Spectroscopic data were in agreement with literature values.[188]

Experimental

Methyl-4-chlorobenzoate, **15c**



Appearance: white solid

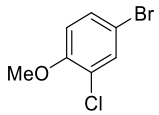
υ_{max} (neat): 3082, 2950, 1723, 1472, 1275, 1089, 814 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ 3.86 (s, 3H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.95 (d, *J* = 8.5 Hz, 2H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 52.3, 128.4, 128.9, 131.0, 138.2, 165.4.

Spectroscopic data were in agreement with literature values.[119]

5-Bromo-2-methoxy-chlorobenzene, **16c**



Appearance: white solid

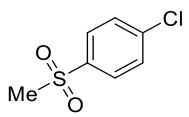
υ_{max} (neat): 3023, 2937, 1749, 1481, 1294, 1055, 877 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ 3.85 (s, 3H), 7.12 (d, *J* = 8.9 Hz, 1H), 7.50 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.66 (d, *J* = 2.4 Hz, 1H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 56.3, 111.6, 114.6, 122.3, 131.0, 131.8, 154.1.

Spectroscopic data were in agreement with literature values.[117]

4-Chlorophenyl methyl sulfone, **17c**



Experimental

Appearance: white solid

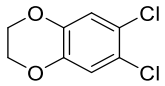
υ_{max} (neat): 3092, 3013, 1710, 1470, 1307, 1087, 966 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ 3.25 (s, 3H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.94 (d, *J* = 8.5 Hz, 2H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 43.4, 54.9, 129.0, 129.5, 138.6, 139.7, 149.9.

Spectroscopic data were in agreement with literature values.[189]

6,7-Dichlorobenzo-1,4-dioxane, **18c**



Appearance: white solid

υ_{max} (neat): 3041, 2943, 1578, 1454, 1121, 1054, 875 cm^{-1}.

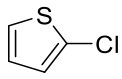
^{1}H NMR (500 MHz, DMSO-d_6): δ 7.17 (s, 2H), 4.27 (s, 4H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 143.2, 122.4, 118.3, 64.1.

HRMS: ($C_8H_6O_2Cl_2$) [M^+] requires 203.9739, found [M^+] 203.9743.

Spectroscopic data were in agreement with literature values.[190]

2-Chlorothiophene, **19c**



Appearance: light yellow liquid

υ_{max} (neat): 3106, 1517, 1413, 1223, 1052, 844 cm^{-1}.

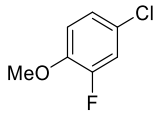
^{1}H NMR (400 MHz, DMSO-d_6): δ 6.99 (dd, *J* = 5.6, 3.7 Hz, 1H), 7.11 (dd, *J* = 3.7, 1.5 Hz, 1H), 7.45 (dd, *J* = 5.6, 1.5 Hz, 1H).

Experimental

^{13}C NMR (125 MHz, $CDCl_3$): δ 125.7, 126.8, 127.2, 128.1.

Spectroscopic data were in agreement with literature values.[191]

2-Fluoro-4-chloroanisole, **46c**



Appearance: light yellow liquid

υ_{max} (neat): 2941, 1589, 1498, 1265, 1128, 1024 cm^{-1}.

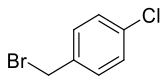
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (dd, *J* = 10.9, 2.5 Hz, 1H), 7.07 – 7.03 (m, 1H), 6.88 (t, *J* = 8.8 Hz, 1H), 3.87 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 152.4 (d, $^1J_{C\text{-}F}$ = 249.4 Hz), 146.8 (d, $^3J_{C\text{-}F}$ = 10.6 Hz), 125.4 (d, $^3J_{C\text{-}F}$ = 8.9 Hz), 124.4 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 117.0 (d, $^2J_{C\text{-}F}$ = 21.7 Hz), 114.3 (d, $^3J_{C\text{-}F}$ = 3.0 Hz), 56.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -132.2.

Spectroscopic data were in agreement with literature values.[192]

4-Chlorobenzylbromide, **47c**



Appearance: colourless solid

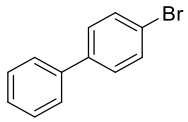
υ_{max} (neat): 1489, 1195, 1087, 833 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 4.45 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4, 134.5, 130.5, 129.1, 32.5.

Spectroscopic data were in agreement with literature values.[193]

4-Bromobiphenyl, **1f**



Appearance: pale yellow solid

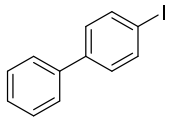
υ_{max} (neat): 3029, 1448, 1395, 1076, 829 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 4H), 7.48 – 7.41 (m, 4H), 7.36 (t, *J* = 7.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 140.3, 132.0, 129.1, 128.9, 127.8, 127.1, 121.7.

Spectroscopic data were in agreement with literature values.[107]

4-Iodobiphenyl, **1g**



Appearance: pale yellow solid

υ_{max} (neat): 3029, 1473, 1390, 998, 757 cm^{-1}.

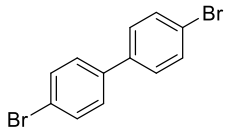
^{1}H NMR (500 Hz, $CDCl_3$): δ 7.78-7.74 (m, 1H), 7.56-7.54 (m, 1H), 7.45-7.42 (m, 1H), 7.38-7.35 (m, 1H), 7.34-7.31 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 140.9, 140.2, 138.0, 129.1, 127.9, 127.1, 93.2.

Spectroscopic data were in agreement with literature values.[178]

Experimental

4,4'-Dibromo-1,1'-biphenyl, **39**



Appearance: pale brown solid

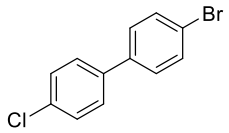
υ_{max} (neat): 2918, 1677, 1519, 1463, 1354 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 – 7.53 (m, 4H), 7.44 – 7.37 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 139.1, 132.2, 128.7, 122.1.

Spectroscopic data were in agreement with literature values.[194]

4-Bromo-4'-chloro-1,1'-biphenyl, **40**



Appearance: yellow solid

υ_{max} (neat): 2820, 1473, 1387, 1093, 811 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 – 7.54 (m, 1H), 7.50 – 7.46 (m, 1H), 7.41 (ddd, *J* = 8.6, 4.1, 2.2 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 139.1, 138.6, 134.0, 132.2, 129.2, 128.7, 128.3, 122.1.

Spectroscopic data were in agreement with literature values.[195]

6.5 Experimental procedures and characterisation for Section 3.1

Results from Figure 10

Reactions carried out according to General Procedure A using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), **$Cu(OTf)_2$ (X mol%)**, **TCICA (Y equiv)** and MeCN (0.25 M, 1 mL) at rt for 16 h.

Entry	X mol% $Cu(OTf)_2$ (mass)	Y equiv. of TCICA (mass)	Isolated yield %
1	5 (5 mg)	0.34 (20 mg)	77
2	5 (5 mg)	0.40 (23 mg)	83
3	5 (5 mg)	0.50 (29 mg)	88
4	5 (5 mg)	0.67 (39 mg)	95
5	10 (9 mg)	0.34 (20 mg)	77
6	10 (9 mg)	0.40 (23 mg)	83
7	10 (9 mg)	0.50 (29 mg)	88
8	10 (9 mg)	0.67 (39 mg)	95

Results from Figure 11

Reactions carried out according to General Procedure A using 4-biphenylboronic acid pinacol ester (1 equiv, 0.25 mmol, 70 mg), **$Cu(OTf)_2$ (X mol%)**, **TCICA (Y equiv)** and MeCN (0.25 M, 1 mL) at rt for 16 h.

Entry	X mol% $Cu(OTf)_2$ (mass)	Y equiv. of TCICA (mass)	Isolated yield %
1	5 (5 mg)	0.34 (20 mg)	4
2	5 (5 mg)	0.40 (23 mg)	4
3	5 (5 mg)	0.50 (29 mg)	4
4	5 (5 mg)	0.67 (39 mg)	6
5	10 (9 mg)	0.34 (20 mg)	5
6	10 (9 mg)	0.40 (23 mg)	8
7	10 (9 mg)	0.50 (29 mg)	4
8	10 (9 mg)	0.67 (39 mg)	7
9	5 (5 mg)	0.34 (20 mg)	21[a]

[a] Reaction at 40 °C.

Results from Table 2

Reactions carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), 1-naphthanylboronic acid pinacol ester (1 equiv, 0.25 mmol, 63 mg), **Chlorinating Agent**, **$Cu(OTf)_2$** and MeCN (0.25 M, 1 mL) at rt for 16 h.

Entry	Source of Chlorine	Copper Catalyst	Equiv (mass)	Conversion %	Selectivity 1c:2c
1	KCl	5 mol% $Cu(OTf)_2$ (5 mg)	1.5 (28 mg)	-	-

2	NaCl	5 mol% $Cu(OTf)_2$ (5 mg)	1.5 (22 mg)	-	-
3	LiCl	5 mol% $Cu(OTf)_2$ (5 mg)	1.5 (16 mg)	-	-
4	$CuCl_2$	-	1.5 (50 mg)	-	-
5	CuCl	-	1.5 (37 mg)	-	-
6	NCS	10 mol% $Cu(OTf)_2$ (9 mg)	2.0 (67 mg)	20	-
7	TCICA	-	0.4 (23 mg)	38	4:1

Results from Table 3

Reactions carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), 1-naphthanylboronic acid pinacol ester (1 equiv, 0.25 mmol, 63 mg), TCICA (0.4 equiv, 0.1 mmol, 23 mg), **$Cu(OTf)_2$** and **Solvent** (0.25 M, 1 mL) at **temperature** for 16 h.

Entry	Copper Catalyst	Temp. (°C)	Solvent	Conversion to 1c (%)	Selectivity 1c:2c
1	-	30	MeCN	42	4.7:1
2	-	50	EtOAc	27	3:1
3	-	50	THF	4	-
4	10 mol% $Cu(OTf)_2$ (9 mg)	50	THF	15	-
5	-	50	PhMe	<1	-
6	-	50	DCM	<1	-

Results from Table 4

Reactions carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), 1-naphthanylboronic acid pinacol ester (1 equiv, 0.25 mmol, 63 mg), TCICA (0.4 equiv, 0.1 mmol, 23 mg) and **MeCN** at 30 °C for 16 h.

Entry	Conc. (volume)	Conversion %	Selectivity 1c:2c
1	0.1 M (2.5 mL)	37	3:1
2	0.25 M (1 mL)	42	4.7:1
3	0.5 M (0.5 mL)	26	2:1
4	1 M (0.25 mL)	24	1.9:1

Results from Table 5

Reactions carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), 1-naphthanylboronic acid pinacol ester (1 equiv, 0.25 mmol, 63 mg), **TCICA**, **$Cu(OTf)_2$** and MeCN (0.25 M, 1 mL) at rt for 16 h.

Entry	$Cu(OTf)_2$ (mass)	Equiv of TCICA (mass)	Conversion %	Selectivity 1c:2c
1	10 mol% (9 mg)	0.34 (20 mg)	52	5.4:1
2	10 mol% (9 mg)	0.40 (23 mg)	31	7.8:1
3	10 mol% (9 mg)	0.50 (29 mg)	52	3:1

4	10 mol% (9 mg)	0.67 (39 mg)	80	4.4:1
5	10 mol% (9 mg)	1.0 (58 mg)	82	5:1
6	5 mol% (5 mg)	0.34 (20 mg)	36	3.3:1
7	5 mol% (5 mg)	0.40 (23 mg)	38	4:1
8	5 mol% (5 mg)	0.50 (29 mg)	72	4:1
9	5 mol% (5 mg)	0.67 (39 mg)	80	5:1
10	5 mol% (5 mg)	1.0 (58 mg)	70	10:1

Results from Table 6

Reactions carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), 1-naphthanylboronic acid pinacol ester (1 equiv, 0.25 mmol, 63 mg), **TCICA**, **$Cu(OTf)_2$** and MeCN (0.25 M, 1 mL) at 30 °C for 16 h.

Entry	**$Cu(OTf)_2$ (mass)**	**Equiv of TCICA (mass)**	**Conversion %**	**Selectivity 1c:2c**
1	10 mol% (9 mg)	0.34 (20 mg)	30	2:1
2	10 mol% (9 mg)	0.40 (23 mg)	36	6:1
3	10 mol% (9 mg)	0.50 (29 mg)	57	8:1
4	10 mol% (9 mg)	0.67 (39 mg)	78	11:1
5	10 mol% (9 mg)	1.0 (58 mg)	92	30:1

6	5 mol% (5 mg)	0.34 (20 mg)	33	5.6:1
7	5 mol% (5 mg)	0.40 (23 mg)	43	6.5:1
8	5 mol% (5 mg)	0.50 (29 mg)	49	7:1
9	5 mol% (5 mg)	0.67 (39 mg)	70	7:1
10	5 mol% (5 mg)	1.0 (58 mg)	94	16:1

Results from Table 7

Reactions carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), 1-naphthanylboronic acid pinacol ester (1 equiv, 0.25 mmol, 63 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg), $Cu(OTf)_2$ (10 mol%, 0.025mmol, 9 mg) and MeCN (0.25 M, 1 mL) at 30 °C for **time**.

Entry	Time (h)	Conversion %	Selectivity 1c:2c
1	2	61	8:1
2	4	72	12:1
3	6	89	30:1
4	16	92	34:1

Results from Table 8

Reactions carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), 1-naphthanylboronic acid pinacol ester

Experimental

(1 equiv, 0.25 mmol, 63 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg), **copper catalyst** and MeCN (0.25 M, 1 mL) at 30 °C for 16 h.

Entry	Copper Catalyst (mass)	Conversion %	Selectivity 1c:2c
1	10 mol% $Cu(OTf)_2$ (9 mg)	92	30:1
2	10 mol% CuBr (4 mg)	95	5:1
3	10 mol% $CuBr_2$ (6 mg)	75	4:1
4	10 mol% $CuCl_2$ (3 mg)	20	-
5	10 mol% CuCl (2 mg)	13	-
6	10 mol% CuI (5 mg)	70	2.1:1
7	10 mol% $Cu(OAc)_2$ (5 mg)	96	28:1
8	10 mol% CuOAc (3 mg)	98	30:1

Results from Table 9

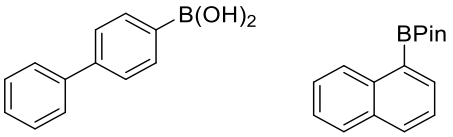
Reactions carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), 1-naphthanylboronic acid pinacol ester (1 equiv, 0.25 mmol, 63 mg), **TCICA**, **$Cu(OAc)_n$** (10 mol%) and MeCN (0.25 M, 1 mL) at **temperature** for **time**.

Entry	$Cu(OAc)_n$ (mass)	X (mass)	Time	Temp.	Conversion to 1c (%)	Selectivity 1c:2c
1	CuOAc (3 mg)	1.00 (58 mg)	6 h	rt	95	26:1

2	CuOAc (3 mg)	1.00 (58 mg)	4 h	rt	93	25:1
3	CuOAc (3 mg)	1.00 (58 mg)	2 h	rt	80	11:1
4	$Cu(OAc)_2$ (5 mg)	1.00 (58 mg)	6 h	rt	92	18:1
5	$Cu(OAc)_2$ (5 mg)	1.00 (58 mg)	4 h	rt	92	22:1
6	$Cu(OAc)_2$ (5 mg)	1.00 (58 mg)	2 h	rt	79	13:1
7	CuOAc (3 mg)	0.67 (39 mg)	4 h	rt	96	50:1

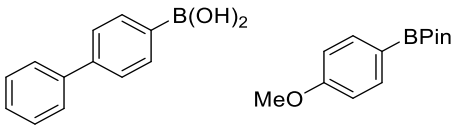
HPLC data for products in Figure 12

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analyzed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (98% conversion, ratio **1c**:**2c** 50:1).

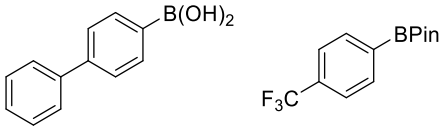
[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 4-methoxyphenylboronic acid, pinacol ester **3b**



Experimental

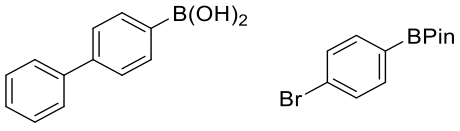
The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv,. 0.25 mmol, 50 mg), 4-methoxyphenylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 59 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (69% conversion, ratio **1c**:**3c** 2:1).

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 4-(trifluoromethyl)phenylboronic acid, pinacol ester **4b**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv,. 0.25 mmol, 50 mg), (4-(trifluoromethyl)phenyl)boronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 69 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (99% conversion, ratio **1c**:**4c** >99:1).

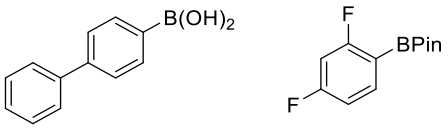
[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 4-bromophenylboronic acid, pinacol ester **5b**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv,. 0.25 mmol, 50 mg), 4-bromophenylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 71 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M)

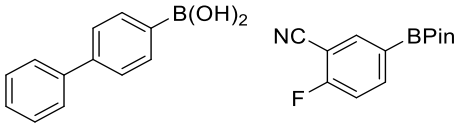
and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (97% conversion, ratio **1c**:**5c** >99:1).

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 2,4-difluorophenylboronic acid, pinacol ester **6b**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv,. 0.25 mmol, 50 mg), (2,4-difluorophenyl)boronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 61 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analyzed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (94% conversion, ratio **1c**:**6c** 7:1).

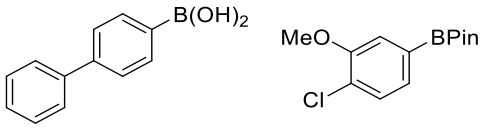
[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 4-fluoro-3-cyanophenylboronic acid, pinacol ester **7b**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), 4-fluoro-3-cyanophenylboronic acid pinacol ester (1.0 equiv, 0.25 mmol, 62 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg),

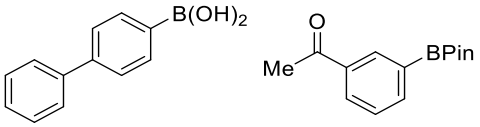
MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (quant.8 ratio **1c**:**7c** >99:1).

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 4-chloro-3-methoxyphenylboronic acid acid, pinacol ester **8b**



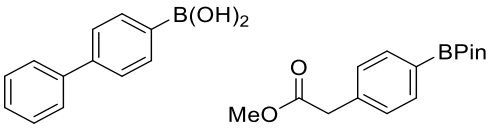
The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), 4-chloro-3-methoxyphenylboronic acid pinacol ester (1.0 equiv, 0.25 mmol, 67 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (98% conversion, ratio **1c**:**8c** >99:1).

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 3-acetylphenylboronic acid, pinacol ester **9b**



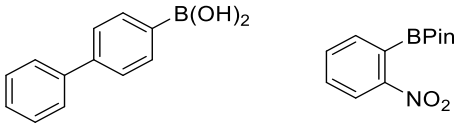
The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), 3-acetylphenylboronic acid pinacol ester (1.0 equiv, 0.25 mmol, 62 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (93% conversion, ratio **1c**:**9c** 47:1).

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. methyl 4-(phenylacetate)boronic acid pinacol ester **10b**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), methyl 4-(phenylacetate)boronic acid pinacol ester (1.0 equiv, 0.25 mmol, 69 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (92% conversion, ratio **1c**:**10c** **>**99:1).

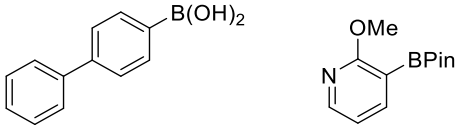
[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 2-nitrophenylboronic acid, pinacol ester **11b**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), (2,4-difluorophenyl)boronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 61 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (88% conversion, ratio **1c**:**11c** >99:1).

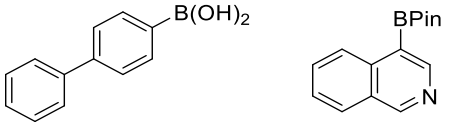
Experimental

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. (2-methoxypyridin-3-yl)boronic acid, pinacol ester **12b**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), (2-methoxypyridin-3-yl)boronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 59 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and purified by flash chromatography (silica gel, 5% Et_2O in petroleum ether) to give 4-chlorobiphenyl **1c** as its only product (46 mg, 97% isolated yield, ratio **1c**:**12c** >99:1).

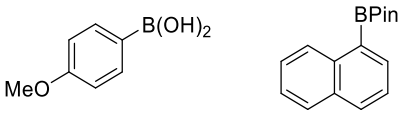
[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. isoquinolin-4-ylboronic acid, pinacol ester **13b**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), isoquinolin-4-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and purified by flash chromatography (silica gel, 5% Et_2O in petroleum ether) to give 4-chlorobiphenyl **1c** as its only product (40 mg, 86% isolated yield, ratio **1c**:**13c** >99:1).

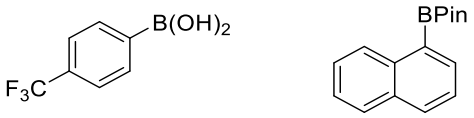
HPLC data for products in Figure 13

4-methoxyphenylboronic acid **3a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



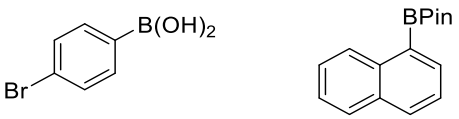
The reaction was carried out according to General Procedure B using (4-methoxyphenyl)boronic acid (1.0 equiv, 0.25 mmol, 45 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chloroanisole **2c** as its major product (quant., ratio **3c**:**2c** >99:1).

4-trifluoromethylphenylboronic acid **4a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure B using 4-trifluoromethylphenylboronic acid (1.0 equiv, 0.25 mmol, 48 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobenzotrifluoride **4c** as its major product (77% conversion, ratio **4c**:**2c** 7:1).

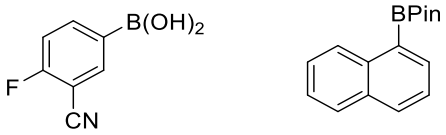
4-bromophenylboronic acid **5a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



Experimental

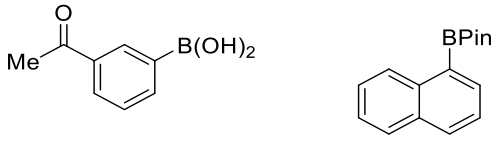
The reaction was carried out according to General Procedure B using 4-bromophenylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobromobenzene **5c** as its major product (40% conversion, ratio **5c**:**2c** 4:1).

4-fluoro-3-cyanophenylboronic acid **7a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure B using 4-fluoro-3-cyanophenylboronic acid (1.0 equiv, 0.25 mmol, 41 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-fluoro-3-cyano-chlorobenzene **7c** as its major product (75% conversion, ratio **7c**:**2c** 3:1).

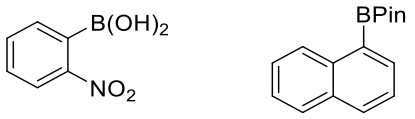
3-acetylphenylboronic acid **9a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure B using 3-acetylphenylboronic acid (1.0 equiv, 0.25 mmol, 41 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M)

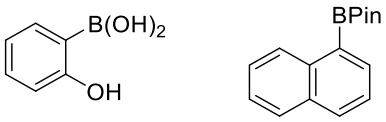
and analysed *via* the HPLC method outlined previously, indicating 4-chloroanisole **9c** as its major product (41% conversion, ratio **9c**:**2c** 2.3:1).

2-nitrophenylboronic acid **11a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure B using 2-nitrophenylboronic acid (1.0 equiv, 0.25 mmol, 42 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chloroanisole **11c** as its major product (42% conversion, ratio **11c**:**2c** 8:1).

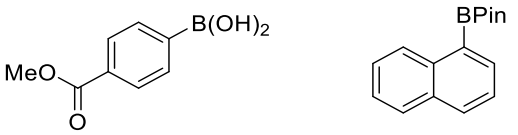
2-hydroxyphenylboronic acid **14a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure B using 2-hydroxyphenylboronic acid (1.0 equiv,. 0.25 mmol, 35 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analyzed *via* the HPLC method outlined previously, indicating 2-chlorophenol **14c** as its major product (76% conversion, ratio **14c**:**2c** 15:1).

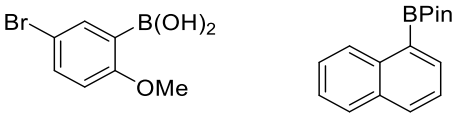
Experimental

4-(methoxycarbonyl)phenylboronic acid **15a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure B using 4-(methoxycarbonyl)phenylboronic acid (1.0 equiv, 0.25 mmol, 45 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-(methoxycarbonyl)chlorobenzene **15c** as its major product (63% conversion, ratio **15c**:**2c** 2.3:1).

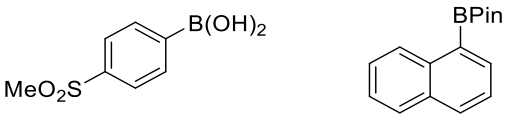
5-bromo-2-methoxyphenylboronic acid **16a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure B using 5-bromo-2-methoxyphenylboronic acid (1.0 equiv, 0.25 mmol, 58 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-bromo-2-chloroanisole **16c** as its major product (43% conversion, ratio **16c**:**2c** 2:1).

Experimental

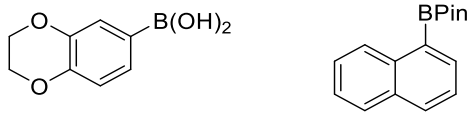
4-(methylsulfonyl)phenylboronic acid **17a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure B using 4-(methylsulfonyl)phenylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-(methylsulfonyl)chlorobenzene **17c** as its major product (23% conversion, ratio **17c**:**2c** 3:1).

Result for product in Scheme 50

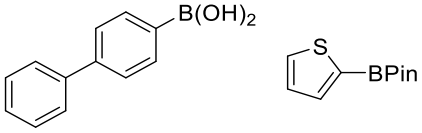
(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)boronic acid **18a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure B using (2,3-dihydrobenzo[b][1,4]dioxin-6-yl)boronic acid (1.0 equiv, 0.25 mmol, 45 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and purified by flash silica chromatography (2%-15% ethyl acetate in petroleum ether), yielding exclusively the product 6,7-dichloro-2,3-dihydrobenzo[b][1,4]dioxine **18c** (42 mg, 82% isolated yield, ratio **18c**:**2c** >99:1).

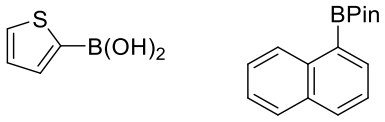
HPLC data for products in Figure 14

4-biphenylboronic acid **1a** vs. thiophen-2-ylboronic acid, pinacol ester **19b**



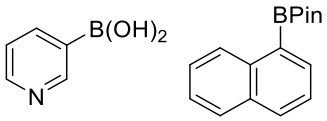
The reaction was carried out according to General Procedure B using 4-biphenylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), thiophen-2-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 53 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analyzed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (10% conversion, ratio **1c**:**19c** >99:1).

Thiophen-2-ylboronic acid **19a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure B using thiophen-2-ylboronic acid (1.0 equiv,. 0.25 mmol, 32 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analyzed *via* the HPLC method outlined previously, indicating 2-chlorothiophene **19c** as its major product (11% conversion, ratio **19c**:**2c** >99:1).

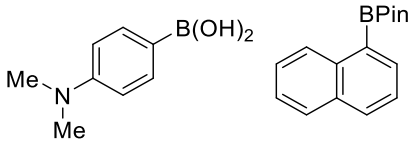
Pyridin-3-ylboronic acid **20a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



Experimental

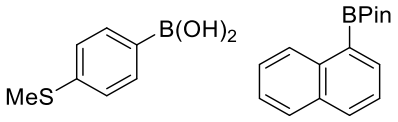
The reaction was carried out according to General Procedure B using pyridin-3-ylboronic acid (1.0 equiv, 0.25 mmol, 32 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analyzed *via* the HPLC method outlined previously, indicating no formation of 3-chloropyridine **20c** product (41% conversion to **2c**).

4-(dimethylamino)phenylboronic acid **21a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure B using 4-(dimethylamino)phenylboronic acid (1.0 equiv, 0.25 mmol, 41 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analyzed *via* the HPLC method outlined previously, indicating decomposition of both starting materials.

4-(methylthio)phenylboronic acid **22a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**

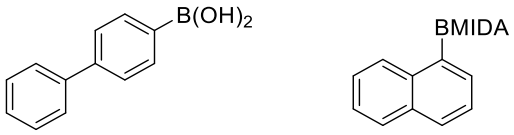


The reaction was carried out according to General Procedure B using 4-(methylthio)phenylboronic acid (1.0 equiv, 0.25 mmol, 42 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00

mL, 0.25 M) and analyzed *via* the HPLC method outlined previously, indicating decomposition of both starting materials.

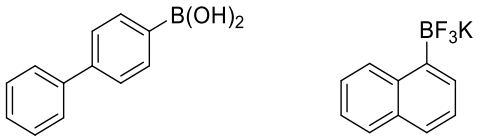
HPLC data for products in Figure 15

[1,1'-biphenyl]-4-ylboronic acid **1a** vs. naphthalen-1-ylboronic acid MIDA ester **2d**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), naphthalen-1-ylboronic acid MIDA ester (1.0 equiv, 0.25 mmol, 71 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.4 equiv, 0.1 mmol, 23 mg), freshly distilled MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl as its major product (35% conversion, ratio **1c**:**2c** 2:1).

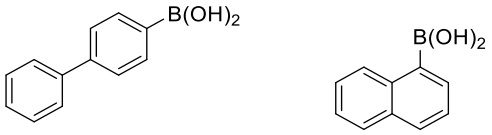
[1,1'-biphenyl]-4-ylboronic acid **1a** vs. potassium naphthalen-1-yltrifluoroborate **2e**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), potassium naphthalen-1-yltrifluoroborate (1.0 equiv, 0.25 mmol, 59 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.4 equiv, 0.1 mmol, 23 mg), freshly distilled MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 1-chloronaphthalene as its major product (quant., ratio **1c**:**2c** 1:11).

Experimental

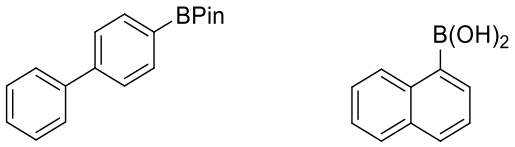
[1,1'-biphenyl]-4-ylboronic acid **1a** vs. naphthalen-1-ylboronic acid **2a**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), naphthalen-1-ylboronic acid (1.0 equiv, 0.25 mmol, 43 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.4 equiv, 0.1 mmol, 23 mg), freshly distilled MeCN (1.00 mL, 0.25 M) and analysed via the HPLC method outlined previously, indicating 4-chlorobiphenyl as its major product (90% conversion, ratio **1c**:**2c** 9:1).

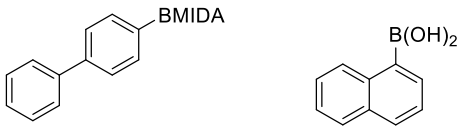
HPLC data for products in Figure 16

[1,1'-biphenyl]-4-ylboronic acid, pinacol ester **1b** vs. naphthalen-1-ylboronic acid **2a**



The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid pinacol ester (1.0 equiv, 0.25 mmol, 70 mg), naphthalen-1-ylboronic acid (1.0 equiv, 0.25 mmol, 43 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 1-chloronaphthalene as its major product (quant., ratio **1c**:**2c** 1:25).

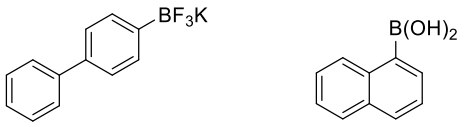
[1,1'-biphenyl]-4-ylboronic acid MIDA ester **1d** vs. naphthalen-1-ylboronic acid **2a**



Experimental

The reaction was carried out according to General Procedure B using [1,1'-biphenyl]-4-ylboronic acid MIDA ester (1.0 equiv, 0.25 mmol, 77 mg), naphthalen-1-ylboronic acid (1.0 equiv, 0.25 mmol, 43 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.4 equiv, 0.1 mmol, 23 mg), freshly distilled MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 1-chloronaphthalene **2c** as its major product (quant., ratio **1c**:**2c** >99:1).

Potassium [1,1'-biphenyl]-4-yltrifluoroborate **1e** vs. naphthalen-1-ylboronic acid **2a**



The reaction was carried out according to General Procedure B using potassium [1,1'-biphenyl]-4-yltrifluoroborate (1.0 equiv, 0.25 mmol, 65 mg), naphthalen-1-ylboronic acid (1.0 equiv, 0.25 mmol, 43 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), TCICA (0.4 equiv, 0.1 mmol, 23 mg), freshly distilled MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 1-chloronaphthalene **2c** as its major product (quant., ratio **1c**:**2c** 1:11).

Results from Table 10

Reactions carried out according to General Procedure C using copper(I) acetate (5 mol%, 0.0125 mmol, 2 mg), 4-chlorobiphenyl (1.0 equiv, 0.25 mmol, 50 mg), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (1 equiv, 0.25 mmol, 69 mg), **additive**, palladium (II) acetate (5 mol%, 0.0125 mmol, 3 mg), SPhos (10 mol%, 0.025 mmol, 10 mg), vaccum oven-dried K_3PO_4 (3.0 equiv, 0.75 mmol, 156 mg), H_2O (5.0 equiv, 1.25 mmol, 23 µL) and MeCN (1mL, 0.25M). The mixture was heated to 90 °C and left to react overnight. The resulting mixture was analysed *via* the HPLC method outlined previously.

Entry	Additive (mass)	Conversion %
1	None	92
2	TCICA (19 mg)	0
3	**23** (22 mg)	56
4	CuOAc (3 mg)	68
5	TCICA (19 mg) + CuOAc (3 mg)	0
6	**23** (22 mg) + CuOAc (3 mg)	49

Results from Figure 19

Reactions carried out according to General Procedure C using copper(I) acetate (5 mol%, 0.0125 mmol, 2 mg), [1,1'-biphenyl]-4-ylboronic acid (1.1 equiv, 0.275 mmol, 54 mg), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (1 equiv, 0.25 mmol, 69 mg), trichloroisocyanuric acid (0.34 equiv, 0.084 mmol, 20 mg) and MeCN (1mL, 0.25M) at rt for 4 h. Then, palladium (II) acetate (5 mol%, 0.0125 mmol, 3 mg), SPhos (10 mol%, 0.025 mmol, 10 mg), vaccum oven-dried **K_3PO_4** and **H_2O** were added, the mixture was heated to 90 °C and left to react overnight. The resulting mixture was analysed *via* the HPLC method outlined previously.

Entry	Equiv. of K_3PO_4 (mass)	Equiv. of H_2O (volume)	Conversion %
1	2 (106 mg)	5 (23 µL)	39
2	2 (106 mg)	10 (45 µL)	22

3	3 (159 mg)	0 (0 µL)	>5
4	3 (159 mg)	3 (14 µL)	>5
5	3 (159 mg)	5 (23 µL)	49
6	3 (159 mg)	7 (32 µL)	53
7	3 (159 mg)	10 (45 µL)	23
8	4 (212 mg)	0 (0 µL)	>5
9	4 (212 mg)	3 (14 µL)	28
10	4 (212 mg)	4 (18 µL)	27
11	4 (212 mg)	5 (23 µL)	81
12	4 (212 mg)	6 (27 µL)	54
13	4 (212 mg)	7 (32 µL)	91
14	4 (212 mg)	8 (36 µL)	37
15	4 (212 mg)	9 (41 µL)	51
16	4 (212 mg)	10 (45 µL)	28
17	5 (265 mg)	0 (0 µL)	27
18	5 (265 mg)	5 (23 µL)	57
19	5 (265 mg)	7 (32 µL)	43
20	5 (265 mg)	10 (45 µL)	22

Results from Table 11

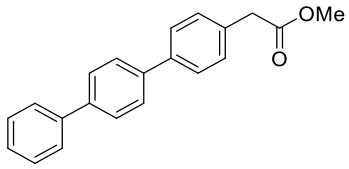
Reactions carried out according to General Procedure C using copper(I) acetate (5 mol%, 0.0125 mmol, 2 mg), [1,1'-biphenyl]-4-ylboronic acid (1.1 equiv, 0.275 mmol, 54 mg), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (1 equiv, 0.25 mmol, 69 mg), trichloroisocyanuric acid (0.34 equiv, 0.084 mmol, 20 mg) and MeCN (1mL, 0.25M) at rt for 4 h. Then, **palladium catalyst**, **Ligand**, vaccum oven-dried **K_3PO_4** and **H_2O** were added, the mixture was heated to 90 °C and left to react overnight. The resulting mixture was analysed *via* the HPLC method outlined previously.

Entry	5 mol% Pd Catalyst (mass)	10 mol% Ligand (mass)	4 equiv. of base (mass)	Conversion %
1	$Pd(OAc)_2$ (3 mg)	SPhos (10 mg)	Cs_2CO_3 (326 mg)	28
2	$Pd(OAc)_2$ (3 mg)	SPhos (10 mg)	K_2CO_3 (138 mg)	24
3	$Pd(OAc)_2$ (3 mg)	DavePhos (10 mg)	K_3PO_4 (212 mg)	19
4	$Pd(OAc)_2$ (3 mg)	CyJohnPhos (9 mg)	K_3PO_4 (212 mg)	19
5	$PdCl_2$ (2 mg)	SPhos (10 mg)	K_3PO_4 (212 mg)	11
6	$Pd(dppf)Cl_2$.DCM (10 mg)	-	K_3PO_4 (212 mg)	16
7	$Pd(PPh_3)_4$ (14 mg)	-	K_3PO_4 (212 mg)	13

Characterisation data for products in Figure 20

Methyl 2-([1,1':4',1''-terphenyl]-4-yl)acetate, **26**

Experimental



The reaction was carried out according to General Procedure D using [1,1'-biphenyl]-4-ylboronic acid (1.1 equiv,. 0.275 mmol, 55 mg), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (1.0 equiv, 0.25 mmol, 69 mg), copper (I) acetate (5 mol%, 0.0125 mmol, 2 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (2%-15% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (69 mg, 90% yield).

ν_{max} (neat): 3030, 2953, 2845, 1734 cm^{-1}.

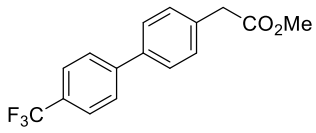
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.59 (m, 8H), 7.49 – 7.43 (m, 2H), 7.40 – 7.34 (m, 3H), 3.73 (s, 3H), 3.69 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2, 140.8, 104.3, 139.8, 133.3, 129.9, 129.0, 127.7, 127.6, 127.5, 127.4, 127.2, 52.3, 41.0, 31.1.

HRMS ($C_{21}H_{18}O_2$): exact calculated mass for [$M+NH_4^+$] requires 320.1645 (100%), 321.1679 (10%); found [$M+NH_4^+$] 320.1646 (100%), 321.1676 (10%).

Spectroscopic data were in agreement with literature values.[141]

Methyl 2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)acetate, **27**



The reaction was carried out according to General Procedure D using 4-trifluoromethylphenylboronic acid (1.1 equiv,. 0.275 mmol, 52 mg), methyl 2-(4-

(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (1.0 equiv, 0.25 mmol, 69 mg), copper (I) acetate (5 mol%, 0.0125 mmol, 2 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (2%-10% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (60 mg, 82% yield).

ν_{max} (neat): 2957, 2930, 1734, 1165 cm^{-1}.

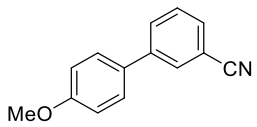
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 – 7.65 (m, 4H), 7.59 – 7.54 (m, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 3.73 (s, 3H), 3.69 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.0, 144.4, 138.8, 134.2, 128.9 (d, $^{1}J_{C-F}$ = 246.8 Hz), 127.5, 125.9 (d, $^{2}J_{C-F}$ = 3.4 Hz), 52.3, 40.9.

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

HRMS ($C_{16}H_{13}F_3O_2$): exact calculated mass for [M+NH_4^+] requires 312.1206 (100%), 313.1240 (20%); found [M+NH_4^+] 312.1209 (100%), 313.1242 (20%).

4'-Methoxy-[1,1'-biphenyl]-3-carbonitrile, **28**



The reaction was carried out according to General Procedure D using 4-methoxyphenylboronic acid (1.1 equiv,. 0.275 mmol, 42 mg), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.0 equiv, 0.25 mmol, 57 mg), copper (I) acetate (5 mol%, 0.0125 mmol, 2 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-7% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (49 mg, 94% yield).

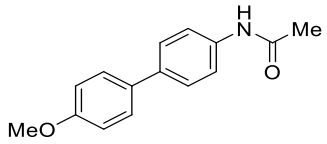
ν_{max} (neat): 2957, 2932, 2358, 2227, 1516, 1250 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.79 – 7.75 (m, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.53 – 7.47 (m, 3H), 7.02 – 6.98 (m, 2H), 3.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.1, 142.2, 131.4, 131.1, 130.3, 130.2, 129.7, 128.3, 119.1, 114.7, 113.0, 55.5.

HRMS ($C_{14}H_{11}NO$): exact calculated mass for [M+H^+] requires 210.0919 (100%), 211.0951 (20%); found [M+H^+] 210.0919 (100%), 211.0946 (20%).

N-(4'-Methoxy-[1,1'-biphenyl]-4-yl)acetamide, **29**



The reaction was carried out according to General Procedure D using 4-methoxyphenylboronic acid (1.1 equiv,. 0.275 mmol, 42 mg), *N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetamide (1.0 equiv, 0.25 mmol, 68 mg), copper (I) acetate (5 mol%, 0.0125 mmol, 2 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-60% ethyl acetate in petroleum ether), to give the desired product as an amorphous off-white solid (43 mg, 72% yield).

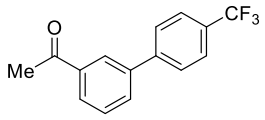
ν_{max} (neat): 3281, 2955, 2922, 2851, 1659 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ 9.97 (s, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.55 (dd, *J* = 10.2, 8.9 Hz, 4H), 6.99 (d, *J* = 8.7 Hz, 2H), 3.78 (s, 3H), 2.05 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 168.2, 158.5, 138.1, 134.4, 132.2, 127.3, 126.3, 119.3, 114.3, 55.1, 24.0.

HRMS ($C_{15}H_{15}NO_2$): exact mass calculated for [M+H$^+$] requires 242.1176 (100%), 243.1209 (20%); found [M+H$^+$] 242.1177 (100%), 243.1211 (20%).

1-(4'-(Trifluoromethyl)-[1,1'-biphenyl]-3-yl)ethan-1-one, **30**



The reaction was carried out according to General Procedure D using 3-acetylphenylboronic acid (1.1 equiv,. 0.275 mmol, 45 mg), 4,4,5,5-tetramethyl-2-(4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (1.0 equiv, 0.25 mmol, 68 mg), copper (I) acetate (5 mol%, 0.0125 mmol, 2 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-8% Et_2O in petroleum ether), to give the desired product as an amorphous white solid (43 mg, 65% yield).

ν_{max} (neat): 2976, 2928, 2851, 1684, 1616 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (t, *J* = 1.7 Hz, 1H), 8.08 – 7.93 (m, 1H), 7.80 (ddd, *J* = 7.7, 1.8, 1.1 Hz, 1H), 7.72 (s, 4H), 7.58 (t, *J* = 7.8 Hz, 1H), 2.67 (s, 3H).

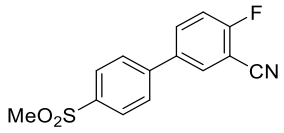
^{13}C NMR (101 MHz, $CDCl_3$): δ 197.9, 143.8, 140.4, 138.0, 130.7 (d, $^1J_{C\text{-}F}$ = 246.6 Hz), 130.1 (q, $^2J_{C\text{-}F}$ = 32.5 Hz), 128.2, 127.7, 127.1, 126.0 (q, $^3J_{C\text{-}F}$ = 3.1 Hz), 26.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.49.

HRMS ($C_{15}H_{11}OF_3$): exact calculated mass for [M+H$^+$] requires 265.0840 (100%), 266.0874 (20%); found [M+H$^+$] 265.0838 (100%), 266.0867 (20%).

Experimental

4-Fluoro-4'-(methylsulfonyl)-[1,1'-biphenyl]-3-carbonitrile, **31**



The reaction was carried out according to General Procedure D using 4-(methylsulfonyl)phenylboronic acid (1.1 equiv,. 0.275 mmol, 55 mg), 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.0 equiv, 0.25 mmol, 62 mg), copper (I) acetate (5 mol%, 0.0125 mmol, 2 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-40% ethyl acetate in petroleum ether), to give the desired product as an amorphous off-white solid (54 mg, 79% yield).

ν_{max} (neat): 2980, 2928, 2235, 1608, 1485 cm^{-1}.

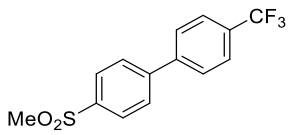
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.5 Hz, 2H), 7.86 – 7.82 (m, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 8.5 Hz, 1H), 3.10 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4 (d, $^{1}J_{C-F}$ = 261.8 Hz), 143.4, 140.6, 136.7 (d, $^{3}J_{C-F}$ = 3.6 Hz), 134.1 (d, $^{3}J_{C-F}$ = 8.4 Hz), 132.4, 128.3 (d, $^{2}J_{C-F}$ = 49.4 Hz), 117.5 (d, $^{2}J_{C-F}$ = 20.0 Hz), 113.6, 102.7 (d, $^{2}J_{C-F}$ = 16.1 Hz), 44.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -106.73.

HRMS ($C_{14}H_{10}NSO_2$): exact calculated mass for [$M+H^+$] requires 276.0494 (100%), 277.0525 (20%), 278.0479 (5%); found [$M+H^+$] 276.0494 (100%), 277.0520 (20%), 278.0469 (5%).

4-(Methylsulfonyl)-4'-(trifluoromethyl)-1,1'-biphenyl, **32**



Experimental

The reaction was carried out according to General Procedure D using 4-(methylsulfonyl)phenylboronic acid (1.1 equiv,. 0.275 mmol, 55 mg), 4,4,5,5-tetramethyl-2-(4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (1.0 equiv, 0.25 mmol, 68 mg), copper (I) acetate (5 mol%, 0.0125 mmol, 2 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-50% Et_2O in petroleum ether), to give the desired product as an amorphous white solid (56 mg, 75% yield).

ν_{max} (neat): 3011, 2928, 2851, 1616, 1593, 1532 cm^{-1}.

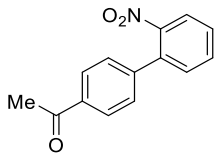
^1H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.80 – 7.68 (m, 6H), 3.11 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.3, 142.8, 140.3, 128.4, 128.3, 127.9, 126.2 (q, $^3J_{C-F}$ = 3.6 Hz), 44.7.

^{19}F NMR (471 MHz, $CDCl_3$): δ -62.65.

HRMS ($C_{14}H_{11}F_3O_2$): exact mass calculated for [M+H^+] requires 301.0510 (100%), 302.0542 (20%), 303.0495 (5%); found [M+H^+] 301.0504 (100%), 302.0535 (20%), 303.0483 (5%).

1-(2'-Nitro-[1,1'-biphenyl]-4-yl)ethan-1-one, **33**



The reaction was carried out according to General Procedure D using 4-acetylphenylboronic acid (1.1 equiv, 0.275 mmol, 45 mg), 4,4,5,5-tetramethyl-2-(2-nitrophenyl)-1,3,2-dioxaborolane (1.0 equiv, 0.25 mmol, 62 mg), copper (I) acetate (5 mol%, 0.0125 mmol, 2 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product

and purified by flash silica chromatography (0%-20% Et_2O in petroleum ether), to give the desired product as an amorphous off-white solid (37 mg, 62% yield).

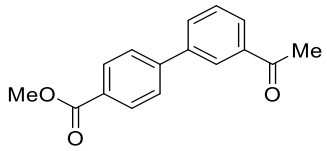
ν_{max} (neat): 2920, 2360, 1676, 1517, 1350 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.04 – 8.00 (m, 2H), 7.94 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.66 (td, *J* = 7.5, 1.4 Hz, 1H), 7.55 (td, *J* = 7.8, 1.5 Hz, 1H), 7.43 (tt, *J* = 8.5, 1.7 Hz, 3H), 2.64 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 197.6, 142.5, 136.8, 135.7, 132.8, 131.9, 129.1, 128.8, 128.4, 124.6, 26.8.

Spectroscopic data were in agreement with literature values.[196]

Methyl 3'-acetyl-[1,1'-biphenyl]-4-carboxylate, **34**



The reaction was carried out according to General Procedure D using 4-(methoxycarbonyl)phenylboronic acid (1.1 equiv,. 0.275 mmol, 50 mg), 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-one (1.0 equiv, 0.25 mmol, 62 mg), copper (I) acetate (5 mol%, 0.0125 mmol, 2 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-20% Et_2O in petroleum ether), to give the desired product as an amorphous white solid (50 mg, 79% yield).

ν_{max} (neat): 3038, 2961, 2926, 1719, 1678 cm^{-1}.

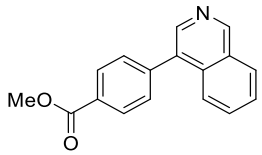
^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (t, *J* = 1.7 Hz, 1H), 8.16 – 8.11 (m, 2H), 8.00 – 7.96 (m, 1H), 7.82 (ddd, *J* = 7.7, 1.9, 1.1 Hz, 1H), 7.73 – 7.64 (m, 2H), 7.61 – 7.52 (m, 1H), 3.95 (s, 3H), 2.67 (s, 3H).

Experimental

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.0, 167.0, 144.7, 140.7, 137.9, 132.0, 130.4, 129.6, 129.4, 128.2, 127.3, 127.2, 52.4, 26.9.

HRMS ($C_{16}H_{14}O_3$): exact calculated mass for [M+H$^+$] requires 255.1016 (100%), 256.1049 (20%); found [M+H$^+$] 255.1019 (100%), 256.1052 (20%).

Methyl 4-(isoquinolin-4-yl)benzoate, **35**



The reaction was carried out according to General Procedure D using 4-(methoxycarbonyl)phenylboronic acid (1.1 equiv,. 0.275 mmol, 50 mg), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (5 mol%, 0.0125 mmol, 2 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-20% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (49 mg, 74% yield).

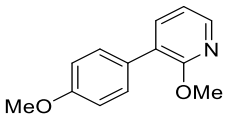
ν_{max} (neat): 3051, 2980, 2951, 2922, 2851, 1721 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.29 (s, 1H), 8.50 (s, 1H), 8.23 – 8.16 (m, 2H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.70 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.62 – 7.58 (m, 2H), 3.98 (d, *J* = 1.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.0, 152.8, 142.9, 142.0, 134.0, 132.5, 131.1, 130.3, 130.0, 129.9, 128.5, 128.2, 127.6, 124.6, 52.4.

HRMS ($C_{17}H_{13}NO_2$): exact calculated mass for [M+H$^+$] requires 264.1019 (100%), 265.1053 (20%); found [M+H$^+$] 264.1022 (100%), 265.1052 (20%).

2-Methoxy-3-(4-methoxyphenyl)pyridine, **36**



The reaction was carried out according to General Procedure D using 4-methoxyphenylboronic acid (1.1 equiv,. 0.275 mmol, 42 mg), 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.0 equiv, 0.25 mmol, 59 mg), copper (I) acetate (5 mol%, 0.0125 mmol, 2 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-7% ethyl acetate in petroleum ether), to give the desired product as an amorphous off-white solid (32 mg, 60% yield).

ν_{max} (neat): 2951, 2922, 2853, 1736 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.58 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.00 – 6.91 (m, 3H), 3.97 (s, 3H), 3.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.0, 167.0, 144.7, 140.7, 137.9, 132.0, 130.4, 129.6, 129.4, 128.2, 127.3, 127.2, 52.4, 26.9.

Spectroscopic data were in agreement with literature values.[197]

6.6 Experimental procedures and characterisation for Section 3.2

Results for Table 12

Reactions carried out according to General Procedure E [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg), **CuOAc (10 mol%, 0.025 mmol)** or **$Cu(OAc)_2$ (10 mol%, 0.025 mmol)** and MeCN (0.25 M, 1 mL) at rt for 4 h and analysed *via* the HPLC method outlined previously.

Entry	TEMPO (mass)	Conversion % with CuOAc (3 mg)	Conversion % with $Cu(OAc)_2$ (5 mg)	Conversion % without catalyst
1	0 equiv (0 mg)	98%	96%	92%
2	1 equiv (39 mg)	92%	90%	94%
3	2 equiv (78 mg)	53%	64%	60%
4	3 equiv (117 mg)	25%	48%	56%
5	5 equiv (195 mg)	20%	40%	38%
6	10 equiv (390 mg)	4%	12%	13%

Results from Table 13

Reactions carried out using an oven-dried 5 mL microwave vial, where 1,1'-biphenyl **41** (1 equiv, 0.25 mmol, 39 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg), CuOAc (10 mol%, 0.025 mmol, 3 mg) and MeCN (0.25 M, 1 mL) were added. The reaction mixture was allowed to react at room temperature for 4 h, in the complete absence of light. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration, affording the desired 4-chlorobiphenyl **1c** compound in 92%, 90% and 94% yield as shown in **page 68**.

Results from Figure 21

(a) Reactions carried out according to General Procedure E using MeCN (0.25 M, 1 mL). The solution has not been any change of colour, either visually and/or by iodine paper indicator.

(b) Reactions carried out according to General Procedure E using trichloroisocyanuric acid (1 equiv, 0.25 mmol, 39 mg) and MeCN (0.25 M, 1 mL). The solution has changed from colourless to dark brown, confirmed by iodine paper indicator.

(c) Reactions carried out according to General Procedure E using trichloroisocyanuric acid (1 equiv, 0.25 mmol, 39 mg), CuOAc (1 equiv, 0.25 mmol, 31 mg) and MeCN (0.25 M, 1 mL). The solution has changed from colourless to dark brown, confirmed by iodine paper indicator.

(d) Reactions carried out according to General Procedure E using trichloroisocyanuric acid (1 equiv, 0.25 mmol, 39 mg), $Cu(OAc)_2$ (1 equiv, 0.25 mmol, 45 mg) and MeCN (0.25 M, 1 mL). The solution has changed from colourless to dark brown, confirmed by iodine paper indicator.

Result from Figure 23

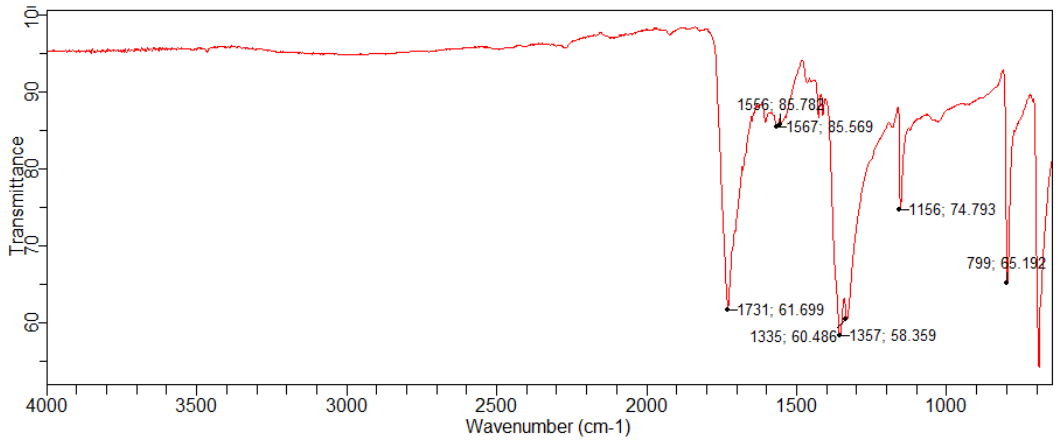
Reactions carried out according to General Procedure F using **TCICA** (0.67 equiv, 0.1675 mmol, 39 mg) and MeCN (0.25 M, 1 mL) at rt for 10 min and analysed *via* the method outlined previously using a Shimadzu IRAffinity-1 machine.

Result from Figure 24

Reactions carried out according to General Procedure F using **TCICA** (0.67 equiv, 0.1675 mmol, 39 mg), **$Cu(OAc)_2$ (1 equiv, 0.25 mmol, 45 mg) or $CuCl_2$ (1 equiv, 0.25 mmol, 34 mg)** and MeCN (0.25 M, 1 mL) at rt for 10 min and analysed *via* the method outlined previously using a Shimadzu IRAffinity-1 machine.

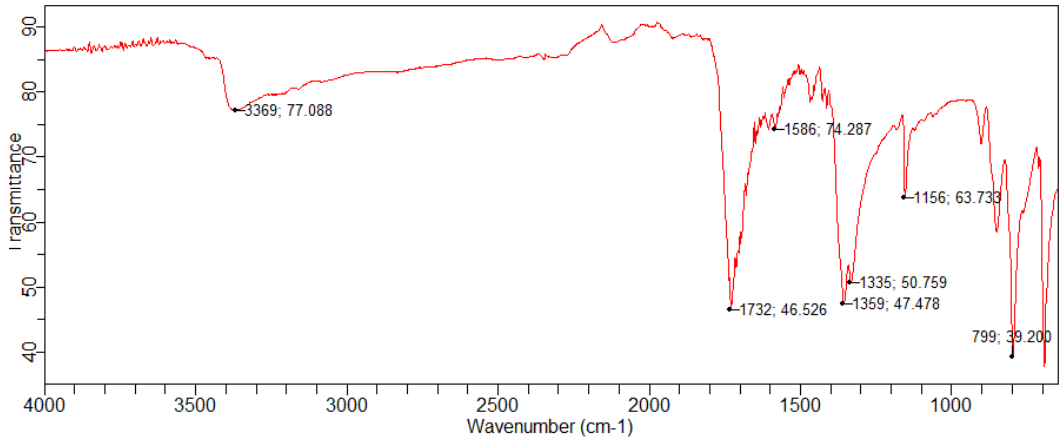
Results from additional IR experiments

Reactions carried out according to General Procedure F using **TCICA** (1 equiv, 0.25 mmol, 56 mg), CuCl (1 equiv, 0.25 mmol, 25 mg) and MeCN (0.25 M, 1 mL) at rt for 10 min and analysed *via* the method outlined previously using a Shimadzu IRAffinity-1 machine.



Scheme 71 - IR spectra of TCICA and CuCl mixture

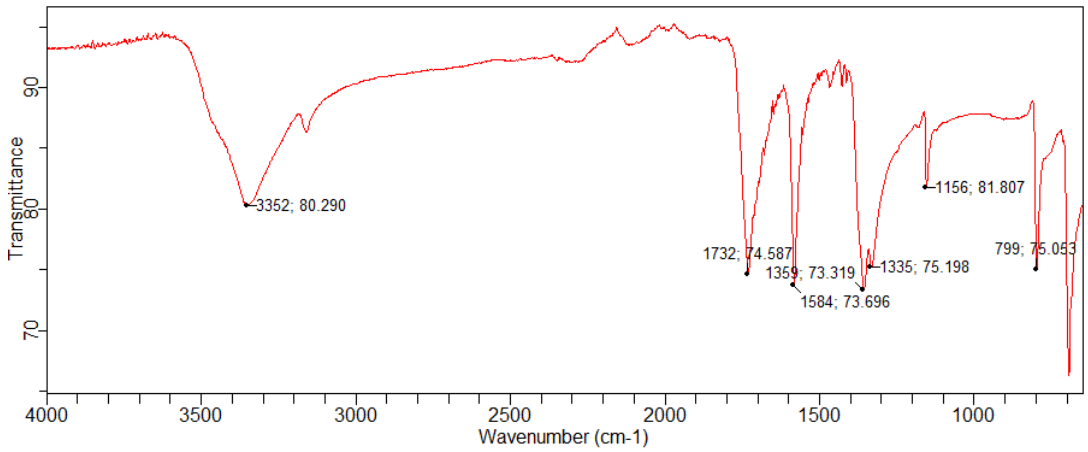
Reactions carried out according to General Procedure F using **TCICA** ((1 equiv, 0.25 mmol, 56 mg), CuOAc (1 equiv, 0.25 mmol, 31 mg) and MeCN (0.25 M, 1 mL) at rt for 10 min and analysed *via* the method outlined previously using a Shimadzu IRAffinity-1 machine.



Scheme 72 - IR spectra of TCICA and CuOAc mixture

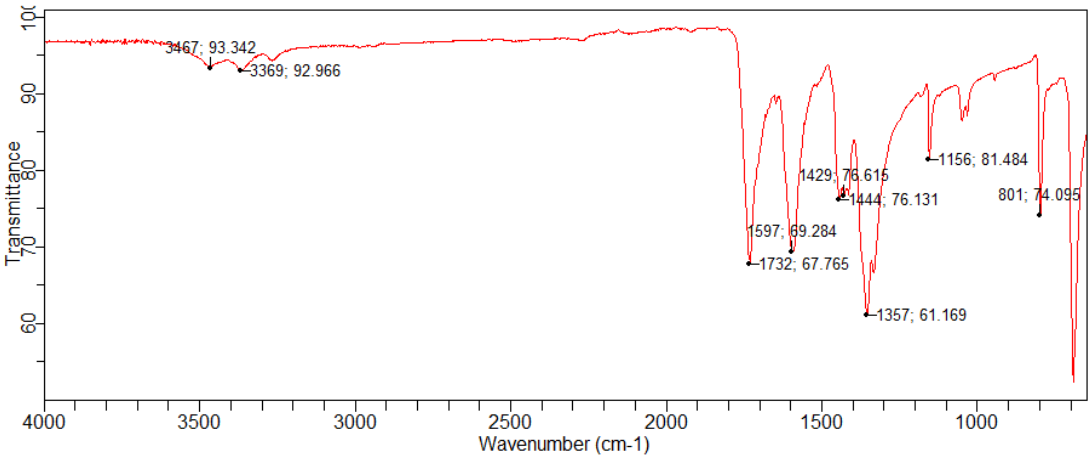
Experimental

Reactions carried out according to General Procedure F using **TCICA** (1 equiv, 0.25 mmol, 56 mg), $CuCl_2$ (1 equiv, 0.25 mmol, 34 mg) and MeCN (0.25 M, 1 mL) at rt for 10 min and analysed *via* the method outlined previously using a Shimadzu IRAffinity-1 machine.



Scheme 73 - IR spectra of TCICA and $CuCl_2$ mixture

Reactions carried out according to General Procedure F using **TCICA** (1 equiv, 0.25 mmol, 56 mg), $Cu(OAc)_2$ (1 equiv, 0.25 mmol, 45 mg) and MeCN (0.25 M, 1 mL) at rt for 10 min and analysed *via* the method outlined previously using a Shimadzu IRAffinity-1 machine.



Scheme 74 - IR spectra of TCICA and $Cu(OAc)_2$ mixture

Results from Scheme 56

(a) Reactions carried out using an oven-dried 5 mL microwave vial, where [1,1'-biphenyl]-4-ylboronic acid **1a** (1 equiv, 0.25 mmol, 50 mg), CuBr (1 equiv, 0.25 mmol, 36 mg) or $CuBr_2$ (1 equiv, 0.25 mmol, 58 mg), and MeCN (0.25 M, 1 mL) were added. The reaction mixture was allowed to react at room temperature for 4 h. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration, showing only starting material remaining in the mixture.

(b) Reactions carried out using an oven-dried 5 mL microwave vial, where [1,1'-biphenyl]-4-ylboronic acid **1a** (1 equiv, 0.25 mmol, 50 mg), CuBr (1 equiv, 0.25 mmol, 36 mg), TCICA (0.7 equiv, 0.1675 mmol, 39 mg), and MeCN (0.25 M, 1 mL) were added. The reaction mixture was allowed to react at room temperature for 4 h. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration, showing full conversion to 4-bromobiphenyl **1f** product.

(c) Reactions carried out using an oven-dried 5 mL microwave vial, where [1,1'-biphenyl]-4-ylboronic acid **1a** (1 equiv, 0.25 mmol, 50 mg), $CuBr_2$ (1 equiv, 0.25 mmol, 58 mg), TCICA (0.7 equiv, 0.1675 mmol, 39 mg), and MeCN (0.25 M, 1 mL) were added. The reaction mixture was allowed to react at room temperature for 4 h. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration, showing full conversion exclusively to 4,4'-dibromobiphenyl **39** product.

Results from Scheme 57

(a) Reactions carried out using an oven-dried 5 mL microwave vial, where using 4-bromobiphenyl **1f** (1 equiv, 0.25 mmol, 58 mg), CuOAc (1 equiv, 0.25 mmol, 28 mg) or $Cu(OAc)_2$ (1 equiv, 0.25 mmol, 45 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg) and MeCN (0.25 M, 1 mL) were added. The reaction mixture was allowed to react at

room temperature for 4 h. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration, showing only starting material remaining in the mixture.

(b) Reactions carried out using an oven-dried 5 mL microwave vial, where using 4-iodobiphenyl **1g** (1 equiv, 0.25 mmol, 70 mg), CuOAc (1 equiv, 0.25 mmol, 28 mg) or $Cu(OAc)_2$ (1 equiv, 0.25 mmol, 45 mg) or CuBr (1 equiv, 0.25 mmol, 36 mg) or $CuBr_2$ (1 equiv, 0.25 mmol, 58 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg) and MeCN (0.25 M, 1 mL) were added. The reaction mixture was allowed to react at room temperature for 4 h. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration, showing only starting material remaining in the mixture.

Results from Scheme 58

Reactions carried out using an oven-dried 5 mL microwave vial, where 4-chlorobiphenyl **1c** (1 equiv, 0.25 mmol, 47 mg), CuBr (1 equiv, 0.25 mmol, 36 mg) or $CuBr_2$ (1 equiv, 0.25 mmol, 58 mg), and MeCN (0.25 M, 1 mL) were added. The reaction mixture was allowed to react at room temperature for 4 h. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration, showing, in both cases, full conversion to 4-Bromo-4'-chloro-1,1'-biphenyl **40** product.

Results from Table 14

Reactions carried out using an oven-dried 5 mL microwave vial, where 1,1’-biphenyl **41** (1 equiv, 0.25 mmol, 39 mg), **copper catalyst (1.0 equiv, 0.25 mmol)**, TCICA (0.67 equiv, 0.1675 mmol, 39 mg) and MeCN (0.25 M, 1 mL) were added. The reaction mixture was allowed to react at room temperature for 4 h. The reaction mixture

was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration and the results as displayed below.

Entry	CuX_n (mass)	Conversion %
1	CuBr (36 mg)	>99% of **1f**
2	$CuBr_2$ (56 mg)	>99% of **36**
3	CuCl (25 mg)	28% of **1c**
4	$CuCl_2$ (34 mg)	80% of **1c**
5	CuOAc (28 mg) or $Cu(OAc)_2$ (49 mg)	traces of **1c**

Results from Table 15

Reactions carried out using an oven-dried 5 mL microwave vial, where 1,1'-biphenyl]-4-ylboronic acid **1a** (1 equiv, 0.25 mmol, 50 mg), **copper catalyst**, **halogen source**, **oxidant (1.2 equiv, 0.3 mmol)** and MeCN (0.25 M, 1 mL) were added. The reaction mixture was allowed to react at room temperature for 4 h. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration and the results as displayed below.

Entry	Conditions (mass)	Conversion %
1	10 mol% CuOAc (3 mg) and 2.0 equiv TBAC (139 mg)	0% of **1c**
2	1.0 equiv CuCl (25 mg)	30% of **1c** (MnO_2 – 26 mg), 64% of **1c** (DTBP – 44 mg), 52% of **1c** (O_2 atm)
3	1.0 equiv NaBr (26 mg)	0% of **1f**
4	1.0 equiv CuBr (36 mg)	45% of **1f** (MnO_2 – 26 mg), 72% of **1f** (DTBP – 44 mg), 17% of **1f** (O_2 atm)

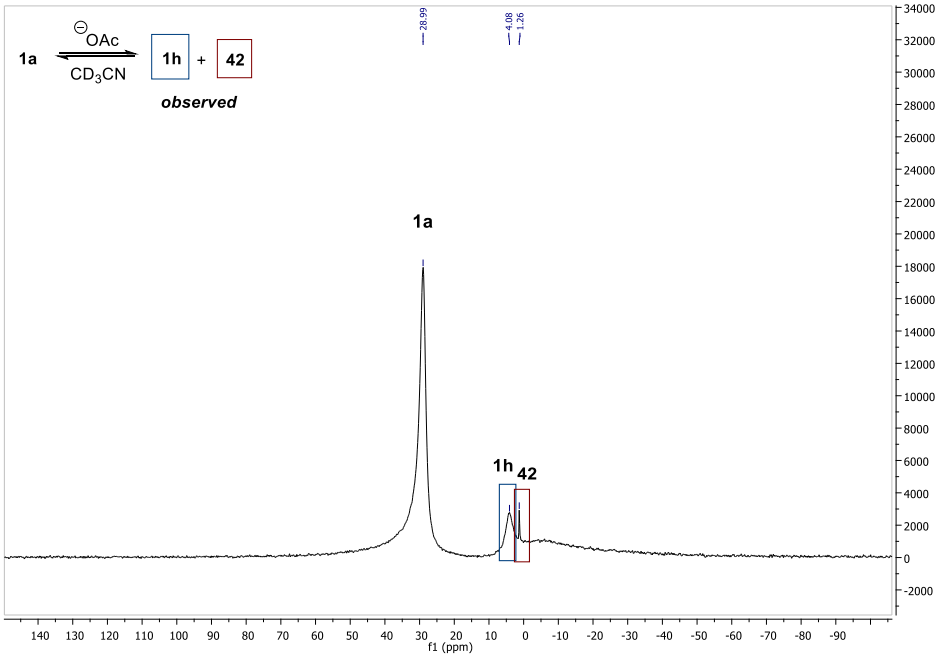
Results from Table 16

Reactions carried out using an oven-dried 5 mL microwave vial, where 1,1'-biphenyl]-4-ylboronic acid **1a** (1 equiv, 0.25 mmol, 50 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg), NaBr (1 equiv, 0.25 mmol, 26 mg), **copper catalyst** and MeCN (0.25 M, 1 mL) were added. The reaction mixture was allowed to react at room temperature for 4 h. The reaction mixture was allowed to cool to room temperature before analysis by HPLC against a caffeine standard of known concentration and the results as displayed below.

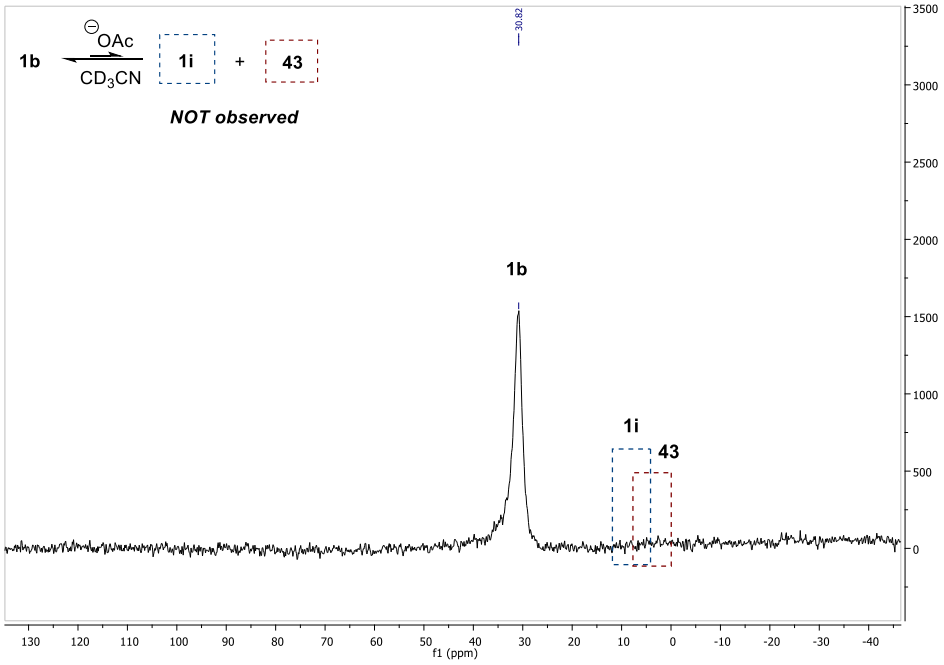
Entry	Copper catalyst (mass)	Conversion[a] %
1	10 mol% CuOAc (3 mg)	72% **1c**, 27% **1f**
2	10 mol% $Cu(OAc)_2$ (5 mg)	70% **1c**, 28% **1f**
3	-	90% **1c**, 10% **1f**

Results from Scheme 61

(a) The NMR experiment was carried out according to General Procedure G [1,1'-biphenyl]-4-ylboronic acid **1a** (1 equiv, 0.125 mmol, 25 mg) and CuOAc (20 mol%, 0.025 mmol, 3 mg) in CD_3CN. A ^{11}B NMR was recorded and analysed, showing boronic acid boronate **1h** formation.

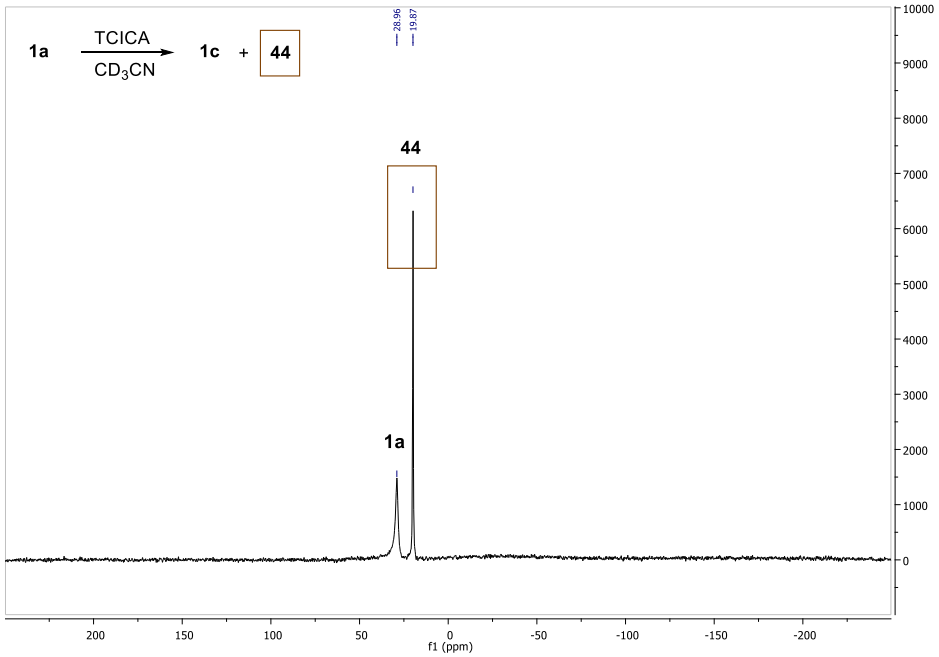


(b) The NMR experiment was carried out according to General Procedure G using [1,1'-biphenyl]-4-ylboronic acid pinacol ester **1b** (1 equiv, 0.125 mmol, 35 mg) and CuOAc (20 mol%, 0.025 mmol, 3 mg) in CD_3CN. A ^{11}B NMR was recorded and analysed, showing no boronic acid pinacol ester boronate **1i** formation.

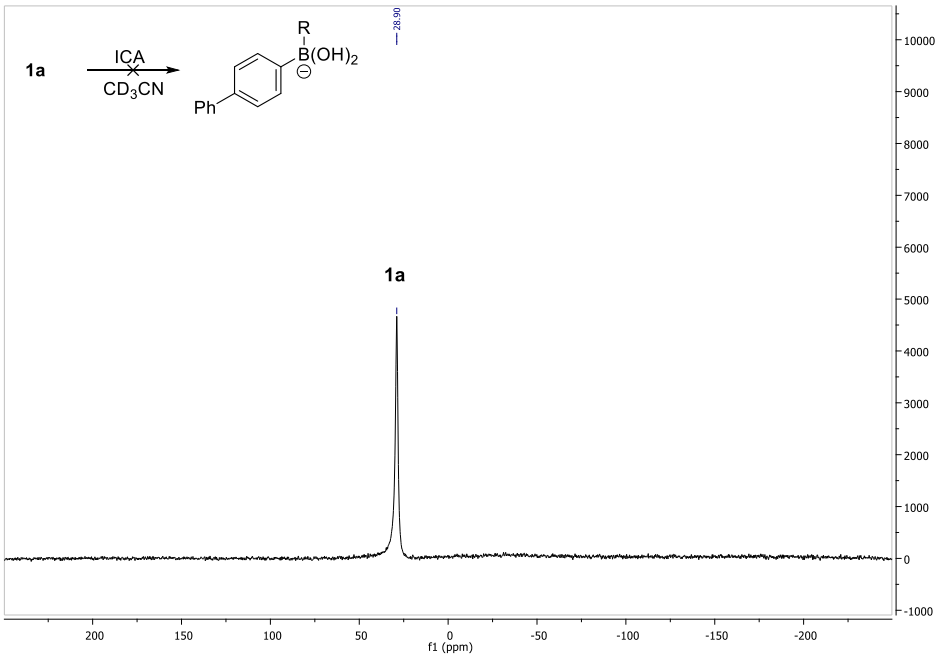


Results from Scheme 62

(a) The NMR experiment was carried out according to General Procedure G using [1,1'-biphenyl]-4-ylboronic acid **1a** (1 equiv, 0.125 mmol, 25 mg) and TCICA (0.67 equiv, 0.084 mmol, 20 mg) in CD_3CN. A ^{11}B NMR was recorded and analysed, showing no formation of boronic acid boronate-type species, only $B(OH)_3$ **44** by-product.

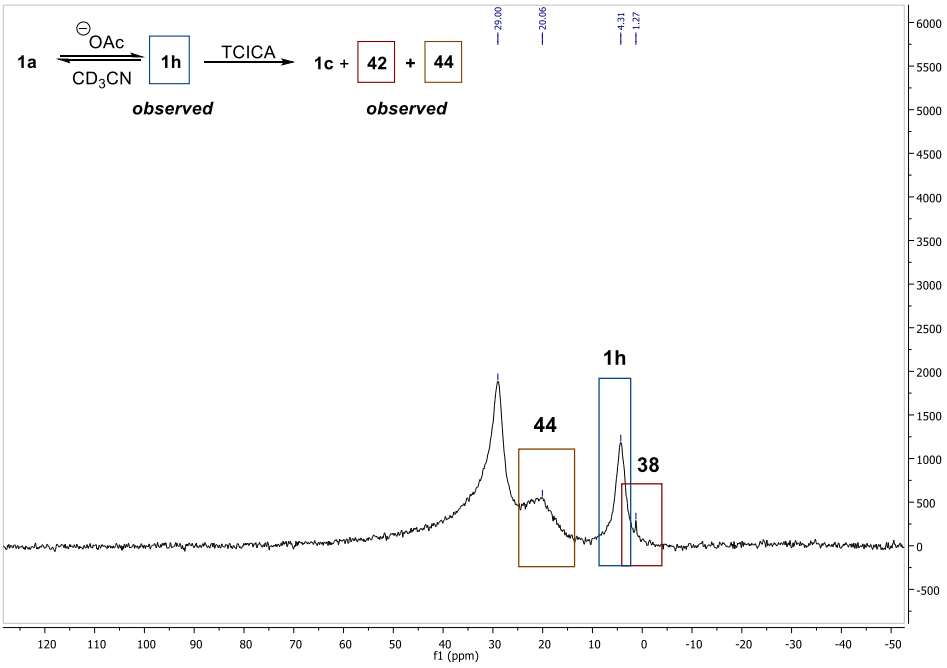


(b) The NMR experiment was carried out according to General Procedure G using [1,1'-biphenyl]-4-ylboronic acid **1a** (1 equiv, 0.125 mmol, 25 mg) and ICA (1 equiv, 0.125 mmol, 16 mg) in CD_3CN. A ^{11}B NMR was recorded and analysed, showing no formation of boronic acid boronate-type species.



Results from Scheme 64

The NMR experiment was carried out according to General Procedure G using [1,1'-biphenyl]-4-ylboronic acid **1a** (1 equiv, 0.125 mmol, 25 mg) and CuOAc (20 mol%, 0.025 mmol, 3 mg) in CD_3CN. A ^{11}B NMR was recorded and analysed, showing boronic acid boronate **1h** formation, together with the by-products $[(OR)B(OH)_3)]^-$ **42** and $B(OH)_3$ **44**.



6.7 Experimental procedures and characterisation for Section 3.3

Results from Table 16

Reactions carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), 1-naphthanylboronic acid pinacol ester (1 equiv, 0.25 mmol, 63 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg), **base** and MeCN (0.25 M, 1 mL) at rt for 4 h.

Entry	Base	X mol% (mass)	Conversion %	Selectivity 1c:2c
1	NaOAc	10 (2 mg)	90	10:1
2	KOAc	10 (3 mg)	94	14:1
3	CsOAc	10 (5 mg)	92	11:1
4	KOAc	20 (6 mg)	96	15:1
5	KOAc	50 (12 mg)	95	14:1
6	KOAc	100 (25 mg)	96	10:1

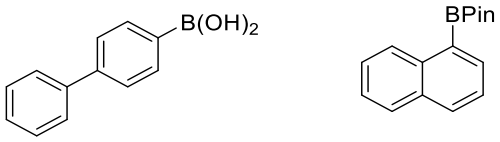
Results from Table 17

Reactions carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), 1-naphthanylboronic acid pinacol ester (1 equiv, 0.25 mmol, 63 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg), **10 mol% base** and MeCN (0.25 M, 1 mL) at rt for **time**.

Entry	10 mol% base (mass)	Time (h)	Conversion %	Selectivity 1c:2c
1	KOAc (3 mg)	4	94	13:1
2	Cs_2CO_3 (8 mg)	4	96	>99:1
3	K_2CO_3 (4 mg)	4	75	12:1
4	K_3PO_4 (5 mg)	4	83	4:1
5	Cs_2CO_3 (8 mg)	2	90	>99:1
6	Cs_2CO_3 (8 mg)	3	97	>99:1

HPLC data for products in Figure 25

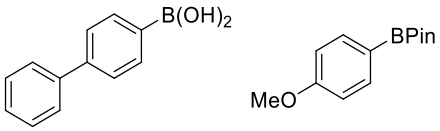
[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (quant., ratio **1c**:**2c** >99:1).

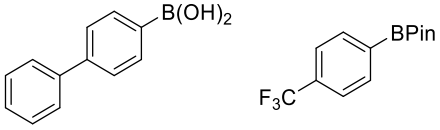
Experimental

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 4-methoxy)phenylboronic acid, pinacol ester **3b**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), 4-(methoxy)phenylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 69 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (79% conversion, ratio **1c**:**3c** 1.6:1).

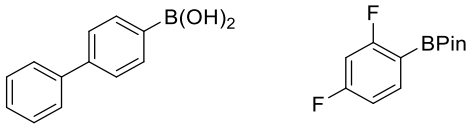
[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 4-(trifluoromethyl)phenylboronic acid, pinacol ester **4b**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), 4-(trifluoromethyl)phenylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 69 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (98% conversion, ratio **1c**:**4c** >99:1).

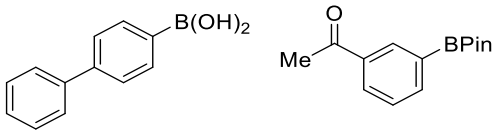
Experimental

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. naphthalen-1-ylboronic acid, pinacol ester **6b**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), (2,4-difluorophenyl)boronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 61 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (97% conversion, ratio **1c**:**6c** >99:1).

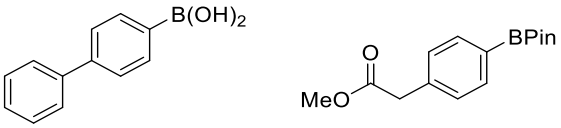
[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 3-acetylphenylboronic acid, pinacol ester **9b**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), 3-acetylphenylboronic acid pinacol ester (1.0 equiv, 0.25 mmol, 62 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (99% conversion, ratio **1c**:**9c** >99:1).

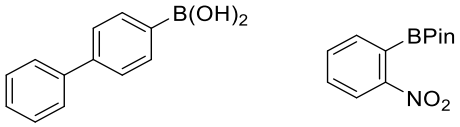
Experimental

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. methyl-4-(acetatephenyl)boronic acid pinacol ester **10b**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), methyl-4-(acetatephenyl)boronic acid pinacol ester (1.0 equiv, 0.25 mmol, 69 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (98% conversion, ratio **1c**:**10c** 5:1).

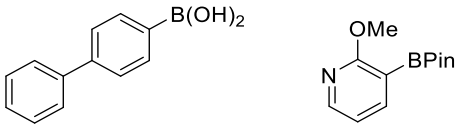
[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 2-nitrophenylboronic acid, pinacol ester **11b**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), (2,4-difluorophenyl)boronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 61 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (quant., ratio **1c**:**11c** >99:1).

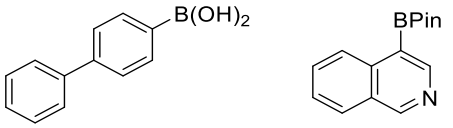
Experimental

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. (2-methoxypyridin-3-yl)boronic acid, pinacol ester **12b**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), (2-methoxypyridin-3-yl)boronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 59 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M), subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (silica gel, 5% Et_2O in petroleum ether) to give 4-chlorobiphenyl **1c** as its only product (47 mg, 99% yield, ratio **1c**:**12c** >99:1).

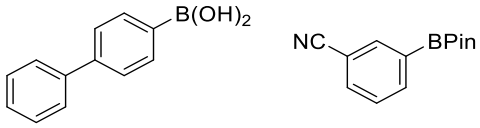
[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. isoquinolin-4-ylboronic acid, pinacol ester **13b**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), isoquinolin-4-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M), subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (silica gel, 5% Et_2O in petroleum ether) to give 4-chlorobiphenyl **1c** as its only product (45 mg, 96% yield, ratio **1c**:**13c** >99:1).

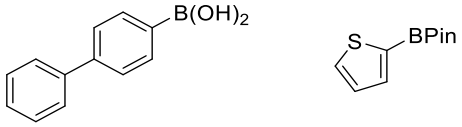
Experimental

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. 3-cyanophenylboronic acid, pinacol ester **45b**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), 3-cyanophenylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 57 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (quant., ratio **1c**:**45c** >99:1).

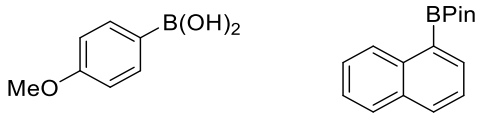
[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. thio-2-phenylboronic acid, pinacol ester **19b**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), thio-2-phenylboronic acid pinacol ester (1.0 equiv, 0.25 mmol, 53 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl **1c** as its major product (46% conversion, ratio **1c**:**19c** 4:1).

HPLC data for products in Figure 26

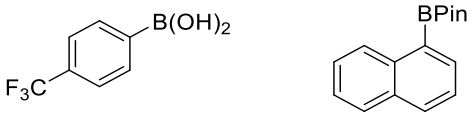
4-Methoxyphenylboronic acid **3a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



Experimental

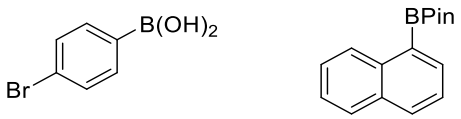
The reaction was carried out according to General Procedure H using (4-methoxyphenyl)boronic acid (1.0 equiv, 0.25 mmol, 45 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chloroanisole **3c** as its major product (quant., ratio **3c**:**2c** 33:1).

4-Trifluoromethylphenylboronic acid **4a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure H using 4-trifluoromethylphenylboronic acid (1.0 equiv, 0.25 mmol, 48 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobenzotrifluoride **4c** as its major product (29% conversion, ratio **4c**:**2c** 4:1).

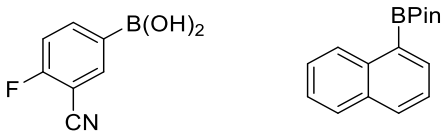
4-Bromophenylboronic acid **5a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure H using 4-bromophenylboronic acid (1.0 equiv,. 0.25 mmol, 50 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M)

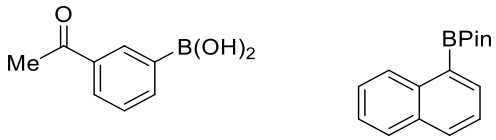
and analysed *via* the HPLC method outlined previously, indicating 4-chlorobromobenzene **5c** as its major product (69% conversion, ratio **5c**:**2c** 4:1).

4-Fluoro-3-cyanophenylboronic acid **7a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure H using 4-fluoro-3-cyanophenylboronic acid (1.0 equiv,. 0.25 mmol, 41 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating (4-fluoro-3-cyano)chlorobenzene **7c** as its major product (50% conversion, ratio **7c**:**2c** 7:1).

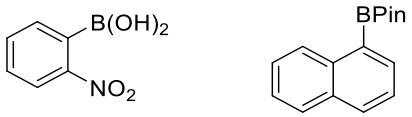
3-Acetylphenylboronic acid **9a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure H using 3-acetylphenylboronic acid (1.0 equiv,. 0.25 mmol, 41 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating (3-acetyl)chlorobenzene **9c** as its major product (34% conversion, ratio **9c**:**2c** 1.3:1).

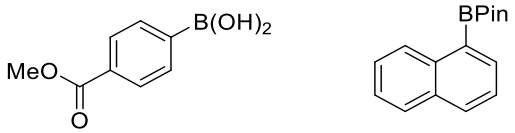
Experimental

2-Nitrophenylboronic acid **11a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure H using 2-nitrophenylboronic acid (1.0 equiv,. 0.25 mmol, 42 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 3% conversion to 2-nitrochlorobenzene **11c** product .

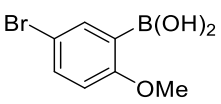
4-(Methoxycarbonyl)phenylboronic acid **15a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**

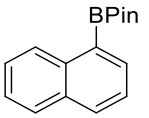


The reaction was carried out according to General Procedure H using 4-(methoxycarbonyl)phenylboronic acid (1.0 equiv,. 0.25 mmol, 45 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-(methoxycarbonyl)chlorobenzene **15c** as its major product (14% conversion, ratio **15c**:**2c** >99:1).

Experimental

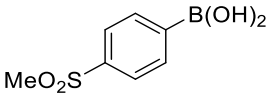
5-Bromo-2-methoxyphenylboronic acid **16a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**

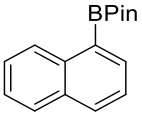




The reaction was carried out according to General Procedure H using 5-bromo-2-methoxyphenylboronic acid (1.0 equiv, 0.25 mmol, 58 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-bromo-2-chloroanisole **16c** as its major product (91% conversion, ratio **16c**:**2c** 30:1).

4-(Methylsulfonyl)phenylboronic acid **17a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**

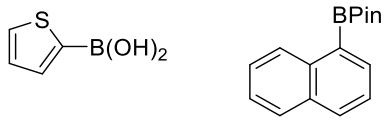




The reaction was carried out according to General Procedure H using 4-(methylsulfonyl)phenylboronic acid (1.0 equiv,. 0.25 mmol, 50 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-(methylsulfonyl)chlorobenzene **17c** as its major product (66% conversion, ratio **17c**:**2c** 9:1).

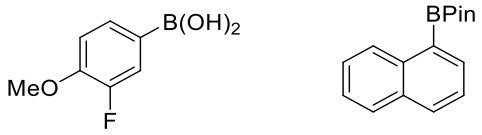
Experimental

Thiophen-2-ylboronic acid **19a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



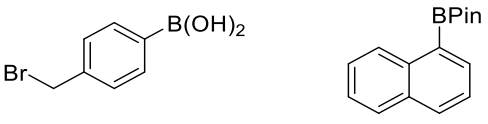
The reaction was carried out according to General Procedure H using thiophen-2-ylboronic acid (1.0 equiv,. 0.25 mmol, 32 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analyzed *via* the HPLC method outlined previously, indicating 2% conversion to 2-chlorothiophene **19c** product.

4-Methoxy-3-fluorophenylboronic acid **46a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



The reaction was carried out according to General Procedure H using 4-methoxy-3-fluorophenylboronic acid (1.0 equiv,. 0.25 mmol, 43 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chloro-2-fluoroanisole **46c** as its major product (96% conversion, ratio **46c**:**2c** 32:1).

4-(Bromomethyl)phenylboronic acid **47a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**

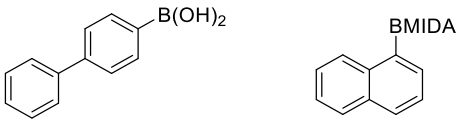


Experimental

The reaction was carried out according to General Procedure H using 4-(bromomethyl)phenylboronic acid (1.0 equiv, 0.25 mmol, 54 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv., 0.1675 mmol, 39 mg) and MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-(bromomethyl)chlorobenzene **47c** as its major product (95% conversion, ratio **47c**:**2c** 24:1).

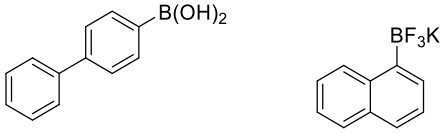
HPLC data for products in Figure 27

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. naphthalen-1-ylboronic acid MIDA ester **2d**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), naphthalen-1-ylboronic acid MIDA ester (1.0 equiv, 0.25 mmol, 71 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.4 equiv, 0.1 mmol, 23 mg), freshly distilled MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl as its major product (60% conversion, ratio **1c**:**2c** 1.5:1).

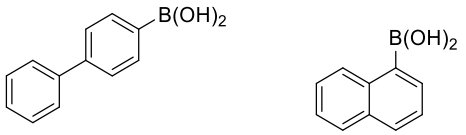
[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. potassium naphthalen-1-yltrifluoroborate **2e**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), potassium naphthalene-1-yltrifluoroborate (1.0 equiv, 0.25 mmol, 59 mg), cesium carbonate (10 mol%, 0.025

mmol, 8 mg), TCICA (0.4 equiv, 0.1 mmol, 23 mg), freshly distilled MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 1-chloronaphthalene as its major product (quant., ratio **1c**:**2c** 1:11).

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. naphthalen-1-ylboronic acid **2a**



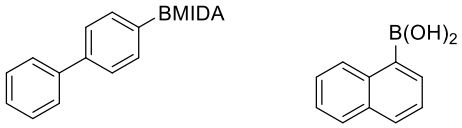
The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), naphthalen-1-ylboronic acid (1.0 equiv, 0.25 mmol, 43 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.4 equiv, 0.1 mmol, 23 mg), freshly distilled MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 4-chlorobiphenyl as its major product (81% conversion, , ratio **1c**:**2c** 27:1).

HPLC data for products in Figure 28

[1,1'-Biphenyl]-4-ylboronic acid, pinacol ester **1b** vs. naphthalen-1-ylboronic acid **2a**

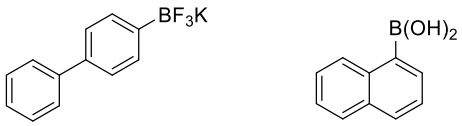
The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid pinacol ester (1.0 equiv, 0.25 mmol, 70 mg), naphthalen-1-ylboronic acid (1.0 equiv, 0.25 mmol, 43 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.67 equiv, 0.1675 mmol, 39 mg), MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 1-chloronaphthalene as its major product (99% conversion, ratio **1c**:**2c** 1:99).

[1,1'-Biphenyl]-4-ylboronic acid MIDA ester **1d** vs. naphthalen-1-ylboronic acid **2a**



The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid MIDA ester (1.0 equiv, 0.25 mmol, 77 mg), naphthalen-1-ylboronic acid (1.0 equiv, 0.25 mmol, 43 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.4 equiv, 0.1 mmol, 23 mg), freshly distilled MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 1-chloronaphthalene **2c** as its major product (93%, ratio **1c**:**2c** 1:12).

Potassium [1,1'-biphenyl]-4-yltrifluoroborate **1e** vs. naphthalen-1-ylboronic acid **2a**



The reaction was carried out according to General Procedure H using potassium [1,1'-biphenyl]-4-yltrifluoroborate (1.0 equiv, 0.25 mmol, 65 mg), naphthalen-1-ylboronic acid (1.0 equiv, 0.25 mmol, 43 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.4 equiv, 0.1 mmol, 23 mg), freshly distilled MeCN (1.00 mL, 0.25 M) and analysed *via* the HPLC method outlined previously, indicating 1-chloronaphthalene **2c** as its major product (92% conversion, ratio **1c**:**2c** 1:14).

Result from Scheme 65

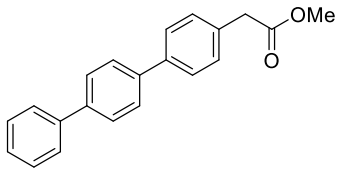
The reaction was carried out according to General Procedure I using 4-biphenylboronic acid (1.1 equiv,. 0.275 mmol, 55 mg), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (1.0 equiv, 0.25 mmol, 69 mg),

cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.34 equiv., 0.0875 mmol, 19 mg) and MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (5%-15% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (58 mg, 76% yield).

For spectral data see above characterisation data for products in Figure 20, Section 6.5.

Characterisation data for products in Figure 29

Methyl 2-([1,1':4',1''-terphenyl]-4-yl)acetate, **26**[141]

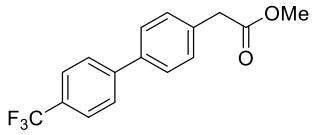


The reaction was carried out according to General Procedure I using 4-biphenylboronic acid (1.1 equiv,. 0.275 mmol, 55 mg), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (1.0 equiv, 0.25 mmol, 69 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.34 equiv., 0.0875 mmol, 19 mg) and MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (5%-15% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (58 mg, 76% yield).

For spectral data see above characterisation data for products in Figure 20, Section 6.5.[141]

Experimental

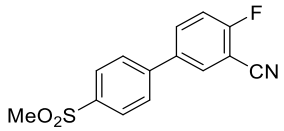
Methyl 2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)acetate, **27**



The reaction was carried out according to General Procedure I using 4-trifluoromethylphenylboronic acid (1.1 equiv,. 0.275 mmol, 52 mg), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (1.0 equiv, 0.25 mmol, 69 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.34 equiv., 0.0875 mmol, 19 mg) and MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (5%-15% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (38 mg, 52% yield).

For spectral data see above characterisation data for products in Figure 20, Section 6.5.

4-Fluoro-4'-(methylsulfonyl)-[1,1'-biphenyl]-3-carbonitrile, **31**

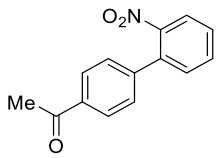


The reaction was carried out according to General Procedure I using 4-(methylsulfonyl)phenylboronic acid (1.1 equiv, 0.275 mmol, 55 mg), 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.0 equiv, 0.25 mmol, 62 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-40% ethyl acetate in petroleum ether), to give the desired product as an amorphous off-white solid (15 mg, 21% yield).

Experimental

For spectral data see above characterisation data for products in Figure 20, Section 6.5.

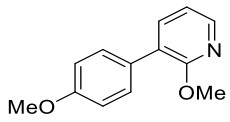
1-(2'-Nitro-[1,1'-biphenyl]-4-yl)ethan-1-one, **33**



The reaction was carried out according to General Procedure I using 4-acetylphenylboronic acid (1.1 equiv,. 0.275 mmol, 45 mg), 4,4,5,5-tetramethyl-2-(2-nitrophenyl)-1,3,2-dioxaborolane (1.0 equiv, 0.25 mmol, 62 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-20% Et_2O in petroleum ether), to give the desired product as an amorphous off-white solid (43 mg, 74% yield).

For spectral data see above characterisation data for products in Figure 20, Section 6.5.

2-Methoxy-3-(4-methoxyphenyl)pyridine, **36**

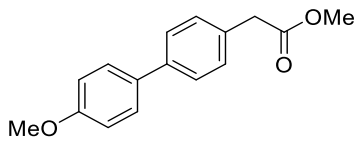


The reaction was carried out according to General Procedure I using 4-methoxyphenylboronic acid (1.1 equiv,. 0.275 mmol, 42 mg), 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.0 equiv, 0.25 mmol, 59 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-7% ethyl acetate in

petroleum ether), to give the desired product as an amorphous off-white solid (48 mg, 89% yield).

For spectral data see above characterisation data for products in Figure 20, Section 6.5.[197]

Methyl 2-(4'-methoxy-[1,1'-biphenyl]-4-yl)acetate, **49**



The reaction was carried out according to General Procedure I using 4-methoxyphenylboronic acid (1.1 equiv,. 0.275 mmol, 42 mg), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (1.0 equiv, 0.25 mmol, 69 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.34 equiv., 0.0875 mmol, 19 mg) and MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (5%-15% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (52 mg, 81% yield).

ν_{max} (neat): 2915, 1738, 1500, 1173 cm^{-1}.

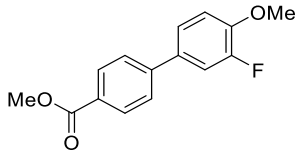
^{1}H NMR (500 MHz, DMSO-d_6): δ 7.60 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.70 (s, 2H), 3.62 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 171.6, 158.9, 138.4, 132.8, 132.2, 129.8, 127.6, 126.1, 114.4, 55.2, 51.7.

HRMS ($C_{16}H_{16}O_3$): exact calculated mass for [$M+H^+$] requires 257.1172 (100%), 258.1206 (20%); found 257. 1175 (100%), 258.1210 (20%).

Experimental

Methyl 3'-fluoro-4'-methoxy-[1,1'-biphenyl]-4-carboxylate, **50**



The reaction was carried out according to General Procedure I using 3-fluoro-4-methoxyboronic acid (1.1 equiv, 0.275 mmol, 47 mg), methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1.0 equiv, 0.25 mmol, 66 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-6% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (56 mg, 87% yield).

ν_{max} (neat): 1708, 1280, 1136, 1012, 767 cm^{-1}.

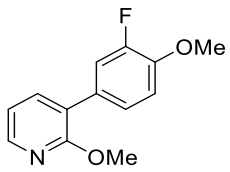
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.34 (m, 2H), 7.05 (t, *J* = 8.7 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.1, 152.8 (d, J_{C-F} = 245.4 Hz), 148.0, 144.2, 133.2 (d, J_{C-F} = 6.3 Hz), 130.4, 129.0, 126.7, 123.1, 115.1 (d, J_{C-F} = 19.2 Hz), 113.9, 56.5, 52.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -134.59

HRMS ($C_{15}H_{13}FO_3$): exact mass calculated for $[M+H]^+$ required *m/z* 261.0921 (100%), 262.0955 (20%); found *m/z* 261.0920 (100%), 262.0955 (20%).

3-(3-Fluoro-4-methoxyphenyl)-2-methoxypyridine, **51**



Experimental

The reaction was carried out according to General Procedure I using (3-fluoro-4-methoxyphenyl)boronic acid (1.1 equiv,. 0.275 mmol, 47 mg), methyl 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.0 equiv, 0.25 mmol, 59 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.34 equiv., 0.0875 mmol, 19 mg) and MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-6% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (46 mg, 78% yield).

ν_{max} (neat): 2950, 1487, 1271 cm^{-1}.

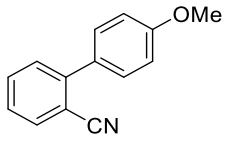
^{1}H NMR (500 MHz, DMSO-d_6): δ 8.47 (d, *J* = 2.3 Hz, 1H), 8.00 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.57 (dd, *J* = 13.0, 2.2 Hz, 1H), 7.45 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.24 (t, *J* = 8.9 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H).

^{19}F NMR (471 MHz, DMSO-d_6): δ -134.83.

^{13}C NMR (126 MHz, DMSO-d_6): δ 162.9, 151.8 (d, $^{1}J_{C\text{-}F}$ = 243.6 Hz), 146.5 (d, $^{2}J_{C\text{-}F}$ = 10.7 Hz), 144.4, 137.2, 130.0, 127.9, 122.4 (d, $^{3}J_{C\text{-}F}$ = 3.2 Hz), 114.4, 113.8 (d, $^{2}J_{C\text{-}F}$ = 18.9 Hz), 110.5, 56.1, 53.2.

HRMS ($C_{13}H_{12}FNO_2$): exact mass calculated for $[M+H]^+$ required *m/z* 234.0925 (100%), 235.0959 (15%); found *m/z* 234.0926 (100%), 235.0958 (15%).

4'-Methoxy-[1,1'-biphenyl]-2-carbonitrile, **52**



The reaction was carried out according to General Procedure I using 4-methoxyphenylboronic acid (1.1 equiv,. 0.275 mmol, 42 mg), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.0 equiv, 0.25 mmol, 57 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.34 equiv., 0.0875 mmol,

19 mg) and MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-8% ethyl acetate in petroleum ether), to give the desired product as an amorphous light yellow solid (39 mg, 75% yield).

ν_{max} (neat): 2991, 2223, 1612, 1480, 1184 cm^{-1}.

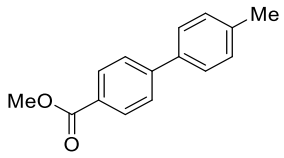
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.62 (td, *J* = 7.7, 1.3 Hz, 1H), 7.53 – 7.47 (m, 3H), 7.40 (td, *J* = 7.7, 1.1 Hz, 1H), 7.04 – 7.00 (m, 2H), 3.87 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 160.2, 145.4, 133.9, 132.9, 130.7, 130.2, 130.0, 127.2, 119.1, 114.4, 111.2, 55.5.

HRMS ($C_{14}H_{11}NO$): exact calculated mass for [$M+H^+$] requires 210.0919 (100%), 211.0951 (20%); found [$M+H^+$] 210.0920 (100%), 211.0947 (20%).

Spectroscopic data were in agreement with literature values.[198]

Methyl 4'-methyl-[1,1'-biphenyl]-4-carboxylate, **53**



The reaction was carried out according to General Procedure I using 4-tolylboronic acid (1.1 equiv,. 0.275 mmol, 37 mg), methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1.0 equiv, 0.25 mmol, 66 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-6% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (38 mg, 67% yield).

ν_{max} (neat): 2920, 1712, 1435, 1269, 1109, 817 cm^{-1}.

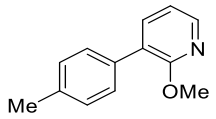
Experimental

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 3.94 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 167.2, 145.7, 138.3, 137.3, 130.2, 129.8, 128.8, 127.3, 126.9, 52.2, 21.3.

Spectroscopic data were in agreement with literature values.[199]

2-Methoxy-3-(*p*-tolyl)pyridine, **54**



The reaction was carried out according to General Procedure I using 4-tolylboronic acid (1.1 equiv,. 0.275 mmol, 37 mg), 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.0 equiv, 0.25 mmol, 59 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg) in MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-7% ethyl acetate in petroleum ether), to give the desired product as an amorphous off-white solid (31 mg, 63% yield).

ν_{max} (neat): 2920, 1581, 1460, 1242, 1010 cm^{-1}.

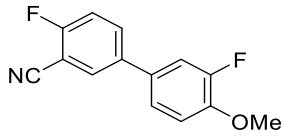
^{1}H NMR (500 MHz, DMSO-d_6): δ 8.15 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.70 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.07 (dd, *J* = 7.3, 5.0 Hz, 1H), 3.87 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6): δ 160.2, 145.4, 138.5, 136.7, 133.3, 128.8, 128.8, 123.7, 117.4, 53.2, 20.7.

Spectroscopic data were in agreement with literature values.[200]

Experimental

3',4-Difluoro-4'-methoxy-[1,1'-biphenyl]-3-carbonitrile, **55**



The reaction was carried out according to General Procedure I using 3-fluoro-4-methoxyphenylboronic acid (1.1 equiv,. 0.275 mmol, 47 mg), 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.0 equiv, 0.25 mmol, 69 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.34 equiv., 0.0875 mmol, 19 mg) and MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-8% ethyl acetate in petroleum ether), to give the desired product as an amorphous off-white solid (30 mg, 49% yield).

ν_{max} (neat): 2912, 2234, 1625, 1491, 1242 cm^{-1}.

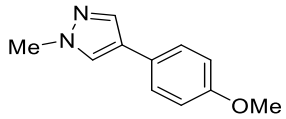
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.25 (dd, *J* = 6.1, 2.5 Hz, 1H), 8.08 (ddd, *J* = 8.9, 5.2, 2.5 Hz, 1H), 7.70-7.66 (m, 1H), 7.62 – 7.57 (m, 1H), 7.57 – 7.53 (m, 1H), 7.27 (t, *J* = 8.8 Hz, 1H), 3.89 (s, 3H).

^{19}F NMR (376 MHz, DMSO-d_6): δ -111.60, -134.73.

^{13}C NMR (101 MHz, DMSO-d_6): δ 163.0, 160.5, 153.0, 150.5, 147.4, 136.1, 133.8 (d, J_{C-F} = 8.7 Hz), 131.4, 129.8, 123.2, 117.0 (d, J_{C-F} = 19.9 Hz), 114.5, 114.3, 114.0, 56.1.

HRMS ($C_{14}H_9F_2NO$): exact calculated mass for [M+H^+] required *m/z* 246.0730 (100%), 247.0763 (20%); found *m/z* 246.0731 (100%), 247.0760 (20%).

4-(4-Methoxyphenyl)-1-methyl-1H-pyrazole, **56**



Experimental

The reaction was carried out according to General Procedure I using 4-methoxyphenylboronic acid (1.1 equiv,. 0.275 mmol, 42 mg), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.0 equiv, 0.25 mmol, 52 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.34 equiv., 0.0875 mmol, 19 mg) and MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-8% ethyl acetate in petroleum ether), to give the desired product as an amorphous off-white solid (22 mg, 45% yield).

ν_{max} (neat): 2924, 1567, 1245, 1028 cm^{-1}.

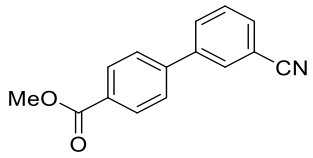
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.52 (s, 1H), 7.41 – 7.36 (m, 2H), 6.94 – 6.86 (m, 2H), 3.93 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.5, 136.6, 126.9, 126.7, 125.5, 123.2, 114.4, 55.5, 39.2.

HRMS ($C_{11}H_{12}N_2O$): exact calculated mass for [$M+H^+$] required *m/z* 189.1022 (100%), 190.1056 (10%); found *m/z* 189.1021 (100%), 190.1053 (10%).

Spectroscopic data were in agreement with literature values.[201]

Methyl 3'-cyano-[1,1'-biphenyl]-4-carboxylate, **57**



The reaction was carried out according to General Procedure I using 4-(methoxycarbonyl)phenylboronic acid (1.1 equiv,. 0.275 mmol, 50 mg), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.0 equiv, 0.25 mmol, 57 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.34 equiv., 0.0875 mmol, 19 mg) and MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the

workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-8% ethyl acetate in petroleum ether), to give the desired product as an amorphous off-white solid (23 mg, 39% yield).

ν_{max} (neat): 2924, 2224, 1715, 1249, 1101 cm^{-1}.

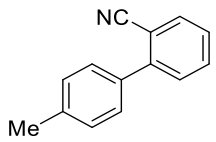
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.90 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 3.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.3, 141.5, 131.7, 131.6, 131.0, 130.6, 130.2, 130.0, 127.3, 118.7, 113.4.

HRMS ($C_{15}H_{11}NO_2$): exact calculated mass for [M+H^+] required *m/z* 238.0868 (100%), 239.0900 (10%); found *m/z* 238.0870 (100%), 239.0898 (10%).

Characterization data for products in Figure 30

4'-Methyl-[1,1'-biphenyl]-2-carbonitrile, **58**



The reaction was carried out according to General Procedure I using 4-tolylboronic acid (1.1 equiv,. 0.275 mmol, 37 mg), 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.0 equiv, 0.25 mmol, 57 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.34 equiv., 0.0875 mmol, 19 mg) and MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (5%-15% ethyl acetate in petroleum ether), to give the desired product as an amorphous off-white solid (43 mg, 89% yield).

ν_{max} (neat): 2915, 2225, 1480, 1186 cm^{-1}.

Experimental

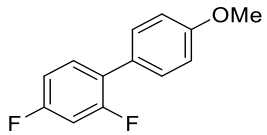
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 – 7.73 (m, 1H), 7.63 (td, *J* = 7.8, 1.1 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.42 (td, *J* = 7.7, 0.8 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 145.7, 138.9, 135.4, 133.9, 132.9, 130.1, 129.6, 128.8, 127.4, 119.0, 111.4, 21.4.

HRMS ($C_{14}H_{11}N$): exact calculated mass for [M+H$^+$] required *m/z* 194.0970 (100%), 195.1002 (20%); found *m/z* 194.0968 (100%), 195.0997 (20%).

Spectroscopic data were in agreement with literature values.[202]

2,4-Difluoro-4'-methoxy-1,1'-biphenyl, **59**



The reaction was carried out according to General Procedure I using 4-methoxyphenylboronic acid (1.1 equiv,. 0.275 mmol, 42 mg), 2-(2,4-difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.0 equiv, 0.25 mmol, 60 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.34 equiv., 0.0875 mmol, 19 mg) and MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-30% ethyl acetate in petroleum ether), to give the desired product as an amorphous white solid (46 mg, 84% yield).

ν_{max} (neat): 2927, 1602, 1490, 1242, 1033 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.41 (m, 2H), 7.36 (td, *J* = 8.7, 6.5 Hz, 1H), 7.00 – 6.96 (m, 2H), 6.95 – 6.85 (m, 2H), 3.85 (s, 3H).

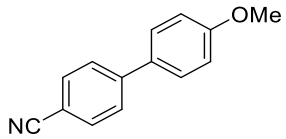
^{19}F NMR (376 MHz, $CDCl_3$): δ -112.40, -113.84.

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.2 (dd, $^1J_{C-F}$ = 237,7, $^3J_{C-F}$ = 11.4 Hz), 159.7 (dd, $^1J_{C-F}$ = 240.2, $^3J_{C-F}$ = 10.3 Hz), 159.42, 131.27 (dd, $^3J_{C-F}$ = 9.3, 4.8 Hz), 130.16 (d, $^3J_{C-F}$ = 2.5 Hz), 127.51, 114.16, 111.58 (dd, $^2J_{C-F}$ = 20.8, $^3J_{C-F}$ = 3.9 Hz), 104.57 (d, $^2J_{C-F}$ = 25.5 Hz), 104.31 (d, $^2J_{C-F}$ = 25.6 Hz), 55.49.

HRMS ($C_{13}H_{10}F_2O$): exact calculated mass for [M+H$^+$] required *m/z* 220.0700 (100%), 221.0733 (20%); found *m/z* 220.0699 (100%), 2221.0729 (20%).

Spectroscopic data were in agreement with literature values.[203]

4'-Methoxy-[1,1'-biphenyl]-4-carbonitrile, **60**



The reaction was carried out according to General Procedure I using 4-methoxyphenylboronic acid (1.1 equiv,. 0.275 mmol, 42 mg), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.0 equiv, 0.25 mmol, 57 mg), cesium carbonate (10 mol%, 0.025 mmol, 8 mg), TCICA (0.34 equiv., 0.0875 mmol, 19 mg) and MeCN (1.00 mL, 0.25 M). The reaction mixture was subjected to the workup procedure outlined previously to afford the crude product and purified by flash silica chromatography (0%-8% ethyl acetate in petroleum ether), to give the desired product as an amorphous off-white solid (51 mg, 98% yield).

ν_{max} (neat): 2991, 2223, 1612, 1480, 1247 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 – 7.67 (m, 2H), 7.66 – 7.62 (m, 2H), 7.57 – 7.52 (m, 2H), 7.03 – 6.98 (m, 2H), 3.87 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.4, 145.4, 132.7, 131.7, 128.5, 127.3, 119.2, 114.7, 110.3, 55.6.

Experimental

HRMS ($C_{14}H_{11}NO$): exact calculated mass for [M+H$^+$] requires 210.0919 (100%), 211.0951 (20%); found [M+H$^+$] 210.0919 (100%), 211.0946 (20%).

Spectroscopic data were in agreement with literature values.[204]

6.8 Experimental procedures and characterisation for Section 3.4

Results from Scheme 66

The reaction was carried out according to General Procedure J using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.3 mmol, 50 mg), NIS (1.2 equiv, 0. equiv, 67 mg) and DMC (0.25 M, 1 mL), conducted at rt for 4 h. The reaction mixture analysed *via* the HPLC method outlined previously, indicating quant. conversion to 4-iodobiphenyl **1g**.

Results from Table 18

Reactions carried out according to General Procedure J using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), NIS (1.05 equiv, 0.2625 equiv, 59 mg), **10 mol% base**, and MeCN (0.25 M, 1 mL) at rt for **time**.

Entry	10 mol% base (mass)	Time	Conversion %
1	NaOAc (2 mg)	4 h	90
2	CsOAc (5 mg)	4 h	95
3	Cs_2CO_3 (8 mg)	4 h	91
4	KOAc (3 mg)	4 h	99

5	KOAc (3 mg)	2 h	98
6	KOAc (3 mg)	1 h	94

Results from Table 19

Reactions carried out according to General Procedure J using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), **NIS**, KOAc (10 mol%, 0.025 equiv, 3 mg), and MeCN (0.25 M, 1 mL) at rt for 2 h.

Entry	Equiv of NIS (mass)	Conversion %
1	1.2 (67 mg)	98
2	1.1 (62 mg)	89
3	1.05 (59 mg)	90
4	1.02 (57 mg)	79

Results from Figure 31

Reactions carried out according to General Procedure K using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), NIS (1.05 equiv, 0.2625 equiv, 59 mg), **KOAc**, and MeCN (0.25 M, 1 mL) at rt for 2 h.

Entry	X mol% of KOAc (mass)	Conversion %
1	0 (0 mg)	40

2	5 (2 mg)	61
3	10 (3 mg)	79
4	20 (6 mg)	80
5	50 (15 mg)	82
6	100 (30 mg)	81

Results from Table 20

Reactions carried out according to General Procedure J using [1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), **NIS**, KOAc (10 mol%, 0.025 equiv, 3 mg), and DMC (0.25 M, 1 mL) at rt for **time**.

Entry	Equiv of NIS (mass)	Time (h)	Conversion (%)
1	1.05 (59 mg)	0.5	73
2	1.05 (59 mg)	1	83
3	1.05 (59 mg)	1.5	85
4	1.05 (59 mg)	2	93
5	1.1 (62 mg)	0.5	80
6	1.1 (62 mg)	1	83
7	1.1 (62 mg)	1.5	84
8	1.1 (62 mg)	2	90

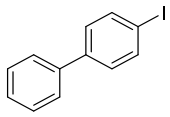
Results from Table 21

Reactions carried out according to General Procedure J using 4[1,1'-biphenyl]-4-ylboronic acid (1 equiv, 0.25 mmol, 50 mg), **Iodinating Agent**, **KOAc** (10 mol%, 0.025 equiv, 3 mg), and DMC (0.25 M, 1 mL) at rt for 2 h.

Entry	Base (mass)	Preparation of iodination agent (mass)	Conversion (%)
1	10 mol% KOAc (3 mg)	NIS (59 mg)	93
2	10 mol% KOAc (3 mg)	*in situ* [NCS (35 mg) + NaI (40 mg)]	98
3	-	NIS (59 mg)	40
4	-	*in situ* [NCS (35 mg) + NaI (40 mg)]	67

Characterisation data for products in Figure 33

4-Iodobiphenyl, **1g**



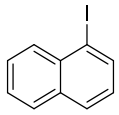
The reaction was carried out according to General Procedure K described in the previous section, using 4-biphenyl boronic acid (1.0 equiv, 0.25 mmol, 50 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 3-cyano-4-iodobiphenyl as an amorphous light yellow solid (65 mg, 92% yield).

Experimental

For spectral data see characterisation data for products in assay, Section 6.4, **page 137**.

Spectroscopic data were in agreement with literature values.[178]

1-Iodonaphthalene, **2g**



The reaction was carried out according to General Procedure K described in the previous section, using 1-naphthyl boronic acid (1.0 equiv, 0.25 mmol, 43 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 1-iodonaphthalene as a yellow liquid (52 mg, 82% yield).

υ_{max} (film): 2921, 1500, 1251, 944, 764 cm^{-1}.

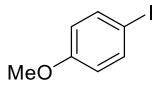
^1H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.58 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.21 – 7.16 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 137.6, 134.5, 134.3, 132.3, 129.1, 128.7, 127.9, 127.0, 126.9, 99.7.

Spectroscopic data were in agreement with literature values.[179]

Experimental

4-Iodoanisole, **3g**



The reaction was carried out according to General Procedure K described in the previous section, using 4-methoxyphenyl boronic acid (1.0 equiv, 0.25 mmol, 38 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 4-iodoanisole as an light yellow liquid (55 mg, 93% yield).

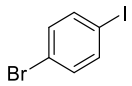
υ_{max} (film): 2837, 1865, 1485, 1240, 1028, 808 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.58-7.54 (m, 2H), 6.70-6.66 (m, 2H), 3.78 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.6, 138.4, 116.5, 82.8, 55.5.

Spectroscopic data were in agreement with literature values.[179]

4-Bromo-iodobenzene, **5g**



The reaction was carried out according to General Procedure K described in the previous section, using 4-bromophenyl boronic acid (1.0 equiv, 0.25 mmol, 50 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica

gel, 1% Et_2O in petroleum ether) to give the desired product 1-iodo-4-bromo-iodobenzene as an yellow liquid (50 mg, 71% yield).

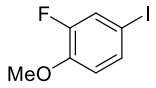
υ_{max} (neat): 2922, 1468, 1377, 998, 801 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ 7.57-7.53 (m, 2H), 7.25-7.21 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.2, 133.6, 122.4, 92.2.

Spectroscopic data were in agreement with literature values.[107]

2-Fluoro-4-iodoanisole, **46g**



The reaction was carried out according to General Procedure K described in the previous section, using 3-fluoro-4-methoxyphenyl boronic acid (1.0 equiv, 0.25 mmol, 43 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 2-fluoro-4-iodoanisole as an amorphous white solid (52 mg, 83% yield).

υ_{max} (neat): 2924, 1580, 1303, 1264 cm^{-1}.

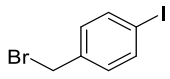
^1H NMR (500 MHz, $CDCl_3$): δ 7.39 (q, *J* = 2.0 Hz, 1H), 7.37 (d, *J* = 2.7 Hz, 1H), 6.71 (t, *J* = 8.7 Hz, 1H), 3.86 (s, 3H).

^{19}F NMR (471 MHz, $CDCl_3$): δ -132.25.

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5 (d, $^1J_{C\text{-}F}$ = 251.3 Hz), 148.1 (d, $^3J_{C\text{-}F}$ = 10.4 Hz), 133.5 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 125.3 (d, $^2J_{C\text{-}F}$ = 20.6 Hz), 115.4, 81.1 (d, $^3J_{C\text{-}F}$ = 7.1 Hz), 56.4.

Spectroscopic data were in agreement with literature values.[205]

1-(Bromomethyl)-4-iodobenzene, **47g**



The reaction was carried out according to General Procedure K described in the previous section, using 4-(bromomethyl)phenyl boronic acid (1.0 equiv, 0.25 mmol, 54 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 1-(bromomethyl)-4-iodobenzene as an amorphous off-white solid (65 mg, 87% yield).

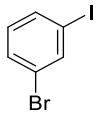
υ_{max} (neat): 2921, 1582, 1480, 1221, 1006, 827 cm^{-1}.

^1H NMR (500 Hz, $CDCl_3$): δ 7.69-7.65 (m, 2H), 7.15-7.11 (m, 2H), 4.42 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.1, 137.6, 131.0, 94.3, 32.6.

Spectroscopic data were in agreement with literature values.[206]

3-Bromo-iodobenzene, **61g**



The reaction was carried out according to General Procedure K described in the previous section, using 3-bromophenyl boronic acid (1.0 equiv, 0.25 mmol, 50 mg),

potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 3-bromo-iodobenzene as an amorphous dark yellow solid (67 mg, 94% yield).

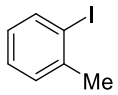
υ_{max} (neat): 2916, 1556, 1452, 1076, 770 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.9, 136.3, 131.5, 131.0, 123.3, 94.6.

Spectroscopic data were in agreement with literature values.[107]

2-Iodotoluene, **62g**



The reaction was carried out according to General Procedure K described in the previous section, using 2-methylphenyl boronic acid (1.0 equiv, 0.25 mmol, 34 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 2-iodotoluene as a colourless liquid (50 mg, 91% yield).

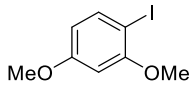
υ_{max} (film): 3049, 1563, 1454, 1015, 742 cm^{-1}.

^{1}H NMR (500 Hz, $CDCl_3$): δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 4.2 Hz, 2H), 7.01-6.63 (m, 1H), 2.43 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.5, 139.1, 129.9, 128.3, 127.5, 101.3, 28.3.

Spectroscopic data were in agreement with literature values.[107]

1-Iodo-2,4-dimethoxybenzene, **63g**



The reaction was carried out according to General Procedure K described in the previous section, using (2,4-dimethoxy)phenyl boronic acid (1.0 equiv, 0.25 mmol, 46 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 1-iodo-2,4-dimethoxybenzene as an amorphous white solid (55 mg, 84% yield).

υ_{max} (neat): 2933, 1575, 1452, 1207, 1030 cm^{-1}.

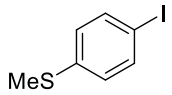
^{1}H NMR (500 MHz, DMSO-d_6): δ 3.82 (s, 3H), 3.88 (s, 3H), 6.35 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.46 (d, *J* = 2.7 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.5, 159.0, 139.3, 107.1, 99.4, 74.9, 56.4, 55.7.

Spectroscopic data were in agreement with literature values.[207]

Experimental

4-(Methylthio)iodobenzene, **64g**



The reaction was carried out according to General Procedure K described in the previous section, using 4-(methylthio)phenyl boronic acid (1.0 equiv, 0.25 mmol, 42 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 4-(methylthio)iodobenzene as an amorphous off-white solid (49 mg, 78% yield).

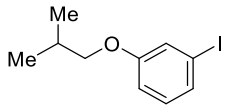
υ_{max} (neat): 2910, 1469, 1381, 1091, 801 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 2.46 (s, 3H), 6.96-7.01 (m, 2H), 7.55-7.59 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.2, 137.2, 127.8, 88.7, 15.2.

Spectroscopic data were in agreement with literature values.[208]

3-Isobutoxy-iodobenzene, **65g**



The reaction was carried out according to General Procedure K described in the previous section, using 3-isobutoxyphenyl boronic acid (1.0 equiv, 0.25 mmol, 49 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica

gel, 1% Et_2O in petroleum ether) to give the desired product 3-isobutoxy-iodobenzene as an amorphous white solid (53 mg, 77% yield).

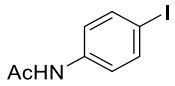
υ_{max} (neat): 2910, 1469, 1381, 1093, 801 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.25 (m, 2H), 7.02 – 6.96 (m, 1H), 6.87 (ddd, *J* = 8.4, 2.3, 1.2 Hz, 1H), 3.69 (d, *J* = 6.5 Hz, 2H), 2.15 – 2.01 (m, 1H), 1.03 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.0, 130.8, 129.7, 123.8, 114.4, 94.5, 74.7, 28.4, 19.3.

Spectroscopic data were in agreement with literature values.[209]

N-(4-Iodophenyl)acetamide, **66g**



The reaction was carried out according to General Procedure K described in the previous section, using 4-acetamidophenyl boronic acid (1.0 equiv, 0.25 mmol, 45 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL). The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product *N*-(4-iodophenyl)acetamide as an amorphous off-white solid (34 mg, 52% yield).

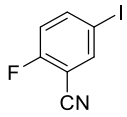
υ_{max} (neat): 2920, 1666, 1527, 1389, 815 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ 10.01 (s, 1H), 7.64 – 7.58 (m, 2H), 7.44 – 7.38 (m, 2H), 2.03 (s, 3H).

^{13}C NMR (101 MHz, DMSO-d_6): δ 168.4, 139.1, 137.3, 121.1, 86.3, 24.0.

Spectroscopic data were in agreement with literature values.[178]

2-Fluoro-5-iodobenzonitrile, **7g**



The reaction was carried out according to General Procedure K described in the previous section, using 3-cyano-4-fluorophenyl boronic acid (1.0 equiv, 0.25 mmol, 41 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 80 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 2-fluoro-5-iodobenzonitrile as an amorphous white solid (42 mg, 68% yield).

υ_{max} (neat): 2921, 1487, 1240, 1117, 823 cm^{-1}.

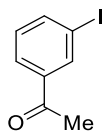
^1H NMR (500 MHz, $CDCl_3$): δ 7.87-7.94 (m, 2H), 7.00 (t, *J* = 8.7 Hz, 1H).

^{19}F NMR (471 MHz, $CDCl_3$): δ -107.42.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.16 (d, $^1J_{C\text{-}F}$ = 261.3 Hz), 144.10 (d, $^3J_{C\text{-}F}$ = 8.0 Hz), 141.75, 118.64 (d, $^2J_{C\text{-}F}$ = 20.0 Hz), 112.43, 86.81.

Spectroscopic data were in agreement with literature values.[210]

3-Iodoacetophenone, **9g**



Experimental

The reaction was carried out according to General Procedure K described in the previous section, using 3-acetylphenyl boronic acid (1.0 equiv, 0.25 mmol, 41 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 80 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 3-iodoacetophenone as an amorphous white solid (44 mg, 72% yield).

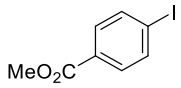
υ_{max} (neat): 2998, 1690, 1354, 1240, 758 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.28 (t, *J* = 1.7 Hz, 1H), 7.90 (ddt, *J* = 9.0, 7.6, 1.3 Hz, 2H), 7.21 (t, *J* = 7.8 Hz, 1H), 2.58 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.0, 139.0, 137.5, 130.5, 127.6, 29.9, 26.7.

Spectroscopic data were in agreement with literature values.[211]

Methyl 4-iodobenzoate, **15g**



The reaction was carried out according to General Procedure K described in the previous section, using 4-(methoxycarbonyl)phenyl boronic acid (1.0 equiv, 0.25 mmol, 45 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 80 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product methyl 4-iodobenzoate as an amorphous white solid (49 mg, 74% yield).

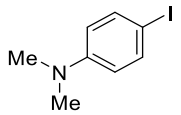
υ_{max} (neat): 2947, 1710, 1273, 1108, 755 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 – 7.78 (m, 2H), 7.76 – 7.72 (m, 2H), 3.91 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 137.9, 131.2, 129.8, 100.8, 52.4.

Spectroscopic data were in agreement with literature values.[179]

(4-Dimethylamino)iodobenzene, **67g**



The reaction was carried out according to General Procedure K described in the previous section, using 4-dimethylaminophenyl boronic acid (1.0 equiv, 0.25 mmol, 41 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 80 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 20% EtOAc in petroleum ether) to give the desired product (4-dimethylamino)iodobenzene as an amorphous dark orange solid (35 mg, 55% yield).

υ_{max} (neat): 2918, 1697, 1492, 1294, 1122 cm^{-1}.

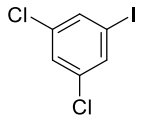
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 – 7.44 (m, 1H), 6.52 – 6.47 (m, 1H), 2.92 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 150.2, 137.7, 114.9, 77.6, 40.5.

Spectroscopic data were in agreement with literature values.[178]

Experimental

1,3-Dichloro-5-iodobenzene, **68g**



The reaction was carried out according to General Procedure K described in the previous section, using 3,5-dichlorophenyl boronic acid (1.0 equiv, 0.25 mmol, 48mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 90 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 1,3-dichloro-5-iodobenzene as an amorphous white solid (44 mg, 65% yield).

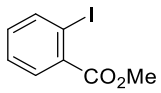
υ_{max} (neat): 3067, 1554, 1407, 1097, 847, 795 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 1.8 Hz, 2H), 7.34 (t, *J* = 1.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 135.7, 128.5, 93.8.

Spectroscopic data were in agreement with literature values.[115]

Methyl 2-iodobenzoate, **69g**



The reaction was carried out according to General Procedure K described in the previous section, using 2-(methoxycarbonyl)phenyl boronic acid (1.0 equiv, 0.25 mmol, 45 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 90 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash

chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product methyl 2-iodobenzoate as an amorphous off-white solid (42 mg, 64% yield).

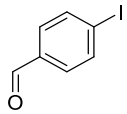
υ_{max} (neat): 2642, 1673, 1266, 1017, 736 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.99 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.40 (td, *J* = 7.7, 1.1 Hz, 1H), 7.15 (td, *J* = 7.7, 1.7 Hz, 1H), 3.93 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.6, 142.4, 142.1, 133.7, 133.3, 132.1, 128.3, 94.9.

Spectroscopic data were in agreement with literature values.[212]

4-Iodobenzaldehyde, **70g**



The reaction was carried out according to General Procedure K described in the previous section, using 4-formylphenyl boronic acid (1.0 equiv, 0.25 mmol, 38 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 90 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 4-iodobenzaldehyde as an amorphous white solid (30 mg, 52% yield).

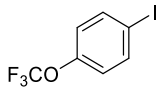
υ_{max} (neat): 2826, 1684, 1582, 1381, 1206, 805 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.61 – 7.57 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 191.6, 138.6, 135.8, 131.0, 103.0.

Spectroscopic data were in agreement with literature values.[179]

1-Iodo-4-(trifluoromethoxy)benzene, **71g**



The reaction was carried out according to General Procedure K described in the previous section, using 4-(trifluoromethoxy)phenyl boronic acid (1.0 equiv, 0.25 mmol, 52 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 90 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) to give the desired product 1-iodo-4-(trifluoromethoxy)benzene as an amorphous white solid (31 mg, 42% yield).

υ_{max} (neat): 2919, 1664, 1495, 1247, 979, 810 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, 1H, *J* = 8.1 Hz), 7.74 – 7.69 (m, 1H).

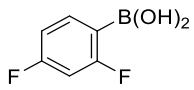
^{19}F NMR (471 MHz, $CDCl_3$): δ -58.02.

^{13}C NMR (126 MHz, $CDCl_3$): δ 142.9, 142.4, 133.6, 128.8 (d, $^3J_{C\text{-}F}$ = 8.2 Hz), 128.3 (d, $^1J_{C\text{-}F}$ = 168.8 Hz), 127.3, 116.0 (d, $^2J_{C\text{-}F}$ = 21.5 Hz).

Spectroscopic data were in agreement with literature values.[213]

Results for reactions from Figure 34

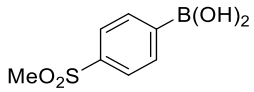
(2,4-Difluorophenyl)boronic acid, **6a**



Experimental

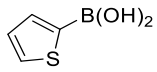
The reaction was carried out according to General Procedure K described in the previous section, using (2,4-difluorophenyl)boronic acid (1.0 equiv, 0.25 mmol, 40 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) and did not afford the desired product.

(4-(Methylsulfonyl)phenyl)boronic acid, **17a**



The reaction was carried out according to General Procedure K described in the previous section, using (4-(methylsulfonyl)phenyl)boronic acid (1.0 equiv, 0.25 mmol, 50 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) and did not afford significant ammounts of the desired product.

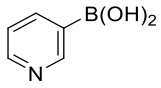
Thiophen-2-ylboronic acid, **19a**



The reaction was carried out according to General Procedure K described in the previous section, using thiophen-2-ylboronic acid (1.0 equiv, 0.25 mmol, 32 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC

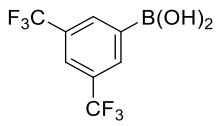
(0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) and did not afford the desired product.

Pyridin-3-ylboronic acid, **20a**



The reaction was carried out according to General Procedure K described in the previous section, using pyridin-3-ylboronic acid (1.0 equiv, 0.25 mmol, 31 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) and did not afford the desired product.

(3,5-Bis(trifluoromethyl)phenyl)boronic acid, **72a**

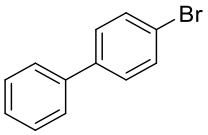


The reaction was carried out according to General Procedure K described in the previous section, using (3,5-bis(trifluoromethyl)phenyl)boronic acid (1.0 equiv, 0.25 mmol, 65 mg), potassium acetate (10 mol%, 0.025 mmol, 3 mg), *N*-chloro succinimide (1.05 equiv, 0.02625 mmol, 35 mg), sodium iodide (1.07 equiv, 0.2675 mmol, 40 mg) and DMC (0.25 M, 1 mL), conducted at 50 °C. The reaction mixture was subjected to the workup procedure outlined previously and purified by flash chromatography (silica gel, 1% Et_2O in petroleum ether) and did not afford significant ammounts of the desired product.

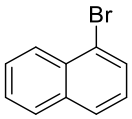
6.9 Experimental procedures and HPLC spectra for Section 5

HPLC data for products in Scheme 70

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



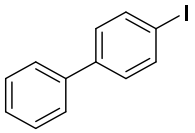
1f



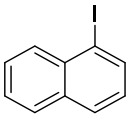
2f

The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), NBS (2.00 equiv, 0.50 mmol, 89 mg), MeCN (1.00 mL, 0.25 M) and analyzed *via* the HPLC method outlined previously, indicating 4-bromobiphenyl **1f** as its major product (quant., ratio **1f**:**2f** >99:1).

[1,1'-Biphenyl]-4-ylboronic acid **1a** vs. naphthalen-1-ylboronic acid, pinacol ester **2b**



1g



2g

The reaction was carried out according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (1.0 equiv, 0.25 mmol, 50 mg), naphthalen-1-ylboronic acid, pinacol ester (1.0 equiv, 0.25 mmol, 64 mg), copper (I) acetate (10 mol%, 0.025 mmol, 3 mg), NIS (2.00 equiv, 0.50 mmol, 112 mg), MeCN (1.00 mL, 0.25 M) and analyzed *via* the HPLC method outlined previously, indicating 4-iodobiphenyl **1g** as its major product (quant., ratio **1g**:**2g** >99:1).

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