Chemoselective Reactions of Organoboron Compounds

John James Molloy

April 2018

Chemoselective Reactions of Organoboron Compounds

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

By

John James Molloy

2018

Declaration of Copyright

This thesis is a result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed: 

Date: April 2018

Publication List

1. "*A Modular Synthesis of Functionalised Phenols Enabled by Controlled Boron Speciation*": J. J. Molloy, R. P. Law, J. W. B. Fyfe, C. P. Seath, D. J. Hirst and A. J. B. Watson, *Org. Biomol. Chem.*, 2015, **13**, 3093–3102.

2. "*Tandem Chemoselective Suzuki-Miyaura Cross-coupling Enabled by Nucleophile Speciation Control*": C. P. Seath, J. W. B. Fyfe, J. J. Molloy and A. J. B. Watson, *Angew. Chem., Int. Ed.*, 2015, **54**, 9976–9979.

3. "*Chemoselective Brown Oxidation of Aryl Organoboron Systems Enabled by Boronic Acid-selective Phase Transfer*": J. J. Molloy, T. A. Clohessy, C. Irving, N. A. Anderson, G. C. Lloyd-Jones and A. J. B. Watson, *Chem. Sci.*, 2017, **8**, 1551–1559.

4. "*Synthesis of Oxindoles and Benzofuranones via Oxidation of 2-Heterocyclic BMIDAs*": C. P. Seath, J. W. B. Fyfe, J. J. Molloy and A. J. B. Watson, *Synthesis*, 2017, **49**, 891–899.

5. "*Interrogating Pd(II) Anion Metathesis using a Bifunctional Chemical Probe: A Transmetalation Switch*": J. J. Molloy, C. P. Seath, M. J. West, C. McLaughlin, N. J. Fazakerley, A. R. Kennedy, D. J. Nelson and A. J. B. Watson, *J. Am. Chem. Soc.*, 2018, **140**, 126–130.

6. "*Contra-Thermodynamic, Photocatalytic E→ Z Isomerization of Styrenyl Boron Species: Vectors to Facilitate Exploration of 2D Chemical Space*": J. J. Molloy, J. B. Metternich, C. G. Daniliuc, A. J. B. Watson and R. Gilmour, *Angew. Chem., Int. Ed.*, 2018, DOI:10.1002/anie.201800286.

7. "*B-Protected Boronic Acids: Methodology Development and Strategic Application*": J. J. Molloy and A. J. B. Watson, in *Boron Reagents in Synthesis*, Chapter 12, 379–413.

Abstract

The Suzuki-Miyaura reaction is a landmark discovery which has revolutionised the field of palladium catalysis. Since its inception, reaction development has not only progressed the range of electrophiles which can be adopted in this transformation but has significantly enhanced the scope of organoboron reagents which can be used, cementing the reaction as the most favoured method for C-C bond formation.[1] Despite these advances, investigation around this key transformation is continuous.

A key highlight of this reaction, which is desirable to the synthetic community, is the chemoselectivity shown between, competing electrophiles, through selective oxidative addition based on electronics and bond dissociation energies, and competing nucleophiles, through selective transmetalation using boron protecting groups. The use of boron protecting groups typically adds several steps to a synthetic sequence and, as such, is an aspect which this investigation looks to address by establishing chemoselectivity between ostensibly equivalent organoboron species. In order to probe this chemoselectivity a workhorse reaction was chosen: The Brown oxidation. This work describes the development of a chemoselective oxidation of competing organoboron species with a thorough investigation into the origin of this observed chemoselectivity. This study serves as a platform for chemoselectivity in other organoboron reactions without the necessity of protecting groups.

A key mechanistic event in the SM reaction which has recently been disclosed in several mechanistic investigations,[2] is the anion metathesis step. Although this critical step has been suitably highlighted in these studies, we believe control of this event would provide a powerful, yet untapped, control vector in Pd^{II} catalysis. The following study highlights how anion metathesis can be regulated to facilitate discrimination between competing Mizoroki-Heck and Suzuki-Miyaura pathways. To interrogate this vinyl BPin, a competent nucleophile in both cross-couplings, is employed as a bifunctional chemical probe.

Ultimately, this thesis will discuss unexplored chemoselectivity of organoboron compounds and how this selectivity can be leveraged for the improvement of synthetic chemistry.

Acknowledgements

I would firstly like to thank my supervisor Dr Allan Watson who has put up with me over the last 4 years and believed in me from day one when I joined as an undergraduate in final year. The years of teaching you have provided me with have been critical in shaping me into the researcher I am today. I truly appreciate your enthusiasm and encouragement, as well as your sarcastic comments and classic one liners which pick me up when I'm feeling down. I have no doubt you will go on to bigger and better things while at St Andrews. A special mention to baby Ava and Dawn too who are awesome!

A huge thanks has to go to my fellow members of the "Boron supremacy", Jamie Fyfe, Ciaran Seath, and Julien Vantourout. Your numerous long discussions about chemistry, be it in the pub or in the office/laboratory, have been invaluable in shaping me into the synthetic chemist I am today. You guys were there always to celebrate the good times and pick me back up during the bad times.

I would also like to acknowledge the previous members of the Watson group; Calum Muir for your endless witty banter, Lisa Stevenson for always believing in me, Diana Castanga for always being there for a chat and a drink, and most of all Mairi Littleson, for always being there for me when I was feeling down or struggling with work, your charisma and drive to become a better chemist is truly inspirational. Some particular thanks has to go to Thomas Clohessy and Craig Irvine for your fantastic work on the oxidation project, your help during this study was greatly appreciated.

I would also like to thank the current members of the Watson group, Matt West (Horse), Eilidh Sood, David Cain, Dr Chao Xu, George Bell (tree beard), and Matthew Ashford. I believe all of you will grow in the group to become fantastic chemists.

I would also like to thank current and previous members of my sister group, Prof Billy Kerr's group, for being extremely welcoming as always. Your support has been excellent throughout the years, in particular Prof. Billy Kerr and Dr David Lindsay have always been extremely helpful with my work.

I would also like to thank my industrial supervisor Dr Neal Fazakerley who has been extremely helpful during discussions about chemistry.

I would also like to thank Dr Jamieson and his previous/current group members who have always been very accommodating and nice throughout my stay in the University of Strathclyde. In particular I would like to highlight Dr. Jamieson's help during my internal examinations which I am extremely grateful for. Also, a special thanks to Peter Campbell and Christopher McPherson who have been there the whole way throughout my PhD with a healthy dose of fun and sass.

I would lastly like to thank Kirsty Wilson, who has always been there for me no matter what the cause. You truly made coming into work worth while over the duration of my PhD and I am extremely grateful. On difficult days when work could be unbearable you would know how to bring me round and make me smile. I can't thank you enough for a wonderful couple of years together and wish you all the best in the future.

Abbreviations

Ac	–	Acetyl
9-BBN	–	9-borabicyclo[3.3.1]nonane
BrettPhos		2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
BPin	–	Boronic acid, pinacolato ester
CBz	–	Carboxybenzyl
CEL	–	Chan-Evans-Lam
COD	–	1,5-Cyclooctaadiene
CPME	–	Cyclopentylmethylether
DA	–	Diels-Alder
DAN	–	1,8-diaminonaphthalene
DavePhos	–	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
DCE	–	Dichloroethane
DCM	–	Dichloromethane
DFT	–	Density functional Theory
DME	–	Dimethoxyethane
DMF	–	Dimethylformamide
DMSO	–	Dimethylsulfoxide
DOS	–	Diversity oriented synthesis
dppf	–	1,1’-Bis(diphenylphosphineo)ferrocene
EDG	–	Electron donating group
EWG	–	Electron withdrawing group
HPLC	–	High-performance liquid chromatography
imid	–	Imidazole
IR	–	Infrared

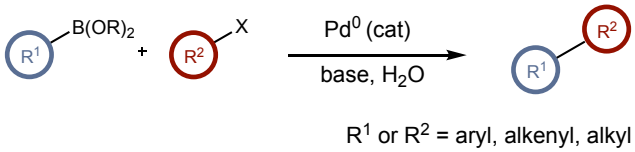
JohnPhos	–	(2-Biphenyl)di-*tert*-butylphosphine
KIE	–	Kinetic isotope effect
*m*CPBA	–	*meta*-Chloroperoxybenzoic acid
MIDA	–	*N*-Methyliminodiacetic acid
MH	–	Mizoroki-Heck
MS	–	Molecular sieves
MVK	–	Methyl vinyl ketone
NMO	–	*N*-Methylmorpholine-*N*-Oxide
NMR	–	Nuclear Magnetic Resonance
NPM	–	*N*-Phenylmaleimide
PSBA	–	Polymer-supported boronic acid
rt	–	Room temperature
SAR	–	Structure activity relationship
Sia	–	disiamylborane
SM	–	Suzuki-Miyaura
SPhos	–	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
THF	–	Tetrahydrofuran
TMEDA	–	Tetramethylethylenediamine
UV	–	Ultraviolet
XPhos	–	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Table of Contents

1 Introduction

1.1 The Suzuki-Miyaura Reaction

The formation of C-C bonds is highly desirable to synthetic chemists across many disciplines, and as a result, the Suzuki-Miyaura (SM) cross-coupling reaction has become arguably the most widely applied reaction to facilitate this bond formation since its inception in 1979.[3] This landmark transformation was suitably recognised in 2010 when Akira Suzuki, one of the two pioneers of this reaction, was awarded the Noble prize in chemistry in 2010. The reaction is a palladium mediated process involving the coupling of an sp^2 or sp^3 nucleophilic organoboron component with an electrophilic sp^2 or sp^3 halide or pseudo halide most often under aqueous basic reaction media (Scheme 1).



Scheme 1: The Suzuki-Miyaura reaction

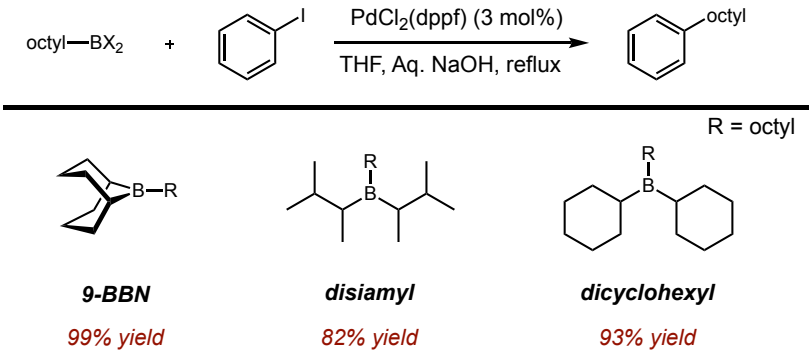
Since the initial discovery by Suzuki and Norio Miyaura, research surrounding the reaction has been continuous in both an industrial and academic setting. Reaction development has led to milder reaction conditions, enhanced reaction rates, and a substantial increase in functionalities tolerated in the transformation. A key highlight of the reaction, indicative of its high uptake in drug discovery, is the use of a relatively benign organoboron reagent as the nucleophilic component. This avoids the use of potentially toxic or highly reactive nucleophiles employed in analogous cross-coupling protocols such as the Stille (organotin), Negishi (organozinc), and Kumada (Gringard reagents) cross-coupling reactions. In medicinal research, where only parts per million quantities of toxic species are tolerated in drug candidates,[4] application of the reaction has been substantial, where greater than 40% of C-C bonds are formed via this transformation.[1,5] Despite the fundamental advances in application over the years, the complex mechanism at hand continues to pose significant questions and remains to be a focus of investigation in academia.

1.2 Boron Reagents in the Suzuki-Miyaura Reaction

The SM reaction possesses many variables which can be suitably adjusted to improve reactivity in tailored systems, such as reaction media, base, palladium catalyst, and choice of ligand. Despite often being overlooked, the organoboron reagent employed in this transformation can significantly affect reagent degradation, competing side reactions, reaction rate, and overall conversion to desired product. This section details the individual properties of possible organoboron reagents which can be used directly in the SM cross-coupling reaction.[6] Synthesis and application of these moieties will also be discussed.

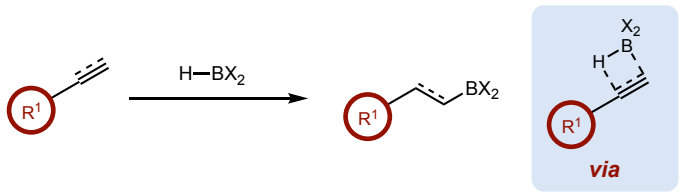
1.2.1 Organoboranes

Organoboranes consist of a tri-substituted trigonal planar neutral boron centre, where each substituent is carbon-based, and are usually derived from BH_3. Of these substituents, bulky secondary ligands such as 9-borabicyclo[3.3.1]nonane (9-BBN), disiamylborane (sia), and dicyclohexylborane are typically employed to enable differentiation between the ligand to be transferred, which is often primary alkyl or alkenyl. The difference in rates between primary and secondary ($1^y >> 2^y$) allows the desired alkyl substituent to engage the palladium centre in transmetalation. Ligands with increasing steric demand provide greater selectivity for the desired substituent which ultimately leads to higher conversion to product. As a result 9-BBN derivatives are typically employed (Scheme 2).[7]



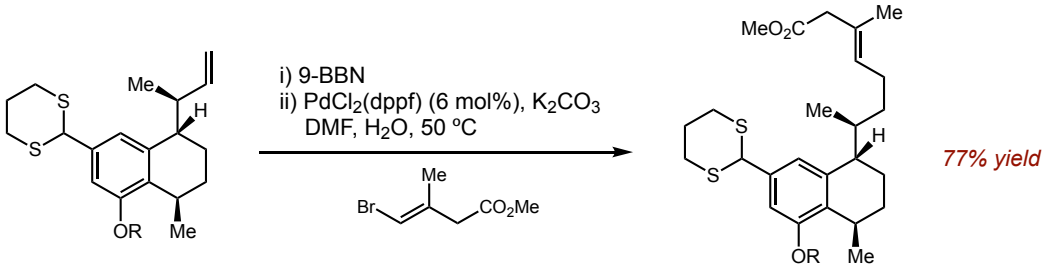
Scheme 2: Application of organoboranes in the SM reaction

The application of organoboranes in the SM reaction dates as far back to seminal studies by Suzuki and Miyaura, where they were employed in the very first study[3] and subsequent mechanistic studies.[8] The early use of these motifs can be attributed to their ease of synthesis through hydroboration from easily accessible alkenes or alkynes (Scheme 3).[9,10] The addition of B-H across an alkene or alkyne is typically rapid and proceeds with excellent regioselectivity and diastereoselectivity meaning the product output can be predicted *a priori*. The *syn*-addition of the B-H bond proceeds via σ-bond metathesis and the addition across alkynes forms specifically *trans* products. These reactions typically form the anti-Markovnikov product which is generated from avoiding energetically unfavourable steric interactions between the approaching boron substituents and the alkene or alkyne substituent, consequently bulky boron substituents such as 9-BBN provide enhanced regioselectivity.



Scheme 3: Hydroboration of alkenes and alkynes

A two-stage, hydroboration/cross-coupling protocol enables the user to rapidly couple two distinct fragments together. Since the initial discovery, this technique has been employed to construct biologically relevant targets as well as natural products.[6] In 1991, Uemura and coworkers employed a two-stage hydroboration/cross-coupling strategy towards the synthesis of diterpenoid, (±)-dihydroxyserrulatic acid, a natural product with known anti-inflammatory activity (Scheme 4).[11]



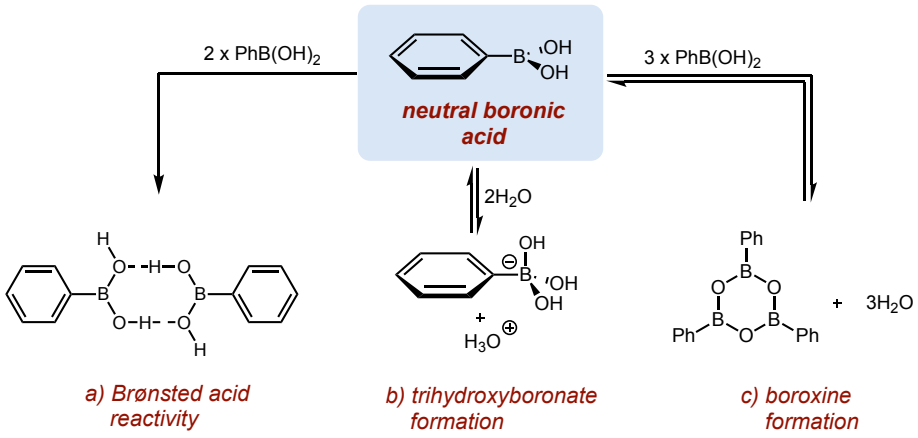
Scheme 4: A two-stage hydroboration/cross-coupling protocol towards the synthesis of (±)-dihidroxyserrulatic acid

Despite being classically employed in SM cross-coupling reactions, the use of organoboranes has diminished as reaction development has progressed. This can be mainly attributed to stability issues faced with the highly electrophilic Lewis acidic boron centre, which can partake in side reactions and, ultimately, leads to reagent degradation. Aerobic oxidation can often be problematic with these motifs and as a result organoboranes are typically employed in degassed solvents in an inert atmosphere.[12] Additionally, dehydroboration as well as protodeboronation in protic solvents can affect reagent integrity.[13] Due to their inherent instability, organoboranes are less readily available from commercial vendors in comparison to analogous organoboron reagents such as boronic acids and esters, which has seen their uptake in the reaction decline. Despite this, organoboranes have played a significant role in the history of the SM reaction and continue to be favourable for the intermolecular and intramolecular cross-coupling of alkyl nucleophiles via a two-stage hydroboration/cross-coupling protocol.[6]

1.2.2 Boronic Acids

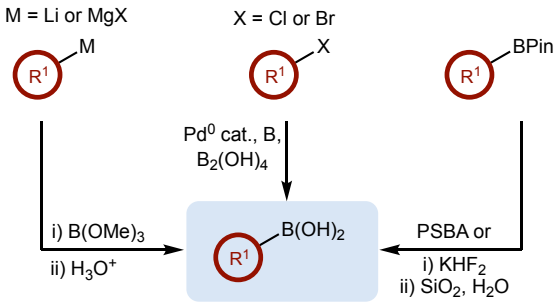
Shortly after the initial discovery, in 1981, boronic acids were shown to be competent nucleophiles in the SM reaction.[14] Boronic acids in their neutral form consist of a trivalent, trigonal planar boron centre containing a carbon-based substituent as well as two hydroxyl substituents. However, boronic acids can often exist as a complex set of equilibria based on the conditions they are exposed to.[15] The hydroxyl groups can serve as Brønsted acid donors/acceptors in the solid state as demonstrated in the crystal structure of phenyl boronic acid which can exist in dimeric (shown in Scheme 5a) and oligiomeric forms.[16] However, in the presence of water, in which boronic acids are partially soluble,[15] the Lewis acidic centre of boron dominates reactivity. From exposure to two water molecules, a hydronium ion can be liberated with concomitant formation of a tetrahedral sp^3 trihydroxyboronate (Scheme 5b).[15] This equilibria can be majorly influenced by pH, with an essentially barrier-less formation of the kinetically favoured trihydroxyboronates at higher pH.[17] Also, under anhydrous conditions, or as a result of extensive drying under vacuum, boronic acids can readily undergo entropically favoured condensation to form partially aromatic boroxines (Scheme 5c).[15] Although often unfavourable, boroxines

are unlikely to affect reactivity of the SM reaction and therefore only restrict characterisation of boronic acids during synthesis and scarcely affect reactivity.[15]



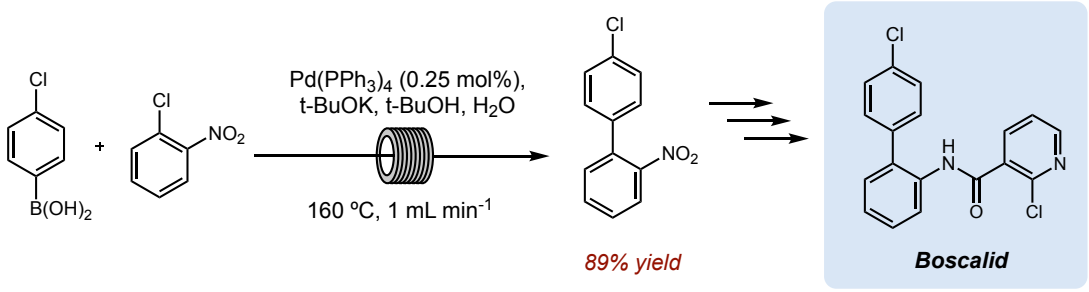
Scheme 5: Speciation of phenyl boronic acid: a) Brønsted acid donors/acceptors; b) Formation of stable trihydroxyboronate; c) Formation of partially aromatic boroxines.

Despite the complexities faced by speciation of these motifs, boronic acids have become one of the main organoboron reagents employed in the SM reaction. This may be attributed to their stability exhibited in the solid state, as well as their ease of preparation. This has ultimately contributed to the widespread availability of a diverse range of boronic acids from many commercial vendors. Boronic acids can be synthesised in a number of ways. The primary method is through the electrophilic trapping of an organometallic reagent, such as an organolithium[18] or a Grignard reagent,[19] with a boric ester, which after *in situ* hydrolysis, reveals the boronic acid (Scheme 6). The use of highly reactive reagents often requires stringent cryogenic conditions with additional limitations on functional group tolerance, however in a bid to circumvent this problem, a palladium catalysed technique, similar to the Miyaura borylation,[20] has been developed by the Molander group using bisboronic acid.[21] Boronic acids can also be generated through direct deprotection of BPins using polymer supported boronic acid (PSBA) to remove the pinacol via diol transfer.[22] Pinacol removal can also be facilitated through a two-stage process using potassium hydrofluoride to stoichiotmetrically form the potassium organotrifluoroborate,[23] subsequent hydrolysis using silica gel generates the desired boronic acid.[24]



Scheme 6: Synthesis of boronic acids

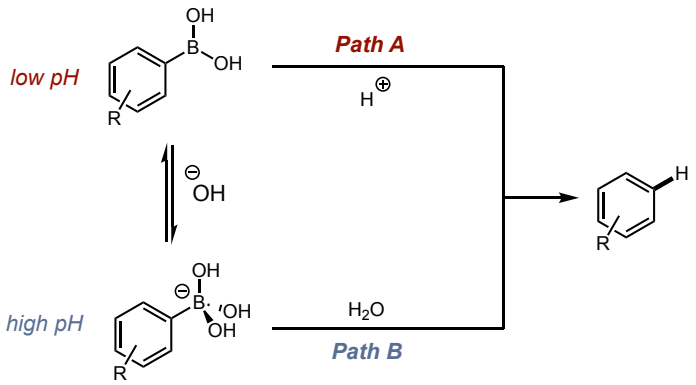
Ultimately, the increased stability and ease of synthesis has seen the uptake of boronic acids in the SM reaction increase over the years. A pertinent example of this is the largest scale SM reaction currently performed (Scheme 7). BASF have developed a multipurpose fungicide, Boscalid, in which more than 1000 tonnes is generated annually.[25] Kappe and coworkers have developed a large scale flow method for the requisite cross-coupling reaction.[26]



Scheme 7: Flow enabled large scale SM reaction towards the synthesis of Boscalid

Despite the inherent utility of boronic acids in comparison to analogous organoboron reagents there are also several undesirable properties such as oxidative and reductive homocoupling, oxidation, and protodeboronation, which plague reactivity.[27] This can often be extremely difficult to attenuate due to the complex equilibria enabled by boron speciation, which can be directly related to pH and water content.[15] Of these particular problems protodeboronation is perhaps the most pertinent and has seen significant investigation over the years. Seminal studies by Kuivila in the 1960's indicated that protodeboronation can proceed by acid-[28] and base-mediated[29] mechanisms which was extrapolated from measuring pH rate profiles (Scheme 8). In the acidic process, it was proposed proton transfer to the aromatic ring of the neutral

boronic acid was the rate determining step based on KIE experiments (path A).[28] In contrast, Kuivila proposed base mediated protodeboronation proceeded via the trihydroxyboronate which subsequently underwent direct protonolysis to form the corresponding protodeboronated product (path B).[29] This was based on Hammet analysis which suggested a build-up of positive charge on the aryl ring.



Scheme 8: Kuivila's proposed acid and base catalysed protodeboronation

Although these landmark studies provided key evidence to aid our understanding of protodeboronation they were carried out well in advance of significant improvements in spectroscopic techniques. During base mediated studies, a limited pH range was explored (pH 5–7) due to competing oxidation above pH 7 which caused interference with UV instrumentation. As such, aqueous association constants were estimated based on UV spectrophotometric analysis of acidic conditions.[29]

Since these seminal studies, the SM reaction has had a profound impact in synthetic chemistry and the application of boronic acids in aqueous basic media in these transformations is common.[30] As a result, a greater understanding of protodeboronation at higher pH would provide insight into the potential suppression of protodeboronation which could ultimately enhance SM reactivity. Buchwald and Perrin have independently investigated 2,6-disubstituted boronic acids at high pH with the latter proposing formation of a boronate anion.[31,32] Recently, Noonan and Leach have divulged a mechanistic proposal for the protodeboronation of neat boronic acids in a pre-organised hydrogen bonding framework.[33] However, perhaps the most pertinent studies have come recently from the Lloyd-Jones group.

The incorporation of heteroaromatics is of paramount importance to drug discovery and the agrochemical industry and these motifs are often delivered via a SM reaction. As heteroaryl boronic acids have been shown to rapidly undergo protodeboronation, generating a greater understanding of the fundamentals behind protodeboronation of these moieties would be extremely beneficial to the synthetic community. In 2016, Lloyd-Jones provided an in-depth study on protodeboronation of heteroaryl boronic acids.[34] Through elegant NMR studies at varying pH, in combination with DFT calculations, it was proposed that formation of zwitterionic species **1**, accelerated protodeboronation through a stabilising effect of the boric acid leaving group at neutral pH (Figure 1a). The energy barrier of an incoming water molecule (**2**), the cause of protodeboronation, was found to be almost identical to zwitterionic species **1** (Figure 1b). The study also demonstrates how the use of Lewis acid additives, such as $CuCl_2$, can supress the rate of protodeboronation through ligation to the basic nitrogen centre, forming adduct **3** (Figure 1c). This then disrupts the boric acid stabilising interaction previously seen in species **1** thereby decreasing the rate of protodeboronation.

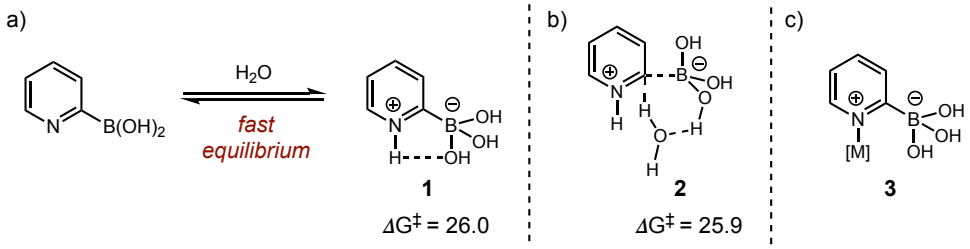
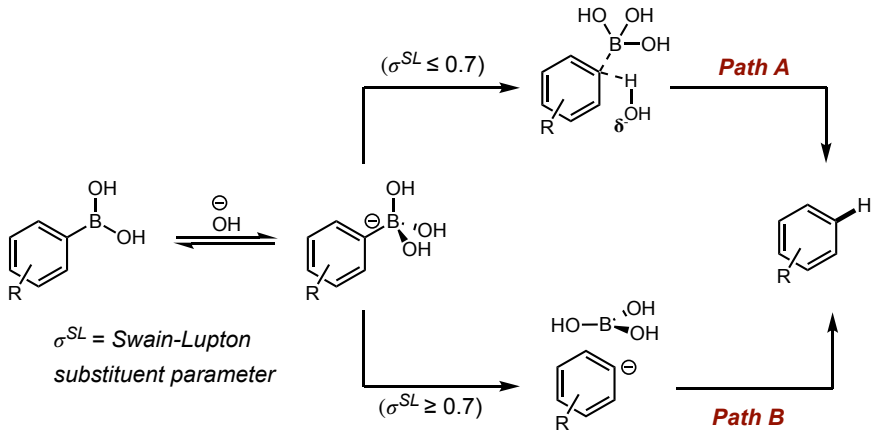


Figure 1: 2-Pyridyl boronic acid protodeboronation: a) Equilibrium formation of zwitterion transition state and associated energy; b) Zwitterion transition state on water approach and associated energy; c) Lewis acid adduct formation

Recently the Lloyd-Jones group have revisited base-catalysed protodeboronation.[35] Through the use of elegant NMR, stopped-flow IR, and rapid quench flow techniques, the group were able to monitor rapidly decaying species (when Ar = C_6F_5, $t_{1/2}$ = 3 msec) and elucidate the mechanism of protodeboronation at high pH. It was proposed that the original mechanism divulged by Kuivila (Scheme 9, path A), concerted *ipso* protonolysis from water, is operational when the combined electron demand of the substituents is below a critical point. However, it was shown that

unimolecular C-B bond cleavage was operational when electron demand is above a critical point (Scheme 9, path B). This dissociative mechanism forms an aryl anion which is immediately quenched by water.



Scheme 9: Base catalysed protodeboronation

1.2.3 Boronic Esters

With a similar analogy to carboxylic acids, substituting the hydroxyl groups of a boronic acid with alkoxy or aryloxy groups provides boronic esters. Through increased electron density via σ-bond donation of the carbon backbone, the lone pairs on the oxygen atoms can donate into the empty Lewis acidic p-orbital of boron. This provides an inherent increase in stability and, by virtue, boronic esters are significantly less Lewis acidic than their boronic acids counterparts.[6] The replacement of hydroxyl, hydrogen bond donors/acceptors with a lipophilic carbon back bone reduces polarity enabling increased solubility in aprotic solvents.[6] The reduced polarity significantly improves the handling and purification of these moieties with column chromatography and distillation of low molecular weight boronic esters common in synthesis.[6] There are a wide range of boronic esters employed in the SM reaction, however, pinacol, neopentyl glycol, and catechol boronic esters are most common due to their cost, stability, and ease of synthesis (Figure 2).

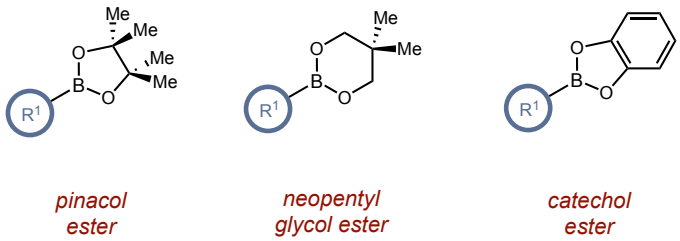
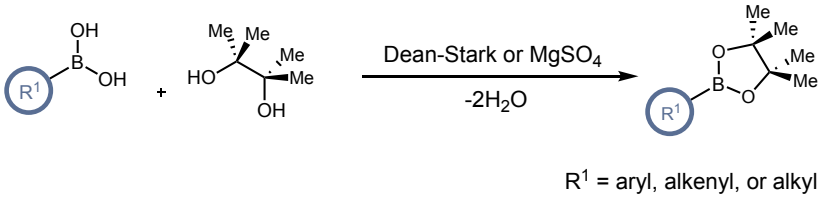


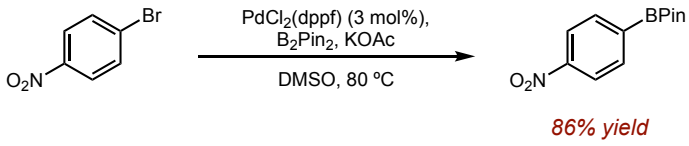
Figure 2: Examples of common boronic esters

The application and uptake of boronic esters in the SM reaction has concomitantly resulted in fundamental advances in their preparation. A common method of synthesis is via diol conjugation to boronic acids, first demonstrated by Kuivila in 1954 (Scheme 10).[36] The overall process is generally in equilibrium, although this can be driven to product formation through the loss of water via Dean-Stark or by employing desiccants such as $MgSO_4$.[15]



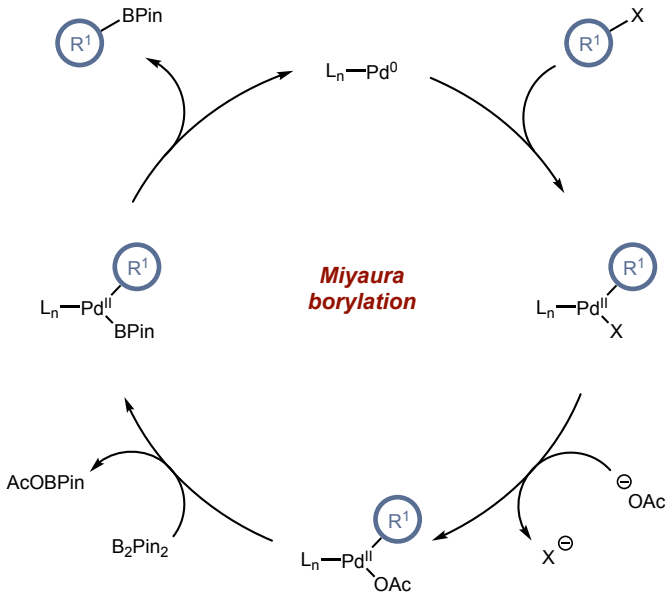
Scheme 10: Diol conjugation to boronic acids

There are numerous other methods to install boronic esters such as transition metal catalysed hydroboration to form alkenyl boronic esters,[37] iridium catalysed C-H borylation to form aryl boronic esters,[38] and direct organometallic addition to boric esters to form aryl or alkenyl boronic esters.[39] However, perhaps the most prevalent method is via the palladium catalysed Miyaura borylation of aryl and alkenyl halides or pseudo halides, first published by Miyaura in 1995 (Scheme 11).[20] The reaction tolerates a wide range of functionality due to the relatively mild conditions employed.



Scheme 11: Miyaura borylation of aryl halides

The reaction proceeds via a Pd^0/Pd^{II} mechanism (Scheme 12), similar to the SM reaction, involving oxidative addition of an organohalide, base mediated anion metathesis, transmetalation of the diboron reagent, and subsequent reductive elimination to generate the desired boronic ester and regenerate Pd^0 for further catalysis. Mechanistic studies provided evidence for the proposed oxo-palladium pathway; there was no boronate species detected throughout the reaction by ^{11}B NMR and the diboron reagent was found to react favourably with a stoichiometric Pd-alkoxide species. Towards the end of the reaction competitive SM cross-coupling of the formed BPin and organo halide starting material can be detrimental to reaction output, however, it was found that use of hard, Lewis basic bases such as potassium acetate or potassium phenoxide supressed SM reactivity.[40]



Scheme 12: Miyaura borylation mechanism

Throughout the years, boronic esters have been employed in SM reactions in key areas of synthetic chemistry such as natural product synthesis,[41] drug discovery,[42] and materials science.[43] This can be attributed to their enhanced stability in comparison to analogous organoboron reagents. In fact, boronic esters are regularly used as replacements where organoboron reagent stability is a concern.[44] A particular point of interest in academia is the comparative hydrolysis and transesterification of boronic esters as it is still unclear if hydrolysis occurs prior to transmetalation,[6] however, this will be discussed in greater detail in section 1.3.2, Transmetalation.

1.2.4 Boronic Acid Protecting Groups

Reactivity of organoboron reagents is principally driven by interaction of a nucleophile with the empty p-orbital of boron. By temporarily occupying this p-orbital with a specific ligand, the organoboron reagent can be protected from incoming nucleophiles and rendered inert to reactivity.[45,46] Such ligands can be considered as boron protecting groups which can be readily installed or removed at the user's discretion. Over the last 30 years, development surrounding boronic acid protecting groups has led to widespread application and accessibility (Figure 3).[45,46] The most commonly employed protecting groups, which will be highlighted in this section, are *N*-methyliminodiacetic acid boronates (BMIDA, **4**), potassium trifluoroborates (BF_3K, **5**), and 1,8-diaminonaphthalene derived aminoboranes (BDAN, **6**). The described "masked" boron species can be retained through standard or modified SM cross-coupling procedures, enabling chemoselective transmetalation of competing unprotected boron species. As a result, the boron protecting groups are primarily employed in iterative cross-coupling processes, however, this topic will be discussed in greater detail in section (Section 1.4.2, Chemoselective Transmetalation – Boronic Acid Protecting Groups).

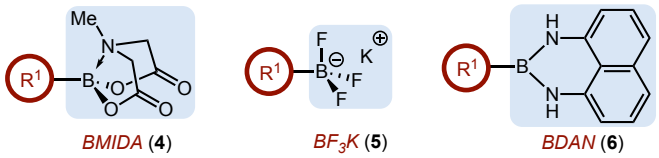
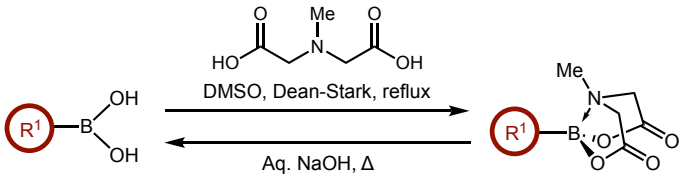


Figure 3: Boronic acid protecting groups

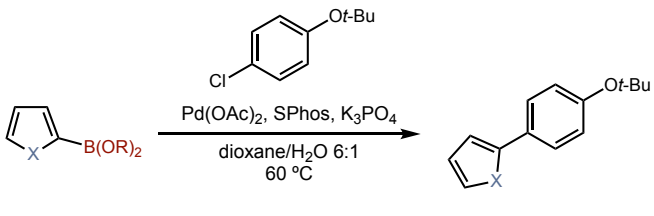
Despite being initially discovered by Contreas and Mancilla in 1986,[47] general uptake of the BMIDA protecting group did not commence until the pioneering studies by the Burke laboratory, employing BMIDAs in iterative synthesis.[48] The protecting group contains two B-O bonds which are formed from the *N*-methyliminodiacetic acid ligand. The tertiary amine backbone forms a strong dative bond with the empty p-orbital of boron resulting in quaternisation of the boron centre to sp^3 hybridised, as a result, BMIDAs tend to be free flowing, monomeric, crystalline solids which are stable to column chromatography. The BMIDA protecting group is commonly accessed through condensation of *N*-

methyliminodiacetic acid with a boronic acid (Scheme 13).[49] Although the protecting group is relatively stable in several reaction media such as weakly basic, acidic, and neutral, it can be easily removed through hydrolysis in the presence of aqueous base at elevated temperatures.[49]



Scheme 13: BMIDA formation and deprotection

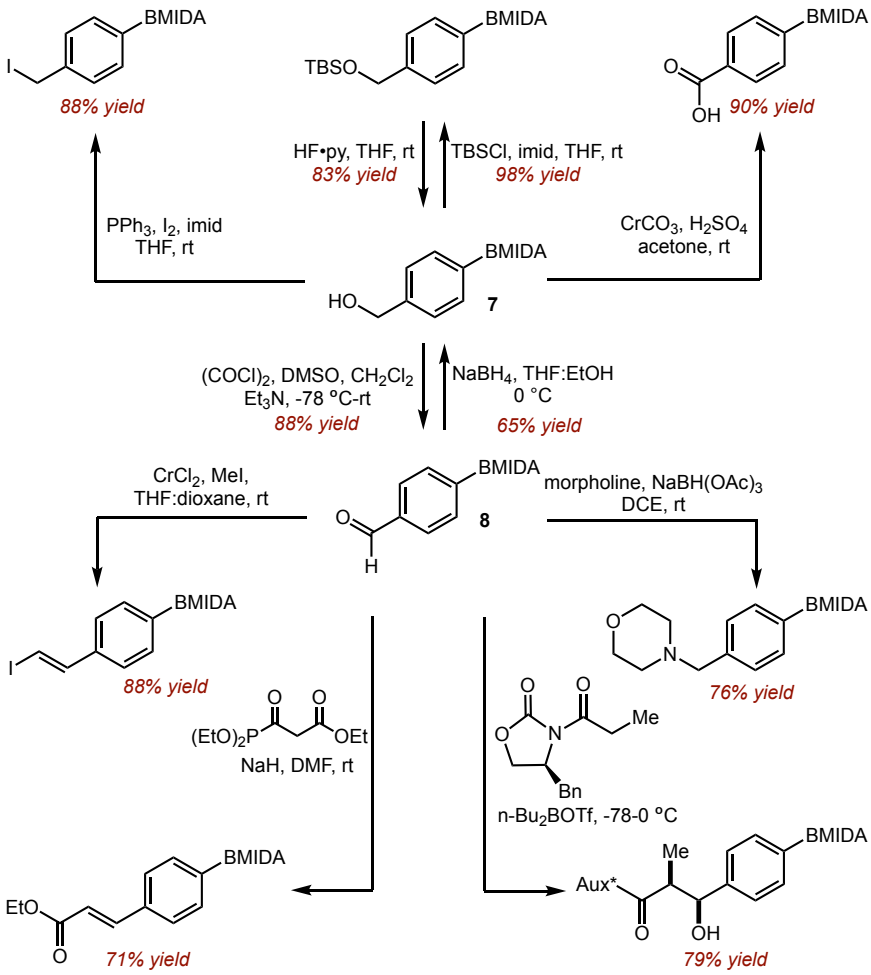
Although the hydrolysis step depicted above appears relatively elementary, the rates of hydrolysis can be drastically different based on reaction media. Recently the Lloyd-Jones, Burke, and Cheong groups have worked collectively to investigate the hydrolysis of BMIDAs, in which it was found hydrolysis could proceed via common ester hydrolysis (aqueous basic) or unexpected B-N bond cleavage (aqueous neutral).[50] A significant finding during this study was the impact of media on hydrolysis. In fully basic biphasic media, MIDA hydrolysis is slow in the bulk organic phase, with rate dependent on stirring and mass transfer rates between phases. This slow hydrolysis can be harnessed by synthetic chemists to aid in the SM reaction of unstable boronic acids (Scheme 14).[51,52] Protodeboronation of unstable boronic acids can be enhanced through self-catalysis when concentrations of the boronic acid are high.[34] In order to avoid high concentrations of boronic acid, boron protecting groups, such as BMIDAs, can be employed. Slow hydrolysis, i.e. "slow release" conditions, limit the amount of active boronic acid present in solution at one time.[27]



X	$B(OH)_2$	BMIDA
X = O	68%	94%
X = S	37%	94%
X = NBoc	61%	90%

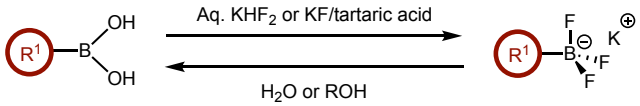
Scheme 14: "Slow release" conditions of the BMIDA protecting group improving SM

Previously, executing a synthetic sequence while retaining a boronic acid functionality throughout, was extremely rare. The advent and application of boronic acid protecting groups, such as BMIDAs, has enabled a host of synthetic manipulations which can be implemented on the "masked" boronic acid as shown by the Burke group (Scheme 15).[53] Benzyl alcohol BMIDA **7** was shown to withstand Swern and Jones oxidations, Appel halogenation, and silyl protection/deprotection. Similarly, the corresponding benzaldehyde BMIDA **8** was resistant to mild reducing conditions using $NaBH_4$, Takai and Horner-Wadsworth-Emmons olefinations, reductive amination, and Evans aldol processes. The Burke group have further demonstrated the stability of the protecting group, carrying out a range of synthetic transformations on vinyl BMIDA,[54] as well as ethynyl BMIDA.[55] In each instance, the BMIDA is retained with high fidelity. After a simple deprotection, the functionalised latent boronic acid can be revealed and employed in subsequent steps.



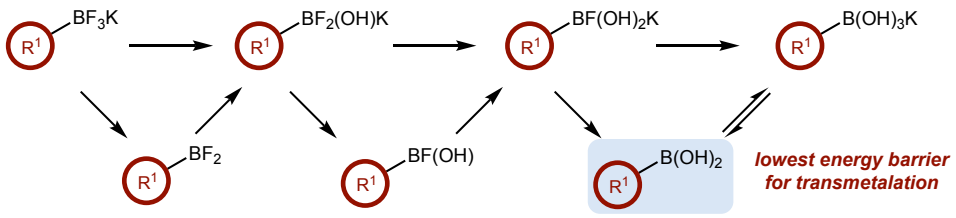
Scheme 15: Distal functionalisation of BMIDAs

Potassium trifluoroborates were first isolated and characterised by Chambers in the 1960's,[56] however, their utility in synthesis was not fully appreciated until the mid 1990's when they were investigated, predominantly by the Molander group.[57] Similar to BMIDA systems, BF_3K species serve as boronic acid protecting groups through formation of a tetrahedral boronate, with a fluoride ligand occupying the reactive boron p-orbital. BF_3K derivatives are salts and are therefore incompatible with column chromatography. Despite this, the salts are often isolated as air-stable, free-flowing, crystalline solids, by precipitation or crystallisation. There are several methods to prepare BF_3K reagents from boronic acids, with the use of aqueous KHF_2 (Vedejs)[58] and KF/tartaric acid (Lloyd-Jones)[59] the most common (Scheme 16). The boronic acid protecting group can be employed in anhydrous acidic, basic, and neutral reaction conditions but can be readily hydrolysed in the presence of water or protic solvents releasing HF. As a result, fluorophiles, such as silica gel or base, are often used to quench excess HF during deprotection.[6]



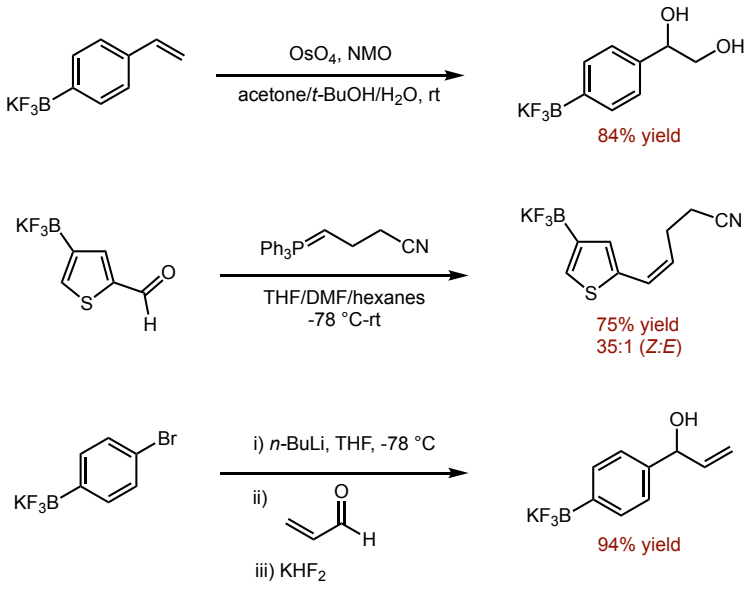
Scheme 16: BF_3K formation and deprotection

Interestingly, the application of BF_3K derivatives in the SM reaction has led to a significant improvement in yields in comparison to boronic acids.[60] As the BF_3K protecting group does not react directly in cross-coupling,[61] it was believed that this enhanced reactivity could be attributed to partial hydrolysis to form a more reactive mixed fluoro/hydroxyl species (Scheme 17).[62] However, this was later ruled out by the Lloyd-Jones group who used DFT calculations to suggest that after full hydrolysis the corresponding neutral boronic acid possessed a more favourable energy barrier for transmetalation.[62] With this information in hand, it can be rationalised that, similar to BMIDA systems, "slow release" of boronic acid through slow hydrolysis is beneficial to the SM reaction.[27] Again, this disrupts the competing side reactions associated with high concentrations of boronic acids, such as oxidation, homocoupling, and protodeboronation. This inherent stability and slow release procedure has also seen alkyl BF_3K reagents employed in typically problematic sp^3-sp^2 cross-coupling.[63]



Scheme 17: Hydrolysis of BF_3K

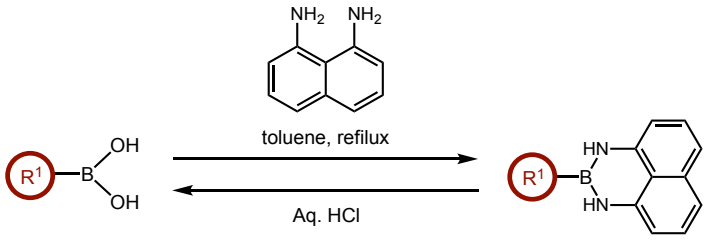
Akin to the BMIDA functionality, BF_3K species have been popularised due to stability exhibited during distal manipulations (Scheme 18). The stability of the motif has been excellently demonstrated with complete retention during dihydroxylation,[64] Wittig olefination,[65] and organometallic processes,[66] however, the latter required a KHF_2 "work up" protocol suggesting protecting group degradation during the reaction.



Scheme 18: Distal functionalisation of BF_3Ks

In contrast to previously described protecting groups, BDANs are trigonal planar.[6,46] The stability of these moieties comes from lone pair donation of the adjacent nitrogen atoms into the empty boron p-orbital donating enough electron density to provide ample protection for many common reagents. BDANs are readily prepared through condensation similar to BMIDAs (Scheme 19).[67] The protecting group is stable to basic conditions and has therefore been employed in iterative synthesis

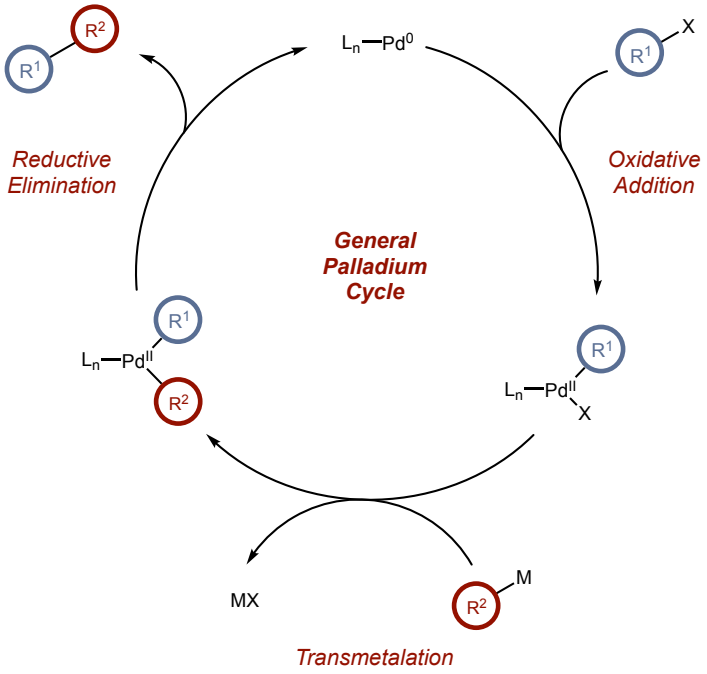
protocols pioneered by Suginome, however, BDANs are acid labile and can be easily cleaved in the presence of aqueous acid.[67]



Scheme 19: BDAN formation and deprotection

1.3 The Mechanism of the Suzuki-Miyaura Reaction

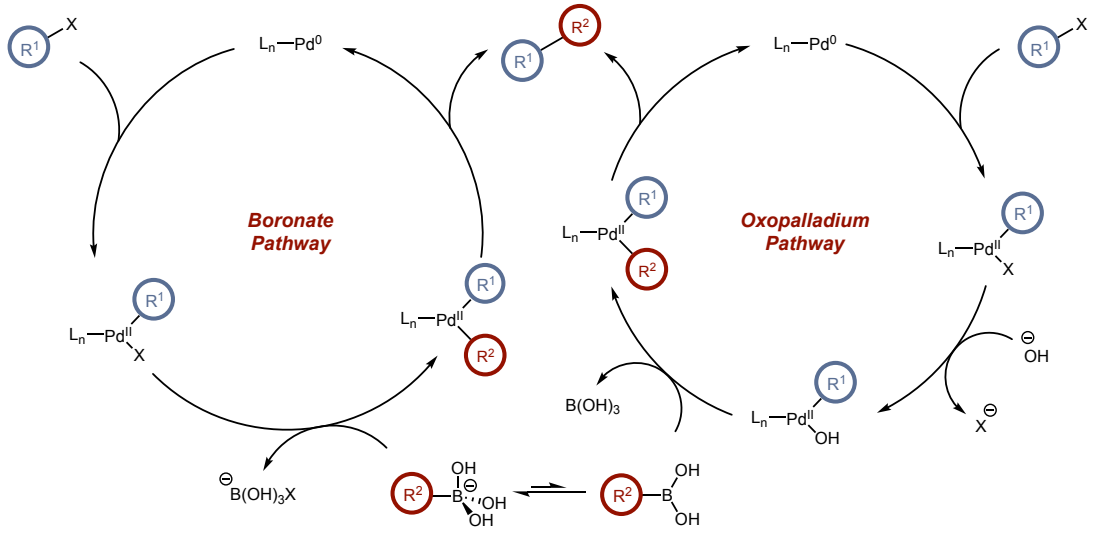
There are many palladium-catalysed reactions which have been developed throughout the years which enable C-C cross-coupling of a nucleophilic component and an electrophilic component. These reactions typically proceed by a closely related general mechanism involving oxidative addition, transmetalation, and reductive elimination (Scheme 20).



Scheme 20: General palladium catalytic cycle

Although it was proposed in seminal studies that the SM reaction proceeds via a boronate pathway, akin to general palladium catalysis, recent studies have provided

strong evidence for an alternative pathway which involves an additional anion metathesis event to form an oxopalladium species (Scheme 21). This is referred to as the oxopalladium pathway and is now firmly recognised as the principal mechanism. The following section will give an overview of the operational mechanisms in the SM reaction including the aspects of the oxidative addition step and the mechanistic dichotomy seen in the transmetalation step.

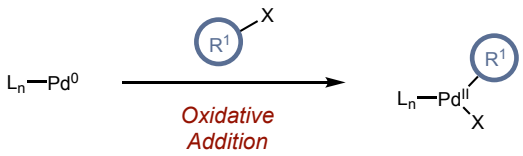


Scheme 21: Mechanism of the SM reaction

1.3.1 Oxidative Addition

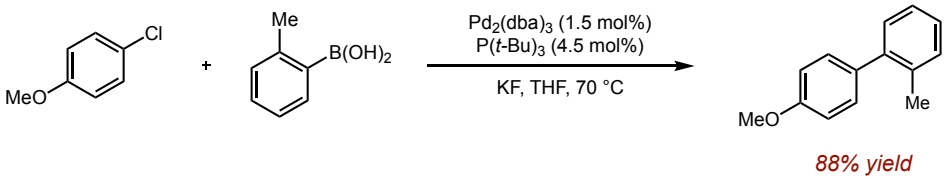
The initial step of both proposed catalytic cycles is oxidative addition, where Pd^0 oxidatively inserts into a carbon-halogen bond to form a Pd^{II} aryl halide intermediate (Scheme 22). This can often be the rate-limiting-step, typically if X = Cl, which can be directly influenced by the properties of the aryl halide or pseudo halide. In seminal studies, Suzuki established an order of reactivity which typically follows I > OTf ≥ Br >> Cl, which unsurprisingly is closely related to the corresponding bond dissociation energies.[30] Of these halides, bromides are most commonly employed in the SM reaction due to their commercial availability in comparison to iodides and triflates and their enhanced reactivity over the less reactive chlorides. Oxidative addition of poor electrophiles, such as chlorides, can be accelerated with electron withdrawing substituents.[30] However, recent advances in ligand design have

significantly improved the oxidative addition step enabling reactivity with even the most unreactive, neutral or electron rich, chloride electrophiles.[68]



Scheme 22: Oxidative addition

Prior to the late 1990's and early 2000's there were no reports of general SM conditions to facilitate the cross-coupling of unactivated aryl chlorides. However, this absence of reactivity was addressed through the introduction of electron rich trialkylphosphine ligands.[69,70] In 2000, Fu developed general SM conditions for neutral, and electron rich aryl chlorides by employing P(*t*-Bu)$_3$ as a ligand (Scheme 23).[71]



Scheme 23: Application of P(*t*-Bu)$_3$ to enable cross-coupling of unactivated chlorides

The use of bulky, electron rich, trialkylphosphines significantly increases electron density at the metal centre, generating a more nucleophilic Pd^0 species. Also, the increased steric saturation not only provides a more stable catalytic system, inhibiting deformation, but enables the generation of a significantly more reactive monoligated Pd^0 species which substantially increases the rate of oxidative addition.[72] This enhanced reactivity is attributed to the smaller size of the monoligated species in comparison to a bis-ligated palladium centre.[68] A smaller ligand sphere enables a closer approach of the aryl halide, which in turn increases reaction rate. It was demonstrated that the palladium to ligand ratio had an impact on the formation of this monoligated species, with more ligand increasing saturation and favouring bis-ligation as expected.[71] As such, palladium to ligand ratio can have a significant effect on reactivity. In pioneering studies by Hartwig, assessing the

complexities of oxidative addition with various ligands, it was found that the monoligated P(*t*-Bu)$_3$ system was preferential for aryl chlorides.[73]

Despite this fundamental advance on reactivity in the SM reaction, the application of P(*t*-Bu)$_3$ as a ligand does have disadvantages as this ligand lacks tunability and is therefore extremely difficult to modify if reactivity is inadequate.[69] The inception of monoligated, bulky, dialkylbiaryl phosphines by the Buchwald group in 1998 suitably addressed this tunability issue.[74] Since this seminal study, a wide range of ligands have been developed with subtle differences to address complications faced with specific transformations (Figure 4).[68,75] The ease of synthesis of these typically crystalline reagents, in combination with their inherent air and thermal stability, has seen them become readily available from commercial vendors allowing wider applications in laboratories around the world.

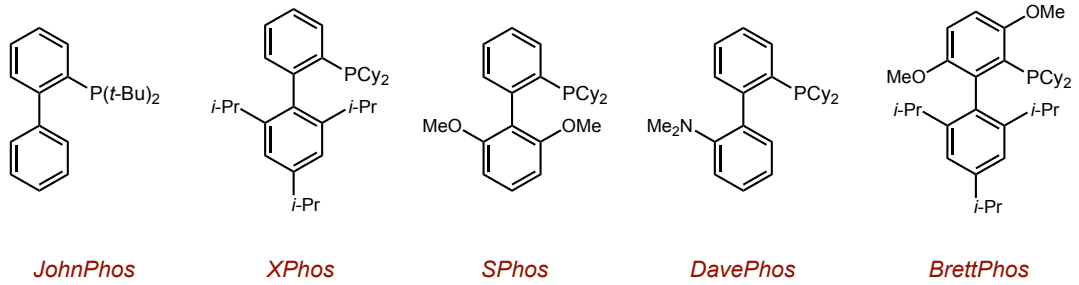


Figure 4: Buchwald ligands employed in SM

Akin to bulky trialkylphosphines, these ligands enhance oxidative addition due to their propensity to favour a monoligated species to palladium which is stabilised by their strong electron donation.[72] It has also been shown that the increase in steric bulk increases the rate of reductive elimination by promoting formation of a critical *cis*-isomer.[76] As a result of significantly enhancing the rate of two of the key steps for most Pd-catalysed processes, Buchwald ligands are now typically the ligands of choice for cross-coupling. The group provided a simplified breakdown of each substituent of the core structure to aid synthetic chemists to tune their catalyst system to suit their synthesis needs (Figure 5).[68,75]

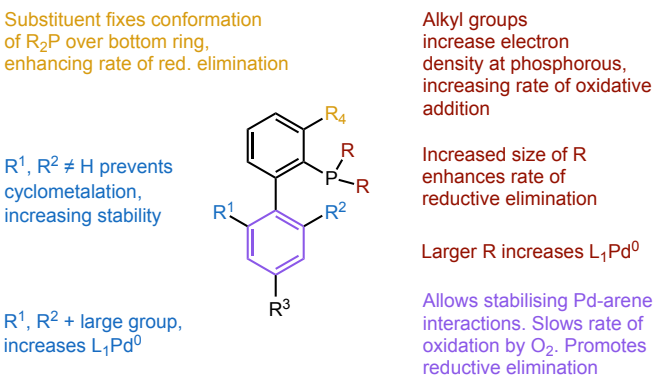
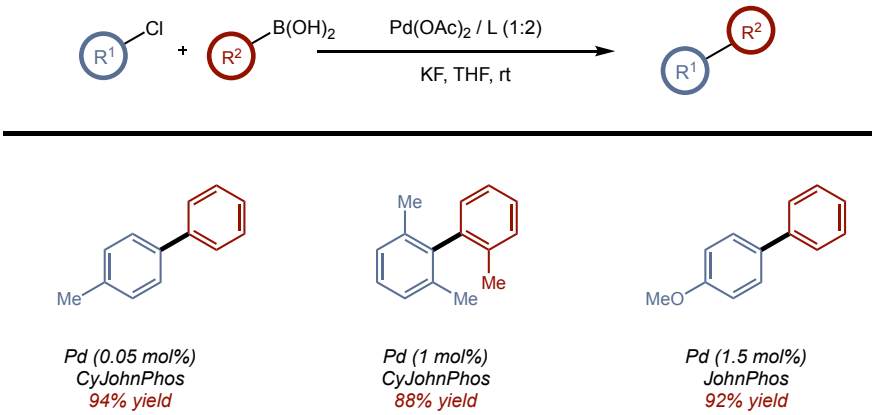


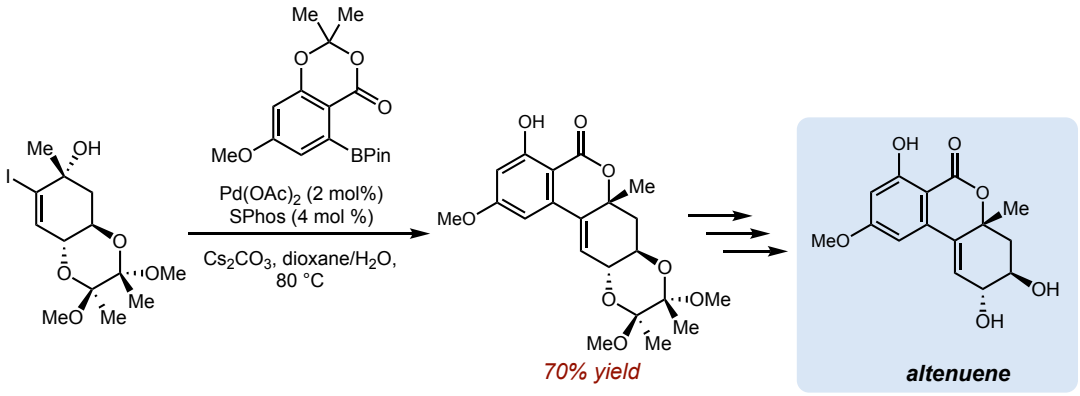
Figure 5: Structural features of Buchwald ligands and their impact on the SM reaction

The applications of Buchwald ligands in palladium catalysis have been very broad. The initial discovery enabled the cross-coupling of previously unreactive electron-rich and sterically congested aryl halides at room temperature with low catalyst loadings (Scheme 24).[77,78]



Scheme 24: Application of Buchwald ligands to enable cross-coupling of unactivated chlorides

The ligands have also been employed in SM reactions to furnish many natural products and biologically active drug targets. For example, in 2006, Podlech made use of the electron rich SPhos ligand to combine two highly functionalised precursors via a SM reaction *en* route towards the total synthesis of the natural product altenuene, a compound with known activity towards HeLa cells (Scheme 25).[79]



Scheme 25: Application of Buchwald ligands in SM towards the total synthesis of altenuene

The Buchwald group has further contributed to the field with the development of several generations of palladacyclic precatalysts (Figure 6).[80,81,82] The application of these catalysts avoids the initial activation of a Pd^{II} species with a ligand to form the catalytically active L_1Pd^0 intermediate, necessary for oxidative addition.

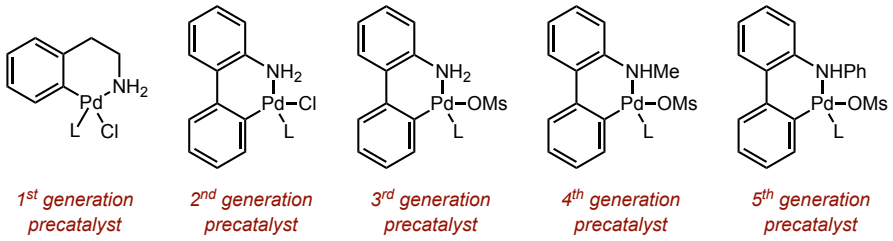
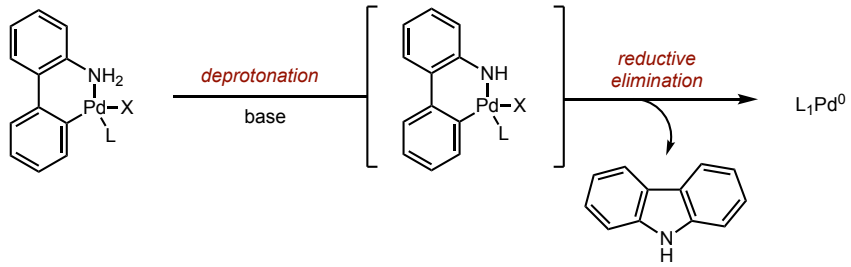


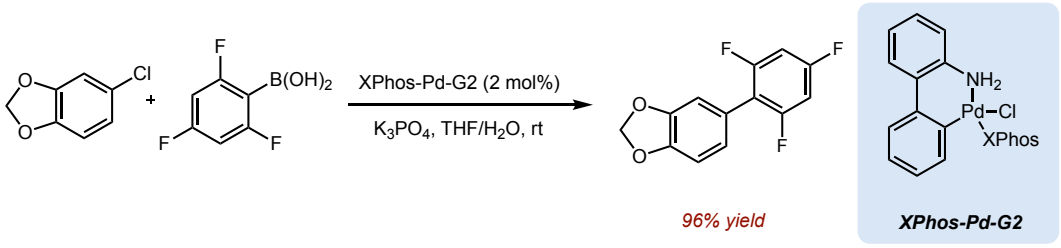
Figure 6: Buchwald precatalysts

The precatalyst enables direct formation of the active L_1Pd^0 through deprotonation and subsequent reductive elimination of the palladacycle, releasing a catalytically inert carbazole in the process (Scheme 26).[80]



Scheme 26: Precatalyst mode of activation

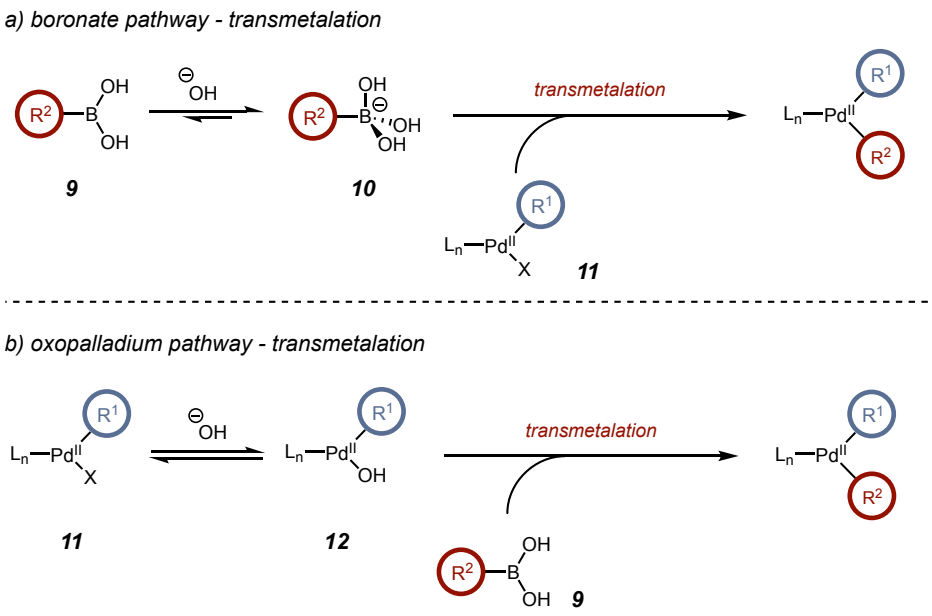
Removal of the catalyst activation step significantly enhances the reaction rate, enabling the successful SM cross-coupling of extremely unstable boronic acids before any degradative side reactions, such as protodeboronation, can compete (Scheme 27).[31] Buchwald has also shown that oxidative addition complexes can be synthesised and readily employed, stoichiometrically, in cysteine bioconjugation.[83]



Scheme 27: Application of precatalysts to improve poor SM reactions

1.3.2 Transmetalation

Although oxidative addition has been relatively well understood and significantly advanced over the years, the transmetalation step has, until recently, been an area of ambiguity. Since the initial discovery, many research groups in academia have presented compelling evidence to demonstrate a mechanistic dichotomy in the transmetalation step.[2] It has been proposed that the reaction can proceed via a boronate pathway (Scheme 28a), where a negatively charged boronate **10**, formed under basic media from a boronic acid **9**, engages a Pd^{II} halide complex **11**, or via an oxopalladium pathway (scheme 28b), where a neutral boronic acid **9**, engages an oxopalladium species **12**, formed via anion metathesis.

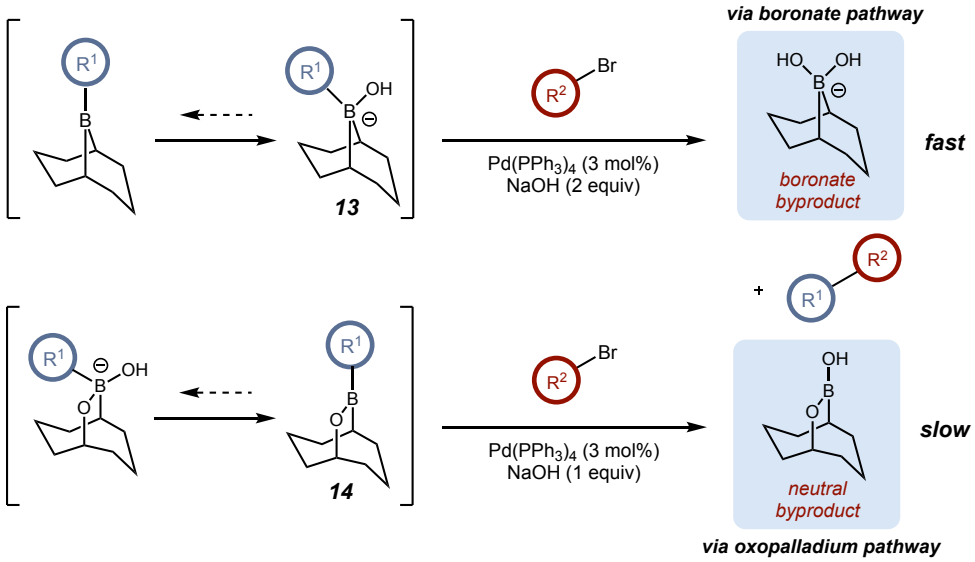


Scheme 28: SM transmetalation: a) boronate pathway; b) oxopalladium pathway

In seminal studies by Suzuki and Miyaura, it was proposed that the reaction proceeded through the boronate pathway.[3] This was proposed due to a neutral three-coordinate boron species showing no reactivity under catalytic conditions, albeit in the absence of base and water. The inactivity was attributed to the neutral species being insufficiently nucleophilic for the transmetalation step. However, on addition of an alkoxide the SM reaction was realised, and it was hypothesised that this was due to the formation of a more nucleophilic "ate" species which could aid transmetalation.

Since these pioneering studies, more groups have provided evidence to support the boronate pathway, such as Maseras and coworkers who compared both pathways computationally.[17] It was shown that formation of a boronate from a neutral boronic acid was practically barrierless and therefore favoured under basic media. The group could also not locate a suitable transition state for the associative displacement of Br with OH and proposed this as evidence in favour of the boronate pathway. Similarly, only Pd^{II} halide **11**, and the four coordinate boronate species **10** could be detected by ESI-MS while monitoring the reaction, suggesting these species are pivotal in reactivity.[84] However, it must be noted that computational studies had to employ simplified models which were inherently different to typical SM conditions in order to extract any information. Also, mass analysis can confirm the presence of key

species but cannot confirm their reactivity characteristics. The most credible evidence for the boronate pathway was divulged in 1998, by Soderquist showing that boronate **13**, reacted significantly faster than the neutral alkylborane **14** (Scheme 29).[85] Both reagents have substantially different Lewis acidities and were proposed to go through contrasting pathways, boronate and oxopalladium, respectively, based on the species they form in solution. It was also shown that the anion metathesis event was inherently slow in the oxopalladium pathway and was therefore deemed the turnover-limiting step. Despite this evidence for preferential reactivity via a boronate pathway, Soderquist was keen to emphasise that pathways are highly dependent on both the organoboron reagent employed and the reaction conditions they are employed in. To this end, many still believe that trialkylboranes proceed through a boronate pathway under certain reaction conditions due to their propensity to favour boronate formation exclusively.



Scheme 29: SM pathways of organoboron species with varying Lewis acidity

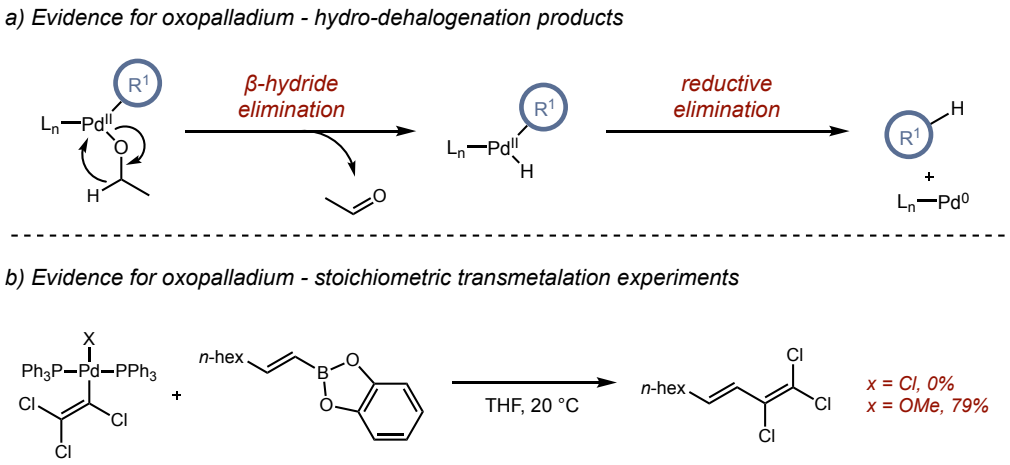
Six years after the initial report from Suzuki, the group postulated that the oxopalladium pathway could in fact be operational.[8] There were several findings which led to this:

1. SM cross-coupling is not effective when Lewis bases, such as triethylamine, are employed. This indicates hydroxide or alkoxides are necessary for reactivity.

2. The use of a preformed methyllithium tetracoordinate boronate salt reacted poorly (9% yield) in the absence of base, whereas the analogous neutral species coupled efficiently (49 - 73%) in the presence of alkoxide bases.

3. Traces of a product derived from hydro-dehalogenation were isolated. It was postulated that this was indicative of a Pd–H species formed through ß-hydride elimination of a palladium alkoxide intermediate (Scheme 30a).

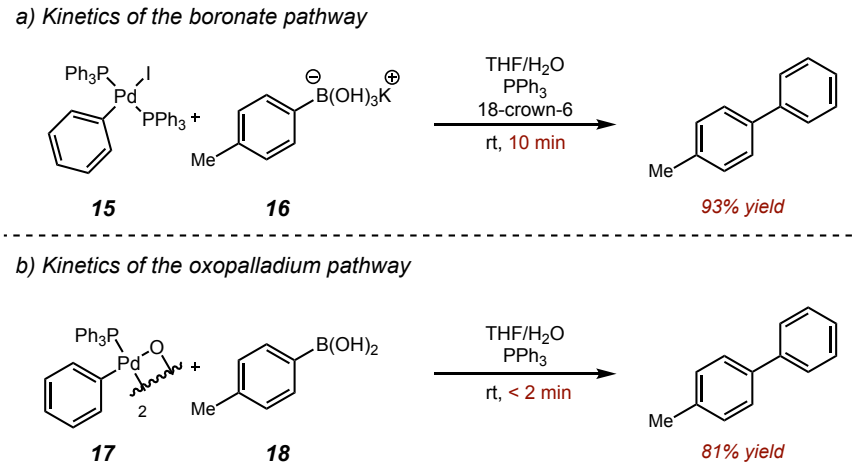
4. Stoichiometric reactions of octenyl boron reagents with isolated palladium halide and oxopalladium complexes provided further evidence suggesting oxopalladium is the operational mechanism with neutral boron species (Scheme 30b).



Scheme 30: Early evidence for oxopalladium: a) formation of hydro-dehalogenation products; b) Stoichiometric transmetalation of oxopalladium complex

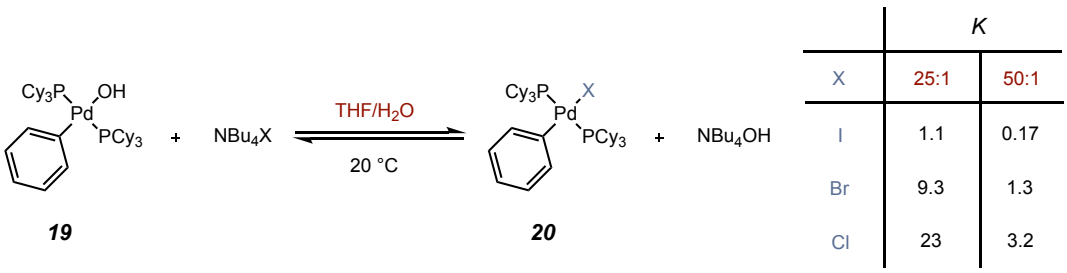
In 2011, a landmark study by Hartwig and coworkers provided substantial evidence that oxopalladium was the operational pathway in the SM reaction.[86] The group measured the rates of stoichiometric transmetalation between both the palladium halide complex **15** and the aryl trihydroxyboronate **16** (reactants in the boronate pathway), as well as oxopalladium species **17** with the neutral aryl boronic acid **18** (reactants in the oxopalladium pathway), monitoring the reaction by ^{31}P NMR

(Scheme 31). Transmetalation of **17** and **18** was found to be four orders of magnitude faster than that of **15** and **16** indicating a clear difference in reactivity in favour of oxopalladium.



Scheme 31: Kinetic measurements of the boronate and oxopalladium pathway

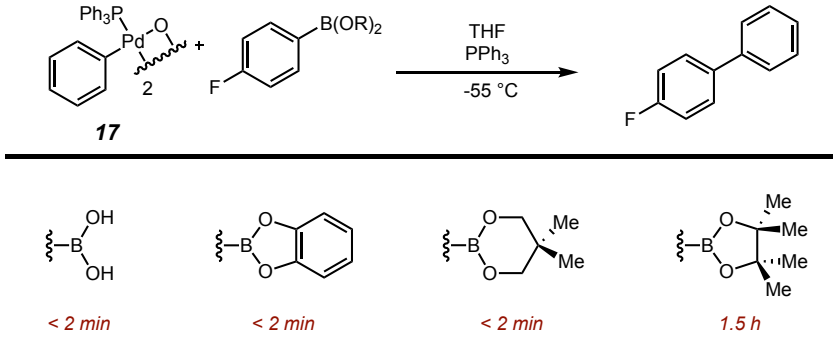
Although the above information demonstrates a clear preference for transmetalation via an oxopalladium species, for this pathway to be shown as operational, the formation of an oxopalladium and neutral boronic acid species under standard reaction conditions must be established. In a bid to address this, the group moved on to probe the complex equilibria generated in the SM reaction.[86] In the presence of water and a weak base (potassium carbonate), it was found that a 1:1 mixture of aryl trihydroxyboronate **16** and aryl boronic acid **17** were formed, confirming the presence of neutral boronic acid critical for oxopalladium transmetalation. The complex equilibrium between Pd^{II} complexes **19** and **20** was also assessed using PCy_3 as a ligand and tetrabutylammonium salts (Scheme 32). The data demonstrates that both palladium species will exist in solution, however, this is majorly influenced by water content. Interestingly, equilibria counterintuitively shifted towards the formation of oxopalladium species **19** when water quantity was decreased. This was attributed to decreased hydration of hydroxide ions. As both the neutral boronic acid and the oxopalladium species have been shown to exist under model reaction conditions, in combination with the significantly enhanced rate of these species in transmetalation, Hartwig proposes that the oxopalladium pathway is favoured.[86]



	K	
X	25:1	50:1
I	1.1	0.17
Br	9.3	1.3
Cl	23	3.2

Scheme 32: Equilibria of 19 and 20 in the presence of base and water

Additionally, the group successfully compared transmetalation of oxopalladium species **17** with a series of organoboron reagents employed in the SM reaction (Scheme 33).[86] The stark difference in reactivity suggests a substantial kinetic window between the inherently fast boronic acid in comparison to bulkier boronic esters.



Scheme 33: Comparative transmetalation of organoboron reagents

Concomitantly to the Hartwig study, Amatore and Jutand also provided clear evidence for the oxopalladium pathway using electrochemical techniques, monitoring the generation/decay of Pd species in solution.[87,88,89] Again, reactivity between the palladium halide species **15** and the trihydroxyboronate **16** was slow. However, on addition of hydroxide, the group noted formation of a rapid equilibrium between **15** and an oxopalladium species (**17**) which enabled transmetalation efficiently with a neutral boron species. Exposing the oxopalladium species to the neutral boronic acid also enabled facile transmetalation. The group were also able to define the antagonistic role of hydroxide in the SM reaction:

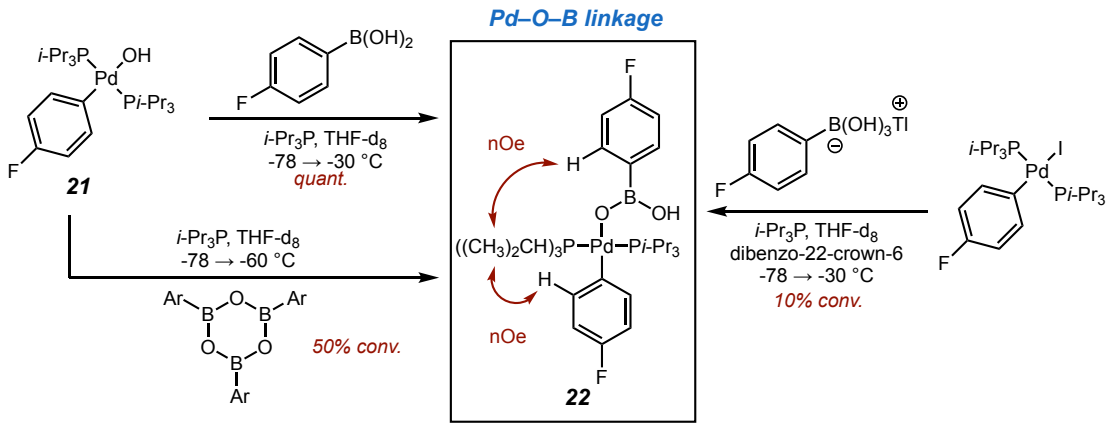
1. Hydroxide is beneficial in generating the desirable oxopalladium species from a palladium halide intermediate through anion metathesis, as previously discussed.

2. The hydroxide base can also enhance reductive elimination through a 5-coordinate intermediate forcing the leaving components into close proximity.

3. However, hydroxide can also have a detrimental role on the SM reaction. The unfavourable formation of a tetracoordinate boronate species has been shown to decrease rates in transmetalation as this cannot engage in the significantly faster oxopalladium process.

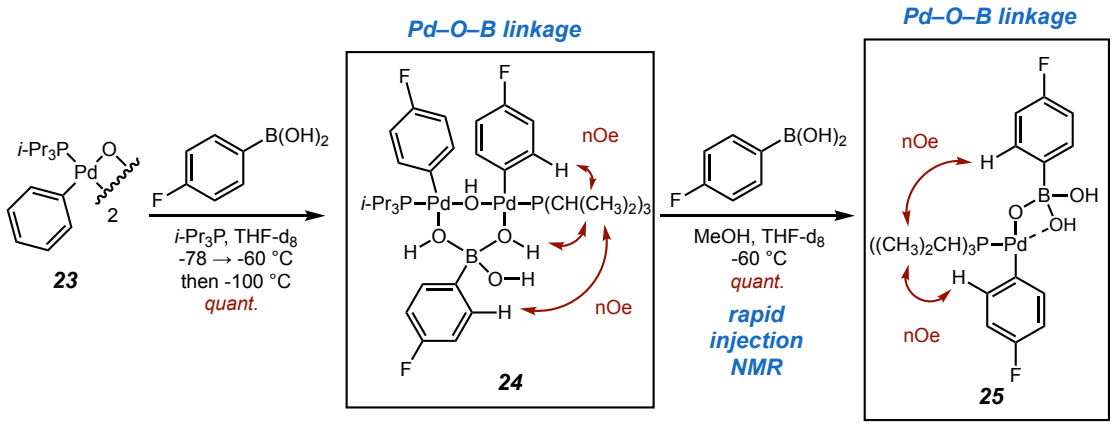
In a distinct but related study, Schmidt was able to draw the same conclusions as Hartwig, and Amatrore and Jutand while using UV analysis to monitor homocoupling of **18**.[90]

Although these landmark studies provided significant evidence to support transmetalation via an oxopalladium species, no technique could define the elusive pre-transmetalation intermediate for the transfer of the organoboron reagent to palladium. Indeed in 2013, Lloyd-Jones proposed that "specialist techniques" would be required to detect pre-transmetalation intermediates.[2] In 2016, Denmark used low temperature rapid injection NMR, independent synthesis, and kinetic studies to unambiguously define the precursors to transmetalation.[91,92] It was demonstrated that bisligated oxopalladium species **21** could form a tricoordinate boron intermediate **22** in the presence of a neutral boronic acid, confirmed by 2D NMR and independent synthesis (Scheme 34).



Scheme 34: Formation of tricoordinate transmetalation precursor containing Pd-O-B linker

However, use of monoligated oxopalladium dimer **23** led to tetracoordinate boron pretransmetalation intermediate **24** containing two palladium units (Scheme 35).[91] Further exposure to the aryl boronic acid formed tetracoordinate precursor **25**, which was significantly faster in transmetalation than precursor **24**.



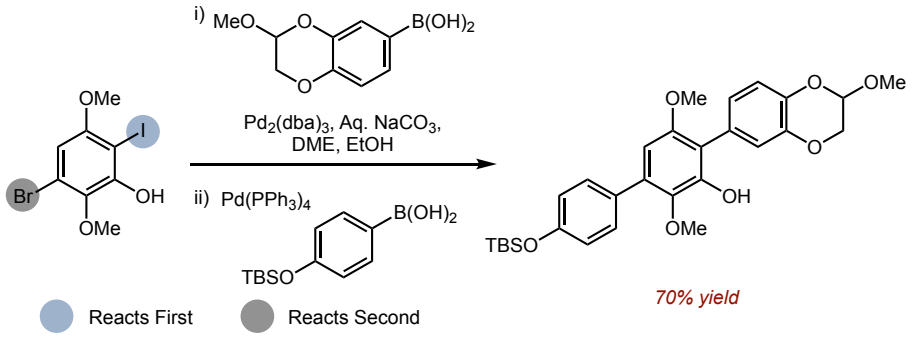
Scheme 35: Formation of tetracoordinate transmetalation precursors containing P-O-B linker

1.4 Chemoselectivity in the Suzuki-Miyaura Reaction

1.4.1 Chemoselective Oxidative Addition

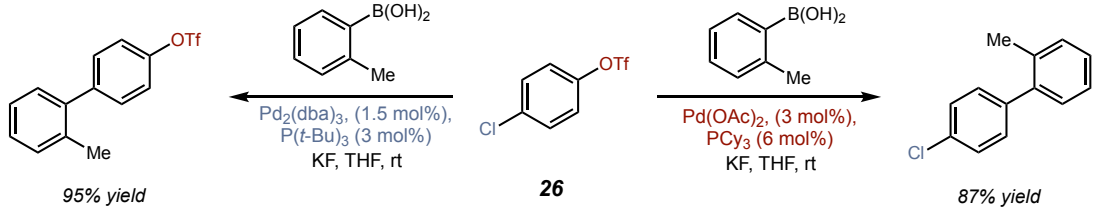
For substrates which contain more than one halide or pseudo halide capable of undergoing oxidative addition, chemoselective monofunctionalisation of these motifs is highly desirable to synthetic chemists. As previously discussed, chemoselectivity can be established based on Suzuki's initial proposal for the order of oxidative addition I > Br ≥ OTf >> Cl.[30] This enables sequential SM reactions to be performed

chemoselectively allowing complete control of site specific manipulations. In 1998, Kawada and Ohtani exploited this order of reactivity carrying out sequential, differentiated SM reactions *en route* to the total synthesis of terprenin, a potent immunoglobulin E antibody suppressant (Scheme 36).[93]



Scheme 36: Chemoselective SM *en route* to the total synthesis of terprenin

Interestingly, in 2000 Fu was able to reverse conventional chemoselectivity of the oxidative addition step by altering the catalyst and ligand choice.[71] The use of $Pd_2(dba)_3$ with a P(*t*-Bu)$_3$ ligand facilitated cross-coupling exclusively at the generally less reactive chloride terminus of substrate **26** (Scheme 37). However, replacing the catalyst system to $Pd(OAc)_2$ and PCy_3 enabled conventional cross-coupling of the more labile triflate residue. Ten years after this interesting observation, Schoenebeck and Houk used computational chemistry to elucidate the origin of this site selectivity switch.[94] It was found that use of $Pd_2(dba)_3$/P(*t*-Bu)$_3$ preferentially forms a monoligated palladium species which undergoes distortion controlled oxidative addition with the chloride. In contrast to this system, $Pd(OAc)_2$/PCy_3 preferentially forms a bisligated palladium species which oxidatively inserts via an interaction controlled mechanism, favouring the triflate terminus. Schoenebeck has also shown how coordinating, polar solvents can directly affect the chemoselectivity between triflates and chlorides.[95]



Scheme 37: Fu's use of ligand to control chemoselective SM reactions

Chemoselectivity in poly-halogenated heteroaromatics is often governed by site specific electronic properties. In 2007, Fairlamb reported a helpful review highlighting which sites of these heteroaromatics preferentially undergo cross-coupling.[96] The review demonstrates how site selectivity can be directly correlated to the strength of the C–X bond. Indeed, Handy and Zhang demonstrated how selectivity could be predicted directly from the ^{1}H NMR signals of the parent, non-halogenated compound (Figure 7).[97] This enables selectivity to be predicted *a priori* allowing the chemist to suitably design their synthetic route.

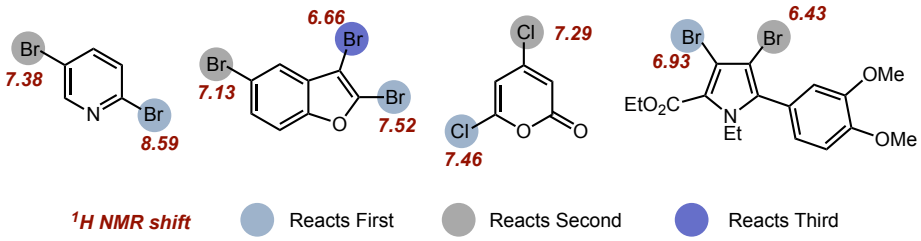
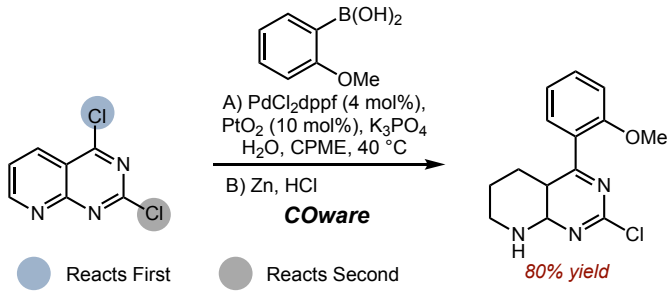


Figure 7: Chemoselective SM of poly-halogenated heteroaromatics

The use of site selective manipulations is paramount in drug discovery where biological targets are rich in heteroaromatics.[98] Recently the Watson group have described a one-pot site selective SM/hydrogenation using COware apparatus to furnish amino-azaheterocycles, key fragments for drug discovery (Scheme 38).[99] The chemoselective SM is favoured in the 4-position of the pyrimidine.

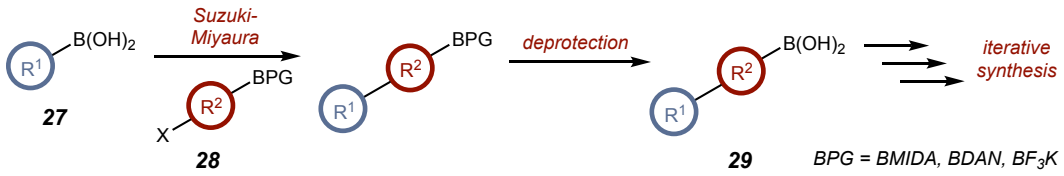


Scheme 38: A one-pot, site selective SM/hydrogenation protocol developed by Watson *et al*

1.4.2 Chemoselective Transmetalation – Boronic Acid Protecting Groups

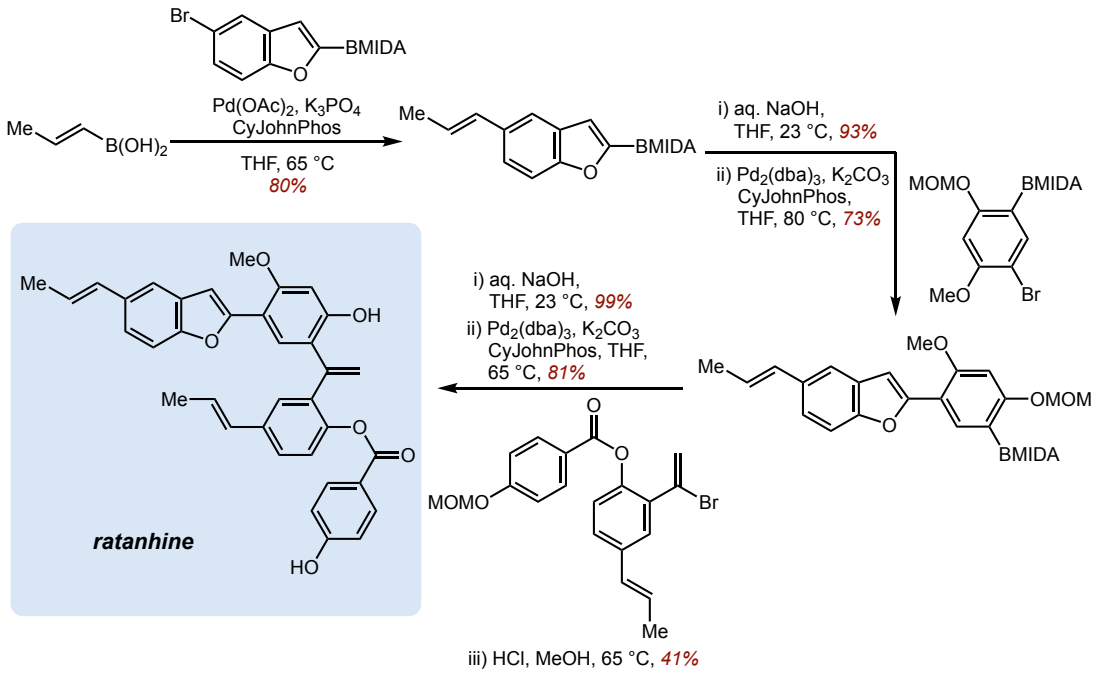
In the past ten years the application of boronic acid protecting groups in synthesis has rapidly expanded. This is due to their ease of synthesis and enhanced stability to

distal manipulations (for a summary of their synthesis and properties refer to section 1.2.4). However, perhaps the most prominent application of these moieties is in iterative synthesis enabled by chemoselective transmetalation (Scheme 39).[100] The observed chemoselectivity derives from the boronic acid protecting group occupying the empty p-orbital of boron rendering this residue inert to the transmetalation step. With this, a neutral unmasked boron species such as a boronic acid **27** can selectively undergo SM cross-coupling in the presence of the boronic acid protecting group **28**. After the initial coupling, the masked boronic acid can be deprotected to reveal the latent boronic acid **29** which can partake in further cross-couplings, permitting an iterative process.



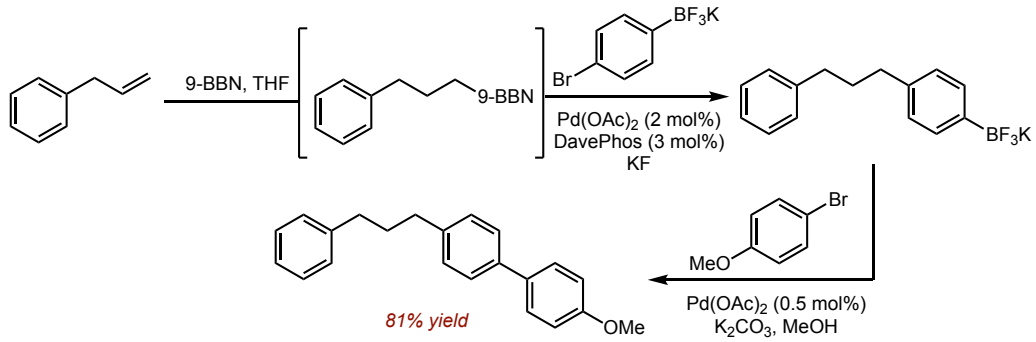
Scheme 39: Use of boron protecting groups in iterative synthesis

In 2007 the Burke group successfully employed the BMIDA protecting group in the synthesis of natural product ratanhine using an iterative SM cross-coupling approach (Scheme 40).[48] The BMIDA intermediates can be hydrolysed under aqueous basic conditions to reveal the latent boronic acid for subsequent SM cross-coupling. Concomitantly, Suginome was also able to employ a similar approach to iterative synthesis using the BDAN "masked" boronic acid which could be readily cleaved in acidic media providing significant complementarity to Burke's approach.[67]



Scheme 40: Synthesis of ratanhine through iterative synthesis

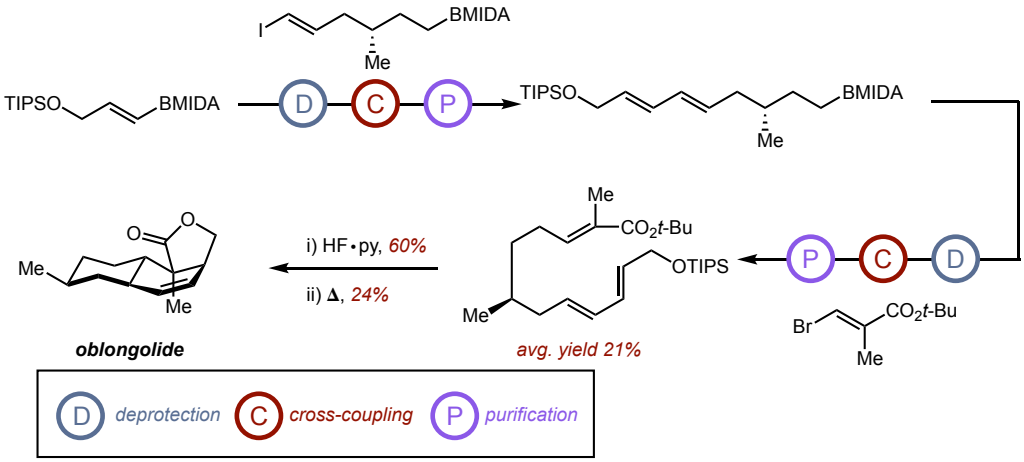
The chemoselective transmetalation of trialkylboranes in the presence of BF_3Ks has also been suitably demonstrated by the Molander group (Scheme 41).[101] This enables an sp^2–sp^3 cross-coupling of the organoborane to proceed with complete retention of the "masked" boron motif for subsequent synthetic manipulations.



Scheme 41: Chemoselective cross-coupling of organoboranes in the presence of BF_3Ks

Since these pioneering studies, the Burke group enabled a fundamental advance in the field of iterative synthesis through the introduction of automation.[102] By virtue of a common automated iteration process, Burke proposes that the carbon framework of any small molecule natural product can be synthetically accessible. The automated process involves an initial deprotection of the BMIDA group (D), cross-coupling of

the latent boronic acid (C), and purification of the newly generated homologated BMIDA species (P) (Scheme 42). After multiple repetitions of the automated procedure Burke was able to form the core carbon framework of the natural product oblongolide, which was easily accessed via subsequent steps. The power of the automated process can be realised by application in drug discovery, enabling rapid structure activity relationship (SAR) of common intermediates to be conducted with the touch of a button.[102]



Scheme 42: Use of automation in iterative synthesis of natural product carbon frameworks

1.4.3 Chemoselective Transmetalation – Vicinal and Geminal Systems

Recently, chemoselective transmetalation has been enabled in sp^3, vicinal and geminal BPin systems. Morken has proposed the potential origin of chemoselectivity in vicinal systems derives from an intramolecular Lewis acid-Lewis base interaction between both BPins (Figure 8).[103] The oxygen atom on the terminal BPin can form a dative bond to the empty p-orbital of the boron on the adjacent internal BPin. This interaction increases the Lewis acidity of the terminal boron species rendering this more activated towards transmetalation, while simultaneously deactivating the adjacent BPin through the dative interaction. The phenomenon can be considered as a neighbouring group activation/protection strategy and can be transcribed to explain the chemoselective reactivity also seen in geminal systems.

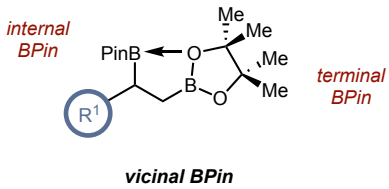
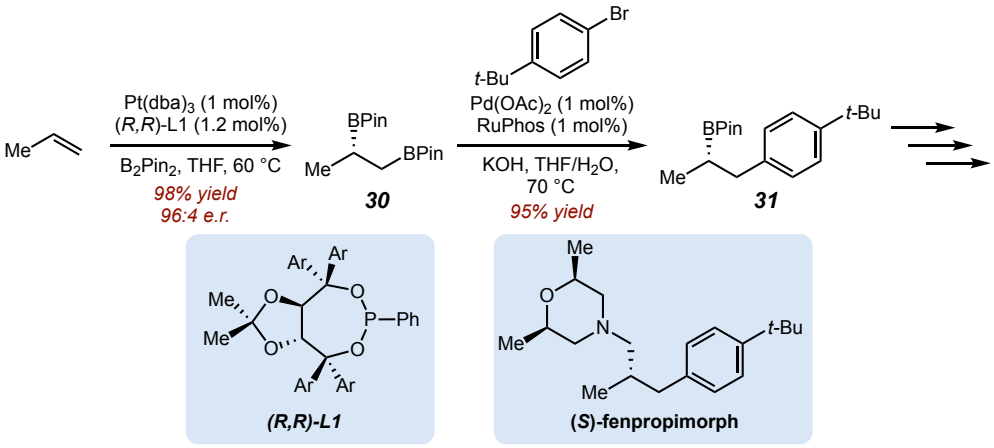


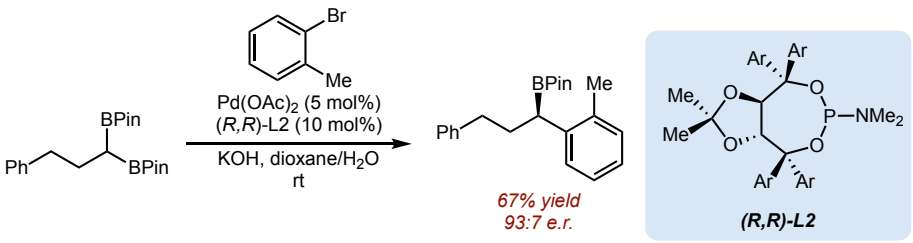
Figure 8: Neighbouring group activation/protection in vicinal BPin systems

The application of this neighbouring group activation/protection was excellently demonstrated by Morken who developed an asymmetric diboration/SM cross-coupling protocol to form chiral BPins (Scheme 43).[103] The group made use of a platinum catalysed enantioselective diboration to form intermediate **30**. After a chemoselective SM reaction with the terminal BPin, chiral BPin species **31** could be formed which, after a few synthetic steps, could be converted to (*S*)-fenpropimorph, a potent fungicide.



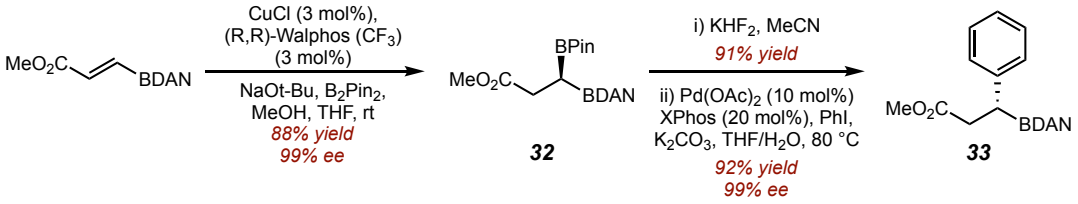
Scheme 43: Asymmetric diboration/SM cross-coupling protocol developed by Morken *et al*

In 2010, Shibata demonstrated that mono cross-coupling via selective transmetalation in geminal systems could be achieved.[104] Since these seminal studies, Morken has developed an enantiotopic group selective cross-coupling protocol to rapidly generate chiral benzylic BPins (Scheme 44).[105] Through the use of a chiral ligand which influences the transmetalation step, a geminal BPin can be readily converted to the chiral BPin through desymmetrisation or dynamic kinetic resolution, as proposed by Morken.



Scheme 44: Enantiotopic group selective cross-coupling of geminal BPins developed by Morken *et al*

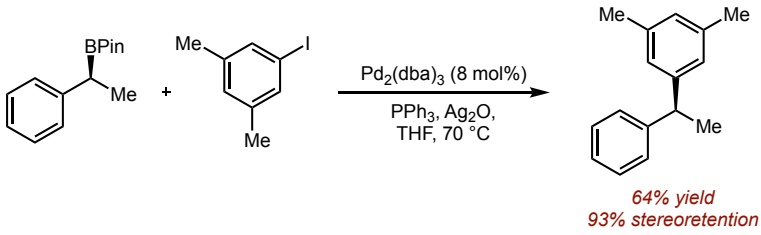
Boron protecting groups have also been utilised to enable chemoselective cross-coupling of geminal systems. In 2011, Hall developed an asymmetric conjugate borylation of ß-boronylacrylates to generate chiral geminal diboron species, with differentiated boron substituents (Scheme 45).[106] The formed BPin component **32** can be readily converted to a BF_3K and employed in a stereoinvertive cross-coupling. The resultant BDAN species **33** can then be used in further synthetic manipulations.



Scheme 45: Asymmetric conjugate borylation

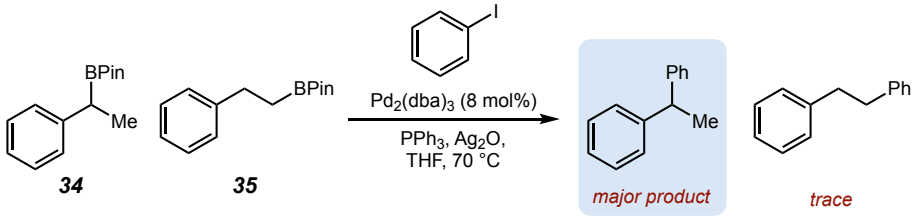
1.4.4 Chemoselective Transmetalation – Use of Silver Additives

The rate-limiting-step of the SM reaction can often be highly dependent on the reagents utilised. Indeed, atypical SM reactions can occasionally be plagued by poor organoboron reactivity resulting in sluggish transmetalation,[85] as opposed to poor oxidative addition of the halide or pseudo halide.[30] A prime example is the poor reactivity observed when employing benzylic BPins, which can be attributed to poor nucleophilicity of the electron deficient boron species. As such, cross-coupling of these motifs is relatively difficult due to poor transmetalation and competing ß-hydride elimination. In 2009, Crudden was able to achieve rapid stereoretentive cross-coupling of chiral benzylic BPins through the use of a silver additive (Scheme 46),[107] an additive known to enhance the rate of the SM reaction by up to 30 orders of magnitude.[108]



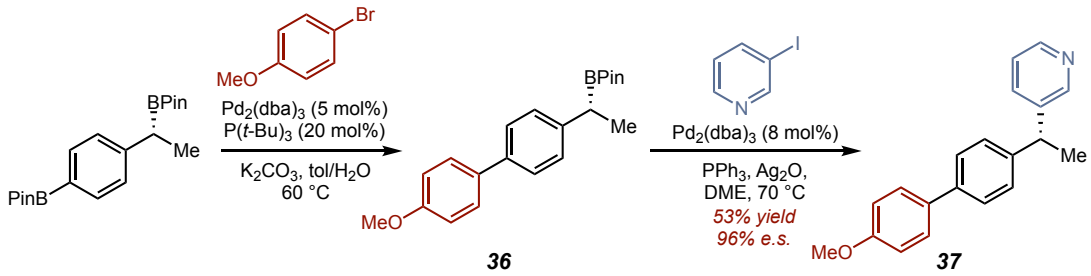
Scheme 46: Stereoretentive SM of benzylic BPins enabled by a silver additive

However, a particular note of interest during this study was the chemoselectivity observed for benzylic BPin **34** over alkyl BPin **35** (Scheme 47).[107] The silver additive enabled selective transmetalation of the less nucleophilic benzylic BPin with only trace amounts of the alkyl cross-coupled product observed.



Scheme 47: Chemoselective SM of benzyl BPins in the presence of alkyl BPins

Years later, Crudden was able to capitalise on this phenomenon further to generate an iterative cross-coupling protocol (Scheme 48).[109] In the absence of the silver additive necessary for benzyl BPin reactivity, a traditional sp^2-sp^2 SM cross-coupling can proceed chemoselectively with complete retention of the benzylic BPin, generating intermediate **36**. The formed benzylic BPin **36** can then undergo a SM reaction in the presence of silver oxide to form triaryl species **37**.

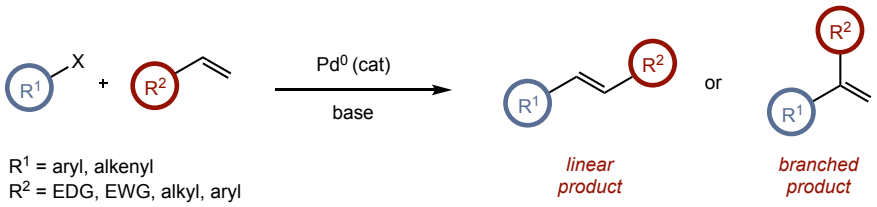


Scheme 48: Sequential chemoselective SM of aryl BPins and benzyl BPins

1.5 The Mizoroki-Heck Reaction

Chapter 2 of this thesis will discuss the use of the Mizoroki-Heck reaction. A full account of this reaction is beyond the scope of this thesis, however, to ensure context, a brief discussion of the mechanism and application of the Mizoroki-Heck reaction follows.

Discovered in the early 1970's in independent studies by Richard Heck[110] and Tstutomu Mizoroki,[111] the Mizoroki-Heck (MH) reaction has become one of the most widely employed palladium catalysed cross-coupling reactions to install alkene substituents. The reaction involves the cross-coupling of an olefinic nucleophile with an aryl or alkenyl halide/pseudo halide electrophile resulting in the formation of linear or branched products (Scheme 49). Since these seminal studies, the reaction has been advanced, enabling regioselective cross-coupling as well as asymmetric variants to grant expedient access to chiral centres and complex carbon frameworks.[112,113] Despite often following a similar series of mechanistic steps, there are a few discrepancies of the proposed catalytic cycle based on mechanistic studies. As such, there have been several proposed mechanisms of the MH reaction. This section will discuss the three operationally similar but distinct MH pathways; neutral, cationic, and anionic.[114] Applications of this fundamental transformation will also be discussed.

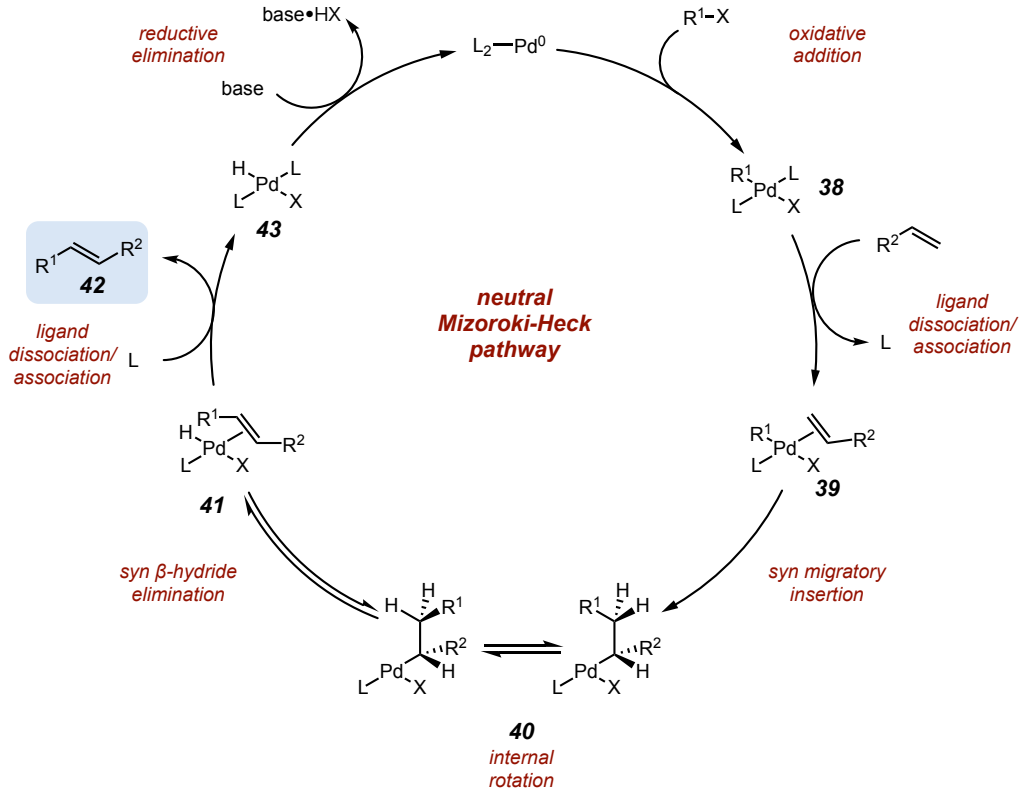


Scheme 49: The Mizoroki-Heck reaction

1.5.1 The Mizoroki-Heck Reaction - Mechanism

Since its inception, there have been three subtly distinct mechanisms proposed for the MH reaction, with each occurring directly as a result of the catalyst and ligands employed.[112] Each pathway is a direct description of the palladium species involved in the catalytic cycle, neutral, cationic, or anionic. The most common reaction

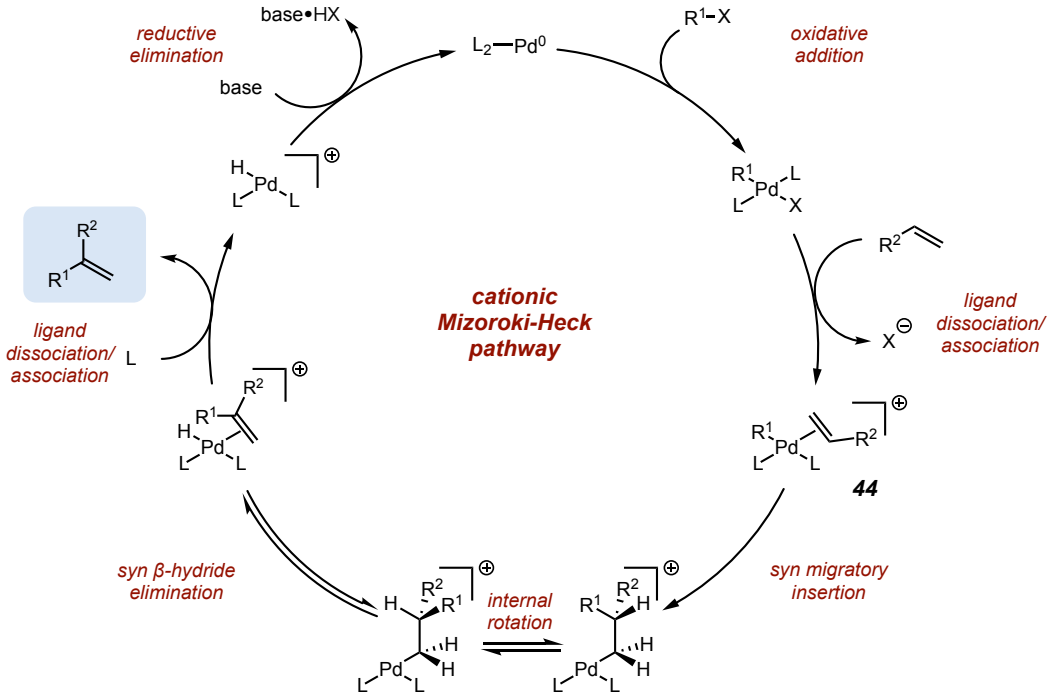
pathway is the neutral pathway in which the catalytic cyclic begins with oxidative addition of an aryl or alkenyl halide to form palladium halide complex **38** (Scheme 50), similar to the SM reaction. Ligand dissociation/association then ensues to form a palladium complex with the datively bound alkene **39** which can then undergo *syn* migratory insertion at the least hindered end of the olefin to form the carbopalladation product **40**. It is this step which governs the *trans* diastereoselectivity in the MH reaction as the previously olefinic C-C bond rotates to minimise steric clash of bulky carbon substituents, enabling stereospecific *syn* ß-hydride elimination to form a palladium complex with a datively bound alkene **41**.[112] Ligand dissociation/association can then proceed to release the desired cross-coupled product **42** and palladium hydride species **43**, with subsequent reductive elimination regenerating the Pd^0 species and basic media quenching the released acid.



Scheme 50: Neutral Mizoroki-Heck mechanism

Several years after the initial discovery, an alternative cationic mechanism was proposed independently by Cabri[115] and Hayashi[116] to describe MH reactions of aryl triflates with bidentate diphosphine ligands (Scheme 51). These ligands bind strongly

to the palladium metal centre generating a chelate effect, meaning phosphine ligand dissociation is unfavourable.[114] Through the use of Ag(I) or Tl(I) additives, which act as halide scavengers, ligand dissociation occurs through abstraction of the halide or ligand dissociation of the weaker triflate leaving an empty coordination site. This prompts the formation of a cationic palladium intermediate **44** after coordination of the alkene, which is stabilised by the electron rich bidentate phosphine ligand. Carbopalladation then proceeds with the cationic palladium attaching to the most electron rich end of the alkene. Similar to the neutral pathway, *syn* ß-hydride elimination, ligand dissociation/association, and base promoted reductive elimination follow to form the 1,1-disubstituted product and active Pd^0 catalyst.[117]



Scheme 51: Cationic Mizoroki-Heck mechanism

As both cationic and neutral pathways preferentially form complimentary regioisomers, different products (branched/linear) can be formed depending on reaction conditions employed. A review by Cabri excellently highlights the observed regioselectivity when using both neutral and cationic conditions (Figure 9).[117] The use of EWGs leads to exclusively linear products irrelevant of which conditions are employed, whereas use of electron donating groups or neutral alkenes can enable

preferential formation of branched or linear products depending on the reaction conditions. This allows synthetic chemists to tailor conditions to suit their needs.

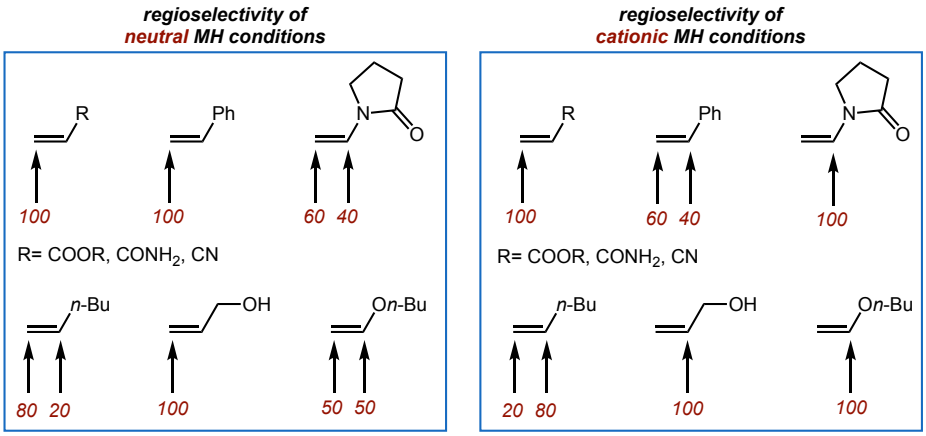
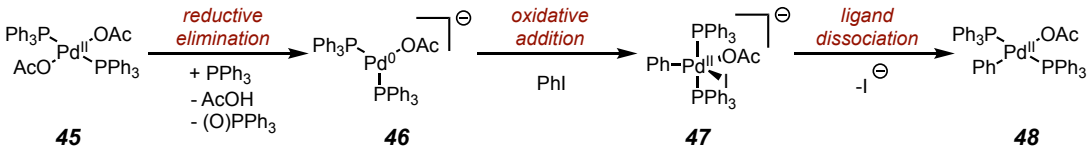


Figure 9: Regioselectivity observed under neutral and cationic MH conditions

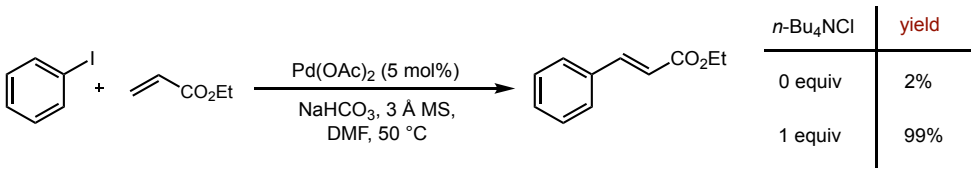
Elegant studies by Amatore and Jutand have highlighted a potential non-innocent role of acetate anions when employing typical $Pd(OAc)_2$ and phosphine ligands in the MH reaction.[118] Experimental evidence has supported a catalytic cycle involving anionic Pd^0 and Pd^{II} intermediates (Scheme 52). During activation, intermediate **45** can lose an acetate ligand to form the tricoordinate anionic palladium species **46**. The nucleophilic species can then undergo oxidative addition to form pentacoordinate species **47**, which after halide dissociation, generates a neutral palladium acetate species **48**, which can continue in the MH mechanism.



Scheme 52: Presence of anionic palladium intermediates in the MH reaction

Recently, Hartwig and Carrow have shown that anionic, ligandless palladium species $[(Ar)PdX_2]_2^{2-}$ are active in the MH reaction and can significantly enhance rates.[119] The group were able to synthesise the palladium complex and extrapolate kinetic data of the MH cross-coupling. Interestingly, additional tetrabutylammonium salt additives, which were used to synthesise the anionic complex, significantly increases reaction rates of standard MH reactions. These conditions were initially pioneered by

Jeffrey and coworkers as phase transfer salts which aid solubility of inorganic bases (Scheme 53),[120] however, the kinetic data from Hartwig suggests the origin of enhanced reactivity may lie with anionic Pd formation.

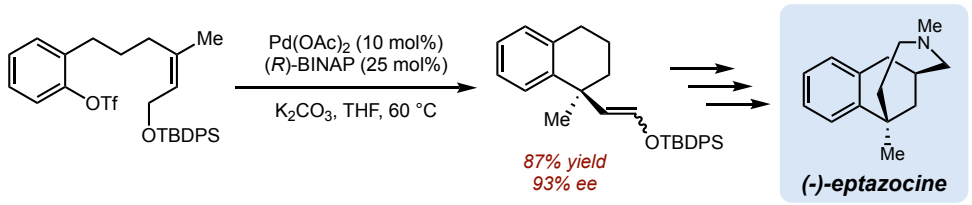


n-Bu_4NCl	yield
0 equiv	2%
1 equiv	99%

Scheme 53: Jeffrey conditions in the MH reaction

1.5.2 The Mizoroki-Heck Reaction - Applications

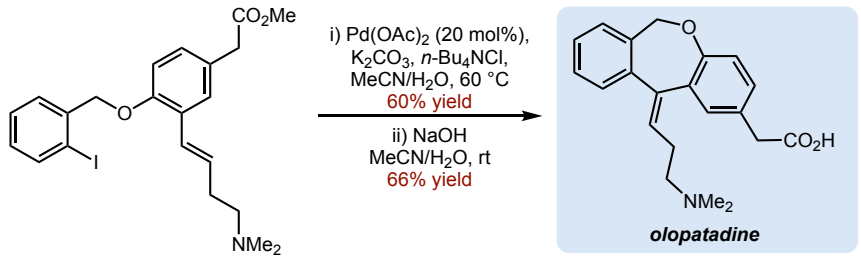
The MH reaction has been employed in synthetic routes to drug candidates as well as natural products. Perhaps the most pertinent example of its application is in the intramolecular asymmetric MH reaction.[113] A chiral centre can be generated during cross-coupling through the use of an axially chiral bidentate ligand, typically under conditions which promote cationic MH. Alkene coordination and migratory insertion have been proposed as the possible enantiodifferentiating steps as both phosphorous atoms are bound to palladium throughout, permitting facial selectivity on approach or induction of stereochemistry during the carbopalladation.[112] The utility of the asymmetric MH reaction was excellently demonstrated by Shibasaki and coworkers who made use of the reaction to form a chiral quaternary centre in high enantiomeric excess (Scheme 54).[121] Interestingly, alkene geometry had a profound effect on ee during optimisation (*Z* = 80% ee, *E* = 51% ee). With additional steps the group were able to synthesise natural product (-)-eptazocine.



Scheme 54: Application of an intramolecular asymmetric MH en route to (-)-eptazocine

The stereospecifity demonstrated in the MH reaction, as a result of *syn* insertion and *syn* elimination, is a highly desirable aspect of the transformation. This is excellently

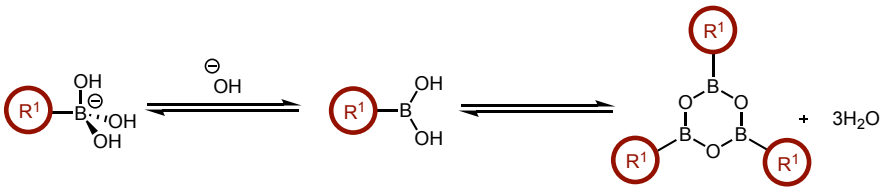
demonstrated by Bosch and coworkers in the synthesis of olopatadine, an antihistaminic drug (Scheme 55).[122] Use of the *trans* starting material led to specifically the desired cis product in high conversion and complete stereoselectivity due to the stereospecific nature of the MH reaction.



Scheme 55: Stereospecific MH cross-coupling towards the synthesis of olopatadine

1.6 Boron Speciation

In solution, organoboron reagents can form highly complex equilibria which is often referred to as boron speciation. As previously discussed, a pertinent example is the dynamic equilibria of boronic acids in solution (Scheme 56). In the presence of aqueous base, through ligand association, a free hydroxide ion can readily occupy the empty p-orbital of boron to generate a new negatively charged, tetrahedral boronate species. The new "ate" species can also readily dissociate in the appropriate media to regenerate the neutral boronic acid. Similarly, in the absence of water, boronic acids readily condense to form entropically driven, partially aromatic boroxines releasing three molecules of water. As a result, at any given time a boronic acid can exist as multiple species.[2]



Scheme 56: Boron speciation of boronic acids

These equilibria, and the concentration of boron intermediates at play, are not only highly pH dependent but can also be influenced by water concentration in solution. The Lloyd-Jones group have shown how the use of inorganic base and small water

quantities in THF can lead to “phase splitting”, in which a minor aqueous phase of high pH and an aqueous THF phase, significantly lower in pH, is generated.[123] As a result of this phenomenon, there is a high concentration of neutral boronic acid, the preferential species for rapid SM, in the organic phase. The base is saturated in the minor aqueous phase behaving as a reservoir of hydroxide ions, which is vital for oxopalladium formation via anion metathesis.[2] The generation of this aqueous basic biphase has significant ramifications on boron speciation, with physical aspects such as stirring, vessel shape, and reaction scale having a profound effect on phase contact and the macroscopic rates of transport between phases.[123] These properties which impact boron speciation must be considered when carrying out SM reactions as formation of undesirable boron species, such as the boronate, can hinder the reaction.

The hydrolysis and diol conjugation equilibrium of boronic esters can also be considered as boron speciation. Although it may appear as a relatively simple equilibrium, it still poses significant questions such as what the active species is in transmetalation when employing boronic esters.[2] In the 1980’s Brown measured the stabilities of various boronic esters through their transesterification equilibrium with pinanediol, a very strong conjugator (Figure 10).[124] In this study six-membered rings were found to be more stable than their five-membered counterparts, presumably due to the enhanced overlap of boron and oxygen enabling superior lone pair donation. The incorporation of increased α-substituents was found to decrease stability of six-membered esters and counterintuitively increase the stability of five-membered esters. A possible explanation is that there is increased σ-bond donation from the carbon substituents or the additional substituents on the more compact five-membered ring may sterically hinder approaching nucleophiles necessary for coordination and subsequent diol cleavage.

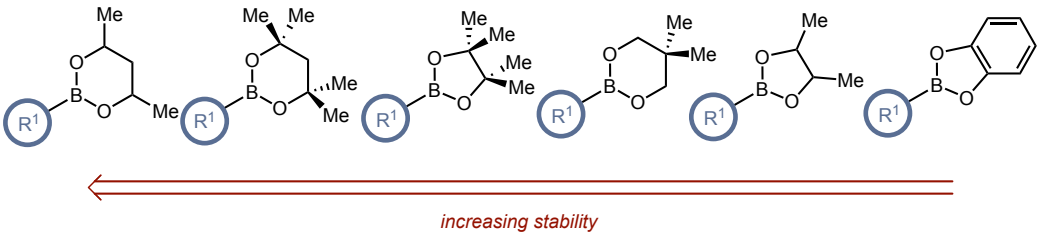
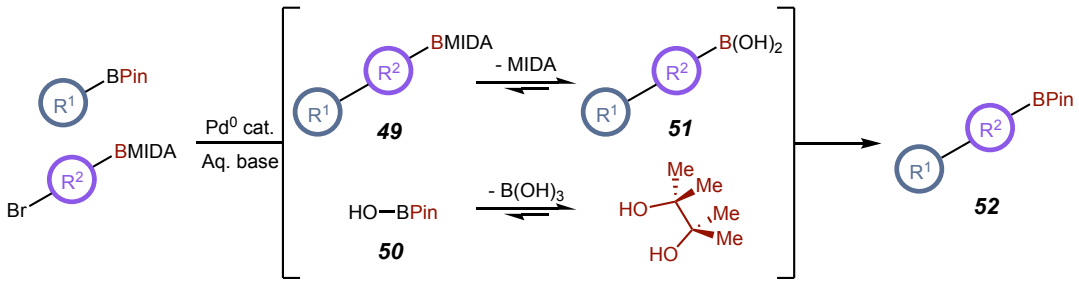


Figure 10: Stabilities of boronic esters based on their transesterification against pinanediol

In contrast to the diol cleavage study by Brown and coworkers, Springsteen and Wang produced an elegant study in 2004, highlighting optimal conditions for diol conjugation. A range of aryl boronic acids with varying pKa (4–9) were investigated at various pH.[125] As the pKa of diols are typically >10, the relative rate of association was found to be greater at higher pH (8–10) with more acidic aryl boronic acids containing EWGs providing enhanced rates of conjugation.

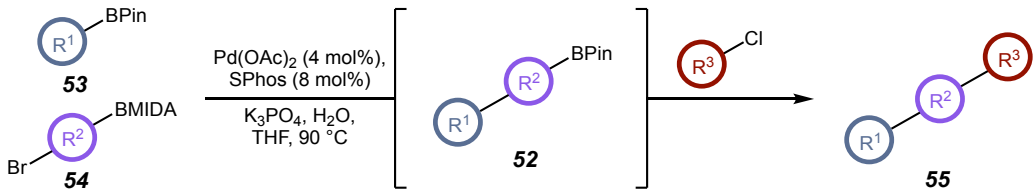
Although inherent control over these equilibria is highly ambitious, if harnessed correctly boron speciation can be utilised for synthetic gain. Recently within the Watson group, through control of boron speciation, a fundamental advance in the use of BMIDAs in iterative synthesis was realised (Scheme 57).[126] Using carefully controlled reaction conditions with limited water and saturated base a rapid chemoselective SM reaction can proceed to form intermediate **49** and HOBPin byproduct **50**. At elevated temperature, in the presence of aqueous base, BMIDA **49** can undergo slow hydrolysis to reveal the latent boronic acid **51**. The basic reaction conditions then promote pinacol hydrolysis of **50** and subsequent conjugation to **51** forming a biaryl homologated BPin **52**. This provides a fundamental advance on traditional iterative processes, bypassing the necessary deprotection stage.[100]



Scheme 57: Biaryl BPin synthesis enabled by speciation control

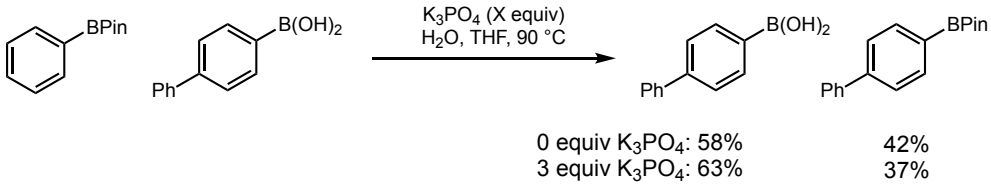
The phenomenon was advanced a year later enabling a one-pot expedient access to triaryl systems (Scheme 58).[127] Chemoselective oxidative addition enables a rapid SM reaction between the aryl BPin **53** and aryl bromide **54** to form a biaryl BPin intermediate **52** after hydrolysis and transesterification similar to previous work (Scheme 57). The newly generated BPin species can partake in a further cross-coupling reaction with the aryl halide to form the desired triaryl scaffold **55**. Chemoselective oxidative addition, chemoselective transmetalation, and boron

speciation enable formation of two new C-C bonds with complete control over reaction outcome.



Scheme 58: Sequential SM reactions enabled by boron speciation and chemoselective oxidative addition/transmetalation

Although boron speciation can be excellently harnessed to enable chemoselective transmetalation and subsequent diol conjugation,[126] the method still requires the use of a boron protecting group to enable chemoselectivity. Indeed, boron speciation is a direct contributing factor as to why chemoselectivity between two reactive boron species, such as a boronic acid and a BPin, has not yet been achieved. This is due to the result of "pinacol scrambling" under aqueous basic conditions (Scheme 59).[128] Under these aqueous basic conditions, critical for SM reactivity, the diol can be readily cleaved enabling conjugation to another boronic acid species which leads to an equilibrium generating an approximately 1:1:1:1 mixture of monoaryl and biaryl boron species (biaryl ratio shown below, Scheme 59).[128] Although direct chemoselective transmetalation would provide a fundamental advance in the SM reaction, in order to achieve direct chemoselectivity between transmetalation active boron species, boron speciation is a fundamental problem which would have to be addressed.



Scheme 59: BPin equilibration under aqueous basic conditions

Additionally, A factor which has not yet been explored is the subtle difference in the transmetalation event of the SM reaction. The necessity for an oxopalladium species for enhanced transmetalation of specifically an organoboron reagent could invoke

chemoselectivity between competing nucleophiles which are active to different modes of transmetalation. A direct mechanistic analysis of the integral anion metathesis step may enable this complex reactivity to be harnessed. Developing chemoselectivity between competing differentiated nucleophiles as a direct function of the catalyst species formed in solution would be a significant advance in the catalysis arena, enabling a platform for divergent synthesis as well as cascade methodologies to generate complex carbon scaffolds.

Chapter 1

Chemoselective Oxidation of Aryl Organoboron Systems

This chapter is based upon the following publication: *Chem. Sci.*, 2017, **8**, 1551–1559.[129]

The enclosed study was carried out with the help of Dr Thomas A. Clohessy who's input during optimisation and in generating a substrate scope of the chemoselective oxidation was greatly appreciated.

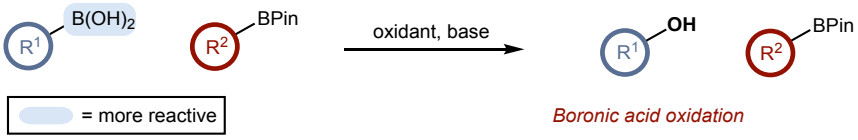
Numbered compounds in chapter 1 will follow the order A1, A2, A3,…. etc.

2 Chapter 1

2.1 Proposed Work

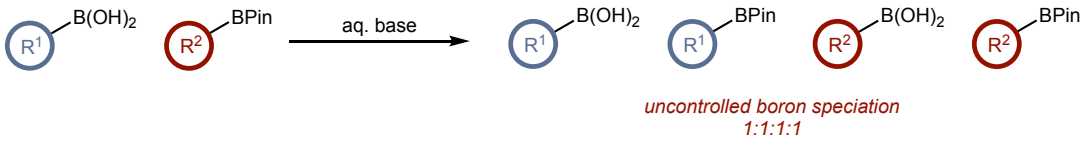
The utility of chemoselectivity in the oxidative addition and transmetalation steps of the SM reaction has modernised C-C bond formation and the subsequent building of carbon frameworks. Although chemoselective oxidative addition is generally governed by the kinetic preference of one specific halide over another, based on electronics and bond dissociation energies,[96] chemoselectivity between competing boron species remains limited to the use of boron protecting groups,[45,46] which preclude competitive transmetalation. Chemoselectivity has been demonstrated on ostensibly equivalent boron species, however, this is restricted to the use of specific systems such as vicinal/geminal systems.[45] As such, enabling chemoselective transmetalation while forgoing the use of boron protecting groups would provide a fundamental advance on current methodologies by avoiding protection/deprotection steps. A recent study by Hartwig included a direct comparison of the rates of transmetalation for both a boronic acid and BPin.[86] The difference in reactivity ($B(OH)_2$ = <2 min, BPin = 1.5 h) suggests a potential kinetic window between two nucleophiles competent in the SM reaction. Despite this, there is a vast expanse of reaction conditions and variables which can be modified in the SM reaction and as a result tailoring conditions to directly achieve chemoselectivity is highly ambitious.

In order to probe chemoselectivity between two ostensibly equivalent non-protected boron species we selected a workhorse reaction: The Brown oxidation. Typically, boron species are rapidly, and indiscriminately oxidised in the presence of oxidants.[130,131] However, with a range of commercial, mild to strong oxidants available it was believed the reaction could be tailored to establish chemoselectivity between competing systems for the first time, based on the kinetic window established by Hartwig (Scheme 60).[86]



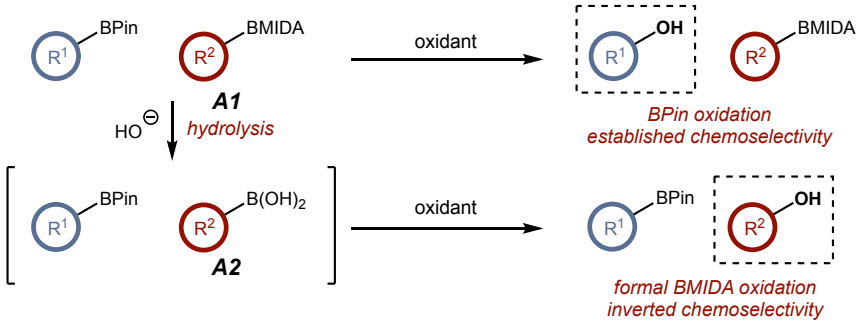
Scheme 60: Chemoselective oxidation of competing aryl organoboron systems

In combination with their rapid oxidation, boronic acids and BPins can readily equilibrate through boron speciation under aqueous basic conditions to generate a complex mixture of species in solution (Scheme 61).[128] As aqueous basic conditions are required for both the above described transformations, in order to obtain any chemoselectivity, boron speciation was a problem we would have to address. It was proposed in depth reaction analysis by NMR/HPLC could interrogate the role of boron speciation and establish the origin of chemoselectivity if achieved.



Scheme 61: Uncontrolled equilibration enabled by boron speciation

If chemoselectivity is established while mitigating boron speciation, it was proposed that traditional chemoselectivity could be inverted (Scheme 62). The *in situ* hydrolysis of BMIDA **A1** would form the requisite boronic acid (**A2**) which could then undergo chemoselective oxidation with complete retention of the BPin throughout. Through this, a formal oxidation of a BMIDA protecting group would be enabled in the presence of an oxidatively labile BPin species. It was also proposed that chemoselectivity between competing aryl boronic acids could be established as a function of their Lewis acidity/solubility, which could potentially be predicted *a priori* by spectroscopic analysis of the reaction mixture. Finally, a stepwise chemoselective oxidation/Chan-Evans-Lam coupling would permit an oxidative nucleophile-nucleophile cross-coupling to provide access to biaryl ethers.

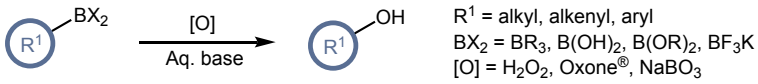


Scheme 62: Inverting conventional chemoselectivity: A formal chemoselective oxidation of BMIDAs

2.2 Results and Discussion

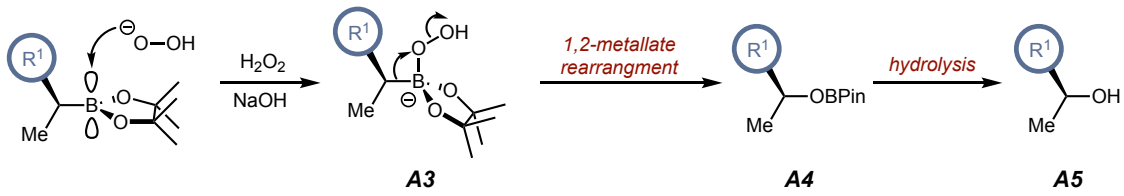
2.2.1 The Brown Oxidation

A landmark transformation which has become ubiquitous in synthetic chemistry is the Brown oxidation.[132] Discovered in the late 1950's/1960's, the Brown oxidation involves the oxidation of a boron species to the corresponding alcohol using a nucleophilic oxidant, typically hydrogen peroxide, in basic media (Scheme 63).[132] The mild reaction provides an elegant method for late stage incorporation of alcohols into carbon frameworks through a hydroboration/oxidation protocol, also developed by Brown.[133] As a result of his synthetic efforts, Brown was awarded the Nobel Prize in chemistry in 1979 for his application of boron in organic synthesis.



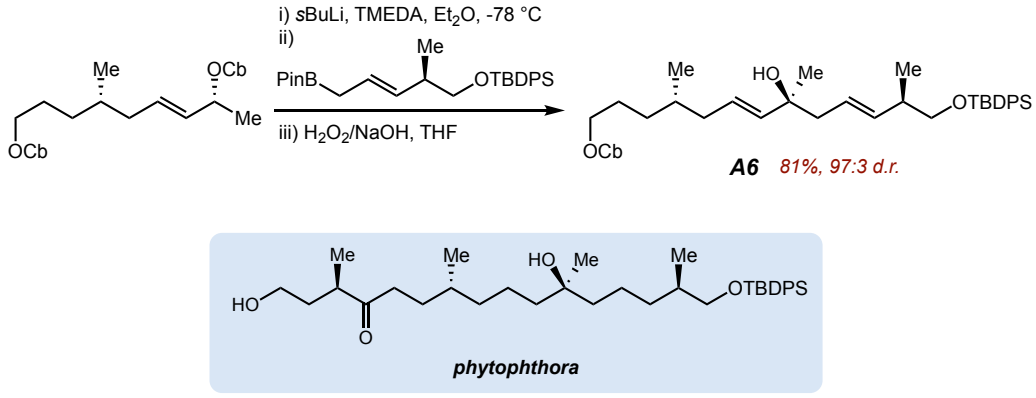
Scheme 63: The Brown oxidation

A key aspect of the Brown oxidation which is particularly desirable to synthetic chemists is the stereospecificity observed. This enables chiral boron species to be cleanly converted to the corresponding chiral alcohol with high fidelity (Scheme 64).[134] The proposed mechanism can be used to rationalise the observed stereoretention. The peroxide anion can attack the empty p-orbital of boron to form a boronate intermediate (**A3**). The boronate can then undergo a 1,2-metallate rearrangement eliminating hydroxide to form the boric ester species **A4**. The nature of the 1,2-metallate rearrangement allows transcription of the stereochemistry from the C-B bond to the newly formed C-O bond. The formed boric ester **A4** can then be hydrolysed under aqueous basic media to reveal the chiral alcohol **A5**.



Scheme 64: Brown Oxidation mechanism

Since the initial discovery, the utility of this protocol is extensive, with many applications in natural product, polyketide synthesis,[135] and synthesis of marketed drugs.[130] In 2014, Aggarwal and coworkers provided an elegant use of the Brown oxidation to generate a chiral alcohol (Scheme 65).[135] The group used a lithiation/borylation/Brown oxidation protocol to form key fragment **A6**, a precursor *en route* to the total synthesis of phytophthora, a universal mating hormone.

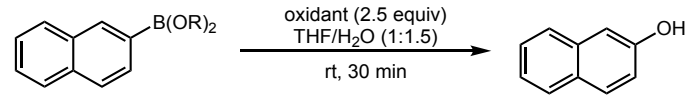


Scheme 65: Use of a lithiation/borylation/Brown oxidation protocol to access chiral alcohols

2.2.2 Reaction Optimisation

In a bid to assess chemoselective oxidation, the oxidation of boronic acid **A7a**, and BPin **A7b** were assessed with a range of oxidants in isolated systems (Table 1). Interestingly, the use of hydrogen peroxide provided poor reactivity with both species (Table 1, entries 1 and 2), presumably due to the absence of a suitable base necessary for reactivity with this peroxide species.[134] The use of sodium perborate and *m*CPBA provided high conversion to product for both boron species (Table 1, entries 3–6). As both species were rapidly oxidised to high conversion, it was believed that chemoselectivity in a shared system using these oxidants would be ambitious as no useful rate discrimination could be extrapolated. Pleasingly, the application of a milder oxidant, Oxone®, which contains potassium peroxymonosulfate as the active oxidant, provided the first indication of a potential rate difference in oxidation. The use of boronic acid **A7a** in the presence of Oxone® provided an excellent 98% conversion to the corresponding phenol (**A7c**) after 30 minutes, whereas the use of the analogous BPin (**A7b**) proceeded to 22% conversion (Table 1, entries 7 and 8).

Table 1: Oxidant study on monoaryl systems



A7a: $B(OR)_2 = B(OH)_2$
A7b: $B(OR)_2 = BPin$

A7c

Entry	Boron Species	Oxidant	Conversion[a] (%)
1	A7a	30% wt. aq. H_2O_2	24
2	A7b	30% wt. aq. H_2O_2	19
3	A7a	$NaBO_3 \bullet 4H_2O$	quant.
4	A7b	$NaBO_3 \bullet 4H_2O$	quant.
5	A7a	50% wt. *m*CPBA	92
6	A7b	50% wt. *m*CPBA	75
7	A7a	Oxone®	98
8	A7b	Oxone®	22

[a] Determined by HPLC against a known internal standard (caffeine)

In a bid to further investigate this contrasting difference in reactivity, the oxidation of **A7a** and **A7b**, using Oxone®, was monitored over time (Chart 1). Interestingly, the oxidation of **A7a** (blue) appeared to show significant conversion in the burst phase in comparison to a more linear trend observed by **A7b** (red).

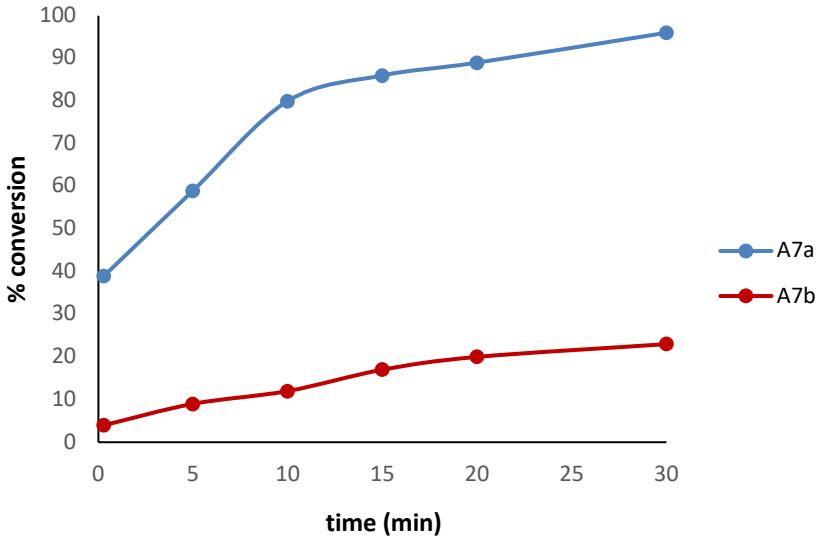
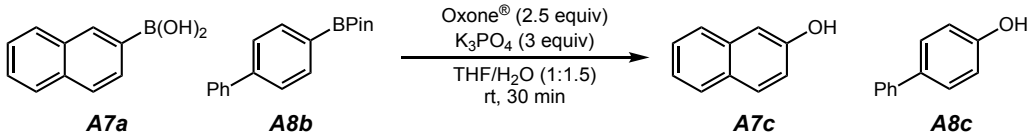


Chart 1: Oxidation of monoaryl A7a/A7b using Oxone® monitored over time

With a difference in reactivity profiles in the non-competitive system established, it was believed chemoselectivity could be leveraged by applying the conditions to a competitive system using **A7a** and **A8b** in one-pot (Table 2). Unfortunately, application of these conditions led to rapid and indiscriminate oxidation, with trace levels of chemoselectivity (Table 2, entry 1). This is presumably due to unfavourable diol equilibration between both species as a result of boron speciation. Removal of water, in a bid to mitigate boron speciation, resulted in complete inhibition of oxidation for both species as a direct result of the insolubility of Oxone® in purely organic media (Table 2, entries 2 and 3). An interesting result was observed with the use of both water and base in the reaction (Table 2, entry 4). The use of K_3PO_4 generated a distinctly biphasic reaction mixture which produced moderate conversion to product for the desired boronic acid with moderate chemoselectivity.

Table 2: Use of Oxone® in the oxidation of competing biaryl systems



A7a ***A8b*** ***A7c*** ***A8c***

Entry	Base	Water	Conversion[a] (%)	A7c:A8c[a]
1	-	Y	95	1.1:1
2	-	-	0	-
3	Y	-	0	-
4	Y	Y	54	14:1

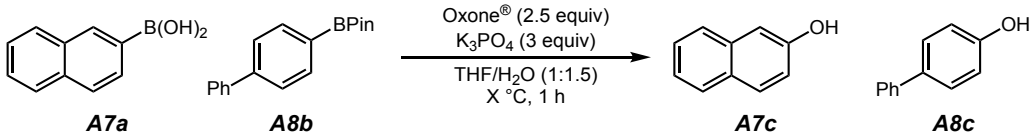
[a] Determined by HPLC against a known internal standard (caffeine)

At this point the use of both Oxone® and K_3PO_4 was further explored. It was believed that increasing the temperature would increase solubility of Oxone® and thereby improve conversion to the desired phenol (Table 3). Reaction times were also extended to one hour in a bid to aid conversion.

To our surprise, not only did increased temperature improve conversion, but it also had an unexpected, significant effect on chemoselectivity. Indeed, chemoselectivity counterintuitively increased with increasing temperature (Table 3). This phenomenon

is unexpected as kinetic favourability of one species over another is typically promoted at lower temperatures.[136] Reactions run at 60 °C and 70 °C provided excellent conversion and good selectivity (Table 3, entries 5 and 6, respectively). However, the reaction at 70 °C exceeds the boiling point of THF and was therefore deemed as suboptimal for further optimisation. Another key point to note is the erosion of chemoselectivity with longer reaction times at room temperature (Table 2, entry 4 vs Table 3, entry 1).

Table 3: Temperature study



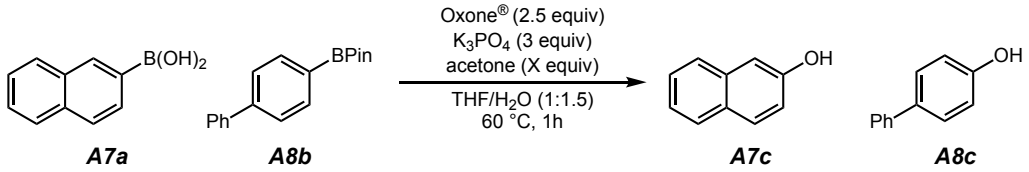
A7a ***A8b*** ***A7c*** ***A8c***

Entry	Temperature (°C)	Conversion[a] (%)	A7c:A8c[a]
1	rt	quant.	2:1
2	30	quant.	5:1
3	40	87	7:1
4	50	62	9:1
5	60	81	18:1
6	70	93	13:1

[a] Determined by HPLC against a known internal standard (caffeine)

Acetone is commonly employed when using Oxone® to aid with solubility of the salt in the organic phase.[137] We decided to interrogate the use of acetone as a potential co-solvent and assess what impact this had on chemoselectivity (Table 4). As demonstrated, additional acetone had a negative impact on chemoselectivity (Table 4, Entries 2–4). This information suggests increased solubility of Oxone® in the organic phase and subsequent distortion of the biphasic media, may indeed be detrimental to chemoselectivity. As a result, investigation into the use of co-solvents to improve conversion was discontinued.

Table 4: Acetone additive study



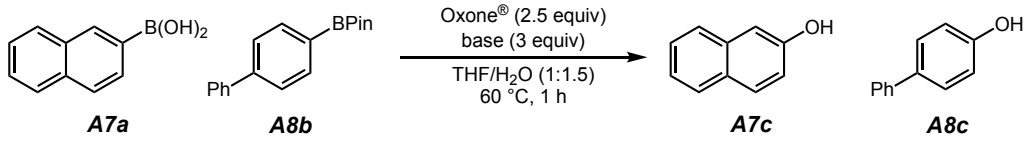
A7a ***A8b*** ***A7c*** ***A8c***

Entry	Acetone (equiv)	Conversion[a] (%)	A7c:A8c[a]
1	-	81	18:1
2	5	54	6:1
3	10	45	3:1
4	20	98	2:1

[a] Determined by HPLC against a known internal standard (caffeine)

A notable factor which has dominated reactivity and chemoselectivity throughout optimisation so far is the necessity for a distinct aqueous basic, biphasic system. With this in mind a range of bases were evaluated in the hope this may impact conversion and selectivity (Table 5). Unfortunately, altering base provided no improvement to chemoselectivity although bases such as Cs_2CO_3 (Entry 2) and K_2CO_3 (Entry 3) did show high levels of chemoselectivity. Any improvement to conversion, as shown with KOAc (Entry 4) and KOH (Entry 5), also led to significant deterioration of selectivity. These results highlight the importance of the aqueous basic media in order to achieve chemoselectivity.

Table 5: Base study



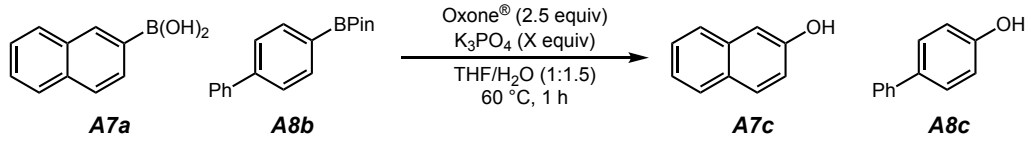
A7a ***A8b*** ***A7c*** ***A8c***

Entry	Base	Conversion[a] (%)	A7c:A8c[a]
1	K_3PO_4	81	18:1
2	Cs_2CO_3	59	14:1
3	K_2CO_3	53	12:1
4	KOAc	quant.	1:1
5	KOH	quant.	1.5:1

[a] Determined by HPLC against a known internal standard (caffeine)

The inherent requirement for basic media was further compounded with a screen of base stoichiometry (Table 6). Reducing the equivalents of base employed in the reaction significantly reduced chemoselectivity of the reaction. This could potentially be attributed to the formation of a less defined aqueous basic biphase.

Table 6: Base equivalents study



A7a ***A8b*** ***A7c*** ***A8c***

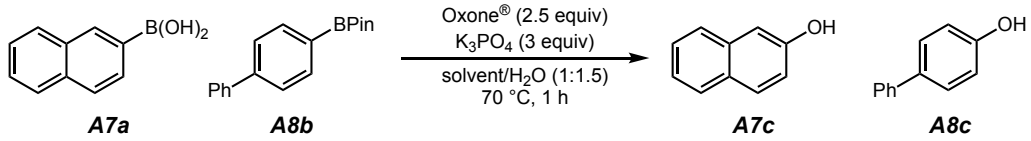
Entry	K_3PO_4 (equiv)	Conversion[a] (%)	A7c:A8c[a]
1	1	81	18:1
2	2	54	6:1
3	3	98	2:1

[a] Determined by HPLC against a known internal standard (caffeine)

At this point in the study it was proposed that solvent may have a significant impact on conversion and selectivity due to initial data indicating the critical role of the biphasic reaction medium. Reactions were carried out at 70 °C due to favourable conversion previously observed at higher temperatures.

A range of solvents were investigated resulting in very distinct, contrasting outcomes (Table 7). The use of highly polar or aprotic solvents, which are typically miscible with water, resulted in high conversions, however, both boron residues were indiscriminately oxidised (Table 7, entries 1–4). The diminished selectivity and high conversion can be attributed to improved miscibility of the reaction medium. Interestingly, the use of less polar solvents led to enhanced chemoselectivity and in some cases enhanced conversion (Table 7, entries 7–11). Notably, cyclopentylmethylether (CPME) and $CHCl_3$ (Entries 11 and 10, respectively) enabled complete conversion to product with full retention of the BPin, **A8b** (quant., 99:1). The completely selective reaction was deemed fully optimised after multiple repititions, and the use of CPME, a bio-derived solvent,[138] was progressed due to its favourable user-friendly properties in comparison to $CHCl_3$.

Table 7: Solvent study



A7a *A8b* *A7c* *A8c*

Entry	Solvent	Conversion[a] (%)	A7c:A8c[a]
1	EtOH	quant.	1:1
2	IPA	quant.	1:1
3	MeCN	quant.	1:1
4	DMF	quant.	1.5:1
5	1,4-dioxane	quant.	2:1
6	THF	73	13:1
7	2-MeTHF	84	47:1
8	EtOAc	quant.	63:1
9	toluene	59	>99:1
10	$CHCl_3$	quant.	>99:1
11	CPME	quant.	>99:1

[a] Determined by HPLC against a known internal standard (caffeine)

At this stage it was clear that formation of a biphasic reaction medium was critical for chemoselectivity. Additionally, increased temperature counterintuitively increased chemoselectivity and conversion. With these interesting observations in hand it was hypothesised that further analysis of the biphasic mixture may aid in elucidating the origin of chemoselectivity.

2.2.3 Determining the Origin of Chemoselectivity

At the outset of this project it was proposed chemoselectivity between a boronic acid and BPin could be leveraged based on a kinetic difference observed in transmetalation.[86] Initially, oxidation on the isolated monoaryl systems suggested this difference in rate could be harnessed for chemoselectivity (Chart 1). However, the conditions were unsuccessful when transferred to a competing biaryl system (Table 2), suggesting a difference in kinetics was not the fundamental basis of chemoselectivity and indeed the overall origin of chemoselectivity may be

significantly more complex than first anticipated. With this information in hand we set out to establish the origin of chemoselectivity observed under optimised conditions and rationalise the unusual trends observed.

During optimisation of the reaction there were several key pieces of data that were notable:

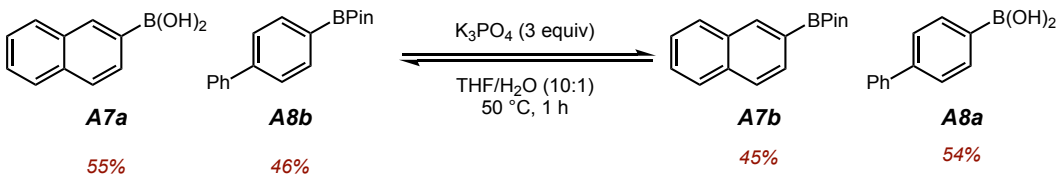
1. The use of base to generate an organic/aqueous basic biphase was critical for chemoselectivity. Reactions in which a defined biphase was not created typically led to rapid, indiscriminate oxidation. This strongly suggests the presence of two distinct phases is necessary in establishing chemoselectivity.

2. In the absence of water, no oxidation was observed which could be the result of the poor solubility of Oxone®. This suggests the oxidant resides in the aqueous layer where it is solubilised and that this is where oxidation proceeds.

3. Under similar reaction conditions with limited water, pinacol equilibration is observed due to boron speciation (Scheme 66). However, no equilibration was observed under the optimised conditions, suggesting both the boronic acid and BPin are physically separated or when residing together there is no water or base present.

4. Chemoselectivity in this system counterintuitively increased with increasing temperature. This is atypical when exploiting a kinetic difference between similar species.

5. Physical aspects, such as shearing, had a profound impact on reactivity. In isolated systems, increasing the stir rate of the BPin oxidation (Chart 2) led to a similar reaction profile of the boronic acid oxidation (Chart 1). This can be attributed to distortion of the organic/water interface, enhancing the surface and thereby increasing the rate of oxidation.



Scheme 66: Speciation equilibria of A7a and A8b under aqueous basic conditions

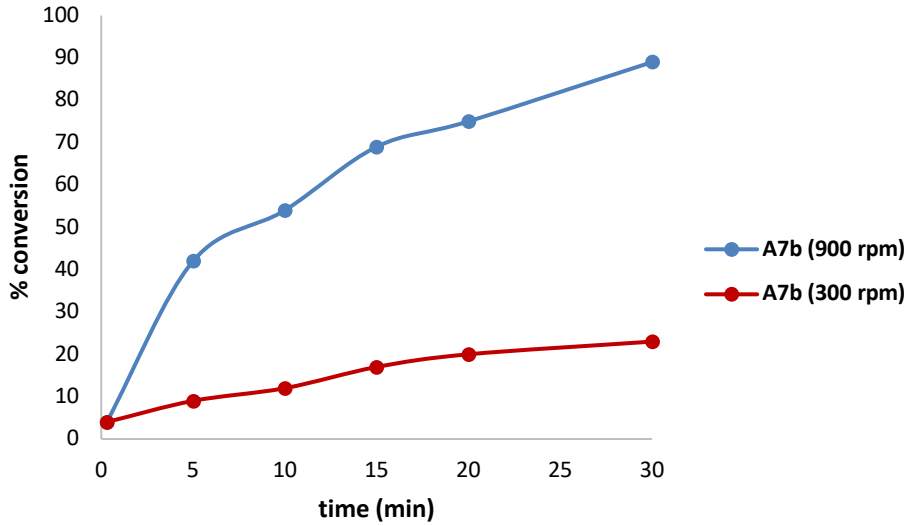
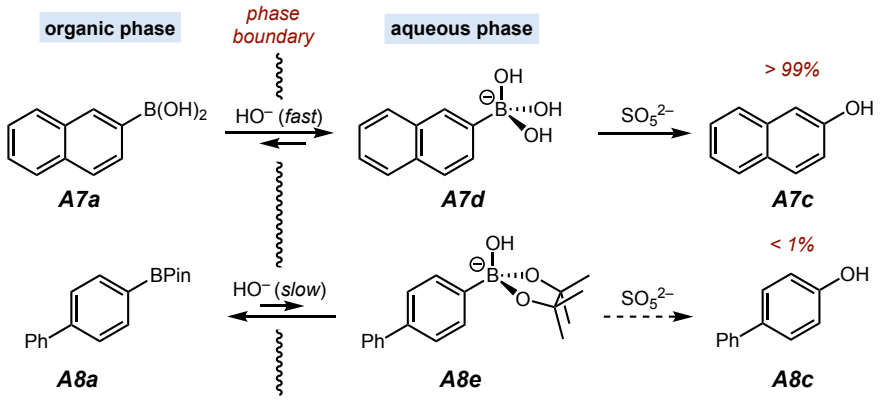


Chart 2: Effect of increased shearing on the rate of oxidation of BPin A7b

Based on all of the above observations, it was proposed that chemoselective oxidation was occurring through selective phase transfer of the boronic acid to the oxidant rich aqueous phase with retention of the BPin in the organic phase (Scheme 67). The cognate hydroxyboronates of organoboron reagents, particularly trihydroxyboronates formed from boronic acids, are significantly more soluble in water than organic media.[15] This factor, in combination with the proposal that trihydroxyboronate formation from the parent boronic acid is essentially barrierless,[17] suggests that the more Lewis acidic boronic acid preferentially forms a trihydroxyboronate which can be readily exchanged to the oxidant rich aqueous phase. In order to probe this hypothesis a series of mechanistic studies were undertaken.

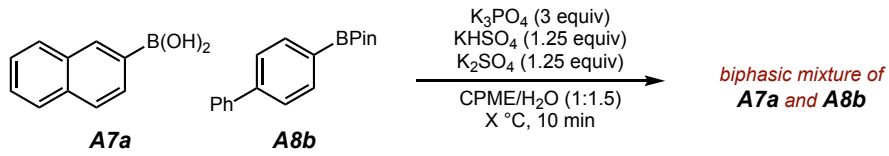


Scheme 67: Proposed origin of chemoselectivity through selective phase transfer

In order to provide conclusive, quantitative data of boron speciation distribution between both phases, HPLC analysis of the biphasic mixture in the absence of the active oxidant, potassium peroxymonosulphate, was explored (Table 8). Reactions were stirred at the specified temperature for 10 minutes and an aliquot of both phases was analysed by HPLC against an internal standard. In the absence of K_3PO_4 and the basic components of Oxone®, both boronic acid (**A7a**) and BPin (**A8b**) reside in the organic phase. This is expected as there is no base to promote boron speciation or phase distribution (Table 8, Entries 1–3). Similar results were obtained in the presence of reaction scale quantities of the basic components of Oxone® ($KHSO_4$ K_2SO_4), in which both boron species remained predominantly in the organic phase at all temperatures (Table 8, Entries 4–6). Interestingly, the use of K_3PO_4 enabled the selective incorporation of **A7a** into the aqueous phase with excellent retention of **A8b** in the organic phase (Table 8, Entries 7–9). Not only does this demonstrate the origin of chemoselectivity, i.e. selective phase transfer of the boronic acid, but also shows that boronic acid transfer to the aqueous phase is increased with increasing temperature, elucidating the counterintuitive optimisation observed previously. The use of all basic components from the model reaction led to similar results as seen with K_3PO_4, with selective transport of the boronic acid to the aqueous phase increasing with increasing temperature (Table 8, Entries 10–12). All of the above information provides quantitative evidence that selective transport of the boronic acid to the aqueous phase occurs with complete retention of the BPin in the organic phase. Although this demonstrates the origin of chemoselectivity, there is still a degree of uncertainty as to the oxidation state of the boron species which is

transferred (i.e. neutral or "ate" species) as this cannot be interrogated by HPLC. It was proposed that ^{11}B NMR could be used to determine which species reside in each phase of the biphasic reaction mixture.

Table 8: HPLC analysis of biphasic reaction media



Entry	Inorganics used	Temp. (°C)	A7a[a,b]	A8b[a,b]
1	-	20	>99:1	>99:1
2	-	50	>99:1	>99:1
3	-	70	>99:1	>99:1
4	$KHSO_4$, K_2SO_4	20	>99:1	>99:1
5	$KHSO_4$, K_2SO_4	50	>99:1	>99:1
6	$KHSO_4$, K_2SO_4	70	98:2	>99:1
7	K_3PO_4	20	54:46	>99:1
8	K_3PO_4	50	46:54	96:4
9	K_3PO_4	70	29:71	98:2
10	K_3PO_4, $KHSO_4$, K_2SO_4	20	67:33	>99:1
11	K_3PO_4, $KHSO_4$, K_2SO_4	50	59:41	>99:1
12	K_3PO_4, $KHSO_4$, K_2SO_4	70	54:46	>99:1

[a]Determined by HPLC, [b] ratios describe product distribution – organic: aqueous

Analysing a single phase of a biphasic mixture by NMR is, to the best of our knowledge, unexplored. It was reasoned that by correctly scaling the reaction, one phase of the biphasic mixture could be monitored by NMR (Figure 11). The receiver/transmitter coil of an NMR magnet has a limited span in which a signal can be detected. If the reaction was scaled to such an extent in an NMR tube, the receiver/transmitter coil would then only detect a single phase (in this case the lower, aqueous phase). It was proposed that through this method, the distribution of boron

species and their oxidation states, could be monitored at various temperatures and times by ^{11}B NMR.

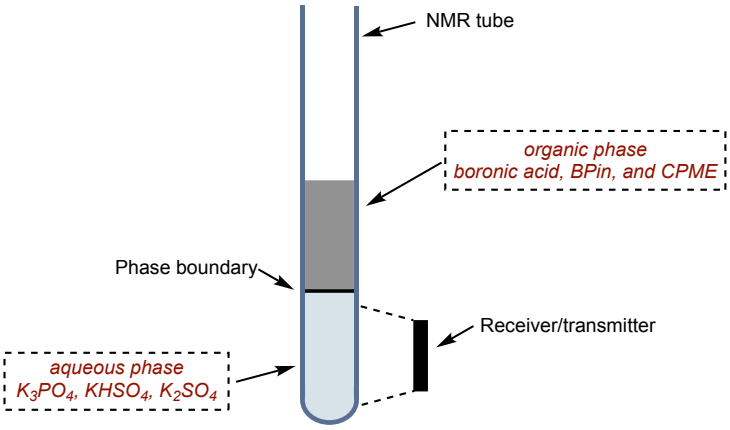


Figure 11: NMR set up for selective analysis of aqueous phase

With a plan in place to selectively analyse the aqueous layer of the biphasic reaction mixture, we set out to establish standard ^{11}B signals of the boron species expected (Figure 12). As shown there is a distinct difference between the neutral boronic acid (**A7a** = 29.7 ppm) and the neutral BPin species (**A8b** = 31.0 ppm). Similarly, signals between their cognate boronates (**A7d** = 3.7 ppm, **A8e** = 6.0 ppm) can also be differentiated. This enables the specific species to be monitored and identified as they cross in to the aqueous layer.

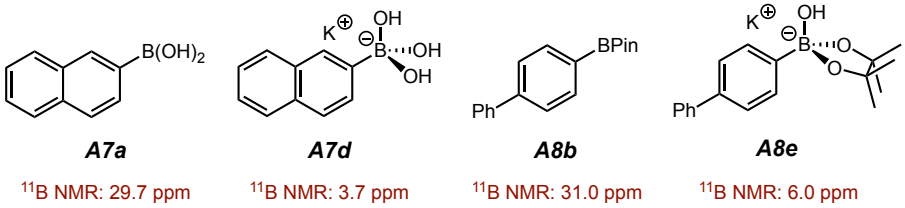
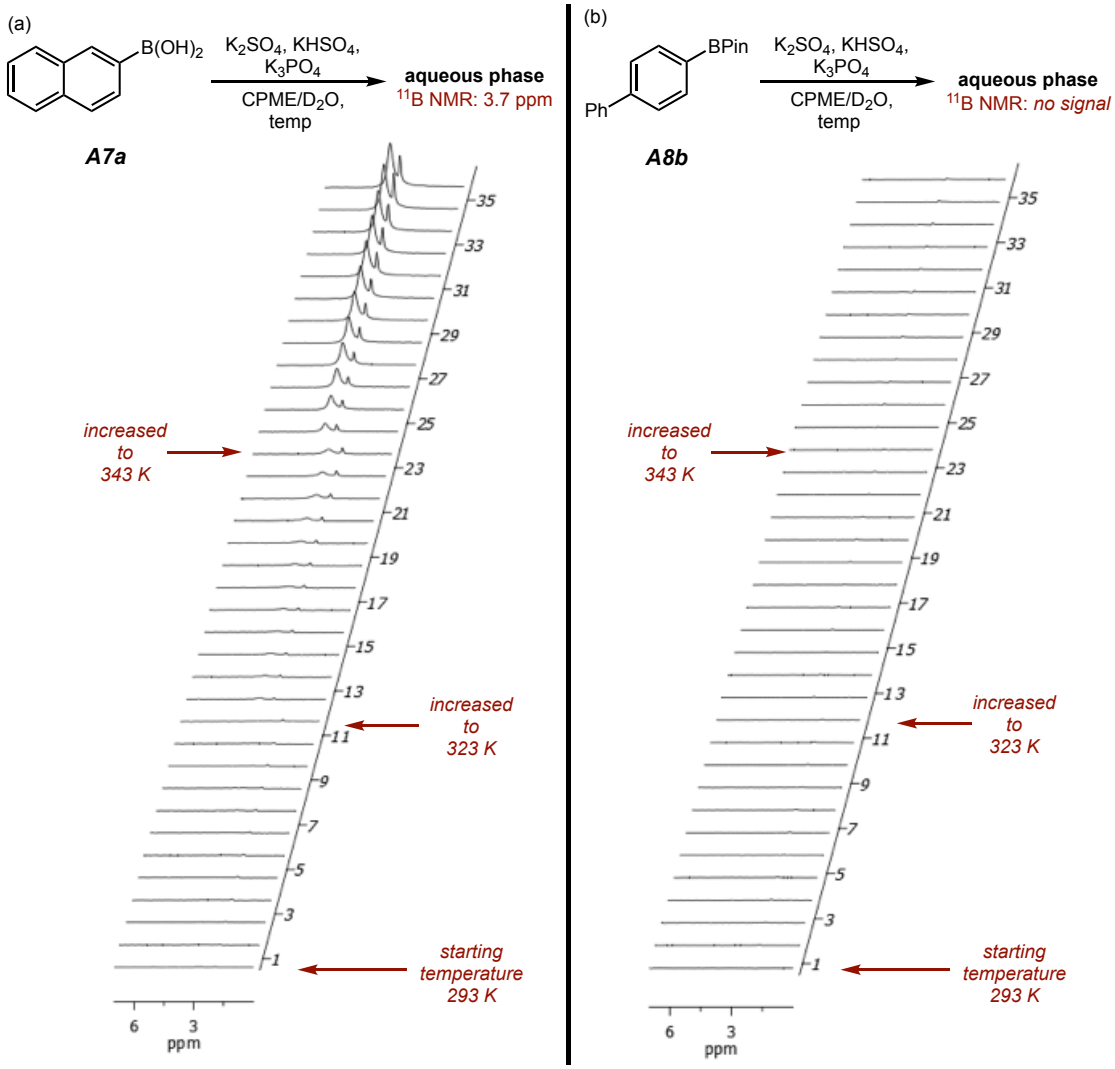


Figure 12: ^{11}B NMR signals of expected species

The NMR study began by analysing the distribution of boron species **A7a** and **A8b** in isolated systems under model reaction conditions (Scheme 68). As demonstrated the reaction of **A7a** shows clear transfer of the boronic acid to the aqueous phase as the trihydroxyboronate **A7d**, as shown in Scheme 68a. Notably the concentration of the boronate species steadily increases with increasing time and temperature similar to previous observations. There was no detection of the neutral species **A7a**. This

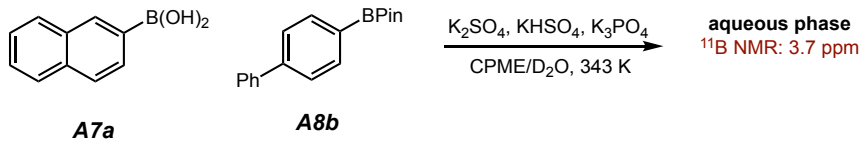
provides qualitative data that the boronic acid resides in the aqueous phase as the boronate. When exposing BPin **A8b** to the reaction conditions no signal was observed by ^{11}B NMR in the aqueous layer as expected (Scheme 68b), providing further evidence that the BPin species resides in the organic layer and is not transferred to the aqueous phase. It must be noted that a shift in signal is observed when increasing temperature due to the effect on relaxation time, which is common to NMR techniques.[139]



Scheme 68: ^{11}B NMR analysis of biphasic mixture containing: a) A7a; b) A8b

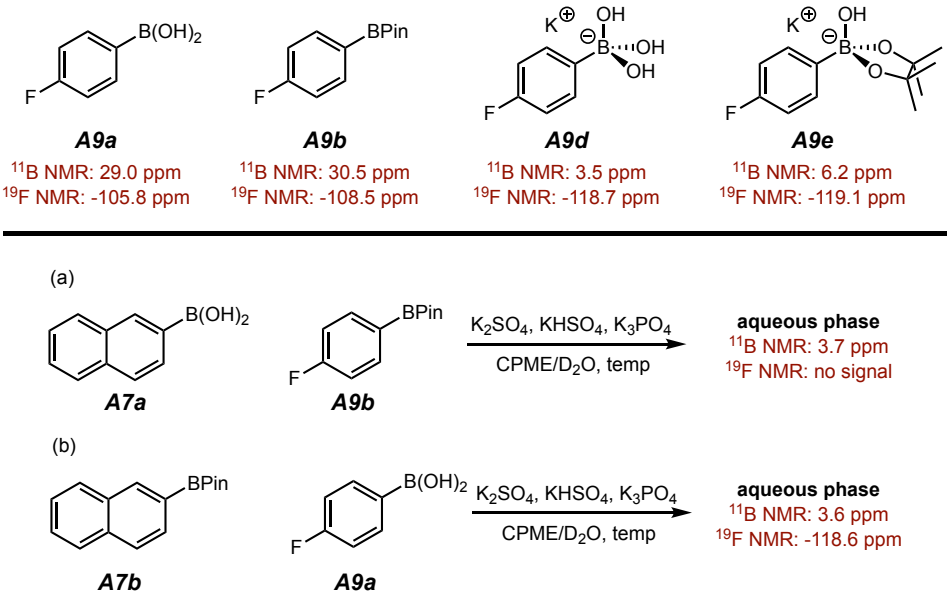
Analysis of the competing biaryl system provided similar results (Scheme 69). In the presence of both boron species, with the potential for all four signals to be observed in the aqueous phase (Figure 12), only trihydroxyboronate **A7d** signal was detected by ^{11}B NMR (3.7 ppm). Again, incorporation of the trihydroxyboronate in to the

aqueous phase increased with increasing temperature. However, the signal could arise from pinacol cleavage to the corresponding biphenyl trihydroxyboronate (**A8d**, 3.6 ppm) and this was a potential doubt we looked to dispel.

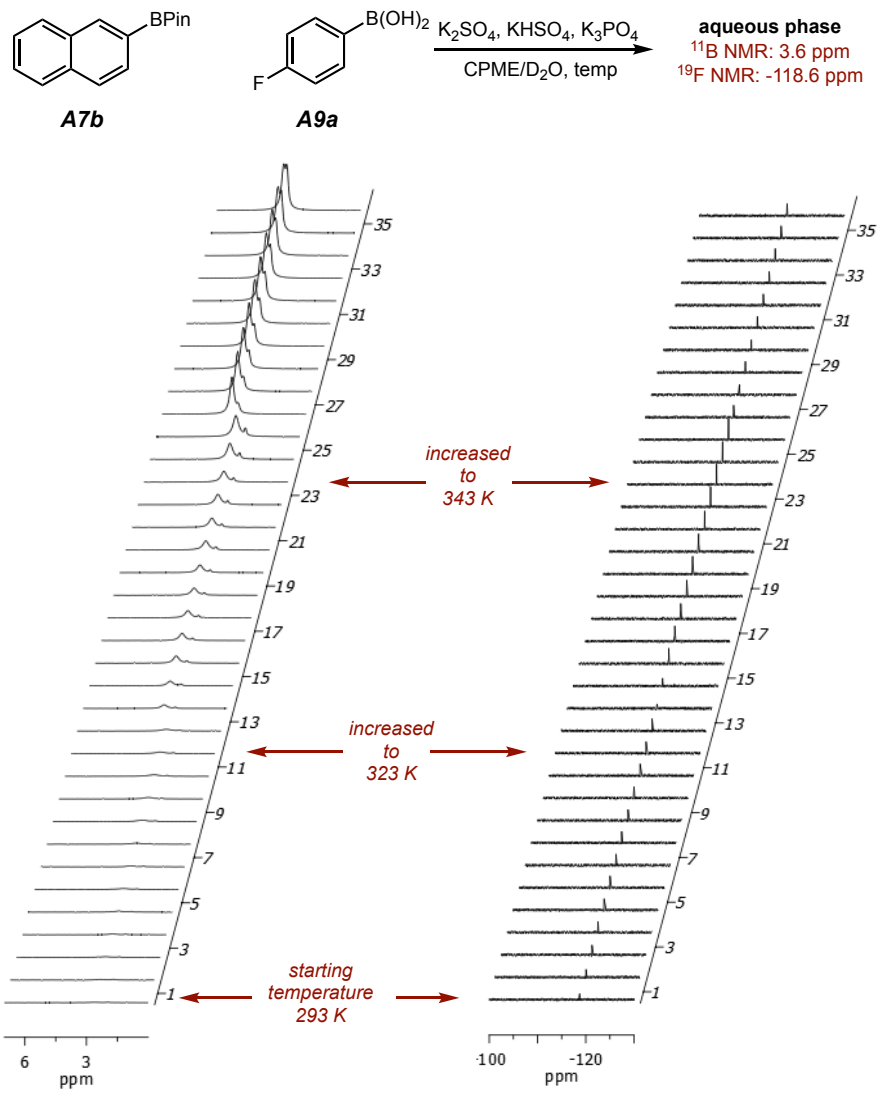


Scheme 69: ^{11}B NMR analysis of biphasic mixture containing competing diboron species A7a and A8b

It was believed incorporating a fluorine tag into the competing biaryl system would provide unambiguous proof of selective transfer of the boronic acid species to the aqueous phase with confirmation via ^{19}F NMR (Scheme 70). The analysis of naphthalene boronic acid **A7a** and 4-fluoro BPin **A9b** provided a boron signal specific to **A7d** (Scheme 70a). However, no fluorine signal was detected by ^{19}F NMR. Switching the fluorine tag and analysing 4-fluoro boronic acid **A9a** and naphthalene BPin **A7b** led to both ^{11}B (3.6 ppm) and ^{19}F (-118.6 ppm) signals (Scheme 71), which correlate to the 4-fluoro trihydroxyboronate species **A9d**. Throughout both experiments no signals which correlate to the BPin species were detected in the aqueous phase, providing further evidence to support our hypothesis.



Scheme 70: ^{11}B and ^{19}F NMR analysis of mono-fluorinated diboron systems under biphasic conditions



Scheme 71: ^{11}B and ^{19}F NMR analysis of biphasic mixture containing competing diboron species A7b and A9a

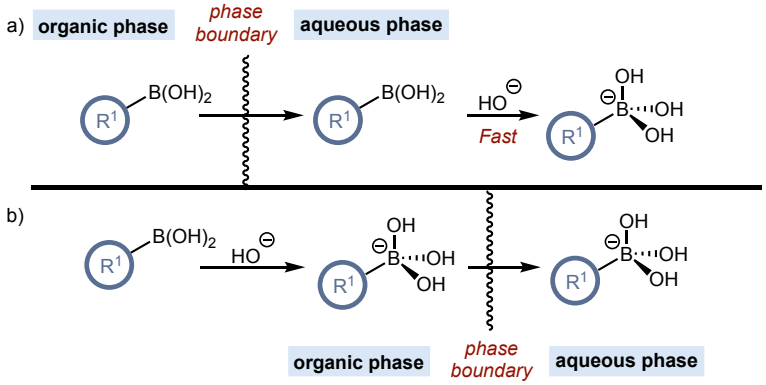
In summary, the use of HPLC has provided quantitative evidence for selective phase transfer of boronic acids in the presence of BPins, supporting our initial hypothesis. Unique NMR experiments have further supported initial HPLC data and have revealed the oxidation state of the boron species which resides in the aqueous layer, a trihydroxyboronate species. Despite this, a key aspect still eludes this study: How exactly is the boronic acid transferred? There are two proposed possibilities of how this could occur (Scheme 72):

1. Boronic acids are partially soluble in aqueous media (for cLogP values please see experimental section, Section 2.5.7 cLogP Parameters for Boron

Species). It is possible that the neutral boronic acid, residing in the organic phase, comes into contact with the aqueous phase at the phase boundary, where it is solubilised. The p-orbital of the Lewis acidic neutral boronic acid is then instantly occupied by a hydroxide anion in the sea of basic media, forming the trihydroxyboronate species (Scheme 72a), which is observed by NMR.

2. It can also be conceived that hydroxide anions are partially solvated in the organic media in which the boronic acid resides. It is proposed that this can enable boronate formation through ligand association in the organic phase, a proposed barrierless process.[17] As boronates are more soluble in aqueous media, it is proposed the boronate can pass to the aqueous layer by diffusion control wherein oxidation occurs (Scheme 72b).

Specialist NMR techniques would be required to elucidate which mode of transportation is operational, as this most probably occurs directly at the phase boundary.



Scheme 72: Proposed methods of boronic acid phase transfer: a) As the neutral boronic acid; b) as the preformed trihydroxyboronate

A side note of particular interest was the detection of boronate species [$B(OH)_4^-$] (3.1 ppm) derived from boric acid, formed as a result of protodeboronation in the absence of active oxidant (Figure 13). This was observed to increase with both time and temperature. Although in this study protodeboronation is inconsequential as oxidation is believed to be rapid in the aqueous phase, this data has significant

ramifications for palladium catalysis in which boronic acids and biphasic conditions are employed, for example, the SM reaction.[62] Formation of a boronate species in the aqueous phase can be detrimental to reactivity in the SM reaction where transmetalation proceeds preferentially via a neutral organoboron species with a presumably largely organic phase-bound catalyst.[2] The data collected also suggests increasing temperature and base equivalents may not enhance SM reactivity, as protodeboronation and boronic acid phase transfer increase as a result.

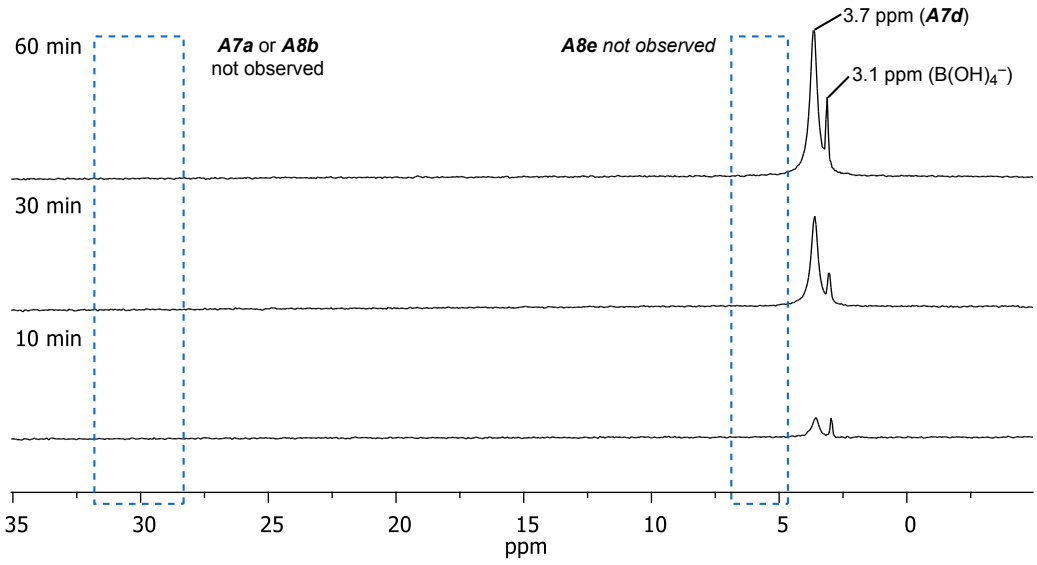
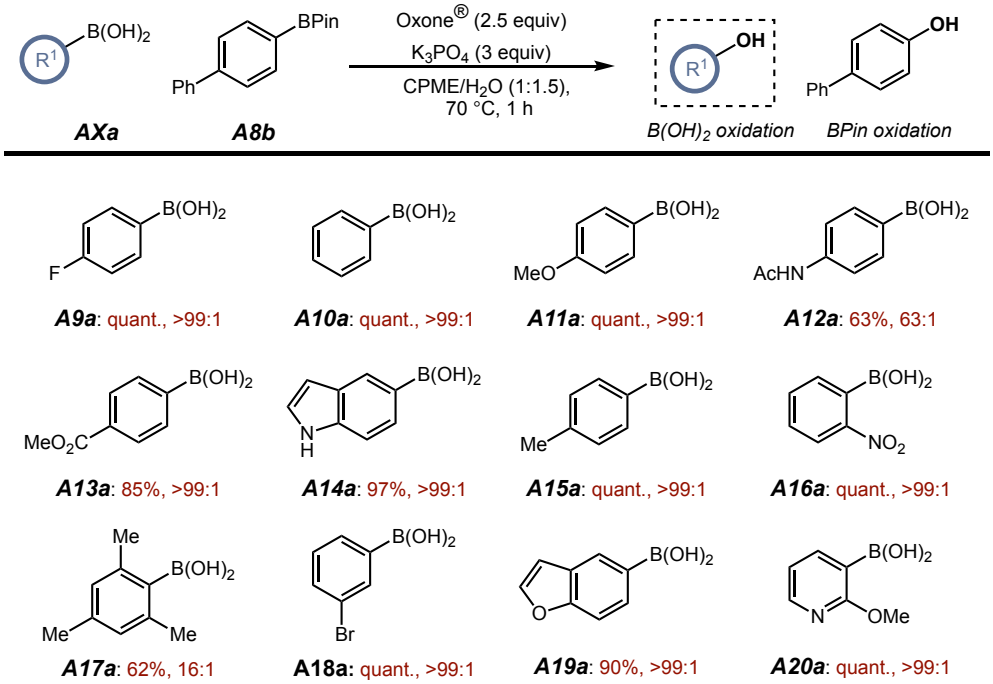


Figure 13: Time proportional concentration of A7d in the aqueous phase

2.2.4 Application

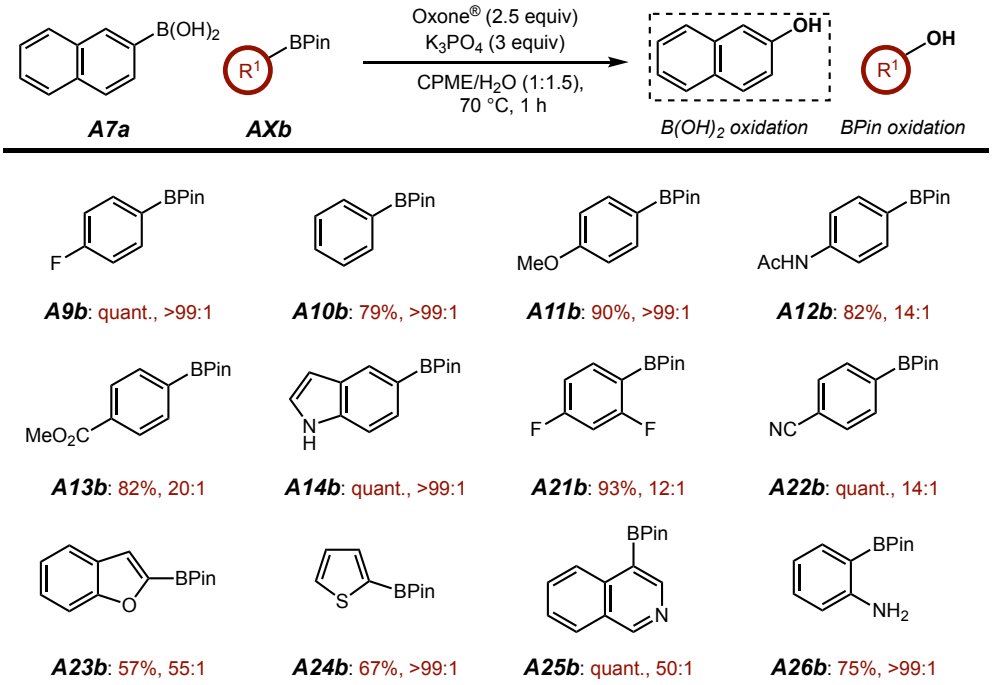
With optimised conditions and a firm understanding of the origin of chemoselectivity in hand, we set out to explore the generality of this process (Scheme 73). The utility of the boronic acid component was first assessed against the standard BPin **A8b**. The reaction typically demonstrated complete selectivity for the boronic acid proceeding with complete conversion in many instances. The reaction tolerated the use of electron donating groups (**A11a**), as well as electron deficient groups (**A9a**, **A13a**, **A16a**, and **A18a**) in *para*, *meta*, and *ortho* positions. Heterocycles could also be employed as the boronic acid component (**A14a**, **A19a**, and **A20a**), with all providing high selectivity for the boronic acid and high conversion of the boronic acid to the corresponding phenol. Interestingly, the highly hindered and lipophilic

boronic acid **A17a** was also preferentially oxidised over the BPin species. However, conversion and selectivity were significantly lower.



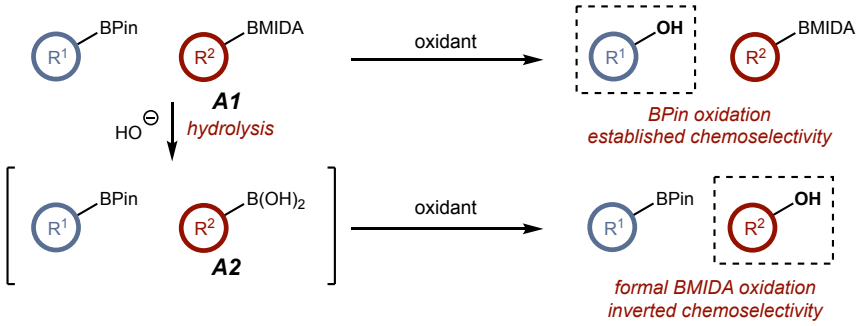
Scheme 73: Chemoselective oxidation of aryl diboron systems – boronic acid scope, ratio given for oxidation of AXa:AXb

A more notable challenge in this project would be to vary the BPin species, as this may affect the associated Lewis acidity/solubility and thereby affect its ionisation and distribution between phases. Using the standard boronic acid (**A7a**) a range of different BPins were trialled under chemoselective oxidation conditions (Scheme 74). Again, conversion was typically high with moderate to excellent chemoselectivity. The use of electron donating groups (**A11b** and **A26b**) led to complete chemoselectivity and conversion. However, it was noted that application of electron deficient BPin species (**A9b**, **A13b**, **A21b**, and **A22b**) often led to diminished chemoselectivity which could be attributed to a more Lewis acidic and aqueous soluble BPin species. Interestingly, heterocyclic species were also retained in the organic phase providing high chemoselectivity in favour of the boronic acid and good conversion to the phenol. The generality across both substrate scopes excellently demonstrates that despite any changes in functionality in both species, chemoselectivity is dominated solely by the boron species employed.



Scheme 74: Chemoselective oxidation of aryl diboron systems – BPin scope, ratio given for oxidation of AXa:AXb

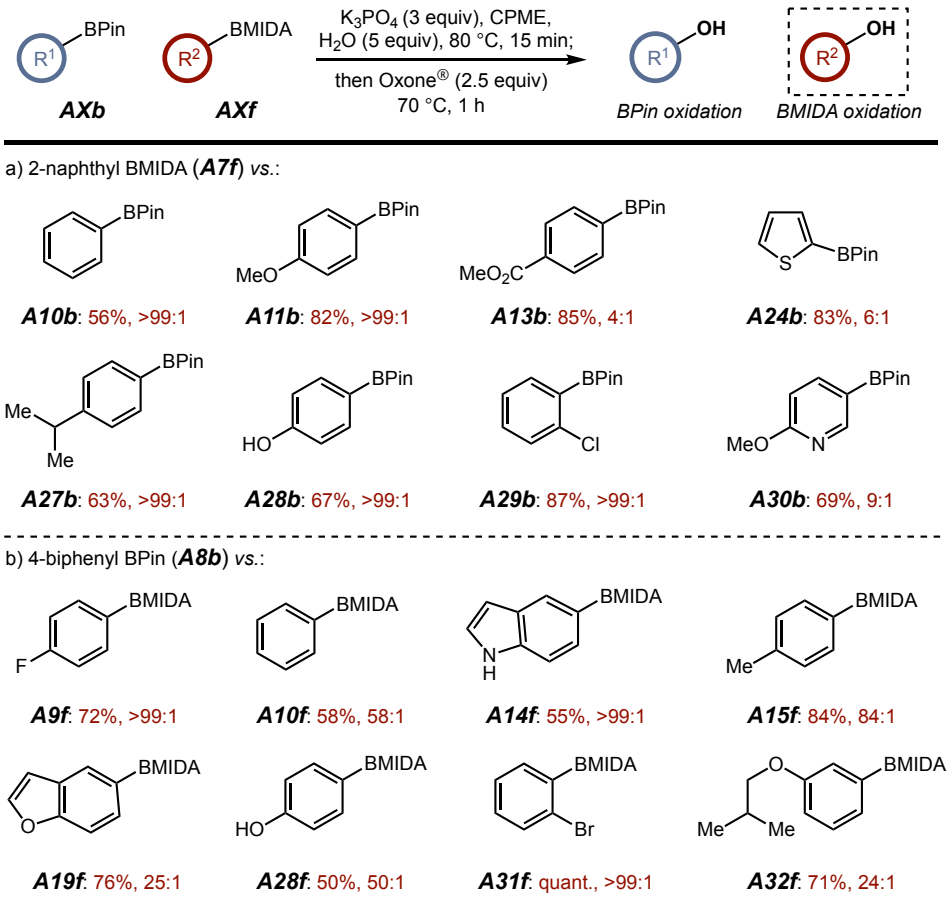
With a substrate scope for chemoselective oxidation of competing organoborons firmly in place, we looked to push the boundaries of this chemistry and challenge established chemoselectivity (Scheme 75).[48] It was proposed that hydrolysis of a BMIDA species (**A1**), while forgoing any boron speciation events, would generate a boronic acid intermediate (**A2**) which could then be chemoselectivity oxidised using our developed conditions. This would provide a formal chemoselective oxidation of a BMIDA protecting group species over a significantly more reactive BPin, inverting traditional chemoselectivity.[130]



Scheme 75: Inverting established chemoselectivity

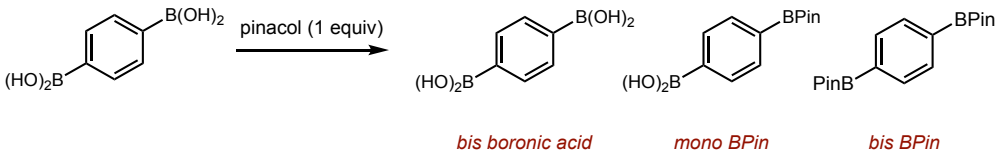
After a brief time and temperature study (see experimental Section 2.5.3 Reaction Optimisation) on the hydrolysis of the BMIDA species in the presence of the BPin, optimised conditions were obtained (Scheme 76). Stirring the reaction at 80 °C in the absence of oxidant enabled clean hydrolysis of the BMIDA species forgoing any boron speciation. A slurry of Oxone® in water could then be added and the standard reaction could proceed at 70 °C for 1 hour.

Altering the BPin component provided varied results with typically electron rich/neutral species (**A10b**, **A11b**, **A27b**, and **A28b**) providing enhanced selectivity with moderate to good conversion (Scheme 76a). However, the application of electron poor/heterocyclic BPins (**A13b**, **A24b**, and **A30b**) led to erosion of selectivity. This could be attributed to their enhanced Lewis acidity leading to pinacol cleavage and subsequent equilibration during the hydrolysis stage of the procedure. Similarly, a range of BMIDAs were selectively oxidised in the presence of standard BPin **A8b** with typically good conversion and selectivity (Scheme 76b). Electron deficient (**A9f** and **A31f**), electron rich (**A28f** and **A32f**), and heterocyclic BMIDA species (**A14f** and **A19f**) all provided excellent selectivity under the reaction conditions with moderate to excellent yield.



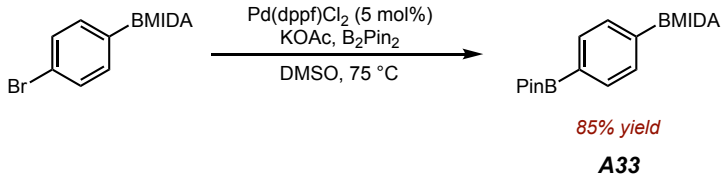
Scheme 76: Chemoselective oxidation of aryl diboron systems – BMIDA oxidation, ratio given for oxidation of AXf:AXb

Unfortunately, during the substrate scope several limitations of the methodology were uncovered. The chemoselective oxidation conditions were examined against a monoaryl system containing two boron substituents which could be readily oxidised. However, synthesis of the boronic acid/BPin species was extremely difficult (Scheme 77). Although the diboron species could be readily formed and seen by crude NMR/TLC. The use of column chromatography (silica, alumina, C_{18}) led to equilibration forming predominantly the bis BPin and bis boronic acid species. As a result, synthesis of this substrate was no longer explored.

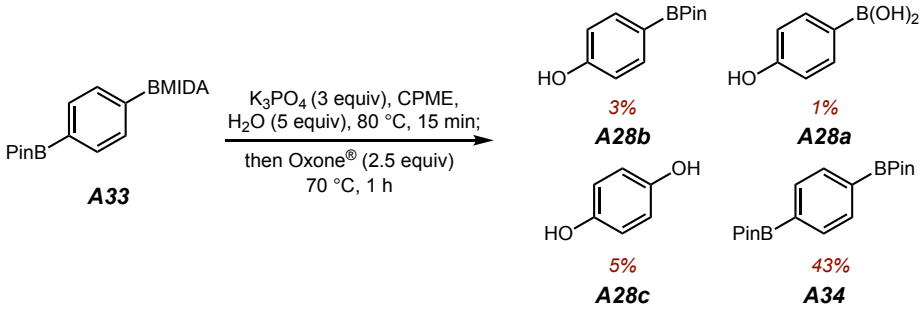


Scheme 77: Unsuccessful synthesis of monoaryl diboron system

Despite this, the equivalent BMIDA species **A33** could be readily accessed via a Miyaura borylation (Scheme 78). However, reacting this substrate under model conditions for BMIDA oxidation further solidified our hypothesis that both boron substituents had to be physically separated to achieve chemoselectivity. The reaction led to a series of by-products which could be identified and quantified by HPLC (Scheme 79). By-product formation was attributed to boron speciation during hydrolysis and only 3% of the desired oxidised product (**A28b**) was observed.



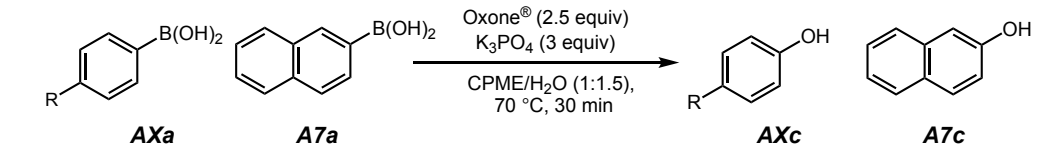
Scheme 78: Miyaura boroylation for the synthesis of diboron species A33



Scheme 79: Unsuccessful chemoselective oxidation of diboron species A33

Chemoselectivity has thus far been readily achieved between dissimilar boron species ($B(OH)_2$ vs BPin, BMIDA vs BPin). As physical properties of organoboron species are governed by their electronics,[125] it was proposed that selective discrimination between competing boronic acids may be achievable by exploiting their differences in boronate formation and aqueous solubility. It was believed that this phenomenon could be predicted *a priori* by HPLC and NMR analysis of the phase distribution of the competing boronic acids system (Scheme 80). As shown, HPLC analysis demonstrated preferential transfer of the monoaryl boronic acid to the aqueous phase, whereas the naphthyl boronic acid **A7a** preferentially resided in the organic layer on each occasion (average 71:29, org/aq, cLogP = 2.64). This can also be correlated by comparing the cLogP values of the parent boronic acids. The boronic acid with the higher calculated aqueous solubility (lower value) is

preferentially oxidised. It should be noted that boronic acid species **A35a** rapidly underwent protodeboronation in the absence of active oxidant leading to distribution between phases being less reliable as an indicator for selectivity.



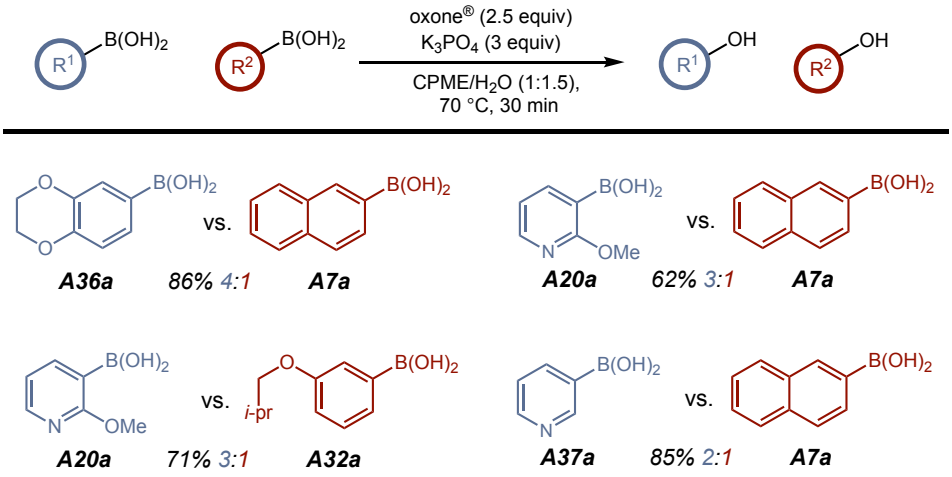
AXa ***A7a*** ***AXc*** ***A7c***

2-naphthyl	MeO-	H-	F-	MeO_2C-	O_2N-
A7a	***A11a***	***A10a***	***A9a***	***A13a***	***A35a***
71/29	0/100	5/95	20/80	9/91	11/14
-	*4:1*	*6.5:1*	*8:1*	*3:1*	*4.5:1*
2.64	*1.39*	*1.64*	*1.74*	*1.79*	*1.59*

HPLC distribution ratio Org/Aq Oxidation ratio (AXc:A7c) cLogP

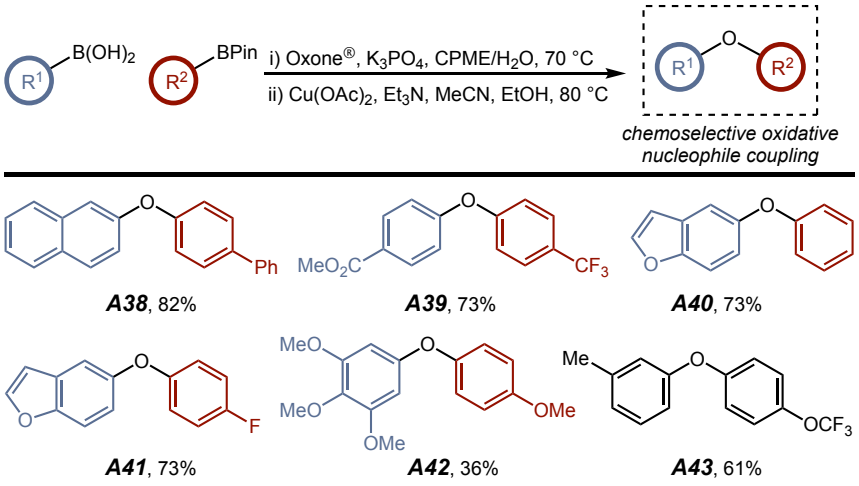
Scheme 80: Phase distribution and chemoselective oxidation of competing boronic acids

Unfortunately, the boronic acid phase distribution ratio did not directly correlate with the ratio of selectivity observed in selective oxidation. However, a range of *para* substituted aryl boronic acids could be selectively oxidised over the 2-naphthyl species with reasonable selectivity. With this selectivity in hand, we sought to explore other competing boronic acids (Scheme 81). Although a range of boronic acids could be selectively oxidised in the presence of a more lipophilic boronic acid species, selectivity was often poor to moderate and conversion after 30 minutes could also be relatively low. However, to the best of our knowledge, this represents the first selective oxidation of two identical species based only on their subtle difference in substituents.



Scheme 81: Selective oxidation of competing aryl boronic acids

It was believed that chemoselective oxidation could be leveraged for synthetic gain. The continuous development of modern catalysis, such as Ir-catalysed C-H activation,[140,141] has allowed expedient access to borylated arenes with substitution patterns which are difficult to access by other means. Due to the continued interest in the Chan-Evans-Lam (CEL) reaction within our laboratory,[142,143] A chemoselective oxidation/CEL etherification protocol to expediently access biaryl ethers was examined (Scheme 82). The oxidative nucleophile cross-coupling enables the synthesis of scaffolds prominent in natural products, pharmaceuticals, and materials.[144] Yields of the two-step process were generally high, with minimal homocoupling of either species observed. A notable example was the synthesis of **A42**, a biaryl ether derivative, combretastatin-A4, with known anticancer activity.[145]

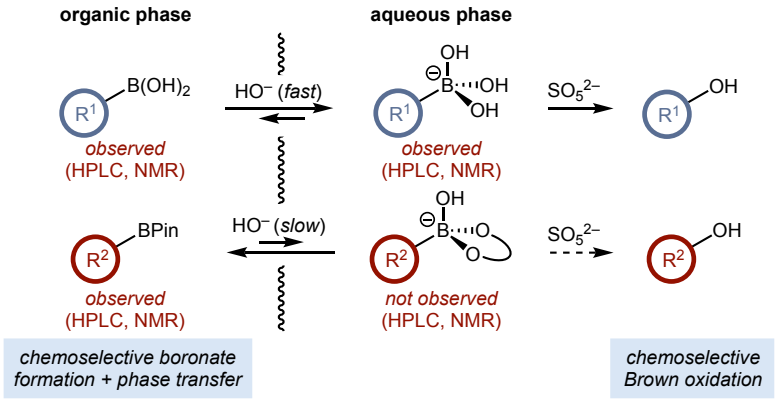


Scheme 82: Chemoselective oxidative nucleophile coupling

2.3 Conclusion

In summary, a chemoselective oxidation of two ostensibly equivalent organoboron species (boronic acid vs. BPin) has been achieved. Although this was initially believed to be enabled by kinetic favourability of the more reactive boronic acid species, spectroscopic investigation by HPLC and NMR concluded that chemoselectivity was a direct result of selective phase transfer of the more Lewis acidic and therefore aqueous soluble boronic acid to an oxidant-rich aqueous phase, while retaining the BPin species in the organic phase (Scheme 83). HPLC and NMR analysis also elucidated the counterintuitive optimisation observed as selectivity increased with increasing temperature, which was due to enhanced phase transfer rates of the boronic acid. The generality of this procedure was thoroughly exemplified through the generation of an expansive substrate scope which showed that chemoselectivity between a boronic acid and a BPin could be achieved irrespective of substituents on both species.

This phenomenon was further advanced to permit a formal chemoselective oxidation of a BMIDA species in the presence of a more reactive BPin. Hydrolysis of the BMIDA species to the corresponding boronic acid, while forgoing any boron speciation events, allowed traditional chemoselectivity to be inverted. Similarly, selectivity between competing boronic acids could also be readily achieved with selectivity being predicted *a priori* through phase distribution analysis by HPLC. The project was completed through the application of a sequential chemoselective oxidation/CEL protocol to grant expedient access to biaryl ethers.

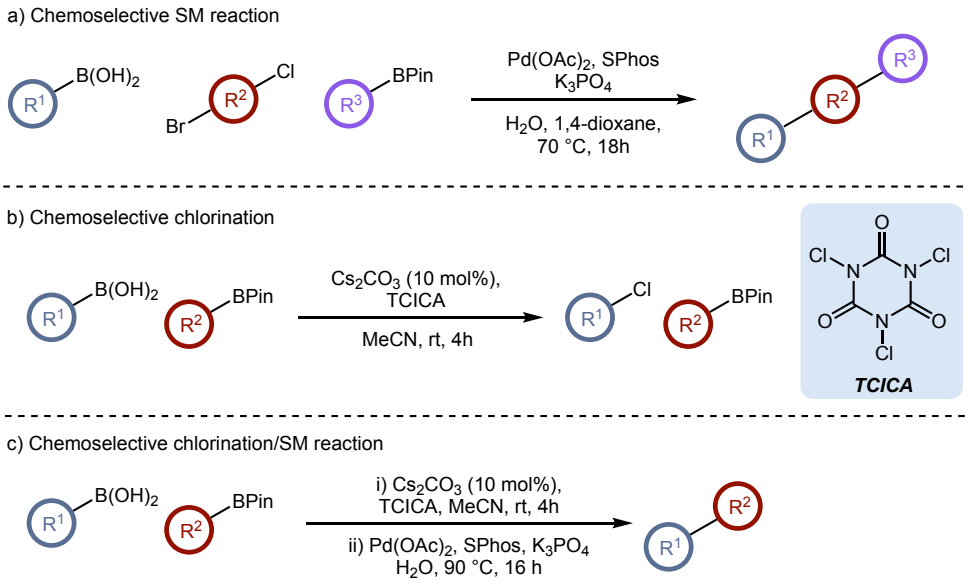


Scheme 83: Chemoselective oxidation of competing diboron systems

A note of particular interest is the concept of boronic acid phase transfer and its effect on the wider synthetic community. In industry, large amounts of water are typically employed in SM reactions in the presence of base which often leads to an aqueous basic biphase.[2] The evidence presented in this thesis shows that use of these conditions may lead to unfavourable boronate formation, protodeboronation, and isolation from the presumably organic-phase bound lipophilic catalyst system. Increasing temperature only enhances these effects and may not improve catalysis.

2.4 Future Work

Pleasingly, these seminal studies have laid down the foundation for chemoselectivity to be achieved between ostensibly equivalent boron species in a series of different transformations (Scheme 84). The group have been able to capitalise on the established kinetic difference between boronic acids and BPins, while avoiding boron speciation and phase transfer obstacles, to enable chemoselective SM without the necessity for boron protecting groups (Scheme 84a).[146] Similarly, the subtle differences in Lewis acidity between boronic acids and BPins was further capitalised upon to enable selective boronate formation/chlorination of boronic acids in the presence of a BPin species (Scheme 84b).[147] In addition, this phenomenon was further enhanced to enable a one-pot chemoselective chlorination/SM cross-coupling protocol (Scheme 84c).[147]



Scheme 84: Chemoselective manipulations of ostensibly equivalent organoborons

While chemoselectivity, and the origin of this chemoselectivity, between competing boron species has been thoroughly established, there remains one fundamental aspect which isn't yet fully understood: The method of phase transfer of the boronic acid species. As stated previously, this would require specialist NMR techniques to unearth the true mode of phase transfer. The Lloyd-Jones group have recently made use of an NMR system which can move vertically up and down a tube and take scans of various parts of the NMR tube. This allows accurate data to be captured in the organic phase, directly at the phase boundary, and in the aqueous phase. The use of this technique may identify the concentration and oxidation state of the boron species directly before the phase transfer, during the phase transfer at the phase boundary, and directly after phase transfer in the aqueous phase. This technique will also allow this process to be monitored over time.

2.5 Experimental

2.5.1 General

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[148]

Purification of Solvents

Dry THF and toluene 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. CH_2Cl_2, Et_2O, CPME, EtOAc, MeCN, 1,4-dioxane, 2-MeTHF, DMF, IPA, $CHCl_3$, and petroleum ether 40-60° for purification purposes were used as obtained from suppliers without further purification.

Drying of Inorganic Bases

K_3PO_4, K_2CO_3, and Cs_2CO_3 were dried in a Heraeus Vacutherm oven at 60 °C under vacuum for a minimum of 24 hours before use.

Experimental Details

Reactions were carried out using conventional glassware (preparation of intermediates) or in capped 5 mL microwave vials (for all other experiments excluding NMR study). Microwave vials were purchased from Biotage (2–5 mL Biotage Microwave Reaction Kit, catalogue number 351521). Magnetic stirrer bars were used as supplied in the Biotage Microwave Reaction Kit. The glassware was oven-dried (150 °C) and purged with N_2 before use. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature was generally *ca.* 20 °C. Reactions were carried out at elevated temperatures in a sand bath using a temperature-regulated hotplate/stirrer. Temperature quoted is a measurement of the sand bath heating block. Temperature-regulated hotplate/stirrers employed over the course of this study were either of the following: An IKA® RCT basic, a Heidolph MR 3004 safety, or Heidolph MR 3002.

Purification of Products

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

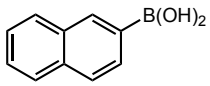
Analysis of Products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{19}F NMR spectra were obtained on a Bruker AV 400 spectrometer (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 101 MHz, respectively, or Bruker Ascend AV(III) HD 500 at 500 MHz and 126 MHz, respectively. ^{11}B NMR was obtained in Norell® natural quartz 5 mm NMR tubes (500 MHz limit). Chemical shifts are reported in ppm and coupling constants are reported in Hz: $CDCl_3$ is referenced at 7.26 (^{1}H) and 77.0 (^{13}C), DMSO-d_6 referenced at 2.50 (^{1}H) and 39.5 (^{13}C). High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University –or at the Mass Spectrometry Facility at Glasgow University. Reversed phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column, which was maintained at a constant temperature of 40 °C. Analysis was performed using a gradient method, eluting with 5–80% MeCN/H_2O over 16 min 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 – with a 1:4 ratio caffeine/product unless stated otherwise. cLogP values were obtained from JChem for excel.[149]

2.5.2 General Experimental Procedures

General Procedure A: Oxidation Study of Monoaryl Boron System (Table 1 and Chart 1)

For example, oxidation of naphthalen-2-ylboronic acid, **A7a**

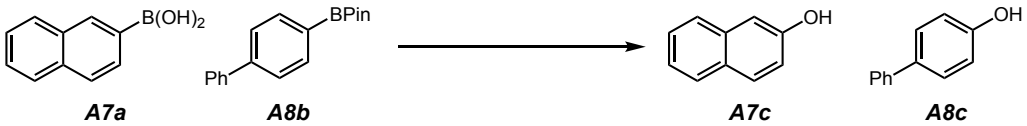


A7a

To an oven-dried microwave vial was added naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv). THF (0.63 mL, 0.25 M) was added followed by a slurry of Oxone® (125 mg, 0.40 mmol, 2.5 equiv) in H_2O (1.28 mL). The reaction mixture was stirred at room temperature for 30 min. Sodium metabisulphite (122 mg, 0.64 mmol, 4 equiv) was added and conversion to product was determined by HPLC against an internal standard (caffeine) indicating oxidation of the naphthalen-2-ylboronic acid (98% conversion).

General Procedure B: Optimized Reaction, Boronic Acid *vs.* BPin or Boronic Acid (Tables 2–7, and Schemes 73, 74, 80, and 81)

For example, selective oxidation of naphthalen-2-ylboronic acid (**A7a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



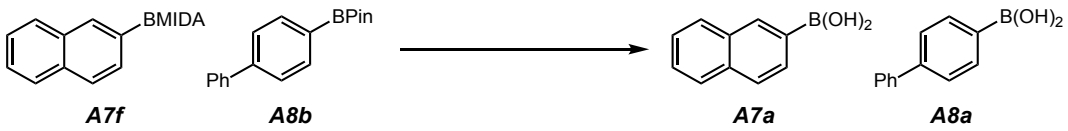
A7a ***A8b*** ***A7c*** ***A8c***

To an oven-dried 5 mL microwave vial was added naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), and K_3PO_4 (103 mg, 0.48 mmol, 3 equiv). CPME (0.63 mL, 0.25 M) was added followed by a slurry of Oxone® (125 mg, 0.40 mmol, 2.5 equiv) in H_2O (1.28 mL) and CPME (0.25 mL). The reaction mixture was then heated to 70 °C with stirring in a sand bath for 1 h. The reaction was allowed to cool to room temperature before addition of sodium metabisulphite (122 mg, 0.64 mmol, 4 equiv). Conversion

to products was determined by HPLC against an internal standard (caffeine) indicating selective oxidation of the naphthalen-2-ylboronic acid (quant., >99:1 selectivity).

General Procedure C: BMIDA Hydrolysis Optimization

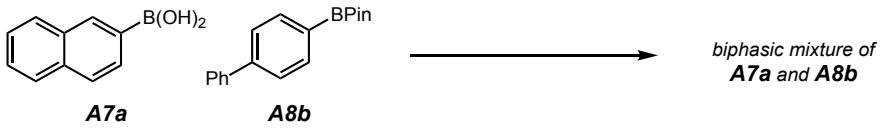
For example, selective hydrolysis of naphthalen-2-ylboronic acid, MIDA ester (**A7f**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



To an oven dried 5 mL microwave vial was added naphthalen-2-ylboronic acid, MIDA ester (45 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), and K_3PO_4 (103 mg, 0.48 mmol, 3 equiv). The vial was then capped and purged with N_2 before addition of CPME (0.63 mL, 0.25 M) and H_2O (14.5 μL, 0.80 mmol, 5 equiv). The reaction mixture was then heated to 80 °C in a sand bath with stirring for 15 min. Conversion to products was determined by HPLC against an internal standard (caffeine) indicating selective hydrolysis of naphthalen-2-ylboronic acid, MIDA ester (86% conversion, 85:1 selectivity).

General Procedure D: Origin of Chemoselectivity – HPLC Analysis (Table 8)

For example, HPLC analysis of a biphasic system for naphthalen-2-ylboronic acid (**A7a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)

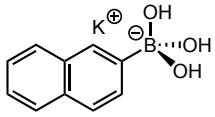


To an oven-dried 5 mL microwave vial was added naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), $KHSO_4$ (27 mg, 0.2 mmol, 1.25 equiv), and K_2SO_4 (34 mg, 0.2 mmol, 1.25 equiv). A mixture of H_2O (1.28 mL) and CPME (0.88 mL) were added and the reaction mixture was heated to 70 °C with

stirring in a sand bath for 10 min. The reaction mixture was removed from agitation and allowed to settle to form a biphase. A 200 µL aliquot was removed from each phase (aqueous and organic) and distribution of products was determined by HPLC against a known quantity of internal standard (caffeine) indicating selective phase transfer of naphthalen-2-ylboronic acid **A7a**, 54:46 (organic/aqueous), **A8b**, >99:1 (organic/aqueous).

General Procedure E: Boronate Formation of Boron Species (Figure 12)

For example, synthesis of potassium trihydroxy(naphthalen-2-yl)borate, **A7d**

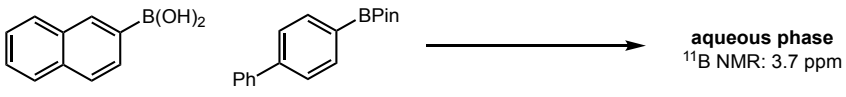


A7d

Naphthalen-2-ylboronic acid (6.1 mg, 0.036 mmol, 1 equiv) and K_3PO_4 (22.7 mg, 0.11 mmol, 3 equiv) were weighed out into a vial. D_2O (0.75 ml) was added and the mixture was sonicated until a solution was formed. The solution was transferred to a quartz NMR tube and a ^{11}B NMR spectrum was recorded at 343 K. Potassium trihydroxy(naphthalen-2-yl)borate provided a signal at 3.7 ppm.

General Procedure F: Origin of Chemoselectivity – NMR Analysis (Scheme 68–71)

For example, NMR analysis of biphasic system for naphthalen-2-ylboronic acid (**A7a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



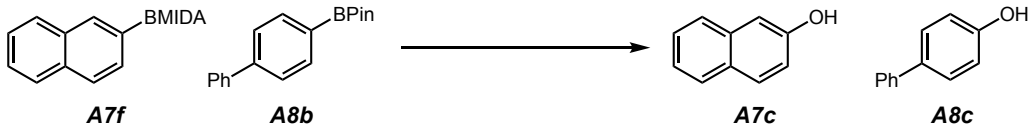
A7a ***A9a***

Naphthalen-2-ylboronic acid (17.2 mg, 0.1 mmol, 1 equiv) and [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (28 mg, 0.1 mmol, 1 equiv) were dissolved in CPME (0.4 mL, 0.25 M) and transferred to a quartz NMR tube (Tube A). K_3PO_4 (63 mg, 0.3 mmol, 3 equiv), $KHSO_4$ (17 mg, 0.125 mmol, 1.25 equiv), and K_2SO_4 (21.5 mg, 0.125 mmol, 1.25 equiv) were weighed out into a vial (Vial A) and were dissolved in

D_2O (0.8 mL) for later use. A D_2O blank (0.8 mL) NMR sample tube (Tube B) was prepared and used as a lock on the NMR machine. After locking (Tube B) was complete, Vial A containing inorganics was transferred slowly via syringe and long needle (needle must reach the bottom of the NMR tube) to Tube A to generate an aqueous biphasic system. The biphasic NMR sample (Tube A) was placed in the magnet and after shimming a data set was recorded every 5 min for 1 h at 293 K (128 scan per data set recording). After 1 h the temperature was increased to 323 K and a data set was recorded every 5 min for 1 h. After 1 h the temperature was further increased to 343 K and a data set was recorded every 5 min for 1 h. (No spinning was used in this NMR study)

General Procedure G: Optimized Reaction BMIDA *vs.* BPin

For example, selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (**A7f**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)

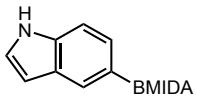


A7f ***A8b*** ***A7c*** ***A8c***

To an oven dried 5 mL microwave vial was added naphthalen-2-ylboronic acid, MIDA ester (45 mg, 0.16 mmol, 1 equiv), phenylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), and K_3PO_4 (103 mg, 0.48 mmol, 3 equiv). The vial was then capped and purged with N_2 before addition of CPME (0.63 mL, 0.25 M) and H_2O (14.5 μL, 0.80 mmol, 5 equiv). The reaction mixture was then heated to 80 °C in a sand bath with stirring for 10 min. The vial was then decapped and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was heated to 70 °C with stirring in a sand bath for 1 h. The reaction was allowed to cool to room temperature before addition of sodium metabisulphite (122 mg, 0.64 mmol, 4 equiv). Conversion to products was determined by HPLC against an internal standard (caffeine) indicating selective oxidation of the naphthalen-2-ylboronic acid, MIDA ester (56% conversion, >99:1 selectivity).

General Procedure H: Synthesis of MIDA Esters from Boronic Acids

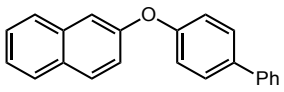
For example, for the preparation of (1*H*-indol-5-yl)boronic acid, MIDA ester, **S1**



A mixture of (1*H*-indol-5-yl)boronic acid (2 g, 12.4 mmol, 1 equiv), *N*-methyliminodiacetic acid (1.9 g, 13.02 mmol, 1.05 equiv) in DMF (50 mL) was heated to 90 °C for 18 h. The reaction mixture was allowed to cool to room temperature and concentrated under vacuum to give an off-white slurry. EtOAc (100 mL) was added and the resulting precipitate was collected by filtration. The precipitate was washed with H_2O (2 × 50 mL) and Et_2O (2 × 50 mL) before being dried under vacuum to give the desired product as a white crystalline solid (3.3 g, 98%).

General Procedure I: Synthesis of Biaryl Ethers via Oxidative Nucleophile Coupling

For example, for the preparation of 2-([1,1'-biphenyl]-4-yloxy)naphthalene,



To an oven-dried 5 mL microwave vial was added naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (225 mg, 0.8 mmol, 5 equiv), and K_3PO_4 (103 mg, 0.48 mmol, 3 equiv). CPME (0.63 mL, 0.25 M) was added followed by a slurry of Oxone® (125 mg, 0.40 mmol, 2.5 equiv) in H_2O (1.28 mL) and CPME (0.25 mL). The reaction mixture was heated to 70 °C with stirring in a sand bath for 1 h. The reaction was allowed to cool to room temperature before addition of sodium metabisulphite (122 mg, 0.64 mmol, 4 equiv). EtOAc (20 mL) was added and organics washed with NH_4Cl (50 mL), H_2O (50 mL), and brine (50 mL). Solvent was removed under reduced pressure and the residue was transferred into an oven-dried 5 mL microwave vial. $Cu(OAc)_2$(58 mg, 0.32 mmol, 2 equiv), powdered activated molecular sieves, MeCN (350 µ*L*), EtOH (16 µL), and Et_3N (45 µL, 0.32 mmol, 2 equiv) were added and the vial was sealed under air. The

reaction mixture was heated to 80 ˚C with stirring for 24 h. The reaction was allowed to cool to room temperature, EtOAc (20 mL) was added, and the mixture was passed through a layer of celite. The filtrate was washed with H_2O (50 mL) and brine (50 ml), dried through a hydrophobic frit, and solvent removed under reduced pressure. The crude product was purified by flash silica chromatography (0-10% EtOAc in petroleum ether) to yield the title compound as a white solid (39.1 mg, 82% yield).

2.5.3 Reaction Optimisation

Oxidation of Monoaryl Boron Systems

Oxidant Study (Table 1)

Reactions were carried out according to General Procedure A using either naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), or naphthalen-2-ylboronic acid, pinacol ester (40.6 mg, 0.16 mmol, 1 equiv), **oxidant** (0.4 mmol, 2.5 equiv), H_2O (1.28 mL), and THF (0.63 mL, 0.25 M). Reactions were run at room temperature for 30 min.

Entry	Boron Species	Oxidant	Conversion[a] (%)
1	A7a	30% wt. aq. H_2O_2 (45.3 µL)	24
2	A7b	30% wt. aq. H_2O_2 (45.3 µL)	19
3	A7a	$NaBO_3 \bullet 4H_2O$ (62 mg)	quant.
4	A7b	$NaBO_3 \bullet 4H_2O$ (62 mg)	quant.
5	A7a	50% wt. *m*CPBA (138.4 mg)	92
6	A7b	50% wt. *m*CPBA (138.4 mg)	75
7	A7a	Oxone® (125 mg)	98
8	A7b	Oxone® (125 mg)	22

[a] Determined by HPLC against a known internal standard (caffeine)

Time Study (Chart 1)

Reactions were carried out according to General Procedure A using either naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), or [1,1'-biphenyl]-4-

ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), Oxone® (125 mg, 0.4 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL), and THF (0.63 mL, 0.25 M). Reactions were run at room temperature for **X** min.

Entry	Boron Species	Time (min)	Conversion[a] (%)
1	A7a	0[b]	39
2	A7a	5	59
3	A7a	10	80
4	A7a	15	86
5	A7a	20	89
6	A7a	30	96
7	A7b	0[b]	4
8	A7b	5	9
9	A7b	10	12
10	A7b	15	17
11	A7b	20	20
12	A7b	30	23

[a] Determined by HPLC against a known internal standard (caffeine), [b] reaction quenched after 10 seconds

Boronic Acid vs BPin Selective Oxidation

Base and Water Study (Table 2)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), **K_3PO_4** (103 mg, 0.48 mmol, 3 equiv), THF (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in **H_2O** (1.28 mL) and THF (0.25 mL). Reactions were run at room temperature for 30 min.

Entry	Base	Water	Conversion[a] (%)	A7c:A8c[a]
1	-	Y	95	1.1:1

2	-	-	0	-
3	Y	-	0	-
4	Y	Y	54	14:1

[a] Determined by HPLC against a known internal standard (caffeine)

Temperature Study (Table 3)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), THF (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and THF (0.25 mL). Reactions were run at **X** °C for 1 h.

Entry	Temperature (°C)	Conversion[a] (%)	A7c:A8c[a]
1	rt	quant.	2:1
2	30	quant.	5:1
3	40	87	7:1
4	50	62	9:1
5	60	81	18:1
6	70	93	13:1

[a] Determined by HPLC against a known internal standard (caffeine)

Acetone Study (Table 4)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), THF (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL), THF (0.25 mL), and acetone (**X** equiv). Reactions were run at 60 °C for 1 h.

Entry	Acetone (volume)	Conversion[a] (%)	A7c:A8c[a]
1	-	81	18:1
2	5 (60 µL)	54	6:1
3	10 (119 µL)	45	3:1

4	20 (239 µL)	98	2:1

[a] Determined by HPLC against a known internal standard (caffeine)

Base Study (Table 5)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), **Base** (0.48 mmol, 3 equiv), THF (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and THF (0.25 mL). Reactions were run at 60 °C for 1 h.

Entry	Base	Conversion[a] (%)	A7c:A8c[a]
1	K_3PO_4 (103 mg)	81	18:1
2	Cs_2CO_3 (157 mg)	59	14:1
3	K_2CO_3 (67 mg)	53	12:1
4	KOAc (47 mg)	quant.	1:1
5	KOH (20 mg)	quant.	1.5:1

[a] Determined by HPLC against a known internal standard (caffeine)

Base Equivalents Study (Table 6)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (**X** equiv), THF (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and THF (0.25 mL). Reactions were run at 60 °C for 1 h.

Entry	K_3PO_4 (equiv)	Conversion[a] (%)	A7c:A8c[a]
1	1 (34 mg)	81	18:1
2	2 (69 mg)	54	6:1
3	3 (103 mg)	98	2:1

[a] Determined by HPLC against a known internal standard (caffeine)

Solvent Study (Table 7)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), **solvent** (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and **solvent** (0.25 mL). Reactions were run at 70 °C for 1 h

Entry	Solvent	Conversion[a] (%)	A7c:A8c[a]
1	EtOH	quant.	1:1
2	IPA	quant.	1:1
3	MeCN	quant.	1:1
4	DMF	quant.	1.5:1
5	1,4-dioxane	quant.	2:1
6	THF	73	13:1
7	2-MeTHF	84	47:1
8	EtOAc	quant.	63:1
9	toluene	59	>99:1
10	$CHCl_3$	quant.	>99:1
11	CPME	quant.	>99:1

[a] Determined by HPLC against a known internal standard (caffeine)

BMIDA Selective Oxidation – Hydrolysis Study

Time Study

Reactions were carried out according to General Procedure C using naphthalen-2-ylboronic acid, MIDA ester (45 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). Reactions were run at 90 °C for **X** min.

Entry	Time (min)	Conversion to A7a (%)[a]	A7a:A8a[a]
1	15	87	86:1

2	30	quant.	5:1
3	45	quant.	2:1
4	60	quant.	2:1
5	75	quant.	2:1
6	90	quant.	2:1

[a] Determined by HPLC against a known internal standard (caffeine)

Temperature Study

Reactions were carried out according to General Procedure C using naphthalen-2-ylboronic acid, MIDA ester (45 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 μL, 0.80 mmol, 5 equiv). Reactions were run at **X °C** for 30 min.

Entry	Temperature (°C)	Conversion to A7a (%)[a]	A7a:A8a[a]
1	70	10	1:1
2	80	quant.	20:1
3	90	quant.	5:1
4	100	quant.	2:1
6	110	quant.	2:1

[a] Determined by HPLC against a known internal standard (caffeine)

2.5.4 Determining the Origin of Chemoselectivity

Boron Speciation Investigation (Scheme 66)

To an oven-dried 5 mL microwave vial was added [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), and K_3PO_4 (103 mg, 0.48 mmol, 3 equiv). A mixture of THF and H_2O (10:1, 0.7 mL) was added and the reaction mixture was heated to 50 °C with stirring in a sand bath for 1 h. The reaction mixture was allowed to cool to room temperature and the conversion to products was determined by HPLC against an

internal standard (caffeine) indicating a 55:46:45:54 mixture of products **A7a**:**A8b**:**A7b**:**A8a**.

Shearing Effect Investigation (Chart 2)

Reactions were carried out according to General Procedure A using [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), Oxone® (125 mg, 0.4 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL), and THF (0.63 mL, 0.25 M). Reactions were run at room temperature with stirring at **X** rpm for **X** min.

Entry	Stir Rate (rpm)	Time (min)	Conversion[a] (%)
1	900	0[b]	4
2	900	5	42
3	900	10	54
4	900	15	69
5	900	20	75
6	900	30	89
7	350	0[b]	4
8	350	5	9
9	350	10	12
10	350	15	17
11	350	20	20
12	350	30	23

[a] Determined by HPLC against a known internal standard (caffeine), [b] reaction quenched after 10 seconds

Determination of Phase Distribution – HPLC Analysis (Table 8)

Reactions were carried out according to General Procedure D using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv) and a mixture of H_2O and CPME (1.28:0.88 mL). Reactions were run at **X** °C for 10 min using varying combinations of the following salts: **K_3PO_4** (103 mg, 0.48 mmol, 3 equiv), **$KHSO_4$** (27 mg, 0.2 mmol, 1.25 equiv), **K_2SO_4** (34 mg, 0.2 mmol, 1.25 equiv).

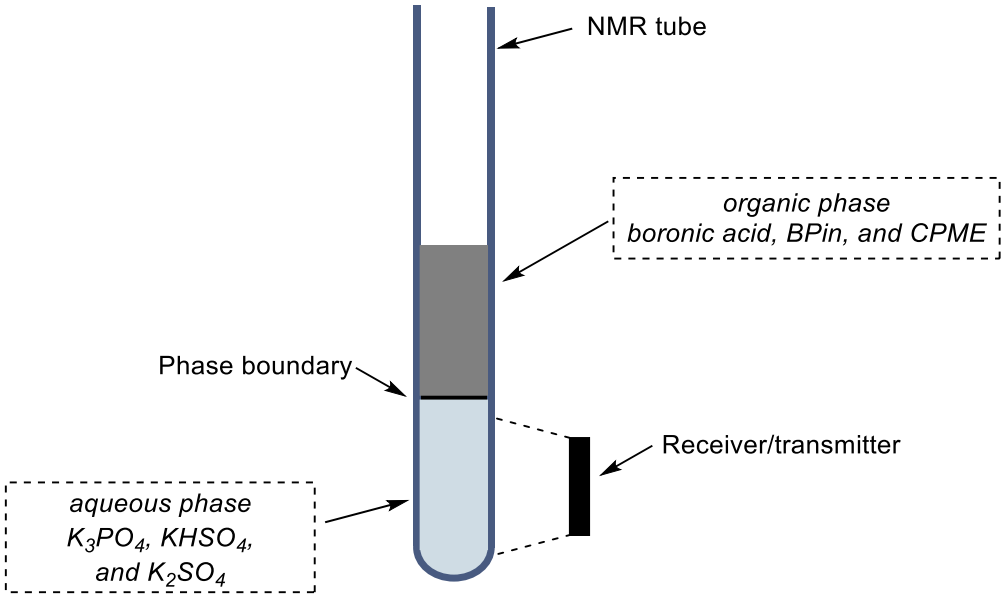
Entry	Inorganics used	Temp. (°C)	A7a[a,b]	A8b[a,b]
1	-	20	>99:1	>99:1
2	-	50	>99:1	>99:1
3	-	70	>99:1	>99:1
4	$KHSO_4$, K_2SO_4	20	>99:1	>99:1
5	$KHSO_4$, K_2SO_4	50	>99:1	>99:1
6	$KHSO_4$, K_2SO_4	70	98:2	>99:1
7	K_3PO_4	20	54:46	>99:1
8	K_3PO_4	50	46:54	96:4
9	K_3PO_4	70	29:71	98:2
10	K_3PO_4, $KHSO_4$, K_2SO_4	20	67:33	>99:1
11	K_3PO_4, $KHSO_4$, K_2SO_4	50	59:41	>99:1
12	K_3PO_4, $KHSO_4$, K_2SO_4	70	54:46	>99:1

[a]Determined by HPLC, [b] ratios describe product distribution – organic: aqueous

Determination of Phase Distribution – NMR Analysis

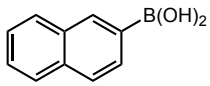
Setup

In order to assess only the aqueous phase during the process it was important to employ a reaction scale in which only the D_2O layer is detected by the receiver/transmitter coil. By ensuring that the D_2O layer and phase boundary of the biphasic system was > 0.5 mL, single analysis of the D_2O layer could be successfully achieved. The aqueous phase was analyzed at various temperatures over time to investigate mass transfer of specific boron species.



NMR Analysis of Monoaryl Boron Systems (Scheme 68)

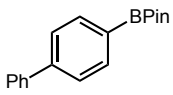
NMR aqueous phase analysis of naphthalen-2-ylboronic acid, **A7a** (Scheme 68)



A7a

The NMR experiment was prepared according to General Procedure F using naphthalen-2-ylboronic acid (17.2 mg, 0.1 mmol, 1 equiv), CPME (0.4 mL, 0.25 M), K_3PO_4 (63 mg, 0.3 mmol, 3 equiv), $KHSO_4$ (17 mg, 0.125 mmol, 1.25 equiv), K_2SO_4 (21.5 mg, 0.125 mmol, 1.25 equiv), and D_2O (0.8 mL). An NMR was recorded (128 scans) at 293 K every 5 min for 1 h. This process was repeated with the same sample at both 323 K and 343 K.

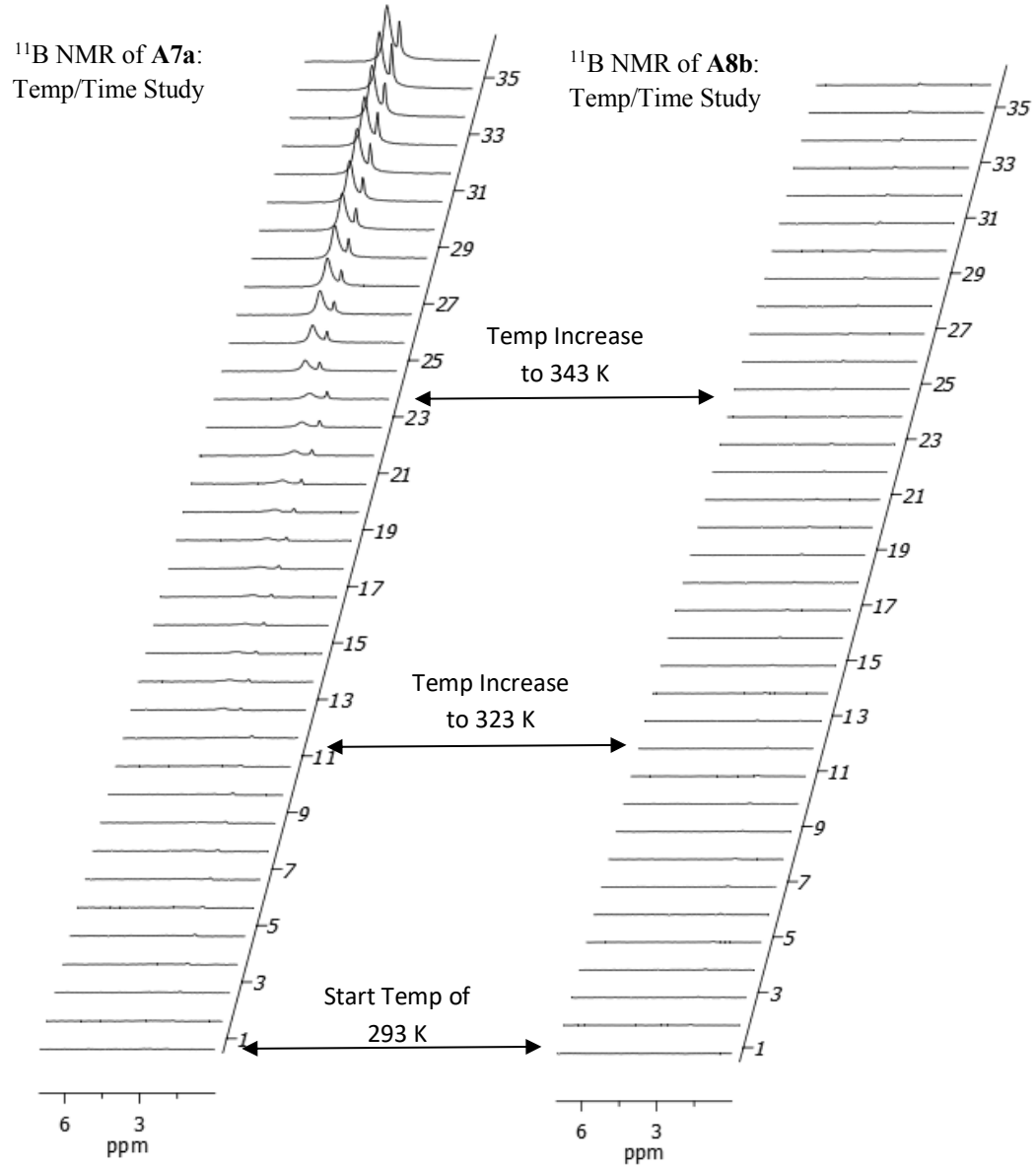
NMR aqueous phase analysis of [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **A8b** (Scheme 68)



A8b

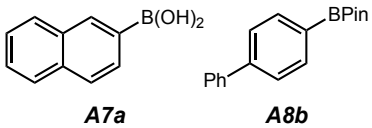
The NMR experiment was prepared according to General Procedure F using [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (28 mg, 0.1 mmol, 1 equiv), CPME (0.4

mL, 0.25 M), K_3PO_4 (63 mg, 0.3 mmol, 3 equiv), $KHSO_4$ (17 mg, 0.125 mmol, 1.25 equiv), K_2SO_4 (21.5 mg, 0.125 mmol, 1.25 equiv), and D_2O (0.8 mL). A ^{11}B NMR was recorded (128 scans) according to the general procedure.



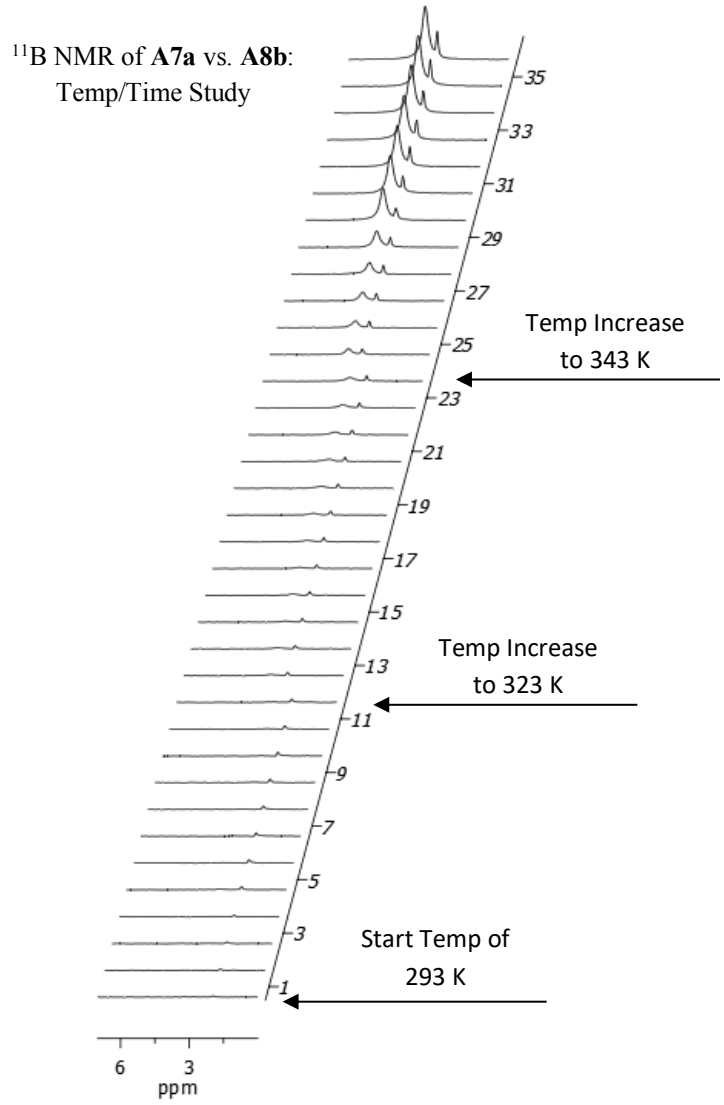
NMR Analysis of Diaryl Boron Systems (Scheme 69–71)

NMR aqueous phase analysis of naphthalen-2-ylboronic acid **A7a** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester **A8b** (Scheme 69)

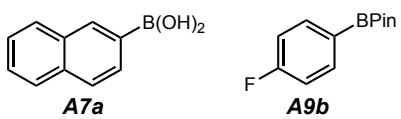


A7a ***A8b***

The NMR experiment was prepared according to General Procedure F using naphthalen-2-ylboronic acid (17.2 mg, 0.1 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (28 mg, 0.1 mmol, 1 equiv), CPME (0.4 mL, 0.25 M), K_3PO_4 (63 mg, 0.3 mmol, 3 equiv), $KHSO_4$ (17 mg, 0.125 mmol, 1.25 equiv), K_2SO_4 (21.5 mg, 0.125 mmol, 1.25 equiv), and D_2O (0.8 mL). A ^{11}B NMR was recorded (128 scans) according to the general procedure.

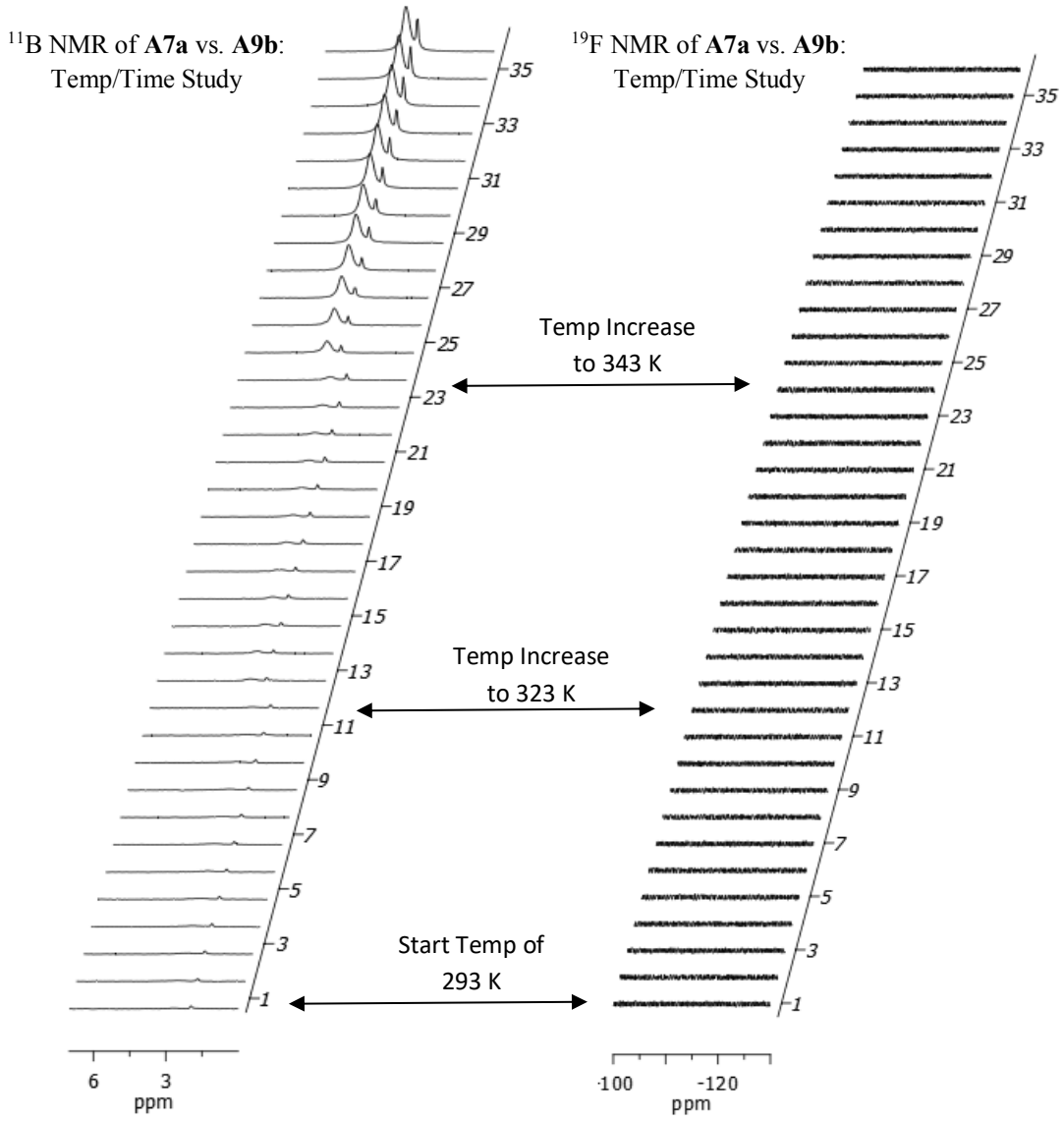


NMR aqueous phase analysis of naphthalen-2-ylboronic acid **A7a** *vs.* (4-fluorophenyl)boronic acid, pinacol ester **A9b** (Scheme 70)

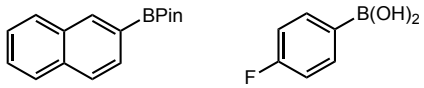


A7a ***A9b***

The NMR experiment was prepared according to General Procedure F using naphthalen-2-ylboronic acid (17.2 mg, 0.1 mmol, 1 equiv), (4-fluorophenyl)boronic acid, pinacol ester (22 mg, 0.1 mmol, 1 equiv), CPME (0.4 mL, 0.25 M), K_3PO_4 (63 mg, 0.3 mmol, 3 equiv), $KHSO_4$ (17 mg, 0.125 mmol, 1.25 equiv), K_2SO_4 (21.5 mg, 0.125 mmol, 1.25 equiv), and D_2O (0.8 mL). A ^{11}B NMR was recorded (128 scans) according to the general procedure. The overall process was repeated on a new sample for ^{19}F NMR (16 scans).

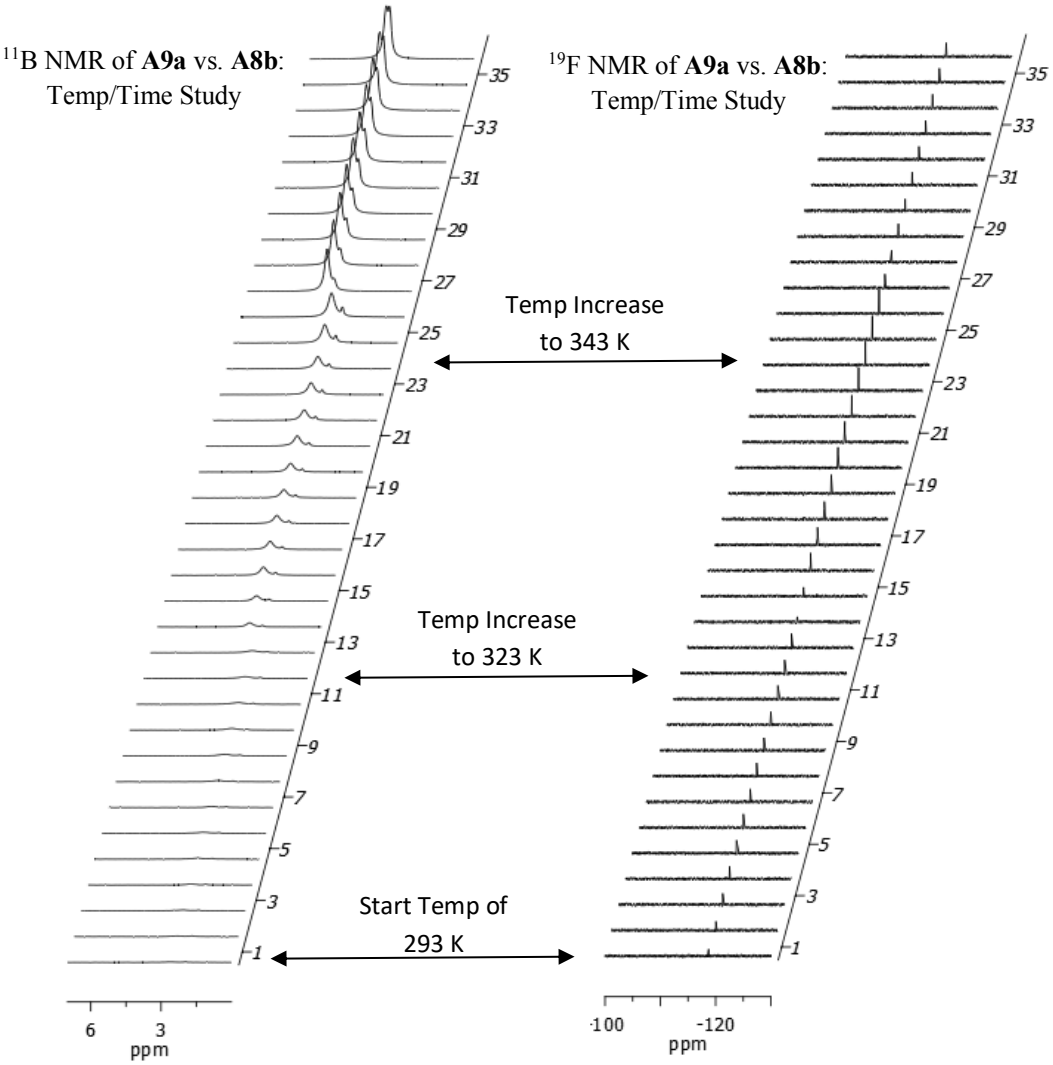


NMR aqueous phase analysis of (4-fluorophenyl)boronic acid **A9a** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester **A8b** (Scheme 70 and 71)



A7b ***A9a***

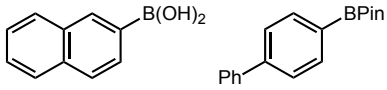
The NMR experiment was prepared according to General Procedure F using (4-fluorophenyl)boronic acid (14 mg, 0.1 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (28 mg, 0.1 mmol, 1 equiv), CPME (0.4 mL, 0.25 M), K_3PO_4 (63 mg, 0.3 mmol, 3 equiv), $KHSO_4$ (17 mg, 0.125 mmol, 1.25 equiv), K_2SO_4 (21.5 mg, 0.125 mmol, 1.25 equiv), and D_2O (0.8 mL). A ^{11}B NMR was recorded (128 scans) according to the general procedure. The overall process was repeated on a new sample for ^{19}F NMR (16 scans).



2.5.5 Chemoselective Oxidation Substrate Scope

Boronic Acid vs. BPin (Scheme 73 and 74)

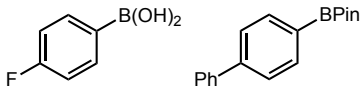
Naphthalen-2-ylboronic acid (**A7a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**),



A7a ***A8b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (quant., >99:1).

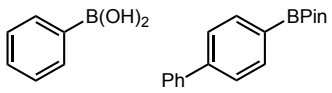
(4-Fluorophenyl)boronic acid (**A9a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A9a ***A8b***

The reaction was carried out according to General Procedure B using (4-fluorophenyl)boronic acid (22 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (4-fluorophenyl)boronic acid (quant., >99:1).

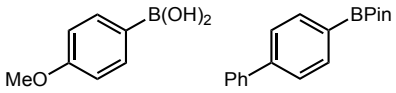
Phenylboronic acid (**A10a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A10a ***A8b***

The reaction was carried out according to General Procedure B using phenylboronic acid (20 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of phenylboronic acid (quant., >99:1).

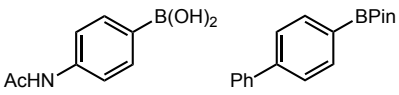
(4-Methoxyphenyl)boronic acid (**A11a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A11a ***A8b***

The reaction was carried out according to General Procedure B using (4-methoxyphenyl)boronic acid (24 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (4-methoxyphenyl)boronic acid (quant., >99:1).

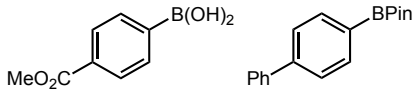
(4-Acetamidophenyl)boronic acid (**A12a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A12a ***A8b***

The reaction was carried out according to General Procedure B using (4-acetamidophenyl)boronic acid (29 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (4-acetamidophenyl)boronic acid (63%, 63:1).

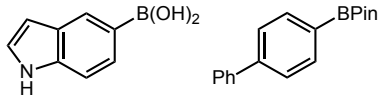
(4-(Methoxycarbonyl)phenyl)boronic acid (**A13a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A13a ***A8b***

The reaction was carried out according to General Procedure B using (4-(methoxycarbonyl)phenyl)boronic acid (29 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (4-(methoxycarbonyl)phenyl)boronic acid (85%, >99:1).

(1*H*-Indol-5-yl)boronic acid (**A14a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)

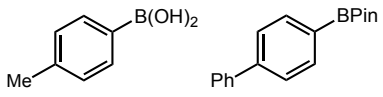


A14a ***A8b***

The reaction was carried out according to General Procedure B using (1*H*-indol-5-yl)boronic acid (26 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv),

CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (1*H*-indol-5-yl)boronic acid (97%, >99:1).

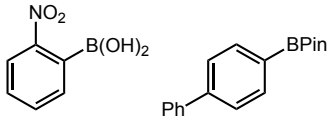
4-Methylphenylboronic acid (**A15a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A15a ***A8b***

The reaction was carried out according to General Procedure B using 4-methylphenylboronic acid (22 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of 4-methylphenylboronic acid (quant., >99:1).

(2-Nitrophenyl)boronic acid (**A16a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)

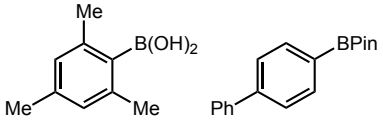


A16a ***A8b***

The reaction was carried out according to General Procedure B using (2-nitrophenyl)boronic acid (27 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general

procedure indicating selective oxidation of (2-nitrophenyl)boronic acid (quant., >99:1).

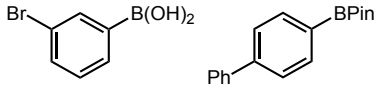
Mesitylboronic acid (**A17a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A17a ***A8b***

The reaction was carried out according to General Procedure B using mesitylboronic acid (26 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of mesitylboronic acid (62%, 16:1).

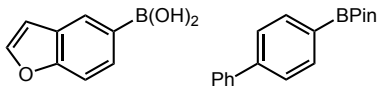
(3-Bromophenyl)boronic acid (**A18a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A18a ***A8b***

The reaction was carried out according to General Procedure B using (3-bromophenyl)boronic acid (32 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (3-bromophenyl)boronic acid (quant., >99:1).

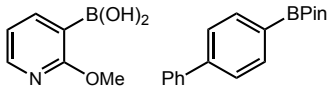
Benzofuran-5-ylboronic acid (**A19a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A19a ***A8b***

The reaction was carried out according to General Procedure B using benzofuran-5-ylboronic acid (26 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of benzofuran-5-ylboronic acid (90%, >99:1).

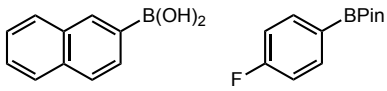
(2-Methoxypyridin-3-yl)boronic acid (**A20a**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A20a ***A8b***

The reaction was carried out according to General Procedure B using (2-methoxypyridin-3-yl)boronic acid (24 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (2-methoxypyridin-3-yl)boronic acid (quant., >99:1).

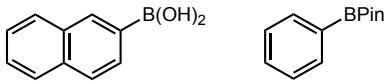
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-fluorophenyl)boronic acid, pinacol ester (**A9b)**



A7a ***A9b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid, pinacol ester (36 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (quant., >99:1).

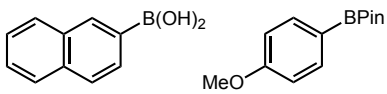
Naphthalen-2-ylboronic acid (**A7a**) *vs.* phenylboronic acid, pinacol ester (**A10b**)



A7a ***A10b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), phenylboronic acid, pinacol ester (33 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (79%, >99:1).

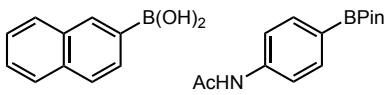
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-methoxyphenyl)boronic acid, pinacol ester (**A11b**)



A7a ***A11b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-methoxyphenyl)boronic acid, pinacol ester (37 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (90%, 85:1).

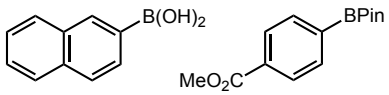
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-acetamidophenyl)boronic acid, pinacol ester (**A12b**)



A7a ***A12b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-acetamidophenyl)boronic acid, pinacol ester (42 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (82%, 14:1).

Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester (**A13b**)

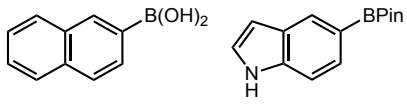


A7a ***A13b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester (42 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h.

Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (82%, 20:1).

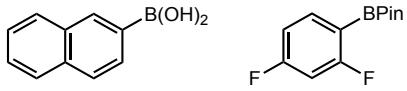
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (1*H*-indol-5-yl)boronic acid, pinacol ester (**A14b**)



A7a ***A14b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (1*H*-indol-5-yl)boronic acid, pinacol ester (39 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (quant., 99:1).

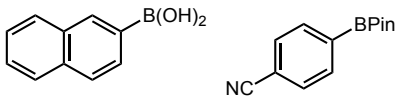
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (2,4-difluorophenyl)boronic acid, pinacol ester (**A21b**)



A7a ***A21b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (2,4-difluorophenyl)boronic acid, pinacol ester (38 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (93%, 12:1).

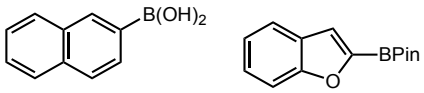
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-cyanophenyl)boronic acid, pinacol ester (**A22b**)



A7a ***A22b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-cyanophenyl)boronic acid, pinacol ester (37 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (quant., 14:1).

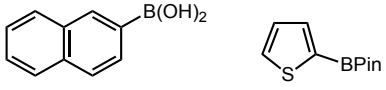
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (benzofuran-2-yl)boronic acid, pinacol ester (**A23b**)



A7a ***A23b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (benzofuran-2-yl)boronic acid, pinacol ester (42 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (57%, 55:1).

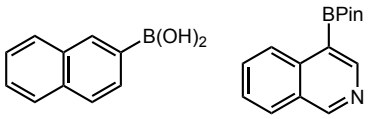
Naphthalen-2-ylboronic acid (**A7a**) *vs.* thiophen-2-ylboronic acid, pinacol ester (**A24b**)



A7a ***A24b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), thiophen-2-ylboronic acid, pinacol ester (34 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (67%, >99:1).

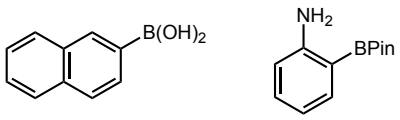
Naphthalen-2-ylboronic acid (**A7a**) *vs.* isoquinolin-4-ylboronic acid, pinacol ester (**A25b**)



A7a ***A25b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), isoquinolin-4-ylboronic acid, pinacol ester (41 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (quant., 50:1).

Naphthalen-2-ylboronic acid (**A7a**) *vs.* (2-aminophenyl)boronic acid, pinacol ester (**A26b**)



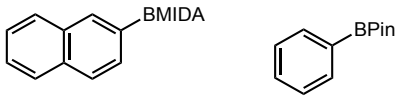
A7a ***A26b***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (2-aminophenyl)boronic acid, pinacol ester (35 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 1 h. Conversion to

products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (75%, >99:1).

BMIDA vs. BPin (Scheme 76)

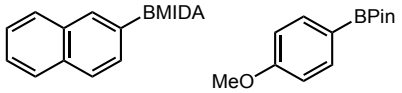
Naphthalen-2-ylboronic acid, MIDA ester (**A7f**) *vs.* phenylboronic acid, pinacol ester (**A10b**)



A7f ***A10b***

The reaction was carried out according to General Procedure G using naphthalen-2-ylboronic acid, MIDA ester (45 mg, 0.16 mmol, 1 equiv), phenylboronic acid, pinacol ester (33 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (56%, >99:1).

Naphthalen-2-ylboronic acid, MIDA ester (**A7f**) *vs.* (4-methoxyphenyl)boronic acid, pinacol ester (**A11b**)

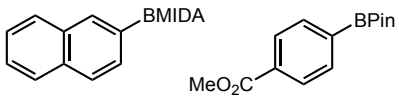


A7f ***A11b***

The reaction was carried out according to General Procedure G using naphthalen-2-ylboronic acid, MIDA ester (45 mg, 0.16 mmol, 1 equiv), (4-methoxyphenyl)boronic acid, pinacol ester (37 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the

general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (82%, >99:1).

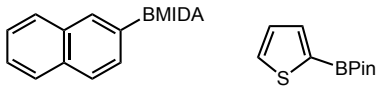
Naphthalen-2-ylboronic acid, MIDA ester (**A7f**) *vs.* (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester (**A13b**)



A7f ***A13b***

The reaction was carried out according to General Procedure G using naphthalen-2-ylboronic acid, MIDA ester (45 mg, 0.16 mmol, 1 equiv), (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester (42 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (85%, 4:1).

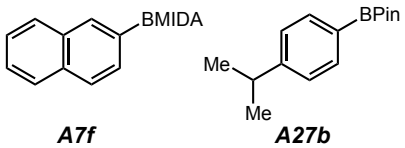
Naphthalen-2-ylboronic acid, MIDA ester (**A7f**) *vs.* thiophen-2-ylboronic acid, pinacol ester (**A24b**)



A7f ***A24b***

The reaction was carried out according to General Procedure G using naphthalen-2-ylboronic acid, MIDA ester (45 mg, 0.16 mmol, 1 equiv), thiophen-2-ylboronic acid (34 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (83%, 6:1).

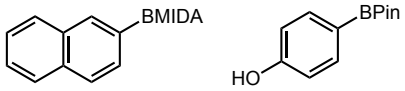
Naphthalen-2-ylboronic acid, MIDA ester (**A7f**) *vs.* (4-isopropylphenyl)boronic acid, pinacol ester (**A27b**)



A7f ***A27b***

The reaction was carried out according to General Procedure G using naphthalen-2-ylboronic acid, MIDA ester (45 mg, 0.16 mmol, 1 equiv), (4-isopropylphenyl)boronic acid (39 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (63%, >99:1).

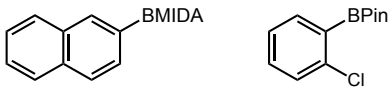
Naphthalen-2-ylboronic acid, MIDA ester (**A7f**) *vs.* (4-hydroxyphenyl)boronic acid, pinacol ester (**A28b**)



A7f ***A28b***

The reaction was carried out according to General Procedure G using naphthalen-2-ylboronic acid, MIDA ester (45 mg, 0.16 mmol, 1 equiv), (4-hydroxyphenyl)boronic acid, pinacol ester (35 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (67%, >99:1).

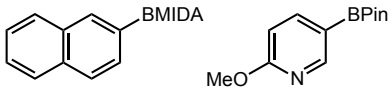
Naphthalen-2-ylboronic acid, MIDA ester (**A7f**) *vs.* (2-chlorophenyl)boronic acid, pinacol ester (**A29b**)



A7f ***A29b***

The reaction was carried out according to General Procedure G using naphthalen-2-ylboronic acid, MIDA ester (45 mg, 0.16 mmol, 1 equiv), (2-chlorophenyl)boronic acid, pinacol ester (38 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (87%, >99:1).

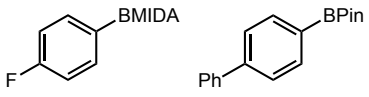
Naphthalen-2-ylboronic acid, MIDA ester (**A7f**) *vs.* (6-methoxypyridin-3-yl)boronic acid, pinacol ester (**A30b**)



A7f ***A30b***

The reaction was carried out according to General Procedure G using naphthalen-2-ylboronic acid, MIDA ester (45 mg, 0.16 mmol, 1 equiv), (6-methoxypyridin-3-yl)boronic acid, pinacol ester (38 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (69%, 9:1).

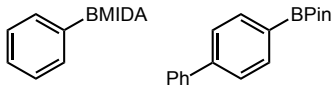
(4-Fluorophenyl)boronic acid, MIDA ester (**A9f**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A9f ***A8b***

The reaction was carried out according to General Procedure G using (4-fluorophenyl)boronic acid, MIDA ester (40 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (4-fluorophenyl)boronic acid, MIDA ester (72%, >99:1).

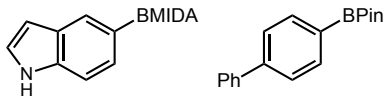
Phenylboronic acid, MIDA ester (**A10f**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A10f ***A8b***

The reaction was carried out according to General Procedure G using phenylboronic acid, MIDA ester (37 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of phenylboronic acid, MIDA ester (58%, 58:1).

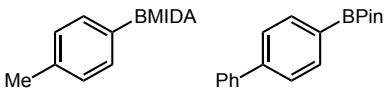
(1*H*-Indol-5-yl)boronic acid, MIDA ester (**A14f**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A14f ***A8b***

The reaction was carried out according to General Procedure G using (1*H*-indol-5-yl)boronic acid, MIDA ester (44 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (1*H*-indol-5-yl)boronic acid, MIDA ester (55%, >99:1).

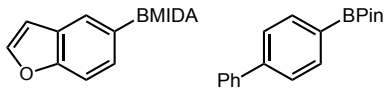
4-Methylphenylboronic acid, MIDA ester (**A15f**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A15f ***A8b***

The reaction was carried out according to General Procedure G using 4-methylphenylboronic acid, MIDA ester (40 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of 4-methylphenylboronic acid, MIDA ester (84%, 84:1).

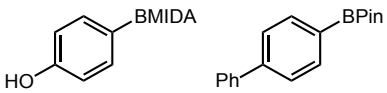
Benzofuran-5-ylboronic acid, MIDA ester (**A19f**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A19f ***A8b***

The reaction was carried out according to General Procedure G using benzofuran-5-ylboronic acid, MIDA ester (44 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of benzofuran-5-ylboronic acid, MIDA ester (76%, 25:1).

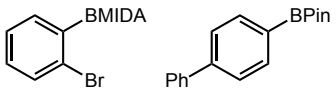
(4-Hydroxyphenyl)boronic acid, MIDA ester (**A28f**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A28f ***A8b***

The reaction was carried out according to General Procedure G using (4-hydroxyphenyl)boronic acid, MIDA ester (40 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (4-hydroxyphenyl)boronic acid, MIDA ester (50%, 50:1).

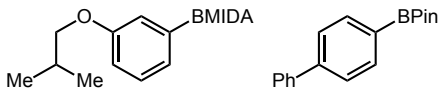
(2-Bromophenyl)boronic acid, MIDA ester (**A31f**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



A31f ***A8b***

The reaction was carried out according to General Procedure G using (2-bromophenyl)boronic acid, MIDA ester (50 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (2-bromophenyl)boronic acid, MIDA ester (quant., >99:1).

(3-Isobutoxyphenyl)boronic acid, MIDA ester (**A32f**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**A8b**)



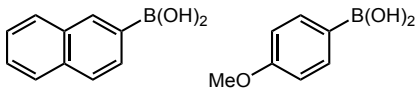
A32f ***A8b***

The reaction was carried out according to General Procedure G using (3-isobutoxyphenyl)boronic acid, MIDA ester (31 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (45 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and H_2O (14.5 µL, 0.80 mmol, 5 equiv). The reaction was run at 80 °C for 15 min. Oxone® (125 mg, 0.40 mmol, 2.5 equiv) was added as a slurry in H_2O (1.6 mL) and CPME (0.25 mL) and the reaction was run at 70 °C for 1 h. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (3-isobutoxyphenyl)boronic acid, MIDA ester (71%, 24:1).

Boronic Acid *vs.* Boronic Acid (Scheme 80 and 81)

Determination of Boronic Acid *vs.* Boronic Acid Phase Distribution – HPLC Analysis

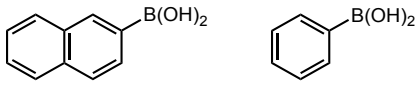
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-methoxyphenyl)boronic acid (**A11a**),



A7a ***A11a***

The reaction was carried out according to General Procedure D using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-methoxyphenyl)boronic acid (24 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), and a mixture of H_2O and CPME (1.28:0.88 mL). The reaction was run at 70 °C for 10 min. Distribution of products was analyzed by HPLC as outlined in the general procedure indicating phase transfer of **A11a**, 0:100 (organic/aqueous), and **A7a**, 72:28 (organic/aqueous).

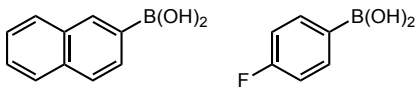
Naphthalen-2-ylboronic acid (**A7a**) *vs.* phenylboronic acid (**A10a**),



A7a ***A10a***

The reaction was carried out according to General Procedure D using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), phenylboronic acid (20 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), and a mixture of H_2O and CPME (1.28:0.88 mL). The reaction was run at 70 °C for 10 min. Distribution of products was analyzed by HPLC as outlined in the general procedure indicating phase transfer of **A10a**, 5:95 (organic/aqueous), and **A7a**, 72:28 (organic/aqueous).

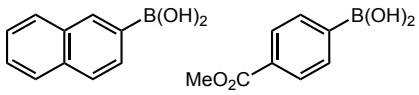
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-fluorophenyl)boronic acid (**A9a**),



A7a ***A9a***

The reaction was carried out according to General Procedure D using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid (22 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), and a mixture of H_2O and CPME (1.28:0.88 mL). The reaction was run at 70 °C for 10 min. Distribution of products was analyzed by HPLC as outlined in the general procedure indicating phase transfer of **A9a**, 20:80 (organic/aqueous), and **A7a**, 63:37 (organic/aqueous).

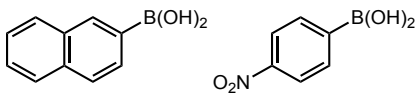
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-(methoxycarbonyl)phenyl)boronic acid (**A13a**),



A7a ***A13a***

The reaction was carried out according to General Procedure D using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-(methoxycarbonyl)phenyl)boronic acid (28 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), and a mixture of H_2O and CPME (1.28:0.88 mL). The reaction was run at 70 °C for 10 min. Distribution of products was analyzed by HPLC as outlined in the general procedure indicating phase transfer of **7a**, 9:91 (organic/aqueous), and **1a**, 85:15 (organic/aqueous).

Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-nitrophenyl)boronic acid (**A35a**),

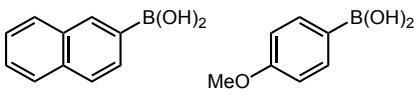


A7a ***A35a***

The reaction was carried out according to General Procedure D using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-nitrophenyl)boronic acid (27 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), and a mixture of H_2O and CPME (1.28:0.88 mL). The reaction was run at 70 °C for 10 min. Distribution of products was analyzed by HPLC as outlined in the general procedure indicating phase transfer of **A35a**, 11:14 (organic/aqueous), and **A7a**, 64:36 (organic/aqueous).

Boronic Acid *vs.* Boronic Acid – Substrate Scope

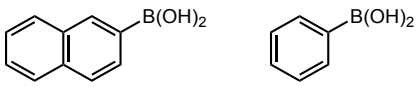
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-methoxyphenyl)boronic acid (**A11a**),



A7a ***A11a***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-methoxyphenyl)boronic acid (24 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 30 min. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (4-methoxyphenyl)boronic acid (quant., 4:1).

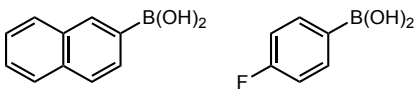
Naphthalen-2-ylboronic acid (**A7a**) *vs.* phenylboronic acid (**A10a**),



A7a ***A10a***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), phenylboronic acid (20 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 30 min. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of phenylboronic acid (88%, 6.5:1).

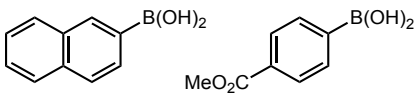
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-fluorophenyl)boronic acid (**A9a**),



A7a ***A9a***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid (22 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 30 min. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (4-fluorophenyl)boronic acid (88%, 8:1).

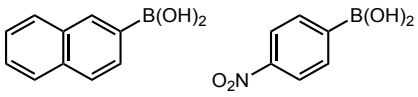
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-(methoxycarbonyl)phenyl)boronic acid (**A13a**),



A7a ***A13a***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-(methoxycarbonyl)phenyl)boronic acid (29 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 30 min. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (4-(methoxycarbonyl)phenyl)boronic acid (58%, 3:1).

Naphthalen-2-ylboronic acid (**A7a**) *vs.* (4-nitrophenyl)boronic acid (**A35a**),

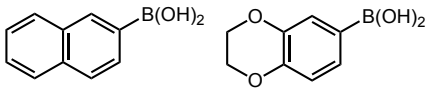


A7a ***A35a***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (4-nitrophenyl)boronic acid (27 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 30 min. Conversion to products was

analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (4-nitrophenyl)boronic acid (77%, 4.4:1).

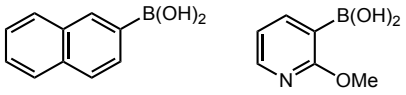
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (2,3-dihydrobenzo[b][1,4]dioxin-6-yl)boronic acid (**A36a**),



A7a ***A36a***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (2,3-dihydrobenzo[b][1,4]dioxin-6-yl)boronic acid (29 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 30 min. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (2,3-dihydrobenzo[b][1,4]dioxin-6-yl)boronic acid (86%, 4:1).

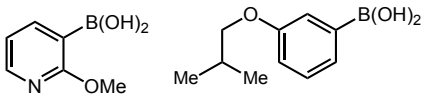
Naphthalen-2-ylboronic acid (**A7a**) *vs.* (2-methoxypyridin-3-yl)boronic acid (**A20a**),



A7a ***A20a***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), (2-methoxypyridin-3-yl)boronic acid (24 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 30 min. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (2-methoxypyridin-3-yl)boronic acid (24 mg, 0.16 mmol, 1 equiv) (62%, 3:1).

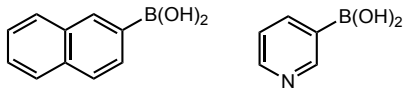
(2-Methoxypyridin-3-yl)boronic acid (**A20a**) *vs.* (3-isobutoxyphenyl)boronic acid (**A32a**),



A20a ***A32a***

The reaction was carried out according to General Procedure B using (2-methoxypyridin-3-yl)boronic acid (24 mg, 0.16 mmol, 1 equiv), (3-isobutoxyphenyl)boronic acid (31 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 30 min. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of (2-methoxypyridin-3-yl)boronic acid (71%, 3:1).

Naphthalen-2-ylboronic acid (**A7a**) *vs.* pyridin-3-ylboronic acid (**A37a**),



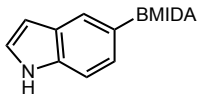
A7a ***A37a***

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), pyridin-3-ylboronic acid (20 mg, 0.16 mmol, 1 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL). The reaction was run at 70 °C for 30 min. Conversion to products was analyzed by HPLC as outlined in the general procedure indicating selective oxidation of pyridin-3-ylboronic acid (85%, 2:1).

2.5.6 Compound Characterization

Data for BMIDA Starting Materials (Scheme 76 and 79)

(1*H*-Indol-5-yl)boronic acid, MIDA ester, **A14f**



Prepared according to General Procedure H using (1*H*-indol-5-yl)boronic acid (2 g, 12.4 mmol, 1 equiv), *N*-methyliminodiacetic acid (1.9 g, 13.02 mmol, 1.05 equiv), and DMF (50 mL) to afford the desired product as a white solid (3.3 g, 98% yield).

υ_{max} (solid): 3401, 3008, 2962, 1766, 1744, 1578, 1455, 1340, 1245, 1236 cm^{-1}.

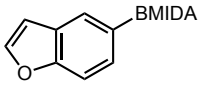
^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.02 (s, 1 H), 7.62 (s, 1 H), 7.37 (d, *J* = 8.2 Hz, 1 H), 7.3 (t, *J* = 2.7 Hz, 1 H), 7.14 (d, *J* = 8.2 Hz, 1 H), 6.41 (s, 1 H), 4.30 (d, *J* = 17.2 Hz, 2 H), 4.08 (d, *J* = 17.2 Hz, 2 H), 2.45 (s, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.5, 136.5, 127.5, 124.9, 124.5, 110.8, 101.1, 61.6, 47.5.

^{11}B NMR ($CDCl_3$, 128 MHz): δ 12.52.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{13}BN_2O_4$) requires *m/z* 273.1041, found *m/z* 273.1045.

(Benzofuran-5-yl)boronic acid, MIDA ester, **A19f**



Prepared according to General Procedure H using (benzofuran-5-yl)boronic acid (200 mg, 0.74 mmol, 1 equiv), *N*-methyliminodiacetic acid (107 mg, 0.77 mmol, 1.05 equiv), and DMF (12 mL) to afford desired product as a white solid (284 mg, 85% yield).

υ_{max} (solid): 3145, 3112, 2967, 1760, 1738, 1340, 1260 cm^{-1}.

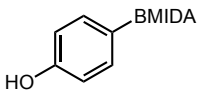
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.96 (d, *J* = 2.1 Hz, 1 H), 7.72 (s, 1 H), 7.55–7.58 (m, 1 H), 7.37 (dd, *J* = 8.2, 1.2 Hz, 1 H), 6.96 (dd, *J* = 2.1, 0.9 Hz, 1 H), 4.34 (d, *J* = 17.4 Hz, 2 H), 4.12 (d, *J* = 17.1 Hz, 2 H), 2.48 (s, 3 H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.4, 155.1, 145.6, 128.5, 126.9, 125.6, 110.5, 106.7, 61.7, 47.6.

^{11}B NMR (DMSO-d_6, 160 MHz): δ 11.72.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{13}BNO_5$) requires *m/z* 274.0881, found *m/z* 274.0886.

4-Hydroxyphenylboronic acid, MIDA ester, **A28f**



Prepared according to General Procedure H using 4-hydroxyphenylboronic acid (1.75 g, 12.7 mmol, 1 equiv), *N*-methyliminodiacetic acid (1.89 g, 12.8 mmol, 1.01 equiv), and DMF (160 mL) to afford the desired product as a white solid (3 g, 95% yield).

υ_{max} (solid): 3361, 3010, 1740, 1610, 1584 cm^{-1}.

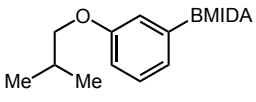
^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.39 (br. s., 1 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 6.74 (d, *J* = 8.6 Hz, 2 H), 4.27 (d, *J* = 17.2 Hz, 2 H), 4.04 (d, *J* = 17.2 Hz, 2 H), 2.46 (s, 3 H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.4, 158.1, 133.6, 114.7, 61.5, 47.4, Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 12.20.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{11}H_{11}NO_5B$) requires *m/z* 248.0736, found *m/z* 248.0730.

(3-Isobutoxyphenyl)boronic acid, MIDA ester, **A32f**



Prepared according to General Procedure H using (3-isobutoxyphenyl)boronic acid (600 mg, 3.1 mmol, 1 equiv), *N*-methyliminodiacetic acid (477 mg, 3.24 mmol, 1.05 equiv), and DMF (30 mL) to afford the desired product as a white solid (900 mg, 95% yield).

υ_{max} (solid): 3004, 2956, 2872, 1768, 1748, 1577, 1457, 1424, 1286, 1253 cm^{-1}.

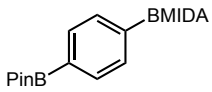
^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.26 (t, *J* = 7.7 Hz, 1 H), 6.99–6.92 (m, 2 H), 6.91 (dd, *J* = 8.1, 2.6 Hz, 1 H), 4.31 (d, *J* = 17.2 Hz, 2 H), 4.10 (d, *J* = 17.2 Hz, 2 H), 3.73 (d, *J* = 6.5 Hz, 2 H), 2.51 (s, 3 H), 2.00 (m, 1 H), 0.98 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.4, 158.3, 128.8, 124.4, 118.2, 114.7, 73.4, 61.8, 47.5, 27.8, 19.1. Carbon bearing boron not observed.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 11.06.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{20}BNO_5$) requires *m/z* 305.1507, found *m/z* 305.1513.

Benzene-1-boronic acid, pinacol ester-4-boronic acid, MIDA ester, **A33**



(4-Bromophenyl)boronic acid, MIDA ester (78 mg, 0.25 mmol, 1 equiv), bis(pinacolato)diboron (91 mg, 0.36 mmol, 1,4 equiv), Pd(dppf)Cl_2·CH_2Cl_2 (10 mg, 0.0125 mmol, 5 mol%), and KOAc (81 mg, 0.825 mmol, 3.3 equiv) were weighed out into an oven-dried 5 mL microwave vial. The vial was capped and purged with nitrogen. DMSO (2 mL, 0.125 M) was added via syringe and the reaction was heated to 75 °C in a sand bath with stirring for 24 h. The reaction was allowed to cool to room temperature and was vented, decapped, and poured into EtOAc (50 mL) and H_2O (40 mL) was added. Organics were separated and washed with water (2 x 40

mL). The aqueous layer was extracted with a further 25 mL EtOAc and both organics combined. Organics were passed through a hydrophobic frit and concentrated under vacuum. Crude product was purified by flash chromatography (silica gel, 10-70% acetone in ether) to afford title compound as a white crystalline solid (76 mg, 85% yield).

υ_{max} (solid): 2978, 1761, 1748, 1517, 1457, 1362 cm^{-1}.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 4.34 (d, *J* = 17.2 Hz, 2H), 4.10 (d, *J* = 17.2 Hz, 2H), 2.46 (s, 3H), 1.29 (s, 12H).

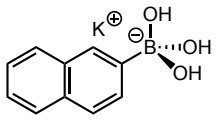
^{13}C NMR (DMSO-d_6, 101 MHz): δ 169.3, 133.6, 131.8, 83.6, 61.8, 47.6, 24.7.

^{11}B NMR (DMSO-d_6, 128 MHz): δ 32.46, 11.78.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{17}H_{22}B_2NO_6$) requires *m/z* 358.1639, found *m/z* 358.1634.

Data for NMR Analysis (Figure 12 and Schemes 68–71)

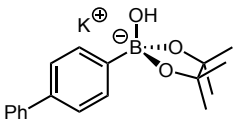
Potassium trihydroxy(naphthalen-2-yl)borate, **A7d**



Prepared according to General Procedure E using naphthalen-2-ylboronic acid (6.1 mg, 0.036 mmol, 1 equiv) and K_3PO_4 (22.7 mg, 0.11 mmol, 3 equiv), and D_2O (0.75 ml). The NMR sample was run at 343 K.

^{11}B NMR (D_2O, 128 MHz): δ 3.67.

Potassium [1,1'-biphenyl]-4-yltrihydroxyborate, pinacol ester, **A8e**

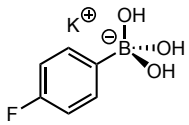


Prepared according to General Procedure E using [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (10 mg, 0.036 mmol, 1 equiv), **base** (0.11 mmol, 3 equiv), and D_2O (0.75 mL). The NMR sample was run at **X** K.

Entry	Base (mass)	Temp (K)	^{11}B Signal
1	K_3PO_4 (22.7 mg)	293	-
2	K_3PO_4 (22.7 mg)	343	-
3	KOH (6 mg)	293	6.0 ppm
4	KOH (6 mg)	343	3.6 ppm

[a] starting material did not form a solution to transfer into the NMR tube, [b] BPin boronate hydrolysis to the corresponding boronic acid boronate occurred.

Potassium (4-fluorophenyl)trihydroxyborate, **A9d**

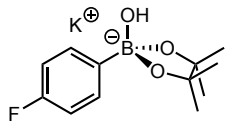


Prepared according to General Procedure E using (4-fluorophenyl)boronic acid (5 mg, 0.036 mmol, 1 equiv) and K_3PO_4 (22.7 mg, 0.11 mmol, 3 equiv), and D_2O (0.75 ml). The NMR sample was run at 343 K.

^{11}B NMR (D_2O, 128 MHz): δ 3.49.

^{19}F NMR (D_2O, 376 MHz): δ –118.65.

Potassium (4-fluorophenyl)trihydroxyborate, pinacol ester, **A9e**



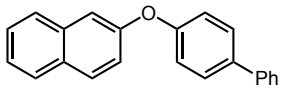
Prepared according to General Procedure E using (4-fluorophenyl)boronic acid (5 mg, 0.036 mmol, 1 equiv) and K_3PO_4 (22.7 mg, 0.11 mmol, 3 equiv), and D_2O (0.75 ml). The NMR sample was run at 343 K. Hydrolysis of BPin boronate was also seen by NMR (3.49 and -188.65 ppm for ^{11}B and ^{19}F NMR respectively).

^{11}B NMR (D_2O, 128 MHz, 343 K): δ 6.24.

^{19}F NMR (D_2O, 376 MHz, 343 K): δ –119.07.

Data for Oxidative Nucleophile Coupling (Scheme 81)

2-([1,1'-Biphenyl]-4-yloxy)naphthalene, **A38**



Prepared according to General Procedure I using naphthalen-2-ylboronic acid (28 mg, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (225 mg, 0.8 mmol, 5 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL), $Cu(OAc)_2$ (58 mg, 0.32 mmol, 2 equiv), powdered activated molecular sieves, MeCN (350 μL), EtOH (16 μL), and Et_3N (45 μL, 0.32 mmol, 2 equiv) to afford title compound as a white solid (39.1 mg, 82% yield).

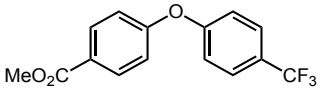
υ_{max} (solid): 3055, 3032, 2922, 2852, 1597, 1588 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (t, *J* = 8.3 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.62–7.56 (m, 4H), 7.50–7.40 (m, 4H), 7.34 (m, 3H), 7.15 (d, *J* = 8.8 Hz, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 156.9, 155.1, 140.7, 136.7, 134.5, 130.4, 130.1, 129.0, 128.7, 127.9, 127.3, 127.2, 127.1, 126.7, 124.9, 120.2, 119.4, 114.5.

HRMS: exact mass calculated for $[M]^+$ ($C_{22}H_{16}O$) requires *m/z* 296.1201, found *m/z* 296.1208.

Methyl 4-(4-(trifluoromethyl)phenoxy)benzoate, **A39**



Prepared according to General Procedure I using (4-(methoxycarbonyl)phenyl)boronic acid (29 mg, 0.16 mmol, 1 equiv), (4-

(trifluoromethyl)phenyl)boronic acid, pinacol ester (217 mg, 0.8 mmol, 5 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL), $Cu(OAc)_2$ (58 mg, 0.32 mmol, 2 equiv), powdered activated molecular sieves, MeCN (350 μ*L*), EtOH (16 μL), and Et_3N (45 μL, 0.32 mmol, 2 equiv) to afford title compound as an off white solid (34.6 mg, 73% yield).

υ_{max} (solid): 3075, 2960, 2922, 1722, 1599, 1506, 1433 cm^{-1}.

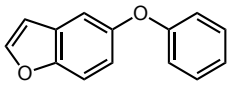
^1H NMR ($CDCl_3$, 400 MHz): δ 8.09–8.03 (m, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.16–7.09 (m, 2H), 7.09–7.02 (m, 2H), 3.92 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.4, 160.2, 158.9, 131.9, 127.4 (q, $^3J_{C-F}$ = 3.1 Hz), 126.2 (app. d, $^2J_{C-F}$ = 33.0 Hz), 125.8, 124.0 (app. d, $^1J_{C-F}$ = 271.4 Hz), 119.2, 118.5, 52.1.

^{19}F NMR ($CDCl_3$, 376 MHz): δ -62.0 (s, 3F).

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{12}F_3O$) requires *m/z* 297.0736, found *m/z* 297.0733.

5-Phenoxybenzofuran, **A40**



Prepared according to General Procedure I using benzofuran-5-ylboronic acid (26 mg, 0.16 mmol, 1 equiv), phenyl boronic acid, pinacol ester (164 mg, 0.8 mmol, 5 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL), $Cu(OAc)_2$ (58 mg, 0.32 mmol, 2 equiv), powdered activated molecular sieves, MeCN (350 μ*L*), EtOH (16 μL), and Et_3N (45 μL, 0.32 mmol, 2 equiv) to afford an inseparable mixture (60:40) of title compound and phenyl boronic acid, pinacol ester, (36.2 mg, 64% NMR yield).

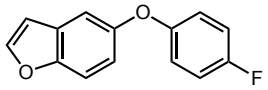
υ_{max} (Film): 3064, 3040, 2922, 1590, 1491, 1457, 1217, 1184 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 2.2 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.36–7.29 (m, 2H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.10–6.97 (m, 4H), 6.72 (dd, *J* = 2.2, 0.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.7, 152.6, 151.7, 146.3, 129.8, 128.5, 122.7, 118.1, 117.2, 112.3, 111.6, 106.9.

HRMS: exact mass calculated for $[M]^+$ ($C_{14}H_{10}O_2$) requires *m/z* 210.0681, found *m/z* 210.0651.

5-(4-Fluorophenoxy)benzofuran, **A41**



Prepared according to General Procedure I using benzofuran-5-ylboronic acid (26 mg, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid, pinacol ester (178 mg, 0.8 mmol, 5 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL), $Cu(OAc)_2$ (58 mg, 0.32 mmol, 2 equiv), powdered activated molecular sieves, MeCN (350 µL), EtOH (16 µL), and Et_3N (45 µL, 0.32 mmol, 2 equiv) to afford an inseparable mixture (80:20) of title compound and (4-fluorophenyl)boronic acid, pinacol ester (33.6 mg, 73% NMR yield).

υ_{max} (Film): 3116, 3073, 2922, 1500, 1461, 1197, 1184 cm^{-1}.

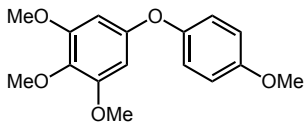
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, *J* = 2.2 Hz, 1H), 7.45 (s, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 7.04–6.93 (m, 5H), 6.72 (dd, *J* = 2.2, 0.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 158.6 (d, $^{1}J_{C\text{-}F}$ = 241.1 Hz), 154.4, 153.2, 151.6, 146.4, 128.5, 119.6 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz), 116.5 (d, $^{2}J_{C\text{-}F}$ = 21.1 Hz), 116.2, 112.3, 110.9, 106.9.

^{19}F NMR ($CDCl_3$, 376 MHz): δ -121.1.

HRMS: exact mass calculated for $[M]^+$ ($C_{14}H_9FO_2$) requires *m/z* 228.0587, found *m/z* 228.0582.

1,2,3-Trimethoxy-5-(4-methoxyphenoxy)benzene, **A42**



Prepared according to General Procedure I using (3,4,5-trimethoxyphenyl)boronic acid (34 mg, 0.16 mmol, 1 equiv), (4-methoxyphenyl)boronic acid, pinacol ester (187 mg, 0.8 mmol, 5 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.6 mL) and CPME (0.25 mL), $Cu(OAc)_2$ (58 mg, 0.32 mmol, 2 equiv), powdered activated molecular sieves, MeCN (350 µL), EtOH (16 µL), and Et_3N (45 µL, 0.32 mmol, 2 equiv) to afford title compound as a clear gum (16.8 mg, 36% yield).

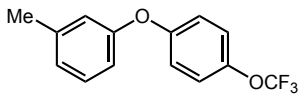
υ_{max} (Film): 3001, 2935, 2837, 1601, 1498, 1213, 1132 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 9.1 Hz, 1H), 6.88 (d, *J* = 9.1 Hz, 1H), 6.20 (s, 1H), 3.81 (d, *J* = 1.4 Hz, 3H), 3.78 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 155.3, 154.1, 153.3, 149.9, 133.1, 119.8, 114.3, 95.1, 60.5, 55.6, 55.2.

HRMS: exact mass calculated for $[M]^+$ ($C_{16}H_{18}O_5$) requires *m/z* 290.1154, found *m/z* 290.1152.

1-Methyl-3-(4-(trifluoromethoxy)phenoxy)benzene, **A43**



Prepared according to General Procedure I using (4-(trifluoromethoxy)phenyl)boronic acid (33 mg, 0.16 mmol, 1 equiv), *m*-tolylboronic acid, pinacol ester (175 mg, 0.8 mmol, 5 equiv), K_3PO_4 (103 mg, 0.48 mmol, 3

equiv), CPME (0.63 mL, 0.25 M), and Oxone® (125 mg, 0.40 mmol, 2.5 equiv) as a slurry in H_2O (1.28 mL) and CPME (0.25 mL), $Cu(OAc)_2$ (58 mg, 0.32 mmol, 2 equiv), powdered activated molecular sieves, MeCN (350 μ*L*), EtOH (16 μL), and Et_3N (45 μL, 0.32 mmol, 2 equiv) to afford title compound as a clear gum (26.2 mg, 61% yield).

υ_{max} (Film): 2926, 1608, 1588, 1502, 1489, 1251, 1193 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.23 (d, *J* = 7.8 Hz, 1H), 7.17 (dd, *J* = 9.0, 0.7 Hz, 2H), 7.01–6.94 (m, 3H), 6.83 (d, *J* = 5.8 Hz, 2H), 2.35 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 156.8, 156.2, 144.5, 140.3, 129.8, 124.8, 122.7, 120.7 (q, $^1J_{C\text{-}F}$ = 256.3 Hz). 120.0, 119.6, 116.3, 21.5.

^{19}F NMR $CDCl_3$, 376 MHz): δ – 58.3 (s, 3F).

HRMS: exact mass calculated for $[M]^+$ ($C_{14}H_{11}F_3O_2$) requires *m/z* 268.0711, found *m/z* 268.0724.

2.5.7 cLogP Parameters for Boron Species

Listed below are cLogP values for neutral boronic acids and boronic acid pinacol esters as well as their potassium boronate derivatives.[149]

Boron Species	cLogP Value
A7a	2.64
A9a	1.78
A10a	1.64
A11a	1.39
A12a	0.97
A13a	1.79
A14a	1.74
A15a	2.11
A16a	1.59
A17a	3.04
A18a	2.43

A19a	1.92
A20a	0.77
A7d	0.50
A9d	- 0.37
A10d	- 0.51
A11d	- 0.76
A12d	- 1.18
A13d	- 0.36
A14d	- 0.41
A15d	- 0.04
A16d	- 0.55
A17d	0.90
A18d	0.29
A19d	- 0.23
A20d	- 1.37
A8b	5.58
A9b	4.04
A10b	3.90
A11b	3.65
A12b	3.23
A13b	4.05
A14b	4.00
A21b	4.18
A22b	3.72
A23b	4.12
A24b	3.49
A25b	3.59
A26b	3.12
A8e	3.44
A9e	1.89
A10e	1.74
A11e	1.50

A12e	1.08
A13e	1.90
A14e	1.86
A21e	2.03
A22e	1.57
A23e	1.98
A24e	1.35
A25e	1.44
A26e	0.97

Chapter 2

Interrogating Pd(II) Anion Metathesis Using Vinyl BPin as a Bifunctional Chemical Probe: A Transmetalation Switch

This chapter is based upon the following publication: *J. Am.Chem. Soc*, 2018, **140**, 126–130.[150]

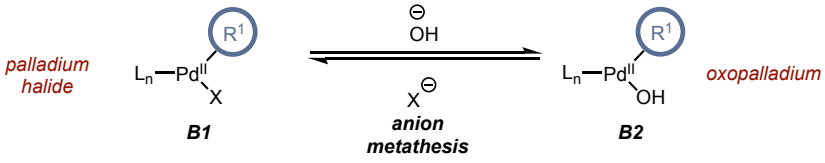
The enclosed study was carried out with the help of Dr Ciaran P. Seath, Matthew West, and Calum McLaughlin. Their input during analysis of palladium speciation and in generating a substrate scope of the transmetalation switch - SM/MH was greatly appreciated.

Numbered compounds in chapter 2 will follow the order B1, B2, B3,…. etc.

3 Chapter 2

3.1 Proposed Work

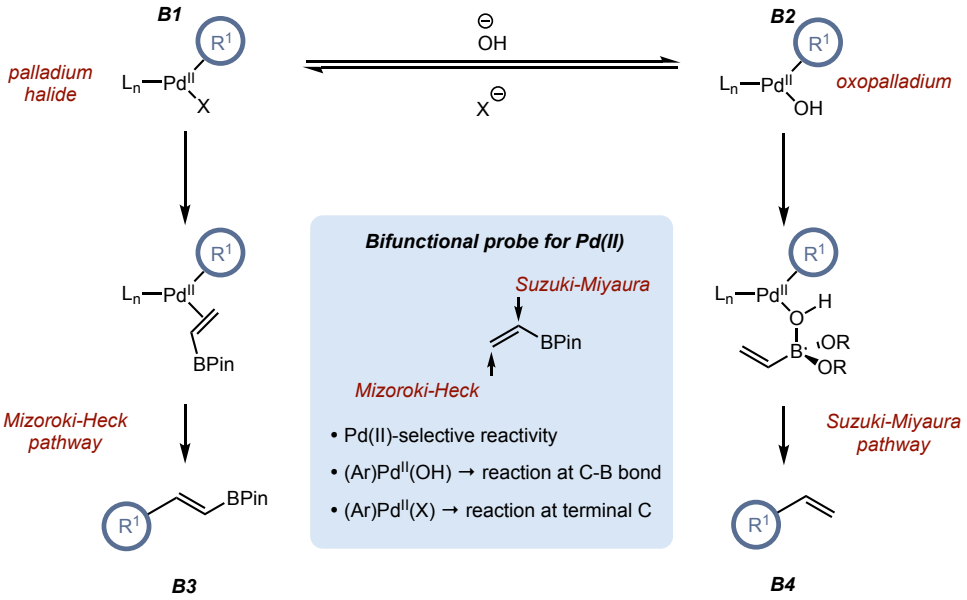
Chemoselectivity in the SM reaction has thus far been established through the electrophilic component, via selective oxidative addition of halides/pseudo halides,[30] and the nucleophilic component, through selective transmetalation of organoboron species.[146] The reactivity and selectivity observed during these mechanistic events is now well understood after years of investigation. Despite this, a key mechanistic event which underpins the SM reaction, and is perhaps underexplored, is the critical anion metathesis event which has recently been elucidated in mechanistic studies.[86,87,91] The step involves the equilibrium between a palladium halide species, (Ar)$Pd^{II}X$ **B1**, and an oxopalladium species (Ar)$Pd^{II}OH$ **B2**, with the formation of **B2** preferential under aqueous basic conditions of the SM reaction (Scheme 85).[86,89]



Scheme 85: Anion metathesis

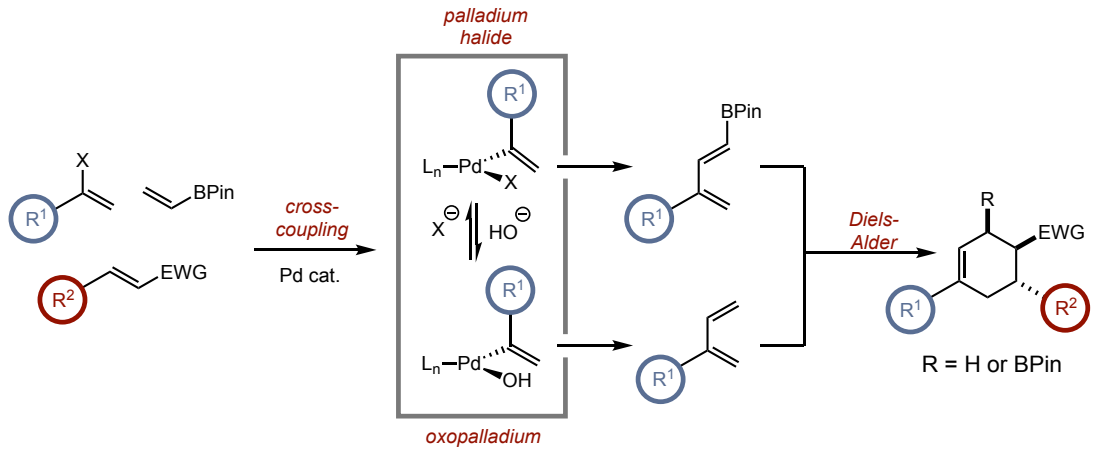
Although the anion metathesis equilibrium has been investigated previously,[86] control over this mechanistic event has not yet been leveraged for synthetic gain. Control over this equilibrium may provide a powerful, yet untapped, control vector for chemoselectivity in palladium catalysis. In order to interrogate this mechanistic event, the use of a bifunctional chemical probe was proposed. Vinyl BPin is a competent organoboron nucleophile in the SM reaction and has also been demonstrated to undergo MH cross-couplings (Scheme 86).[151] It was believed that this divergence is a direct result of catalyst speciation and through a thorough investigation of anion metathesis we could enable discrimination of competing synthetic pathways and facilitate a transmetalation switch as a function of anion metathesis. To probe this, stoichiometric palladium species would require synthesis, and the anion metathesis event investigated under various reaction media. Once differentiation of palladium species was established, these conditions could be used in the presence of vinyl BPin to generate a range of divergent substrates, with

styrenyl BPin products (**B3**) formed under palladium halide favouring conditions, and styrenyl products (**B4**) under oxopalladium promoting conditions (Scheme 86).



Scheme 86: A transmetalation switch at Pd^{II} via control of anion metathesis

Establishing divergent conditions as a direct function of anion metathesis will set up a platform for cascade events. It was postulated that cross-coupling of vinyl BPin with vinyl halides/pseudo halides could form diene intermediates which could then engage a dienophile in a Diels-Alder (DA) reaction (Scheme 87). The cascade triene annulation would allow rapid access to complex non-borylated and borylated carbon frameworks. The complex borylated scaffolds could serve as key intermediates in synthesis, with a plethora of organic transformations established on organoborons.

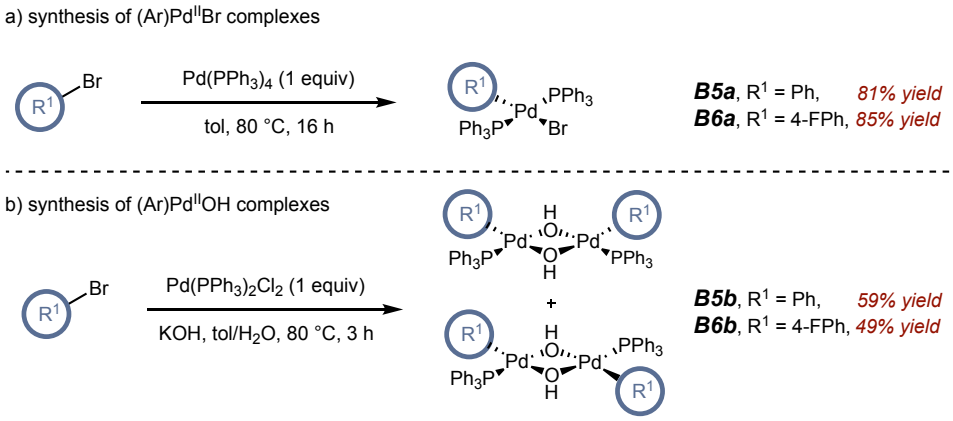


Scheme 87: (Non)borylated carbocycles from anion metathesis-controlled cascade annulation

3.2 Results and Discussion

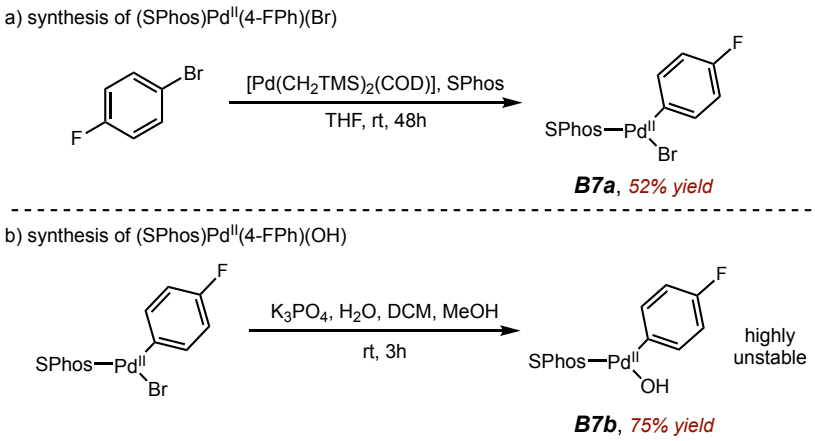
3.2.1 Stoichiometric Transmetalation – Proof of Concept

At the outset of this project the bifunctional reactivity of vinyl BPin with the two proposed palladium species involved in anion metathesis had to be suitably demonstrated. To do this, it was necessary to synthesise the requisite palladium halide complexes, in order to assess MH transmetalation, and oxopalladium complexes, to probe SM reactivity. Palladium halide complexes **B5a** and **B6a** were easily accessed on a large scale through stoichiometric oxidative addition of the aryl bromide with $Pd(PPh_3)_4$ (Scheme 88a). These complexes were found to be air stable and could be readily stored under air at room temperature. Similarly, oxopalladium complexes (**B5b** and **B6b**) could be synthesised as their *cis* and *trans* bridged dimers through oxidative addition of the aryl halide and subsequent anion metathesis in the presence of KOH (Scheme 88b).



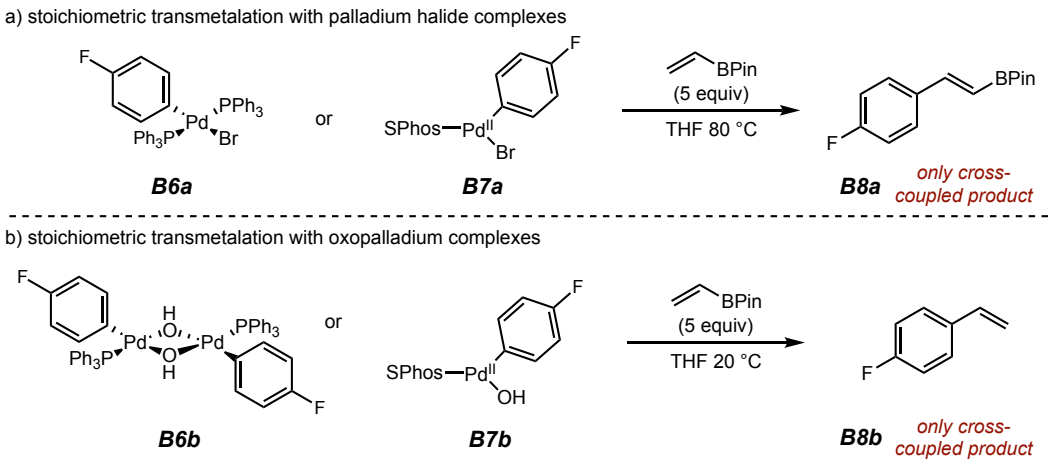
Scheme 88: Synthesis of stoichiometric Pd^{II} species: a) palladium halide; b) oxopalladium

Although the above complexes are commonly employed in catalytic SM reactions, reactivity with many aryl chloride electrophiles can be poor.[68] In a bid to address this issue and expand the scope of electrophile throughout this study, we looked to synthesise the significantly more active SPhos, palladium halide complex **B7a** and oxopalladium complex (**B7b**, Scheme 89). However, the oxopalladium complex **B7b** was extremely unstable to air and non-degassed solvents and was deemed as suboptimal for an in-depth investigation of anion metathesis.



Scheme 89: Synthesis of SPhos complexes: a) B7a; b) B7b

At this point in the study vinyl BPin was reacted with each palladium complex and establish a preferred mode of transmetalation (Scheme 90). Pleasingly, palladium halide complexes **B6a** and **B7a** provided styrenyl BPin **B8a** as the only cross-coupled product (Scheme 90a) demonstrating that the MH pathway is preferred for this palladium complex. It must be noted that significant amounts of fluorobenzene (< 30 %) were detected during these reactions as a result of protodepalladation. However, no styrene products, as a result of SM transmetalation, were detected. In contrast, exposing vinyl BPin to the corresponding oxopalladium species (**B6b** and **B7b**) led to formation of styrenyl product **B8b** as the only cross-coupled product (Scheme 90b). Both results clearly show that if anion metathesis is properly regulated a transmetalation switch (MH vs. SM) of the bifunctional vinyl BPin can be readily achieved.



Scheme 90: Stoichiometric transmetalation of vinyl BPin with Pd^{II} complexes

During these stoichiometric transmetalation reactions a stark difference in reactivity was noted. The MH reaction with **B6a** and **B7a** required elevated temperatures for meaningful conversion whereas the SM transmetalation with both oxopalladium species (**B6b** and **B7b**) was complete <10 min at room temperature. To provide a rough comparison of the difference in relative rates, the half-life of both metal complexes **B6a** and **B6b** with vinyl BPin were examined (Chart 3 and 4). As shown $t_{1/2}$ of vinyl BPin with **B6a** was ~ 50 min at 80 °C (Chart 3), while < 2 min was observed for vinyl BPin with **B6b** at room temperature (Chart 4). This immense difference in the relative rates highlights the superior rate of organoboron transmetalation with the oxopalladium species, in comparison to the MH with

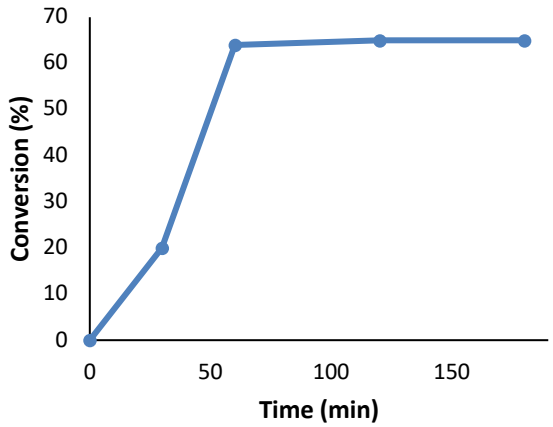


Chart 3: $t_{1/2}$ of B6a with vinyl BPin at 80 °C

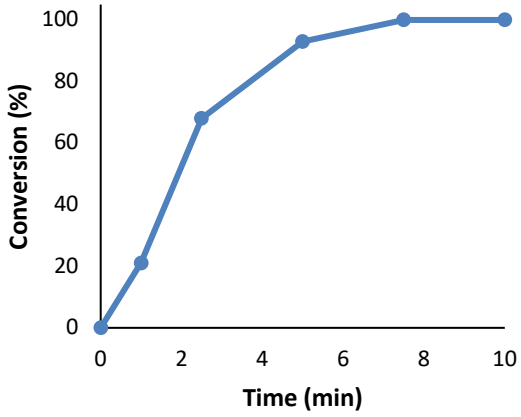


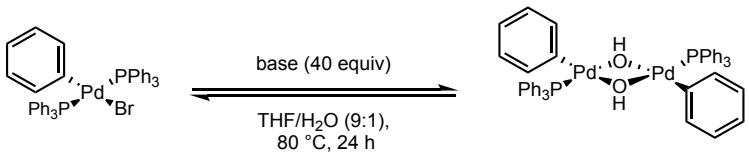
Chart 4: $t_{1/2}$ of B6b with vinyl BPin at 20 °C

3.2.2 Controlling Anion Metathesis

With evidence that differentiated products can be accessed via the contrasting palladium complexes involved in anion metathesis, we set out to analyse the complex equilibrium of this critical event and interrogate if anion metathesis can be directly regulated by reaction media. It was believed the variable which would have the most profound impact on the distribution of palladium species was base as this is critical for oxopalladium formation.[89] A series of bases were exposed to palladium halide complex **B5a** (on typical reaction scale - 40 equiv of base) in both aqueous and anhydrous conditions, and the distribution of palladium complexes were monitored by ^{31}P NMR (Table 9). In the absence of water, formation of oxopalladium species **B5b** was unfavoured for most bases and palladium halide species **B5a** remained as

the major complex in solution (Table 9, Entries 3, 5, 7, and 9). The preferential formation of **B5a** suggests MH reactivity could be favoured under these reaction conditions. In contrast, on addition of water, KOH was found to predominantly form the oxopalladium species (Table 9, Entry 2). Similarly, inorganic bases such as K_3PO_4, K_2CO_3, and KOAc formed substantial quantities of their respective oxopalladium species (Table 9, Entry 4, 6, and 10). Of particular note was the preference of **B5a** for weaker organic bases, such as Et_3N, irrespective of water content (Table 9, Entries 7 and 8). Weaker organic bases preferentially lying to **B5a** of the equilibrium suggest these systems may be superior for MH reactivity. Similarly, use of aqueous inorganic base forms substantial amounts of **B5b** and is therefore better suited for SM transmetalation.

Table 9: Effect of base and water on anion metathesis equilibrium



B5a ***B5b***

Entry	Base	Water	Pd(Br)%[a]	Pd(OH)%[a]
1	KOH	-	81	19
2	KOH	Y	8	92
3	K_3PO_4	-	99	1
4	K_3PO_4	Y	68	32
5	K_2CO_3	-	93	7
6	K_2CO_3	Y	77	23
7	Et_3N	-	99	1
8	Et_3N	Y	99	1
9	KOAc	-	96	4[b]
10	KOAc	Y	66	34[b]

[a] Determined by ^{31}P NMR as a ratio, [b] $(PPh_3)_2(Ph)Pd^{II}(OAc)$ oxopalladium species formed

Interestingly, the use of KOH led to a complete switch of the dominant species in solution based on the presence of water (Table 9, Entries 1 and 2), as such, this was a base we intended to interrogate further and establish other effects which may

influence anion metathesis equilibria. It was believed water content would have a significant impact on the distribution of palladium species. Palladium complex **B5a** was employed in a series of reactions with KOH and varied THF/water ratios (Chart 5). Interestingly, formation of oxopalladium complex **B5b** counterintuitively increased with decreasing water content. However, this trend was in agreement with literature data,[86] and can be attributed to the reduced solvation of hydroxide ions with decreasing water content, enhancing nucleophilic displacement of the halide.

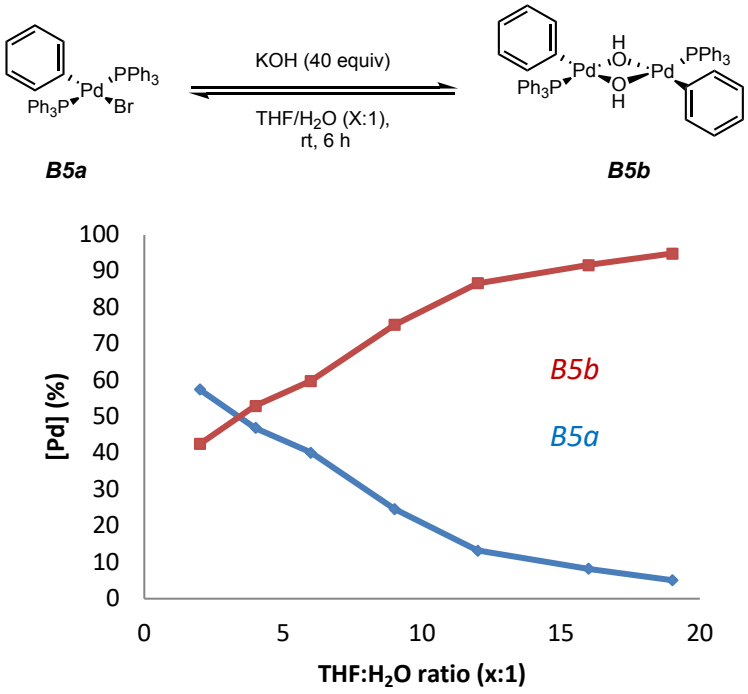
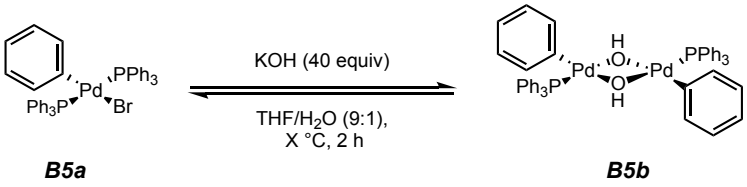


Chart 5: Interrogating the effect of water on anion metathesis by ^{31}P NMR

A similar study was conducted with varying temperature (Chart 6). As expected, the equilibrium shifted from **B5a** to **B5b** with increasing temperature, presumably due to improved nucleophilic displacement. Both the water and temperature studies highlight the favourability of oxopalladium species at lower water content and higher temperatures. Although increasing temperature in the presence of aqueous base increases unfavourable properties associated with SM reactivity such as boronate formation and phase transfer of boronic acids, the use of small water quantities also increases oxopalladium allowing this to be avoided. In addition to this phenomenon, a landmark study on the SM reaction by Lloyd-Jones and coworkers demonstrated that lower concentrations of water favours the neutral boronic acid, critical for

oxopalladium transmetalation. [62,123] As such, low water content appears most favourable for SM reactivity.



B5a ***B5b***

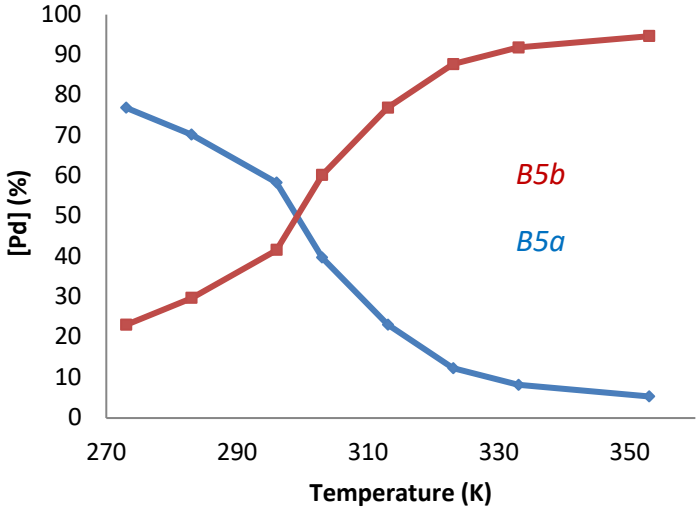


Chart 6: Interrogating the effect of water on anion metathesis

3.2.3 A Transmetalation Switch

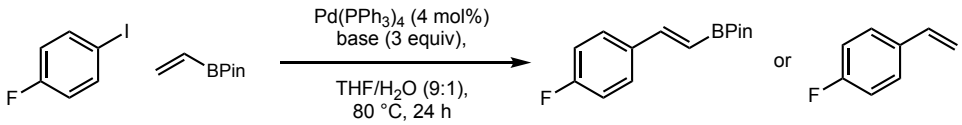
Of the data generated thus far there are two implications for both pathways to be feasible with one catalytic system:

1. For organoboron transmetalation a neutral boron species and oxopalladium complex are required.[91] Both these critical species are preferentially formed at small water quantities with inorganic base suggesting these conditions as optimal for the SM reaction.[62]

2. Elevated temperatures are necessary for MH transmetalation. However, the concentration of oxopalladium is shown to increase with increasing temperature in the presence of water (Chart 6). As such, conditions would have to be completely anhydrous in order to achieve any selectivity for MH.

With a mechanistic understanding of how anion metathesis can be manipulated to enable discrimination between synthetic pathways, we examined the use of vinyl BPin in a catalytic scenario. Unfortunately use of $Pd(PPh_3)_4$ provided inconsistency and poor reactivity with aryl bromides under a number of conditions. However, the use of aryl iodides provided more consistent results (Table 10). The use of inorganic bases generally favoured formation of SM product **B8b** irrespective of water content (Table 10, Entries 1–8). This could be attributed to incorporation of adventitious water as a result of the hygroscopic nature of the bases. Interestingly, the use of Et_3N enabled a transmetalation switch in the absence of water preferentially forming the MH product **B8a** (Table 10, Entry 9), demonstrating the suitable discrimination of synthetic pathways as a function of regulating anion metathesis. However, the use of Et_3N in the presence of water provided an unexpected result. Although water and Et_3N formed no oxopalladium complex visible by NMR during the anion metathesis study (Table 9, Entry 8), the SM product was favoured in the catalytic scenario (Table 10, Entry 10). It could be possible that small quantities of oxopalladium is formed during the reaction, and due to the inherent difference in relative rates, organoboron transmetalation is favoured. Of course, due to Le Chateliers principle, consummation of the oxopalladium species will only alter the equilibrium and generate more of the species, subsequently pushing reactivity towards SM transmetalation. Similarly, MH and subsequent protodeboronation to form the SM product cannot be ruled out at this stage.

Table 10: Variation of base and water in a catalytic scenario – $Pd(PPh_3)_4$



B8a ***B8b***

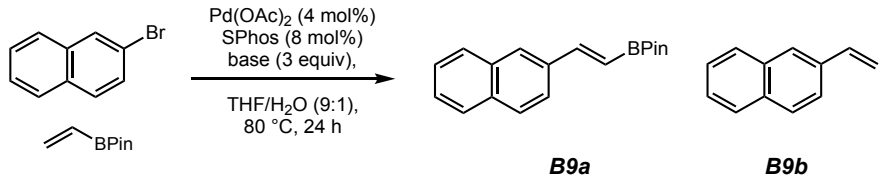
Entry	Base	Water	B8a (%)[a]	B8b (%)[a]
1	KOH	-	0	100
2	KOH	Y	0	100
3	K_3PO_4	-	0	100
4	K_3PO_4	Y	0	100
5	K_2CO_3	-	11	89
6	K_2CO_3	Y	14	86
7	KOAc	-	14	86
8	KOAc	Y	12	88
9	Et_3N	-	81	19
10	Et_3N	Y	11	89

[a] percentage ratio of products established by ^{19}F NMR

In a bid to extend the scope of the electrophile for both pathways, we carried out a base and water study with a commonly employed $Pd(OAc)_2$/SPhos catalyst system, analysing product ratios by ^1H NMR against a known standard (Table 11). Similar trends were observed, as SM product **B9b** was favoured with strong hygroscopic inorganic bases regardless of water content (Table 11, Entries 1–4). Interestingly with this catalyst system, weaker inorganic bases favoured MH in the absence of water (Table 11, Entries 5 and 7). However, K_2CO_3 provided low conversions. This data suggests anion metathesis of the SPhos complex may require stronger bases (hydroxide) to form the necessary oxopalladium complex for SM reactivity. Also, as MH conversion has generally improved, the SPhos, palladium halide complex formed after oxidative addition may be more active to transmetalation with MH nucleophiles. The use of Et_3N provided good conversion to the MH product **B9a** in the absence of water showing a clear transmetalation switch based on manipulation of anion metathesis (Table 11, Entry 9). However, similar to the tetrakis catalyst system (Table 10, Entry 10), employing Et_3N in the presence of water led,

predominantly, to the SM product **B9b** (Table 11, Entry 10). Again, this could be attributed to small quantities of oxopalladium being formed in the presence of water and preferential organoboron transmetalation based on the stark difference on the relative rates.

Table 11: Variation of base and water in a catalytic scenario – $Pd(OAc)_2$/SPhos

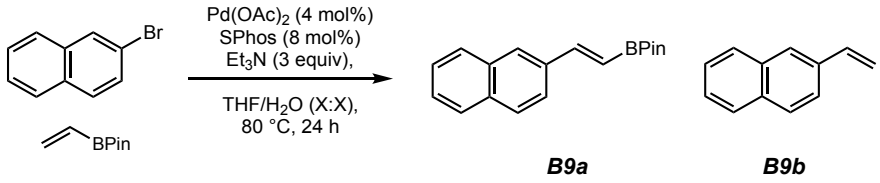


Entry	Base	Water	Conversion to B9a (%)[a]	Conversion to B9b (%)[a]
1	KOH	-	0	100
2	KOH	Y	0	100
3	K_3PO_4	-	1	92
4	K_3PO_4	Y	0	100
5	K_2CO_3	-	21	2
6	K_2CO_3	Y	0	100
7	KOAc	-	81	19
8	KOAc	Y	12	55
9	Et_3N	-	98	2
10	Et_3N	Y	0	82

[a] Determined by ^1H NMR against a known internal standard (1,4-dinitrobenzene)

The transmetalation switch demonstrated with Et_3N based on the presence/absence of water was a phenomenon we wanted to investigate further. A study on water content suitably showed that any additional water in the system resulted in a transmetalation switch favouring organoboron transmetalation to form **B9b** (Table 12). In the absence of water, formation of **B9a** dominates.

Table 12: Water effect on transmetalation when employing Et_3N as base

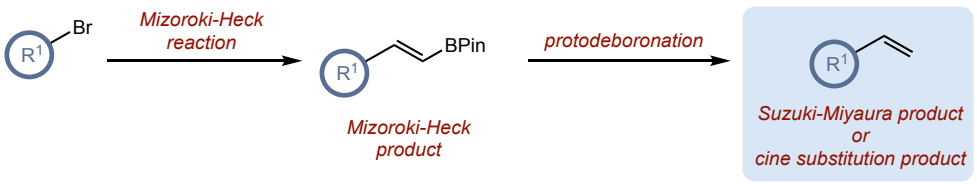


Entry	THF/H_2O	Conversion to B9a (%)[a]	Conversion to B9b (%)[a]
1	1:0	98	2
2	40:1	18	72
3	20:1	14	72
4	9:1	2	78
5	4:1	0	100

[a] Determined by ^1H NMR against a known internal standard (1,4-dinitrobenzene)

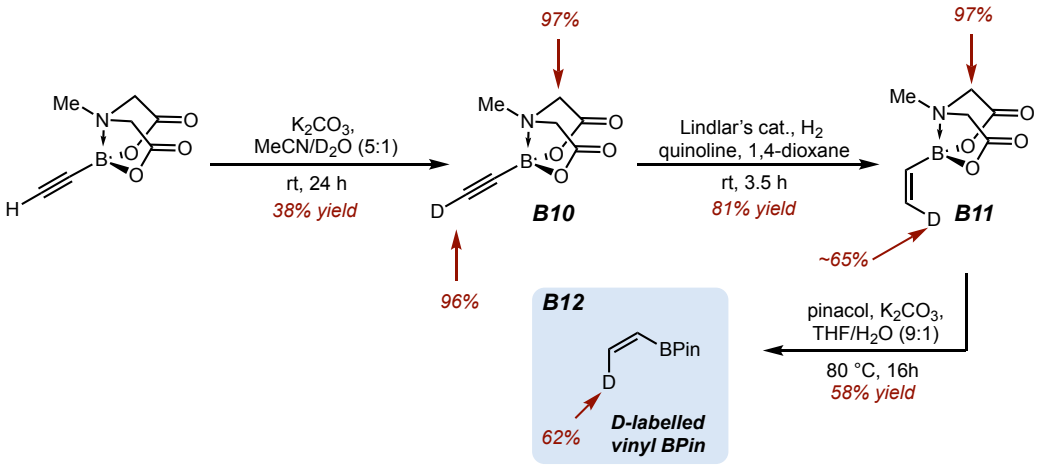
In summary, it was demonstrated that aqueous inorganic bases enable rapid organoboron transmetalation by promoting formation of an oxopalladium species in the anion metathesis equilibrium. In contrast, anhydrous conditions using organic base enabled MH transmetalation via a palladium halide species through inhibition of anion metathesis. This phenomenon provides a transmetalation switch of the bifunctional vinyl BPin species based on solution control of the anion metathesis event in catalysis.

With a transmetalation switch leading to differentiated products as a function of anion metathesis in hand, we set out to dispel any doubt as to the origin of diversified products. It could be proposed that in a cine substitution manner,[152] a MH reaction and subsequent protodeboronation of the BPin residue could afford the SM product (Scheme 91). This would imply both products are formed via a common intermediate and only differentiate in protodeboronation.



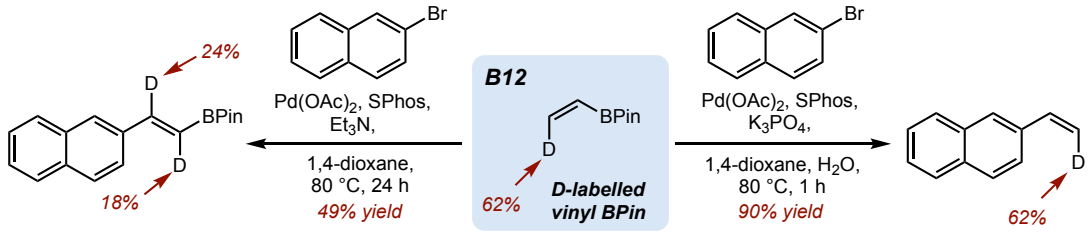
Scheme 91: Possible cine substitution mechanism in the formation of SM products

In order to rule out cine substitution as the origin of styrenyl product formation, we aimed to synthesise mono-deuterium labelled vinyl BPin and monitor incorporation of deuterium into the product (Scheme 92). The synthesis began by exposing acetylene BMIDA to D_2O and base at room temperature allowing the formation of **B10**, with 96% incorporation in the desired alkyne position.[153] Deuterium was also incorporated into the CH_2 position (97% incorporation) of the MIDA protecting group back bone, although this was inconsequential as this would be removed in future synthetic steps. Following a literature procedure,[55] **B10** could be easily reduced to the corresponding alkene **B11** using Lindlar's catalyst. However, unfortunately during this transformation deuterium incorporation at the desired site was diminished through proton exchange. Despite this, the level of incorporation was deemed acceptable to demonstrate the absence of cine substitution and the synthetic sequence was continued. Conversion of **B11** to D-labelled vinyl BPin via step-wise hydrolysis and pinacol conjugation was initially unsuccessful, presumably due to the instability of the vinyl boronic acid intermediate which could not be isolated. Diol conjugation to boronic acids is favoured at high pH,[125] as is MIDA hydrolysis in the presence of aqueous base.[50] Pleasingly, **B11** could be converted to the desired D-labelled vinyl BPin (62% D-incorporation) via a one-pot hydrolysis/pinacol conjugation sequence allowing isolation of the unstable vinyl boronic acid intermediate to be avoided. Great care had to be taken during isolation of the potentially volatile product.



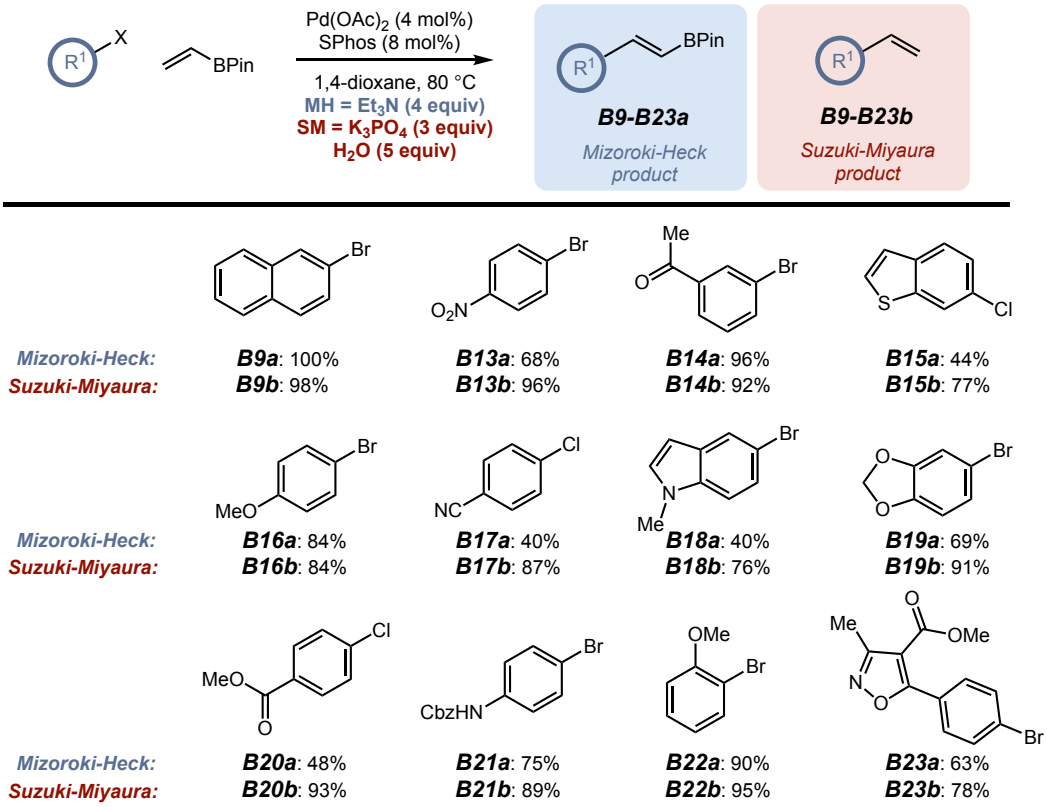
Scheme 92: Synthesis of D-labelled vinyl BPin

At this point D-labelled vinyl BPin **B12** under both MH and SM conditions was examined. Under MH conditions, scrambling of the deuterium was observed (Scheme 93). This observation is not unusual as the β-hydride elimination and carbopalladation steps are reversible in the MH mechanism.[114] Pleasingly, the use of D-labelled vinyl BPin under SM promoting reaction conditions led to full transcription of deuterium to the appropriate site as shown (Scheme 93). The incorporation of deuterium in the correct position shows that transmetalation occurs directly through the organoboron species and not via a cine substitution mechanism.



Scheme 93: Use of D-labelled vinyl BPin in MH and SM reactions with 2-bromonaphthalene

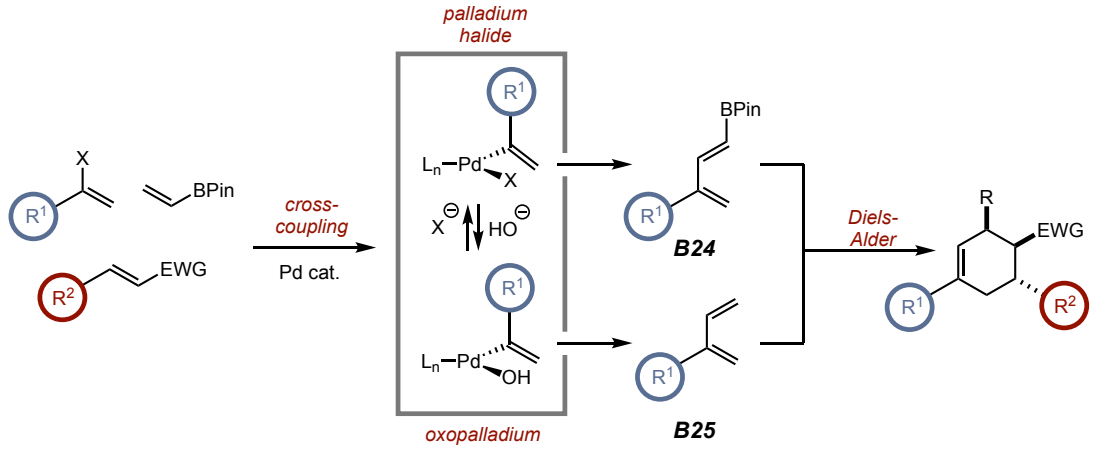
With confidence that discrimination between competing synthetic pathways was a result of MH reactivity with a (Ar)$Pd^{II}X$ species and SM transmetalation with (Ar)$Pd^{II}OH$, we looked to assess the generality of this transmetalation switch on a range of different aryl electrophiles analysing conversion to products by ^{1}H NMR (Scheme 94). Pleasingly a transmetalation switch with high fidelity was enabled for all aryl halides with most proceeding to high conversions. Aryl bromides with electron withdrawing groups (**B13** and **B14**) and electron donating groups (**B16**, **B19**, and **B22**) were well tolerated in both MH and SM selective reactions. The use of heteroaryl halides was also tolerated (**B15, B18**, and **B23**) in both transformations. However, the yield of the MH was typically low due to poor reactivity of these species. Interestingly, the use of a more active catalyst system enabled the cross-coupling of aryl chlorides (**B15**, **B17**, and **B20**) under both reaction conditions, although MH coupling led to poor conversions again with these halides.



Scheme 94: Transmetalation switch substrate scope

3.2.4 Cascade Triene Annulation

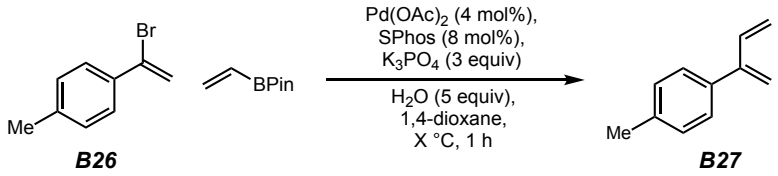
With control of Pd^{II} in a catalytic scenario established, this transmetalation switch phenomenon was explored in a cascade protocol. It was believed that a one-pot cascade cross-coupling/DA procedure would enable the rapid synthesis of complex borylated and non-borylated carbon frameworks (Scheme 95). Discriminating between MH and SM cross-coupling would allow the formation of key diene intermediates (**B24** and **B25**). In the presence of a dienophile, the formed diene intermediates can then undergo a DA reaction to form the cyclohexene core.



Scheme 95: Cascade triene annulation to form borylated and non-borylated carbocycles mediated by Pd^{II} species

The initial aim was to ensure our SM conditions transcribed to a vinyl/vinyl cross-coupling manifold (Table 13). Vinyl bromide **B26** was exposed to vinyl BPin at varied temperatures for one hour. Pleasingly, the conditions were transferable, and the reaction proceeded to very high conversion of the diene **B27** at low temperatures, with 50 °C chosen as optimal conditions. Higher temperatures led to product degradation. This is presumably due to competing homo-DA of the diene species with another molecule of itself.

Table 13: Vinyl/vinyl SM optimisation - temperature study

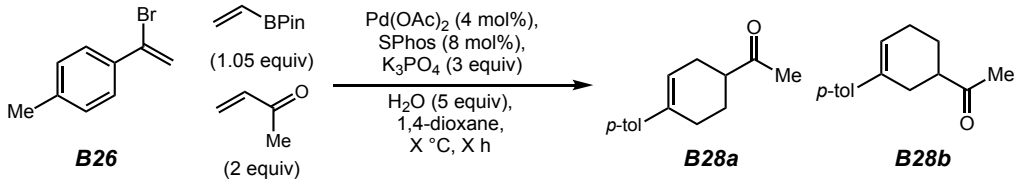


Entry	Temperature (°C)	Conversion to B27 (%)[a]
1	rt	88
2	30	94
3	50	97
4	70	93
5	90	88
6	110	80

[a] Determined by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene)

As the vinyl/vinyl SM cross-coupling was relatively facile the proposed cascade SM/DA triene annulation using methyl vinyl ketone (MVK) as the dienophile was interrogated in a bid to investigate regioselectivity (Table 14). Unfortunately, allowing the reaction to run for longer at 50 °C led to poor conversion to the cyclised products likely due to insufficient thermal energy to promote DA cyclisation (**B28**, Table 14, Entry 1). However, regioselectivity was reasonable in comparison to previous studies in the literature.[154] Similarly, conducting the reaction at higher temperatures for longer led to decreased conversion (Table 14, Entry 2). This was tentatively attributed to higher temperatures promoting competing side reactions during the initial SM step. Regioselectivity could not be properly assigned by ^{1}H NMR due to multiple species in the crude mixture. Pleasingly, running the reaction for 1 hour and subsequently increasing the temperature allowed increased conversion to the DA cycloadduct (Table 14, Entries 3–5). Despite this, increasing the temperature to a certain extent led to deterioration of regioselectivity (Table 14, Entry 5). Although the DA reaction is a concerted process it is highly asynchronous enabling regioselectivity in unsymmetrical dienophiles,[155] increasing the temperature enables increased reactivity and promotes cyclisation before any orbital interactions occur. As a result, typical regioselectivity can be diminished.

Table 14: Cascade SM/DA protocol – Temperature/time study

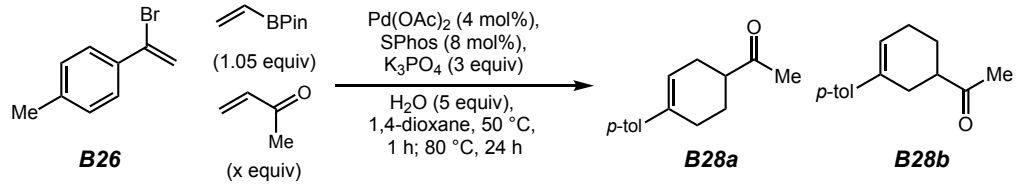


Entry	Conditions	Conversion (%)[a]	B28a:B28b[a]
1	50 °C, 24 h	42	8:1
2	80 °C, 24 h	63	-
3	50 °C, 1 h; 80 °C, 24 h	78	7:1
4	50 °C, 1 h; 120 °C, 24 h	81	6:1
5	50 °C, 1 h; 150 °C, 24 h	71	4:1

[a] Determined by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene)

At this point we began to implement a temperature change after one hour and alter other variables in a bid to increase conversion (Table 15). It was believed increasing the dienophile equivalents would enhance DA reactivity as we had already shown that the SM went to complete conversion after 1 hour (Table 13, Entry 3). It was proposed increasing vinyl BPin equivalents would provide a competitive dienophile for MVK and hinder DA reactivity. As such, this variable was not assessed. Pleasingly, increasing the dienophile equivalents led to excellent conversion and the reaction was deemed optimal for further exploration of a substrate scope (Table 15, Entry 3).

Table 15: Cascade SM/DA protocol – Dienophile equivalents study



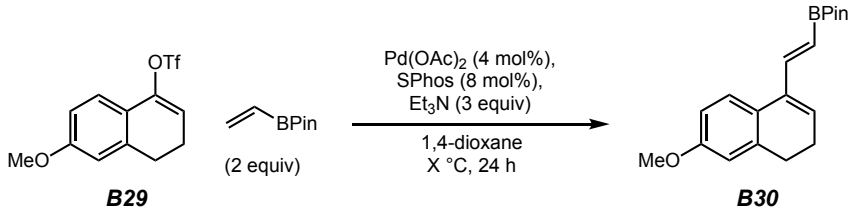
Entry	MVK (equiv)	Conversion (%)[a]	B28a:B28b[a]
1	1 equiv	42	6:1
2	2 equiv	78	7:1

3	3 equiv	91	6:1
4	5 equiv	87	6:1

[a] Determined by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene)

With a cascade SM/DA protocol enabling the rapid synthesis of non-borylated carbon scaffolds optimised, we looked to apply our transmetalation switch methodology and ensure MH conditions were transferrable to a vinyl/vinyl cross-coupling system in order to grant access to borylated analogues. Unfortunately, the reaction conditions were not successful when employed in the vinyl/vinyl system (Table 16). An initial temperature study using vinyl triflate **B29** provided poor results suggesting elevated temperatures were detrimental to conversion. For reactions at 40 °C and above, full consumption of the starting vinyl triflate **B29** was observed indicating there was little room for improvement of reactivity (Table 16, entries 2–4). It appears the formed diene BPin intermediate **B30** is unstable in the reaction mixture at elevated temperatures and this was confirmed by monitoring the reaction over time. As such, reactions at 40 °C were taken forward for further investigation.

Table 16: Vinyl/vinyl MH optimisation – Temperature Study



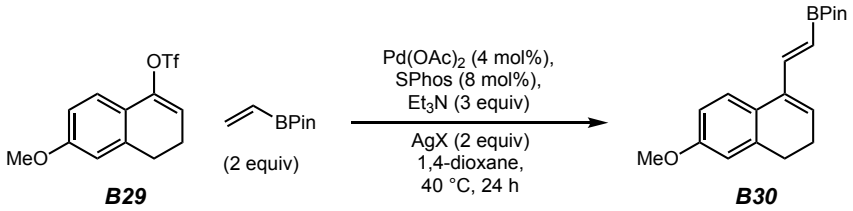
Entry	Temp. (°C)	Conversion to B30 (%)[a]	Starting Material (%)[a]
1	rt	15	62
2	40	31	0
3	60	23	0
4	80	18	0

[a] Determined by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene)

Further solvent, concentration, and base equivalent studies provided no improvement on conversion to product at 40 °C. The use of additives, such as silver, have been known to enhance palladium-catalysed reactions.[108] Attention then turned to the use

of silver additives in a final attempt to improve MH reactivity on the vinyl/vinyl cross-coupling system (Table 17). To our delight, reactivity was significantly improved, with anhydrous AgOAc providing the optimal conditions (Table 14, Entry 3). It must be noted that the silver additive only enhanced reactivity and had no effect on SM/MH selectivity. It must also be noted that the diene BPin species **B30** was extremely unstable to silica and could not be isolated for full characterisation, although the allylic BPin generated from a subsequent DA reaction allowed full characterisation.

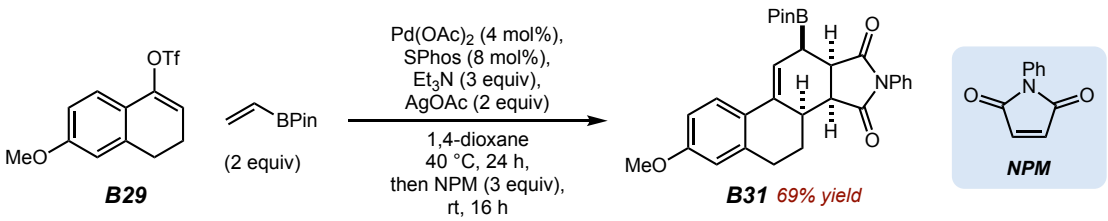
Table 17: Vinyl/vinyl MH optimisation – Silver additive study



Entry	AgX	Conversion to B30 (%)[a]
1	Ag_2CO_3	40
2	Ag_3PO_4	54
3	AgOAc	67

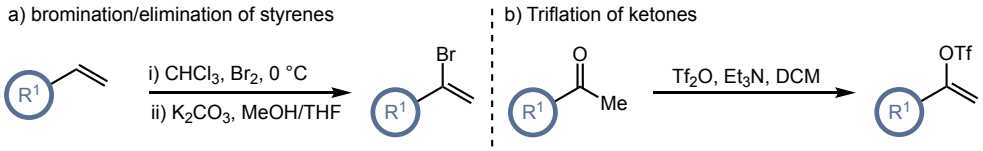
[a] Determined by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene)

With improved MH reactivity, introduction of a dienophile to the newly found conditions was next examined. Of course, selective MH between two competing olefins has not yet been established and as a result the dienophile would have to be added sequentially. Pleasingly the use of *N*-phenyl maleimide (NPM) as a dienophile at room temperature allowed complete conversion of the intermediate diene BPin to the borylated DA adduct (Scheme 96).



Scheme 96: Optimised cascacde MH/DA reaction to synthesis borylated carbocycles

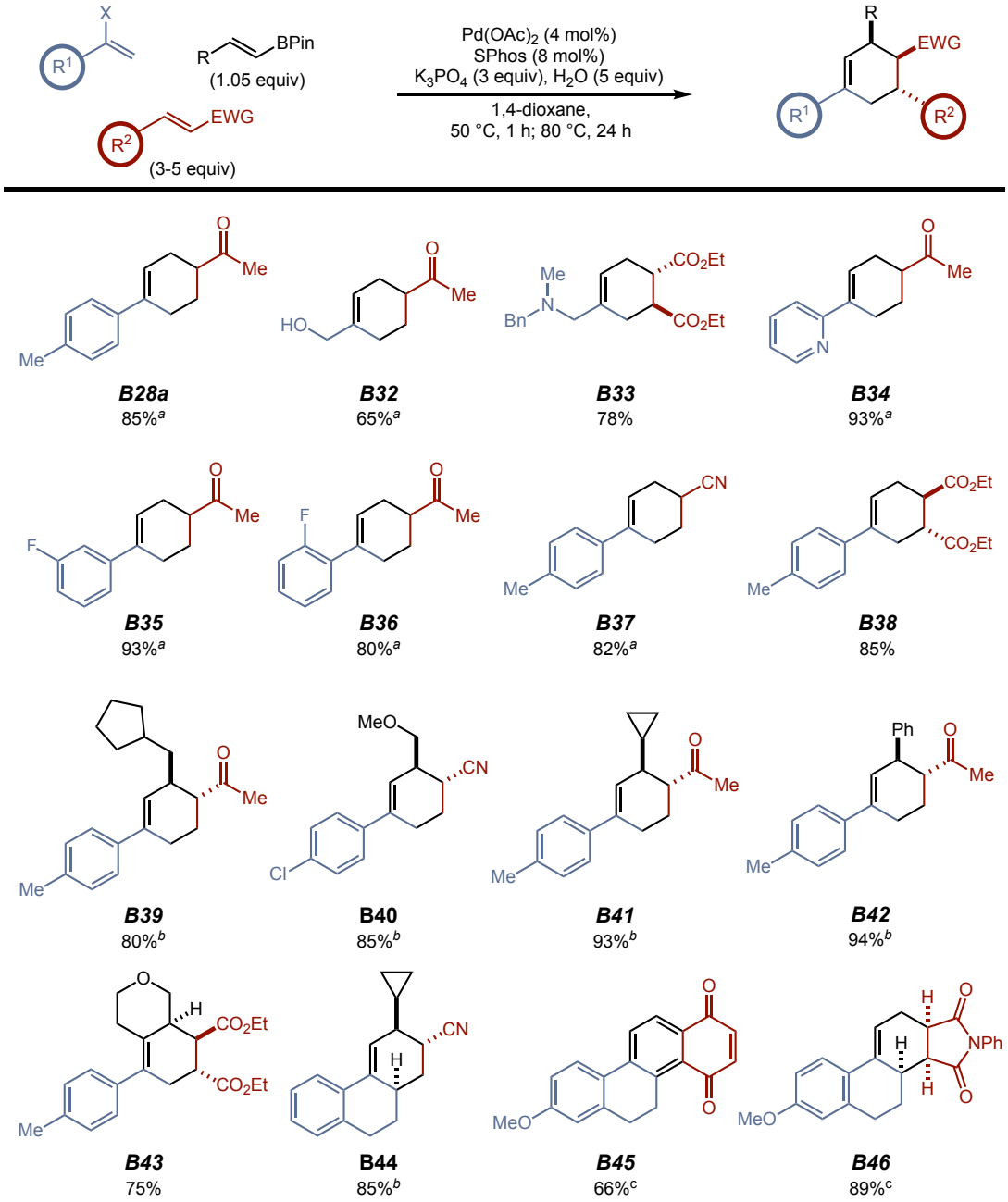
At this point we aimed to capitalise on this divergent platform enabled by control of Pd^{II} and generate a substrate scope around both cascade processes. To do this, we needed facile synthesis of vinyl halide/pseudo halide starting materials (Scheme 97). Vinyl bromides could be easily accessed via a two-step bromination/elimination procedure (Scheme 97a).[156,157] Formation of vinyl triflates was also relatively facile through a triflation procedure in the presence of organic base (Scheme 97b).[158] All other vinyl BPin and dienophile species are commercially available from known suppliers.



Scheme 97: Synthesis of vinyl halide/pseudo halide starting materials

As an accessible route to the necessary starting materials was established, the next aim was to explore the generality of the SM/DA cascade protocol (Scheme 98). Pleasingly, all substrates were successfully converted to the desired product with high fidelity. On each occasion SM was preferential to form a non-borylated diene, and subsequent cyclisation afforded a wide range of carbocycles. The use of alkyl vinyl halides were well tolerated, to produce monocyclic products (**B32** and **B33**). Similarly, a host of bicyclic products could be accessed with the use of styrenyl vinyl halides and unsubstituted vinyl BPin (**B28a**, and **B34**–**B38**). Substitution on the vinyl BPin species was also permitted, allowing the formation of bicyclic species (**B39**–**B42**) and tricyclic carbon scaffolds (**B43** and **B44**). A notable output of this method was the expedient synthesis of steroidal structures. Compounds **B45** and **B46** contain a similar A,B,C,D tetracyclic structure as many steroids,[159] excellently demonstrating the power of this methodology. Although most substrates are high yielding, there are some fundamental drawbacks of the chemistry. The use of monosubstituted dienophiles, such as acrylonitrile and MVK, led to a mixture of regioisomers, ranging from 3:1 to 9:1 (major regioisomer shown), when used alongside unsubstituted vinyl BPin (**B28a**, **B32**, **B34**, and **B35**–**B37**). However, regioselectivity was comparative, and on most occasions superior, to previous literature.[154] Admittedly this regioselectivity can be improved through the use of Lewis acids,[160]

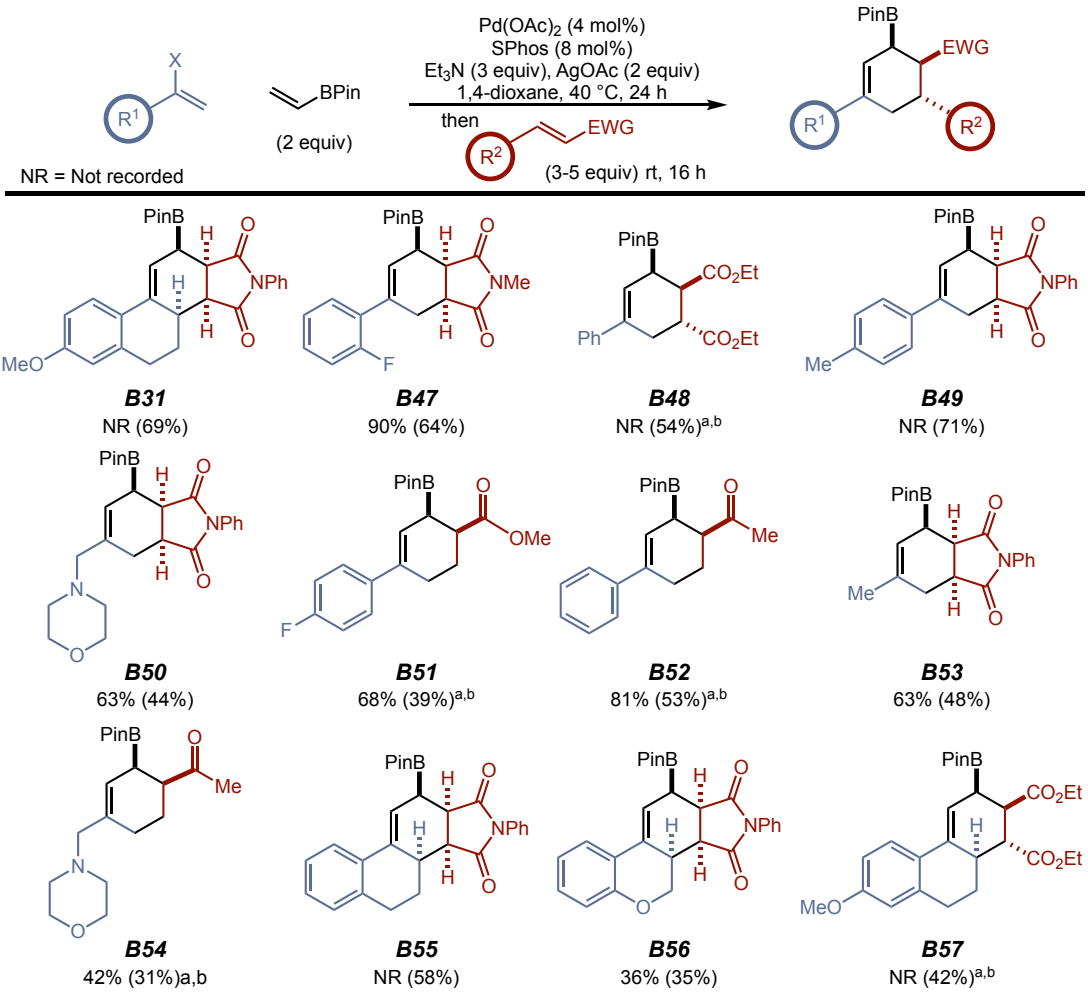
however, it was deemed that use of these catalysts would affect SM reactivity and, as a result, this avenue was not explored. Although introducing substituents on the vinyl BPin species led to complete regioselectivity (**B39**–**B44**), these reactions were not diastereoselective and led to 1:1 mixtures (regioselectivity and diastereoselectivity confirmed by 2D NMR, see experimental, Section 3.5.6 Structure Elucidation by 2D NMR). It was believed the aqueous basic media enabled epimerisation of the acidic proton adjacent to the carbonyl deteriorating any diastereoselectivity obtained from the DA reaction. Use of a more reactive dienophile (NPM) facilitated DA at room temperature and no racemisation was observed, leading only to the *endo* product (**B46**). However, the use of highly reactive dienophiles was detrimental to SM reactivity but could be avoided by sequential addition (**B45** and **B46**).



Scheme 98: Cascade SM/DA substrate scope, [a] mixture of regioisomers obtained (main regioisomer shown; [b] mixture of diastereomers (1:1); [c] dienophile added after 1 h

With the cascade SM/DA process thoroughly assessed we aimed to evaluate the analogous MH/DA protocol (Scheme 99). Unfortunately yields were not comparable to the SM/DA process and this was attributed to a poor initial MH reaction. Additionally, the allyl BPin products were notoriously difficult to isolate, often leading to protodeboronation when exposed to silica gel. As a result, ^{1}H NMR conversion was often recorded against an internal standard prior to purification.

Despite this, a series of complex scaffolds, containing an allyl BPin for further synthetic manipulation, could be accessed, including monocyclic **B54** and bicyclic (**B50** and **B53**) DA cycloadducts from alkyl vinyl halides. As well as bicyclic (**B48**, **B51**, and **B52**) and tricyclic (**B47** and **B49**) frameworks derived from styrenyl halides. Tetralone derived vinyl triflates could also be employed to form complex tricyclic borylated carbocycles **B57**. However, the most notable output from the developed methodology was the expedient access to tetracyclic, borylated, steroidal scaffolds (**B31**, **B55**, and **B56**). To form such complex structures, containing a functional boron handle, in a single synthetic process is of high importance to synthetic chemists. An unfortunate drawback was experienced when employing dienophiles other than maleimides (**B48**, **B51**, **B52**, **B54**, and **B57**). Application of these dienophiles required an increase in thermal energy in order to facilitate DA cyclisation. As it was already established that the generated allyl BPin intermediate was unstable to the MH reaction mixture at elevated temperature, these substrates required an aqueous "work up" prior to the DA step. Interestingly, mono substituted dienophiles led to completely regioselective and diastereoselective *endo* products (**B51**, **B52**, and **B54**). Similarly, use of symmetrical disubstituted dienophiles led to a single diastereomer (**B31**, **B47**–**B50**, **B53**, and **B55**–**B57**) This could potentially be attributed to an additional dative interaction between the carbonyl of the dienophile and the empty p-orbital of the BPin species directing regioselectivity.[161] The interaction could also be conceived as the origin of diastereoselectivity with the dative interaction enabling facial selectivity on dienophile approach leading to both substituents being located on the same side (*endo* approach). Diastereomers and regioisomers were confirmed by 2D NMR studies (See experimental for comprehensive 2D NMR analysis of a representative substrate for each scaffold, other substrates were assigned by analogy).



Scheme 99: Cascade MH/DA substrate scope, yields are conveyed as follows: NMR yield (isolated yield), [a] aqueous work up required after MH reaction; [b] DA reaction run at 80 °C

Although all products were completely assigned by 2D NMR, other methods were considered to provide confidence in our assignment. Pleasingly, an X-ray crystal structure of **B31** was obtained (Figure 14). The 3D structure shows the *endo* adduct has been formed with both the dienophile and BPin species in a *syn* relationship.

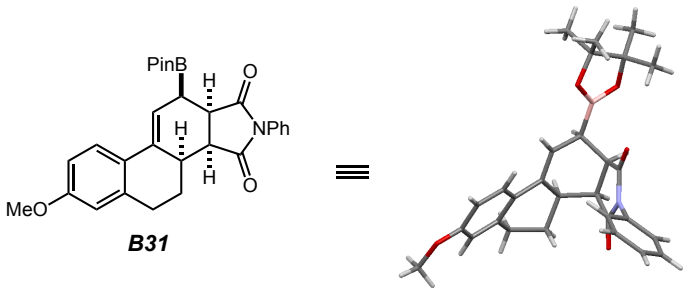
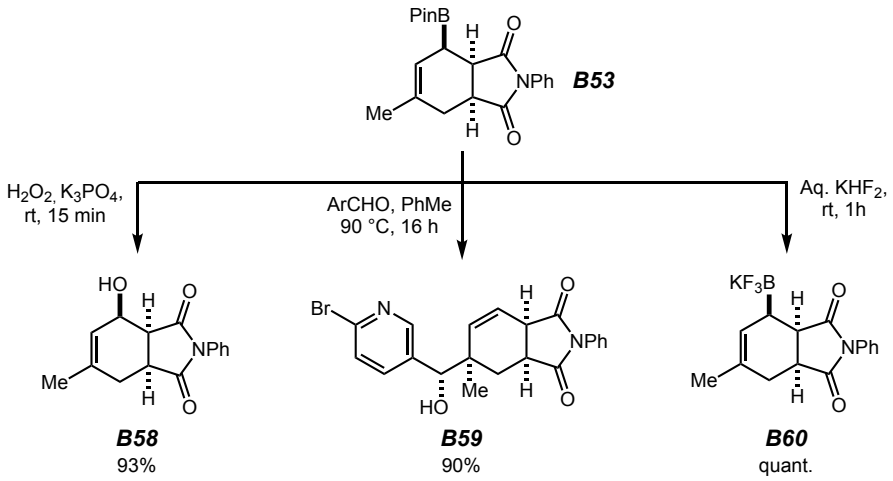


Figure 14: X-ray crystal structure of MH/DA product B31

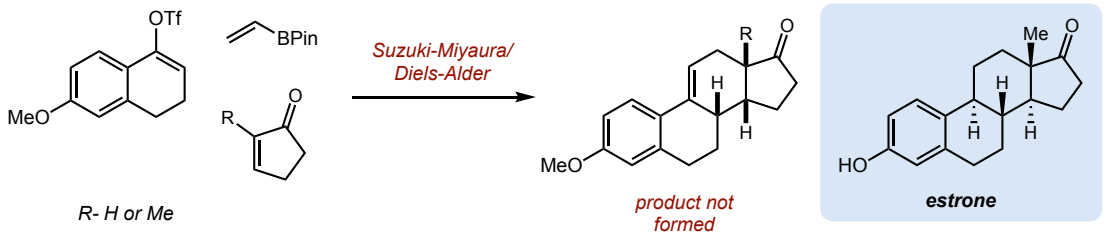
The developed cascade MH/DA methodology allows expedient access to allyl BPin motifs, incorporated in complex carbon scaffolds. There are a plethora of synthetic manipulations which can be employed on organoboron species. As such, this allyl BPin core serves as an excellent functional handle for further synthetic manipulation. In a bid to explore these transformations and demonstrate how the allyl BPin species can serve as a functional handle for SAR and diversity oriented synthesis (DOS) studies of core structures, compound **B53** was assessed in subsequent transformations (Scheme 100). The allyl BPin species **B53** could undergo a facile oxidation process to form the corresponding allylic alcohol **B58**. Perhaps the most pertinent application of allyl BPins is in nucleophilic allylation reactions with aldehydes.[161] This transformation was feasible to form the Vaultier-Hoffmann-type product **B59** in high yields. The application of sp^3 BF_3K species has increased in recent years with the advent of photoredox cross-coupling reactions.[162] Through a simple functional group interconversion, the BPin could be converted to the BF_3K **B60** in excellent yield. Unfortunately, established methodology in which allylic BPins can be cross-coupled at the boron bearing terminus, as well as the allylic position, was unsuccessful in our hands.[163]



Scheme 100: Derivitisation of allyl BPin product B53

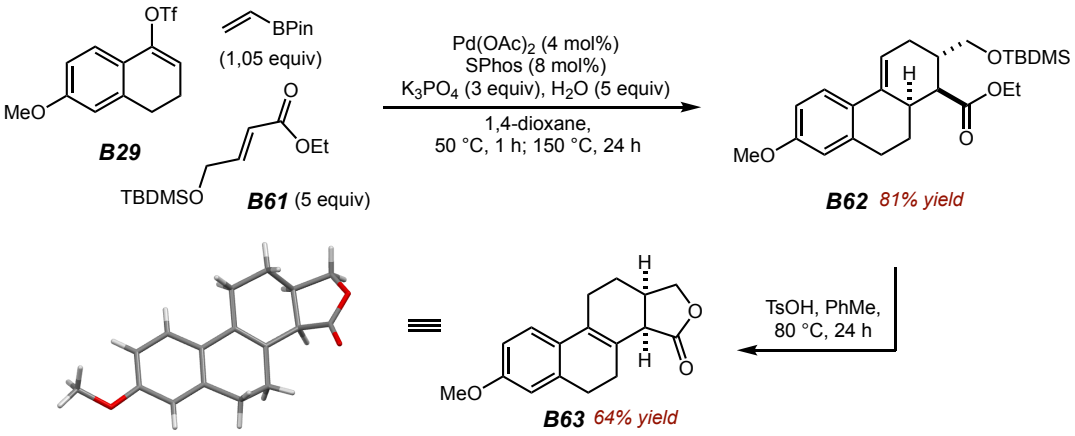
An unfortunate drawback experienced during development of the methodology was the poor reactivity of cyclopentenone-type dienophiles (Scheme 101). An obvious application of the methodology would be in the rapid synthesis of known steroids, such as estrone, a previously prescribed hormone for women.[164] This would allow rapid access to (non) borylated analogues. In order to form this scaffold via our

methodology, a regioselective DA of cyclopentenone or 2-methylcyclopenteneone would be required. Unfortunately, despite synthetic efforts, no cyclisation of these dienophiles was observed, even at temperatures greater than 150 °C. It was deemed that Lewis acid catalysis would be required to facilitate this DA reaction.



Scheme 101: Unsuccessful application of cyclopentenone derivatives in a cascade SM/DA

Despite this, an interesting result was observed when attempting a stepwise SM/DA and subsequent cyclisation procedure to form steroidal scaffolds (Scheme 102). The use of dienophile **B61** with vinyl triflate **B29** and vinyl BPin formed an intermediate **B62** which could not be properly characterised by spectroscopic means. However, on exposure to acid, cyclised product **B63** was formed in moderate yield. This suggests previously observed regioselectivity which is typically governed by electronics is not operational and regioselectivity is controlled by sterics to form intermediate **B62**. On exposure to acid intermediate **B62** can be deprotected with concomitant epimerisation of the acidic centre to allow both substituents necessary for lactonisation to have a *syn* relationship. Subsequent lactonisation delivers product **B63**. Notably during this process, the olefin migrates to form a more stable styrenyl product under the acidic conditions. An X-ray crystal structure was obtained to confirm the 3D structure.



Scheme 102: Flipping conventional regioselectivity to synthesis steroidal scaffolds

3.3 Conclusion

In summary, a series of Pd^{II} complexes were successfully synthesised in order to assess transmetalation with the bifunctional probe, vinyl BPin. A proof of concept was suitably demonstrated as aryl palladium halide complexes of type $(Ar)Pd^{II}X$ were shown to transmetalate at the carbon terminus via a MH reaction, and oxopalladium species of type $(Ar)Pd^{II}OH$ via organoboron transmetalation as predicted. The stark difference in reactivity of these two transmetalation steps was shown by generating a half-life of each complex with vinyl BPin (**B6a**, $t_{1/2}$ = 50 min at 80 °C; **B6b**, < 2 min at rt).

As discrimination between the competing synthetic pathways required preferential formation of the contrasting Pd^{II} species in solution, a thorough investigation into the key anion metathesis event with Pd^{II} complexes with varied base and water content was carried out. Preferential formation of each species in the complex equilibrium was successfully established. It was found that oxopalladium formation was preferential with inorganic bases, specifically at low water content, and palladium halide complexes were preferred in the absence of water and with organic bases.

The knowledge gained from initial studies on stoichiometric palladium complexes was successfully transcribed to a catalytic scenario. Optimal SM and MH conditions were developed as a direct result of the anion metathesis study enabling divergence as a function of this critical event. The developed conditions were then applied to generate a substrate scope for each opposing reaction, generating a wide range of styrene and styrenyl BPins with a range of functionalities incorporated, including electron withdrawing groups, electron donating groups, and hetereocycles.

Discriminating between competing synthetic pathways as a function of anion metathesis was further enhanced through the application in a cascade triene synthesis. Sequential Pd^{II} speciation controlled cross-coupling/DA allowed the rapid synthesis of complex borylated and non-borylated carbocyclic scaffolds which would be otherwise, difficult to access. A notable output was the expedient access to steroidal structures demonstrating the power of the developed methodology. The

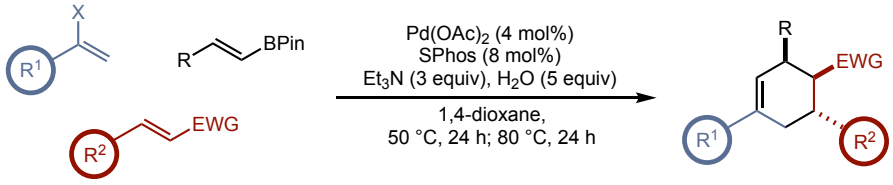
synthetic utility of the allyl BPin functional handle was suitably demonstrated through the synthesis of several analogues.

Overall, vinyl BPin has been employed as a bifunctional chemical probe to suitably demonstrate the key mechanistic event in the SM reaction, anion metathesis, can be controlled to enable discrimination between competing synthetic pathways

3.4 Future Work

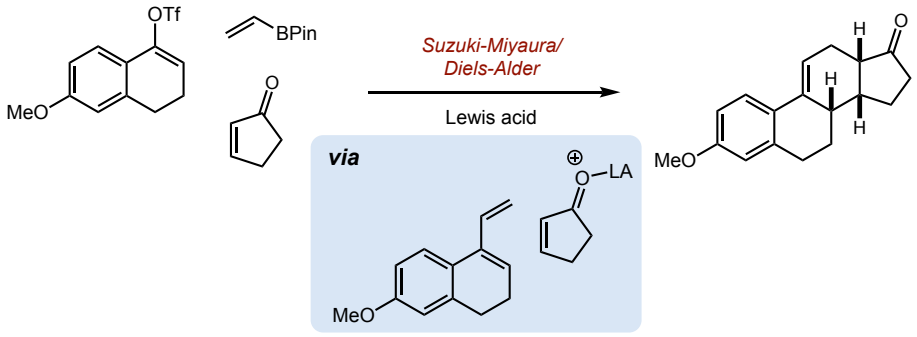
Although half-life experiments robustly demonstrate the difference in relative rates of the two competing transmetalation events (MH and SM), they do not provide an exact rate. In addition to this, the rate of transmetalation is influenced by the bound ligand (application of SPhos in a catalytic scenario showed improved reactivity for MH). As a result, exact kinetic data for the transmetalation of vinyl BPin with a series of ligand bound palladium halide complexes, and oxopalladium complexes would be useful to the synthetic community. Admittedly, this may be difficult as organoboron transmetalation is rapid and therefore specialist techniques may be required.

It was noted that use of substituted BPins in the cascade SM/DA process led to a mixture of diastereomers (Scheme 98). This was tentatively attributed to the aqueous basic media generating hydroxide and promoting epimerisation of the acidic centre. However, during analysis of transmetalation in a catalytic scenario, weaker bases were shown to facilitate a SM reaction (Table 11, Entry 10). The use of triethylamine in the presence of water enabled conversion to the SM product albeit over a longer reaction period. Use of this weaker base in the cascade manifold may inhibit epimerisation and, as a result, enhance diastereoselectivity of the process (Scheme 103).



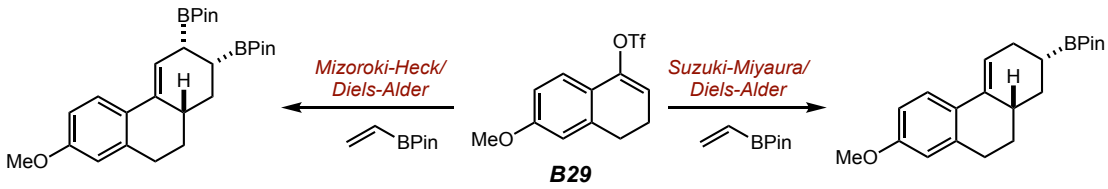
Scheme 103: Use of a weaker base to mitigate epimerisation in cascade SM/DA

Similarly, use of poorly reactive dienophiles has been an issue in the cascade triene annulation (Scheme 101). Application of a suitable, reaction compatible, Lewis acid may enable the synthesis of known steroids by improving reactivity and regioselectivity (Scheme 104).



Scheme 104: Use of Lewis acids to enhance DA reactivity and regioselectivity

Progressing the cascade triene annulation to the formation of new products through exhaustive use of vinyl BPin in a cascade SM/DA or MH/DA protocol would enable the formation of complex scaffolds containing one or two boron units for further synthetic manipulation (Scheme 105). This would enable expedient access to scaffolds containing useful synthetic handles.



Scheme 105: Exhaustive use of vinyl BPin in cascade MH/DA and SM/DA reactions to form complex borylated carbocycles

3.5 Experimental

3.5.1 General

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[148]

Purification of Solvents

Dry THF, CH_2Cl_2, and PhMe 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. 1,4-Dioxane was distilled over $LiAlH_4$ and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves, and purged with and stored under nitrogen. CH_2Cl_2, Et_2O, CPME, EtOAc, MeCN, 1,4-dioxane, EtOH, $CHCl_3$, and petroleum ether 40-60° for purification purposes were used as obtained from suppliers without further purification. Solvents were degassed by sonication under a weak vacuum before refilling with nitrogen (this sequence was carried out three times).[165]

Drying of Inorganic Bases

K_3PO_4, K_2CO_3, and Cs_2CO_3 were dried in a Heraeus Vacutherm oven at 60 °C under vacuum for a minimum of 24 hours before use.

Experimental Details

Reactions were carried out using conventional glassware (preparation of intermediates) or in capped 5/20 mL microwave vials (all substrates and reaction optimization). Microwave vials were purchased from Biotage (2–5 mL Biotage Microwave Reaction Kit, catalogue number 351521; 10-20 mL Biotage Microwave Reaction Kit, catalogue number 354833). Magnetic stirrer bars were used as supplied in the Biotage Microwave Reaction Kit. The glassware was oven-dried (150 °C) and purged with nitrogen before use. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature was generally *ca.* 20 °C. Reactions were carried out at

elevated temperatures in a sand bath using a temperature-regulated hotplate/stirrer. Temperatures quoted are of the sand bath.

Purification of Products

Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light or developed using potassium permanganate or vanilin solutions. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 μm silica gel. Isolated regioisomers/diastereomers were obtained via either column chromatography, Chiral preparative-HPLC, or a reduction/separation/oxidation protocol. Reported data is that of the major regioisomer/diastereomer.

Analysis of Products

Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{19}F NMR spectra were obtained on a Bruker AV 400 spectrometer (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 101 MHz, respectively, or Bruker Ascend AV(III) HD 500 at 500 MHz and 126 MHz, respectively. Chemical shifts are reported in ppm and coupling constants are reported in Hz: $CDCl_3$ is referenced at 7.26 (^{1}H) and 77.2 (^{13}C), DMSO-d_6 at 2.50 (^{1}H) and 39.5 (^{13}C), and THF-d_8 at 1.73, 3.58 (^{1}H) and 25.4, 67.6 (^{13}C). High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University or at the Mass Spectrometry Facility at the University of Glasgow. Reversed phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column, which was maintained at a constant temperature of 40 °C. Analysis was performed using a gradient method, eluting with 5-80% MeCN/H_2O over 16 min 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/product. Reaction HPLC samples used a 1:4 ratio caffeine/product unless stated otherwise. NMR conversion was obtained through addition of a known standard (1,4-dinitrobenzene) to the crude reaction mixture. Solvent was removed under reduced pressure and conversion against the internal standard was determined by ^{1}H NMR.

3.5.2 General Procedures

General Procedure A: Measurement of cross-coupling chemoselectivity/half-life experiments (Scheme 90, and Chart 3 and 4)

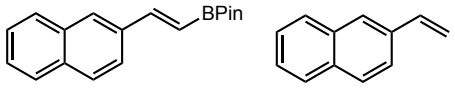
In an argon filled glovebox, a 2 mL screw cap vial was charged with Pd complex (0.015 mmol, 1 equiv) and a Teflon coated stirrer bar. The Pd complex was diluted with dry, degassed THF before being sealed with a Teflon cap. The vial was removed from the glovebox before the addition of vinyl BPin (12 mg, 0.075 mmol, 5 equiv). The reaction was stirred at a set temperature until completion. The reaction was vented and decapped. The resulting solution was filtered through cotton wool into an NMR tube, and topped up with 100 µL of THF-d_8. The ratio of products was determined by ^{19}F NMR against established chemical shifts.

General Procedure B: Measurement of anion metathesis of Pd^{II} complexes (Table 9, and Chart 5 and 6)

In an argon filled glovebox, a 2 mL screw cap vial was charged with Pd complex (0.015 mmol, 1 equiv), base (0.6 mmol, 40 equiv) and a Teflon coated stirrer bar. The Pd complex was diluted with dry, degassed THF before being sealed with a Teflon cap. The vial was removed from the glovebox before the addition of degassed H_2O. The reaction was stirred at a set temperature until completion. The reaction was vented and decapped. The resulting solution was transferred to an NMR tube and topped up with 100 µL of THF-d_8. The ratio of products was determined by ^{31}P NMR against established chemical shifts.

General Procedure C: Effect of base on product distribution with vinylBPin and 2- bromonaphthalene (Table 11 and 12)

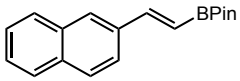
For example, formation of compounds **B9a** and **B9b**



To an oven-dried microwave vial was added 2-bromonaphthalene (51.8 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), Pd(OAc)2 (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The vial was capped and purged with nitrogen before addition of THF/H_2O (1 mL, 0.25 M, 9:1 or 1:0). The reaction mixture was heated at 80 °C for 24 h. The vial was then decapped, diluted with EtOAc (5 mL) and passed through a layer of Celite. A known standard (1,4-dinitrobenzene) was added to the crude residue as a solution, solvent was removed under reduced pressure and conversion to product was measured by ^{1}H NMR analysis against the internal standard (caffeine).

General Procedure D: Mizoroki-Heck cross-coupling of vinyl BPin (Scheme 94)

For example, synthesis of compound **B9a**

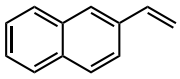


To an oven-dried microwave vial was added 2-bromonaphthalene (51.8 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), and SPhos (8.2 mg, 0.02 mmol, 8 mol%). The vial was capped and purged with nitrogen before the addition of 1,4-dioxane (1 mL, 0.25 M) and distilled Et_3N (140 µL, 1 mmol, 4 equiv). The reaction mixture was heated at 80 °C for 24 h. The vial was then decapped, diluted with EtOAc (10 mL), passed through a layer of Celite and concentrated under vacuum. A solution of 1,4-dinitrobenzene in MeCN (1 mL, 62.5 mM) was added, the resulting solution was concentrated under vacuum and the conversion measured via ^{1}H NMR relative to the

intensity of the 1,4-dinitrobenzene peak. For characterization, the solution was concentrated under vacuum and resultant solid was diluted with a minimum volume of DCM and purified by column chromatography (silica gel, 100% petroleum ether 40-60°). The appropriate fractions were combined and concentrated under vacuum to provide the desired product as a yellow oil.

General Procedure E: Suzuki-Miyaura cross-coupling of vinyl BPin (Scheme 94)

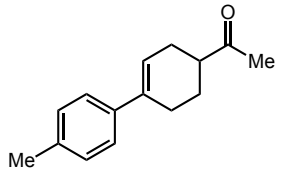
For example, synthesis of compound **B9b**



To an oven-dried microwave vial was added 2-bromonaphthalene (51.8 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The vial was capped and purged with nitrogen before the addition of 1,4-dioxane (1 mL, 0.25 M) and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was heated at 80 °C for 1 h. The vial was then decapped, diluted with EtOAc and passed through a layer of Celite. The resultant solution was concentrated under vacuum and diluted with EtOAc (10 mL). The organics were washed with H_2O (3 x 10 mL) followed by brine (10 mL) and the organic phases collected. The organic phase was dried over Na_2SO_4, filtered, and concentrated under vacuum. A solution of 1,4-dinitrobenzene in MeCN (1 mL, 62.5 mM) was added, the resulting solution was concentrated under vacuum and the conversion measured *via* ^1H NMR relative to the intensity of the 1,4-dinitrobenzene peak. For characterization, the solution was concentrated under vacuum and resultant solid was diluted with a minimum volume of DCM and purified by column chromatography (silica gel, 100% petroleum ether 40-60°). The appropriate fractions were combined and concentrated under vacuum to give the desired product as an off-white solid.

General Procedure F: Suzuki-Miyaura/Diels-Alder annulation (Table 14 and 15, and Scheme 98)

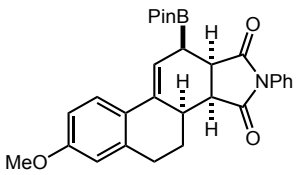
For example, synthesis of compound **B28a**



To an oven-dried microwave vial was added $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-methylbenzene (49.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), and K_3PO_4 (159 mg, 0.75 mmol, 3 equiv). The vial was capped and purged with nitrogen before addition of 1,4-dioxane (1 mL, 0.25 M), methyl vinyl ketone (67.8 µL, 0.75 mmol, 3 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was heated at 50 °C with stirring. After 1 h the temperature was increased to 80 °C and the reaction was stirred for 24 h. After the reaction was complete the vial was allowed to cool to room temperature, vented, and decapped. The reaction mixture was diluted with EtOAc (5 mL) and passed through a layer of Celite eluting the product with EtOAc (2 x 10 mL). The filtrate was washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude residue was purified by column chromatography (silica gel, 0-10% Et_2O in petroleum ether 40-60°) to afford the desired product as a clear oil (46.8 mg, 65%) 7:1 regioselectivity. Main regioisomer was separated for characterization by General Procedure I.

General Procedure G: Mizoroki-Heck/Diels-Alder annulation, procedure 1 (Scheme 96 and 99)

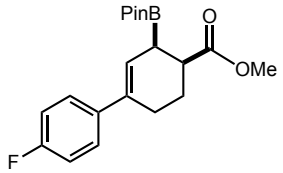
For example, synthesis of compound **B31**



To an oven-dried microwave vial was added $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (77.2 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), and anhydrous AgOAc (83 mg, 0.5 mmol, 2 equiv). The vial was capped and purged with nitrogen before addition of 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (105 µL, 0.75 mmol, 3 equiv). The reaction mixture was heated at 40 °C with stirring for 24 h. The vial was allowed to cool to room temperature, vented, and decapped. *N*-phenyl maleimide (130 mg, 0.75 mmol, 3 equiv) was added and the reaction was stirred at room temperature for 16 h. Once the reaction was complete the reaction mixture was diluted with EtOAc (5 mL) and passed through a layer of Celite, eluting the product with EtOAc (2 x 10 mL). The filtrate was washed with H_2O (50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude residue was purified by column chromatography (silica gel, 0-20% EtOAc in petroleum ether 40-60°) to afford the desired product as a yellow solid (84.4 mg, NMR yield not recorded, 69% product yield).

General Procedure H: Heck Diels-Alder annulation, procedure 2 (Scheme 99)

For example, synthesis of compound **B51**

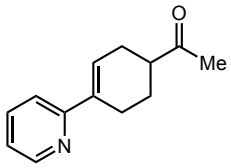


To an oven-dried microwave vial was added $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-fluorobenzene (50.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), and AgOAc (83 mg, 0.5 mmol, 2 equiv). The vial was capped and purged with nitrogen before addition of 1,4-dioxane (1 mL, 0.25 M) and distilled Et_3N (105 µL, 0.75 mmol, 3 equiv). The reaction mixture was heated at 40 °C with stirring for 24 h. The vial was allowed to cool to room temperature, vented and decapped. The reaction mixture was diluted with EtOAc (5 mL) and passed through a layer of celite eluting the product with EtOAc (2 x 10 mL). The filtrate was washed with H_2O (50

mL), brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. The crude residue was transferred in 1,4-dioxane (2 mL, 0.125 M) to an oven-dried microwave vial. The vial was capped and purged with nitrogen before addition of methyl acrylate (113 µL, 1.25 mmol, 5 equiv). The reaction mixture was heated to 80 °C with stirring for 16 h. Solvent was removed under vacuum and crude residue was purified by column chromatography (silica gel, 0-15% EtOAc in petroleum ether 40-60°) to afford the desired product as a yellow solid (35.4 mg, 68% NMR yield, 39% isolated yield).

General Procedure I – reduction/separation/oxidation sequence for the separation of diastereomers/regioisomers (Scheme 98)

For example, isolation of major regioisomer of compound **B34**



Sodium borohydride (70.5 mg, 1.86 mmol, 1.5 equiv) was added in small portions to a mixture of the regioisomeric mixture of **B34** (250 mg, 1.24 mmol, 1 equiv) in MeOH (4.1 mL, 0.3 M) at 0 °C. The reaction was stirred at room temperature for 2 h. Water (20 mL) and EtOAc (20 mL) were added sequentially and organics were separated, washed with brine, and dried over Na_2SO_4. The crude mixture was purified by column chromatography (silica gel, 0-15% EtOAc in petroleum ether 40-60°). Single fractions were collected, and solvent was removed under vacuum to afford a single regioisomer as the corresponding alcohol. The major regioisomer (90 mg, 0.44 mmol, 1 equiv) was dissolved in dry DCM (15 mL, 0.03 M) and was degassed by bubbling nitrogen. DMP (282 mg, 0.66 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with 1:1 mixture of saturated aq. sodium thiosulphate and saturated aq. sodium bicarbonate until a transparent solution was formed. The compound was extracted in Et_2O (2 x 25 mL), dried over $NaSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography to afford a single regioisomer of the desired compound permitting full characterization.

3.5.3 Mechanistic Investigation

Preparation and reactivity of $L_nPd(II)(Ar)(X)$ complexes: General

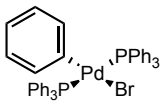
Handling and purification of Pd(II) complexes was performed under air, with no specialist techniques required. The complexes were stored in an argon filled glovebox but were found to be bench/air stable in the solid state for weeks. All solvents used were distilled according to standard laboratory procedures and freshly degassed before use.[148]

KOH was powdered, dried in a vacuum oven for 16 h and transferred to an argon filled glovebox before use. K_3PO_4 and K_2CO_3 were dried in a vacuum oven for 16 h and transferred to an argon filled glovebox before use. KOAc was dried through heating under reduced pressure until melting. Clean, dry, KOAc crystals were obtained upon cooling which were immediately transferred to an argon filled glovebox.

Preparation of $(PPh_3)_2Pd(II)(Ar)(Br)$

$(PPh_3)_2Pd(II)(Ar)(Br)$ complexes were prepared according to literature procedures.[166,167]

$(PPh_3)_2Pd(II)(Ph)(Br)$, **B5a**



In an argon filled glovebox, a 20 mL microwave vial was charged with $Pd(PPh_3)_4$ (880 mg, 0.78 mmol, 1 equiv) and a Teflon coated stirrer bar, before being capped. The vial was removed from the glovebox and dry, freshly degassed, PhMe (6 mL) was added, followed by bromobenzene (0.5 mL, 4.68 mmol, 6 equiv). The resulting solution was stirred at 80 °C for 16 h before being cooled to room temperature. The vial was vented, decapped, and the white solid was left to settle out of solution. The yellow mother liquor was carefully pipetted off, leaving a white powder. The white powder was transferred into a 250 mL round bottomed flask with PhMe (3 x 15 mL). The suspension was concentrated under reduced pressure to provide an off white

solid. The solid was triturated with Et_2O (3 x 20 mL) to remove any yellow colouring until the washings ran clear. The white powder was dried under high vacuum to remove any trace solvent impurities and provide the desired compound (500 mg, 81%).

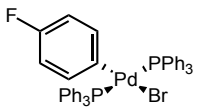
^{1}H NMR (THF-d_8, 500 MHz): δ 7.60 – 7.52 (m, 12H), 7.34 (t, J = 7.4 Hz, 6H), 7.29 – 7.21 (m, 12H), 6.71 – 6.65 (m, 2H), 6.35 (t, J = 7.2 Hz, 1H), 6.22 (t, J = 7.4 Hz, 2H).

^{13}C NMR (THF-d_8, 101 MHz): δ 135.9, 134.3 (t, J = 6.3 Hz), 131.7, 131.5, 131.3, 128.9, 127.0 (t, J = 4.9 Hz), 126.9, 120.9.

^{31}P NMR (THF-d_8, 162 MHz): δ 23.77.

Spectroscopic data in agreement with literature values.[166,167]

$(PPh_3)_2$Pd(II)(4-FPh)(Br), **B6a**



In an argon filled glovebox, a 20 mL microwave vial was charged with $Pd(PPh_3)_4$ (880 mg, 0.78 mmol, 1 equiv) and a Teflon coated stirrer bar, before being capped. The vial was removed from the glovebox and dry, freshly degassed, PhMe (6 mL) was added, followed by 4-fluorobromobenzene (0.5 mL, 4.5 mmol, 5.8 equiv). The resulting solution was stirred at 80 °C for 16 h before being cooled to room temperature. The vial was vented, decapped, and the white solid was left to settle out of solution. The yellow mother liquor was carefully pipetted off, leaving a white powder. The white powder was transferred into a 250 mL round bottomed flask with PhMe (3 x 15 mL). The suspension was concentrated under reduced pressure to provide an off white solid. The solid was triturated with Et_2O (3 x 20 mL) to remove any yellow colouring until the washings ran clear. The white powder was dried under high vacuum to remove any trace solvent impurities and provide the desired compound (530 mg, 85%).

^{1}H NMR (THF-d_8, 400 MHz) δ 7.63 – 7.53 (m, 12H), 7.36 (t, J = 7.4 Hz, 6H), 7.32 – 7.24 (m, 12H), 6.60 (ddd, J = 8.4, 4.9, 1.6 Hz, 2H), 6.04 (t, J = 9.1 Hz, 2H).

^{13}C NMR (THF-d_8, 101 MHz): δ 159.7 (d, J = 239.7 Hz), 149.4 (d, J = 3.0 Hz), 135.8 (d, J = 5.1 Hz), 134.3 (t, J = 6.4 Hz), 131.3 (t, J = 22.8 Hz), 129.1 (s), 127.1 (t, J = 4.8 Hz), 113.5 (d, J = 19.0 Hz).

^{31}P NMR (THF-d_8, 162 MHz): δ 23.72.

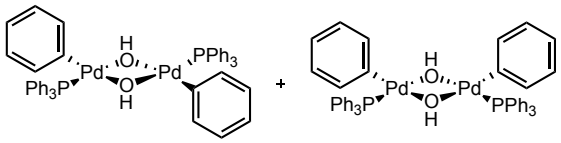
^{19}F NMR (THF-d_8, 471 MHz): δ –125.64.

Spectroscopic data in agreement with literature values.[168]

Preparation of $(PPh_3)_2Pd(II)(Ar)(OH)$

$(PPh_3)_2Pd(II)(Ar)(OH)$ complexes were prepared according to literature procedure.[169]

$[(PPh_3)_2Pd(II)(Ph)(\mu\text{-}OH)]_2$, **B5b**



A 20 mL microwave vial was charged with $Pd(PPh_3)_2Cl_2$ (490 mg, 0.7 mmol, 1 equiv), KOH (2 g, 35 mmol, 50 equiv) and a Teflon coated stirrer bar, before being capped. Freshly degassed, PhMe (10 mL) was added, followed by bromobenzene (0.37 mL, 3.5 mmol, 5 equiv) and H_2O (2 mL). The resulting solution was stirred at 80 °C for 3 h before being cooled to room temperature. The vial was vented, decapped, and the organic layer was separated and the aqueous layer washed with PhMe (2 x 15 mL). The combined organics were filtered through a cotton wool plug to provide a light yellow solution that was concentrated under reduced pressure. The resulting light yellow solid was triturated with acetone (3 x 20 mL) to remove any yellow colouring until the washings ran clear. The resulting white powder was dried under high vacuum to remove any trace solvent impurities and provide the desired compound (300 mg, 59%).

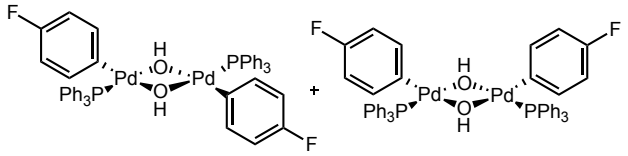
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 – 7.52 (m, 12H), 7.34 (t, *J* = 7.4 Hz, 6H), 7.29 – 7.21 (m, 12H), 6.71 – 6.65 (m, 2H), 6.35 (t, *J* = 7.2 Hz, 1H), 6.22 (t, *J* = 7.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 131.1, 129.2 – 128.6 (m), 126.9 (d, *J* = 10.3 Hz), 126.7 (d, *J* = 2.5 Hz), 125.1 (d, *J* = 13.3 Hz), 123.2 (dd, *J* = 19.5, 11.6 Hz), 121.7 – 121.1 (m), 108.1.

^{31}P NMR ($CDCl_3$, 162 MHz): 33.53, 32.83 (*cis*/*trans* isomers).

Spectroscopic data in agreement with literature values.[92]

$[(PPh_3)_2Pd(II)(4\text{-F-Ph})(\mu\text{-OH})]_2$, **B6b**



A 20 mL microwave vial was charged with $Pd(PPh_3)_2Cl_2$ (490 mg, 0.7 mmol, 1 equiv), KOH (2 g, 35 mmol, 50 equiv) and a Teflon coated stirrer bar, before being capped. Dry, freshly degassed, PhMe (10 mL) was added, followed by 4-fluorobromobenzene (0.38 mL, 3.5 mmol, 5 equiv) and H_2O (2 mL). The resulting solution was stirred at 80 °C for 3 h before being cooled to room temperature. The vial was vented, decapped, and the solution was separated and the aqueous layer washed with PhMe (2 x 15 mL). The organics were filtered through a cotton wool plug to provide a light yellow solution that was concentrated under reduced pressure. The resulting light yellow solid was triturated with acetone (3 x 20 mL) to remove any yellow colouring until the washings ran clear. The resulting white powder was dried under high vacuum to remove any trace solvent impurities and provide the desired compound (260 mg, 49%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 – 7.65 (m, 1H), 7.61 – 7.45 (m, 6H), 7.45 – 7.31 (m, 3H), 7.30 – 7.20 (m, 5H), 7.12 – 6.91 (m, 2H), 6.72 – 6.37 (m, 2H).

^{13}C NMR (DMSO-d_6, 101 MHz): δ 135.5, 133.9 (d, J = 11.4 Hz), 131.5 (d, J = 9.5 Hz), 130.5, 130.01 (d, J = 49.2 Hz), 128.8 (d, J = 11.8 Hz), 128.3 (d, J = 10.6 Hz), 126.9.

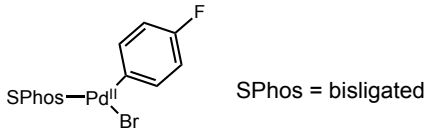
^{31}P NMR ($CDCl_3$, 162 MHz): δ 33.41, 32.63(*cis*/*trans* isomers).

^{19}F NMR (THF-d_8, 471 MHz): –123.02 – –123.63 (m) (*cis*/*trans* isomers).

Spectroscopic data in agreement with literature values.[92]

Preparation of (SPhos)Pd(II)(4-F-Ph)(Br) and (SPhos)Pd(II)(4-F-Ph)(OH)

(SPhos)Pd(II)(4-F-Ph)(Br), **B7a**



[Pd($CH_2TMS)_2$(COD)] was prepared according to a literature procedure.[170]

Prepared using a modification of a literature procedure.[171] In an argon-filled glovebox, a Schlenk flask was charged with [Pd($CH_2TMS)_2$(COD)] (406.0 mg, 1.044 mmol), SPhos (343.0 mg, 0.835 mmol), 4-bromo-1-fluorobenzene (0.8 mL, 502.2 mg, 2.87 mmol), and anhydrous THF (25 mL). The orange solution was allowed to stand for 48 hours, then the flask was removed from the glovebox, attached to the Schlenk line, and the solution was layered with anhydrous hexane (75 mL). The crystals that formed were recovered by cannula filtration, and washed with anhydrous hexane (3 x 10 mL). Upon drying under high vacuum, a green powder was formed (300 mg, 52%).

υ_{max} (solid): 3089, 3052, 3007, 2929, 2847, 2832, 1584, 1473, 1452, 1428, 1248, 1207, 1106 cm^{-1}.

^{1}H NMR (THF-d_8, 400 MHz): δ 7.35 (t, J = 7.5 Hz, 1H), 7.24 (t, J = 8.4 Hz, 1H), 7.16 – 7.10 (m, 1H), 7.07 (t, J = 7.7 Hz, 1H), 6.92 – 6.72 (m, 3H), 6.66 (br. d, J = 8.0 Hz, 2H), 6.39 (br. t, J = 8.0 Hz, 2H), 3.82 (br. s, 6H), 3.00 (br. s, 2H), 2.06 – 1.93 (m,

2H), 1.88 – 1.68 (m, 6H), 1.68 – 1.54 (m, 4H), 1.51 – 1.36 (m, 2H), 1.34 – 1.17 (m, 2H), 1.14 – 0.92 (m, 4H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.2 (d, $^{1}J_{CF}$ = 241 Hz), 158.6, 140.5 (d, J = 8.5 Hz), 137.2, 134.9 (d, J = 8.9 Hz), 133.5 (d, J = 3.3 Hz), 129.9, 129.4, 129.3, 129.0, 126.3 (d, J = 7.8 Hz), 119.2, 113.0 (d, J = 18.7 Hz), 104.7, 56.1, 39.2, 33.2, 31.2 (d, J = 6.9 Hz), 29.0 (d, J = 15.2 Hz), 28.7 (d, J = 8.6 Hz), 27.3.

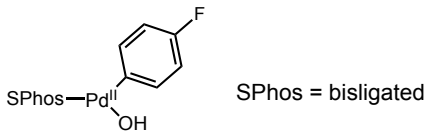
^{31}P NMR ($CDCl_3$, 162 MHz): δ 38.8 (br), 37.8 (br), 32.0

^{19}F NMR (THF-d_8, 471 MHz): δ -124.8.

HRMS: exact mass calculated for $[M\text{-}Br]^+$ ($C_{32}H_{39}FO_2PPd$) requires *m/z* 611.1707, found *m/z* 611.1760.

Analogous complexes of this type have been reported,[172] and are known to exhibit broad signals on the ^{1}H NMR and ^{31}P NMR spectra, and complex ^{13}C{^{1}H} NMR spectra.

(SPhos)Pd(II)(4-F-Ph)(OH), **B7b**



Prepared using a literature procedure. In an argon-filled glovebox, a microwave tube was charged with (SPhos)Pd(II)(4-F-Ph)(Br) (54.5 mg, 79 μmol), equipped with a magnetic stir bar, and closed with a crimp cap fitted with a septum. On the Schlenk line, the complex was dissolved in anhydrous and degassed DCM (0.5 mL). Anhydrous and degassed methanol (2 mL) was added, followed by K_3PO_4 (1.22 g, 5.75 mmol, 73 equiv.) dissolved in degassed water (1.3 mL). The reaction was stirred at room temperature for 3 h, and then diluted with methanol (2.5 mL) and degassed water (1.3 mL). The resulting grey precipitate was isolated by filtration and washed with methanol (1.3 mL), then water (1.3 mL), and then methanol again (1.3 mL). After drying on the frit, the product was obtained as an off-white solid (35.9 mg, 72%).

The product is contaminated with approximately 20% of the starting material, and is unstable in dry degassed THF-d_8 at room temperature. As the material is an 80:20 mixture of (unstable) palladium hydroxide and palladium bromide complexes, there are many overlapping signals and $^{13}C\{^1H\}$ NMR analysis is precluded, but some diagnostic signals can be identified.

υ_{max} (solid): 3619, 3050, 2920, 2849, 1588, 1569, 1473, 1248, 1205, 1110 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.72 (t, J = 9.3 Hz), 6.97 (t, J = 6.9 Hz), 6.77 (d, J = 7.9 Hz), 3.91 (br. s), 3.70 (s), 2.49 (br. app. t, J = 8.8 Hz), –1.79 (s), –2.93 (d, J = 2.1 Hz), –4.41 (s).

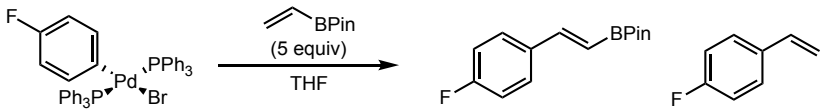
^{31}P NMR ($CDCl_3$, 162 MHz): δ 44.2.

^{19}F NMR (THF-d_8, 471 MHz): δ –125.2 – –125.4 (m).

HRMS: exact mass calculated for $[M\text{-}OH]^+$ ($C_{32}H_{39}FO_2PPd$) requires *m/z* 611.1707, found *m/z* 611.1766.

Transmetalation Study and Half-Life Experiments

$(PPh_3)_2Pd(II)(Ar)(Br)$, **B6a** (Scheme 90a)



B6a ***B8a*** ***B8b***

Performed according to the General Procedure A using $(PPh_3)_2Pd(II)(4\text{-}F\text{-}Ph)(Br)$ (12.1 mg, 0.015 mmol, 1 equiv), vinyl boronic acid, pinacol ester (12 mg, 0.075 mmol, 5 equiv), and THF (500 μL). The reactions were stirred at **temperature** for 24 h before analysis by ^{19}F NMR.

Entry	Temperature (°C)	Ratio (B8a:B8b)[a]
1	23	1:0
2	50	1.8:1
3	80	1:0

[a] Ratio determined by ^{19}F NMR

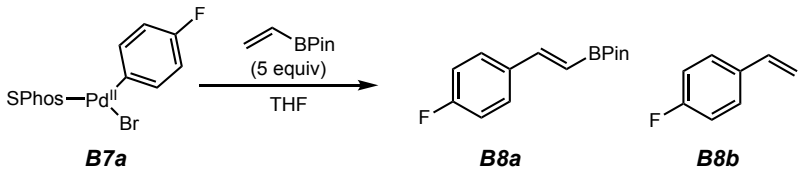
Determination of half life (Chart 3)

Performed according to the General Procedure A using $(PPh_3)_2Pd(II)(4\text{-}F\text{-}Ph)(Br)$ (12.1 mg, 0.015 mmol, 1 equiv), vinyl boronic acid, pinacol ester (12 mg, 0.075 mmol, 5 equiv), and THF (500 µL). The reactions were stirred at 80 °C for varying time intervals before being quenched by HCl in MeOH (100 µL, 2 M) and analyzed by ^{19}F NMR.

Entry	Time (min)	Conversion to B8a (%)
1	30	20
2	60	64
3	120	65
4	180	64

Half life = ~ 52 min

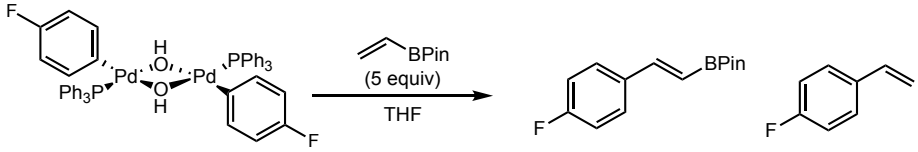
(SPhos)Pd(II)(4-F-Ph)(Br), **B7a** (Scheme 90a)



B7a ***B8a*** ***B8b***

Performed according to the General Procedure A using (SPhos)Pd(II)(4-F-Ph)(Br) (10 mg, 0.015 mmol, 1 equiv), vinyl boronic acid, pinacol ester (12 mg, 0.075 mmol, 5 equiv), and THF (500 µL). The reactions were stirred at 80 °C for 24 h before analysis by ^{19}F NMR. NMR analysis showed **B8a** to be the sole cross-coupled product of the reaction showing complete selectivity over **B8b**.

$(PPh_3)_2Pd(II)(Ar)(OH)$, **B6b** (Scheme 90b)



B6b ***B8a*** ***B8b***

Performed according to the General Procedure A using $[(PPh_3)_2Pd(4\text{-}F\text{-}Ph)(\mu\text{-}OH)]_2$ (11.1 mg, 0.015 mmol, 1 equiv), vinyl boronic acid, pinacol ester (12 mg, 0.075

mmol, 5 equiv), and THF (500 μL). The reactions were stirred at room temperature for 24 h before being analyzed by ^{19}F NMR. NMR analysis showed **B8b** to be the sole product of the reaction.

Note

When using $[(PPh_3)_2Pd(Ar)(\mu\text{-}OH)]_2$ under any conditions, **B8b** was the major product with no **B8a** observed under any circumstance. When the reaction was performed at increased temperature, the product of protodepalladation (fluorobenzene) was also observed.

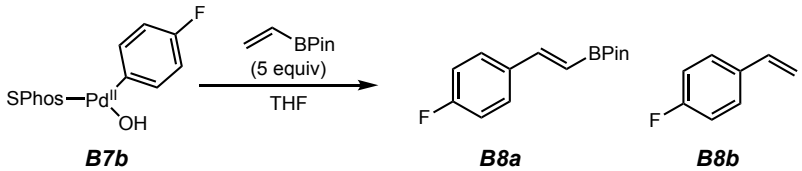
Determination of half life (Chart 4)

Performed according to the General Procedure A using $[(PPh_3)_2Pd(4\text{-}F\text{-}Ph)(\mu\text{-}OH)]_2$ (11.1 mg, 0.015 mmol, 1 equiv), vinyl boronic acid, pinacol ester (12 mg, 0.075 mmol, 5 equiv), and THF (500 μL). The reactions were stirred at room temperature for varying time intervals before being quenched by HCl in MeOH (100 μL, 2 M) and analyzed by ^{19}F NMR.

Entry	Time (min)	Conversion to B8b (%)
1	1	21
2	2.5	68
3	5	93
4	7.5	100
5	10	100

Half life = ~ 2 min

(SPhos)Pd(II)(4-F-Ph)(OH), **B7b** (Scheme 90b)



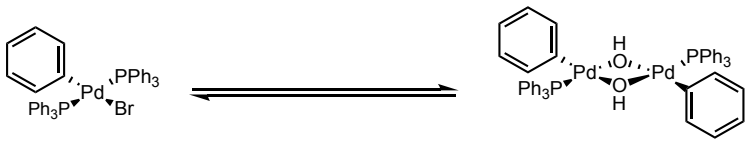
B7b ***B8a*** ***B8b***

Performed according to the General Procedure A using (SPhos)Pd(II)(4-F-Ph)(OH) (10 mg, 0.015 mmol, 1 equiv), vinyl boronic acid, pinacol ester (12 mg, 0.075 mmol, 5 equiv), and THF (500 μL). The reactions were stirred at 80 °C for 24 h before

analysis by ^{19}F NMR. NMR analysis showed **B8b** to be the sole product of the reaction.

Anion Metathesis Study

Base Study (Table 9)



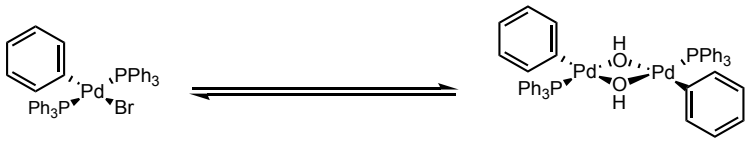
B5a ***B5b***

Performed according to the General Procedure B using $(PPh_3)_2Pd(II)(Ph)(Br)$ (11.8 mg, 0.015 mmol, 1 equiv), **base** (0.6 mmol, 40 equiv), THF (450 µL or 500 µL), and **H_2O** (50 µL or no water) the reactions were stirred at 80 °C for 24 h before analysis by ^{31}P NMR.

Entry	Base	Water	Pd(Br)%[a]	Pd(OH)%[a]
1	KOH (33.6 mg)	-	81	19
2	KOH (33.6 mg)	Y	8	92
3	K_3PO_4 (127.2 mg)	-	99	1
4	K_3PO_4 (127.2 mg)	Y	68	32
5	K_2CO_3 (83 mg)	-	93	7
6	K_2CO_3 (83 mg)	Y	77	23
7	Et_3N (84 µL)	-	99	1
8	Et_3N (84 µL)	Y	99	1
9	KOAc (58.8 mg)	-	96	4[b]
10	KOAc (58.8 mg)	Y	66	34[b]

[a] Determined by ^{31}P NMR as a ratio, [b] $(PPh_3)_2(Ph)Pd^{II}(OAc)$ oxopalladium species formed

Effect of water on equilibrium (Chart 5)



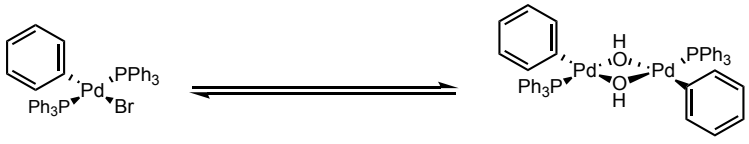
B5a ***B5b***

Performed according to the General Procedure B using $(PPh_3)_2Pd(II)(Ph)(Br)$ (11.8 mg, 0.015 mmol, 1 equiv), KOH (33.6 mg, 0.6 mmol, 40 equiv), **THF**, and **H_2O**. The reactions were stirred at room temperature for 6 h before analysis by ^{31}P NMR.

Entry	THF:H_2O (µL: µL)	B5a:B5b N=1[a]	B5a:B5b N=2[a]	B5a:B5b N=3[a]	Mean	Std Dev
1	2 (333 µL: 166 µL)	56:44	59:41	57:43	57:43	1.53
2	4 (400 µL: 100 µL)	47:53	47:53	47:53	47:53	0.33
3	6 (430 µL: 70 µL)	44:56	38:62	39:61	40:60	3.18
4	9 (450 µL: 50 µL)	23:77	26:74	25:75	25:75	1.28
5	12 (460 µL: 40 µL)	13:87	17:83	11:89	13:87	3.18
6	16 (470 µL: 30 µL)	9:91	9:91	7:93	8:92	1.13
7	19 (475 µL: 25 µL)	5:95	5:95	5:95	5:95	0.06

[a] Ratio determined by ^{31}P NMR

Effect of temperature on equilibrium (Chart 6)



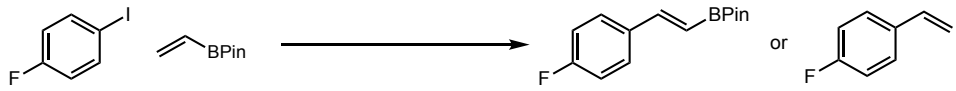
B5a ***B5b***

Performed according to the General Procedure B using $(PPh_3)_2Pd(II)(Ph)(Br)$ (11.8 mg, 0.015 mmol, 1 equiv), KOH (33.6 mg, 0.6 mmol, 40 equiv), THF (450 µL), and H_2O (50 µL). The reactions were stirred at temperature for 2 h before analysis by ^{31}P NMR.

Entry	Temp (K)	B5a:B5b N=1[a]	B5a:B5b N=2[a]	B5a:B5b N=3[a]	Mean	Std Dev
1	273	76:24	76:24	79:21	77:23	1.58
2	283	71:29	67:33	74:26	70:30	3.46
3	296	56:44	61:39	58:42	58:42	2.64
4	303	33:67	50:50	39:61	40:60	8.30
5	313	28:72	28:72	17:83	23:77	6.33
6	323	12:88	13:87	12:88	12:88	0.89
7	333	8:92	7:93	10:90	8:92	1.73
8	353	4:96	7:93	5:95	5:95	1.53

[a] Ratio determined by ^{31}P NMR

Effect of water on reaction output, $Pd(PPh_3)_4$ (Table 10)



B8a ***B8b***

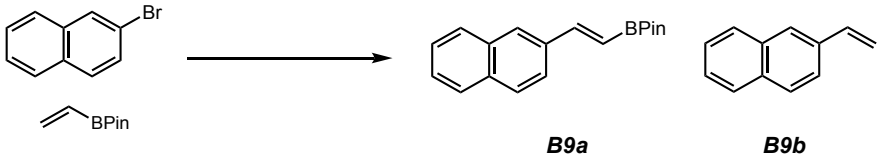
To an oven-dried microwave vial was added 4-fluoroiodobenzene (55.5 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol, 4 mol%), and **base** (0.75 mmol, 3 eq). The vial was capped and purged with nitrogen before addition of THF/H_2O (1 mL, 0.25 M, 9:1 or 1:0), and trifluorotoluene (30.7 µL, 0.25 mmol, 1 equiv). The reaction mixture was heated at 80 °C for 24 h. The vial was then decapped, diluted with $CDCl_3$ (0.5 mL) and passed through a layer of Celite. The ratio of products **B8a** and **B8b** were measured by ^{19}F NMR

Entry	Base	H_2O (µL)	B8a:B8b[a]
1	KOH (42.2 mg)	-	0:100
2	KOH (42.2 mg)	100 µL	0:100

3	K_3PO_4 (159 mg)	-	0:100
4	K_3PO_4 (159 mg)	100 µL	0:100
5	K_2CO_3 (103.7 mg)	-	11:89
6	K_2CO_3 (103.7 mg)	100 µL	14:86
7	KOAc (73.7 mg)	-	14:86
8	KOAc (73.7 mg)	100 µL	12:88
9	Et_3N (105 µL)	-	81:19
10	Et_3N (105 µL)	100 µL	11:89

[a] Ratio determined by ^{19}F NMR

Effect of water on reaction output, $Pd(OAc)_2$ and SPhos (Table 11)



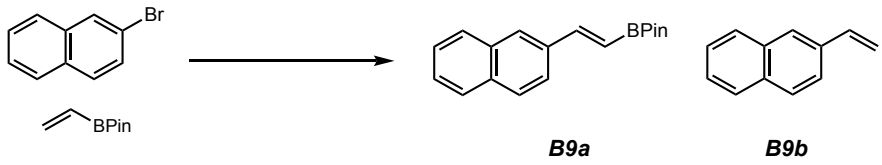
B9a ***B9b***

Performed according to the General Procedure C using 2-bromonaphthalene (51.8 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), **base** (0.75 mmol, 3 equiv), H_2O (100 µL or no water), and THF (900 µL or 1 mL, 0.25 M) the reactions were stirred at 80 °C for 24 h before analysis by ^1H NMR against a known internal standard (1,4 dinitrobenzene).

Entry	Base	H_2O (µL)	B9a:B9b[a]
1	KOH	-	0:100
2	KOH	100 µL	0:100
3	K_3PO_4	-	1:92
4	K_3PO_4	100 µL	0:100
5	K_2CO_3	-	21:2
6	K_2CO_3	100 µL	0:100
7	KOAc	-	81:19
8	KOAc	100 µL	12:55

9	Et_3N	-	98:2
10	Et_3N	100 µL	0:82

Effect of water on reaction output, Et_3N (Table 12)



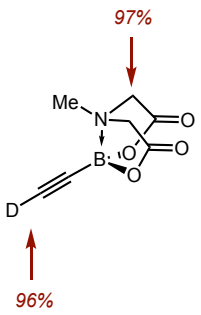
Performed according to the General Procedure C using 2-bromonaphthalene (51.8 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), and Et_3N (105 µL, 0.75 mmol, 3 equiv), THF/H_2O (**x:x** ratio, 1 mL, 0.25 M). The reactions were stirred at 80 °C for 24 h before analysis by ^1H NMR against a known internal standard (1,4 dinitrobenzene).

Entry	THF:H_2O	B9a:B9b[a]
1	1:0	98:2
2	40:1	18:72
3	20:1	14:72
4	9:1	2:78
5	4:1	0:100

Deuterium labelling investigation

Preparation of D-VinylBPin,

(Ethynyl-*d*) boronic acid, MIDA ester (**B10**)



To an oven-dried flask was added ethynyl boronic acid, MIDA ester (2.2 g, 12 mmol, 1 equiv) and K_2CO_3 (2.5 g, 18 mmol, 1.5 equiv). The flask was sealed and purged with nitrogen before the addition of distilled MeCN (120 mL, 0.1 M) and D_2O (20 mL, 80 equiv). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (200 mL) and the organic layer was separated, dried with Na_2SO_4, filtered, and solvent was concentrated under vacuum. The crude residue was purified by column chromatography (silica gel, 0-20% acetone in EtOAc) to afford the desired product as a white solid (832 mg, 38% yield) indicating 96% deuterium incorporation in the desired (acetylinic) position.

υ_{max} (solid): 2572, 1941, 1765, 1460, 1290 cm^{-1}.

^1H NMR of parent compound (CD_3CN, 400 MHz): δ 3.93 (dd, J = 50.3, 17.0 Hz, 4H), 3.03 (s, 3H), 2.68 (s, 1H).

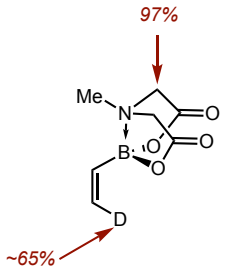
Deuterium labelling expected at δ 3.93 and 2.68 ppm, incorporation established against δ 3.03 ppm.

^{13}C NMR of parent compound (CD_3CN, 101 MHz): δ 168.7, 90.2, 62.4, 48.8.

^{11}B NMR of parent compound (CD_3CN, 128 MHz): δ 5.63.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_7H_3D_5BNO_4Na$) requires *m/z* 209.0752, found *m/z* 209.0751.

(Vinyl-*d*) boronic acid, MIDA ester (**B11**)



Prepared according to a similar literature procedure.[55] To an oven-dried flask was added (ethynyl-*d*) boronic acid, MIDA ester (465 g, 2.5 mmol, 1 equiv) and Lindlar catalyst (25 mg). The flask was sealed before the addition of distilled 1,4-dioxane

(12.5 mL, 0.2 M) and quinoline (148 µL, 0.5 equiv). The reaction mixture was purged with hydrogen and stirred at room temperature for 3.5 h. The reaction mixture was diluted with MeCN (5 mL) filtered through Celite, and concentrated under vacuum. The crude residue was purified by column chromatography (silica gel, 0-20% acetone in EtOAc) to afford the desired product as a white solid (383 mg, 81% yield) indicating 60-70% deuterium incorporation in the desired position.

υ_{max} (solid): 2959, 2270, 2246, 1737, 1592, 1454, 1307, 1173, 1015 cm^{-1}.

^{1}H NMR of parent compound (CD_3CN, 400 MHz): δ 5.93 (dd, *J* = 19.1, 13.6 Hz, 1H), 5.79 (s, 1H), 5.68 (dd, *J* = 19.2, 3.5 Hz, 1H), 3.87 (dd, *J* = 67.0, 16.9 Hz, 4H), 2.78 (s, 3H).

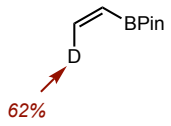
Deuterium labelling expected at δ 5.68 and 3.87 ppm, incorporation established against δ 2.78 ppm.

^{13}C NMR of parent compound (CD_3CN, 101 MHz): δ 167.9, 128.7, 116.8, 60.9, 46.2.

^{11}B NMR of parent compound (CD_3CN, 128 MHz): δ 10.29.

HRMS: exact mass calculated for $[M]^+$ ($C_7H_5D_5BNO_4$) requires *m/z* 188.1017, found *m/z* 188.1009.

(Vinyl-*d*) boronic acid, pinacol ester (**B12**)



To an oven-dried 20 mL microwave vial was added (vinyl-*d*) boronic acid, MIDA ester (329 g, 1.8 mmol, 1 equiv), pinacol (620 mg, 5.3 mmol, 3 equiv), and K_2CO_3 (726 mg, 5.3 mmol, 3 equiv). The vial was sealed and purged with nitrogen before the addition of THF/H_2O (9:1, 7 mL, 0.25 M). The reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was allowed to cool to room temperature and was vented and decapped. Et_2O (20 mL) and H_2O (10 mL) were added and organics were separated, washed with brine (20 mL), dried with Na_2SO_4, filtered, and concentrated under vacuum (using an ice bath, with pressure always above 300 mbar). The crude

residue was purified by column chromatography (silica gel, 0-5% Et_2O in *n*-pentane) and concentrated under vacuum (using an ice bath, with pressure always above 300 mbar) to afford the desired product, and (ethane-*d*)BPin (2:1, vinylBPin:ethaneBPin) as a clear oil (158 mg, 58% yield) indicating 62% deuterium incorporation in the desired position of vinylBPin.

υ_{max} (film): 2977, 2931, 1592, 1380, 1372, 1320, 1264, 1143 cm^{-1}.

^1H NMR of parent compound ($CDCl_3$, 400 MHz): δ 6.15 (dd, *J* = 19.5, 4.1 Hz, 1H), 6.05 – 5.96 (m, 1H), 5.85 (dd, *J* = 19.5, 13.7 Hz, 1H), 1.27 (s, 12H).

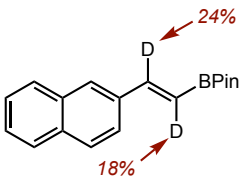
Deuterium labelling expected at δ 6.15, incorporation established against δ 5.85 ppm.

^{13}C NMR of parent compound ($CDCl_3$, 101 MHz): δ 137.2, 83.5, 24.9.

^{11}B NMR of parent compound ($CDCl_3$, 128 MHz): δ 29.68.

HRMS: exact mass calculated for $[M]^+$ ($C_8H_{15}DBO_2$) requires *m/z* 155.1228, found *m/z* 155.1301.

Compound B9a(D)



Prepared according to General Procedure D, using 2-bromonaphthalene (51.8 mg, 0.25 mmol, 1 equiv), (vinyl-*d*) boronic acid, pinacol ester (as a mixture with (ethane-*d*)BPin, 66% purity, 116.8 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (140 µL, 1 mmol, 4 equiv). The reaction mixture was diluted with EtOAc (5 mL) and passed through a layer of Celite eluting the product with EtOAc (2 x 10 mL). The filtrate was washed with H_2O (25 mL), brine (25 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude residue was purified by column chromatography (silica gel, 0-5% EtOAc in petroleum ether 40-60°) to afford the

desired product as a yellow oil (17.3 mg, 49%) with deuterium labelling in both alkene positions.

Note

Deuterium scrambling can be attributed to reinsertion of $L_n(X)Pd(II)(D)$. Formation of the *trans*-BPin product with high fidelity indicates *cine* substitution is not operational under Mizoroki-Heck conditions.

υ_{max} (film): 3052, 2973, 2925, 1620, 1610, 1365, 1320, 1142 cm^{-1}.

^1H NMR of parent compound ($CDCl_3$, 400 MHz): δ 7.86 – 7.79 (m, 4H), 7.71 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.58 (d, *J* = 18.4 Hz, 1H), 7.50 – 7.44 (m, 2H), 6.30 (d, *J* = 18.4 Hz, 1H), 1.34 (s, 12H).

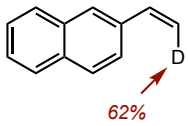
Deuterium labelling expected at δ 7.58 and 6.30, incorporation established against δ 7.71 ppm.

^{13}C NMR of parent compound ($CDCl_3$, 101 MHz): δ 149.5, 135.0, 133.7, 133.4, 128.4, 128.2, 128.0, 127.7, 126.4, 126.3, 123.4, 83.4, 24.8.

^{11}B NMR of parent compound ($CDCl_3$, 128 MHz): δ 30.42.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{18}H_{20}DBNaO_2$) requires *m/z* 304.1590, found *m/z* 304.1579.

Compound B9b(D)



Prepared according to General Procedure E, using 2-bromonaphthalene (51.8 mg, 0.25 mmol, 1 equiv), (vinyl-*d*) boronic acid, pinacol ester (as a mixture with (ethane-*d*)BPin, 66% purity, 64.1 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). The reaction mixture was diluted with EtOAc (5 mL) and passed through a layer of Celite

eluting the product with EtOAc (2 x 10 mL). The filtrate was washed with H_2O (25 mL), brine (25 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude residue was purified by column chromatography (silica gel, 100% petroleum ether 40-60°) to afford the desired product as a white solid (17.5 mg, 90%) with 62% labelling incorporated in the designated position.

Note

The incorporation of deuterium in one position only, strongly supports that *cine* substitution is not operational under Suzuki-Miyaura conditions.

υ_{max} (film): 3052, 3016, 2925, 2371, 1508 cm^{-1}.

^1H NMR of parent compound ($CDCl_3$, 400 MHz): δ 7.84 – 7.80 (m, 3H), 7.77 (s, 1H), 7.65 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.50 – 7.43 (m, 2H), 6.90 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.89 (dd, *J* = 17.6, 0.6 Hz, 1H), 5.35 (dd, *J* = 10.9, 0.5 Hz, 1H).

Deuterium labelling expected at δ 5.89, incorporation established against δ 7.65 ppm.

^{13}C NMR of parent compound ($CDCl_3$, 101 MHz): δ 149.5, 135.0, 133.7, 133.4, 128.4, 128.2, 128.0, 127.7, 126.4, 126.3, 123.4, 83.4, 24.8.

HRMS: exact mass calculated for $[M]^+$ ($C_{12}H_9D$) requires *m/z* 155.0845, found *m/z* 155.0837.

3.5.4 Reaction Optimisation

Vinyl/Vinyl Suzuki-Miyaura Cross-coupling (Table 13)

Prepared according to General Procedure E, using 1-(1-bromovinyl)-4-methylbenzene (49.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction was run at the specified temperature for 1 h. The reaction mixture was then concentrated under vacuum and was analysed by ^1H NMR against an internal standard (1,4-dinitrobenzene).

Entry	Temperature (°C)	Conversion to B27 (%)[a]
1	rt	88
2	30	94
3	50	97
4	70	93
5	90	88
6	110	80

[a] Determined by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene)

Cascade Suzuki-Miyaura/Diels Alder

Temperature Study (Table 14)

Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-methylbenzene (49.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), methyl vinyl ketone (45.2 µL, 0.5 mmol, 2 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was passed through a layer of Celite, concentrated under vacuum, and analysed by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	Conditions	Conversion (%)[a]	B28a:B28b[a]
1	50 °C, 24 h	42	8:1
2	80 °C, 24 h	63	-
3	50 °C, 1 h; 80 °C, 24 h	78	7:1
4	50 °C, 1 h; 120 °C, 24 h	81	6:1
5	50 °C, 1 h; 150 °C, 24 h	71	4:1

[a] Determined by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene)

Dienophile Stoiciometry Study (Table 15)

Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-methylbenzene (49.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), methyl vinyl ketone (X µL, X mmol, X equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was passed through a layer of Celite, concentrated under vacuum, and analysed by ^1H NMR against a known internal standard (1,4-dinitrobenzene).

Entry	MVK (equiv)	Conversion (%)[a]	B28a:B28b[a]
1	1 equiv (22.6 µL)	42	6:1
2	2 equiv (45.2 µL)	78	7:1
3	3 equiv (67.8 µL)	91	6:1
4	5 equiv (113 µL)	87	6:1

[a] Determined by ^1H NMR against a known internal standard (1,4-dinitrobenzene)

Vinyl/Vinyl Mizoroki-Heck Cross-coupling

Temperature Study (Table 16)

Prepared according to General Procedure D, using 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (77.2 mg, 0.25 mmol, 1 equiv),, vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (105 µL, 0.75 mmol, 3 equiv). The reactions were run for 24 hour at the specified temperature. The reaction mixture was then concentrated under vacuum and analysed by ^1H NMR against an internal standard (1,4-dinitrobenzene).

Entry	Temp. (°C)	Conversion to B30 (%)[a]	Starting Material (%)[a]
1	rt	15	62
2	40	31	0
3	60	23	0

4	80	18	0

[a] Determined by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene)

Silver Additive Study (Table 17)

Prepared according to General Procedure D, using 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (77.2 mg, 0.25 mmol, 1 equiv),, vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), **AgX** (0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (105 μL, 0.75 mmol, 3 equiv). The reactions were run at 40 °C for 24 h. The reaction mixture was then concentrated under vacuum and analysed by ^{1}H NMR against an internal standard (1,4-dinitrobenzene).

Entry	AgX	Conversion to B30 (%)[a]
1	Ag_2CO_3 (138 mg)	40
2	Ag_3PO_4 (210 mg)	54
3	AgOAc (83 mg)	67

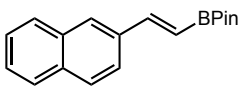
[a] Determined by ^{1}H NMR against a known internal standard (1,4-dinitrobenzene)

3.5.5 Compound characterization

Mizoroki-Heck and Suzuki-Miyaura Substrate Scope (Scheme 94)

Compound B9a

(*E*)-(2-(Naphthalen-2-yl)vinyl)boronic acid, pinacol ester



Prepared according to General Procedure D, using 2-bromonaphthalene (51.8 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (140 μL, 1 mmol, 4 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 100% by NMR assay. The reaction mixture was then purified by column

chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a yellow oil.

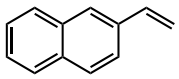
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 – 7.79 (m, 4H), 7.71 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.58 (d, *J* = 18.4 Hz, 1H), 7.50 – 7.44 (m, 2H), 6.30 (d, *J* = 18.4 Hz, 1H), 1.34 (s, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 149.5, 135.0, 133.7, 133.4, 128.4, 128.2, 128.0, 127.7, 126.4, 126.3, 123.4, 83.4, 24.8.

The spectral data were consistent with those previously reported in the literature.[173]

Compound B9b

2-Vinylnaphthalene



Prepared according to General Procedure E, using 2-bromonaphthalene (51.8 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 98% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 100% petroleum ether 40-60°) for characterization data to give the desired product as an off-white solid.

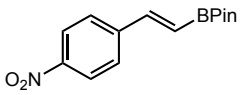
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84 – 7.80 (m, 3H), 7.77 (s, 1H), 7.65 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.50 – 7.43 (m, 2H), 6.90 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.89 (dd, *J* = 17.6, 0.6 Hz, 1H), 5.35 (dd, *J* = 10.9, 0.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 136.9, 135.0, 133.6, 133.2, 128.1, 128.0, 127.7, 126.4, 126.2, 125.9, 123.2, 114.2.

The spectral data were consistent with those previously reported in the literature.[174]

Compound B13a

(*E*)-(4-Nitrostyryl)boronic acid, pinacol ester



Prepared according to General Procedure D, using 1-bromo-4-nitrobenzene (50.5 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and Et_3N distilled (140 μL, 1 mmol, 4 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 68% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as an orange solid.

ν_{max} (solid): 2975, 2927, 2853, 1627, 1595, 1519, 1419, 1335, 1147 cm^{-1}.

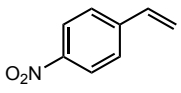
^1H NMR ($CDCl_3$, 400 MHz): δ 8.22 – 8.18 (m, 2H), 7.62 – 7.58 (m, 2H), 7.41 (d, J = 18.4 Hz, 1H), 6.33 (d, J = 18.4 Hz, 1H), 1.32 (s, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 147.7, 146.6, 143.6, 127.5, 124.0, 83.8, 24.8.

HRMS: exact mass calculated for $[M]^+$ ($C_{14}H_{18}BNO_4$) requires *m/z* 275.1329, found *m/z* 275.1316.

Compound B13b

1-Nitro-4-vinylbenzene



Prepared according to General Procedure E, using 1-bromo-4-nitrobenzene (50.5 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was then concentrated under

vacuum and was determined to give a yield of 96% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as an orange solid.

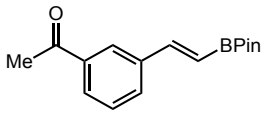
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 – 8.16 (m, 2H), 7.55 – 7.51 (m, 2H), 6.78 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.93 (d, *J* = 17.6 Hz, 1H), 5.50 (d, *J* = 10.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 147.2, 143.8, 135.0, 126.8, 123.9, 118.6.

The spectral data were consistent with those previously reported in the literature.[174]

Compound B14a

(*E*)-(3-Acetylstyryl)boronic acid, pinacol ester



Prepared according to General Procedure D, using 3'-bromoacetophenone (49.8 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (140 μL, 1 mmol, 4 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 96% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-20% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a yellow oil.

ν_{max} (film): 2975, 2927, 2853, 1687, 1627, 1430, 1344, 1142 cm^{-1}.

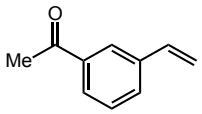
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (t, *J* = 1.7 Hz, 1H), 7.89 – 7.86 (m, 1H), 7.67 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.45 – 7.41 (m, 2H), 6.24 (d, *J* = 18.4 Hz, 1H), 2.60 (s, 3H), 1.31 (s, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 197.8, 148.3, 137.9, 137.5, 131.2, 128.9, 128.5, 127.0, 83.5, 26.6, 24.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{21}BO_3$) requires *m/z* 273.1657, found *m/z* 273.1652.

Compound B14b

1-(3-Vinylphenyl)ethan-1-one



Prepared according to General Procedure E, using 3'-bromoacetophenone (49.8 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 92% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a yellow oil.

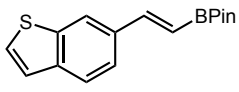
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.98 (t, *J* = 1.8 Hz, 1H), 7.85 – 7.82 (m, 1H), 7.59 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 6.72 (dd, 17.6, 10.9 Hz, 1H), 5.78 (d, *J* = 17.6 Hz, 1H), 5.34 (d, *J* = 10.6 Hz, 1H), 2.62 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 198.1, 138.0, 137.4, 136.0, 130.6, 128.8, 127.7, 126.0, 115.3, 26.7.

The spectral data were consistent with those previously reported in the literature.[174]

Compound B15a

(*E*)-(2-(Benzo[b]thiophen-6-yl)vinyl)boronic acid, pinacol ester



Prepared according to General Procedure D, using 6-chlorobenzo[*b*]thiophene (42.0 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2

equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (140 μL, 1 mmol, 4 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 44% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-5% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a white solid.

ν_{max} (solid): 2973, 2925, 1618, 1450, 1342, 1142 cm^{-1}.

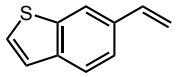
^1H NMR ($CDCl_3$, 400 MHz): δ 7.95 (d, *J* = 0.6 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.55 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.49 (s, 1H), 7.45 (d, *J* = 5.4 Hz, 1H), 7.31 (dd, *J* = 5.4, 0.6 Hz, 1H), 6.24 (d, *J* = 18.4 Hz, 1H), 1.33 (s, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 149.4, 140.1, 140.0, 134.0, 127.5, 123.7, 123.6, 122.9, 121.6, 83.3, 24.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}BO_2S$) requires *m/z* 285.1236, found *m/z* 285.1235.

Compound B15b

6-Vinylbenzo[b]thiophene



Prepared according to General Procedure E, using 6-chlorobenzo[*b*]thiophene (42.0 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction vial was heated at 80 °C for 4 h. The reaction mixture was then concentrated under vacuum and was determined to give a yield of 77% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, petroleum ether 40-60°) for characterization data to give the desired product as a white solid.

ν_{max} (solid): 3090, 2918, 2849, 1681, 1592, 1023 cm^{-1}.

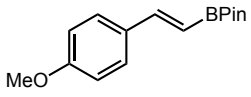
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (s, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.49 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.43 (d, *J* = 5.4 Hz, 1H), 7.32 (d, *J* = 5.4 Hz, 1H), 6.84 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.83 (d, *J* = 17.6 Hz, 1H), 5.30 (d, *J* = 10.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 140.2, 139.2, 136.8, 134.0, 126.7, 126.7, 123.5, 122.4, 120.5, 113.7.

HRMS: exact mass calculated for $[M]^+$ ($C_{10}H_8S$) requires *m/z* 160.0347, found *m/z* 160.0345.

Compound B16a

(*E*)-(4-Methoxystyryl)boronic acid, pinacol ester



Prepared according to General Procedure D, using 4-bromoanisole (46.7 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (140 μL, 1 mmol, 4 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 84% by NMR assay. The reaction mixture was then purified by reverse phase chromatography (C18 silica gel, 5-60% MeCN in H_2O) for characterization data to give the desired product as a colorless oil.

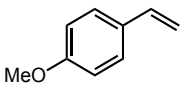
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 – 7.42 (m, 2H), 7.35 (d, *J* = 18.4 Hz, 1H), 6.88 – 6.85 (m, 2H), 6.01 (d, *J* = 18.4 Hz, 1H), 3.81 (s, 3H), 1.31 (s, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 160.3, 149.0, 130.4, 128.5, 114.0, 83.2, 55.3, 24.8.

The spectral data were consistent with those previously reported in the literature.[173]

Compound B16b

1-Methoxy-4-vinylbenzene



Prepared according to General Procedure E, using 4-bromoanisole (46.7 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 84% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a colorless oil.

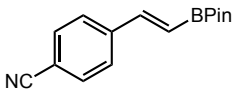
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 – 7.33 (m, 2H), 6.89 – 6.85 (m, 2H), 6.67 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.61 (dd, *J* = 17.6, 0.9 Hz, 1H), 5.13 (dd, *J* = 10.9, 0.9 Hz, 1H), 3.82 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz,): δ 159.4, 136.2, 130.5, 127.4, 113.9, 111.6, 55.3.

The spectral data were consistent with those previously reported in the literature.[174]

Compound B17a

(*E*)-(4-Cyanostyryl)boronic acid, pinacol ester



Prepared according to General Procedure D, using 4-chlorobenzonitrile (34.4 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (140 μL, 1 mmol, 4 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 40% by NMR assay. The reaction mixture was then purified by reverse phase chromatography (C18 silica gel, 0-35% MeCN in H_2O) for characterization data to give the desired product as a colorless oil.

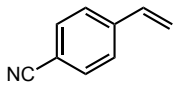
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 – 7.61 (m, 2H), 7.56 – 7.53 (m, 2H), 7.36 (d, *J* = 18.4 Hz, 1H), 6.28 (d, *J* = 18.4 Hz, 1H), 1.32 (s, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 147.1, 141.7, 132.4, 127.4, 118.8, 112.0, 83.7, 24.8.

The spectral data were consistent with those previously reported in the literature.[175]

Compound B17b

4-Vinylbenzonitrile



Prepared according to General Procedure E, using 4-chlorobenzonitrile (34.4 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction vial was heated at 80 °C for 4 h. The reaction mixture was then concentrated under vacuum and was determined to give a yield of 87% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-5% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a colorless oil.

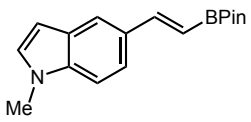
^{1}H NMR ($CDCl_3$, 500 MHz,): δ 7.61 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 6.73 (dd, J = 17.6, 10.9 Hz, 1H), 5.87 (d, J = 17.6 Hz, 1H), 5.45 (d, J = 10.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 141.9, 135.4, 132.4, 126.7, 118.9, 117.7, 111.1.

The spectral data were consistent with those previously reported in the literature.[174]

Compound B18a

(*E*)-(2-(1-Methyl-1H-indol-5-yl)vinyl)boronic acid, pinacol ester



Prepared according to General Procedure D, using 5-bromo-1-methyl-1*H*-indole (52.5 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (140 μL, 1 mmol, 4 equiv). The reaction mixture was then concentrated under vacuum and was determined to

give a yield of 40% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) followed by reverse phase chromatography (C18 silica gel, 0-35% MeCN in H_2O) for characterization data to give the desired product as a colorless oil.

ν_{max} (film): 2973, 2927, 1687, 1608, 1447, 1316, 1140 cm^{-1}.

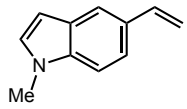
^1H NMR ($CDCl_3$, 400 MHz,): δ 7.72 (d, *J* = 1.5 Hz, 1H), 7.55 (d, *J* = 18.4 Hz, 1H), 7.47 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.03 (t, *J* = 3.0 Hz, 1H), 6.49 (dd, *J* = 3.1, 0.8 Hz, 1H), 6.12 (d, *J* = 18.4 Hz, 1H), 3.77 (s, 3H), 1.33 (s, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 151.1, 137.2, 129.4, 129.3, 128.5, 120.9, 120.5, 109.3, 101.7, 83.1, 32.9, 24.8.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{22}BNO_2$) requires *m/z* 284.1925, found *m/z* 284.1925.

Compound B18b

1-Methyl-5-vinyl-1H-indole



Prepared according to General Procedure E, using 5-bromo-1-methyl-1*H*-indole (52.5 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 76% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a colorless oil.

ν_{max} (film): 2921, 2849, 1687, 1627, 1489, 1246, 1110 cm^{-1}.

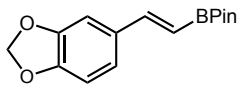
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (s, 1H), 7.39 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 3.1 Hz, 1H), 6.86 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.49 – 6.48 (m, 1H), 5.72 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.15 (dd, *J* = 10.9, 0.9 Hz, 1H), 3.79 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 137.9, 136.6, 129.3, 129.3, 128.6, 119.7, 119.3, 110.7, 109.2, 101.3, 32.9.

HRMS: exact mass calculated for $[M]^+$ ($C_{11}H_{11}N$) requires *m/z* 157.0891, found *m/z* 157.0893.

Compound B19a

(*E*)-(2-(Benzo[d][1,3]dioxol-5-yl)vinyl)boronic acid, pinacol ester



Prepared according to General Procedure D, using 3,4-(methylenedioxy)bromobenzene (50.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (140 μL, 1 mmol, 4 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 69% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a colorless oil.

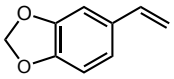
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (d, *J* = 18.3 Hz, 1H), 7.03 (d, *J* = 1.6 Hz, 1H) 6.93 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.01 – 5.93 (m, 3H), 1.30 (s, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 149.0, 148.4, 148.1, 132.2, 122.6, 108.2, 105.9, 101.2, 83.3, 24.8.

The spectral data were consistent with those previously reported in the literature.[176]

Compound B19b

5-Vinylbenzo[d][1,3]dioxole



Prepared according to General Procedure E, using 3,4-(methylenedioxy)bromobenzene (50.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 91% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, petroleum ether 40-60°) for characterization data to give the desired product as a colorless oil.

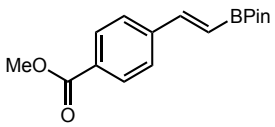
^1H NMR ($CDCl_3$, 400 MHz): δ 6.97 (d, *J* = 1.7 Hz, 1H), 6.84 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.63 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.95 (s, 2H), 5.58 (dd, *J* = 17.5, 0.7 Hz, 1H), 5.13 (dd, *J* = 10.9, 0.7 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 148.0, 147.4, 136.4, 132.1, 121.0, 112.0, 108.2, 105.4, 101.0.

The spectral data were consistent with those previously reported in the literature.[177]

Compound B20a

(*E*)-(4-(Methoxycarbonyl)styryl)boronic acid, pinacol ester



Prepared according to General Procedure D, using methyl 4-chlorobenzoate (42.5 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (140 μL, 1 mmol, 4 equiv).

The reaction mixture was then concentrated under vacuum and was determined to give a yield of 48% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-8% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a white solid.

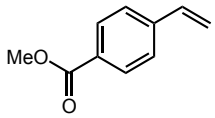
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 – 7.99 (m, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 18.4 Hz 1H), 6.27 (d, *J* = 18.4 Hz, 1H), 3.91 (s, 3H), 1.30 (s, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.8, 148.1, 141.7, 130.1, 129.9, 127.0, 83.6, 52.1, 24.8.

The spectral data were consistent with those previously reported in the literature.[178]

Compound B20b

Methyl 4-vinylbenzoate



Prepared according to General Procedure E, using methyl 4-chlorobenzoate (42.5 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction vial was heated at 80 °C for 4 h. The reaction mixture was then concentrated under vacuum and was determined to give a yield of 93% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-20% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a colorless oil.

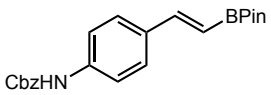
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 – 7.98 (m, 2H), 7.47 – 7.44 (m, 2H), 6.75 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.86 (dd, *J* = 17.6, 0.7 Hz, 1H), 5.38 (dd, *J* = 10.9, 0.6 Hz, 1H), 3.91 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.8, 141.9, 136.0, 129.9, 129.3, 126.1, 116.4, 52.0.

The spectral data were consistent with those previously reported in the literature.[174]

Compound B21a

(*E*)-(4-(((Benzyloxy)carbonyl)amino)styryl)boronic acid, pinacol ester



Prepared according to General Procedure D, using benzyl (4-bromophenyl)carbamate (76.5 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (140 μL, 1 mmol, 4 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 75% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a colorless oil.

ν_{max} (film): 2976, 2358, 1734, 1712, 1589, 1521, 1311, 1142 cm^{-1}.

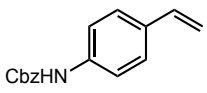
^1H NMR ($CDCl_3$, 400 MHz): δ 7.45 – 7.32 (m, 10H), 6.73 (s, 1H), 6.07 (d, *J* = 18.4 Hz, 1H), 5.20 (s, 2H), 1.31 (s, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 153.1, 148.7, 138.3, 135.9, 132.9, 128.6, 128.4, 128.4, 127.9, 118.5, 83.3, 67.1, 24.8.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{22}H_{26}BNO_4$) requires *m/z* 402.1853, found *m/z* 402.1841.

Compound B21b

Benzyl (4-vinylphenyl)carbamate



Prepared according to General Procedure E, using benzyl (4-bromophenyl)carbamate (76.5 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M),

and H_2O (22.5 μL, 1.25 mmol, 5 equiv).The reaction mixture was then concentrated under vacuum and was determined to give a yield of 89% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a white solid.

ν_{max} (solid): 3314, 3095, 3037, 1703, 1586, 1527 cm^{-1}.

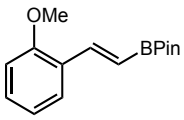
^1H NMR ($CDCl_3$, 400 MHz): δ 7.42 – 7.32 (m, 9H), 6.66 (dd, *J* = 17.6, 10.9 Hz, 2H), 5.67 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.21 (s, 2H), 5.18 (dd, *J* = 10.9, 0.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 153.2, 137.3, 136.1, 136.0, 133.0, 128.6, 128.3, 128.3, 126.9, 118.6, 112.7, 67.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{16}H_{15}NO_2$) requires *m/z* 254.1176, found *m/z* 254.1178.

Compound B22a

(*E*)-(2-Methoxystyryl)boronic acid, pinacol ester



Prepared according to General Procedure D, using 2-bromoanisole (46.7 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (140 μL, 1 mmol, 4 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 90% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a colorless oil.

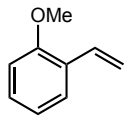
^1H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 18.6 Hz, 1H), 7.55 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.29 – 7.24 (m, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.18 (d, *J* = 18.6 Hz, 1H), 3.85 (s, 3H), 1.31 (s, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 157.3, 144.1, 129.9, 127.1, 126.6, 120.5, 110.9, 83.2, 55.3, 24.8.

The spectral data were consistent with those previously reported in the literature.[173]

Compound B22b

1-Methoxy-2-vinylbenzene



Prepared according to General Procedure E, using 2-bromoanisole (46.7 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 95% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a colorless oil.

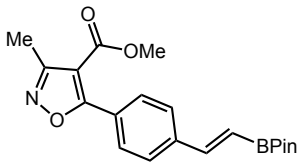
^1H NMR ($CDCl_3$, 400 MHz): δ 7.47 (dd, J = 7.6, 1.7 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.05 (dd, J = 17.8, 11.2 Hz, 1H), 6.94 (t, J = 7.8 Hz, 1H), 6.88 (dd, J = 8.3, 0.8 Hz, 1H), 5.74 (dd, J = 17.8, 1.6 Hz, 1H), 5.26 (dd, J = 11.2, 1.6 Hz, 1H), 3.85 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 156.7, 131.7, 128.8, 126.8, 126.5 120.6, 114.0, 110.5, 55.0.

The spectral data were consistent with those previously reported in the literature.[179]

Compound B23a

(*E*)-(4-(4-(Methoxycarbonyl)-3-methylisoxazol-5-yl)styryl)boronic acid, pinacol ester



Prepared according to General Procedure D, using methyl 5-(4-bromophenyl)-3-methylisoxazole-4-carboxylate (74.0 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.1 mg, 0.5 mmol, 2 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1,4-dioxane (1 mL, 0.25 M), and distilled Et_3N (140 μL, 1 mmol, 4 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 63% by NMR assay. The reaction mixture was then purified by reverse phase chromatography (C18 silica gel, 0-35% MeCN in H_2O) for characterization data to give the desired product as an orange solid.

ν_{max} (solid): 2975, 2923, 2951, 1720, 1625, 1580, 1350, 1316, 1216 cm^{-1}.

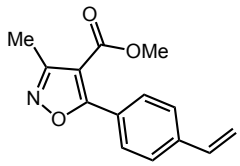
^1H NMR ($CDCl_3$, 400 MHz): δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 18.4 Hz, 1H), 6.27 (d, *J* = 18.4 Hz, 1H), 3.84 (s, 3H), 2.50 (s, 3H), 1.32 (s, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.6, 162.6, 160.8, 148.1, 140.1, 129.3, 127.0, 126.9, 83.5, 51.8, 29.7, 24.8, 12.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{24}BNO_5$) requires *m/z* 370.1820, found *m/z* 370.1813.

Compound B23b

Methyl 3-methyl-5-(4-vinylphenyl)isoxazole-4-carboxylate



Prepared according to General Procedure E, using methyl 5-(4-bromophenyl)-3-methylisoxazole-4-carboxylate (74.0 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (42.3 mg, 0.275 mmol, 1.1 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction mixture was then concentrated under vacuum and was determined to give a yield of 78% by NMR assay. The reaction mixture was then purified by column chromatography (silica gel, 0-10% EtOAc in petroleum ether 40-60°) for characterization data to give the desired product as a white solid.

ν_{max} (solid): 2949, 1720, 1592, 1413, 1311, 1229, 1093 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.89 – 7.86 (m, 2H), 7.52 – 7.48 (m, 2H), 6.75 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.86 (d, *J* = 17.6 Hz, 1H), 5.37 (d, *J* = 10.9 Hz, 1H), 3.84 (s, 3H), 2.50 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.7, 162.6, 160.7, 140.3, 135.9, 129.3, 126.1, 126.0, 116.1, 107.9, 51.7, 12.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{13}NO_3$) requires *m/z* 244.0968, found *m/z* 244.0962.

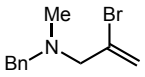
Synthesis of starting materials

Triflate electrophiles were prepared according to a literature procedure.[158]

Vinyl bromide electrophiles were prepared according to literature procedures.[156,157]

Synthesis of novel starting materials

N-Benzyl-2-bromo-*N*-methylprop-2-en-1-amine (**S1**), starting material for compound **B33**



To a solution of 2,3-dibromoprop-1-ene (500 mg, 2.5 mmol, 1 equiv) in THF (8.3 mL, 0.3 M) was added *N*-methyl-1-phenylmethanamine (646 µL, 5 mmol, 2 equiv) via syringe. The reaction mixture was heated to 35 °C for 4 h. Once the reaction was complete, H_2O (25 mL) was added and the organics were extracted with Et_2O (25 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography (silica gel, 20-50% EtOAc in petroleum ether) to afford the title compound as a clear oil (485 mg, 81%).

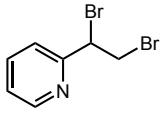
υ_{max} (film): 3026, 2977, 2946, 2786, 1631, 1454, 1028 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 (dt, J = 13.0, 7.4 Hz, 4H), 7.26 (t, J = 3.5 Hz, 1H), 5.91 (s, 1H), 5.60 (s, 1H), 3.58 (s, 2H), 3.22 (s, 2H), 2.25 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 138.1, 131.3, 128.4, 127.8, 126.6, 118.0, 64.8, 60.7, 41.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{11}H_{15}N^{79}Br$) requires *m/z* 242.0362, found *m/z* 242.0360.

2-(1,2-Dibromoethyl)pyridine (**S2**), starting material for compound **B34**

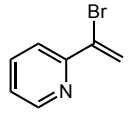


To an oven dried 10 mL round-bottomed flask charged with 2-vinylpyridine (512 µL, 4.8 mmol, 1 equiv) and $CHCl_3$ (2 mL, 1.9 M) was added bromine (280 µL, 2.15 mmol, 1.15 equiv) dropwise under nitrogen at 0 °C. The reaction was allowed to reach room temperature and was then diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous sodium metabisulfite solution (10 mL), H_2O (10 mL), and brine (10 mL). The organics were passed through a hydrophobic frit and concentrated to afford the desired product as a clear oil (980 mg, 78%). Product is highly air sensitive and was used immediately after NMR analysis.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.67 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.71 (td, *J* = 7.7, 1.8 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.25 – 7.28 (m, 1H), 5.20 (dd, *J* = 11.0, 4.6 Hz, 1H), 4.40 (dd, *J* = 11.0, 9.8 Hz, 1H), 4.04 (dd, *J* = 9.8, 4.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 156.8, 150.6, 137.1, 123.9, 123.4, 50.0, 33.3.

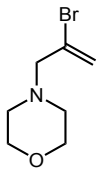
2-(1-Bromovinyl)pyridine (**S3**), starting material for compound **B34**



To an oven dried 10 mL round-bottomed flask charged with 2-(1,2-dibromoethyl)pyridine (478 mg, 1.8 mmol, 1 equiv) as a solution in MeOH/THF (1/1, 6 mL) was added K_2CO_3 (500 mg, 3.6 mmol, 2 equiv). The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with water (10 mL) and volatiles were removed under reduced pressure. Organics were extracted with Et_2O (2 x 10 mL). The combined organics were washed with brine (2 x 10 mL), passed through a hydrophobic frit and concentrated to afford the desired product as a light sensitive yellow oil (202 mg, 61%), which was immediately used in subsequent reactions without further purification. Product is extremely air sensitive and was used immediately after NMR analysis.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.60 (d, *J* = 4.6 Hz, 1H), 7.81 – 7.69 (m, 2H), 7.24 (ddd, *J* = 6.9, 5.7, 3.3 Hz, 1H), 6.85 (d, *J* = 1.6 Hz, 1H), 5.99 (d, *J* = 1.6 Hz, 1H).

4-(2-Bromoallyl)morpholine (**S4**), starting material for compound **B50**



To a solution of 2,3-dibromoprop-1-ene (500 mg, 2.5 mmol, 1 equiv) in THF (8.3 mL, 0.3 M) was added morpholine (432 µL, 5 mmol, 2 equiv) via syringe. The reaction mixture was stirred at room temperature for 24 h. Once the reaction was complete, H_2O (25 mL) was added and the organics were extracted with Et_2O (25 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography (silica gel, 20-80% EtOAc in petroleum ether) to afford the title compound as a clear oil (342 mg, 66%).

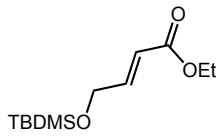
υ_{max} (film): 2926, 2854, 2808, 1631, 1454, 1294, 1117 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 5.87 (s, 1H), 5.60 (s, 1H), 3.78 – 3.69 (m, 4H), 3.18 (s, 2H), 2.51 – 2.46 (m, 4H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 130.1, 119.1, 66.9, 66.8, 53.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_7H_{13}{}^{79}BrNO$) requires *m/z* 208.0155, found *m/z* 208.0155.

Ethyl (*E*)-4-((*tert*-butyldimethylsilyl)oxy)but-2-enoate (**B61**), starting material for compound **B63**



(Carbethoxymethylene)triphenylphosphorane (7.5 g, 21.5 mmol, 1.5 equiv) was weighed into an oven-dried round bottom flask. The flask was sealed and purged with nitrogen before addition of PhMe (47.8 mL, 0.3 M) and 2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde (2.5 g, 14.3 mmol, 1 equiv).The reaction mixture was heated to 70 °C for 16 h. The reaction was allowed to cool to room

temperature and the crude mixture was concentrated under vacuum. Et_2O (30 mL) was added and precipitates were filtered and washed with cold Et_2O (30 mL). The filtrate was concentrated under vacuum and the crude residue was purified by column chromatography (silica gel, 3% EtOac in petroleum ether 40-60 °) to afford the desired product as a clear oil (1.6 g, 46%).

υ_{max} (film): 2955, 2929, 2856, 1720 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ 6.99 (dt, *J* = 15.5, 3.5 Hz, 1H), 6.09 (dt, *J* = 15.5, 2.3 Hz, 1H), 4.33 (dd, *J* = 3.5, 2.3 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.30 (d, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 6H).

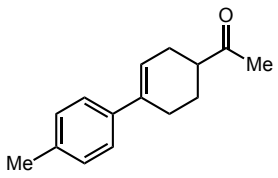
^{13}C NMR ($CDCl_3$, 101 MHz): δ 166.8, 147.5, 119.8, 62.3, 60.4, 26.0, 18.9, 14.4, –5.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{12}H_{25}O_3Si$) requires *m/z* 245.1567, found *m/z* 245.1569.

Compounds from Scheme 98

Compound B28a

1-(4'-Methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-yl)ethan-1-one



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-methylbenzene (49.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), methyl vinyl ketone (67.8 µL, 0.75 mmol, 3 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (product eluting in 0-10% EtOAc in petroleum ether 40-60°) to afford the desired product as an off white solid (46.8 mg,

85%, 7:1 regioselectivity). Main regioisomer was separated by reduction/oxidation protocol.

υ_{max} (film): 3026, 2920, 2849 1709 cm^{-1}.

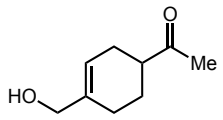
^1H NMR ($CDCl_3$, 500 MHz): δ 7.17 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 5.98 (dd, *J* = 3.1, 1.6 Hz, 1H), 2.60 – 2.51 (m, 1H), 2.51 – 2.34 (m, 2H), 2.34 – 2.25 (m, 2H), 2.24 (s, 3H), 2.12 (s, 3H), 2.09 – 2.02 (m, 1H), 1.69 – 1.57 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 211.0, 138.3, 136.1, 135.7, 128.5, 124.4, 121.3, 46.5, 27.6, 27.1, 26.6, 24.6, 20.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}O$) requires *m/z* 201.1274, found *m/z* 201.1271.

Compound B32

1-(4-(Hydroxymethyl)cyclohex-3-en-1-yl)ethan-1-one



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 2-bromoprop-2-en-1-ol (20.7 µL, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), methyl vinyl ketone (67.8 µL, 0.75 mmol, 3 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 20-60% Et_2O in petroleum ether 40-60°) to afford the desired product as a clear oil (25.2 mg, 65%; 3:1 regioselectivity). Main regioisomer was separated by column chromatography.

υ_{max} (film): 3401, 2920, 2840, 1700, 1354 cm^{-1}.

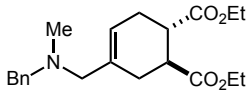
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.70 (d, *J* = 3.8 Hz, 1H), 4.00 (s, 2H), 2.58 (d, *J* = 6.8 Hz, 1H), 2.21 (ddd, *J* = 8.5, 4.2, 2.4 Hz, 2H), 2.18 (s, 3H), 2.15 – 2.07 (m, 2H), 2.07 – 1.99 (m, 1H), 1.65 – 1.50 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 211.6, 137.4, 121.2, 67.1, 47.4, 28.2, 26.7, 25.2, 24.7.

HRMS: exact mass calculated for $[M+NH_4]^+$ ($C_9H_{18}O_2N$) requires *m/z* 172.1332, found *m/z* 172.1333.

Compound B33

Diethyl (1S*,2S*)-4-((benzyl(methyl)amino)methyl)cyclohex-4-ene-1,2-dicarboxylate



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), *N*-benzyl-2-bromo-*N*-methylprop-2-en-1-amine (60.1 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), diethyl fumarate (123 µL, 0.75 mmol, 3 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 20-80% EtOAc in petroleum ether 40-60°) to afford the desired product as a clear oil (70.4 mg, 78%).

υ_{max} (film): 2979, 2933, 2838, 2784, 1731, 1454, 1179 cm^{-1}.

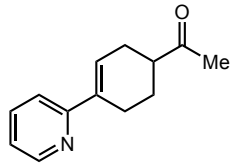
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 4H), 7.24 (dd, *J* = 8.7, 4.2 Hz, 1H), 5.61 (d, *J* = 3.0 Hz, 1H), 4.20 – 4.08 (m, 4H), 3.42 (d, *J* = 4.9 Hz, 2H), 2.90 – 2.78 (m, 4H), 2.54 – 2.40 (m, 2H), 2.24 – 2.14 (m, 2H), 2.10 (s, 3H), 1.28 – 1.22 (m, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.0, 175.0, 139.4, 134.7, 129.0, 128.3, 127.0, 122.2, 64.1, 61.9, 60.7, 42.3, 41.9, 41.7, 29.9, 28.1, 14.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{30}NO_4$) requires *m/z* 360.2169, found *m/z* 360.2171.

Compound B34

1-(4-(Pyridin-2-yl)cyclohex-3-en-1-yl)ethan-1-one



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 2-(1-bromovinyl)pyridine (46 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), methyl vinyl ketone (67.8 µL, 0.75 mmol, 3 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether 40-60°) to afford the desired product as an off white solid (47 mg, 93%; 7:1 regioselectivity). Main regioisomer was separated for characterisation by reduction/oxidation general procedure.

υ_{max} (film): 2999, 2921, 2838, 1705, 1584, 1467, 1432 cm^{-1}.

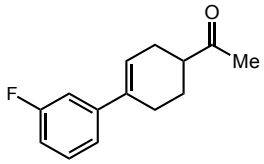
^1H NMR ($CDCl_3$, 500 MHz) δ 8.55 – 8.53 (m, 1H), 7.64 – 7.59 (m, 1H), 7.38 – 7.35 (m, 1H), 7.13 – 7.08 (m, 1H), 6.69 – 6.65 (m, 1H), 2.76 – 2.65 (m, 2H), 2.59 – 2.48 (m, 1H), 2.47 – 2.42 (m, 2H), 2.22 (s, 3H), 2.21 – 2.14 (m, 1H), 1.79 – 1.68 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 211.3, 158.2, 148.9, 136.4, 127.7, 126.4, 121.8, 119.1, 47.0, 28.2, 27.6, 25.6, 25.1.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{13}H_{16}NO$) requires *m/z* 202.1226, found *m/z* 202.1224.

Compound B35

1-(3'-Fluoro-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-yl)ethan-1-one



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-3-fluorobenzene (50.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), methyl vinyl ketone (67.8 µL, 0.75 mmol, 3 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (product eluting in 0-10% EtOAc in petroleum ether 40-60°) to afford the desired product as a yellow oil (50.7 mg, 93%, 6:1 regioselectivity). Main regioisomer was separated by reduction/oxidation protocol.

υ_{max} (film): 3457, 3070, 2927, 1705, 1586, 1437 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.29 – 7.22 (m, 1H), 7.14 (d, J = 7.9 Hz, 1H), 7.09 – 7.02 (m, 1H), 6.92 (td, J = 8.3, 1.9 Hz, 1H), 6.15 (td, J = 3.1, 1.6 Hz, 1H), 2.70 – 2.62 (m, 1H), 2.55 – 2.44 (m, 2H), 2.40 (ddd, J = 9.2, 5.9, 3.3 Hz, 2H), 2.23 (s, 3H), 2.20 – 2.13 (m, 1H), 1.79 – 1.68 (m, 1H).

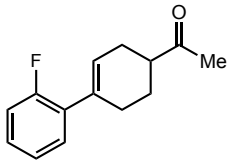
^{13}C NMR ($CDCl_3$, 101 MHz): δ 211.3, 163.1 (d, $^1J_{CF}$ = 244.5 Hz), 144.1 (d, $^3J_{CF}$ = 7.5 Hz), 135.5, 129.8 (d, $^3J_{CF}$ = 8.2 Hz), 124.0, 120.7 (d, $^4J_{CF}$ = 2.2 Hz), 113.7 (d, $^2J_{CF}$ = 21.1 Hz), 112.1 (d, $^2J_{CF}$ = 21.8 Hz), 46.9, 28.2, 27.6, 27.0, 25.1.

^{19}F NMR ($CDCl_3$, 376 MHz): δ -113.68.

HRMS: exact mass calculated for $[M]^+$ ($C_{14}H_{15}FO$) requires *m/z* 219.1185, found *m/z* 219.1200.

Compound B36

1-(2'-Fluoro-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-yl)ethan-1-one



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-2-fluorobenzene (50.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), methyl vinyl ketone (67.8 µL, 0.75 mmol, 3 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (product eluting in 0-10% EtOAc in petroleum ether 40-60°) to afford the desired product as a yellow oil (43.7 mg, 80%, 4:1 regioselectivity). Main regioisomer was separated by reduction/oxidation protocol.

υ_{max} (film): 3043, 3066, 2927, 1705, 1489, 1450, 1355 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.25 – 7.15 (m, 2H), 7.08 (td, J = 7.5, 1.1 Hz, 1H), 7.03 – 6.98 (m, 1H), 5.94 (d, J = 1.2 Hz, 1H), 2.75 – 2.65 (m, 1H), 2.55 – 2.35 (m, 4H), 2.22 (s, 3H), 2.17 – 2.08 (m, 1H), 1.80 – 1.65 (m, 1H).

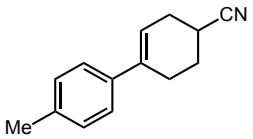
^{13}C NMR ($CDCl_3$, 101 MHz): δ 211.4, 160.1 (d, $^1J_{CF}$ = 247.5 Hz), 133.6, 130.7 (d, $^2J_{CF}$ = 14.0 Hz), 129.4 (d, $^3J_{CF}$ = 4.6 Hz), 128.4 (d, $^3J_{CF}$ = 8.1 Hz), 126.3 (d, $^4J_{CF}$ = 2.7 Hz), 124.1 (d, $^3J_{CF}$ = 4.0 Hz), 115.88 (d, $^2J_{CF}$ = 23.0 Hz), 46.92, 28.39 (d, $^4J_{CF}$ = 3.3 Hz), 28.2, 27.5, 25.2.

^{19}F NMR ($CDCl_3$, 376 MHz): δ -113.68.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{14}H_{16}FO$) requires *m/z* 219.1180, found *m/z* 219.1180.

Compound B37

4'-Methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carbonitrile



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-methylbenzene (49.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), acrylonitrile (50 μL, 0.75 mmol, 3 equiv), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (product eluting in 0-10% EtOAc in petroleum ether 40-60°) to afford the desired product as a yellow solid (40.3 mg, 82%, 10:1 regioselectivity). Main regioisomer was separated by chiral prep HPLC, 60% MeOH /H_2O (+ 0.1% formic acid), f = 40mL/min, λ = 215 nm, column = 30 mm x 2.1 mm BEH C_{18} (1.7 μm).

υ_{max} (film): 3037, 2951, 2934, 2921, 2841, 2239, 1517, 1435 cm^{-1}.

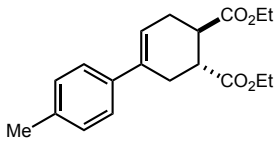
^1H NMR ($CDCl_3$, 400 MHz): δ 7.25 (d, *J* = 7.3 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.99 (d, *J* = 3.7 Hz, 1H), 2.90 – 2.83 (m, 1H), 2.68 – 2.56 (m, 2H), 2.56 – 2.44 (m, 2H), 2.34 (s, 3H), 2.20 – 2.12 (m, 1H), 2.10 – 1.99 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 138.4, 137.3, 136.8, 129.2, 125.1, 122.5, 119.6, 29.1, 26.1, 25.5, 24.7, 21.2.

HRMS: exact mass calculated for $[M]^+$ ($C_{14}H_{15}N$) requires *m/z* 197.1205, found *m/z* 197.1211.

Compound B38

Diethyl (3R*,4R*)-4'-methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-3,4-dicarboxylate



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-methylbenzene (49.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), diethyl fumarate (123 µL, 0.75 mmol, 3 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (product eluting in 0-30% EtOAc in petroleum ether 40-60°) to afford the desired product as an off white solid (46.8 mg, 85%).

υ_{max} (film): 2979, 2933, 1727, 1179, 1164 cm^{-1}.

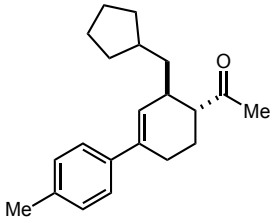
^1H NMR ($CDCl_3$, 500 MHz): δ 7.25 (d, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.07 – 6.00 (m, 1H), 4.22 – 4.12 (m, 4H), 3.00 (td, *J* = 10.9, 5.3 Hz, 1H), 2.91 (td, *J* = 10.8, 5.6 Hz, 1H), 2.81 (dd, *J* = 17.0, 5.3 Hz, 1H), 2.67 – 2.51 (m, 2H), 2.40 – 2.31 (m, 4H), 1.27 (tt, *J* = 5.2, 2.6 Hz, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.3, 174.3, 137.5, 136.5, 134.4, 128.5, 124.5, 120.6, 60.2, 60.2, 41.5, 40.7, 29.7, 28.2, 20.5, 13.7.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{25}O_4$) requires *m/z* 317.1747, found *m/z* 317.1748.

Compound B39

1-((4R*,5R*)-5-(Cyclopentylmethyl)-4'-methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-yl)ethan-1-one



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-methylbenzene (49.3 mg, 0.25 mmol, 1 equiv), (*E*)-(3-cyclopentylprop-1-en-1-yl)boronic acid, pinacol ester (62 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), methyl vinyl ketone (67.8 µL, 0.75 mmol, 3 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether 40-60°) to afford the desired product, a yellow solid, as a 1:1 mixture of diastereoisomers (59.5 mg, 80%). Diastereoisomers could be separated by reduction/oxidation general procedure.

υ_{max} (solid): 2949, 2931, 2910, 2858, 1700, 1354 cm^{-1}.

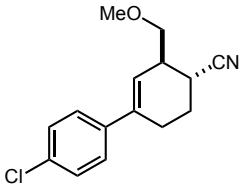
^1H NMR ($CDCl_3$, 400 MHz): δ 7.31 – 7.26 (m, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.24 – 6.19 (m, 1H), 2.84 – 2.72 (m, 2H), 2.58 – 2.48 (m, 1H), 2.43 – 2.33 (m, 4H), 2.18 (s, 3H), 2.00 – 1.83 (m, 4H), 1.79 – 1.72 (m, 1H), 1.63 – 1.48 (m, 5H), 1.14 – 1.00 (m, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 211.2, 139.2, 136.8, 136.5, 129.1, 126.5, 125.3, 51.6, 38.3, 37.6, 35.7, 33.9, 32.2, 28.8, 27.3, 25.3, 25.1, 21.1, 19.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{29}O$) requires *m/z* 297.2213, found *m/z* 297.2214.

Compound B40

(4R*,5R*)-4'-chloro-5-(methoxymethyl)-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carbonitrile



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-chlorobenzene (54.4 mg, 0.25 mmol, 1 equiv), (*E*)-(3-methoxyprop-1-en-1-yl)boronic acid, pinacol ester (52 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), acrylonitrile (50 µL, 0.75 mmol, 3 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether 40-60°) to afford the desired product, a yellow oil, as a 1:1 mixture of diastereoisomers (55.7 mg, 85%). Diastereoisomers could be separated by column chromatography.

υ_{max} (film): 2981, 2929, 2873, 2830, 2239, 1495 cm^{-1}.

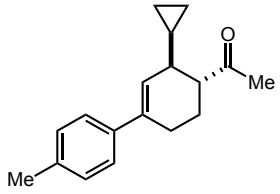
^1H NMR ($CDCl_3$, 500 MHz): δ 7.29 (s, 4H), 6.00 – 5.89 (m, 1H), 3.55 – 3.48 (m, 2H), 3.39 (s, 3H), 2.89 – 2.83 (m, 1H), 2.82 – 2.77 (m, 1H), 2.52 (dd, *J* = 22.1, 3.8 Hz, 2H), 2.28 – 2.20 (m, 1H), 2.03 (dd, *J* = 9.3, 5.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 138.7, 136.6, 132.8, 128.0, 126.0, 122.6, 121.4, 73.3, 58.6, 39.4, 26.2, 25.0, 24.1.

HRMS: exact mass calculated for $[M+Na]^+$ ($C_{15}H_{16}{}^{35}ClNONa$) requires *m/z* 284.0815, found *m/z* 284.0813.

Compound B41

1-((4R*,5R*)-5-Cyclopropyl-4'-methyl-2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-yl)ethan-1-one



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-methylbenzene (49.3 mg, 0.25 mmol, 1 equiv), (*E*)-(2-cyclopropylvinyl)boronic acid, pinacol ester (50.9 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), methyl vinyl ketone (67.8 μL, 0.75 mmol, 3 equiv), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether 40-60°) to afford the desired product, a white solid, as a 1:2 mixture of diastereoisomers (56 mg, 93%). Diastereoisomers could be separated by column chromatography.

υ_{max} (film): 3078, 2998, 2921, 2856, 1709, 1514, 1359 cm^{-1}.

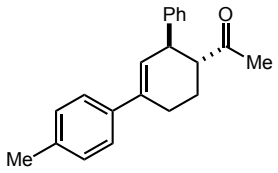
^1H NMR ($CDCl_3$, 400 MHz): δ 7.32 – 7.27 (m, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.08 – 6.02 (m, 1H), 2.71 – 2.61 (m, 1H), 2.49 – 2.42 (m, 2H), 2.34 (s, 3H), 2.29 (s, 3H), 2.04 – 1.95 (m, 1H), 1.93 – 1.82 (m, 1H), 1.82 – 1.69 (m, 1H), 0.69 – 0.57 (m, 1H), 0.52 – 0.42 (m, 2H), 0.29 – 0.15 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 213.1, 138.9, 136.8, 135.7, 129.1, 126.9, 125.1, 53.9, 43.3, 30.4, 27.0, 26.0, 21.2, 16.8, 4.9, 3.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{18}H_{23}O$) requires *m/z* 255.1749, found *m/z* 255.1748.

Compound B42

1-((3'R*,4'R*)-4-Methyl-3',4',5',6'-tetrahydro-[1,1':3',1''-terphenyl]-4'-yl)ethan-1-one



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-methylbenzene (49.3 mg, 0.25 mmol, 1 equiv), (*E*)-styrylboronic acid, pinacol ester (60.3 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), methyl vinyl ketone (67.8 µL, 0.75 mmol, 3 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether 40-60°) to afford the desired product, a white solid, as a 1:1 mixture of diastereoisomers (68.5 mg, 94%). Diastereoisomers could be separated by column chromatography.

υ_{max} (film): 3024, 2921, 2858, 1709 cm^{-1}.

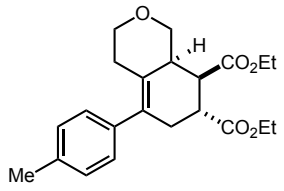
^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 – 7.28 (m, 4H), 7.22 (dd, *J* = 5.0, 2.9 Hz, 3H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.05 (s, 1H), 3.90 – 3.86 (m, 1H), 2.86 – 2.77 (m, 1H), 2.65 – 2.58 (m, 2H), 2.35 (s, 3H), 2.14 – 2.08 (m, 1H), 1.95 (d, *J* = 5.9 Hz, 3H), 1.94 – 1.87 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 211.7, 144.6, 138.6, 137.0, 136.2, 129.2, 128.7, 128.3, 126.8, 126.7, 125.2, 55.6, 44.8, 30.3, 27.1, 25.9, 21.2.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{23}O$) requires *m/z* 291.1749, found *m/z* 291.1746.

Compound B43

Diethyl (7R*,8R*,8aS*)-5-(*p*-tolyl)-3,4,6,7,8,8a-hexahydro-1H-isochromene-7,8-dicarboxylate



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-methylbenzene (49.3 mg, 0.25 mmol, 1 equiv), (3,6-dihydro-2H-pyran-4-yl)boronic acid, pinacol ester (62 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), diethyl fumarate (123 μL, 0.75 mmol, 3 equiv), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-40% EtOAc in petroleum ether 40-60°) to afford the desired product as a yellow oil, as a single diastereomer (70 mg, 75%).

υ_{max} (solid): 2960, 2923, 2903, 2847, 1722 cm^{-1}.

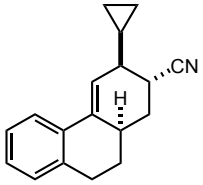
^1H NMR ($CDCl_3$, 400 MHz): δ 7.14 (d, *J* = 7.8 Hz, 2H), 7.06 – 7.00 (m, 2H), 4.21 – 4.10 (m, 4H), 3.91 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.73 (dd, *J* = 10.3, 4.4 Hz, 1H), 3.40 – 3.29 (m, 1H), 3.28 – 3.08 (m, 2H), 3.02 – 2.85 (m, 2H), 2.68 (dd, *J* = 17.1, 5.0 Hz, 1H), 2.34 (s, 3H), 1.55 (s, 3H), 1.26 (dd, *J* = 11.8, 7.1 Hz, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 174.8, 172.9, 138.4, 136.8, 131.9, 130.1, 129.2, 128.5, 71.4, 70.2, 60.9, 60.8, 43.5, 39.7, 39.6, 35.1, 33.2, 21.3, 14.4, 14.3.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{22}H_{29}O_5$) requires *m/z* 373.2010, found *m/z* 373.2009.

Compound B44

(2R*,3R*,10aR*)-3-Cyclopropyl-1,2,3,9,10,10a-hexahydrophenanthrene-2-carbonitrile



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (69.5 mg, 0.25 mmol, 1 equiv), (*E*)-(2-cyclopropylvinyl)boronic acid, pinacol ester (50.9 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), acrylonitrile (50 µL, 0.75 mmol, 3 equiv), and H_2O (22.5 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether 40-60°) to afford the desired product, a white solid, as a 3:2 mixture of diastereoisomers (53 mg, 85%). Main diastereomer was separated by chiral prep HPLC, 60% MeOH /H_2O (+ 0.1% formic acid), f = 40mL/min, λ = 215 nm, column = 30 mm x 2.1 mm BEH C_{18} (1.7 µm).

υ_{max} (film): 3068, 3001, 2925, 2856, 2237, 1485, 1458 cm^{-1}.

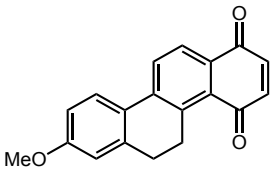
^1H NMR ($CDCl_3$, 500 MHz): δ 7.61 (dd, *J* = 5.9, 3.3 Hz, 1H), 7.20 – 7.13 (m, 2H), 7.13 – 7.07 (m, 1H), 6.24 (dd, *J* = 4.5, 1.9 Hz, 1H), 3.07 – 2.85 (m, 3H), 2.69 – 2.61 (m, 1H), 2.15 (dt, *J* = 13.3, 5.1 Hz, 1H), 2.05 (d, *J* = 12.6 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.82 – 1.74 (m, 1H), 1.55 (dd, *J* = 12.7, 5.2 Hz, 1H), 0.77 (dd, *J* = 8.6, 4.1 Hz, 1H), 0.62 (dd, *J* = 8.4, 3.9 Hz, 1H), 0.54 (dd, *J* = 8.2, 4.4 Hz, 1H), 0.42 – 0.29 (m, 2H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 136.8, 136.7, 133.9, 129.5, 127.6, 126.2, 123.9, 122.3, 119.5, 44.3, 33.0, 30.6, 29.9, 29.8, 29.6, 16.5, 4.6, 4.0.

HRMS: exact mass calculated for $[M]^+$ ($C_{18}H_{19}N$) requires *m/z* 249.1517, found *m/z* 249.1523.

Compound B45

8-Methoxy-5,6-dihydrochrysene-1,4-dione



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (77.2 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction was run at 50 °C for 1h. The vial was vented, decapped, and *p*-benzoquinone (135.4 mg, 1.25 mmol, 5 equiv) was added to the reaction mixture. The vial was sealed, purged with nitrogen and heated at 60 °C for 24 h with stirring. After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether 40-60 °) to afford the desired product as a bright red solid (48.1 mg, 66% (contains < 5% unknown aromatic impurity)).

υ_{max} (solid): 3070, 3013, 2925, 2832, 1653, 1608, 1575, 1558 cm^{-1}.

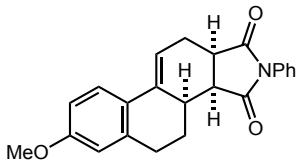
^1H NMR ($CDCl_3$, 500 MHz): δ 8.05 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 6.90 – 6.86 (m, 3H), 6.80 (d, *J* = 2.6 Hz, 1H), 3.86 (s, 3H), 3.56 – 3.45 (m, 2H), 2.84 – 2.77 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 187.9, 185.1, 160.7, 141.7, 140.8, 139.9, 139.9, 137.1, 131.3, 129.7, 127.9, 126.4, 126.0, 126.0, 113.2, 113.1, 55.5, 28.6, 25.5.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{15}O_3$) requires *m/z* 291.1021, found *m/z* 291.1027.

Compound B46

(3aS*,3bR*,11aR*)-7-Methoxy-2-phenyl-3a,3b,4,5,11,11a-hexahydro-1H-naphtho[2,1-e]isoindole-1,3(2H)-dione



Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (77.2 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction was run at 50 °C for 1h. The vial was vented, decapped, and *N*-phenyl maleimide (130.1 mg, 0.75 mmol, 3 equiv) was added to the reaction mixture. The vial was sealed, purged with nitrogen and stirred at room temperature for 24 h. After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether 40-60 °) to afford the desired product as a yellow solid (80.3 mg, 89%).

υ_{max} (solid): 2972, 2929, 1705, 1488, 1372, 1140 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.39 (t, *J* = 8.5 Hz, 3H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.14 – 7.08 (m, 2H), 6.72 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.28 – 6.21 (m, 1H), 3.79 (s, 3H), 3.38 – 3.31 (m, 2H), 3.01 (ddd, *J* = 15.6, 7.4, 1.2 Hz, 1H), 2.81 – 2.71 (m, 2H), 2.68 – 2.57 (m, 1H), 2.47 – 2.30 (m, 2H), 2.20 – 2.09 (m, 1H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 179.1, 177.0, 159.1, 139.7, 138.2, 132.1, 129.2, 128.6, 126.9, 126.7, 124.7, 117.8, 113.1, 112.9, 55.4, 43.8, 41.4, 37.1, 30.5, 25.4, 24.5.

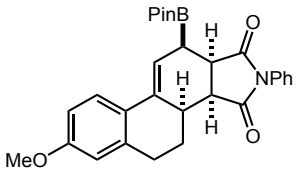
HRMS: exact mass calculated for $[M+H]^+$ ($C_{23}H_{22}NO_3$) requires *m/z* 360.1594, found *m/z* 360.1597.

Compounds from Scheme 99

Due to degradation of allylic BPin products by protodeboronation during silica chromatography the yields were calculated by analysis of the crude material by ^{1}H NMR using a 1,4 dinitrobenzene standard. Isolation of clean material was then performed to provide an isolated yield and analytical data. Yields will be presented as follows (mass, NMR yield, isolated yield).

Compound B31

((3aS*,3bR*,11R*,11aR*)-7-methoxy-1,3-dioxo-2-phenyl-2,3,3a,3b,4,5,11,11a-octahydro-1H-naphtho[2,1-e]isoindol-11-yl)boronic acid, pinacol ester



Prepared according to General Procedure G using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (77.2 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), AgOAc (83 mg, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), Et_3N (105 µL, 0.75 mmol, 3 equiv), and then *N*-phenyl maleimide (130 mg, 0.75 mmol, 3 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether 40-60°) to afford the desired product as an off white solid (84.4 mg, NMR yield not recorded, 69% isolated yield (contains residual EtOAc)).

υ_{max} (solid): 2972, 2929, 2834, 1707, 1603, 1495, 1370, 1236, 1140 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (d, *J* = 8.6 Hz, 1H), 7.38 – 7.30 (m, 3H), 7.07 – 7.01 (m, 2H), 6.70 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.62 (d, *J* = 2.6 Hz, 1H), 6.48 (t, *J* = 3.4 Hz, 1H), 3.78 (s, 3H), 3.66 (dd, *J* = 8.8, 4.6 Hz, 1H), 3.35 (dd, *J* = 8.7, 7.4 Hz, 1H), 2.79 – 2.69 (m, 2H), 2.64 – 2.54 (m, 1H), 2.27 – 2.14 (m, 2H), 1.99 – 1.94 (m, 1H), 1.35 (d, *J* = 3.6 Hz, 12H).

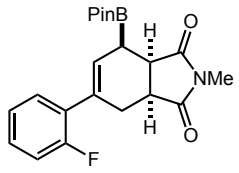
^{13}C NMR ($CDCl_3$, 101 MHz): δ 179.0, 177.1, 159.0, 139.5, 137.8, 132.2, 129.2, 128.6, 127.3, 126.9, 125.3, 121.1, 112.8, 112.8, 84.2, 55.4, 44.8, 44.8, 37.7, 30.5, 25.3, 24.9, 24.5.

^{11}B NMR ($CDCl_3$, 160 MHz): δ 34.93.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{29}H_{33}BNO_5$) requires *m/z* 486.2451, found *m/z* 486.2433.

Compound B47

((3aR*,4R*,7aS*)-6-(2-Fluorophenyl)-2-methyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)boronic acid, pinacol ester



Prepared according to General Procedure G using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-2-fluorobenzene (50.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), AgOAc (83 mg, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), Et_3N (105 μL, 0.75 mmol, 3 equiv), and then *N*-methyl maleimide (83.3 mg, 0.75 mmol, 3 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether 40-60°) to afford the desired product as a yellow solid (62 mg, 90% NMR yield, 64% isolated yield).

υ_{max} (solid): 3037, 2975, 2933, 1692, 1435, 1374, 1136 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.20 – 7.15 (m, 1H), 7.14 – 7.11 (m, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.01 – 6.94 (m, 1H), 6.25 (dd, *J* = 5.0, 1.5 Hz, 1H), 3.34 (dd, *J* = 9.1, 6.1 Hz, 1H), 3.23 – 3.18 (m, 1H), 2.94 – 2.86 (m, 4H), 2.68 – 2.60 (m, 1H), 2.17 (t, *J* = 5.2 Hz, 1H), 1.29 (d, *J* = 2.4 Hz, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 180.3, 180.1, 159.8 (d, $^{1}J_{CF}$ = 247.1 Hz), 135.3, 129.5 (d, $^{3}J_{CF}$ = 14.3 Hz), 129.3, 128.9 (d, $^{3}J_{CF}$ = 8.3 Hz), 124.1 (d, $^{3}J_{CF}$ = 3.3 Hz), 115.8 (d, $^{2}J_{CF}$ = 22.4 Hz), 115.2 (d, $^{2}J_{CF}$ = 21.2 Hz), 84.2, 48.2, 41.9, 40.6, 29.0 (d, $^{4}J_{CF}$ = 2.5 Hz), 25.0, 24.8.

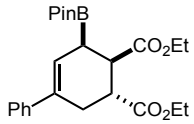
^{19}F NMR ($CDCl_3$, 376 MHz): δ –115.72 (s).

^{11}B NMR ($CDCl_3$, 160 MHz): δ 32.66.

HRMS: exact mass calculated for $[M]^+$ ($C_{21}H_{25}BFNO_4$) requires *m/z* 385.1861, found *m/z* 385.1865.

Compound B48

((3R*,4R*,5R*)-4,5-bis(Ethoxycarbonyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)boronic acid, pinacol ester



Prepared according to General Procedure H using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), (1-bromovinyl)benzene (45.8 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), AgOAc (83 mg, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), Et_3N (105 µL, 0.75 mmol, 3 equiv), and then 1,4-dioxane (2 mL, 0.125 M), and diethylfumarate (205 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether 40-60°) to afford the desired product as a yellow solid (57.4 mg, NMR yield not recorded, 54% isolated yield).

υ_{max} (film): 3024, 2927, 2931, 1733, 1372, 1335 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 2H), 7.21 (s, 1H), 6.14 (dd, *J* = 3.3, 1.6 Hz, 1H), 4.26 – 4.10 (m, 4H), 3.25 (dd, *J* =

8.9, 6.1 Hz, 1H), 3.17 (dd, *J* = 9.6, 6.0 Hz, 1H), 2.75 – 2.61 (m, 2H), 2.49 (t, *J* = 5.3 Hz, 1H), 1.27 (t, *J* = 3.6 Hz, 6H), 1.23 (d, *J* = 11.3 Hz, 12H).

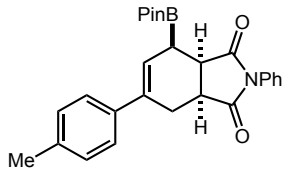
^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.4, 174.2, 141.6, 133.3, 128.4, 125.0, 125.3, 123.8, 83.7, 60.8, 60.7, 42.2, 40.6, 30.0, 24.9, 24.8, 14.4, 14.3.

^{11}B NMR ($CDCl_3$, 160 MHz): δ 33.10.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{24}H_{34}BO_6$) requires *m/z* 429.2443, found *m/z* 429.2437.

Compound B49

((3aR*,4R*,7aS*)-1,3-Dioxo-2-phenyl-6-(p-tolyl)-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)boronic acid, pinacol ester



Prepared according to General Procedure G using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-methylbenzene (49.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), AgOAc (83 mg, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), Et_3N (105 μL, 0.75 mmol, 3 equiv), and then *N*-phenyl maleimide (130 mg, 0.75 mmol, 3 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether 40-60°) to afford the desired product as an off white solid (79 mg, NMR yield not recorded, 71% isolated yield).

υ_{max} (solid): 2975, 2923, 2248, 1705, 1501, 1372, 1142 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (dd, *J* = 10.4, 4.8 Hz, 2H), 7.37 – 7.31 (m, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.18 – 7.11 (m, 4H), 6.39 (dd, *J* = 5.2, 1.7 Hz, 1H), 3.53 (dd, *J* = 9.3, 6.0 Hz, 1H), 3.40 – 3.36 (m, 1H), 3.13 (dd, *J* = 15.1, 4.1 Hz, 1H), 2.72

(dd, J = 15.1, 7.6 Hz, 1H), 2.34 (s, 3H), 2.24 (t, J = 5.4 Hz, 1H), 1.30 (d, J = 8.0 Hz, 12H).

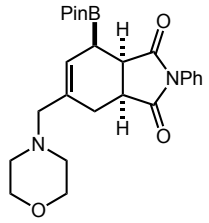
^{13}C NMR ($CDCl_3$, 101 MHz): δ 179.4, 179.2, 139.3, 137.8, 137.1, 132.3, 129.2, 129.1, 128.5, 126.7, 125.5, 124.8, 84.2, 42.2, 41.0, 28.3, 25.0, 24.8, 21.2.

^{11}B NMR ($CDCl_3$, 160 MHz): δ 32.89.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{27}H_{31}BNO_4$) requires *m/z* 444.2341, found *m/z* 444.2328.

Compound B50

((3aR*,4R*,7aS*)-6-(Morpholinomethyl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)boronic acid, pinacol ester



Prepared according to General Procedure G using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 4-(2-bromoallyl)morpholine (51.5 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), AgOAc (83 mg, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), Et_3N (105 µL, 0.75 mmol, 3 equiv), and then *N*-phenyl maleimide (130 mg, 0.75 mmol, 3 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether 40-60°) to afford the desired product as a clear oil (50.2 mg, 63% NMR yield, 44% isolated yield).

υ_{max} (film): 2955, 2927, 2853, 2802, 1705, 1357, 1143 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42 (t, J = 7.7 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.23 (d, J = 7.5 Hz, 2H), 5.98 (d, J = 4.5 Hz, 1H), 3.59 (d, J = 3.9 Hz, 4H), 3.42 (dd, J =

9.5, 6.3 Hz, 1H), 3.26 – 3.19 (m, 1H), 2.89 (s, 2H), 2.69 (dd, *J* = 15.3, 4.5 Hz, 1H), 2.39 (dd, *J* = 15.3, 8.3 Hz, 1H), 2.30 (s, 4H), 2.14 (t, *J* = 5.3 Hz, 1H), 1.25 (d, *J* = 4.9 Hz, 12H).

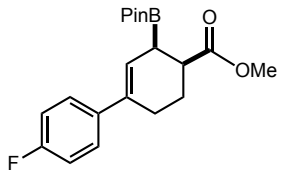
^{13}C NMR ($CDCl_3$, 101 MHz): δ 179.3, 179.2, 137.1, 132.3, 129.1, 128.5, 126.3, 126.3, 84.1, 67.0, 64.7, 53.7, 53.7, 42.2, 40.4, 27.1, 25.0, 24.8.

^{11}B NMR ($CDCl_3$, 160 MHz): δ 33.03.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{25}H_{34}BN_2O_5$) requires *m/z* 453.2556, found *m/z* 453.2549.

Compound B51

((3R*,4S*)-4'-Fluoro-4-(methoxycarbonyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)boronic acid, pinacol ester



Prepared according to General Procedure H using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 1-(1-bromovinyl)-4-fluorobenzene (50.3 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), AgOAc (83 mg, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), Et_3N (105 µL, 0.75 mmol, 3 equiv), and then 1,4-dioxane (2 mL, 0.125 M), and methyl acrylate (113 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether 40-60°) to afford the desired product as a yellow solid (35.4 mg, 68% NMR yield, 39% isolated yield).

υ_{max} (film): 2977, 2949, 2929, 1731, 1510, 1357, 1326, 1225 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (dd, *J* = 8.7, 5.5 Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 6.11 (d, *J* = 4.7 Hz, 1H), 3.69 (s, 3H), 2.85 – 2.76 (m, 1H), 2.44 (dd, *J* = 7.9, 3.7 Hz, 2H), 2.32 (s, 1H), 2.19 – 2.15 (m, 2H), 1.23 (d, *J* = 3.1 Hz, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.9, 161.9 (d, $^{1}J_{CF}$ = 245.0 Hz), 138.4 (d, $^{4}J_{CF}$ = 3.1 Hz), 134.1, 126.6 (d, $^{3}J_{CF}$ = 7.8 Hz), 123.9, 115.0 (d, $^{2}J_{CF}$ = 21.2 Hz), 83.5, 51.8, 40.5, 26.9, 25.0, 24.7, 24.3.

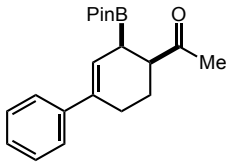
^{19}F NMR ($CDCl_3$, 376 MHz): δ –116.68 (s).

^{11}B NMR ($CDCl_3$, 160 MHz): δ 32.37.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{20}H_{25}BFO_4$) requires *m/z* 359.1830, found *m/z* 359.1833.

Compound B52

((3R*,4S*)-4-Acetyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)boronic acid, pinacol ester



Prepared according to General Procedure H using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), (1-bromovinyl)benzene (45.8 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), AgOAc (83 mg, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), Et_3N (105 µL, 0.75 mmol, 3 equiv), and then 1,4-dioxane (2 mL, 0.125 M), and methyl vinyl ketone (113 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether 40-60°) to afford the desired product as a clear oil (43.4 mg, 81% NMR yield, 53% isolated yield).

υ_{max} (film): 2975, 2931, 1709, 1448, 1372, 1329, 1145 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 – 7.33 (m, 2H), 7.29 (t, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 7.3 Hz, 1H), 6.18 (d, *J* = 4.8 Hz, 1H), 2.87 – 2.78 (m, 1H), 2.59 – 2.44 (m, 2H), 2.27 – 2.12 (m, 6H), 1.25 (d, *J* = 1.7 Hz, 12H).

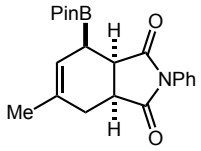
^{13}C NMR ($CDCl_3$, 101 MHz): δ 211.3, 142.3, 134.4, 128.3, 126.6, 125.1, 124.4, 83.2, 49.9, 27.3, 27.1, 25.0, 24.9, 24.8.

^{11}B NMR ($CDCl_3$, 160 MHz): δ 32.55.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{20}H_{28}BO_3$) requires *m/z* 327.2135, found *m/z* 327.2135.

Compound B53

((3aR*,4R*,7aS*)-6-Methyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)boronic acid, pinacol ester



Prepared according to General Procedure G using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 2-bromoprop-1-ene (66.6 µL, 0.75 mmol, 3 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), AgOAc (83 mg, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), Et_3N (105 µL, 0.75 mmol, 3 equiv), and then *N*-phenyl maleimide (43.3 mg, 0.25 mmol, 1 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether 40-60°) to afford the desired product as a yellow solid containing a 5% *N*-phenyl maleimide impurity (44.5 mg, 63% NMR yield, 48% isolated yield).

υ_{max} (solid): 2973, 2940, 2923, 2905, 1705, 1365, 1331, 1205, 1136 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 (dd, *J* = 10.9, 4.5 Hz, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.24 – 7.20 (m, 2H), 5.83 – 5.79 (m, 1H), 3.41 (dd, *J* = 9.3, 6.0 Hz, 1H), 3.26 –

3.19 (m, 1H), 2.54 (dd, *J* = 15.2, 4.0 Hz, 1H), 2.35 (dd, *J* = 15.1, 8.0 Hz, 1H), 2.05 (d, *J* = 2.7 Hz, 1H), 1.78 (s, 3H), 1.27 (d, *J* = 5.0 Hz, 12H).

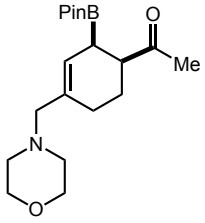
^{13}C NMR ($CDCl_3$, 101 MHz): δ 179.0, 178.8, 135.7, 131.8, 128.5, 127.9, 126.0, 121.8, 83.4, 41.5, 39.8, 29.2, 24.4, 24.1, 22.7.

^{11}B NMR ($CDCl_3$, 160 MHz): δ 33.40.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{27}BNO_4$) requires *m/z* 368.2037, found *m/z* 368.2037.

Compound B54

((1R*,6S*)-6-Acetyl-3-(morpholinomethyl)cyclohex-2-en-1-yl)boronic acid, pinacol ester



Prepared according to General Procedure H using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 4-(2-bromoallyl)morpholine (51.5 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), AgOAc (83 mg, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), Et_3N (105 µL, 0.75 mmol, 3 equiv), and then 1,4-dioxane (2 mL, 0.125 M), and methyl vinyl ketone (113 µL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether 40-60°) to afford the desired product as a clear oil (26.9 mg, 42% NMR yield, 31% isolated yield).

υ_{max} (film): 2955, 2927, 2853, 2802, 1705, 1357, 1143 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.62 (d, *J* = 4.0 Hz, 1H), 3.67 (t, *J* = 4.6 Hz, 4H), 2.86 – 2.74 (m, 3H), 2.32 (s, 4H), 2.19 – 2.15 (m, 3H), 2.09 – 2.07 (m, 1H), 2.05 – 1.98 (m, 2H), 1.94 – 1.84 (m, 1H), 1.56 – 1.59 (m, 1H), 1.21 (d, *J* = 2.4 Hz, 12H).

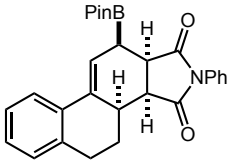
^{13}C NMR ($CDCl_3$, 101 MHz): δ 211.5, 132.2, 125.3, 83.1, 67.3, 66.1, 53.7, 50.3, 27.2, 26.4, 24.9, 24.8, 24.2.

^{11}B NMR ($CDCl_3$, 160 MHz): δ 32.65.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{19}H_{33}BNO_4$) requires *m/z* 350.2497, found *m/z* 350.2489.

Compound B55

((3aS*,3bR*,11R*,11aR*)-1,3-Dioxo-2-phenyl-2,3,3a,3b,4,5,11,11a-octahydro-1H-naphtho[2,1-e]isoindol-11-yl)boronic acid, pinacol ester



Prepared according to General Procedure G using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (69.6 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), AgOAc (83 mg, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), Et_3N (105 µL, 0.75 mmol, 3 equiv), and then *N*-phenyl maleimide (130 mg, 0.75 mmol, 3 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether 40-60°) to afford the desired product as a yellow solid (65.9 mg, N/A, 58% isolated yield).

υ_{max} (solid): 2977, 2929, 1705, 1499, 1372, 1140 cm^{-1}.

1H NMR ($CDCl_3$, 500 MHz) δ 7.60 – 7.56 (m, 1H), 7.38 – 7.33 (m, 2H), 7.32 – 7.27 (m, 1H), 7.17 – 7.07 (m, 3H), 7.06 – 7.02 (m, 2H), 6.62 (t, *J* = 3.4 Hz, 1H), 3.68 (dd, *J* = 8.8, 4.7 Hz, 1H), 3.37 (dd, *J* = 8.7, 7.5 Hz, 1H), 2.83 – 2.71 (m, 2H), 2.66 – 2.57 (m, 1H), 2.24 – 2.15 (m, 2H), 2.02 – 1.95 (m, 1H), 1.35 (d, *J* = 5.2 Hz, 12H).

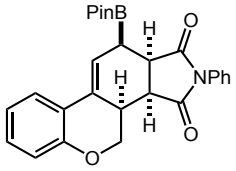
^{13}C NMR ($CDCl_3$, 101 MHz): δ 178.9, 176.9, 138.3, 138.0, 134.2, 132.1, 129.1, 128.6, 128.1, 127.2, 126.8, 126.6, 123.8, 123.6, 84.2, 44.8, 44.7, 37.8, 30.2, 25.2, 24.9, 24.4.

^{11}B NMR ($CDCl_3$, 160 MHz): δ 33.72.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{28}H_{31}BNO_4$) requires *m/z* 456.2341, found *m/z* 456.2327.

Compound B56

((3aS*,3bR*,11R*,11aR*)-1,3-Dioxo-2-phenyl-1,2,3,3a,3b,4,11,11a-octahydrochromeno[3,4-e]isoindol-11-yl)boronic acid, pinacol ester



Prepared according to General Procedure G using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 2*H*-chromen-4-yl trifluoromethanesulfonate (70.1 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), AgOAc (83 mg, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), Et_3N (105 μL, 0.75 mmol, 3 equiv), and then *N*-phenyl maleimide (130 mg, 0.75 mmol, 3 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-20% EtOAc in petroleum ether 40-60°) to afford the desired product as a white solid (39.7 mg, 36% NMR yield, 35% isolated yield).

υ_{max} (film): 3066, 3039, 2975, 2927, 1705, 1482, 1370, 1140 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.62 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.40 – 7.27 (m, 3H), 7.16 – 7.06 (m, 3H), 6.96 – 6.87 (m, 2H), 6.61 (t, *J* = 3.3 Hz, 1H), 4.54 (dd, *J* = 11.4, 5.8 Hz, 1H), 4.40 – 4.27 (m, 1H), 3.70 (dd, *J* = 9.0, 4.7 Hz, 1H), 3.45 (t, *J* = 8.6 Hz, 1H), 3.04 – 2.94 (m, 1H), 1.98 (d, *J* = 2.3 Hz, 1H), 1.36 (d, *J* = 3.6 Hz, 12H).

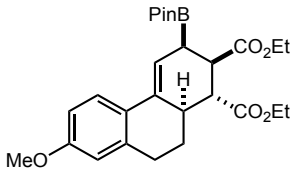
^{13}C NMR ($CDCl_3$, 101 MHz): δ 178.3, 176.2, 155.3, 132.2, 131.8, 129.1, 128.7, 128.6, 126.5, 123.6, 123.2, 122.1, 122.0, 117.6, 84.2, 67.2, 43.2, 42.3, 35.9, 25.1, 24.8.

^{11}B NMR ($CDCl_3$, 160 MHz): δ 33.60.

HRMS: exact mass calculated for [M+H] ($C_{27}H_{29}BNO_5$) requires *m/z* 458.2144, found *m/z* 458.2143.

Compound B57

((1R*,2R*,3R*,10aR*)-1,2-bis(Ethoxycarbonyl)-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthren-3-yl)boronic acid



Prepared according to General Procedure H using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (77.2 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (77.2 mg, 0.5 mmol, 2 equiv), AgOAc (83 mg, 0.5 mmol, 2 equiv), 1,4-dioxane (1 mL, 0.25 M), Et_3N (105 μL, 0.75 mmol, 3 equiv), and then 1,4-dioxane (2 mL, 0.125 M), and diethylfumarate (205 μL, 1.25 mmol, 5 equiv). After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-15% EtOAc in petroleum ether 40-60°) to afford the desired product as a yellow oil (51.2 mg, NMR yield not recorded, 42% isolated yield).

υ_{max} (film): 2977, 2933, 1731, 1608, 1502, 1465, 1447, 1372, 1255 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48 (d, *J* = 8.8 Hz, 1H), 6.72 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.58 (d, *J* = 2.6 Hz, 1H), 6.16 (d, *J* = 3.9 Hz, 1H), 4.21 – 4.05 (m, 4H), 3.78 (s, 3H), 3.08 (dd, *J* = 11.6, 5.8 Hz, 1H), 2.87 – 2.82 (m, 3H), 2.52 (dd, *J* = 11.2, 8.0 Hz, 2H), 2.19 – 2.10 (m, 1H), 1.62 (dd, *J* = 7.1, 4.9 Hz, 1H), , 1.25 (t, *J* = 7.1 Hz, 6H), 1.19 (d, *J* = 4.2 Hz, 12H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 175.9, 174.0, 158.7, 137.2, 133.3, 127.6, 125.3, 117.5, 113.2, 112.9, 83.7, 60.8, 60.6, 55.4, 47.5, 43.0, 39.9, 30.1, 29.0, 24.9, 24.7, 14.4, 14.3.

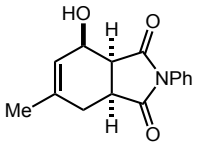
^{11}B NMR ($CDCl_3$, 160 MHz): δ 32.53.

HRMS: exact mass calculated for $[M-H]^+$ ($C_{27}H_{36}BNO_7$) requires *m/z* 483.2553, found *m/z* 483.2536.

Products from Scheme 100 and 101

Compound B58

(3aS*,4R*,7aS*)-4-Hydroxy-6-methyl-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione



To a solution of Allyl BPin **B53** (55.1 mg, 0.15 mmol, 1 equiv) and K_3PO_4 (95.4 mg, 0.45 mmol, 3 equiv) in THF (0.6 mL, 0.25 M) was added hydrogen peroxide, 30% w/v (153.2 µL, 1.5 mmol, 10 equiv) dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 15 min. After the reaction was complete, sodium metabisulfite was added at 0 °C until effervescence had ceased. Sat. aq. NH_4Cl (10 mL) and Et_2O (10 mL) were added and organics were separated, washed with brine (10 mL), dried over $NaSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by column chromatography (silica gel, 20-80% EtOAc in petroleum ether) to afford the desired product as a white solid (35.9 mg, 93%).

υ_{max} (solid): 3472, 2964, 2921, 2853, 1705, 1501, 1387 cm^{-1}.

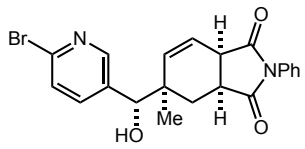
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47 (dd, *J* = 10.4, 4.8 Hz, 2H), 7.42 – 7.36 (m, 1H), 7.24 – 7.21 (m, 2H), 5.90 – 5.73 (m, 1H), 4.54 (s, 1H), 3.40 – 3.32 (m, 2H), 3.32 – 3.26 (m, 1H), 2.66 (dd, *J* = 16.0, 3.0 Hz, 1H), 2.34 (dd, *J* = 16.0, 8.2 Hz, 1H), 1.81 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 178.9, 178.6, 136.9, 131.8, 129.4, 129.0, 126.6, 126.6, 66.5, 44.7, 38.3, 28.6, 23.3.

HRMS: exact mass calculated for $[M-H]^-$ ($C_{15}H_{14}NO_3$) requires *m/z* 256.0979, found *m/z* 256.0976.

Compound B59

(3aS*,5R*,7aR*)-5-((S*)-(6-Bromopyridin-3-yl)(hydroxy)methyl)-5-methyl-2-phenyl-3a,4,5,7a-tetrahydro-1H-isoindole-1,3(2H)-dione



To an oven-dried microwave vial was added, allyl BPin **B53** (55.1 mg, 0.15 mmol, 1 equiv) and 6-bromonicotinaldehyde (83.7 mg, 0.45 mmol, 3 equiv). The vial was capped and purged with nitrogen before addition of dry PhMe (0.6 mL, 0.25M). The reaction mixture was heated to 90 °C with stirring overnight. After the reaction was complete solvent was removed under reduced pressure. The crude residue was purified by column chromatography (silica gel, 20-80% EtOAc in petroleum ether) to afford the desired product as white solid (90% NMR yield).

υ_{max} (solid): 3463, 3063, 2952, 2927, 2252, 1705, 1501, 1380, 1181 cm^{-1}.

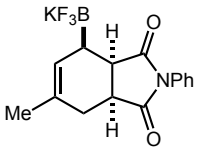
1H NMR ($CDCl_3$, 500 MHz) δ 8.62 (d, *J* = 2.1 Hz, 1H), 7.80 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 1H), 6.05 (dd, *J* = 10.1, 3.9 Hz, 1H), 5.98 (dd, *J* = 10.1, 2.4 Hz, 1H), 4.49 (s, 1H), 3.60 – 3.53 (m, 1H), 3.28 – 3.19 (m, 1H), 2.06 (dd, *J* = 13.6, 9.2 Hz, 1H), 1.73 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.00 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 178.4, 175.2, 156.7, 149.0, 138.2, 137.0, 131.3, 128.7, 128.1, 125.9, 123.4, 120.2, 119.3, 78.0, 40.0, 39.8, 36.6, 29.7, 21.6.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{21}H_{20}{}^{79}BrN_2O_3$) requires *m/z* 427.0652, found *m/z* 427.0653.

Compound B60

((3aR*,4R*,7aS*)-6-Methyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)boronic acid, potassium trifluoroborate salt



KHF_2 (70.3 mg, 0.90 mmol, 6 equiv) was stirred as a solution H_2O (0.3 mL) for 5 min before dropwise addition of allyl BPin **B53** (55.1 mg, 0.15 mmol, 1 equiv) as a solution in acetone (1.5 mL). The reaction mixture was stirred at room temperature for 1 h. Solvent was removed under vacuum adding acetone for azeotropic removal of H_2O. The crude residue was washed with hot acetone (3 x 5 mL) and filtered. The filtrate was concentrated under vacuum and the resulting solid was washed with hexane (5 mL) and Et_2O (5 mL) to afford the desired product as an off white solid (52.1 mg, quant.).

υ_{max} (solid): 2925, 2851, 1700, 1501, 1387, 1184 cm^{-1}.

^1H NMR (CD_3CN, 400 MHz): δ 7.47 – 7.41 (m, 2H), 7.38 (d, *J* = 7.4 Hz, 1H), 7.26 – 7.21 (m, 2H), 5.69 (dd, *J* = 5.7, 0.8 Hz, 1H), 3.25 – 3.16 (m, 1H), 3.00 (dd, *J* = 8.7, 7.3 Hz, 1H), 2.46 (dd, *J* = 15.4, 3.9 Hz, 1H), 2.19 (d, *J* = 8.4 Hz, 1H), 1.71 (s, 3H), 1.49 (t, *J* = 12.2 Hz, 1H).

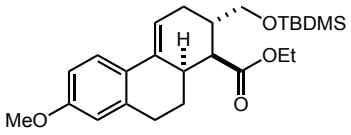
^{13}C NMR (CD_3CN, 101 MHz): δ 181.9, 181.4, 134.6, 132.1, 129.8, 128.9, 128.6, 128.3, 43.1, 42.3, 28.5, 23.7.

^{19}F NMR (CD_3CN, 376 MHz): δ –140.27 (s).

^{11}B NMR (CD_3CN, 128 MHz): δ 4.29.

HRMS: exact mass calculated for $[M\text{-}K]^-$ ($C_{15}H_{14}BF_3NO_2$) requires *m/z* 308.1075, found *m/z* 308.1077.

Compound B62

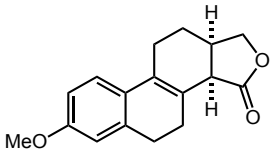


Prepared according to General Procedure F using $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 4 mol%), SPhos (8.2 mg, 0.02 mmol, 8 mol%), 6-methoxy-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (77.2 mg, 0.25 mmol, 1 equiv), vinyl boronic acid, pinacol ester (40.5 mg, 0.26 mmol, 1.05 equiv), K_3PO_4 (159 mg, 0.75 mmol, 3 equiv), 1,4-dioxane (1 mL, 0.25 M), ethyl (*E*)-4-((*tert*-butyldimethylsilyl)oxy)but-2-enoate (183 mg, 0.75 mmol, 3 equiv), and H_2O (22.5 μL, 1.25 mmol, 5 equiv). The reaction was run at 50 °C for 1h and then raised to 150 °C for 24 h. After the reaction was complete it was subjected to the purification method outlined in the General Procedure (silica gel, 0-10% EtOAc in petroleum ether 40-60 °) to afford the desired product, a yellow gum, as an uncharacterizable, complex mixture (87.2 mg, 81%). Characterization via conversion to compound **B63**.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{25}H_{39}O_4Si$) requires *m/z* 431.2612, found *m/z* 431.2608.

Compound B63

(3aR*,11aR*)-7-Methoxy-3a,4,5,10,11,11a-hexahydrophenanthro[1,2-c]furan-3(1H)-one



To an oven-dried microwave-vial was added **B62** (50 mg, 0.12 mmol, 1 equiv) and *p*-toluenesulfonic acid monohydrate (4.4 mg, 0.02 mmol, 20 mol%). The vial was capped and purged with nitrogen before the addition of PhMe (1.7 mL, 0.07 M). The reaction mixture was heated at 80 °C, with stirring for 24 h. After the reaction was compete, solvent was removed under vacuum and the crude residue was purified

directly by column chromatography (silica gel, 0-20% EtOAc in petroleum ether 40-60 °) to afford the desired product as a white solid (19.9 mg, 64%).

υ_{max} (solid): 2999, 2944, 2893, 2832, 1761, 1607, 1499 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.12 (d, *J* = 9.2 Hz, 1H), 6.75 – 6.70 (m, 2H), 4.37 (dd, *J* = 9.0, 6.0 Hz, 1H), 4.10 (dd, *J* = 9.0, 2.2 Hz, 1H), 3.80 (s, 3H), 3.08 (d, *J* = 7.3 Hz, 1H), 2.91 – 2.80 (m, 2H), 2.80 – 2.65 (m, 2H), 2.52 – 2.33 (m, 2H), 2.26 – 2.13 (m, 1H), 2.06 – 1.94 (m, 1H), 1.75 – 1.63 (m, 1H).

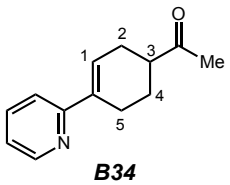
^{13}C NMR ($CDCl_3$, 101 MHz): δ 176.0, 158.0, 137.2, 129.1, 127.9, 124.3, 122.6, 112.9, 110.5, 70.5, 54.7, 43.5, 34.0, 28.0, 26.0, 23.7, 23.0.

HRMS: exact mass calculated for $[M+H]^+$ ($C_{17}H_{19}O_3$) requires *m/z* 271.1329, found *m/z* 271.1331.

3.5.6 Structure Elucidation by 2D NMR

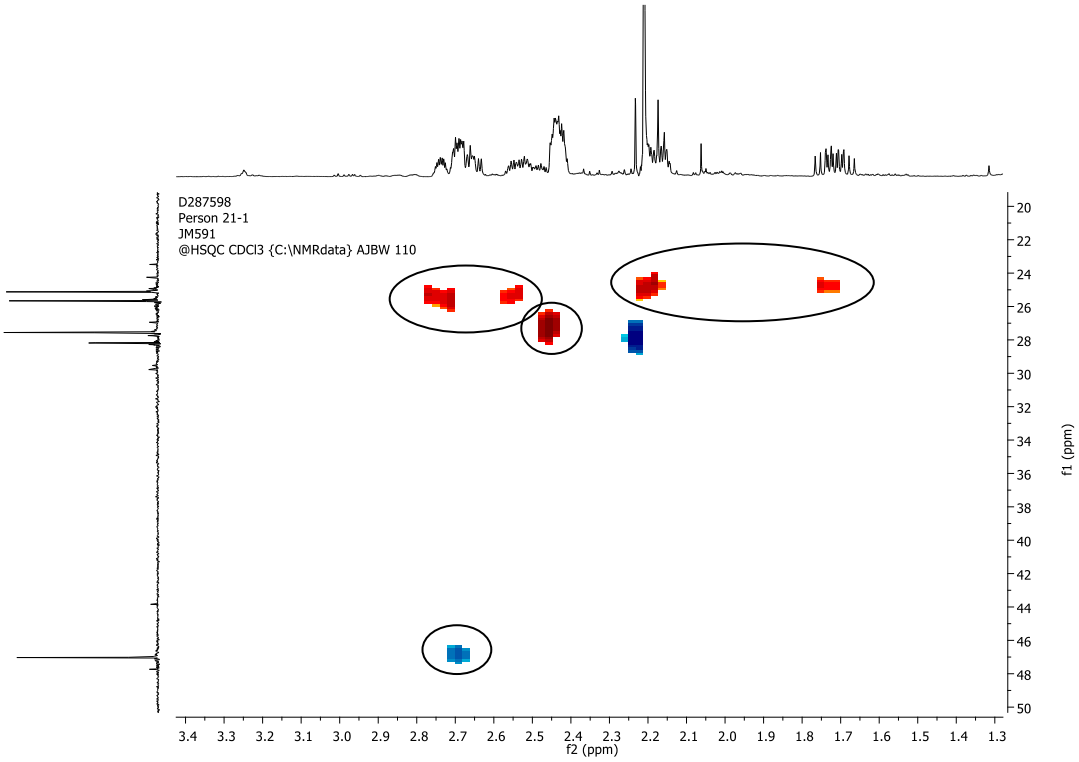
Elucidation of Main Regioisomer

Distribution of regioisomers has been demonstrated previously in the literature for similar Diels-Alder adducts.[154] Confirmation of the structure of the main regioisomer could be obtained by 2D NMR. For this we analysed the main regioisomer of the compound below.

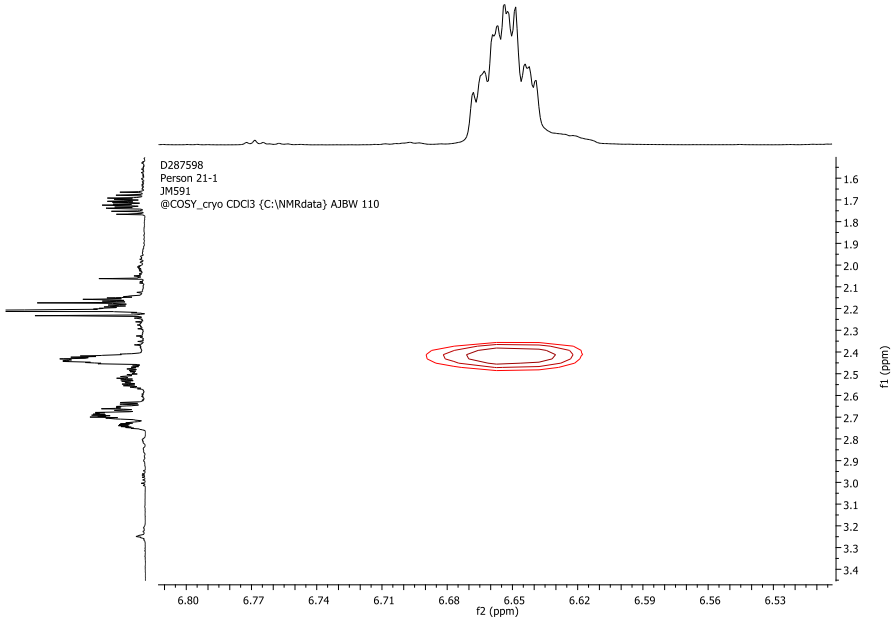


B34

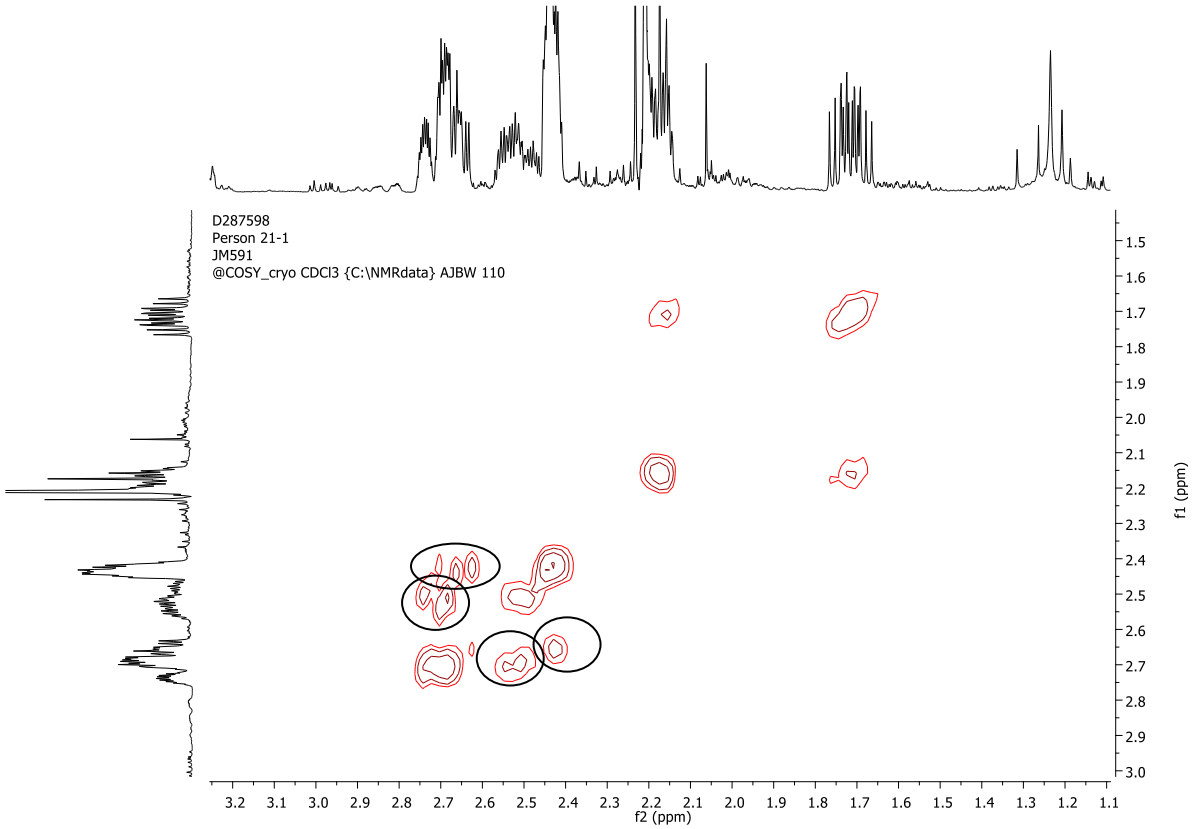
The HSQC of the molecule demonstrates the presence of one CH in the aliphatic region (C3) and three CH_2 groups (C2/C4/C5).



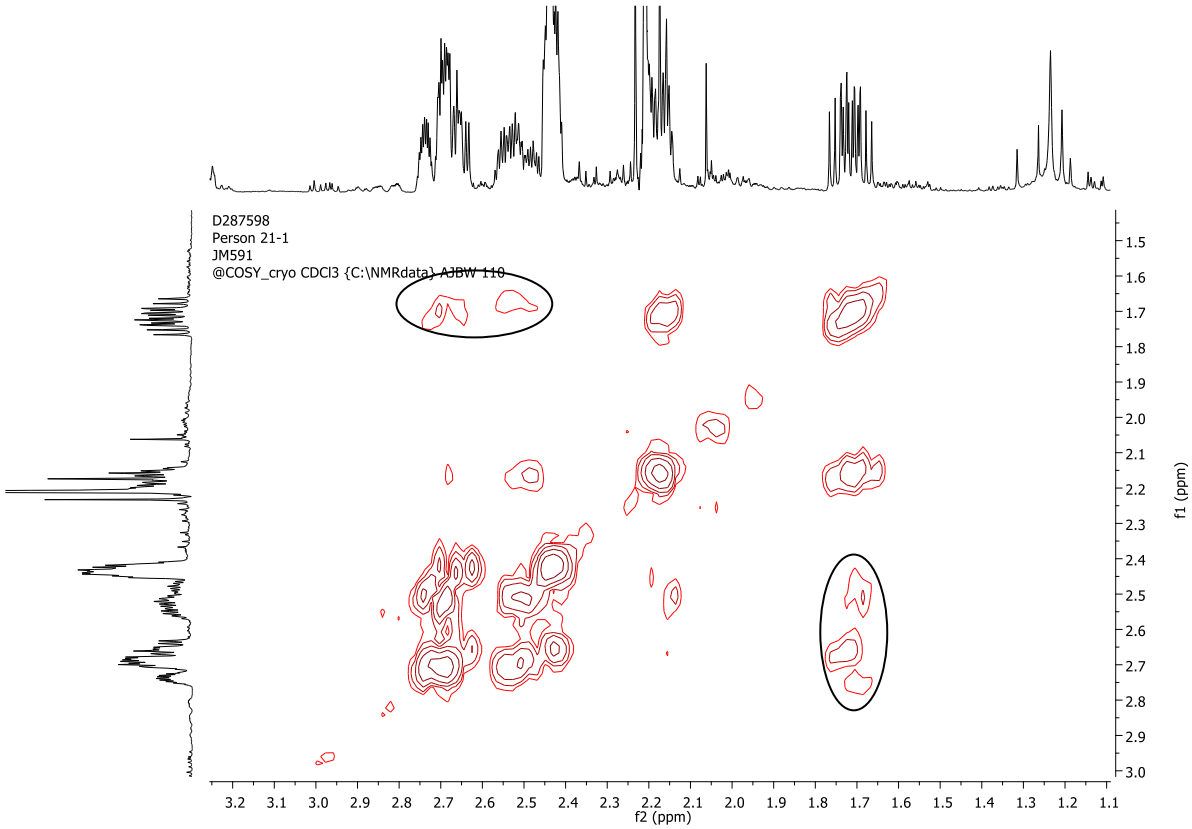
Analysis of the COSY spectrum shows a clear through bond correlation between the alkene CH (C1) and a CH_2 component (C2) showing each atoms are adjacent.



The CH (C3) has a clear through bond correlation with the CH_2 groups (C2, 2.43 ppm; C4, 2.68 ppm).

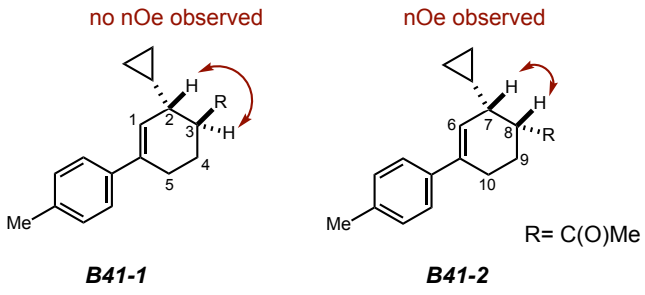


It is also clear that C4 has a correlation with C5. These through bond correlations are also supported by nOe data demonstrating through space correlations. These data, and literature data,[154] support the structure depicted above (**B34**).



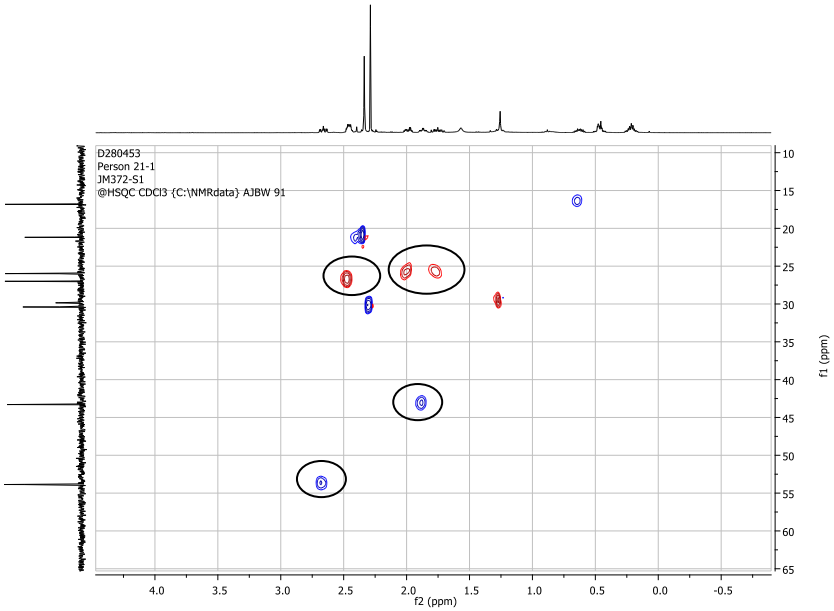
Formation of Diastereomers with Substitution of the BPin Component

Substituting the vinyl BPin component of the SM/DA often led to mixtures of two structures, similar by NMR, which could often be separated by column chromatography. Under aqueous basic conditions epimerization of the enolizable methine was possible leading to diasteromers at the methine position. An example of this is for structure **B41-1** and the corresponding diastereomer **B41-2**.

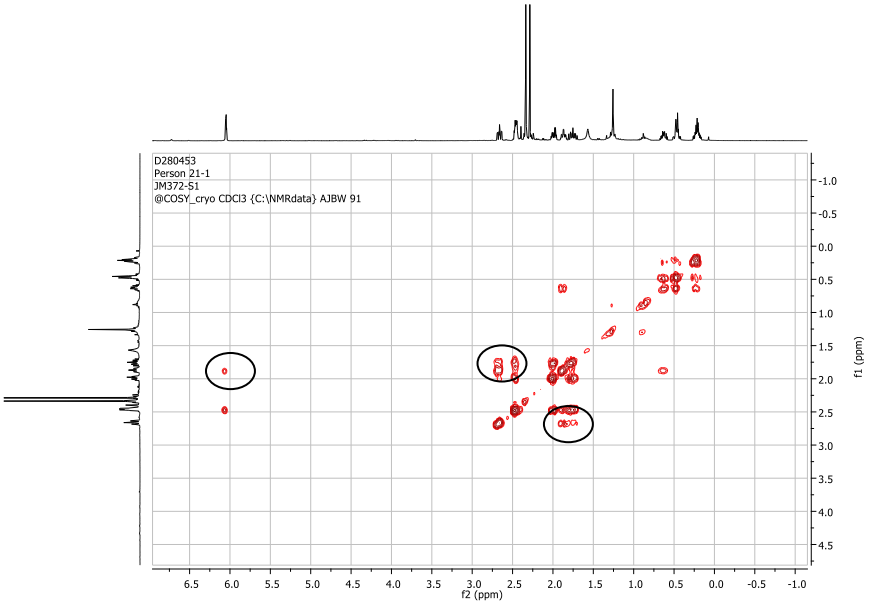


B41-1 ***B41-2***

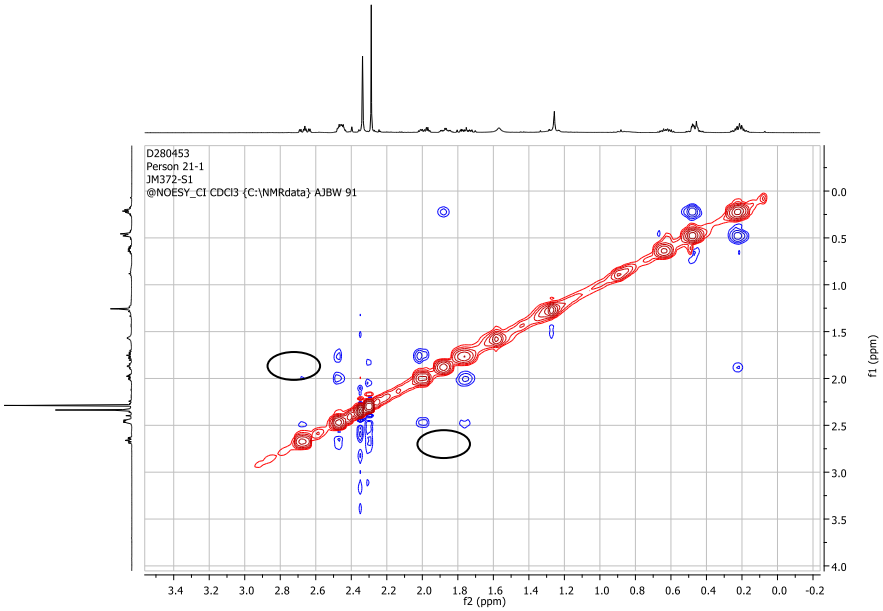
The HSQC of **B41-1** shows the presence of two CH groups (C2 and C3), a diastereotopic CH_2 (C4), and an adjacent CH_2 group in the cyclohexene ring (C5), which supports the correct regioselectivity as shown above.



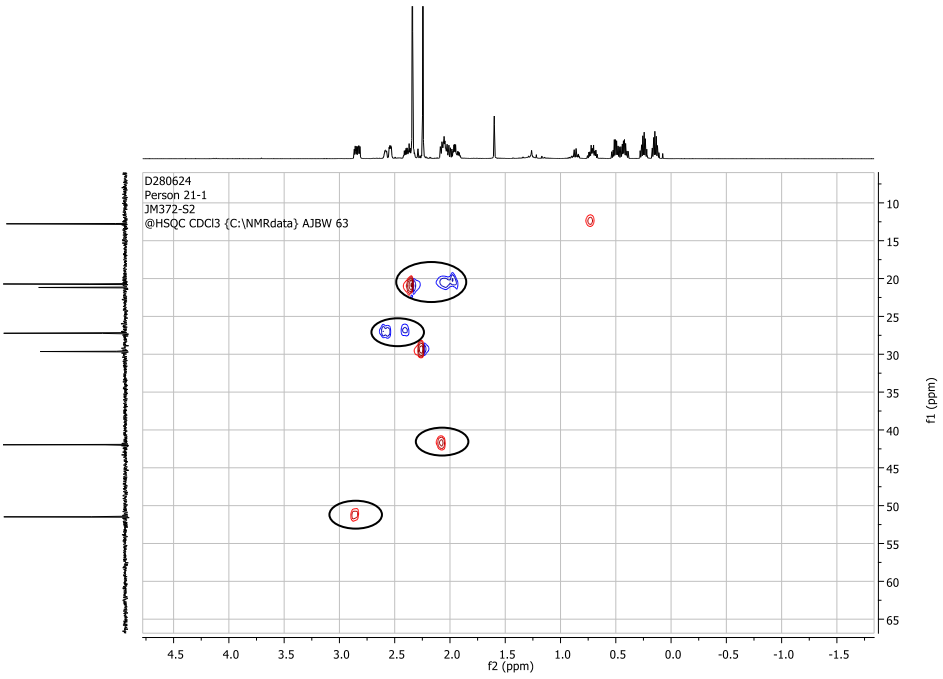
COSY was used to determine the difference between both CH components. A through bond correlation can be seen between the alkene CH and the CH peak at 1.87 ppm. This signal equates to C2. For confirmation, a through bond correlation can be seen between CH (C2) and the CH (C3) at 2.66 ppm.



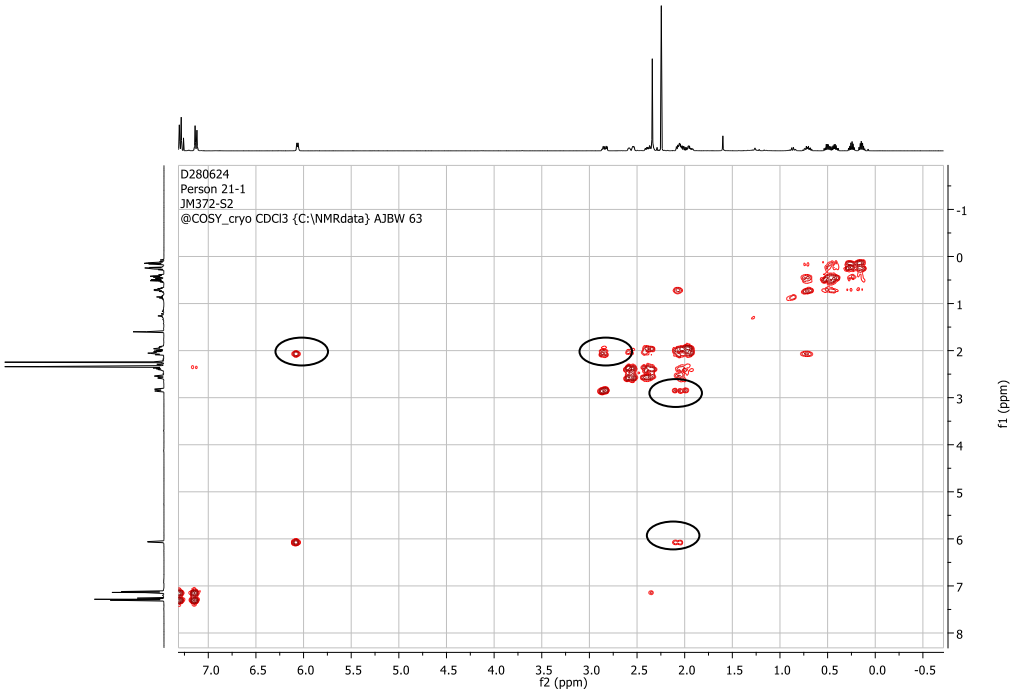
nOe was used to spectra to assign *syn* or *anti* relationship. No nOe was observed and this structure was therefore assigned as the *anti* diastereoisomer.



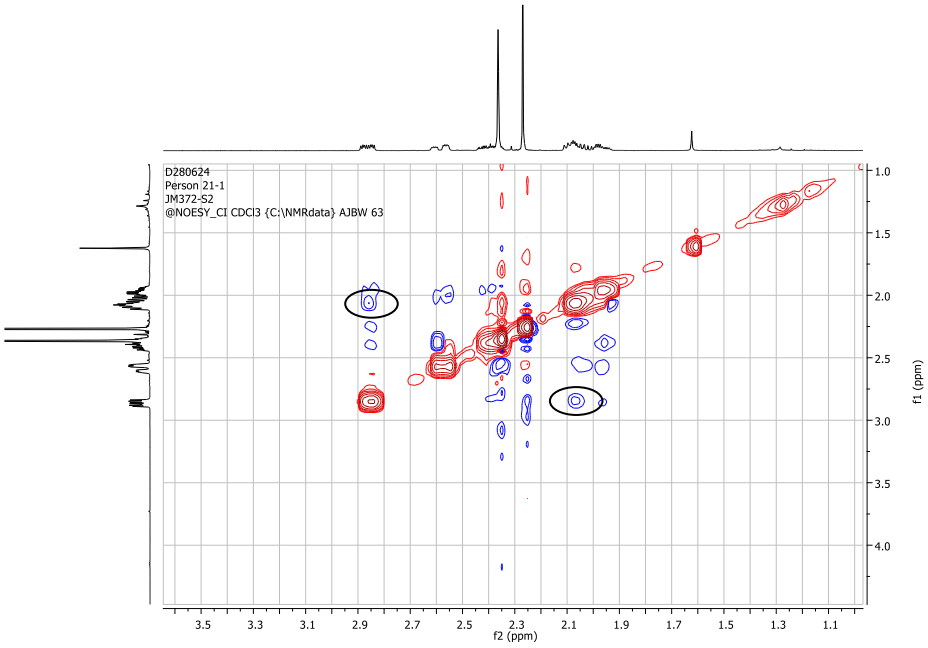
For completeness, **B41-2** was evaluated by 2D NMR. Again, the HSQC for this structure demonstrates the presence of two CH signals (C7 and C8), two CH_2 signals (C9 and C10).



A clear through bond interaction can be seen between the alkene CH and the CH (C7) group present at 2.08 ppm. A through bond correlation can also be seen between C7 and C8 at 2.84 ppm. This supported that **B41-2** had the regiochemistry as indicated.

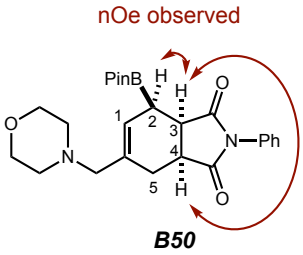


nOe was used to establish if a through space interaction was present and to confirm that the structure was the corresponding diastereoisomer. An interaction between the *syn* protons can be seen by the nOe spectra, supporting the proposed structure as depicted above.

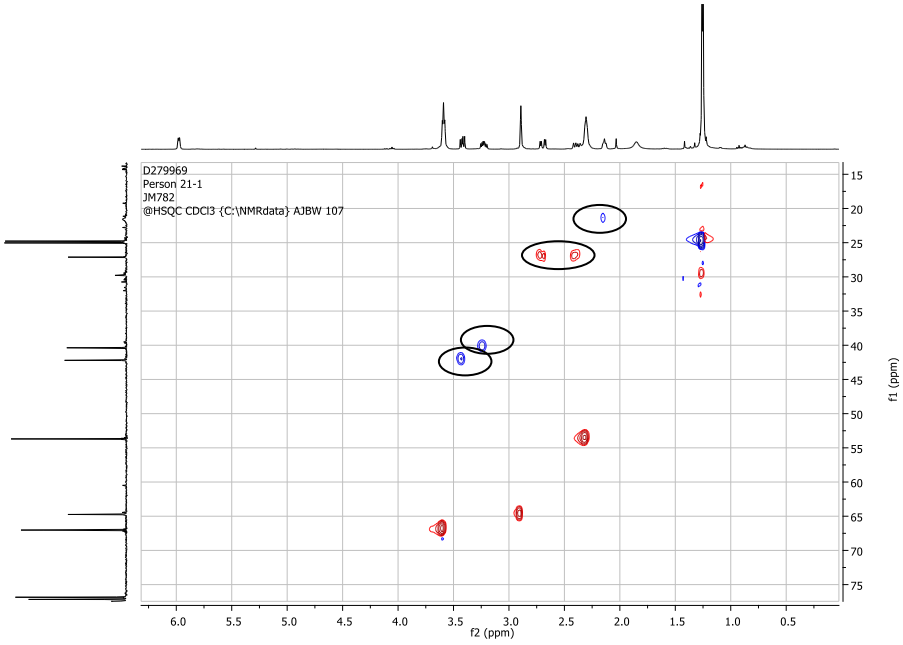


Determining the Diastereoselectivity of Various Dienophiles in the Heck/DA Protocol

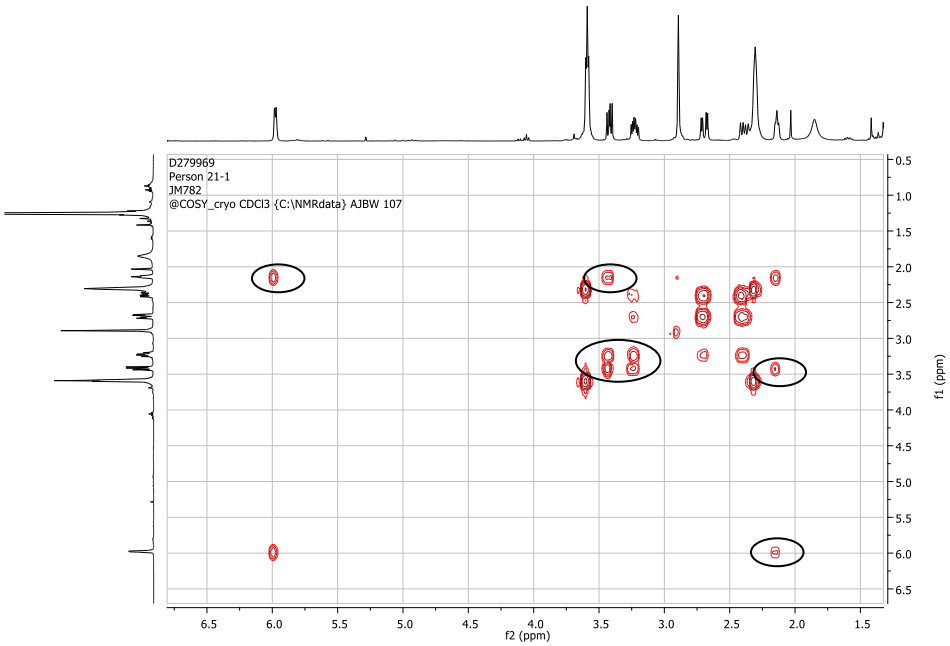
Three different types of dienophile were employed in the Mizoroki-Heck/Diels-Alder process. 2D NMR was used to elucidate the stereochemical outcomes of these transformations.



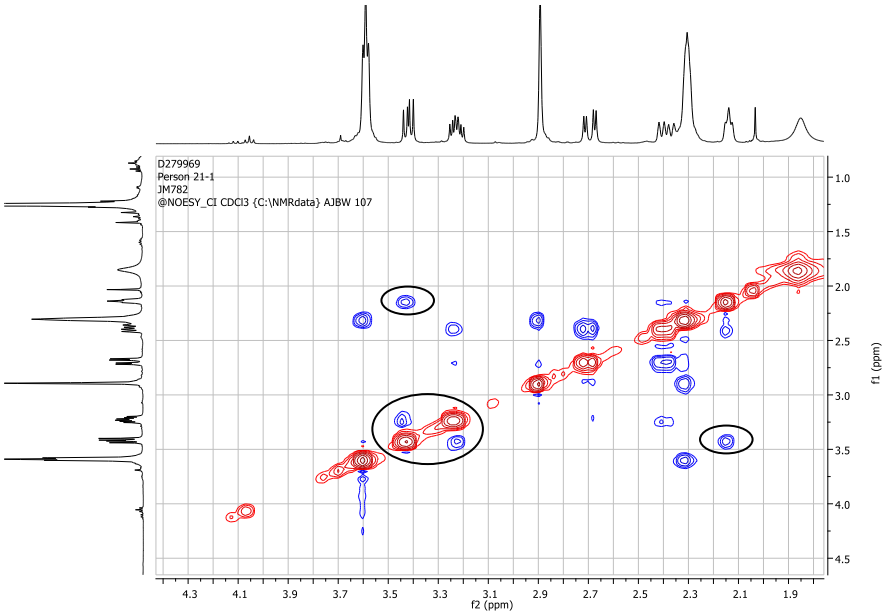
The use of maleimides was shown to generate a single diastereoisomer (*endo*). The HSQC trace shows three aliphatic CH signals (C2, C3, and C4) and a diastereotopic CH_2 (C5) signal of the cyclohexene.



COSY was used to differentiate between CH signals. The CH alkene signal has a clear through bond correlation with a CH signal at 2.14 ppm (C2). C2 also has a correlation with the CH signal at 3.44 ppm (C3). C3 and C4 also have a through bond correlation (C4 is at 3.25 ppm).

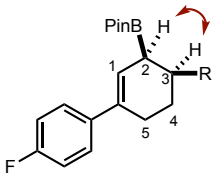


nOe then established that the CH signals have a through space interaction, supporting assignment as the *endo* adduct.



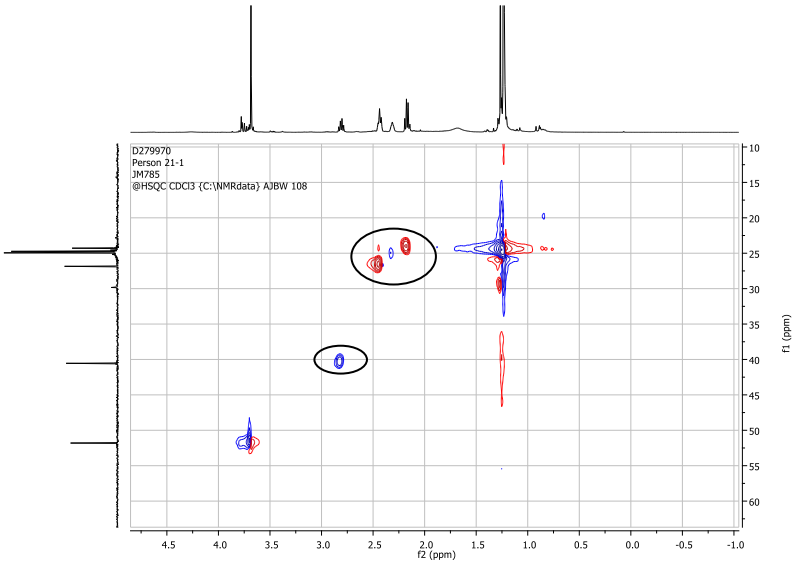
Similarly, the stereochemical outcome was established using mono-substituted dienophiles, such as methyl acrylate.

nOe observed

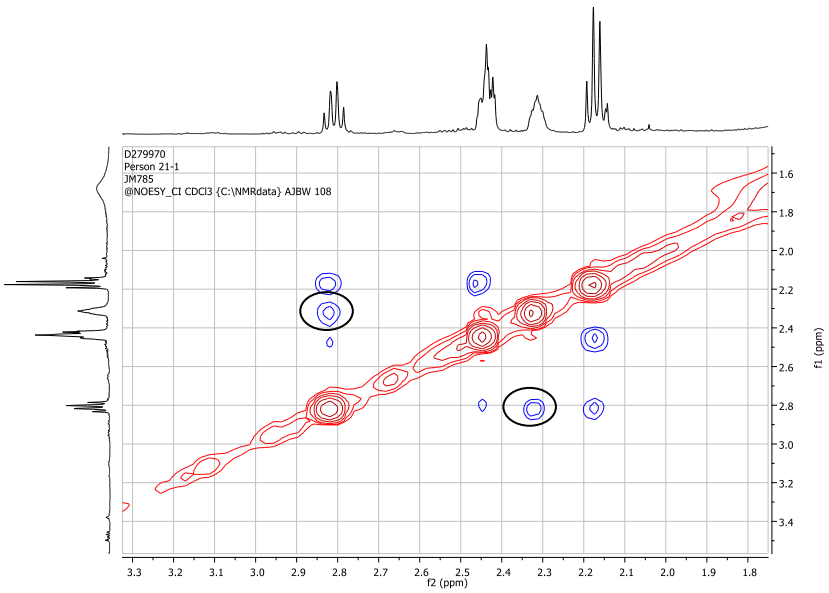


B51

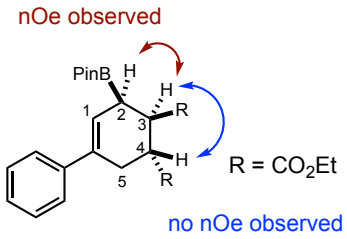
HSQC demonstrates two CH_2 groups (C4 and C5) and two CH groups (C2 and C3).



nOe then established that the CH signals have a through space interaction, supporting assignment as the *endo* adduct.

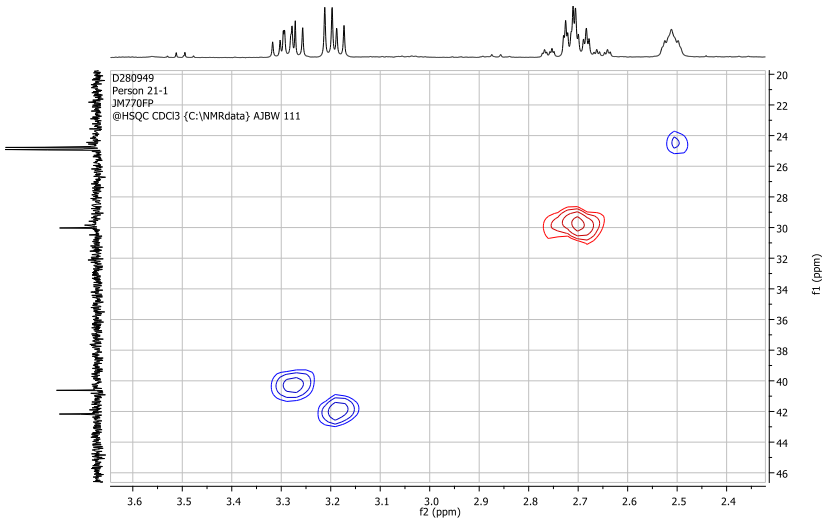


The diethyl maleate products were similarly assessed.

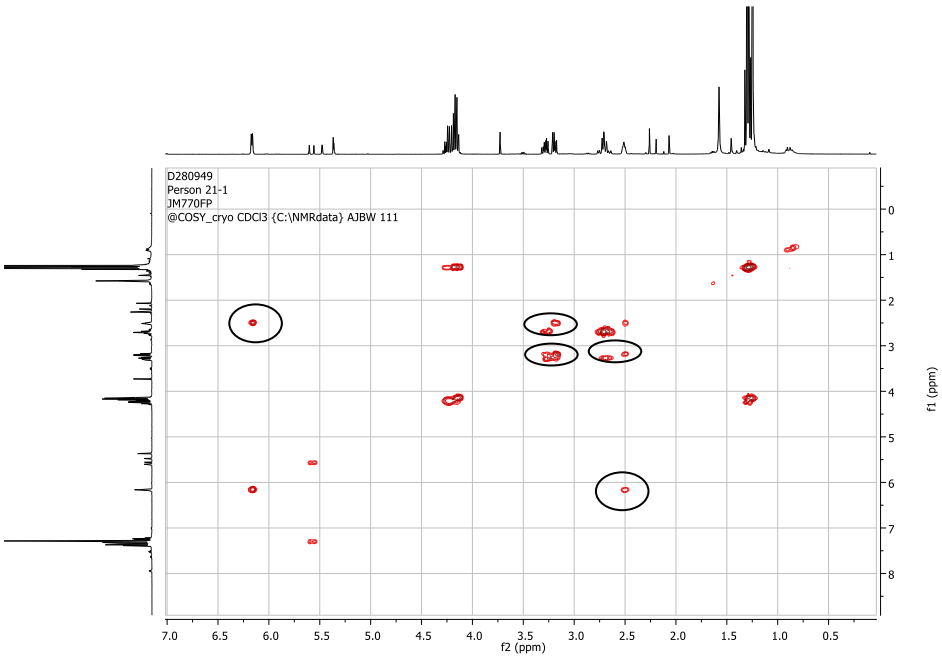


B52

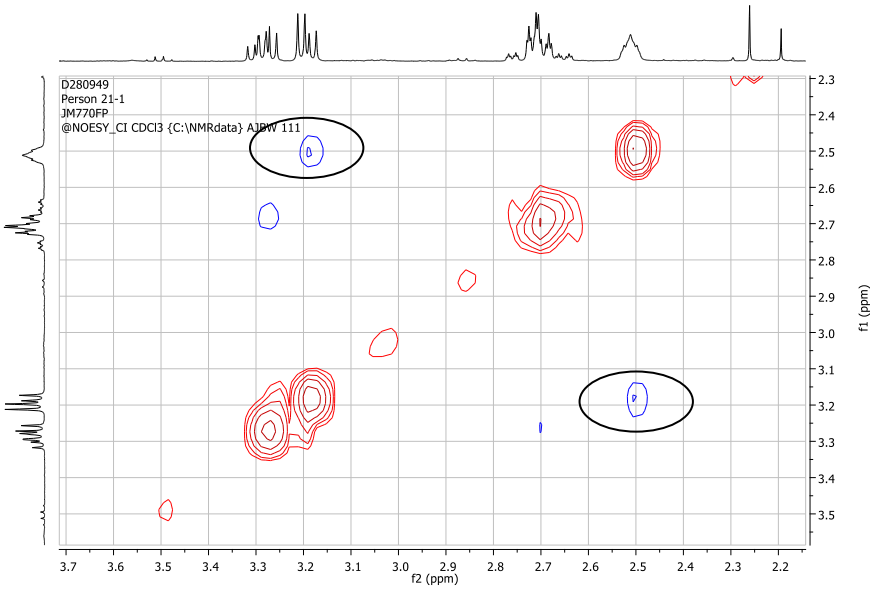
HSQC was used to identify the three CHs (C2, C3, and C4) and one CH_2 functional group of the cyclohexene ring.



COSY was used to distinguish between CH signals. The alkene CH has a clear through bond correlation with CH at 2.51 ppm (C2). C2 has a through bond correlation with the CH signal at 3.19 ppm (C3). The atom adjacent to C3 (C4, 3.28 ppm) also has a clear through bond correlation.

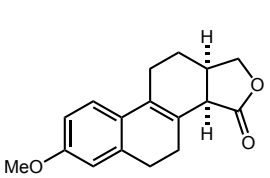


nOe then established that the CH signals do not have a through space interaction, supporting assignment of an *anti* relationship.

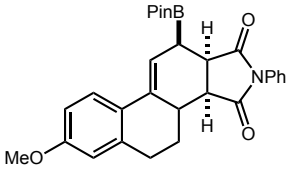


3.5.7 Crystallographic Data

Single-crystal data were measured at with Oxford Diffraction CCD Diffractometers and with graphite monochromated radiation. The structures were solved by direct methods (SIR92, SHELXS) and refined to convergence on F^2 and against all independent reflections by full-matrix least-squares using SHELXL programs.[180,181] All non-hydrogen atoms were refined anisotropically and hydrogen atoms were geometrically placed and allowed to ride on their parent atoms. Table S1 contains selected metrics, crystallographic and refinement data for **B63** and **B31**. CCDC-1579862 (**B63**) and CCDC-1579863 (**B31**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



B63



B31

Table S1. Selected crystallographic and refinement data for **B63** and **B31**.

	B63	**B31**
Formula	$C_{17}H_{18}O_3$	$C_{29}H_{32}BNO_5$
Fw	270.31	485.37
Cryst. System	Monoclinic	Monoclinic
Space Group	$P2_1/n$	$P2_1/c$
Wavelength/Å	1.54184	0.71073
a/Å	12.8554(8)	13.381(4)
b/Å	8.6634(3)	14.344(6)
c/Å	13.3612(8)	13.503(4)
α/°	90	90
β/°	118.093(8)	103.20(2)
γ/°	90	90
Volume/Å^3	1312.74(15)	2523.2(15)
Z	4	4
Temp./K	123(2)	150(2)
Refls. Collect.	5244	9497

$2\theta_{max}$	145.9	50.0
Refls. Ind.	2579	4430
Refls. Obs.	2259	2616
R_{int}	0.0164	0.0729
Goodness of fit	1.034	0.995
$R[F^2>2\sigma]$, F	0.0425	0.0636
R_w (all data), F^2	0.1202	0.1304

4 References

1 D. G. Brown and J. Boström, *J. Med. Chem.*, 2016, **59**, 4443–4458.

2 A. J. J. Lennox and G. C. Lloyd-Jones, *Angew. Chem. Int. Ed.*, 2013, **52**, 7362–7370.

3 N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.*, 1979, **20**, 3437–3440.

4 C. E. Garrett and K. Prasad, *Adv. Synth. Catal.*, 2004, **346**, 889–900.

5 S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451–3479.

6 A. J. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev.*, 2014, **43**, 412–443.

7 N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Sato and A. Suzuki, *J. Am. Chem. Soc.*, 1989, **111**, 314–321.

8 N. Miyaura, K. Yamada, H. Suginome and A. Suzuki, *J. Am. Chem. Soc.*, 1985, **107**, 972–980.

9 E. R. Burkhardt and K. Matos, *Chem. Rev.*, 2006, **106**, 2617–2650.

10 K. Burgess and M. J. Ohlmeyer, *Chem. Rev.*, 1991, **91**, 1179–1191.

11 M. Uemura, H. Nishimura, T. Minami and Y. Hayashi, *J. Am. Chem. Soc.*, 1991, **113**, 5402–5410.

12 C. Ollivier and P. Renaud, *Chem. Rev.*, 2001, **101**, 3415–3434.

13 H. C. Brown and G. A. Molander, *J. Org. Chem.*, 1986, **51**, 4512–4514.

14 N. Miyaura, T. Yanagi and A. Suzuki, *Synth. Commun.*, 1981, **11**, 513–519.

15 D. G. Hall, in *Boronic Acids*, Wiley-VCH Verlag GmbH & Co. KGaA, 2011, pp. 1–133.

16 S. J. Rettig and J. Trotter, *Can. J. Chem.*, 1977, **55**, 3065–3070.

17 A. A. C. Braga, N. H. Morgon, G. Ujaque and F. Maseras, *J. Am. Chem. Soc.*,

2005, **127**, 9298–9307.

18 W. Li, D. P. Nelson, M. S. Jensen, R. S. Hoerrner, D. Cai, R. D. Larsen and P. J. Reider, *J. Org. Chem.*, 2002, **67**, 5394–5397.

19 D. C. Gerbino, S. D. Mandolesi, H.-G. Schmalz and J. C. Podestá, *European J. Org. Chem.*, 2009, **2009**, 3964–3972.

20 T. Ishiyama, M. Murata and N. Miyaura, *J. Org. Chem.*, 1995, **60**, 7508–7510.

21 G. A. Molander, S. L. J. Trice and S. D. Dreher, *J. Am. Chem. Soc.*, 2010, **132**, 17701–17703.

22 T. E. Pennington, C. Kardiman and C. A. Hutton, *Tetrahedron Lett.*, 2004, **45**, 6657–6660.

23 J. M. Murphy, C. C. Tzschucke and J. F. Hartwig, *Org. Lett.*, 2007, **9**, 757–760.

24 G. A. Molander, L. N. Cavalcanti, B. Canturk, P.-S. Pan and L. E. Kennedy, *J. Org. Chem.*, 2009, **74**, 7364–7369.

25 C. Torborg and M. Beller, *Adv. Synth. Catal.*, 2009, **351**, 3027–3043.

26 T. N. Glasnov and C. O. Kappe, *Adv. Synth. Catal.*, 2010, **352**, 3089–3097.

27 A. J. J. Lennox and G. C. Lloyd-Jones, *Isr. J. Chem.*, 2010, **50**, 664–674.

28 H. G. Kuivila and K. V Nahabedian, *J. Am. Chem. Soc.*, 1961, **83**, 2159–2163.

29 H. G. Kuivila, J. F. R. Jr. and J. A. Mangravite, *Can. J. Chem.*, 1963, **41**, 3081–3090.

30 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483.

31 T. Kinzel, Y. Zhang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 14073–14075.

32 J. Lozada, Z. Liu and D. M. Perrin, *J. Org. Chem.*, 2014, **79**, 5365–5368.

33 G. Noonan and A. G. Leach, *Org. Biomol. Chem.*, 2015, **13**, 2555–2560.

34 P. A. Cox, A. G. Leach, A. D. Campbell and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2016, **138**, 9145–9157.

35 P. A. Cox, M. Reid, A. G. Leach, A. D. Campbell, E. J. King and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2017, **139**, 13156–13165.

36 H. G. Kuivila, A. H. Keough and E. J. Soboczenski, *J. Org. Chem.*, 1954, **19**, 780–783.

37 S. Pereira and M. Srebnik, *Organometallics*, 1995, **14**, 3127–3128.

38 J. F. Hartwig, *Acc. Chem. Res.*, 2012, **45**, 864–873.

39 H. C. Brown, N. G. Bhat and M. Srebnik, *Tetrahedron Lett.*, 1988, **29**, 2631–2634.

40 J. Takagi, K. Takahashi, T. Ishiyama and N. Miyaura, *J. Am. Chem. Soc.*, 2002, **124**, 8001–8006.

41 D. Gao and G. A. O'Doherty, *Org. Lett.*, 2010, **12**, 3752–3755.

42 F. Wakenhut, T. D. Tran, C. Pickford, S. Shaw, M. Westby, C. Smith-Burchnell, L. Watson, M. Paradowski, J. Milbank, D. Stonehouse, K. Cheung, R. Wybrow, F. Daverio, S. Crook, K. Statham, D. Leese, D. Stead, F. Adam, D. Hay, L. R. Roberts, J.-Y. Chiva, C. Nichols, D. C. Blakemore, G. H. Goetz, Y. Che, I. Gardner, S. Dayal, A. Pike, R. Webster and D. C. Pryde, *ChemMedChem*, 2014, **9**, 1387–1396.

43 A. Yokoyama, H. Suzuki, Y. Kubota, K. Ohuchi, H. Higashimura and T. Yokozawa, *J. Am. Chem. Soc.*, 2007, **129**, 7236–7237.

44 J. Z. Deng, D. V Paone, A. T. Ginnetti, H. Kurihara, S. D. Dreher, S. A. Weissman, S. R. Stauffer and C. S. Burgey, *Org. Lett.*, 2009, **11**, 345–347.

45 L. Xu and P. Li, *Synlett*, 2014, **25**, 1799–1802.

46 J. J. Molloy and A. J. B. Watson, in *Boron Reagents in Synthesis*, pp. 379–413.

47 T. Mancilla, R. Contreras and B. Wrackmeyer, *J. Organomet. Chem.*, 1986, **307**, 1–6.

48 E. P. Gillis and M. D. Burke, *J. Am. Chem. Soc.*, 2007, **129**, 6716–6717.

49 J. Li, A. S. Grillo and M. D. Burke, *Acc. Chem. Res.*, 2015, **48**, 2297–2307.

50 J. A. Gonzalez, O. M. Ogba, G. F. Morehouse, N. Rosson, K. N. Houk, A. G. Leach, P. H.-Y. Cheong, M. D. Burke and G. C. Lloyd-Jones, *Nat. Chem.*, 2016, **8**, 1067.

51 D. M. Knapp, E. P. Gillis and M. D. Burke, *J. Am. Chem. Soc.*, 2009, **131**, 6961–6963.

52 G. R. Dick, E. M. Woerly and M. D. Burke, *Angew. Chem. Int. Ed.*, 2012, **51**, 2667–2672.

53 E. P. Gillis and M. D. Burke, *J. Am. Chem. Soc.*, 2008, **130**, 14084–14085.

54 B. E. Uno, E. P. Gillis and M. D. Burke, *Tetrahedron*, 2009, **65**, 3130–3138.

55 J. R. Struble, S. J. Lee and M. D. Burke, *Tetrahedron*, 2010, **66**, 4710–4718.

56 R. D. Chambers, H. C. Clark and C. J. Willis, *J. Am. Chem. Soc.*, 1960, **82**, 5298–5301.

57 G. A. Molander, *J. Org. Chem.*, 2015, **80**, 7837–7848.

58 E. Vedejs, R. W. Chapman, S. C. Fields, S. Lin and M. R. Schrimpf, *J. Org. Chem.*, 1995, **60**, 3020–3027.

59 A. J. J. Lennox and G. C. Lloyd-Jones, *Angew. Chem. Int. Ed.*, 2012, **51**, 9385–9388.

60 G. A. Molander and B. Canturk, *Angew. Chem. Int. Ed.*, 2009, **48**, 9240–9261.

61 G. A. Molander and B. Biolatto, *J. Org. Chem.*, 2003, **68**, 4302–4314.

62 M. Butters, J. N. Harvey, J. Jover, A. J. J. Lennox, G. C. Lloyd-Jones and P. M. Murray, *Angew. Chem. Int. Ed.*, 2010, **49**, 5156–5160.

63 G. A. Molander and T. Ito, *Org. Lett.*, 2001, **3**, 393–396.

64 G. A. Molander and R. Figueroa, *Org. Lett.*, 2006, **8**, 75–78.

65 G. A. Molander and R. Figueroa, *J. Org. Chem.*, 2006, **71**, 6135–6140.

66 G. A. Molander and N. M. Ellis, *J. Org. Chem.*, 2006, **71**, 7491–7493.

67 H. Noguchi, K. Hojo and M. Suginome, *J. Am. Chem. Soc.*, 2007, **129**, 758–759.

68 R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461–1473.

69 C. A. Fleckenstein and H. Plenio, *Chem. Soc. Rev.*, 2010, **39**, 694–711.

70 A. F. Littke and G. C. Fu, *Angew. Chem. Int. Ed.*, 1998, **37**, 3387–3388.

71 A. F. Littke, C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 4020–4028.

72 U. Christmann and R. Vilar, *Angew. Chem. Int. Ed.*, 2005, **44**, 366–374.

73 F. Barrios-Landeros, B. P. Carrow and J. F. Hartwig, *J. Am. Chem. Soc.*, 2009, **131**, 8141–8154.

74 D. W. Old, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 9722–9723.

75 D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27–50.

76 T. E. Barder and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 12003–12010.

77 J. P. Wolfe and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 1999, **38**, 2413–2416.

78 J. P. Wolfe, R. A. Singer, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 9550–9561.

79 M. Altemöller, J. Podlech and D. Fenske, *European J. Org. Chem.*, 2006, **2006**, 1678–1684.

80 N. C. Bruno, M. T. Tudge and S. L. Buchwald, *Chem. Sci.*, 2013, **4**, 916–920.

81 C. W. Cheung and S. L. Buchwald, *Org. Lett.*, 2013, **15**, 3998–4001.

82 N. C. Bruno, N. Niljianskul and S. L. Buchwald, *J. Org. Chem.*, 2014, **79**, 4161–4166.

83 E. V Vinogradova, C. Zhang, A. M. Spokoyny, B. L. Pentelute and S. L. Buchwald, *Nature*, 2015, **526**, 687.

84 A. O. Aliprantis and J. W. Canary, *J. Am. Chem. Soc.*, 1994, **116**, 6985–6986.

85 K. Matos and J. A. Soderquist, *J. Org. Chem.*, 1998, **63**, 461–470.

86 B. P. Carrow and J. F. Hartwig, *J. Am. Chem. Soc.*, 2011, **133**, 2116–2119.

87 C. Amatore, A. Jutand and G. Le Duc, *Chem. Eur. J.*, 2011, **17**, 2492–2503.

88 C. Amatore, A. Jutand and G. Le Duc, *Chem. Eur. J.*, 2012, **18**, 6616–6625.

89 C. Amatore, G. Le Duc and A. Jutand, *Chem. Eur. J.*, 2013, **19**, 10082–10093.

90 A. F. Schmidt, A. A. Kurokhtina and E. V Larina, *Russ. J. Gen. Chem.*, 2011, **81**, 1573.

91 A. A. Thomas and S. E. Denmark, *Science*, 2016, **352**, 329–332.

92 A. A. Thomas, H. Wang, A. F. Zahrt and S. E. Denmark, *J. Am. Chem. Soc.*, 2017, **139**, 3805–3821.

93 K. Kawada, A. Arimura, T. Tsuri, M. Fuji, T. Komurasaki, S. Yonezawa, A. Kugimiya, N. Haga, S. Mitsumori, M. Inagaki, T. Nakatani, Y. Tamura, S. Takechi, T. Taishi, J. Kishino and M. Ohtani, *Angew. Chem. Int. Ed.*, 1998, **37**, 973–975.

94 F. Schoenebeck and K. N. Houk, *J. Am. Chem. Soc.*, 2010, **132**, 2496–2497.

95 F. Proutiere and F. Schoenebeck, *Angew. Chem. Int. Ed.*, 2011, **50**, 8192–8195.

96 I. J. S. Fairlamb, *Chem. Soc. Rev.*, 2007, **36**, 1036–1045.

97 S. T. Handy and Y. Zhang, *Chem. Commun.*, 2006, 299–301.

98 J. Almond-Thynne, D. C. Blakemore, D. C. Pryde and A. C. Spivey, *Chem. Sci.*, 2017, **8**, 40–62.

99 T. A. Clohessy, A. Roberts, E. S. Manas, V. K. Patel, N. A. Anderson and A. J. B. Watson, *Org. Lett.*, 2017, **19**, 6368–6371.

100 J. P. G. Rygus and C. M. Crudden, *J. Am. Chem. Soc.*, 2017, **139**, 18124–18137.

101 G. A. Molander and D. L. Sandrock, *J. Am. Chem. Soc.*, 2008, **130**, 15792–15793.

102 J. Li, S. G. Ballmer, E. P. Gillis, S. Fujii, M. J. Schmidt, A. M. E. Palazzolo, J. W. Lehmann, G. F. Morehouse and M. D. Burke, *Science*, 2015, **347**, 1221–1226.

103 S. N. Mlynarski, C. H. Schuster and J. P. Morken, *Nature*, 2013, **505**, 386.

104 K. Endo, T. Ohkubo, M. Hirokami and T. Shibata, *J. Am. Chem. Soc.*, 2010, **132**, 11033–11035.

105 C. Sun, B. Potter and J. P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 6534–6537.

106 J. C. H. Lee, R. McDonald and D. G. Hall, *Nat. Chem.*, 2011, **3**, 894.

107 D. Imao, B. W. Glasspoole, V. S. Laberge and C. M. Crudden, *J. Am. Chem. Soc.*, 2009, **131**, 5024–5025.

108 J. Uenishi, J. M. Beau, R. W. Armstrong and Y. Kishi, *J. Am. Chem. Soc.*, 1987, **109**, 4756–4758.

109 C. M. Crudden, C. Ziebenhaus, J. P. G. Rygus, K. Ghozati, P. J. Unsworth, M. Nambo, S. Voth, M. Hutchinson, V. S. Laberge, Y. Maekawa and D. Imao, *Nat. Commun.*, 2016, **7**, 11065.

110 R. F. Heck and J. P. Nolley, *J. Org. Chem.*, 1972, **37**, 2320–2322.

111 M. Tsutomu, M. Kunio and O. Atsumu, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 581.

112 A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945–2964.

113 D. Mc Cartney and P. J. Guiry, *Chem. Soc. Rev.*, 2011, **40**, 5122–5150.

114 I. P. Beletskaya and A. V Cheprakov, *Chem. Rev.*, 2000, **100**, 3009–3066.

115 W. Cabri, I. Candiani, S. DeBernardinis, F. Francalanci, S. Penco and R. Santo, *J. Org. Chem.*, 1991, **56**, 5796–5800.

116 F. Ozawa, A. Kubo and T. Hayashi, *J. Am. Chem. Soc.*, 1991, **113**, 1417–1419.

117 W. Cabri and I. Candiani, *Acc. Chem. Res.*, 1995, **28**, 2–7.

118 C. Amatore and A. Jutand, *Acc. Chem. Res.*, 2000, **33**, 314–321.

119 B. P. Carrow and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 79–81.

120 T. Jeffery, *Tetrahedron*, 1996, **52**, 10113–10130.

121 T. Takemoto, M. Sodeoka, H. Sasai and M. Shibasaki, *J. Am. Chem. Soc.*, 1993, **115**, 8477–8478.

122 J. Bosch, J. Bachs, A. M. Gómez, R. Griera, M. Écija and M. Amat, *J. Org. Chem.*, 2012, **77**, 6340–6344.

123 A. J. J. Lennox and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2012, **134**, 7431–7441.

124 C. D. Roy and H. C. Brown, *J. Organomet. Chem.*, 2007, **692**, 784–790.

125 J. Yan, G. Springsteen, S. Deeter and B. Wang, *Tetrahedron*, 2004, **60**, 11205–11209.

126 J. W. B. Fyfe, C. P. Seath and A. J. B. Watson, *Angew. Chem. Int. Ed.*, 2014, **53**, 12077–12080.

127 C. P. Seath, J. W. B. Fyfe, J. J. Molloy and A. J. B. Watson, *Angew. Chem. Int. Ed.*, 2015, **54**, 9976–9979.

128 J. W. B. Fyfe, E. Valverde, C. P. Seath, A. R. Kennedy, J. M. Redmond, N. A.

Anderson and A. J. B. Watson, *Chem. Eur. J.*, 2015, **21**, 8951–8964.

129 J. J. Molloy, T. A. Clohessy, C. Irving, N. A. Anderson, G. C. Lloyd-Jones and A. J. B. Watson, *Chem. Sci.*, 2017, **8**, 1551–1559.

130 J. J. Molloy, R. P. Law, J. W. B. Fyfe, C. P. Seath, D. J. Hirst and A. J. B. Watson, *Org. Biomol. Chem.*, 2015, **13**, 3093–3102.

131 C. P. Seath, J. W. B. Fyfe, J. J. Molloy and A. J. B. Watson, *Synthesis*, 2017, **49**, 891–898.

132 H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1961, **83**, 2544–2551.

133 H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, 1960, **82**, 4708–4712.

134 C. Sandford and V. K. Aggarwal, *Chem. Commun.*, 2017, **53**, 5481–5494.

135 A. P. Pulis, P. Fackler and V. K. Aggarwal, *Angew. Chem. Int. Ed.*, 2014, **53**, 4382–4385.

136 H. O. House and B. M. Trost, *J. Org. Chem.*, 1965, **30**, 1341–1348.

137 K. S. Webb and S. J. Ruszkay, *Tetrahedron*, 1998, **54**, 401–410.

138 V. Antonucci, J. Coleman, J. B. Ferry, N. Johnson, M. Mathe, J. P. Scott and J. Xu, *Org. Process Res. Dev.*, 2011, **15**, 939–941.

139 R. E. Hoffman, *Magn. Reson. Chem.*, 2006, **44**, 606–616.

140 M. A. Larsen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 4287–4299.

141 M. A. Larsen, C. V Wilson and J. F. Hartwig, *J. Am. Chem. Soc.*, 2015, **137**, 8633–8643.

142 J. C. Vantourout, R. P. Law, A. Isidro-Llobet, S. J. Atkinson and A. J. B. Watson, *J. Org. Chem.*, 2016, **81**, 3942–3950.

143 J. C. Vantourout, H. N. Miras, A. Isidro-Llobet, S. Sproules and A. J. B. Watson, *J. Am. Chem. Soc.*, 2017, **139**, 4769–4779.

144 Z. Huang and J.-P. Lumb, *Angew. Chem. Int. Ed.*, 2016, **55**, 11543–11547.

145 N. J. Lawrence, D. Rennison, M. Woo, A. T. McGown and J. A. Hadfield, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 51–54.

146 J. W. B. Fyfe, N. J. Fazakerley and A. J. B. Watson, *Angew. Chem. Int. Ed.*, 2017, **56**, 1249–1253.

147 C. P. Frias, *PhD Thesis*.

148 W. L. F. Armarego and C. Chai, *Purification of Labratory Chemicals*, Elsevier, Oxford, 7th Editio., 2013.

149 JChem for Excel 15.12.1400.458, 2008-2015, ChemAxon, (http://www.chemaxon.com)

150 J. J. Molloy, C. P. Seath, M. J. West, C. McLaughlin, N. J. Fazakerley, A. R. Kennedy, D. J. Nelson and A. J. B. Watson, *J. Am. Chem. Soc.*, 2018, **140**, 126–130.

151 A. P. Lightfoot, S. J. R. Twiddle and A. Whiting, *Synlett*, 2005, **2005**, 529–531.

152 V. Farina and M. A. Hossain, *Tetrahedron Lett.*, 1996, **37**, 6997–7000.

153 C. P. Seath, G. A. Burley and A. J. B. Watson, *Angew. Chem. Int. Ed.*, 2017, **56**, 3314–3318.

154 L. Wang and M. E. Welker, *J. Org. Chem.*, 2012, **77**, 8280–8286.

155 E. Goldstein, B. Beno and K. N. Houk, *J. Am. Chem. Soc.*, 1996, **118**, 6036–6043.

156 S. Song, X. Li, X. Sun, Y. Yuan and N. Jiao, *Green Chem.*, 2015, **17**, 3285–3289.

157 A. Gonzalez-de-Castro and J. Xiao, *J. Am. Chem. Soc.*, 2015, **137**, 8206–8218.

158 D. Chang, Y. Gu and Q. Shen, *Chem. Eur. J.*, 2015, **21**, 6074–6078.

159 E. G. Mackay and M. S. Sherburn, *Synthesis*, 2015, **47**, 1–21.

160 H. B. Kagan and O. Riant, *Chem. Rev.*, 1992, **92**, 1007–1019.

161 M. Vaultier, F. Truchet, B. Carboni, R. W. Hoffmann and I. Denne, *Tetrahedron Lett.*, 1987, **28**, 4169–4172.

162 J. C. Tellis, C. B. Kelly, D. N. Primer, M. Jouffroy, N. R. Patel and G. A. Molander, *Acc. Chem. Res.*, 2016, **49**, 1429–1439.

163 B. W. Glasspoole, K. Ghozati, J. W. Moir and C. M. Crudden, *Chem. Commun.*, 2012, **48**, 1230–1232.

164 H. Kuhl, *Climacteric*, 2005, **8**, 3–63.

165 W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng and S. L. Buchwald, *J. Org. Chem.*, 2008, **73**, 7603–7610.

166 P. Fitton and E. A. Rick, *J. Organomet. Chem.*, 1971, **28**, 287–291.

167 W. R. Moser, A. W. Wang and N. K. Kildahl, *J. Am. Chem. Soc.*, 1988, **110**, 2816–2820.

168 L. A. Perego, L. Grimaud and F. Bellina, *Adv. Synth. Catal.*, 2016, **358**, 597–609.

169 V. V Grushin and H. Alper, *Organometallics*, 1993, **12**, 1890–1901.

170 H. G. Lee, P. J. Milner and S. L. Buchwald, *Org. Lett.*, 2013, **15**, 5602–5605.

171 B. P. Fors, D. A. Watson, M. R. Biscoe and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 13552–13554.

172 P. L. Arrechea and S. L. Buchwald, *J. Am. Chem. Soc.*, 2016, **138**, 12486–12493.

173 E. A. Romero, R. Jazzar and G. Bertrand, *J. Organomet. Chem.*, 2017, **829**, 11–13.

174 C. R. Smith and T. V RajanBabu, *Tetrahedron*, 2010, **66**, 1102–1110.

175 C. Feng, H. Wang, L. Xu and P. Li, *Org. Biomol. Chem.*, 2015, **13**, 7136–

7139.

176 C. Tanaka, K. Nakamura and T. Nishikata, *Tetrahedron*, 2017, **73**, 3999–4003.

177 T. Iwasaki, Y. Miyata, R. Akimoto, Y. Fujii, H. Kuniyasu and N. Kambe, *J. Am. Chem. Soc.*, 2014, **136**, 9260–9263.

178 H. E. Ho, N. Asao, Y. Yamamoto and T. Jin, *Org. Lett.*, 2014, **16**, 4670–4673.

179 Q.-Y. Lin, X.-H. Xu and F.-L. Qing, *J. Org. Chem.*, 2014, **79**, 10434–10446.

180 A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Crystallogr.*, 1994, **27**, 435.

181 G. M. Sheldrick, *Acta Crystallogr. Sect. C*, 2015, **71**, 3–8.