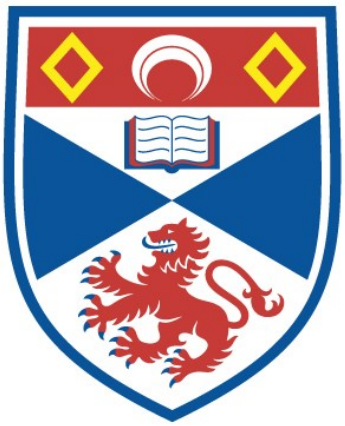
On the discovery and applications of a palladium-catalysed organoboron homologation

Kane Alan Clayton Bastick

A thesis submitted for the degree of PhD
at the
University of St Andrews



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Many people speak of just 'surviving' a PhD. For a lucky few in the right place with the right people, it can be an opportunity to thrive. I have been one of those lucky people.

I owe no greater thanks than to my supervisor, Professor Allan Watson, for giving me the opportunity to pursue my PhD with him at St. Andrews. Your dedication to both chemistry and the group members that you lead will continue to be a source of inspiration as I navigate my career. I'll never reach the upper echelons of being a true 'weegie, but I like to think after over three years this Englishman at least carries carry the grace, decorum, and vernacular of one. I'll never cease to be impressed by your faith in me to extrapolate the results of a 24-hour reaction an hour after we discussed it, or how you managed to get into 'that' outfit courtesy of Jeremy. Keep peddling faster, Winston.

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I would like to thank John Halford-McGuff, my year group partner in crime, for being an absolute titan of knowledge and ideas throughout my PhD. You have made my organic chemistry understanding that little bit better, and my quality of banter that much worse. I don't think I'll be able to hear a word ending in –er and not think of you mate.

I have been fortunate enough to have shared this PhD rollercoaster with an eclectic mix of people who have made my time in the Watson Group unforgettable. Dr Eva Israel and Dr Jeremy Brals, my energetic French musketeers, you reminded me to not take myself too seriously and that the lab is always a place for class style. My lab 337 couple, Tim Hilton and Tom Richardson, thank you for putting up with all the drum and bass I could legally get away with in the lab, while providing me opportune times to laugh at your charming marriage. Marek 'MVIDA' Varga, the most chill dude in all PhDLand, I wish you all the best in your pursuit of borylated alkynes. Maria Mazhuga, thank you for always being ready to listen out for the 'tea', and Misa Cerna, thank you for your keeping us on our toes with your incredible emails. I extend my thanks to older members of the group who I encountered when I first joined, whose names are now cemented into Watson Group folklore: Dr George Bell, Dr Matthew Coles, and Dr David Cain. I also wish our freshest faces, Joanna Urbanczyk and Louis Beaumont, the best of luck riding the Watson wave.

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I owe a special thanks to everyone at the University of St Andrews Olympic Weightlifting Club, particularly Ella Coulter, Abi Driscoll, and Jack Fernando. Lifting heavy circles over my head with you always felt like light work after a day of chemistry – I don't think I would have been able to achieve so much in one facet if it wasn't for the other.

Finally, I thank my family for their constant encouragement as I have navigated this strange but enriching world that is academia. You haven't always followed my rambles about boron and stuff, but your wholehearted support has always been cherished.

I dedicate this thesis to my mum, Wendy Patricia Bastick. For being my counsel, speaking your mind, and being a tenacious fighter. This document won't fix the notorious 'wobbly leg' of yours, but perhaps it might help someone else do it in the future.

Abstract

Organoboron compounds have become a cornerstone of contemporary synthetic chemistry. Classical methods towards their preparation typically require the use of stoichiometric quantities of organometallic reagents; namely, by metalation-borylation or Matteson homologations. The latter transformation exploits a facile 1,2-metalate rearrangement of a boronate complex, where a leaving group is appended to the α-boryl carbon atom. As a conceptually distinct approach to the Matteson homologation, this thesis will discuss how a carbanion surrogate can be applied under palladium catalysis to homologate arylboronic acids. Rather than relying upon a 1,2-metalate rearrangement used in classical boron homologation, this reaction involves a rare oxidative addition of an α-halogenated boronic ester to palladium.

Following a review of the literature surrounding boron homologation and related reactions of α-halogenated boronic esters, the first results section shall describe the development of the palladium-catalysed homologation of boronic acids. This reaction is remarkably chemoselective at the transmetalation step, with one organoboron reagent being selected out of a possible four, including a byproduct formed due to boron speciation. The generality of the process is discussed, including the disclosure of current limitations in the methodology.

The second results section will consider the mechanism of the developed palladium-catalysed homologation in relation to the Suzuki–Miyaura cross-coupling. In an analogous manner to Matteson's original empirical observations made during nucleophilic substitution reactions, α-halogenated organoboron reagents exhibit a remarkable level of electrophilicity: the oxidative addition of an α-boryl C(sp^3)–Br bond is more facile than the C(sp^2)–Br bond of bromobenzene. This 'α-boryl electrophile effect' is explored further in a series of empirical control studies.

The third results section will demonstrate the synthetic potential of the developed homologation process by using the benzyl boronic esters as a general synthetic platform for the formation of benzylic C–X bonds, including several active pharmaceutical ingredients, with limitations of each operation disclosed.

PhD Publications List

* Denotes publications that contain the work presented as part of this thesis.

1. *Copper (II) Fluoride, CuF_2: First update*; Bastick, K. A. C.; Watson, A. J. B. *EROS*, Wiley-VCH, **2021**.
2. *Bastick, K. A. C.; Watson, A. J. B. Pd-catalyzed organometallic-free homologation of arylboronic acids enabled by chemoselective transmetalation. *ACS Catal*. **2023**, *13*, 7013.
3. *Bastick, K. A. C.; Watson, A. J. B. Pd-catalyzed homologation of arylboronic acids as a platform for the diversity-orientated synthesis of benzylic C–X Bonds. *Synlett* **2023,** *34*, 2097–2104.
4. Bastick, K. A. C.; Watson, A. J. B. Multiborylated alkanes in synthetic methodology: implicit or exquisite value? *Submitted*.

Abbreviations

Abbreviation	Word
4CzIPN	1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
Å	Ångström
Ac	acetyl
addn.	addition
AIBN	azobisisobutyronitrile
am	amyleneglycolato
app.	apparent
aq.	aqueous
Ar	aryl or argon
bipy	2,2'-bipyridine
Bn	benzyl
Boc	*tert*-butoxycarbamoyl
Bu	butyl
cat	catecholato
cataCXium A	di(adamantylalkyl)phosphine
CBS	Corey–Bakshi–Shibata
COD	1,5-cyclooctadiene
CPME	cyclopentylmethyl ether
Cy	cyclohexyl
dba	dibenzylideneacetone
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DMA	*N*,*N*-dimethylacetamide
DMF	dimethylformamide
DMPU	*N,N'*-dimethylpropyleneurea
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
eg	ethyleneglycolato
equiv	equivalent
es	enantiospecificity
Et	ethyl
h	hour
HEH	diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate
Het	heterocycle
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single coherence spectroscopy

Abbreviations (continued)

Abbreviation	Word
Inv	inversion
IR	infrared
L	undefined ligand
LDA	lithium diisopropylamide
LED	light emitting diode
M	molar
MandyPhos	(S_P,S'_P)-1,1'-bis[bis(4-methoxy-3,5-dimethylphenyl)phosphino]-2,2'-bis[(*R*)-α-(dimethylamino)benzyl]ferrocene
Me	methyl
Mes	mesityl
MIDA	*N*-methyliminodiacetic acid
min	minute
MOM	methoxymethyl
MS	molecular sieves
Ms	methanesulfonic
Ms	methanesulfonyl
MTBE	methyl *tert*-butyl ether
n.d.	not determined
NBS	*N*-bromosuccinimide
neo	neopentylglycolato
nm	nanometre
NMR	nuclear magnetic resonance
OCb	*N,N*-diisopropylcarbamate
OTIB	2,4,6-triisopropylbenzoate
ovn.	overnight
PEPPSI	pyridine-enhanced precatalyst preparation stabilisation and initiation
pg	propylyeneglycolato
Ph	phenyl
pin	pinacolato
Pr	propyl
R	variable group
Ret	retentive
rt	room temperature
SET	single electron transfer
sp.	sparteine
SPhos	2-(2',6'-dimethoxybiphenyl)-dicyclohexylphosphine
TBAF	tetra-*N*-butylammonium fluoride
tcep	tris(cyanoethyl)phosphine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIB	1,3,5-triisopropylbenzoate
TLC	thin layer chromatography

Abbreviations (continued)

Abbreviation	Word
TMS	trimethylsilyl
Tol	tolyl
t_R	residence time
Troc	2,2,2-trichloroethoxycarbonyl
UV	ultraviolet
W	Watt
XantPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

Table of contents

1. Introduction

1.1 Organoboron chemistry

Boron is the fifth element in the periodic table and was first isolated from the mineral borax.[1] The inception of organoboron chemistry, the study of the formation and manipulation of C–B bonds, can be traced as far back as 1860 when Frankland and coworkers prepared and oxidised "boric ethide",[2] or ethyl boronic acid using modern nomenclature (Figure 1.1).[3] The preparation of reagents such as borane and metal borohydrides in the early 1900s allowed new syntheses of organoboron compounds to emerge,[4] but it was Brown's hydroboration of olefins,[5] and Suzuki and Miyaura's palladium-catalysed cross-coupling of catechol boronic esters,[6] which are typically attributed to the popularisation of organoboron chemistry. Between these two transformations, sharing one-half and one-third of the 1979 and 2010 Nobel Prizes in chemistry, respectively,[4,7] Matteson pioneered the homologation and α-displacement of boronic esters.[8] This latter transformation is the topic of this thesis.

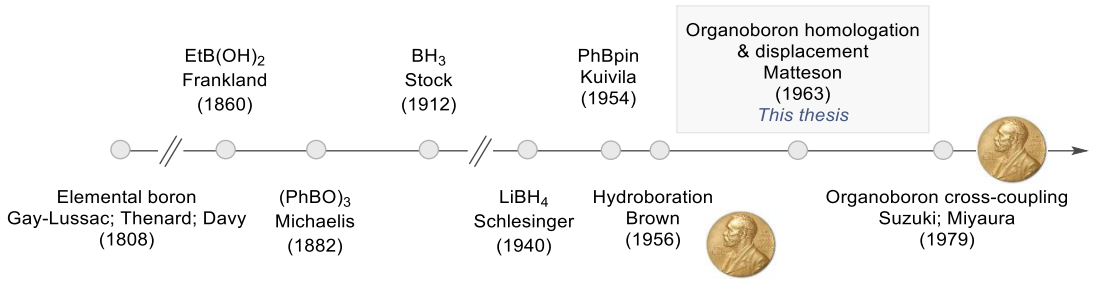


Figure 1.1: Early history of organoboron chemistry.

Boron only exists in natural products as complexes of tetrahydroxyborate, making organoboron chemistry an entirely human invention.[9] As such, the evolution of organoboron compounds has been entirely directed by synthetic methodology. The focus of this thesis will cover organoboron compounds as reagents; however, modern synthesis has also incorporated boron into additives,[10,11] catalysts,[10,11] materials,[12] and active pharmaceutical ingredients (Figure 1.2).[13,14]

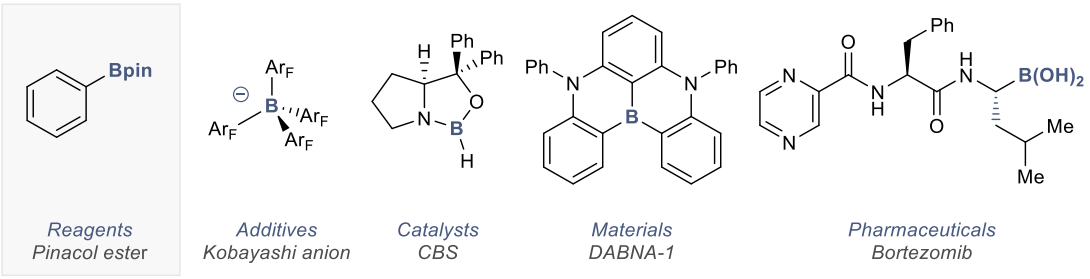


Figure 1.2: Examples of organoboron classes. Ar_F = 3,5-bis(trifluoromethyl)phenyl; DABNA-1 = 5,9-diphenyl-5,9-diaza-13b-boranaphtho[3,2,1-*de*]anthracene.

Organoboron compounds can be electrophilic or nucleophilic depending on their hybridisation (Figure 1.3). When sp^2-hybridised, the vacant *p*-orbital orthogonal to the substituent plane renders them electrophilic. When the *p*-orbital becomes occupied, the resulting tetrahedral boronate (often abbreviated as 'ate) is considered nucleophilic and can lead to displacement reactions *via* the directed expulsion of the nucleophile. This concept is exemplified in the Matteson reaction,[8] which shall be discussed further below.

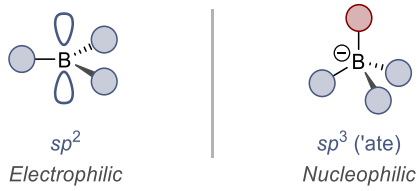


Figure 1.3: Organoboron hybridisation.

Throughout this thesis, a variety of organoboron protecting groups are discussed. Abbreviations based on common nomenclature are routinely used and their structures are provided below (Figure 1.4).[3] In general, complete structures will only be drawn out when these ligands need to be emphasised for a given transformation.

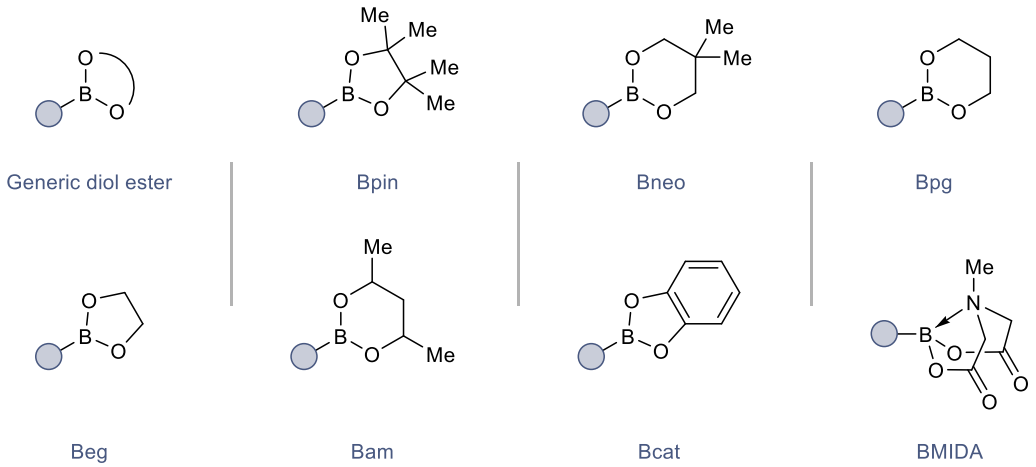
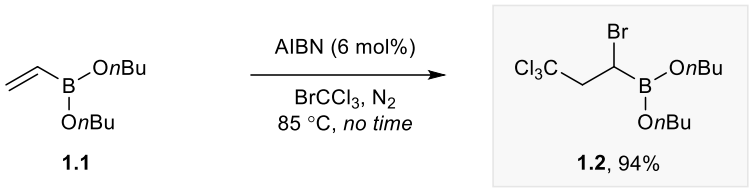


Figure 1.4: Structures of common organoboron protecting groups used throughout this thesis.

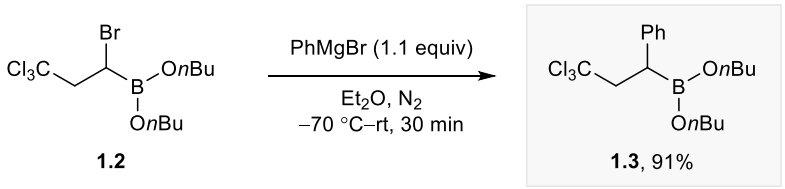
1.2 The Matteson reaction

In 1960, Matteson prepared an α-haloalkaneboronic ester **1.2** using a radical addition of bromo(trichloro)methane to vinyl boronic acid dibutyl ester (Scheme 1.1).[8]



Scheme 1.1: Seminal preparation of an α-bromoalkane boronic ester.

Three years later, Matteson and Mah would report a series of nucleophilic displacement reactions using these α-haloalkaneboronic esters, derived from an initial reaction using phenylmagnesium bromide as the nucleophile (Scheme 1.2).[15]

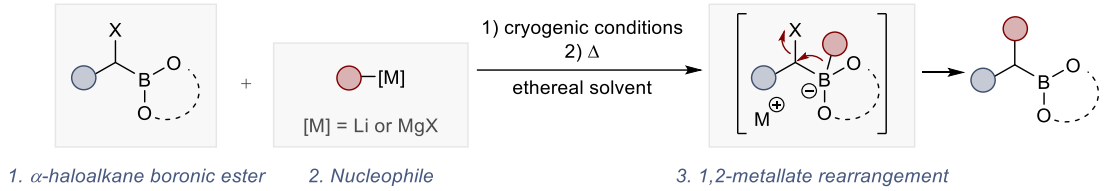


Scheme 1.2: Seminal nucleophilic substitution of an α-bromoalkane boronic ester.

The first Section of this literature review shall cover the generalities of the Matteson reaction, including the Aggarwal-type chiral anion approach.[8,16] Modern examples from the last decade have then been selected that show mechanistic variations, conceptually new approaches, or provide bespoke products from 1,2-metalate rearrangements, and are shown by the appropriate subcategory in chronological order.

1.2.1 Overview and generalities

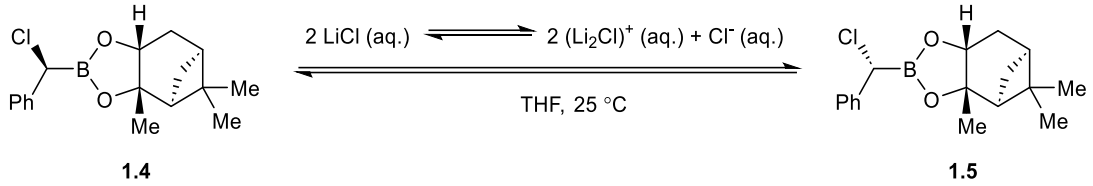
The named Matteson reaction can be described loosely as any nucleophilic substitution where the leaving group is located on the α-carbon of an organoboron compound.[17] The reaction can be broken down into three main components: (1) the α-haloalkane boronic ester;[18] (2) the nucleophile;[17–19] and (3) the 1,2-metalate rearrangement.[8,17,18,20] Each of these reaction elements are detailed in the following Sections (Scheme 1.3).



Scheme 1.3: Overview of the Matteson reaction. X = Br or Cl.

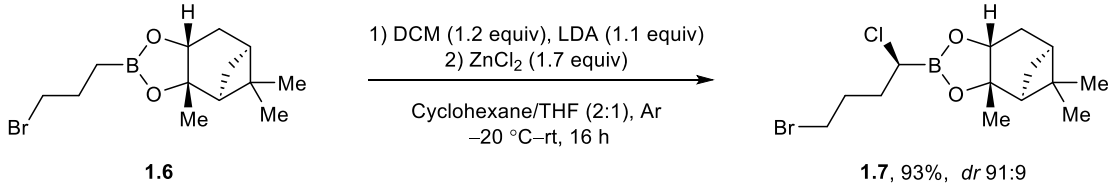
1.2.1.1 The α-haloalkane boronic ester

α-Haloalkane boronic esters are routinely prepared by Matteson's homologation of a boronic ester with (halomethyl)lithium reagents. This reaction typically proceeds with excellent stereospecificity and products are typically trivial to purify by vacuum distillation. Aqueous workup was by Matteson and coworkers to reduce the rate of epimerisation at the stereogenic centre *via* halide ion exchange (*i.e.*, **1.4** to **1.5**, Scheme 1.4).



Scheme 1.4: Epimerization of crude α-chloroboronic esters under aqueous conditions.

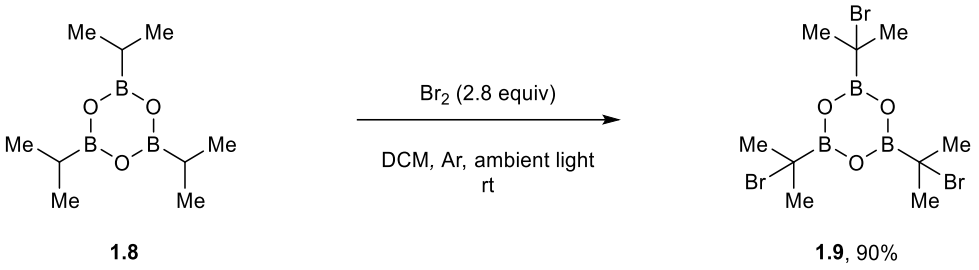
Matteson's above method to prepare α-haloalkaneboronic esters was robust towards functional groups at least two carbons away from the C–B bond; including acetals,[21] azides,[21] esters,[21] and nitriles.[22] Halogens, *i.e.*, **1.6**, were also tolerated when the (halomethyl)lithium was prepared using lithium diisopropylamide, which avoided any unwanted *in situ* lithium-halogen exchange from unreacted organolithiums, with no competitive rearrangements observed (Scheme 1.5).[23,24]



Scheme 1.5: Preparation of α-haloalkane boronic esters.

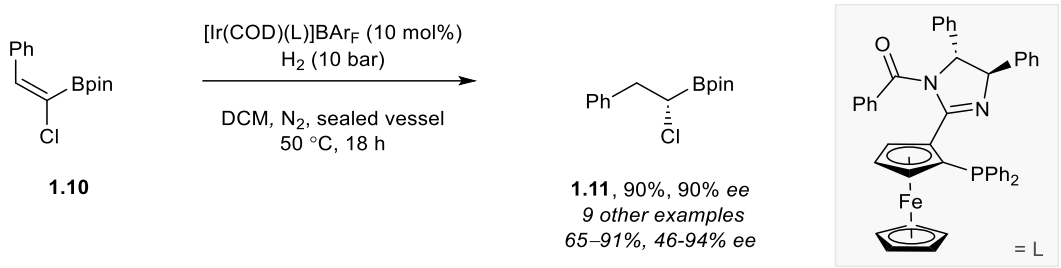
Some α-bromoalkaneboronic esters may be prepared by radical bromination.[22] While this reaction is facile under ambient (fumehood) lighting, it is limited to secondary alkylboronic esters (*i.e.*, **1.8** Scheme 1.6). The reaction was particularly fast using boroxines, although the exact time was not given by the authors.[22] The same method was operative when boronic esters were used, [25] and a Finkelstein reaction using sodium iodide can be used to provide

the corresponding α-iodoalkaneboronic ester.[26] Radical additions of C–Br bonds across vinyl organoboron compounds is generally challenging, with Matteson's original report being a notable exception (*i.e.*, Scheme 1.1).[15]



Scheme 1.6: Radical method for the preparation of tertiary α-bromoalkaneboronic esters.

α-Chloroalkaneboronic esters can be prepared in a high enantiomeric excess using iridium-catalysed asymmetric hydrogenations, rather than relying on chiral substrate approaches *(i.e.*, **1.10** Scheme 1.7).[27,28] Notably this method also accesses the desired reagents in high enantiomeric excess without the requirement for stoichiometric quantities of organometallic reagents, or cryogenic conditions, with the caveat of requiring 10 bar pressure of hydrogen. The methodology was later applied to 1-bromo-1-alkenylboronic esters by the same group.[29]



Scheme 1.7: Catalytic enantioselective hydrogenation of chlorovinylboronic esters.

Ar_F = tetrakis[(3,5-bis(trifluoromethyl)phenyl].

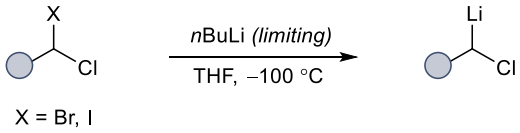
Other methods for the preparation of α-haloalkaneboronic esters, such as the use of highly toxic (halomethyl)mercuric halides,[30] have been made obsolete by Matteson's addition of (halomethyl)lithiums and Casar's catalytic asymmetric hydrogenations.[31]

1.2.1.2 The organometallic nucleophile

Organometallic nucleophiles contain carbon–metal bonds. In the context of the Matteson reaction, these nucleophiles are typically organolithiums or organomagnesium halides.[17–19] The latter (Grignard) reagents are prepared by refluxing the requisite halide with magnesium and their preparation will not be discussed further.[3,32] This Section will detail the preparation

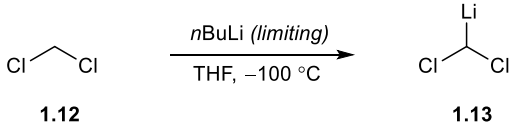
of Matteson-type organolithium reagents required for subsequent 1,2-metalate rearrangements. The preparation of chiral lithiated carbanions from carbamates and benzoate esters is distinct from the original Matteson reaction in terms of both scope and the origins of stereoselectivity, so is presented in its own Section later.

The two most common nucleophiles used in Matteson reactions are (chloromethyl)lithiums, used for homologations, and (dichloromethyl)lithium, used for the preparation of α-chloroboronic esters.[31] (Chloromethyl)lithiums can be prepared by lithium-halogen exchange of the C–Br bond in 1-bromo,1-chloromethanes under cryogenic conditions in an inert atmosphere using *n*-butyllithium.[33,34] (Chloromethyl)lithium can also be prepared from chloroiodomethane, although this starting material is typically more expensive (Scheme 1.8).[35] Butyllithium is used in limiting stoichiometries to prevent unwanted additions into the boronic ester.[31] The equivalent (bromomethyl)lithium can be prepared in an analogous manner using dibromomethane.[36]



Scheme 1.8: General preparation of (chloromethyl)lithiums.

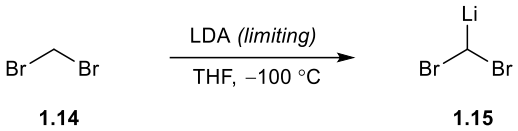
(Dichloromethyl)lithium **1.13** can be prepared using the solvent dichloromethane in reagent quantities with *n*-butyllithium (Scheme 1.9). The preparation of some substituted (dichloromethyl)lithiums, such as (1,1-dichloroethyl)lithium, is known; however, the yields and diastereoselectivity acquired so far have been insufficient to become adopted into general Matteson reactions.[37]



Scheme 1.9: General preparation of (dichloromethyl)lithium.

The stability of (dichloromethyl)lithium is a point of contention in the literature.[21,38–41] The original report states that the reagent is stable in tetrahydrofuran at −65 °C,[38] but modern methods typically use temperatures set with an ethanol-liquid nitrogen slush bath (~−110 °C) to avoid decomposition.[39–42] To make the preparation of (dichloromethyl)lithium scalable for industrial applications, lithium diisopropylamide was used at ~−20 °C; however, this lowered the diastereomeric ratio of the obtained product to 9:1.[24] When preparations of

(dichloromethyl)lithium are conducted at (~−110 °C), chiral halomethyl boronic ester products can be afforded in diastereomeric ratios greater than 99:1.[31] (Dibromomethyl)lithium **1.15** must be made from dibromomethane using lithium diisopropylamide to avoid lithium-halogen exchange (Scheme 1.10), which would form (bromomethyl)lithium.



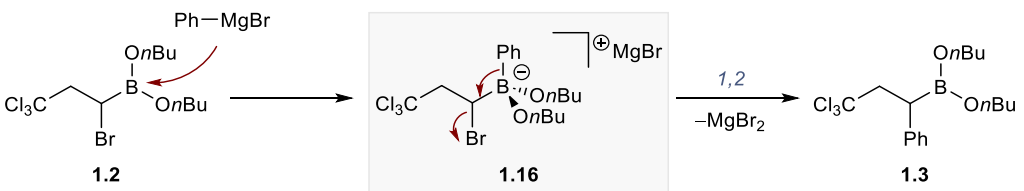
1.14 **1.15**

Scheme 1.10: General preparation of (dibromomethyl)lithium.

It is worth noting at this stage that the exact chemical procedures to prepare each class of the described organolithiums for Matteson reactions can be particularly capricious. It is commonplace for notes describing exact internal temperatures and allowed fluctuations, the precise rate of butyllithium addition, and even the position of the syringe needle with reference to the reaction flask, to be included in experimental Sections.[17,18,31] When adequately controlled, these reagents are powerful tools in the fields of organoboron homologation and asymmetric synthesis. The following Section shall describe the mechanism behind this precise stereocontrol — the 1,2-metalate rearrangement.

1.2.1.3 The 1,2-metalate rearrangement

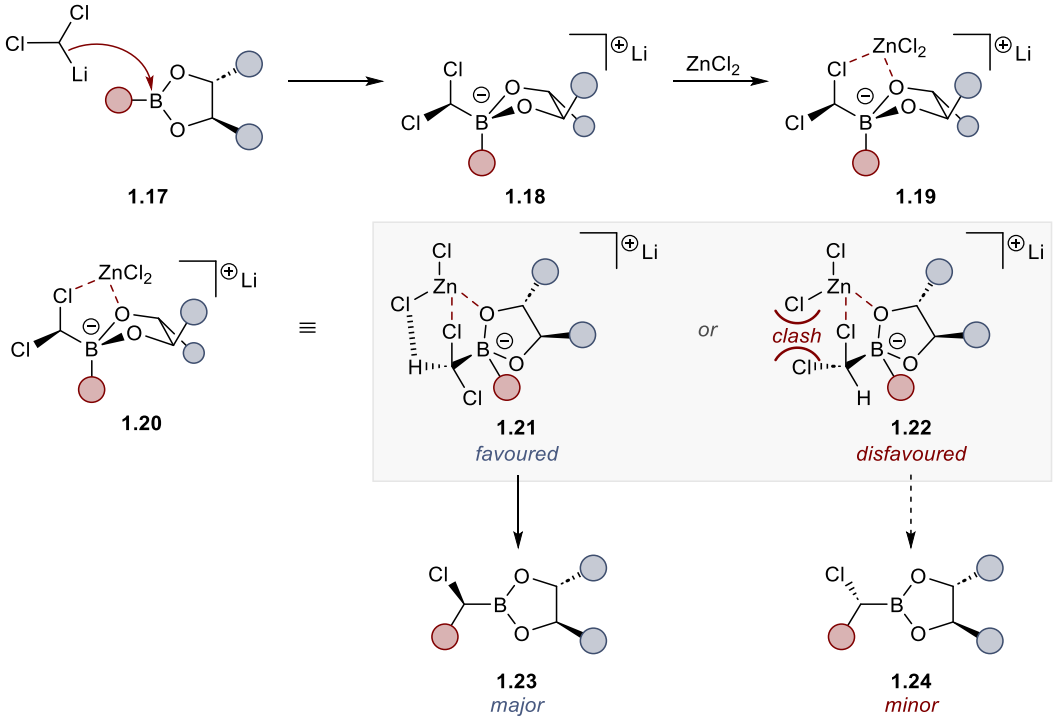
Boronic esters are sp^2 hybridised at the boron atom and highly electrophilic. The formation of a B–C bond is thermodynamically more favourable than the formation of a C–C bond by approximately 48 kJ mol^{-1};[43] this causes a nucleophile, such as phenylmagnesium Grignard, to intercept the vacant *p*-orbital on a boron atom to form a tetracoordinate boronate complex (*i.e.*, **1.16**, Scheme 1.11).[8,17–19,21,31] The subsequent concerted migration of the boron-bound nucleophile and displacement of the requisite leaving group, the 1,2-metalate rearrangement, is highly exothermic.[31,44,45] This general reaction sequence is exemplified in Matteson's seminal report (Scheme 1.11).[8]



1.2 **1.16** **1.3**

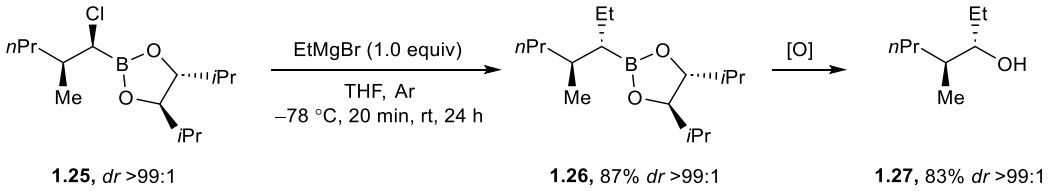
Scheme 1.11: The 1,2-metalate rearrangement. Alternative Grignard species may be present.[46–48]

When chiral ligands are used on the boronic ester reagents, 1,2-metalate rearrangements are highly diastereoselective. Typically, zinc chloride is used as an additive in these transformations.[17,19,39] Upon the formation of a boronate complex using (dichloromethyl)lithium (*e.g.*, **1.18**, Scheme 1.12), zinc chloride will promote the migration of the nucleophile by forming an association complex **1.19** to the most accessible oxygen atom bound to the boron atom and facilitate the departure of the leaving group (*i.e.*, chloride).[31] This retains the configuration of the migrating C–B bond (*i.e.*, red sphere, Scheme 1.12) which is set by the zinc chloride-boronate complex, thus inverting the configuration at the carbon where displacement occurs.



Scheme 1.12: The diastereoselective 1,2-metalate rearrangement.

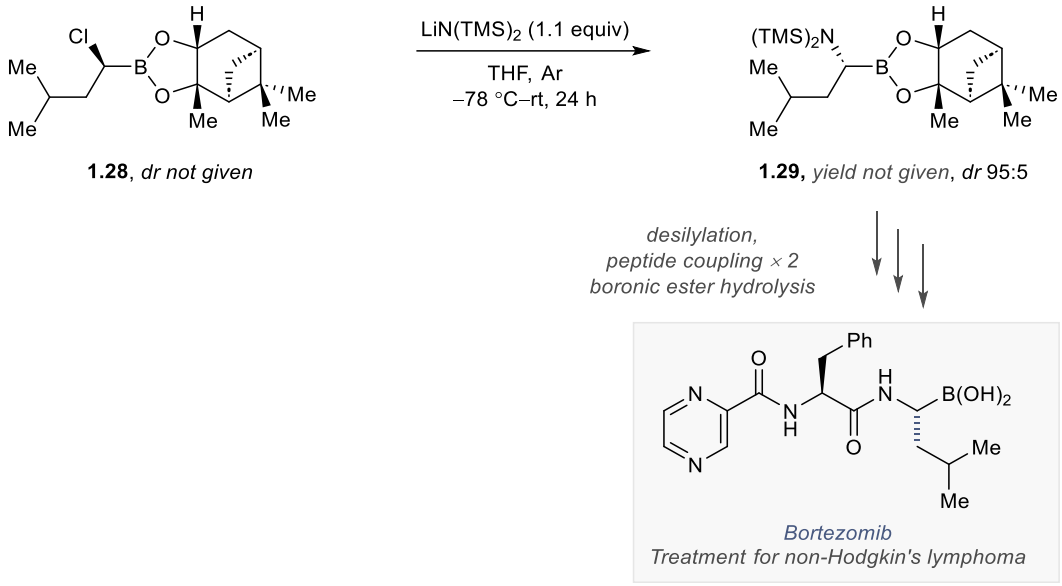
Subsequent Matteson displacement reactions of the obtained α-haloboronic ester product with carbon nucleophiles emphasises the stereochemical outcome of the diastereoselective 1,2-metalate rearrangement.[21] Treatment of the chiral α-chloroboronic ester **1.25** with ethylmagnesium bromide, followed by an oxidation of the requisite boronic ester **1.26**, yields the insect pheromone **1.27** in high yield and diastereomeric ratio (Scheme 1.13).[49]



1.25, *dr* >99:1 **1.26,** 87% *dr* >99:1 **1.27,** 83% *dr* >99:1

Scheme 1.13: Stereospecific nucleophilic displacement of α-chloroboronic esters.

Heteroatom nucleophiles may also participate in 1,2-metalate rearrangements. Typical nucleophiles include dialkylamines,[30] trialkylamines,[50] and alkoxides;[8,51–53] although mercaptides,[8,49,54] thioureas,[54] phosphines,[55] and lithium trialkylstannane examples are all known.[56] In the synthesis of bortezomib, a treatment for non-Hodgkin's lymphoma,[57] a pinanediol α-chloroboronic ester **1.28** is treated with *N*-lithiohexamethyldisilazane to install a protected amine group (Scheme 1.14). The remaining synthesis is completed by desilylation and peptide couplings or the aminated product, **1.29**.[58]



1.28, *dr not given* **1.29,** *yield not given*, *dr* 95:5

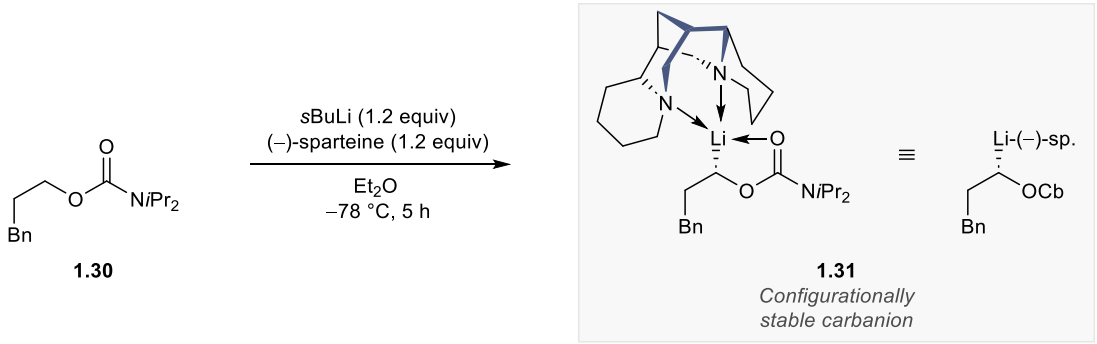
Scheme 1.14: Heteroatom 1,2-metalate rearrangement in the synthesis of bortezomib.

First disclosed over six decades ago, the Matteson reaction is the hallmark example of organoboron synthesis utilizing the two distinct hybridisations of the boron atom to facilitate a highly predictable 1,2-metalate rearrangement. A considerable limitation of this initial work was the preparation of tertiary boronic esters. This next Section will discuss how their synthesis was overcome by using an approach distinct from the original Matteson reports, which is largely attributed to the Aggarwal group. Landmark applications towards total synthesis are also summarised.

1.2.2 Chiral anion approach

In Matteson's classical displacement reactions, the origins of stereocontrol are substrate based using a chiral auxiliary (*i.e.*, located on the boronic ester). A notable disadvantage of this strategy is in the case of multiple homologations, where the selection of orientation at the next stereogenic centre can require a change of boronic ester ligand. An alternative approach using methodology discovered by Hoppe and Beak, but elaborated considerably by Aggarwal, uses a configurationally stable chiral carbanion to facilitate the stereospecific 1,2-metalate rearrangement of a boronic ester containing achiral ligands.

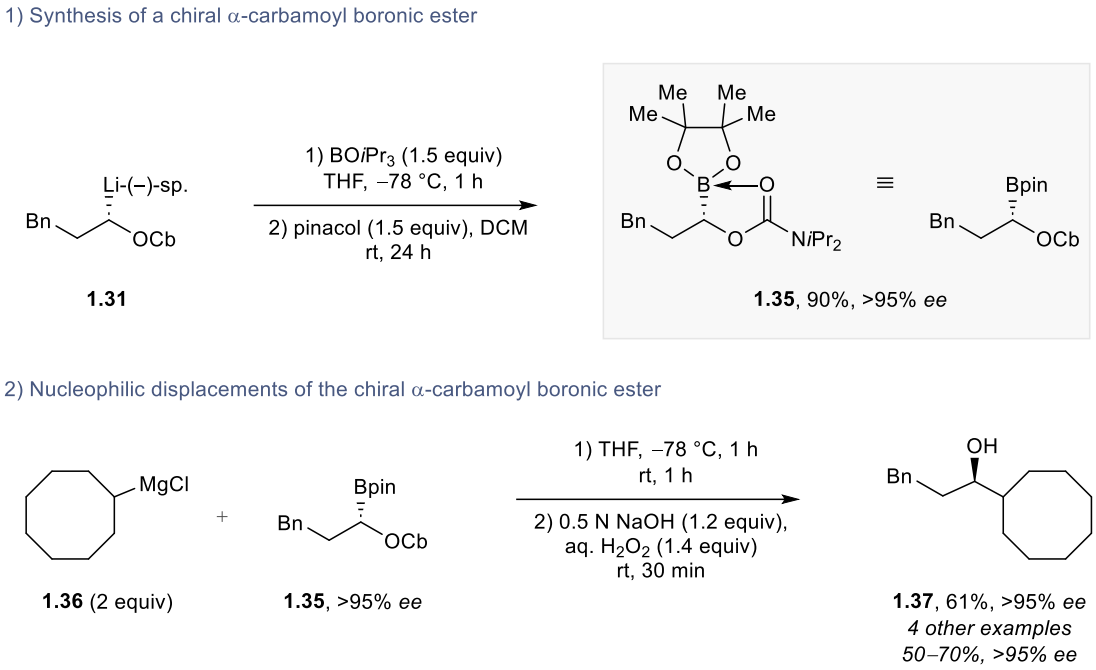
In 2004, Hoppe and coworkers reported the preparation of chiral secondary boronic esters derived from a configurationally stable chiral lithiated carbamate (*i.e.*, **1.31**, Scheme 1.15.1).[59] The 'Hoppe-type' carbamate is produced *via* asymmetric deprotonation using *s*-butyllithium and the chiral diamine lupin alkaloid, sparteine.[60–62] A synthetically-derived surrogate was made available by the O'Brien group in 2002,[63] but it gained popularity around 2010 during well-documented commercial supply shortages of (−)-sparteine.[60,64–66] Although O'Brien's analogue looks more structurally akin to (+)-sparteine, the stereochemistry of the resultant lithium complex is the same as when (−)-sparteine is used (Scheme 1.15.2).[63]



Scheme 1.15: (Top) preparation of Hoppe's configurationally stable lithiated carbamate. (Bottom) structures of sparteine isomers and O'Brien's analogue.

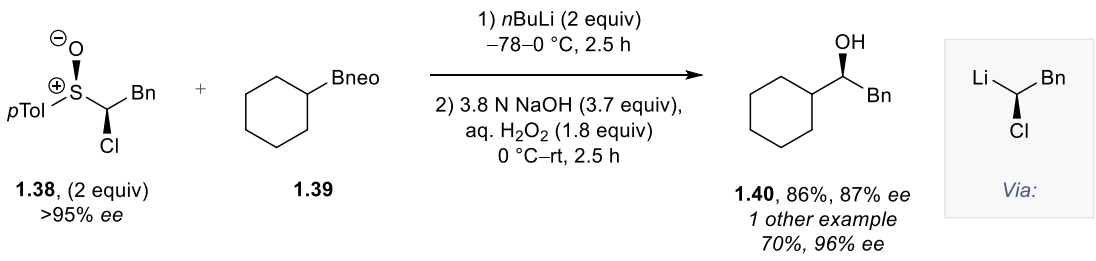
In the same study, Hoppe and coworkers trapped the chiral lithiated complex **1.31** with triisopropyl borate and pinacol to afford the α-carbamoyl boronic ester **1.35** (Scheme 1.16.1).[59] The carbamate is sufficiently electron withdrawing to behave as a leaving group for

the 1,2-metalate rearrangement with a Grignard reagent without the requirement for additives, such as zinc chloride (Scheme 1.16.2).[8,17,31]



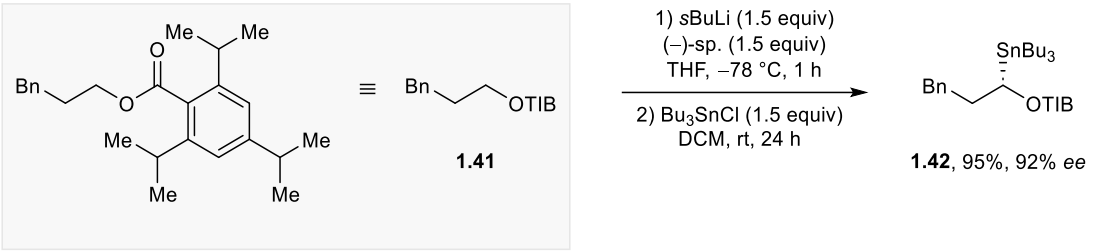
Scheme 1.16: Synthesis and nucleophilic displacement of chiral α-carbamoyl boronic esters.

In 2006, Blakemore and coworkers treated a chiral α-chlorosulfoxide with ethylmagnesium bromide or *n*-butyllithium to afford a configurationally stable α-chlorinated organometallic reagent (organolithium, as shown, or Grignard), which was trapped with achiral boronic esters (*e.g.*, **1.39,** Scheme 1.17).[67] The synthesis of the chiral α-chlorosulfoxide **1.38** required four steps to be made and three recrystallisations in the final step to afford an acceptable diastereomeric ratio for use in stereospecific reactions with achiral boronic esters. An alternative method reported a year later required only three steps and no recrystallisations;[68] however, the final chlorination step took between five and ten days. This approach to chiral carbanions has been largely relinquished in the literature.[16,31]



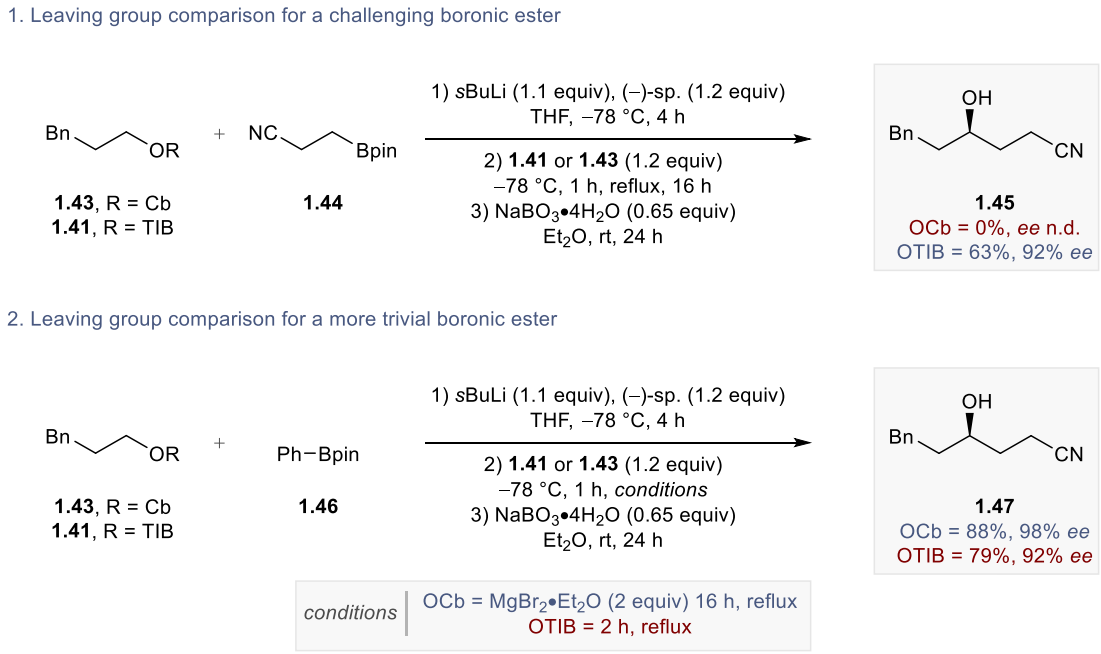
Scheme 1.17: Nucleophilic displacement using Blakemore's chiral α-chlorosulfoxide.

Functional groups can be slow to migrate from boronate complexes containing the Hoppe carbamates. In 2011, Aggarwal addressed this problem by preparing chiral lithiated stannanes from 'Beak-type' benzoate esters (*i.e.*, **1.42**, Scheme 1.18).[69] This used Beak's originally reported 2,4,6-triisopropylphenyl benzoate ester **1.41** with sparteine in replacement of tetramethylenediamine as the ligand to set the lithiated stereocentre,[70] which was isolated by forming the requisite stannane from tributyltin chloride.



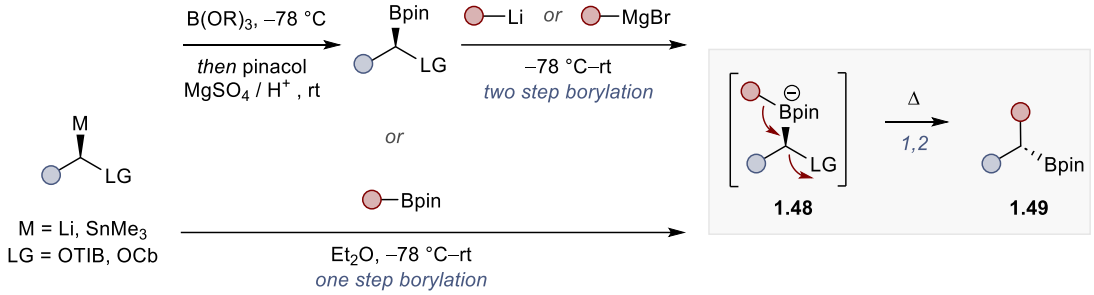
Scheme 1.18: Aggarwal's preparation of a Beak-type chiral α-stannyl benzoate ester.

In the same study, the benefits of the Beak-type benzoate esters over the Hoppe-type carbamates were demonstrated when attempting to migrate boronic esters containing β-electron withdrawing groups (*e.g.*, **1.44**, Scheme 1.19.1). Interestingly, Hoppe-type carbamates can still perform with slightly higher yields and enantioselectivities than the Beak-type benzoates when the reaction times are increased and Lewis acids are added, such as magnesium bromide etherate (Scheme 1.19.2).[69]



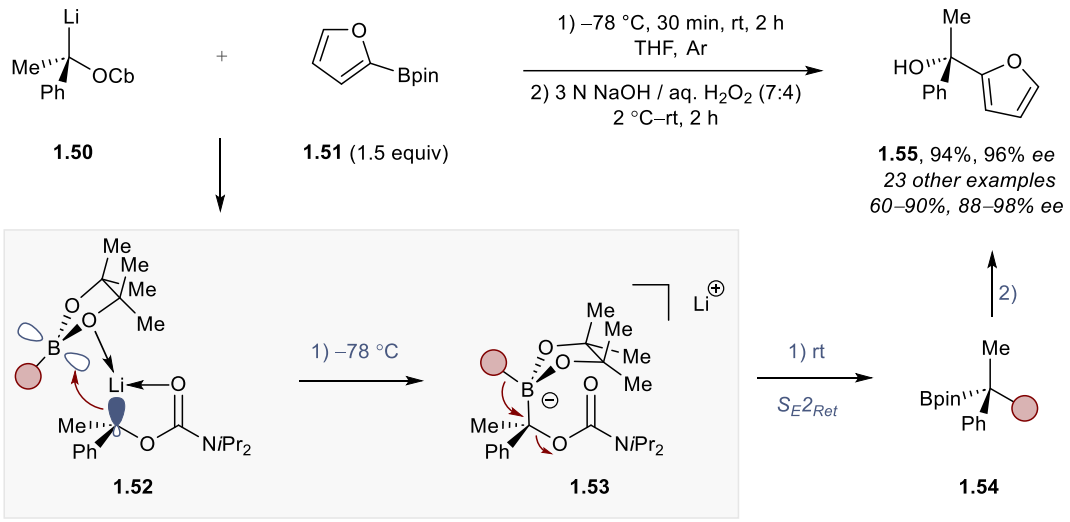
Scheme 1.19: Head-to-head studies comparing OCb and OTIB leaving groups.

Both Hoppe-type carbamates and Beak-type benzoates continue to be used heavily in the preparation of chiral carbanions. A notable point of evolution was the transition from earlier two-step borylation protocols, where the chiral carbanion is trapped with a borate then intercepted with an organometallic nucleophile, to the one-step borylation approach (Scheme 1.20). This latter approach as disclosed above, coined by Aggarwal as 'lithiation-borylation',[16] introduces a boronic ester directly, where the leaving group on the chiral anion can be selected based on the difficulty of migration.[69]



Scheme 1.20: Summary of one-step and two-step approaches to chiral secondary boronic esters. Ester ligands can also be varied.

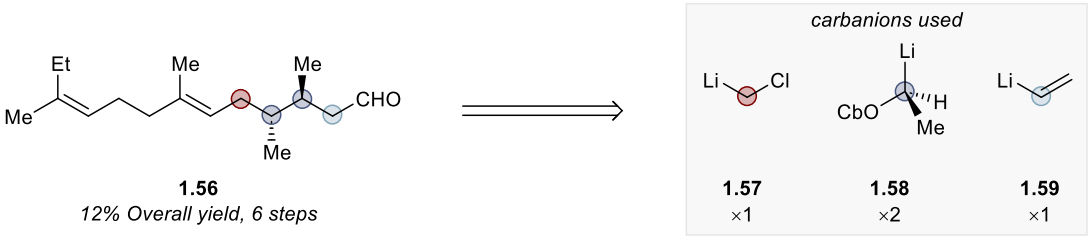
Tertiary and quaternary boronic esters are particularly desirable products because they are structurally complex and cannot be accessed by typical borylation methods,[16] such as hydroboration and Matteson's displacement reactions.[5,8,31] In 2008, Aggarwal and coworkers prepared asymmetrically-lithiated secondary carbamates to furnish tertiary boronic esters (Scheme 1.21).[71] Notably, the reaction proceeds with retention of configuration (S_E2_{Ret}), because a boronic ester oxygen atom can coordinate to the set lithium atom and deliver the nucleophile accordingly. Quaternary boronic esters can also be prepared and the stereochemical course proceeds in an analogous manner,[72] with iterative homologations furnishing densely functionalised products.[73]



Scheme 1.21: Synthesis of chiral tertiary boronic esters and alcohols with retention of stereochemistry.

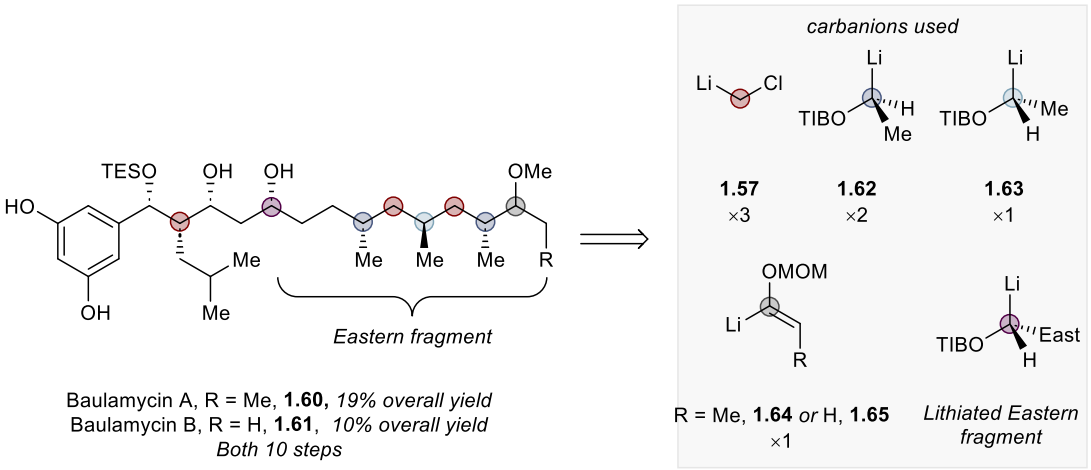
The development of chirally-lithiated carbamates and benzoates has enabled the synthesis of contiguous stereocentres through iterative lithiation-borylations, without the requirement for ligand interconversions on the boronic ester.[16,74] This level of reagent control enables the user to select the desired stereocentre with each extension to the carbon chain. Moreover, purification is not required after every iteration, permitting several homologations before an aqueous workup or chromatography is required. Subsequent campaigns exploiting this general synthesis platform have afforded many concise total syntheses of natural products, with step counts being reduced by up to 70% compared to previous efforts.[75] In the synthesis of (+)-faranal **1.56**, optimal yields were obtained when two homologations, a vinylation, and a hydroboration-oxidation reaction are all performed in a single operation (Scheme 1.22.1).[76] A similar approach was used to prepare (−)-stemaphylline,[77] (+)-tatanan A,[78] (+)-invictolide,[79] and serricornin.[79] In the total synthesis of Baulamycins **1.60** and **1.61**, five different carbanions were used over seven homologations (Scheme 1.22.2).[80] An impressive sixteen iterative homologations were performed during the synthesis of (+)-hydroxyphthioceranic acid **1.66**, across only four purifications, with each 1,2-metalate rearrangement performing with over 99% conversion and 99:1 stereocontrol (Scheme 1.22.3).[75] This methodology has been used to identify and correct previously misassigned configurations of a natural product by independently synthesising all possible diastereoisomer-enantiomer combinations at ambiguous positions.[80]

1. (+)-Faranal



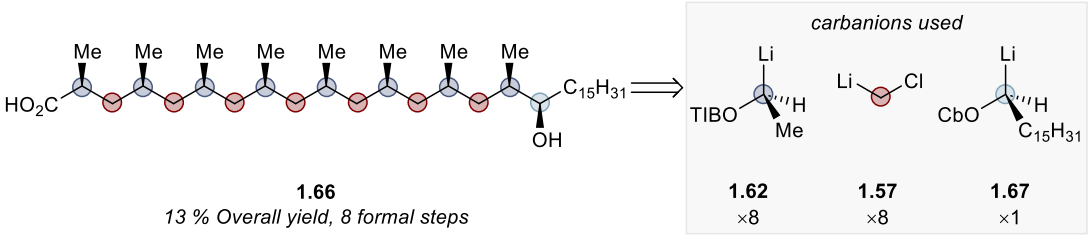
1.56
12% Overall yield, 6 steps

2. Baulamycins A and B



Baulamycin A, R = Me, **1.60,** *19% overall yield*
Baulamycin B, R = H, **1.61**, *10% overall yield*
Both 10 steps

3. (+)-Hydroxyphthioceranic acid



1.66
13 % Overall yield, 8 formal steps

Scheme 1.22: Applications of the chiral anion approach to total synthesis. Coloured spots indicate the source carbanion used. In 3, 'formal' steps refers to the inclusion of a workup and purification during the otherwise iterative homologation sequence.

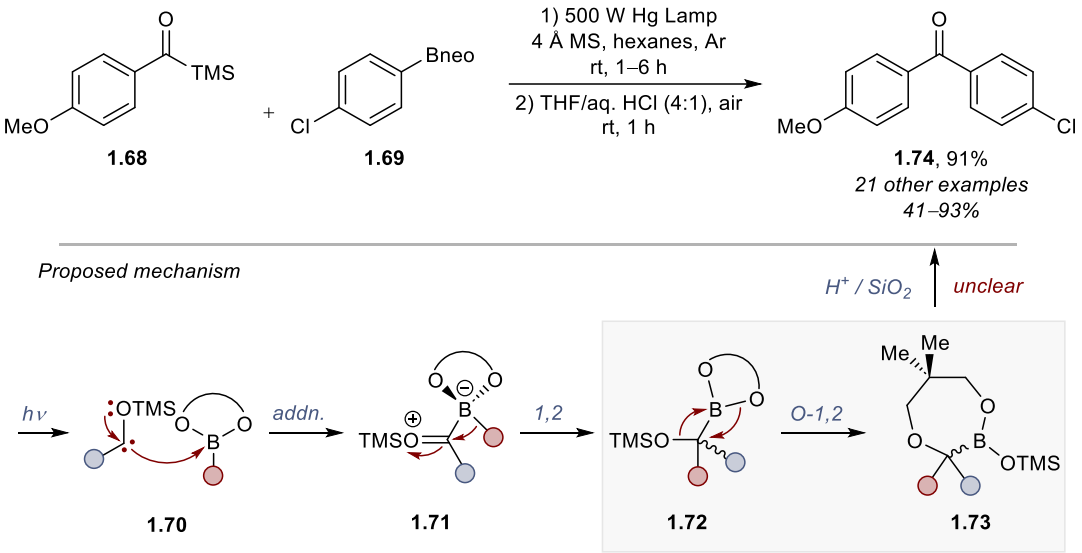
Modern chiral anion approaches have several drawbacks worth highlighting. Asymmetric deprotonations often use superstoichiometric quantities of sparteine to afford sufficient enantioenrichment of the lithiated carbanion, which can be problematic in terms of cost, supply, and atom economy.[64,65] Subsequent 1,2-metalate rearrangements can suffer from diminished enantiopurity and conversion due to competing interactions with excess sparteine, which is overcome by isolating the chiral stannane, then retreating with butyllithium — an unusual caveat to an otherwise efficient assembly line process. Finally, the level of functional group tolerance achieved by the chiral anion approach is no better than

the original Matteson-type reactions which all require the use of stoichiometric organometallic reagents.

The following Sections shall discuss conceptually new approaches to the 1,2-metalate rearrangement, following from the original Matteson reaction and chiral anion approaches. Literature was selected based on either mechanistic distinction or newly accessed functional group patterns and is presented chronologically when discussed in detail. In general, any initial treatment of a boronic ester with an organometallic reagent is omitted from reaction drawings because conceptual novelties arise after the formation of the boronate complex, so it is shown as the requisite starting material for simplicity.

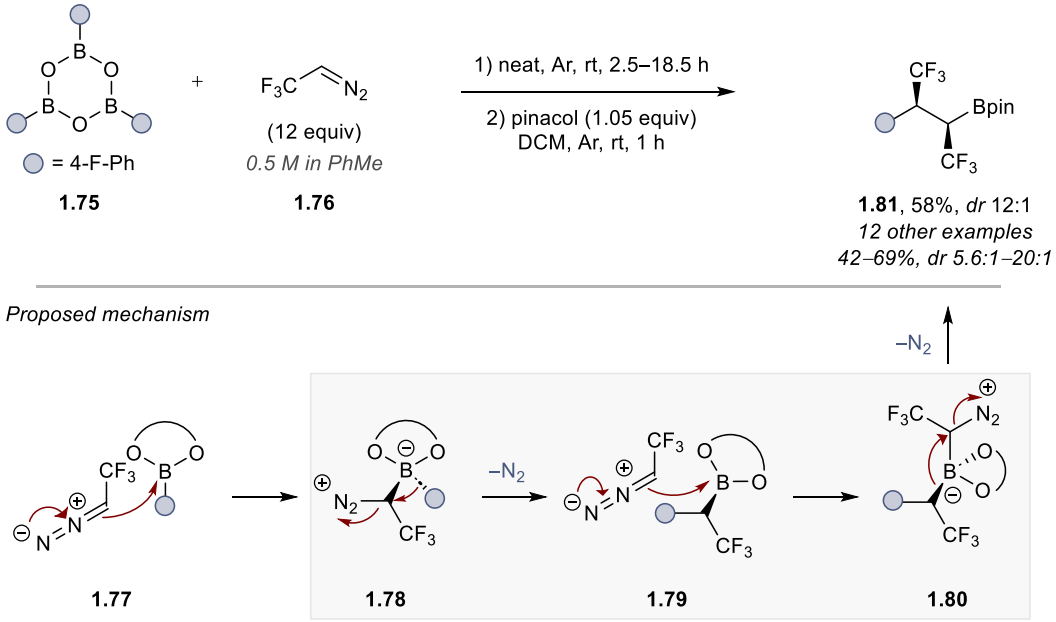
1.2.3 Selected variations of the 1,2-metalate rearrangement

Acylsilanes are synthetic precursors to siloxycarbenes which form under light irradiation through a 1,2-shift of the silyl group.[81–83] In 2011, Kusama and coworkers reported the 1,2-metalate rearrangement of boronate complexes **1.71** generated from siloxycarbenes, furnishing a variety of asymmetric ketones (*i.e.*, **1.74**, Scheme 1.23).[84] Notably this 1,2-metalate rearrangement occurs without the requirement for organometallic reagents. An unusual second insertion of one neopentyl glycol C–O bond into the C–B bond was postulated to occur based on related rearrangements,[85,86] forming a seven-membered ring intermediate **1.73** which could be characterised from crude reaction mixtures. Surprisingly, the scope tolerated halide-containing arenes, including chloride- (*e.g.,* **1.69**), bromide-, and iodide-, despite requiring a high-power mercury lamp to form the acylcarbene *in situ*.



Scheme 1.23: Organometallic-free 1,2-metalate rearrangement using siloxycarbenes.

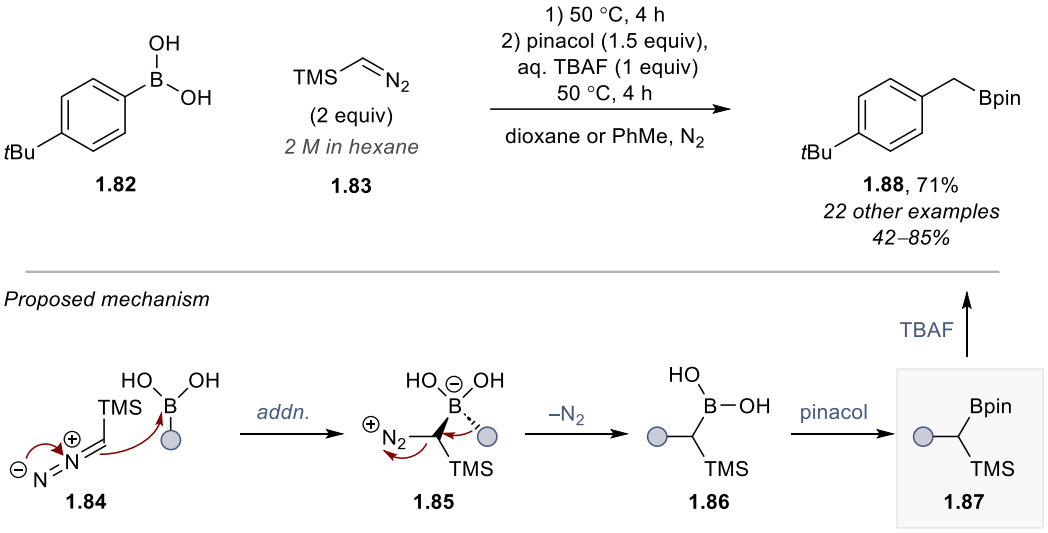
In 2013, Molander and coworkers prepared a series of bench-stable α-trifluoromethylated organoboron compounds from the insertion of trifluorodiazoethane into potassium trifluoroborate salts.[87] In the year that followed, the same group reported a double insertion trifluorodiazoethane **1.76** to prepare *syn* vicinal bis(trifluoromethylated) organoboron compounds from boroxines (Scheme 1.24).[88] Notably, the leaving group in this 1,2-metalate rearrangement is nitrogen gas and is another example where organometallic reagents have been avoided. The use of boroxines (*i.e.*, **1.75**), as opposed to the hydrated boronic acids or diol boronic esters, was essential to obtaining the desired double addition of trifluorodiazoethane without competing β-fluoride elimination (*i.e.*, **1.77** and **1.79**). By the admission of the authors, this significantly limited the available substrate scope because many boronic acids underwent protodeboronation during azeotropic dehydration to prepare the respective boroxines. The origins of diasteroselectivity were proposed to arise from a transition state prior to 1,2-metalate shift that avoids *syn*-pentane interactions between the two trifluoromethyl groups.[88]



Scheme 1.24: Diastereoselective synthesis of vicinal bis(trifluoromethylated) organoboron compounds.

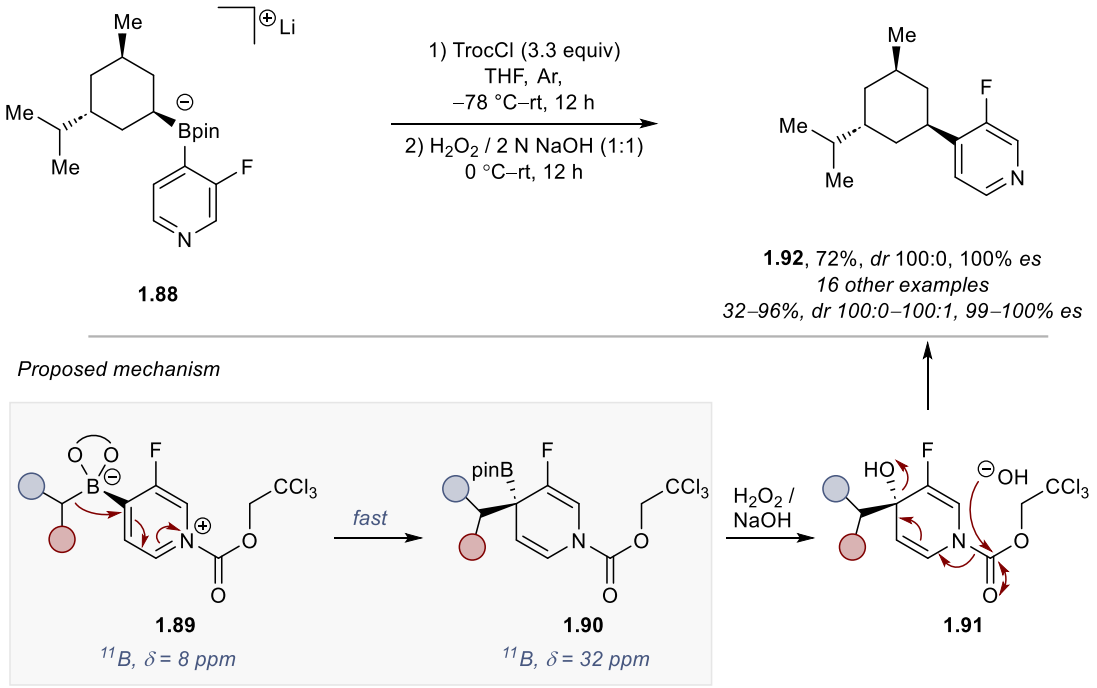
In 2016, Wang and coworkers used a similar trimethylsilyldiazomethane reagent **1.83** to homologate arylboronic acids into benzyl boronic acid pinacol esters (Scheme 1.25) in the absence of organometallic reagents. The reaction proceeds in a similar manner to the above processes by Molander and coworkers,[88] with subsequent expulsion of nitrogen and esterification with pinacol yielding intermediate **1.87**. Despite this intermediate being both

isolable and synthetically interesting,[89,90] the Authors chose to initially protodesilylate the reaction mixture by using tetrabutylammonium fluoride. The Authors later followed up the study with a second set of conditions to deliver the same products which were cross-coupled with aryl iodides;[91] however, this required heating highly toxic trimethylsilyldiazomethane **1.83** to 100 °C to afford more synthetically appreciable yields.[92] Later density functional theory and experimental studies by Ley and coworkers provided evidence to suggest that boroxines formed *in situ*, rather than the boronic acids such as **1.82**, are the more reactive organoboron species which engage with trimethylsilyldiazomethane,[93] akin to Molander's previous observations (*i.e.*, Scheme 1.24).[88]



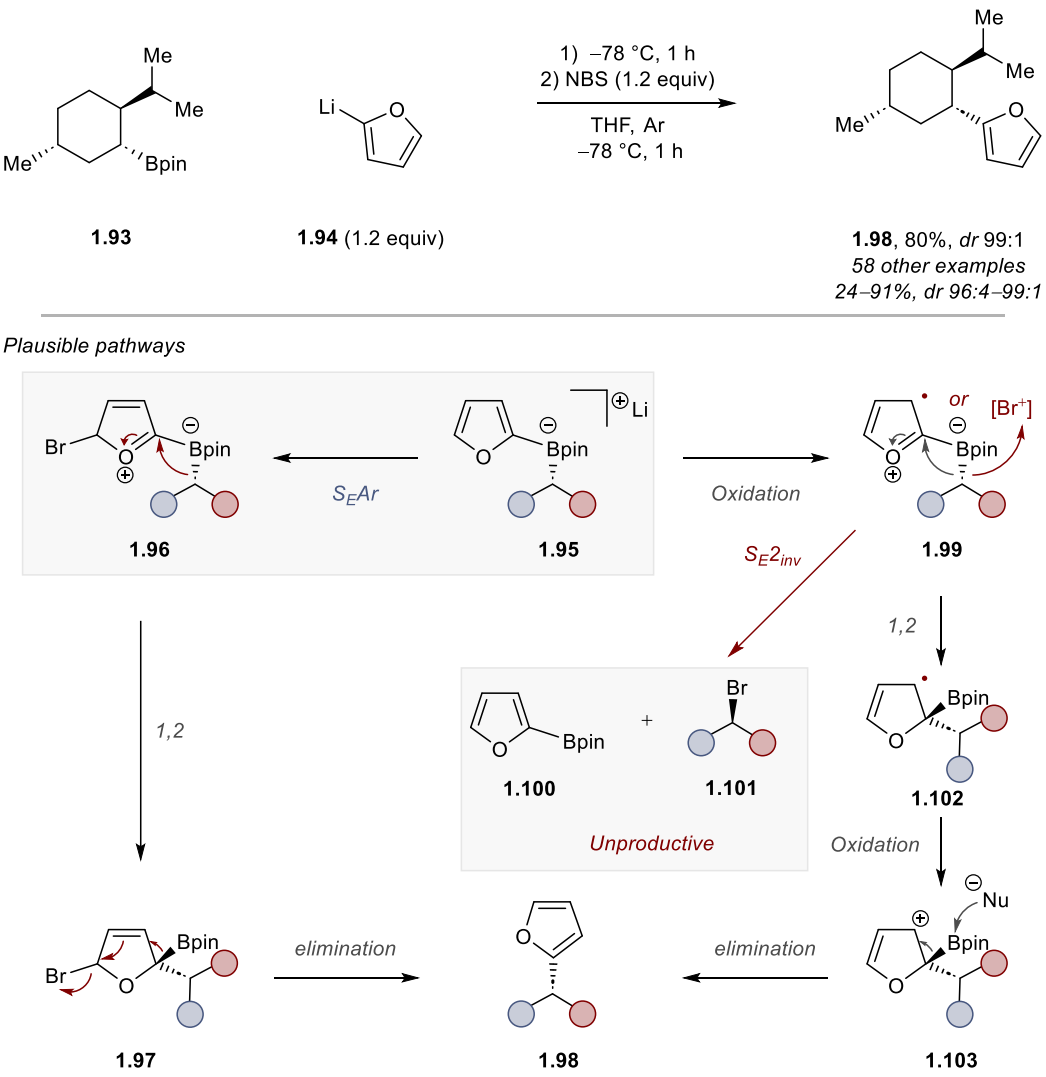
Scheme 1.25: Homologation of arylboronic acids using trimethylsilyldiazomethane.

In 2014, Aggarwal and coworkers developed a stereospecific cross-coupling of lithiated heteroaromatics using chiral secondary and tertiary boronic esters (Scheme 1.26).[94,95] The reaction could be followed by ^{11}B NMR and infrared spectroscopy, where the collapse of the boronate **1.89** by 1,2-metalate shift into a dihydropyridine **1.90** was rapid upon the addition of trichloroethoxycarbonyl chloride.[95] While still relying upon stochiometric metalation using organometallic reagents, these two studies together represent a landmark redesign of C–C bond-forming strategies which has historically relied on transition metal catalysis.[3,94–96] Unlike previous 1,2-metalate rearrangements,[16,20,31] oxidative workup is required as part of the coupling process to rearomatize the heteroaromatic (*i.e.*, **1.91**), so no boronic ester is retained in the products. In a follow up study using *ortho*-lithiated benzylamines, Aggarwal and coworkers used a similar strategy which could retain the boronic ester motif *via* a subsequent 1,3-borotropic shift after 1,2-migration.[97]



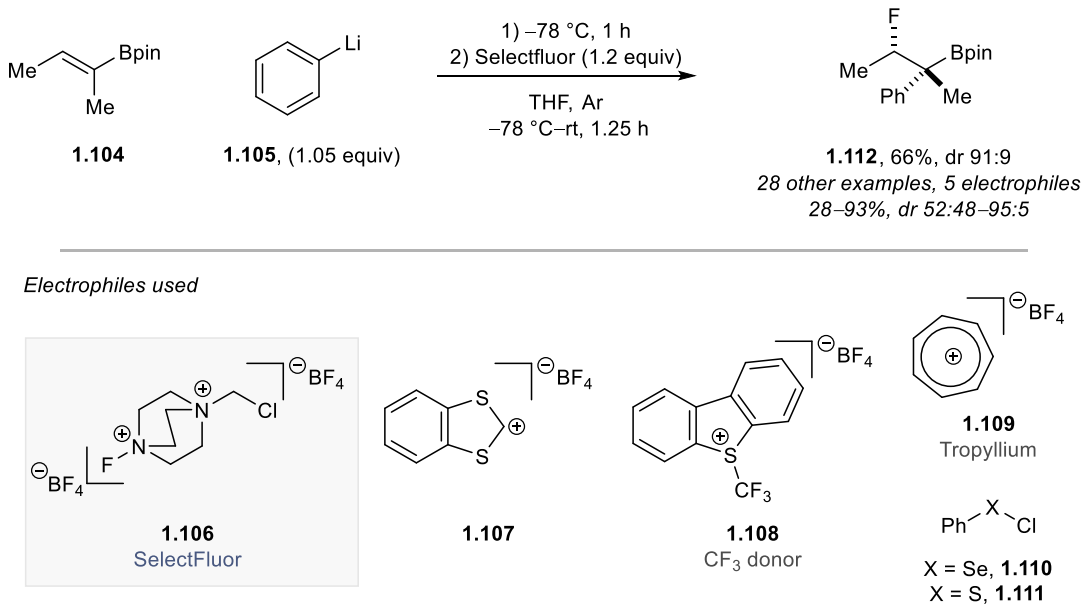
Scheme 1.26: Stereospecific coupling of lithiated heteroaromatics with secondary boronic esters.

In 2016, the Aggarwal group disclosed a full experimental and computational study based on their original stereospecific coupling of chiral secondary and tertiary alkyl boronic esters with electron-rich aryllithiums (Scheme 1.27).[94,98] From a mechanistic standpoint, the protocol is a cascade reaction comprising of an electrophilic aromatic substitution, 1,2-metalate rearrangement, then an elimination. *N*-bromosuccinimide can serve as either an electrophile in S_EAr reactions, or as an oxidant (Scheme 1.27, left *versus* right); however, density functional theory studies showed that the substitution path is favoured in more polar solvents.[98] Overoxidation can lead to early C–B bond cleavage and unproductive elimination, which was previously observed when 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was used (*i.e.*, **1.100** and **1.101**). Bromination must be directed in the *ortho* (*i.e.*, **1.96**) or *para* positions (when appropriate rings are used) to facilitate the appropriate elimination reaction and the reaction requires electron-rich lithiated aromatics to facilitate the desired electrophilic aromatic substitution pathway. Later work expanded operative substrates to *para*-alkynyl lithiated aromatics, which form an extended bromoallene intermediate.[99]



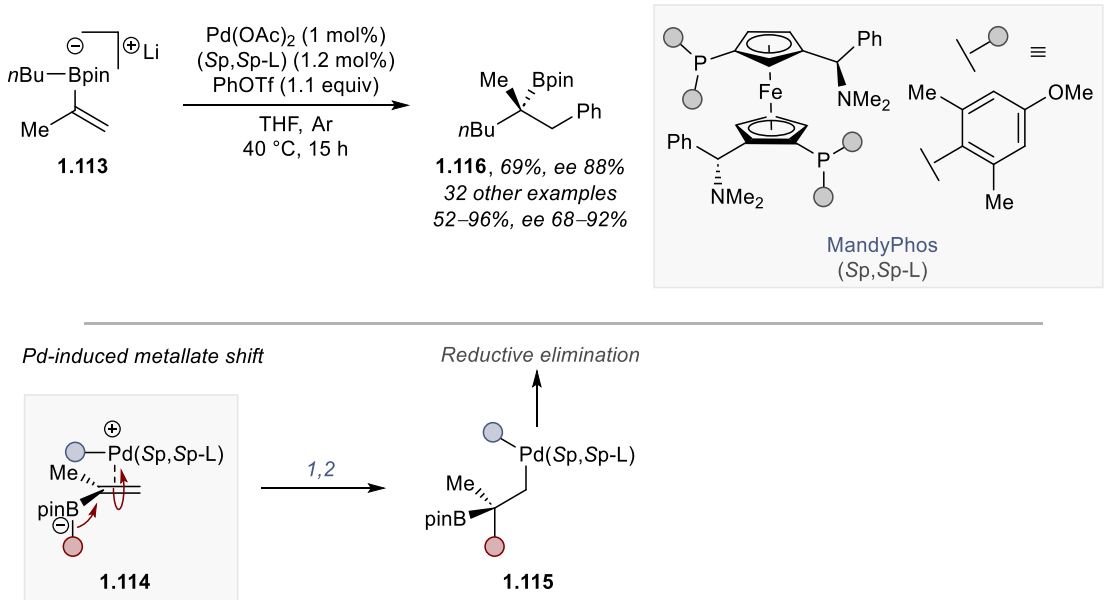
Scheme 1.27: Enantiospecific coupling of secondary boronic esters *via* an S_EAr-1,2-metalate-rearrangement-elimination cascade.

The above two-electron pathway has previously been used by the Aggarwal group to facilitate direct stereospecific 1,2-metalate rearrangements of arylboronates with electrophiles such as *N*-bromosuccinimide, trichloroisocyanuric acid, iodine, tropylium, Eschenmoser's salts, and Selectfluor.[20,100] In 2017, a similar process was reported using vinylboronate complexes (Scheme 1.28).[101] No new electrophiles were reported between the two studies.[20,101] The latter transformation represents a three-component diastereoselective coupling; however, some charged electrophiles (*e.g.*, tropylium, **1.,109**) exhibit partially eroded diastereoselectivity by competing *syn* migration as bond formation becomes increasingly asynchronous. Hydrogen and methyl were the only α-substituents used for the vinyl organoboron reagents, which likely reduced the chance of competing elimination reactions with increasing steric bulk.[101]



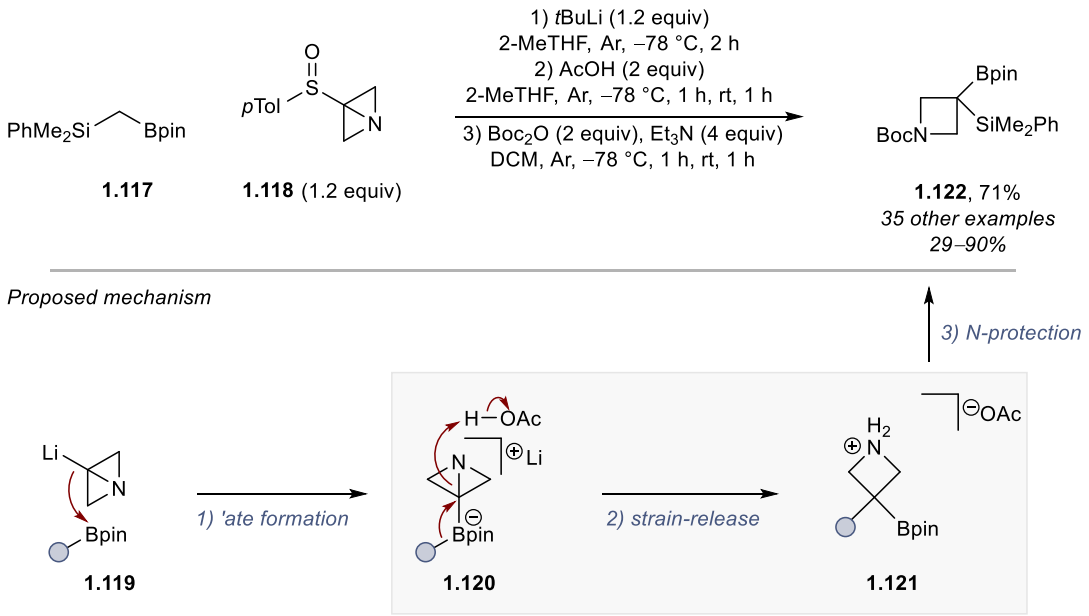
Scheme 1.28: Diastereoselective three-component coupling of vinyl organoborons.

Transition metal catalysis can offer a complementary approach to enable the asymmetric synthesis of complex molecules.[102] In 2018, Morken and coworkers reported a catalytic enantioselective cross-coupling of vinyl lithium boronates and aryl triflates using palladium catalysis and a very sterically-demanding MandyPhos ligand (Scheme 1.29).[103] Following rate-limiting oxidative addition of the aryl triflate,[6] the vinylboronate complex **1.114** is proposed to undergo a palladium-induced 1,2-metalate shift prior to reductive elimination.[103]



Scheme 1.29: Palladium-induced 1,2-metalate shift.

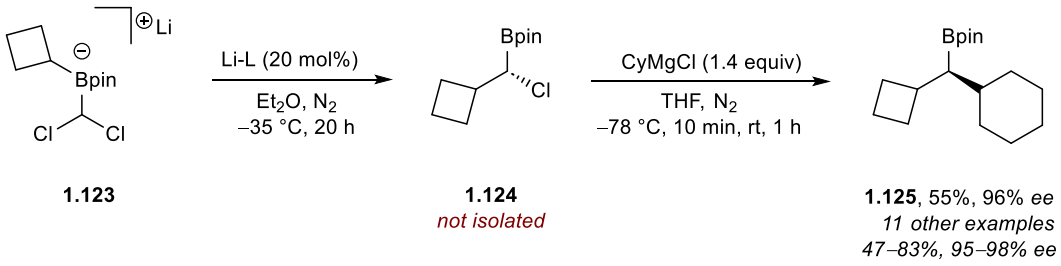
In 2018, Aggarwal and coworkers prepared a strained bicyclo[1.1.0]butyl boronate complex which could undergo C–C σ-bond carbopalladation, with the same palladium acetate / MandyPhos combination as the above report by Morken and coworkers,[103] to deliver chiral 1,1,3-trisubstituted cyclobutanes.[104] In an analogous study, the same group prepared an azabicyclo[1.1.0]butane **1.118** to forge substituted azetidines (Scheme 1.30).[105] The trapping of azabicyclo[1.1.0]butyl lithium **1.119** with a boronic ester (e.g., **1.117**) formed a highly strained boronate complex **1.120** which could undergo a facile strain-driven 1,2-metalate rearrangement. A convenient 'silica-catch' method could separate the intermediate azetidine salt **1.121** from the sulfoxide byproduct, which was isolated through an *N*-protection operation. Although azabicyclo[1.1.0]butyl lithium **1.119** can be prepared from azabicyclo[1.1.0]butane using *s*-butyllithium, the Authors elected to isolate the azabicyclo[1.1.0]butyl lithium equivalent **1.118** by treatment with methyl 4-methylbenzenesulfinate. This prepared an easy-to-handle salt for use in parallel reactions, but the regeneration of azabicyclo[1.1.0]butyl lithium **1.119** requires superstoichiometric *t*-butyllithium. Similar strain-promoted 1,2-metalate rearrangements were subsequently reported by the group using epoxides,[106] propellanes,[107] and cyclopropanes.[108]



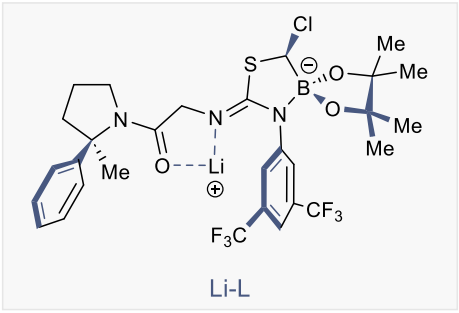
Scheme 1.30: Strain-promoted 1,2-metalate rearrangement.

In 2020, Jacobsen and coworkers reported a catalytic, enantioselective, 1,2-metalate rearrangement of boronate complexes (Scheme 1.31).[109] A unique isothiourea-boronic ester complex, whose synthesis was particularly exigent, was used as the catalyst to discriminate between the two enantiotopic chlorine atoms located on the requisite boronate complex **1.123**. Following Matteson's chiral auxillaries,[17,18,31,110] and Beak's and Hoppe's chiral anion

reagents,[59,70,111,112] this transformation was the first example of a chiral catalyst approach being applied to the 1,2-metalate rearrangement. Despite α-chloroboronic esters (*i.e.*, **1.124**) being configurationally stable,[67] the Authors did not isolate these products and immediately treated them with Grignard reagents.



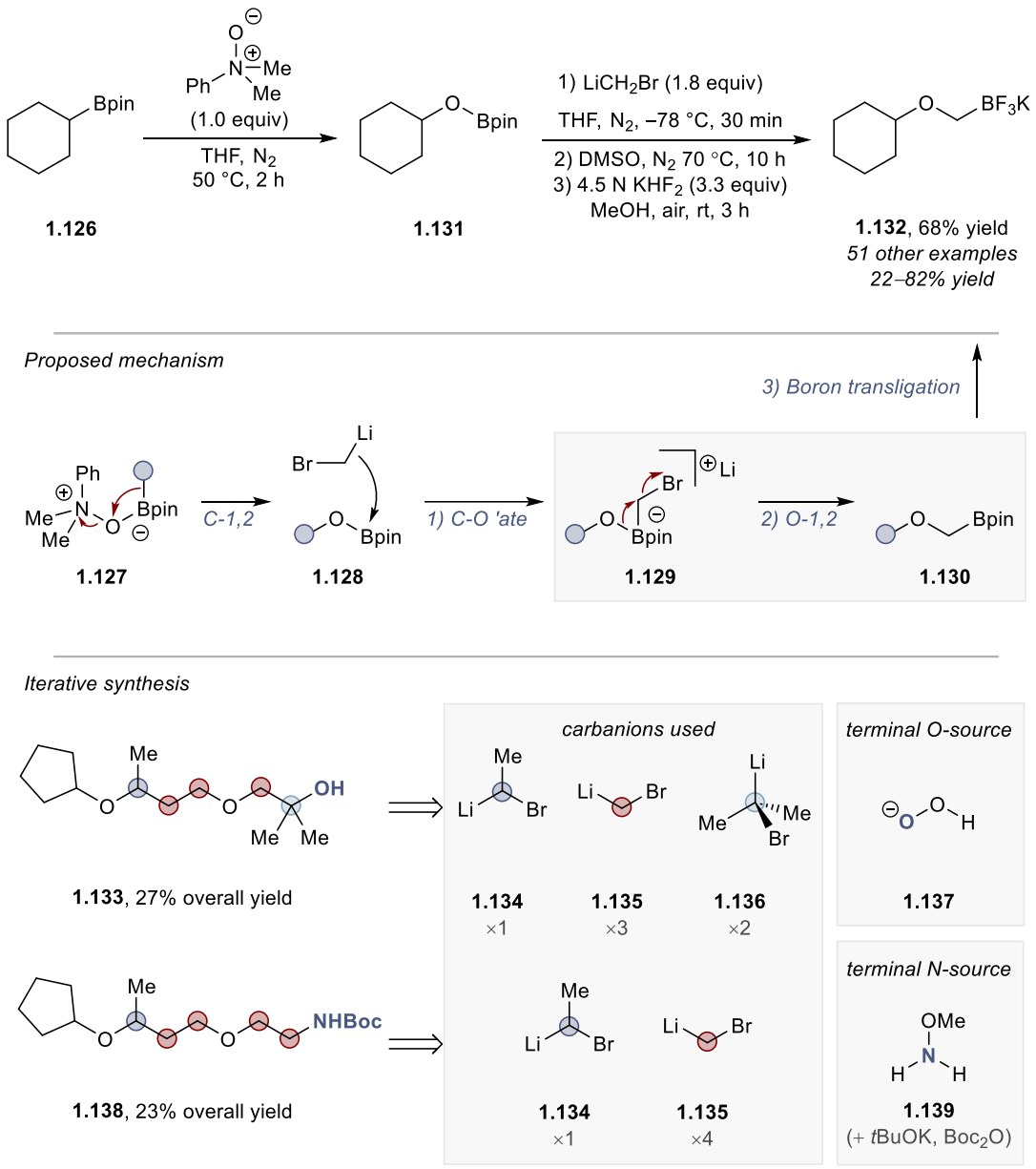
Lithium-isothiourea-boronate catalyst



Scheme 1.31: Catalytic, enantioselective, 1,2-metalate rearrangement.

In 2022, Dong and coworkers reported a Matteson-like homologation of boronic esters to yield alkyl ethers (Scheme 1.32).[113] The reaction involves sequential C–O and B–O insertion reactions (sequential *C*-1,2- and *O*-1,2-metalate rearrangements) using an oxygen donor and typical carbanion fragments (*i.e.*, **1.134**–**1.136**).[16,36,113] The latter B–O insertion is especially challenging because the migrating B–O bond is less nucleophilic than a C–B bond, and the cleavage of the B–O bond comes at a high enthalpic cost.[43] The B–O bond cleavage is typically a minor (and undesired) pathway in Matteson-type rearrangements,[31] so it is unsurprising the Authors had to heat the oxyboronic ester **1.131** to 70 °C for ten hours to achieve the described transformation. The Authors also reported a series of four Aggarwal-type iterative homologations using their methodology,[16,74] with up to four manipulations taking place in one pot.[113] Notably, each oxygen homologation took place at least two carbons away from the preceding one, and it unclear whether the Authors directed the synthesis in this manner for a particular reason. This action may have been taken to avoid competitive migrations if the ethers were too close together.[73,84] Conveniently, oxidation of the *B*-terminus could provide a terminal alcohol (*i.e.*, **1.133**), or treatment with *O*-methoxyhydroxylamine **1.139**

under basic conditions with di-*t*-butyl-dicarbonate could furnish a terminal amine (*i.e.*, **1.138**).



Scheme 1.32: Oxa-Matteson reaction and iterative synthesis of polyethers.

Since its inception over sixty years ago,[8] the 1,2-metalate rearrangement of organoboronate complexes has continued to inspire the synthesis community.[31,76] Modern variations of this reaction have enabled a plethora of complex products to be prepared, which evolved in the last decade into a general platform for iterative molecular construction.[16,68,74,76,113,114] From a broader conceptual standpoint, most metalate rearrangements rely upon an α-boryl leaving group to facilitate the heterolytic bond cleavage of a B–C and C–X bond to forge a new C–X bond,[31] with exceptions to this rule already discussed.[105,106,113] The following Section of this

literature review shall consider wider reactions of organoboron compounds bearing α-boryl leaving groups, namely halogens, that undergo C–X homolytic bond cleavage (radical generation), or undergo discrete on-metal transformations within transition metal catalysis.

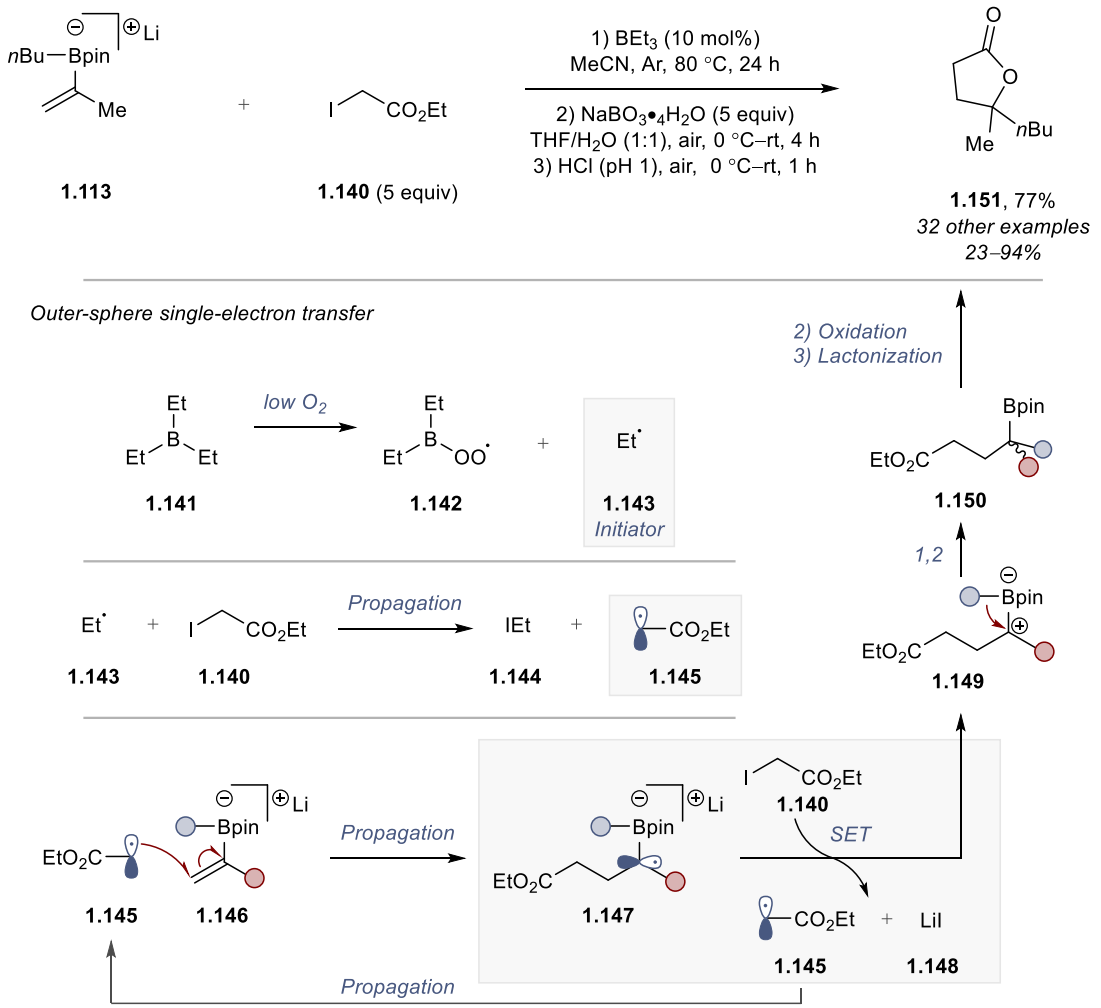
1.3 Other reactions of α-halogen organoboron compounds

1.3.1 Radical generation

Photochemistry is over a century old and uses various wavelengths of ultraviolet and visible light to obtain reactive intermediates that are generally inaccessible through classical (thermal) pathways.[115,116] In the last decade, photoredox catalysis has emerged as a distinct field where a transition metal- or organic-based catalyst either donates, or abstracts, electrons to prepare organic radicals.[117–119] Subsequent oxidations or reductions of these radicals can generate carbocations and carbanions — a process generally referred to as 'radical-polar crossover'.[120–122] These general reaction paradigms have transcended across various organic subdisciplines, including organoboron chemistry. As photoredox chemistry has continued to evolve, new methods have emerged that require no transition metal photocatalyst to access these processes.[123] The reactions of α-boryl radicals, generally prepared by homolytic bond cleavage of α-halogen organoboron compounds, are summarised in the following Section.

In 2017, Studer and coworkers first demonstrated how radical-polar crossover could be applied to organoboron compounds to generate α-boryl radicals (Scheme 1.33).[124] Triethylborane **1.141** and oxygen forms an ethyl radical **1.143** which serves as an initiator.[125] Chain propagation with the C–X bond-containing electrophile (*e.g.*, **1.140**, perfluoroiodoalkyl, iodomethylnitrile) generates the desired alkyl radical (*i.e.*, **1.145**) which is trapped by a vinyl boronate complex at the β-position. Subsequent radical-polar crossover of this adduct with superstoichiometric quantities of the electrophile yields a zwitterion **1.149** which can undergo a 1,2-metalate rearrangement. This outer sphere radical electron transfer process, as opposed to an inner sphere 1,2-metalate rearrangement of an *in situ* α-halogen boronate, was confirmed with an alternate substrate to **1.140**, which cannot liberate halide ions. The boronic ester can be retained in the products; alternatively, they can undergo typical oxidation reactions. Further acid hydrolysis of the ester moiety can furnish substituted γ-lactones (*i.e.*, **1.151**). Similar studies by Aggarwal have used light rather than triethylborane as a radical initiator.[126,127] In the following year, the Studer group used secondary and tertiary chiral boronic esters to demonstrate a stereospecific radical-induced

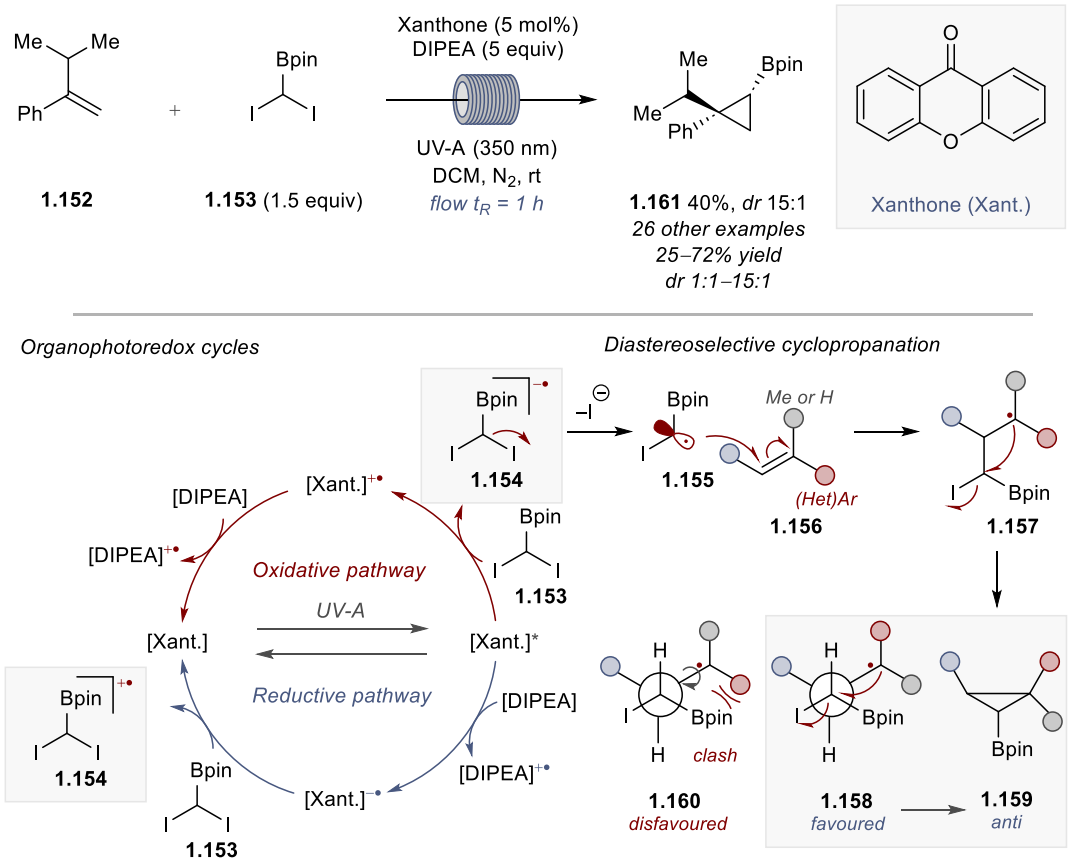
1,2-migration where subsequent oxidation provided enantioenriched α-ketones.[128] Proceeding reactions of α-boryl radicals which do not use a α-halogen organoboron compounds are generally out of the scope of this review,[123,129–131] so will not be discussed further.



Scheme 1.33: Radical-polar crossover reaction of vinylboronate complexes to prepare γ-lactones.

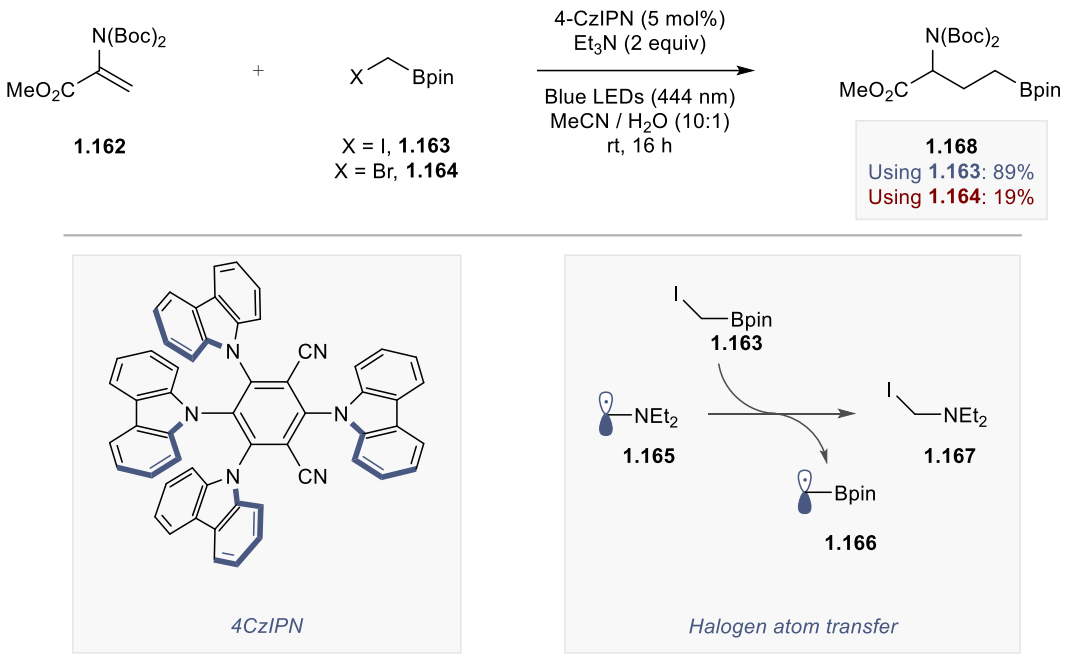
In 2018, Charette and coworkers reported a borocyclopropanation of styrenes under ultraviolet light (Scheme 1.34).[132] Unlike Studer and coworkers, who generated the α-boryl radical from a B(sp^3)–C vinylboronate,[124] the authors used the homolytic C–I bond fission of a B(sp^2)–C diiodomethylboronic ester **1.153**.[128] The reaction could be run in a continuous flow setup but still required the use of high-energy ultraviolet light and an exogenous photocatalyst to form the α,α-iodomethylboryl radical (*i.e.*, **1.154**). Good *trans* diastereoselectivity was observed, which followed that the termination step was under general steric control (*i.e.*, **1.158** *versus* **1.160**).[133,134] The analyses of Stern-Volmer

experiments and reduction potentials revealed both oxidative and reductive quenching pathways to be thermodynamically feasible.



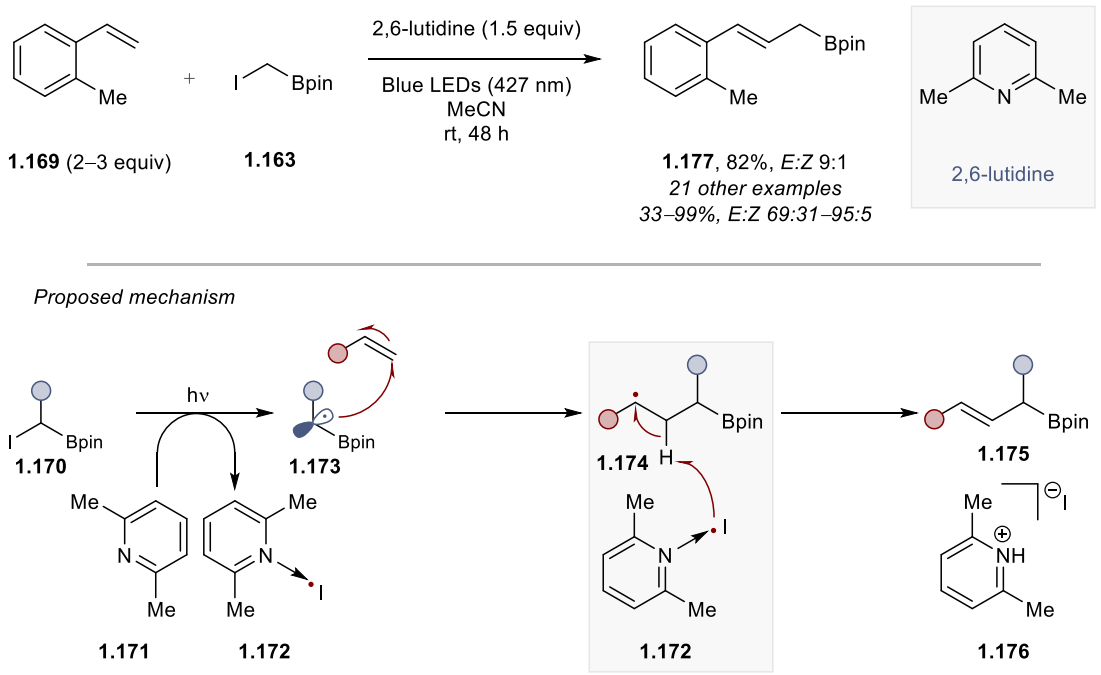
Scheme 1.34: Diastereoselective cyclopropanation using a diiodomethyl boronic acid pinacol ester. In structure **1.159**, 'anti' is with respect to the boronic ester.

In 2020, Leonori and coworkers used amines to generate aminoalkyl radicals which could promote C–X homolytic bond cleavage or aryl and alkyl halides without typical initiators such as tin or silicon reagents,[135–137] or ultraviolet light.[132] This mode of radical formation through the abstraction of a halogen using a suitable transfer reagent is known as halogen atom transfer.[138] Within the reported scope, a single example used a halomethyl boronic acid pinacol ester as the halide counterpart (Scheme 1.35).[139] A stark difference in reactivity was observed between the bromide **1.163** and iodide **1.164**, although radicals derived from alkylborane oxidation also struggle to serve as efficient initiators for alkyl bromides.[125]



Scheme 1.35: Generation of α-boryl radicals via aminoalkyl radicals.

In 2023, Molloy and coworkers reported a stereodivergent synthesis of *trans*-allylic boronic esters prepared from halomethyl organoboron reagents and styrenes (Scheme 1.36).[140] Unlike Leonori's process using aminoalkyl radicals,[139] the α-boryl radical is formed *in situ* using a Lewis base — 2,6-lutidine — and no photocatalyst. The mechanism of single electron transfer is reportedly dichotomous to Studer's original report using vinyl boronates,[124] where an iodide radical is involved as opposed to a second molecule of the alkyl iodide.



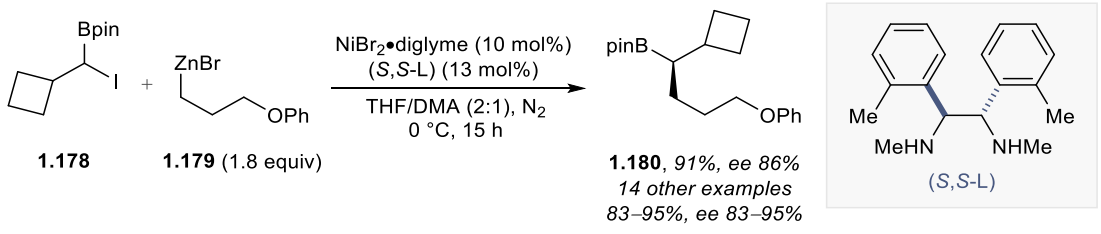
Scheme 1.36: Synthesis of *trans*-allylic boronic esters.

1.3.2 Reactions under transition metal catalysis

Transition metal catalysis is often considered one of the central pillars of modern organic chemistry, both in academic and industrial settings.[7,102,119,141–144] The ability of transition metals to activate a plethora of bonds through two-electron or single-electron pathways continues to unlock novel transformations, which has been acknowledged by three Nobel Prizes in the past two decades.[7,145,146] Moreover, the advent of photocatalysis has enabled a variety of dual "metallaphotoredox" processes to emerge.[147–149] Nickel and palladium continue to dominate this reaction space in the transformations of α-halogen organoboron reagents. These reactions are summarised chronologically below, with discussion focussing on the manipulations of α-halogen organoboron reagents with respect to the transition metal catalyst. A more thorough mechanistic discussion around transition metal (Suzuki–Miyaura) cross-coupling will be presented in later Sections.

1.3.2.1 Nickel catalysis

In 2016, Fu and coworkers reported an asymmetric nickel-catalysed cross-coupling of α-halogenated boronic esters with organozinc reagents (Scheme 1.37).[150] Generally excellent yields and enantioselectivities were observed using a simple diamine ligand and mild conditions, although the loading of nickel catalyst was relatively high. The organozinc reagents (*i.e.*, **1.179**) were prepared in a separate operation at 70 °C for 12 h. In comparison to Jacobsen's later work, which used a chiral catalyst to influence a 1,2-metalate rearrangement,[109] this was the first example of a chiral catalyst being applied to achieve a net Matteson-type displacement of an α-halogenated boronic ester. Although not explicitly proven by the Authors, the reaction is analogous to a Negishi coupling where the α-iodinated boronic ester **1.178** is assumed to undergo oxidative addition to nickel(0).[141,151]

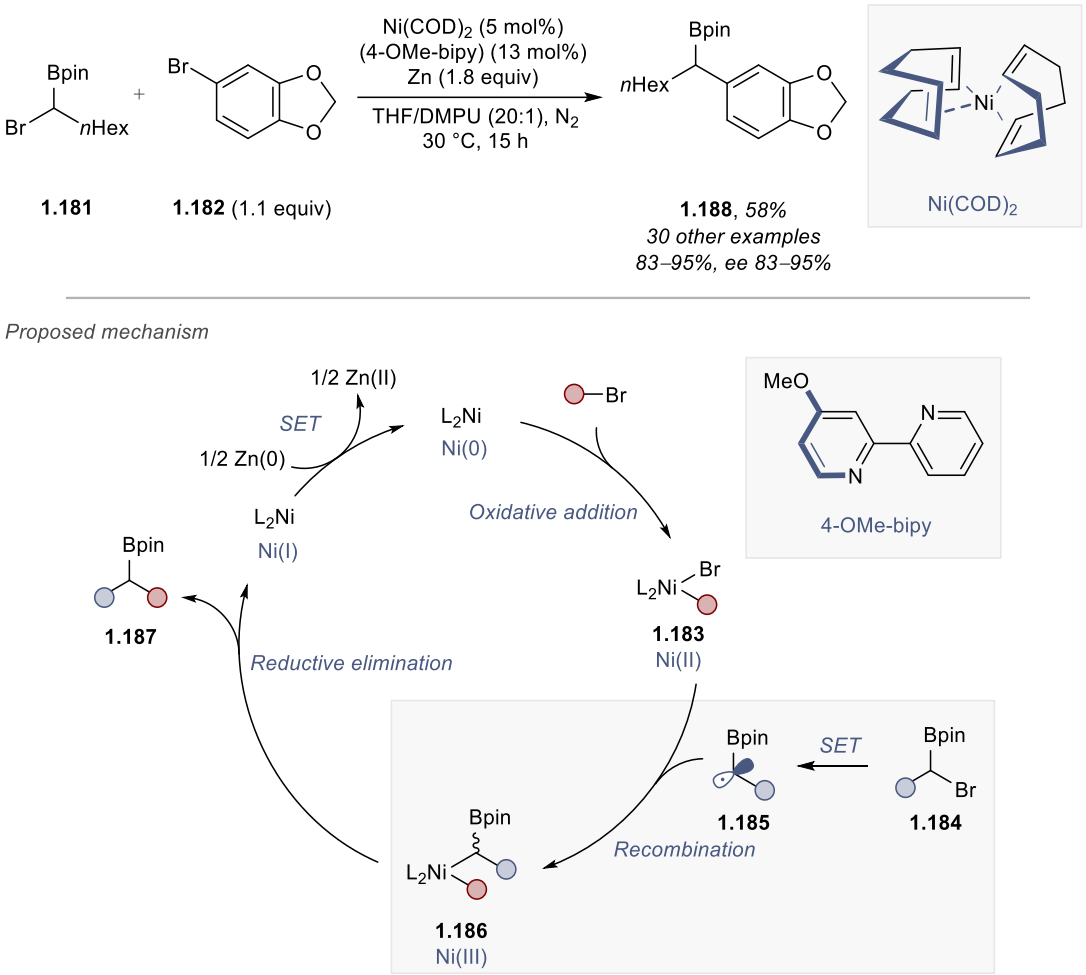


1.178 **1.179** (1.8 equiv) **1.180**, *91%, ee 86%*
14 other examples
83–95%, ee 83–95%

Scheme 1.37: Asymmetric nickel-catalysed cross-coupling of α-halogenated boronic esters.

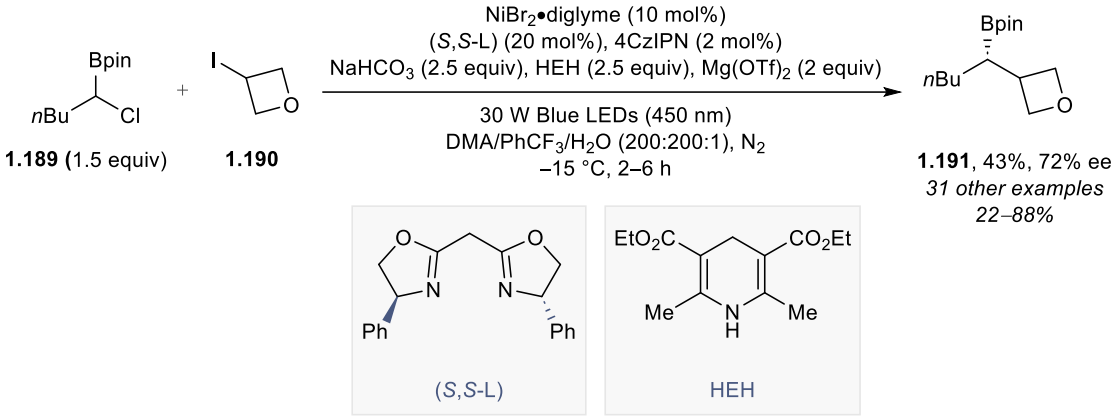
In 2018, Martin and coworkers reported a nickel-catalysed arylation of α-bromomethyl boronic esters (*e.g.*, **1.181**, Scheme 1.38).[152] Under these conditions, the α-halogenated boronic ester does not participate in the oxidative addition step, thereby reversing the

polarity of the cross-coupling originally reported by Fu and coworkers.[150] Instead, a single electron transfer event forms an α-boryl radical (*i.e.*, **1.185**), which can recombine with the oxidative addition complex **1.183**. Subsequent reductive elimination from nickel(III) to nickel(I) affords the coupled product (*i.e.*, **1.187**/**1.188**), which was supported by the requirement for zinc(0) to act as a sacrificial reductant to close the catalytic cycle.[152] A similar transformation was reported by the same group in 2018 using olefins rather than aryl halides, but the mechanistic outlook was unclear between a similar single electron transfer event from an α-boryl radical, or a two-electron transfer of a nickel hydride intermediate.[153]



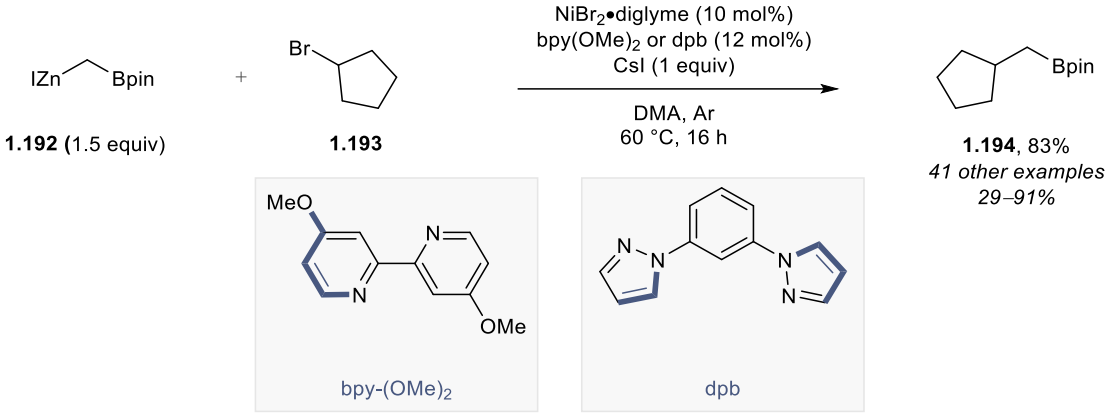
Scheme 1.38: Nickel-catalysed arylation of α-bromomethyl boronic esters.

In 2023, Xu and coworkers reported an enantioselective reductive cross-coupling of alkyl halides and α-chloromethyl boronic esters using dual nickel/photoredox catalysis (Scheme 1.39).[154] Simple reductants to turnover the photocatalyst, such as zinc,[152] were ineffective and a Hantzsch ester (HEH) was essential. The exact species involved in the catalytic cycle were unclear, with both oxidative addition and single electron transfer events proposed with reference to the α-chloromethyl boronic ester **1.189**.



Scheme 1.39: Enantioselective reductive cross-coupling of α-chloromethyl boronic esters.

In the month following Xu and coworkers' report,[154] Zhan and coworkers reported a Negishi-type coupling of alkyl halides and an α-borylated organozinc reagent **1.192**, derived from the requisite α-bromomethyl boronic ester (Scheme 1.40).[155] The polarity of the cross-coupling is flipped in comparison to Fu's original report,[150] with the tolerance towards secondary and tertiary alkyl halides being a notable improvement. When tertiary alkyl halides were used, zirconium tetrachloride was used as an additive instead of caesium iodide.[155]

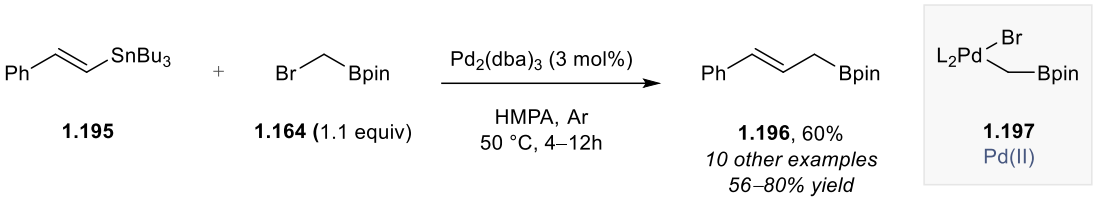


Scheme 1.40: Coupling of an α-borylorganozinc reagent with secondary and tertiary halides.

1.3.2.2 Palladium catalysis

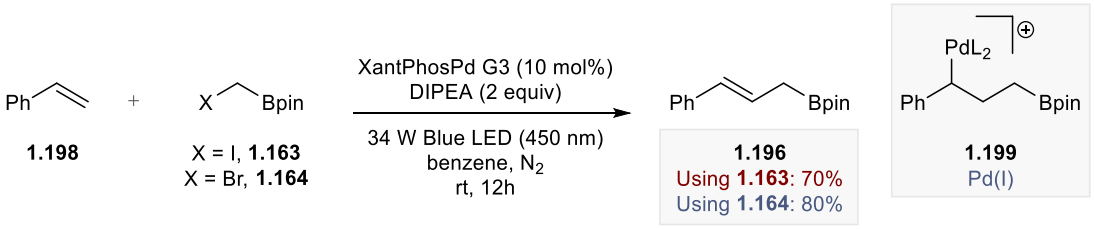
Palladium catalysis was first employed in reactions with α-halomethyl boronic esters far earlier than nickel catalysis but is otherwise less explored. In 1999, Falck and coworkers reported a Stille coupling between styryl and aryl stannanes, and an α-bromomethyl boronic ester (*i.e.*, **1.164** , Scheme 1.41).[156] It is likely that hexamethylphosphoramide was used to behave as a cooperative ligand to palladium, although no mechanistic information or optimisation was provided.[157] Assuming that the reaction follows a mechanism analogous to Stille's cross-coupling,[158,159] the α-bromomethyl boronic ester oxidatively adds to

palladium(0). It is likely that the use of highly toxic stannanes facilitates rapid transmetalation in this unusual C(sp^3)–C(sp^2) coupling.[142,159]



Scheme 1.41: Stille reaction of $BrCH_2Bpin$ *via* oxidative addition.

In 2017, Gevorgyan and coworkers reported a visible-light promoted Heck reaction of alkyl halides and styrenes.[160] Within the scope, an example was disclosed using an α-halomethyl boronic ester **1.163** (Scheme 1.42). A radical-based mechanism was proposed which, in the context of **1.163** or **1.164**, would generate an α-boryl radical and a palladium(I) species, which can add to styrene **1.198** and afford a cationic palladium(I) intermediate **1.199**. Notably the Authors used two sets of conditions — using either those outlined to afford product **1.196**, or palladium(II) acetate, XantPhos, and caesium carbonate — but only conducted mechanistic experiments using the latter, which were never applied to the α-halomethyl boronic esters **1.163** or **1.164**. This is problematic because, in contrast to Leonori's single electron transfer example,[139] the α-iodomethylboronic ester **1.163** performed worse than the equivalent α-bromomethylboronic ester **1.164**. Intriguingly, the same palladium catalyst and conditions were reported by Gevorgyan and coworkers a year later for the Heck reaction of a tertiary α-iodomethylboronic ester, but with no light activation.[26] No further mechanistic investigation was performed.



Scheme 1.42: Light-induced Heck reaction of XCH_2Bpin *via* single electron transfer.

2. Research outline

Beyond Matteson's initial displacement reaction and Aggarwal's lithiation-borylation strategy, the reactions of α-functionalised organoboron reagents, namely α-halogenated organoboron reagents, can be classified into one of three reaction modes: 1) Boronate formation; 2) Radical formation; and 3) Oxidative addition to transition metals (Figure 2.1). Some reactions vary this dogma by nesting in between these reaction modes, such as transition metal-catalysed reactions that operate *via* single-electron pathways. Nearly all boronate reactions, and several radical-based reactions, require the use of stoichiometric organometallic reagents to facilitate the desired transformation.

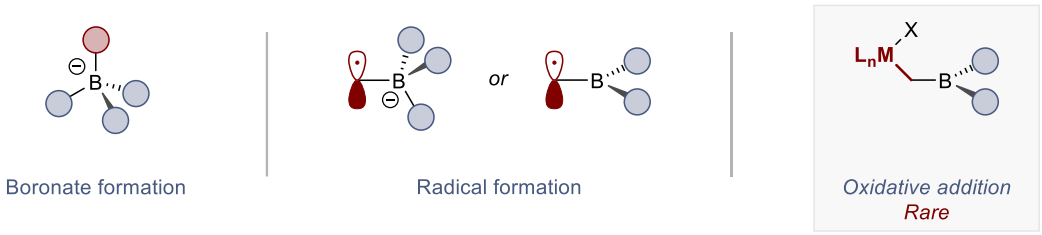
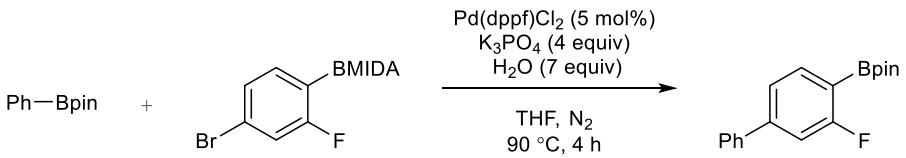


Figure 2.1: General reaction modes of α-halogenated organoboron reagents.

The least explored reaction mode — both methodologically and mechanistically — is the oxidative addition of α-halogenated organoboron reagents to transition metals. To date, the Stille coupling reported by Falck and coworkers is the only example of direct oxidative addition of this reagent class to palladium and there have been no mechanistic investigations reported.[156]

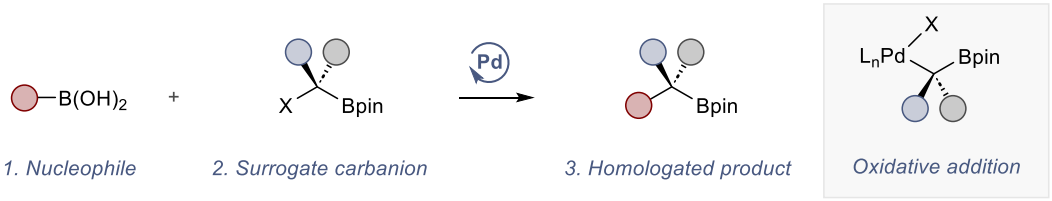
Previous work in the Watson group has utilised the controlled hydrolysis of organoboron protecting groups to facilitate chemoselective Suzuki–Miyaura C(sp^2)-C(sp^2) cross-couplings under palladium catalysis (Scheme 2.2).[161] The behaviour and exchange of organoboron ligands in solution is generally referred to as 'speciation'.[161–165]



2.1 **2.2** **2.3**, 83%
20 other examples
46–84%

Scheme 2.2: Watson-type speciation control of organoboron reagents in Suzuki–Miyaura couplings.

Following a review of boron homologation and the use of α-functionalised organoboron reagents in synthetic methodology, it was proposed that a Suzuki–Miyaura cross-coupling of an α-functionalised organoboron reagent with a boronic acid could enable a net, Matteson-like, organoboron homologation. Rather than relying upon a 1,2-metalate rearrangement and stoichiometric quantities of organometallic reagents, the α-functionalised organoboron reagent would serve as a stable carbanion surrogate and undergo oxidative addition to palladium. Unlike previous efforts using nickel catalysis or Falck's Stille coupling, the proposed homologation would be contingent on the control of three organoboron species in a single reaction: 1) The organoboron nucleophile; 2) The surrogate carbanion; and 3) The homologated product (Scheme 2.3).



Scheme 2.3: Proposed reaction design.

It was anticipated that the controlled transmetalation of these three organoboron species in solution could be overcome by speciation control. Using a halomethyl boronic acid pinacol ester as the surrogate carbanion and a boronic acid nucleophile would deliver a homologated pinacol ester. By tuning the reaction conditions, it was hypothesised that the boronic acid could undergo chemoselective transmetalation without the hydrolysis of either the boronic ester starting material or product. This reaction consideration was essential because, if the homologated product could hydrolyse, uncontrolled homologations could persist and lead to polymerisation.

Based upon the literature review and research outline, a clear set of goals were established for this study:

1. Investigate whether a palladium-catalysed organoboron homologation is operative.
2. Discover the reaction scope and underlying limitations.
3. Gather any new mechanistic insight where appropriate.
4. Demonstrate the synthetic utility of the new homologation strategy.

The results of this thesis are presented in three Sections. The first Section shall describe goals 1–2: The discovery of the palladium-catalysed homologation from hit to scope, including the

current limitations of the methodology. The second shall describe Goal 3: A mechanistic investigation into the oxidative addition of α-halogenated organoboron reagents. The third Section shall discuss goal 4: The onward synthetic utility of the developed homologation process based upon a series of C–C, C–N and C–O bond-forming reactions.

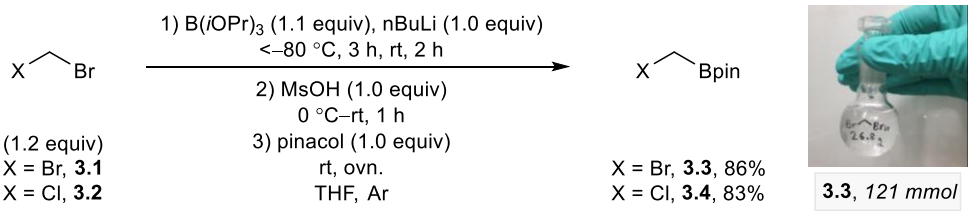
3. Results and discussion

Any compounds that have appeared in the previous Sections have been renumbered for clarity. All compounds in this results and discussion Section are assigned as **3.X**. In the Research Data Management System Repository, all synthesised compounds are just referred to by their **X** component.

3.1 Discovery of the palladium-catalysed boron homologation

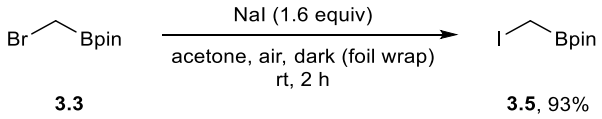
3.1.1 Reaction development

Work began by preparing the relevant starting materials. Both arylboronic acids and the bromomethyl boronic ester **3.3** are commercially available; however, it was more economical to prepare **3.3** by the borylation of dibromomethane**,** based on a modified procedure from Aggarwal and coworkers (Scheme 3.1).[166] The internal temperature of the reaction was kept carefully below −80 °C throughout the formation of the triisopropylborate complex to prevent unwanted degradation of bromomethyllithium,[33,35,36] but the reaction was robust; a reaction at 141 mmol afforded 121 mmol (26.8 g) of compound **3.3** in 86% yield. Anticipating that the electrophile appended to the carbanion surrogate would be investigated during the optimisation, the chloromethyl boronic ester **3.4** was prepared in an analogous manner using bromochloromethane.[35]



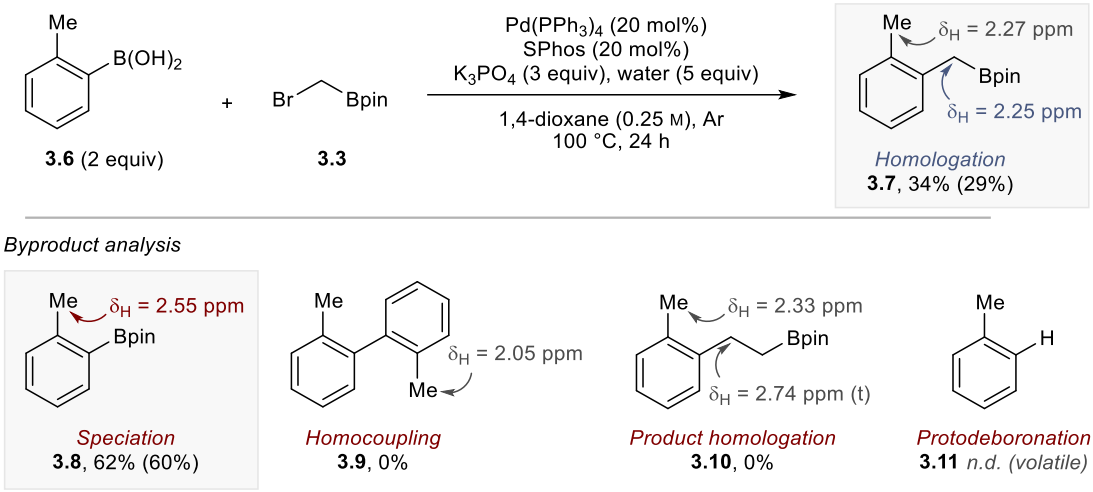
Scheme 3.1: Preparation of the bromine and chlorine carbanion surrogates.

The iodomethylboronic ester **3.5** could be prepared *via* a Finklestein reaction between **3.3** and sodium iodide (Scheme 3.2).[167] The compound has been previously used to prepare α-boryl radicals,[139,140] so the synthesis was performed using a foil-wrapped flask with the fumehood lights turned off to prevent any unpredictable reactivity, then stored accordingly.



Scheme 3.2: Preparation of the iodine carbanion surrogate.

Commercially available *ortho*-tolylboronic acid was selected as the workhorse nucleophile for the model reaction. Using 1,4-dioxane as a typical ethereal solvent for Suzuki–Miyaura cross-couplings that provides an adequate thermal range for heating,[3,11] and a base / water combination commonly employed by our Group as a starting point,[161,163–165] an initial screening campaign identified the below hit and demonstrated that the desired homologation was operative (Scheme 3.3).



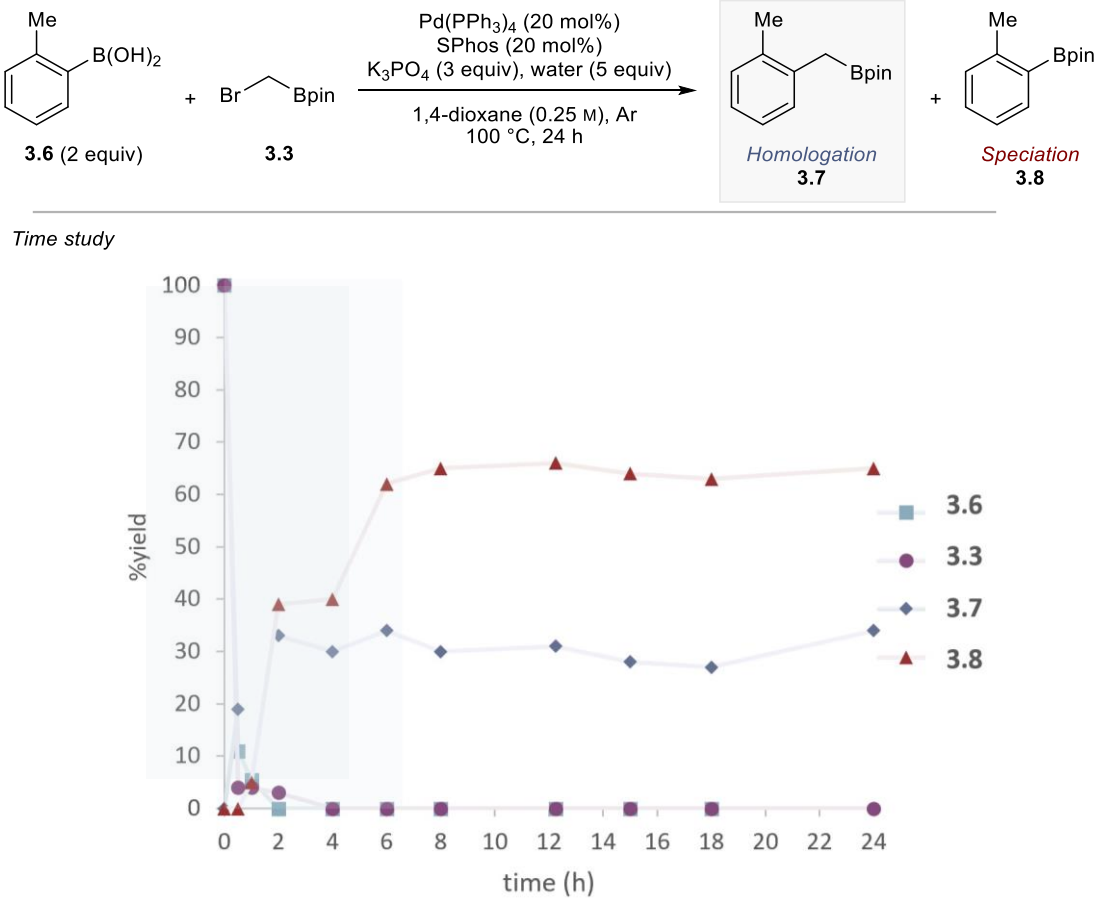
Scheme 3.3: Homologation hit reaction. ^{1}H NMR yields given, isolated yields in parenthesis.

The methylene proton shift of the desired product **3.7** was distinct from any tolyl byproduct peaks to enable identification by ^{1}H NMR assay for subsequent reaction screening (*i.e.*, **3.8**–**3.11**, Scheme 3.4). Specifically, the ^{1}H NMR yield of the desired product **3.7** was obtained by integration of methylene CH_2 (followed by division by two) and the speciated byproduct **3.8** by division of the methylene CH_3 (followed by division by three, for more details see the Experimental) The hit reaction was encouraging for several reasons, other than the formation of the desired product **3.7**. No homocoupling was observed (*i.e.*, **3.9**), and the desired product **3.7** did not re-engage with the palladium catalyst to form the product **3.10** or any related polymers, which implied that a homologation sequence could be adequately controlled. The mass balance of the reaction was tracked by the formation of a speciated byproduct **3.8**, caused by the transesterification reaction of pinacol between the two starting materials **3.3** and **3.6**.[161,163] At this stage, it was unclear whether the fate of excess boronic

acid (*i.e.*, **3.6**) was benign, being filtered off during the workup procedure, or was undergoing a protodeboronation reaction to yield toluene (*i.e.*, **3.11**) which was removed upon evaporation of the crude reaction mixture. Irrespective of route, this simplified the analysis of byproducts.

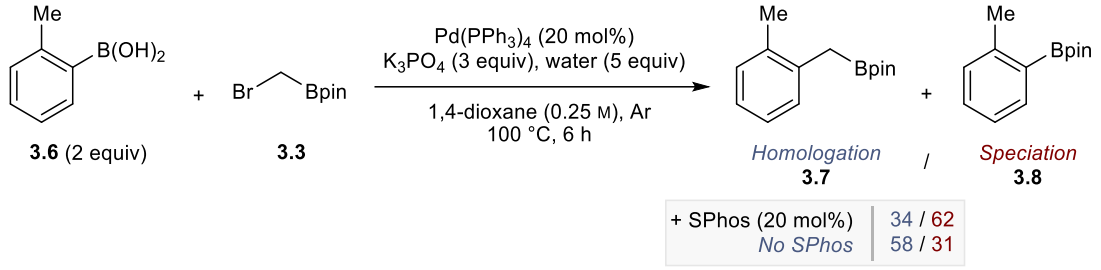
It should be noted that the isolated yields reported in the initial hit reaction were only achieved after several methods were trialled to separate boronic esters **3.7** and **3.8** by silica gel or alumina chromatography. It was essential to overcome this initial isolation challenge early on to develop a synthetically meaningful protocol. A procedure reported by Snaddon and coworkers to prepare silica gel 'capped' with boric acid significantly reduced boronic ester streaking during column chromatography.[168] More details can be found in the Experimental Section.

A time study revealed that the formation of both products reached a plateau after approximately six hours (Scheme 3.4).



Scheme 3.4: Time study of the homologation hit. ^{1}H NMR yields are given using trichloroethylene as an internal ^{1}H NMR standard, and each time point was recorded from an independent reaction.

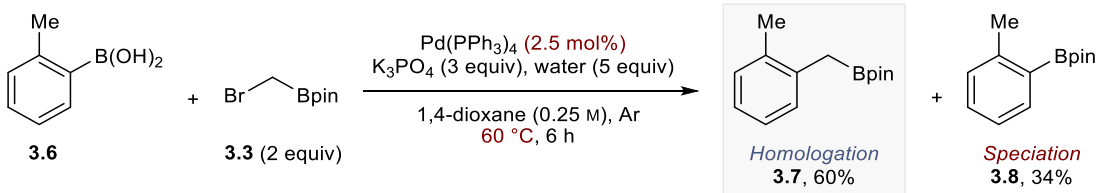
Initially, SPhos was added as an exogenous ligand to prepare an electron-rich palladium complex *in situ*. The reaction was quickly simplified by removing SPhos from the reaction mixture entirely (Scheme 3.5). Strikingly, the removal of SPhos significantly increased the yield of the desired homologation (Scheme 3.5). The rationale behind this result is addressed in later Sections.



Scheme 3.5: Effect of SPhos removal. ^{1}H NMR yields are given using trichloroethylene as an internal standard.

For the remainder of the optimisation presented in this chapter, all yields are quoted based on ^{1}H NMR assay and were the mean average of two independent reactions. When reactions were not concordant (within ~5% yield), a third reaction was run. All ^{1}H NMR assays were performed using trichloroethylene as an internal standard, with exact details found in the Experimental Section.

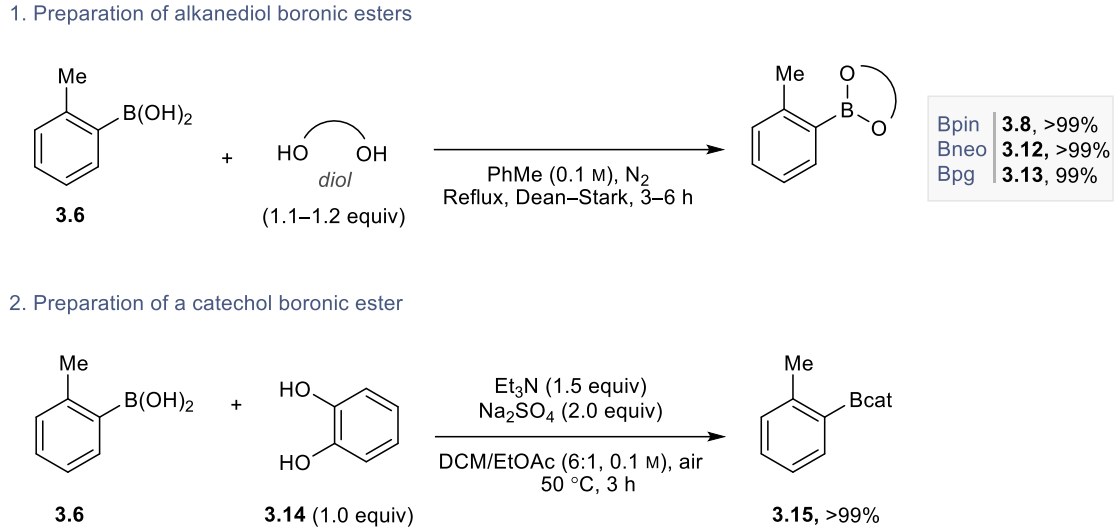
Several optimisation parameters were investigated by Iona Meier, which arrived at the below conditions following the exclusion of SPhos — this was independently verified (Scheme 3.6). Gratifyingly, the loading of palladium catalyst was significantly reduced while retaining the same yield afforded above (compare Scheme 3.5). The reaction could also tolerate a lower temperature, which was hypothesised to reduce the rate of unwanted speciation.



Scheme 3.6: Verified reaction conditions after optimisation by Iona Meier.

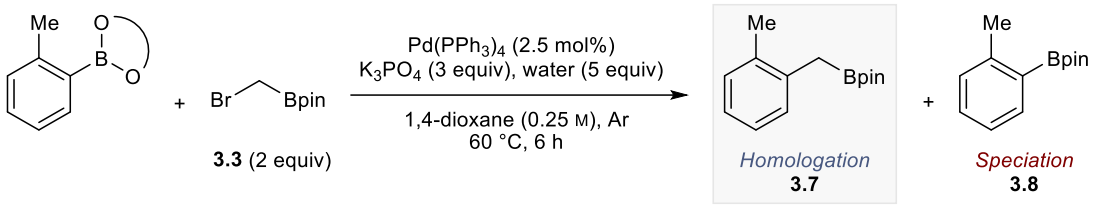
Arylboronic esters are known to undergo direct transmetalation to palladium without the requirement for hydrolysis under certain conditions.[169] Based on the concomitant formation of both **3.7** and **3.8** throughout the time study, it appeared unlikely that the homologation

reaction was proceeding *via* speciation of the arylboronic acid **3.6** to the pinacol ester **3.8** prior to transmetalation. To determine whether the pinacol ester **3.8** could lead to the productive formation of **3.7**, a sample of the boronic ester was prepared alongside several others to investigate speciation control (Scheme 3.7). All boronic esters were prepared according to literature procedures.[170,171]

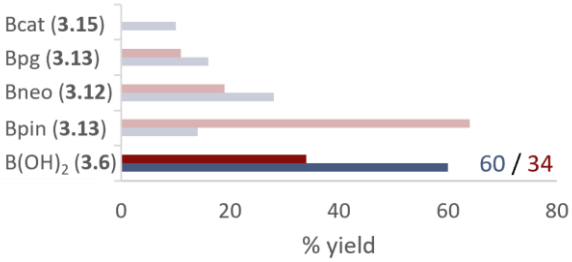


Scheme 3.7: Preparation of arylboronic esters.

The variation of the boron group on the nucleophile was unproductive compared to the boronic acid (Scheme 3.8). In cases where the combined yield of **3.7** and **3.8** was low, the starting material boronic ester remained (*e.g.*, Bcat, **3.15**). The low yield when the pinacol ester (*i.e.*, **3.8**) was used demonstrated that its formation as a speciation byproduct cannot re-engage with the palladium catalyst, which would still lead to a productive homologation. As such, the formation of **3.8** by speciation between **3.3** and **3.6** represents a dead-end pathway in the homologation reaction, which needed to be overcome by alternative means. While the use of propylene glycol and neopentyl glycol esters lead to reduced speciation (*i.e.*, Bneo **3.12** and Bpg **3.13**),[3] these reagents did not transmetalate effectively to afford the desired product.

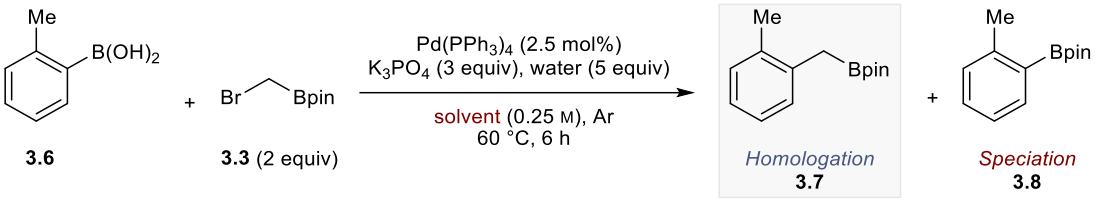


Boron group variation (nucleophile)

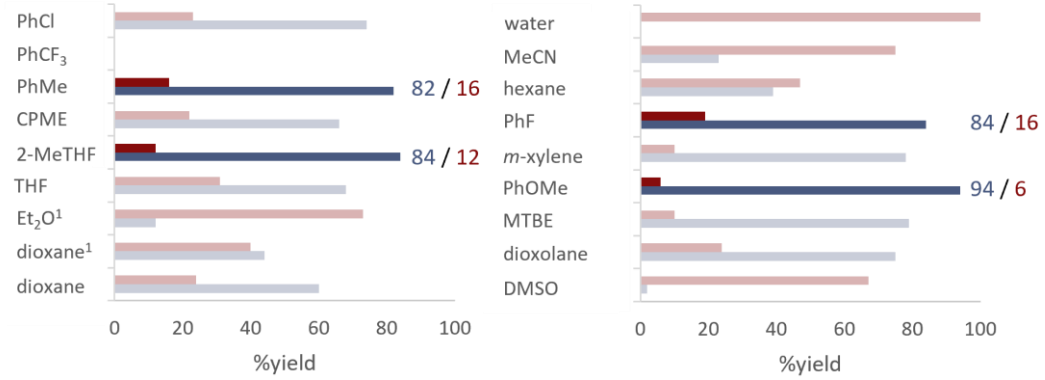


Scheme 3.8: Variation of the nucleophile organoboron protecting group.

The solvent was varied (Scheme 3.9). The use of water lead to quantitative formation of the speciation byproduct **3.8** by facilitating the hydrolysis of compound **3.3**. The use of α,α,α-trifluorotoluene lead to none of the desired product **3.7** or speciated product **3.8** but homocoupling was detected (*i.e.*, **3.9**, 31%) and the reason for this was unclear. To offer a direct comparison of solvent efficacy, both 1,4-dioxane and diethyl ether were used at 40 °C; both the switch to diethyl ether and the reduction of temperature was detrimental to the reaction. In general, polar aprotic solvents performed well, with anisole affording the greatest yield (94%). This observation can be largely rationalised by adequate solubilisation of the boronic acid. Toluene is far less polar than anisole or 2-methyltetrahydrofuran and can lead to boroxine formation *via* dehydration of the boronic acid.[3] This would liberate three equivalents of water thus adjusting the water stoichiometry of the reaction in a manner that benefitted the homologation reaction under these conditions. The 'one variable at a time approach' during optimisation can sometimes lead to false optimums,[172,173] so solvents that performed the best after anisole were noted to screen a broader reaction space in later experiments (*i.e.*, toluene, 2-methyl-tetrahydrofuran). For commercial reasons, fluorobenzene was ruled out.

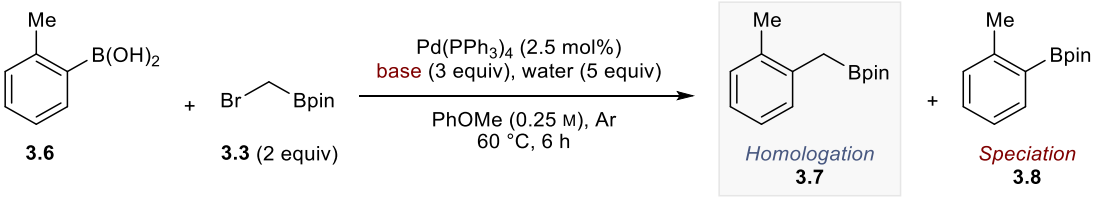


Solvent variation

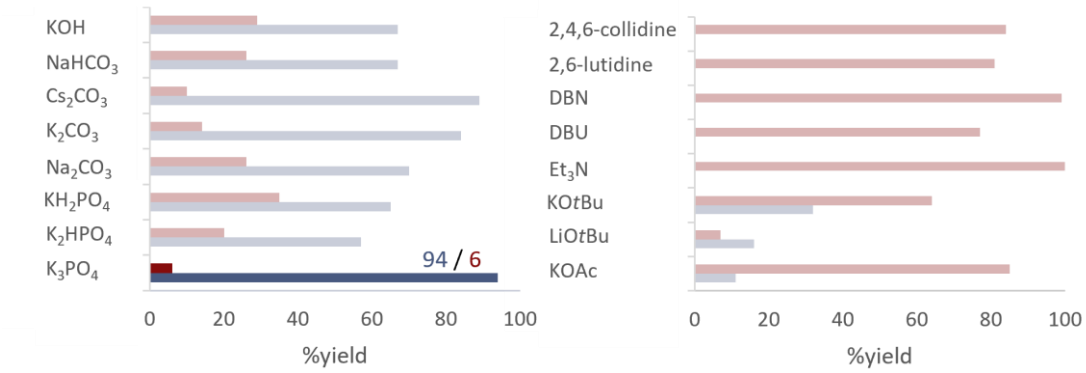


Scheme 3.9: Variation of the solvent.[1] The reactions were performed at 40 °C.

The base was varied (Scheme 3.10). All organic bases were detrimental to the reaction, which could be rationalised by competing reactions with compound **3.3** in conjunction with Matteson's original nucleophilic displacements.[8,50] Similar effects were observed when alkoxide bases were used, whose reactions with the carbanion surrogate **3.3** are also known.[8,51–53] When the remaining non-nucleophilic inorganic bases were assessed, a general positive trend was observed between the yield of the homologated product **3.7** and increasing the pK_a of the conjugate base used (Figure 3.1). This was somewhat surprising given that increasing basicity can influence rates of speciation in Suzuki–Miyaura couplings;[174] however, the use of stoichiometric water likely enabled adequate control of speciation.[161,163] A notable outlier was dibasic potassium phosphate, which gave a lower conversion than its monobasic counterpart. This caveat has previously been observed in Suzuki–Miyaura cross-couplings and can be explained by the reduced aqueous solubility of the dibasic potassium phosphate.[161]



Base variation



Scheme 3.10: Variation of the base.

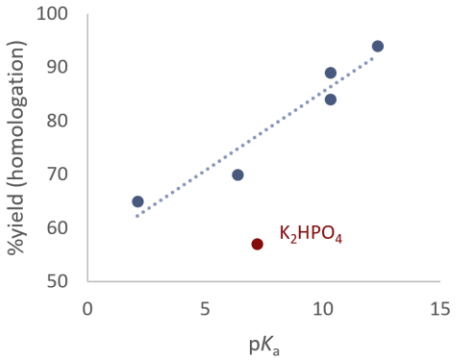
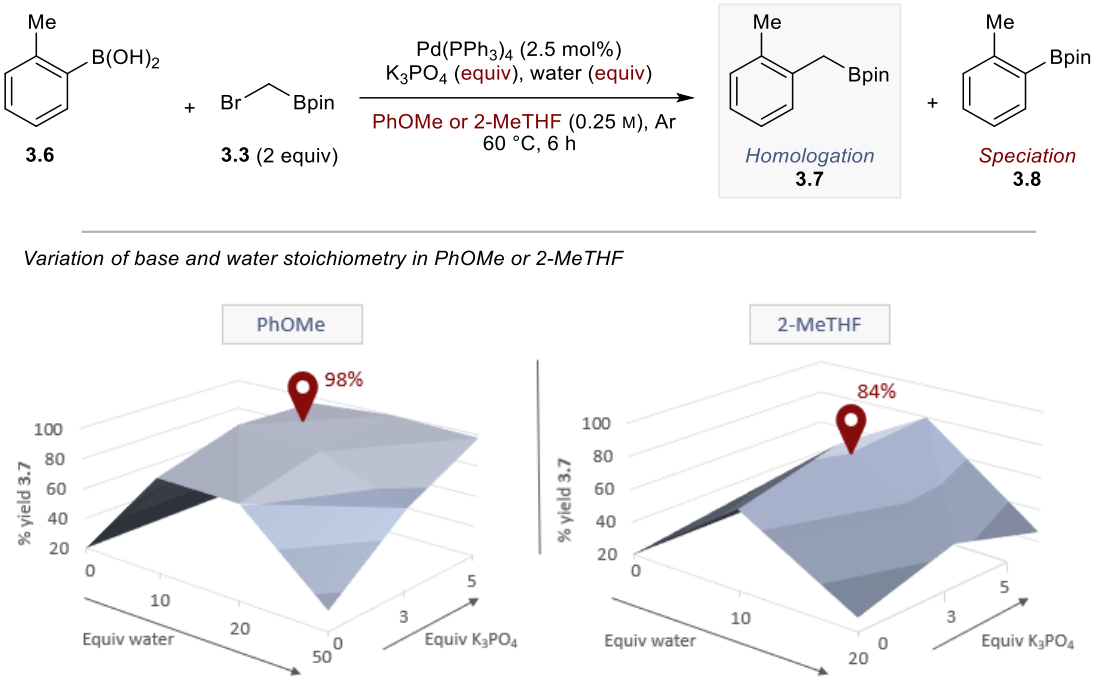


Figure 3.1: Variation of non-nucleophilic bases as a measurement of p*K*a.

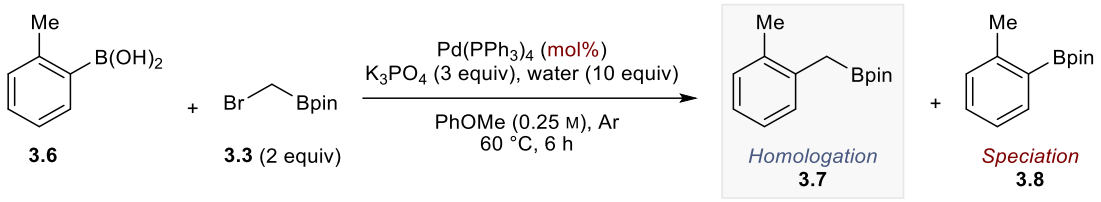
To probe speciation effects further, the stoichiometries of water and tribasic potassium phosphate were varied by selecting a series of variable combinations in both anisole and 2-methyltetrahydrofuran (Scheme 3.11). The developed response surface plot indicated that increasing the water equivalents improved the reaction up to ten equivalents; however, yields declined significantly beyond twenty equivalents. This sensitivity to water loading beyond twenty equivalents generally agreed with previous reactions of boronic esters with MIDA boronates, where oligomerisation of starting materials occurred beyond 25 equivalents of water due to poor speciation control.[161] Likewise, a balance of potassium phosphate loading was essential, and deviations above or below three equivalents lead to drops in the yield of the desired homologation. In general, equivalent combinations of base and water performed better in anisole than 2-methyltetrahydrofuran, with three equivalents of base and ten equivalents of water both offering the best yields (98% *versus* 84%). Reactions using 2-methyltetrahydrofuran were generally more sensitive to slight deviations in base and water stoichiometries – notably, a drop from 84% to 44% yield was observed when the loading of water increased from ten to twenty equivalents. In anisole, an optimised 'plateau' was reached where deviations from 5–20 equivalents of water and 3–5 equivalents

of base all afforded yields of the desired homologation in the range of 92–98%. These differences in sensitivity to water loading may arise from the slightly lower solubility of 2-methyltetrahydrofuran in water compared to anisole, thus creating a more well-defined aqueous biphase that can pool a higher concentration of hydroxide ions.[174]

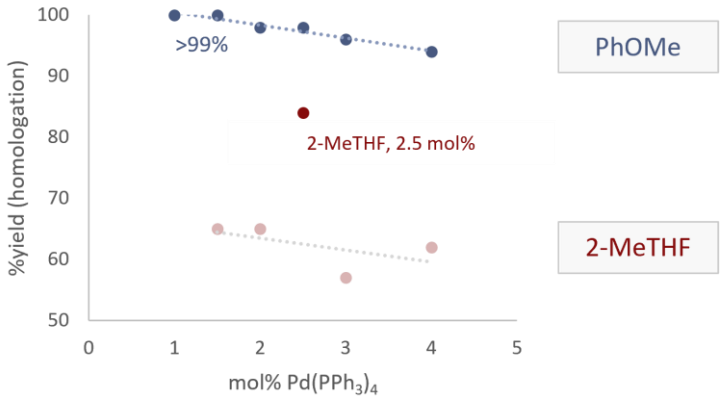


Scheme 3.11: Variation to base and water stoichiometry. Only data for the formation of desired homologation product **3.7** is shown. In general, the mass balance of all reactions was accounted for quantitatively by the combined yields for homologation **3.7** and speciation **3.8**.

A practical limitation of using anisole was the high boiling point. Trial purifications found that anisole coeluted with the boronic ester during column chromatography, so the only reliable method of removal was high vacuum. To circumvent this problem and gather more data about other reaction parameters, optimisation continued using both anisole and 2-methyltetrahydrofuran. The loading of palladium catalyst was investigated and, gratifyingly, could be reduced to just 1% in anisole (Scheme 3.12). The benefits of further reducing catalyst loading, which could not be done in 2-methyltetrahydrofuran, outweighed the drawbacks of removing anisole by high vacuum.

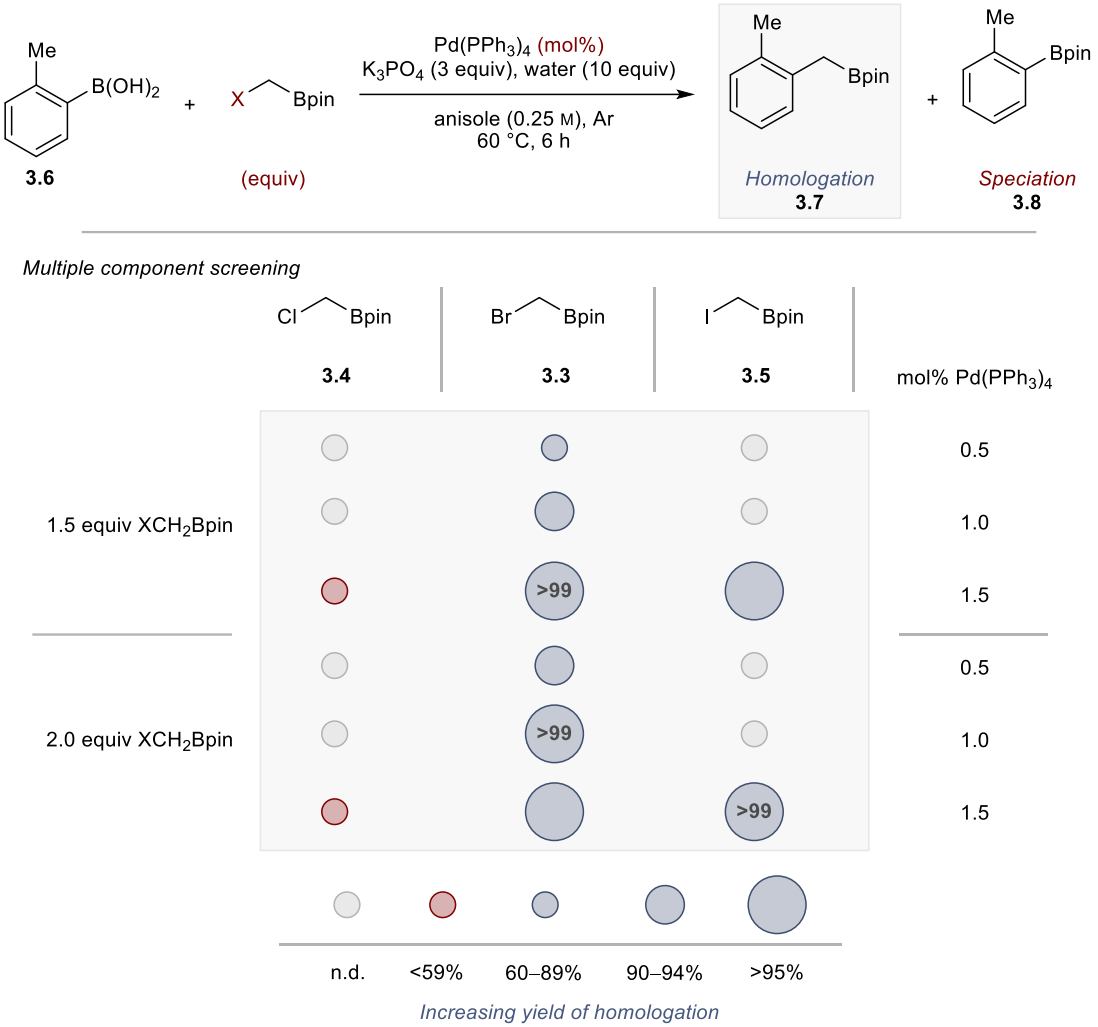


Variation of catalyst loading in PhOMe or 2-MeTHF



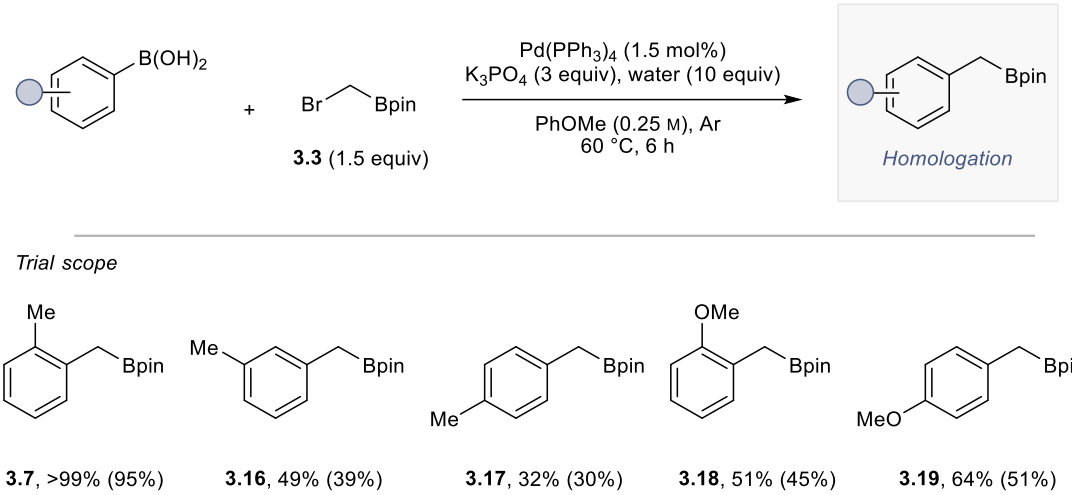
Scheme 3.12: Variation to catalyst loading. Only data for the formation of the desired homologation product **3.7** is plotted. In general, the mass balance of all reactions was accounted for quantitatively by the combined yields for homologation **3.7** and speciation **3.8**.

A panel of multiple component variations were setup by varying the halide appended to the carbon donor, its stoichiometry, and the loading of palladium catalyst (Scheme 3.13).[172,173] The chloride **3.4** performed much worse than the bromide **3.3** at 1.5 mol% catalyst loading so was not investigated further (59% *versus* >99%). Gratifyingly, the loadings of both the bromide **3.3** and iodide **3.5** could be reduced to 1.5 equivalents; however, using less than 1.5 mol% catalyst loading was either less effective or furnished inconsistent results. When used at 1.5 equivalents for 1.5 mol% catalyst loading, the bromide **3.3** only slightly outperformed the iodide **3.5** (>99% *versus* 96% yield); however, the iodide **3.5** must be made over two steps which affirmed the optimised conditions using **3.3**.



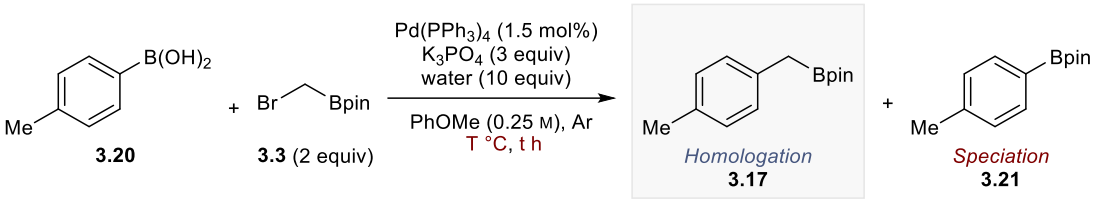
Scheme 3.13: Variation of donor and catalyst loadings. In general, the mass balance of all reactions was accounted for quantitatively by the combined yields for homologation **3.7** and speciation **3.8**.

The developed homologation conditions were tested for generality using four commercially available boronic acids (Scheme 3.14). Yields were disappointing; the switch from *ortho*- to *meta*- or *para*-substitution lead to a significant drop in yield (*i.e.*, **3.16** and **3.17**), although in the case of *para*-substitution this could be partially fixed using an electron-donating substituent (*i.e.*, **3.19** *versus* **3.17**). Given the generally excellent yields afforded using traditional Matteson- and Aggarwal-type boron homologations,[16,17,19,20,30,31,99,110,166] reoptimisation was required to achieve a competitive process. *Para*-tolyl boronic acid was selected as the new workhorse substrate because it was both available in sufficient quantities for screening and performed the worst in the trial scope (*i.e.*, product **3.17**).

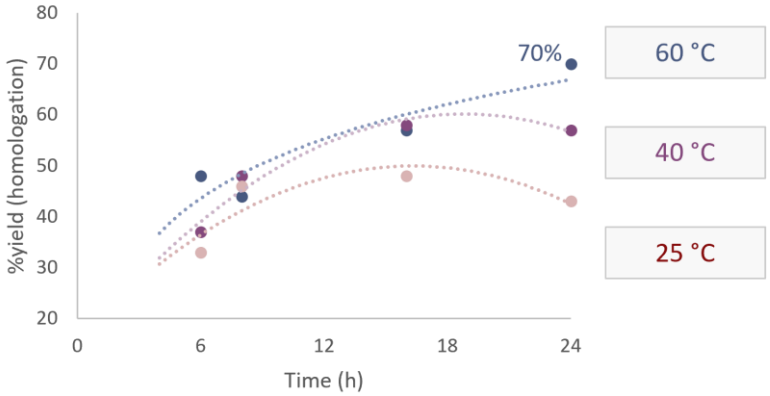


Scheme 3.14: Trial substrate scope. ^{1}H NMR assay yields are given using trichloroethylene as an internal standard, with isolated yields in parentheses. More details can be found in the Experimental Section.

It was hypothesised that some substrates were reacting more slowly than others, so the time was extended (Scheme 3.15). Gratifyingly, simply leaving the reaction for 24 hours using *p*-tolyl boronic acid increased the yield from 32% to 70%. The remainder of the mass balance could still be tracked by the unwanted speciation reaction. It was hypothesised that lowering the temperature of the reaction could reduce the rate of speciation, yielding a greater quantity of the desired product. In an analogous manner to the study at 60 °C, the reaction time was extended at 40 °C and 25 °C. No further improvements in yield were made, with little changes to the yield of homologation product **3.17** after eight hours.

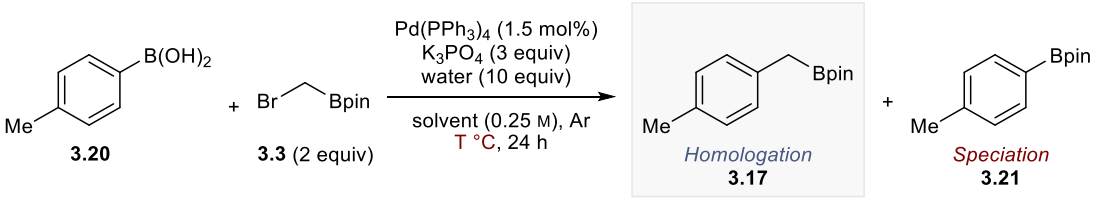


Variation of temperature and time

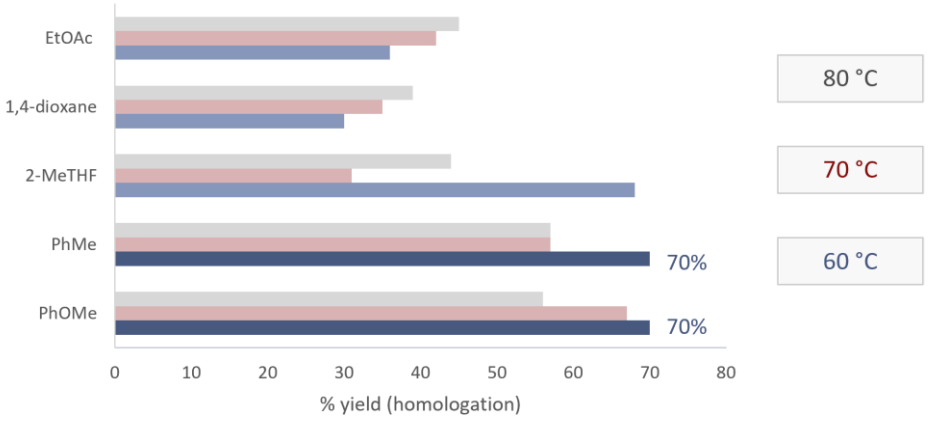


Scheme 3.15: Variation of temperature and time. Individual reactions were run for each time point.

The temperature was increased with varying solvents (Scheme 3.16). No further improvements to the yield of **3.17** were achieved with an elevated temperature, suggesting that 60 °C provided optimal reactivity without degrading **3.3**. Following the first round of screening, toluene and anisole remained the superior solvent choices.

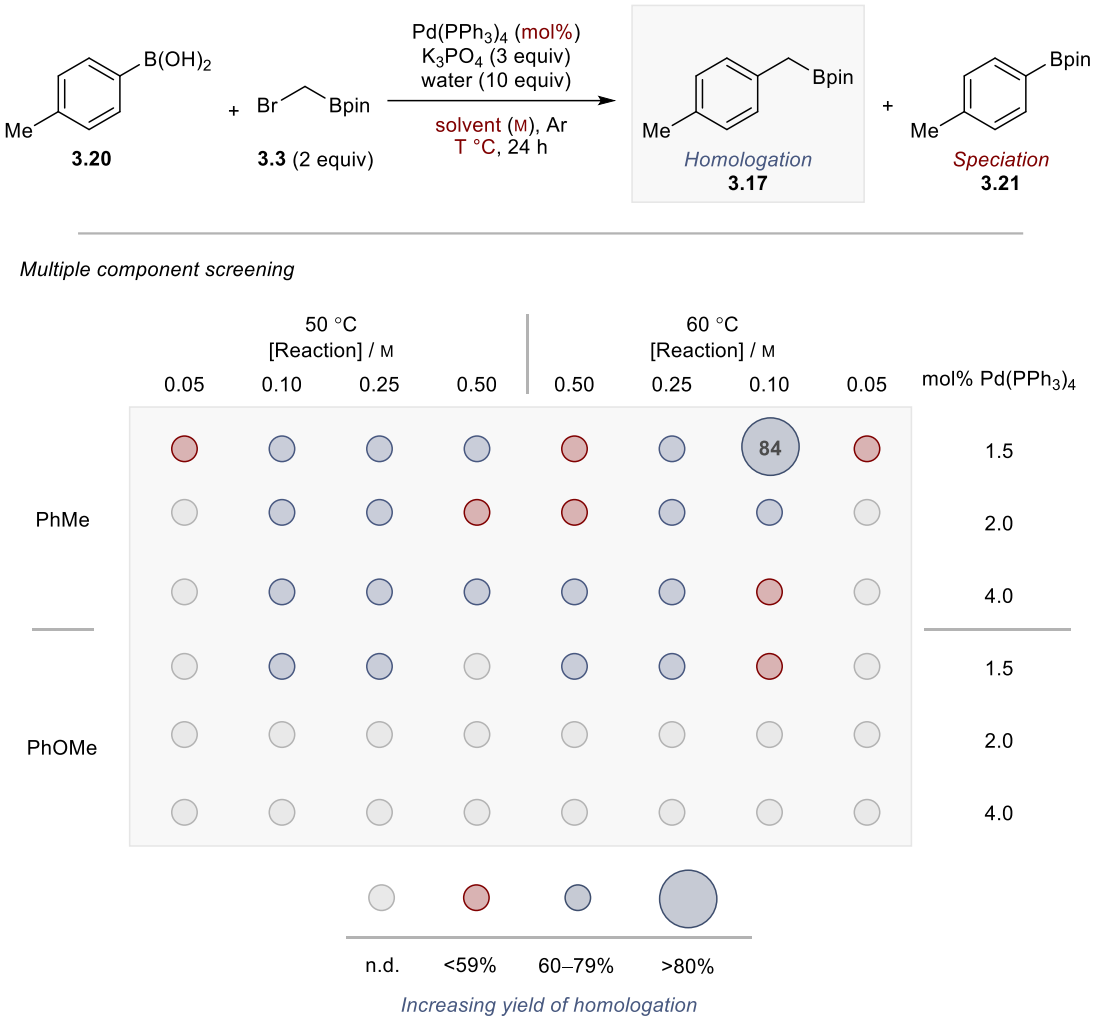


Variation of temperature and solvent



Scheme 3.16: Variation of temperature and solvent.

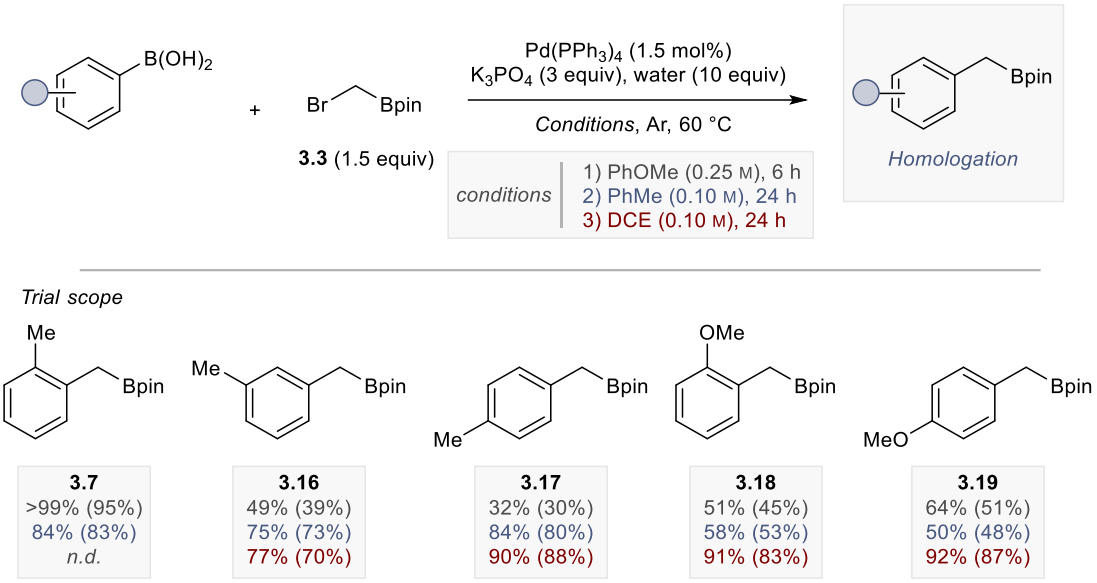
Catalyst loading, concentration, and temperature were varied in both toluene and anisole, with reaction combinations selected based on responses from six runs at a time (Scheme 3.17). Toluene was superior in comparison to anisole and benefitted from a reduced reaction concentration (0.1 M) to afford an assay yield of 84% for the formation of **3.17**, although this could not be further improved by increasing the loading of catalyst. Reactions at 50 °C generally followed the same trends to concentration and solvent but at a reduced yield, further demonstrating the balance of reactivity achieved at 60 °C.



Scheme 3.17: Variation of concentration, temperature, and catalyst loading in toluene and anisole.

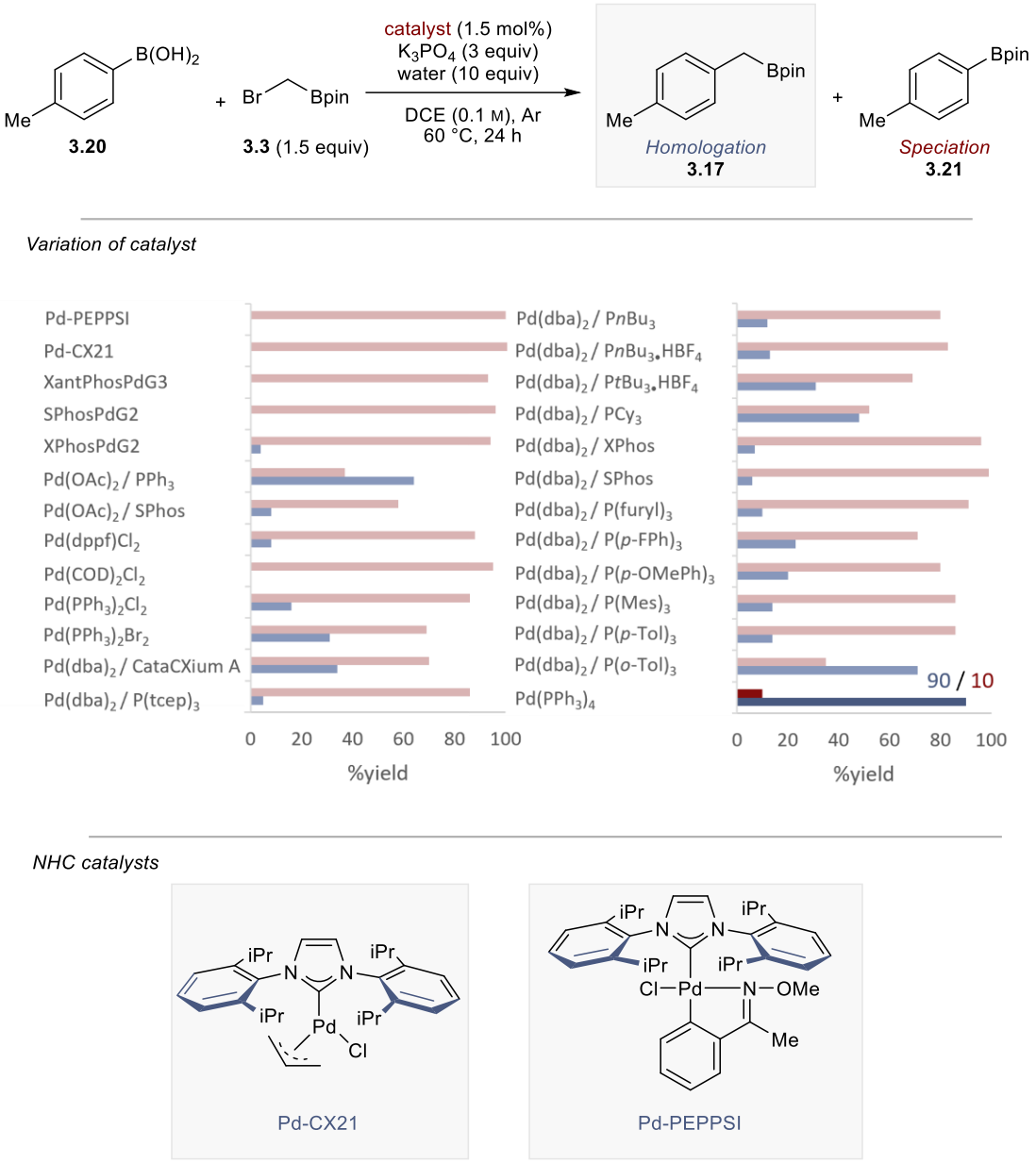
The reaction conditions were re-evaluated against the test substrates again (Scheme 3.18). In general, yields were improved significantly, although some decreased compared to the previous anisole conditions (*i.e.*, **3.7** and **3.19**). Fortuitously, a simple change of solvent from toluene to 1,2-dichlorethane afforded generally excellent yields (>90%, **3.17**–**3.19**). It was

unclear what the exact cause of this was, although it was noticed during reaction setup that reaction mixtures appeared more homogenous than those using toluene or anisole.



Scheme 3.18: Trial substrate scope.

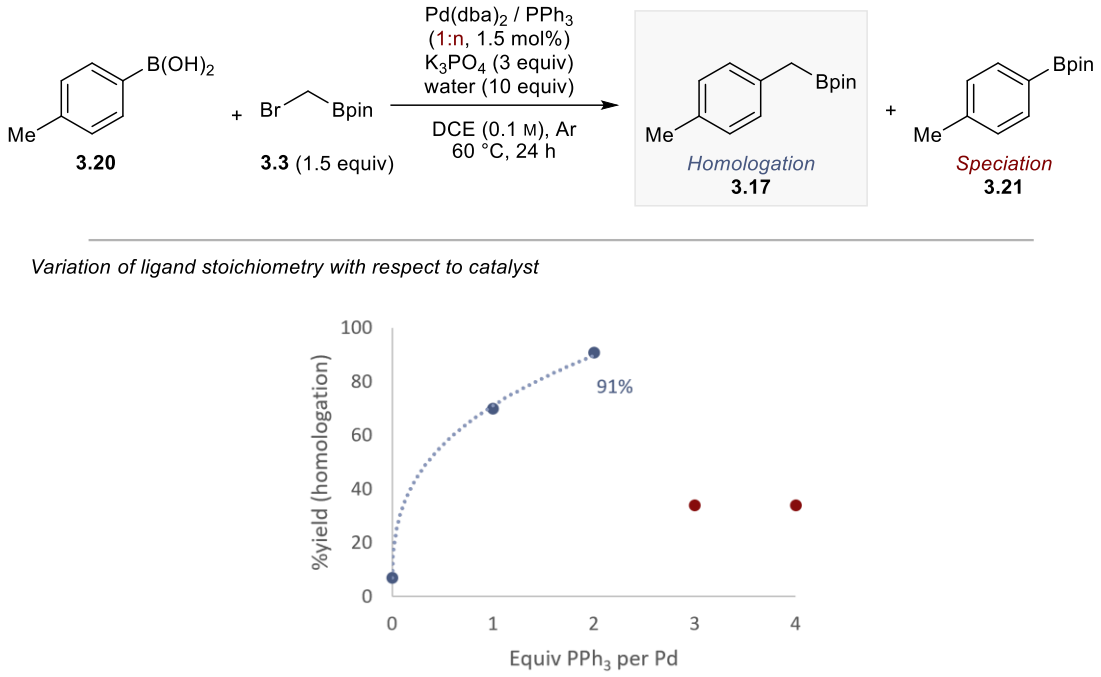
To identify a hit for the homologation process, the catalyst was initially varied (*i.e.*, Scheme 3.3). With all other reaction components investigated during the main optimisation phase, it was pertinent to reevaluate the role of the palladium catalyst again. A series of palladium(0) and palladium(II) catalysts were varied alongside various ligand combinations (Scheme 3.19). The results were striking: nearly all deviations to the catalyst lead to a significant drop in the yield of the desired homologation product **3.17**. This finding was highly unusual; not only did preactivated palladium(II) catalysts fail entirely *(i.e.*, G2 and G3 catalysts, NHC-based catalysts Pd-CX21 and Pd-PEPPSI), but the outright best performing catalyst —tetrakis(triphenylphosphine)palladium(0) — is one of the most simple and commercially abundant catalysts utilised in Suzuki–Miyaura cross-couplings.[142,177] While this makes the developed reaction conditions synthetically attractive towards cost-effective industrial applications, the underlying rationale behind these observations were unclear at this stage but is elaborated on in later Sections.



Scheme 3.19: Variation of palladium catalyst. A 2:1 ligand/palladium ratio was used for all reactions using an exogenous ligand source.

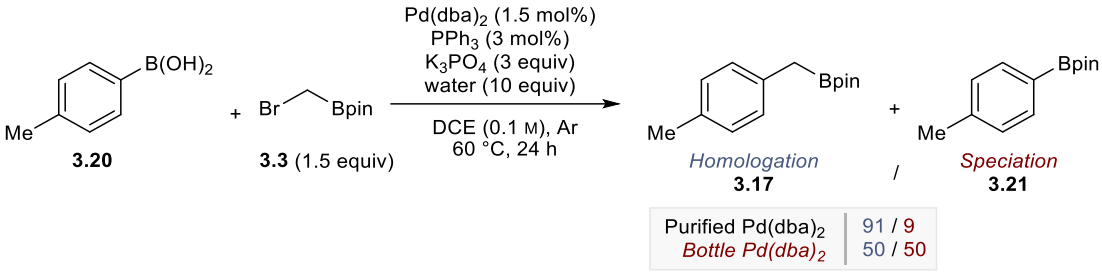
Similar results could be achieved compared to tetrakis(triphenylphosphine)palladium(0) by using triphenylphosphine and bis(dibenzylideneacetone)palladium(0). The stoichiometry of triphenylphosphine with respect to palladium(0) was detrimental to the reaction (Scheme 3.20). In the Suzuki–Miyaura cross-couplings of benzyl boronic esters, Crudden and coworkers required a threefold excess of triphenylphosphine when using tri(dibenzylideneacetone)dipalladium(0) (*i.e.*, 12:1 phosphine:palladium),[178] whereas this homologation reaction only required the theoretical minimum amount of triphenylphosphine to furnish a 14-electron complex (*i.e.*, 2:1 phosphine:palladium). Unlike

Falck's original reaction conditions for the homologation of stannanes,[156] bis(dibenzylideneacetone)palladium(0) alone was insufficient. As previously noted during the Introduction (Section 1.3.2), this finding highlights the plausible non-innocent nature of using hexamethylphosphoramide as a solvent in Falck's original report which still required twice the loading of palladium catalyst. For safety reasons, no reactions were undertaken using hexamethylphosphoramide for this homologation.



Scheme 3.20: Variation of ligand loading with respect to palladium(0).

It is worth highlighting that the yields obtained using exogenous triphenylphosphine and bis(dibenzylideneacetone)palladium(0) could only be obtained when the palladium catalyst was recrystallised twice from chloroform/water, then dried and placed in an argon-filled glovebox (Scheme 3.21). As such, the use of preformed tetrakis(triphenylphosphine)palladium(0) was more practically appropriate and reliable for onward use. Further discussion surrounding ligand effects can be found in Sections 3.1.3 and 3.2.



Scheme 3.21: Discrepancy between yields obtained using bis(dibenzylideneacetone)palladium(0).

The developed set of conditions provided sufficient confidence to enter a full substrate scope with encouraging and synthetically valuable yields. The outcome of this scope shall be detailed in the following Section.

3.1.2 Example scope and limitations

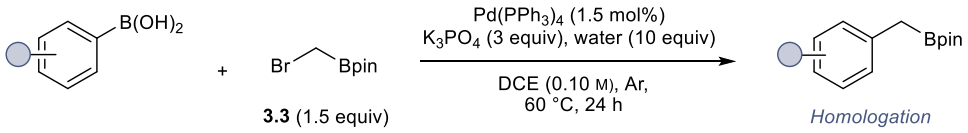
This Section shall explore the generality of the developed palladium catalysed homologation reaction and discuss the underlying limitations. All substrates were attempted using each of the three reaction conditions outlined during the final trial screen (*i.e.*, Scheme 3.18), to eliminate any ambiguity in cases where the obtained yield was moderate or poor. For all substrates, ^{1}H NMR yields were determined using trichlorethylene as an internal standard prior to column chromatography on boric acid-capped silica gel. More details can be found in the Experimental Section.

The conditions using 1,2-dichloroethane outperformed the conditions using toluene or anisole in 93% of successful cases. In unsuccessful cases, there was no difference in outcome between the three sets of reaction conditions and these limitations are outlined later on in this Section. As such, the conditions using 1,2-dichlorethane (0.1 M, 60 °C, 24 h) were taken as the standard reaction conditions for the remainder of the study, including all robustness and mechanistic investigations outlined in later Sections.

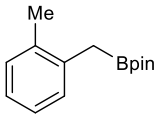
The generality of the developed reaction was first examined using a range of arylboronic acids (Scheme 3.22). The reaction conditions generally accommodated steric substitution around the boronic acid well (*e.g.*, **3.7, 3.24, 3.49**). Electron-rich examples were also well tolerated, including alkyl- (**3.18**, **3.19**, and **3.33**–**3.35**), fluoroalkyl- (**3.41**) and silyl- ethers (**3.28**, **3.29**), as were electron-neutral examples bearing heteroatoms such as thioalkyl (**3.36**, **3.38**) and silyl (**3.37**). Vinyl groups were also tolerated (*i.e.*, **3.30** and **3.31**) without any competing reactions with the alkene and palladium catalyst. Of note was the continued positive impact of *ortho*-substitution (*e.g.*, **3.7, 3.18, 3.30, 3.38, 3.45**), first observed during

the optimisation phase using anisole as a solvent. For *ortho*-substituents bearing lone pairs (*e.g.*, **3.18** and **3.29**) it is possible that these substituents benefitted from an interaction with the boronic acid that reduces the rate of unwanted speciation, which has previously been observed in our Group.[161] Gratifyingly, boronic acids containing chlorides were tolerated when used at a reduced reaction temperature (**3.46**–**3.48**), although a bromide-containing substrate performed poorly (*i.e.*, **3.49**). The very good yield obtained by chloride-containing substrate **3.44** using the standard conditions may be explained by the beneficial effect of the 6-alkyoxy functional group, in an analogous manner to above commentary regarding *ortho*-substituted heteroatoms.[161]

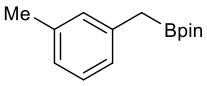
The tolerance of the homologation reaction towards chlorides requires further commentary. Firstly, this presented the initial evidence that the developed homologation could also proceed with chemoselectivity in favour of the carbanion surrogate **3.3** at oxidative addition, which later prompted further mechanistic study (see Section 3.2). Secondly, while (halomethyl)lithiums have been used with aryl electrophiles containing chloride substituents *in situ*, such as aldehydes[179–181] and benzyl halides,[182] yields in these processes have been moderate or poor in yield and remain generally uncommon. In cases where yields are similar to the aryl chlorides used in this scope, the convenience of setting up the developed homologation in comparison to the preparation and addition of (halomethyl)lithiums (temperatures below −80 °C, monitoring over hours, *i.e.*, discussions outlined in Sections 1.2.1 and 1.2.2) is clear.[16,31] This is without the overarching feature of most organoboron homologations to date, which is the requirement for stoichiometric quantities of organometallic reagents (*i.e.*, Section 1.2). While the tolerance of (halomethyl)lithiums towards electrophiles containing aryl bromides is known,[183,184] this is much less common than aryl chlorides. Unfortunately, aryl bromides continue to remain a problematic functional group for the developed homologation reaction, likely due to competing oxidative addition events (*i.e.*, **3.49**, Scheme 3.22). Further limitations of the homologation shall be discussed later in this Section.



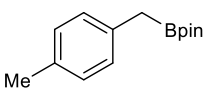
Aryl scope



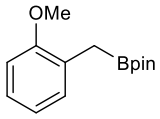
3.7, >99% (95%)[1]



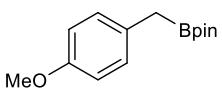
3.16, 77% (70%)



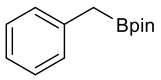
3.17, 90% (88%)



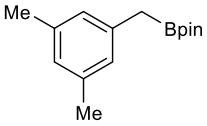
3.18, 91% (83%)



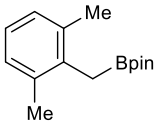
3.19, 92% (87%)



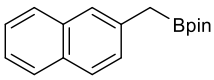
3.22, 75% (63%)[2]



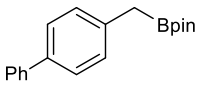
3.23, 91% (84%)



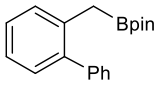
3.24, 57% (48%)



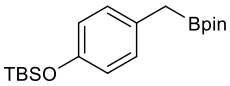
3.25, 71% (69%)



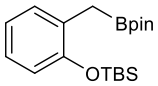
3.26, 63% (59%)



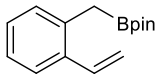
3.27, 90% (85%)



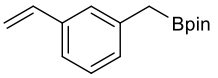
3.28, >99% (96%)



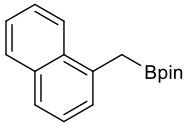
3.29, 98% (91%)



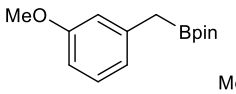
3.30, 70% (67%)



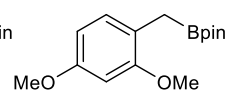
3.31, 69% (72%)



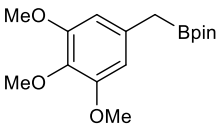
3.32, 91% (87%)



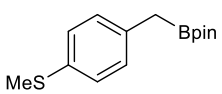
3.33, 86% (82%)



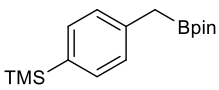
3.34, 86% (81%)



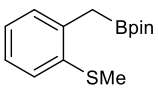
3.35, 69% (58%)



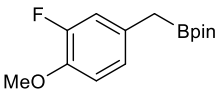
3.36, 61% (50%)



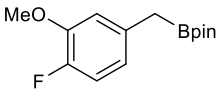
3.37, 87% (84%)



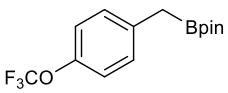
3.38, 81% (74%)



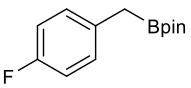
3.39, 80% (78%)



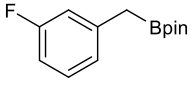
3.40, 78% (73%)



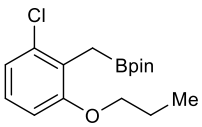
3.41, 74% (65%)



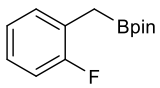
3.42, 81% (69%)



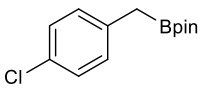
3.43, 60% (47%)[2]



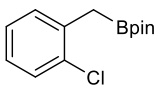
3.44, 72% (76%)



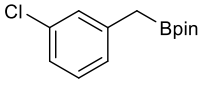
3.45, 60% (32%)



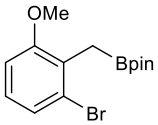
3.46, 77% (71%)[3]



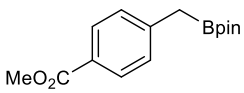
3.47, 50% (47%)[3]



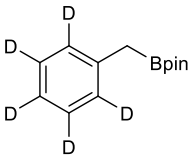
3.48, 57% (52%)[3]



3.49, 29% (32%)



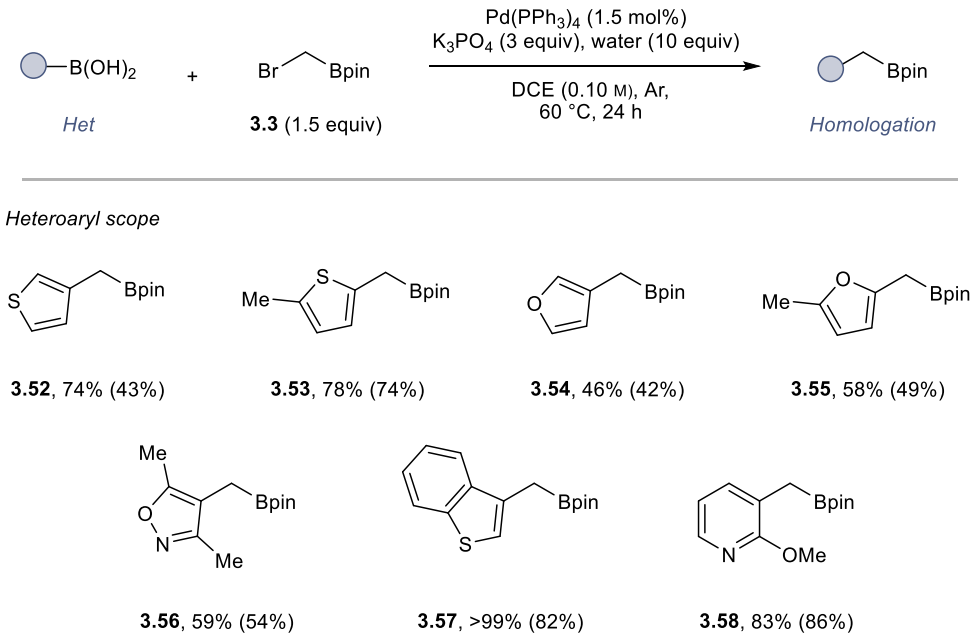
3.50, 54% (29%)



3.51, 70% (64%)

Scheme 3.22: Substrate scope with variations to the arylboronic acid. ^{1}H NMR yields are given, with isolated yields in parentheses. [1] PhOMe (0.25 M), 6 h; [2] PhMe (0.1 M), 24 h; [3] 45 °C, 36 h.

The reaction accommodates several heterocycles (Scheme 3.23). In all cases, the optimal conditions used 1,2-dichlorethane as the solvent. Thiophenes (**3.52**, **3.53**, **3.57**) and furans (**3.54**, **3.55**) were tolerated, although isolated yields were generally poor due to product volatility (*e.g.*, **3.52**, 31% difference between ^{1}H NMR and isolated yield). It was surprising that 2-thiophene- and 2-furyl-boronic acids each performed better than their 3-substituted counterparts given that the former are more protodeboronation prone (*i.e.*, **3.54**, **3.55** *versus* **3.52**, **3.54**) and it is unclear whether other interactions (namely, those involved with speciation) influenced this result.[185] An isoxazole (**3.56**) and pyridine (**3.58**) were also tolerated. The pyridine (**3.58**) afforded a particularly high yield and it was unclear at this stage whether this was the result of the *ortho*-methoxy substitution or the pyridine; this is discussed later in this Section. Excluding heteroatom-based nucleophilic displacements, [8,49–55,186] the use of heterocycles as non-participating functional groups in traditional Matteson-type homologations is generally uncommon,[77,187–189] although this has been supplemented by Aggarwal's strain-promoted methods more recently.[105,108] As such, the inclusion of several heterocycles in the developed catalytic homologation process was encouraging.

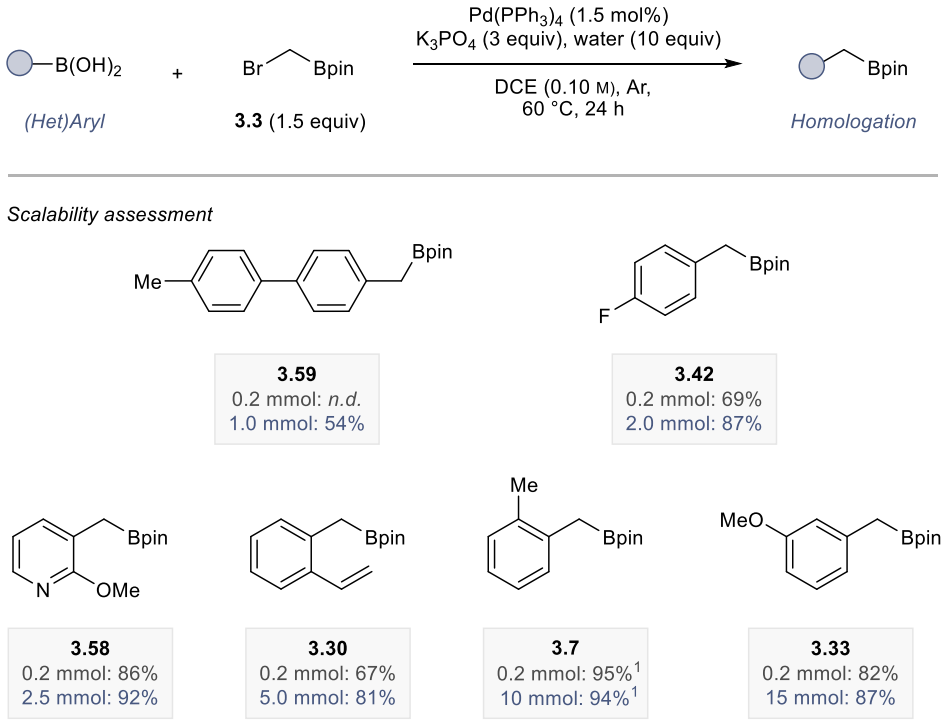


Scheme 3.23: Substrate scope with variations to the heteroarylboronic acid. ^{1}H NMR yields are given, with isolated yields in parentheses.

Variations with respect to the carbanion surrogate have formed the basis for mechanistic discussions, so is presented in Section 3.2.

The standard homologation reactions reported in the above two scopes were performed at 0.2 mmol; however, the reactions were also effective at elevated scales (Scheme 3.24). A

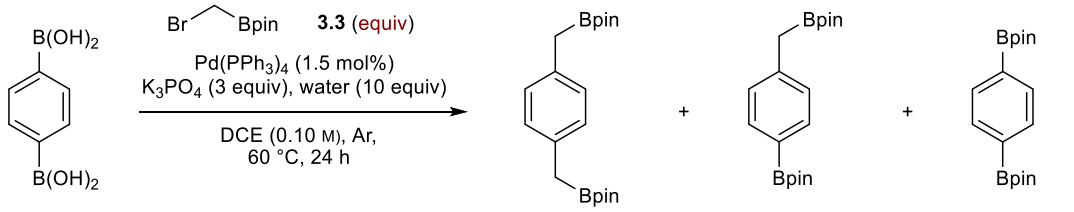
75-fold increase in the standard scale afforded 3.22 g of **3.33** in 87% yield. Reactions above 10 mmol were performed in a flame-dried two-necked flask setup as opposed to the standard microwave vial setup (see Experimental for details). It is unclear whether the variation in setup accounted for the generally higher yields afforded on scaleup as opposed to the standard 0.2 mmol reaction due to improved oxygen removal, although this observation was also noted at 2.0 mmol (*i.e.*, 69% *versus* 87% yield, **3.42**). Regardless, the improved performance at scale demonstrated that the developed process could be an effective method of arylboronic acid homologation to yield sufficient quantities of benzyl boronic esters for onward reactions. Note that the products obtained from these scaleup reactions were later used as the starting materials in Section 3.3.



Scheme 3.24: Substrate scope with respect to scalability. All yields are isolated. [1] Anisole (0.25 M), 6 h.

Several reactions delivered complex mixtures that warranted further analysis. The homologation of a bisboronic acid (*i.e.*, **3.60**) was attempted using the standard reaction conditions with elevated quantities of **3.3** (Scheme 3.25). The desired product, where both boronic acids were homologated (*i.e.*, **3.61**) was only ever observed in trace quantities in the crude ^{1}H NMR spectrum. The dominant product in all cases was the byproduct **3.63**, where both boronic acid units underwent transesterification with **3.3** — a sample was isolated for completeness. Although the product of a single homologation (*i.e.*, **3.62**) could be detected

in the ^{1}H NMR with reference to the literature, it could never be isolated from the crude reaction mixture containing four different boronic esters. During early optimisation work, Iona Meier noted that increasing the stoichiometry of the carbanion surrogate **3.3** beyond four equivalents was detrimental to the reaction yield of a single homologation reaction using *ortho*-tolylboronic acid. It is likely that the increased quantity of **3.3** in solution permits faster speciation because there is an increased bulk quantity of released pinacol. As such, simply increasing the equivalents of carbanion surrogate **3.3** was insufficient to homologate both boronic acids (*i.e.*, furnishing **3.63**) at all, and the single homologation yield (*i.e*, **3.62**) was very poor.

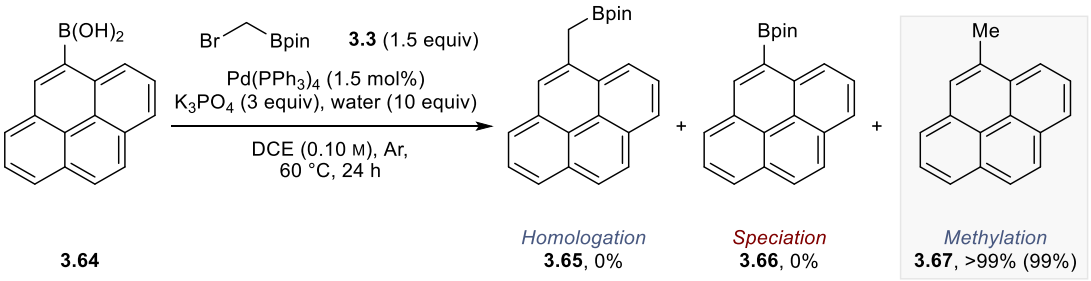


3.60

	Homologation/ Homologation **3.61**	*Homologation/ Speciation* **3.62**	*Speciation/ Speciation* **3.63**
2 equiv **3.3**:	0%	10%	58%
4 equiv **3.3**:	trace	26%	59%
6 equiv **3.3**:	trace	24%	74% (73%)

Scheme 3.25: Attempted homologation of a bisboronic acid. ^{1}H NMR yields are given, with an isolated yield of byproduct **3.63** in parenthesis.

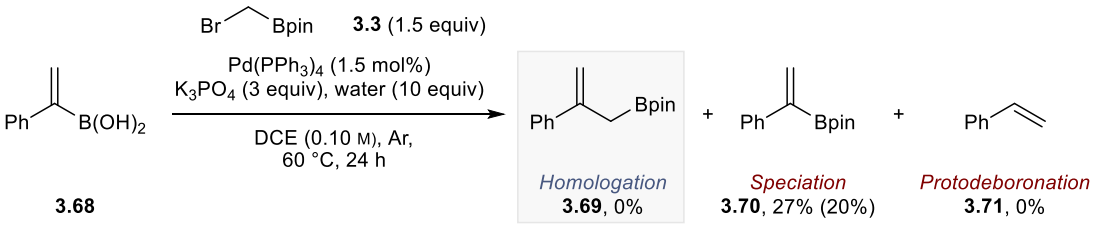
In an unusual case, the attempted homologation of 1-pyrene boronic acid lead to methylation with no change to the reaction conditions, which was purified using standard silica gel chromatography (Scheme 3.26). The expected boronic ester (*i.e.*, **3.65**) is unknown in the literature and it is plausible that, after successful homologation of the starting material, the product immediately protodeboronated to yield **3.67**.[3] Although this does not retain the desired boronic ester, so is not a boron homologation, the reaction offers the same net transformation as cross-couplings of aryl halides with potassium methyltrifluoroborate in opposite reagent polarity.[176,190,191] This example is the only case of homologation-protodeboronation being observed throughout the scope, although in other cases the resultant products may have been volatile (*e.g.*, 3-methylfuran).



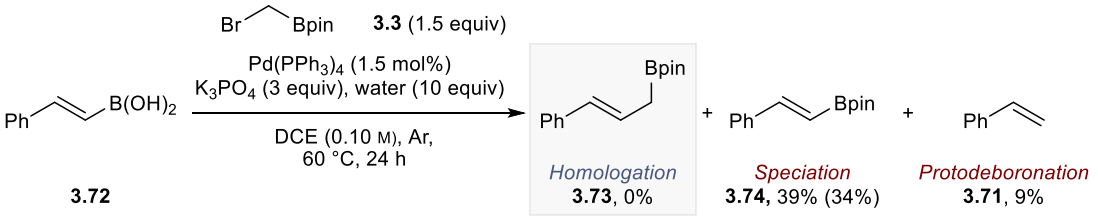
Scheme 3.26: Homologation-protodeboronation of 1-pyreneboronic acid.

Shortly after Matteson's first reports on the nucleophilic displacements of boronic esters,[8] Zweifel and coworkers reported an olefination reaction where an alkenyl borane was treated with sodium hydroxide and iodine.[192] Independent work from Evans and Matteson later expanded the scope of this reaction using boronic esters that were treated with vinyl lithium, affording vinylated products.[193–195] It was hoped that, by using the same vinyl organoboron starting materials in an analogous manner to Evans and Matteson, homologated olefins that retain the boronic ester could be furnished using the developed methodology. 1-Styrl- and 2-(*E*)-styryl-boronic acid were selected as test substrates to expand the scope of the homologation, but both formed complex mixtures of products (Schemes 3.27.1, 3.27.2). The speciated byproducts (*i.e.*, **3.70**, **3.74**) could be isolated from the crude reaction mixtures, but it was unclear whether the desired products (*i.e.*, **3.69**, **3.73**) were forming, or were being lost during isolation. As such, analytical standards of products **3.69** and **3.73** were prepared according to literature procedures (Schemes 3.27.3, 3.27.4).[196] Stacking of ^{1}H NMR spectra with the crude reaction mixtures confirmed that the desired products were not present in the crude reaction mixtures, and only a small amount of protodeboronation (yielding styrene, *i.e.*, **3.71**) was detected. As such, styrene boronic acids are a current limitation of the developed methodology. It is plausible that this intolerance is caused by the palladium complex coordinating to the styryl boron unit in an interaction that does not permit productive oxidative addition and/or transmetalation steps with **3.3** or the boronic acid, in an analogous manner to the 1,2-metalate shift reported by Morken and coworkers.[103] Conversely, other interactions specific to styrene boronic acids may be involved, given that boronic acids containing vinyl groups were tolerated in the arylboronic acid scope (*i.e.*, **3.30**, **3.31**, Scheme 3.22).

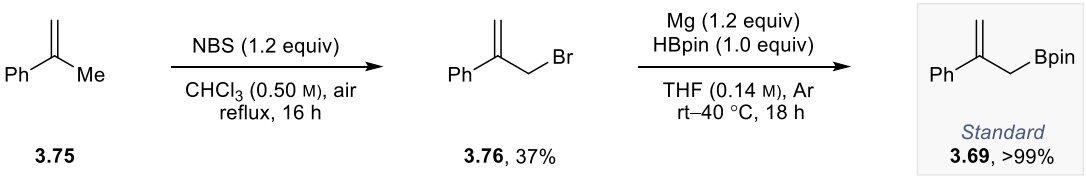
1. Attempted homologation of 1-styrylboronic acid[1]



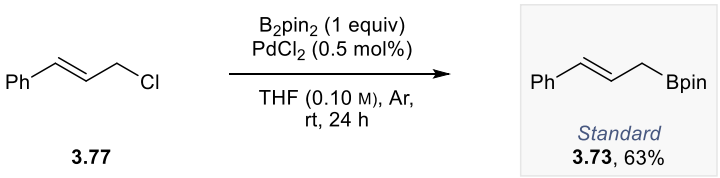
2. Attempted homologation of 2-(E)-styrylboronic acid[1]



3. Synthesis of an analytical standard for the homologation of 1-styrylboronic acid[2]



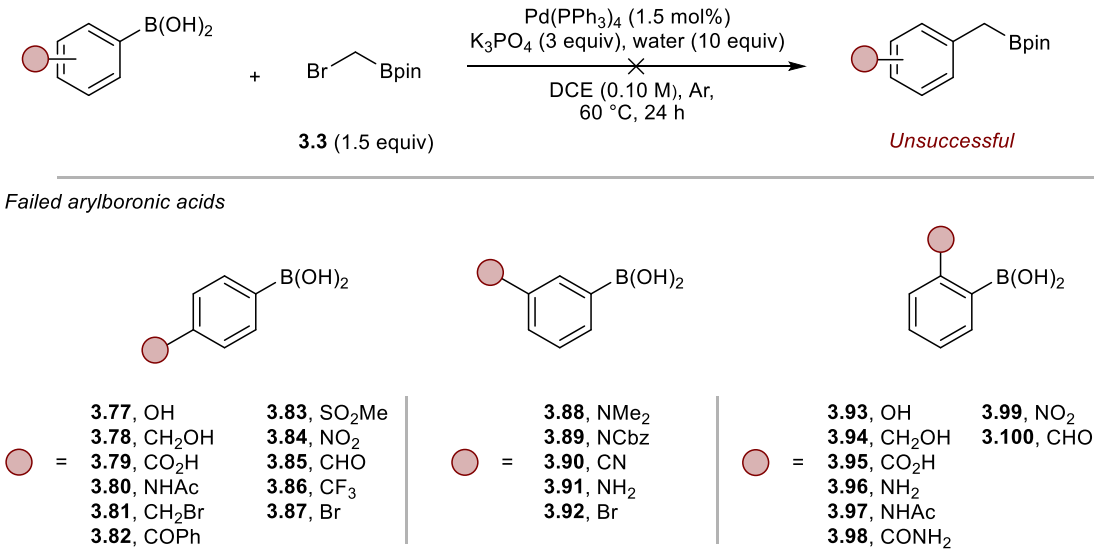
4. Synthesis of an analytical standard for the homologation of 2-(E)-styrylboronic acid[2]



Scheme 3.27: Attempted homologations of styryl boronic acids (1,2) and preparations of analytical standards (3,4).[1]H NMR yields given with isolated yields in parentheses; [2] isolated yields given.

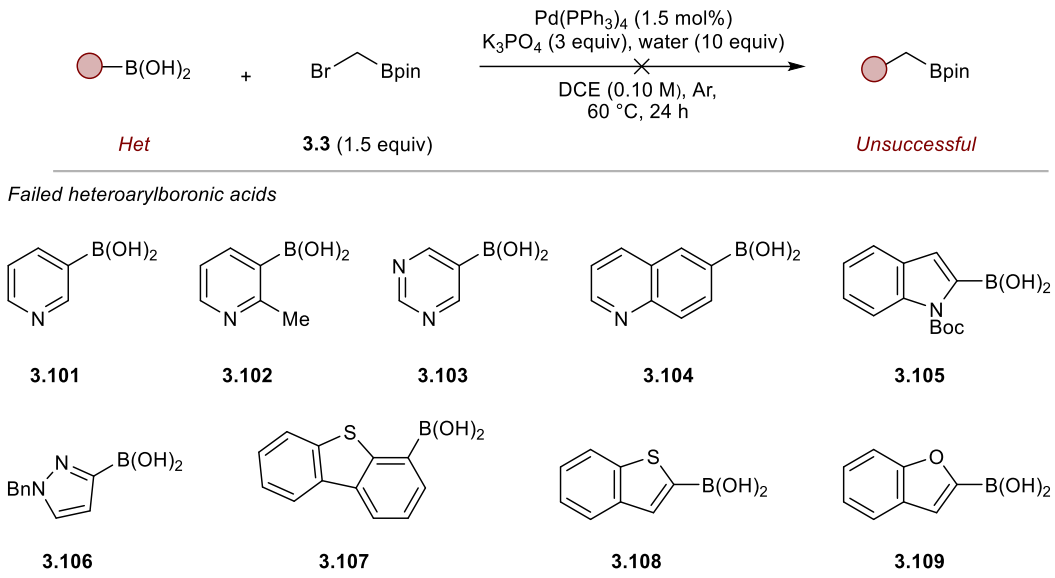
Numerous functional groups were incompatible with the desired homologation reaction (Scheme 3.28). Functional groups bearing unprotected heteroatoms were recalcitrant at all positions of substitution, including alcohol (**3.77**, **3.78**, **3.93**), acid (**3.79, 3.95**), amine (**3.91, 3.96**), and amide (**3.98**). Based on Mattesons original reports,[8,19,19,50,54,186] it is plausible that these substrates underwent nucleophilic displacement reactions with compound **3.3**, sequestering it from oxidative addition. Protected amines, with groups including acetate (**3.80**, **3.97**), dimethyl (**3.88**), and carbazole (**3.89**), were also ineffective. It is possible that some heteroatom-containing functional groups poison the palladium catalyst — this is investigated further in later Sections. Bromide-containing substrates (*i.e.*, **3.81, 3.87, 3.92**) all afforded low quantities of product by analysis of the crude ^{1}H NMR spectrum (5–15%); however, reaction mixtures were generally very complex and none of the desired products

could be successfully isolated by column chromatography. Retrospectively, the isolable bromide **3.49** disclosed in the substrate scope was likely partially rescued by the *ortho*-methoxy group (Scheme 3.22). Other intolerant functional groups were mesyl (**3.83**), nitro (**3.84**, **3.99**), aldehyde (**3.85**, **3.100**), trifluoromethyl (**3.86**), and nitrile (**3.90**) and these effects are less clear. Regretfully, many of the intolerant functional groups disclosed here are the same as those that are typically limited by Matteson- and Aggarwal-type boron homologations that use stoichiometric organometallic reagents,[16,17,31] although the origins of the functional group intolerance here likely rests with the palladium catalyst. Therefore, expanding the substrate scope to tolerate more diverse functional groups remains an ongoing challenge in classical organoboron homologation.



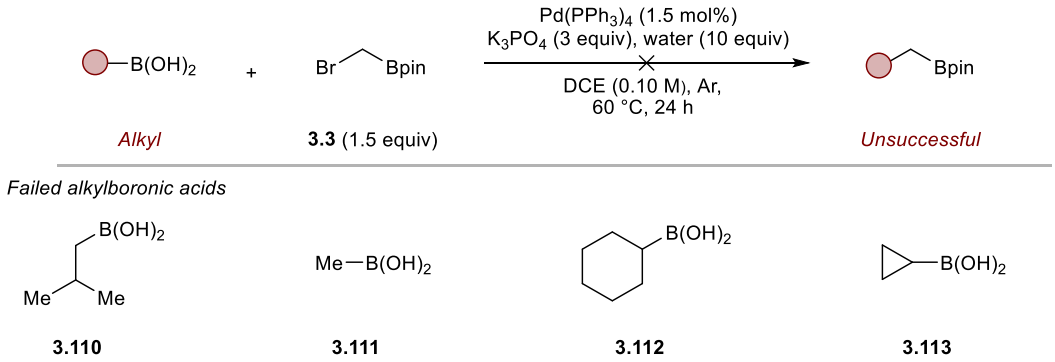
Scheme 3.28: Unsuccessful homologations of arylboronic acids.

Several heterocycles were obstinate (Scheme 3.29). Of note was the intolerance towards pyridines (**3.101, 3.102**), especially in the context of the very successful *ortho*-methoxy-3-pyridyl substrate (**3.58**, Scheme 3.22). An *ortho*-methyl group alone was insufficient to rescue the pyridine substrate (*i.e.*, **3.102**), which further supported the hypothesis that lone pair donation from an *ortho*-functional group into a boronic acid can reduce speciation.[161] Moreover, substrate **3.58** benefits from the boronic acid sitting in the 3-position, which is relatively slow to protodeboronate,[197] especially in comparison to the notorious 2-pyridyl position.[3,185,198,199] Other intolerant heterocycles bearing a nitrogen atom included pyrimidine (**3.103**), indole (**3.105**), and pyrazole (**3.106**); moving the nitrogen atom to an adjacent aromatic ring was also ineffective (*i.e.*, 6-quinoline, **3.104**). Other protodeboronation-prone 2-heterocyclic boronic acids,[185] including indole (**3.105**), benzothiophene (**3.108**), and benzofuran (**3.109**), were also ineffective.



Scheme 3.29: Unsuccessful homologations of heteroarylboronic acids.

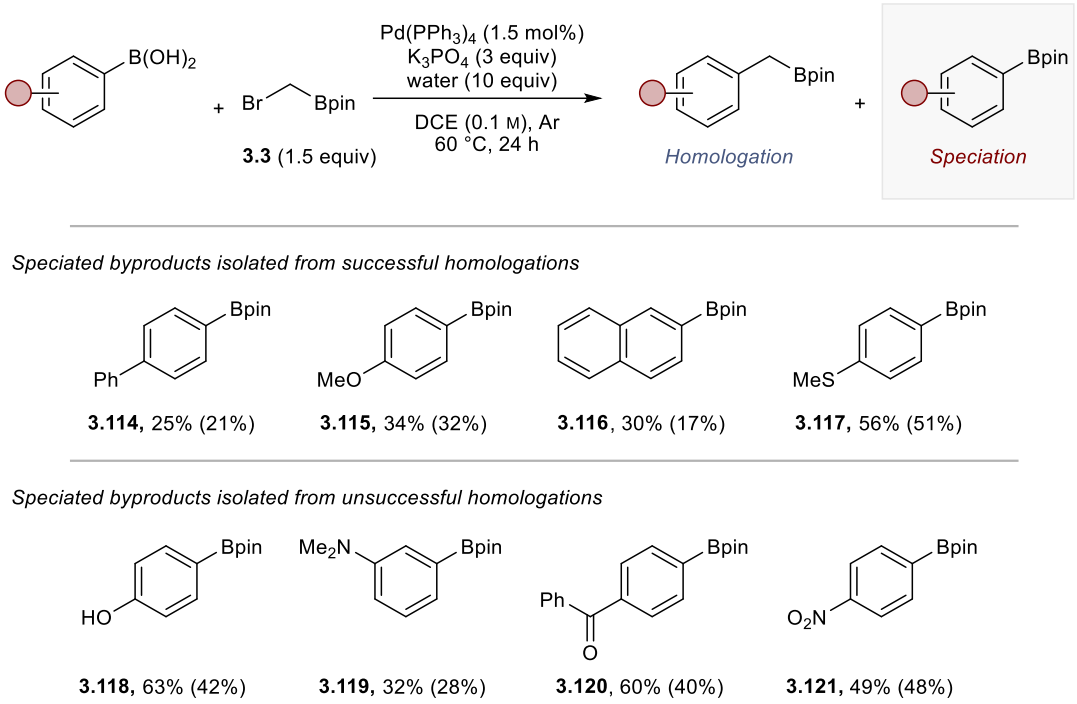
All attempts to homologate primary- (**3.110**, **3.111**) and secondary- (**3.112**, **3.113**) alkyl boronic acids under the standard conditions were unsuccessful (Scheme 3.30). While the cyclopropylboronic acid **3.113** is partially C(sp^2)–B in character,[200] couplings of C(sp^3)–B boronic acids are challenging in a general sense because of protodeboronation, slow transmetalation, and β-hydride elimination.[3,11] As such, these observations were disappointing but unsurprising. In terms of wider organoboron homologation strategies, this is a significant drawback of the developed transition metal-catalysed approach compared to classical boronate rearrangements,[16,31] which usually proceed excellently with alkyl boronic esters.



Scheme 3.30: Unsuccessful homologations of alkyl boronic acids.

To demonstrate that the speciation of pinacol from compound **3.3** was not an isolated problem for the workhorse boronic acids **3.6** and **3.20**, a series of the speciated byproducts were also isolated from the crude reaction mixtures part of the scope campaign (Scheme

3.31). In cases where the homologation reaction was successful, >88% of the total mass balance could be tracked by the sum of the homologation and speciation products (*i.e.*, **3.114**–**3.117**). In cases where the homologation reaction was unsuccessful, the tracked mass balance was generally poor (<60%, *i.e.*, **3.118**–**3.121**), which suggested that other non-isolable byproducts were forming.



Scheme 3.31: Isolation of speciated byproducts from selected reactions.

In summary, a palladium-catalysed homologation of aryl and heteroarylboronic acids has been developed using low loadings of a widely commercially available catalyst. Not only does the process negate the requirement for complex ligand systems, but these appear to be detrimental to the fate of the reaction. Conditions are generally milder than Matteson- and Aggarwal- type organoboron homologations, requiring a shorter period of hands-on setup time and no cryogenic conditions; however, functional group limitations that typically arise from classical methods remain troublesome in the developed protocol. One of the dominant byproducts throughout the homologation was the C(sp^2)–B boronic ester of the requisite boronic acid starting material, caused by the speciation of pinacol from compound **3.3**. In cases where the homologation was ineffective, the mass balance was generally very poor and suggested that other byproducts were also forming.

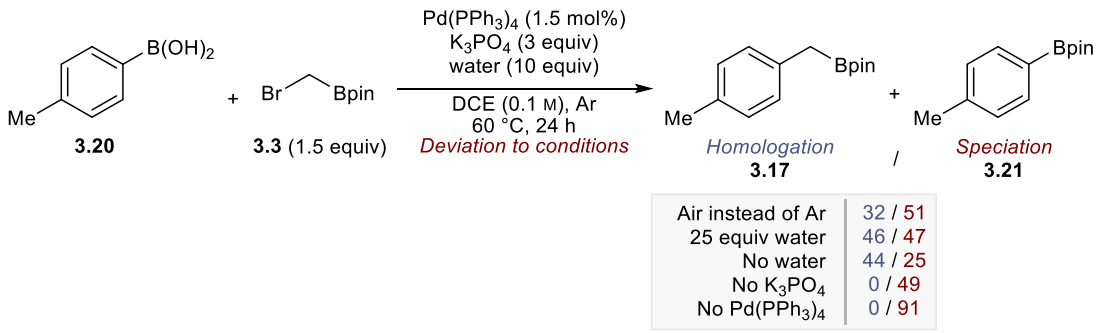
The following Section shall examine how other byproducts from the developed homologation may form by inputting recalcitrant functional groups as additives in the form of a robustness

screen, which may provide an explanation for failed substrates in the above reaction scopes and provide relevant information for possible industrial applications.

3.1.3 Robustness screening

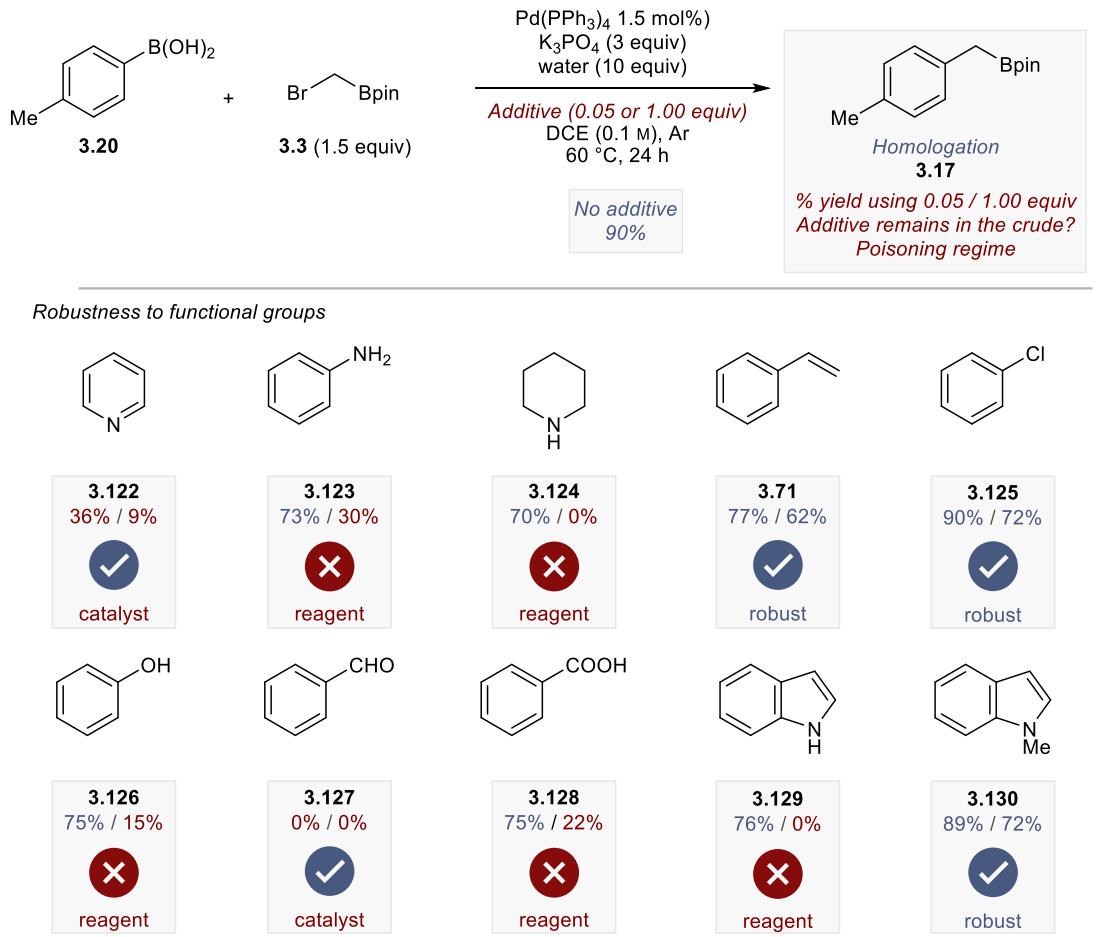
One of the principle aims of synthetic organic chemistry is the application of methodology towards real-world applications.[201] Understanding changes to parameters beyond those explored during the optimisation phase of a developed process can enable synthetic chemists to foresee challenges during process development.[202,203] In academic methodology, tolerance to scale is one of the few factors of a developed protocol that is routinely explored. The use of additives to probe further reaction details that are relevant to industrial processes can enable the smoother transition of new methodologies into practical applications. The standardisation of this practice, generally referred to as robustness screening, has recently been popularised by the Glorius and MacMillan groups.[204,205] This Section shall describe a series of robustness and additive mapping studies for the developed homologation process.

The first study confirmed the requirement for all reaction components and examined deviations to water content (Scheme 3.32). Surprisingly, some of the desired product **3.17** could still be afforded under an air atmosphere. The total tracked mass balance — the combined yields of the desired product **3.17** and byproduct **3.21** — under an air atmosphere was 83%. This agreed with early optimisation screening that oxidative homocoupling was generally not a problem for this Suzuki–Miyaura coupling. The reaction was very sensitive to the loading of water. Typical Suzuki–Miyaura couplings list water as part of the solvent ratio whereas the precise stoichiometry of water was critical in the presented homologation, in an analogous manner to previous couplings under speciation control.[3,11,161,163,206] It is likely that a delicate balance of water stoichiometry is required to facilitate the desired coupling without accelerating the hydrolysis of compound **3.3**. As such, both raising the stoichiometry of water by 2.5-fold and eliminating it from the reaction conditions was detrimental. In retrospect of earlier optimisation data, it would also appear that the sensitivity to water loading can be affected by solvent selection (*i.e.*, Scheme 3.11). Finally, the exclusion of base or palladium catalyst was detrimental and ruled out other unexpected reaction pathways. Importantly, the near quantitative formation of the speciated byproduct in the absence palladium catalyst demonstrated that speciation likely occurs off from the palladium cycle. More details pertaining to the reaction mechanism and formation of byproducts is outlined in Section 3.2.



Scheme 3.32: Robustness to air, water, and removal of reaction components.

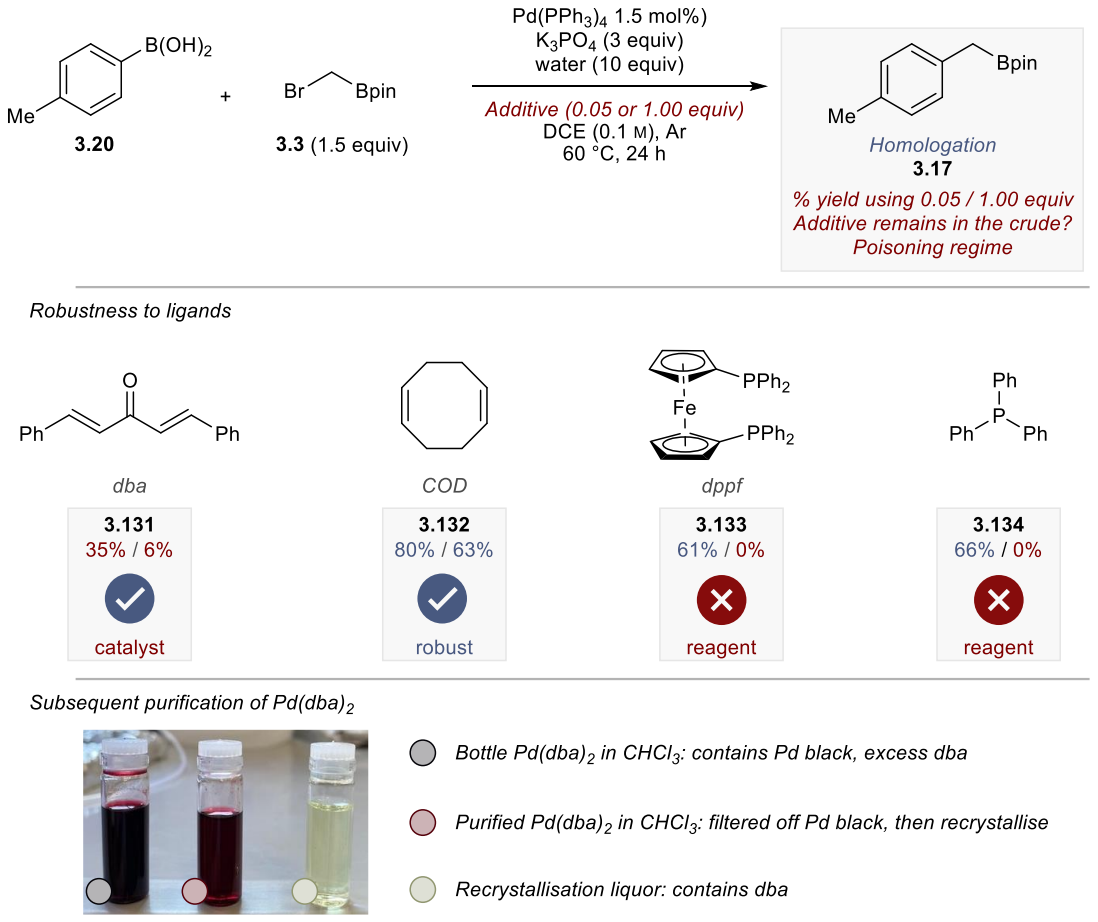
The standard homologation reaction using the benchmark arylboronic acid **3.20** was repeated using a series of additives (Scheme 3.33). To establish whether an additive was influencing the yield *via* a reagent- or catalysed-based poisoning regime, either 1.00 or 0.05 equivalents (*i.e.*, 5 mol%) of a given additive were applied. Additives were selected based on the functional groups that were troublesome during the reported substrate scope (*i.e.*, pyridine (**3.101**), amine (**3.91**, **3.96**), alcohol (**3.77**), aldehyde (**3.85**), or acid (**3.95**), or functional groups that were present in the substrate scope but it was unclear whether deleterious interactions occurred (*e.g.*, vinyl (**3.30**), chloride (**3.46**). The addition of pyridine **3.122** was detrimental to the yield of **3.17** at 5 mol% (9% yield) which implied that a catalyst poisoning regime was involved. In contrast, primary (**3.123**) and secondary amines (**3.124**) were generally tolerated at catalytic loading (70–73% yield), but the yield loss at stoichiometric loading implied a reagent-based poisoning regime (0–30% yield). The addition of styrene **3.71** was generally robust, which was in agreement with the success of vinyl substrates **3.30** and **3.31** from the scope (Scheme 3.22). Chlorobenzene was particularly robust, the maintained yield at stochiometric loading supported the tolerance of chlorides in the substrate scope (*i.e.*, **3.44**, **3.46**–**3.48**, Scheme 3.22) and that oxidative addition could be chemoselective (*i.e.*, **3.3** over **3.125**). Phenol (**3.126**), benzaldehyde (**3.127**), and benzoic acid (**3.128**) all caused significant poisoning at stoichiometric loading, in agreement with the recalcitrance of these functional groups within the substrate scope. The consumption of phenol and benzoic acid as additives also agreed with the generally poor tracking of mass balance in these reactions. The addition of benzaldehyde was particularly ruinous and was not tolerated at either catalytic or stoichiometric loading; the discrepancy between this result and benzoic acid was unclear. Finally, the intolerance to unprotected heteroatoms could be demonstrated by the dichotomous reactions using indole **3.129** and *N*-methylindole **3.130**. While the reaction was robust using *N*-methylindole as an additive, removal of the methyl protecting group led to a reagent poisoning regime.



Scheme 3.33: Robustness test against functional groups.

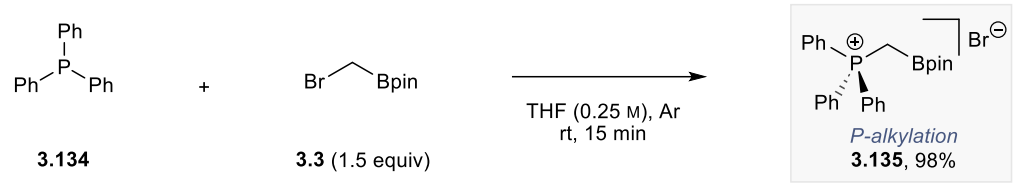
Throughout the optimisation phase of the study, it was noted that an excess of ligand could be detrimental to the reaction outcome (Scheme 3.20). Moreover, the inconsistency in yields obtained with bis(dibenzylideneacetone)palladium(0) unless recrystallised suggested a non-innocent role of some ligands during the homologation reaction. In an analogous manner to the initial robustness study (Scheme 3.33), four ligands used during the optimisation were applied as additives to the benchmark reaction (Scheme 3.34.1). Remarkably, only a 5 mol% excess of dibenzylideneactetone **3.131** was detrimental to the reaction, and stoichiometric quantities shut the reaction down almost entirely (*i.e.*, 6% yield). Retrospectively, this highlighted that the likely reason why bis(dibenzylideneacetone)palladium(0) must be recrystallised prior to use is to remove any excess dibenzylideneactetone (*i.e.*, Scheme 3.34.2). In contrast, cyclooctadiene **3.132** was benign, even at stoichiometric loading. This was consistent with the previous robustness study where the addition of styrene was also uneventful (**3.71** Scheme 3.33). Both bidentate (**3.133**) and monodentate (**3.134**) phosphines were robust at catalytic loading, and the observed decrease in yield (66–61%) was in agreement with optimisation studies (*i.e.*, Scheme 3.19). The stochiometric addition of both

phosphine ligands was detrimental to the reaction, which signposted to a reagent poisoning scenario.



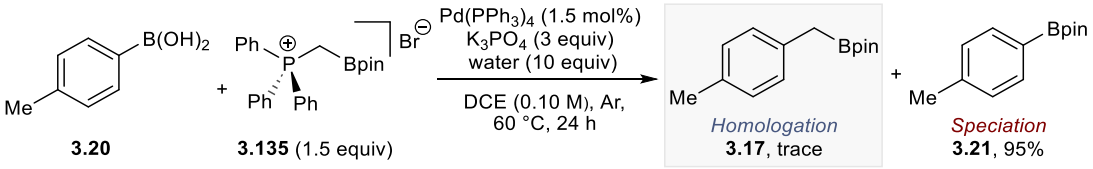
Scheme 3.34: Robustness tests against excess ligands.

The mechanism by which the reagent poisoning regime is most likely to operate is with respect to the donor **3.3**, rather than the boronic acid. Based on the literature,[8,49–55,186] nitrogen and oxygen-based additives likely undergo nucleophilic displacement reactions with **3.3**, thus displacing the halide and preventing oxidative addition from taking place. The reagent poisoning by the phosphine ligands was more intriguing because only a single example exists of a nucleophilic displacement of an α-halogenated boronic ester by a trialkylphosphine.[55] In reactions quoting reagent poisoning regimes, including the trialkylphosphines, white solids were often filtered off from the crude reaction mixtures. The nucleophilic displacement of carbanion surrogate **3.3** by triphenylphosphine **3.134** was confirmed by an independent synthesis (Scheme 3.35). The reaction was particularly rapid, and a white solid was observed almost immediately after the addition of **3.3** to the solution containing triphenylphosphine, affording the phosphonium salt **3.135** in quantitative yield.



Scheme 3.35: Ligand alkylation by compound **3.3**.

Based on the deligation of triphenylphosphine from palladium, less than 6% of the triphenylphosphonium salt would ever be present in solution during the homologation reaction at any one time. To rule out whether the phosphonium salt could serve as a competent homologating agent formed *in situ*, a control reaction was run using **3.135** in reagent quantities (Scheme 3.36). Only traces of the desired product (*i.e.*, **3.17**) could be detected in the crude, which ruled out alternative unexpected reaction pathways. More discussion surrounding the mechanism of the reaction can be found in Section 3.2.



Scheme 3.36: Control reaction for the homologation reaction using the phosphonium salt **3.135**.

The results of the robustness study have allowed several challenges associated with the developed homologation to be clarified and rationalised. The two major conclusions were the general incompatibility of unprotected heteroatoms with compound **3.3**, and the non-innocent nature of excess ligand that persisted throughout the optimisation phase. Both observations can be traced back to Matteson's original nucleophilic displacements with heteroatom-based nucleophiles. Although the exact mechanism is unclear, the inconsistencies associated with using bis(dibenzylidene)acetonepalladium(0) have been addressed, which highlights the fortuitous nature of using the commercially available catalyst tetrakis(triphenylphosphine)palladium(0) as part of the optimised conditions, where no complex ligands were required.

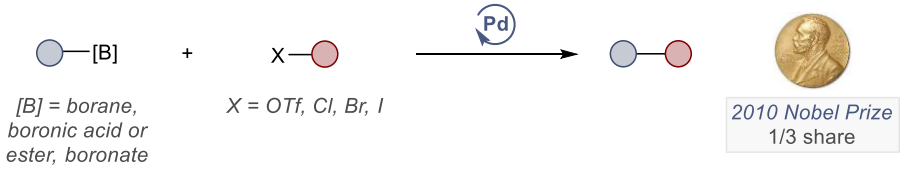
With a set of benchmark conditions for the desired homologation and an example scope in hand, fulfilling Goals 1–2 of this study, more detailed mechanistic information surrounding the reactivity of α-halogenated boronic esters towards palladium was sought. The oxidative addition of a C(sp^3)–X halide such as **3.3**, to palladium is rare and has never been subject to a mechanistic study. The following Section shall aim to probe this event with a series of

informative control studies. This Section is split into two parts; the first will provide a brief mechanistic overview of the Suzuki–Miyaura cross coupling and the second Section will deliver the results of the mechanistic study.

3.2 Mechanistic investigation of the palladium-catalysed boron homologation

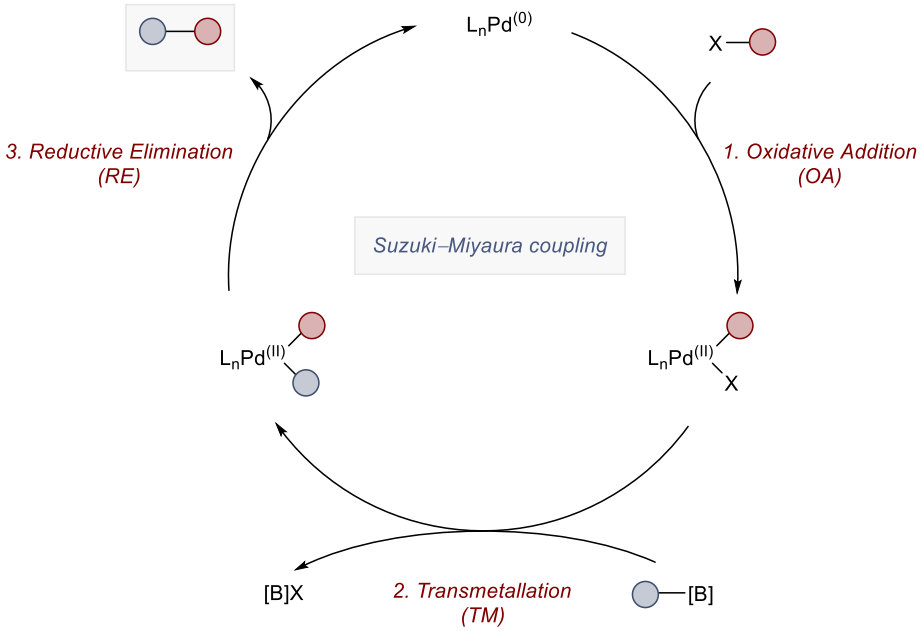
3.2.1 The Suzuki–Miyaura cross-coupling

In 1975, Heck and Dieck observed that boronic acids were competent cross-coupling nucleophiles with aryl halide electrophiles in the presence of stochiometric quantities of palladium.[207] Four years later, Suzuki and Miyaura would report the cross-coupling of aryl bromides with alkenyl boronic acid catechol esters under a catalytic regime.[6] The cross-coupling of (pseudo)organohalide electrophiles with organoboron nucleophiles now carries Suzuki's and Miyaura's names, and is a ubiquitous reaction across synthetic chemistry;[3,7,141,177] approximately 40% of C–C bond formations in industry are thought to be made using the developed methodology (Scheme 3.37).[142] While the Suzuki–Miyaura reaction was first disclosed under palladium catalysis, which is also the paradigm relevant to this study, other transition metals have been used — namely, nickel, [141,142] cobalt,[208,209] and iron.[210] Note that while organofluorides are generally not considered a typical (pseudo)halide coupling partner, conditions have been developed to also adopt these electrophiles in recent years.[211,212]



Scheme 3.37: Overview of the Suzuki−Miyaura cross-coupling.

The general mechanism of the Suzuki–Miyaura cross-coupling is synonymous with other palladium-catalysed couplings involving different nucleophile partners; namely, the Stille (organostannane), Corriu–Kumada (organomagnesium), Murahashi (organolithium), Negishi (organozinc), and Hiyama (organosilicon) couplings.[141–143] The catalytic cycle can be broken into three constituent parts: 1) Oxidative addition; 2) Transmetalation; and 3) Reductive elimination (Scheme 3.38).[3,10,11,141–143,177]

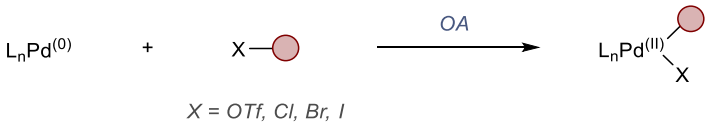


Scheme 3.38: Mechanistic overview of the Suzuki-Miyaura cross–coupling.

Due to the popularity of the Suzuki-Miyaura coupling, extensive research has taken place to uncover detailed mechanistic information to improve reaction efficacy and scope, which is reported in a vast quantity of literature. The following section shall provide an overview of the steps involved in the catalytic cycle and relevant considerations for this study, with a focus on oxidative addition.

3.2.1.1 Oxidative addition

The catalytic cycle of the Suzuki–Miyaura cross-coupling begins with oxidative addition. A carbon–(pseudo)halide bond is broken in exchange for a metal–carbon and a metal–(pseudo)halide bond, resulting in a net oxidation of the active catalyst from palladium(0) to palladium(II) (Scheme 3.39).[3,177]



Scheme 3.39: Oxidative addition.

Oxidative addition is often the rate limiting step of a Suzuki–Miyaura cross-coupling and is most directly influenced by the dissociation energy of the carbon–(pseudo)halide bond of the electrophile, which generally follows the order I > OTf > Br >> Cl.[177,213,214] The C–F bond is very strong (~ 533 kJ mol^{-1}) and does not typically undergo oxidative addition unless tailored

catalysts or ligand systems are applied.[43,211,212] Based on commercial availability and price, bromides are typically the electrophiles of choice for the Suzuki–Miyaura cross-coupling.[141]

Sagacious ligand selection can enable facile oxidative addition of organohalides by increasing the electron density around palladium centre, thus increasing the nucleophilicity of the metal. Fu and coworkers employed tri-(*tert*-butyl)phosphine and tri(cyclohexyl)phosphine as bulky electron-rich alkyl phosphine ligands to enable the couplings of aryl chlorides,[215] overcoming a significant limitation of Suzuki's and Miyaura's seminal work.[6,177,216] Buchwald's ligands emerged concomitantly, using a common electron-rich biaryl backbone (Figure 3.2).[176,185] The anatomy of these ligands, published over eleven years,[215,217–220] were tweaked to facilitate both oxidative addition and reductive elimination steps. A prominent feature of this ligand class is that a monoligated palladium(0) complex will dominate over the bisligated complex.[221] As such, the combined features of an electron rich monodentate ligand alongside a larger vacant coordination space around the palladium(0) centre can enable more straightforward oxidative addition because the complex can reach closer to the (pseudo)halide C–X bond.[176] The *ortho*-substitution of the ring bearing the alkylphosphine can stabilise the conformation of the ligand by directing the phosphine to sit above the π-system of the lower pendent arene. This interaction can stabilise the more reactive monoligated palladium(0) complex while promoting reductive elimination in later steps.[221]

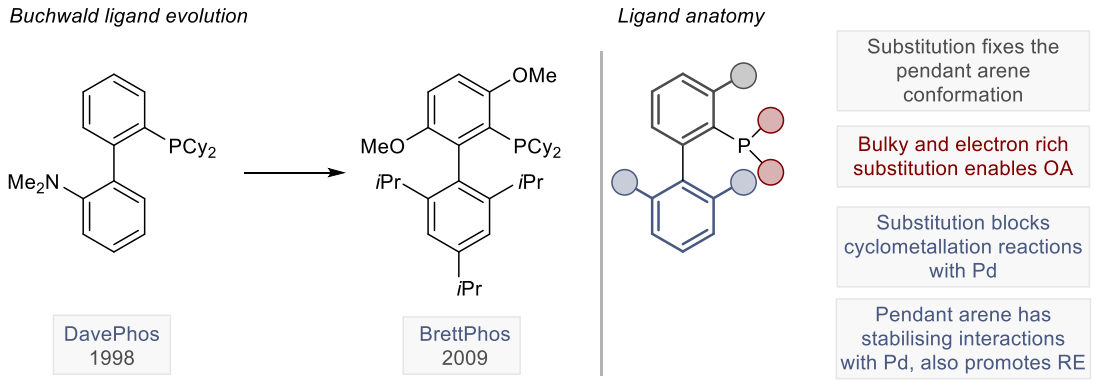
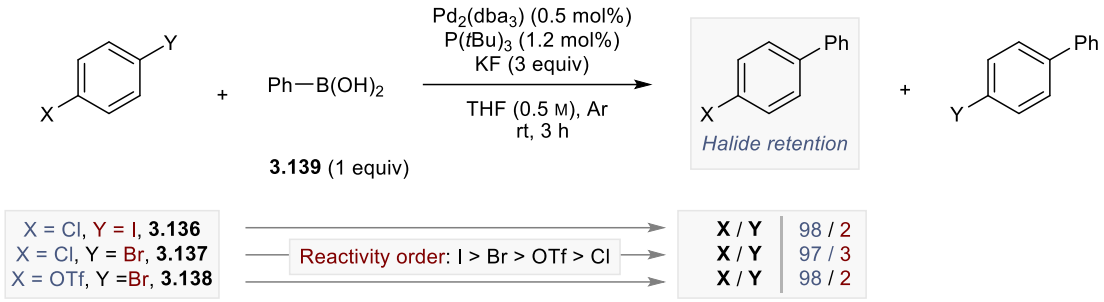


Figure 3.2: Evolution and design rationale of Buchwald-type phosphine ligands.

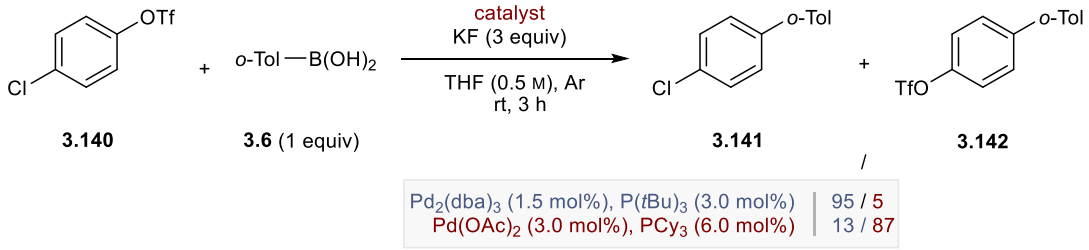
Oxidative addition can be chemoselective using either different (psueodo)halides, or different chemical environments around the same halide. The synthetic utility of chemoselective cross-couplings are evident because the remaining halide can be used in further couplings to build molecular complexity iteratively,[164,206] which is conceptually similar to Aggarwal's assembly line approach.[16] Some chemoselective cross-couplings take advantage of the differences in C–X bond strength, as demonstrated by Fu and coworkers

(Scheme 3.40).[215] Notably the established reactivity order did not fully match the bond dissociation energies of each halide; specifically, the bromide reacted selectively over the triflate of **3.138** to deliver the triflate product (halide retention triflate/bromide = 98/2).



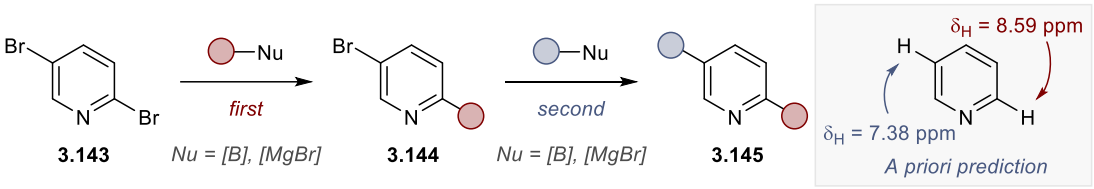
Scheme 3.40: Chemoselective cross-couplings based on halide bond dissociation energies.

The judicious choice of ligand can also change the outcome of chemoselectivity. In the same landmark study, Fu and coworkers could flip the selectivity of oxidative addition between chlorides *versus* triflates simply by changing the palladium catalyst and ligand combination (Scheme 3.41).[215] It was proposed that the initial conditions exploited the steric bulk of tri-(*tert*)butylphosphine, which occludes the monoligated palladium centre from being within close enough proximity to the C–OTf bond. Instead, the C–Cl bond can form a stabilising interaction with the monoligated palladium centre. When tri(cyclohexyl)phosphine is used, Schoenebeck,[222,223] Houk,[222] and Sigman[224] have shown that the bisligated palladium speciates dominates which is more nucleophilic and undergoes facile insertion into the weaker C–OTf bond.



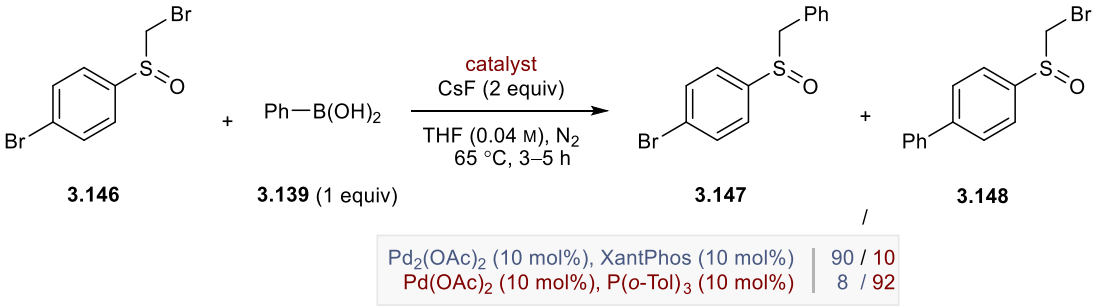
Scheme 3.41: Chemoselective oxidative addition of a dihalide based on catalyst/ligand selection.

Chemoselective oxidative addition can also take place based on the different chemical environments surrounding the same halide. Conveniently, the order of reactivity can be determined *a priori* based upon the ^{1}H NMR chemical shifts at the site of the parent compound where the halide would be located (Scheme 3.42).[225,226]



Scheme 3.42: Chemoselective oxidative addition of a dibromide based on chemical environments.

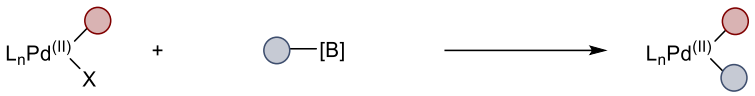
Electrophiles can also be discriminated based upon hybridisation. An experimental and computational study from Mareras and coworkers used a bromomethylsulfoxide appended to a bromobenzene (*i.e.*, **3.146**) to explore C(sp^2)–Br *versus* C(sp^3)–Br oxidative addition (Scheme 3.43).[227] When a bidentate ligand is used (*i.e.*, XantPhos), selectivity arises for the stronger C–Br bond because it is more accessible. When a monodentate ligand is used, (*i.e.*, tri(*o*-tolyl)phosphine), a monoligated palladium complex can dominate which selects the weaker C(sp^2)–Br bond, which would be the product predicted using Zhang's shift method alone.[225] Intriguingly, these results seemed dichotomous with respect to the role of the sulfoxide; computed geometries indicated that no oxygen-palladium interactions could form in the presence of XantPhos, despite full chemoselectivity being observed for the Br–C(sp^3)–SO bromide. It should be noted that tri-(*o*-tolyl)phosphine can also behave as a bidentate ligand where the tolyl C–H bond becomes palladated.[228]



Scheme 3.43: Chemoselective oxidative addition of a dibromide based on hybridisation.

3.2.1.2 Transmetalation

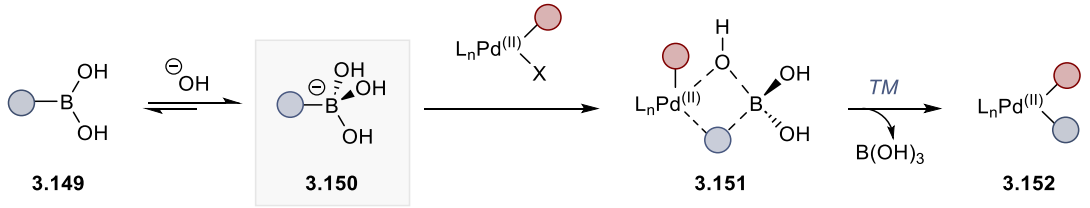
Transmetalation is the intermediary step between oxidative addition and reductive elimination where an organometallic (*e.g.*, organomagnesium, organozinc, or organotin) or an organometalloid (organosilicon or organoboron) transfers its organic fragment onto a transition metal (Scheme 3.44). In comparison to other nucleophiles, transmetalation of organoboron compounds is more challenging because the boron metalloid is more electronegative (Pauling 2.0) than organometallic partners (*e.g.*, magnesium, zinc, tin, Pauling 1.2–1.8).[3,43,177]



Scheme 3.44: Transmetalation.

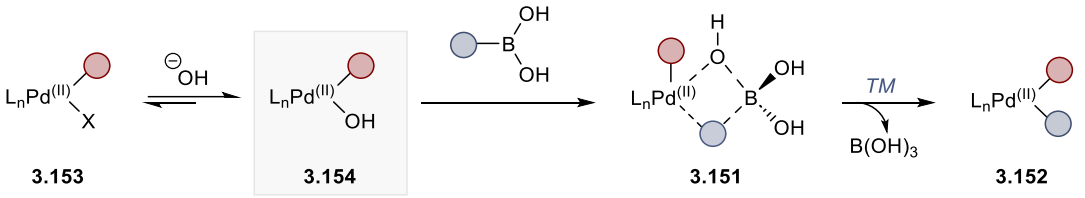
Compared to oxidative addition, and transmetalation in other palladium-catalysed cross-couplings, transmetalation in the Suzuki−Miyaura cross-coupling remains a topic of contention.[174] This typically can be reduced into two competing pathways; the boronate pathway, *versus* the oxo-palladium pathway. Many detailed mechanistic investigations on the Suzuki–Miyaura cross-coupling have focussed on transmetalation due to this dichotomy, which reach beyond the scope of this overview. As such, both pathways are summarised in brief. Note that, owing to the homologation reaction described in this thesis, only the transmetalation of boronic acids and boronic esters will be considered.

Boronate was the first pathway considered by Suzuki and Miyaura in 1979 and is characterised by an anionic, sp^3-hybridised, boronate that intercepts a palladium(II) halide oxidative addition complex (Scheme 3.45).[6] The charged organoboron species forms *in situ* under basic conditions and was hypothesised to make the organoboron nucleophilic enough to transmetalate. Following boronate formation, an oxygen atom can displace the halide from the palladium(II) complex, forming a four-membered palladacycle intermediate, **3.151**. The subsequent collapse of the palladacycle and liberation of boric acid to deliver the pre-reductive elimination complex (*i.e.*, **3.152**) is the common step in both the boronate and oxo-palladium pathways. The unambiguous assignment of a pre-transmetalation complex containing a Pd–O–B linkage akin to structure **3.151** would not come until 2016.[229]



Scheme 3.45: The boronate pathway in transmetalation.

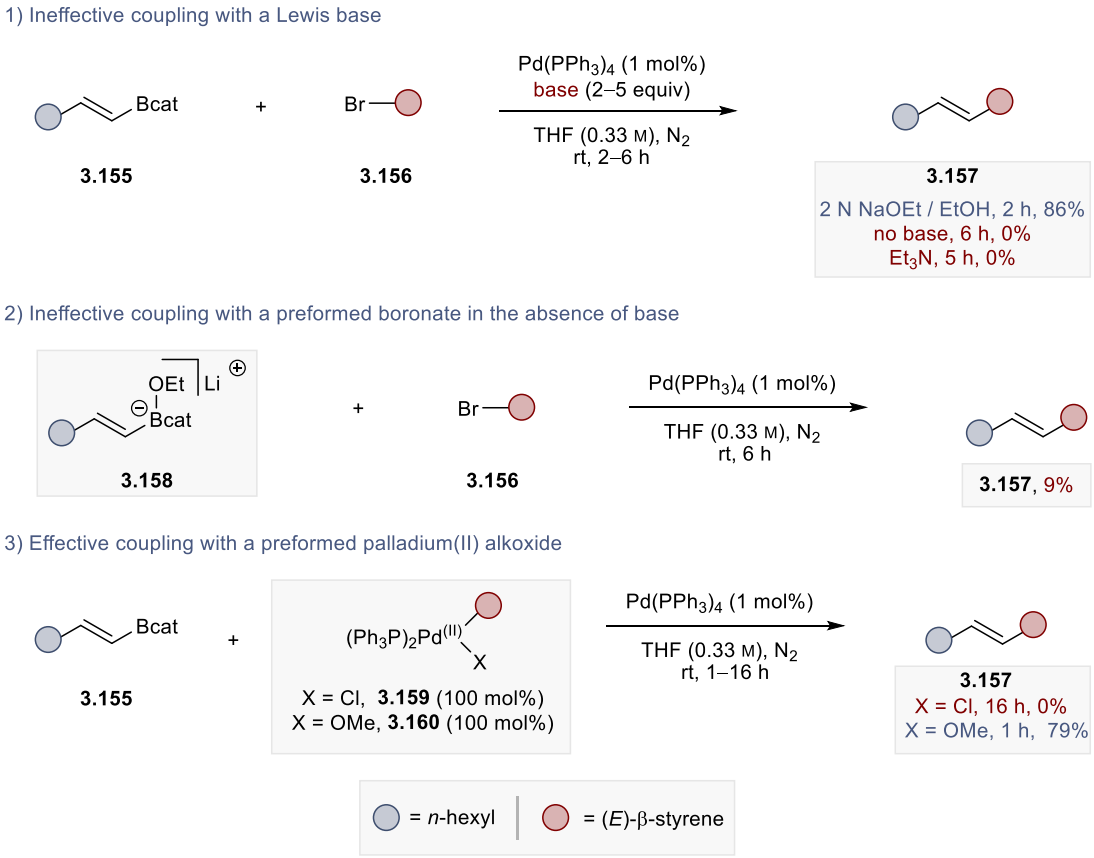
Suzuki and Miyaura later postulated the oxo-palladium pathway, which is characterised by the base-mediated anion metathesis of the palladium(II) halide complex to yield a palladium(II) hydroxide complex (*i.e.*, **3.154**, Scheme 3.46). Subsequent coordination of the neutral, sp^2-hybridised, organoboron compound forms the common palladacycle **3.151**, which completes the transmetalation step upon collapse.



Scheme 3.46: The oxo-palladium pathway in transmetalation.

Several investigations have been conducted to elucidate the dominant pathway in transmetalation step following Suzuki's and Miyaura's initial work.[6,216] The most prominent investigations were later contributed by Amatore and Jutand,[230] and Hartwig,[229,231] which has been reviewed by Lennox and Lloyd-Jones.[174] These are summarised below.

Initial studies by Suzuki and Miyaura indicated that alkenyl-alkenyl couplings of stryl catechol boronic esters were ineffective when triethylamine was used as a Lewis base (Scheme 3.47).[216] When a preformed ethoxyboronate (*i.e.*, **3.158**) was used, couplings were ineffective in the absence of base; whereas the neutral catechol ester (*i.e.*, **3.155**) was an effective coupling partner in the presence of an alkoxide base. When stoichiometric quantities of a preformed palladium(II) alkoxide were applied (*i.e.*, **3.160**) in the absence of base, the coupling was effective, whereas the parent palladium(II) halide (*i.e.*, **3.159**) was not. The conclusions drawn from these empirical observations were that the alkoxide-palladium(II) intermediates must form from metathetical displacement of the palladium(II)-halide by the alkoxide base, which captures the neutral boronic ester.



Scheme 3.47: Control studies by Suzuki and Miyaura that suggested a boronate pathway.

Electrochemical studies by Amatore and Jutand have supported the oxo-palladium pathway.[230] By determining the concentrations of reactive intermediates throughout the palladium cycle, rate constants could be extrapolated for both palladium(II) hydroxide and palladium(II) halide species. The concentration of the palladium(II) hydroxide complex (*i.e.*, **3.154**, Figure 3.3), analogous to Suzuki and Miyaura's palladium(II) alkoxide complex (*i.e.*, **3.158**, Scheme 3.47.2),[216] was determined to be dependent on the relative concentration of hydroxide ions in solution.[230] However, unlike Suzuki and Miyaura's studies using the catechol boronic ester,[216] Amatore and Jutand used a boronic acid and found that the formation of the trihydroxyboronate was also dependent on hydroxide concentration but this could not undergo productive transmetalation (*i.e.*, **3.150**).[230] These combined observations can be used to explain why Suzuki–Miyaura reactions can be sensitive to both high and low concentrations of base.

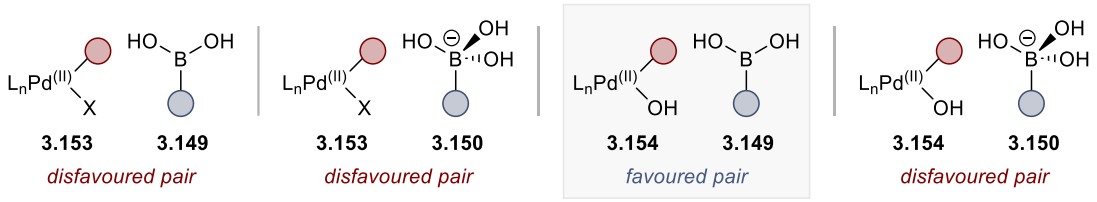
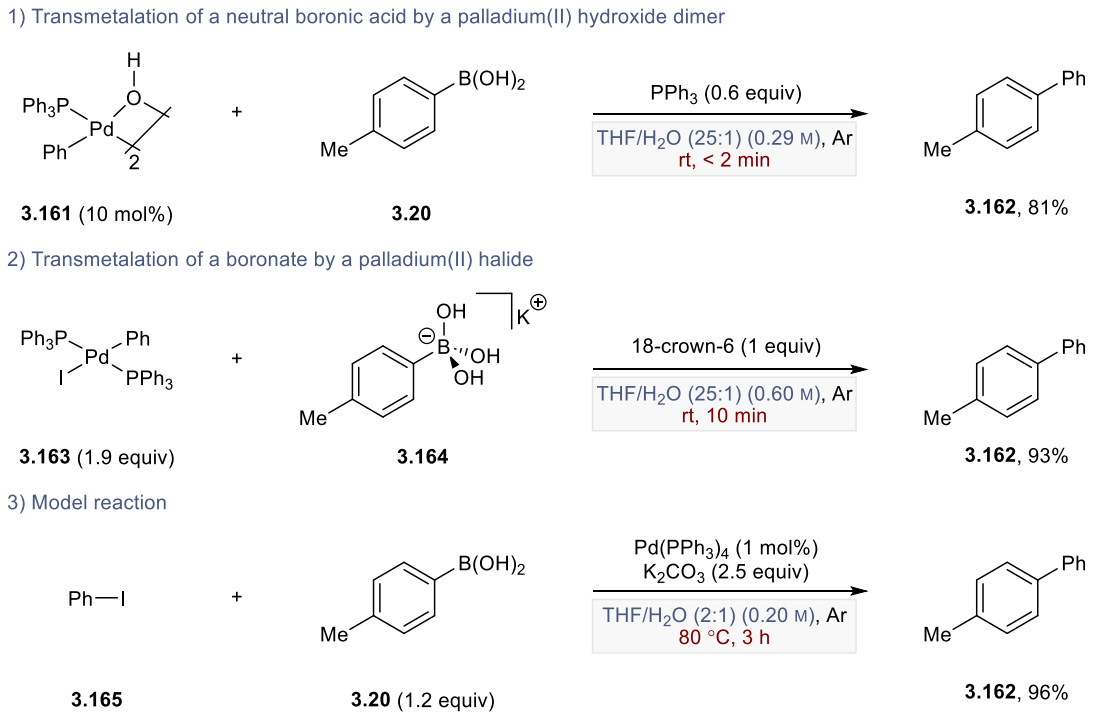


Figure 3.3: Favoured transmetalation pair based on kinetic data.

A study from Hartwig and Carrow reported in the same year found that both boronate and oxo-palladium pathways were feasible, but at different rates (Scheme 3.48).[231] A palladium(II) hydroxide dimer **3.161** could undergo facile coupling with a boronic acid **3.20** in just two minutes at room temperature, whereas the equivalent coupling from a palladium(II) iodide **3.163** and potassium trihydroxyboronate **3.164** took over ten minutes. Intriguingly, the model reaction took over three hours at elevated temperature, which implied that both reactions could be feasible over the timeframe. The authors did not address the differences in reaction concentration or water loading used; which could have generated an undesired excess of hydroxide ions and reduced the overall reaction rate.[3,161,174] Later work taken by Hartwig and Thomas to identify pretransmetalation intermediates containing the elusive Pd–O–B linkage arrived at a similar conclusion; while a palladium(II) iodide and thallium trihydroxyboronate could furnish a Pd–O–B pre-transmetalation complex. The yield was only 10%, compared to quantitative using a palladium(II) hydroxide and a boronic acid.[229]

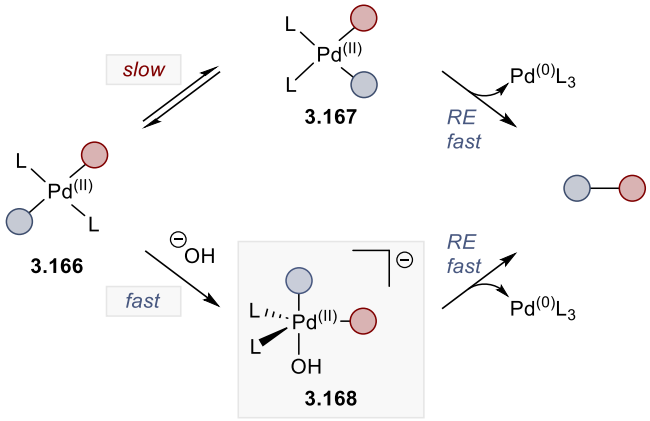


Scheme 3.48: Hartwig's evidence for both oxo-palladium and boronate pathways.

It is worth highlighting that it remains challenging to completely rule out the boronate pathway in favour of the oxo-palladium pathway. Subtle parameter changes, such as the selection of organoboron reagent used,[3,169,231] can influence whether the boronate pathway is feasible. As such, it is unwise to label transmetalation as a binary reaction course (*i.e.*, exclusively oxo-palladium or boronate). Instead, it is better to consider which pathway dominates over the other.

3.2.1.3 Reductive elimination

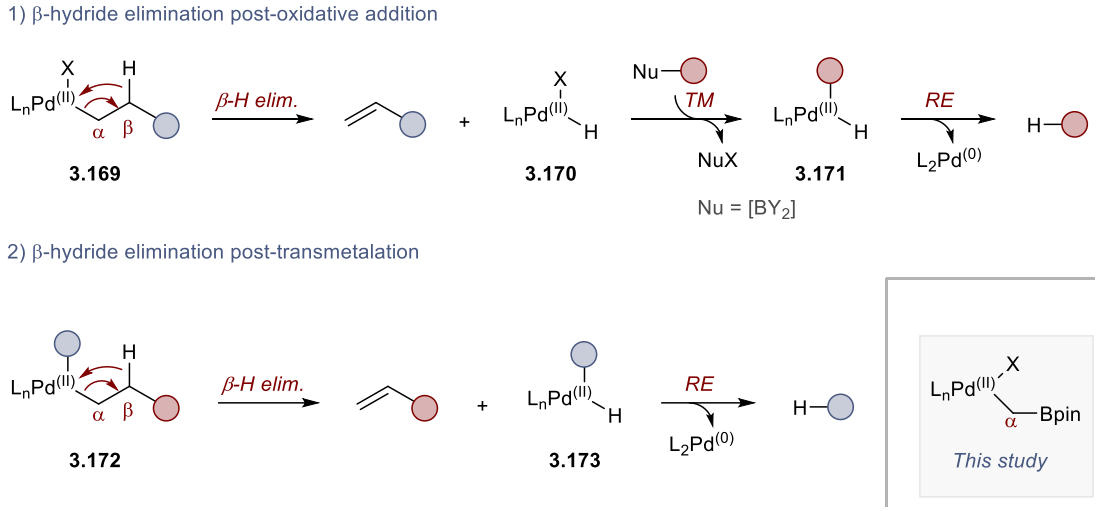
The reductive elimination step of the Suzuki–Miyaura cross-coupling can be conceptualised as the opposite of the oxidative addition step, whereby two bonds to the palladium centre are broken in exchange for one C–C bond. This causes the catalyst to be reduced from palladium(II) back to palladium(0), closing the catalytic cycle.[3,174] Reductive elimination can only occur when the two coupling partners are *cis* to one another on the palladium complex, which is thermodynamically less favourable than the *trans* isomer initially formed post-transmetalation (*i.e.* **3.167** *versus* **3.166**, Scheme 3.49). As such, the use of bulky phosphine ligands can facilitate reductive elimination by forcing substrates closer together.[176,185] During Amatore and Jutand's landmark studies on transmetalation, a third role of hydroxide ion was proposed where coordination to palladium would form a pentavalent anionic complex *(i.e.*, **3.168**) which could enable facile reductive elimination by circumventing the barrier towards *trans*/*cis* isomerisation.[230]



Scheme 3.49: Role of hydroxide in reductive elimination.

The use of a C(sp^3) component in the Suzuki–Miyaura cross-coupling would typically require discussion on one of their principal challenges, β-hydride elimination (*i.e.*, Scheme 50). This pathway can occur as a result of sluggish oxidative addition or reductive elimination, which is often overcome using more complex ligand systems designed to facilitate these steps;

namely, by providing steric bulk or electron density that can donate into the palladium centre.[3,141,177] Based on the developed homologation reaction outlined in Section 3.1, this mechanistic consideration is not relevant because the carbanion surrogate (*i.e.*, **3.3**) does not contain a β-hydrogen to eliminate and therefore exceeds the confines of this overview.



Scheme 3.50: Overview of β-hydride elimination in respect of this study.

The following Sections will aim to develop a more comprehensive insight into the developed Suzuki–Miyaura organoboron homologation, beginning with a mechanistic overview based upon empirical observations made during optimisation. Owing to the general lack of information regarding the use of α-boryl electrophiles in transition metal catalysis, Section 3.2.3 will focus on the oxidative addition step with a series of control studies.

3.2.2 Mechanistic overview for the palladium-catalysed homologation

Several observations made during the optimisation campaign for the palladium-catalysed homologation can help to deliver an overall *likely* mechanism (Scheme 3.51). As alluded to during the general overview of the Suzuki–Miyaura reaction, several reaction steps contain multiple plausible pathways that cannot be ruled out entirely, but the most complete outlook is presented herein. Discussion is broken into six steps, with four on-cycle:

(0) **Ligand dissociation.** During the optimisation phase it was noted that two equivalents of triphenylphosphine were required with respect to bis(dibenzylidene)acetone palladium(0) (Scheme 3.20). While at least two vacant coordination sites are required to enable oxidative addition, it is unclear whether two equivalents of triphenyphosphine were required to form the monoligated complex, or all

triphenylphosphine displaced the dibenzylidene(acetone) to yield the bisligated complex. Therefore, it is unclear whether two or three deligations of tetrakis(triphenylphosphine)palladium(0) occurs in the optimisation reaction (*i.e.*, n=1 or 2). As such, any *cis*/*trans* isomerisation (when n=2) in subsequent steps has been left out of the mechanism. Liberated triphenylphosphine can alkylate the carbenoid equivalent **3.3** to yield a phosphonium salt (*i.e.*, **3.135**); however, a control study showed that this product was not competent in the reaction (Scheme 3.36), so has been omitted from the overall mechanism drawing.

(1) **Oxidative addition** of the carbanion surrogate **3.3** affords a palladium(II) halide complex, **3.177**. It was unclear whether the structure of the carbanion surrogate **3.3** influences the ease of this C(sp^3)–X oxidative addition step, which is typically challenging and requires more complex ligand systems than triphenylphosphine. This step forms the basis of later control studies.

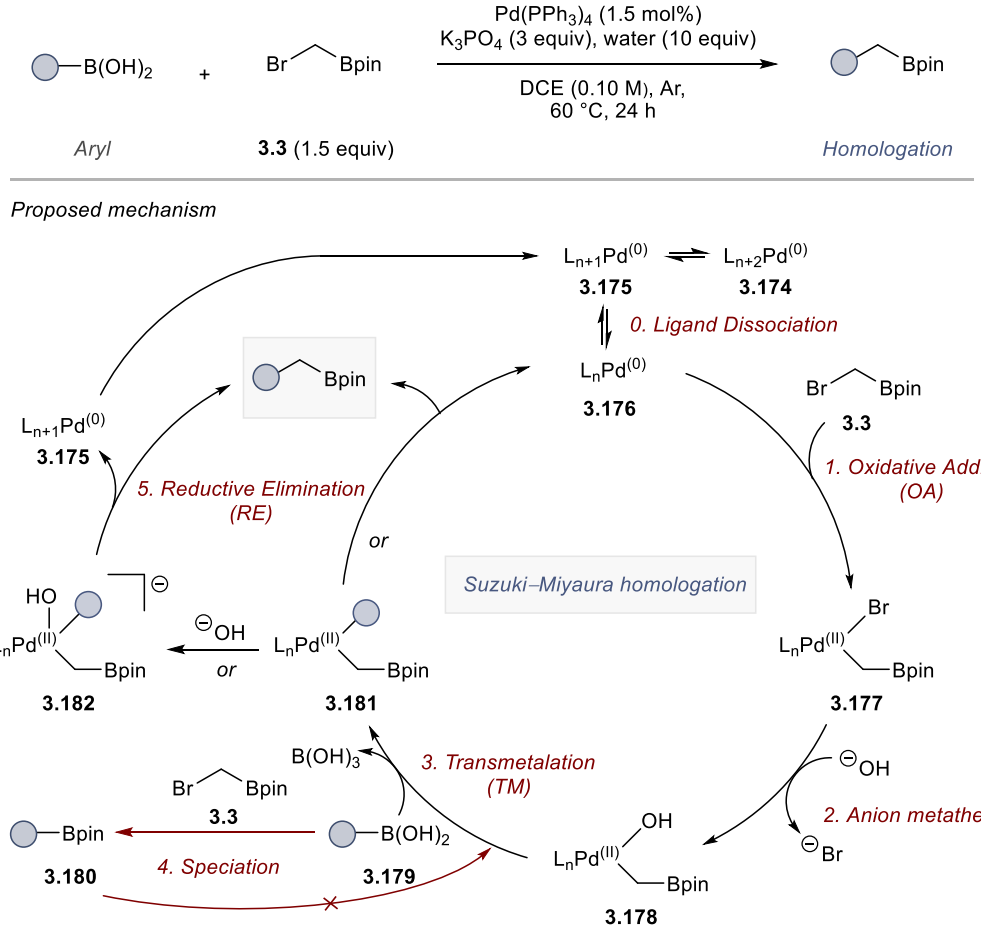
(2) ***Likely*** **anion metathesis** of the palladium(II) halide complex **3.177** affords the palladium(II) hydroxide complex, **3.178**. During the optimisation screening, no organic bases afforded any of the desired product (*e.g.* triethylamine, Scheme 3.10) which was consistent with Suzuki and Miyaura's observations using the same tetrakis(triphenylphosphine)palladium(0) catalyst, pointing towards an oxo-palladium pathway. While a transmetalation step involving the palladium(II) halide complex **3.177** cannot be ruled out (*i.e.*, a boronate pathway), the remaining cycle shown has depicted the oxo-palladium pathway as the dominant route.

(3) **Transmetalation** of the arylboronic acid **3.179** onto the palladium(II) hydroxide complex **3.178** affords the pre-reductive elimination palladium(II) complex, **3.181**, liberating boric acid. There is no evidence for the transmetalation of any boronic esters in the reaction mixture (*i.e.*, **3.3**, **3.180**, and the homologated product), indicating that transmetalation is wholly chemoselective for the desired metathetical displacement of the arylboronic acid.

(4) **Speciation** between compound **3.3** and arylboronic acid **3.179** is an unproductive event, leading to the byproduct **3.180**. A control study that eliminated palladium from the reaction and delivered the speciated byproduct in quantitative yield indicates that the speciation reaction very likely occurs in solution (*i.e.*, off-palladium). Moreover, there is a 67- and 100-fold excess of boronic acid **3.179** and compound **3.3** with respect to palladium, so there is greater statistical likelihood of

this reaction occurring off the palladium cycle. The fate of **3.3** following speciation of pinacol is discussed later in this Section.

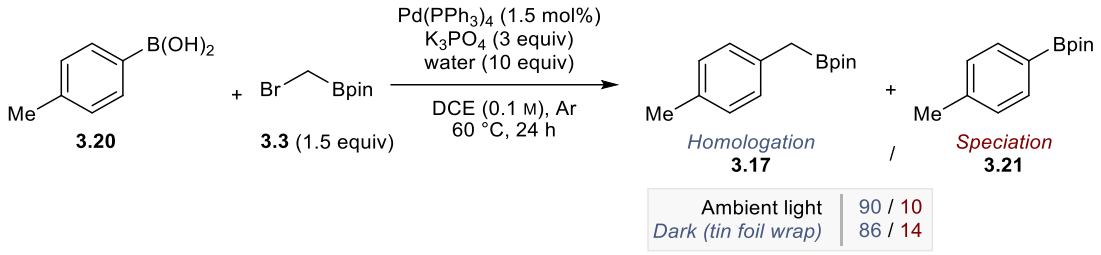
(5) **Reductive elimination** affords the desired homologation product. Based on whether the palladium(II) complex contains one or two triphenylphosphine ligands (*i.e.*, **3.181**, n = 1 or 2) it is unclear whether hydroxide is required to form the anionic palladium(II) hydroxide complex **3.182** to facilitate reductive elimination, akin to Amatore and Jutand's observations also using tetrakis(triphenylphosphine)palladium(0).[230] As such, both pathways are depicted in the reaction mechanism. Importantly, the desired homologation product cannot re-enter the catalytic cycle under the prescribed homologation conditions (*i.e.*, it cannot transmetalate). Overall, this represents a remarkable level of selectivity achieved at transmetalation, whereby only one organoboron transfers to palladium(II) from a possible four.



Scheme 3.51: Proposed mechanism for the developed homologation. n = 1 or 2.

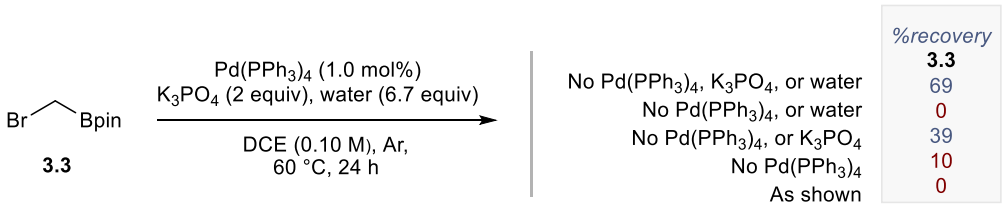
To rule out an alternate single electron pathway in respect of Gevorgyan and coworkers' Heck reaction involving single electron transfer of an α-boryl radical,[160] the reaction was repeated

by excluding all ambient light (Scheme 3.52). No discernible change to the product distribution was observed, thus failing to provide evidence of such a pathway in this homologation reaction.



Scheme 3.52: Control for a light-mediated reaction pathway.

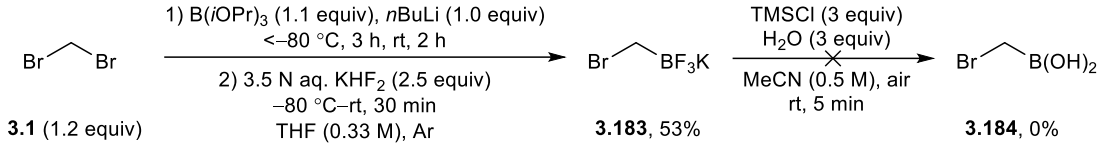
Several control studies were conducted to determine the fate of the excess amount of halomethyl boronic ester. Compound **3.3** was subjected to each of the reaction conditions in the absence of any boronic acid and stoichiometries were adjusted to maintain the same ratio as the standard homologation reaction (Scheme 3.53). In the absence of any aqueous base or palladium catalyst, **3.3** showed good recovery (69%), with ~30% likely being lost due to thermal degradation. This was consistent with the optimised conditions requiring 1.5 equivalents of **3.3**. Base was detrimental and none of the material could be recovered even in the absence of water, with solvent being dried using standard techniques (see the Experimental Section). The partial recovery of **3.3** when only water was added (39%) implied that the degradation is likely to be mediated by basic conditions (*i.e.*, hydroxide formed with tribasic potassium phosphate). The negligible difference in recovery under aqueous basic conditions with the inclusion or exclusion of palladium catalyst provided further evidence to support that the speciation and degradation of compound **3.3** occurs independently of the palladium cycle.



Scheme 3.53: Stability assessment of compound **3.3**. ^{1}H NMR yields.

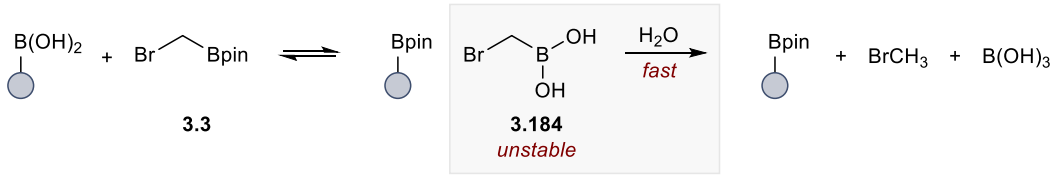
It was hypothesised that the degradation pathway of **3.3** occurred *via* hydrolysis to yield the boronic acid (*i.e.*, **3.184**), which degrades. Throughout the optimisation process, none of the excess homologating agent **3.3** or the parent boronic acid were ever detected in the crude reaction mixtures, which was consistent with the above control studies (Scheme 3.53). A

study to establish the degradation pathway was to be performed using the independently synthesised boronic acid **3.184** *via* the deprotection of the potassium trifluoroborate (*i.e.*, **3.183**, Scheme 3.54). The potassium trifluoroborate **3.183** was prepared using a modified lithiation-borylation protocol akin to the reagent **3.3** but quenching the lithium isopropylboronate complex with aqueous potassium hydrogen fluoride, instead of pinacol. Subsequent deprotection to the boronic acid using a standard literature technique caused the immediate formation of a cloudy suspension that warmed the flask to the touch,[232] but the only detectable compound in the crude reaction mixture was boric acid.



Scheme 3.54: Attempted preparation of the bromomethylboronic acid *via* the trifluoroborate.

It is likely that the boronic acid **3.184** is very unstable and can undergo rapid protodeboronation after pinacol ester hydrolysis (Scheme 3.55). This would yield boric acid and bromomethane. While the exact pathway may be unclear, it can provide an adequate explanation why none of compound **3.3** is present in the crude reaction mixtures of the homologation reaction, unless a significant excess is used (*e.g.*, Scheme 3.25)



Scheme 3.55: Protodeboronation of the carbenoid surrogate post-speciation.

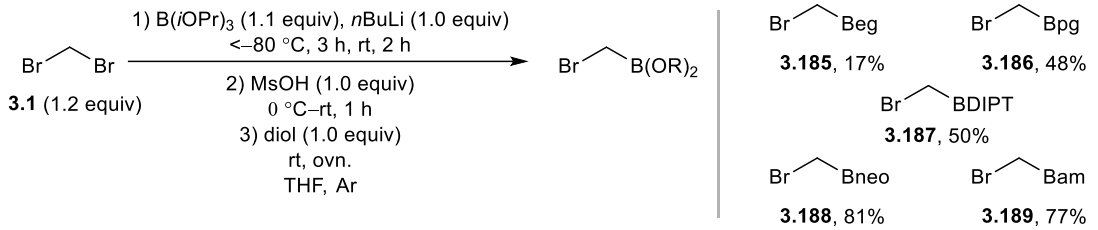
To summarise, the above mechanistic synopsis and controls have gathered a general overview of the palladium-catalysed homologation and provided a more comprehensive outlook regarding the degradation path of the homologating agent under the prescribed conditions. The following section will aim to gather a greater understanding of α-boryl electrophiles under palladium catalysis by assessing how the presence of the boron atom can influence oxidative addition. Contextualisation with respect to Matteson's observations made during his original displacement reactions highlight that the positioning of the boron atom at the α-position of an electrophile leads to remarkable electrophilicity, which is exploited during oxidative addition rather than a classical 1,2-metalate rearrangement. This reactivity is casually referred to as an 'α-boryl effect'.

3.2.3 The oxidative addition of α-boryl electrophiles to palladium

A series of modified homologating agents were prepared as relevant probes for deeper mechanistic investigation. Their syntheses are all summarised first, followed by the relevant control studies. Unless otherwise stated, all yields reported during the preparation of starting materials (Section 3.2.3.1) were isolated and yields obtained during control studies were obtained by ^{1}H NMR assay (Section 3.2.3.2, see Experimental for details).

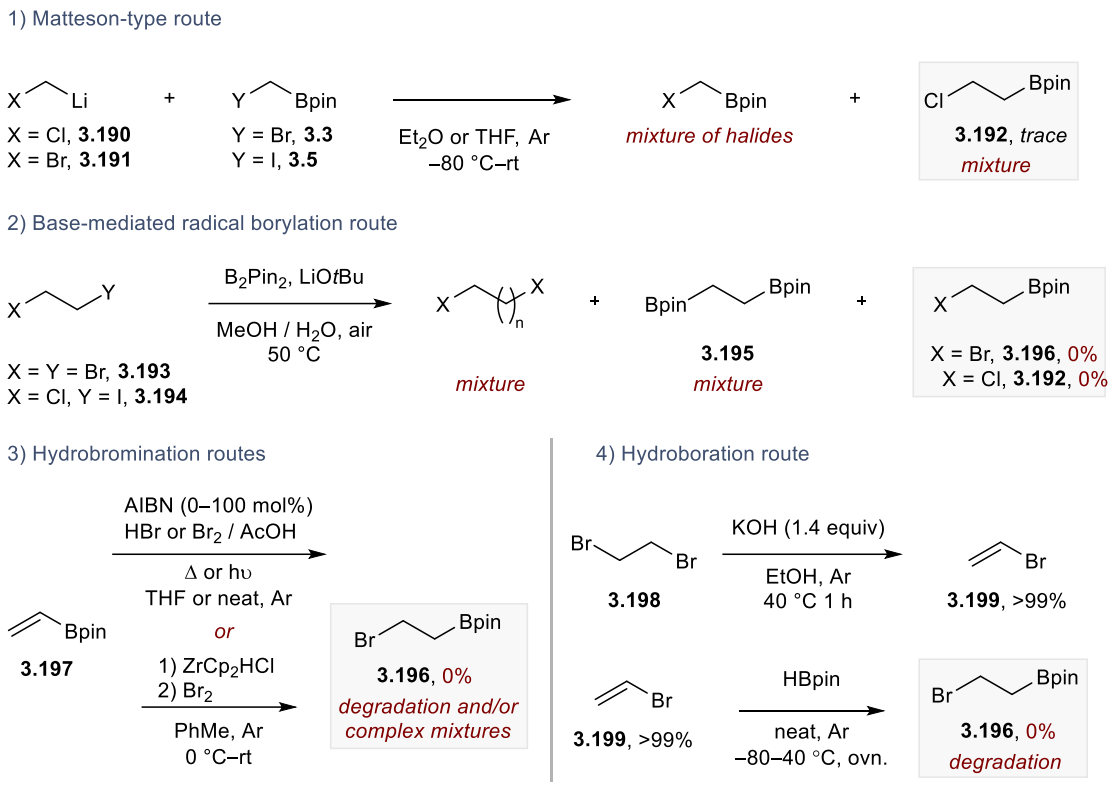
3.2.3.1 Preparation of starting materials

Variations to the ester component of the carbanion were made using the previous lithiation-borylation procedure and changing the relevant diols (Scheme 3.56). The poor yields associated with the ethylene and propylene glycol esters (*i.e.*, **3.185** and **3.186**) can be explained by challenges during vacuum distillation. Distillation without vacuum can result in degradation.



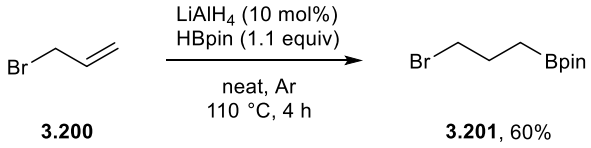
Scheme 3.56: Preparation of homologating agents with varying boronic esters. Isolated yields.

It was sought to investigate the relationship between the positions of the C–B and C–X bond by preparing two compounds with extended chain lengths (*i.e.*, **3.196** and **3.201**). The β-bromoethyl pinacol ester could not be prepared using a variety of synthetic methods, including: 1) Matteson-type displacements using (halomethyl)lithiums; 2) base-mediated radical borylation of alkyl halides; 3) hydrobromination of vinyl boronic acid pinacol ester **3.197**; or 4) hydroboration of freshly made vinyl bromide **3.199** (Scheme 3.57). The full details for these reactions are not shown for brevity, but more details are included in the Experimental Section. A commercial supplier also attempted to prepare **3.196** and were unsuccessful. While the synthesis of pinacol ester **3.196** is unreported in the literature at the time of writing this thesis, β-haloethyl boronic esters in general are notoriously unstable and are reported to undergo a β-elimination-protodeboronation reaction to yield ethylene and boric acid.[31,233]



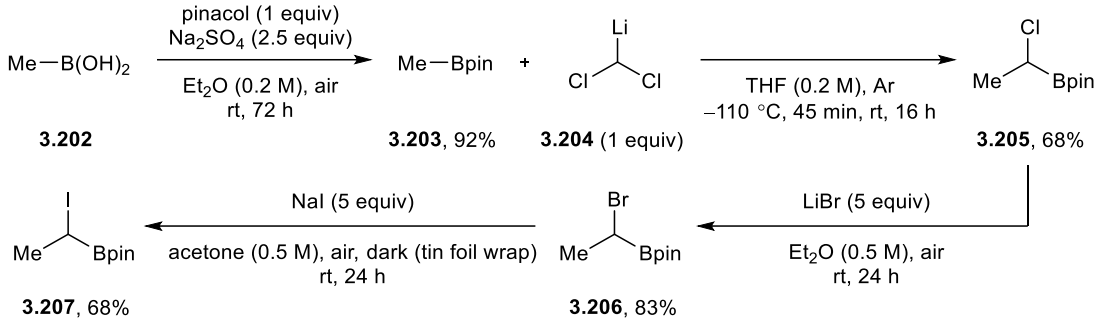
Scheme 3.57: Summary of failed syntheses of β-haloalkyl pinacol esters.

The hydroboration of allyl bromide to prepare the γ-bromopropyl pinacol ester **3.201** was initially unsuccessful; however, this could be remedied by employing catalytic lithium aluminium hydride in a procedure developed by Thomas and coworkers (Scheme 3.58).[234]



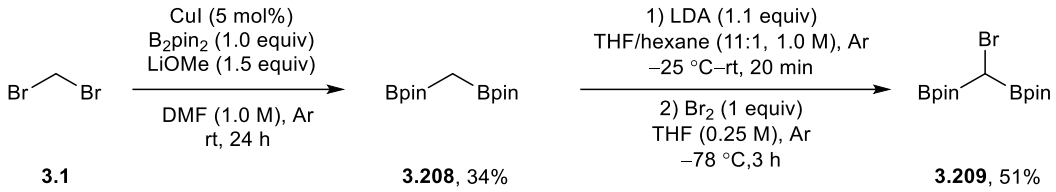
Scheme 3.58: Preparation of a γ-bromopropyl pinacol ester.

A series of α-haloethyl pinacol esters were prepared in a linear fashion from methylboronic acid **3.202** (Scheme 3.59). Following esterification to the pinacol ester (*i.e.*, **3.203**), a Matteson reaction with (dichloromethyl)lithium **3.204** afforded the α-chloroboronic ester, **3.205**, in good yield.[38] While sodium bromide was ineffective, lithium bromide afforded the α-bromoboronic ester, **3.206**, in very good yield. A Finklestein reaction subsequently afforded the α-iodoboronic ester, **3.207**.[167]



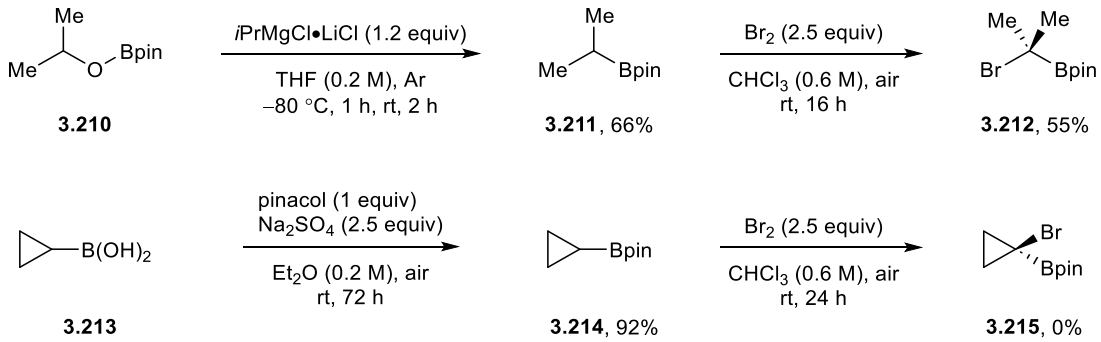
Scheme 3.59: Preparation of α-haloethyl pinacol esters.

An α-brominated bisboronic ester, **3.209**, was prepared over two steps by the diborylation of dibromomethane using a literature procedure to afford **3.208**,[235] followed by a modified telescoped bromination reaction where the intermediate (diborylmethyl)lithium was trapped with bromine *in situ* (Scheme 3.60).[236] Yields were low and moderate, but were consistent with the literature for both transformations.[235,236]



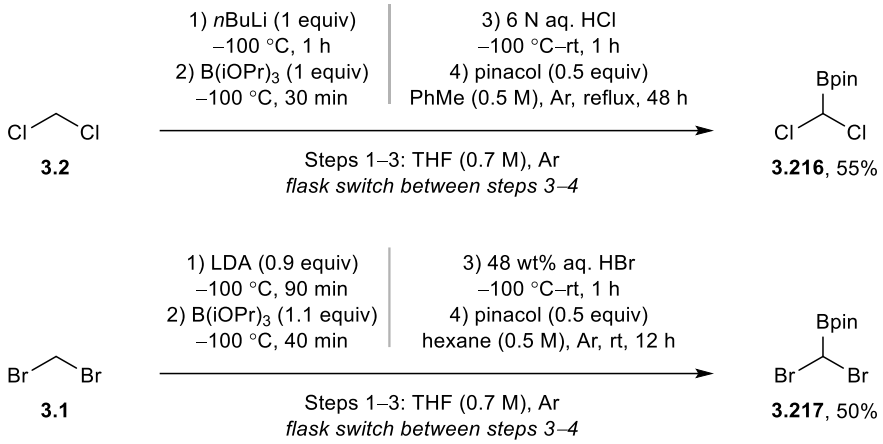
Scheme 3.60: Preparation of an α-brominated bisboronic ester.

The synthesis of two tertiary α-brominated pinacol esters was attempted (Scheme 3.61). The isopropyl boronic ester **3.211** was first prepared by displacement of isopropanol from isopropoxy pinacol ester **3.210** using Turbo Grignard.[237] The cyclopropyl boronic ester **3.214** was prepared by esterification. While a radical-based bromination method from Morken and coworkers furnished the α-brominated isopropyl pinacol ester *(i.e.,* **3.212**) in moderate yield,[25] the analogous reaction with the cyclopropyl boronic ester **3.214** was ineffective and the pursuit of substrate **3.215** was not taken further.



Scheme 3.61: Attempted preparations of tertiary α-brominated pinacol esters.

Two α,α-dihalogenated boronic esters, **3.216** and **3.217**, were prepared *via* the *in-situ* formation of (dichloromethyl)lithium and (dibromomethyl)lithium (Scheme 3.62). Both yields were in agreement with the modified literature procedures.[238]

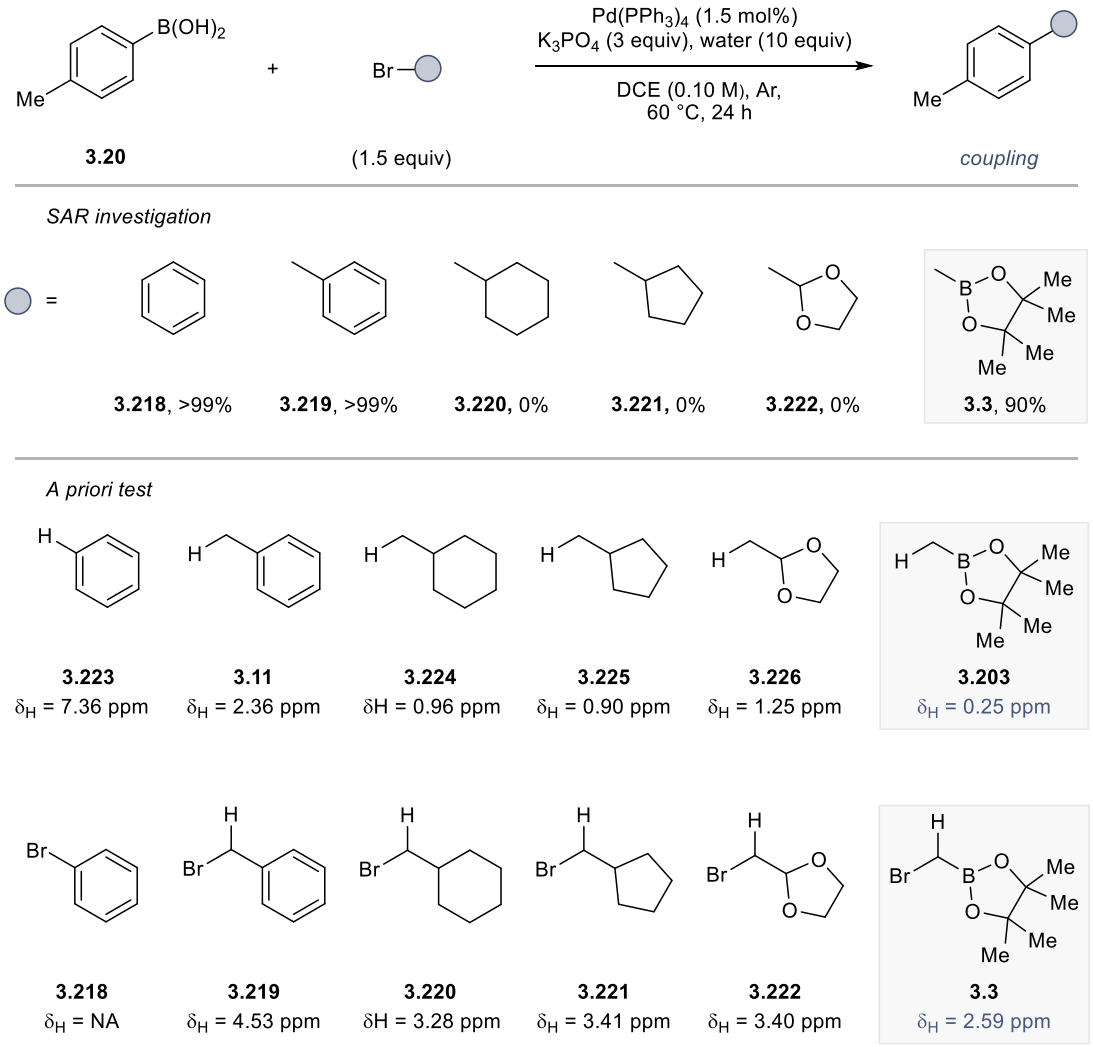


Scheme 3.62: Preparation of α,α-dihalogenated boronic esters.

3.2.3.2 Control studies

A series of control reactions were performed using either the above prepared starting materials or commercially available halides to establish the empirical behaviour of the homologating agent and any further limitations of the developed homologation process.

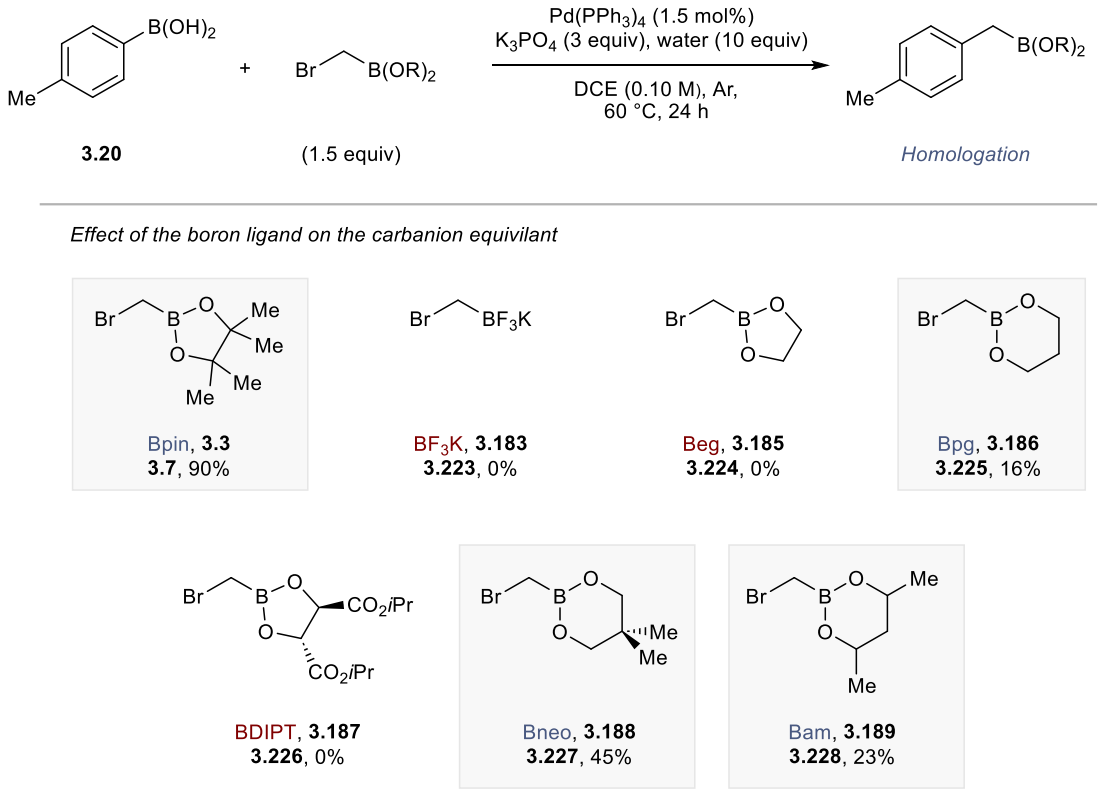
To determine whether the structure of the boronic ester was critical to the reactivity observed the C(sp^3)–C(sp^2) coupling, the bromide was varied (Scheme 3.63). C(sp^2)–Br bromobenzene **3.218** and activated C(sp^3)–Br benzyl bromide **3.219** coupled effectively; however, unactivated C(sp^3)–Br bromides with increasing structural resemblance to **3.3** were ineffective (*i.e.*, **3.220**–**3.222**). The incompetence of the 1,3-dioxolane variant **3.222**, which could be recovered from the reaction mixture quantitatively compared to compound **3.3**, suggested that the presence of the boron atom was critical to enable the oxidative addition of compound **3.3**. Notably, the observed oxidative addition of **3.3** and subsequent homologation reaction cannot be predicted *a priori* by using Zhang's ^{1}H NMR shift test from either the parent compounds (**3.11, 3.203, 3.223**–**3.226**) or the α-hydrogen of the bromides (**3.219**–**3.222**).[225]



Scheme 3.63: Structure-activity relationship test. Comparison of ^{1}H NMR shifts for parent compounds and bromides analogous to Zhang's method. Compound numbers refer to the bromide used.

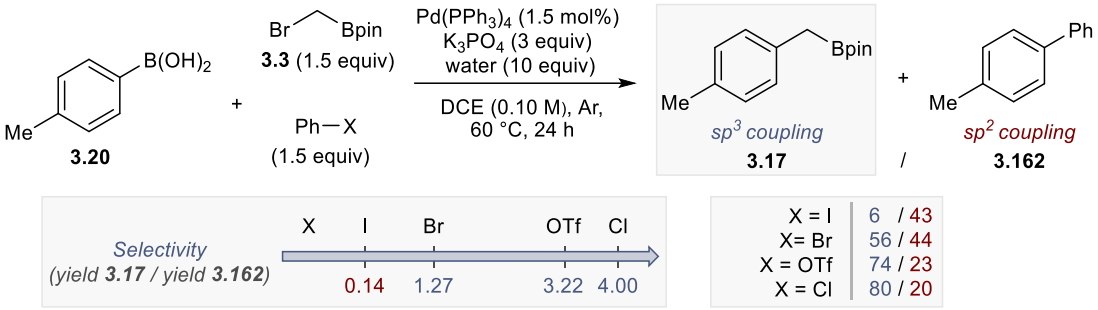
The anatomy of the boronic ester component of the homologating agent was examined (Scheme 3.64). The change from the pinacol ester **3.3** to other boron protecting groups **3.185**–**3.189** was generally detrimental to the reaction, although the propylene- (**3.186**), neopentyl- (**3.188**) and amylene- (**3.189**) glycol esters all showed evidence of coupling in the crude reaction mixtures to varying degrees. The poor assay yields obtained in these cases were unclear; although the selection of boronic ester has been detrimental in other reactions of α-boryl electrophiles, such as Charette's borocyclopropanation of styrenes.[132] The intolerance of the trifluoroborate **3.183** is possibly expected based on the general requirement for B(sp^2)–C hybridisation to stabilise decreased electron density around the α-carbon atom.[123] The ethylene glycol ester **3.185** is very labile so quantitative conversion to the speciated byproduct was expected.[3] The reluctance for the diisopropyl tartrate ester

3.187 is possibly expected based on the intolerance of these functional groups during the robustness study, otherwise this was unclear.



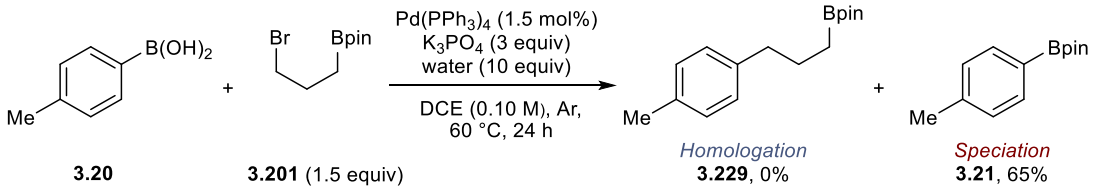
Scheme 3.64: Variation of the boron ligand.

To gauge the overall reactivity of compound **3.3** towards oxidative addition, a series of competition experiments were run using phenyl (pseudo)halides (Scheme 3.65). The selectivity score was determined by the fraction of the desired homologation reaction (sp^3 coupling, **3.17**) over the coupling with the phenyl (pseudo)halide, where both halides were pre-mixed to avoid any bias (see Experimental for further details). While the conditions were selective for iodobenzene, compound **3.3** outcompeted bromo-, trifluoromethylsulfonyl- and chlorobenzene. The excellent chemoselectivity for **3.3** over chlorobenzene was consistent with previous control studies which tolerated the addition of chlorobenzene, even when added before **3.3** (Scheme 3.33). The apparent enhanced weakening of the C–Br bond in **3.3** compared to bromobenzene was also consistent with Matteson's original discussions in nucleophilic displacement reactions, where an α-boryl halide reacts "*300–700 times as fast as the analogous carboxylic ester*".[8] As such, the observed α-boryl effect in nucleophilic substitution (Matteson) reactions is likely to also be applicable to oxidative addition, which has been exploited in this homologation reaction.



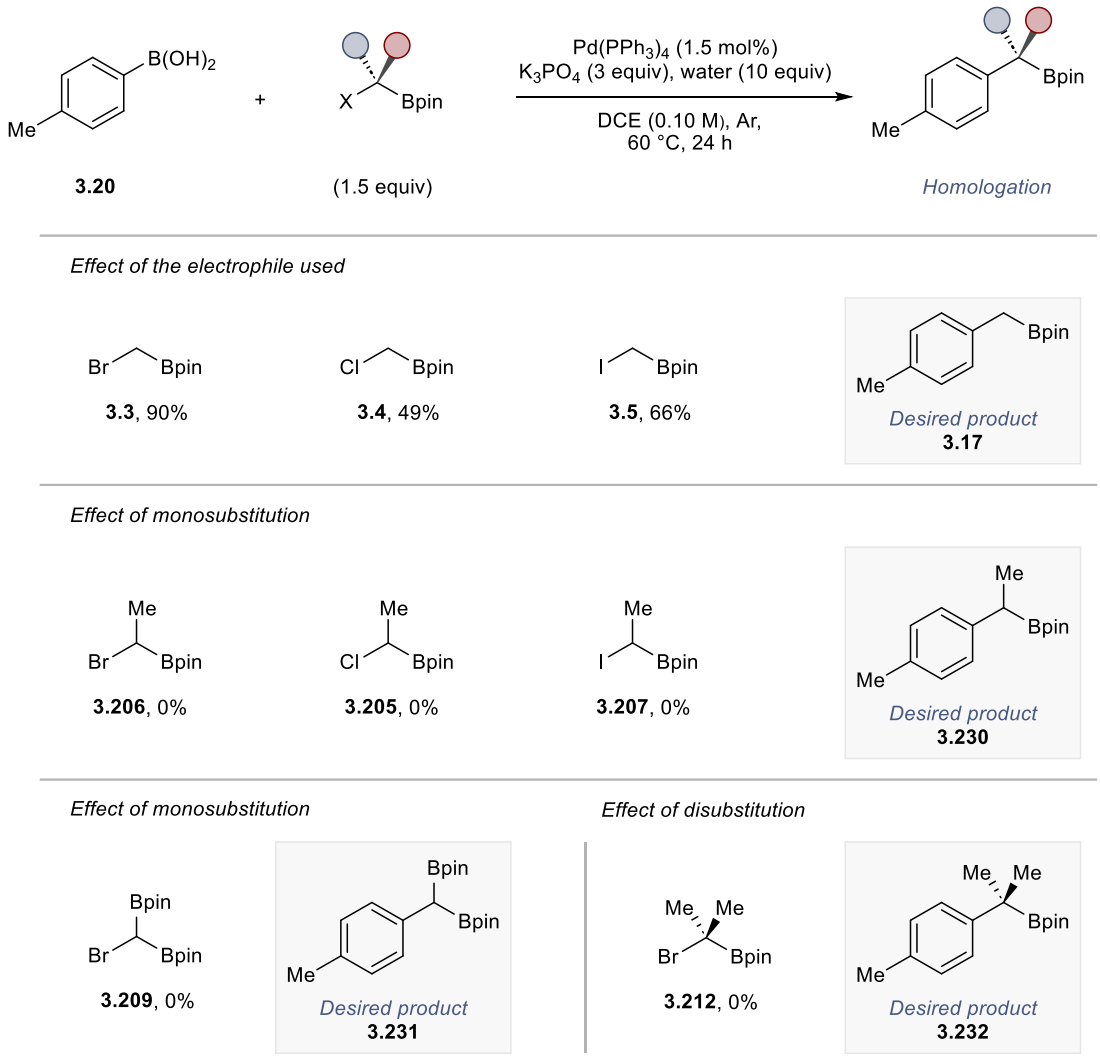
Scheme 3.65: Competition experiments between the carbanion surrogate **3.3** and aryl halides.

The optimised conditions were applied to the γ-bromopropylboronic ester **3.201** to establish whether the boron atom and electrophile must be held in the α-position to permit effective coupling (Scheme 3.66). None of the desired product **3.229** could be obtained, and the reduced yield of the byproduct **3.21** suggested that the speciation of pinacol may also be influenced by the proximity of the halogen atom. While the β-bromoethylboronic ester **3.196** is currently synthetically inaccessible so its coupling cannot be ruled out, it appears based on the available data that the facile oxidative addition of **3.3** is enabled by the boron and halogen atoms being in the α-position to one another.



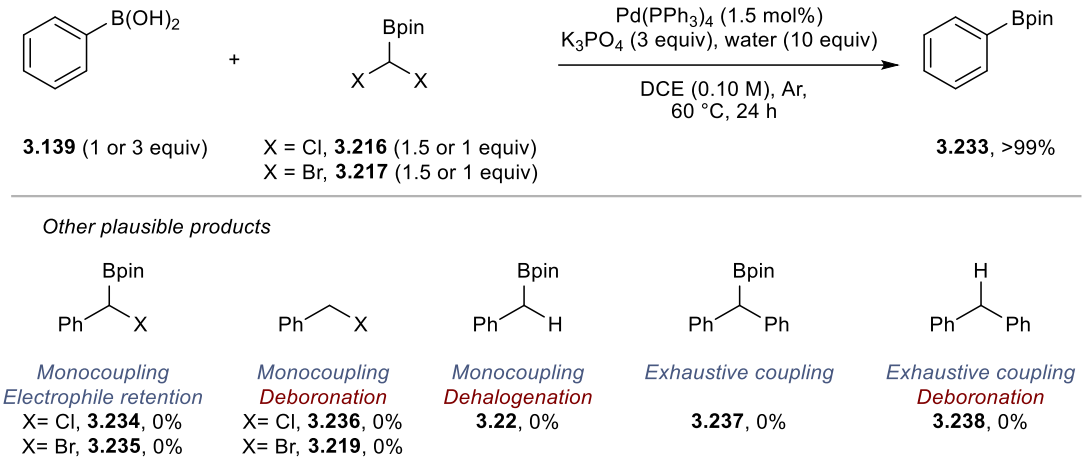
Scheme 3.66: Attempted coupling of γ-bromopropylboronic ester **3.201**.

To determine whether the perceived α-boryl effect at oxidative addition was general, the homologation reaction was run using *para*-tolyl boronic acid **3.20** and a scope of substituted homologating agents (Scheme 3.67). The halide was previously varied during optimisation, so the chloride **3.4** and iodide **3.5** were applied to the optimised conditions. Both were effective but at diminished yields, which suggested that the bromide **3.3** likely possesses a combination of reactivity and stability to the reaction conditions to allow effective cross-coupling. Mono substitution was detrimental and varying the halide was ineffective (*i.e.*, **3.205**–**3.207**). Using the bisboronic ester **3.209** also failed to couple, suggesting that a second boronic ester was counterproductive towards the α-boryl effect. In a similar manner, disubstitution using **3.212** was also ineffective.



Scheme 3.67: Effect of substitution on the homologating agent.

It was hypothesised that reducing the bulk of the added substituent could permit effective coupling. Based on A-values in comparison to methyl, dichloride **3.216**, and dibromide **3.217** were selected as smaller substituents (Scheme 3.68).[43] Sherburn and Sinclair have previously controlled monocoupling *versus* exhaustive coupling of C(sp^2)–X dihalides using different bases and boron protecting groups,[239] so it was unclear which coupling would dominate using C(sp^3)–X dihalides **3.216** and **3.217**. Phenylboronic acid **3.139** was used to assay for all plausible products using available literature data (*i.e.*, **3.22**, **3.219**, **3.234**–**3.238**). In all four cases, varying the reagent stoichiometry or halide was ineffective and only the speciated product could form (for further details, see Experimental). Based on these observations and those outlined in Scheme 3.67, it appears that the perceived α-boryl electrophile effect is highly sensitive to substitution at the α-position. Disappointingly, this sensitivity is not observed during Matteson's nucleophilic displacements.[8]



Scheme 3.68: Attempted couplings of α,α-dihalogenated boronic esters.

To conclude this Section, the assimilation of optimisation data and a series of control experiments have provided a more complete outlook on the idiosyncrasies associated with the developed palladium-catalysed homologation of arylboronic acids using α-halogenated boronic esters, fulfilling Goal 3 of this study. The oxidative addition of the α-brominated boronic ester **3.3** is remarkably facile and shows greater comparative reactivity to bromobenzene; however, substituted variants are recalcitrant and currently limit the overall generality of the developed process. Aside from a disruption of the perceived α-boryl effect, the underlying rationale behind these limitations remain unclear. The impressive reactivity of **3.3**, a B(sp^2)–C(sp^3)–X halide, is consistent with Matteson's original displacement reactions, although specific boronic ester effects observed in this study are less clear. Despite an off-cycle speciation event forming an additional boronic ester byproduct, transmetalation remains wholly chemoselective for the desired homologation (*i.e.*, the boronic acid).

The following Section will use the products successfully obtained from the developed homologation process as synthetic precursors towards more complex products, with a focus towards medicinal chemistry applications.

3.3 Synthetic applications of benzyl boronic esters

The Introduction literature review established that boronic esters are often made by metalation-borylation protocols;[3,16] however, benzyl boronic esters generally cannot be made in this manner due to the instability of the intermediates towards degradation. Miyaura borylations,[240] a typical method to prepare arylboronic esters that does not require stoichiometric organometallic reagents,[3,11] are generally poor when benzyl halides are used

under typical conditions.[241] As such, one of the few methods to reliably prepare benzyl boronic esters before this study was by using Matteson's homologation protocol, which requires prolonged cryogenic control of stoichiometric organometallic reagents.[31]

The possible industrial impact of the catalytic homologation reaction was probed further. A structure search of organoboron compounds from four major commercial suppliers found a significant discrepancy between the number of available aryl boronic acids and esters *versus* benzyl boronic acids and esters, which was interpreted as a general synthetic problem for industrial synthesis (Figure 3.4). This quickly provided evidence that the designed protocol could fulfil a current synthetic bottleneck where onward reactions of benzyl boronic esters, prepared using mild conditions, could be used to assemble novel and complex products in a rapid and modular fashion.

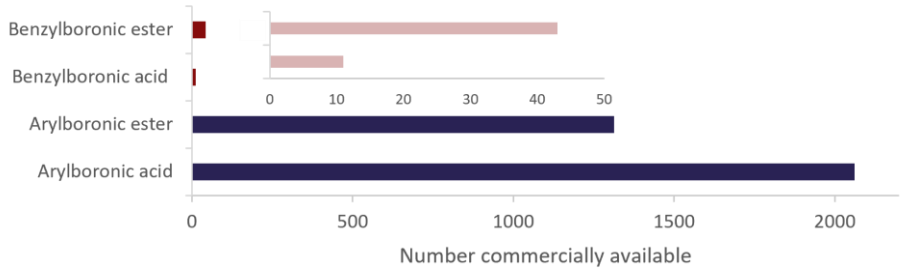


Figure 3.4: Commercial availability of benzyl *versus* aryl organoboron reagents. Data was collected on 20/07/2023 using compiled structure searches from Fluorochem, Sigma Aldrich, Alfa Aesar, and TCI.

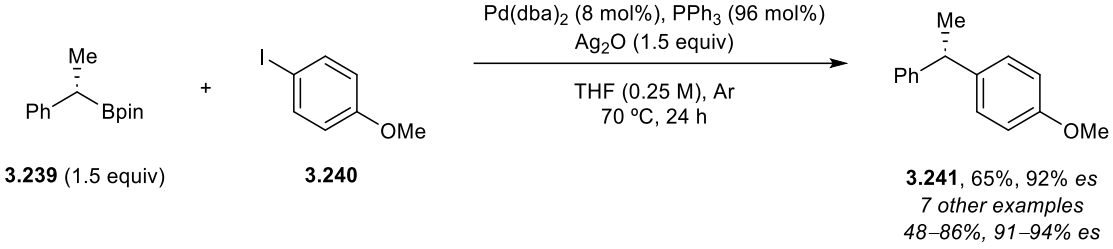
The following section will detail the use of benzyl boronic ester products as a reagent pool for onward synthetic diversification using palladium- and copper-promoted processes to forge benzylic C–C, C–O, and C–N bonds. Possible industrial applications are further demonstrated by accessing substituted diarylmethane pharmacophores.

3.3.1 C–C bond formation

3.3.1.1 Suzuki–Miyaura benzylation

The developed conditions for the palladium-catalysed homologation reaction *via* a Suzuki–Miyaura cross coupling was contingent on the stability of the benzyl boronic ester product. By tuning the reaction conditions, it was hoped that the controlled transmetalation of the benzylic organoboron products could facilitate a sequential Suzuki–Miyaura benzylation reaction.

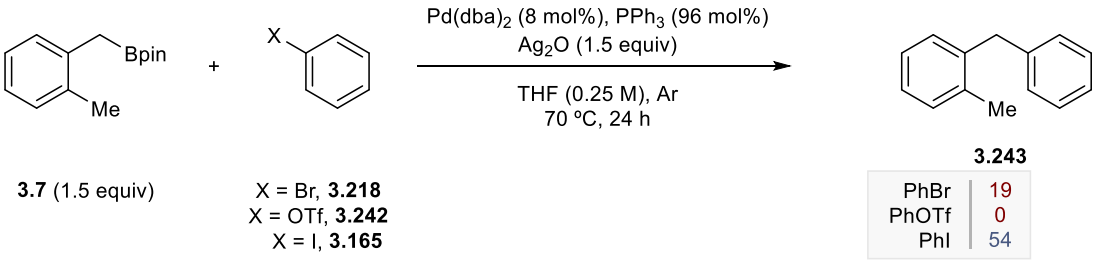
Crudden and coworkers have previously reported a Suzuki–Miyaura cross-coupling of chiral secondary benzyl boronic esters with retention of configuration using silver(I) oxide as an additive (Scheme 3.69).[178]



3.239 (1.5 equiv) **3.240** **3.241**, 65%, 92% *es*
7 other examples
48–86%, 91–94% es

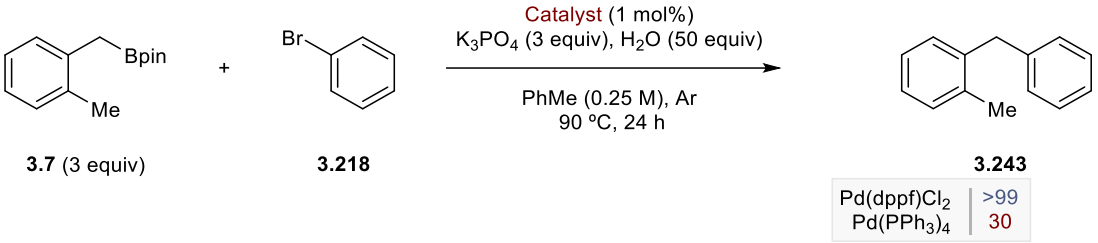
Scheme 3.69: Suzuki–Miyaura cross-coupling of secondary benzylic boronic esters.

The relatively low loading of palladium catalyst with a simple ligand system reported by Crudden and coworkers was attractive to begin work on the Suzuki–Miyaura benzylation of primary benzyl boronic esters for this study. As a product of the developed homologation reaction, benzylboronic acid pinacol ester **3.7** was selected as an appropriate test substrate; however, the assay yield was disappointing using bromobenzene **3.218** as a standard electrophile (Scheme 3.70). The use of phenyl triflate **3.242** was completely ineffective. While the switch back to iodobenzene **3.165** improved the yield significantly, the yield remained moderate for a simplified model reaction and the requirement for aryl iodides would likely reduce the number of available substrates for the developed protocol.[141] Intriguingly, Crudden's report also later quoted significantly poorer isolated yields in comparison to the assay yields (38–64% compared to 48–86%), for reasons that were not explained.[178] Crudden,[178] and others,[242–244] have postulated various roles of silver oxide in coupling reactions of organoboron reagents. The formation of insoluble silver halide salts, rather than typical alkali metal salts,[3] was thought to accelerate the rate of transmetalation based on observations made by Hiyama and Kishi.[178,245,246] Historically, observations as early as 1882 from Michaelis and Becker have clearly demonstrated the use of silver salts as oxidants of organoboron reagents.[247] As such, it is possible that the observed poor yield obtained in the above trial reaction could also be caused by several complex challenges that reach beyond the scope of this study. Moreover, silver salts are generally very toxic so may be inappropriate for future industrial applications. For these reasons, an alternative procedure was sought.



Scheme 3.70: Attempted Suzuki–Miyaura benzylations under Crudden-type conditions. Yields based on ^{1}H NMR assay.

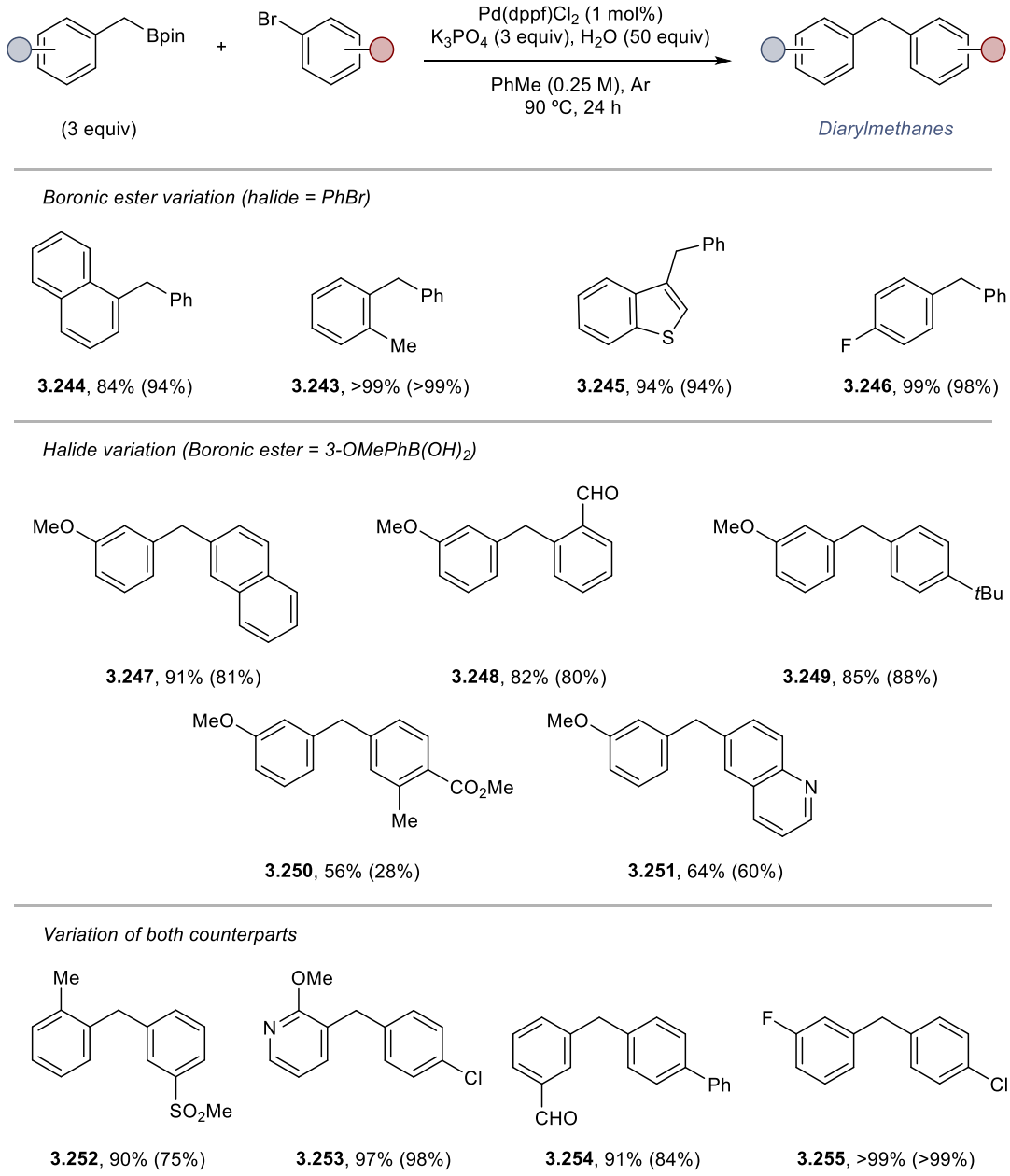
The Watson Group has employed stoichiometric quantities of water to achieve kinetic control of organoboron transmetalation in C(sp^2)–C(sp^2) Suzuki–Miyaura cross-couplings.[161,163–165,206] Based upon these reports, and optimisation data for the homologation reaction showing product hydrolysis when fifty equivalents of water were used (*i.e.*, Scheme 3.71), an alternative set of conditions were trialled which was quantitative using the model substrates (*i.e.*, **3.7** and **3.218**, Scheme 3.71). The use of (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride as a simple and commercially abundant catalyst system alongside a particularly low loading in comparison to Crudden's conditions was attractive from an industrial viewpoint.[178] Moreover, iodides were not required to achieve quantitative conversion and the more widely available aryl bromides could be employed. Disappointingly, the use of tetrakis(triphenylphosphine)palladium(0) was ineffective, so a one-pot homologation-benzylation procedure using a single catalyst for both steps was not possible. The development of such a tandem reaction remains an ongoing methodological project in our laboratory and exceeds the confines of this initial study.



Scheme 3.71: Suzuki–Miyaura benzylation using stoichiometric water. Yields based on ^{1}H NMR assay.

With a quantitative conversion of the model substrates in hand, no further optimisation was performed and a substrate scope was explored by varying the boronic ester, aryl bromide, and both counterparts (Scheme 3.72). In general, a variety of electronic and steric substitution was tolerated at very good to excellent yields. Of note was the tolerance towards heterocycles from either the boronic ester component (*e.g.*, **3.245**, **3.253**) or bromide (**3.251**), and several heteroatom-containing functional groups were tolerated including

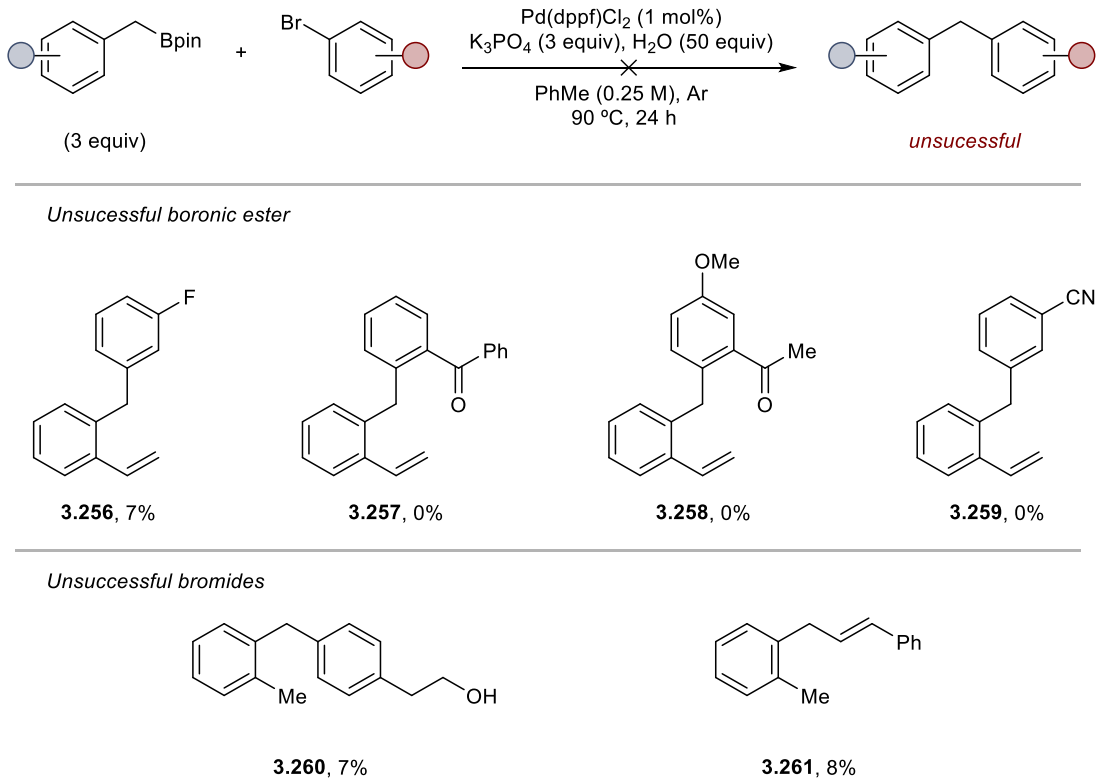
aldehydes (*e.g.*, **3.248**, **3.254**), esters (**3.250**), and sulfonates (**3.252**). Electrophile chemoselectivity was also observed using either boronic esters containing chlorides (*i.e.*, **3.255**) or aryl bromides containing chlorides (*i.e.*, **3.253**) leading to products suitable for further cross-coupling. Substitution at the *ortho*-position was generally well tolerated (*e.g.*, **3.243**, **3.248**, **3.252**, **3.253**), generating several sterically crowded products.



Scheme 3.72: Scope of the Suzuki–Miyaura benzylation. ^{1}H NMR yields are given, with isolated yields in parentheses.

Several Suzuki–Miyaura benzylations were unsuccessful (Scheme 3.73). Most notable was the obstinacy of the *ortho*-vinylbenzylboronic acid pinacol ester towards cross-coupling with

several aryl bromides (*i.e.*, products **3.246**–**3.259**). The reason for this was unclear and crude ^{1}H NMR analysis failed to identify any possible byproducts formed by interactions made between the vinyl group and palladium catalyst. Although the *ortho*-tolylbenzylboronic acid pinacol ester was well-tolerated for several substrates (*i.e.*, products **3.243** and **3.252**, Scheme 3.22), couplings with an unprotected alcohol located on the bromide (product 3.260), or β-bromostyrene (product **3.261**) were ineffective.



Scheme 3.73: Limitations of the Suzuki–Miyaura benzylation. ^{1}H NMR yields are given for non-zero values with respect to the literature. No attempts were made to isolate.

An operationally simple Suzuki–Miyaura procedure has been applied to a reagent pool of benzyl boronic esters that have been prepared *via* the developed palladium-catalysed homologation procedure. This serves as a general method to prepare unsymmetrical diarylmethanes from a previous bottleneck of benzyl boronic esters. The elaboration of these products to assemble substituted diarylmethane pharmacophores is detailed in the following Section.

3.3.1.2 Synthesis of diarylmethane pharmacophores

Diarylmethanes are a common scaffold that is present in natural products, agrochemicals, and active pharmaceutical ingredients. The general reactivity of the benzylic position from

either the diarylmethane or benzyhydrol often directs the onwards elaboration of these scaffolds into complex trisubstituted products.[248] Indeed, many clinically approved treatments contain this motif (Figure 3.5).

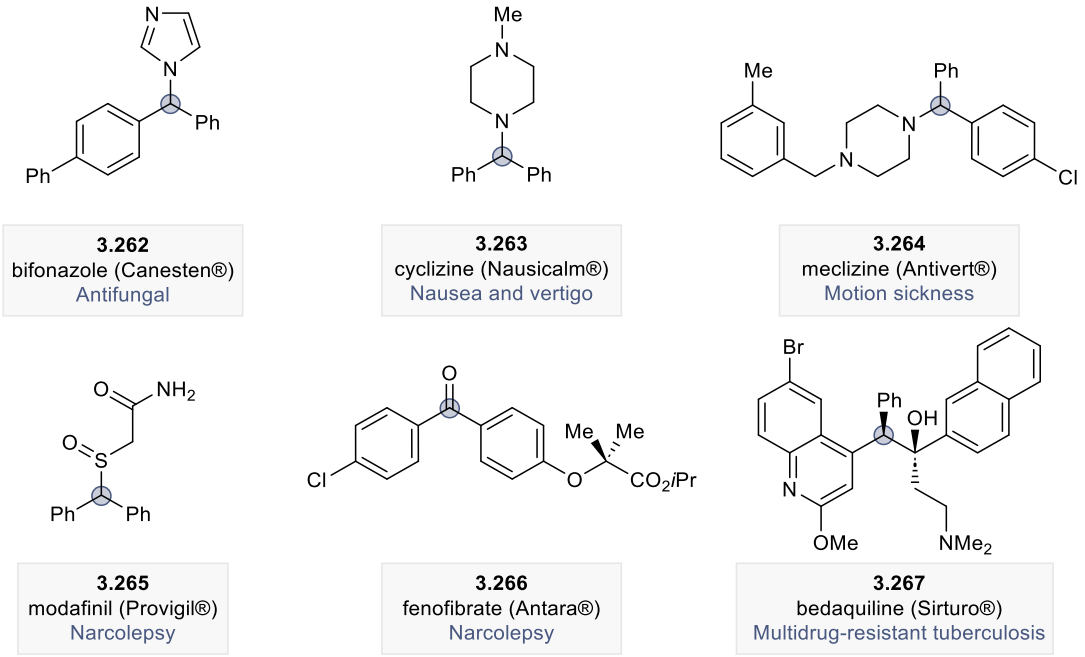
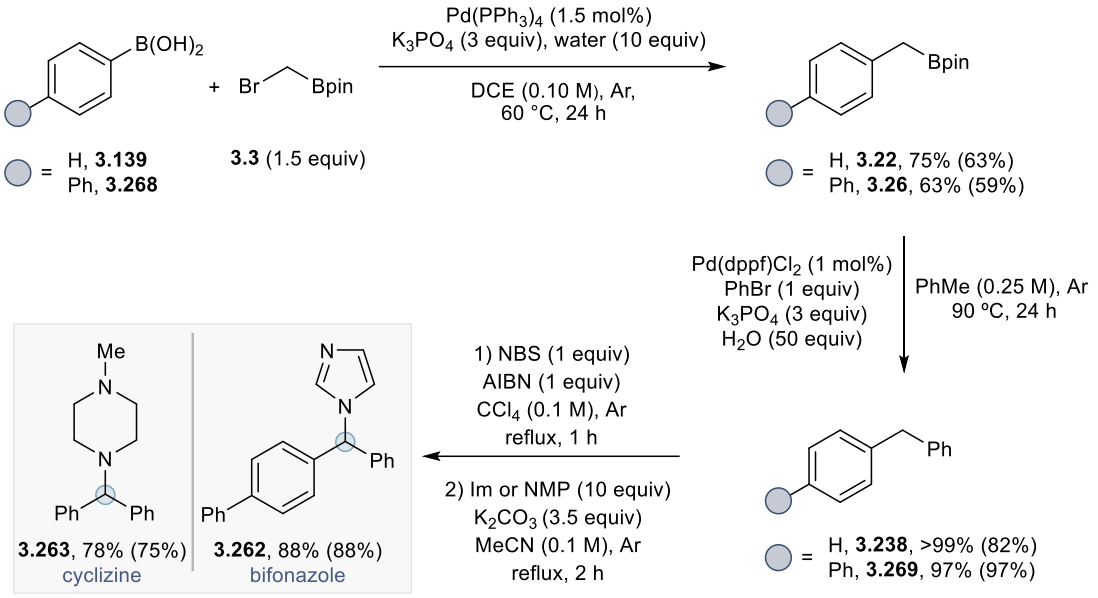


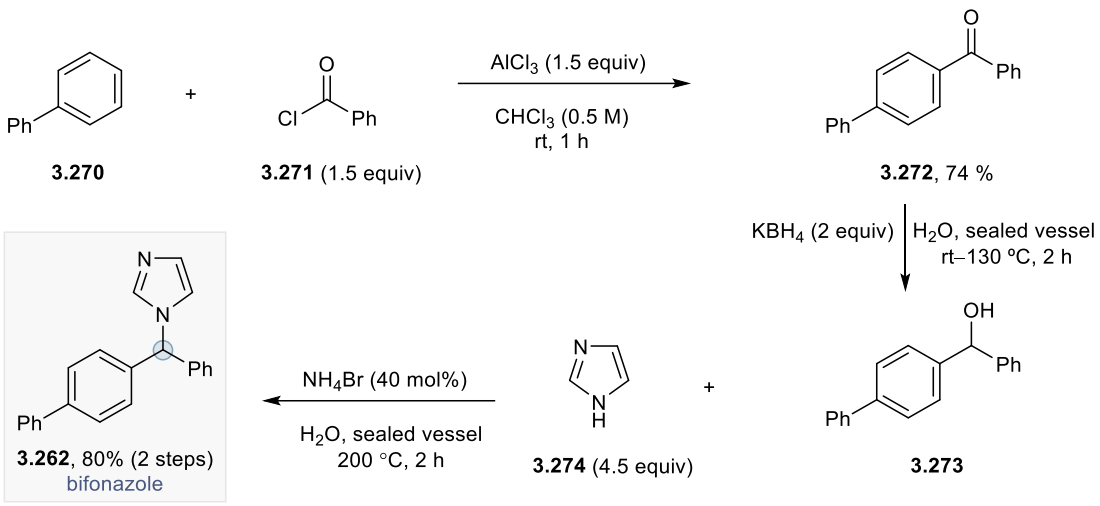
Figure 3.5: Clinically approved active pharmaceutical ingredients containing a diarylmethane.

Bifonazole **3.262** and cyclizine **3.263** were selected as targets for two concise syntheses beginning with the developed catalytic homologation reaction (Scheme 3.74). The intermediate diarylmethanes **3.238** and **3.269** could be prepared from the previously accessed benzyl boronic esters **3.22** and **3.26** — their syntheses, outlined in Section 3.1.2, is shown again for completeness. A one-pot Wohl–Ziegler bromination and nucleophilic substitution was performed on the diarylmethane products using imidazole and *N*-methylpiperazine, respectively, which both proceeded smoothly to yield bifonazole **3.262** and cyclizine **3.263**.[249,250] Overall, bifonazole was accessed in 50% yield, and cyclizine was accessed in 39% yield, each over three isolated steps. No stoichiometric organometallic reagents were required throughout these syntheses from commercially abundant arylboronic acid starting materials and simple catalysts were used at low loadings throughout.



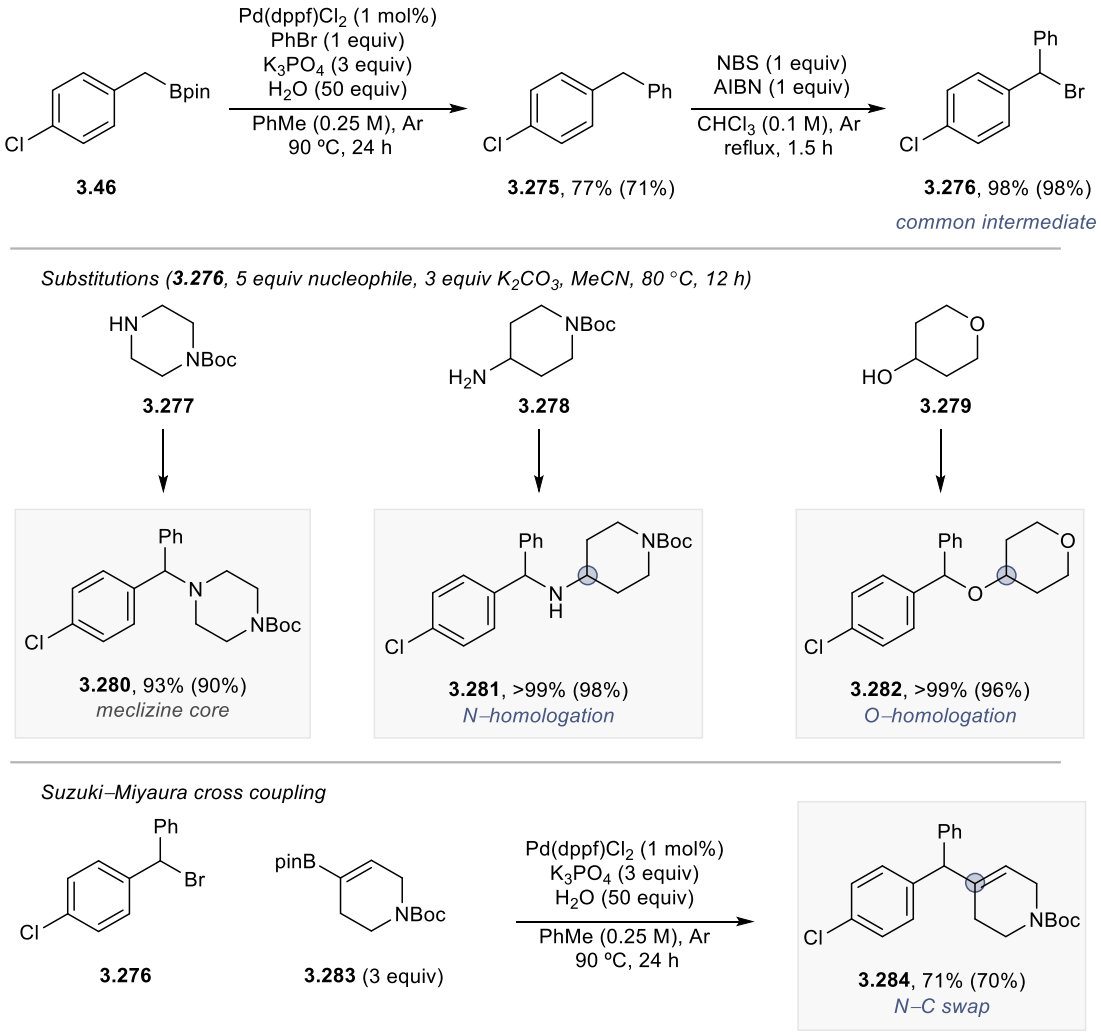
Scheme 3.74: Syntheses of cyclizine and bifonazole *via* the developed catalytic homologation reaction. ^{1}H NMR yields are given, with isolated yields in parentheses. Im = Imidazole; NMP = *N*-methyl piperazine.

To contextualise the potential industrial impact of the developed homologation process further, a search of the patent literature was carried out with respect to the synthesis of bifonazole. The most established route patented by Bayer (DE10332684B3) utilises a similar nucleophilic displacement reaction using imidazole; however, the method requires thionyl chloride and three steps to the asymmetric substituted benzydrol starting material. The most concise patented route found, assuming biphenyl **3.270** as a readily available starting material, involves a Friedel–Crafts acylation (PL170632) followed by a one-pot reduction-substitution reaction that is catalysed by ammonium bromide at high temperatures in a sealed vessel (CN107459486, Scheme 3.75). Over two isolated steps bifonazole can be accessed in 59% yield; however, there are also associated safety drawbacks (*e.g.*, use of acyl chlorides, excess borohydride under prolonged heating, very high temperatures) which are not encountered using the homologation-benzylation-substitution route above. As such, an isolated yield of 50% under generally milder conditions could offer a commercially viable alternative route to bifonazole.



Scheme 3.75: A commercial route to bifonazole.

Synthetic methodology is typically directed towards the synthesis of novel products that have fortuitous properties over existing molecules. As such, the modular preparation of diverse libraries using relatively simple techniques to access new chemical space is a cornerstone of modern synthesis, including pharmaceutical development.[251] This approach was applied towards the derivatization of meclizine (Scheme 3.76). Following the homologation-benzylation-bromination sequence previously used for the synthesis of bifonazole and cyclizine, both amine (*i.e*, **3.277** and **3.278**) and alcohol (**3.279**) nucleophiles could be applied to furnish the meclizine core (*i.e.*, **3.280**) or structurally analogous compounds (*e.g.*, **3.281** or **3.282**) that would be appropriate for potency screening against meclizine to determine a structure-activity relationship. A Suzuki–Miyaura coupling of the crude benzyl bromide **3.276** and the tetrahydropyridyl boronic ester **3.283** using the previously applied conditions also afforded a derivative of the meclizine core where a nitrogen atom has been swapped for carbon (*i.e.*, **3.284**). Yields were generally excellent throughout.



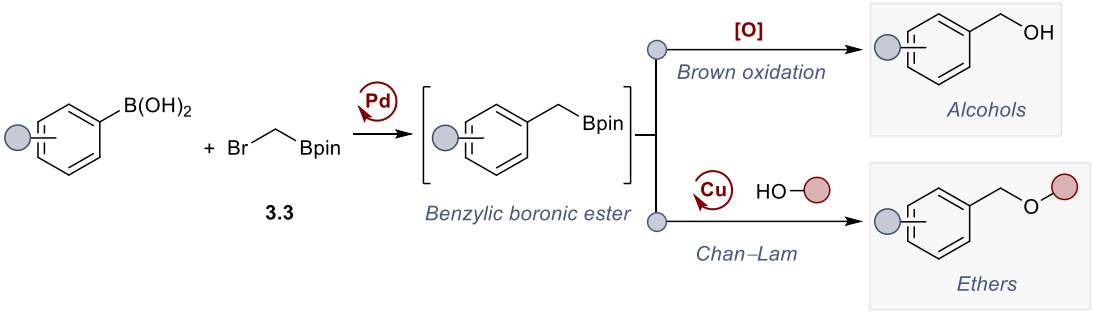
Scheme 3.76: Divergent synthesis of the meclizine core for structure-activity relationship determination. ^{1}H NMR yields are given, with isolated yields in parentheses.

The developed Suzuki–Miyaura benzylation procedure of commercially uncommon benzyl boronic esters has been applied towards the syntheses of substituted diarylmethane pharmacophores and related derivatives in a simple, modular, fashion. Conditions are generally mild throughout and the developed route to access this motif offers a potential alternative compared with existing commercial methods that obtain similar yields under harsher conditions. The following two sections will continue to explore the applications of the catalytic homologation of arylboronic acids to forge C–O and C–N bonds.

3.3.2 C–O bond formation

The preparation of organoboron compounds is often synonymous with the preparation alcohols. The oxidation of organoboron compounds to alcohols is typically attributed to Brown following his hydroboration methodology developed in 1956,[5] although organoboron

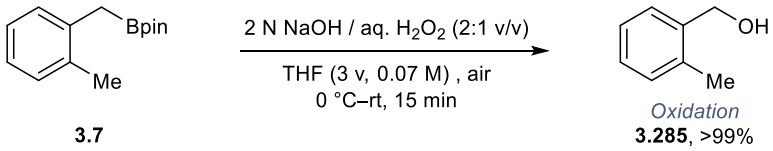
oxidation was first demonstrated by Frankland in 1860.[2] An oxidation reaction performed in the same reaction vessel as the developed homologation reaction would be a convenient method to prepare benzyl alcohols from arylboronic acids (Scheme 3.77). Following the oxidation of the C–B bond into a C–O bond, a Williamson synthesis could be used to prepare more structurally diverse ether products. An alternative method would be to convert the benzyl boronic esters into the corresponding ethers directly, which could be realised using a Chan–Lam coupling.[252,253] This section will detail the applications of benzylic boronic esters towards the synthesis of alcohols and ethers.



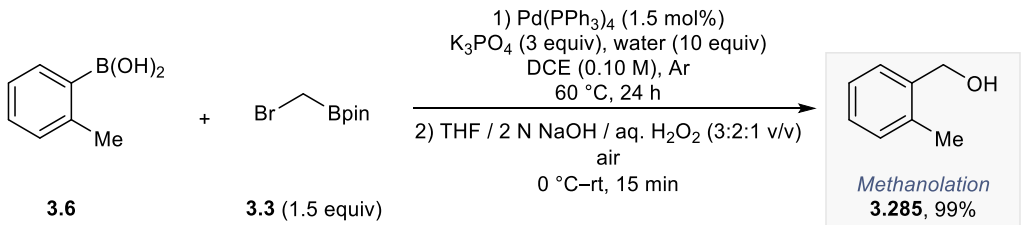
Scheme 3.77: Designed application of the catalytic homologation to prepare benzylic C–O bonds.

Work began with the one-pot homologation-oxidation reaction using *ortho*-tolyl benzyl boronic acid pinacol ester **3.7** as the workhorse substrate (Scheme 3.78). A Brown oxidation using a typical ethereal solution of basic hydrogen peroxide was quantitative.[5] The one-pot process was then applied using the parent boronic acid as the starting material, which also proceeded smoothly to afford the benzyl alcohol, **3.285**.

1. Trial Brown oxidation from the benzyl boronic ester

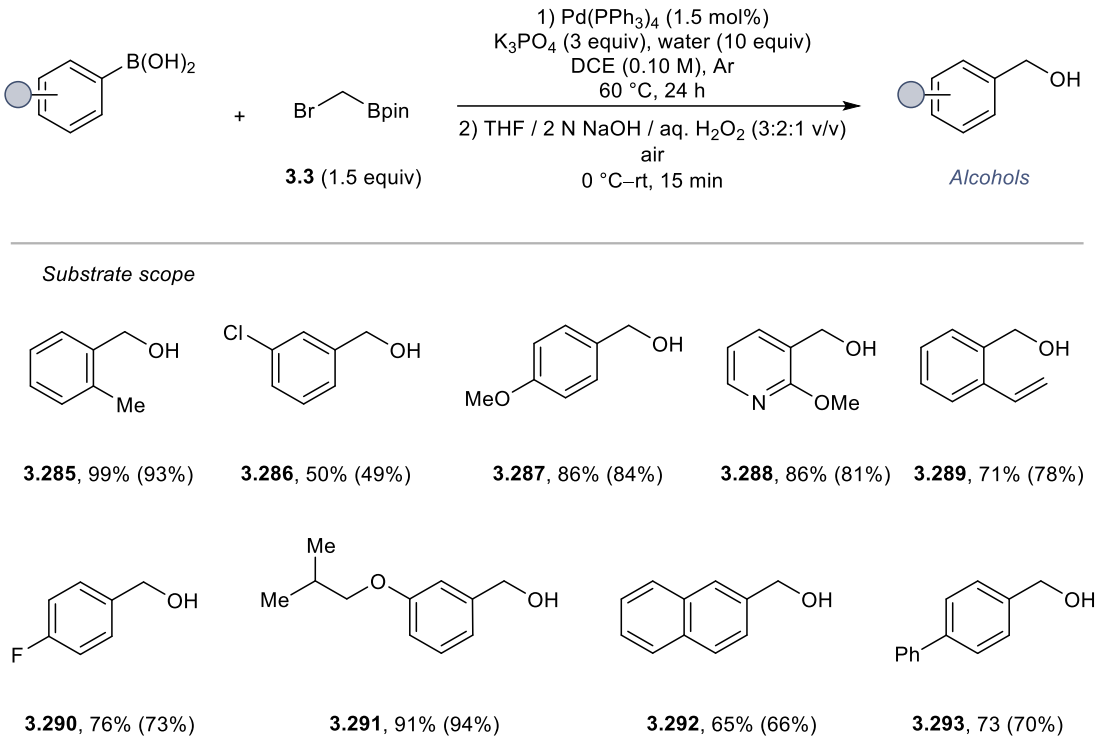


2. Trial one-pot homologation-oxidation procedure



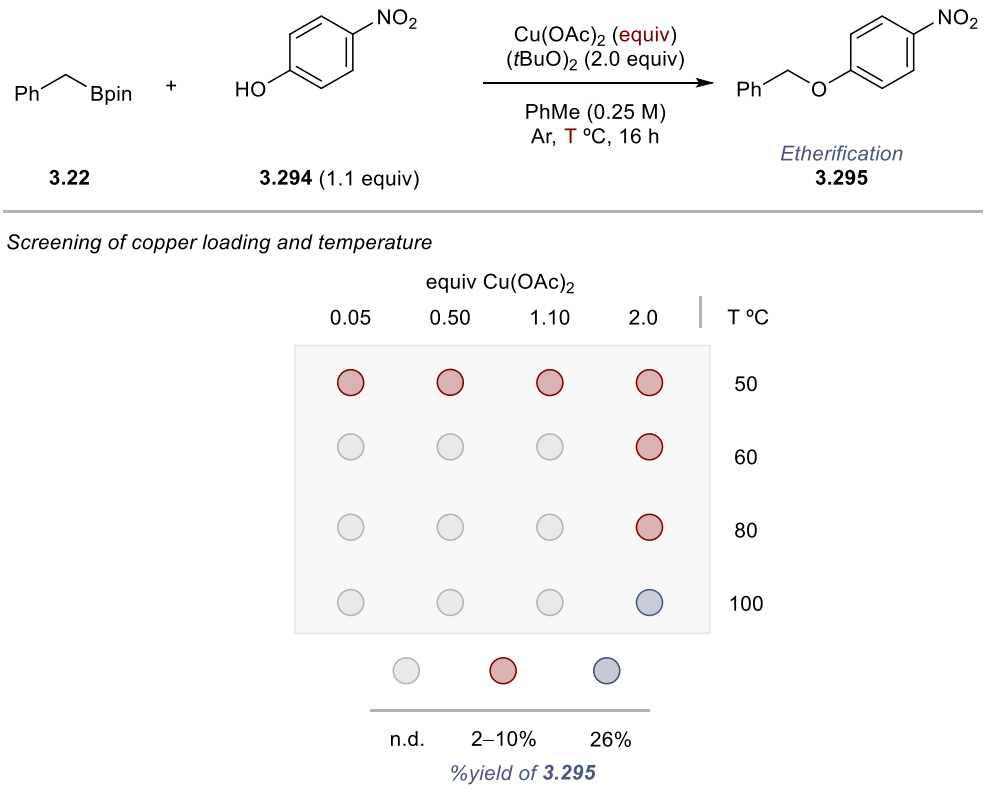
Scheme 3.78: Trial reactions to prepare benzylic alcohols from the developed homologation process. ^{1}H NMR yields are displayed.

Using a sample of competent arylboronic acids discovered during the initial homologation process (*i.e.*, Section 3.1.2), a scope of benzyl alcohols was prepared (Scheme 3.79). All substrates that were trialled proceeded smoothly, with yields generally reflecting the conversion obtained from the homologation reaction followed by quantitative oxidation. More sensitive functional groups, such as pyridine (**3.288**) or vinyl (**3.289**), were unaffected.



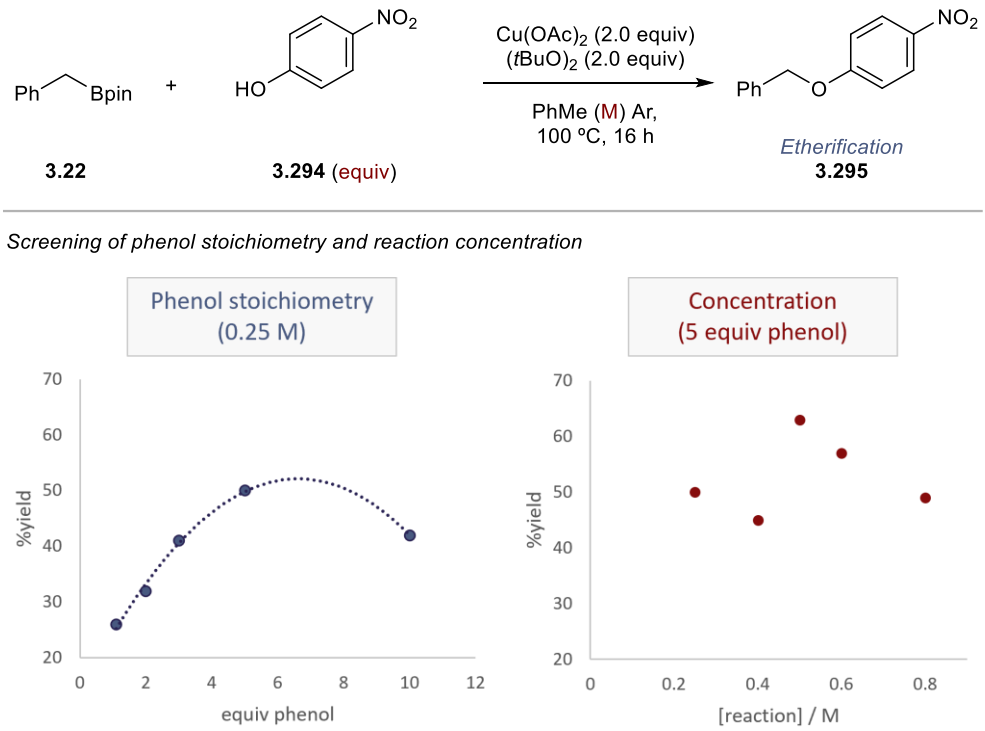
Scheme 3.79: Scope of benzyl alcohols. ^{1}H NMR yields are given, with isolated yields in parentheses.

The Chan–Lam etherification was investigated next. A literature search identified a set of conditions reported by Kuninobu that were applied to primary benzylic boronic esters and seven electron-deficient alcohols.[254] A trial reaction using benzylboronic acid pinacol ester **3.22** and *para*-nitrophenol **3.294** was ineffective in our laboratory (3%, Scheme 3.80). Copper(II) acetate is an abundant and cheap copper source that is generally the reagent of choice in Chan–Lam couplings. While many methodological investigations of the Chan–Lam coupling have focussed on the catalytic process, there is a notable trade-off between more bespoke reagents and harsher conditions as opposed to reactions that simply use stochiometric quantities of copper(II) acetate.[255] With the principal focus of this work leaning towards industrial methodology, the use of stoichiometric copper(II) acetate appeared favourable. At elevated temperatures, modest conversion to the desired product could be afforded using stoichiometric copper(II) acetate (26%).



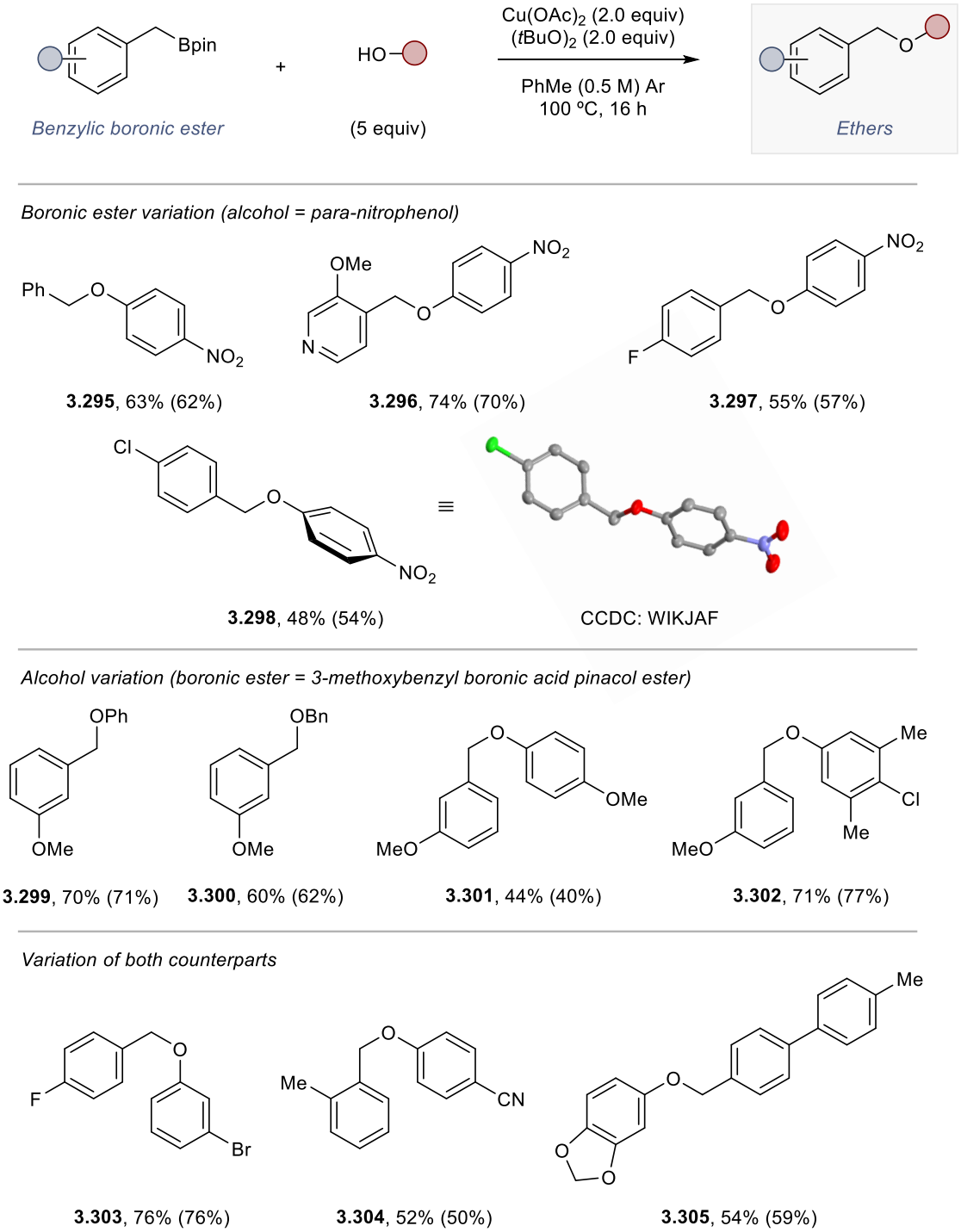
Scheme 3.80: Screening of copper(II) acetate loading and temperature for the Chan–Lam etherification. ^{1}H NMR assay yields are given.

Increasing the stoichiometry of phenol was also effective (left, Scheme 3.81). Throughout the screening process other typical byproducts, formed by the oxidation of the boronic ester or oxidative homocoupling,[255] typically accounted for less than 10% of the tracked mass balance. Increasing the concentration of the reaction up to 0.5 M further increased the yield to 63% (right, Scheme 3.81). Beyond this concentration, most of the copper(II) acetate was out of solution and likely impeded the overall conversion. Based on typical yields obtained for Chan–Lam couplings and a significant improvement made with reference to Kuninobu's original report, no further optimisation was undertaken.



Scheme 3.81: Screening of phenol stoichiometry and concentration for the Chan–Lam etherification. ^{1}H NMR assay yields are given.

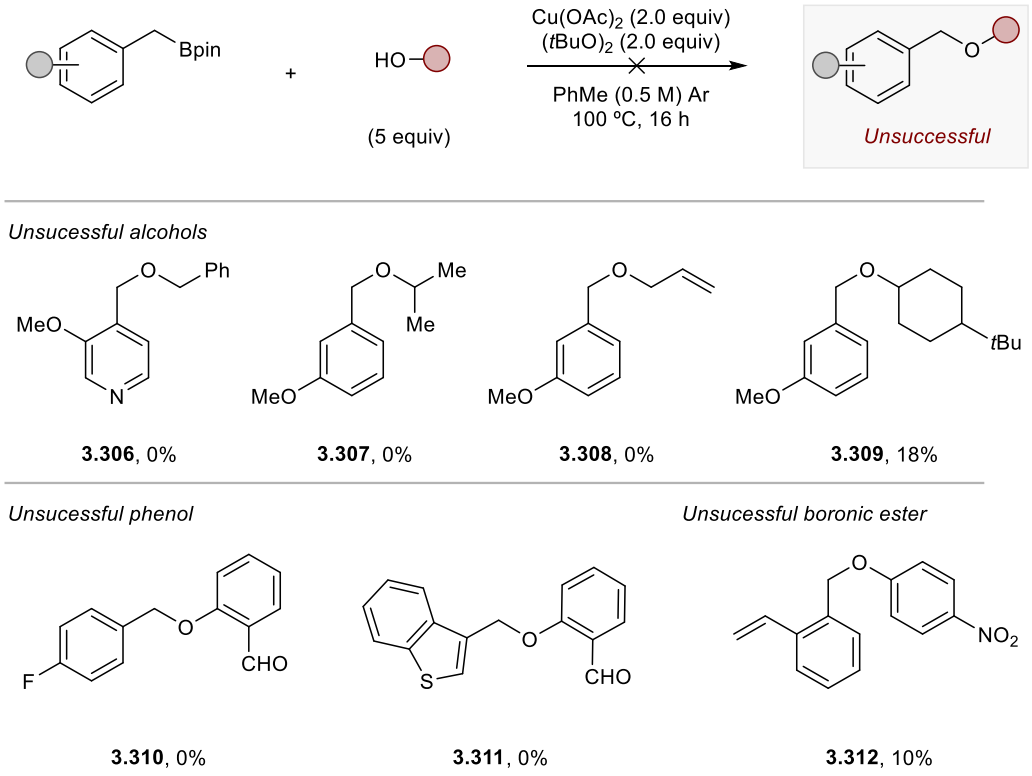
A scope of benzylic ethers was prepared by varying the boronic ester, alcohol, and both counterparts using the developed protocol (Scheme 3.82). The reaction was generally immune to changes in the boronic ester (*i.e.*, **3.295**–**3.298**), with the structure of **3.298** unambiguously confirmed by X-ray crystallography. The reaction was effective with electron-withdrawing (*e.g.*, products **3.295**–**3.298**, **3.302**, **3.304**) phenols; however, electron-rich phenols (*e.g.*, product **3.301**) tended to give lower yields along with a series of unidentified side products that were not isolated. While benzyl alcohol was tolerated to deliver product **3.300**, this was generally an exception (see below for further details). Gratifyingly, a variety of functional groups that could be used in further manipulations were tolerated such as bromide (*e.g.*, **3.303**), chloride (*e.g.*, **3.298**, **3.302**) and nitrile (**3.304**). Many of the obtained products are also novel, demonstrating that new chemical space can be accessed from the developed homologation protocol where benzylboronic esters are a generally uncommon reagent pool.



Scheme 3.82: Scope of benzyl ethers. ^{1}H NMR yields are given, with isolated yields in parentheses.

Several Chan–Lam etherifications were unsuccessful (Scheme 3.83). Although one example was achieved using benzyl alcohol (*i.e.*, **3.300**, Scheme 3.82), other examples were recalcitrant at either stoichiometric loading or when used in solvent quantities (*i.e.*, products **3.306**–**3.308**, Scheme 3.83). The use of *ortho*-hydroxybenzaldehyde was unsuccessful and it was unclear whether this was caused by the aldehyde functional group, *ortho*-substitution,

or both factors. In an analogous observation to the Suzuki–Miyaura benzylation, the *ortho*-vinylbenzyl boronic ester was ineffective using the benchmark phenol (*i.e.*, product **3.312**).

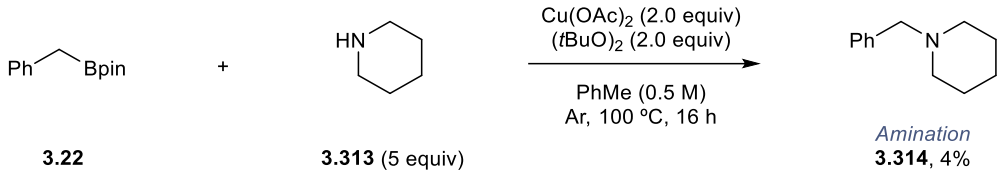


Scheme 3.83: Limitations of the Chan–Lam etherification. ^{1}H NMR yields are given for non-zero values. No attempts were made to isolate.

The products of the developed catalytic homologation of arylboronic acids have been applied towards the synthesis of C–O bonds. Conveniently, the synthesis of benzyl alcohols can be performed in a single operation from the arylboronic acid. The developed Chan–Lam etherification can offer good yields of products using stoichiometric quantities of abundant and inexpensive copper(II) acetate without the requirement for bespoke ligands and limitations have been disclosed. The following Section will continue to use the Chan–Lam coupling to extend the scope of products towards the synthesis of benzylic amines.

3.3.3 C–N bond formation

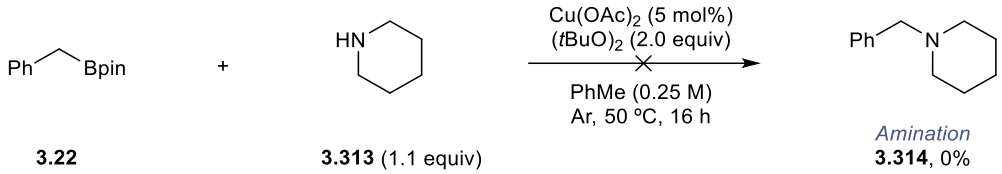
The application of benzylboronic esters prepared from the catalytic homologation reaction was applied towards the synthesis of benzylamines. Naturally, the first set of conditions trialled were those applied to the previous Chan–Lam etherification reaction. Using benzyl boronic acid pinacol ester **3.22** and piperidine as the benchmark substrates, these conditions were completely ineffective (Scheme 3.84).



3.22 **3.313** (5 equiv) **3.314**, 4%

Scheme 3.84: Attempted Chan–Lam amination based on the developed etherification. ^{1}H NMR yield.

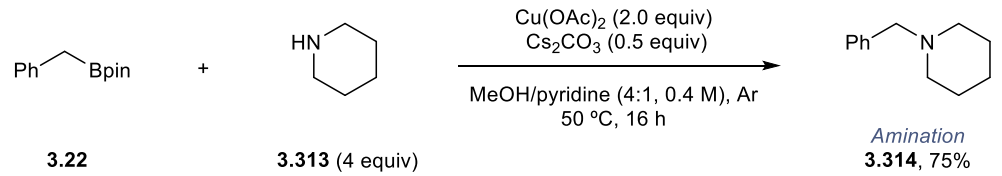
Returning to the initial amination and etherification conditions disclosed by Kuninobu and coworkers was equally ineffective in our laboratory (Scheme 3.85).[254]



3.22 **3.313** (1.1 equiv) **3.314**, 0%

Scheme 3.85: Attempted Chan–Lam amination using conditions reported by Kuninobu and coworkers.

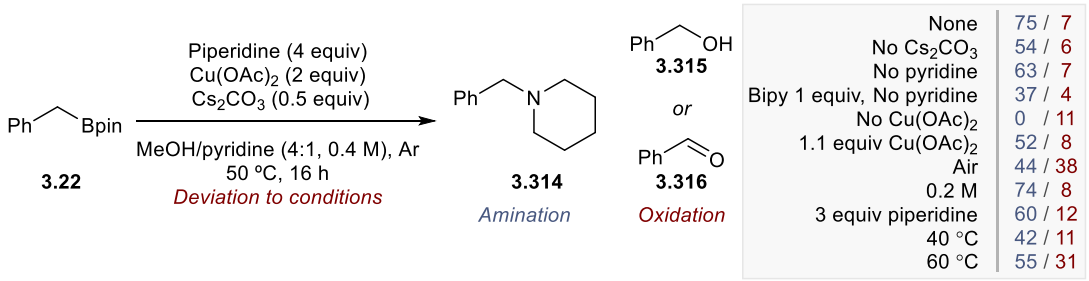
A literature search identified a similar Chan–Lam amination of secondary benzylic boronic esters reported by Partridge and coworkers, where a single primary boronic ester was also reported.[256] Gratifyingly, these conditions were effective (Scheme 3.86).



3.22 **3.313** (4 equiv) **3.314**, 75%

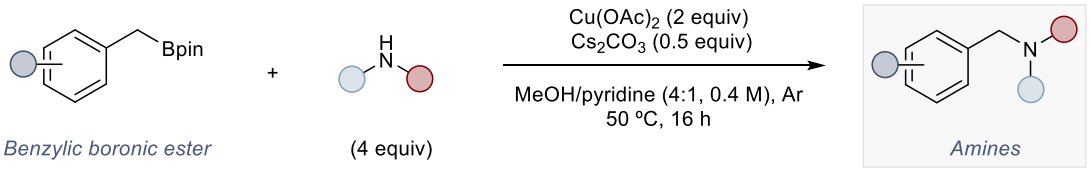
Scheme 3.86: Chan–Lam amination using conditions disclosed by Partridge and coworkers. ^{1}H NMR yield.

To try to simplify the reaction operation, a series of control reactions were performed to determine the effect of all reaction components and conditions (Scheme 3.87). Inorganic base and pyridine were both essential, where the latter likely serves as a ligand for copper(II) acetate.[255] Contrastingly, bipyridine was an ineffective ligand in the absence of pyridine. Air is typically used as a terminal oxidant in catalytic Chan–Lam couplings,[255] but an inert atmosphere was essential to reduce the formation of oxidation byproducts under these conditions. Diluting the reaction lead to no yield improvement, and superstoichiometric loadings of cheap amine were essential. A reaction temperature of 50 °C provided a balance of desired reactivity without competing oxidation of the boronic ester.

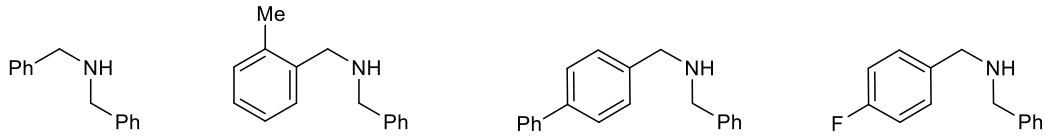


Scheme 3.87: Analysis of reaction components for the applied Chan–Lam amination. ^{1}H NMR yields.

With Partridge's amination conditions proving most effective for the primary benzylic boronic esters prepared in this study, a scope of benzyl amines were prepared (Scheme 3.88). When varying the boronic ester component using benzylamine, the negative impact of *ortho*-substitution became apparent (*i.e.*, **3.318**, **3.327**). Changes to the electronics of substituents were generally less noticeable (*i.e.*, **3.319**, **3.320**, **3.321**, **3.324**). A variety of amines were tolerated with very good yields maintained throughout; including benzyl amine (*i.e.*, **3.317**–**3.320**) primary (*e.g.*, **3.321**, **3.324**, **3.326**) and secondary (**3.322**, **3.327**) anilines, piperazine (**3.323**), piperidine (**3.314**), and tetrahydroquinoline (**3.325**).

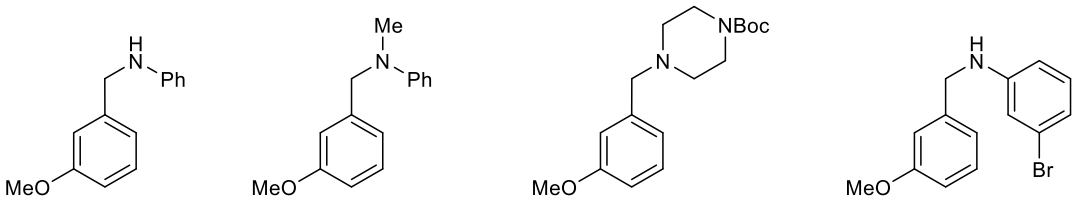


Boronic ester variation (amine = benzylamine)



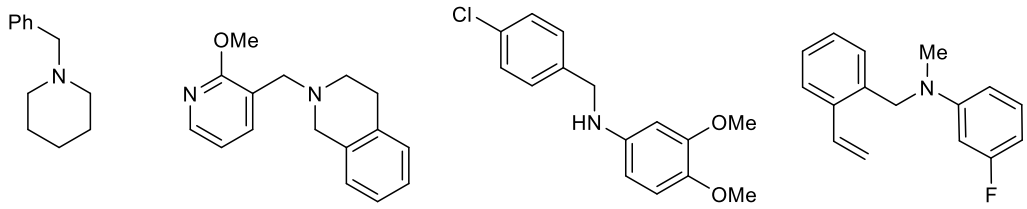
3.317, 54% (50%) **3.318**, 24% (23%) **3.319**, 60% (51%) **3.320**, 51% (53%)

Amine variation (boronic ester = 3-methoxybenzyl boronic acid pinacol ester)



3.321, 61% (61%) **3.322**, 73% (65%) **3.323**, 78% (82%) **3.324**, 76% (58%)

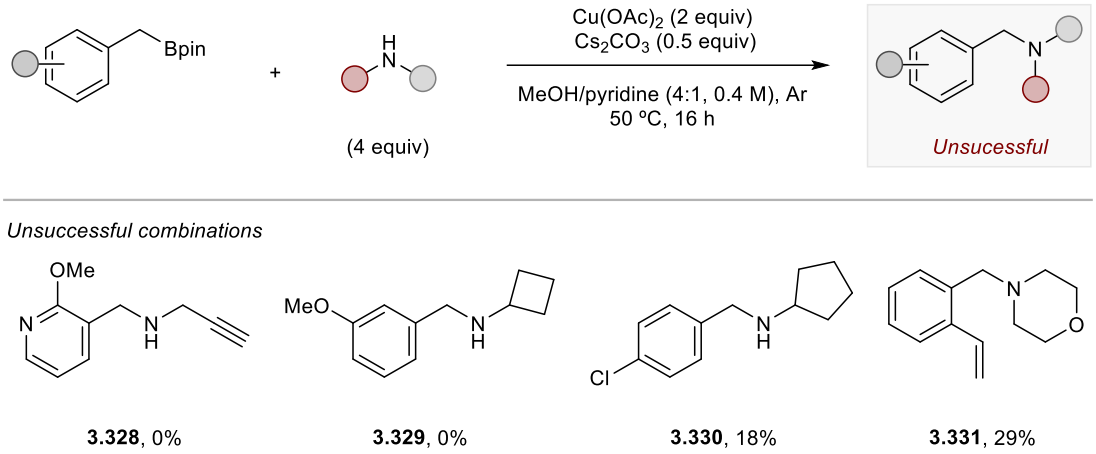
Variation of both counterparts



3.314, 75% (71%) **3.325**, 66% (64%) **3.326**, 80% (68%) **3.327**, 48% (38%)

Scheme 3.88: Scope of benzyl amines. ^{1}H NMR yields are given, with isolated yields in parentheses.

Four attempted Chan–Lam aminations were unsuccessful (Scheme 3.89). Some alkyl amines were challenging including propargyl amine (*i.e.*, product **3.328**) and alicyclic amines (*i.e.*, **3.329**, **3.330**), where the respective boronic esters were tolerated within the scope above. Morpholine was also a poor nucleophile in Partridge's initial report,[256] and coupled poorly with the generally intractable *ortho*-vinylbenzyl boronic ester to yield product **3.331** which could not be isolated from the reaction mixture.



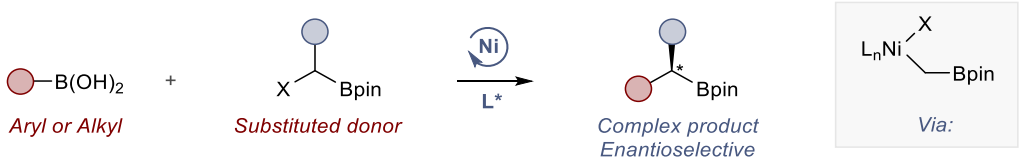
Scheme 3.89: Limitations of the Chan–amination. ^{1}H NMR yields are given for non-zero values. Attempts to isolate the desired products **3.330** and **3.331** were unsuccessful.

The products of the developed catalytic homologation of arylboronic acids have been applied toward the synthesis of C–N bonds. The Chan–Lam amination could offer good yields of primary and secondary benzyl amines using mild conditions and inexpensive reagents, in an analogous manner to the developed Chan–Lam etherification. Overall, this Section has prepared more complex products using a common reagent pool of benzylboronic esters, which are a current synthetic bottleneck in industry. This has been exemplified by preparing several active pharmaceutical scaffolds, derivatizing them, and appraising the developed routes with respect to contemporary methods used in industry, fulfilling Goal 4 of the study.

5. Conclusions and outlook

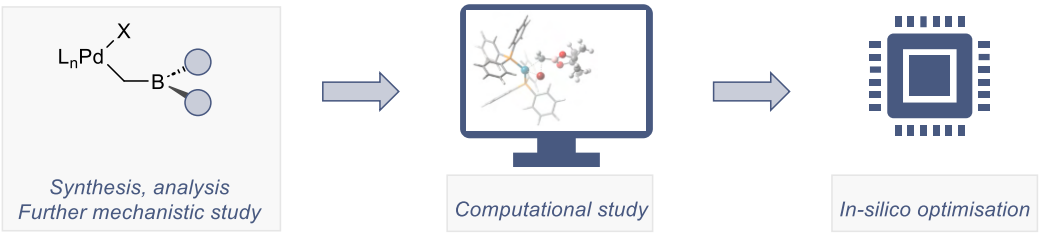
A formal Matteson-like homologation of arylboronic acids to prepare the corresponding benzyl boronic esters has been developed. Rather than relying upon 1,2-metalate rearrangements or radical generation from stoichiometric organometallic reagents encountered in typical methodologies, this work has applied an α-halogenated boronic ester under palladium catalysis. After Falck's Stille coupling, this is the second study to disclose the oxidative addition of α-halogenated boronic esters to palladium, and the only study to fully explore factors effecting reactivity by varying the anatomy of the electrophile. The benzyl boronic ester products are currently uncommon reagents prepared by commercial suppliers and their synthetic potential has been demonstrated in a series of C–C, C–O, and C–N bond-forming processes at the benzylic position, which rapidly provides access to several pharmacophores. As a testament to the mild conditions used in comparison to classical boron homologation, the developed homologation process has received commercial interest for process-scale applications by a pharmaceutical company.

Throughout the exploration of the substrate scope of the homologation process, a general intolerance to substitution was encountered with respect to the homologating reagent. In comparison to modern boron homologation, namely, Aggarwal's assembly-line synthesis, this is a significant limitation of the developed methodology towards the synthesis of more complex organoboron compounds. The origins of this general 'substitution problem' are currently unclear. Nickel catalysis has been used to oxidatively add α-halogenated organoboron reagents in reductive couplings, but a methodology involving organoboron reagents to achieve the equivalent homologation disclosed in this thesis is currently unknown (Scheme 4.1). Solving the substitution problem would also unlock potential asymmetric couplings to prepare enantioenriched boronic esters, one of the hallmark features of Matteson's original homologation and Aggarwal's assembly-line synthesis. The development of a nickel-catalysed protocol is currently a fledging project in our laboratory.



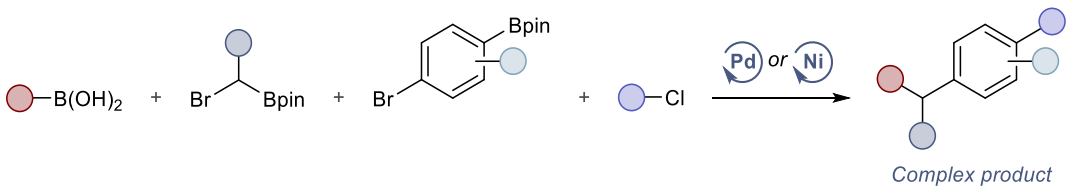
Scheme 4.1: A nickel-catalysed asymmetric boron homologation.

A series of mechanistic controls aimed at oxidative addition have revealed that the apparent α-boryl electrophile effect, first observed by Matteson during alkylation reactions, can also facilitate oxidative addition. While these empirical observations can be related to one another, a general increased propensity towards displacements on carbons that are in the α-position to a boron atom, detailed underpinning rationale remains unclear. A collaboration is currently focussed on computing barriers towards oxidative addition for α-borylated electrophiles and any dominant orbital interactions that can account for an apparent weakening of C–X bonds in the α-position to a halide. Future experimental work to compliment this computational investigation would prepare, characterise and conduct further manipulations of oxidative addition complexes bearing a Pd–C–B centre (Scheme 4.2). While this study focussed on the behaviour of α-halogenated organoboron compounds at oxidative addition from a mechanistic perspective, this future work could enable a greater understanding of the homologation reaction pathway during the elusive transmetalation step, which could also offer an insight to tackle the substitution problem.



Scheme 4.2: Workflow for complementary experimental and theoretical investigations.

The mechanistic investigation revealed that the homologation reaction could be chemoselective at both oxidative addition and transmetalation. A benzylation using a different palladium catalyst could prepare diarylmethanes, but an ideal protocol would apply a boronic acid, the α-brominated boronic ester, and an electrophile in a single operation. Using our Group's previous work on speciation control, the use of an additional coupling partner would offer a mild route to complex products in a series of chemoselective couplings (Scheme 4.3).



Scheme 4.3: Chemoselective multiple component couplings.

5. Experimental

5.1 General

Purification of reagents and solvents

Reagents and solvents were obtained from commercial suppliers and were not further purified unless otherwise stated. THF and PhMe were obtained from a PureSolv SPS-400-5 solvent purification system. DCE was stored over 4 Å molecular sieves for at least 24 h prior to degassing by freeze-pump-thaw (3 cycles, Ar). All boronic acids were purchased from commercial suppliers (Fluorochem, Sigma Aldrich, Alfa Aesar or Apollo Scientific) and were used as received. All amine substrates used in the Chan–Lam amination were purified, either as neat liquids or solutions in CH_2Cl_2, by passing through a short pipette of silica gel before use. Inorganic bases were ground using a pestle and mortar then stored in a Heraeus Vacutherm vacuum oven at 60 °C for at least 48 h prior to use. Triisopropyl borate (Fluorochem) was stored on 180 °C oven-dried 4 Å molecular sieves in a flame-dried flask for at least 24 h before use. $Pd(PPh_3)_4$ and $Pd(dba)_2$ were stored in an Ar-filled glovebox and removed in ~100 mg portions, which could be stored in an Ar-purged vial fitted with a septum for up to six weeks in a −20 °C freezer. $Pd(dba)_2$ was purified by recrystallisation ($CHCl_3$/water, 2×) prior to use. Lithium diisopropylamide was prepared fresh for use on the same day by dropwise addition of *n*BuLi (1 equiv) into diisopropylamine (freshly distilled over KOH, 1 equiv) in the appropriate solvent at 0 °C and stirring for 30 min at 0 °C.

Experimental details

Reactions were carried out in borosilicate round-bottomed flasks or microwave vials with septum caps. For inert reactions, glassware was flame-dried with a blowtorch under a vacuum and cooled under an atmosphere of Ar. Microwave vials were stored in an oven at 180 °C prior to use. Room temperature was approximately 18−20 °C. Reactions at elevated temperatures were conducted using a sand bath (vial or flask immersion depth was approximately twice the reaction volume) or a DrySyn insert. Reactions performed at temperatures <0 °C were done using an ice slurry with saturated brine solution. Reactions performed at <−78 °C were done using an acetone slurry with liquid N_2. Reactions performed at <−90 °C were done using an absolute EtOH slurry with liquid N_2. Degassing was performed by the freeze-pump-thaw technique over three cycles. Additions over times greater than 10 min were performed using a World Precision Instruments Aladdin-220 syringe pump, unless otherwise stated.

Details for ^{1}H NMR assays

To determine ^{1}H NMR yields, crude residues were suspended in ~0.3 mL $CDCl_3$ and trichloroethylene was added based on the scale of the reaction (18 μL, 0.20 mmol or 9.0 μL, 0.10 mmol). The solution made homogenous by pipette agitation, then a sample of this liquor was taken and diluted in fresh $CDCl_3$ to be analysed by ^{1}H NMR spectroscopy.

Chromatographic details

TLC was carried out using Merck aluminium-backed silica gel plates coated with F_{254} fluorescent indicator, analysed under UV light and/or developed using ethanolic vanillin or aq. $KMnO_4$ solutions and applying a heat gun as appropriate. Column chromatography was performed using silica gel (40−62 μm, Fluorochem) and porosity grade 2 or 3 sintered disks. Purifications of benzyl boronic esters were carried out using boric acid capped silica gel (B-SiO_2), prepared in a procedure outlined below. When used as an eluent, Et_2O (Fisher Scientific, Honeywell) was distilled using a rotary evaporator.

Analysis of products

IR spectra were recorded on a Shimadzu IR Affinity-1 Fourier transform IR (FT-IR) spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). The spectra were recorded as films using CH_2Cl_2, or as solids. Transmittance was recorded with maximal absorption wavenumbers given as cm^{-1}. Electrospray ionisation (ESI) and chemical impact ionisation (CI) HRMS was recorded on either a Bruker Microtof II or a Bruker 12T FT mass spectrometer at the University of Edinburgh mass spectrometry facility (SIRCAMS). Electron impact ionisation (EI) and chemical impact ionisation (CI) HRMS was recorded on a Thermo Mat 99xl sector instrument at the University of Edinburgh mass spectrometry facility (SIRCAMS). ^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H}, and ^{31}P{^{13}C} spectra were recorded on either a Bruker AV-III HD 500 fitted with a SmartProbe BBFO+ probe (^{1}H 500 MHz; ^{13}C 126 MHz; ^{19}F 470 MHz, ^{31}P 202 MHz), a Bruker AVIII 500 fitted with a CryoProbe Prodigy BBO probe (^{1}H 500 MHz; ^{13}C 126 MHz), or a Bruker AVIII 700 fitted with a CryoProbe Prodigy TCI probe (^{1}H 700 MHz; ^{13}C 176 MHz). ^{11}B NMR spectra were obtained on a Bruker AV 300 fitted with a BBFO probe (^{11}B 96 MHz). All spectra were recorded at rt with the deuterated solvents used as a lock for spectra and internal reference ($CDCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.16 ppm; DMSO-d_6: ^{1}H, 2.50 ppm; ^{13}C 39.52 ppm; CD_3CN: ^{1}H, 1.94 ppm, ^{13}C, 118.26 ppm; THF-d_8: ^{1}H, 3.58 ppm; ^{13}C, 67.57 ppm). For ^{1}H NMR assays performed during reaction development and mechanistic controls, trichloroethylene was used as the integration standard throughout (δ_H = 6.47 ppm, 0.20

mmol = 18 μL). For ^{11}B NMR analysis, samples were either run using a standard borosilicate tube and the spectra baselines corrected during processing, or using a quartz tube when the signal-to-noise ratio was poor. All ^{11}B NMR spectra were externally referenced to $F_3B{\bullet}OEt_2$ in $CDCl_3$ (^{11}B, 0.00 ppm) and, unless otherwise stated, all boron-bearing carbons were not observed by ^{13}C NMR due to quadrupolar relaxation. All chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent peak. Multiplicity is given as br (broad), s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), hept. (heptet), or m (multiplet), or combinations thereof. Signals which overlap with one another are described as multiplets. All coupling constants, *J*, are quoted in Hz and are $^3J_{HH}$ unless otherwise stated.

Assignment of products

Assignments of spectra are given in all unambiguous cases based on the labelled chemical environment with respect to the numbered carbon atom. In ambiguous cases due to overlapping peaks, details on the chemical environment may be provided without specific assignment such as alkyl, benzyl, aryl (Ar), naphthyl (Nap), or quaternary (quart.).

5.2 Use of boric acid-capped silica gel

In many instances, the purification of crude reaction mixtures from the palladium-catalysed homologation reaction by standard chromatographic techniques failed to separate the desired homologation product from the undesired speciated product; despite separation being visible by silica gel TLC using vanillin stain (*i.e.*, Figure 5.1). When both products are observed, the R_f value of the desired homologated product is typically lower (R_f = 0.3–0.4) than that of the speciated byproduct (R_f = 0.4–0.5).

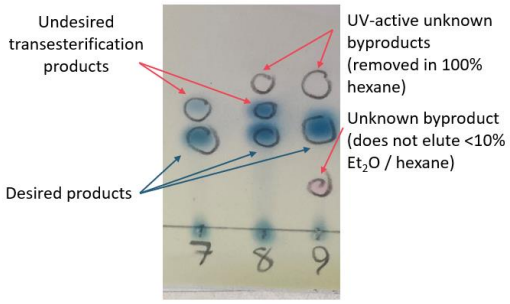


Figure 5.1: Stained TLC plates (vanillin) of three crude reaction mixtures.

To remedy products from streaking, the separation of any compound containing a benzylic boronic acid pinacol ester was achieved using boric acid-capped silica gel (B-SiO_2) which also

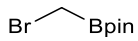
maintained good isolated yields of the products in comparison to obtained NMR yields (loss typically <15%).

B-SiO_2 was prepared according to a procedure adapted from Snaddon and coworkers.[168] Boric acid (82.5 g) was suspended in absolute EtOH (1.65 L, 5% v/v) in a 2.5 L glass beaker and stirred (mechanical overhead) at rt until the mixture became homogenous (~1 h). 450 g of SiO_2 was added portion wise over 5 min and the suspension stirred for 1 h. The silica was filtered off using a 500 mL sintered funnel and washed with Et_2O (3×400 mL). The damp silica was then transferred portion wise to a 2 L round bottom flask, which was then fitted with a sintered bump guard and the silica dried at reduced pressure. When the silica gel appeared free flowing, the flask was placed in a vacuum oven at 60 °C for several hours (*safety: to remove remaining Et_2O*) before placing in a 180 °C oven and leaving overnight to remove any residual EtOH.

5.3 General synthetic procedures

General Procedure A: Preparation of halomethylboronic esters

For example, 2-(bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.3**)



A procedure adapted from Aggarwal and coworkers.[166] To a flame-dried three-necked flask backfilled under an atmosphere of Ar was added dry THF (~0.3 M), the dihalide *e.g.,* dibromomethane (1.20 equiv), then triisopropyl borate (1.10 equiv). The solution was cooled to <–80 °C (internal thermometer temperature) then *n*BuLi in hexanes (1.00 equiv) was added dropwise using a syringe pump over 2 h at <–80 °C. *The purity and yield of the final product is significantly affected if the internal temperature is allowed to rise above ~ –75 °C at this stage*. *nBuLi should be added by dropping directly into the reaction mixture, not by running down the side of the flask*. The resulting mixture was stirred for 1 h at −80 °C, and then the cooling bath was removed, allowed to warm to rt (~ 30 min), then stirred for 2 h at rt. The reaction mixture was cooled to 0 °C and methanesulfonic acid (1.00 equiv) was added dropwise over 10 min, then the reaction mixture was warmed to rt, stirred for 1 h, and the diol, *e.g.,* pinacol (1.00 equiv) was added in a single portion. The septum was returned, and the reaction was stirred overnight at rt whereupon the volatiles were removed at reduced pressure. The cream residue was triturated with CH_2Cl_2 (~¼ reaction volume) and the suspension filtered, washing the LiBr filter cake with CH_2Cl_2 (3 x ~¼ reaction volume). The

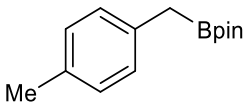
liquor was concentrated at reduced pressure to yield the crude. Desired products were purified by vacuum distillation with the bay and fume cupboard lights turned off.

General Procedure B: Optimisation of the palladium-catalysed homologation

To an oven-dried microwave vial equipped with a stir bar was added the reaction solids at a 0.20 mmol scale, in the following order: base, boronic acid, catalyst, and any exogenous ligand or additive, as appropriate. The vial was capped and purged with Ar (3×) prior to the addition of degassed solvent, then the halomethyl boronic ester, water, and any liquid additive. The microwave vial was heated to the appropriate temperature and stirred for the appropriate time, then vial was decapped. The reaction mixture was diluted in CH_2Cl_2 (5 mL) then filtered through a short pipette of silica gel, eluting with CH_2Cl_2 and concentrated at reduced pressure to afford a crude residue where the ^{1}H NMR assay procedure was applied (0.20 mmol, see General).

General Procedure C: palladium-catalysed homologation of boronic acids

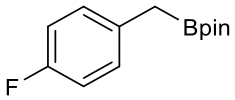
For example, 4,4,5,5-tetramethyl-2-(4-methylbenzyl)-1,3,2-dioxaborolane (**3.17**)



To an oven-dried microwave vial equipped with a stir bar was added in the following order: dry K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), the boronic acid, *e.g. p*-tolylboronic acid (27.2 mg, 0.20 mmol, 1.0 equiv), and $Pd(PPh_3)_4$ (3.5 mg, 0.003 mmol, 1.5 mol%), then the vial was capped and purged with Ar prior to the addition of DCE (2.0 mL, 0.1 M), then $BrCH_2Bpin$ **3.3** (54 μL, 0.30 mmol, 1.5 equiv), then water (36 μL, 2.0 mmol, 10 equiv) and the microwave vial heated to 60 °C and stirred for 24 h (unless otherwise stated). The reaction mixture was cooled to rt and diluted in CH_2Cl_2 (5 mL) then filtered through a short pad of silica gel, eluting with CH_2Cl_2 and concentrated at reduced pressure to afford the crude residue, where the ^{1}H NMR assay procedure was applied (0.20 mmol, see General). The products were purified by silica gel chromatography as required.

General Procedure D: palladium-catalysed homologations of boronic acids ≥ 2.5 mmol

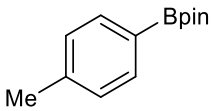
For example, 2-(4-fluorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.42**)



To a flame-dried two-necked flask equipped with a reflux condenser and septum cooled under an atmosphere of Ar was added dry K_3PO_4 (3.0 equiv), the boronic acid, *e.g.*, 4-fluorobenzeneboronic acid (1.0 equiv), and $Pd(PPh_3)_4$ (1.5 mol%), then the flask evacuated and backfilled with Ar thrice prior to the addition of DCE (0.1 M), then $BrCH_2Bpin$ **3.3** (1.5 equiv), then water (10 equiv). The reaction mixture was heated to 60 °C and stirred for 24 h. The reaction mixture was diluted in CH_2Cl_2 and filtered through a short pad of silica gel, eluting with CH_2Cl_2, then concentrated at reduced pressure. The products were purified by silica gel chromatography as required.

General Procedure E: Preparation of boronic esters from boronic acids

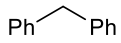
For example, 4,4,5,5-tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane (**3.21**)



An open flask fitted with a stir bar was charged with the boronic acid, *e.g.*, *p*-tolyboronic acid (1.0 equiv), the diol, *e.g.*, pinacol (1.1 equiv) and Na_2SO_4 (2.5 equiv) followed by Et_2O (~0.2 M) and the flask fitted with a septum and needle inlet (air). The flask was stirred at ambient temperature overnight (16–24 h), filtered and concentrated at reduced pressure, then resuspended in CH_2Cl_2 (100 mL) and warm water (~40 °C, 50 mL, *solubilises excess diol*). The organics were extracted with CH_2Cl_2 (2×) then dried (Na_2SO_4), filtered and concentrated at reduced pressure. The products were purified by silica gel chromatography as required.

General Procedure F: Suzuki–Miyaura benzylation

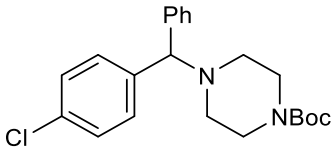
For example, diphenylmethane (**3.238**)



To an oven-dried microwave vial fitted with a stir bar was added dried K_3PO_4 (63 mg, 0.30 mmol, 3.0 equiv), then the benzyl boronic ester (0.10 mmol, 3.0 equiv), then $Pd(dppf)Cl_2$ (1 mg, 0.001 mmol, 1 mol%), and the vial capped and purged thrice with Ar prior to the addition of PhMe (0.40 mL, 0.25 M), then the halide, bromobenzene (0.10 mmol, 1.0 equiv), then water (90 μL, 5.0 mmol, 50 equiv) and the reaction mixture stirred at 90 °C for 24 h. When the benzyl boronic ester or bromide were solids at rt, these were added prior to capping. The vial was decapped and the crude reaction mixture was filtered through a short pad of silica gel, eluting with CH_2Cl_2, and concentrated at reduced pressure to afford the crude residue, where the ^{1}H NMR assay procedure was applied (0.10 mmol, see General). The products were purified by silica gel chromatography as required.

General procedure G: Nucleophilic substitution of isolated benzyl bromides

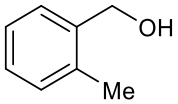
For example, *tert*-butyl 4-((4-chlorophenyl)(phenyl)methyl)piperazine-1-carboxylate (**3.280**)



In an open oven-dried microwave vial fitted with a stir bar was made a solution of K_2CO_3 (83 mg, 0.60 mmol, 3.0 equiv) in MeCN (2.0 mL, 0.1 M). Compound **3.276 (**0.20 mmol, 1.0 equiv), was then added in one portion, followed by the nucleophile *e.g.*, *tert*-butyl piperazine-1-carboxylate **3.277** (1.0 mmol, 5.0 equiv). The vial was capped and stirred at 80 °C for 12 h, then cooled to rt and the vial decapped. The reaction mixture was diluted into brine 5 mL and the organics extracted into CH_2Cl_2 (3×) which were collected and washed with brine (1×) then dried (Na_2SO_4) and concentrated at reduced pressure to afford the crude, , where the ^{1}H NMR assay procedure was applied (0.20 mmol, see General). The products were purified by silica gel chromatography as required.

General procedure H: One-pot preparation of benzyl alcohols from arylboronic acids

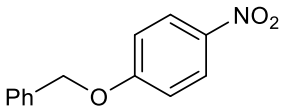
For example, *o*-tolylmethanol (**3.285**)



To an oven-dried 20 mL microwave vial equipped with a stir bar was added, dry K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), the boronic acid *e.g.*, *o*-tolylboronic acid (0.20 mmol, 1.0 equiv), then $Pd(PPh_3)_4$ (3.5 mg, 0.003 mmol, 1.5 mol%) and the vial capped and purged with Ar prior to the addition of DCE (2.0 mL, 0.1 M), $BrCH_2Bpin$ **3.3** (54 μL, 0.30 mmol, 1.5 equiv), then water (36 μL, 2.0 mmol, 10 equiv). The reaction mixture was heated to 60 °C and the reaction stirred for 24 h. The vial was cooled to 0 °C and decapped then THF (3.0 mL) was added in one portion followed by dropwise addition of a 2:1 solution of 2 N aq. NaOH / 30% aq. H_2O_2 (3.0 mL). The cooling bath was removed and the reaction mixture was stirred at rt for 15 min (air), then the reaction mixture was extracted into CH_2Cl_2 (3×). The collected organic phases were washed with brine (1×), dried (Na_2SO_4), and concentrated at reduced pressure to afford the crude, , where the ^{1}H NMR assay procedure was applied (0.20 mmol, see General). The products were purified by silica gel chromatography as required.

General procedure I: Chan–Lam etherification

For example, 1-(benzyloxy)-4-nitrobenzene (**3.295**)

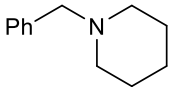


To an oven-dried microwave vial fitted with a stir bar was added $Cu(OAc)_2$ (2.0 equiv) and the freshly ground solid alcohol *e.g.*, *p*-nitrophenol (1.0 mmol, 5.0 equiv). The vial was capped and purged thrice with Ar prior to the addition of PhMe (0.5 M), the benzyl boronic ester *e.g.*, benzylboronic acid pinacol ester **2.22** (0.20 mmol, 1.0 equiv), then *tert*-butylperoxide (23 μL, 0.20 mmol, 2.0 equiv) and the reaction mixture stirred at 100 °C for 16 h (*safety: the reaction was placed behind a blast shield as a precaution, heating of $(tBuO)_2$).** The vial was cooled to rt, decapped, and the crude reaction mixture was diluted in Et_2O ~10 mL and washed with 10% aq. ammonia (3×, or until the aqueous phase was no longer green-blue), then brine (1×), then the collected organic layer was dried (Na_2SO_4) and concentrated at reduced pressure to afford the crude, where the ^{1}H NMR assay procedure was applied (0.20 mmol, see General). The products were purified by silica gel chromatography as required.

*At the scales performed in this study (≤0.20 mmol), sealed reaction mixtures never showed evidence of significant pressure build up from the use of peroxide. The reaction setup may need modifying to safely accommodate significant increases in reaction scale.

General procedure J: Chan–Lam amination

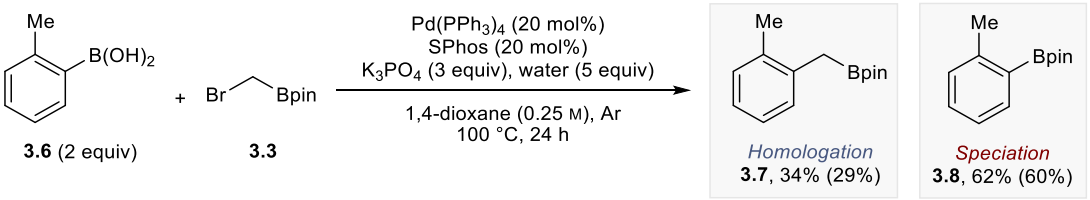
For example, 4-benzylpiperidine (**3.314**)



To an oven-dried microwave vial fitted with a stir bar was added $Cu(OAc)_2$ (2.0 equiv) and dried Cs_2CO_3 (0.5 equiv). The vial was capped and purged thrice with Ar prior to the addition of MeOH/ pyridine (4:1, 0.50 mL, 0.40 M), the liquid benzyl boronic ester *e.g.*, benzylboronic acid pinacol ester **3.22** (0.20 mmol, 1.0 equiv), then the liquid amine *e.g.*, piperidine (0.80 mmol, 4.0 equiv), and the reaction mixture stirred at 50 °C for 16 h. When the benzyl boronic ester or bromide were solids at rt, these were added prior to capping. The vial was decapped and the crude reaction mixture was diluted in Et_2O ~10 mL and washed with 10% aq. ammonia (3×, or until the aqueous phase was no longer blue), then brine (1×), then the collected organic layer was dried (Na_2SO_4) and concentrated at reduced pressure to afford the crude, where the ^{1}H NMR assay procedure was applied (0.20 mmol, see General). The products were purified by silica gel chromatography as required.

5.4 Details and tabulated results of assay reactions

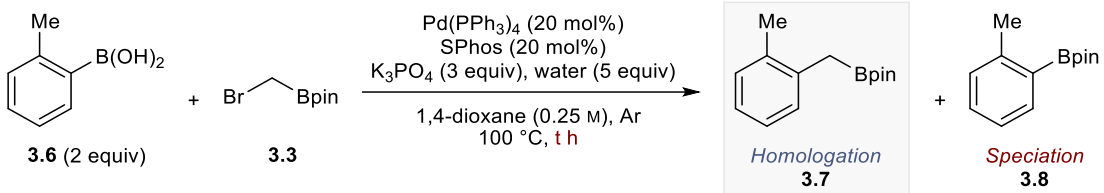
Homologation hit (Scheme 3.3)



General Procedure B was followed using dry K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), o-tolylboronic acid, (54.4 mg, 0.40 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (47 mg, 0.040 mmol, 20 mol%), and SPhos (16.4 mg, 0.040 mmol, 20 mol%), 1,4-dioxane (0.80 mL, 0.25 M), $BrCH_2Bpin$ **3.3** (36 mL, 0.20 mmol, 1.0 equiv) and water (18 μL, 1.0 mmol, 5 equiv) at 100 °C for 24 h. Following workup, the crude contained a mixture of **3.7** and **3.8** in 34% yield and 62% yield, respectively, by ^{1}H NMR assay. The hit was confirmed by isolation using column chromatography on B-SiO_2 (0–2% Et_2O in hexane) to afford **3.7** as a colourless oil (13.5 mg, 29%) and **3.8** as a colourless oil (26.2 mg, 60%). Characterisation is presented following optimisation.

Time study (Scheme 3.4)

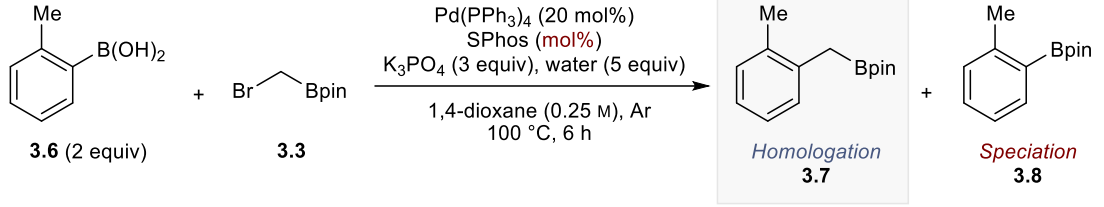
General Procedure B was followed using dry K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *o*-tolylboronic acid, (54.4 mg, 0.40 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (47 mg, 0.040 mmol, 20 mol%), SPhos (16.4 mg, 0.040 mmol, 20 mol%), 1,4-dioxane (0.80 mL, 0.25 M), $BrCH_2Bpin$ **3.3** (36 µL, 0.20 mmol, 1.0 equiv), and water (18 µL, 1.0 mmol, 5 equiv) at 100 °C for the specified time.



Entry	h	%3.7	%3.8	Entry	h	%3.7	%3.8
1	0.5	19	0	**6**	6	8	30
2	1	26	5	**7**	7	12.25	31
3	2	33	39	**8**	8	15	28
4	4	30	40	**9**	9	18	27
5	6	34	62	**10**	10	24	28

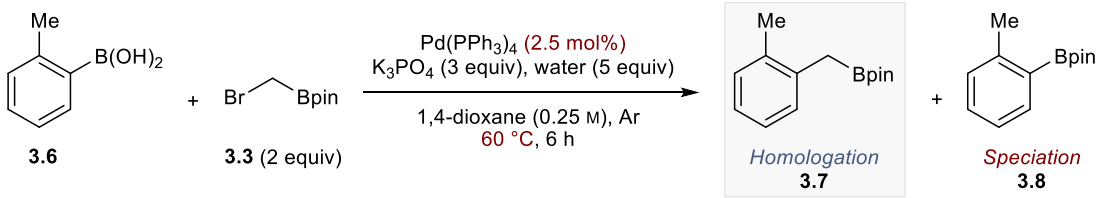
SPhos exclusion (Scheme 3.5)

General Procedure B was followed using dry K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *o*-tolylboronic acid, (54.4 mg, 0.40 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (47 mg, 0.040 mmol, 20 mol%), SPhos (mol% varied), 1,4-dioxane (0.80 mL, 0.25 M), $BrCH_2Bpin$ **3.3** (36 µL, 0.20 mmol, 1.0 equiv), and water (18 µL, 1.0 mmol, 5 equiv) at 100 °C and stirred for 6 h.



Entry	Mol% SPhos (mg)	%3.7	%3.8
1	20 (16.4)	34	62
2	0	58	31

Verified reaction conditions after Iona Meier's study (Scheme 3.6)

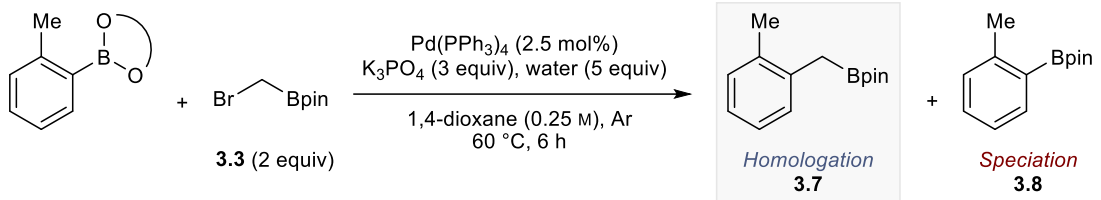


General Procedure B was followed using dry K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *o*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (5.9 mg, 0.050 mmol, 2.5 mol%),

1,4-dioxane (0.80 mL, 0.25 M), $BrCH_2Bpin$ **3.3** (72 μL, 0.40 mmol, 2.0 equiv), and water (18 μL, 1.0 mmol, 5 equiv) at 100 °C for 6 h. The crude contained a mixture of **3.7** and **3.8** in 60% yield and 34% yield, respectively.

Boron nucleophile variation (Scheme 3.8)

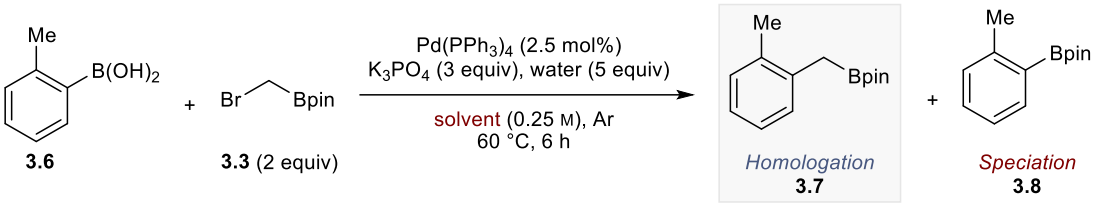
General Procedure B was followed using dry K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), the varied organoboron nucleophile (0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (5.9 mg, 0.0050 mmol, 2.5 mol%), 1,4-dioxane (0.80 mL, 0.25 M), $BrCH_2Bpin$ **3.3** (72 μL, 0.40 mmol, 2.0 equiv), and water (18 μL, 1.0 mmol, 5 equiv) at 60 °C for 6 h.



Entry	Nucleophile	Mass (mg)	%3.7	%3.8
1	$B(OH)_2$ (**3.6**)	27.2	60	34
2	Bpin (**3.8**)	43.6	14	64
3	Bneo (**3.12**)	40.8	28	19
4	Bpg (**3.13**)	35.2	16	11
5	Bcat (**3.15**)	42.0	10	0

Solvent variation (Scheme 3.9)

General Procedure B was followed using dry K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *o*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (5.9 mg, 0.0050 mmol, 2.5 mol%), the varied solvent (0.80 mL, 0.25 M), $BrCH_2Bpin$ **3.3** (72 μL, 0.40 mmol, 2.0 equiv), and water (18 μL, 1.0 mmol, 5 equiv) at 60 °C for 6 h.

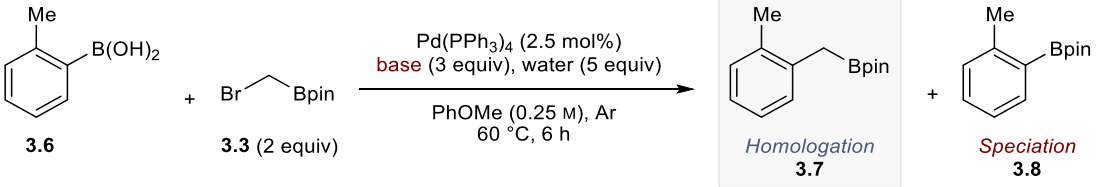


Entry	Solvent	%3.7	%3.8	Entry	Solvent	%3.7	%3.8
1	1,4-dioxane	60	24	**10**	DMSO	2	67
2*	1,4-dioxane	44	40	**11**	1,3-dioxolane	75	24
3*	Et_2O	12	73	**12**	MTBE	79	10
4	THF	68	31	**13**	PhOMe	94	6
5	2-MeTHF	84	12	**14**	*m*-xylene	78	10
6	CPME	66	22	**15**	PhF	84	19
7	PhMe	82	16	**16**	Hexane	39	47
8	$PhCF_3$	0	0	**17**	MeCN	23	75
9	PhCl	74	23	**18**	H_2O	0	100

**Entries 2–3 were performed at 40 °C.*

Base variation (Scheme 3.10)

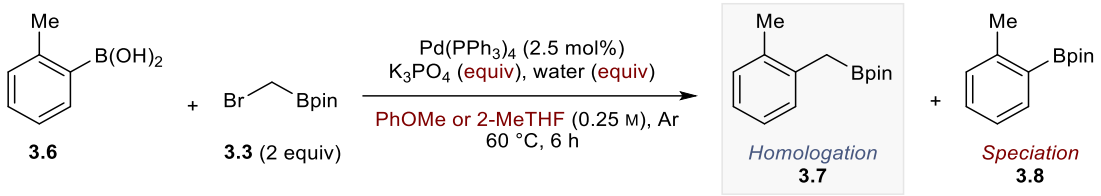
General Procedure B was followed using dry solid base (0.60 mmol, 3.0 equiv), *o*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (5.9 mg, 0.050 mmol, 2.5 mol%), PhOMe (0.80 mL, 0.25 M), $BrCH_2Bpin$ **3.3** (72 µL, 0.40 mmol, 2.0 equiv), and water (18 µL, 1.0 mmol, 5 equiv) at 60 °C for 6 h. When the base was a liquid, this was added last after capping.



Entry	Base (mg)	%3.7	%3.8	Entry	Base (quantity)	%3.7	%3.8
1	K_3PO_4 (127)	94	6	**9**	KOAc (59 mg)	11	85
2	K_2HPO_4 (104)	57	20	**10**	LiO*t*Bu (48 mg)	16	7
3	KH_2PO_4 (82)	65	35	**11**	KO*t*Bu (67 mg)	32	64
4	Na_2CO_3 (63)	70	26	**12**	Et_3N (84 µL)	0	100
5	K_2CO_3 (83)	84	14	**13**	DBU (90 µL)	0	77
6	Cs_2CO_3 (195)	89	10	**14**	DBN (74 µL)	0	99
7	$NaHCO_3$ (50)	67	26	**15**	2,6-lutidine (70 µL)	0	81
8	KOH (34)	67	29	**16**	2,4,6-collidine (78 µL)	0	84

Variation to base and water stoichiometry in PhOMe and 2-MeTHF (Scheme 3.11)

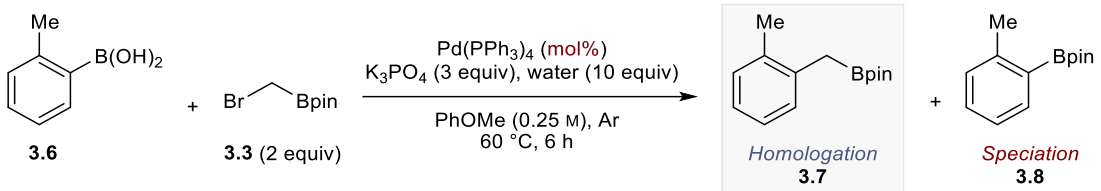
General Procedure B was followed using dried K_3PO_4 (equiv varied), *o*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (5.9 mg, 0.0050 mmol, 2.5 mol%), PhOMe or 2-MeTHF (0.80 mL, 0.25 M), $BrCH_2Bpin$ **3.3** (72 μL, 0.40 mmol, 2.0 equiv), and water (equiv varied) at 60 °C for 6 h.



Entry	Solvent	Equiv K_3PO_4 (mg)	Equiv H_2O (μL)	%3.7	%3.8
1	PhOMe	2 (85)	5 (18)	82	20
2	PhOMe	2 (85)	10 (36)	82	21
3	PhOMe	2 (85)	20 (72)	81	15
4	PhOMe	2 (85)	50 (180)	33	69
5	PhOMe	3 (127)	5 (18)	94	0
6	PhOMe	3 (127)	10 (36)	98	0
7	PhOMe	3 (127)	20 (72)	94	12
8	PhOMe	3 (127)	50 (180)	73	31
9	PhOMe	5 (212)	5 (18)	89	15
10	PhOMe	5 (212)	10 (36)	96	9
11	PhOMe	5 (212)	20 (72)	105	2
12	PhOMe	5 (212)	50 (180)	98	7
13	2-MeTHF	2 (85)	5 (18)	54	35
14	2-MeTHF	2 (85)	10 (36)	68	36
15	2-MeTHF	2 (85)	20 (72)	28	82
16	2-MeTHF	3 (127)	5 (18)	72	22
17	2-MeTHF	3 (127)	10 (36)	84	12
18	2-MeTHF	3 (127)	20 (72)	44	65
19	2-MeTHF	5 (212)	5 (18)	85	20
20	2-MeTHF	5 (212)	10 (36)	80	14
21	2-MeTHF	5 (212)	20 (72)	26	79

Variation to catalyst loading in PhOMe and 2-MeTHF (Scheme 3.12)

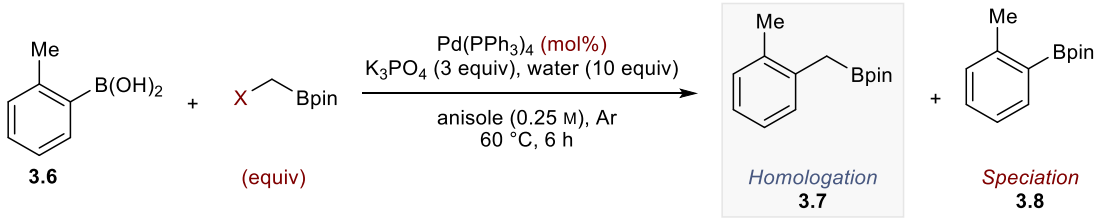
General Procedure B was followed using dried K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *o*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (mol% varied, PhOMe or 2-MeTHF (0.80 mL, 0.25 M), $BrCH_2Bpin$ **3.3** (72 μL, 0.40 mmol, 2.0 equiv), and water (36 μL, 1.0 mmol, 10 equiv) at 60 °C for 6 h.



Entry	Solvent	mol% (mg)	%3.7	%3.8
1	PhOMe	1.5 (3.5)	100	0
2	PhOMe	2.0 (4.6)	98	0
3	PhOMe	2.5 (5.8)	98	0
4	PhOMe	3.0 (7.0)	96	0
5	PhOMe	4.0 (9.3)	94	5
6	2-MeTHF	1.5 (3.5)	65	32
7	2-MeTHF	2.0 (4.6)	65	30
8	2-MeTHF	2.5 (5.8)	84	12
9	2-MeTHF	3.0 (7.0)	57	29
10	2-MeTHF	4.0 (9.3)	62	39

Variation of the donor and catalyst loading (Scheme 3.13)

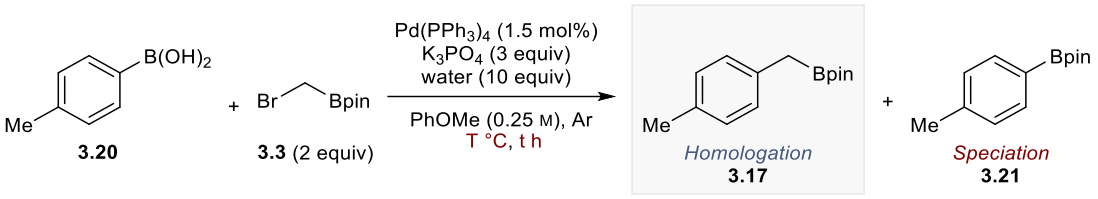
General Procedure B was followed using dried K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *o*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (mol% varied), PhOMe (0.80 mL, 0.25 M), the varied halide donor (equiv varied), and water (36 μL, 1.0 mmol, 10 equiv) at 60 °C for 6 h.



Entry	XCH_2Bpin	Equiv XCH_2Bpin (mg)	mol% $Pd(PPh_3)_4$ (mg)	%3.7	%3.8
1	$ClCH_2Bpin$ (**3.4**)	2.0 (71)	1.5 (3.5)	59	39
2	$ClCH_2Bpin$ (**3.4**)	1.5 (53)	1.5 (3.5)	25	53
3	$BrCH_2Bpin$ (**3.3**)	2.0 (88)	1.5 (3.5)	>99	0
4	$BrCH_2Bpin$ (**3.3**)	2.0 (88)	1.0 (2.3)	101	0
5	$BrCH_2Bpin$ (**3.3**)	2.0 (88)	0.5 (1.2)	84	14
6	$BrCH_2Bpin$ (**3.3**)	1.5 (66)	1.5 (3.5)	>99	0
7	$BrCH_2Bpin$ (**3.3**)	1.5 (66)	1.0 (2.3)	95	7
8	$BrCH_2Bpin$ (**3.3**)	1.5 (66)	0.5 (1.2)	60	23
9	ICH_2Bpin (**3.5**)	2.0 (110)	1.5 (3.5)	99	15
10	ICH_2Bpin (**3.5**)	1.5 (80)	1.5 (3.5)	95	9

Variation of reaction temperature and time using *p*-tolylboronic acid (Scheme 3.15)

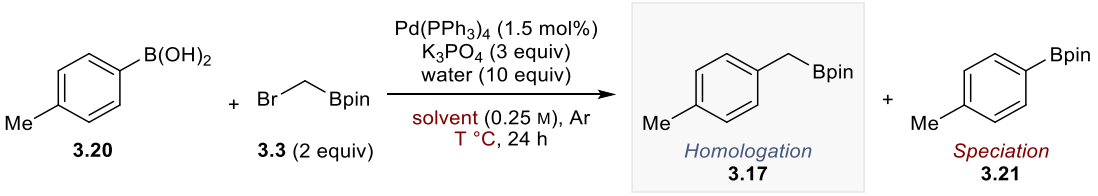
General Procedure B was followed using dried K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *p*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (3.5 mg, 0.0030 mmol, 1.5 mol%), PhOMe (0.80 mL, 0.25 M), $BrCH_2Bpin$ **3.3** (66.3 mg, 54 µL, 0.30 mmol, 1.5 equiv), and water (36 µL, 1.0 mmol, 10 equiv) at the given temperature for the listed time.



Entry	°C	h	%3.17	%3.21	Entry	°C	h	%3.17	%3.21
1	60	6	48	30	**7**	40	16	58	39
2	60	8	44	35	**8**	40	24	57	45
3	60	16	57	36	**9**	25	6	23	23
4	60	24	70	31	**10**	25	8	46	36
5	40	6	37	32	**11**	25	16	48	40
6	40	8	63	32	**12**	25	24	43	42

Variation of reaction temperature and solvent (Scheme 3.16)

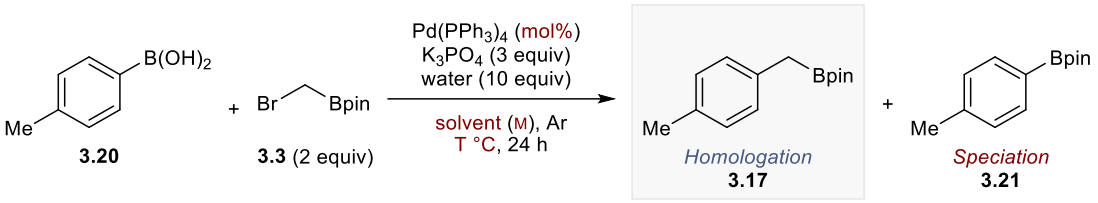
General Procedure B was followed using dried K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *p*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (3.5 mg, 0.0030 mmol, 1.5 mol%), varied solvent (0.80 mL, 0.25 M), $BrCH_2Bpin$ **3.3** (66.3 mg, 54 µL, 0.30 mmol, 1.5 equiv), and water (36 µL, 1.0 mmol, 10 equiv) at the given temperature for 24 h.



Entry	°C	solvent	%3.17	%3.21	Entry	°C	solvent	%3.17	%3.21
1	60	PhOMe	70	31	**9**	70	2-MeTHF	31	85
2	60	PhMe	70	39	**10**	70	1,4-dioxane	35	72
3	60	2-MeTHF	68	19	**11**	70	EtOAc	42	64
4	60	1,4-dioxane	30	19	**12**	70	DCE	74	41
5	60	EtOAc	36	76	**13**	80	PhOMe	56	45
6	60	DCE	71	34	**14**	80	PhMe	57	46
7	70	PhOMe	67	32	**15**	80	2-MeTHF	44	52
8	70	PhMe	57	50	**16**	80	1,4-dioxane	39	65

Variation of reaction temperature and solvent, concentration, and catalyst loading (Scheme 3.17)

General Procedure B was followed using dried K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *p*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (mol% varied), varied solvent (concentration varied), $BrCH_2Bpin$ **3.3** (66.3 mg, 54 μL, 0.30 mmol, 1.5 equiv), and water (36 μL, 1.0 mmol, 10 equiv) at the given temperature for 24 h.

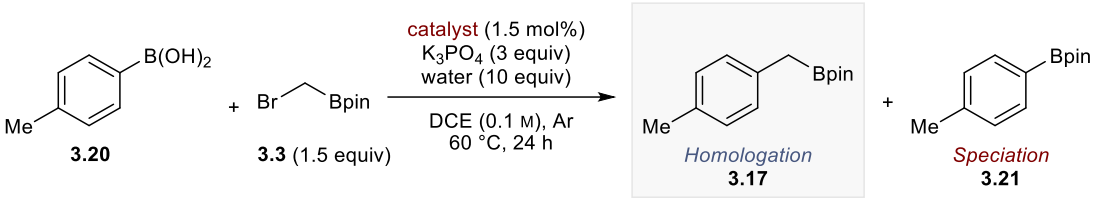


Entry	mol% (mg)	Solvent (mL, M)	°C	%3.17	%3.21
1	1.5 (3.5)	PhMe (0.8, 0.25)	60	70	39
2	1.5 (3.5)	PhMe (2.0, 0.1)	60	84	19
3	1.5 (3.5)	PhMe (0.4, 0.50)	60	57	51
4	2.0 (4.7)	PhMe (0.8, 0.25)	60	64	39
5	2.0 (4.7)	PhMe (2.0, 0.1)	60	64	54
6	2.0 (4.7)	PhMe (0.4, 0.5)	60	44	66
7	4.0 (9.3)	PhMe (0.8, 0.25)	60	69	35
8	4.0 (9.3)	PhMe (2.0, 0.1)	60	56	44
9	4.0 (9.3)	PhMe (0.4, 0.5)	60	67	28
10	1.5 (3.5)	PhMe (0.8, 0.25)	50	72	20
11	1.5 (3.5)	PhMe (2.0, 0.1)	50	74	21
12	1.5 (3.5)	PhMe (0.4, 0.5)	50	67	33
13	2.0 (4.7)	PhMe (0.8, 0.25)	50	67	34
14	2.0 (4.7)	PhMe (2.0, 0.1)	50	76	57
15	2.0 (4.7)	PhMe (0.4, 0.5)	50	50	62
16	4.0 (9.3)	PhMe (0.8, 0.25)	50	74	47
17	4.0 (9.3)	PhMe (2.0, 0.1)	50	77	54
18	4.0 (9.3)	PhMe (0.4, 0.5)	50	60	51
19	1.5 (3.5)	PhOMe (0.8, 0.25)	60	70	39
20	1.5 (3.5)	PhOMe (2.0, 0.1)	60	49	45
21	1.5 (3.5)	PhOMe (0.4, 0.5)	60	63	37
22	1.5 (3.5)	PhOMe (2.0, 0.1)	50	65	35
23	1.5 (3.5)	PhOMe (0.8, 0.25)	50	68	30
24	1.5 (3.5)	PhOMe (0.4, 0.5)	50	60	36

Variation of catalyst (Scheme 3.19)

General Procedure B was followed using dried K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *p*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), varied catalyst (0.0030 mmol, 1.5 mol%), varied exogenous ligand where appropriate (0.0060 mmol, 3.0 mol%), varied solvent

(concentration varied), $BrCH_2Bpin$ **3.3** (66.3 mg, 54 μL, 0.30 mmol, 1.5 equiv), and water (36 μL, 1.0 mmol, 10 equiv) at 60 °C for 24 h.

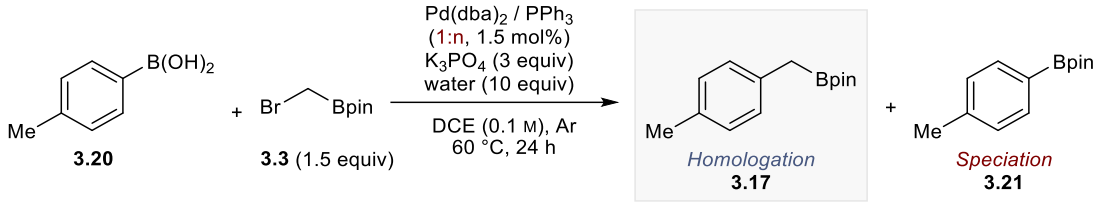


Entry	Catalyst (mg)	Ligand (mg)	%3.17	%3.21
1	$Pd(PPh_3)_4$ (3.5)	-	90	10
2	$Pd(dba)_2$ (2.8)	-	7	93
3	$Pd(dba)_2$ (2.8)	PPh_3 (1.6)	91	9
4	$Pd(dba)_2$ (2.8)	P(*o*-Tol)$_3$ (1.8)	71	35
5	$Pd(dba)_2$ (2.8)	P(*p*-Tol)$_3$ (1.8)	14	86
6	$Pd(dba)_2$ (2.8)	$PMes_3$ (2.3)	14	86
7	$Pd(dba)_2$ (2.8)	P(*p*-OMePh)$_3$ (2.0)	20	80
8	$Pd(dba)_2$ (2.8)	P(*p*-OMePh)$_3$ (1.7)	23	71
9	$Pd(dba)_2$ (2.8)	P(Furyl)$_3$ (1.4)	10	91
10	$Pd(dba)_2$ (2.8)	SPhos (1.2)	6	99
11	$Pd(dba)_2$ (2.8)	XPhos (1.3)	7	96
12	$Pd(dba)_2$ (2.8)	PCy_3 (1.7)	48	52
13	$Pd(dba)_2$ (2.8)	P(*t*Bu)$_3$•HBF_4 (1.7)	31	69
14	$Pd(dba)_2$ (2.8)	P(*n*Bu)$_3$•HBF_4 (1.7)	13	83
15	$Pd(dba)_2$ (2.8)	P(*n*Bu)$_3$ (1.7)	12	80
16	$Pd(dba)_2$ (2.8)	P(tcep)$_3$ (1.2)	5	86
17	$Pd(dba)_2$ (2.8)	CataCXium A (2.2)	34	70
18	$PdBr_2(PPh_3)_2$ (2.4)	-	31	69
19	$PdCl_2(PPh3)_2$ (2.1)	-	16	86
20	$PdCl_2$ (0.8)	PPh_3 (1.6)	17	83
21	$PdCl_2(COD)_2$ (0.9)	-	0	95
22	$PdCl_2$ (0.8)	-	0	101
23	$Pd(dppf)Cl_2$ (2.2)	-	8	88
24	$Pd(OAc)_2$ (0.7)	SPhos (1.2)	8	58
25	$Pd(OAc)_2$ (0.7)	PPh_3 (1.6)	64	37
26	XphosPdG2 (2.2)	-	4	94
27	SPhosPdG2 (2.3)	-	0	96
28	XantPhosPdG3 (2.2)	-	0	93
29	PdCX21 (1.6)	-	0	107
30	PdPEPPSI (20)	-	0	100

Variation of ligand stoichiometry (Scheme 3.20)

General Procedure B was followed using dried K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *p*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(dba)_2$ (2.8 mg, 0.0030 mmol, 1.5 mol%),

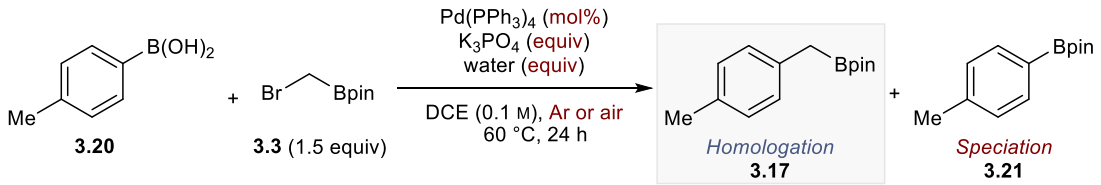
PPh_3 (varied stoichiometry wrt $Pd(dba)_2$), DCE (2.0 mL, 0.1 M), $BrCH_2Bpin$ **3.3** (66.3 mg, 54 μL, 0.30 mmol, 1.5 equiv), and water (36 μL, 1.0 mmol, 10 equiv) at 60 °C for 24 h.



Entry	1:n (mg PPh_3)	%3.17	%3.21	Entry	1:n (mg PPh_3)	%3.17	%3.21
1	0	7	93	**4**	3 (2.4)	34	68
2	1 (0.8)	70	30	**5**	4 (3.2)	34	66
3	2 (1.6)	91	9	-	-	-	-

Robustness to air, water, and removal of reaction components (Scheme 3.32)

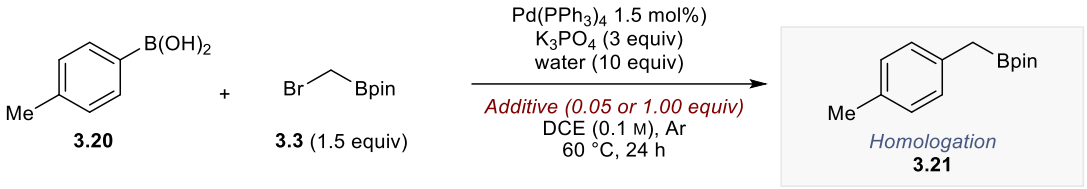
General Procedure B was followed using dried K_3PO_4 (equiv varied), *p*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (mol% varied), DCE (2.0 mL, 0.1 M), $BrCH_2Bpin$ **3.3** (66.3 mg, 54 μL, 0.30 mmol, 1.5 equiv), and water (equiv varied) at 60 °C for 24 h.



Entry	mol% (mg)	Equiv K_3PO_4 (mg)	Equiv H_2O (μL)	Atm.	%3.17	%3.21
1	1.5 (3.5)	3 (127)	10 (36)	Air	32	51
2	1.5 (3.5)	3 (127)	25 (90)	Ar	46	47
3	1.5 (3.5)	3 (127)	0	Ar	44	25
4	1.5 (3.5)	0	10 (36)	Ar	0	49
5	0	3 (127)	10 (36)	Ar	0	91

Robustness to additives (Scheme 3.33)

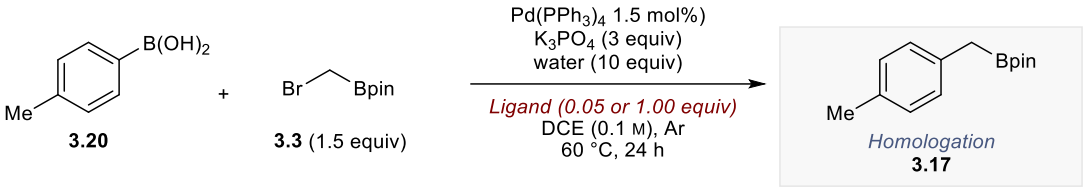
General Procedure B was followed using dried K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *p*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (3.5 mg, 0.0030 mmol, 1.5 mol%), the solid additive (0.05 or 1.00 equiv), DCE (2.0 mL, 0.1 M), $BrCH_2Bpin$ **3.3** (66.3 mg, 54 μL, 0.30 mmol, 1.5 equiv), and water (36 μL, 1.0 mmol, 10 equiv) at 60 °C for 24 h. When the additive was a liquid, this was added first after capping.



Entry	Additive	Equiv (quantity)	%3.21
1	Pyridine (**3.122**)	1.0 (15 μL)	36
2	Pyridine (**3.122**)	0.05 (0.8 μL)	9
3	Aniline (**3.123**)	1.0 (19 μL)	73
4	Aniline (**3.123**)	0.05 (0.9 μL)	30
5	Piperidine (**3.124**)	1.0 (20 μL)	70
6	Piperidine (**3.124**)	0.05 (1 μL)	0
7	Styrene (**3.71**)	1.0 (23 μL)	77
8	Styrene (**3.71**)	0.05 (1 μL)	62
9	Chlorobenzene (**3.125**)	1.0 (23 μL)	90
10	Chlorobenzene (**3.125**)	0.05 (1 μL)	72
11	Phenol (**3.126**)	1.0 (19 mg)	75
12	Phenol (**3.126**)	0.05 (0.9 mg)	15
13	Benzaldehyde (**3.127**)	1.0 (20 μL)	0
14	Benzaldehyde (**3.127**)	0.05 (1 μL)	0
15	Benzoic acid (**3.128**)	1.0 (24 mg)	75
16	Benzoic acid (**3.128**)	0.05 (1 mg)	22
17	Indole (**3.129**)	1.0 (23 mg)	76
18	Indole (**3.129**)	0.05 (1 mg)	0
19	*N*-methylindole (**3.130**)	1.0 (26 mg)	89
20	*N*-methylindole (**3.130**)	0.05 (1 mg)	72

Robustness to ligands (Scheme 3.34)

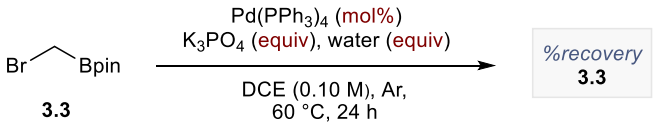
General Procedure B was followed using dried K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *p*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (3.5 mg, 0.0030 mmol, 1.5 mol%), the ligand (0.05 or 1.00 equiv), DCE (2.0 mL, 0.1 M), $BrCH_2Bpin$ **3.3** (66.3 mg, 54 μL, 0.30 mmol, 1.5 equiv), and water (36 μL, 1.0 mmol, 10 equiv) at 60 °C for 24 h.



Entry	Ligand	Equiv (mg)	%3.17
1	dba (**3.131**)	0.05 (2)	35
2	dba (**3.131**)	1.0 (47)	6
3	COD (**3.132**)	0.05 (1)	80
4	COD (**3.132**)	1.0 (22)	63
5	dppf (**3.133**)	0.05 (6)	61
6	dppf (**3.133**)	1.0 (110)	0
7	PPh_3 (**3.134**)	0.05 (3)	66
8	PPh_3 (**3.134**)	1.0 (53)	0

Stability of compound 3.3 (Scheme 3.53)

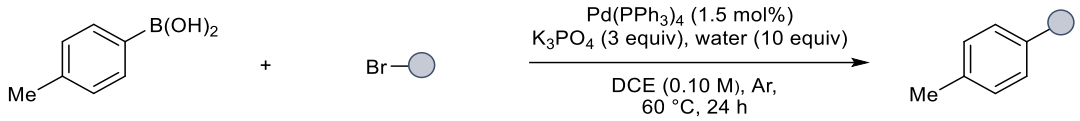
To an oven-dried microwave vial equipped with a stir bar was added in the following order: dried K_3PO_4 (equiv varied), $Pd(PPh_3)_4$ (mol% varied) then the vial was capped and purged with Ar prior to the addition of DCE (2.0 mL, 0.1 M), then $BrCH_2Bpin$ **3.3** (66.3 mg, 54 μL, 0.30 mmol, 1.0 equiv), then water (equiv varied) and the microwave vial heated to 60 °C and stirred for 24 h. The reaction mixture was cooled to rt and diluted in CH_2Cl_2 (5 mL) then filtered through a short pipette of silica gel, eluting with CH_2Cl_2 and concentrated at reduced pressure.



Entry	mol% (mg)	Equiv K_3PO_4 (mg)	Equiv H_2O (μL)	%3.3
1	0	0	0	69
2	0	2 (127)	0	0
3	0	0	6.7 (36)	39
4	0	2 (127)	6.7 (36)	10
5	1.0 (3.5)	2 (127)	6.7 (36)	0

Structure-activity relationship compound 3.3 (Scheme 3.63)

General Procedure C was followed with a slight modification using *p*-tolylboronic acid (27.2 mg, 0.20 mmol, 1.0 equiv) and $BrCH_2Bpin$ **3.3** was replaced with the varied bromide (0.30 mmol, 1.5 equiv).

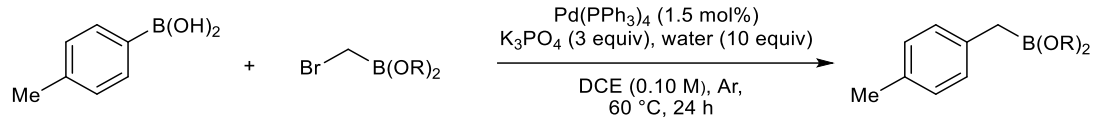


3.20 (1.5 equiv) *coupling*

Entry	Bromide (μL)	%yield
1	Bromobenzene, **3.218** (32)	>99
2	Benzyl bromide, **3.219** (36)	>99
3	Cyclohexyl bromide, **3.220** (38)	0
4	Cyclopentyl bromide, **3.221** (38)	0
5	2-(Bromomethyl)-1,3-dioxolane, **3.222** (21)	0
6	$BrCH_2Bpin$, **3.3** (54)	90

Variation of the boron ligand (Scheme 3.64)

General Procedure C was followed with a slight modification using *p*-tolylboronic acid (27.2 mg, 0.20 mmol, 1.0 equiv) and $BrCH_2Bpin$ **3.3** was replaced with the varied bromide (0.30 mmol, 1.5 equiv). When the bromide is a solid (*i.e.*, **3.183**), this were added prior to capping.



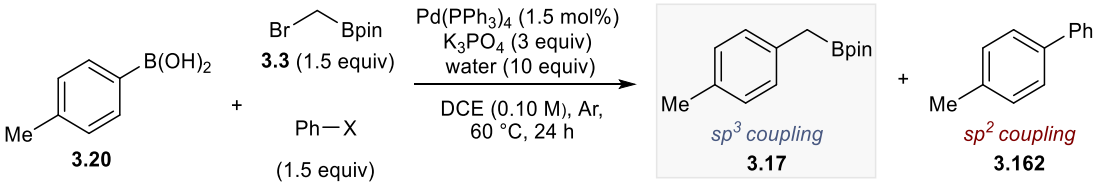
3.20 (1.5 equiv) *Homologation*

Entry	$BrCH_2B(OR)_2$ (quantity)	%yield
1	Bpin, **3.3** (54 μL)	90
2	BF_3K, **3.183** (81 mg)	0
3	Beg, **3.185** (54 μL)	0
4	Bpg, **3.186** (54 μL)	0
5	BDIPT, **3.187** (54 μL)	0
6	Bneo, **3.188** (54 μL)	45
7	Bam, **3.189** (54 μL)	23

Competition reactions between electrophiles (Scheme 3.65)

To an oven-dried microwave vial equipped with a stir bar was added in the following order: dried K_3PO_4 (127 mg, 0.60 mmol, 3.0 equiv), *p*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv), and $Pd(PPh_3)_4$ (3.5 mg, 0.0030 mmol, 1.5 mol%) then the vial was capped and purged with Ar. A separate microwave vial equipped with a stir bar was capped and purged with Ar prior to the addition of DCE (2.0 mL, 0.1 M), then $BrCH_2Bpin$ **3.3** (66.3 mg, 54 μL, 0.30 mmol, 1.5 equiv), then the varied aryl (pseudo)halide (0.30 mmol, 1.5 equiv) and the solution stirred at rt for <1 min. The halide mixture was transferred by syringe to the microwave vial containing the boronic acid, then water (36 μL, 1.0 mmol, 10 equiv) was added and the reaction mixture heated to 60 °C and stirred for 24 h. The reaction mixture was cooled to rt and diluted in CH_2Cl_2 (5 mL) then filtered through a short pipette of silica gel, eluting with

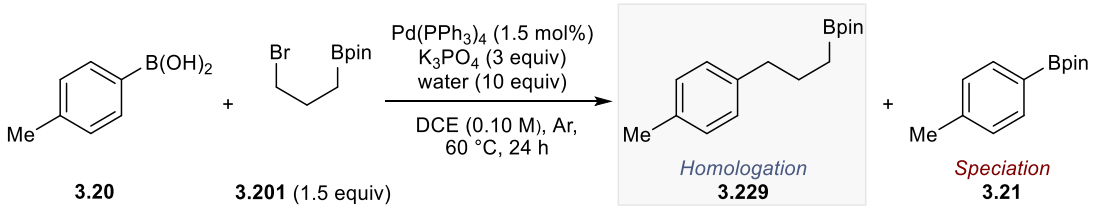
CH_2Cl_2 and concentrated at reduced pressure. The detection of the sp^2 coupling product **3.162** was done in reference to the literature.[257]



Entry	Aryl (psueodo)halide (μL)	%3.17	%3.162
1	Iodobenzene, **3.165** (33)	6	43
2	Bromobenzene, **3.218** (31)	56	44
3	Phenyl triflate, **3.242** (49)	74	23
4	Chlorobenzene, **3.125** (30)	80	20

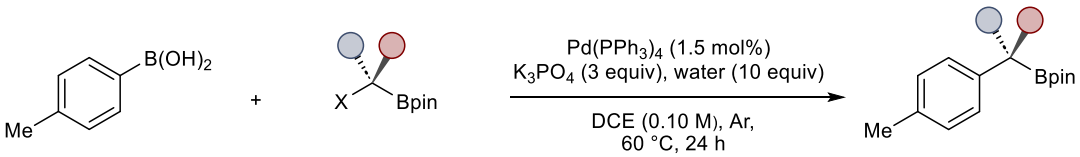
Attempted homologation using a γ-bromopropylboronic ester (Scheme 3.66)

General Procedure C was followed with a slight modification using *p*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv) as the substrate and $BrCH_2Bpin$ **3.3** was replaced with γ-bromopropylboronic acid pinacol ester **3.201** (74 mg, 0.30 mmol, 1.5 equiv). Following workup, analysis of the crude by ^1H NMR identified none of the desired compound **3.229**, and byproduct **3.21** (65%)



Variation of the electrophile (Scheme 3.67)

General Procedure C was followed with a slight modification using *p*-tolylboronic acid, (27.2 mg, 0.20 mmol, 1.0 equiv) as the substrate and $BrCH_2Bpin$ **3.3** was replaced by the appropriate homologating agent (0.30 mmol, 1.5 equiv).

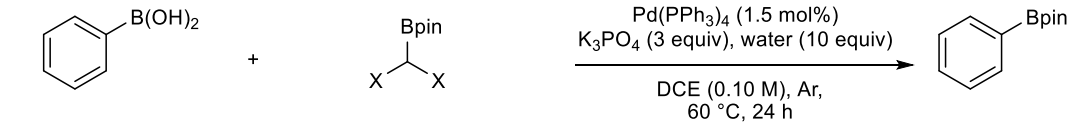


3.20 (1.5 equiv) *Homologation*

Entry	Homologating agent (quantity)	Expected product (%yield)
1	$BrCH_2Bpin$, **3.3** (54 μL)	**3.17** (90)
2	$ClCH_2Bpin$, **3.4** (53 mg)	**3.17** (49)
3	ICH_2Bpin, **3.5** (80 mg)	**3.17** (66)
4	BrCHMeBpin, **3.206** (75 mg)	**3.230** (0)
5	ClCHMeBpin, **3.205** (62 mg)	**3.230** (0)
6	ICHMeBpin, **3.207** (89 mg)	**3.230** (0)
7	$BrCH(Bpin)_2$, **3.209** (109 mg)	**3.231** (0)
8	$BrCMe_2Bpin$, **3.212** (79 mg)	**3.232** (0)

Attempted exhaustive couplings (Scheme 3.68)

General Procedure C was followed with a slight modification using phenylboronic acid (equiv varied) as the substrate and $BrCH_2Bpin$ **3.3** was replaced by the appropriate dihalide (equiv varied). In all cases, analysis of the crude by ^1H NMR identified byproduct **3.233** (>99%) and no other reaction products.



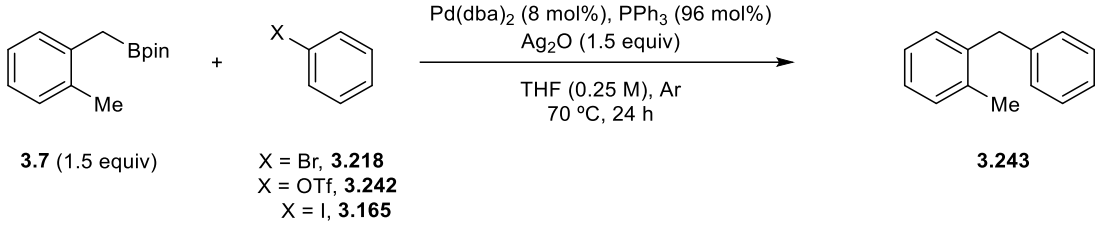
3.139 (1 or 3 equiv) X = Cl, **3.216** (1.5 or 1 equiv) X = Br, **3.217** (1.5 or 1 equiv) **3.233**, >99%

Entry	Equiv $PhB(OH)_2$ (mg)	Dihalide	Equiv dihalide (mg)
1	1.0 (24)	$CHCl_2Bpin$, **3.216**	1.5 (68)
2	3.0 (73)	$CHCl_2Bpin$, **3.216**	1.0 (45)
3	1.0 (24)	$CHBr_2Bpin$, **3.217**	1.5 (94)
4	3.0 (73)	$CHBr_2Bpin$, **3.217**	1.0 (63)

Suzuki–Miyaura benzylations based on Crudden-type conditions (Scheme 3.70)

Based on a procedure from Crudden and coworkers, with slight modifications.[178] To an oven-dried microwave vial equipped with a stir bar was added compound **3.7** (34 mg, 0.15 mmol, 1.50 equiv), freshly ground PPh_3 (25.2 mg, 0.096 mmol, 96 mol%) and Ag_2O (35 mg, 0.15 mmol, 1.50 equiv). The vial was taken into an Ar-filled glovebox where $Pd(dba)_2$ (7 mg, 0.008 mmol, 8 mol%) and THF (0.40 mL, 0.25 M) were added, then the vial was capped and taken out of the glovebox. The varied (pseudo)halide (0.10 mmol, 1.0 equiv) was added in one portion and the reaction mixture was stirred at 70 °C for 24 h (*Safety: the reaction was placed*

behind a blast shield as a precaution, bp THF ~66 °C). The vial was cooled to rt, decapped, diluted in CH_2Cl_2 and the reaction mixture filtered through a plug of silica gel and concentrated at reduced pressure.



3.7 (1.5 equiv)

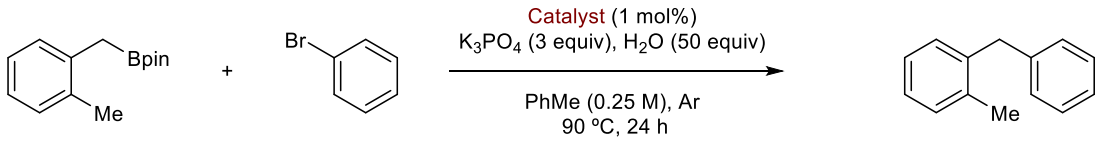
X = Br, **3.218**
X = OTf, **3.242**
X = I, **3.165**

3.243

Entry	Aryl (psueodo)halide (μL)	%3.243
1	Bromobenzene, **3.218** (11)	19
2	Phenyl triflate, **3.242** (16)	0
3	Iodobenzene, **3.165** (11)	54

Suzuki–Miyaura benzylations based on Watson-type conditions (Scheme 3.71)

To an oven-dried microwave vial fitted with a stir bar was added dried K_3PO_4 (127 mg, 0.30 mmol, 3.0 equiv), then compound **3.7** (69.6 mg, 0.30 mmol, 3.0 equiv), then the catalyst (1.0 mol%), and the vial capped and purged thrice with Ar prior to the addition of PhMe (0.4 mL, 0.25 M), then bromobenzene (11 μL, 0.10 mmol, 1.0 equiv), then water (90 μL, 5 mmol, 50 equiv) and the reaction mixture stirred at 90 °C for 24 h. The vial was decapped and the crude reaction mixture was filtered through a short pad of silica gel, eluting with CH_2Cl_2, and concentrated at reduced pressure.



3.7 (3 equiv)

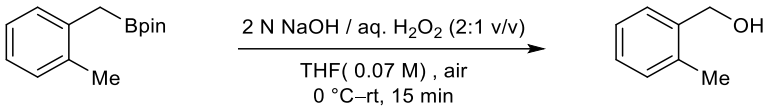
3.218

3.243

Entry	Catalyst (mg)	%3.243
1	$Pd(dppf)Cl_2$ (0.8)	>99
2	$Pd(PPh_3)_4$ (1.2)	30

Stepwise Brown oxidation (Scheme 3.78.1)

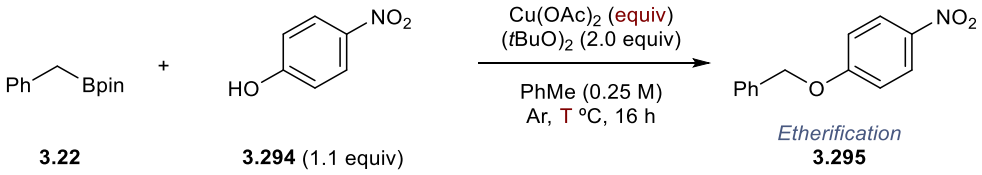
To an oven-dried 20 mL microwave vial equipped with a stir bar was added THF (3 mL) and compound **3.7** (46 mg, 0.20 mmol, 1.0 equiv). The vial was cooled to 0 °C followed by dropwise addition of a 2:1 solution of 2 N aq. NaOH / 30% aq. H_2O_2 (3 mL). The cooling bath was removed and the reaction mixture was stirred at rt for 15 min (air), then the reaction mixture was extracted into CH_2Cl_2 (3×). The collected organic phases were washed with brine (1×), dried (Na_2SO_4), and concentrated at reduced pressure. Following workup, analysis of the crude by ^1H NMR identified the desired compound **3.285** (>99%).



3.7 **3.285**

Variation of Cu loading and temperature for the Chan–Lam etherification (Scheme 3.80)

To an oven-dried microwave vial fitted with a stir bar was added $Cu(OAc)_2$ (equiv varied) and ground *p*-nitrophenol (15 mg, 0.11 mmol, 1.1 equiv). The vial was capped and purged with Ar prior to the addition of PhMe (0.40 mL, 0.25 M), benzylboronic acid pinacol ester **3.22** (20 µL, 22 mg, 0.10 mmol, 1.0 equiv), then *tert*-butylperoxide (23 µL, 0.20 mmol, 2.0 equiv), and the reaction mixture stirred at the appropriate temperature for 16 h (*Safety: the reaction was placed behind a blast shield as a precaution, heating of peroxides*). The vial was cooled to rt, decapped, and the crude reaction mixture was diluted in Et_2O ~10 mL and washed with 10% aq. ammonia (3×, or until the aqueous phase was no longer green-blue), then brine (1×), then the collected organic layer was dried (Na_2SO_4) and concentrated at reduced pressure.

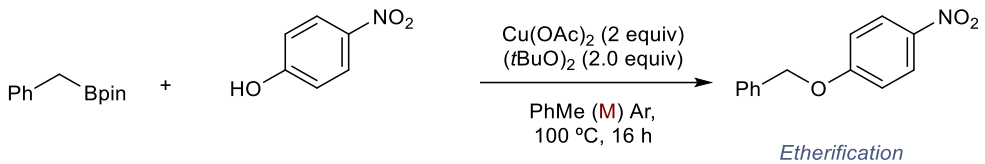


3.22 **3.294** (1.1 equiv) **3.295**

Entry	Equiv (mg)	°C	%3.295	Entry	Equiv (mg)	°C	%3.295
1	0.05 (1)	50	3	**5**	2.0 (36)	60	2
2	0.5 (9)	50	3	**6**	2.0 (36)	80	9
3	1.1 (20)	50	4	**7**	2.0 (36)	100	26
4	2.0 (36)	50	3	-	-	-	-

Variation of phenol stoichiometry and concentration (Scheme 3.81)

To an oven-dried microwave vial fitted with a stir bar was added $Cu(OAc)_2$ (36 mg, 0.20 mmol, 2.0 equiv) and ground *p*-nitrophenol (equiv varied). The vial was capped and purged with Ar prior to the addition of PhMe (concentration varied), benzylboronic acid pinacol ester **3.22** (20 µL, 22 mg, 0.10 mmol, 1.0 equiv), then *tert*-butylperoxide (23 µL, 0.20 mmol, 2.0 equiv), and the reaction mixture stirred at 100 °C for 16 h (*Safety: the reaction was placed behind a blast shield as a precaution, heating of peroxides*). The vial was cooled to rt, decapped and the crude reaction mixture was diluted in Et_2O ~10 mL and washed with 10% aq. ammonia (3×, or until the aqueous phase was no longer green-blue), then brine (1×), then the collected organic layer was dried (Na_2SO_4) and concentrated at reduced pressure.

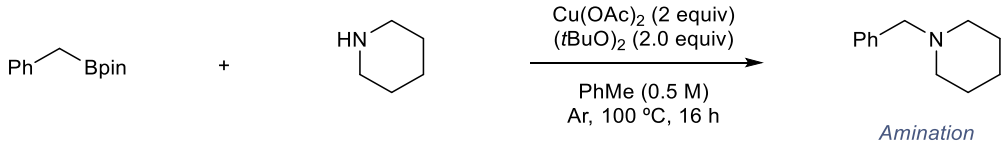


3.22 **3.294** (equiv) *Etherification* **3.295**

Entry	Equiv (mg)	mL (M)	%3.295
1	1.1 (15)	0.40 (0.25)	26
2	2.0 (27)	0.40 (0.25)	32
3	3.0 (41)	0.40 (0.25)	41
4	5.0 (68)	0.40 (0.25)	50
5	10 (140)	0.40 (0.25)	42
6	5.0 (68)	1.00 (0.10)	51
7	5.0 (68)	0.25 (0.40)	45
8	5.0 (68)	0.20 (0.50)	63
9	5.0 (68)	0.17 (0.6)	57
10	5.0 (68)	0.13 (0.8)	49

Chan–Lam amination based on etherification conditions (Scheme 3.84)

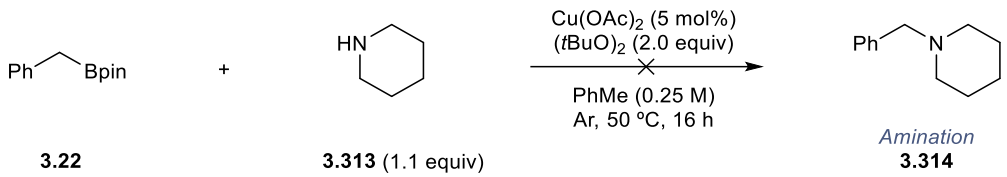
General Procedure I was followed with a slight variation using benzylboronic acid pinacol ester **3.22** (20 µL, 22 mg, 0.10 mmol, 1.0 equiv) and the alcohol was replaced with piperidine (49 µL, 0.50 mmol, 5.0 equiv) Following workup, analysis of the crude by ^{1}H NMR identified the desired compound **3.314** (4%).



3.22 **3.313** (5 equiv) *Amination* **3.314**

Chan–Lam amination based on Kuninobu-type conditions (Scheme 3.85)

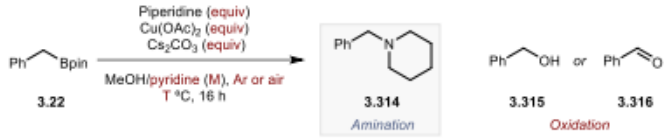
To an oven-dried microwave vial fitted with a stir bar was added $Cu(OAc)_2$ (1 mg, 0.005 mmol, 5 mol%). The vial was capped and purged with Ar prior to the addition of PhMe (0.40 mL, 0.25 M), benzylboronic acid pinacol ester **3.22** (20 µL, 22 mg, 0.10 mmol, 1.0 equiv), then *tert*-butylperoxide (23 µL, 0.20 mmol, 2.0 equiv), then piperidine (11 µL, 0.11 mmol, 1.1 equiv) and the reaction mixture stirred at 50 °C for 16 h (*Safety: the reaction was placed behind a blast shield as a precaution, heating of peroxides*). The vial was cooled to rt, decapped and the crude reaction mixture was diluted in Et_2O ~10 mL and washed with 10% aq. ammonia (3×, or until the aqueous phase was no longer green-blue), then brine (1×), then the collected organic layer was dried (Na_2SO_4) and concentrated at reduced pressure. Following workup, analysis of the crude by ^{1}H NMR identified none of the desired compound **3.314**.



3.22 **3.313** (1.1 equiv) **3.314**

Deconstruction of Partridge-type Chan–Lam amination components (Scheme 3.87)

To an oven-dried microwave vial fitted with a stir bar was added $Cu(OAc)_2$ (equiv varied), dried Cs_2CO_3 (equiv varied) and bipy (equiv varied). The vial was capped and purged with Ar or air prior to the addition of MeOH/ pyridine (4:1, 0.40 M), then benzylboronic acid pinacol ester **3.22** (20 µL, 22 mg, 0.10 mmol, 1.0 equiv), then piperidine (equiv varied), and the reaction mixture stirred at the given temperature for 16 h. The vial was decapped and the crude reaction mixture was diluted in Et_2O (10 mL) and washed with 10% aq. ammonia (3×, or until the aqueous phase was no longer blue), then brine (1×), then the collected organic layer was dried (Na_2SO_4) and concentrated at reduced pressure.

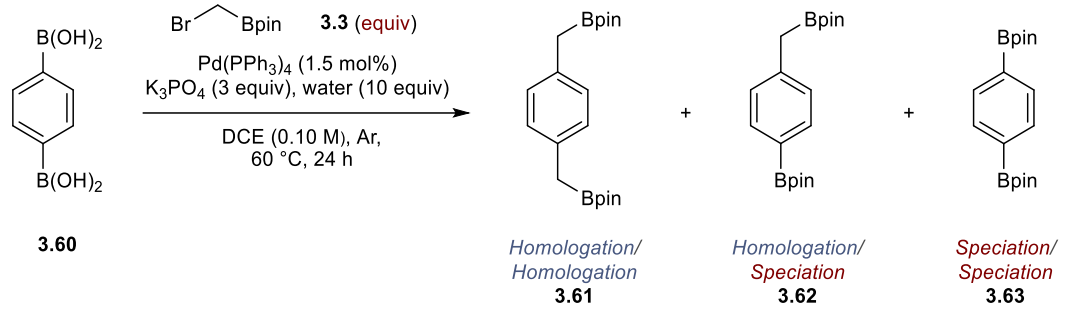


Entry	Equiv $Cu(OAc)_2$ (mg)	Equiv Cs_2CO_3 (mg)	Equiv bipy (mg)	MeOH (µL)	Pyridine (µL)	Equiv Piperidine (µL)	°C	Ar/Air	%3.314	%3.315	%3.316
1	2 (36)	0.5 (16)	0	200	50	4 (40)	50	Ar	75	7	0
2	2 (36)	0	0	200	50	4 (40)	50	Ar	54	5	1
3	2 (36)	0.5 (16)	0	200	0	4 (40)	50	Ar	63	5	2
4	0	0.5 (16)	0	200	50	4 (40)	50	Ar	0	10	1
5	2 (36)	0.5 (16)	0	200	50	4 (40)	50	Air	44	18	20
6	1.1 (2)	0.5 (16)	0	200	50	4 (40)	50	Ar	52	6	2
7	2 (36)	0.5 (16)	0	100	50	4 (40)	50	Ar	74	8	0
8	2 (36)	0.5 (16)	0	200	50	3 (30)	50	Ar	60	10	2
9	2 (36)	0.5 (16)	1 (16)	200	0	4 (40)	50	Ar	37	4	0
10	2 (36)	0.5 (16)	0	200	50	4 (40)	40	Ar	42	8	3
11	2 (36)	0.5 (16)	0	200	50	4 (40)	60	Ar	55	28	3

5.5 Experimental details of described unsuccessful syntheses

Double homologation attempts (Scheme 3.25)

General Procedure C was followed with a slight modification using benzene-1,4-diboronic acid (33 mg, 0.20 mmol, 1.0 equiv), where $BrCH_2Bpin$ **3.3** equivalents were varied.



3.60

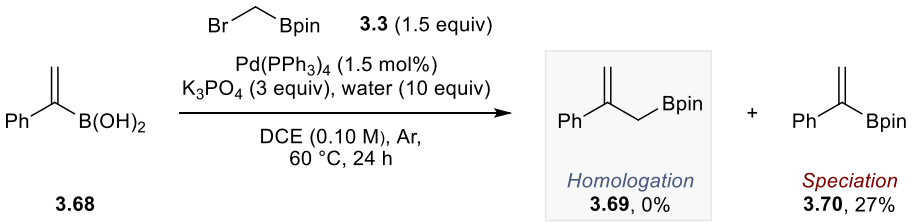
Homologation/ Homologation **3.61**

Homologation/ Speciation **3.62**

Speciation/ Speciation **3.63**

Entry	Equiv $BrCH_2Bpin$ (µL)	%3.61	%3.62	%3.63
1	2.0 (72)	0	10	58
2	4.0 (140)	<2	26	59
3	6.0 (220)	<2	24	74

Attempted homologation of 1-styrylboronic acid (Scheme 3.27.3)



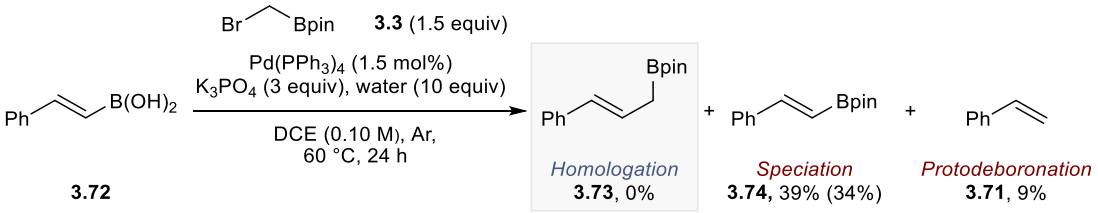
3.68

Homologation **3.69**, 0%

Speciation **3.70**, 27%

General Procedure C was followed using (1-phenylvinyl) boronic acid (30.4 mg, 0.20 mmol, 1.0 equiv). Following workup, analysis of the crude by ^{1}H NMR identified byproduct **3.70** (27%) and none of the desired compound **3.69**.

Attempted homologation of 2-(*E*)-styrylboronic acid (Scheme 3.27.4)



3.72

Homologation **3.73**, 0%

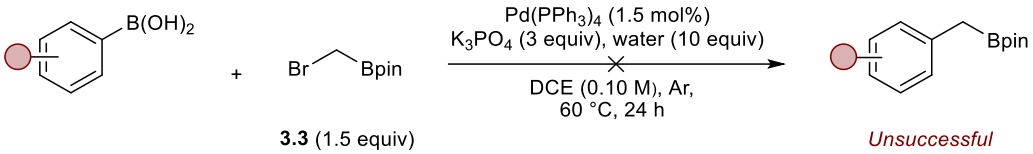
Speciation **3.74**, 39% (34%)

Protodeboronation **3.71**, 9%

General Procedure C was followed using *trans*-2-phenylvinylboronic acid (30.4 mg, 0.20 mmol, 1.0 equiv). Following workup, analysis of the crude by ^{1}H NMR identified byproducts **3.74** (39%) and **3.71** (9%) and none of the desired compound **3.73**.

Unsuccessful palladium-catalysed homologations of arylboronic acids (Scheme 3.28)

General Procedure C was followed using the listed arylboronic acid (0.20 mmol, 1.0 equiv). Following workup, analysis of the crude by ^{1}H NMR failed to identify the expected homologation product.



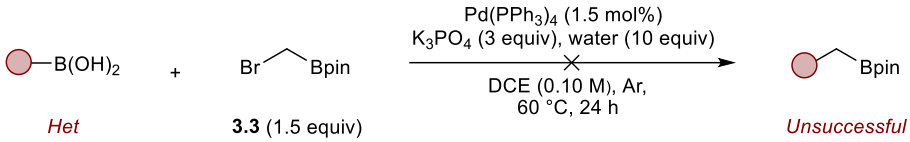
3.3 (1.5 equiv)

Unsuccessful

Entry	Arylboronic acid (mg)
1	4-Hydroxyphenylboronic acid, **3.77** (27.6)
2	4-(Hydroxymethyl)phenylboronic acid, **3.78** (30.4)
3	4-Carboxybenzeneboronic acid, **3.79** (33.2)
4	4-Acetamidophenylboronic acid, **3.80** (35.8)
5	4-Bromomethylphenylboronic acid, **3.81** (43.0)
6	4-benzoylphenyl)boronic acid, **3.82** (45.2)
7	4-(Methanesulfonyl)phenylboronic acid, **3.83** (40.0)
8	4-Nitrobenzeneboronic acid, **3.84** (33.4)
9	4-Formylphenylboronic acid, **3.85** (30.0)
10	4-(Trifluoromethyl)phenylboronic acid, **3.86** (38.0)
11	4-Bromobenzeneboronic acid, **3.87** (40.2)
12	3-(dimethylamino)phenylboronic acid, **3.88** (33.0)
13	(3-(9*H*-Carbazol-9-yl)phenyl)boronic acid, **3.89** (57.4)
14	3-Cyanophenylboronic acid, **3.90** (29.4)
15	3-Aminophenylboronic acid, **3.91** (27.4)
16	3-Bromophenylboronic acid, **3.92** (40.2)
17	2-Hydroxyphenylboronic acid, **3.93** (27.6)
18	2-(Hydroxyphenyl)boronic acid, **3.94** (30.4)
19	2-carboxybenzene boronic acid, **3.95** (33.2)
20	2-Aminophenylboronic acid, **3.96** (27.4)
21	2-acetamidobenzeneboronic acid, **3.97** (35.8)
22	2-Carbamoylbenzeneboronic acid, **3.98** (33.0)
23	2-Nitrophenylboronic acid, **3.99** (33.4)
24	2-Formylbenzeneboronic acid, **3.100** (30.0)

Unsuccessful palladium-catalysed homologations of heteroarylboronic acids (Scheme 3.29)

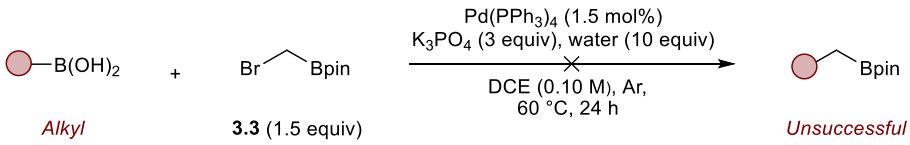
General Procedure C was followed using the listed heteroarylboronic acid (0.20 mmol, 1.0 equiv). Following workup, analysis of the crude by ^{1}H NMR failed to identify the expected homologation product.



Entry	Heteroarylboronic acid (mg)
1	3-Pyridinylboronic acid, **3.101** (24.6)
2	(2-Methylpyridin-3-yl)boronic acid, **3.102** (27.4)
3	Pyrimidine-5-boronic acid, **3.103** (24.8)
4	Quinoline-6-boronic acid, **3.104** (34.6)
5	(1-(*tert*-Butoxycarbonyl)-1*H*-indol-2-yl)boronic acid, **3.105** (52.2)
6	1-Benzyl-1*H*-pyrazole-4-boronic acid, **3.106** (40.4)
7	4-Dibenzothienylboronic acid, **3.107** (45.6)
8	Benzo[*b*]thien-2-ylboronic acid, **3.108** (35.6)
9	Benzo[*b*]furan-2-boronic acid, **3.109** (32.4)

Unsuccessful palladium-catalysed homologations of alkylboronic acids (Scheme 3.30)

General Procedure C was followed using the listed alkylboronic acid (0.20 mmol, 1.0 equiv). Following workup, analysis of the crude by ^{1}H NMR failed to identify the expected homologation product.

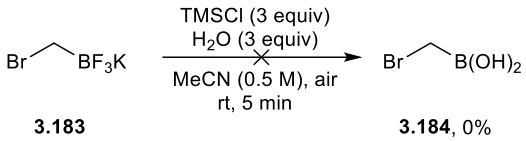


Entry	Alkylboronic acid (mg)
1	(2-methylpropyl)boronic acid, **3.110** (20.4)
2	Methylboronic acid, **3.111** (12.0)
3	Cyclohexylboronic acid, **3.112** (25.6)
4	Cyclopropylboronic acid, **3.113** (17.2)

Attempted preparation of bromomethylboronic acid (Scheme 3.54, step 2)

Based on part of a procedure by Hutton and coworkers.[232] To an oven-dried round-bottomed flask was added $BrCH_2BF_3K$ **3.183** (100 mg, 0.50 mmol, 1.0 equiv) followed by MeCN (2.0 mL, 0.25 M) under air. While stirring at rt, TMSCl (0.19 mL, 1.5 mmol, 3.0 equiv) was added in a single portion, followed by water (27 μL, 1.5 mmol, 3.0 equiv). The reaction mixture was concentrated at reduced pressure then resuspended in Et_2O (20 mL), dried (Na_2SO_4), filtered,

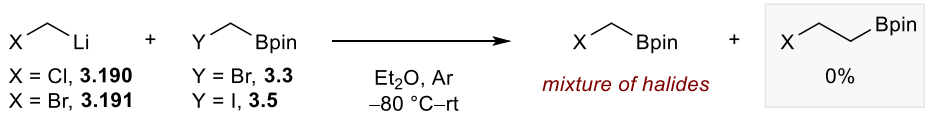
and the liquor concentrated at reduced pressure. Analysis of the crude by ^{1}H NMR failed to identify the expected product, **3.184**.



3.183 **3.184**, 0%

Attempted preparations of β-chloroethylboronic acid pinacol ester (Scheme 3.57.1)

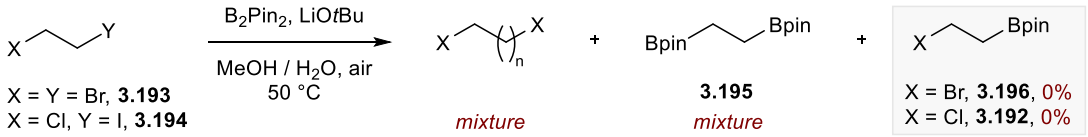
In a flamed-dried flask under Ar a solution of the dihalide (1.2 equiv) in dry Et_2O (0.2 M) was cooled to −80 °C then *n*BuLi in hexanes (1.05 equiv) was added dropwise by hand such that the reaction temperature never exceeded −75 °C, this took 30 min. The reaction mixture was stirred for 15 min prior to the addition of the halomethylboronic ester **3.3** or **3.5** (1 equiv) in one portion, then the reaction mixture stirred at −80 °C for 30 min, warmed to 35 °C, then stirred for 1 h. The reaction mixture was concentrated at reduced pressure then resuspended in CH_2Cl_2 ~50 mL and insoluble salts filtered off, washed with CH_2Cl_2, then the liquor concentrated at reduced pressure to afford a yellow oil. Analysis of the crude by ^{1}H NMR failed to identify the desired β-haloethyl boronic ester products**.** The starting material boronic esters and a halide exchange byproduct were observed as below.



Entry	mmol	Dihalide (mL)	XCH_2Bpin (mL)	XCH_2Bpins in crude (%)
1	10	$BrCH_2Cl$ (1.17)	$ClCH_2Bpin$, **3.4** (1.73)	Cl **3.4** (76), Br **3.3** (16)
2	5	CH_2Br_2 (0.79)	$BrCH_2Bpin$, **3.3** (0.89)	Br **3.3** (83)
3	5	CH_2Br_2 (0.79)	ICH_2Bpin, **3.5** (0.91)	I **3.5** (86) Br **3.3** (14)

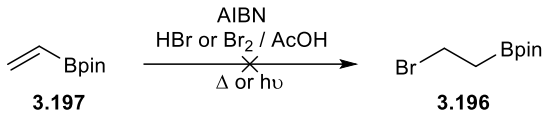
Attempted radical preparations of β-haloethylboronic acid pinacol esters (Scheme 3.57.2)

A flame-dried Schlenk tube fitted with a stir bar and cooled under Ar was charged with B_2pin_2 (5.33 g, 21.0 mmol, 4.0 equiv) and Li*O*t*Bu* (841 mg, 10.5 mmol, 2.0 equiv) and the top sealed with a septum then evacuated and backfield with Ar (3×). To the solids were added MeOH (10.5 mL), then water (53 μL, 2.91 mmol) and the reaction stirred at rt until homogenous (~3 min) then the dihalide (1.0 equiv) was added in a single portion. The reaction mixture was stirred at rt for 72 h, then concentrated at reduced pressure. Analysis of the crude by ^{1}H NMR failed to identify the desired β-haloethyl boronic ester products **3.192** or **3.196**. Several byproducts were identified including dihalide polymers and a double-displacement adduct (*i.e.*, **3.195**) but were not quantified due to overlapping signals.



Entry	Dihalide (mL)	Desired product
1	1-Chloro-2-iodoethane (0.64)	$ClCH_2CH_2Bpin$, **3.192**
2	1,2-Dibromoethane (0.43)	$BrCH_2CH_2Bpin$, **3.196**

Attempted radical hydrobrominations of vinylboronic acid pinacol ester (Scheme 3.57.3)



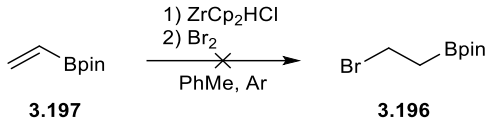
Procedure with AcOH

To a Schlenk tube fitted with a stir bar, vinylboronic acid pinacol ester **3.197** (0.85 mL, 5.00 mmol, 1.0 equiv) was dissolved in hexane (9.0 mL). 48% aq. HBr (0.54 mL, 10.0 mmol) was then added in one portion at rt, then AcOH (1.0 mL) and the solution stirred at rt under air for 18 h, then diluted in hexane 20 mL. The reaction mixture was washed with aq. $Na_2S_2O_3$ (3×), brine (3×) then the collected organic phase dried (Na_2SO_4) and concentrated at reduced pressure to afford a colourless oil, which was solely starting material.

Procedures with AIBN

A flame-dried Schlenk tube equipped with a stir bar and backfilled with Ar was charged with AIBN (820 mg, 5.0 mmol, 1.0 equiv) then the septum returned and the flask purged with Ar prior to the addition of hexane (15 mL), 48% aq. HBr (0.54 mL, 10.0 mmol), and vinylboronic acid pinacol ester **3.197** (0.85 mL, 5.00 mmol, 1.0 equiv) at rt. The Schlenk tube was either 1) set up with two 25 W compact fluorescent lamps side by side ~ 3 cm from the flask and a thermometer that read ~35 °C and the reaction stirred for 18 h; or 2) heated to reflux, then both were cooled to rt and diluted in hexane 20 mL. The reaction mixtures were washed with aq. $Na_2S_2O_3$ (3×), brine (3×) then the collected organic phase dried (Na_2SO_4) and concentrated at reduced pressure where none of the desired product (*i.e.*, **3.196**) was found in each case.

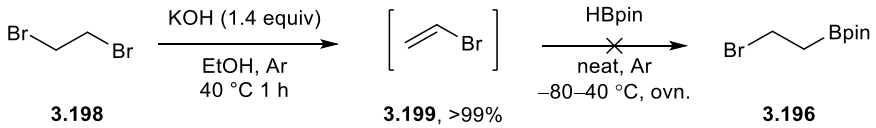
Attempted hydrobromination using Schwartz reagent (Scheme 3.57.4, top)



3.197 **3.196**

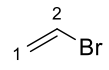
In an Ar-filled glovebox Schwartz reagent (520 mg, 2.0 mmol, 2.0 equiv) was added to a Schlenk tube fitted with a stir bar. The tube was sealed with a septum and electrical tape, then removed from the glovebox where PhMe (10.0 mL, 0.1 M) was added and the solution cooled to 0 °C. Vinylboronic acid pinacol ester **3.197** (0.17 mL, 1.0 mmol, 1.0 equiv) was added in one portion at rt and the reaction mixture stirred for 2 h, then the reaction mixture cooled to 0 °C prior to the addition of Br_2 (0.16 mL, 1.5 mmol, 1.5 equiv) in one portion. The reaction mixture was warmed to rt, stirred for 15 min then diluted in Et_2O (10 mL), quenched with aq. $Na_2S_2O_3$ (10 mL). The organic phase was extracted using Et_2O (3×) and the organics washed with brine (5×), dried (Na_2SO_4) and concentrated at reduced pressure where none of the desired product (*i.e.*, **3.196**) was found.

Attempted hydroboration of vinyl bromide (Scheme 3.57.4, bottom)



3.198 **3.199**, >99% **3.196**

Safety: Vinyl bromide is extremely toxic and volatile, a respirator was used during this synthesis and characterisation of trapped vinyl bromide was performed in a J. Young's NMR tube. A two-necked flask fitted with a septum and a 20 cm Vigreux column was charged with freshly ground KOH (1.57 g, 28 mmol, 1.4 equiv) and EtOH (40 mL). The mixture was warmed to 40 °C and stirred until homogeneous (~5 min) prior to the dropwise addition of 1,2-dibromoethane (1.7 mL, 20 mmol, 1.0 equiv) over 15 min. The reaction mixture was warmed to 60 °C and stirred for 1 h whereupon vinyl bromide **3.199** was collected as a 2:1 solution in EtOH using a flask *cooled in a liquid N_2 bath and the condenser cooled to ~1 °C using a pad of cotton wool periodically soaked in liquid N_2* (3.31 g, >99%) and was stored in a Schlenk tube at −80 °C and used on the same day.



Chemical Formula: C_2H_3Br
Exact Mass: 105.9418

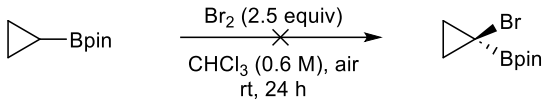
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 15.0, 7.1 Hz, 1 H, H_2), 5.99 (dd, *J* = 7.2, 1.9 Hz, 1 H, $H_{1\text{-}cis}$), 5.86 (dd, *J* = 15.1, 1.9 Hz, 1 H, $H_{1\text{-}trans}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 122.1 (C_1), 114.1 (C_2).

A flame-dried Schlenk tube equipped with a stir bar and backfilled with Ar was cooled to −80 °C then charged with the ethanolic solution of vinyl bromide **3.199** (1.20 mL, 17.0 mmol,

1.70 equiv). HBpin (1.45 mL, 10.0 mmol, 1.00 equiv) was added dropwise at −80 °C, then the reaction mixture was stirred at −80 °C for 1 h, warmed to rt, and stirred for 14 h. The reaction mixture warmed to 40 °C and the septum removed, stirring for 1 h under strong fumehood extraction to vent excess vinyl bromide (*safety: the fume cupboard sash was fully shut and the bay was left unoccupied during venting*). The solution was cooled back down to 0 °C, diluted in Et_2O 5 mL and quenched with 2 M HCl solution 5 mL and stirred at rt for 15 min. The organics were extracted into ether (3×) and the collected organics washed with brine (2×), dried (Na_2SO_4) and concentrated at reduced pressure. The desired product (*i.e.*, **3.196**) was not obtained.

Attempted preparation of 2-(1-bromocyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Scheme 3.61, bottom, step 2)

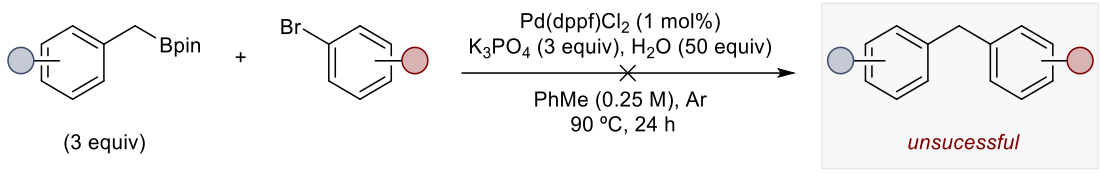


3.214 **3.215**, 0%

A flame-dried two necked flask cooled under an atmosphere of Ar was fitted with a septum and an aq. $NaHCO_3$ scrubber was charged with $CHCl_3$ (5.0 mL, 0.6 M) and cyclopropylboronic acid pinacol ester **3.214** (0.571 mL, 3.00 mmol, 1.0 equiv). Br_2 (0.39 mL, 7.50 mmol, 2.5 equiv) was added in a single portion at rt. The flask was stirred at rt for 16 h then diluted in CH_2Cl_2 10 mL, transferred to a single-necked flask and concentrated at reduced pressure. Analysis of the crude by ^1H NMR showed full decomposition of the starting material.

Unsuccessful Suzuki–Miyaura benzylations (Scheme 3.73)

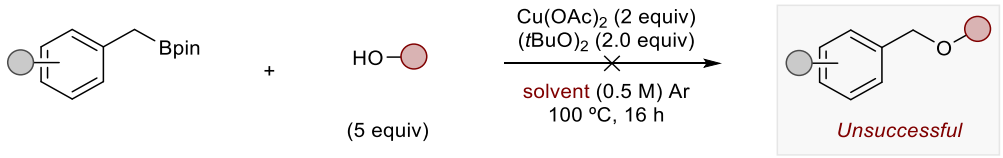
General Procedure F was followed using the listed benzyl boronic ester (0.30 mmol, 3.0 equiv) and bromide (0.10 mmol, 1.0 equiv). Following workup, analysis of the crude by ^{1}H NMR failed to identify the expected benzylation product.



Entry	Bpin (mg)	Halide (μL)	Product
1	**3.30** (73)	1-Bromo-3-fluorobenzene (11)	**3.256**
2	**3.30** (73)	2-Bromobenzophenone (18)	**3.257**
3	**3.30** (73)	1-(2-Bromo-5-methoxyphenyl)ethanone (16)	**3.258**
4	**3.30** (73)	3-Bromobenzonitrile (12)	**3.259**
5	**3.7** (70)	2-(4-Bromo-phenyl)-ethanol (14)	**3.260**
6	**3.7** (70)	β-Bromostyrene (13)	**3.261**

Unsuccessful Chan–Lam etherifications (Scheme 3.83)

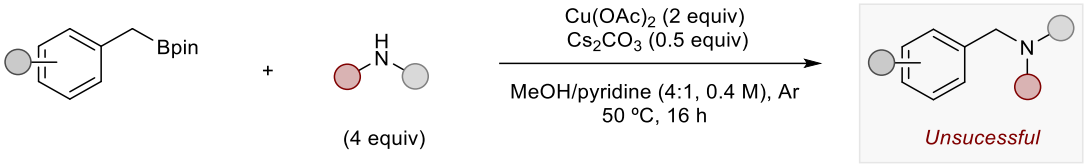
General Procedure I was followed using the listed benzyl boronic ester (0.20 mmol, 1.0 equiv) and alcohol (1.0 mmol, 5.0 equiv). Alternatively, the alcohol replaced PhMe as the solvent (0.4 mL, 0.5 M) Following workup, analysis of the crude by ^{1}H NMR failed to identify the expected etherification product.



Entry	Bpin (mg)	Alcohol (quantity)	Solvent	Product
1	**3.58** (50)	Benzyl alcohol (100 μL)	PhMe	**3.306**
2	**3.58** (50)	-	Benzyl alcohol	**3.306**
3	**3.33** (50)	Isopropanol (47 μL)	PhMe	**3.307**
4	**3.33** (50)	-	Isopropanol	**3.307**
5	**3.33** (50)	Allyl alcohol (34 μL)	PhMe	**3.308**
6	**3.33** (50)	-	Allyl alcohol	**3.308**
7	**3.33** (50)	4-*tert*-Butylcyclohexanol (160 mg)	PhMe	**3.309**
8	**3.42** (47)	Salicaldehyde (110 μL)	PhMe	**3.310**
9	**3.57** (54)	Salicaldehyde (110 μL)	PhMe	**3.311**
10	**3.30** (49)	4-nitrophenol (139 mg)	PhMe	**3.312**

Unsuccessful Chan–Lam aminations (Scheme 3.89)

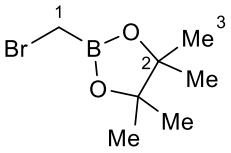
General Procedure J was followed using the listed benzyl boronic ester (0.20 mmol, 1.0 equiv) and amine (0.80 mmol, 4.0 equiv). Following workup, analysis of the crude by ^{1}H NMR failed to identify the expected amination product.



Entry	Bpin (mg)	Amine (μL)	Product
1	**3.58** (50)	Propargyl amine (51)	**3.328**
2	**3.33** (50)	Cyclobutylamine (68)	**3.329**
3	**3.46** (49)	Cyclopentylamine (51)	**3.330**
4	**3.30** (49)	Morpholine (86)	**3.331**

5.6 Synthesis and characterisation of isolated starting materials and products

2-(bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3)



Chemical Formula: $C_7H_{14}BBrO_2$
Exact Mass: 220.0270

Prepared according to General procedure A using THF (500 mL), dibromomethane (11.9 mL, 169 mmol, 1.20 equiv), triisopropyl borate (35.8 mL, 155 mmol, 1.10 equiv) and *n*BuLi 2.45 M in hexanes (57.6 mL, 141 mmol, 1.00 equiv), methanesulfonic acid (9.15 mL, 141 mmol, 1.00 equiv) and pinacol (15.6 g, 141 mmol, 1.00 equiv). Following workup, the desired product was purified by vacuum distillation (55–57 °C, 6–7 mbar, lit 42–44 °C, 3.5–5.1 mbar[166]) and was stored in the freezer in the absence of light as a colourless liquid (26.8 g, 86%). *Safety: At this scale the product is a lachrymator.*

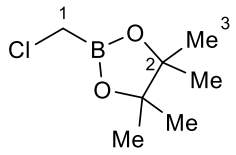
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 2 H, H_1), 1.29 (s, 12 H, H_3).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 84.7 (C_2), 24.7 (C_3).

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.09.

The spectral data were consistent with the literature.[166]

2-(chloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.4)



Chemical Formula: $C_7H_{14}BClO_2$
Exact Mass: 176.0775

Prepared according to General Procedure A using THF (250 mL), bromochloromethane (2.34 mL, 36.0 mmol, 1.20 equiv), triisopropyl borate (7.62 mL, 33.0 mmol, 1.10 equiv) and *n*BuLi 2.46 M in hexanes (12.2 mL, 30.0 mmol, 1.00 equiv), methanesulfonic acid (1.95 mL, 30.0 mmol, 1.00 equiv) and pinacol (3.55 g, 30.0 mmol, 1.00 equiv). Following workup, the desired product was purified by vacuum distillation (42–44 °C, 5 mbar, lit 80–82 °C, 19 mbar) and was stored in the freezer in the absence of light as a colourless liquid (7.77 g, 83%).

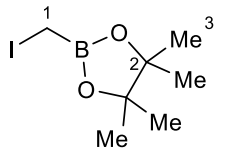
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96 (s, 2 H, H_1), 1.29 (s, 12 H, H_3).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 84.7 (C_2), 63.7 (C_1), 24.7 (C_3).

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.56.

The spectral data were consistent with the literature.[76]

2-(iodomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.5)



Chemical Formula: $C_7H_{14}BIO_2$
Exact Mass: 268.0132

To $BrCH_2Bpin$ **3.3** (2.25 g, 10.2 mmol, 1.00 equiv) in acetone (20 mL), was added NaI (2.44 g, 16.3 mmol, 1.6 equiv) in one portion at rt, and the mixture stirred at rt in the dark (tin foil wrapped flask) for 2 h. Insoluble salts were filtered off and the flask rinsed with acetone (40 mL), and the solvents were evaporated under reduced pressure to afford a residue that was triturated in hexane (50 mL) and the insoluble material filtered off, washing with hexane (2×25 mL). The liquor was concentrated under reduced pressure to obtain the product as a pale-yellow liquid (2.55 g, 93%) which was stored in the freezer in the absence of light.

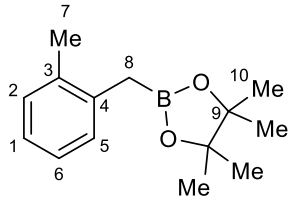
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (2 H, s, H_1), 1.27 (12 H, s, H_3).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 84.3 (C_2), 74.6 (C_1), 24.5 (C_3).

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.83.

The spectral data were consistent with the literature.[258]

4,4,5,5-tetramethyl-2-(2-methylbenzyl)-1,3,2-dioxaborolane (3.7)



Chemical Formula: $C_{14}H_{21}BO_2$
Exact Mass: 232.1635

Prepared according to General Procedure C with a slight modification using *o*-tolylboronic acid (27.2 mg, 0.20 mmol) as the substrate, but PhOMe (0.8 mL, 0.25 M) was used as the solvent and the reaction time was 6 h. The crude (>99% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (41.1 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (m, 4 H, $H_{1,2,5,6}$), 2.27 (s, 3 H, H_7), 2.25 (s, 2 H, H_8), 1.22 (s, 12 H, H_{10}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 137.7 (C_{Ar}), 136.1 (C_{Ar}), 129.9 (C_{Ar}), 129.6 (C_{Ar}), 126.0 (C_{Ar}), 125.3 (C_{Ar}), 83.5 (C_9), 24.9 (C_{10}), 20.2 (C_7).

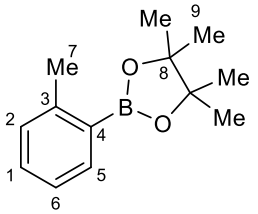
^{11}B NMR (96 MHz, $CDCl_3$) δ 32.96.

The spectral data were consistent with the literature.[259]

The compound was also prepared according to General Procedure C with a slight modification using *o*-tolylboronic acid (27.2 mg, 0.20 mmol) as the substrate, but PhMe (2.0 mL, 0.1 M) was used as the solvent. The crude (84% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (35.9 mg, 83%).

The compound was according to General Procedure D with a slight modification using *o*-tolylboronic acid (1.36 g, 10 mmol, 1.0 equiv) as the substrate, but PhOMe (40 mL, 0.25 M) was used as the solvent and the reaction time was 6 h. The crude oil was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless liquid (2.03 g, 95%).

4,4,5,5-tetramethyl-2-(*o*-tolyl)-1,3,2-dioxaborolane (3.8)



Chemical Formula: $C_{13}H_{19}BO_2$
Exact Mass: 218.1478

Prepared according to general procedure E using *o*-tolylboronic acid (1.36 g, 10.0 mmol, 1.0 equiv) and pinacol (1.54 g, 12 mmol, 1.2 equiv) The reaction time was 3 h. The title compound was obtained as a straw-coloured oil without further purification (2.18 g, >99%).

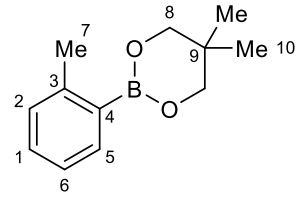
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.74 (m, 1 H, H_5), 7.37−7.29 (m, 1 H, H_6), 7.21–7.11 (m, 2 H, $H_{1\text{-}2}$), 2.55 (s, 3 H, H_7), 1.35 (s, 12 H, H_9).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.0 (C_3), 136.0 (C_5), 130.9 (C_6), 129.9 (C_2), 124.8 (C_1), 83.5 (C_8), 25.0 (C_9), 22.4 (C_7).

^{11}B NMR (96 MHz, $CDCl_3$) δ 30.90.

The spectral data were consistent with the literature.[260]

5,5-dimethyl-2-(*o*-tolyl)-1,3,2-dioxaborinane (3.12)



Chemical Formula: $C_{13}H_{19}BO_2$
Exact Mass: 218.1478

Prepared according to General Procedure E using *o*-tolylboronic acid (412 mg, 3.03 mmol, 1.0 equiv) and neopentylglycol (347 mg, 3.33 mmol, 1.1 equiv) The reaction time was 6 h. The title compound was obtained as a colourless oil without further purification (619 mg, >99%).

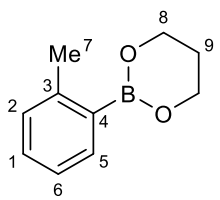
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.4, 1.6 Hz, 1 H, H_1), 7.30 (td, *J* = 7.5, 1.7 Hz, 1 H, H_6), 7.21–7.16 (m, 2 H, $H_{2,5}$), 3.79 (s, 4 H, H_8), 2.54 (s, 3 H, H_7), 1.05 (s, 6 H, H_{10}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.1 (C_3), 135.0 (C_1), 130.2 (C_{Ar}), 130.1 (C_{Ar}), 124.8 (C_{Ar}), 72.4 (C_8), 31.8 (C_9), 22.5 (C_7), 22.0 (C_{10}).

^{11}B NMR (96 MHz, $CDCl_3$) δ 27.42.

The spectral data were consistent with the literature.[171]

2-(*o*-tolyl)-1,3,2-dioxaborinane (3.13)



Chemical Formula: $C_{10}H_{13}BO_2$
Exact Mass: 176.1009

Prepared according to General Procedure E using *o*-tolylboronic acid (412 mg, 3.03 mmol, 1.0 equiv) and propane-1,3,-diol (0.24 mL, 3.33 mmol, 1.1 equiv). The reaction time was 6 h. The crude was subjected to silica gel chromatography (10–40% Et_2O in hexane) to afford the title compound as a white solid (527 mg, 99%).

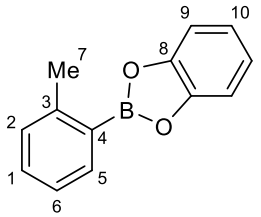
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78−7.82 (m, 1 H, H_2), 7.33−7.35 (m, 1 H, H_6), 7.25–7.18 (m, 2 H, $H_{1,5}$), 4.30–4.12 (t, *J* = 5.3 Hz, 4 H, H_8), 2.59 (s, 3 H, H_7), 2.08 (p, *J* = 5.5 Hz, 2 H, H_9).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 144.0 (C_3), 134.9 (C_2), 130.1 (C_{Ar}), 130.0 (C_{Ar}), 124.7 (C_{Ar}), 61.9 (C_8), 27.5 (C_9), 22.5 (C_7).

^{11}B NMR (96 MHz, $CDCl_3$) δ 28.39.

The spectral data were consistent with the literature.[261]

2-(*o*-tolyl)benzo[*d*][1,3,2]dioxaborole (3.15)



Chemical Formula: $C_{13}H_{19}BO_2$
Exact Mass: 218.1478

An oven-dried flask equipped with a stir bar was charged with catechol (330 mg, 3.00 mmol, 1.00 equiv) and *o*-tolylboronic acid (412 mg, 3.03 mmol, 1.01 equiv) and the solution dissolved in CH_2Cl_2 (30.0 mL). The solution was stirred at rt where EtOAc was added until the solution became homogenous (5 mL) whereupon Et_3N (0.63 mL, 4.5 mmol, 1.5 equiv) and Na_2SO_4 (850 mg, 6.0 mmol, 2.0 equiv) were added. The reaction mixture was heated to 50 °C and stirred for 3 h, then cooled to rt, filtered and concentrated at reduced pressure to yield a rose residue. The residue was dissolved in a minimum volume of EtOAc and precipitated from hexane, then filtered and dried at reduced pressure to obtain the product as a pink solid (635 mg, >99%). Residual solvent could not be removed after prolonged high vacuum and an unknown impurity is present in the ^1H NMR spectrum. The compound is unstable to silica chromatography and was used without further purification.

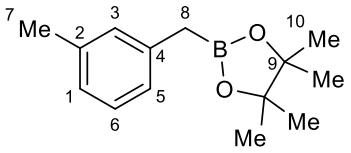
^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 6.9 Hz, 1 H, H_5), 7.44 (t, *J* = 7.6 Hz, 1 H, H_6), 7.35–7.26 (m, 4 H, H_{Ar}), 7.17–7.08 (m, 2 H, H_{Ar}), 2.74 (br s, 3 H, H_7).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 148.7 (C_8), 145.5 (C_3), 136.5 (C_5), 132.0 (C_6), 130.4 (C_2), 125.3 (C_1), 122.6 (C_9), 112.5 (C_{10}), 22.6 (C_7).

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.22.

The spectral data were consistent with the literature.[170]

4,4,5,5-tetramethyl-2-(3-methylbenzyl)-1,3,2-dioxaborolane (3.16)



Chemical Formula: $C_{14}H_{21}BO_2$
Exact Mass: 232.1635

Prepared according to General Procedure C using *m*-tolylboronic acid (27.2 mg, 0.20 mmol). The crude (78% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (30.3 mg, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (t, *J* = 7.4 Hz, 1 H, H_6), 6.99 (d, *J* = 8.6 Hz, 2 H, $H_{1,5}$), 6.94 (d, *J* = 7.6 Hz, 1 H, H_3), 2.30 (s, 3 H, H_7), 2.26 (s, 2 H, H_8), 1.24 (s, 12 H, H_{10}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.6 (C_4), 137.9 (C_2), 130.0 (C_{Ar}), 128.3 (C_6), 126.1 (C_{Ar}), 125.7 (C_3), 83.5 (C_9), 24.9 (C_{10}), 21.6 (C_7).

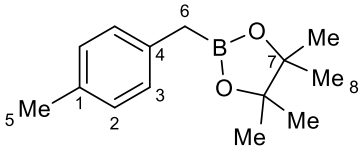
^{11}B NMR (96 MHz, $CDCl_3$) δ 32.97.

The spectral data were consistent with the literature.[259]

Also prepared according to General Procedure C with a slight modification using *m*-tolylboronic acid (27.2 mg, 0.20 mmol) as the substrate, but PhOMe (0.8 mL, 0.25 M) was used as the solvent and the reaction time was 6 h. The crude (49% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (16.9 mg, 39%).

Also prepared according to General Procedure C with a slight modification using *m*-tolylboronic acid (27.2 mg, 0.20 mmol) as the substrate, but PhMe (2.0 mL, 1.0 M) was used as the solvent. The crude (75% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (31.6 mg, 73%).

4,4,5,5-tetramethyl-2-(4-methylbenzyl)-1,3,2-dioxaborolane (3.17)



Chemical Formula: $C_{14}H_{21}BO_2$
Exact Mass: 232.1635

Prepared according to General Procedure C using *p*-tolylboronic acid (27.2 mg, 0.20 mmol). The crude (90% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (40.9 mg, 88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (m, $H_{2,3}$), 2.30 (s, 3 H, H_5), 2.25 (s, 2 H H_6), 1.23 (s, 12 H, H_8).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 135.5 (C_{Ar}), 134.3 (C_{Ar}), 129.1 (C_{Ar}), 129.0 (C_{Ar}), 83.5 (C_7), 24.9 (C_8), 21.1 (C_5).

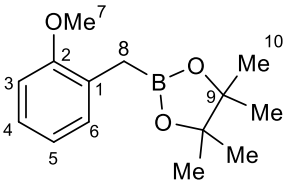
^{11}B NMR (96 MHz, $CDCl_3$) δ 33.00.

The spectral data were consistent with the literature.[259]

Also prepared according to General Procedure C with a slight modification using *p*-tolylboronic acid (27.2 mg, 0.20 mmol) as the substrate, but PhOMe (0.8 mL, 0.25 M) was used as the solvent and the reaction time was 6 h. The crude (32% ^1H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (13.0 mg, 39%).

Also prepared according to General Procedure C with a slight modification using *p*-tolylboronic acid (27.2 mg, 0.20 mmol) as the substrate, but PhMe (2.0 mL, 0.10 M) was used as the solvent. The crude (84% ^1H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (26.7 mg, 80%).

2-(2-methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.18)



Chemical Formula: $C_{14}H_{21}BO_3$
Exact Mass: 248.1584

Prepared according to General Procedure C using 2-methoxybenzeneboronic acid (24.0 mg, 0.14 mmol). The crude (91% ^1H NMR yield) was subject to column chromatography on silica gel (1–4% Et_2O in hexane) to afford the title compound as a white solid (41.0 mg, 83%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.4 Hz, 2 H, $H_{3,6}$) 6.88 (td, *J* = 7.4, 1.2 Hz, 1 H, H_4), 6.84–6.79 (m, 1 H, H_5), 3.82 (s, 3 H, H_7), 2.21 (s, 2 H, H_8), 1.26 (s, 12 H, H_{10}).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.2 (C_2), 130.5 (C_6), 128.0 (C_1), 126.3 (C_3), 120.5 (C_4), 109.7 (C_5), 83.1 (C_9), 55 .1 (C_7), 24.7 (C_{10}), 15.3 (br., C_8). C_8 weak and confirmed by the HSQC cross-peak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.57.

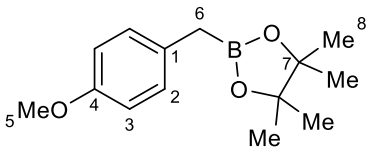
The spectral data were consistent with the literature.[262]

Also prepared according to General Procedure C with a slight modification using 2-methoxybenzeneboronic acid (30.4 mg, 0.20 mmol) as the substrate, but PhOMe (0.8 mL, 0.25 M) was used as the solvent and the reaction time was 6 h. The crude (51% ^1H NMR yield)

was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (21.4 mg, 45%).

Also prepared according to General Procedure C with a slight modification using 2-methoxybenzeneboronic acid (30.4 mg, 0.20 mmol) as the substrate, but PhMe (2.0 mL, 0.10 M) was used as the solvent. The crude (58% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (25.2 mg, 53%).

2-(4-methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.19)



Chemical Formula: $C_{14}H_{21}BO_3$
Exact Mass: 248.1584

Prepared according to General Procedure C using 4-methoxybenzeneboronic acid (30.4 mg, 0.20 mmol). The crude (92% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5–1% Et_2O in hexane) to afford the title compound as a white solid (43.0 mg, 87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13–7.06 (m, 2 H, H_2), 6.82–6.76 (m, 2 H, H_3), 3.77 (s, 3 H, H_5), 2.22 (s, 2 H, H_6), 1.23 (s, 12 H, H_8).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.2 (C_4), 130.6 (C_1), 129.9 (C_3), 113.9 (C_2), 83.5 (C_7), 55.3 (C_5), 24.9 (C_8), *ca*. 19.1 (C_6). C_6 weak and broad and was confirmed by the HSQC cross-peak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.47.

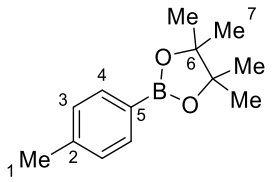
The spectral data were consistent with the literature.[259]

Also prepared according to General Procedure C with a slight modification using 4-methoxybenzeneboronic acid (30.4 mg, 0.20 mmol) as the substrate, but PhOMe (0.8 mL, 0.25 M) was used as the solvent and the reaction time was 6 h. The crude (64% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (25.2 mg, 51%).

Also prepared according to General Procedure C with a slight modification using 4-methoxybenzeneboronic acid (30.4 mg, 0.20 mmol) as the substrate, but PhMe (1.0 mL, 0.10 M) was used as the solvent. The crude (50% ^{1}H NMR yield) was subject to column

chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (23.7 mg, 48%).

4,4,5,5-tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane (3.21)



Chemical Formula: $C_{13}H_{19}BO_2$
Exact Mass: 218.1478

Prepared according to General Procedure E using 4-tolyboronic acid (3.00 g, 22.1 mmol, 1.00 equiv) and pinacol (2.87 g, 24.3 mmol, 1.10 equiv) and Na_2SO_4 (7.84 g, 55.2 mmol, 2.5 equiv) with THF as the solvent. Following workup, the desired product was obtained as a white solid and no further purification was required (4.98 g, quant.).

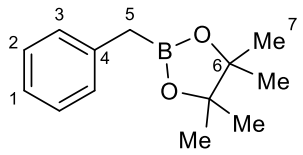
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73–7.68 (m, 2 H, H_3), 7.21–7.16 (m, 2 H, H_4), 2.36 (s, 3 H, H_1), 1.34 (s, 12 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 141.6 (C_2), 134.9 (C_3), 128.7 (C_4), 83.8 (C_6), 25.0 (C_1), 21.9 (C_7).

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.24.

These data were consistent with that of the literature.[263]

2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.22)



Chemical Formula: $C_{13}H_{19}BO_2$
Exact Mass: 218.1478

Prepared according to General Procedure C using phenylboronic acid (24.4 mg, 0.20 mmol) and PhMe (2.0 mL, 0.10 M) was the solvent. The crude (75% ^{1}H NMR yield) was subject to column chromatography on silica gel (1–2% Et_2O in hexane) to afford the title compound as a colourless oil (27.5 mg, 63%).

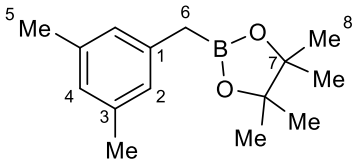
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.5 Hz, 2 H, H_3), 7.21–7.16 (m, 2 H, H_2), 7.15–7.10 (m, 1 H, H_1), 2.30 (s, 2 H, H_5), 1.24 (s, 12 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.8 (C_4), 129.1 (C_2), 128.4 (C_3), 125.0 (C_1), 83.5 (C_6), 24.9 (C_7), 20.4 (br., C_5). C_5 identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.26.

The spectral data were consistent with the literature.[264]

2-(3,5-dimethylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.23)



Chemical Formula: $C_{15}H_{23}BO_2$
Exact Mass: 246.1791

Prepared according to General Procedure C using (3,5-dimethylphenyl)boronic acid (39.6 mg, 0.20 mmol). The crude (91% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (23.8 mg, 48%).

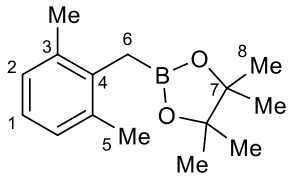
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (s, 2 H, H_2), 6.77 (s, 1 H, H_4), 2.27 (s, 6 H, H_5), 2.22 (s, 2 H, H_6), 1.24 (s, 12 H, H_8).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.5 (C_4), 137.7 (C_1), 127.0 (C_2), 126.7 (C_4), 83.5 (C_7), 24.8 (C_8), 21.4 (C_5), 19.8 (C_6). C_6 identified by the HSQC cross-peak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.92.

The spectral data were consistent with the literature.[262]

2-(2,6-dimethylbenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.24)



Chemical Formula: $C_{15}H_{23}BO_2$
Exact Mass: 246.1791

Prepared according to General Procedure C using (2,6-dimethylphenyl)boronic acid (30.0 mg, 0.20 mmol). The crude (57% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.1–0.5% Et_2O in hexane) to afford the title compound as a white solid (21.9 mg, 44%).

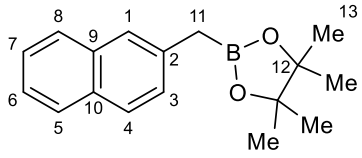
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01–6.92 (m, 3 H, $H_{1,2}$), 2.39 (s, 6 H, H_5), 2.25 (s, 2 H, H_6), 1.21 (s, 12 H, H_8).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.7 (C_4), 135.8 (C_3), 127.7 (C_2), 124.6 (C_1), 83.4 (C_7), 24.8 (C_8), 21.0 (C_5), *ca*. 14.8 (C_6). C_6 identified by the HSQC crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.06.

The spectral data were consistent with the literature.[259]

4,4,5,5-tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborolane (3.25)



Chemical Formula: $C_{17}H_{21}BO_2$
Exact Mass: 268.1635

Prepared according to General Procedure C using 2-naphthaleneboronic acid (24.0 mg, 0.14 mmol). The crude (71% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a white solid (25.8 mg, 69%).

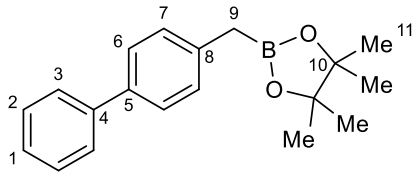
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.70 (m, 3 H, $H_{4,5,8}$), 7.68–7.59 (m, 1 H, H_1), 7.46–7.30 (m, 3 H, $H_{3,6,7}$), 2.46 (s, 2 H, H_{11}), 1.24 (s, 12 H, H_{13}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.3 (C_2), 133.8, 131.5, 128.2, 127.7, 127.56, 127.3, 126.6 (C_1), 125.7, 124.70, 83.5 (C_{12}), 20.3 (C_{11}), 24.8 (C_{13}). C_{11} identified by the HSQC cross-peak due to quadrupolar relaxation of the α-boron atom. For those unassigned, C_{Ar}.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.43.

The spectral data were consistent with the literature.[265]

2-([1,1'-biphenyl]-4-ylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.26)



Chemical Formula: $C_{19}H_{23}BO_2$
Exact Mass: 294.1791

Prepared according to General Procedure C using 4-biphenylboronic acid (39.6 mg, 0.20 mmol). The crude (63% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a white solid (34.7 mg, 59%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.55 (m, 2 H, H_3), 7.52–7.46 (m, 2 H, H_7), 7.46–7.38 (m, 2 H, H_2), 7.36–7.28 (m, 1 H, H_1), 7.28–7.23 (m, 2 H, H_2) 2.34 (s, 2 H, H_9), 1.26 (s, 12 H, H_{11}).

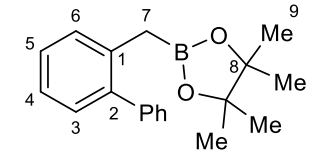
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 141.4 (C_8), 138.0 (C_{Ar}), 137.9 (C_{Ar}), 129.5 (C_6), 128.8 (C_2), 127.2 (C_7), 127.1 (C_3), 127.0 (C_1), 83.6 (C_{10}), 24.9 (C_{11}), 19.8 (C_9). C_9 identified by the HSQC cross-peak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.89.

The spectral data were consistent with the literature.[266]

The substrate was also prepared according to General Procedure D using 4-biphenylboronic acid (990 mg, 5.0 mmol). The crude was subject to column chromatography on silica gel (0–1% Et_2O in hexane) to afford the title compound as a white solid (691 mg, 47%). The loss of yield on scaleup was accounted for by coelution with the speciated byproduct.

2-([1,1'-biphenyl]-2-ylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.27)



Chemical Formula: $C_{19}H_{23}BO_2$
Exact Mass: 294.1791

Prepared according to General Procedure C using 4-biphenylboronic acid (39.6 mg, 0.20 mmol). The crude (90% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (50.0 mg, 85%).

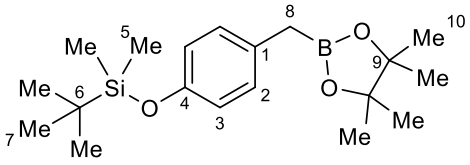
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.29 (m, 5 H, H_{Ar}), 7.23–7.17 (m, 2 H, H_{Ar}), 2.29 (s, 2 H, H_7), 1.15 (s, 12 H, H_9).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 142.4, 141.8 (C_1), 136.7, 130.3, 130.1, 129.6, 128.1, 127.4, 126.8, 125.3, 83.4 (C_8), 24.9 (C_9), 18.7 (C_7). C_7 identified by the HSQC cross-peak due to quadrupolar relaxation of the α-boron atom. For those unassigned, C_{Ar}.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.58.

The spectral data were consistent with the literature.[259]

***tert*-butyldimethyl(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)phenoxy)silane (3.28)**



Chemical Formula: $C_{19}H_{33}BO_3Si$
Exact Mass: 348.2292

Prepared according to General Procedure C using 4-(*tert*-butyldimethylsilyl)phenylboronic acid (50.4 mg, 0.20 mmol). The crude (93% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a white solid (58.6 mg, 84%).

IR (ATR, film) υ 2930, 2859, 2361, 2342, 1508, 1256, 1144, 916, 839 cm^{-1}.

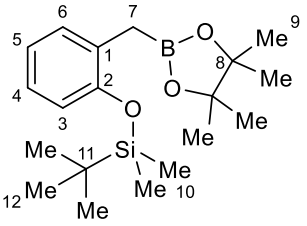
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05–7.00 (m, 2 H, H_2), 6.74–6.68 (m, 2 H, H_3), 2.21 (s, 2 H, H_8), 1.22 (s, 12 H, H_{10}), 0.97 (s, 9 H, H_7), 0.17 (s, 6 H, H_5).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.1 (C_4), 131.2 (C_1), 129.9 (C_2), 120.0 (C_3), 83.5 (C_9), 29.9 (C_6), 25.9 (C_7), 24.8 (C_{10}), 19.0 (C_8), 18.3, −4.3 (C_5). C_8 identified by the HSQC crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.96.

HRMS (EI) Exact mass calculated for $C_{19}H_{33}BO_4Si$ $[M+O]^{+\bullet}$ *m/z* = 364.2236; found 364.2225.

***tert*-butyldimethyl(2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)phenoxy)silane (3.29)**



Chemical Formula: $C_{19}H_{33}BO_3Si$
Exact Mass: 348.2292

Prepared according to General Procedure C using 2-((*tert*-butyldimethylsilyl)oxy)phenyl)boronic acid (50.4 mg, 0.20 mmol). The crude (98% ^1H NMR yield) was subject to column chromatography on silica gel (0–1% Et_2O in hexane) to afford the title compound as a white residue (62.1 mg, 91%).

IR (ATR, film) υ 2361, 2342, 1489, 1327, 1252, 1144, 924, 837, 779 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 7.5, 1.8 Hz, 1 H, H_6), 7.01 (td, *J* = 7.7, 1.8 Hz, 1 H, H_4), 6.85 (t, *J* = 7.4 Hz, 1 H, H_5), 6.76 (d, *J* = 8.0 Hz, 1 H, H_3), 2.24 (s, 2 H, H_7), 1.22 (s, 12 H, H_9), 1.01 (s, 9 H, H_{12}), 0.22 (s, 6 H, H_{10}).

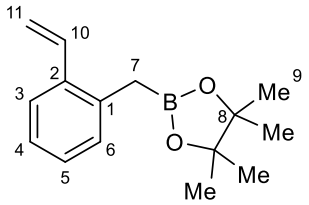
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.4 (C_1), 130.8 (C_6), 130.1 (C_2), 126.0 (C_4), 121.1 (C_5), 118.6 (C_3), 83.3 (C_8), 26.1 (C_{12}), 24.9 (C_9), 18.5 (C_{11}), 14.7 (br, C_7), −4.0 (C_{10}). C_7 was confirmed by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 34.07

HRMS (EI) Exact mass calculated for $C_{19}H_{33}BO_3Si$ $[M]^{+\bullet}$ *m/z* = 348.22865; found 348.22810.

The substrate was also prepared according to General Procedure C using 2-((*tert*-butyldimethylsilyl)oxy)phenyl)boronic acid (504 mg, 2.0 mmol). The crude was subject to column chromatography on silica gel (1–2% Et_2O in hexane) to afford the title compound as a colourless oil (990 mg, 81%).

4,4,5,5-tetramethyl-2-(2-vinylbenzyl)-1,3,2-dioxaborolane (3.30)



Chemical Formula: $C_{15}H_{21}BO_2$
Exact Mass: 244.1635

Prepared according to General Procedure C using 2-vinylphenylboronic acid (29.6 mg, 0.20 mmol). The crude (70% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5–1% Et_2O in hexane) to afford the title compound as a colourless oil (32.8 mg, 67%).

IR (ATR, film) υ 2978, 2361, 2342, 1329, 1141, 966, 847 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 7.2 Hz, 1 H, H_{Ar}), 7.14 (d, J = 10.9 Hz, 3 H, H_{Ar}), 6.96 (dd, J = 17.3, 10.9 Hz, 1 H, H_{10}), 5.64–5.57 (m, 1 H, $H_{11\text{-}trans}$), 5.26 (d, J = 10.9 Hz, 1 H, $H_{11\text{-}cis}$), 2.33 (s, 2 H, H_7), 1.22 (s, 12 H, H_9).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.8 (C_2), 136.7 (C_{10}), 135.5 (C_{Ar}), 130.2 (C_{Ar}), 127.9 (C_1), 125.7 (C_{Ar}), 125.6 (C_{Ar}), 115.3 (C_{11}), 83.6 (C_8), 24.9 (C_9), *ca*. 18.4 (C_7). C_7 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

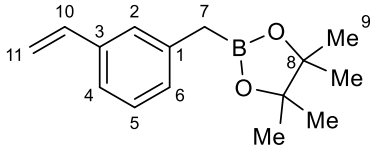
^{11}B NMR (96 MHz, $CDCl_3$) δ 33.16.

HRMS (EI) Exact mass calculated for $C_{15}H_{21}BO_2$ $[M]^{+\bullet}$ m/z = 244.1629; found 244.1631.

The substrate was also prepared according to General Procedure D using 2-vinylphenylboronic acid (990 mg, 5.0 mmol). The crude was subject to column chromatography on silica gel (0–1% Et_2O in hexane) to afford the title compound as a colourless oil (990 mg, 81%).

4,4,5,5-tetramethyl-2-(3-vinylbenzyl)-1,3,2-dioxaborolane (3.31)

Prepared according to General Procedure C using 3-vinylphenylboronic acid (29.6 mg, 0.20 mmol). The crude (69% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5% Et_2O in hexane) to afford the title compound as a colourless oil (35.2 mg, 72%).



Chemical Formula: $C_{15}H_{21}BO_2$
Exact Mass: 244.1635

IR (ATR, film) υ 2978, 2926, 2361, 2342, 1329, 1141, 989, 669 cm^{-1}.

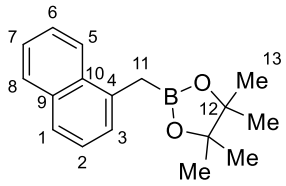
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (br s, 1 H, H_2), 7.23–7.15 (m, 2 H, $H_{4,6}$), 7.09 (dt, J = 6.9, 2.0 Hz, 1 H, H_5), 6.68 (dd, J = 17.6, 10.9 Hz, 1 H, H_{10}), 5.72 (dd, J = 17.6, 1.0 Hz, 1 H, $H_{11\text{-}trans}$), 5.20 (dd, J = 10.9, 1.0 Hz, 1 H, $H_{11\text{-}cis}$), 2.29 (s, 2 H, C_7), 1.23 (s, 12 H, C_9).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 139.0 (C_1), 137.6 (C_3), 137.3 (C_{10}), 128.7 (C_5), 128.6 (C_4), 127.1 (C_2), 123.0 (C_6), 113.5 (C_{11}), 83.6 (C_8), 24.9 (C_9), 20.0 (C_7). C_7 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.32.

HRMS (EI) Exact mass calculated for $C_{15}H_{21}BO_2$ $[M]^{+\bullet}$ *m/z* = 244.1629; found 244.1634.

4,4,5,5-tetramethyl-2-(naphthalen-1-ylmethyl)-1,3,2-dioxaborolane (3.32)



Chemical Formula: $C_{17}H_{21}BO_2$
Exact Mass: 268.1635

Prepared according to General Procedure C using 1-naphthylboronic acid (34.4 mg, 0.20 mmol). The crude (91% ^1H NMR yield) was subject to column chromatography on silica gel (0–5% Et_2O in hexane) to afford the title compound as a colourless oil (46.7 mg, 87%).

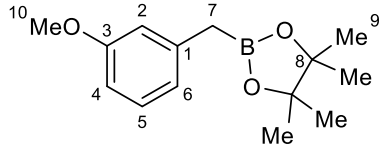
^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.2, 1.6 Hz, 1 H, H_8), 7.84 (dd, *J* = 7.6, 1.7 Hz, 1 H, H, H_5), 7.70–7.65 (m, 1 H, H_1), 7.48 (dqd, *J* = 8.2, 6.8, 1.5 Hz, 2 H, $H_{6,7}$), 7.42–7.33 (m, 2 H, $H_{2,3}$), 2.71 (s, 2 H, H_{11}), 1.21 (s, 12 H, H_{13}).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 135.7 (C_4), 133.9 (C_9), 132.6 (C_{10}), 128.6 (C_5), 126.6 (C_3), 125.9 (C_1), 125.7(C_2), 125.5 (C_6), 125.5 (C_7), 124.6 (C_8), 83.7 (C_{12}), 24.8 (C_{13}).

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.28.

The spectral data were consistent with the literature.[267]

2-(3-methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.33)



Chemical Formula: $C_{14}H_{21}BO_3$
Exact Mass: 248.1584

Prepared according to General Procedure C using 3-methoxybenzeneboronic acid (30.4 mg, 0.20 mmol). The crude (86% ^1H NMR yield) was subject to column chromatography on silica gel (0.5–1% Et_2O in hexane) to afford the title compound as a colourless oil (40.7 mg, 82%).

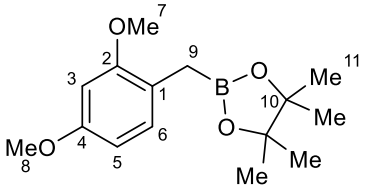
^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.8 Hz, 1 H, H_5), 6.80–6.73 (m, 2 H, $H_{4,6}$), 6.68 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1 H, H_2), 3.78 (s, 3 H, H_{10}), 2.27 (s, 2 H, H_7), 1.24 (s, 12 H, H_9).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.7 (C_3), 140.3 (C_1), 129.3 (C_5), 121.7 (C_4), 114.8 (C_6), 110.6 (C_2), 83.6 (C_8), 55.2 (C_{10}), 24.9 (C_9), 20.2 (C_7). C_7 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.13.

The spectral data were consistent with the literature.[265]

2-(2,4-dimethoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.34)



Chemical Formula: $C_{15}H_{23}BO_4$
Exact Mass: 278.1689

Prepared according to General Procedure C using 2,4-dimethoxybenzeneboronic acid (36.4 mg, 0.20 mmol). The crude (86% ^1H NMR yield) was subject to column chromatography on silica gel (1–4% Et_2O in hexane) to afford the title compound as a white solid (45.1 mg, 81%).

IR (ATR, film) υ 2361, 2342, 1558, 1506, 1207, 1146 cm^{-1}.

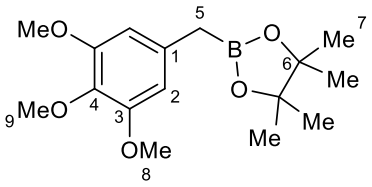
^1H NMR (500 MHz, $CDCl_3$) δ 7.06–7.00 (m, 1 H, H_6), 6.41 (d, *J* = 2.5 Hz, 1 H, H_3), 6.39 (dd, *J* = 8.1, 2.5 Hz, 1 H, H_5), 3.77 (br. s 6 H, $H_{7,8}$), 2.10 (s, 2 H, H_9), 1.23 (s, 12H, H_{11}).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 158.7 (C_4), 158.0 (C_1), 130.5 (C_6), 120.3 (C_2), 103.9 (C_5), 98.4 (C_3), 83.2 (C_{10}), 55.4 (C_{OMe}), 55.2 (C_{OMe}), 24.8 (C_{11}), *ca*. 14.3 (C_9). C_9 identified by the HSQC cross-peak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 34.34.

HRMS (EI) Exact mass calculated for $C_{15}H_{23}BO_4$ $[M]^{+\bullet}$ *m/z* = 294.1633; found 294.1643.

4,4,5,5-tetramethyl-2-(3,4,5-trimethoxybenzyl)-1,3,2-dioxaborolane (3.35)



Chemical Formula: $C_{16}H_{25}BO_5$
Exact Mass: 308.1795

Prepared according to General Procedure C using 3,4,5-trimethoxyphenylboronic acid (42.4 mg, 0.20 mmol). The crude (69% ^1H NMR yield) was subject to column chromatography on silica gel (0.5–4% Et_2O in hexane) to afford the title compound as a colourless oil (35.7 mg, 58%).

IR (ATR, film) υ 2976, 2930, 2361, 2342, 1587, 1506, 1456, 1323, 1123, 1009, 962, 847 cm^{-1}.

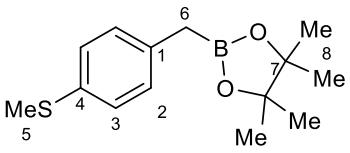
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (s, 2 H, H_2), 3.86 (s, 6 H, H_8), 3.84 (s, 3 H, H_9), 2.26 (s, 2 H, H_5), 1.28 (s, 12 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.1 (C_3), 135.5 (C_1), 134.3 (C_4), 106.0 (C_2), 83.6 (C_6), 61.0 (C_9), 56.1 (C_8), 24.9 (C_7), *ca*. 20.4 (C_5). C_5 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.32.

HRMS (EI) Exact mass calculated for $C_{16}H_{25}BO_5$ $[M+O]^{+\bullet}$ *m/z* = 324.1734; found 324.1749.

4,4,5,5-tetramethyl-2-(4-(methylthio)benzyl)-1,3,2-dioxaborolane (3.36)



Chemical Formula: $C_{14}H_{21}BO_2S$
Exact Mass: 264.1355

Prepared according to General Procedure C using 4-(methylthio)benzeneboronic acid (33.6 mg, 0.20 mmol). The crude (61% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (26.4 mg, 50%).

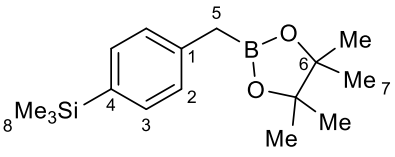
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19–7.14 (m, 2 H, H_3), 7.14–7.08 (m, 2 H, H_2), 2.45 (s, 3 H, H_5), 2.25 (s, 2 H. H_6), 1.23 (s, 12 H, H_8).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.9 (C_1), 134.0 (C_4), 129.6 (C_2), 127.4 (C_3), 83.5 (C_7), 24.7 (C_8), *ca*. 19.4 (C_6), 16.5 (C_5). C_6 identified by the HSQC cross-peak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.26.

The spectral data were consistent with the literature.[268]

trimethyl(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)phenyl)silane (3.37)



Chemical Formula: $C_{16}H_{27}BO_2Si$
Exact Mass: 290.1873

Prepared according to General Procedure C using 4-(trimethylsilyl)phenylboronic acid (38.8 mg, 0.20 mmol). The crude (87% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.2% Et_2O in hexane) to afford the title compound as a colourless oil (48.8 mg, 84%).

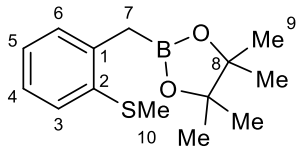
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.33 (m, 2 H, H_3), 7.22–7.14 (m, 2 H, H_2), 2.29 (s, 2 H, H_5), 1.24 (s, 12 H, H_7), 0.24 (s, 9 H, H_8).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 139.5 (C_1), 136.1 (C_4), 133.5 (C_3), 128.7 (C_2), 83.6 (C_6), 24.9 (C_7), 20.1 (C_5), −0.9 (C_8). C_7 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the a-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.60.

The spectral data were consistent with the literature.[264]

4,4,5,5-tetramethyl-2-(2-(methylthio)benzyl)-1,3,2-dioxaborolane (3.38)



Chemical Formula: $C_{14}H_{21}BO_2S$
Exact Mass: 264.1355

Prepared according to General Procedure C using 2-(methylthio)phenylboronic acid (33.6 mg, 0.20 mmol). The crude (81% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5% Et_2O in hexane) to afford the title compound as a colourless oil (38.9 mg, 74%).

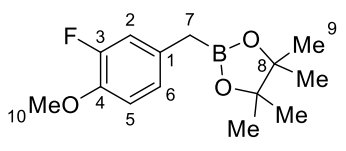
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 7.8, 1.4 Hz, 1 H, H_6), 7.14 (dq, *J* = 7.6, 7.0, 3.1 Hz, 2 H, $H_{4,5}$), 7.07 (td, *J* = 7.4, 1.4 Hz, 1 H, H_3), 2.44 (s, 3 H, H_{10}), 2.37 (s, 2 H, H_7), 1.24 (s, 12 H, H_9).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.4 (C_2), 137.0 (C_1), 129.8 (C_4), 126.8 (C_5), 126.1 (C_6), 125.5 (C_3), 83.6 (C_8), 24.9 (C_9), 16.7 (C_{10}).

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.05.

The spectral data were consistent with the literature.[269]

2-(3-fluoro-4-methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.39)



Chemical Formula: $C_{14}H_{20}BFO_3$
Exact Mass: 266.1490

Prepared according to General Procedure C using 3-fluoro-4-methoxyphenylboronic acid (34.0 mg, 0.20 mmol). The crude (80% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5% Et_2O in hexane) to afford the title compound as a colourless oil (41.5 mg, 78%).

IR (ATR, film) υ 2979, 2927, 2355, 1514, 1348, 1328, 1269, 1142, 846 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (dd, *J* = 12.6, 2.0 Hz, 1 H, H_2), 6.86 (dd, *J* = 8.5, 2.0 Hz, 1 H, H_5), 6.83 (t, *J* = 8.2 Hz, 1 H, H_6), 3.84 (s, 3 H, H_{10}), 2.21 (s, 2 H, H_7), 1.23 (s, 12 H, H_9).

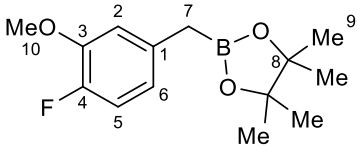
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.3 (d, $^1J_{CF}$ = 244.4 Hz, C_3), 145.1 (d, $^2J_{CF}$ = 10.9 Hz, C_4), 131.8 (d, $^3J_{CF}$ = 6.7 Hz, C_1), 124.5 (d, $^3J_{CF}$ = 3.5 Hz, C_5), 116.9 (d, $^2J_{CF}$ = 18.1 Hz, C_2), 113.6 (d, $^4J_{CF}$ = 2.4 Hz, C_6), 83.7 (C_8), 56.5 (C_{10}), 24.9 (C_9), 19.0 (C_7). C_7 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.94.

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ −136.07.

HRMS (EI) Exact mass calculated for $C_{14}H_{20}BFO_3$ $[M]^{+\bullet}$ *m/z* = 266.14840; found 266.1245.

2-(4-fluoro-3-methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.40)



Chemical Formula: $C_{14}H_{20}BFO_3$
Exact Mass: 266.1490

Prepared according to General Procedure C using 4-fluoro-3-methoxyphenylboronic acid (34.0 mg, 0.20 mmol). The crude (78% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5% Et_2O in hexane) to afford the title compound as a colourless oil (38.9 mg, 73%).

IR (ATR, film) υ 2978, 2933, 2361, 2342, 1608, 1516, 1329, 1142, 1036, 847 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 11.4, 8.2 Hz, 1 H, H_5), 6.79 (dd, *J* = 8.3, 2.1 Hz, 1 H, H_6), 6.68 (ddd, *J* = 8.2, 4.3, 2.1 Hz, 1 H, H_2), 3.86 (s, 3 H, H_{10}), 2.24 (s, 2 H, H_7), 1.24 (s, 12 H, H_9).

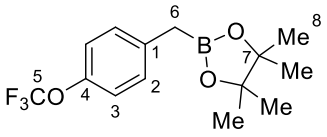
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.50 (d, $^1J_{CF}$ = 241.6 Hz, C_4), 147.19 (d, $^2J_{CF}$ = 10.8 Hz, C_3), 134.85 (d, $^4J_{CF}$ = 3.8 Hz, C_1), 121.05 (d, $^3J_{CF}$ = 6.4 Hz, C_2), 115.71 (d, $^2J_{CF}$ = 17.9 Hz, C_5), 114.25 (d, $^3J_{CF}$ = 1.5 Hz, C_6), 83.7, (C_8), 56.2 (C_{10}), 24.9 (C_9) *ca*. 19.9 (C_7). C_7 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.99.

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ −141.34.

HRMS (ESI+) Exact mass calculated for $C_{14}H_{21}BFO_3$ $[M+H]^+$ *m/z* = 267.1562; found 267.1571.

4,4,5,5-tetramethyl-2-(4-(trifluoromethoxy)benzyl)-1,3,2-dioxaborolane (3.41)



Chemical Formula: $C_{14}H_{18}BF_3O_3$
Exact Mass: 302.1301

Prepared according to General Procedure C using 4-(trifluoromethoxy)phenylboronic acid (36.4 mg, 0.20 mmol). The crude (74% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5% Et_2O in hexane) to afford the title compound as a white solid (39.3 mg, 65%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.15 (m, 2 H, H_2), 7.11–7.04 (m, 2 H, H_3), 2.29 (s, 2 H, H_6), 1.24 (s, 12 H, H_8).

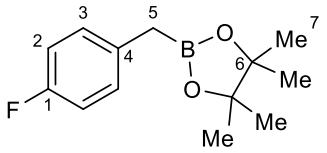
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 146.9 (C_4), 137.6 (C_1), 130.3 (C_2), 121.0 (C_3), 120.7 (q, $^1J_{CF}$ = 256.24 Hz, C_5) 83.7 (C_7), 24.9 (C_8), 19.5 (C_6). C_6 identified by the HSQC cross-peak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.03.

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ −57.91.

The spectral data were consistent with the literature.[265]

2-(4-fluorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.42)



Chemical Formula: $C_{13}H_{18}BFO_2$
Exact Mass: 236.1384

Prepared according to General Procedure C using 4-fluorobenzeneboronic acid (28.0 mg, 0.20 mmol). The crude (81% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–5% Et_2O in hexane) to afford the title compound as a colourless oil (32.6 mg, 69%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.08 (m, 2 H, H_3), 6.97–6.88 (m, 2 H, H_2), 2.25 (s, 2 H), 1.23 (s, 12 H).

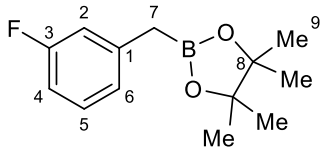
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.9 (d, $^1J_{CF}$ = 242.0 Hz, C_1), 134.2 (d, $^4J_{CF}$ = 3.4 Hz, C_4), 130.3 (d, $^3J_{CF}$ = 7.6 Hz, C_3) 115.1 (d, $^2J_{CF}$ = 21.2 Hz, C_2), 83.6 (C_6), 24.9 (C_7).

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.69.

^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −119.37.

The spectral data were consistent with the literature.[259]

2-(3-fluorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.43)



Chemical Formula: $C_{13}H_{18}BFO_2$
Exact Mass: 236.1384

Prepared according to General Procedure C using 3-fluorobenzeneboronic acid (28.0 mg, 0.20 mmol). Anisole (0.8 mL, 0.25 M) were used as the solvent and the reaction time was 6 h. The crude (60% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–10% Et_2O in hexane) to afford the title compound as a colourless oil (22.0 mg, 47%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (td, *J* = 7.9, 6.2 Hz, 1 H, H_5), 6.97–6.92 (m, 1 H, C_6), 6.90 (dt, *J* = 10.3, 2.1 Hz, 1 H, H_2), 6.81 (td, *J* = 8.4, 2.4 Hz, 1 H, H_4), 2.29 (s, 2 H, H_7), 1.24 (s, 12 H, H_9).

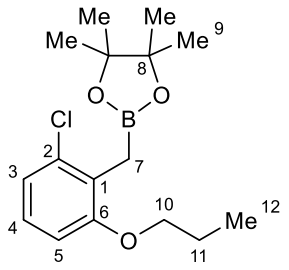
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) d 163.01 (d, $^1J_{CF}$ = 244.3 Hz, C_3), 141.41 (d, $^3J_{CF}$ = 7.7 Hz, C_1), 129.64 (d, $^3J_{CF}$ = 8.6 Hz, C_5), 124.82 (d, $^4J_{CF}$ = 2.7 Hz, C_6), 115.98 (d, $^2J_{CF}$ = 21.0 Hz, C_2), 111.87 (d, $^2J_{CF}$ = 21.1 Hz, C_4), 83.72 (C_8), *ca*. 20.0 (C_7) 24.86 (C_9).

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.77.

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ −114.32.

The spectral data were consistent with the literature.[267]

2-(2-chloro-6-propoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.44)



Chemical Formula: $C_{16}H_{24}BClO_3$
Exact Mass: 310.1507

Prepared according to General Procedure C using 2-chloro,6-propoxyphenylboronic acid (42.9 mg, 0.20 mmol). The crude (72% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5% Et_2O in hexane) to afford the title compound as a colourless oil (40.0 mg, 64%).

IR (ATR, film) υ 2976, 2930, 2361, 2342, 1348, 1327, 1144, 982, 662 cm^{-1}.

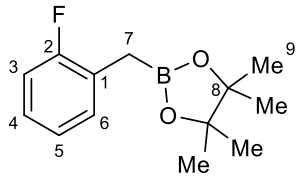
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 2.6 Hz, 1 H, H_3), 7.04 (dd, *J* = 8.6, 2.7 Hz, 1 H, H_4), 6.69 (d, *J* = 8.6 Hz, 1 H, H_5), 3.87 (t, *J* = 6.6 Hz, 2 H, H_{10}), 2.18 (s, 2 H, H_7), 1.80 (dtd, *J* = 14.0, 7.4, 6.5 Hz, 2 H, H_{11}), 1.23 (s, 12 H, H_9), 1.04 (t, *J* = 7.4 Hz, 3 H, H_{12}).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 155.5 (C_6), 130.3 (C_3), 130.2 (C_1), 125.9 (C_4), 125.0 (C_2), 112.0 (C_5), 83.4 (C_8), 69.9 (C_{10}), 24.9 (C_9), 22.9 (C_{11}), *ca*. 15.0 (C_7) 10.7 (C_{12}). C_7 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.60.

HRMS (EI) Exact mass calculated for $C_{16}H_{24}B^{35}ClO_4$ $[M+O]^{+\bullet}$ *m*/*z* = 326.1451; 326.1462.

2-(2-fluorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.45)



Chemical Formula: $C_{13}H_{18}BFO_2$
Exact Mass: 236.1384

Prepared according to General Procedure C using 3-fluorobenzeneboronic acid (28.0 mg, 0.20 mmol). The crude (60% ^1H NMR yield) was subject to column chromatography on silica gel (0.5–1.5% Et_2O in hexane) to afford the title compound in 74:26 ratio mixture with the undesired starting material pinacol ester (20.7 mg, 32% yield of desired product). Loss of yield was caused by partial decomposition during chromatography. Attempts to completely isolate the desired product from the starting material speciated pinacol ester (0.1% Et_2O in hexane) resulted in full decomposition upon concentration, so the mixture was characterised.

^1H NMR (500 MHz, $CDCl_3$) δ 7.22–7.16 (m, 1 H, H_6), 7.14–7.07 (m, 1 H, H_4), 7.04–6.95 (m, 2 H, $H_{5,6}$), 2.26 (s, 2 H, H_7), 1.24 (s, 12 H, H_9).

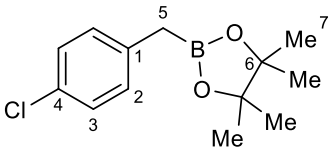
$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 161.2 (d, *J* = 243.6 Hz, C_2), 131.5 (d, *J* = 4.9 Hz, C_6), 126.8 (d, *J* = 7.9 Hz, C_4), 126.2 (d, *J* = 16.9 Hz, C_1), 124.0 (d, *J* = 3.6 Hz, C_5), 115.0 (d, *J* = 22.1 Hz, C_3), 83.7 (C_8), 24.8 (C_9).

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.40.

$^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ −116.87.

The spectral data were consistent with the literature.[259]

2-(4-chlorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.46)



Chemical Formula: $C_{13}H_{18}BClO_2$
Exact Mass: 252.1088

Prepared according to General Procedure C using 4-chlorobenzeneboronic acid (31.3 mg, 0.20 mmol) with a slight modification at 45 °C for 36 h. The crude (65% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5% Et_2O in hexane) to afford the title compound as a colourless oil (29.3 mg, 58%).

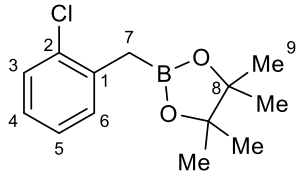
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.16 (m, 2 H, H_3), 7.14–7.07 (m, 2 H, H_2), 2.25 (s, 2 H, H_5), 1.23 (s, 12 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 137.3 (C_1), 130.7 (C_4), 130.4 (C_2), 128.4 (C_3), 83.7 (C_6), 24.9 (C_7), 19.6 (br, C_5). C_5 was confirmed by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.87.

The spectral data were consistent with the literature.[267]

2-(2-chlorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.47)



Chemical Formula: $C_{13}H_{18}BClO_2$
Exact Mass: 252.1088

Prepared according to General Procedure C using 2-chlorobenzeneboronic acid (31.3 mg, 0.20 mmol) with a slight modification at 45 °C for 36 h. The crude (45% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5% Et_2O in hexane) to afford the title compound as a white solid (21.6 mg, 43%).

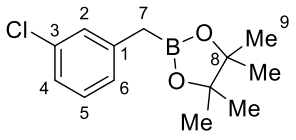
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.8, 1.4 Hz, 1 H, H_3), 7.22 (dd, *J* = 7.5, 1.8 Hz, 1 H, H_6), 7.14 (td, *J* = 7.4, 1.4 Hz, 1 H, H_5), 7.08 (td, *J* = 7.6, 1.8 Hz, 1 H, H_4), 2.38 (s, 2 H, H_7), 1.24 (s, 12 H, H_9).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 137.7 (C_1), 134.0 (C_2), 131.0 (C_6), 129.2 (C_3), 126.8 (C_5), 126.6 (C_4), 83.7 (C_8), 24.9 (C_9), 19.1 (C_7). C_7 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.09.

The spectral data were consistent with the literature.[267]

2-(3-chlorobenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.48)



Chemical Formula: $C_{13}H_{18}BClO_2$
Exact Mass: 252.1088

Prepared according to General Procedure C using 3-chlorobenzeneboronic acid (31.3 mg, 0.20 mmol) with a slight modification at 45 °C for 36 h. The crude (54% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5% Et_2O in hexane) to afford the title compound as a white solid (21.2 mg, 42%).

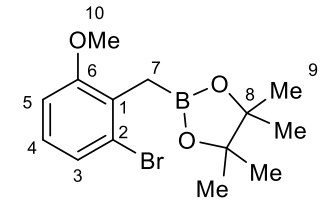
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16–7.18 (m, 1 H, H_2), 7.15 (br. d, *J* = 7.7 Hz, 1 H, H_4), 7.10 (dt, *J* = 8.1, 1.7 Hz, 1 H, H_5), 7.06 (ddt, *J* = 7.5, 1.7, 0.8 Hz, 1 H, H_6), 2.27 (s, 2 H, H_7), 1.23 (s, 12 H, H_9).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.9 (C_1), 134.0 (C_3), 129.6 (C_2), 129.2 (C_4), 127.3 (C_6), 125.2 (C_5), 83.8 (C_8), 24.9 (C_9), 20.0 (br, C_7). C_7 was confirmed by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.83.

The spectral data were consistent with the literature.[265]

2-(2-bromo-6-methoxybenzyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.49)



Chemical Formula: $C_{14}H_{20}BBrO_3$
Exact Mass: 326.0689

Prepared according to General Procedure C using 2-bromo,6-methoxyphenylboronic acid (46.2 mg, 0.20 mmol). The crude (29% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.2–2% Et_2O in hexane) to afford the title compound as a colourless oil (20.9 mg, 32%).

IR (ATR, film) υ 2978, 2928, 2359, 2342, 1489, 1348, 1242, 669 cm^{-1}.

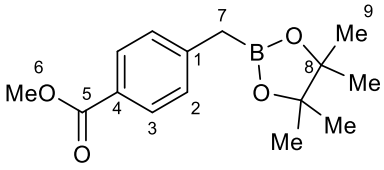
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.18 (m, 2 H, H_{Ar}), 6.66 (d, *J* = 8.6 Hz, 1 H, H_{Ar}), 3.77 (s, 3 H, H_{10}), 2.14 (s, 2 H, H_7), 1.23 (s, 12 H, H_9).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.5 (C_6), 133.2 (C_{Ar}), 130.6 (C_2), 129.0 (C_{Ar}), 112.8 (C_1), 111.4 (C_{Ar}), 83.4 (C_8), 55.4 (C_{10}), 24.8 (C_9). *ca*. 15.3 (C_7). C_7 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.52.

HRMS (EI) Exact mass calculated for $C_{14}H_{21}B^{79}BrO_3$ $[M+H]^{+\bullet}$ m/z = 327.0762; found 327.0762.

methyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)benzoate (3.50)



Chemical Formula: $C_{15}H_{21}BO_4$
Exact Mass: 276.1533

Prepared according to General Procedure C using 4-methoxycarbonylphenyl boronic acid (36.0 mg, 0.20 mmol): The crude (54% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5–1% Et_2O in hexane) to afford the title compound as a white solid (16.0 mg, 29%).

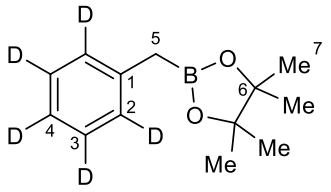
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95–7.86 (m, 2 H, H_2), 7.25–7.22 (m, 2 H, H_3), 3.89 (s, 3 H, H_6), 2.35 (s, 2 H, H_7), 1.22 (s, 12 H, H_9).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.5 (C_5), 144.9 (C_4), 129.8 (C_2), 129.1 (C_3), 127.0 (C_1), 83.8 (C_8), 52.1 (C_6), 24.8 (C_9), 20.4 (C_7).

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.30.

The spectral data were consistent with the literature.[265]

4,4,5,5-tetramethyl-2-((phenyl-*d*$_5$)methyl)-1,3,2-dioxaborolane (3.51)



Chemical Formula: $C_{13}H_{14}D_5BO_2$
Exact Mass: 223.1792

Prepared according to General Procedure C using phenylboronic acid-*d*$_5$ (25.3 mg, 0.20 mmol). The crude (81% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5–1% Et_2O in hexane) to afford the title compound as a colourless oil (26.8 mg, 64%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 2 H, H_5), 1.23 (s, 12 H, H_7).

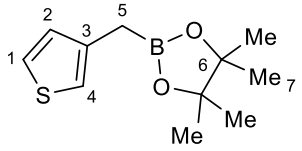
^{2}H NMR (77 MHz, $CHCl_3$) δ 7.17–7.29 (br. m, 5 D, $D_{2–4}$).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.6, 128.7 (t, $^1J_{CD}$ = 23.8 Hz), 127.9 (t, $^1J_{CD}$ = 23.3 Hz), 124.4 (t, $^1J_{CD}$ = 23.8 Hz), 83.5 (C_6), 24.9 (C_7).

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.36.

The spectral data were consistent with the literature.[270]

4,4,5,5-tetramethyl-2-(thiophen-3-ylmethyl)-1,3,2-dioxaborolane (3.52)



Chemical Formula: $C_{11}H_{17}BO_2S$
Exact Mass: 224.1042

Prepared according to General Procedure C using thiophene-3-boronic acid (25.6 mg, 0.20 mmol). The crude (74% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5–1% Et_2O in hexane) to afford the title compound as a colourless oil (19.4 mg, 43%).

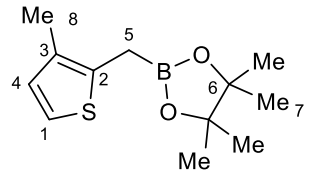
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 4.9, 3.0 Hz, 1 H, H_1), 6.98–6.91 (m, 2 H, $H_{2,4}$), 2.28 (s, 2 H, H_5), 1.25 (s, 12 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 137.7 (C_3), 129.6 (C_2), 124.9 (C_1), 120.2 (C_4), 83.6 (C_8), 24.9 (C_7), 13.9 (C_5). C_5 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.94.

The spectral data were consistent with the literature.[268]

4,4,5,5-tetramethyl-2-((3-methylthiophen-2-yl)methyl)-1,3,2-dioxaborolane (3.53)



Chemical Formula: $C_{12}H_{19}BO_2S$
Exact Mass: 238.1199

Prepared according to General Procedure C using 5-methylthiophene-2-boronic acid (28.4 mg, 0.20 mmol). The crude (78% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5–1% Et_2O in hexane) to afford the title compound as a colourless oil (33.8 mg, 71%).

IR (ATR, film) υ 2978, 2361, 2342, 1363, 1333, 1141, 996, 669 cm^{-1}.

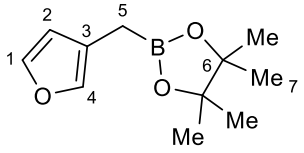
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (d, *J* = 3.3 Hz, 1 H, H_1), 6.51 (d, *J* = 3.4 Hz, 1 H, H_4), 2.40 (br s, 5 H, $H_{5,8}$), 1.27 (s, 12 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.0 (C_3), 137.1 (C_2), 125.0 (C_4), 124.7 (C_1), 83.8 (C_6), 24.9 (C_7), 15.4 (C_8).

^{11}B NMR (96 MHz, $CDCl_3$) δ 34.23. Boric acid (δ_B = 22.53 ppm) can be seen in the spectrum.

HRMS (EI) Exact mass calculated for $C_{12}H_{19}BO_2{}^{32}S$ $[M]^{+\bullet}$ *m/z* = 238.1193; found 238.10325.

2-(furan-3-ylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.54)



Chemical Formula: $C_{11}H_{17}BO_3$
Exact Mass: 208.1271

Prepared according to General Procedure C using furan-3-boronic acid (22.4 mg, 0.20 mmol). The crude (46% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5% Et_2O in hexane) to afford the title compound as a colourless oil (17.5 mg, 42%).

IR (ATR, film) υ 2920, 2851, 2359, 2342, 1261, 750, 669 cm^{-1}.

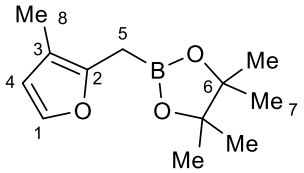
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 1.7 Hz, 1 H, H_1), 7.27–7.24 (br m, 1 H, H_4), 6.30–6.24 (m, 1 H, H_2), 2.01 (s, 2 H, H_5), 1.26 (s, 12 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 142.5 (C_1), 139.4 (C_4), 120.2 (C_3), 112.6 (C_2), 83.6 (C_6), 24.9 (C_7).

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.13.

HRMS (CI) Exact mass calculated for $C_{11}H_{18}BO_3$ $[M+H]^+$ *m/z* = 209.1344; found 209.1343.

4,4,5,5-tetramethyl-2-((3-methylfuran-2-yl)methyl)-1,3,2-dioxaborolane (3.55)



Chemical Formula: $C_{12}H_{19}BO_3$
Exact Mass: 222.1427

Prepared according to General Procedure C using 5-methylfuran-2-boronic acid (25.2 mg, 0.20 mmol). The crude (58% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5% Et_2O in hexane) to afford the title compound as a colourless oil (21.8 mg, 49%).

IR (ATR, film) υ 3210, 2922, 2361, 2342, 1458, 764, 750, 669 cm^{-1}.

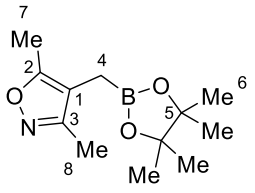
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (dd, *J* = 2.9, 1.3 Hz, 1 H, H_1), 5.82 (dd, *J* = 2.9, 1.3 Hz, 1 H, H_4), 2.25 (s, 2 H, H_5), 2.23 (s, 3 H, H_8), 1.27 (s, 12 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.5 (C_4), 150.1 (C_1), 106.2 (C_{Het}), 106.1 (C_{Het}), 83.8 (C_6), 24.9 (C_7), 13.7 (C_8), 11.8 (C_5). C_5 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.70. Boric acid (δ_B = 22.47 ppm) can be seen in the spectrum.

HRMS (CI) Exact mass calculated for $C_{12}H_{20}BO_3$ $[M+H]^+$ *m/z* = 223.1506; found 223.1508.

3,5-dimethyl-4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)isoxazole (3.56)



Chemical Formula: $C_{12}H_{20}BNO_3$
Exact Mass: 237.1536

Prepared according to General Procedure C using 3,5-dimethylisoxazole-4-boronic acid (28.2 mg, 0.20 mmol). The crude (59% ^{1}H NMR yield) was subject to column chromatography on silica gel (1–5% Et_2O in hexane) to afford the title compound as a colourless oil (25.8 mg, 54%).

IR (ATR, film) υ 2978, 2924, 2361, 2342, 1352, 1167, 1141, 669 cm^{-1}.

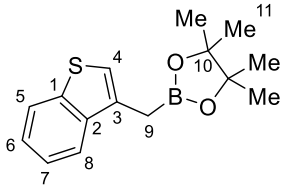
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3 H, H_7), 2.19 (s, 3 H, H_8), 1.81 (s, 2 H, H_4), 1.23 (s, 12 H, H_6).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.9, 160.0, 109.9, 83.8 (C_5), 24.9 (C_6), 11.2, 10.5.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.76.

HRMS (EI) Exact mass calculated for $C_{12}H_{20}BNO_3$ $[M+]^{+\bullet}$ *m/z* = 237.1531; found 237.11267.

2-(benzo[*b*]thiophen-3-ylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.57)



Chemical Formula: $C_{15}H_{19}BO_2S$
Exact Mass: 274.1199

Prepared according to General Procedure C using benzo[*b*]thien-3-ylboronic acid (35.6 mg, 0.2 mmol). The crude (80% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5–1% Et_2O in hexane) to afford the title compound as a pale-yellow oil (37.0 mg, 67%).

IR (ATR, film) υ 2361, 2342, 1146, 763, 669, 656, 650 cm^{-1}.

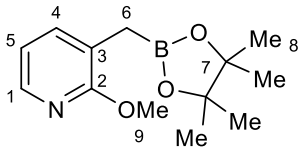
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.9 Hz, 1 H, H_8), 7.75 (d, *J* = 7.9 Hz, 1 H, H_5), 7.43–7.33 (m, 1 H, H_{Ar}), 7.36–7.29 (m, 1 H, H_{Ar}), 7.19 (s, 1 H, H_4), 2.44 (s, 2 H, H_9), 1.25 (s, 12 H, H_{11}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.3 (C_1), 139.9 (C_2), 132.4 (C_3), 124.0 (C_{Ar}), 123.7 (C_{Ar}), 122.8 (C_8), 122.1 (C_5), 121.3 (C_4), 83.8 (C_{10}), 24.9 (C_{11}), 12.2 (C_9). C_9 identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.98.

HRMS (EI) Exact mass calculated for $C_{15}H_{19}BO_2{}^{32}S$ $[M]^{+\bullet}$ *m/z* = 274.1193; found 227.1200.

2-methoxy-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pyridine (3.58)



Chemical Formula: $C_{13}H_{20}BNO_3$
Exact Mass: 249.1536

Prepared according to General Procedure C using 2-methoxy-3-pyridinylboronic acid (30.6 mg, 0.20 mmol). The crude (83% ^{1}H NMR yield) was subject to column chromatography on silica gel (CH_2Cl_2) to afford the title compound as a pale-yellow oil (42.8 mg, 86%).

IR (ATR, film) υ 2978, 2359, 1587, 1252, 1414, 1350, 1142, 1109, 846, 773 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 5.1, 1.9 Hz, 1 H, H_1), 7.38 (ddt, *J* = 7.1, 1.8, 0.8 Hz, 1 H, H_4), 6.77 (dd, *J* = 7.1, 5.1 Hz, 1 H, H_5), 3.92 (s, 3 H, H_9), 2.13 (s, 2 H, H_6), 1.24 (s, 12 H, H_8).

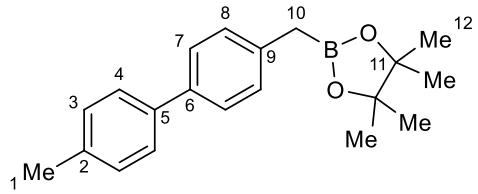
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.2 (C_2), 143.5 (C_1), 138.3 (C_4), 122.5 (C_3), 117.0 (C_5), 83.5 (C_7), 53.2 (C_9), 24.8 (C_8) *ca*. 14.9 (C_6). C_6 was identified by the HSQC-crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.54.

HRMS (EI) Exact mass calculated for $C_{13}H_{20}BNO_3$ $[M]^{+\bullet}$ *m/z* = 249.1531; found 249.15372.

The substrate was also prepared according to General Procedure D from 2-methoxy-3-pyridinylboronic acid (382 mg, 2.50 mmol). The crude was subject to column chromatography on silica gel (CH_2Cl_2) to afford the title compound as a colourless oil (573 mg, 92%).

4,4,5,5-tetramethyl-2-((4'-methyl-[1,1'-biphenyl]-4-yl)methyl)-1,3,2-dioxaborolane (3.59)



Chemical Formula: $C_{20}H_{25}BO_2$
Exact Mass: 308.1948

Prepared according to General Procedure C using (4'-methyl-[1,1'-biphenyl]-4-yl)boronic acid (210 mg, 1.0 mmol, 1.0 equiv). Following concentration, the crude was subject to column chromatography on silica gel (1% Et_2O in hexane) to afford the title compound as a white solid (168 mg, 54%).

IR (film) ν 2978, 2361, 2342, 1501, 1331, 1142, 849, 804, 669, 650 cm^{-1}.

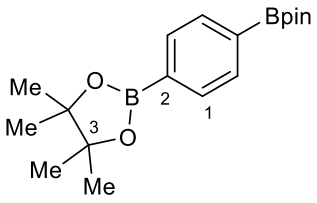
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.45 (m, 4 H, $H_{3,4}$), 7.27–7.21 (m, 4 H, $H_{7,8}$), 2.39 (s, 3 H, H_1), 2.34 (s, 2 H, H_{10}), 1.26 (s, 12 H, H_{12}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.5 (C_2), 137.8 (C_6), 137.6 (C_{10}), 136.6 (C_2), 129.5, 129.5, 127.0, 126.9, 83.6 (C_{11}), 30.4 (C_{14}), 24.9 (C_1), 21.2 (C_{12}). For those unassigned, C_{Ar}.

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.09.

HRMS (ESI+) exact mass calcd. for $C_{20}H_{25}BO_2Na$ $[M+Na]^+$ m/z = 331.1841; found 331.1836.

1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (3.63)



Chemical Formula: $C_{18}H_{28}B_2O_4$
Exact Mass: 330.2174

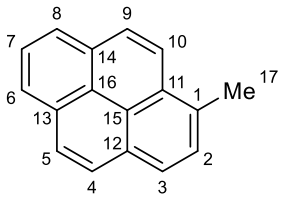
Prepared according to General Procedure C with a slight modification using benzene-1,4-diboronic acid (33.1 mg, 0.20 mmol, 1.0 equiv.) and $BrCH_2Bpin$ **3.3** (0.21 mL, 1.2 mmol, 6.0 equiv) The crude (74% ^{1}H NMR yield) was subject to column chromatography on silica gel (1% Et_2O in hexane) to afford the title compound as a white solid (48.2 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 4 H, H_1), 1.35 (s, 24 H, H_4).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 134.0 (C_1), 84.0 (C_3), 25.0 (C_4).

The spectral data were consistent with the literature.[271]

1-methylpyrene (3.67)



Chemical Formula: $C_{17}H_{12}$
Exact Mass: 216.0939

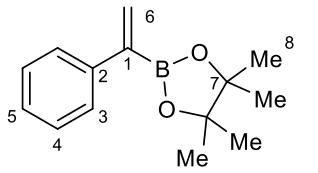
Prepared according to General Procedure C using pyrene-1-boronic acid (49.2 mg, 0.20 mmol). The crude (>99% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.2% Et_2O in hexane) to afford the title compound as white solid (43.0 mg, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.1 Hz, 1 H, H_6), 8.22–8.14 (m, 2 H, $H_{3,4}$), 8.14– 8.07 (m, 3 H, H_{Ar}), 8.07–7.97 (m, 3 H,. H_{Ar}), 7.88 (dd, *J* = 7.7, 0.8 Hz, 1 H, H_9), 2.99 (s, 3 H, H_{17}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 132.4 ($C_{quart.}$), 131.6 ($C_{quart.}$), 131.3 ($C_{quart.}$), 131.1 ($C_{quart.}$), 129.9 ($C_{quart.}$), 129.3 ($C_{quart.}$), 128.0 ($C_{quart.}$), 127.7, 127.5, 127.2, 126.6, 126.0, 125.9, 125.1, 125.0, 124.9, 124.9, 124.8, 123.8, 20.0 (C_{17}). For those unassigned, C_{Ar}.

The spectral data were consistent with the literature.[272]

4,4,5,5-tetramethyl-2-(1-phenylvinyl)-1,3,2-dioxaborolane (3.70)



Chemical Formula: $C_{14}H_{19}BO_2$
Exact Mass: 230.1478

Prepared according to General Procedure C using 1-phenylvinylboronic acid (29.6 mg, 0.20 mmol). The crude (27% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5–2% Et_2O in hexane) to afford the title compound as a white solid (9.2 mg, 20%).

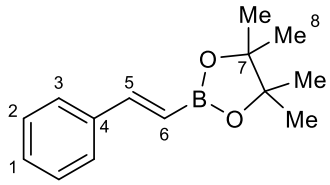
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.44 (m, 2 H, H_3), 7.36–7.28 (m, 2 H, H_4), 7.28–7.20 (m, 1 H, H_5), 6.11–6.03 (m, 2 H, H_6), 1.33 (s, 12 H, H_8).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 141.5 (C_2), 131.1 (C_6), 128.3 (C_4), 127.3 (C_3), 127.2 (C_5), 83.9 (C_7), 24.9 (C_8).

^{11}B NMR (96 MHz, $CDCl_3$) δ 30.72.

The spectral data were consistent with the literature.[273]

(*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (3.74)



Chemical Formula: $C_{14}H_{19}BO_2$
Exact Mass: 230.1478

Prepared according to General Procedure C using *trans*-2-phenylvinylboronic acid (29.6 mg, 0.20 mmol). The crude (39% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–1% Et_2O in hexane) to afford the title compound as a white solid (15.9 mg, 34%).

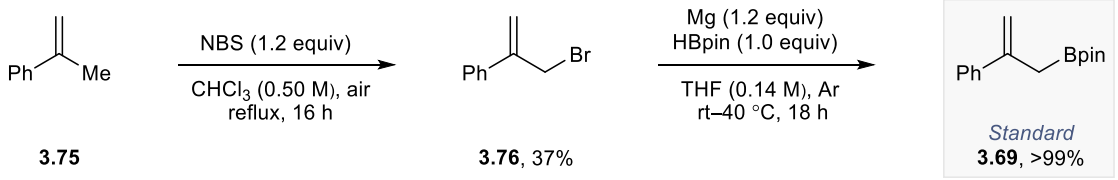
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.42 (m, 2 H, H_3), 7.39–7.27 (m, 4 H, $H_{1,2,5}$), 6.17 (d, *J* = 18.4 Hz, 1 H, H_6), 1.32 (s, 12 H, H_8).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.7, 137.6 (C_4), 129.0, 128.7, 127.20, 116.3 (C_6), 83.5 (C_7), 25.0 (C_8). C_6 identified by the HSQC crosspeak due to quadrupolar relaxation of the α-boron atom. For those left unassigned, C_{Ar}. C_5 also overlaps.

^{11}B NMR (96 MHz, $CDCl_3$) δ 29.73.

The spectral data were consistent with the literature.[274]

Preparation of 4,4,5,5-tetramethyl-2-(2-phenylallyl)-1,3,2-dioxaborolane (3.69)



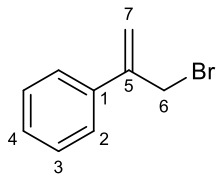
3.75

3.76, 37%

3.69, >99%

Prepared according to a telescoped two-step procedure from Wang and coworkers.[196] To a solution of α-methylstyrene (0.65 mL, 5.0 mmol, 1.0 equiv) in $CHCl_3$ (10 mL, 0.5 M), NBS (1.07 g, 6.00 mmol, 1.20 equiv) was added in one portion. The resulting mixture was heated to reflux (air) for 16 h, cooled to rt, then concentrated under reduced pressure. The crude was suspended in dry Et_2O 30 mL and the resulting precipitate was filtered off, then the filtrate concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (hexane) to afford α-bromomethylstyrene **3.76** as colourless oil (366 mg, 37%). A two-neck round-bottom flask equipped with a stir bar and condenser was charged with Mg turnings (14.6 mg, 0.60 mmol, 1.20 equiv) and fitted with a rubber septum. The flask was flame dried under vacuum and purged with Ar, then charged with dry THF (3.0 mL, 0.14 M) followed by HBpin (73 mL, 0.50 mmol, 1.0 equiv) in one portion. α-Bromomethylstyrene (98.5 mg, 0.50 mmol, 1.0 equiv) as a solution in THF (0.5 mL) was added dropwise with constant stirring over 5 min at rt. After 30 min stirring at rt, α-bromomethylstyrene (98.5 mg, 0.50 mmol, 1.0 equiv) as a solution in THF (0.5 mL) was added again in one portion. After 1.5 h stirring at rt the reaction was then warmed to 40 °C and stirred for 16 h. The reaction mixture was diluted with hexane 5 mL and quenched with aq. 0.1 N HCl (10 mL), then extracted with hexane (3×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated at reduced pressure to afford **3.69** as a colourless oil without further purification required (125 mg, >99%).

α-bromomethylstyrene (3.76)



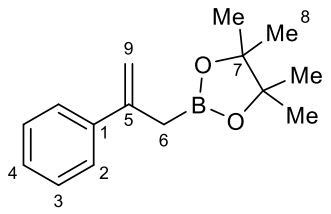
Chemical Formula: C_9H_9Br
Exact Mass: 195.9888

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.47 (m, 2 H, H_2), 7.41–7.31 (m, 3 H, $H_{3,4}$), 5.56 (s, 1 H, H_7), 5.50 (s, 1 H, $H_{7'}$), 4.39 (s, 2 H, H_6).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.4 (C_1), 137.7 (C_5), 128.7 (C_3), 128.4 (C_4), 126.2 (C_2), 117.4 (C_7), 34.34 (C_6).

The spectral data were consistent with the literature.[196]

4,4,5,5-tetramethyl-2-(2-phenylallyl)-1,3,2-dioxaborolane (3.69)



Chemical Formula: $C_{15}H_{21}BO_2$
Exact Mass: 244.1635

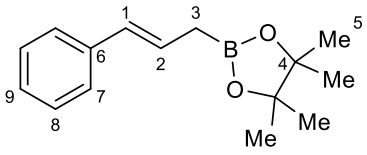
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.44 (m, 2 H, H_2), 7.37–7.28 (m, 2 H, H_3), 7.26–7.19 (m, 1 H, H_4), 5.37 (d, *J* = 1.5 Hz, 1 H, $H_{9\text{-}cis}$), 5.11 (d, *J* = 1.4 Hz, 1 H, $H_{9\text{-}trans}$), 2.17 (d, *J* = 3.8 Hz, 2 H, H_6), 1.17 (s, 12 H, H_8). H_9 protons were assigned by ^{1}H-^{1}H COSY NMR against H_6.

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.5 (C_1), 141.9 (C_5), 128.2 (C_3), 127.3 (C_4), 126.0 (C_2), 112.4 (C_9), 83.5 (C_7), 24.7 (C_8).

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.07.

The spectral data were consistent with the literature.[196]

2-cinnamyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.73)



Chemical Formula: $C_{15}H_{21}BO_2$
Exact Mass: 244.1635

Prepared according to Morken and coworkers.[275] An oven-dried microwave vial equipped with a stir bar was charged with $PdCl_2$ (0.9 mg, 0.005 mmol, 0.5 mol%) and B_2pin_2 (250 mg, 1.0 mmol, 1.0 equiv). The vial was capped and purged with Ar (3×). THF (0.5 mL, 0.5 M) was added, followed by cinnamyl chloride (0.13 mL, 1.0 mmol, 1.0 equiv) and the reaction mixture stirred at 60 °C for 12 h. The reaction mixture was cooled to rt and concentrated at reduced pressure. The crude (86% ^{1}H NMR yield) was subject to column chromatography (1–6% Et_2O in hexane) to afford the desired product as a colourless oil (153 mg, 63%). Partial degradation of the product occurred during chromatography.

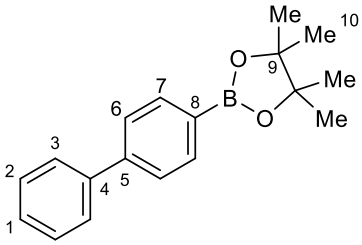
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.30 (m, 2 H, H_7), 7.30–7.23 (m, 2 H, H_8), 7.21–7.13 (m, 1 H, H_9), 6.41–6.34 (m, 1 H, H_1), 6.28 (dt, *J* = 15.7, 7.3 Hz, 1 H, H_2), 1.87 (d, *J* = 7.3 Hz, 2 H, H_3), 1.26 (s, 12 H, H_5).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.4 (C_6), 130.4 (C_1), 128.5 (C_8), 126.6 (C_2), 126.5 (C_9), 126.0 (C_7), 83.5 (C_4), 25.0 (C_5).

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.34.

The spectral data were consistent with the literature.[275]

2-([1,1'-biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.114)



Chemical Formula: $C_{18}H_{21}BO_2$
Exact Mass: 280.1635

Prepared according to General Procedure C using 4-biphenylboronic acid (39.6 mg, 0.20 mmol). The crude (25% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a white solid (27.1 mg, 21%).

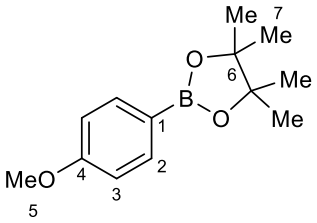
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92–7.85 (m, 2 H, H_7), 7.68–7.57 (m, 4 H, $H_{3,6}$), 7.51–7.39 (m, 2 H, H_2), 7.39–7.31 (m, 1 H, H_1), 1.37 (s, 12 H, H_{10}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.0 (C_{Ar}), 141.2 (C_{Ar}), 135.4 (H_7), 128.9 (H_2), 127.7 (C_1), 127.4 (C_{Ar}), 126.6 (C_{Ar}), 84.0 (C_9), 25.0 (C_{10}).

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.20.

The spectral data were consistent with the literature.[276]

2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.115)



Chemical Formula: $C_{13}H_{19}BO_3$
Exact Mass: 234.1427

Prepared according to General Procedure C using 4-methoxybenzeneboronic acid (30.4 mg, 0.20 mmol). The crude (34% ^{1}H NMR yield) was subject to column chromatography on silica gel (1–2% Et_2O in hexane) to afford the title compound as a white solid (15.0 mg, 32%).

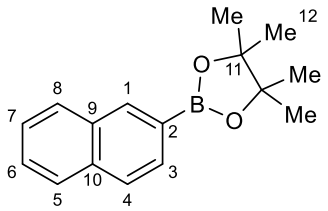
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78–7.72 (m, 2 H, H_3), 6.93–6.86 (m, 2 H, H_2), 3.83 (s, 3 H, H_5), 1.33 (s, 12 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.3 (C_4), 136.7 (C_3), 120.3 (C_1), 113.4 (C_2), 83.7 (C_6), 55.2 (C_5), 25.0 (C_7).

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.50.

The spectral data were consistent with the literature.[276]

4,4,5,5-tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborolane (3.116)



Chemical Formula: $C_{16}H_{19}BO_2$
Exact Mass: 254.1478

Prepared according to General Procedure C using 2-naphthaleneboronic acid (24.0 mg, 0.20 mmol). The crude (30% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.5–2% Et_2O in hexane) to afford the title compound as a white solid (6.0 mg, 17%).

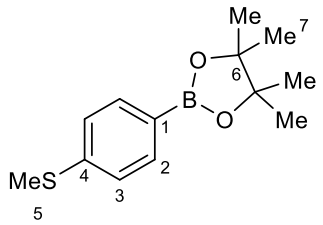
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (br s, 1 H, H_1), 7.91–7.86 (m, 1 H, H_3), 7.84 (td, *J* = 3.8, 2.3 Hz, 3H, $H_{6–8}$), 7.48–7.50 (m, 2 H, $H_{4,5}$), 1.40 (s, 12 H, H_{12}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.4 (C_1), 135.2 (C_9), 132.9 (C_{10}), 130.5, 128.8 (C_3), 127.9, 127.1, 125.9, 84.1 (C_{11}), 25.1 (C_{12}). For those left unassigned, C_{Ar}.

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.09.

The spectral data were consistent with the literature.[276]

4,4,5,5-tetramethyl-2-(4-(methylthio)phenyl)-1,3,2-dioxazborolane (3.117)



Chemical Formula: $C_{13}H_{19}BO_2S$
Exact Mass: 250.1199

Prepared according to General Procedure C using 4-(methylthio)benzeneboronic acid (33.6 mg, 0.20 mmol). The crude (56% ^{1}H NMR yield) was subject to column chromatography on silica gel (0.2–2% Et_2O in hexane) to afford the title compound as a colourless oil (25.5 mg, 51%).

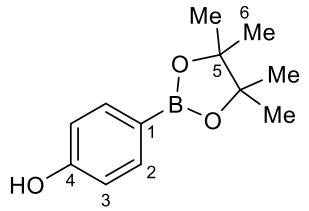
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–7.67 (m, 2 H, H_3), 7.26–7.19 (m, 2 H, H_2), 2.49 (s, 3 H, H_5), 1.34 (s, 12 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 142.7 (C_4), 135.2 (C_3), 125.1 (C_2), 83.9 (C_6), 25.0 (C_7), 15.2 (C_5).

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.31.

The spectral data were consistent with the literature.[160]

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (3.118)



Chemical Formula: $C_{12}H_{17}BO_3$
Exact Mass: 220.1271

Prepared according to General Procedure C using and 4-hydroxybenzeneboronic acid (27.6 mg, 0.20 mmol). The crude (63% ^{1}H NMR yield) was subject to column chromatography on silica gel (CH_2Cl_2) to afford the title compound as a colourless oil (18.6 mg, 42%).

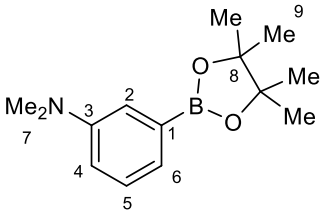
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.68 (m, 2 H, H_2), 6.86–6.79 (m, 2 H, H_3), 5.19 (br s, OH), 1.33 (s, 12 H, H_6).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.4 (C_4), 136.9 (C_2), 120.4 (C_1) 114.9 (C_3), 83.8 (C_5), 25.0 (C_6). C_1 identified by the HMBC crosspeak due to quadrupolar relaxation of the α-boron atom.

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.22.

The spectral data were consistent with the literature.[276]

***N*,*N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.119)**



Chemical Formula: $C_{14}H_{22}BNO_2$
Exact Mass: 247.1744

Prepared according to General Procedure C using 3-(*N*,*N*-dimethylamino)phenylboronic acid (30.4 mg, 0.20 mmol). The crude (32% ^{1}H NMR yield) was subject to column chromatography on silica gel (5–20% EtOAc in hexane) to afford the title compound as a white solid (13.8 mg, 28%).

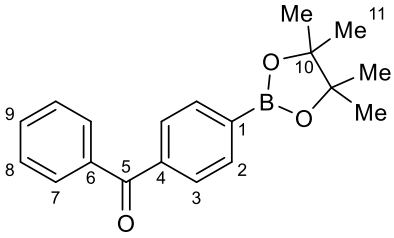
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.22 (m, 1 H, H_6), 7.22–7.15 (m, 2 H, $H_{4,5}$), 6.90–6.82 (m, 1 H H_2), 2.96 (s, 6 H, H_7), 1.34 (s, 12 H, H_9).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.0 (C_3), 128.5 (C_5), 123.3 (C_6), 118.7 (C_4), 115.8 (C_2), 83.6 (C_8), 40.8 (C_7), 24.8 (C_9).

^{11}B NMR (96 MHz, $CDCl_3$) δ 30.82.

The spectral data were consistent with the literature**.**[277]

phenyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (3.120)



Chemical Formula: $C_{19}H_{21}BO_3$
Exact Mass: 308.1584

Prepared according to General Procedure C using 4-benzoylphenyl)boronic acid (45.2 mg, 0.20 mmol). The crude (60% ^{1}H NMR yield) was subject to column chromatography on silica gel (1–4% Et_2O in hexane) to afford the title compound as a white solid (24.7 mg, 40%).

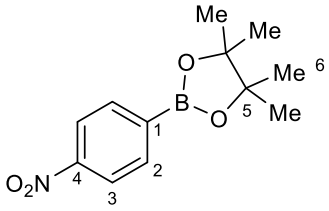
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95–7.89 (m, 2 H, H_2), 7.83–7.74 (m, 4 H, $H_{3,7}$), 7.58–7.60 (m, 1 H, H_9), 7.51–7.44 (m, 2 H, H_8), 1.37 (s, 12 H, H_{11}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 197.1 (C_5), 139.9, 137.6, 134.7 (C_2), 132.7 (C_9), 130.3, 129.2, 128.4 (C_8), 84.3 (C_{10}), 25.0 (C_{11}). For those left unassigned, C_{Ar}.

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.04.

The spectral data were consistent with the literature.[160]

4,4,5,5-tetramethyl-2-(4-nitrophenyl)-1,3,2-dioxaborolane (3.121)



Chemical Formula: $C_{12}H_{16}BNO_4$
Exact Mass: 249.1172

Prepared according to General Procedure C using 4-nitrophenylboronic acid (33.4 mg, 0.20 mmol). The crude (49% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the title compound as a colourless oil (23.9 mg, 48%).

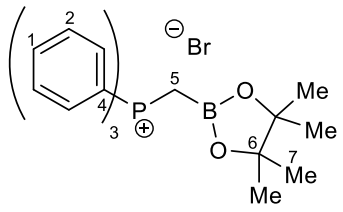
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22–8.16 (m, 2 H, H_2), 7.99–7.93 (m, 2 H, H_3), 1.37 (s, 12 H, H_6).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.0 (C_4), 135.8 (C_3), 122.6 (C_2), 84.8 (C_5), 25.0 (C_6).

^{11}B NMR (96 MHz, $CDCl_3$) δ 30.76.

The spectral data were consistent with the literature.[160]

triphenyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-λ⁴-phosphane bromide (3.135)



Chemical Formula: $C_{25}H_{29}BBrO_2P$
Exact Mass: 482.1187

In an Ar-filled glovebox, ground PPh_3 (260 mg, 1.0 mmol, 1.0 equiv) was added to a microwave vial fitted with a stir bar and capped. The vial was removed from the glovebox and dry THF (4.0 mL, 0.25 M) was added. The mixture was stirred at rt until homogenous (~2 min) prior to the addition of $BrCH_2Bpin$ **3.3** (0.20 mL, 1.1 mmol, 1.1 equiv) in one portion. The reaction mixture was stirred at rt for 15 min then transferred to a flask (THF) and concentrated at reduced pressure. The white solid was washed with ice-cold hexane (3×5 mL) then dried under high vacuum (1 h) to afford the desired product as a white solid (474 mg, 98%).

IR (solid) ν 2368, 2353, 646 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 7.82–7.70 (m, 15 H, H_{1-3}), 3.17 (d, $^2J_{HP}$ = 14.6 Hz, 2 H, H_5), 1.15 (s, 12 H).

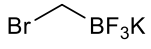
^{13}C{^{1}H} NMR (126 MHz, DMSO-*d*$_6$) δ 134.8 (d, $^4J_{CP}$ = 3.1 Hz), 133.3 (d, $^3J_{CP}$ = 10.9 Hz), 130.1 (d, $^2J_{CP}$ = 12.7 Hz), 119.9 (d, $^1J_{CP}$ = 88.5 Hz), 81.4, 24.5, 7.3 (d, $^1J_{CP}$ = 55.5 Hz).

^{11}B NMR (96 MHz, THF-*d*$_8$) δ 28.90.

^{31}P{^{13}C} NMR (202 MHz, DMSO-*d*$_6$) δ 22.70.

HRMS (ESI+) Exact mass calcd. for $C_{19}H_{18}P$ [M−Bpin]$^+$ *m*/*z* = 277.1141; found 277.1141.

potassium bromomethyltetrafluoroborate (3.183)



Chemical Formula: CH_2BBrF_3K
Exact Mass: 199.9022

Prepared according to General Procedure A, with some slight modifications. A solution of dibromoethane (1.75 mL, 25.0 mmol, 1.2 equiv) and triisopropyl borate (5.31 mL, 23.0 mmol, 1.10 equiv) in dry THF (75 mL) was cooled to −80 °C. *n*BuLi 2.32 M in hexanes (9.05 mL, 21.0 mmol, 1.00 equiv) was added dropwise over 1 h. After the addition, the solution was stirred vigorously for 1 h at –78 °C, then at rt for 1 h. The reaction mixture was cooled back to –80 °C whereupon KHF_2 (4.08 g, 52.9 mmol, 2.50 equiv) was added in a single portion. The septum was returned and water (15 mL) was added dropwise over 10 min. The reaction was warmed to 25 ℃, then vigorously stirred for 30 min. The cloudy suspension was

transferred to a single necked flask, rinsing with THF, concentrated, then left on high vacuum overnight to afford an off-white solid. The crude was dissolved an excess of acetone and the insoluble salts (excess KHF_2, KF) filtered off, then the liquor was concentrated at reduced pressure to afford a white solid. The solid was in a minimum volume of hot acetone (*ca*. 45 °C), then precipitated with ice-cold diethyl ether which was filtered off then dried on the high vacuum to afford the title compound as a white hygroscopic solid (2.25 g, 53%).

^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 2.28–2.09 (m, 2 H).

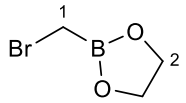
^{13}C{^{1}H} NMR (126 MHz, $(CD_3)_2CO$) δ no peaks.

^{11}B NMR (96 MHz, $(CD_3)_2CO$) δ 2.59 (q, $^{1}J_{BF}$ = 50.7 Hz).

^{19}F{^{1}H} NMR (470 MHz, $(CD_3)_2CO$) δ −145.69 (q, $^{1}J_{FB}$ = 49.4 Hz).

The spectral data were consistent with the literature.[278]

2-(bromomethyl)-1,3,2-dioxaborolane (3.185)



Chemical Formula: $C_3H_6BBrO_2$
Exact Mass: 163.9644

Prepared according to General Procedure A using THF (40 mL), dibromomethane (0.84 mL, 12.0 mmol, 1.20 equiv), triisopropyl borate (2.42 mL, 10.5 mmol, 1.05 equiv), *n*BuLi 11 M in hexanes (0.91 mL, 10.0 mmol, 1.00 equiv), methanesulfonic acid (0.65 mL, 10.0 mmol, 1.00 equiv) and ethyleneglycol (0.56 mL, 10.0 mmol, 1.00 equiv). Following workup, the desired product was purified by vacuum distillation (33–35 °C, 1.2 mbar) and was stored in the freezer in the absence of light as a colourless liquid (290 mg, 17%). *Note: partial loss of material occurred during vacuum distilation.*

IR (film) ν 2357, 2342, 1418, 1325, 764, 750, 669 cm^{-1}.

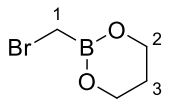
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (s, 4 H, C_2), 2.66 (s, 2 H, C_1).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 66.5 (C_2).

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.01.

HRMS (CI) Exact mass calcd. for $C_3H_6BO_2$ $[M-Br]^+$ *m/z* = 85.0455; found 85.0458.

2-(bromomethyl)-1,3,2-dioxaborinane (3.186)



Chemical Formula: $C_4H_8BBrO_2$
Exact Mass: 177.9801

Prepared according to General Procedure A using THF (40 mL), dibromomethane (0.84 mL, 12.0 mmol, 1.20 equiv), triisopropyl borate (2.42 mL, 10.5 mmol, 1.05 equiv), *n*BuLi 11 M in hexanes (0.91 mL, 10.0 mmol, 1.00 equiv), methanesulfonic acid (0.65 mL, 10.0 mmol, 1.00 equiv) and 1,3 propanediol (0.72 mL, 10.0 mmol, 1.00 equiv). Following workup, the desired product was purified by vacuum distillation (39–41 °C, 1.2 mbar) and was stored in the freezer in the absence of light as a colourless liquid (862 mg, 48%). *Note: partial loss of material occurred during vacuum distillation.*

IR (film) ν 2953, 2899, 2361, 2342, 1431, 1279, 1155, 932, 758 cm^{-1}.

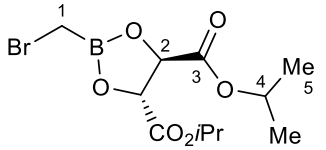
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (t, *J* = 5.5 Hz, 4 H, H_2), 2.52 (s, 2 H, H_1), 1.98 (p, *J* = 5.5 Hz, 2 H, H_3).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 62.5 (C_2), 27.1 (C_3).

^{11}B NMR (96 MHz, $CDCl_3$) δ 27.80.

HRMS (EI) Exact mass calcd. for $C_4H_8B^{79}BrO_2$ $[M]^{+\bullet}$ *m*/*z* = 177.9780; found 177.9801.

diisopropyl (4*R*, 5*R*)-2-(bromomethyl)-1,3,2-dioxaborolane-4,5-dicarboxylate (3.187)



Chemical Formula: $C_{11}H_{18}BBrO_6$
Exact Mass: 336.0380

Prepared according to General Procedure A using THF (30 mL), dibromomethane (1.77 mL, 25.2 mmol, 1.20 equiv), triisopropyl borate (5.33 mL, 23.1 mmol, 1.10 equiv), *n*BuLi 1.98 M in hexanes (10.6 mL, 21.0 mmol, 1.00 equiv), methanesulfonic acid (1.36 mL, 21.0 mmol, 1.00 equiv) and (+)-diisopropyl *L*-tartrate, 99% *e*.*e*. (4.92 g in 10 mL THF, 21.0 mmol, 1.00 equiv). Following workup, the desired product was purified by vacuum distillation (6–7 mbar, 150–152 °C) afforded the product as a straw-coloured liquid (3.71 g, 50%).

$[\alpha]_D^{20}$ = – 41.0° (*c* = 1.0, $CHCl_3$).

IR (film) ν 2361, 2342, 1736, 1271, 1103, 669 cm^{-1}.

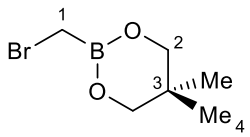
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13 (hept, *J* = 6.3 Hz, 2 H, H_4), 4.87 (s, 2 H, H_2), 2.75 (s, 2 H, H_2), 1.31 (d, *J* = 6.3 Hz, 12 H, H_5).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.6 (C_3), 78.3 (C_2), 70.5 (C_4), 21.8 (C_5), 21.7 (C_5).

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.40.

HRMS (EI) exact mass calcd. for $[M]^+$ ($C_{11}H_{18}{}^{11}B^{79}BrO_6$) *m/z* = 336.03743; found *m/z* 336.03668.

2-(bromomethyl)-5,5-dimethyl-1,3,2-dioxaborinane (3.188)



Chemical Formula: $C_6H_{12}BBrO_2$
Exact Mass: 206.0114

Prepared according to General Procedure A using THF (40 mL), dibromomethane (0.84 mL, 12.0 mmol, 1.20 equiv), triisopropyl borate (2.42 mL, 10.5 mmol, 1.05 equiv), *n*BuLi 11 M in hexanes (0.91 mL, 10.0 mmol, 1.00 equiv), methanesulfonic acid (0.65 mL, 10.0 mmol, 1.00 equiv) and neopentylglycol (1.04 g, 10.0 mmol, 1.00 equiv). Following workup, the desired product was purified by vacuum distillation (56–58 °C, 1.2 mbar) and was stored in the freezer in the absence of light as a colourless liquid (1.68 g, 81%).

IR (film) ν 2963, 2361, 2342, 1479, 1292, 1260, 1146, 1007, 814, 745, 654, 546 cm^{-1}.

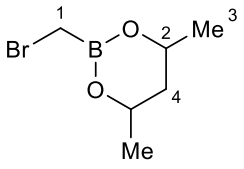
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (s, 4 H, H_2), 2.53 (s, 2 H, H_1), 0.97 (s, 6 H, H_4).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 72.6 (C_2), 31.9 (C_3), 21.8 (C_4).

^{11}B NMR (96 MHz, $CDCl_3$) δ 27.39.

HRMS (EI) Exact mass calcd. for $C_6H_{12}B^{79}BrO_2$ $[M]^{+\bullet}$ *m/z* = 206.0108; found 206.0103.

2-(bromomethyl)-4,6-dimethyl-1,3,2-dioxaborinane (3.189)



Chemical Formula: $C_6H_{12}BBrO_2$
Exact Mass: 206.0114

Prepared according to General Procedure A using THF (40 mL), dibromomethane (0.84 mL, 12.0 mmol, 1.20 equiv), triisopropyl borate (2.42 mL, 10.5 mmol, 1.05 equiv), *n*BuLi 11 M in hexanes (0.91 mL, 10 mmol, 1.0 equiv), methanesulfonic acid (0.65 mL, 10 mmol, 1.0 equiv) and 2,4-pentanediol (2.19 mL, 10.0 mmol, 1.00 equiv). Following workup, the desired product was purified by vacuum distillation (45–47 °C, 4 mbar) and was stored in the freezer in the absence of light as a colourless liquid (1.59 g, 77%, *dr* 53:47). No attempt was made to separate the diastereomers.

IR (film) ν 2361, 2342, 1418, 1290, 1152, 750, 679 cm^{-1}.

^{11}B NMR (96 MHz, $CDCl_3$) δ 27.62.

HRMS (EI) Exact mass calcd. for $C_6H_{12}BBrO_2$ $[M]^{+\bullet}$ *m/z* = 206.0114; found 206.0116.

Major diastereomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (dp, *J* = 12.3, 5.9 Hz, 2 H, H_2), 2.52 (s, 2 H, H_1), 1.74–1.77 (m, 2 H, H_2), 1.27 (d, *J* = 6.2 Hz, 6 H, H_3).

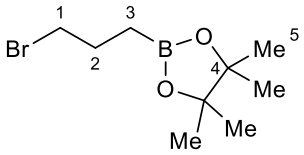
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 68.9 (C_2), 42.3 (C_4), 23.0 (C_3).

Minor diastereomer

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (ddt, *J* = 12.5, 6.3, 5.0 Hz, 2 H, H_2), 2.52 (s, 2 H, H_1), 1.89–1.95 (m, 2 H, H_2), 1.30 (d, *J* = 6.4 Hz, 6 H, H_3).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 65.4 (C_2), 39.0 (C_4), 22.5 (C_3).

2-(3-bromopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.201)



Chemical Formula: $C_9H_{18}BBrO_2$
Exact Mass: 248.0583

Prepared according to a procedure from Thomas and coworkers.[234] Allyl bromide (0.44 mL, 5.0 mmol, 1.0 equiv) then HBpin (0.80 mL, 5.5 mmol, 1.1 equiv) were added to a flame dried Young's tube containing $LiAlH_4$ (19 mg, 0.50 mmol, 10 mol%) at rt under an atmosphere of Ar. *Safety: gas evolution*. The reaction mixture was stirred for 4 h at 110 °C, then cooled to rt, opened to air, and filtered through a short pad of silica gel, eluting with CH_2Cl_2 20 mL. The crude was subject to column chromatography on silica gel (0−10% EtOAc in hexane) to afford the desired product as a straw oil (750 mg, 60%).

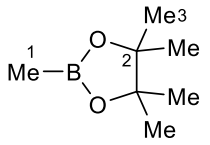
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.42 (t, *J* = 6.9 Hz, 2 H, H_1), 2.01–1.92 (m, 2 H, H_2), 1.24 (s, 12 H, H_5), 0.94−0.90 (td, *J* = 7.5, 2.3 Hz, 2 H, H_3).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 83.4 (C_4), 36.4 (C_1), 27.7 (C_2), 25.0 (C_5).

^{11}B NMR (96 MHz, $CDCl_3$) δ 34.03.

The spectral data were consistent with the literature.[234]

2,4,4,5,5-pentamethyl-1,3,2-dioxaborolane (3.203)



Chemical Formula: $C_7H_{15}BO_2$
Exact Mass: 142.1165

An open flask charged with a stir bar was added methylboronic acid (4.79 g, 80.0 mmol, 1.00 equiv), pinacol (9.55 g, 80.8 mmol, 1.01 equiv), Na_2SO_4 (28.4 g, 200 mmol, 2.50 equiv) followed by Et_2O (320 mL) and the flask fitted with a septum and needle inlet (air). The reaction mixture was stirred at rt for 72 h, filtered, and rinsed with Et_2O (3×) then concentrated at reduced pressure (≥300 mbar, 30 °C water bath) to afford the desired product as a colourless oil (10.5 g, 92%). *The product is volatile.*

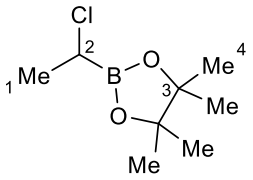
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 12 H, H_3), 0.25 (s, 3 H, H_1).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 25.0 (C_3), 83.1 (C_2).

^{11}B NMR (96 MHz, $CDCl_3$) δ 34.04.

The spectral data were consistent with the literature.[279]

2-(1-chloroethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.205)



Chemical Formula: $C_8H_{16}BClO_2$
Exact Mass: 190.0932

To a flame dried three-necked flask equipped with a stir bar, cooled under Ar and fitted with a thermometer and septum, was added a solution of dichloromethane (3.53 mL, 55.0 mmol, 1.10 equiv) in THF (100 mL, 0.2 M) which was cooled to -110 °C. *n*BuLi 11.0 M in hexane (4.55 mL, 50.0 mmol, 1.0 equiv) was precooled to in an acetone bath dosed with liquid nitrogen (bath temperature −40 °C) and the bottle lightly shaken before use to ensure homogeneity, then added dropwise by hand over 15 min. *The needle containing the nBuLi was placed such that the solution ran down the side of the flask before making contact with the reaction mixture to ensure adequate cooling*. After 30 min stirring <−100 °C, a solution of MeBpin **3.203** (7.46 g, 52.5 mmol, 1.05 equiv) in THF (5 mL), precooled to −80 °C, was added to the centre of the reaction flask in one portion. The solution was stirred for a further 15 min at −100 °C, then the cooling bath was removed and the reaction mixture was stirred at rt for 16 h. The solution was concentrated at reduced pressure, then resuspended in pentane (150 mL) and insoluble salts were filtered off, washing the LiCl filter cake with pentane (2×). The solution was concentrated at reduced pressure to afford a cream

which was subject to vacuum distillation (68–70 °C, 11 mbar) to afford a colourless liquid (6.47 g in >99% purity, 68%).

*Technical note: After the *n*BuLi addition and stirring for 30 min the reaction mixture should remain colourless or straw yellow. A darker yellow or orange colour can be indicative of carbenoid degradation and the reaction must be restarted. Formation of (chloromethyl)lithium can be tested by removing a ~0.2 mL aliquot of the straw-coloured reaction mixture and watching the solution flash black in the syringe barrel, which is discarded.

IR (film) ν 2980, 2363, 2342, 1379, 1348, 1142, 1030, 972, 870, 840, 640 cm^{-1}.

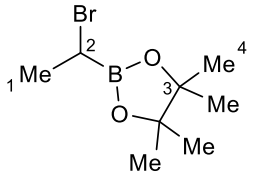
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51 (q, *J* = 7.6 Hz, 1 H, H_2), 1.54 (d, *J* = 7.6 Hz, 3 H, H_1), 1.29 (s, 12 H_4).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 84.5 (C_3), 24.7 (C_1), 20.5 (C_4).

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.51.

HRMS (EI) Exact mass calcd. for $C_8H_{16}B^{35}ClO_2$ $[M]^{+\bullet}$ *m/z* = 190.0926; found 190.0927.

2-(1-bromoethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.206)



Chemical Formula: $C_8H_{16}BBrO_2$
Exact Mass: 234.0427

The reaction was performed with the bay and fumehood lights turned off. To a round bottomed flask wrapped in tin foil and equipped with a stir bar was added MeCHClBpin **3.205** (952 mg, 5.00 mmol, 1.00 equiv) which was dissolved in Et_2O (10.0 mL, 5.0 M) prior to the addition of LiBr (2.17 g, 25.0 mmol, 5.00 equiv) in one portion. The flask was stirred at rt for 24 h, then diluted in Et_2O 50 mL and insoluble salts filtered off. The liquor was concentrated at reduced pressure, then resuspended in hexane 15 mL and any remaining salts filtered off, then the liquor concentrated at reduced pressure to afford the desired product as a pale yellow oil (975 mg, 83%).

The compound is known from a mixture but has not been fully characterised. [280]

IR (film) ν 2980, 2361, 2342, 1371, 1167, 1134, 970, 841, 669 cm^{-1}.

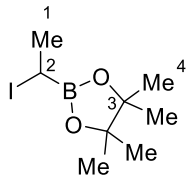
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.43 (q, *J* = 7.6 Hz, 1 H, H_2), 1.70 (d, *J* = 7.5 Hz, 3 H, H_1), 1.28 (d, *J* = 1.3 Hz, 12 H, H_4).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 84.4 (C_3), 24.6 (2 × s, C_4), 20.7 (C_1). Two observed C_4 signals are consistent with *syn* and *anti* Bpin methyl groups wrt the C−Br bond.

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.37.

HRMS (EI) Exact mass calcd. for $C_8H_{16}B^{79}BrO_2$ $[M]^{+\bullet}$ *m/z* = 234.0421; found 234.0414.

2-(1-iodoethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.207)



Chemical Formula: $C_8H_{16}BIO_2$
Exact Mass: 282.0288

The reaction was performed with the bay and fumehood lights turned off. To a round bottomed flask wrapped in tin foil and equipped with a stir bar was added NaI (3.75 g, 25.0 mmol, 5.00 equiv) and acetone (10.0 mL) and the reaction stirred at rt for 3 min until MeCHBrBpin **3.206** (952 mg, 5.00 mmol, 1.00 equiv) was added in one portion. The reaction mixture was stirred at rt for 16 h then the reaction mixture filtered and concentrated at reduced pressure (30 °C, flask wrapped in tin foil) to afford a yellow solid which was triturated with CH_2Cl_2 (25 mL) and the solid filtered off, washing with (CH_2Cl_2) in 10 mL portions until the filtered solid turned white (excess NaI). The liquor was concentrated at reduced pressure to afford the desired product as a yellow oil (958 mg, 68%). The compound is known as an intermediate but has not been fully characterised.[281]

IR (film) ν 2978, 2361, 2342, 1366, 1331, 1144, 1105, 970, 841, 669 cm^{-1}.

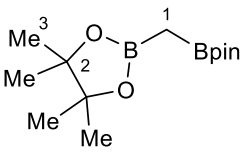
^1H NMR (500 MHz, $CDCl_3$) δ 3.36 (q, *J* = 7.5 Hz, 1 H, H_2), 1.84 (d, *J* = 7.5 Hz, 3 H, H_1), 1.27 (s, 12 H, H_4).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 84.1 (C_3), 24.5 (C_4), 24.4 ($C_{4'}$), 21.8 (C_1). Two observed C_4 signals are consistent with *syn* and *anti* Bpin methyl groups wrt the C−Br bond.

^{11}B NMR (96 MHz, $CDCl_3$) δ 32.07.

HRMS (EI) Exact mass calcd. for $C_8H_{16}BIO_2$ $[M]^{+\bullet}$ *m/z* = 282.0283; found 282.0292.

1,1-diborylmethane pinacol ester (3.208)



Chemical Formula: $C_{13}H_{26}B_2O_4$
Exact Mass: 268.2017

Prepared according to Morken and coworkers.[235] A flame-dried Schlenk tube equipped with a stir bar was charged with CuI (295 mg, 1.5 mmol, 5.0 mol%), LiOMe (1.77 g, 47 mmol, 1.5 equiv) and B_2pin_2 (7.87 g, 31 mmol, 1.0 equiv) under a flow of Ar. The flask was sealed with a rubber septum and purged with Ar (3×), followed by the addition of DMF (31 mL, 1.0 M). After stirring at room temperature for 10 min, dibromomethane (2.18 mL, 31.0 mmol, 1.0 equiv) was added via syringe at rt to the black solution. The reaction mixture was stirred at rt for 24 h whereupon Et_2O (50 mL) was added. The slurry was filtered through a silica gel plug (5×5 cm), rinsed with Et_2O (200 mL), and the liquor was concentrated at reduced pressure. The crude DMF solution was diluted with hexane (150 mL), washed with H_2O (4×50 mL) and the collected organic phase dried (Na_2SO_4), then concentrated at reduced pressure to yield the product as a white solid (2.85 g, 34%).

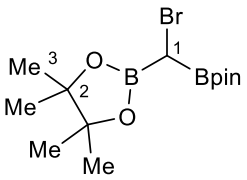
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 24 H, H_3), 0.35 (s, 2 H, H_1).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 83.2 (C_2), 24.9 (C_3).

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.31.

The spectral data were consistent with the literature.[235]

2,2'-(bromomethylene)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.209)



Chemical Formula: $C_7H_{13}BBrO_2$
Exact Mass: 219.0192

A telescoped procedure based on two preparations by Cho and coworkers.[236] To a Schlenk tube equipped with a stir bar inside an Ar-filled glovebox was added $CH_2(Bpin)_2$ **3.208** (1.34 g, 5.00 mmol, 1.0 equiv) and dry hexane (0.50 mL) and the tube was sealed with a septum and electrical tape before removing from the glovebox and cycling onto an Ar Schlenk line. To this solution, freshly prepared LDA 1 M in THF (5.50 mL, 5.50 mmol, 1.1 equiv), stirred at −25 °C in a MeCN/dry ice slush bath for 1 h prior to use, was added in one portion. After stirring for 20 min stirring was stopped and the white solid ($CH(Bpin)_2Li$) was allowed to settle to the bottom of the tube. A syringe was used to remove most of the solvent. The solid was rinsed with dry hexane (3×25 mL) using the same method under a high flow of Ar. The

remaining solvent was removed on the high vacuum for 30 min (*$CH(Bpin)_2Li$ is a very fine powder, bumping can be minimized by keeping the Schlenk line warm with a water bath/hands and very gently opening the line to vacuum*). The solid was dissolved in dry degassed THF (20.0 mL, 0.25 M) and the solution was cooled to <−78 °C, then a solution of Br_2 (0.26 mL, 5.00 mmol) in THF (5 mL, pre-cooled to −78 °C) was added dropwise and stirred for 3 h at <−78 °C. The reaction mixture was suspended in hexane (75 mL, pre-chilled to <−78 °C), filtered through a short pad of silica gel, washed with hexane (75 mL, pre-chilled to <−78 °C), and concentrated under reduced pressure. The crude mixture was re-dissolved in hexane (75 mL, pre-chilled to <−78 °C), filtered through a short pad of 1:1 silica gel/$MgSO_4$, washed with hexane (75 mL, pre-chilled to <−78 °C), and concentrated under reduced pressure (rt water bath, bay lights switched off) to afford the desired product as a white solid (890 mg, 51%).

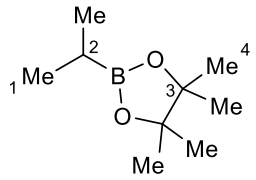
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.53 (s, 1 H, H_1), 1.26 (s, 24 H, H_3).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 84.7 (C_2), 24.7 (C_3), 24.6 ($C_{3'}$). Two observed C_3 signals are consistent with *syn* and *anti* Bpin methyl group wrt C−Br bond and is consistent with data reported by Cho and coworkers.[236]

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.95.

The spectral data were consistent with the literature.[236]

2-isopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.211)



Chemical Formula: $C_9H_{19}BO_2$
Exact Mass: 170.1478

A flame-dried three-necked flask equipped with a stir bar and backfilled with Ar was charged with THF (50.0 mL, 0.2 M) and *i*PrOBpin (2.04 mL, 10.0 mmol, 1.0 equiv) then cooled to −80 °C prior to the dropwise addition of Turbo Grignard solution 1.2 M in THF (10.0 mL, 12.0 mmol, 1.2 equiv) over 15 min. The reaction was stirred at −80 °C for 1 h then warmed to rt and stirred for 2 h. The reaction mixture was cooled down to 0 °C and treated with 2 N aq. HCl (25 mL) and stirred at rt for 1 h. The organics were extracted into Et_2O (3×) and the collected organics washed with brine (2x), dried (Na_2SO_4) and concentrated at reduced pressure, then resuspended in hexane (100 mL) and any insoluble salts filtered off, rinsing with hexane (50 mL). The liquor was concentrated at reduced pressure to afford the desired product as a colourless liquid (1.13 g, 66%). *The product is volatile.*

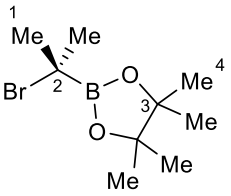
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 12 H, H_4), 1.13–1.03 (m, 1 H, H_2), 0.98 (br d, *J* = 6.9 Hz, 6 H, H_1).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 83.0 (C_3), 24.9 (C_4), 18.1 (C_1).

^{11}B NMR (96 MHz, $CDCl_3$) δ 34.82.

The spectral data were consistent with the literature.[237]

2-(2-bromopropan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.212)



Chemical Formula: $C_9H_{18}BBrO_2$
Exact Mass: 248.0583

Based on a procedure by Morken and coworkers.[25] A flame-dried two necked flask cooled under an atmosphere of Ar was fitted with a septum and an aq. $NaHCO_3$ scrubber was charged with $CHCl_3$ (5.0 mL, 0.6 M) and $CHMe_2Bpin$ **3.211** (0.571 mL, 3.00 mmol, 1.0 equiv). Br_2 (0.39 mL, 7.50 mmol, 2.5 equiv) was added in a single portion at rt. The flask was stirred at rt for 16 h then concentrated at reduced pressure. The oil was diluted in CH_2Cl_2 (2 mL) and filtered through a pipette pad of a short pad of silica gel (3 cm), eluting with CH_2Cl_2 (10 mL), then concentrated to afford the desired product as a pale orange oil (412 mg, 55%) which was stored in the freezer in the absence of light. Yield loss was attributed to the instability of the product to silica gel which was used remove residual Br_2. The compound is known but full characterisation was incomplete.[25]

IR (film) ν 1728, 1462, 1364, 1364, 1140, 854 cm^{-1}.

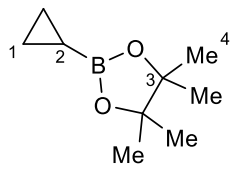
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.77 (s, 6 H, H_1), 1.28 (s, 12 H, H_4).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 84.3 (C_3), 30.4 (C_1), 24.5 (C_4).

^{11}B NMR (96 MHz, $CDCl_3$) δ 31.48.

HRMS (CI) Exact mass calcd. for $C_9H_{18}B^{79}BrO_2$ $[M]^+$ *m/z* = 249.0656; found 249.0648.

2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.214)



Chemical Formula: $C_9H_{17}BO_2$
Exact Mass: 168.1322

An open flask charged with a stir bar was added cyclopropylboronic acid (429 mg, 5.00 mmol, 1.00 equiv), pinacol (597 mg, 5.05 mmol, 1.01 equiv), Na_2SO_4 (1.78 g, 12.5 mmol) followed by Et_2O (20.0 mL) and the flask fitted with a septum and needle inlet (air). The flask was stirred at ambient temperature for 16 h, filtered and rinsed with Et_2O (3×) then concentrated at reduced pressure to afford the desired product as a straw-coloured oil (717 mg, 85%). No further purification was required. *The product is volatile.*

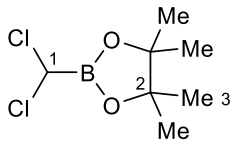
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 12 H, H_4), 0.61 (app. dt, *J* = 9.2, 2.8 Hz, 2 H, H_1), 0.50 (dq, *J* = 6.1, 3.3 Hz, 2 H, $H_{1'}$), −0.19 (tt, *J* = 9.3, 6.1 Hz, 1 H, H_2).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 83.0 (C_3), 24.8 (C_4), 4.0 (C_1).

^{11}B NMR (96 MHz, $CDCl_3$) δ 33.71.

The spectral data were consistent with the literature. [282]

2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.216)



Chemical Formula: $C_7H_{13}BCl_2O_2$
Exact Mass: 210.0386

Based on a procedure adapted from Rathke and coworkers, with some modifications.[42] To a flame-dried three-necked flask cooled under Ar and fitted with a septum and thermometer was added dry CH_2Cl_2 (1.60 mL, 25.0 mmol, 1.00 equiv) in dry THF (35 mL). The solution was cooled to −100 ˚C and *n*BuLi 2.04 M in hexanes (12.3 mL, 25.0 mmol, 1.00 equiv) was added dropwise over 20 min. The resulting mixture was stirred at −100 ˚C for 30 min. Triisopropyl borate (5.77 mL, 25.0 mmol, 1.00 equiv) was added in a single portion and the resulting mixture was stirred at −100 ˚C for a further 30 min. 6 N aq. HCl (50 mL) was added in a single portion and the mixture was stirred vigorously and allowed to warm to rt over 1 h. The reaction mixture was extracted into Et_2O (3×), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated at reduced pressure. *For the remainder of the preparation, the bay and fume cupboard lights were switched off.* The residue was dissolved in PhMe (50 mL, 0.5 M) and transferred to a flame-dried two-necked flask fitted with a septum and reflux condenser and cooled under Ar. Pinacol (2.95 g, 25.0 mmol, 1.00 equiv) was added in a single portion

and the resulting mixture was stirred under vigorous reflux (hotplate temperature 140 °C) for 48 h. The resulting solution was concentrated at reduced pressure (bath temp 30 °C, foil wrapped flask). Purification by vacuum distillation (b.p. 90−92 °C, 1.2 mbar, lit 64–66 °C, 0.2 mbar[238]) afforded the desired product as a colourless oil (2.92 g, 55%).

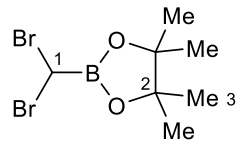
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (s, 1 H, H_1), 1.33 (s, 12 H, H_3).

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 85.9 (C_2), 24.6 (C_3).

^{11}B NMR (96 MHz, $CDCl_3$) δ 29.01.

The spectral data was consistent with the literature.[42]

2-(dibromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.217)



Chemical Formula: $C_7H_{13}BBr_2O_2$
Exact Mass: 297.9375

Based on a procedure adapted from Hoffmann and coworkers[238]. Using a flame dried Schlenk tube cooled under Ar, 1 M LDA was prepared in Et_2O (20 mL, 20 mmol, 0.9 equiv) then diluted into dry THF (15 mL) and cooled to −100 °C. In a separate flame-dried Schlenk tube, a solution of dibromomethane (1.50 mL, 21.0 mmol 1.1 equiv) in THF (10 mL) was prepared then added to the above reaction mixture at −100 °C over 1 h, then kept stirring for a further 30 min at this temperature. Triisopropyl borate (4.94 mL, 21.4 mmol, 1.07 equiv) was then added in a single portion. After 40 min of stirring at −100 °C, 48 wt% aq. HBr (4.55 mL, 40.2 mmol, 1.02 equiv) was added in a single portion then the cooling bath was removed, and the reaction was warmed to rt while stirring for 1 h. *For the remainder of the preparation, the bay and fume cupboard lights were switched off.* The amine hydrobromide salt was filtered off and washed with Et_2O (3×). The organic liquor was concentrated at reduced pressure (water bath temperature 30 °C) and the residue resuspended in Et_2O (50 mL) and transferred to a flame-dried two-necked flask cooled under Ar and fitted with a septum. Pinacol (2.36 g, 20.0 mmol, 1.00 equiv) was followed by the addition of hexane (50 mL, 0.5 M). After stirring for 12 h at rt, the reaction mixture was washed with water (4×) and the collected organics dried (Na_2SO_4) then concentrated at reduced pressure (bath temp 30 °C, foil wrapped flask). Bulb-to-bulb distillation (1.1 mbar, 8 cm vertical path height, 120 °C sand bath) of the crude yellow oil afforded a colourless oil that turned into a white foam upon standing at rt under Ar. Subsequent drying on the high vacuum for 1 h afforded the desired product as a white

hygroscopic solid that was stored in an Ar-filled glovebox freezer (−20 °C) in the absence of light (2.97 g, 50%).

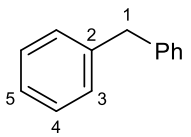
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (s, 1 H, H_1), 1.27 (s, 12 H, H_3).

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 83.4 (C_2) 24.7 (C_3).

^{11}B NMR (96 MHz, $CDCl_3$) δ 22.40.

The spectral data was consistent with the literature.[238]

diphenylmethane (3.238)



Chemical Formula: $C_{13}H_{12}$
Molecular Weight: 168.2390

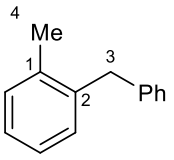
Prepared according to General Procedure F using benzyl boronic acid pinacol ester **3.22** (131 mg, 6.0 mmol, 3.0 equiv) and bromobenzene (0.21 mL, 2.0 mmol, 1.00 equiv). The crude (>99% ^{1}H NMR yield) was subject to column chromatography on silica gel (2% EtOAc in hexane) to afford the desired product as a white solid (276 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.20 (m, 4 H, H_2), 7.18−7.23 (m, 6 H, $H_{4,5}$), 4.00 (s, 2 H, H_1).

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 141.3 (C_2), 129.1 (C_3), 128.6 (C_4), 126.2 (C_5), 42.1 (C_1).

The spectral data were consistent with the literature.[283]

1-benzyl-2-methylbenzene (3.243)



Chemical Formula: $C_{14}H_{14}$
Exact Mass: 182.1096

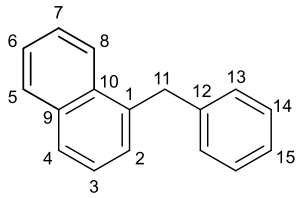
Prepared according to general procedure F using compound **3.7** (70 mg, 0.30 mmol, 3.0 equiv) and bromobenzene (11 μL, 0.10 mmol, 1.0 equiv). The crude (>99% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–1% Et_2O in hexane) to afford the desired product as a colourless oil (18.8 mg, >99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2 H), 7.23–7.09 (m, 7 H), 4.00 (s, 2 H, H_3), 2.25 (s, 3 H, H_4). For those unassigned, H_{Ar}.

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 140.5 ($C_{quart.}$), 139.1 ($C_{quart.}$), 136.8 (C_1), 130.4, 130.1, 128.9, 128.5, 126.6, 126.1, 126.1, 39.6 (C_3), 19.8 (C_4). For those unassigned, C_{Ar}.

The spectral data were consistent with the literature.[284]

1-benzylnaphthalene (3.244)



Chemical Formula: $C_{17}H_{14}$
Exact Mass: 218.1096

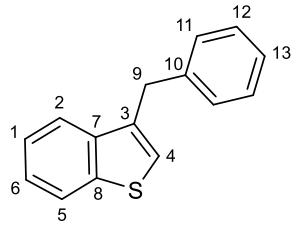
Prepared according to General Procedure F using compound **3.32** (80 mg, 0.30 mmol, 3.0 equiv) and bromobenzene (11 mL, 0.10 mmol, 1.0 equiv). The crude (84% ^{1}H NMR yield) was subject to column chromatography on silica gel (hexane) to afford the desired product as a white solid (20.6 mg, 94%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05–7.97 (m, 1 H, H_5), 7.91–7.83 (m, 1 H, H_8), 7.78 (d, *J* = 8.2 Hz, 1 H, H_4), 7.49–7.42 (m, 3 H, H_{Ar}), 7.33–7.26 (m, 3 H, H_{Ar}), 7.23–7.18 (m, 3 H, $H_{14,15}$), 4.48 (s, 2 H, H_{11}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.8 (C_1), 136.8 (C_9), 134.1 (C_{10}), 132.3 (C_{12}), 128.9, 128.8, 128.6, 127.5, 127.5, 127.3, 126.2, 126.1, 125.7, 124.4 (H_5), 39.2 (C_{11}). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[284]

3-benzylbenzo[*b*]thiophene (3.245)



Chemical Formula: $C_{15}H_{12}S$
Exact Mass: 224.0660

Prepared according to General Procedure F using compound **3.57** (82 mg, 0.30 mmol, 3.0 equiv) and bromobenzene (11 mL, 0.10 mmol, 1.0 equiv). The crude (94% ^{1}H NMR yield) was subject to column chromatography on silica gel (2% Et_2O in hexane) to afford the desired product as a colourless oil (21.1 mg, 94%).

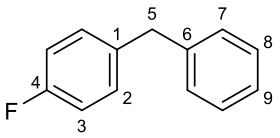
IR (film) ν 2361, 2342, 1494, 727, 696, 669 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.82 (m, 1 H, H_5), 7.75–7.67 (m, 1 H, H_2), 7.39–7.20 (m, 7 H, $H_{1,6,11–13}$), 7.01 (br t, *J* = 1.1 Hz, 1 H, H_4), 4.20 (s, 2 H, H_9).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.7 (C_7), 139.5 (C_{10}), 139.0 (C_8), 135.7 (C_3), 129.0, 128.7, 126.5 (C_{13}), 124.4 (C_1), 124.1 (C_6), 123.2 (C_4), 123.0 (C_5), 122.1 (C_2), 35.1 (C_9). C_{11} and C_{12} could not be unambiguously assigned.

HRMS (ESI+) exact mass calcd. for $C_{15}H_{12}{}^{32}S$ $[M]^+$ m/z = 225.0733; found 225.0734.

1-benzyl-4-fluorobenzene (3.246)



Chemical Formula: $C_{13}H_{11}F$
Exact Mass: 186.0845

Prepared according to General Procedure F using compound **3.42** (71 mg, 0.30 mmol, 3.0 equiv) and bromobenzene (11 μL, 0.10 mmol, 1.0 equiv). The crude (97% ^{1}H NMR yield) was subject to column chromatography on silica gel (1–3% Et_2O in hexane) to afford the desired product as a white solid (16.1 mg, 91%).

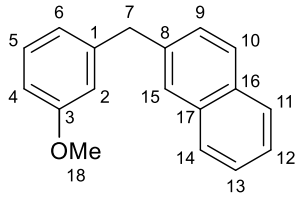
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2 H, H_3), 7.25–7.20 (m, 1 H, H9), 7.20–7.13 (m, 4 H, $H_{2,7}$), 7.01–6.95 (m, 2 H, H_8), 3.97 (s, 2 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.6 (d, $^1J_{CF}$ = 244.5 Hz, C_4), 141.1 (C_6), 136.9 (d, $^4J_{CF}$ = 2.4 Hz, C_1), 130.4 (d, $^3J_{CF}$ = 7.9 Hz, C_2), 129.0 (C_9), 128.7 (C_7), 126.3 (C_6), 115.3 (d, $^2J_{CF}$ = 21.2 Hz), 41.2 (C_5).

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ −117.41.

The spectral data were consistent with the literature.[285]

2-(3-methoxybenzyl)naphthalene (3.247)



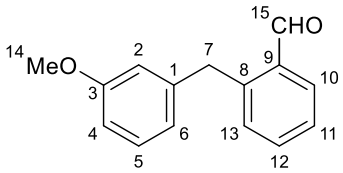
Chemical Formula: $C_{18}H_{16}O$
Exact Mass: 248.1201

Prepared according to General Procedure F using compound **3.33** (74 mg, 0.30 mmol, 3.0 equiv) and 2-bromonaphthalene (21 mg, 0.10 mmol, 1.0 equiv). The crude (64% ^{1}H NMR yield) was subject to column chromatography on silica gel (3% Et_2O in hexane) to afford the desired product as a white solid (20.2 mg, 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.71 (m, 3 H, $H_{11, 14, 15}$), 7.67–7.62 (m, 1 H, H_{10}), 7.46–7.38 (m, 2 H, $H_{12,13}$), 7.34–7.30 (m, 1 H, H_9), 7.22 (t, *J* = 7.8 Hz, 1 H, H_5), 6.83–6.84 (m, 1 H, H_6), **^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$)** δ 159.9 (C_3), 142.7 (C_1), 138.6 (C_8), 133.7($C_{Nap\text{-}quart}$), 132.2 ($C_{Nap\text{-}quart}$), 129.6 (C_5), 128.2 ($C_{Nap\text{-}CH}$), 127.8 ($C_{Nap\text{-}CH}$), 127.7 (2C, $C_{Nap\text{-}CH}$), 127.2 (C_{10}), 126.1 ($C_{Nap\text{-}CH}$), 125.5 ($C_{Nap\text{-}CH}$), 121.6 (C_6), 115.0 ($C_{Ar\text{-}CH}$), 111.5 ($C_{Ar\text{-}CH}$), 55.3 (C_{18}), 42.3 (C_7). Full assignment was not possible due to overlapping signals in ^{13}C NMR and 2D NMR.

The spectral data were consistent with the literature.[286]

2-(3-methoxybenzyl)benzaldehyde (3.248)



Chemical Formula: $C_{15}H_{14}O_2$
Exact Mass: 226.0994

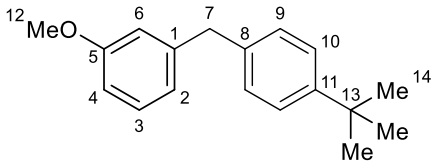
Prepared according to General Procedure F using compound **3.33** (74 mg, 0.30 mmol, 3.0 equiv) and 2-bromobenzaldehyde (12 mL, 0.10 mmol, 1.0 equiv). The crude (82% ^{1}H NMR yield) was subject to column chromatography on silica gel (3–5% Et_2O in hexane) to afford the desired product as a colourless solid (18.2 mg, 80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.25 (s, 1 H, H_{15}), 7.86 (dd, *J* = 7.7, 1.5 Hz, 1 H, H_{10}), 7.53 (td, *J* = 7.5, 1.2 Hz, 1 H, H_{12}), 7.42 (td, *J* = 7.5, 1.2 Hz, 1 H, H_{11}), 7.28 (br s, 1 H, H_{13}), 7.24–7.16 (m, 1 H, H_5), 6.78– 6.70 (m, 2 H, $H_{4,6}$), 6.68 (t, *J* = 2.2 Hz, 1 H, H_2), 4.43 (s, 2 H, H_7), 3.76 (s, 3 H, H_{14}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 192.6 (C_{15}), 159.9 (C_3), 142.9 (C_9), 142.3 (C_8), 134.1 (2C, $C_{1,12}$), 132.1 (C_{10}), 131.8 (C_{13}), 129.7 (C_5), 127.2 (C_{11}), 121.3 (C_6), 114.9 (C_2), 111.5 (C_4), 55.3 (C_{14}), 38.2 (C_7).

The spectral data were consistent with the literature.[287]

1-(4-(*tert*-butyl)benzyl)-3-methoxybenzene (3.249)



Chemical Formula: $C_{18}H_{22}O$
Exact Mass: 254.1671

Prepared according to General Procedure F using compound **3.33** (74 mg, 0.30 mmol, 3.0 equiv) and 1-bromo-4-(*tert*-butyl)benzene (17 μL, 0.10 mmol, 1.0 equiv). The crude (85% ^{1}H NMR yield) was subject to column chromatography on silica gel (2% Et_2O in hexane) to afford the desired product as a colourless solid (22.4 mg, 88%).

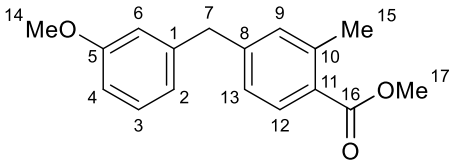
IR (film) ν 2961, 2361, 2342, 1599, 1584, 1487, 1258, 1051, 777 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2 H, H_{10}), 7.23–7.16 (m, 1 H, H_3), 7.14–7.09 (m, 2 H, H_9), 6.82–6.77 (m, 1 H, H_2), 6.73–6.75 (m, 2 H, $H_{4,6}$), 3.92 (s, 2 H, H_7), 3.78 (s, 3 H, H_{12}), 1.30 (s, 9 H, H_{14}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.8 (C_5), 149.0 (C_{11}), 143.0 (C_1), 138.0 (C_8), 129.5 (C_3), 128.6 (C_9), 125.5 (C_{10}), 121.6 (C_2), 115.0 (C_6), 111.3 (C_4), 55.3 (C_{12}), 41.6 (C_7), 34.5 (C_{13}), 31.5 (C_{14}).

HRMS (ESI+) exact mass calcd. for $C_{18}H_{23}O$ $[M+H]^+$ m/z = 255.1743; found 255.1736.

methyl 4-(3-methoxybenzyl)-2-methylbenzoate (3.250)



Chemical Formula: $C_{17}H_{18}O_3$
Exact Mass: 270.1256

Prepared according to General Procedure F using compound **3.33** (74 mg, 0.30 mmol, 3.0 equiv) and 4-bromo-2-methylbenzoate (17 mL, 0.10 mmol, 1.0 equiv). The crude (56% ^{1}H NMR yield) was subject to column chromatography on silica gel (1–5% Et_2O in hexane) to afford the desired product as a colourless solid (7.6 mg, 28%).

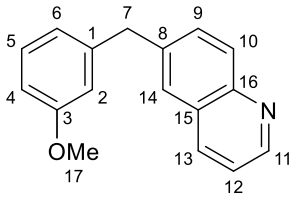
IR (film) ν 2949, 2924, 2361, 2342, 1719, 1597, 1258, 1084, 1049 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 1 H, H_{12}), 7.21 (t, *J* = 8.0 Hz, 1 H, H_3), 7.05–7.07 (m, 2 H, $H_{9,13}$), 6.75–6.77 (m, 2 H, $H_{4,6}$), 6.71 (br s, 1 H, H_2), 3.94 (s, 2 H, H_7), 3.87 (s, 3 H, H_{17}), 3.77 (s, 3 H, H_{14}), 2.56 (s, 3 H, H_{15}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.1 (C_{16}), 159.9 (C_5), 145.3 (C_1), 142.0 (C_8), 140.7 (C_{11}), 132.4 (C_{10}), 131.1 (C_{12}), 129.7 (C_3), 127.5 (C_{13}), 126.4 (C_9), 121.5 (C_6), 114.8 (C_2), 111.6 (C_4), 55.3 (C_{14}), 51.9 (C_{17}), 41.9 (C_7), 22.0 (C_{15}).

HRMS (ESI+) exact mass calcd. for $C_{17}H_{18}O_3Na$ $[M+Na]^+$ m/z = 293.1148; found 293.1151.

6-(3-methoxybenzyl)quinoline (3.251)



Chemical Formula: $C_{17}H_{15}NO$
Exact Mass: 249.1154

Prepared according to General Procedure F using compound **3.33** (74.4 mg, 0.30 mmol, 3.0 equiv) and 6-bromoquinoline (14 μL, 0.10 mmol, 1.0 equiv). The crude (64% ^{1}H NMR yield) was subject to column chromatography on silica gel to afford the desired product as a yellow solid (15.0 mg, 60%).

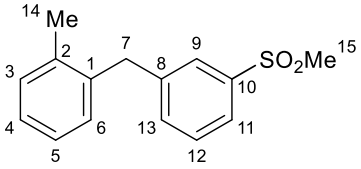
IR (film) ν 2927, 2361, 2342, 1595, 1584, 1489, 1260, 1049, 837, 770, 694 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (dd, *J* = 4.3, 1.7 Hz, 1 H, H_{11}), 8.13–8.05 (m, 1 H, H_{13}), 8.04–7.99 (m, 1 H, H_{10}), 7.62–7.53 (m, 2 H, $H_{9,14}$), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1 H), 7.25–7.18 (m, 1 H, H_5), 6.83 (dd, *J* = 7.8, 1.4 Hz, 1 H, H_6), 6.80–6.73 (m, 2 H, $H_{4,2}$), 4.14 (s, 2 H, H_7), 3.77 (s, 3 H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.0 (C_3), 150.0 (C_{11}), 147.4 (C_{16}), 142.1 (C_{15}), 139.5 (C_1), 135.9 (C_8), 131.4 (C_{13}), 129.7, 129.7, 126.9, 121.6, 121.3 (C_5), 115.1 (C_6), 113.4 (C_2), 111.7 (C_4), 55.3 (C_{17}), 42.0 (C_7). For those left unassigned, C_{Nap}.

HRMS (ESI+) exact mass calcd. for $C_{17}H_{15}NO$ $[M]^+$ m/z = 250.1226; found 250.1224.

1-methyl-2-(3-(methylsulfonyl)benzyl)benzene (3.252)



Chemical Formula: $C_{15}H_{16}O_2S$
Exact Mass: 260.0871

Prepared according to General Procedure F using compound **3.7** (70 mg, 0.30 mmol, 3.0 equiv) and 1-bromo-3-(methylsulfonyl)benzene (23.5 mg, 0.10 mmol, 1.0 equiv). The crude (90% ^{1}H NMR yield) was subject to column chromatography on silica gel (3–30% Et_2O in hexane) to afford the desired product as a white solid (19.6 mg, 28%).

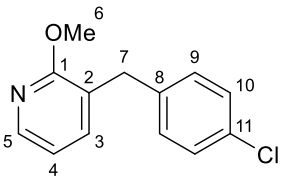
IR (film) ν 2924, 2359, 2340, 1595, 1456, 1299, 1142, 777, 741, 532 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.74 (m, 2 H, $H_{Ar\text{-}sulfonyl}$), 7.52–7.44 (m, 2 H, $H_{Ar\text{-}sulfonyl}$), 7.23 (t, *J* = 7.9 Hz, 1 H, H_5), 6.81–6.73 (m, 2 H, $H_{4,6}$), 6.71 (t, *J* = 2.1 Hz, 1 H, H_3), 4.03 (s, 2 H, H_7), 3.78 (s, 3 H, H_{15}), 3.03 (s, 3 H, H_{14}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.0 (C_{10}), 143.0 (C_8), 141.2 (C_1), 140.8 (C_2), 134.4 ($C_{Ar\text{-}sulfonyl}$), 129.6 ($C_{Ar\text{-}sulfonyl}$), 127.6 ($C_{Ar\text{-}sulfonyl}$), 125.3 ($C_{Ar\text{-}sulfonyl}$), 121.2 (C_6), 119.8 (C_5), 115.3 (C_3), 111.8 (C_4), 55.3 (C_{15}), 44.6 (C_{14}), 41.8 (C_7).

HRMS (ESI+) exact mass calcd. for $C_{15}H_{17}O_3{}^{32}S$ $[M+OH]^+$ m/z = 277.0893; found 277.0898.

3-(4-chlorobenzyl)-2-methoxypyridine (3.253)



Chemical Formula: $C_{13}H_{12}ClNO$
Exact Mass: 233.0607

Prepared according to General Procedure F using compound **3.58** (75 mg, 0.30 mmol, 3.0 equiv) and 1-bromo-4-chlorobenzene (19 mg, 0.10 mmol, 1.0 equiv). The crude (97% ^{1}H NMR yield) was subject to column chromatography on silica gel to afford the desired product as a white solid (22.8 mg, 98%).

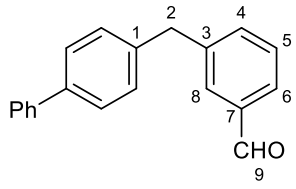
IR (film) ν 2359, 2338, 1585, 1464, 1408, 1016 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03–8.05 (m, 1 H, H_5), 7.32–7.22 (m, 3 H, $H_{3,9}$), 7.16–7.09 (m, 2 H, H_{10}), 6.77–6.82 (m, 1 H, H_4), 3.95 (s, 3 H, H_6), 3.87 (s, 2 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.0 (C_1), 145.0 (C_5), 138.3 ($C_{quart.}$), 138.1 (C_{ArCH}), 132.1 ($C_{quart.}$), 130.5 (C_{10}), 128.7 (C_{ArCH}), 123.6 ($C_{quart.}$), 116.9 (C_4), 53.5 (C_6), 35.2 (C_7). Full assignment was not possible due to overlapping signals in the 2D NMR.

HRMS (ESI+) exact mass calcd. for $C_{13}H_{12}{}^{35}ClNO$ $[M]^+$ m/z = 234.0680; found 234.0674.

3-([1,1'-biphenyl]-4-ylmethyl)benzaldehyde (3.254)



Chemical Formula: $C_{20}H_{16}O$
Exact Mass: 272.1201

Prepared according to General Procedure F using compound **3.26** (88 mg, 0.30 mmol, 3.0 equiv) and 3-bromobenzaldehyde (19 mg, 12 μL, 0.10 mmol, 1.0 equiv). The crude (94% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane) to afford the desired product as a colourless oil (21.1 mg, 94%).

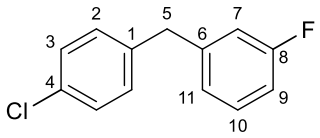
IR (film) ν 3725, 2849, 2359, 2341, 1697, 1603, 1450, 669, 760, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1 H, H_9), 7.79–7.69 (m, 2 H, $H_{6,8}$), 7.61–7.39 (m, 9 H), 7.27–7.26 (m, 1 H), 7.37–7.31 (m, 1 H), 4.11 (s, 2 H, H_2). For those left unassigned, H_{Ar}.

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 192.6 (C_9), 142.3 ($C_{quart.}$), 140.9 (C_3), 139.6 ($C_{quart.}$), 139.3 ($C_{quart.}$), 136.8 ($C_{7.}$), 135.3, 130.1, 129.1 129.4, 128.9, 128.1, 127.6, 127.4, 127.2, 41.4 (C_2). For those left unassigned, C_{Ar}.

HRMS (ESI+) exact mass calcd. for $C_{20}H_{17}NO$ $[M+H]^+$ m/z = 273.1274; found 273.1275.

1-(4-chlorobenzyl)-3-fluorobenzene (3.255)



Chemical Formula: $C_{13}H_{10}ClF$
Exact Mass: 220.0455

Prepared according to General Procedure F using compound **3.46** (76 mg, 0.30 mmol, 3.0 equiv) and 1-bromo-3-fluorobenzene (18 mg, 0.10 mmol, 1.0 equiv). The crude (>99% ^{1}H NMR yield) was subject to column chromatography on silica gel (1% Et_2O in hexane) to afford the desired product as a colourless oil (22.1 mg, >99%).

IR (film) ν 2363, 2338, 1589, 1489, 1449, 1092, 781, 748 cm^{-1}.

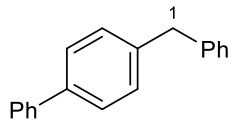
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.22 (m, 3 H, $H_{3,10}$), 7.13–7.08 (m, 2 H, H_2), 6.96–6.87 (m, 2 H, $H_{9,11}$), 6.83–6.86 (m, 1 H, H_7), 3.94 (s, 2 H, H_5).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.1 (d, $^1J_{CF}$ = 245.9 Hz, C_8), 143.2 (d, $^3J_{CF}$ = 7.2 Hz, C_6), 138.9 (C_4), 132.3 (C_3), 130.4 (C_2), 130.1 (d, $^3J_{CF}$ = 8.3 Hz, C_{10}), 128.8, 124.6 (d, $^4J_{CF}$ = 2.8 Hz, C_{11}), 115.9 (d, $^2J_{CF}$ = 21.2 Hz, C_7), 113.4 (d, $^2J_{CF}$ = 21.0 Hz, C_9), 41.1 (C_5).

^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) δ −113.25.

HRMS (ESI−) exact mass calcd. for $C_{13}H_9{}^{35}ClF$ $[M-H]^-$ m/z = 225.0733; found 225.0734.

4-benzyl-1,1'-biphenyl (3.269)



Chemical Formula: $C_{19}H_{16}$
Molecular Weight: 244.3370

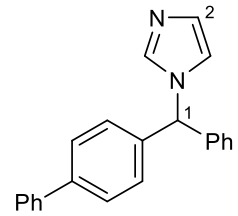
Prepared according to General Procedure F using **3.26** (221 mg, 0.75 mmol, 3.0 equiv) and bromobenzene (26.3 mL, 0.25 mmol, 1.00 equiv). The crude (97% ^{1}H NMR yield) was subject to column chromatography on silica gel (hexane) to afford the desired product as a white solid (59.1 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.55 (m, 2 H), 7.55–7.50 (m, 2 H), 7.43 (dd, *J* = 8.5, 7.0 Hz, 2 H), 7.35–7.29 (m, 3 H), 7.29–7.19 (m, 4 H), 4.03 (s, 2 H, H_1). For those left unassigned, H_{Ar}

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 141.1 ($C_{quart.}$), 140.4 ($C_{quart.}$), 139.2 ($C_{quart.}$), 129.5 ($C_{quart.}$), 129.1, 129.0, 128.9, 128.7, 127.4, 127.2, 127.2, 126.3, 41.7 (C_9). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[288]

bifonazole (3.262)



Chemical Formula: $C_{22}H_{18}N_2$
Molecular Weight: 310.4000

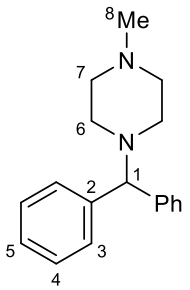
To an oven dried flask fitted with a stir bar that was evacuated and backfilled under Ar was added **3.269** (44.0 mg, 0.18 mmol, 1.00 equiv), NBS (32.0 mg, 0.18 mmol, 1.0 equiv), AIBN (29.6 mg, 0.18 mmol, 1.0 equiv) and the flask purged with Ar (3×). The flask was quickly transferred to a reflux condenser fitted with a septum and Ar balloon prior to the addition of CCl_4 (2.25 mL) and the solution was refluxed for 1 h, then cooled to rt. The reaction mixture was diluted in hexane (3 mL) and insoluble solids filtered off, washing with hexane, then the liquor concentrated at reduced pressure. To the flask containing the crude yellow solid was added dry K_2CO_3 (87.1 mg, 0.63 mmol, 3.5 equiv), imidazole (123 mg, 1.80 mmol, 10 equiv) and MeCN (4.50 mL). The reaction mixture was refluxed for 2 h. After cooling to rt, the reaction was diluted in MeCN (5 mL), filtered through Celite, and the liquor concentrated at reduced pressure. The crude (88% ^{1}H NMR yield) was subject to column chromatography on silica gel (20–40% EtOAc in hexane) to afford the desired product as a white solid (49.1 mg, 88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.8 Hz, 4 H), 7.48–7.42 (m, 3 H), 7.42–7.32 (m, 4 H), 7.20–7.10 (m, 5 H), 6.90 (br. s, 1 H, H_2), 6.57 (br. s, 1 H, H_1). For those left unassigned, H_{Ar}

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 141.4 ($C_{quart.}$), 140.3 ($C_{quart.}$), 139.2 ($C_{quart.}$), 138.2 ($C_{quart.}$), 137.6 ($C_{quart.}$), 129.6, 129.0, 129.0, 128.6, 128.6, 128.2, 127.76, 127.7, 127.2, 119.5 (C_2), 64.9 (C_1). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[289]

cyclizine (3.263)



Chemical Formula: $C_{18}H_{22}N_2$
Molecular Weight: 266.3880

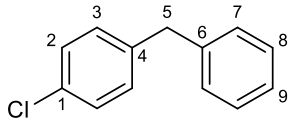
To an oven dried flask fitted with a stir bar that was evacuated and backfilled under Ar was added **3.238** (33.6 mg, 0.18 mmol, 1.00 equiv), NBS (32.0 mg, 0.18 mmol, 1.0 equiv), AIBN (29.6 mg, 0.18 mmol, 1.0 equiv) and the flask purged three times under Ar. The flask was quickly transferred to a reflux condenser fitted with a septum and Ar balloon prior to the addition of CCl_4 (2.25 mL) and the solution was refluxed for 1 h. After cooling to rt, the reaction mixture was diluted in hexane 3 mL and insoluble solids filtered off, washing with hexane (2×) then the liquor concentrated at reduced pressure. To the flask containing the crude solid was added dry K_2CO_3 (87.1 mg, 0.63 mmol, 3.5 equiv), *N*-methylpiperazine (0.20 mL, 2.0 mmol, 10 equiv) and MeCN (4.50 mL). The reaction mixture was refluxed for 2 h, then cooled to rt. The reaction mixture was diluted in MeCN 5 mL, filtered through Celite, and the liquor concentrated at reduced pressure. The crude (78% ^1H NMR yield) was subject to column chromatography on silica gel (CH_2Cl_2) to afford the desired product as a colourless oil (40.0 mg, 75%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.38 (m, 4 H, H_3), 7.29–7.23 (m,I 4 H, H_4), 7.22–7.13 (m, 2 H, H_5), 4.23 (s, 1 H, H_1), 2.73–2.24 (m, 8 H, $H_{6,7}$), 2.36 (s, 3 H, H_8). For those left unassigned, H_{Ar}.

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 142.6 (C_2), 128.7 (C_4), 127.9 (C_3), 127.2 (C_5), 76.2 (C_1), 55.2 (C_7), 51.3 ($C_{7'}$), 45.9 (C_6), 45.5 (C_8). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[290]

1-benzyl-4-chlorobenzene (3.275)



Chemical Formula: $C_{13}H_{11}Cl$
Exact Mass: 202.0549

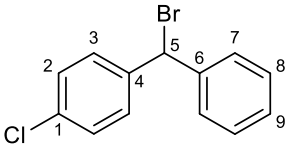
Prepared according to general procedure F using **3.46** (152 mg, 0.600 mmol, 3.00 equiv) and bromobenzene (21 mL, 0.20 mmol, 1.0 equiv). Following workup, the crude (98% ^{1}H NMR yield) was subject to column chromatography on silica gel (1% Et_2O in hexane) to afford the desired product as a colourless oil (39.8 mg, 98%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.31 (m, 2 H, H_2), 7.26–7.19 (m, 3 H, $H_{7–9}$), 7.16 (d, *J* = 7.5 Hz, 2 H, H_3), 7.12 (d, *J* = 8.1 Hz, 2 H, H_2), 3.95 (s, 2 H, H_5).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.7 (C_6), 139.7 (C_4), 132.0 (C_1), 130.4 (C_2), 129.0, 128.7 (2C), 126.4, 41.4 (C_5). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[31]

1-(bromo(phenyl)methyl)-4-chlorobenzene (3.276)



Chemical Formula: $C_{13}H_{10}BrCl$
Exact Mass: 279.9654

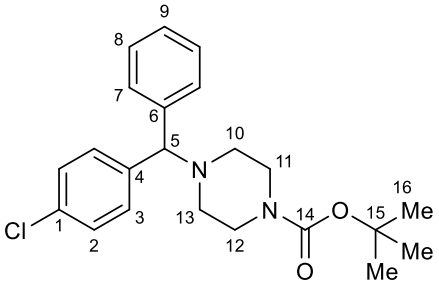
A flame-dried two-necked flask charged with a stir bar fitted with a reflux condenser and septum was cooled under Ar then charged with AIBN (820 mg, 5.00 mmol, 1.0 equiv), NBS (890 mg, 5.00 mmol, 1.0 equiv). The solids were purged with Ar (3×), then $CHCl_3$ (20. mL) was added, followed by **3.275** (1.01 g, 5.00 mmol, 1.00 equiv). The reaction mixture was heated to vigorous reflux (hotplate 90 °C) and stirred for 1.5 h, then cooled to rt and concentrated at reduced pressure. The yellow solid was suspended in hexane (50 mL) and the solids were filtered off, washing with hexane (3×). The collected liquor was concentrated at reduced pressure to afford the desired product as a dark yellow oil without further purification (1.34 g, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.29 (m, 9 H, $H_{2,3,7–9}$), 6.24 (s, 1 H, H_5).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.7 ($C_{quart.}$), 139.8 ($C_{quart.}$), 134.1 (C_1), 130.0, 128.9, 128.8, 128.5, 128.6, 54.4 (C_5). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[32]

***tert*-butyl 4-((4-chlorophenyl)(phenyl)methyl)piperazine-1-carboxylate (3.280)**



Chemical Formula: $C_{22}H_{27}ClN_2O_2$
Exact Mass: 386.1761

Prepared according to General Procedure G using **3.276** (56 mg, 0.20 mmol, 1.00 equiv) and **3.280** (186 mg, 1.00 mmol, 5.00 equiv). Following workup, the crude (93% ^{1}H NMR yield) was subject to column chromatography on silica gel (1–20% Et_2O in hexane) to afford the desired product as a colourless oil (69.6 mg, 90%).

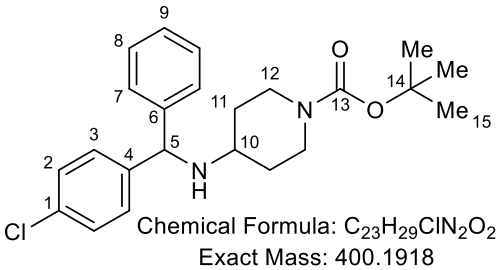
IR (film) ν 2974, 2361, 2342, 1244, 1167, 1121, 999, 758, 720, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.31 (m, 4 H), 7.23–7.29 (m, 4 H), 7.20 (t, *J* = 7.3 Hz, 1 H, H_9), 4.20 (s, 1 H, H_5), 3.41 (br s, 4 H, $H_{11,12}$), 2.32 (br s, 4 H, $H_{10,13}$), 1.43 (s, 9 H, H_{16}). For those left unassigned, H_{Ar}.

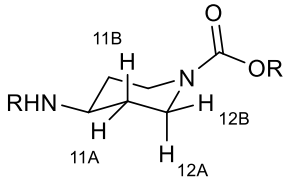
^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.9 (C_{14}), 142.0 ($C_{quart.}$), 141.2 ($C_{quart.}$), 132.8 (C_1), 129.3, 128.9, 128.8, 127.9, 127.4 (C_9), 79.7 (C_{15}), 75.5 (C_5), 51.8 ($C_{11,12}$), 44.0 (br, C_{NBoc}), 43.4 (br, C_{NBoc}) 28.5 (C_{16}). Piperazinyl (br) carbons were confirmed by ^{1}H-^{13}C HSQC crosspeaks due to broadening. For those left unassigned, C_{Ar}.

HRMS (ESI+) exact mass calcd. for $C_{22}H_{28}ClN_2O_2$ $[M+H]^+$ m/z =341.1148; found 341.1146.

***tert*-butyl 4-(((4-chlorophenyl)(phenyl)methyl)amino)piperidine-1-carboxylate (3.281)**



Chemical Formula: $C_{23}H_{29}ClN_2O_2$
Exact Mass: 400.1918



Prepared according to General Procedure G using **3.276** (56 mg, 0.20 mmol, 1.00 equiv) and **3.281** (200 mg, 0.60 mmol, 3.0 equiv). Following workup, the crude (>99% ^{1}H NMR yield) was subject to column chromatography on silica gel (1–10% Et_2O in hexane) to afford the desired product as a pale-yellow oil (76.1 mg, 98%).

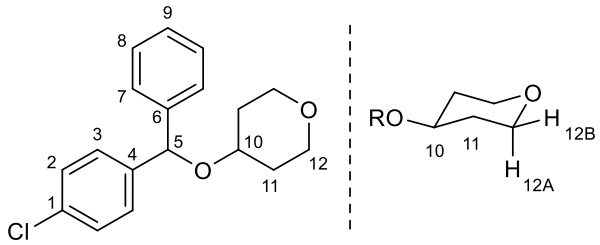
IR (film) ν 3734, 2976, 2931, 2852, 2359, 2338, 1686, 1234, 1169, 1140, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.19 (m, 9 H, $H_{2,3,7–9}$), 4.99 (s, 1 H, H_5), 3.98 (br s, 2 H, H_{12A}), 2.78–2.66 (m, 2 H, H_{12B}), 2.55 (tt, *J* = 10.3, 3.9 Hz, 1 H, H_{10}), 1.88 (br s, 2 H, H_{11A}), 1.44 (s, 9 H, H_{15}), 1.27–1.24 (m, 2 H, H_{11B}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.9 (C_{13}), 144.0 ($C_{quart.}$), 143.0 ($C_{quart.}$), 132.8 (C_1), 128.8 (3C), 127.4, 127.3, 79.5 (C_{14}), 63.2 (C_5), 52.5 (C_{10}), 42.8 (br, C_{12}), 32.9 (C_{11}), 28.6 (C_{15}). For those left unassigned, C_{Ar}.

HRMS (ESI+) exact mass calcd. for $C_{23}H_{29}{}^{35}ClN_2O_2Na$ $[M+Na]^+$ m/z =423.1810; found 423.1814.

4-((4-chlorophenyl)(phenyl)methoxy)tetrahydro-2*H*-pyran (3.282)



Chemical Formula: $C_{18}H_{19}ClO_2$
Exact Mass: 302.1074

Prepared according to General Procedure G using **3.276** (56 mg, 0.20 mmol, 1.00 equiv) and compound **3.282** (102 mg, 0.600 mmol, 3.00 equiv). Following workup, the crude (>99% ^{1}H NMR yield) was subject to column chromatography on silica gel (1–10% Et_2O in hexane) to afford the desired product as a colourless oil (58.3 mg, 96%).

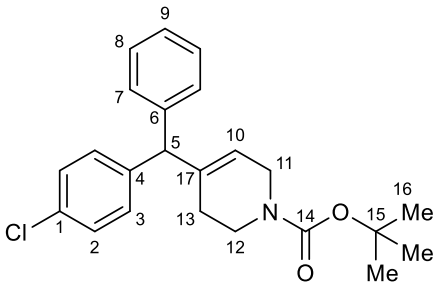
IR (film) ν 2949, 2853, 2359, 2365, 2342, 1489, 1086, 1013, 756, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.26 (m, 9 H $H_{2,3,7–9}$), 5.49 (s, 1 H, H_5), 3.95–3.88 (m, 2 H, H_{12A}), 3.55 (tt, *J* = 8.5, 4.0 Hz, 1 H, H_{10}), 3.39–3.35 (m, 2 H, H_{12B}), 1.90–1.81 (m, 2 H, H_{11}), 1.68–1.63 (m, 2 H, $H_{11'}$).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.6($C_{quart.}$), 142.4 ($C_{quart.}$), 142.2 ($C_{quart.}$), 141.4 ($C_{quart.}$), 133.3 (C_1), 133.3 ($C_{1'}$), 128.8, (2C), 128.6, 128.5, 128.0 (2C), 127.8, 127.1, 126.6, 79.5 (C_5), 71.7 (C_{10}), 65.7 (C_{12}), 32.7 (C_{11}), 32.5 ($C_{11'}$). For those left unassigned, C_{Ar}.

HRMS (ESI+) exact mass calcd. for $C_{18}H_{19}{}^{35}ClO_2Na$ $[M+Na]^+$ m/z =325.0966; found 325.0969.

***tert*-butyl 4-((4-chlorophenyl)(phenyl)methyl)-3,6-dihydropyridine-1(2*H*)-carboxylate (3.284)**



Chemical Formula: $C_{23}H_{26}ClNO_2$
Exact Mass: 383.1652

Prepared according to General Procedure F using **3.276** (56 mg, 0.20 mmol, 1.00 equiv) and **3.283** (186 mg, 0.600 mmol, 3.00 equiv). Following workup, the crude (71% ^{1}H NMR yield) was subject to column chromatography on silica gel (1–3% Et_2O in hexane) to afford the desired product as a pale-yellow oil (51.4 mg, 70%).

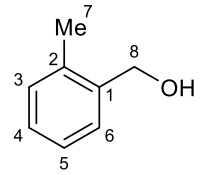
IR (film) ν 2976, 2926, 2361, 2342, 1653, 1165, 1475, 1456, 754, 700, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5 H, $H_{7–9}$), 7.13–7.10 (m, 2 H, H_3), 7.05–7.09 (m, 2 H, H_2), 5.12 (br s, 2 H, H_{10}), 4.64 (s, 1 H, H_5), 3.89 (br s, 2 H, H_{12}), 3.48 (d, *J* = 6.7 Hz, 2 H, H_{11}), 2.05 (br s, 2 H, H_{13}), 1.46 (s, 9 H, H_{16}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.6 (C_{14}), 141.5 ($C_{quart.}$), 140.6 ($C_{quart.}$), 132.4 (C_1), 130.7 (C_2), 129.3 (C_3), 128.8 (2C), 128.6 (2C), 128.0 (C_{10}), 126.8, 126.7, 79.7, 75.8 (C_{15}), 57.6 (C_5), 28.6 (C_{16}). For those left unassigned, C_{Ar}.

HRMS (ESI+) exact mass calcd. for $C_{23}H_{26}{}^{35}ClNO_2Na$ $[M+Na]^+$ m/z =406.1544; found 406.1546.

2-tolylmethanol (3.285)



Chemical Formula: $C_8H_{10}O$
Exact Mass: 122.0732

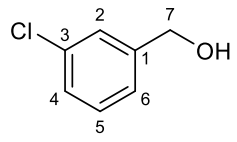
Prepared according to General Procedure H using *o*-tolylboronic acid (27.2 mg, 0.20 mmol, 1.0 equiv). Following workup, the crude (99% ^{1}H NMR yield) was subject to column chromatography (CH_2Cl_2) to afford the desired product as a white solid (22.7 mg, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 6.1, 2.8 Hz, 1 H, H_3), 7.25–7.16 (m, 3 H, $H_{4–6}$), 4.71 (d, *J* = 5.8 Hz, 2 H, H_8), 2.37 (s, 3 H, H_7), 1.51 (t, *J* = 5.8 Hz, 1 H, OH).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.8 (C_1), 136.3 (C_2), 130.5 (C_3), 128.0 (C_{Ar}) 127.7 (C_3), 126.2 (C_{Ar}), 63.8 (C_8), 18.8 (C_7).

The spectral data were consistent with the literature.[291]

(3-chlorophenyl)methanol (3.286)



Chemical Formula: C_7H_7ClO
Exact Mass: 142.0185

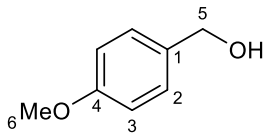
Prepared according to General Procedure H using (3-chlorophenyl)boronic acid (31.3 mg, 0.20 mmol, 1.0 equiv) with a modified reaction temperature (45 °C) and time (36 h) for the homologation step. Following workup, the crude (50% ^{1}H NMR yield) was subject to column chromatography (3–5% Et_2O in hexane) to afford the desired product as a colourless oil (14.1 mg, 49%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.35 (m, 1 H, H_2), 7.33–7.20 (m, 3 H, $H_{4–6}$), 4.69 (d, *J* = 5.9 Hz, 2 H, H_7), 1.71 (t, *J* = 6.0 Hz, 1 OH).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.0 (C_1), 134.6 (C_3), 130.0, 127.9, 127.1 (C_2), 125.0, 64.7 (C_7). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[284]

(4-methoxyphenyl)methanol (3.287)



Chemical Formula: $C_8H_{10}O_2$
Exact Mass: 138.0681

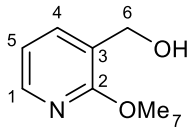
Prepared according to General Procedure H using (4-methoxyphenyl)boronic acid (30.4 mg, 0.20 mmol, 1.0 equiv). Following workup, the crude (86% ^{1}H NMR yield) was subject to column chromatography (2–5% Et_2O in hexane) to afford the desired product as a white solid (23.2 mg, 84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.26 (m, 2 H, H_2), 6.93–6.86 (m, 2 H, H_3), 4.62 (s, 2 H, H_5), 3.81 (s, 3 H, H_6), 1.64 (br s, 1 OH).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.3 (C_4), 133.2 (C_1), 128.8 (C_2), 114.1 (C_3), 65.2 (C_5), 55.4 (C_6).

The spectral data were consistent with the literature.[284]

(2-methoxypyridin-3-yl)methanol (3.288)



Chemical Formula: $C_7H_9NO_2$
Exact Mass: 139.0633

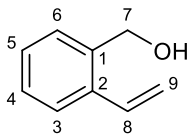
Prepared according to General Procedure H using (2-methoxypyridin-3-yl)boronic acid (30.6 mg, 0.20 mmol, 1.0 equiv). Following workup, the crude (86% ^{1}H NMR yield) was subject to column chromatography (10–30% Et_2O in hexane) to afford the desired product as a colourless oil (22.5 mg, 81%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 5.1, 1.9 Hz, 1 H, H_1), 7.61–7.54 (m, 1 H, H_4), 6.89 (dd, *J* = 7.2, 5.1 Hz, 1 H, H_5), 4.65 (d, *J* = 6.1 Hz, 2 H, H_6), 3.99 (s, 3 H, H_7), 2.29 (t, *J* = 6.4 Hz, 1 OH).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.8 (C_2), 146.0 (C_1), 136.7 (C_4), 123.4 (C_3), 117.0 (C_5), 61.3 (C_6), 53.5 (C_7).

The spectral data were consistent with the literature.[292]

(2-vinylphenyl)methanol (3.289)



Chemical Formula: $C_9H_{10}O$
Exact Mass: 134.0732

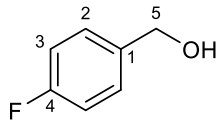
Prepared according to General Procedure H using (2-vinylphenyl)boronic acid (29.6 mg, 0.20 mmol, 1.0 equiv). Following workup, the crude (74% ^{1}H NMR yield) was subject to column chromatography (5–15% Et_2O in hexane) to afford the desired product as a colourless oil (21.0 mg, 78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.4, 1.8 Hz, 1 H, H_5), 7.37 (dd, *J* = 7.2, 1.8 Hz, 1 H, H_6), 7.32 (dd, *J* = 7.4, 1.8 Hz, 2 H, $H_{3,4}$), 7.06 (dd, *J* = 17.4, 11.0 Hz, 1 H, H_8), 5.71 (dd, *J* = 17.4, 1.4 Hz, 1 H, $H_{9\text{-}trans}$), 5.37 (dd, *J* = 11.0, 1.3 Hz, 1 H, $H_{9\text{-}cis}$), 4.77 (d, *J* = 5.1 Hz, 2 H, H_7), 1.56 (t, *J* = 6.1 Hz, 1 OH).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 137.7 (C_1), 136.8 (C_2), 133.9 (C_8), 128.5, 128.4, 128.1, 126.1, 116.7 (C_9), 63.6 (C_7). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[293]

(4-fluorophenyl)methanol (3.290)



Chemical Formula: C_7H_7FO
Exact Mass: 126.0481

Prepared according to General Procedure H using (4-fluoroophenyl)boronic acid (28.0 mg, 0.20 mmol, 1.0 equiv). Following workup, the crude (76% ^1H NMR yield) was subject to column chromatography (2–6% Et_2O in hexane) to afford the desired product as a colourless oil (18.3 mg, 73%).

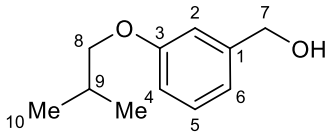
^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.29 (m, 2 H, H_2), 7.09–7.00 (m, 2 H, H_3), 4.66 (br s, 2 H, H_5), 1.73 (br s, 1 OH).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 162.5 (d, $^1J_{CF}$ = 245.4 Hz, C_4), 136.7 (d, $^4J_{CF}$ = 3.2 Hz, C_1), 128.9 (d, $^3J_{CF}$ = 8.0 Hz, C_2), 115.5 (d, $^2J_{CF}$ = 21.4 Hz, C_3), 64.8 (C_5).

$^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ −144.88.

The spectral data were consistent with the literature.[294]

(3-isobutoxyphenyl)methanol (3.291)



Chemical Formula: $C_{11}H_{16}O_2$
Exact Mass: 180.1150

Prepared according to General Procedure H using (3-isobutoxyphenyl)boronic acid (38.8 mg, 0.20 mmol, 1.0 equiv). Following workup, the crude (91% ^1H NMR yield) was subject to column chromatography (5–15% Et_2O in hexane) to afford the desired product as a colourless oil (33.9 mg, 94%).

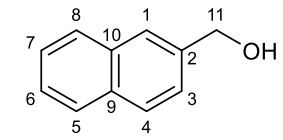
IR (film) ν 3325, 2957, 2872, 2361, 2342, 1472, 1263, 1036 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.22 (m, 1 H, H_2), 6.97–6.89 (m, 2 H, $H_{5,6}$), 6.86–6.79 (m, 1 H, H_4), 4.67 (br s, 2 H, H_7), 3.73 (d, *J* = 6.6 Hz, 2 H, H_8), 2.03–2.14 (m, 1 H, H_9), 1.68, (br, 1 OH), 1.03 (d, *J* = 6.7 Hz, 6 H, H_{10}).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.7 (C_3), 142.6 (C_1), 129.7 (C_2), 119.0, 114.0 (C_4), 113.1, 74.5 (C_8), 65.5 (C_7), 28.4 (C_9), 19.4 (C_{10}). For those left unassigned, C_{Ar}.

HRMS (ESI+) exact mass calcd. for $C_{11}H_{17}O_2$ $[M+Na]^+$ m/z = 203.1043; found 203.1045.

naphthalen-2-ylmethanol (3.292)



Chemical Formula: $C_{11}H_{10}O$
Exact Mass: 158.0732

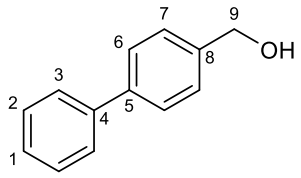
Prepared according to General Procedure H using naphthalen-2-ylboronic acid (34 mg, 0.20 mmol, 1.0 equiv). Following workup, the crude (65% ^{1}H NMR yield) was subject to column chromatography (1–5% Et_2O in hexane) to afford the desired product as a white solid (21.0 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89–7.79 (m, 4 H, $H_{1,4,5,8}$), 7.53–7.44 (m, 3 H, $H_{3,6,7}$), 4.87 (d, *J* = 5.7 Hz, 2 H, H_{11}), 1.78 (t, *J* = 5.9 Hz, 1 OH).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.4 (C_2), 133.5 ($C_{quart.}$), 133.1($C_{quart.}$), 128.5, 128.0, 127.9, 126.3, 126.1, 125.6, 125.3, 65.7 (C_{11}). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[295]

[1,1'-biphenyl]-4-ylmethanol (3.293)



Chemical Formula: $C_{13}H_{12}O$
Exact Mass: 184.0888

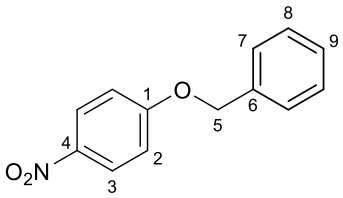
Prepared according to General Procedure H using [1,1'-biphenyl]-4-ylboronic acid (39.6 mg, 0.20 mmol, 1.0 equiv). Following workup, the crude (73% ^{1}H NMR yield) was subject to column chromatography (5% Et_2O in hexane) to afford the desired product as a white solid (25.8 mg, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64–7.56 (m, 4 H, $H_{6,7}$), 7.49–7.41 (m, 4 H, $H_{2,3}$), 7.40–7.32 (m, 1 H, H_1), 4.75 (s, 2 H, H_9), 1.80 (br s, 1 OH).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 141.0 ($C_{quart.}$), 140.8 ($C_{quart.}$), 140.0 (C_8), 128.9 (C_6), 128.7, 127.6, 127.5 (C_7), 127.2, 65.3 (C_9). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[296]

1-(benzyloxy)-4-nitrobenzene (3.295)



Chemical Formula: $C_{13}H_{11}NO_3$
Exact Mass: 229.0739

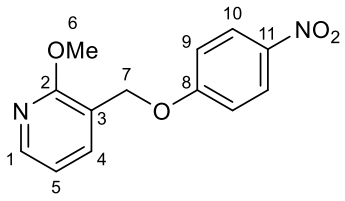
Prepared according to General Procedure I using **3.22** (21.8 mg, 20.0 μL, 0.10 mmol, 1.0 equiv) and 4-nitrophenol (69.6 mg, 0.50 mmol, 5.0 equiv). Following workup, the crude (63% ^{1}H NMR yield) was subject to column chromatography on silica gel (5% Et_2O in hexane) to afford the desired product as a yellow oil (14.3 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25–8.17 (m, 2 H, H_3), 7.46–7.33 (m, 5 H, $H_{7–9}$), 7.07–6.99 (m, 2 H, H_2), 5.17 (s, 2 H, H_5).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.8 (C_4), 141.8 (C_1), 135.6 (C_6), 129.0, 128.7 (C_9), 127.7, 126.1 (C_3), 115.0 (C_2), 70.8 (C_5). C_7 and C_8 could not be unambiguously assigned.

The spectral data were consistent with the literature.[254]

2-methoxy-3-((4-nitrophenoxy)methyl)pyridine (3.296)



Chemical Formula: $C_{13}H_{12}N_2O_4$
Exact Mass: 260.0797

Prepared according to General Procedure I using **3.58** (49.8, 0.20 mmol, 1.0 equiv) and 4-nitrophenol (139 mg, 1.00 mmol, 5.0 equiv). Following workup, the crude (74% ^{1}H NMR yield) was subject to column chromatography on silica gel (1–5% Et_2O in hexane) to afford the desired product as a white solid (36.4 mg, 70%).

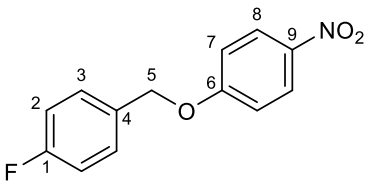
IR (film) ν 2365, 2357, 1589, 1508, 1458, 1341, 1258, 1111, 1026, 752, 669 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24–8.20 (m, 2 H, H_{10}), 8.16 (dd, *J* = 5.0, 1.9 Hz, 1H, H_4), 7.70 (ddt, *J* = 7.3, 1.7, 0.8 Hz, 1 H, H_5), 7.09–7.01 (m, 2 H, H_9), 6.93 (dd, *J* = 7.3, 5.0 Hz, 1 H, H_1), 5.16 (s, 2 H, H_7), 4.01 (s, 3 H, H_6).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.6 (C_8), 161.1 (C_2), 146.7 (C_4), 141.9 (C_{11}), 136.7 (C_5), 126.1 (C_{10}), 118.5 (C_3), 117.0 (C_1), 115.0 (C_9), 65.3 (C_7), 53.7 (C_6).

HRMS (ESI+) exact mass calcd. for $C_{13}H_{12}O_4N_2Na$ $[M+Na]^+$ m/z = 283.0689; found. 283.0687.

1-fluoro-4-((4-nitrophenoxy)methyl)benzene (3.297)



Chemical Formula: $C_{13}H_{10}FNO_3$
Exact Mass: 247.0645

Prepared according to General Procedure I using **3.42** (47.2 mg, 0.20 mmol, 1.0 equiv) and 4-nitrophenol (139 mg, 1.00 mmol, 5.0 equiv). Following workup, the crude (55% ^{1}H NMR yield) was subject to column chromatography on silica gel (2–4% Et_2O in hexane) to afford the desired product as a white solid (28.3 mg, 57%).

IR (film) ν 2357, 2342, 1593, 1516, 1497, 1337, 1258, 912, 748 cm^{-1}.

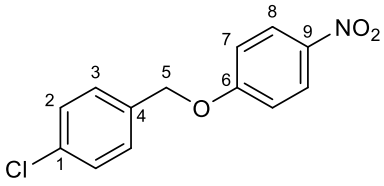
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25–8.17 (m, 2 H, H_8), 7.45–7.36 (m, 2 H, H_3), 7.15–7.06 (m, 2 H, H_2), 7.06–6.95 (m, 2 H, H_7), 5.12 (s, 2 H, H_5).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.6 (C_6), 162.9 (d, $^1J_{CF}$ = 247.4 Hz, C_1), 141.9 (C_9), 131.4 (d, $^4J_{CF}$ = 3.2 Hz, C_4), 129.6 (d, $^3J_{CF}$ = 8.2 Hz, C_3), 126.12 (C_8), 115.9 (d, $^2J_{CF}$ = 21.7 Hz, C_2), 115.0 (C_7), 70.1 (C_5).

$^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) −113.11.

HRMS (EI) exact mass calcd. for $C_{13}H_{10}FNO_2$ $[M-O]^-$ m/z = 231.0690; found 231.0692.

1-chloro-4-((4-nitrophenoxy)methyl)benzene (3.298)



Chemical Formula: $C_{13}H_{10}ClNO_3$
Exact Mass: 263.0349

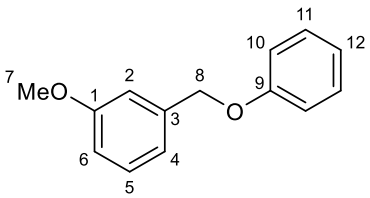
Prepared according to General Procedure I using **3.46** (50.5 mg, 0.20 mmol, 1.0 equiv) and 4-nitrophenol (139 mg, 1.00 mmol, 5.0 equiv). Following workup, the crude (48% ^{1}H NMR yield) was subject to column chromatography on silica gel (2–4% Et_2O in hexane) to afford the desired product as a white solid (28.6 mg, 54%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25–8.17 (m, 2 H, H_8), 7.43–7.33 (m, 4 H, $H_{2,3}$), 7.06–6.98 (m, 2 H, H_7), 5.13 (s, 2 H, H_5).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.5 (C_6), 142.0 (C_9), 134.6 (C_4), 134.1 (C_1), 129.2, 129.0, 126.1 (C_8), 115.0 (C_7), 70.0 (C_5). C_2 and C_3 could not be unambiguously assigned.

The spectral data were consistent with the literature.[297]

1-methoxy-3-(phenoxymethyl)benzene (3.299)



Chemical Formula: $C_{14}H_{14}O_2$
Exact Mass: 214.0994

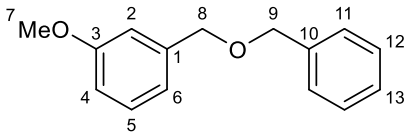
Prepared according to General Procedure I using **3.33** (49.6 mg, 0.20 mmol, 1.0 equiv) and phenol (94.1 mg, 1.00 mmol, 5.0 equiv). Following workup, the crude (70% ^{1}H NMR yield) was subject to column chromatography on silica gel (3–5% Et_2O in hexane) to afford the desired product as a white solid (30.6 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (ddd, *J* = 11.3, 6.2, 3.2 Hz, 3 H, $H_{4–6}$), 7.05–6.93 (m, 5 H, $H_{10–12}$), 6.87 (dd, *J* = 8.2, 2.6 Hz, 1 H, H_2), 5.05 (s, 2 H, H_8), 3.83 (s, 3 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.0 (C_1), 158.9 (C_9), 138.8 (C_3), 129.8, 129.6, 129.4, 121.1, 119.8, 115.0, 113.6 (C_2), 113.0, 69.9 (C_8), 55.4 (C_7). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[298]

1-((benzyloxy)methyl)-3-methoxybenzene (3.300)



Chemical Formula: $C_{15}H_{16}O_2$
Exact Mass: 228.1150

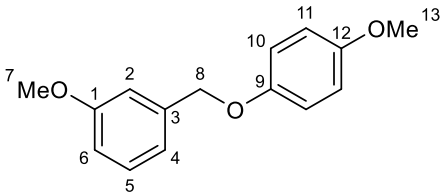
Prepared according to General Procedure I with a slight modification using **3.33** (49.6 mg, 0.20 mmol, 1.0 equiv). Benzyl alcohol was used in solvent quantities (0.40 mL, 3.85 mmol, 19.2 equiv) with the exclusion of PhMe. Following workup, the crude (60% ^{1}H NMR yield) was subject to column chromatography on silica gel (5% Et_2O in hexane) to afford the desired product as a white solid (28.4 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.33 (m, 4 H, $H_{11,12}$), 7.33–7.27 (m, 2 H), 7.02–6.92 (m, 2 H), 6.88–6.81 (m, 1 H, H_2), 4.56 (s, 2 H, H_8), 4.55 (s, 2 H, H_9), 3.82 (s, 3 H, H_7). Remaining aromatic protons could not be unambiguously assigned.

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.9 (C_3), 140.1 (C_{10}), 138.4 (C_3), 129.6, 128.6, 128.0, 127.8, 120.1, 113.4, 113.2, 72.2 (C_{Benzyl}), 72.1 (C_{Benzyl}), 55.4 (C_7). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[299]

1-methoxy-3-((4-methoxyphenoxy)methyl)benzene (3.301)



Chemical Formula: $C_{15}H_{16}O_3$
Exact Mass: 244.1099

Prepared according to General Procedure I using **3.33** (49.6 mg, 0.20 mmol, 1.0 equiv) and 4-methoxyphenol (124 mg, 1.00 mmol, 5.0 equiv). Following workup, the crude (44% ^{1}H NMR yield) was subject to column chromatography on silica gel (2–5% Et_2O in hexane) to afford the desired product as a white solid (19.7 mg, 40%).

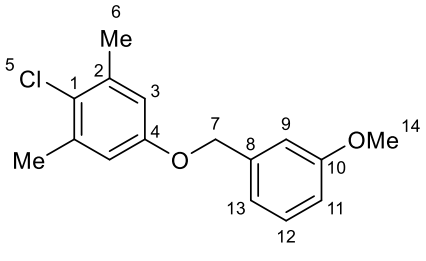
IR (film) ν 2930, 2833, 1506, 1458, 1267, 1227, 1038, 824, 764, 691 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.27 (m, 1 H, H_5), 7.04–6.96 (m, 2 H, H_{10}), 6.93–6.89 (m, 2 H, H_{11}), 6.88–6.81 (m, 3 H, $H_{2,4,6}$), 5.00 (s, 2 H, H_8), 3.82 (s, 3 H, H_{13}), 3.77 (s, 3 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.9 (C_1), 154.1 (C_{12}), 153.0 (C_9), 139.0 (C_3), 129.7, 119.8, 116.0, 114.8, 113.6, 113.0 (C_{11}), 70.7 (C_8), 55.9 (C_7), 55.4 (C_{13}). For those left unassigned, C_{Ar}.

HRMS (ESI+) exact mass calcd. for $C_{15}H_{16}O_3Na$ $[M+Na]^+$ m/z =297.0992; found 267.0988.

2-chloro-5-((3-methoxybenzyl)oxy)-1,3-dimethylbenzene (3.302)



Chemical Formula: $C_{16}H_{17}ClO_2$
Exact Mass: 276.0917

Prepared according to General Procedure I using **3.33** (49.6 mg, 0.20 mmol, 1.0 equiv) and 4-chloro-3,5-dimethylphenol (157 mg, 1.00 mmol, 5.0 equiv). Following workup, the crude (71% ^{1}H NMR yield) was subject to column chromatography on silica gel (2–4% Et_2O in hexane) to afford the desired product as a light green oil (19.7 mg, 77%).

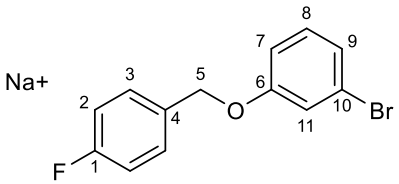
IR (film) ν 2361, 2342, 1462, 679, 669 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.9 Hz, 1 H, H_{12}), 7.03–6.94 (m, 2 H, $H_{11,13}$), 6.87 (dd, *J* = 8.3, 2.6 Hz, 1 H, H_9), 6.72 (s, 2 H, H_3), 4.99 (s, 2 H, H_7), 3.82 (s, 3 H, H_{14}), 2.34 (s, 6 H, H_6).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.0 (C_{10}), 156.7 (C_4), 138.6 (C_8), 137.3 (C_2), 129.8 (C_{12}), 126.6 (C_1), 119.7 (C_{13}), 114.9 (C_3), 113.6 (C_9), 113.0 (C_{11}), 70.1 (C_7), 55.4 (C_{14}), 21.1 (C_6).

HRMS (ESI+) exact mass calcd. for $C_{16}H_{17}{}^{35}ClO_2Na$ $[M+Na]^+$ m/z =299.0809; found 299.0819.

1-bromo-3-((4-fluorobenzyl)oxy)benzene (3.303)



Chemical Formula: $C_{13}H_{10}BrFO$
Exact Mass: 279.9899

Prepared according to General Procedure I using **3.42** (47.2 mg, 0.20 mmol, 1.0 equiv) and 3-bromophenol (173 mg, 1.00 mmol, 5.0 equiv). Following workup, the crude (76% ^1H NMR yield) was subject to column chromatography on silica gel (2–4% Et_2O in hexane) to afford the desired product as a colourless oil (42.8 mg, 76%).

IR (film) ν 2401, 2378, 2361, 1602, 1551, 1508, 1259, 1102, 770 cm^{-1}.

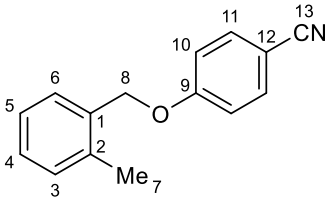
^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (ddd, *J* = 8.5, 5.4, 2.6 Hz, 2 H), 7.18–7.04 (m, 5 H), 6.89 (ddd, *J* = 8.1, 2.5, 1.1 Hz, 1 H, H_{11}), 5.00 (s, 2 H, H_5). For those left unassigned, H_{Ar}.

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 162.7 (d, $^1J_{CF}$ = 246.6 Hz, C_{10}), 159.5 (C_6), 132.25 (d, $^4J_{CF}$ = 3.2 Hz, C_4), 130.6, 129.5 (d, $^3J_{CF}$ = 8.2 Hz), 124.3, 123.0 (C_{10}), 118.3, 115.7 (d, $^2J_{CF}$ = 21.7 Hz, C_2), 113.9, 69.7 (C_5). For those left unassigned, C_{Ar}.

$^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −113.83.

HRMS (ESI+) exact mass calcd. for $C_{13}H_{10}{}^{79}BrFO$ $[M+Na]^+$ m/z =302.9791; found 302.9799.

4-((2-methylbenzyl)oxy)benzonitrile (3.304)



Chemical Formula: $C_{15}H_{13}NO$
Exact Mass: 223.0997

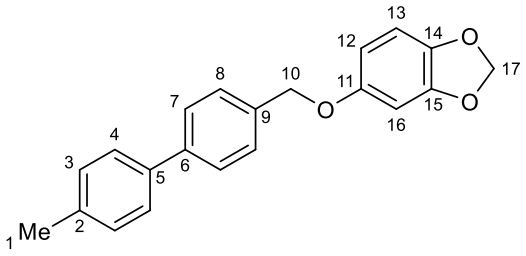
Prepared according to General Procedure I using **3.7** (46.4, 0.20 mmol, 1.0 equiv) and 4-hydroxybenzonitrile (119 mg, 1.00 mmol, 5.0 equiv). Following workup, the crude (52% ^1H NMR yield) was subject to column chromatography on silica gel (3–5% Et_2O in hexane) to afford the desired product as a white solid (22.2 mg, 50%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.65–7.56 (m, 2 H, H_{11}), 7.39–7.35 (m, 1 H, H_3), 7.31–7.27 (m, 1 H, H_4), 7.26–7.20 (m, 2 H, $H_{5,6}$), 7.07–6.99 (m, 2 H, H_{10}), 5.09 (s, 2 H, H_8), 2.37 (s, 3 H, H_7).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 162.2 (C_9), 136.9 (C_1), 134.2 (C_{11}), 133.7 (C_2), 130.8, 128.9, 128.8, 126.3, 119.4 (C_{13}), 115.6 (C_{10}), 104.3 (C_{12}), 69.1 (C_8), 19.0 (C_7). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[300]

5-((4'-methyl-[1,1'-biphenyl]-4-yl)methoxy)benzo[*d*][1,3]dioxole (3.305)



Chemical Formula: $C_{21}H_{18}O_3$
Exact Mass: 318.1256

Prepared according to General Procedure I using **3.59** (61.6 mg, 0.20 mmol, 1.0 equiv) and sesmol, benzo[*d*][1,3]dioxol-5-ol, (138 mg, 1.00 mmol, 5.0 equiv). Following workup, the crude (54% ^{1}H NMR yield) was subject to column chromatography on silica gel (2–5% Et_2O in hexane) to afford the desired product as a colourless oil (37.8 mg, 59%).

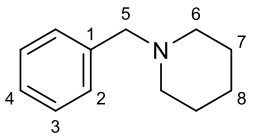
IR (film) ν 2365, 2357, 2342, 1734, 943, 889, 762 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.57 (m, 2 H, H_8), 7.52–7.45 (m, 4 H, $H_{4,7}$), 7.25 (br s, 2 H, H_3), 6.72 (d, *J* = 8.5 Hz, 1 H, H_{13}), 6.58 (d, *J* = 2.5 Hz, 1 H, H_{16}), 6.42 (dd, *J* = 8.4, 2.5 Hz, 1 H, H_{12}), 5.92 (s, 2 H, H_{17}), 5.02 (s, 2 H, H_{10}), 2.40 (s, 3 H, H_1).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.4 (C_{11}), 148.4 (C_{14}), 142.0 (C_{15}), 141.0 ($C_{quart.}$), 138.0 ($C_{quart.}$), 137.3 (C_2), 135.8, 129.7 (C_3), 128.1, 127.3, 127.1, 108.1 (C_{13}), 106.2 (C_{12}), 101.3 (C_{17}), 98.6 (C_{16}), 70.9 (C_{10}), 21.3 (C_1).). For those left unassigned, C_{Ar}.

HRMS (ESI+) exact mass calcd. for $C_{21}H_{18}O_3Na$ $[M+Na]^+$ m/z =341.1148; found 341.1146.

1-benzylpiperidine (3.314)



Chemical Formula: $C_{12}H_{17}N$
Exact Mass: 175.1361

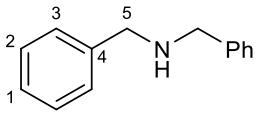
Prepared according to General Procedure I using **3.22** (21.8 mg, 20 μL, 0.10 mmol, 1.0 equiv) and piperidine (34.1 mg, 39.5 mL, 0.40 mmol, 4.0 equiv). Following workup, the crude (75% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–5% Et_2O in hexane containing 0.1% Et_3N) to afford the desired product as a colourless oil (12.5 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.30 (m, 4 H, $H_{2,3}$), 7.27–7.23 (m, 1 H, H_4), 3.51 (s, 2 H, H_5), 2.41 (br s, 4 H, H_6), 1.60 (quint., *J* = 5.6 Hz, 4 H, H_7), 1.46–1.43 (m, 2 H, H_8).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.0 (br, C_1), 129.5 (C_2), 128.3 (C_3), 127.1 (C_4), 63.9 (C_5), 54.5 (C_6), 25.9 (C_7), 24.4 (C_8).

The spectral data were consistent with the literature.[301]

dibenzylamine (3.317)



Chemical Formula: $C_{14}H_{15}N$
Exact Mass: 197.1204

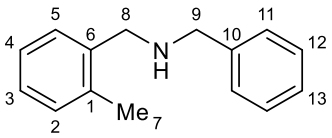
Prepared according to General Procedure I using **3.33** (21.8 mg, 20.0 μL, 0.10 mmol, 1.0 equiv) and benzylamine (42.9 mg, 43.6 mL, 0.40 mmol, 4.0 equiv). Following workup, the crude (54% ^{1}H NMR yield) was subject to column chromatography on silica gel (5% Et_2O in hexane) to afford the desired product as a colourless oil (9.9 mg, 50%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.31 (m, 8 H, $H_{2,3}$), 7.31–7.21 (m, 2 H, H_1), 3.82 (s, 4 H, H_5).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.5 (C_4), 128.5 (C_3), 128.3 (C_2), 127.1 (C_1), 53.3 (C_5).

The spectral data were consistent with the literature.[291]

***N*-benzyl-1-(*o*-tolyl)methanamine (3.318)**



Chemical Formula: $C_{15}H_{17}N$
Exact Mass: 211.1361

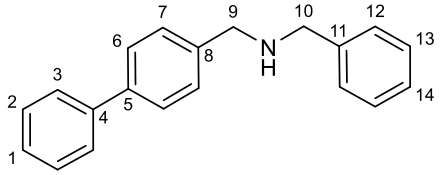
Prepared according to General Procedure I using **3.7** (46 mg, 0.20 mmol, 1.0 equiv) and benzylamine (86 mg, 87 μL, 0.80 mmol, 4.0 equiv). Following workup, the crude (24% ^{1}H NMR yield) was subject to column chromatography on silica gel (3% Et_2O in hexane) to afford the desired product as a white solid (9.6 mg, 23%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5 H, $H_{11–13}$), 7.29-7.24 (m, 1 H, H_2), 7.19–7.13 (m, 3 H, $H_{3,4,5}$), 3.86 (s, 2 H, H_9), 3.79 (s, 2 H, H_8), 2.33 (s, 3 H, H_7), 1.47 (s, 1 NH).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.6 (C_{10}), 138.4 (C_6), 136.6 (C_1), 130.4, 128.5, 128.3, 127.1 (2C), 126.1, 53.8 (C_9), 51.1 (C_8), 19.1 (C_7). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[302]

1-([1,1'-biphenyl]-4-yl)-*N*-benzylmethanamine (3.319)



Chemical Formula: $C_{20}H_{19}N$
Exact Mass: 273.1517

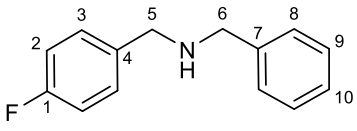
Prepared according to General Procedure I using **3.26** (58.8 mg, 0.20 mmol, 1.0 equiv) and benzylamine (85.7 mg, 87.2 μL, 0.80 mmol, 4.0 equiv). Following workup, the crude (60% ^{1}H NMR yield) was subject to column chromatography on silica gel (10-40% CH_2Cl_2 in hexane) to afford the desired product as a yellow solid (29.7 mg, 54%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.54 (m, 4 H, $H_{2–3}$), 7.45–7.41 (m, 4 H, $H_{6–7}$), 7.39–7.33 (m, 5 H, $H_{1–3}$), 7.29–7.25 (m, 1 H, H_{14}), 3.86 (2× s, 4 H, $H_{9,10}$), 2.40 (br s, 1 NH).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 141.1 (C_{quart}), 140.2 (C_{quart}), 139.1 (C_{quart}), 138.9 (C_{quart}), 128.9, 128.9, 128.6, 128.4, 127.3, 127.3, 127.2, 53.1 (C_{benzyl}), 52.7 (C_{benzyl}). For those left unassigned, C_{Ar}.

One carbon atom could not be distinguished. The spectral data were consistent with the literature.[302]

***N*-benzyl-1-(4-fluorophenyl)methanamine (3.320)**



Chemical Formula: $C_{14}H_{14}FN$
Exact Mass: 215.1110

Prepared according to General Procedure I using **3.42** (42.7 mg, 0.20 mmol, 1.0 equiv) and benzylamine (85.7 mg, 87.2 mL, 0.80 mmol, 4.0 equiv). Following workup, column chromatography could not isolate the desired product from the crude (51% ^1H NMR yield). The crude residue was subject to a Brown oxidation by dissolving in THF (2 mL) followed by dropwise addition of 2 N aq. NaOH / aq. H_2O_2 (2:1, 3 mL) at rt. The reaction mixture was stirred at rt for 10 min then diluted in CH_2Cl_2 10 mL and brine 10 mL. The organics were extracted into CH_2Cl_2 (3x), then the collected phases dried (Na_2SO_4) and concentrated at reduced pressure. The residue was subject to column chromatography on silica gel (3–5% Et_2O in hexane) to afford the desired product as a colourless oil (11.1 mg, 53%).

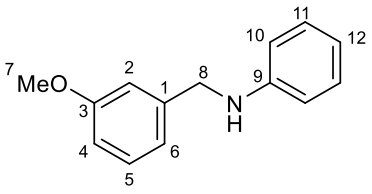
^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.28 (m, 6 H, $H_{3,8,9}$), 7.27–7.23 (m, 1 H, H_{10}), 7.04–6.99 (t, *J* = 8.5 Hz, 2 H, H_2), 3.80 (s, 2 H, H_5), 3.78 (s, 2 H, H_6).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 162.1 (d, $^1J_{CF}$ = 244.4 Hz, C_1), 140.3 (C_7), 136.2 (d, $^4J_{CF}$ = 3.1 Hz, C_4), 129.8 (d, $^3J_{CF}$ = 8.0 Hz, C_3), 128.6, 128.3, 127.2 (C_{10}), 115.3 (d, $^2J_{CF}$ = 21.3 Hz, C_2), 53.3 (C_5), 52.5 (C_6). For those left unassigned, C_{Ar}.

$^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$) δ −116.12.

The spectral data were consistent with the literature.[302]

***N*-(3-methoxybenzyl)aniline, (3.321)**



Chemical Formula: $C_{14}H_{15}NO$
Exact Mass: 213.1154

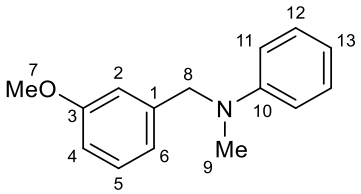
Prepared according to General Procedure I using **3.33** (49.6 mg, 0.20 mmol, 1.0 equiv) and aniline (74.5 mg, 73.0 mL, 0.80 mmol, 4.0 equiv). Following workup, the crude (61% ^1H NMR yield) was subject to column chromatography on silica gel (0−3% Et_2O in hexane containing 0.1% Et_3N, as eluent) to afford the desired product as a colourless oil (26.0 mg, 61%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.24 (m, 1 H, H_4), 7.21–7.15 (m, 2 H, H_{11}), 6.98–6.95 (m, 1 H, H_5), 6.93–6.94 (m, 1 H, H_2), 6.82 (dd, *J* = 8.3, 2.7, 1 H, H_6), 6.72 (tt, *J* = 7.3, 1.1 Hz, 1 H, H_{12}), 6.66–6.62 (m, 2 H, H_{10}), 4.31 (s, 2 H, H_8), 4.04 (br s, 1 NH), 3.80 (s, 3 H, H_7).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.0 (C_3), 148.23 (C_9), 141.3 (C_1), 129.8 (C_4), 129.4 (C_{11}), 119.9 (C_5), 117.7 (C_{12}), 113.1 (C_2), 113.0 (C_6), 112.8 (C_{10}), 55.4 (C_7), 48.5 (C_8).

The spectral data were consistent with the literature.[302]

***N*-(3-methoxybenzyl)-*N*-methylaniline (3.322)**



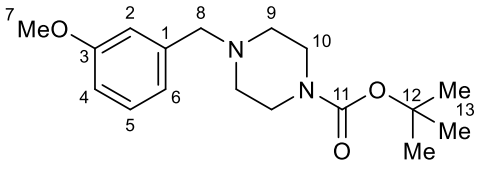
Prepared according to General Procedure I using **3.33** (49.6 mg, 0.20 mmol, 1.0 equiv) and *N*-methylaniline (85.7 mg, 86.7 μL, 0.80 mmol, 4.0 equiv). Following workup, the crude (73% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–2% Et_2O in hexane containing 0.1% Et_3N, as eluent) to afford the desired product as a pale-yellow oil (29.6 mg, 65%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.20 (m, 3 H), 6.86–6.82 (m, 1 H, H_2), 6.81–6.70 (m, 5 H), 4.51 (s, 2 H, H_8), 3.78 (s, 3 H, H_7), 3.02 (s, 3 H, H_9). For those left unassigned, H_{Ar}.

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.0 (C_3), 149.9 (C_1), 141.4 (C_{10}), 129.7, 129.3, 119.1 (C_2), 116.7, 112.5 (2C), 112.2, 56.8 (C_8), 55.3 (C_7), 38.7 (C_9). For those left unassigned, C_{Ar}.

The spectral data were consistent with the literature.[303]

***tert*-butyl 4-(3-methoxybenzyl)piperazine-1-carboxylate (3.323)**



Chemical Formula: $C_{17}H_{26}N_2O_3$
Exact Mass: 306.1943

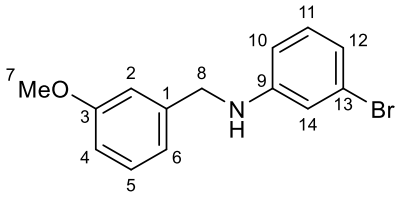
Prepared according to General Procedure I using **3.3** (49.6 mg, 0.20 mmol, 1.0 equiv) and *N*-Boc-piperazine (149 mg, 0.80 mmol, 4.0 equiv). Following workup, the crude (78% ^{1}H NMR yield) was subject to column chromatography on silica gel (0–3% Et_2O in hexane) to afford the desired product as a white solid (50.2 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, *J* = 8.0 Hz, 1 H, H_5), 6.93–6.86 (m, 2 H, $H_{4,6}$), 6.80 (dd, *J* = 8.8, 2.4 Hz, 1 H, H_2), 3.81 (s, 3 H, H_7), 3.48 (s, 2 H, H_8), 3.42 (br s, 4 H, H_{10}), 2.38 (t, *J* = 5.1 Hz, 4 H, H_9), 1.45 (s, 9 H, H_{13}).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.8 (C_3), 155.0 (C_1), 139.7 (C_{11}), 129.4 (C_5), 121.6, 114.7, 112.6 (C_2), 79.7 (C_{12}), 63.1 (C_8), 55.3 (C_7), 53.0 (C_9), 43.6 (C_{10}) (28.6 (C_{13}). C_{10} was estimated based on ^1H-^{13}C HSQC crosspeaks due to significant broadening. C_4 and C_6 could not be unambiguously assigned.

The spectral data were consistent with the literature.[304]

3-bromo-*N*-(3-methoxybenzyl)aniline (3.324)



Chemical Formula: $C_{14}H_{14}BrNO$
Exact Mass: 291.0259

Prepared according to General Procedure I using **3.3** (49.6 mg, 0.20 mmol, 1.0 equiv) and 3-bromoaniline (138 mg, 87.1 mL, 0.80 mmol, 4.0 equiv). Following workup, the crude (76% ^1H NMR yield) was subject to column chromatography on silica gel (1–5% Et_2O in hexane) to afford the desired product as a colourless oil (33.9 mg, 58%).

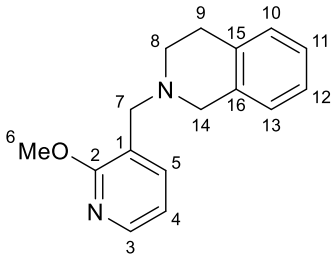
IR (film) ν 3420, 2957, 2920, 2361, 2342, 1593, 1489, 1481, 1261, 1155, 1067 986, 764, 669 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 1 H, H_5), 7.00 (t, *J* = 8.0 Hz, 1 H, H_{12}), 6.94–6.92 (m, 1 H, H_{11}), 6.90 (t, *J* = 2.1 Hz, 1 H, H_{10}), 6.85–6.80 (m, 2 H, $H_{4,6}$), 6.78 (t, *J* = 2.1 Hz, 1 H, H_2), 6.53 (dd, *J* = 8.2, 2.3 Hz, 1 H, H_{14}), 4.28 (d, *J* = 4.8 Hz, 2 H, H_8), 4.10 (br s, 1 NH), 3.80 (s, 3 H, H_7).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.1 (C_3), 149.5 (C_1), 140.5 (C_9), 130.7 (C_{12}), 129.9 (C_5), 123.4 (C_{13}), 120.5, 119.8 (C_{11}), 115.5 (C_2), 113.2 (C_{10}), 112.9, 111.7 (C_{14}), 55.4 (C_7), 48.2 (C_8). C_4 and C_6 could not be distinguished.

HRMS (ESI+) exact mass calcd. for $C_{14}H_{15}{}^{79}BrNO$ $[M+H]^+$ m/z = 292.03315; found 292.0332.

2-((2-methoxypyridin-3-yl)methyl)-1,2,3,4-tetrahydroisoquinoline (3.325)



Chemical Formula: $C_{16}H_{18}N_2O$
Exact Mass: 254.1419

Prepared according to General Procedure I using **3.3** (49.8 mg, 0.20 mmol, 1.0 equiv) and 1,2,3,4-tetrahydroisoquinoline (107, 0.80 mmol, 4.0 equiv). Following workup, the crude (66% ^1H NMR yield) was subject to column chromatography on silica gel (10–20% Et_2O in hexane) to afford the desired product as a white residue (32.5 mg, 64%).

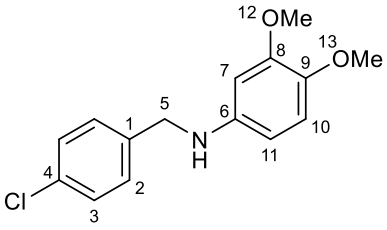
IR (film) ν 2947, 2918, 2361, 1653, 1587, 1462, 1412, 1250, 1088, 1020, 741 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 5.0, 1.9 Hz, 1 H, H_3), 7.74 (ddt, *J* = 7.2, 1.9, 0.9 Hz, 1 H, H_5), 7.16–7.09 (m, 3 H, $H_{10–12}$), 7.04–6.96 (m, 1 H, H_{13}), 6.88 (dd, *J* = 7.2, 5.0 Hz, 1 H, H_4), 3.98 (s, 3 H, H_6), 3.70 (s, 2 H, H_{14}), 3.68 (s, 2 H, H_7), 2.93 (t, *J* = 5.9 Hz, 2 H, H_9), 2.79 (t, *J* = 5.9 Hz, 2 H, H_8).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.3 (C_2), 145.2 (C_3), 138.2 (C_5), 135.1, 134.5, 128.9, 126.7 (C_{13}), 126.3 (C_{10}), 125.7, 121.2 (C_1), 116.9 (C_4), 56.3 (C_{14}), 55.6 (C_7), 53.5 (C_6), 51.0 (C_8), 29.3 (C_9). For those left unassigned, C_{Ar}.

HRMS (ESI+) exact mass calcd. for $C_{16}H_8N_2O$ $[M]^+$ m/z =255.1492; found 255.1493.

N-(4-chlorobenzyl)-3,4-dimethoxyaniline (3.326)



Chemical Formula: $C_{15}H_{16}ClNO_2$
Exact Mass: 277.0870

Prepared according to General Procedure I using **3.46** (50.5 mg, 0.20 mmol, 1.0 equiv) and 3,4-dimethoxyaniline (123 mg, 0.80 mmol, 4.0 equiv). Following workup, the crude (80% ^{1}H NMR yield) was subject to column chromatography on silica gel (5–20% Et_2O in hexane) to afford the desired product as a yellow residue (38.0 mg, 68%).

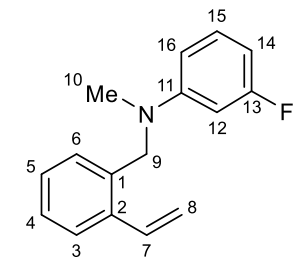
IR (film) ν 2978, 2897, 2390, 2336, 1275, 1267, 764, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29–7.27 (m, 2 H, H_3), 7.18–7.15 (m, 2 H, H_2), 6.72 (d, *J* = 8.8 Hz, 1 H, H_7), 6.33 (d, *J* = 2.9 Hz, 1 H, H_{10}), 6.23 (dd, *J* = 8.8, 2.8 Hz, 1 H, H_{11}), 4.47 (s, 2 H, H_5), 3.78 (s, 3 H, H_{13}), 3.71 (s, 3 H, H_{12}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.8 (C_8), 144.0 (C_6), 141.9 (C_9), 137.3 (C_1), 132.8 (C_4), 128.9 (C_2), 128.6 (C_3), 112.9 (C_7), 105.7 (C_{11}), 100.1 (C_{10}), 56.6 (C_{13}), 55.9 (C_{12}), 55.0 (C_5).

HRMS (ESI+) exact mass calcd. for $C_{15}H_{16}{}^{35}ClNO_2Na$ $[M+Na]^+$ m/z = 300.0762; found 300.0759.

3-fluoro-*N*-methyl-*N*-(2-vinylbenzyl)aniline (3.327)



Chemical Formula: $C_{16}H_{16}FN$
Exact Mass: 241.1267

Prepared according to General Procedure I using **3.30** (48.8 mg, 0.20 mmol, 1.0 equiv) and 3-fluoro-*N*-methylaniline (100 mg, 0.80 mmol, 4.0 equiv). Following workup, the crude (48% ^{1}H NMR yield) was subject to column chromatography on silica gel (1–3% Et_2O in hexane) to afford the desired product as a yellow oil (18.4 mg, 38%).

IR (film) ν 2920, 2361, 2342, 1618, 1502, 1234, 1159, 772, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.6, 1.5 Hz, 1 H, H_3), 7.28–7.24 (m, 1 H, H_4), 7.21 (td, *J* = 7.5, 1.5 Hz, 1 H, H_{15}), 7.18–7.06 (m, 2 H, $H_{5–6}$), 6.92 (dd, *J* = 17.3, 11.0 Hz, 1 H, H_7), 6.47–6.32 (m, 3 H, $H_{12,14,16}$), 5.68 (dd, *J* = 17.3, 1.4 Hz, 1 H, $H_{8\text{-}trans}$), 5.35 (dd, *J* = 10.9, 1.4 Hz, 1 H, $H_{8\text{-}cis}$), 4.56 (s, 2 H, H_9), 3.01 (s, 3 H, H_{10}).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.3 (d, $^{1}J_{CF}$ = 241.7 Hz, C_{13}), 151.4 (d, $^{3}J_{CF}$ = 10.8 Hz, C_{11}), 136.6 (C_2), 134.8 (C_1), 133.7 (C_7), 130.3 (d, $^{3}J_{CF}$ = 10.4 Hz, C_{15}), 128.1 (C_{16}), 127.4 (C_4), 126.6 (C_5), 126.4 (C_3), 116.7 (C_8), 107.8 (d, $^{4}J_{CF}$ = 2.2 Hz, C_{16}), 103.0 (d, $^{2}J_{CF}$ = 21.7 Hz, C_{12}), 99.2 (d, $^{2}J_{CF}$ = 26.1 Hz, C_{14}), 54.5 (C_9), 38.6 (C_{10}).

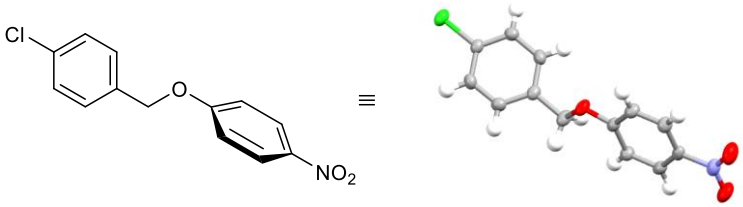
^{19}F{^{1}H} NMR (470 MHz, $CDCl_3$) −113.06.

HRMS (ESI+) exact mass calcd. for $C_{16}H_{17}FN$ $[M+H]^+$ m/z = 242.1340; found. 242.1341.

5.7 X-ray crystallography

A single crystal of **3.298** was prepared by vapour diffusion between acetone and water. The data for compound **3.298** were collected using a Rigaku FR-X Ultrahigh Brilliance Microfocus

RA generator/confocal optics with XtaLAB P200 diffractometer. CCDC ref WIKJAF contains the supplementary crystallographic data for this structure and can be accessed via the Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/structures.



3.298 CCDC: WIKJAF

Crystal data	**Compound 3.298**
Identification code	KB1071KBAW11XRD
Empirical formula	$C_{13}H_{10}ClNO_3$
Formula weight	263.67
Temperature/K	173
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	5.7102(2)
b/Å	12.4488(3)
c/Å	16.6542(4)
α/°	90.0000
β/°	93.567(2)
γ/°	90.0000
Volume/Å^3	1181.57(6)
Z	4
ρ_{calc}g/cm^3	1.482
μ/mm^{-1}	0.322
F(000)	544.0
Crystal size/mm^3	0.24×0.08×0.02
Radiation	Mo Kα (λ=0.71073)
2Θ range for data collection/°	4.088−58.882
Index ranges	−7 ≤ h ≤ 7, −16 ≤ k ≤ 13, −22 ≤ l ≤ 21
Reflections collected	25298
Independent reflections	2913 [R_{int} = 0.0336, R_σ = 0.0236]
Data/restraints/parameters	2913/0/163
Goodness of fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0346, wR_2 = 0.0814
Final R indexes [all data]	R_1 = 0.0477, wR_2 = 0.0858
Largest diff. peak/hole / e Å^{-3}	0.24/−0.19

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