University of Strathclyde

Department of Pure and Applied Chemistry

The development of chemo- and regioselective reactions of boron systems

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

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

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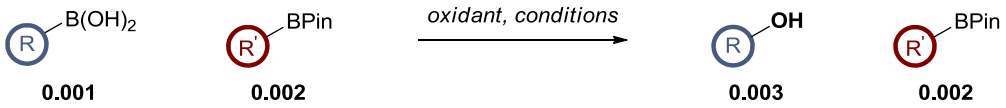
Abstract

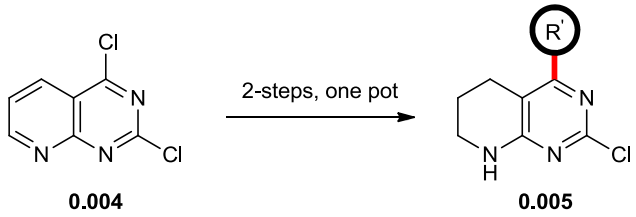
This thesis describes an evolution in the chemo- and regioselective reactions of boron species. The first chapter details the chemoselective oxidation of an aryl organoboron species in the presence of a second oxidisable aryl organoboron moiety (Scheme 0.01).



Scheme 0.01 Chemoselective oxidation of aryldiboron systems.

Comprehensive reaction optimisation led to the discovery of basic biphasic reaction conditions where, upon further analysis, selective boronic acid boronate formation occurs enabling the differentiation of boron species. Furthermore, inversion of conventional protecting group strategies can be facilitated by the biphasic system, allowing for the chemoselective oxidation of boronic acid, *N*-methyliminodiacetic acid (BMIDA) species over normally more reactive boronic acid pinacol (BPin) ester substrates. Chemoselective oxidation can be further expanded to diboronic acid systems where the extent of chemoselectivity can be predicted *via* prior HPLC analysis.

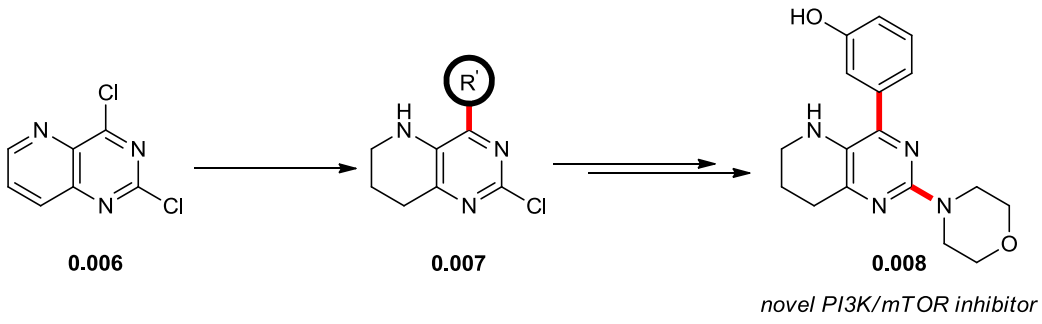
The second chapter focuses on the use of new technologies in a drug discovery environment. In particular the use of COware, a two-chamber glassware system for the *in situ* production and consumption of low molecular weight gases, and the role that it can play in facilitating multistep reaction sequences in one-pot. This idea was exemplified by achieving a high-yielding, one-pot regioselective Suzuki-Miyaura/hydrogenation reaction sequence (Scheme 0.02).



0.004 **0.005**

Scheme 0.02 Synthesis of substituted tetrahydropyridopyrimidines enabled by COware.

The use of COware technology allows for a simple experimental procedure. Expedient access to a plethora of motifs demonstrates the applicability of this approach to a drug discovery environment. The resulting bicyclic core contains two sites of orthogonal reactivity for further synthetic manipulation. The applicability of COware methodology was further demonstrated in the syntheses of two semi-saturated inhibitors from the literature (Scheme 0.03).



0.006 **0.007** **0.008**

Scheme 0.03 One-pot PI3K/mTOR inhibitor synthesis.

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I would like to thank my industrial supervisor Dr. Niall Anderson and my academic supervisor Dr. Allan Watson for their continued support over the course of my PhD. I am particularly grateful for the assistance, creative suggestions, and counsel of Dr. Watson. His vast knowledge of synthetic chemistry has been crucial to the project. The advice and support given by Dr. Anderson has been enormously helpful. His ideas and time have been very much appreciated.

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Mum, Dad, Ann, and Jack thanks for putting up with minimal contact over the past few years; must try harder. Finally, Roxanne, thank you so much for all you have done.

Abbreviations

Å	angstrom/s
Ac	acetyl
AKI	adenosine kinase inhibitor
amu	atomic mass unit
aq.	aqueous
atm	atmosphere/s
9-BBN	9-borabicyclo(3.3.1)nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butoxycarbonyl
brsm	based on recovered starting material
BSA	bovine serum albumin
°C	degrees Celsius
Cat	catechol
cat.	catalyst
Cb	*N*,*N*-diisopropylcarbamoyl
CBS	Corey-Bakshi-Shibata
CHI	chromatographic hydrophobicity index
CLND	chemiluminescence nitrogen detector
cod	cyclooctadiene
conv.	conversion
COSY	correlation spectroscopy
CPME	cyclopentyl methyl ether
m-CPBA	*meta*-chloroperoxybenzoic acid

Cy	cyclohexyl
CYP450	cytochrome P450
D	distribution coefficient
δ	chemical shift in parts per million downfield from tetramethylsilane
DAN	1,8-diaminonaphthalene
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DEPT	distortionless enhancement by polarization transfer
Dip	1,3-diisopropylbenzene
DIPEA	*N*,*N*-diisopropylethylamine
DiPrPF	(1,1′-bis(diisopropylphosphino)ferrocene)
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1’-bis(diphenylphosphino)ferrocene
dtbpy	4,4’di-*tert*-butyl bipyridine
E	entgegen
EDG	electron donating group
ee	enantiomeric excess
EPSRC	engineering and physical sciences research council
equiv	equivalents
ESI	electrospray ionisation
EWG	electron withdrawing group
fsp^3	fraction of sp^3

FTIR	Fourier transform infrared
g	gram/s
G I	Grubbs 1st generation catalyst: benzylidene-bis(tricyclohexylphosphine)dichlororuthenium
h	hour/s
Hg	hexyleneglycol
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
H-G II	Hoveyda-Grubbs 2nd generation catalyst: (1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSA	human serum albumin
HSQC	heteronuclear single quantum coherence
Hz	hertz
i	*iso*
IPA	isopropanol
Ipc	isopinocampheyl
IR	infrared
J	coupling constant (in NMR spectrometry)
$J \cdot mol^{-1}$	Joules per mole
K	Kelvin
L	litre/s
λ	wavelength
LCMS	liquid chromatography mass spectrometry

Leu	leucine
LeuRS	leucyl-tRNA synthetase
lit.	literature
LG	leaving group
m	metre/s
M	molar
MCR	multicomponent reaction
MDAP	mass directed automatic purification
Mes	mesityl
MIDA	*N*-methyliminodiacetic acid
min/s	minute/s
mol.	mole/s
m.p.	melting point
mTOR	mechanistic target of rapamycin
µw	microwave
m/*z*	mass-to-charge ratio
N	normal
Npg	neopentylglycol
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
org	organic
PBM	Petasis borono-Mannich
PCC	pyridinium chlorochromate
PDE	phosphodiesterase

PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
PFI	property forecast index
PG	protecting group
Ph	phenyl
PI3K	phosphatidylinositol-4,5-bisphosphate 3-kinase
PIDA	(diacetoxyiodo)benzene
Pin	pinacolato
Piv	pivaloyl
ppm	parts per million
quant.	quantitative
®	registered trademark
rpm	revolutions per minute
rt	room temperature
R_t	retention time
RuPhos	2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
s	sec
SAR	structure activity relationship
Sia	disiamyl
S_NAr	nucleophilic aromatic substitution
t	*tert*
TBDMS	*tert*-butyldimethylsilyl
TBME	*tert*-butyl methyl ether
tetrakis	tetrakis(triphenylphosphine)palladium(0)
Tf	triflate

TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
Th	thexyl
THF	tetrahydrofuran
THPP	tetrahydropyridopyrimidine
TKI	tyrosine kinase inhibitor
TLC	thin-layer chromatography
™	unregistered trademark
TMAO	trimethylamine *N*-oxide
TMG	2-*tert*-butyl-1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
tRNA	transfer ribonucleic acid
UPLC	ultra-performance liquid chromatography
UV	ultraviolet
v/v	volume/volume
wt.	weight
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
xs	excess
Z	zusammen

Contents

Introduction

1 Boron

Since its discovery in 1808 independently by Gay-Lussac and Thénard in France and Davy in England, boron has become of fundamental importance to the world as we know it.[1,2] In fact, over 4000 years ago boron compounds were employed by the Babylonian civilization for use as a flux for working gold.[3] From its use in drug molecules,[4] to its incorporation into borosilicate glass (Pyrex®),[5] and its use as a rocket fuel igniter,[6] boron, and compounds derived from it, play a pivotal role in modern day society.[2] Furthermore, molecules containing boron can perform a plethora of chemical transformations, many of which are essential in current synthetic organic chemistry.[7]

Despite the pivotal role that boron compounds have, elemental boron is not very abundant.[3] The earth's crust comprises only 10 mg/kg of boron, representing 0.001% of the elemental composition of earth.[3] This is relatively small for a low atomic weight element when compared to carbon (480 mg/kg) and nitrogen (25 mg/kg).[8] Moreover, this composition drops to 4.5 mg/kg in groundwater around active volcanic and geothermal activity and even further to a maximum 0.5 mg/kg in freshwater.[3]

Boron never occurs naturally as a free element; it is primarily found in the form of oxygenated minerals, a point illustrated by the fact that pure boron wasn't isolated until over 100 years after its initial discovery.[3] A wide variety of natural boron sources exist including: borax, ulexite, and sassolite, to name a few, which are generally found as deposits in areas of desert (Figure 1.01).[3]

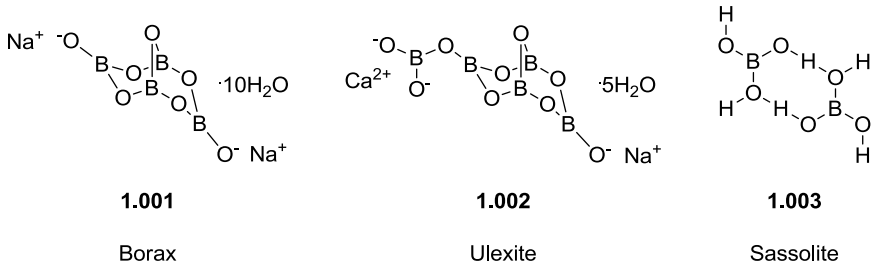
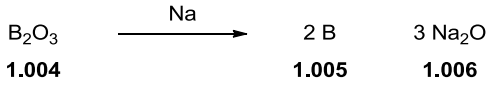


Figure 1.01 Oxygenated boron minerals.[3]

Boron is the fifth element in the periodic table and has an atomic mass of 10.81 amu.[3] Amorphous boron can be obtained from boron oxides through its reduction with sodium (Scheme 1.01).[3] Elemental boron is a black solid at room temperature and pressure and is composed of five isotopes: ^{8}B, ^{10}B, ^{11}B, ^{12}B, and ^{13}B.[3] Of these, the most stable isotopes are ^{10}B which is approximately 20% abundant, and ^{11}B accounting for the remaining 80%.[3] Both of these naturally occurring nuclei are nuclear magnetic resonance (NMR) active, a useful property for compound analysis: ^{10}B has a spin of 3 and ^{11}B has a spin of 3/2.[9]

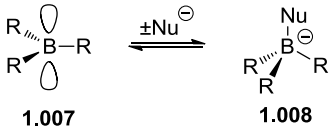


Scheme 1.01 Elemental boron production.[3]

The chemical nature of boron is influenced by its small size (covalent radius 0.80−1.01 Å), high ionisation energy (344.2 kJ·mol^{-1}), and high affinity for oxygen.[3] These properties explain the propensity of boron to form covalent interactions, primarily with oxygen, and explain the fact that boron mainly exists in compounds with other elements.

The valence electronic structure of boron is $1s^2 2s^2 2p^1$: there are three outer shell electrons. This occurs as a direct consequence of its position in group 13 of the periodic table, where it is the only non-metal in the group.[3] Therefore, the majority of boron moieties are trivalent at the boron centre and, as a result, possess trigonal planar geometry.[10] Accordingly, trivalent boron centres are sp^2 hybridised with a vacant, low energy, p-orbital. This results in the boron centre containing six valence electrons.[10] Consequently, boron compounds tend to be electron deficient and Lewis-

acidic giving them the ability to coordinate Lewis-basic molecules, a key aspect of the chemistry of boron (Scheme 1.02).[11]

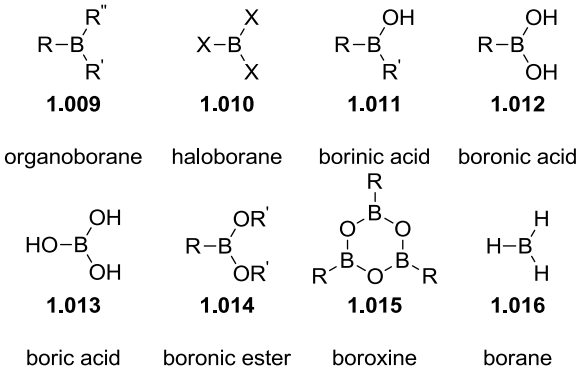


1.007 **1.008**

Scheme 1.02 General Lewis-acidic reactivity of boron species.[10]

Boronate complexes, of type **1.008**, contain a full octet of valence electrons. A carbon-like tetrahedral configuration is adopted with a formal negative charge on boron, which can be stabilised through dissociation onto electron-withdrawing ligands. The electron-rich boronate species generally engage in intra- or intermolecular ligand transfer reactions due to the highly congested environment around the relatively small boron centre.[3]

There are numerous classes of boron compounds known, including but not exclusively, boranes (B_xH_y), borides (compounds of boron with more electropositive atoms), and borates (boron-containing oxyanions).[12] However, the majority of these compounds are of no use to the synthetic organic chemist. In general, compounds with a boron-carbon bond, termed organoboranes, and those that contain one or more boron-hydroxide functionality are synthetically valuable (Figure 1.02).[13]

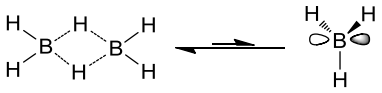


1.009 organoborane
1.010 haloborane
1.011 borinic acid
1.012 boronic acid
1.013 boric acid
1.014 boronic ester
1.015 boroxine
1.016 borane

Figure 1.02 Synthetically important boron compounds.[13]

1.1 Boron hydrides

The most simple boron-containing compound, borane, consists of one central boron atom bonded to three hydrogen atoms (Scheme 1.03).[10] In reality, borane exists as a mixture of diborane dimer, **1.017**, containing two, three-centre two-electron bonds, and the borane monomer **1.018**.[10] The two moieties are in rapid equilibrium.[10] Borane also exists in complexes with Lewis bases such as tetrahydrofuran (THF), phosphines, tertiary amines, and dimethyl sulfide which stabilise the reactive, electron-deficient, boron species through coordination to the empty p-orbital.[14]

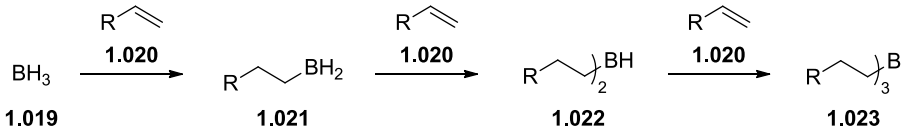


Scheme 1.03 Structure of borane.[10]

Borane is an important reagent for the synthetic chemist. Seminal studies by Herbert C. Brown showed that organoboron compounds could be synthesised through hydroboration of olefins using borane.[15] Furthermore, borane can be used to perform a variety of carbonyl reductions.[16] Reactions of borane will be discussed over the upcoming sections.

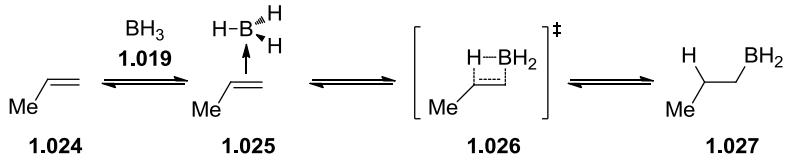
1.1.1 Hydroboration

The first incorporation of boron into organic compounds was accomplished *via* the hydroboration of olefins whereby boron adds across the carbon-carbon double bond (Scheme 1.04).[15] The process is difficult to control when unhindered alkenes are treated with borane; the resulting organoborane (**1.021**) adds rapidly to another molecule of the alkene, forming **1.022**, and then potentially to a third alkene (**1.023**).[10] There is potential to control the extent of hydroboration when more hindered di-, tri-, and tetrasubstituted alkenes are subjected to the reaction conditions.[7]



Scheme 1.04 Hydroboration of an unhindered olefin.[10]

Hydroboration proceeds *via* a concerted asynchronous mechanism (Scheme 1.05).[10] This asynchronicity leads to predictable regiochemistry which is kinetically governed at standard reaction temperatures (0 °C to ambient temperature). The same is true for reaction stereochemistry.[10] The relative electropositivity of boron leads to formal Markovnikov addition of borane to the olefin.[17] The mechanism proceeds by initial formation of a π-complex (**1.025**) between the nucleophilic alkene (**1.024**) and electrophilic borane (**1.019**) which is followed by asynchronous addition of boron to the less substituted end of the alkene (**1.026**). The electropositive boron stabilises the negative charge being generated in the transition state, dictating the regiochemistry of addition. Concurrently, the hydrogen atom is transferred from the boron centre to the opposite end of the alkene. Both boron and hydrogen add to the same face of the alkene leading to overall *syn*-addition (**1.027**).[10]



Scheme 1.05 Hydroboration mechanism.[10]

One caveat with the use of borane in hydroboration reactions is the tendency of the boron species to react multiple times (c*f.* Scheme 1.04).[10] A number of carbon-substituted boron reagents have been synthesised to alleviate this issue (Figure 1.03). By design, dialkylboranes can only hydroborate once, and alkylboranes twice. Thexyl borane ($ThBH_2$, **1.028**) will only add once to the majority of sterically hindered tetrasubstituted alkenes while the dialkylborane, disiamyl borane (Sia_2BH, **1.029**) will not add further to trisubstituted alkenes. Both 9-borabicyclo[3.3.1]nonane (9-BBN, **1.030**) and catechol borane (HBCat, **1.031**) are incredibly selective for the

terminal position and can differentiate between alkenes within the same molecule.[7] Another useful hydroborating agent is pinacol borane (HBPin) **1.032**.

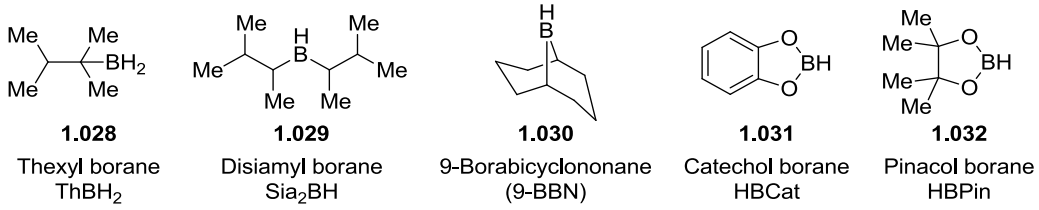
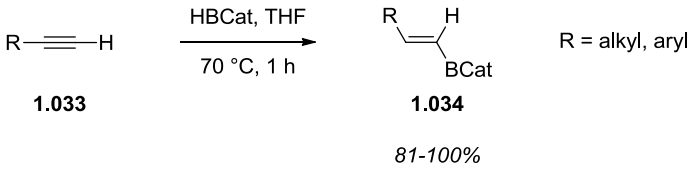


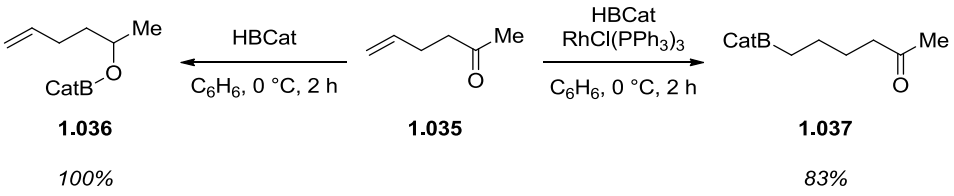
Figure 1.03 Selective hydroborating reagents.[7]

Hydroboration is not limited to olefins. Alkynes can also be hydroborated to generate vinylboranes.[18] HBCat, **1.031**, is effective at mono-hydroborating alkynes with high regioselectivity (Scheme 1.06).[18]



Scheme 1.06 Alkyne hydroboration.[18,19]

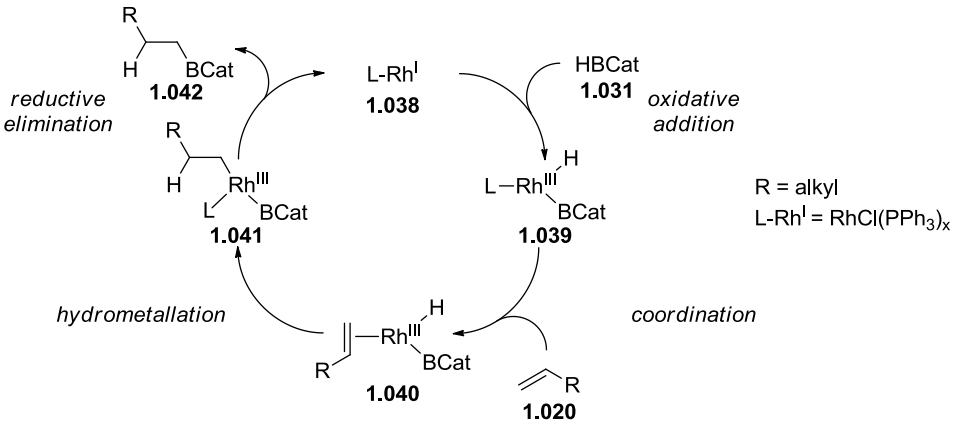
Despite the high reactivity of organoboron compounds in the absence of metals, a number of metal-catalysed hydroboration reactions have been developed.[14] Metal catalysts can be extremely useful in order to control the regioselectivity of reactions when more than one electrophilic functional group is present *e.g.*, olefin and ketone (Scheme 1.07).[20] Rhodium catalysis leaves the more reactive ketone group untouched while hydroborating the alkene to **1.037**.[20]



Scheme 1.07 Metal-catalysed hydroboration.[20]

Markovnikov addition is observed when rhodium is present, which is readily explained when the mechanism is considered (Scheme 1.08). Rhodium insertion into

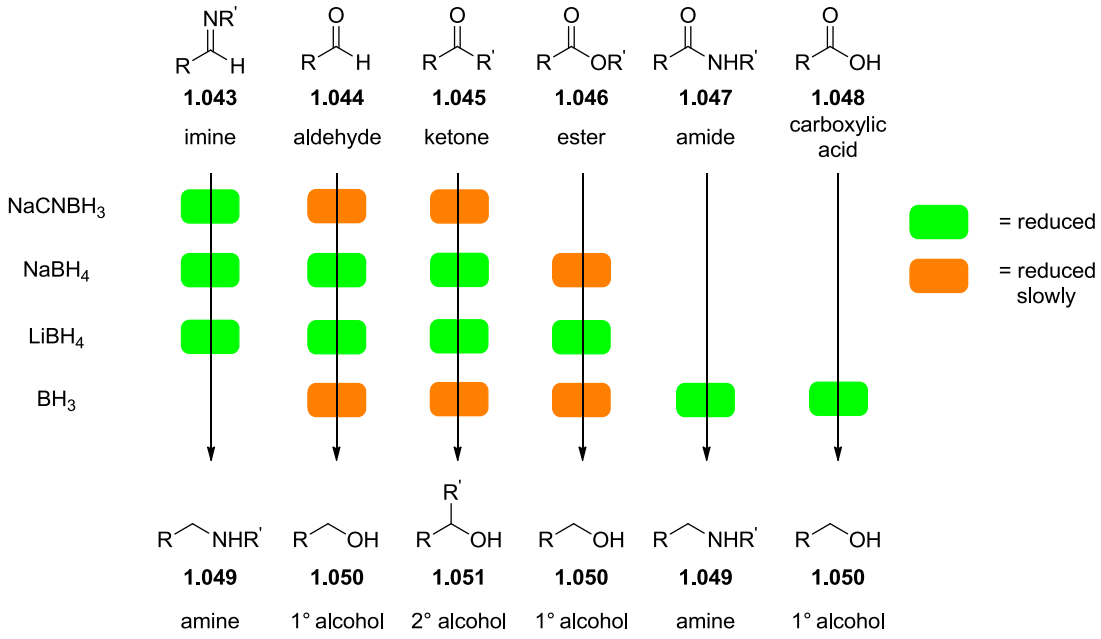
the boron-hydrogen bond generates intermediate **1.039**. This is followed by coordination of the olefin to the metal centre and hydrometallation. Reductive elimination regenerates the rhodium(I) catalyst and produces the desired hydroborated product **1.042**. Hydrometallation is the regiochemistry-controlling step where the large, ligated metal prefers to add to the least sterically hindered end of the alkene.[20]



Scheme 1.08 Rhodium-catalysed hydroboration.[20]

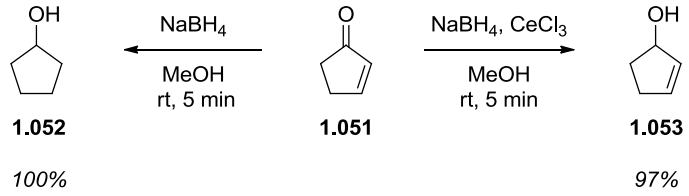
1.1.2 Reduction

Beyond hydroboration, borane has found use in the reduction of unsaturated systems, namely carbonyls, carboxylic acids, and halogens.[16] Other nucleophilic boron hydride compounds, known as borohydrides, are also widely used for carbonyl reduction.[16] These nucleophilic hydride sources have varying degrees of reactivity. Careful selection of reducing agents allows for chemoselective functional group reduction (Scheme 1.09).[16]



Scheme 1.09 Summary of reduction by boron hydride reducing agents.[16]

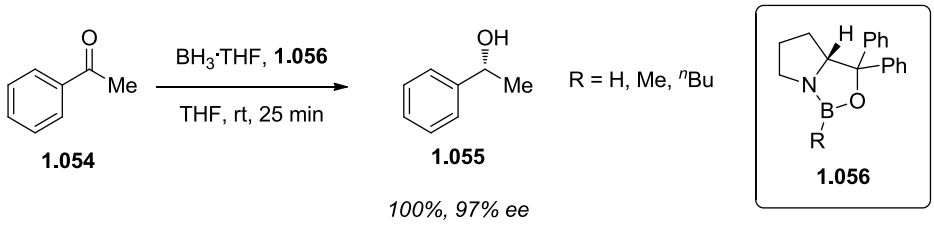
Cerium trichloride can be a useful additive to these reductive reactions as it increases the selectivity for ketone reduction in the presence of an olefin, even when both are in conjugation *e.g.*, enones (Scheme 1.10).[21] This is explained through hard-soft acid-base theory. Initially, sodium borohydride is rapidly converted into an alkoxide species, increasing the hardness of the nucleophile.[22] Furthermore, the carbonyl moiety is activated through the Lewis-acidic cerium trichloride. The hard borohydride nucleophile then preferentially attacks the hard, activated, carbonyl group preferentially.[22]



Scheme 1.10 Luche reduction of cyclopentenone.[21]

Further reductive transformations can also be performed with borane in combination with oxazaborolidines, namely the Corey-Bakshi-Shibata (CBS) reduction, which allows the enantioselective reduction of prochiral ketones to provide chiral alcohols

(Scheme 1.11).[23] Both enantiomers of the catalyst are commercially available, thus the pair of product enantiomers can be accessed.



Scheme 1.11 Enantioselective CBS reduction.[24]

The absolute stereochemistry and outstanding enantioselectivity can be explained by a mechanistic model (Figure 1.04). Initial complexation of borane to the Lewis-basic nitrogen activates BH_3 as a hydride donor. The resulting strongly Lewis-acidic complex then binds to the carbonyl group which minimizes unfavourable steric interactions between the substrate and the oxazaborolidine. This aligns the borane and ketone for face-selective hydride transfer to form the desired product.[24]

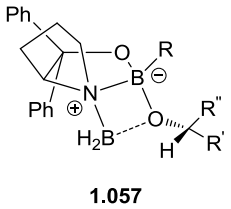
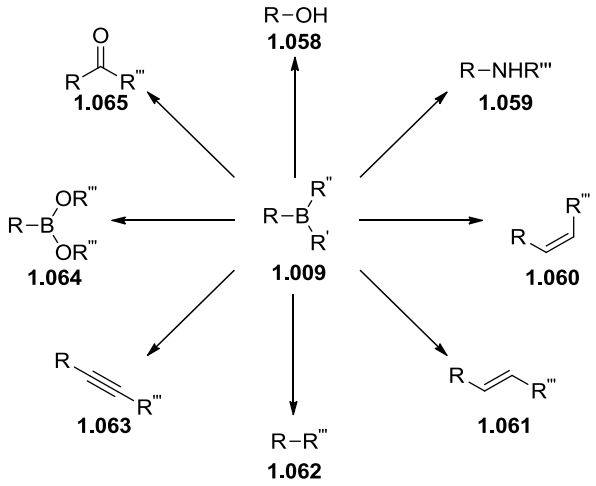


Figure 1.04 CBS reduction intermediate.[24]

1.2 Organoboranes

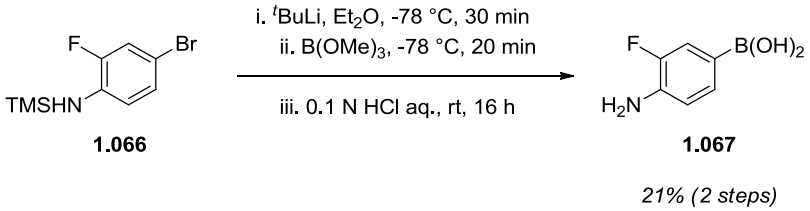
Organoboranes are fundamental reagents or catalysts for a plethora of chemical transformations (Scheme 1.12).[23] Conversion of organoboranes to a wide variety of functional groups including alcohols, amines, olefins, acetylenes, and ketones can be accomplished without difficulty.[23]



Scheme 1.12 Versatile organoboranes.[23]

1.2.1 Synthesis of organoboranes

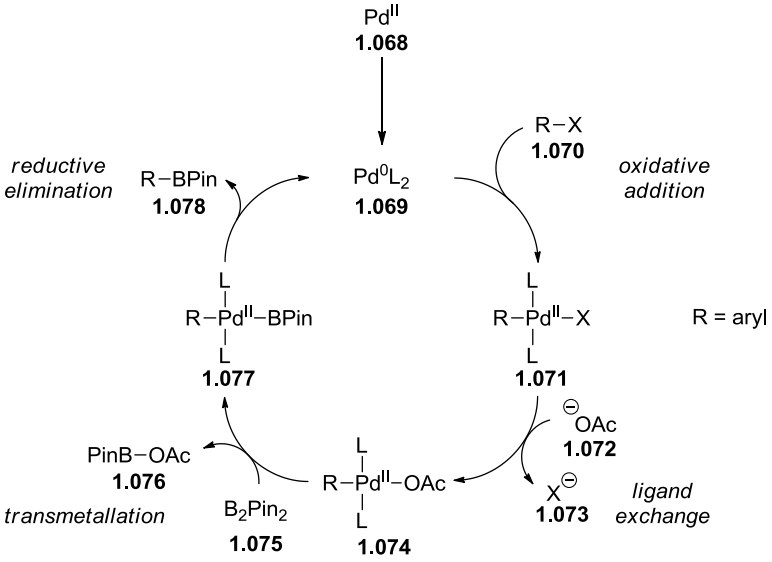
Hydroboration, although one of the most widely-utilized reactions in organic synthesis, is not the only method of introducing boron into organic molecules. Organometallic substitution reactions with electrophilic boron sources have steadily become more popular. In particular, trialkoxide boron sources are widely used to trap organometallic intermediates.[13,25] This method is particularly prevalent due to the high availability and relative affordability of the starting arylhalides (Scheme 1.13).[26] Initial protection of the aniline moiety to generate **1.066** with a silane protecting group renders the basic centre unreactive. Installation of the boronic acid functionality through lithium-halogen exchange and quenching with trimethoxyborane then ensues. Finally, global deprotection yields the desired boronic acid **1.067**.



Scheme 1.13 Boron incorporation *via* organometallic substitution.[27]

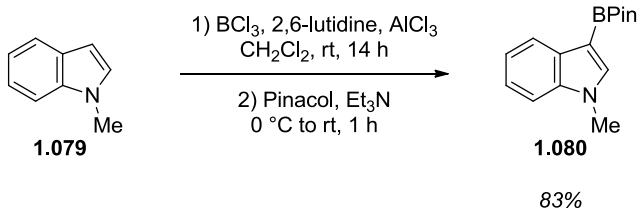
The Miyaura borylation is another metal-catalysed method of preparing boronic esters.[28] Treatment of an aryl or alkenyl halide with a palladium catalyst and a boron

source, for example B_2Pin_2, generates the corresponding boron species (Scheme 1.14).[28–30] The reaction proceeds though a palladium(II)/palladium(0) cycle with four distinct steps; oxidative addition of the aryl (pseudo)halide to the palladium catalyst giving **1.071**, ligand exchange between the (pseudo)halide and acetoxy ligands, transmetallation with B_2Pin_2, and reductive elimination to form the borylated product **1.078**. The choice of base is crucial to ensure that no cross-coupling occurs between the aryl halide and borylated product. Hard Lewis bases (*e.g.*, acetoxy) have been shown to give greatest selectivity for the Miyaura borylation over the closely-related Suzuki-Miyaura cross-coupling reaction.[29]



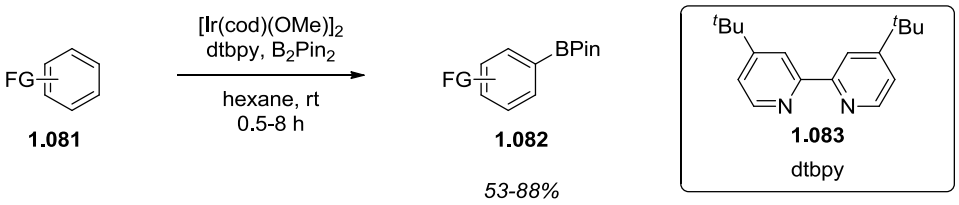
Scheme 1.14 Miyaura borylation reaction mechanism.[25]

Boron trihalides can be utilized in electrophilic substitution reactions, which eliminates the need to use cryogenic conditions (Scheme 1.15).[31] Furthermore, no prior substitution is required which promotes the synthetic utility of the reaction.



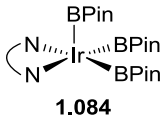
Scheme 1.15 Boron addition through electrophilic aromatic substitution.[31]

Where electrophilic substitution is not possible, metal-catalysed C-H activation can be used to install boronic esters (Scheme 1.16). The regiochemistry of borylation is primarily determined by the steric environment present in the system; that is, the least sterically hindered position is selectively borylated. This method can also be used to borylate heteroaromatics.[32] The mechanism of the reaction is depicted in Scheme 1.17.



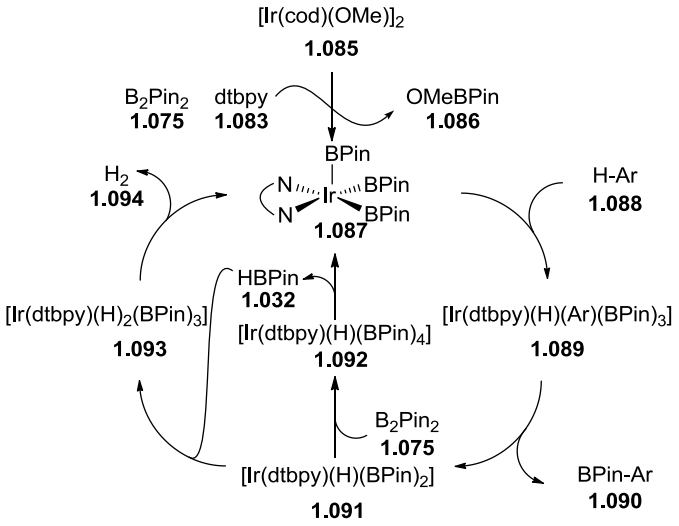
Scheme 1.16 Iridium catalysed C-H borylation.[32]

Initially, the active catalytic species **1.084** is generated from the iridium catalyst **1.085**, B_2Pin_2, and a bipyridine ligand, **1.083** (Figure 1.05 and Scheme 1.17).[32] Cyclooctadiene (cod) then reversibly dissociates from the metal centre generating **1.087** which can undergo oxidative addition or σ-bond metathesis with an aryl C-H bond. Reductive elimination gives the desired borylated product **1.090** and an iridium (III) intermediate **1.091**. The catalytic species **1.087** can then be regenerated through oxidative addition of B_2Pin_2 to give **1.092** and reductive elimination of HBPin or oxidative addition of HBPin forming **1.093** and the elimination of hydrogen gas.[32]



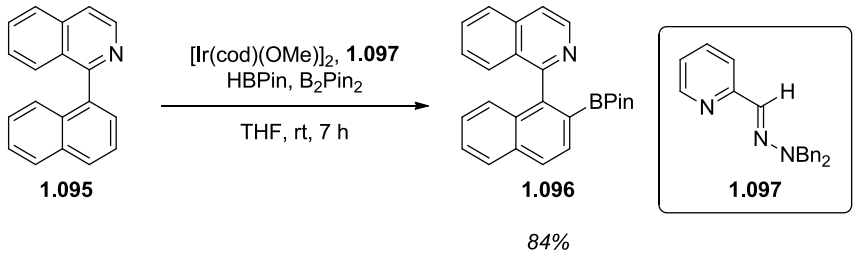
1.084

Figure 1.05 Active catalytic species generated from $[Ir(cod)(OMe)]_2$, dtbpy, and B_2Pin_2.



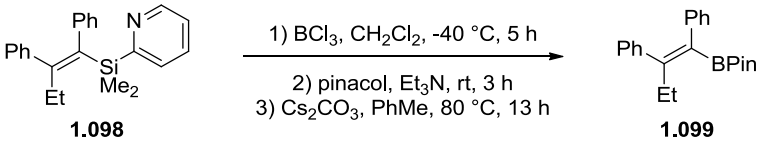
Scheme 1.17 Iridium catalysed C-H activation mechanism.[32]

Interestingly, borylation can also be directed through coordination of a neighbouring group to the iridium catalyst system, thus overcoming the rigid steric demands of the previous system (Scheme 1.18).[33]



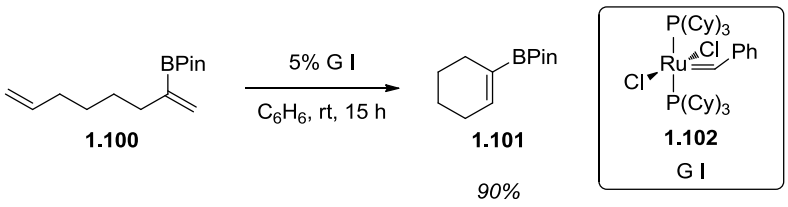
Scheme 1.18 Directed C-H borylation.[33]

Organoboranes can also be synthesised from alkylsilane derivatives. Preparation of tetrasubstituted alkenylboron species has been accomplished through transmetallation with boron halides (Scheme 1.19).[34] The resulting organoboranes can be transformed to boronic esters by treatment with the corresponding diol and base.[34]



Scheme 1.19 Organoborane synthesis *via* transmetallation.[34]

The advent of efficient alkene metathesis catalysts has unlocked new possibilities for the synthesis of organoboranes.[35] In particular, the synthesis of cyclic alkenylboronic acids and esters is possible using ring closing metathesis (Scheme 1.20).[36] These targets are synthesised in good yield using the first-generation Grubbs catalyst (G I).



Scheme 1.20 Organoborane synthesis by ring closing metathesis.[36]

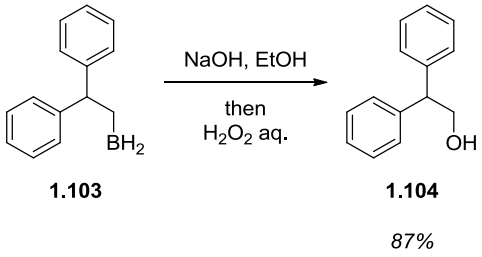
1.3 Reactions of organoboron species

1.3.1 Oxidation

Commonly, organoboron compounds are handled under a nitrogen atmosphere as they are sensitive to aerobic oxidation.[25] The oxidation reaction is thermodynamically favoured due to the high strength of the boron-oxygen bond (480–565 kJ·mol^{-1}) relative to the boron-carbon bond (350–400 kJ·mol^{-1}).[7] However, the oxidative cleavage of the boron-carbon bond is kinetically slow, allowing for a degree of aerial stability.[13] Furthermore, boron derivatives, most notably boronic acids, are transiently protected from autoxidation when in aqueous basic solution *via* boronate formation through coordination of hydroxide into the vacant p-orbital.[25]

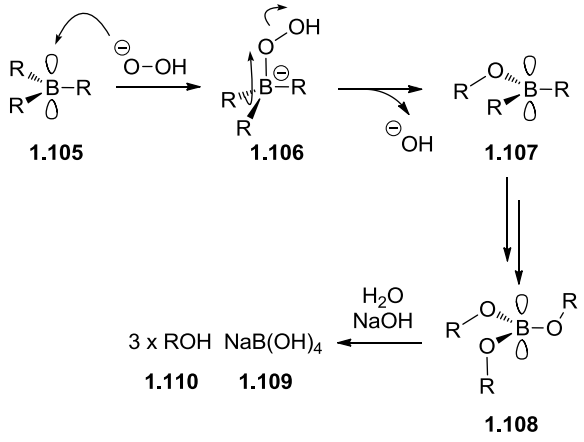
Seminal work on the oxidation of boron compounds was performed by Herbert C. Brown, for which he was awarded, jointly with Georg Wittig, the Nobel prize in chemistry in 1979.[15] Treatment of alkylboranes with potent oxidants such as an alkaline hydrogen peroxide solution produces alcohols (Scheme 1.21).[15] Importantly,

the stereochemistry at the carbon atom adjacent to the boron is maintained throughout the reaction, meaning that enantiopure alcohols can be prepared from a chiral starting organoborane.[10]



Scheme 1.21 Brown's seminal oxidation of organoboranes.[15]

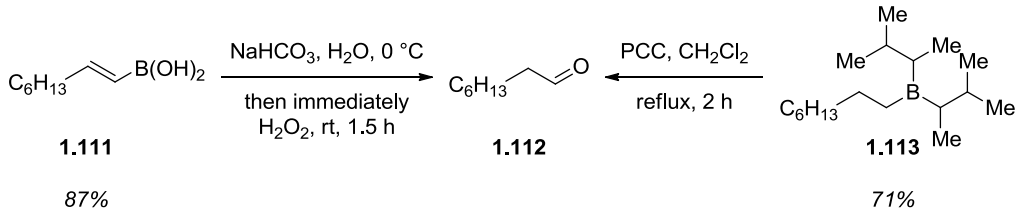
The retention of stereochemistry can be explained by the mechanism of the reaction (Scheme 1.22). A hydroperoxide anion attacks the vacant p-orbital of the electrophilic species **1.105**. The boronate complex formed undergoes a 1,2-alkyl shift, breaking the weak oxygen-oxygen bond in the process, resulting in the loss of hydroxide. Critically, this migratory process occurs with retention of stereochemistry of the alkyl group.[10] Depending on the nature of the substituents on boron, the reaction can occur multiple times to produce trialkoxide species **1.108**. Subsequent hydrolysis of the boron-oxygen generates the desired phenol **1.110**.



Scheme 1.22 Mechanism of the Brown oxidation.[7]

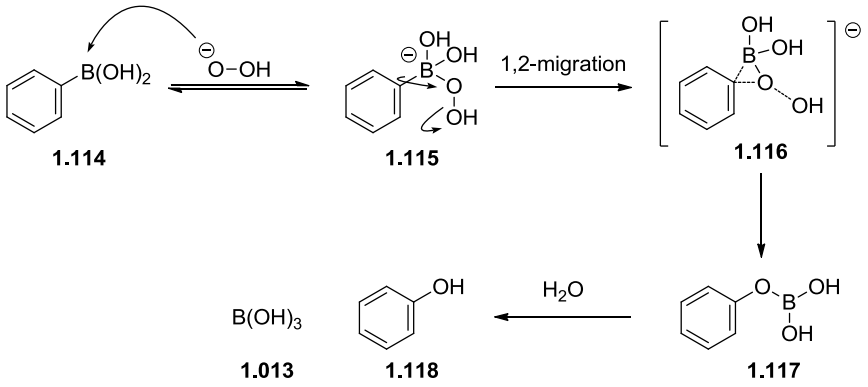
More recently, a wide variety of oxidising agents have been utilized to perform the same transformation, including, but not exclusive to, *meta*-chloroperoxybenzoic acid (*m*-CPBA), sodium perborate, Oxone® (potassium peroxymonosulfate),

trimethylamine *N*-oxide (TMAO), (diacetoxyiodo)benzene (PIDA), and sodium hypochlorite.[37] Furthermore, oxidation of alkenylborates produces enols which tautomerise to carbonyl compounds (Scheme 1.23). Oxidation of alkylborates with pyridinium chlorochromate (PCC) also generates carbonyl species as a result of the *in situ* oxidation of the intermediate alcohol.[38,39]



Scheme 1.23 Carbonyl compounds produced from boron oxidation.[38,39]

The synthesis of aliphatic chiral alcohols *via* an asymmetric hydroboration oxidation procedure is a synthetically useful transformation. The same process can also be carried out on aromatic boron centres generating phenol derivatives. The mechanism was probed by Kuivila *et al.* and was determined to be first order in both boronic acid and hydroperoxide ion.[40,41] This led to the proposal of an *ipso*-1,2-migration as the key bond forming step (Scheme 1.24).

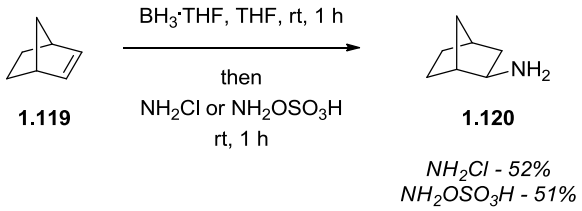


Scheme 1.24 Arylboronic acid oxidation mechanism.[40,41]

1.3.2 Amination

Carbon-boron bond cleavage is not limited to oxidation but can also be facilitated by a variety of heteroatoms including halogens, nitrogen, and hydrogen isotopes.[7] Primary amines can be synthesised through the reaction of an alkylborane with an

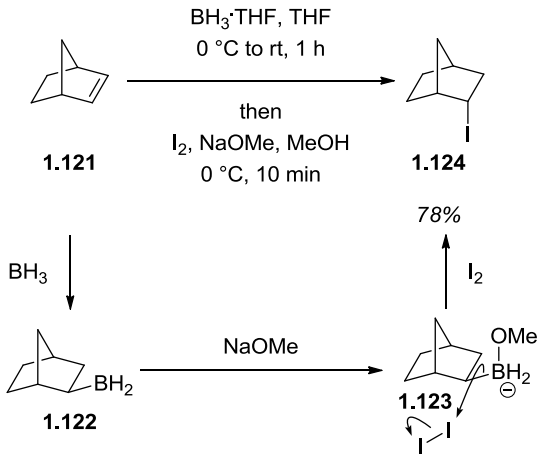
amine bearing a leaving group (Scheme 1.25).[7] The stereochemistry at the carbon atom is maintained *via* the same migratory mechanism that facilitates organoborane oxidation (Scheme 1.22).



Scheme 1.25 Functional group interconversion – amination.[7,42]

1.3.3 Halogenation

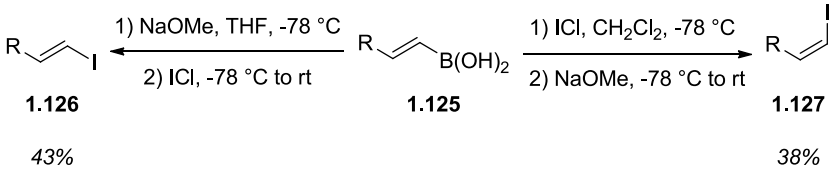
Anti-Markovnikov addition of hydrogen halides to olefins can be facilitated by successive hydroboration and halogenation reactions. Iodination and bromination of alkylboranes proceeds with clean inversion of configuration, in stark contrast to previous functional group interconversions described *e.g.*, amination, oxidation.[7] The mechanism is predicted to proceed through boronate formation and subsequent alkyl group migration (Scheme 1.26).



Scheme 1.26 *Anti*-Markovnikov addition of iodine to an olefin.[7,43]

Vinylboron compounds react with halogens in differing fashions depending on the order of reagent addition (Scheme 1.27).[44] Initially, addition of methoxide to the reaction facilitates boronate formation and a 1,2-migration once the halogen is added. As previously observed, the stereochemistry is conserved to form the *E*-olefin, **1.126**.

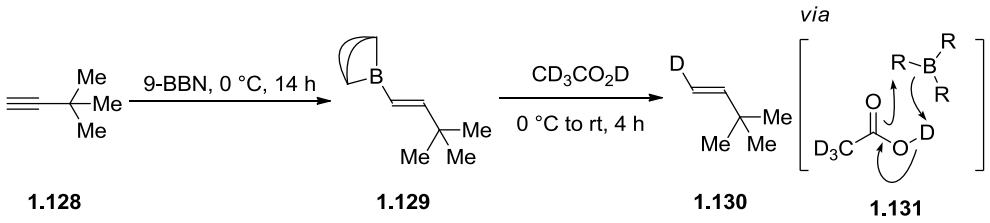
However, if an iodine source is added first, then the *Z*-olefin, **1.127**, is generated *via* iodonium formation and ring opening.[44]



Scheme 1.27 Iodination of vinylboron compounds.[44]

1.3.4 Protonolysis

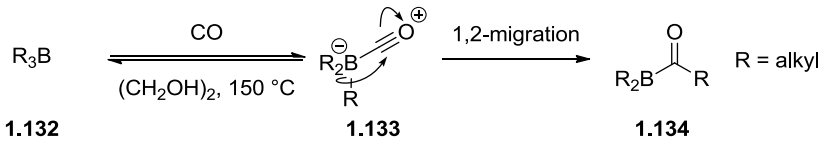
Protonolysis of alkylboron compounds is readily achieved by heating in excess carboxylic acid, usually propanoic or ethanoic acid (Scheme 1.28).[7] No reaction occurs when aqueous acid or base is used and the stereochemistry of the alkenyl group is retained during the reaction. These observations point to a concerted mechanism and also allow for the introduction of deuterium into organoboron species through the use of deuterated acids.[7]



Scheme 1.28 Functional group interconversion – protonolysis.[7,45]

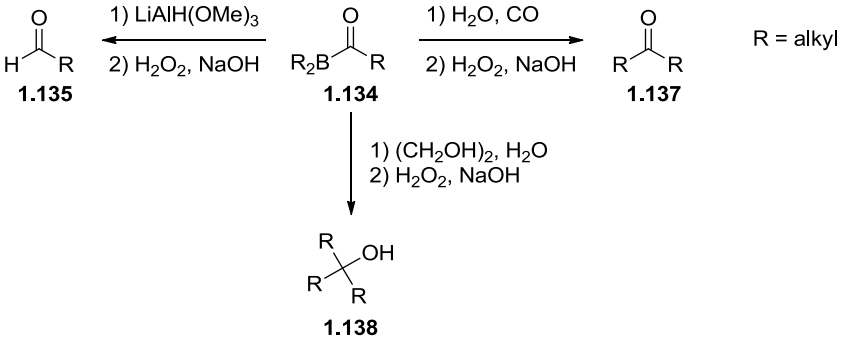
1.3.5 Carbonylation

Alkylboranes can be converted into numerous products including aldehydes, ketones, and tertiary alcohols through boron carbonylation chemistry.[7] An alkylboron species reacts with carbon monoxide in a similar fashion to other electrophilic boron reactions (*vide infra*) (Scheme 1.29). The resulting organoborate readily transfers an alkyl group to the carbonyl group, forming acyl borane intermediate **1.134**.[7]



Scheme 1.29 Acyl borane formation.[7,46]

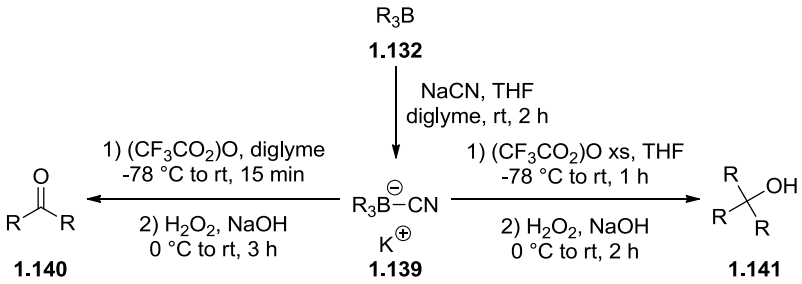
Treatment of acyl borane **1.134** with different nucleophilic reagents can promote the formation of a variety of products (Scheme 1.30).[7] Addition of lithium trimethoxyaluminium hydride facilitates aldehyde synthesis *via* boronate formation and migration of hydride to the carbonyl. In a similar fashion, an increase in carbon monoxide pressure and addition of water forces alkyl migration, yielding ketones of type **1.137**. Finally, addition of ethylene glycol promotes the migration of a further alkyl group to the carbon centre. Subsequent oxidation reveals tertiary alcohols.



Scheme 1.30 Aldehyde, ketone, and tertiary alcohol synthesis from acyl boranes.[7]

1.3.6 Cyanation

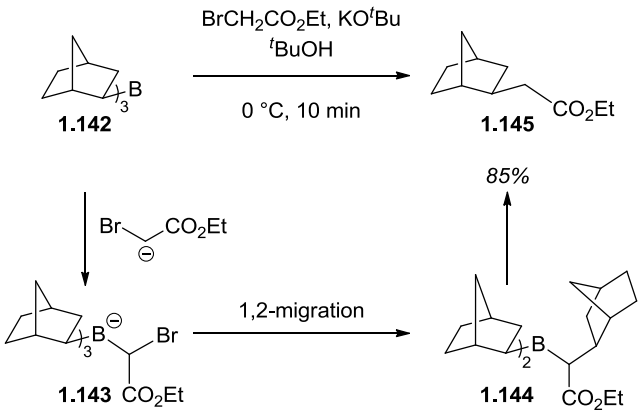
Cyanation is a viable alternative to the harsh carbonylation conditions needed to synthesise carbonyl compounds from alkylborates (Schemes 1.30 and 1.31). A negatively-charged boron complex is initially formed through addition of cyanide into the vacant p-orbital. On treatment with trifluoroacetic anhydride, two alkyl groups then undergo migration to the cyanide moiety if the reaction is performed below ambient temperature.[7] Oxidation then generates ketones of type **1.140**. A third migration can be forced if an excess of trifluoroacetic anhydride is used and the reaction is heated. Subsequent oxidation produces tertiary alcohols.



Scheme 1.31 Ketone and tertiary alcohol synthesis through alkylborane cyanation.[7,47,48]

1.3.7 Reactions with *α*-halocarbonyl compounds

Reaction of an alkylborane with *α*-halocarbonyl compounds in the presence of a base leads to the replacement of the halogen atom with an alkyl group from the borane (Scheme 1.32). The mechanism follows the usual pathway of addition to the electrophilic boron moiety and then 1,2-migration.[49] Addition of the enolate anion to the alkylborane initiates the reaction. Transfer of one alkyl group then occurs, releasing bromide, and the resulting boryl ester tautomerises to an alkenyloxyborane, **1.144**. Hydrolysis then releases the alkylated ester **1.145**.

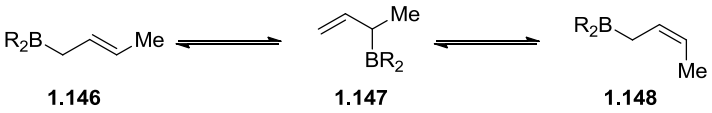


Scheme 1.32 Alkylation of alkylboranes by ethyl bromoacetate.[49]

9-BBN is often used in this type of reaction as only one alkyl group migrates.[7] This avoids the wastage of a valuable alkyl group as 9-BBN shows an very low migratory aptitude.[7]

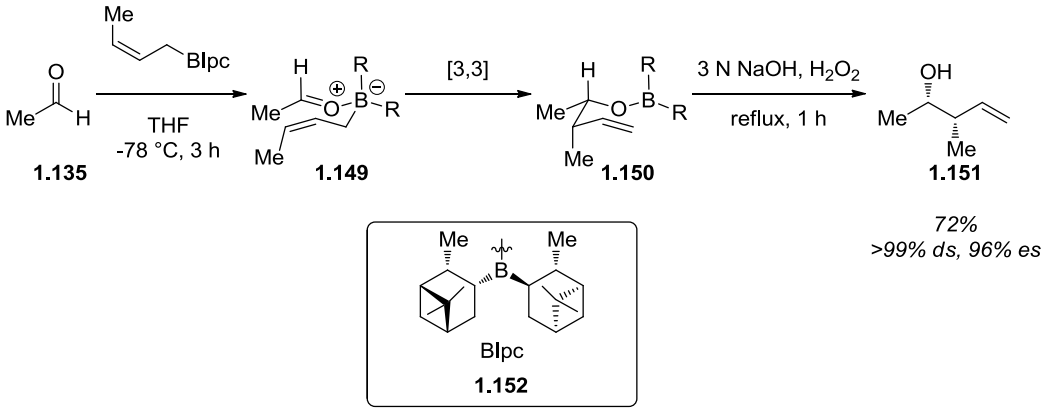
1.3.8 Allylboranes in organic synthesis

Allylboranes can be unstable at ambient temperature.[7] The pendent nucleophilic olefin can react with an electrophilic boron residue (Scheme 1.33).[7] The presence of π-donating substituents on boron, *e.g.*, oxygen, reduces electron deficiency and suppresses the rearrangement.[7] As a result, aryl- and alkenylboronic acids and ester derivatives are comparatively stable at room temperature.



Scheme 1.33 Allylborane rearrangement.[7]

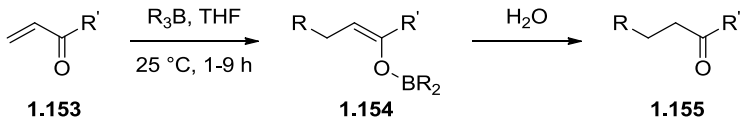
Allylboranes react with carbonyl compounds in a different way to other alkylboranes. Initially, coordination between the Lewis-acidic boron and Lewis-basic carbonyl occurs which increases the electrophilicity of the carbonyl and weakens the carbon-boron bond (Scheme 1.34).[10] The negatively-charged boronate intermediate **1.149** also increases the nucleophilicity of the olefin. A [3,3]-rearrangement then ensues. The reaction proceeds through a stepwise chair-like transition state which leads to high stereoselectivity and stereospecificity.[50] The short boron-oxygen bond leads to a compressed transition state which maximises any 1,3-diaxial interactions, heightening the stereoselectivity of the reaction. Hydrolysis then affords the free alcohol.



Scheme 1.34 Allylborane rearrangement mechanism.[50]

1.3.9 Boron conjugate addition

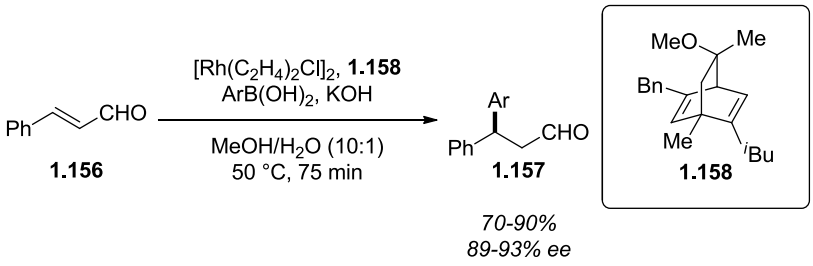
Organoboron compounds can also add to activated double bonds, in a similar fashion to the hydroboration of olefins.[14] The presence of water in the reaction medium from the outset can afford the carbonyl product, **1.155**, in one-pot (Scheme 1.35).[14] A terminal alkene is pivotal to the success of the reaction, however, the reaction can also be induced with controlled addition of oxygen or by the use of ultraviolet (UV) light.[14]



1.153 **1.154** **1.155**

Scheme 1.35 Conjugate addition of alkylboranes.[14]

More recently, metal-catalysed conjugate additions have been performed using rhodium, palladium, bismuth, and nickel catalysts.[51–55] Conjugate additions can be carried out asymmetrically with the use of chiral 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), chiral dienes, and phosphoramidite ligands (Scheme 1.36).[51] High levels of enantioselectivity can be achieved and, unlike earlier examples, both electron-deficient and electron-rich enones have equal reactivity.[51]

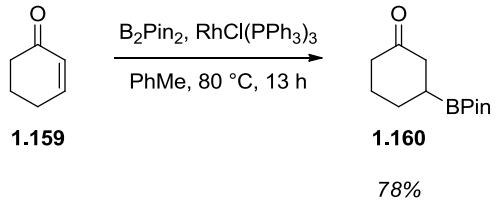


1.156 **1.157** **1.158**

70-90%
89-93% ee

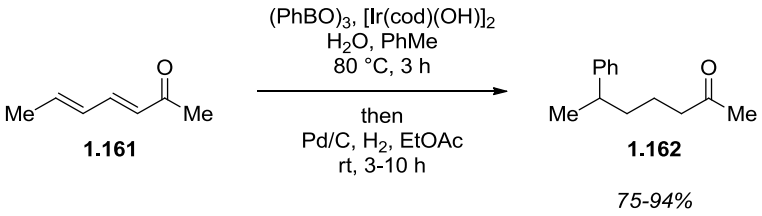
Scheme 1.36 Enantioselective boronic acid conjugate addition.[51]

Boronic ester moieties can themselves be added to electron deficient olefins in a rhodium-catalysed process (Scheme 1.37).[56] The reaction is thought to proceed through oxidative addition of the diboron reagent to rhodium and insertion into the olefin. Most likely, these reactions progress through a free radical process as the presence of radical inhibitors vastly reduces the reaction yield.[57]



Scheme 1.37 Conjugate addition of boron compounds.[56]

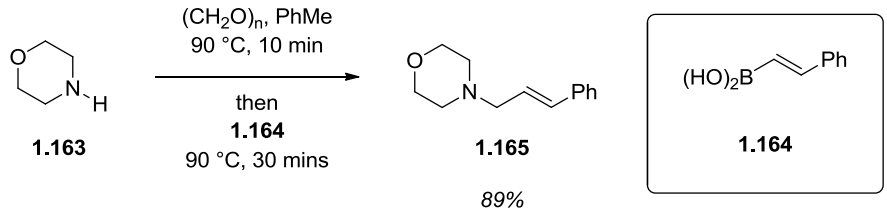
Conjugate addition is not solely limited to *α,β*-unsaturated carbonyls; 1,6-additions to *α,β,γ,δ*-unsaturated systems have been reported.[58] However, there are significant regiochemical issues that arise when previously employed 1,4-selective conditions are applied to an extended unsaturated system. The catalytic addition of aryl boronic acids to electron-deficient dienes was realised by the use of an iridium catalyst, giving excellent 1,6-selectivity (Scheme 1.38).[58]



Scheme 1.38 Iridium catalysed 1,6-conjugate addition of boronic acids.[58]

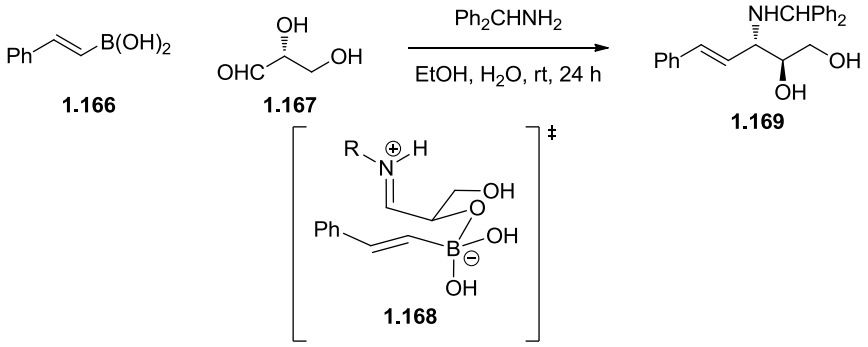
1.3.10 Petasis reaction

The Petasis reaction, or Petasis borono-Mannich reaction (PBM), comprises of the addition of an amine, an aldehyde, and a boronic acid to form substituted amines (Scheme 1.39).[59] The multicomponent reaction (MCR) is a variation of the conventional Mannich reaction and is particularly useful for the synthesis of functionalised *α*-amino acids.[60] The reaction is classified as a type II MCR whereby there is only one irreversible step in the reaction mechanism.[60] In the case of the Petasis reaction, the carbon-carbon bond-forming step is irreversible.



Scheme 1.39 Petasis reaction.[59]

The prevailing mechanism initiates through imine formation from condensation of the amine and aldehyde.[61] A pendent alcohol can then form an intermediate 'ate' (**1.168**) complex which then reacts *via* a chair-like transition state (Scheme 1.40).[61] The key carbon-carbon bond-forming step occurs with high levels of stereocontrol.[61] Vinylboronic acids are often employed in Petasis reactions due to the high migratory aptitude of the vinyl group which, in turn, lowers the transition state energy in the rate determining step.



Scheme 1.40 Stereocontrolled PBM reaction.[61]

1.3.11 Boron enolate chemistry

Boron-containing compounds also play an important role as Lewis acids, particularly in the formation and reaction of boron enolates (Figure 1.06).[7] Depending on the organoboron component used, both (*E*)- and (*Z*)-enolate geometries can be formed. Large alkyl groups (*e.g.*, dicyclohexyl{[(trifluoromethyl)sulfonyl]oxy}borane) force (*E*)-enolate formation due to a steric clash with the pendent methyl group, whereas a spatially smaller 9-BBN derivative can be aligned away from the alkene allowing for (*Z*)-enolate formation.[7]

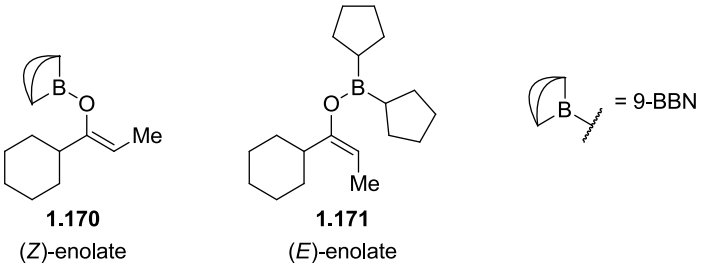
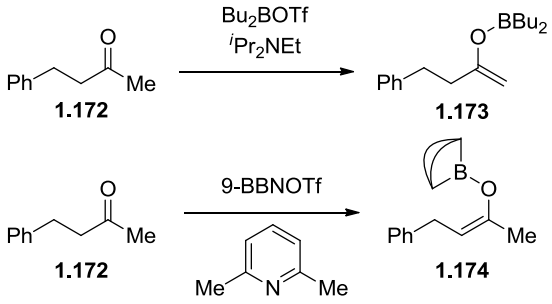


Figure 1.06 Boron enolate geometries.

Boron enolates react with aldehydes and ketones to form aldol type products.[7] Control of base and alkylboron species allows for regiochemical control of the boron enolate geometry (Scheme 1.41). This regiochemistry is maintained in the subsequent aldol reaction. Furthermore, enolate geometry and facial selectivity can be further controlled by the use of a chiral auxiliary in combination with a boron Lewis acid. The most commonly used auxiliaries in boron enolate chemistry are Evans oxazolidinones.[62]



Scheme 1.41 Regioselective boron enolate formation.[7]

Diastereoselectivity can also be controlled through selective enolate formation. A chair-like transition state ensues wherein the aldehyde substituent occupies an equatorial position (Figure 1.07). The geometry of the product can then be explained. The use of boron enolates as opposed to other Lewis acids, lithium or aluminium for example, generates products with high diastereoselectivity. This is attributed to the short boron-oxygen bond enhancing unfavourable 1,3-diaxial interactions.[7]

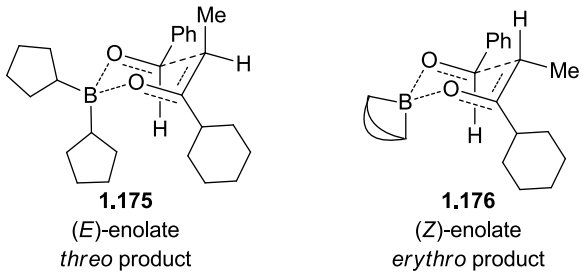
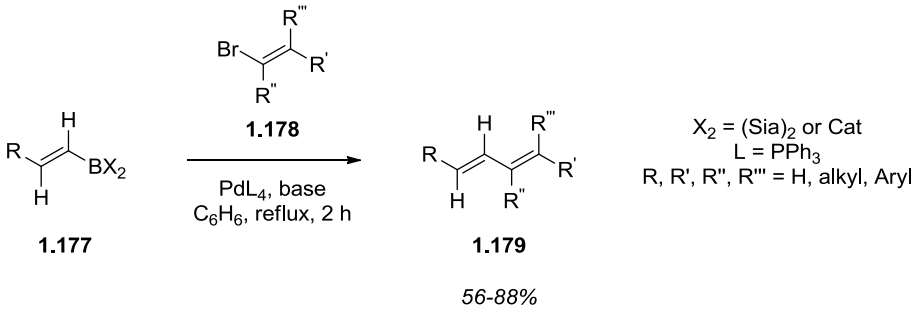


Figure 1.07 Transition states of boron enolate aldol reactions.[7]

1.3.12 Suzuki-Miyaura reaction

Perhaps the most common use of boron within preparative chemistry is as an organometallic nucleophile in the Suzuki-Miyaura reaction.[63] That is, the coupling of an aryl-, vinyl-, or alkyl(pseudo)halide with an aryl-, vinyl-, or alkylboronic acid, or derivative thereof, under transition metal catalysis. The widespread use of the reaction is due to the relative inertness of boronic acid/ester species compared to other organometallic species, the commercial availability of boron species, mild reaction conditions used, and the low toxicity of boron.[3]

The initial discovery by Suzuki and Miyaura in 1979 described a palladium(0)-catalysed coupling between alkenyl boron species and aryl halides in the presence of base in high yield (Scheme 1.42).[63] Different boron species used in the seminal work were catechol (BCat) and disiamyl ($BSia_2$) boranes and a variety of bases were shown to be successful, including sodium hydroxide, methoxide, ethoxide, and acetate.[63] The only palladium source utilized was tetrakis(triphenylphosphine)palladium(0) (tetrakis).



Scheme 1.42 Initial Suzuki-Miyaura discovery.[63]

In the following years a plethora of optimisation studies have been conducted studying every parameter of the reaction including catalyst, ligand, base, solvent, and additives.[64–69] A notable advancement is the ability to use a wide variety of boronic esters in the carbon-carbon bond forming process (Figure 1.08).[25]

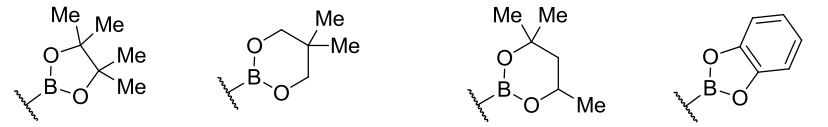
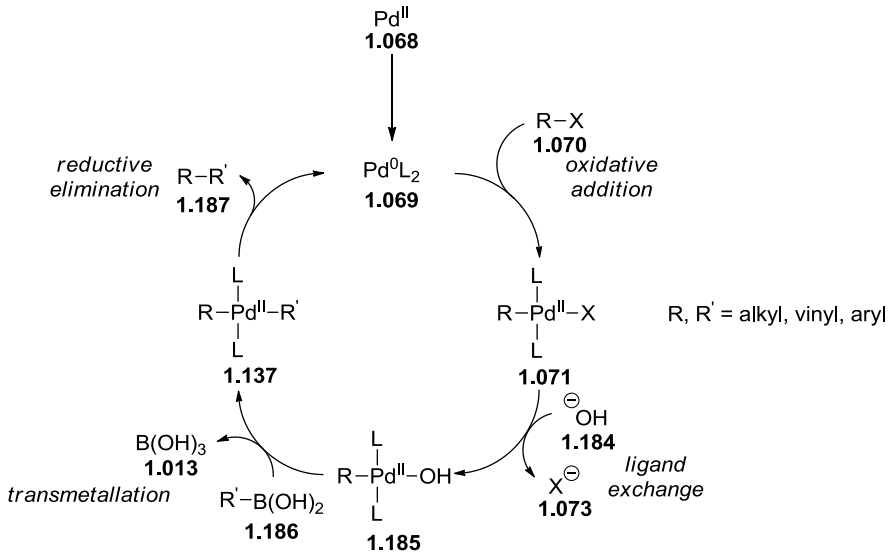
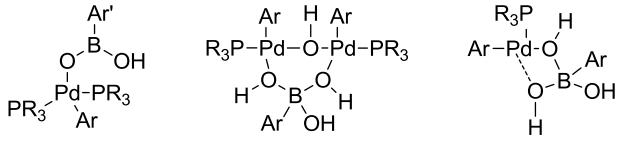


Figure 1.08 Common boronic esters.[13]

A large amount of research had been conducted into the exact mechanism of the reaction, in particular the transmetallation step.[70] It is widely accepted that palladium(0) is the active catalytic species and undergoes oxidative addition to the arylhalide bond (Scheme 1.43). Ligand exchange with the base then occurs to yield oxopalladium species **1.185**. Denmark and co-workers have analysed this transmetallation process using rapid injection NMR revealing the mechanisms of transmetallation and the exact nature of the boron-oxygen substituents formed (Scheme 1.44).[71] Hartwig has shown that species **1.185** undergoes transmetallation with the neutral boron nucleophile to generate boric acid (**1.013**).[70] *Cis*/*trans* isomerism followed by reductive elimination forms the desired carbon-carbon bond and regenerates the palladium(0) catalyst.



Scheme 1.43 Proposed Suzuki-Miyaura reaction mechanism.[70]



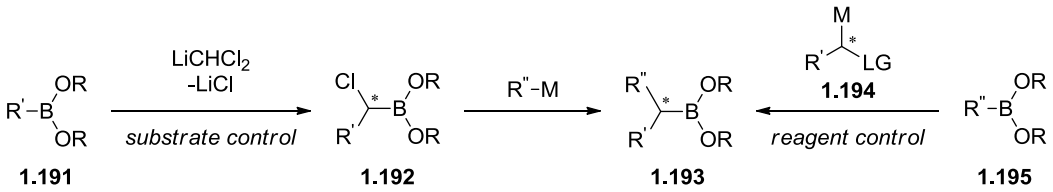
Scheme 1.44 Oxopalladium species detected by NMR.[71]

Despite the wide synthetic utility of the reaction, there are a number of limitations. Firstly, protolytic deboronation exacerbated by the basic conditions and transition metal catalyst can affect certain *ortho*-substituted and electron-poor arylboronic acids.[13,72] Furthermore, homo-coupling of the arylboron species is also known to occur.[13] To counter these events milder reaction conditions have been developed such as the use of non-aqueous conditions and milder bases.[13]

1.3.13 Boronate ester homologations

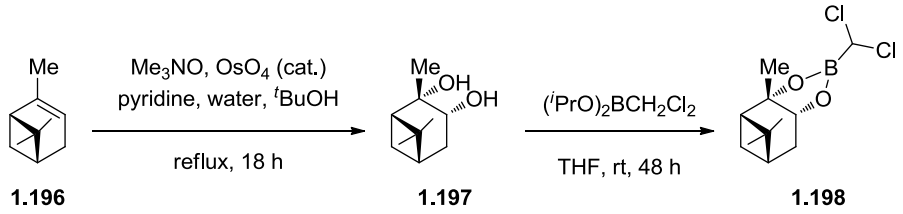
Homologation of boronic esters is known to occur when treated with dichloromethyllithium or a Grignard reagent.[73] Pivotal work in this area conducted by Matteson *et al.*[74,75] revealed that a chiral auxiliary embedded in the boronic ester could lead to homochiral organoboranes (Schemes 1.45 and 1.46). The stereochemistry of the product is directed by the substrate and as a result this approach is termed substrate controlled. A complementary approach pioneered by

Aggarwal and co-workers[73] uses a chiral reagent to form a chiral boronic ester. As such, this type of homologation termed is reagent controlled. Addition of an organometallic reagent forms a boronate species which can then undergo a 1,2-metallate rearrangement to furnish homochiral organoboranes (Scheme 1.45).



Scheme 1.45 Homochiral organoborane synthesis.[73,74]

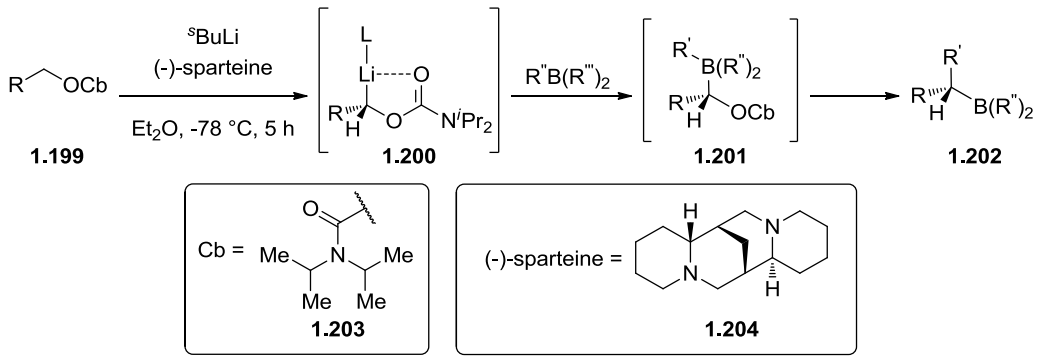
Chiral boronic ester moieties can be synthesised through the reaction of boronic acids with pinene derivatives (Scheme 1.46).[7] Both (+)- and (-)-α-pinene can be dihydroxylated using osmium tetroxide. On reaction with a boronic acid, the homochiral boronic ester is readily formed.[7] Once synthesised these derivatives can be employed in Matteson homologation procedures. Addition of (dichloromethyl)lithium rapidly forms a boronate complex at –78 °C. On warming to ambient temperature, rearrangement occurs, leading to an α-chloroboronic ester with high diastereomeric purity. A second nucleophile can then be added which once again forms a boronate species. Stereospecific migration then ensues to generate homochiral organoboranes of type **1.193** (Scheme 1.45).[73,74]



Scheme 1.46 Homochiral boronic ester synthesis.[7,76]

More recently, Aggarwal has developed the use of chiral carbanions to synthesise the same homochiral products described above (Scheme 1.47, **1.202**).[77] Elegant examples of this chemistry use a chiral base to deprotonate a prochiral substrate **1.199**. Quenching of the carbanion with a boron source forms chiral boron species of

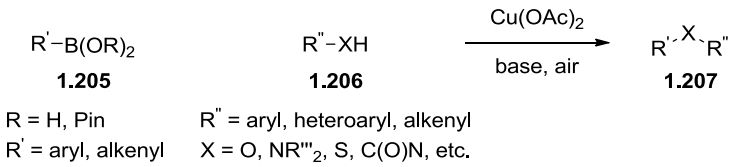
type **1.201** (Scheme 1.47). These can then undergo a 1,2-metallate rearrangement to furnish homochiral organoboron species **1.202**.[73]



Scheme 1.47 Homochiral organoborane synthesis *via* lithiation-borylation.[73,78]

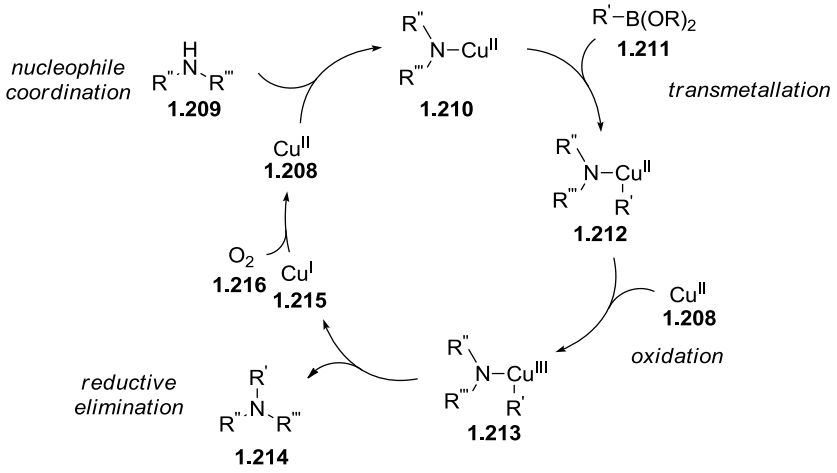
1.3.14 Chan-Evans-Lam coupling

The copper-mediated carbon-heteroatom bond forming reaction was independently reported by the groups of Chan, Evans, and Lam.[79–81] Aryl- and alkenylboronic acids react with mildly acidic functional groups under stoichiometric copper catalysis to form products of type **1.207** (Scheme 1.48). Catalytic copper can be employed if an oxidant is added to reoxidise the copper species. More recently, the substrate scope has been expanded to include BPin esters as reaction substrates.[82–85]



Scheme 1.48 General Chan-Evan-Lam reaction scheme.[13]

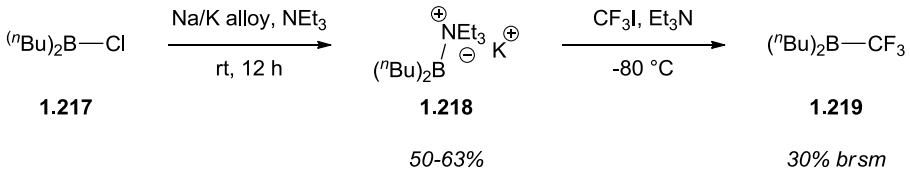
The proposed mechanism of the reaction is as follows (Scheme 1.49); initial nucleophile coordination to copper(II) lowers the copper(II)/copper(III) redox potential.[86] Transmetallation then occurs with the boronic acid derivative. This is irreversible and turn-over limiting.[86] The copper centre is then oxidised which promotes reductive elimination, generating the carbon-heteroatom bond. Finally, copper(I) is reoxidised to copper(II). [86]



Scheme 1.49 Copper oxidase Cham-Evans-Lam reaction mechanism.[86]

1.4 Boron nucleophiles in organic synthesis

Generally, boron acts as an electrophilic centre due to its electron-deficient nature, (*vide infra*). As a result, examples of boron centred nucleophiles are elusive within the chemical literature. The first example of a so called boryl anion was described by Parsons *et al.* (Scheme 1.50).[87] A Lewis acid-Lewis base interaction between triethylamine and the boron centre produces a boron species with a full octet of valence electrons. Treatment with a sodium-potassium alloy facilitates the formation of boryl anion **1.218**. The species was then proved to be nucleophilic through reaction with trifluoromethyl iodide, generating trifluoromethyl compound **1.219** in 30% yield based on recovered starting material (brsm).



Scheme 1.50 Formation and reaction of a boron nucleophile.[87]

In a similar fashion Nozaki and Yamashita rationally designed boryl anions of type **1.220**.[88] Stabilisation of the electron-deficient boron species through π-donation from adjacent nitrogen atoms coupled with their σ-acceptor capabilities allows for the formation of boryllithium species (Figure 1.09).[89] These boryllithium species can be reacted with a wide variety of electrophiles including, but not exclusively to,

aldehydes, ketones, aryl and alkyl halides, and carbon dioxide to form a variety of borylated products (Scheme 1.51).[88,89]

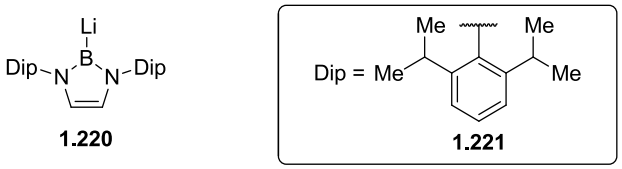
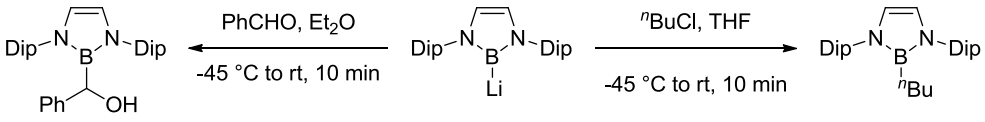


Figure 1.09 Stable boryllithium species.[89]



1.222 **1.220** **1.223**

40% *78%*

Scheme 1.51 Reactions of boryllithium species.[89]

1.5 Organoboranes in drug molecules

It should be noted that most boron compounds are thought to have low toxicity, including when exposure is through inhalation, when taken orally, or *via* skin contact.[3] Current data suggests that boron has no mutagenic activity and that there is no link between the element and cancer.[3] In fact, boron intake has been found to be essential in humans where inadequate intake was found to result in decreased activities of several hormones.[3]

Despite this, there are very few boron-containing compounds that are considered for use as drugs. However, investigations have been carried out using boron containing drugs, such as diazoborines, to treat tuberculosis.[90] Furthermore, studies have been completed on boronic acids as steroid mimics in order to treat hepatitis C and as antibiotics in order to inhibit β-lactamase.[4] Despite this research, only a couple of drug molecules containing boron have come to market. Bortezomib, **1.224** (Figure 1.10), sold as Velcade® or Cytomib® by Millennium Pharmaceuticals, is a proteasome inhibitor used to treat multiple myeloma.[91] The selective and potent boronic acid dipeptide binds reversibly to the proteasome. The Lewis-acidic boron atom binds to the catalytic site of the proteasome to inhibit its mechanism of action.[92]

The boronic acid moiety is essential for the selectivity of the drug over cysteine proteases.[93] Lewis hard-soft acid-base principles ensure that the boron atom covalently interacts with the hard oxygen lone pair in the desired proteasome as opposed to the softer sulfur lone pairs in cysteines.[94] In Bortezomib, the boronic acid also forms a covalent tetrahedral adduct with a serine residue in an oxyanion hole.

Tavaborole, **1.225**, is a known leucyl-tRNA synthetase (LeuRS) inhibitor; a new class of antibacterial that inhibits a novel target (Figure 1.10).[95] It is sold by Anacor Pharmaceuticals for the treatment of toenail onychomycosis.[95] The electrophilic boron atom covalently binds to hydroxyl groups in LeuRS, in a similar fashion to bortezomib. This covalent inhibition is irreversible which inactivates the protein and disrupts fungal protein synthesis.[95] It should also be mentioned that other boron containing compounds are a new class of molecules that demonstrate antiseptic, antifungal, and anti-viral properties.[96]

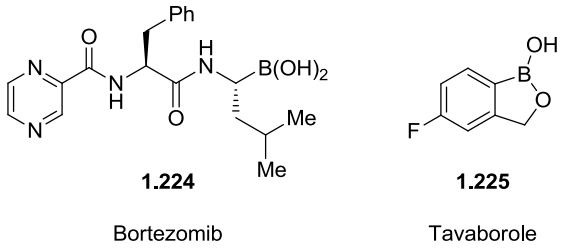


Figure 1.10 Boron containing drugs.[97]

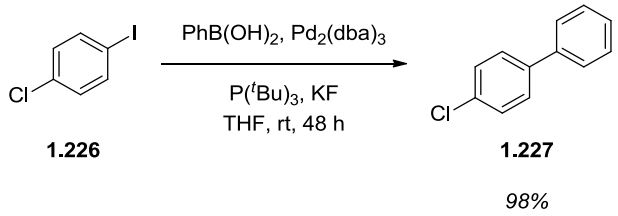
1.6 Chemoselective reactions of organoboranes

Chemoselectivity is the preferential reaction of a chemical reagent with one of two or more functional groups.[98] Increasing interest over the past several decades in organoborane compounds has led to the development of chemoselective reactions of diboron systems.[99] Research has inevitably focused on the widely utilized Suzuki-Miyaura reaction with a variety of elegant strategies to achieve chemoselectivity demonstrated, details of which will be discussed herein.[99]

1.6.1 Chemoselective oxidative addition

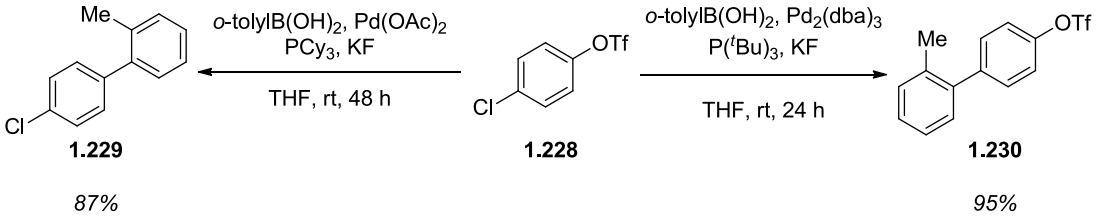
Within the Suzuki-Miyaura reaction, chemoselectivity can be achieved through exploiting the relative rates of aryl (pseudo)halide oxidative addition.[64] Generally,

the rate aligns with the carbon (pseudo)halide bond strength. That is I > Br > OTf > Cl.[64] For example, Fu and co-workers have shown exquisite chemoselectivity when reacting dihaloaryls with an arylboronic acid (Scheme 1.52).[100]



Scheme 1.52 Chemoselective oxidative addition.[100]

Interestingly, the established chemoselectivity can be inverted by careful choice of ligand (Scheme 1.53).[100,101] This so called ligand-controlled regioselectivity is dictated by the method of oxidative addition whether it be *via* pre-coordination to the π-system or by direct addition.[101]



Scheme 1.53 Ligand-controlled chemoselectivity.[100,101]

1.6.2 Chemoselectivity in diboron systems

Discrimination between two boron systems is pivotal to achieving chemoselectivity. One such way of accomplishing this is by the use of boron protecting groups such as 1,8-diaminonaphthalene (DAN), *N*-methyliminodiacetic acid (MIDA), and potassium trifluoroborate salts (BF_3K) (Figure 1.11).

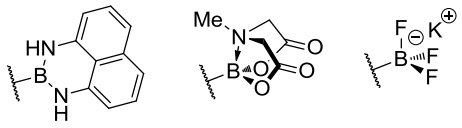
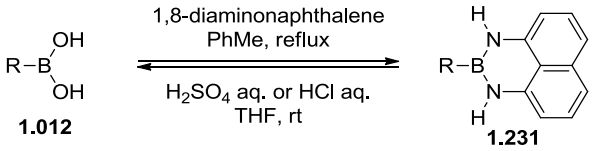


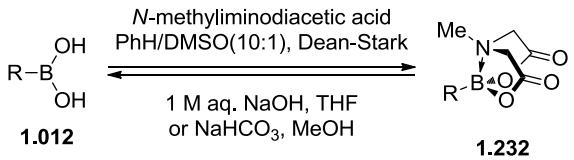
Figure 1.11 Protected boron species.

The DAN protecting group, pioneered by Suginome *et al.*, lowers the Lewis acidity of the boron centre through partial delocalisation of the nitrogen lone pairs into the vacant p-orbital.[102] This increases their stability towards hydrolysis in strongly basic conditions including those employed in the Suzuki-Miyaura reaction.[99,103,104] The diamine can be easily installed through refluxing in toluene with azeotropic removal of water and removed once utilised through stirring in strong acid (Scheme 1.54).[102]



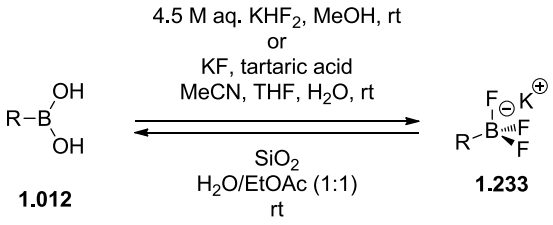
Scheme 1.54 Transformation of boronic acids into the protected BDAN species.[103]

Concurrently, the base-sensitive, acid-stable MIDA protecting group was reintroduced by Burke *et al.* following its initial discovery in the early 1980's (Figure 1.11).[105,106] The nitrogen-boron dative bond alters the hybridisation of the boron centre from sp^2 to sp^3, enforcing tetrahedral geometry.[99] This nullifies the electrophilic boron, rendering it unreactive in a wide variety of conditions including Suzuki-Miyaura, Stille, and Negishi cross-coupling reactions. The species are bench-stable and survive chromatographic methods while remaining straightforward to deprotect on treatment with base (Scheme 1.55).[103]



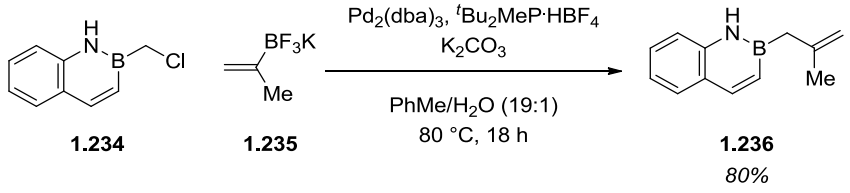
Scheme 1.55 Transformation of boronic acids into the protected BMIDA species.[103]

In a similar fashion, boron potassium trifluoroborate salts also form a tetrahedral boronate centre which is deactivated to both transmetallation and nucleophilic attack.[107] The first preparation of such species was reported by Vedejs *et al.* (Scheme 1.56). Treatment of boronic acids with potassium bifluoride revealed the corresponding trifluoroborate salt.[107] However, significant glass etching was reported which led to Lloyd-Jones and Lennox proposing a combination of potassium fluoride and tartaric acid which avoids such problems.[108] Reversal of the procedure is synthetically simple. Addition of an aqueous fluorophore (*e.g.*, SiO_2) reveals the parent boronic acid.[109]



Scheme 1.56 Transformation of boronic acids into the protected BF_3K species.[108–110]

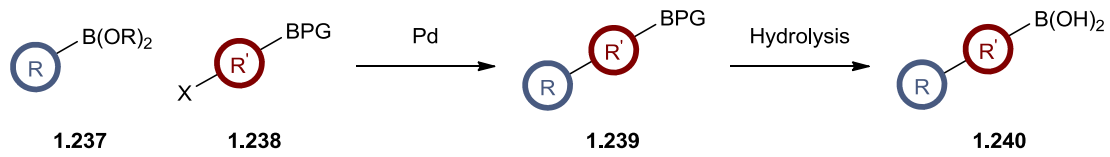
Organotrifluoroborate salts are stable to anhydrous conditions and as such can be employed as protecting groups in Suzuki-Miyaura reactions.[110] Conversely, aqueous basic conditions can facilitate hydrolysis, rendering the trifluoroborate the most reactive boron species (Scheme 1.57).[111]



Scheme 1.57 Hydrolysis and reaction of potassium trifluoroborate salts.[111]

As mentioned, the majority of the reported uses of boron protecting groups is in the Suzuki-Miyaura reaction.[25,99,104] A protected boron species containing a (pseudo)halide, such as **1.238**, can allow for chemoselective reaction between the carbon-(pseudo)halide bond and a free boronic acid or ester group on another molecule, leaving the boron protecting group intact. Subsequent hydrolysis can

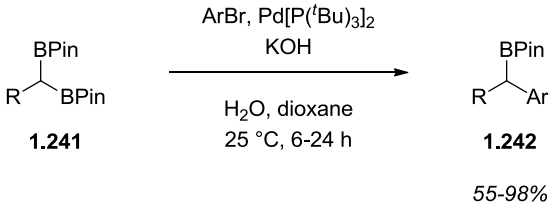
reveal the parent boronic acid, **1.240**, which can undergo further functional group interconversion (Scheme 1.58).[99,104]



Scheme 1.58 General scheme depicting chemoselectivity in diboron systems.[104]

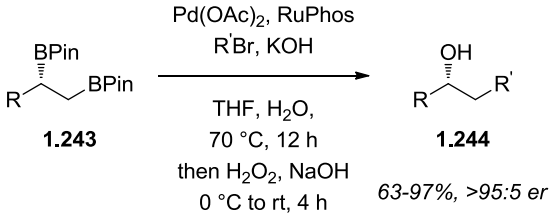
1.6.3 Chemoselectivity in diboron compounds

The use of protecting groups in organic synthesis is discouraged wherever possible as it introduces two additional steps into a sequence, increasing cost and time investment along with reducing the overall yield of the process.[112] One such method of avoiding protecting groups is by the self-activation/protection mechanism invoked in geminal and vicinal diboron systems.[104] Pioneering work in the area performed by Shibata *et al.* demonstrated that geminal BPins could be chemoselectively cross-coupled (Scheme 1.59).[113] Furthermore, Morken has demonstrated that an enantioselective process is possible by the use of a chiral ligand.[114]



Scheme 1.59 Chemoselective coupling of 1,1-diborylalkanes.[113]

This methodology can be expanded to vicinal diboron species. Morken and co-workers have developed conditions that enable chemo- and stereoselective Suzuki-Miyaura coupling of enantioenriched starting materials (Scheme 1.60).[115]



Scheme 1.60 Chemoselective coupling of vicinalBPin compounds.[115]

It is proposed that chemoselectivity in these reactions arises from a Lewis acid-Lewis base interaction between the two boron species.[115] The terminal BPin donates electron density into the proximal boron (Figure 1.12). This activates the terminal BPin and increases its relative rate of transmetallation. In turn, the more Lewis-basic proximal BPin is deactivated.[104] As a result this process is termed self-activation/protection.

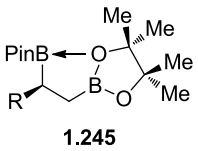


Figure 1.12 Self-activation/protection of vicinal alkylBPin compounds.[115]

1.7 Aims

One void in the chemical literature is the inability to chemoselectively discriminate between unprotected diboron compounds. Consequently, the aims of the project described in chapter one are to:

1. Develop conditions that enable chemoselective reaction of diboron compounds.

2. Invert the established chemoselectivity by employing a suitable protecting group.

3. Probe the mechanism by which chemoselectivity is achieved.

Research into boron chemistry is then continued in chapter two through the application of new technology to the Suzuki-Miyaura reaction. Specifically incorporation of novel glassware (COware) which allows regioselective cross-coupling and subsequent hydrogenation to occur in one reaction vessel. As such, the aims of the project are to:

1. Develop a one-pot Suzuki-Miyaura/hydrogenation procedure utilizing COware that is applicable to a wide variety of substrates.

2. Apply the new methodology to synthesise a series of semi-saturated drug analogues to compare physicochemical properties.

Chapter 1

Chemoselective oxidation of aryl diboron systems enabled by boronic acid-selective phase transfer

This chapter is based on the publication 'Chemoselective Brown Oxidation of Aryl Organoboron Systems Enabled by Boronic Acid-selective Phase Transfer.' (Appendix 1)

1 Introduction

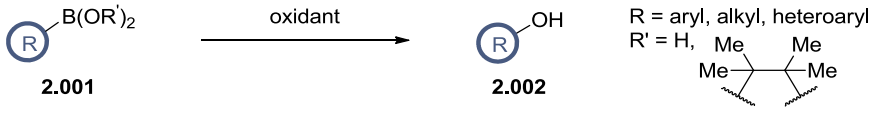
Boron protecting groups are the most widely adopted strategy for accomplishing chemoselective reactions of diboron systems, that is, systems containing two separate boron compounds (*cf.* section 1.6.2). The most prevalent boron protecting groups used in synthetic organic chemistry are BMIDA, BDAN, and BF_3K due to their complementary reactivity and ease of protection and removal.[102–111] Protecting groups are generally used for achieving chemoselective reactions of boron species within diboron systems.[25,99,102–104,110,116–123] Chemoselectivity in alkyl diboron systems can be achieved through similar protecting group methodology although the more elegant self-activation/protection mechanism invoked in geminal/vicinal diboron systems is also applicable within alkyl systems (*cf.* section 1.6.3).[99,103,104,113–117,124–126]

Therefore, the only current method of performing chemoselective reactions of aryl diboron systems is through the use of a suitable protecting group strategy. However, as discussed previously, using protecting groups in organic synthesis is lengthy and decreases overall synthetic sequence yield.[127] In order to avoid the use of protecting groups in reactions comprising multiple boron moieties, two unprotected boron species with differing reactivity could be used, for example a boronic acid and a boronic ester. Both of these species have broadly similar reactivity and undergo the same synthetic transformations, *e.g.*, cross-coupling, oxidation, and halogenation under similar reaction conditions.[13]

However, boronic acids and their ester derivatives experience complex system solution equilbria.[13,55,85,128–138] This so-called speciation must be controlled in order to facilitate a chemoselective reaction. Control of equilibrium processes was investigated in a chemoselective oxidation process of an arylboronic acid over an arylboronic ester. This would be the first example of a chemoselective reaction in an aryl diboron system without the use of boron protecting groups.

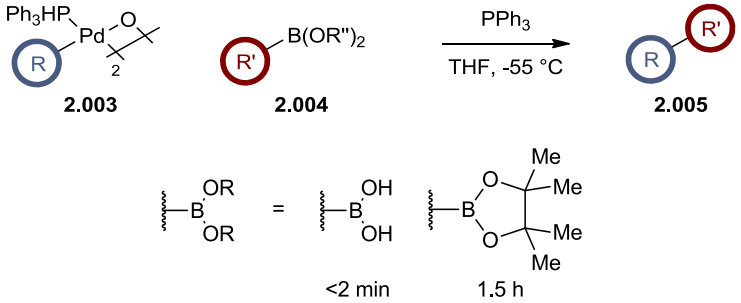
2 Results and discussion

The Brown oxidation of an organoboron compound to the corresponding alcohol or phenol is a fundamental transformation within the synthetic organic chemistry toolbox (Scheme 2.01).[13,15,39] A variety of oxidants have been utilised to facilitate this transformation including basic hydrogen peroxide, *meta*-chloroperoxybenzoic acid (*m*-CPBA), sodium perborate ($NaBO_3$), Oxone® (potassium peroxymonosulfate), trimethylamine *N*-oxide (TMAO), (diacetoxyiodo)benzene (PIDA), and sodium hypochlorite.[139]



Scheme 2.01 Brown oxidation of organoboron compounds.[13,15,39]

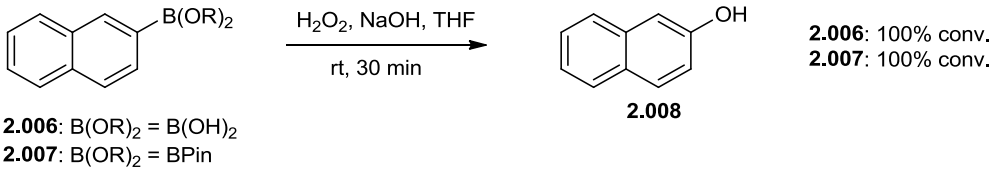
Typically, boronic acids and esters are rapidly and indiscriminately oxidised under classical oxidative conditions.[13,140,141] Consequently, chemoselective reactions, specifically oxidation, of these unprotected diboron systems is unknown. However, small differences in the reactivity of boronic acids and esters have been observed in non-competitive systems (Scheme 2.02).[70] Data from the Hartwig group demonstrates that the transmetallation of arylboronic acids occurs at a rate approximately 45 times faster than that of pinacol esters.[70] However, reproducibility in diboron systems is unknown as this data was generated in monoboron systems.[142]



Scheme 2.02 Differing reactivity of boron species in the Suzuki-Miyaura reaction.[70]

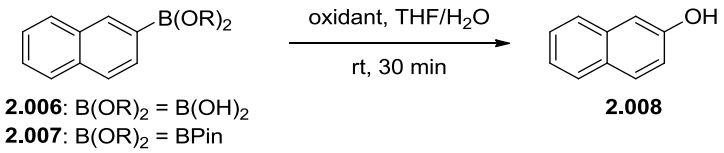
Initially, the difference in reactivity of boronic acids and esters was explored in an oxidation reaction. Monoboron systems containing naphthalen-2-ylboronic acid,

2.006, and naphthalen-2-ylboronic acid, pinacol ester, **2.007**, were initially subjected to classical Brown oxidation conditions employing basic hydrogen peroxide as oxidant (Scheme 2.03).[15] Extremely rapid and uncontrollable oxidation of both species ensued at ambient temperature when stirred for 30 minutes.



Scheme 2.03 Indiscriminant oxidation of boron species.

Subsequently, a range of oxidants and reaction conditions were surveyed to determine if any difference in oxidation rate could be obtained (Table 2.01). Initial removal of base from the reaction mixture significantly slowed the rate of the reaction with just 24% conversion of naphthalen-2-ylboronic acid **2.006** being observed after one hour (Table 2.01, entry 1). Only 19% conversion was observed when the corresponding pinacol ester **2.007** was used (entry 2). Altering the oxidant to sodium perborate showed indiscriminant oxidation of both boronic acid **2.006** and pinacol ester **2.007** (entries 3 and 4). The use of *m*-CPBA yielded a small degree of selectivity for boronic acid oxidation (entries 5 and 6).



entry	boron species	oxidant	conversion[a]
1	**2.006**	30% wt. aq. H_2O_2	24%
2	**2.007**	30% wt. aq. H_2O_2	19%
3	**2.006**	$NaBO_3{\cdot}4H_2O$	quant.
4	**2.007**	$NaBO_3{\cdot}4H_2O$	quant.
5	**2.006**	50% wt. *m*-CPBA	92%
6	**2.007**	50% wt. *m*-CPBA	75%
7	**2.006**	Oxone®	98%
8	**2.007**	Oxone®	22%

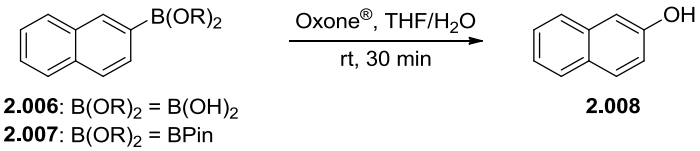
[a]Determined by HPLC analysis using an internal standard.

Table 2.01 Oxidation of monoboron systems – oxidant study.

Finally, a small rate difference favouring a more rapid oxidation of **2.006** was found using Oxone® in THF and water (Table 2.01, entries 7 and 8). This rate difference was more profound than when *m*-CBPA was employed as oxidant (entries 5 and 6). Oxone®, a triple salt consisting of potassium peroxymonosulfate ($KHSO_5$), the active oxidant, and degradation products potassium bisulfate ($KHSO_4$) and potassium sulfate (K_2SO_4), is a versatile oxidant in organic synthesis.[143] Its nature as a white, weighable, crystalline solid enhances the synthetic utility of the substance.[143] Excellent conversion of boronic acid **2.006** to naphthol **2.008** was observed when

Oxone® was employed as the oxidant, however, only 22% of the corresponding pinacol ester was oxidised under identical reaction conditions.

More focused analysis of the oxidation through analysis of the reaction over a range of time points revealed significant rate information about the individual reactions (Chart 2.01). Using identical conditions to those in Scheme 2.04, oxidation of boronic acid **2.006** appeared to show significant conversion in the burst phase (approximately 0–10 mins) of the reaction, where conversion to product is rapid, before steady state conditions are established (approximately 10–30 mins). Oxidation of pinacol ester **2.007** exhibited a more linear profile throughout the entire reaction.



2.006: $B(OR)_2 = B(OH)_2$
2.007: $B(OR)_2$ = BPin

2.008

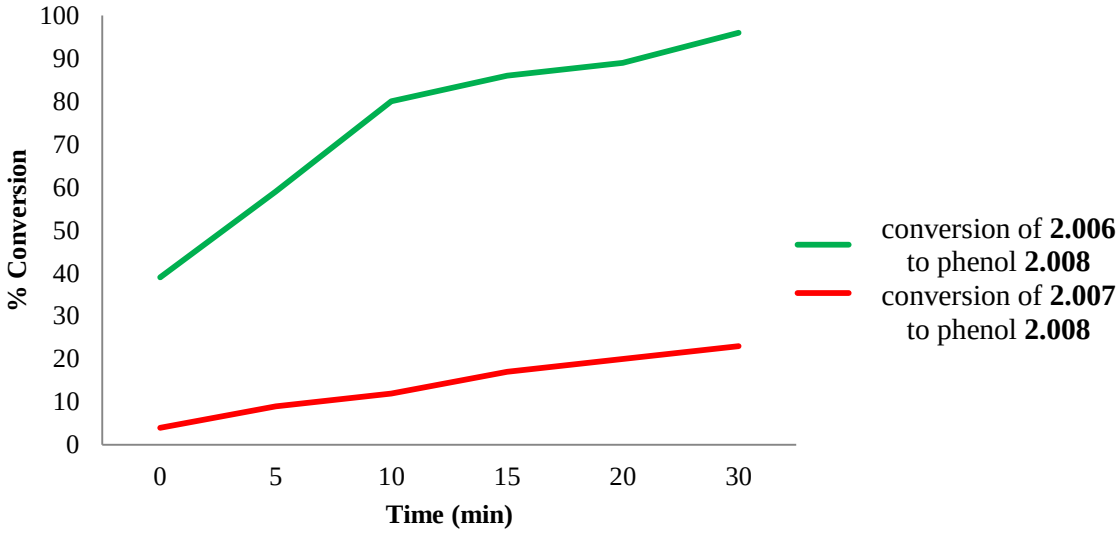
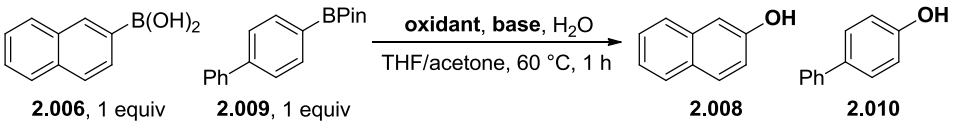


Chart 2.01 Oxidation of **2.006** and **2.007** using Oxone® under biphasic reaction conditions (THF/H_2O) over 30 min at 350 rpm.

All reactions performed thus far have featured isolated monoboron systems *i.e.*, containing either boronic acid or pinacol ester. A difference in the rate of the reaction when using Oxone® as an oxidant has been observed (Chart 2.01) but is this difference in rate still prevalent in competitive diboron systems? Initially, to trial this hypothesis, identical reaction conditions to those in which kinetic discrimination

was observed in monoboron systems (Table 2.01, entries 7 and 8) were employed in a diboron system (Table 2.02). Good conversion of both boronic acid **2.006** and pinacol ester **2.007** moieties was observed (entry 1); however, minimal chemoselectivity was observed (1.1:1). An elevated temperature (60 °C) was then employed to increase the rate of the kinetically slow Oxone®-mediated reaction (entry 2). Interestingly, conversion significantly decreased (56%); however, a level of chemoselective boronic acid oxidation was observed (5:1). Using the original oxidant, hydrogen peroxide, with no base significantly improved conversion in the diboron system, however, there was no observable chemoselectivity (entry 3). Addition of potassium hydroxide into the reaction mixture increased conversion from 90% to quantitative (entries 3 and 4). Alteration of the base present from potassium hydroxide to tripotassium phosphate maintained excellent conversion and allowed a small amount of selectivity for boronic acid oxidation to be leveraged (entry 5).



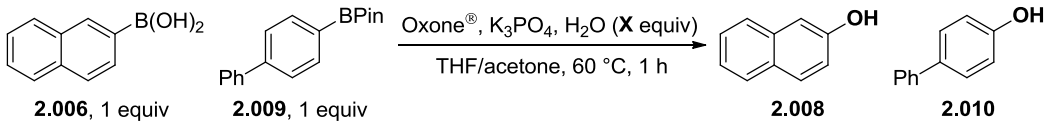
entry	base	oxidant	conversion[a]	**2.008**:**2.010**[a]
1[b,c]	---	Oxone® (2.5 equiv) in H_2O:THF (5:1)	95%	1.1:1
2[c]	K_3PO_4 (3 equiv)	Oxone® (2.5 equiv) in H_2O:THF (5:1)	56%	5:1
3	---	30% wt. aq. H_2O_2 (2.5 equiv)	90%	1:1
4	KOH (3 equiv)	30% wt. aq. H_2O_2 (2.5 equiv)	quant.	1:1
5	K_3PO_4 (3 equiv)	30% wt. aq. H_2O_2 (2.5 equiv)	quant.	1.1:1

[a]Determined by HPLC analysis using an internal standard. [b]Reaction conducted at ambient temperature. [c]Oxone was added as a slurry in acetone.

Table 2.02 Oxidation optimisation – oxidant study.

A moderate level of chemoselectivity (5:1) was observed utilising Oxone® in a trisolvent reaction mixture consisting of THF, acetone, and water (Table 2.02, entry 2). As such, the reaction medium composition was originally examined through altering the water content of the reaction mixture (Table 2.03). Significantly decreasing the amount of water to 100 or 200 equivalents mediated indiscriminate oxidation of both boron species **2.006** and **2.009** (Table 2.03, entries 1 and 2). Increasing the water content of the solvent mixture to 300, 400, or 500 equivalents yielded improved conversion to the desired phenol, **2.008**; however, no chemoselectivity was obtained (entries 3, 4, and 5). A small amount of

chemoselectivity was observed through raising the amount of water present to 550 equivalents (entry 7). However, only slight levels (3:1) of chemoselectivity were achieved as significant boronic ester oxidation was also occurring. Analysis of the water content of the reaction mixture did not allow for significant improvement in the overall conversion or chemoselectivity of the reaction (*cf.* Table 2.02, entry 2 *vs.* Table 2.03, entry 7). As such, other components of the reaction medium were investigated to try and improve the chemoselectivity of oxidation.



2.006, 1 equiv **2.009**, 1 equiv **2.008** **2.010**

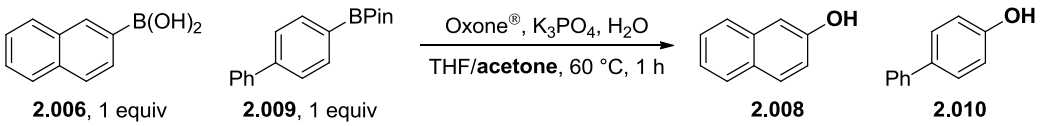
entry	water	conversion[a]	**2.008**:**2.010**[a]
1	100 equiv	72%	1:1
2	200 equiv	77%	1.1:1
3	300 equiv	quant.	1:1
4	400 equiv	quant.	1.1:1
5	450 equiv	91%	1.5:1
6	500 equiv	quant.	1:1
7	550 equiv	62%	3:1

[a]Determined by HPLC analysis using an internal standard.

Table 2.03 Oxidation optimisation – water study.

Acetone was initially added to the reaction mixture to aid the solubility of Oxone® in the reaction medium. This enhanced the yield of the oxidation reaction; however, levels of chemoselectivity were only slender (Table 2.03, entry 7). Consequently, the amount of acetone in the reaction mixture was investigated (Table 2.04). Decreasing

the equivalents from twenty, to ten, and then further to five equivalents reduced overall conversion by a factor of two from 98% to 54% (Table 2.04, entries 1–3). However, chemoselectivity gradually increased over the same measurements from 2:1 to 6:1. Finally, a reaction medium consisting of only THF and water recovered conversion to 81% and greatly enhanced chemoselectivity to 18:1 in favour of boronic acid oxidation (entry 4).



2.006, 1 equiv **2.009**, 1 equiv **2.008** **2.010**

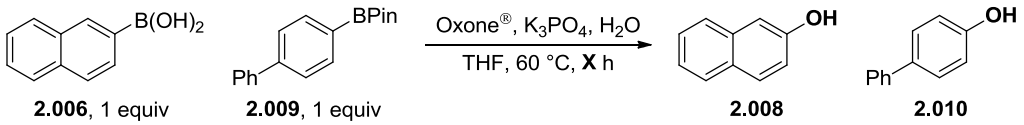
entry	acetone	conversion[a]	**2.008**:**2.010**[a]
1	20 equiv	98%	2:1
2	10 equiv	45%	3:1
3	5 equiv	54%	6:1
4	---	81%	18:1

[a]Determined by HPLC analysis using an internal standard.

Table 2.04 Oxidation optimisation – acetone study.

The timeframe of the reaction was previously unknown, with all reactions being conducted over a one hour period (Tables 2.03 and 2.04). The reaction time was thus shortened to investigate if oxidation was complete before the one hour mark (Table 2.05). After 30 minutes, the reaction was quenched and conversion determined to be lower than that obtained after one hour (entry 1 *vs.* entry 3). However, enhanced chemoselectivity was observed, 25:1 *vs.* 18:1. Further increasing the reaction time to 45 minutes improved conversion to levels similar to that after one hour, 78% *vs.* 81%, while chemoselectivity was maintained (entries 2 and 3). Chemoselectivity significantly decreased between 30 and 45 minutes which is presumably due to the relative rate of oxidation of the two species. Increasing the duration of the reaction

allows for more boronic ester oxidation to occur. Furthermore, as boronic acid **2.006** is oxidised, the relative concentration of boronic ester **2.009** increases, meaning that the boronic ester is more likely to be oxidised as the reaction progresses. Consequently, the reaction time was kept constant at one hour to ensure full conversion to the desired naphthol, **2.008**. Any attempts to further increase the reaction time resulted in no improvement in conversion or chemoselectivity (entry 4).



2.006, 1 equiv **2.009**, 1 equiv **2.008** **2.010**

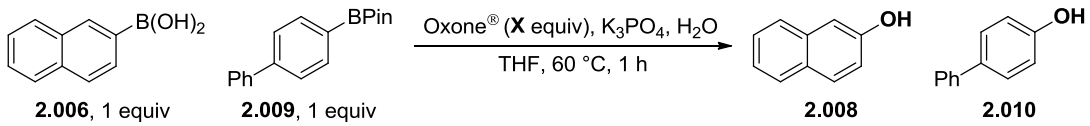
entry	time (h)	conversion[a]	**2.008**:**2.010**[a]
1	0.5	66%	25:1
2	0.75	78%	18:1
3	1	81%	18:1
4	2	64%	19:1

[a]Determined by HPLC analysis using an internal standard.

Table 2.05 Oxidation optimisation – time study.

Two and a half equivalents of the oxidant were used in all reactions in order to ensure that there was sufficient oxidant present in the reaction mixture so that both boron species could be oxidised. Therefore, the equivalents of Oxone® employed were not lowered below 2.5 equivalents. Instead, an increase in the quantity of oxidant used was investigated in order to determine the optimum amount (Table 2.06). Somewhat counter-intuitively, levels of conversion decreased with increasing equivalents of oxidant present, from 81% to 61% (entries 1−3). As expected, chemoselectivity also decreased, from 18:1 to 8:1. Furthermore, the presence of additional salts in the form of Oxone® could cause a subtle change in the pH of the

reaction mixture. The change in pH may facilitate more facile speciation and as a result more boronic ester oxidation. Consequently, the amount of oxidant used was not altered from the previously used 2.5 equivalents in further studies.



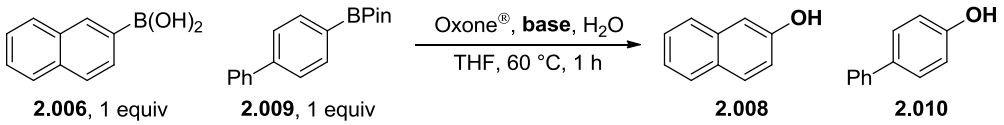
2.006, 1 equiv **2.009**, 1 equiv **2.008** **2.010**

entry	Oxone®	conversion[a]	**2.008**:**2.010**[a]
1	2.5 equiv	81%	18:1
2	3.5 equiv	71%	16:1
3	4.5 equiv	61%	8:1

[a]Determined by HPLC analysis using an internal standard.

Table 2.06 Oxidation optimisation – Oxone® equivalents study.

Despite the good conversion and selectivity already achieved when employing tripotassium phosphate in the reaction, a range of bases were surveyed in an attempt to improve the conversion and chemoselectivity of the oxidation procedure (Table 2.07, entry 1). Carbonate bases maintained similar levels of chemoselectivity to tripotassium phosphate, while oxidation levels were slightly diminished, 81% *vs.* 53% (entries 1−3). Stronger potassium bases evaluated provided enhanced conversion but no discrimination between boron species (entries 4 and 5). Consequently, tripotassium phosphate was retained in the reaction mixture as it provided optimal conversion and chemoselectivity.



2.006, 1 equiv **2.009**, 1 equiv **2.008** **2.010**

entry	base	conversion[a]	**2.008**:**2.010**[a]
1	K_3PO_4	81%	18:1
2	Cs_2CO_3	59%	14:1
3	K_2CO_3	53%	12:1
4	KOAc	quant.	1:1
5	KOH	quant.	1.5:1

[a]Determined by HPLC analysis using an internal standard.

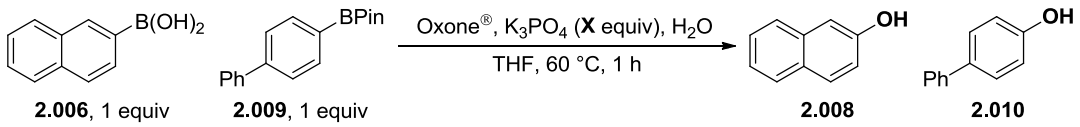
Table 2.07 Oxidation optimisation – base study.

The conversion and chemoselectivites calculated can be aligned with the pK_aH of the bases used in the reaction (Table 2.08). Basic potassium hydroxide facilitates rapid pinacol hydrolysis[144] and consequently no chemoselectivity is observed (entry 1). Conversion is high due to the kinetically fast oxidation of boronic acid. Tripotassium phosphate is not as basic as hydroxide, so much so that ester hydrolysis does not occur, and boronic acid boronate formation can take place. Selective phase transport of the boronic acid boronate into the aqueous phase then ensues. This leads to excellent chemoselectivity in the reaction. Crucially, phosphate is more basic than both carbonate and acetate which show poorer levels of chemoselectivity and, in the case of potassium carbonate, diminished conversion *i.e.*, carbonate bases do not allow for rapid boronate formation and as such conversion in lowered.

entry	base	pK_aH
1	KOH	15.71
2	K_3PO_4	12.32, 7.21, 2.21
3	K_2CO_3	10.33, 6.35
4	KOAc	4.76

Table 2.08 pK_{aH} of bases present in the oxidation reaction mixture.

With the optimal base identified, a short study was conducted into whether a large excess of base, three equivalents, was necessary in order to maintain levels of chemoselectivity (Table 2.09). As expected, lowering the equivalents of base present significantly decreased the levels of chemoselectivity observed in the reaction, correlating with earlier examples where removal of all base reduced overall conversion (Table 2.09, entries 1 and 2 and Table 2.02, entries 2 and 3).



2.006, 1 equiv **2.009**, 1 equiv **2.008** **2.010**

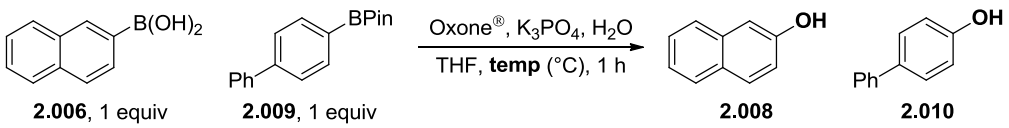
entry	base	conversion[a]	**2.008**:**2.010**[a]
1	1 equiv	quant.	2:1
2	2 equiv	67%	4:1
3	3 equiv	81%	18:1

[a]Determined by HPLC analysis using an internal standard.

Table 2.09 Oxidation optimisation – base equivalents study.

The impact of reaction temperature on chemoselectivity was then investigated (Table 2.10). Quantitative oxidation was obtained at low reaction temperatures, ambient

temperature and 30 °C, with minimal chemoselectivity, 2:1 and 5:1, respectively (Table 2.10, entries 1 and 2). In general, chemoselectivity improved as the reaction temperature was increased (entries 1−6). However, conversion to the desired phenol initially lowered on raising the temperature (entries 1−6). Conversion improved upon further heating of the reaction mixture to 60 °C and 70 °C (entries 5 and 6). No attempt to further increase the reaction temperature above 70 °C was made in order to prevent evaporation of the solvent mixture. Further reaction screening was carried out at 70 °C due to the enhanced conversion and good level of chemoselectivity observed.



2.006, 1 equiv **2.009**, 1 equiv **2.008** **2.010**

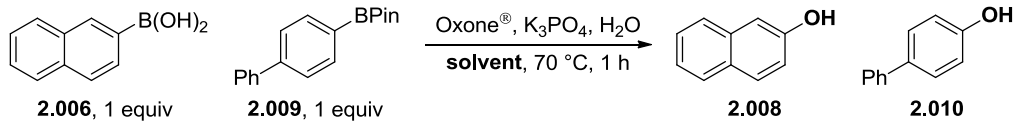
entry	temperature (°C)	conversion[a]	**2.008**:**2.010**[a]
1	20	quant.	2:1
2	30	quant.	5:1
3	40	87%	7:1
4	50	62%	9:1
5	60	81%	18:1
6	70	93%	13:1

[a]Determined by HPLC analysis using an internal standard.

Table 2.10 Oxidation optimisation – temperature study.

Finally, after a solvent screen, cyclopentyl methyl ether (CPME) was determined to be optimal for the reaction as it allowed quantitative oxidation of boronic acid **2.006** and with near perfect chemoselectivity (Table 2.11, entry 1). Excellent conversion and chemoselectivity was also observed when chloroform ($CHCl_3$) was employed

(entry 8). CPME was carried forward as the solvent of choice as there are significant environmental, health, and safety risks associated with the use of $CHCl_3$.[145] Other hydrophobic solvents, 2-methyltetrahydrofuran (2-MeTHF) and toluene (PhMe) also demonstrated good levels of chemoselectivity, confirming the requirement of a non-polar solvent to achieve a chemoselective reaction (entries 2 and 3). This was further exemplified by the water-miscible solvents isopropanol (IPA), ethanol (EtOH), *N*,*N*-dimethylformamide (DMF) and acetonitrile (MeCN) showing no chemoselectivity as well as quantitative oxidation of both species (entries 6, 7, 9, and 10).



2.006, 1 equiv **2.009**, 1 equiv **2.008** **2.010**

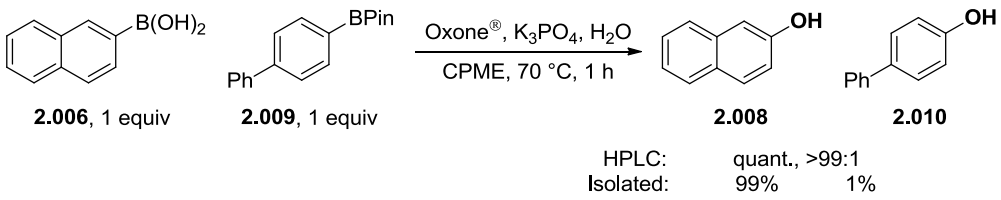
entry	solvent	conversion[a]	**2.008**:**2.010**[a]
1	CPME	quant.	>99:1
2	2-MeTHF	84%	47:1
3	toluene	59%	>99:1
4	1,4-Dioxane	quant.	2:1
5	EtOAc	quant.	63:1
6	IPA	quant.	1:1
7	EtOH	quant.	1:1
8	$CHCl_3$	quant.	>99:1
9	DMF	quant.	1.5:1
10	MeCN	quant.	1:1
11	THF	93%	13:1

[a]Determined by HPLC analysis using an internal standard.

Table 2.11 Oxidation optimisation – solvent study.

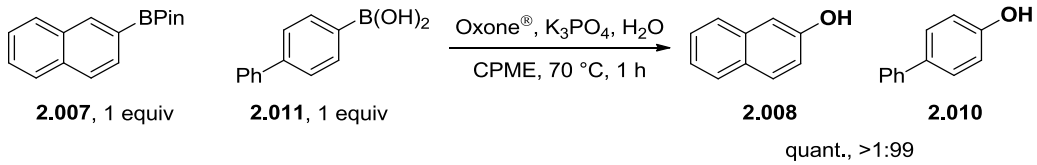
After optimisation of the oxidation reaction, optimal conditions were identified for the oxidation of boronic acid **2.006** *vs.* boronic ester **2.009**, providing excellent conversion and chemoselectivity (Scheme 2.04). To ensure that HPLC yields were reflective of the reaction, the individual components were isolated. Pleasingly, the

same conversion and chemoselectivity were observed with naphthalene-2-ol, **2.008**, isolated in 99% yield and 4-phenylphenol **2.010** in 1% yield.



Scheme 2.04 Optimal chemoselective oxidation reaction conditions.

Furthermore, the boronic acid and boronic ester substituents were switched in order to rule out any electronic bias between the two starting boron species (Scheme 2.05). Gratifyingly, quantitative conversion and excellent chemoselectivity was maintained pointing to no electronic bias contributing to chemoselectivity.

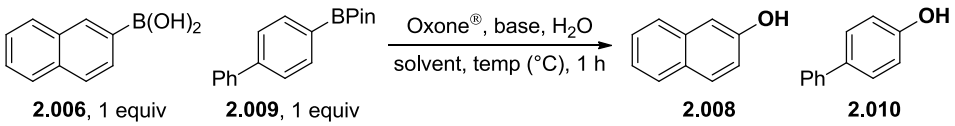


Scheme 2.05 Reversal of boron substituents.

2.1 Determination of the origin of chemoselectivity

With optimum reaction conditions determined, (Scheme 2.06) attention was then turned to investigation into the origins of the observed chemoselectivity. Initially, chemoselectivity was observed in non-competitive monoboron systems (Scheme 2.06). This approximate 5:1 ratio of boronic acid:boronic ester oxidation was reflected when similar reaction conditions were trialled using diboron systems (Table 2, entry 2). This could imply the ability to leverage chemoselectivity based on the kinetic reactivity of both boron species. However, one factor that did change between the two sets of reaction conditions was the reaction temperature (20 °C to 60 °C). On studying the impact of temperature on the reaction (Table 2.10) it was observed that this kinetic discrimination was not apparent in diboron systems at ambient temperature (entry 1).

A number of themes were noticed while performing the optimisation reactions. Firstly, that Oxone® is poorly soluble in organic solvents[146] and, in the absence of water, no reaction was observed (Table 2.12, entries 2 and 3). Oxidation is facile when water is present in the reaction mixture (entry 1 *vs*. entry 2) and, as such, water clearly plays a key role in achieving chemoselectivity. On further analysis of the reaction vessel, a biphase was also observed.



2.006, 1 equiv **2.009**, 1 equiv **2.008** **2.010**

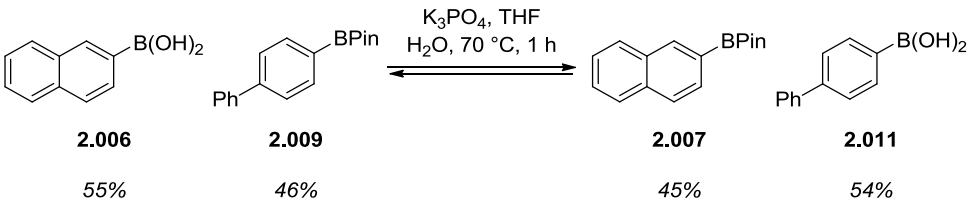
entry	base	temperature (°C)	solvent	**2.008**:**2.010**[a]
1	---	20	THF/H_2O (1:1)	95% (1.1:1)
2	---	20	THF	0%
3	K_3PO_4	20	THF	0%

[a]Determined by HPLC analysis using an internal standard.

Table 2.12 Chemoselective oxidation of boronic acid **2.006** *vs*. BPin ester **2.009**: reaction optimisation.

Secondly, speciation behavior of boronic acid **2.006** and boronic ester **2.009** was observed in similar basic biphasic reaction media, resulting in pinacol transfer to produce a mixture of **2.006**, **2.007**, **2.010**, and **2.011** in approximately a 1:1:1:1 ratio (Scheme 2.06).[13,147] This process cannot be occurring in the reaction medium as otherwise a mixture of phenol products would be expected. This suggested the physical separation of boronic acid and boronic ester moieties may take place; *i.e.*, one species is present in the aqueous phase and the other in the organic phase. It is likely that both species will reside in the organic phase. However, rapid boronic acid boronate formation ensues, which enables the negatively charged species to be

transported to the aqueous phase to be oxidised. Meanwhile, no boronic ester boronate is formed and as such the species is confined to the organic phase.



Scheme 2.06 Speciation equilibria of boronic acid **2.006** and boronic ester **2.009** in a basic biphasic medium.

Furthermore, chemoselectivity counter-intuitively increased with increasing reaction temperature (Table 2.10, entries 4, 5, and 6). Finally, shearing profoundly impacted the chemoselectivity of oxidation with high stirring rates resulting in lower chemoselectivity and *vice versa*. The impact of stirring rate was clearly seen in the change of kinetics of boronic ester, **2.009**, oxidation where increasing the stirring rate changed the reaction profile from linear (at 350 rpm) to exhibiting a burst phase (at 900 rpm) (Chart 2.02).[148] This initial burst phase is then followed by a linear profile.[149]

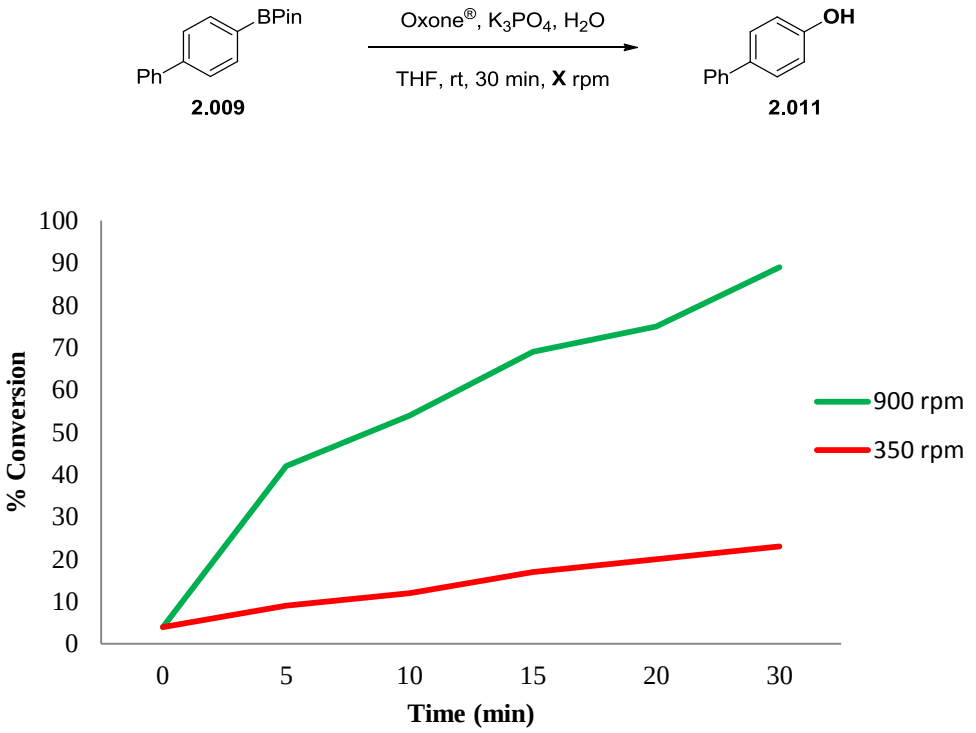
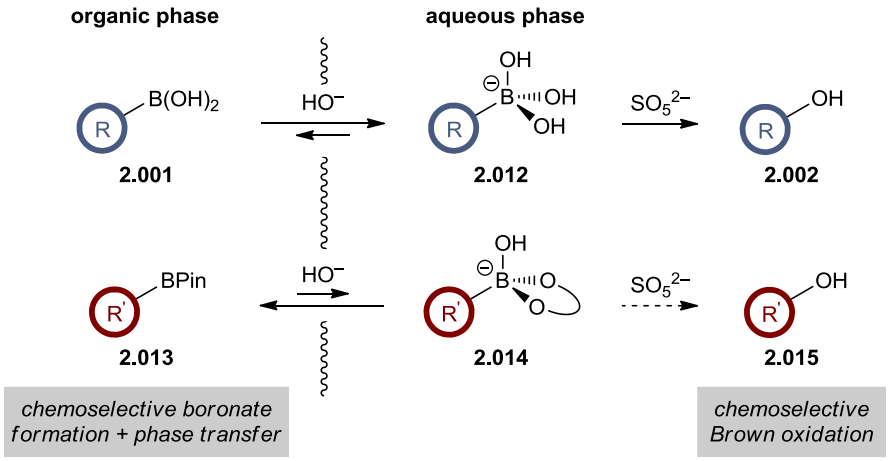


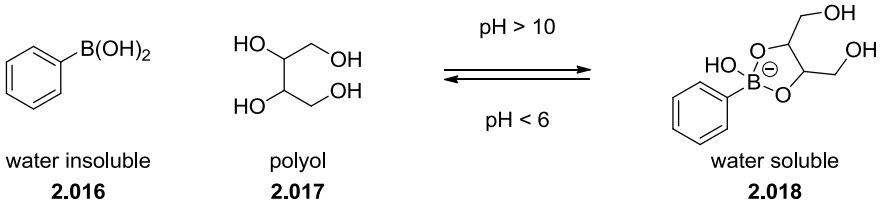
Chart 2.02 Oxidation of boronic ester **2.009** to phenol **2.011** using Oxone® under biphasic reaction conditions (THF/H_2O) over 30 min at varying stirring rates.

Based on all of the above, it was suspected that oxidation was taking place *via* a phase transfer process where boronic acid **2.001** was selectively transported to and oxidised in the aqueous phase with the equivalent process for boronic ester **2.015** much slower in comparison (Scheme 2.07). It was therefore theorised that both boron species would only be transported to the aqueous phase in their boronate form under the basic reaction conditions. Consequently, boronic acid boronate, **2.012**, is selectively formed in the presence of tripotassium phosphate in the organic phase or on the phase boundary. The equivalent boronic ester boronate, **2.014**, does not form in the organic phase. Consequently, this species cannot be transported into the aqueous phase. The active oxidant, potassium peroxymonosulfate, is only present in the aqueous phase due to its poor solubility in organic solvents.[146] Therefore, the only boron species that can be oxidised is boronic acid **2.001**.



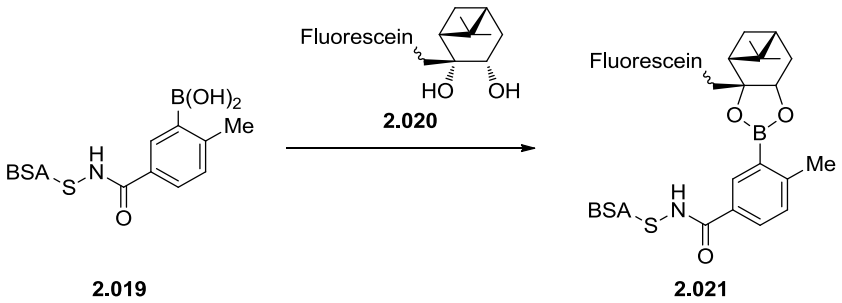
Scheme 2.07 Proposed chemoselective oxidation mechanism.

Hall and co-workers have shown that polyols can be used to stoichiometrically transfer boronic acids to an aqueous phase as their boronate derivatives (Scheme 2.08).[150,151] This pH-driven phase transfer technique has been utilised to purify boronic acids *via* phase separation.[150,151]



Scheme 2.08 Formation of water soluble boronate derivatives using polyols.[150]

The rapidly-formed covalent linkages present in water soluble polyol boronates also allow for the fast introduction of fluorescent tags to boronic acid derivatives. This can be especially useful of in the synthesis of bioconjugation systems that can have significant applications in chemical biology (Scheme 2.09).[152]

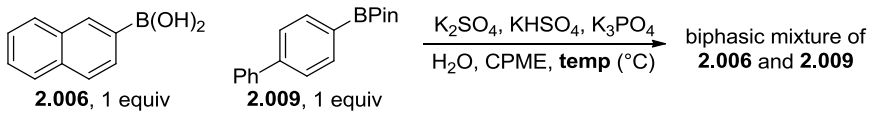


Scheme 2.09 Boron ligation of bovine serum albumin (BSA).

In our case, no such phase-transfer catalyst was employed in the oxidation of diboron systems. However, boronates are considerably more soluble in aqueous media than in organic media.[13] This suggests that chemoselective boronate formation (boronic acid over boronic ester) is taking place while avoiding speciation processes in the basic biphasic medium. It is known that boronic esters are less Lewis-acidic than boronic acids.[25] Therefore, selective boronate formation must be under kinetic control. Boronate formation itself is typically very rapid, practically barrier-less.[153] To confirm the selective boronate formation hypothesis, detailed analysis of the basic biphasic reaction mixture was undertaken.

2.2 HPLC analysis

Initially, HPLC analysis of the individual aqueous and organic phases was conducted (Table 2.13). This was performed through stirring the workhorse reaction components, naphthalene-2-boronic acid, **2.006**, and biphenylBPin, **2.009**, in reaction-like conditions with various additives that are present in the reaction mixture, without the addition of the active oxidising species, potassium peroxymonosulfate. The individual phases were then sampled and analysed using an internal standard to assess the phase distribution of the boron-containing components.



entry	inorganics	temperature (°C)	organic:aqueous (%)[a]	
			2.006[b]	**2.009**[b]
1	---	20, 50, 70	>99:1	>99:1
2	K_3PO_4	20	54:46	>99:1
3	K_3PO_4	50	46:54	96:4
4	K_3PO_4	70	29:71	98:2
5	K_2SO_4, $KHSO_4$	20	>99:1	>99:1
6	K_2SO_4, $KHSO_4$	50	>99:1	>99:1
7	K_2SO_4, $KHSO_4$	70	98:2	>99:1
8	K_2SO_4, $KHSO_4$, K_3PO_4	20	67:33	>99:1
9	K_2SO_4, $KHSO_4$, K_3PO_4	50	59:41	>99:1
10	K_2SO_4, $KHSO_4$, K_3PO_4	70	54:46	>99:1

[a]Determined by HPLC analysis using an internal standard. [b]Ratios describe product distribution - organic:aqueous (%).

Table 2.13 Phase distribution of boronic acid **2.006** and boronic ester **2.009** in the presence of relevant inorganics and with temperature variation.

At first, no inorganic compounds were added to the reaction mixture (entry 1). At a variety of temperatures, including the optimal reaction temperature, 70 °C, both boron compounds were confined to the organic phase. This aligns with the earlier

hypothesis that boronate formation facilitates phase transfer. When no base is present in the reaction mixture, boronate formation is not possible. The addition of tripotassium phosphate into the reaction medium vastly altered the distribution of the organic components (entry 2). Boronic acid **2.006** was split between the two phases in an approximate 1:1 ratio at ambient temperature while boronic ester **2.009** was confined to the organic phase. As the temperature was increased, first to 50 °C and then to 70 °C, the amount of **2.006** in the aqueous phase increased to over 70% (entries 3 and 4). The phase distribution of **2.009** does not alter significantly over the same temperature range. This finding starts to explain the temperature dependence of the oxidation reaction observed previously, whereby chemoselectivity increased with increasing reaction temperature (Table 2.10).

Oxone® is a mixture of salts containing potassium peroxymonosulfate, potassium sulfate, and potassium bisulfate. As such, the inorganic components of Oxone® that are not the active oxidant could have an effect on the phase distribution of the boron components in the reaction mixture as they themselves are bases. This was investigated through the addition of potassium sulfate and potassium bisulfate to the reaction mixture, initially at room temperature (entry 5). No effect on the phase distribution was observed. Increasing the reaction temperature has no influence on the phase distribution when the same two bases are present (entries 6 and 7). Therefore, chemoselectivity in the reaction can be attributed to the presence of tripotassium phosphate in the reaction mixture. This, in turn, is aligned with the pK_b of the respective bases (Table 2.14).

entry	base	pK_aH
1	K_3PO_4	12.32, 7.21, 2.21
2	$KHSO_4$	1.99
3	K_2SO_4	-3.00, 1.99

Table 2.14 pK_{aH} and pK_b of bases present in the oxidation reaction mixture.

Tripotassium phosphate is the strongest base out of the three bases present (entry 1). For that reason, it is more likely to affect the overall pH of the system and, consequently, have an impact on the phase distribution of these species due to the extent of boronate formation. Potassium bisulfate and potassium sulfate are not sufficiently strong bases to facilitate the creation of boronate species and, consequently, no phase transfer occurs.

When all three inorganic components: tripotassium phosphate, potassium bisulfate, and potassium sulfate, are added to the reaction mixture, boronic acid **2.006** was found to distribute in both phases at ambient temperature (entry 8). However, the extent to which the boronic acid is in the aqueous phase is considerably lower than when only tripotassium phosphate is added to the reaction mixture (entry 2 *vs.* entry 8). The lower concentration of **2.006** in the aqueous phase in the presence of all inorganics may be attributable to a buffering effect caused by the presence of potassium sulfate and potassium bisulfate. Increasing the temperature to 50 °C enhanced the concentration of boronic acid **2.006** in the aqueous phase as observed with solely tripotassium phosphate (entry 9). At the reaction temperature, 70 °C, **2.006** distributed in both phases in an approximately 1:1 ratio (entry 10). Throughout the temperature range boronic ester **2.009** was confined to the organic phase (entries 8–10). Finally, speciation behavior, as explained earlier (Scheme 2.06) was not observed by HPLC in any case.

The HPLC analysis conducted provides a good explanation of the phase distribution of boron species in the reaction mixture. The outcome of the experiments confirms the selective phase transfer theory postulated (Scheme 2.07) and explains the chemoselectivity observed in the reaction.

2.3 NMR analysis

The HPLC analysis previously conducted (Table 2.13) allows for the quantities of both boron species present in each phase of the biphasic reaction mixture to be determined. However, HPLC analysis cannot identify whether the boron species present exist as neutral boronic acids or esters, or as charged boronate species in either aqueous or organic phases. The form in which the boron species are present is

crucially important in order to gain further mechanistic insight into the reaction. This information will determine if the base and other inorganic materials present play an important role in achieving a chemoselective reaction. To this end, NMR analysis was conducted as it enabled differentiation between the boron species present (Figure 2.01).

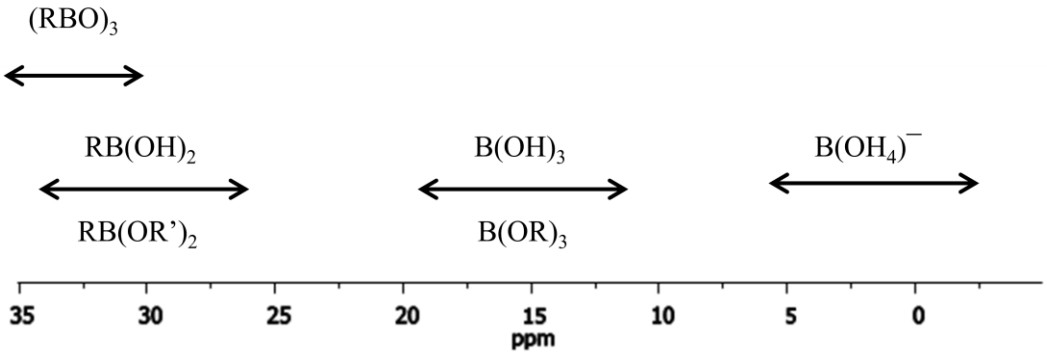


Figure 2.01 ^{11}B NMR shifts of different boron species.

It is essential to only observe one phase of the basic biphasic reaction mixture, in order to determine what boron species are present in that phase. To assess only the aqueous phase during the NMR experiment it was important to employ a reaction scale in which only the D_2O layer is detected by the receiver/transmitter coil (Figure 2.02). Individual analysis of the D_2O layer could be successfully achieved by ensuring that the D_2O phase of the biphasic system was greater than 0.5 mL. The organic phase of the reaction can also be solely observed through the use of $CDCl_3$ in the NMR experiment. Excellent conversion and chemoselectivity are also observed when $CDCl_3$ is used as the reaction solvent (Table 2.11, entry 8).

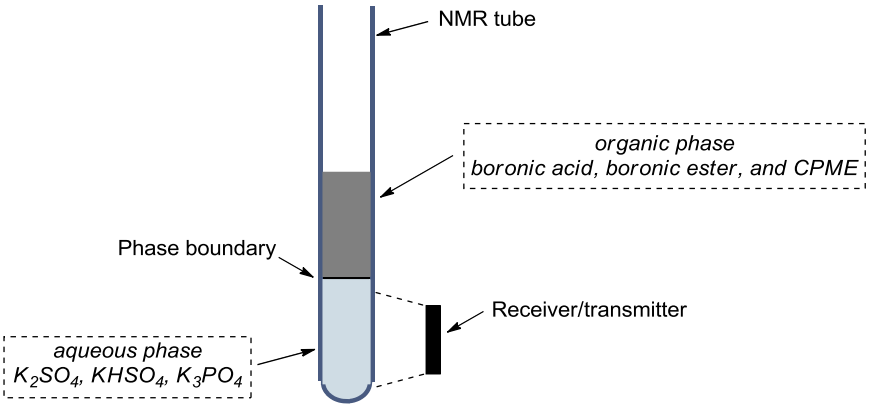
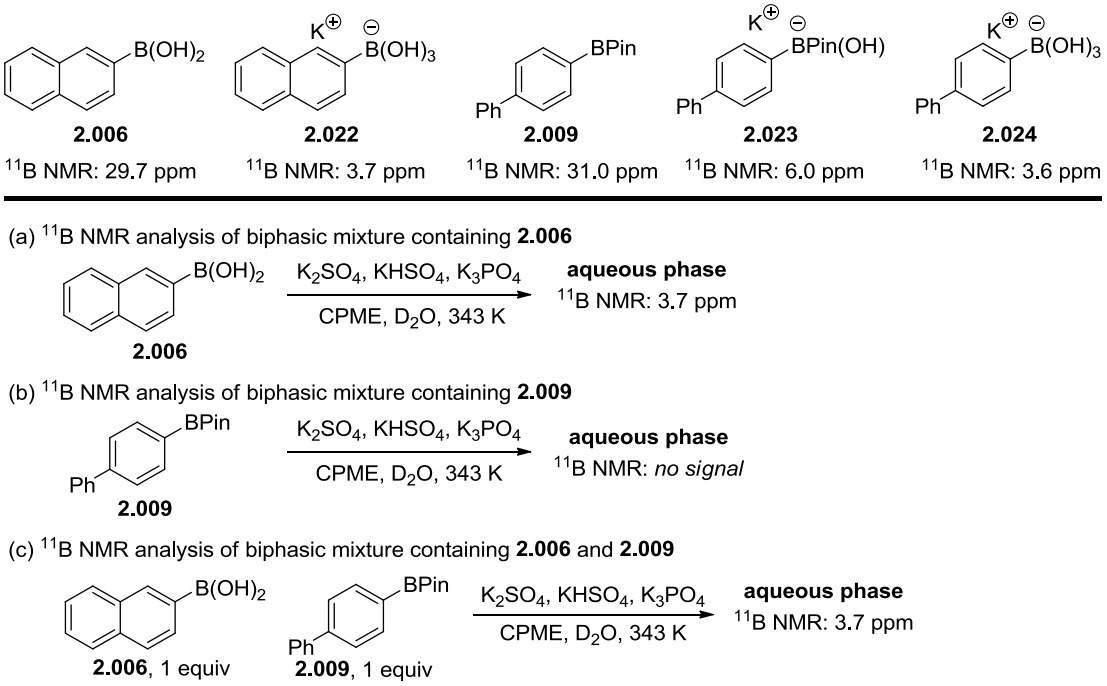


Figure 2.02 ^{11}B NMR experimental set up.

Initially, monoboron systems containing boronic acid **2.006** and boronic ester **2.009** were analysed using the NMR technique described above (Scheme 2.10). Similar biphasic reaction conditions were employed to the optimal reaction medium determined previously without any active oxidant present in the reaction mixture. ^{11}B NMR analysis of the aqueous phase of the biphasic monoboron system containing **2.006** and relevant inorganics, potassium bisulfate, potassium sulfate, and tripotassium phosphate, showed the presence of a single boron species with a resonance at 3.7 ppm, consistent with boronate **2.022** (Scheme 2.10a). No signal was detected in the aqueous phase for the equivalent experiment using only **2.009** (Scheme 2.10b) meaning that the boronic ester is not transferred to the aqueous phase. Analysis of the corresponding model diboron system containing both **2.006** and **2.009** revealed a single signal in the aqueous phase at 3.7 ppm, consistent with boronic acid boronate **2.022** (Scheme 2.10c). This analysis agreed with the HPLC data (Table 2.13), but also supported selective phase transport of boronic acid **2.006** to the aqueous phase as its boronate derivative, **2.022**.

Interestingly, pinacol ester boronate **2.023** was only observed upon treatment with aqueous potassium hydroxide (Scheme 2.10). The reaction conditions also led to pinacol ester hydrolysis.[144] Boronate **2.024** formed rapidly under the aqueous basic conditions. This finding led to the confirmation of the hypothesis that boronic acid boronates can be selectively formed under the chemoselective reaction conditions as pinacol ester hydrolysis and subsequent boronate formation is not observed. This allows for selective phase transport and subsequent chemoselective oxidation.

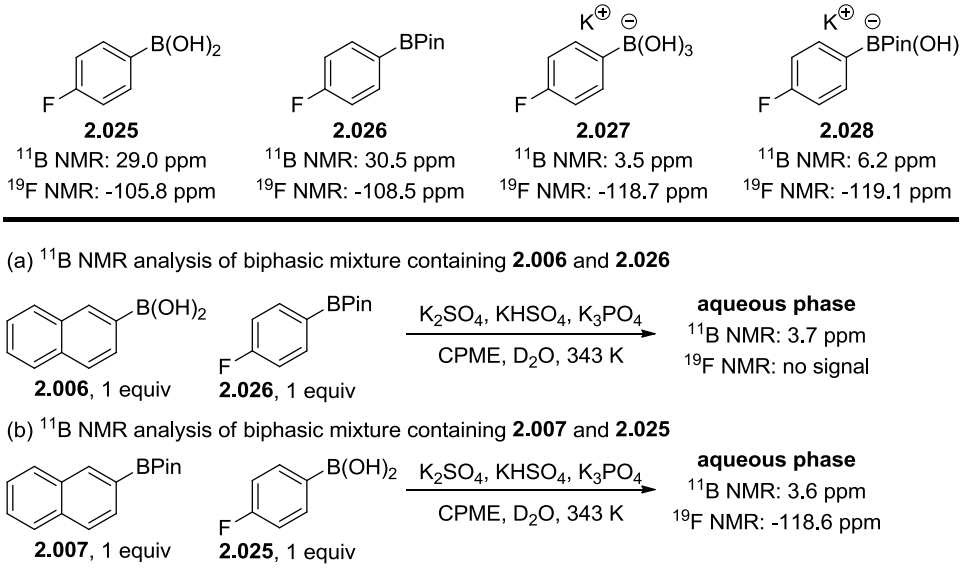


Scheme 2.10 ^{11}B NMR analysis of mono- and diboron systems of **2.006** and **2.009** under biphasic reaction conditions.

Boronates **2.022** and **2.023** are distinguishable by ^{11}B NMR and the assignment of the observed ^{11}B NMR signal at 3.7 ppm was attributed to **2.022**. However, it is conceivable that *in situ* hydrolysis of **2.009** could occur to deliver biphenylboronic acid **2.011** and ultimately its boronate derivative, **2.024**, which has a similar ^{11}B NMR resonance to boronic acid boronate **2.022**. The boronic ester boronate signal may be obscured by **2.022**, preventing detection at low concentration. To ensure that no speciation was occurring, two mono-fluorinated diboron systems were analysed by ^{11}B and ^{19}F NMR (Scheme 2.11).

^{11}B and ^{19}F NMR analysis of the aqueous phase of the diboron system containing boronic acid **2.006** and fluorinated boronic ester **2.026** revealed a single ^{11}B NMR signal at 3.7 ppm, consistent with boronic acid boronate **2.022**; no ^{19}F NMR signals were detected (Scheme 2.11a). Conversely, analysis of the mixture of boronic ester **2.007** and fluorinated boronic acid **2.025** showed one ^{11}B NMR signal at 3.6 ppm and one ^{19}F NMR signal at -118.6 ppm, both of which were consistent with boronate

2.027 (Scheme 2.11b). Thus, these experiments support the hypothesis of selective boronic acid boronate formation with inhibited speciation.



Scheme 2.11 ^{11}B and ^{19}F NMR analysis of mono-fluorinated diboron systems under representative biphasic conditions.

Variable temperature NMR helped to explain the observed chemoselectivity of the reaction. Firstly, individual analysis of monoboron systems (Figure 2.03) revealed considerable amounts of boronic acid boronate in the aqueous phase. The concentration increased with increasing temperature, as seen by the improving chemoselectivity in the temperature optimisation of the reaction (Table 2.10). No boronic ester could be detected in same phase at ambient or elevated temperature. As previously discussed, monoboron systems are not representative of the optimal reaction conditions. Consequently, a diboron system containing **2.006** and **2.009** was analysed.

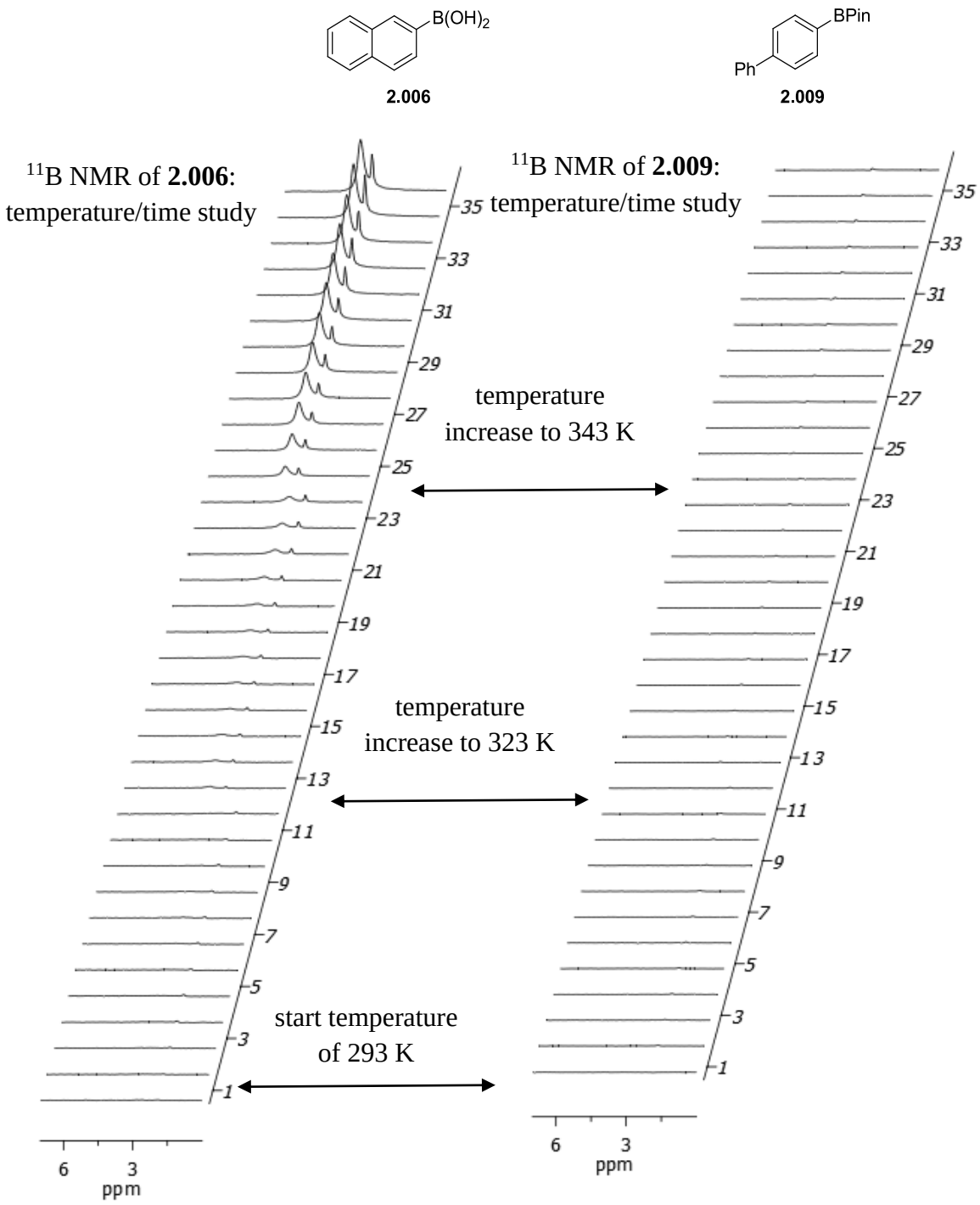


Figure 2.03 NMR aqueous phase analysis of naphthalen-2-ylboronic acid, **2.006**, and [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**.

The monoboron systems were then combined (Figure 2.04). Consistent with the HPLC analysis (Table 2.13), variable temperature ^{11}B NMR revealed that the concentration of boronic acid boronate, **2.022**, increased with temperature, with no

detectable increase in the concentration of boronic acid **2.006**, boronic ester **2.009**, or boronic ester boronate, **2.023** (Figure 2.04).[154] In this case there is a significant downfield shift in both boronic acid boronate, **2.022**, and boric acid peaks.[155] This is because chemical shifts are temperature-dependent.[155] The non-intuitive increase in chemoselectivity can be explained by increasing concentrations of boronic acid boronate, **2.022**, in the aqueous phase at higher temperature as observed by both HPLC and NMR. This increase, combined with the absence of any boronic ester boronate, **2.023**, in the aqueous phase at elevated reaction temperatures, aligns with the enhanced chemoselectivity observed.

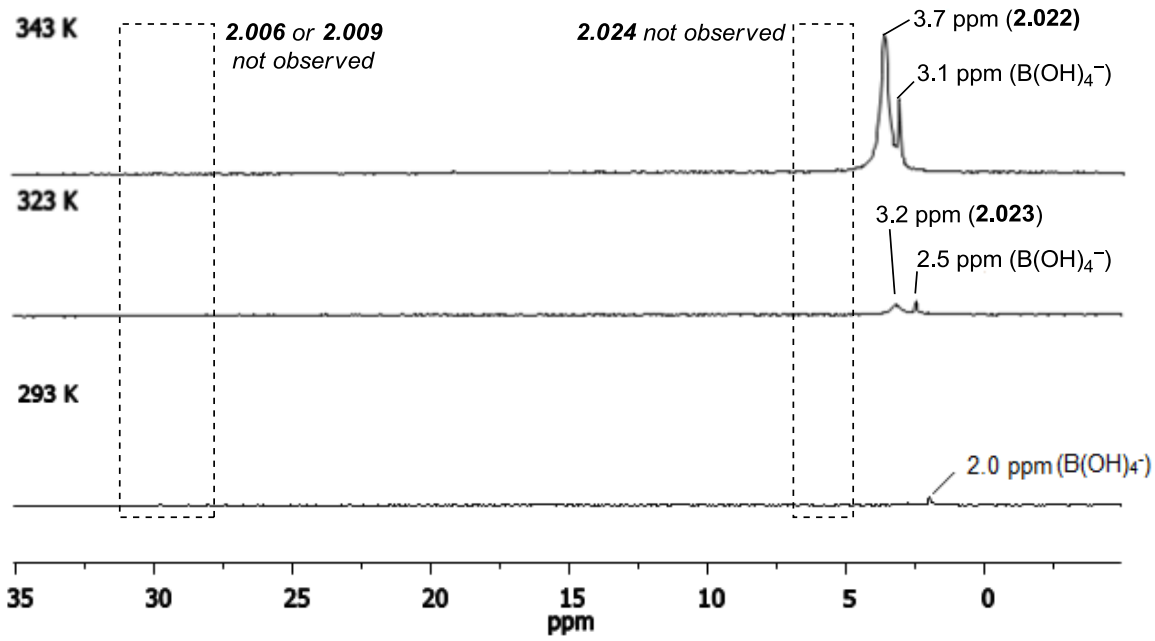


Figure 2.04 Temperature-proportional concentrations of **2.022** in the aqueous phase by ^{11}B NMR analysis.

Diffusion of **2.006** into the aqueous phase (as its boronate **2.022**) also increased over time (Figure 2.05). The low concentration of boronic acid boronate in the aqueous phase after 30 minutes correlates well with the enhanced conversion observed as reaction time was increased from 30 minutes to one hour during reaction optimisation (Table 2.05).

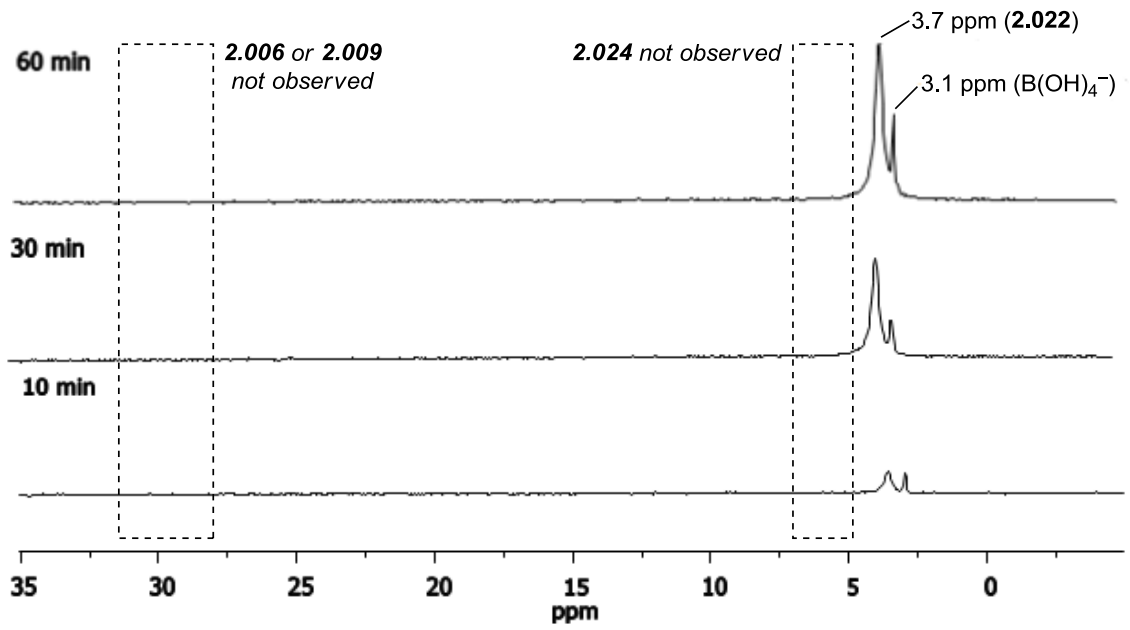


Figure 2.05 Time-proportional concentrations of **2.022** in the aqueous phase by ^{11}B NMR analysis.

When no active oxidant was present in the reaction mixture, protodeboronation was observed to occur. This was determined from the presence of boric acid boronate ($B(OH)_4^-$) in the NMR spectra (peak at 3.1 ppm) (Figures 2.04 and 2.05). The concentration of boric acid boronate increases with both time and temperature. Protodeboronation is not a problem in oxidation reactions of boron species due to the rapid rate of reaction. However, significant levels of protodeboronation could have implications for reactions of boron species conducted in basic biphasic media, namely the Suzuki-Miyaura cross-coupling reaction.[156]

Fluorinated systems were also subjected to temporal profiling to confirm the transport of boronic acid boronate into the aqueous phase (Figures 2.06 and 2.07). The fluorinated boronic ester substrate **2.026** is clearly confined to the organic phase whereas a clear fluorine peak is observed when the boronic acid is fluorinated, confirming the hypothesis. Furthermore, the intensity of the ^{11}B NMR peak increases with temperature, aligning with the same phenomenon of increasing amounts of boronic acid boronate present in the aqueous layer, as observed previously for non-fluorine tagged systems.

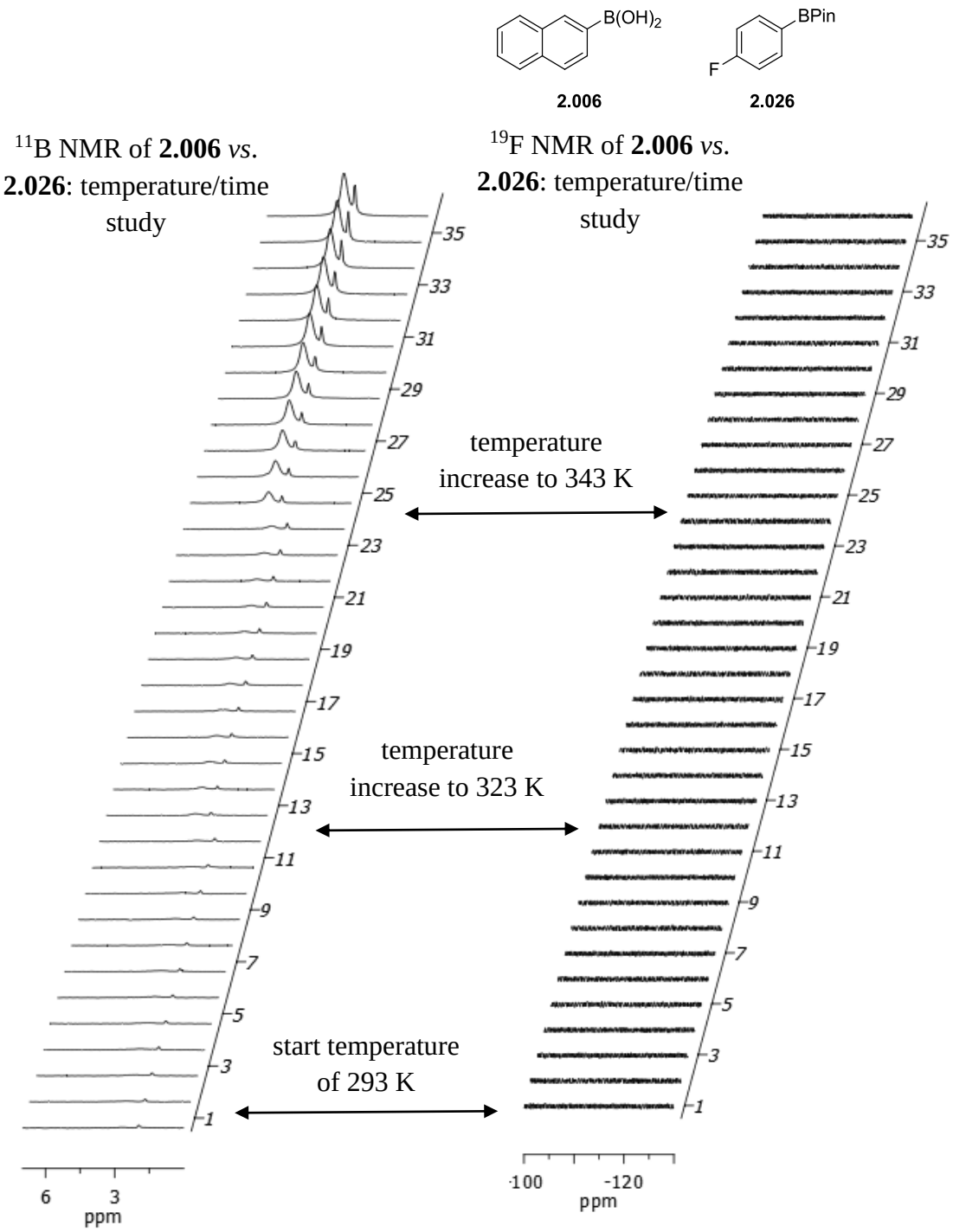


Figure 2.06 NMR aqueous phase analysis of naphthalen-2-ylboronic acid (**2.006**) *vs.* (4-fluorophenyl)boronic acid, pinacol ester (**2.026**).

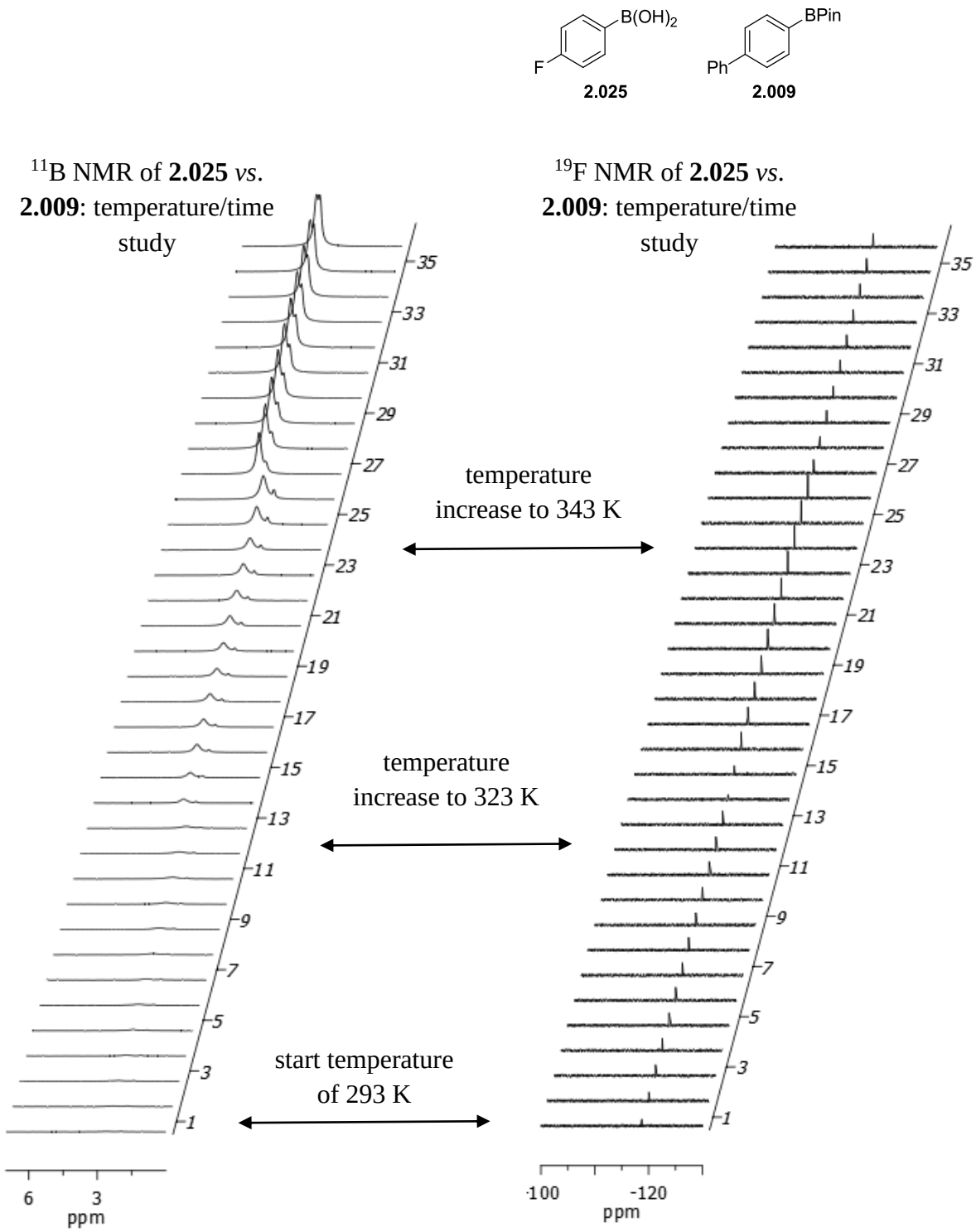
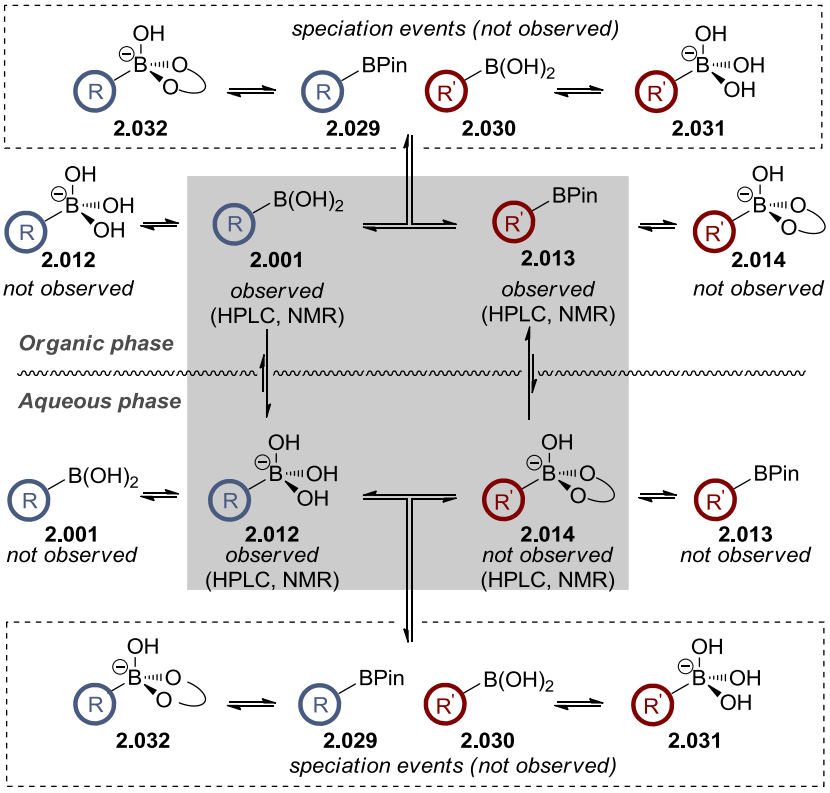


Figure 2.07 NMR aqueous phase analysis of (4-fluorophenyl)boronic acid (**2.025**) *vs*. [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**2.009**).

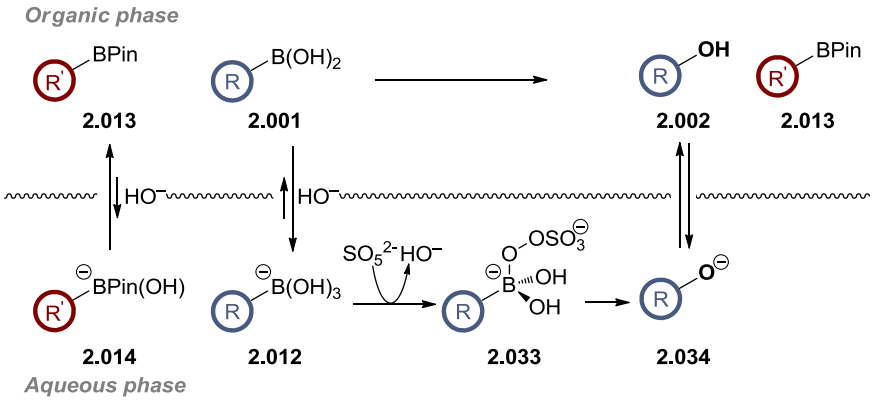
The results of the combined HPLC and NMR summaries reveal the presence of a variety of boron species in the biphasic reaction mixture (Scheme 2.12). Both boron species **2.001** and **2.013** are observable in the organic phase by HPLC (Table 2.13). There is no boronate formation detectable in the organic phase, and speciation events are well controlled throughout the process. Only the boronic acid, in the form of its boronate, **2.012**, is detected in the aqueous phase with the boronic ester boronate **2.014** not being detected. The only boron species observable in the aqueous phase are in the form of negatively charged boronate compounds by NMR. In a similar fashion to the organic phase, no speciation events occur in the aqueous phase.



Scheme 2.12 Observable organoboron species by HPLC and NMR.

The rate of oxidation was found to be rapid in the burst phase of the reaction (see Chart 2.01). As such, the rate-determining process for oxidation under the reaction conditions appears to be phase transfer of the organoboron species to the aqueous phase. Accordingly, chemoselective oxidation in the diboron system is achieved since boronic acid phase transfer is significantly more favorable than boronic ester transfer.

The above information allows a mechanistic operation of the chemoselective oxidation to be proposed (Scheme 2.13). Since oxidation takes place in the aqueous phase, chemoselectivity arises from selective phase transfer of the boronic acid to the aqueous phase. Oxidation of the boronic acid boronate **2.012** then ensues, forming phenolate **2.034** which is then protonated.



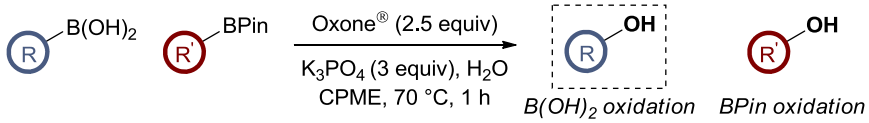
Scheme 2.13 Proposed mechanism facilitating chemoselective reaction.

2.4 Generality of the chemoselective oxidation process

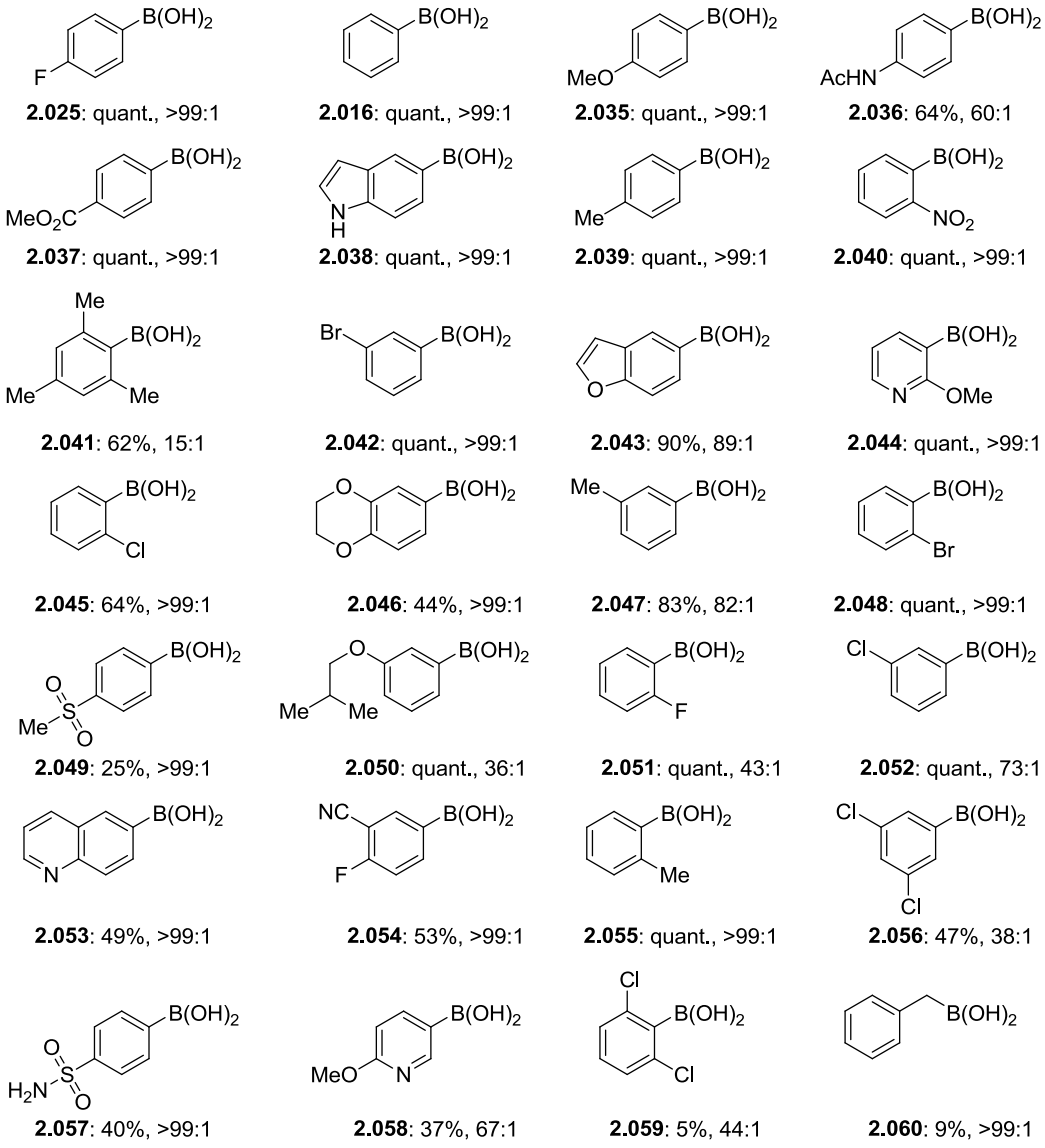
With the reaction mechanism determined, a number of aryl groups were trialled to observe how they would affect the phase distribution of the reaction mixture and, in turn, the overall chemoselectivity of the process. Initially, the boronic ester, 4-biphenyl BPin, was kept constant and the boronic acid was altered (Scheme 2.14). The biphasic reaction conditions were found to be general across a wide variety of arylboronic acid and pinacol ester reaction partners. Conversion to products over a one hour reaction time was generally high. The chemoselectivity for boronic acid oxidation was typically >20:1, and was exclusively selective (>99:1) in many cases, regardless of functionality or regiochemistry. A number of heterocyclic boronic acids, **2.038**, **2.043**, **2.044**, **2.053**, and **2.058**, were also oxidised chemoselectively but some specific heterocycles showed diminished conversion relative to the naphthalene-2-boronic acid, **2.006**. Oxidisable functional groups including nitrile, **2.054**, amide, **2.036**, and sulfonamide, **2.057**, were also tolerated in the reaction. The regiochemistry of substitution around the aromatic ring appears to be inconsequential

to the chemoselectivity of the reaction *cf.*, *ortho*-, *meta*-, and *para*-tolylboronic acids, **2.055**, **2.047**, and **2.039** respectively.

Significant decreases in the overall conversion were observed when the phenylboronic acid was 2,6-disubstiuted with halogens, **2.059**, and when a benzyl boronic acid was employed, **2.060**. Direct comparison of **2.059** with mesitylboronic acid, **2.041**, highlights the presence of halogen substituents *ortho*- to the boronic acid have an important role in lowering the substrates electrophilicity, possibly due to an intermolecular Lewis acid-Lewis base interaction. Reactivity is regained, albeit only moderately, when 3,5-dichlorophenylboronic acid, **2.056**, was subjected to the oxidation conditions providing further evidence for this theory.



4-biphenyl BPin (**2.009**) *vs.*:



2.025: quant., >99:1 | **2.016**: quant., >99:1 | **2.035**: quant., >99:1 | **2.036**: 64%, 60:1

2.037: quant., >99:1 | **2.038**: quant., >99:1 | **2.039**: quant., >99:1 | **2.040**: quant., >99:1

2.041: 62%, 15:1 | **2.042**: quant., >99:1 | **2.043**: 90%, 89:1 | **2.044**: quant., >99:1

2.045: 64%, >99:1 | **2.046**: 44%, >99:1 | **2.047**: 83%, 82:1 | **2.048**: quant., >99:1

2.049: 25%, >99:1 | **2.050**: quant., 36:1 | **2.051**: quant., 43:1 | **2.052**: quant., 73:1

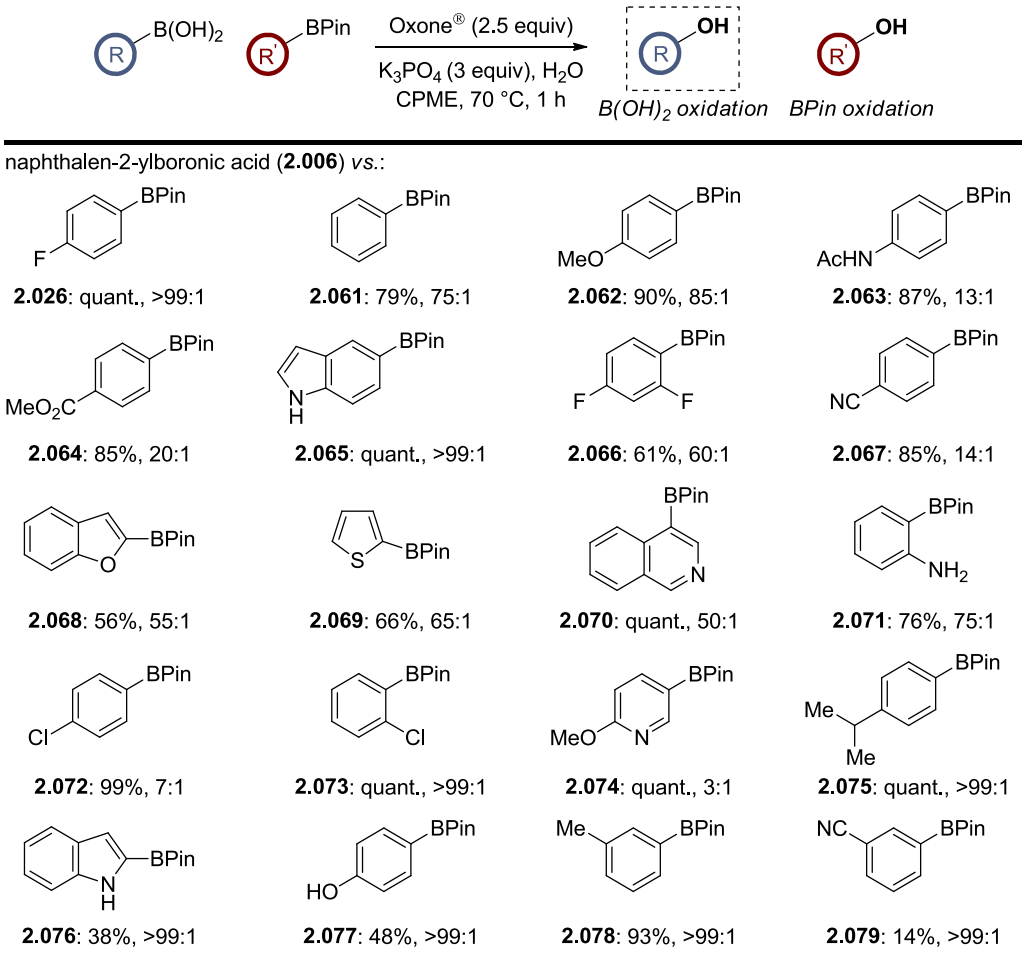
2.053: 49%, >99:1 | **2.054**: 53%, >99:1 | **2.055**: quant., >99:1 | **2.056**: 47%, 38:1

2.057: 40%, >99:1 | **2.058**: 37%, 67:1 | **2.059**: 5%, 44:1 | **2.060**: 9%, >99:1

Scheme 2.14 Chemoselective oxidation of aryl diboron system: $B(OH)_2$ *vs.* BPin substrate scope. Ratio given for oxidation of boronic acid:pinacol ester. Determined by HPLC.

The boronic acid moiety, naphthalen-2-ylboronic acid, was next kept constant while altering the pinacol ester (Scheme 2.15). Good to excellent conversions and chemoselectivities were observed when a number of *para*-substituted arylboronic esters were employed. Electron-poor, **2.026**, **2.064**, **2.067**, and **2.072,** and electron-rich, **2.062**, **2.063**, and **2.077**, aryl groups were well tolerated as well as difluorinated

derivative **2.066**. A number of heterocyclic derivatives, **2.065**, **2.068**, **2.069**, **2.070**, **2.074**, and **2.076**, were also successfully employed in the reaction, albeit with slightly diminished chemoselectivity.

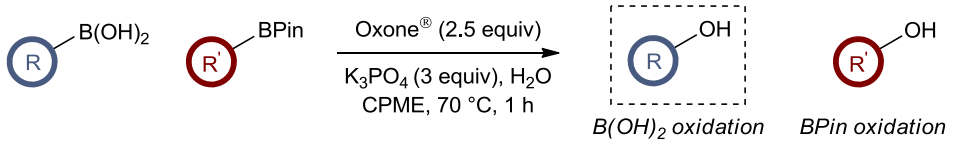


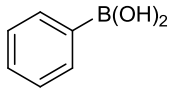
Scheme 2.15 Chemoselective oxidation of aryl diboron system: $B(OH)_2$ *vs.* BPin substrate scope. Ratio given for oxidation of boronic acid:pinacol ester. Determined by HPLC.

A variety of arylboronic acid and ester substituents were then explored (Scheme 2.16). Phenylboronic acid, **2.016**, was oxidised with outstanding chemoselectivity when in competition with a variety of electron-rich and electron-poor arylboronic esters. The conversion was excellent in all cases. (4-(Methoxycarbonyl)phenyl)boronic acid, **2.037**, was also chemoselectively oxidised in the presence of a number of *ortho*- and *para*-substituted boronic esters. In general, the conversion to the desired phenol was excellent except for when (4-

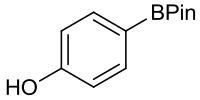
hydroxyphenyl)boronic acid, pinacol ester, **2.077**, and (2-fluorophenyl)boronic acid, pinacol ester, **2.080**, were used. Boronic ester **2.077**, also limits conversion in other cases, *e.g.*, when in the same pot as (2-fluorophenyl)boronic acid, **2.082**. The presence of a free phenol in the aqueous basic conditions could facilitate boronate formation and prevent phase transfer of the boronic acid substrate, limiting conversion. Also, the acidic phenol functional group could be altering the pH of the system. This subtle effect could affect boronate formation which in turn would lower the chemoselectivity of the reaction.

Electron-deficient boronic acid, **2.040**, is also preferentially oxidised in the presence of a plethora of pinacol esters. Conversion is excellent in all cases but chemoselectivity is diminished in certain examples. Electron-deficient boron species would be expected to undergo rapid boronate formation, and consequently phase transfer, due to the highly Lewis-acidic boron centre. This may facilitate a rapid chemoselective oxidation. Leaving the reaction for one hour may be too long for these substrates and speciation of could start to occur, accounting for the inferior chemoselectivity observed. There are no such issues for electron-rich boronic acids **2.035** and **2.083** which react with excellent conversion and chemoselectivity. However, when *ortho*-substituted boronic acid, **2.045**, is used, conversion is greatly diminished. This may be due to the intramolecular Lewis-acid, Lewis-base interaction discussed earlier. On the whole, excellent chemoselectivity was maintained throughout with good to excellent yields, regardless of functionality on the boronic acid and boronic ester moieties.



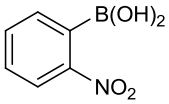


2.016

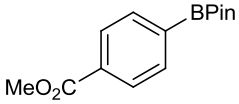


2.077

98%, >99:1

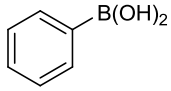


2.040

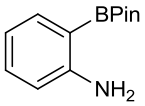


2.064

quant., 21:1

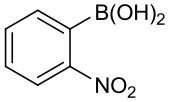


2.016

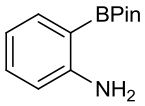


2.071

99%, >99:1

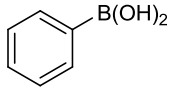


2.040

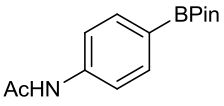


2.071

quant., >99:1

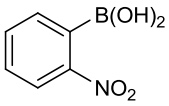


2.016

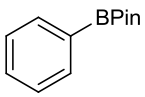


2.063

quant., 47:1

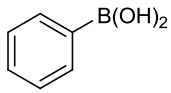


2.040

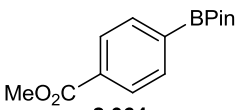


2.061

quant., >99:1

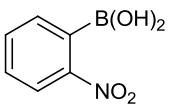


2.016



2.064

quant., >99:1



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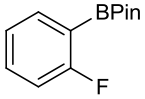
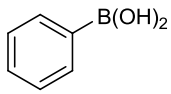
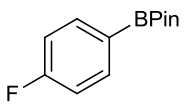


2.080

quant., 8:1

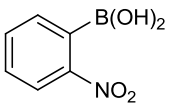


2.016

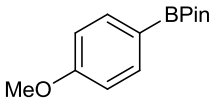


2.026

93%, >99:1

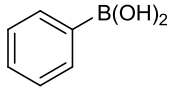


2.040

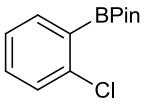


2.062

85%, >99:1

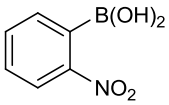


2.016

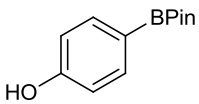


2.073

92%, >99:1

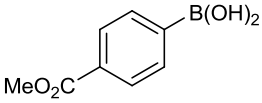


2.040

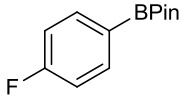


2.077

quant, >99:1

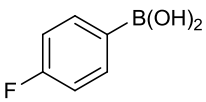


2.037

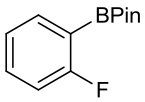


2.026

quant., >99:1

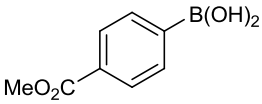


2.025

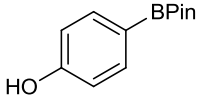


2.080

quant., 11:1

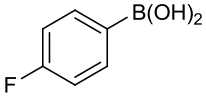


2.037

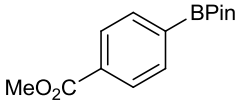


2.077

44%, >99:1

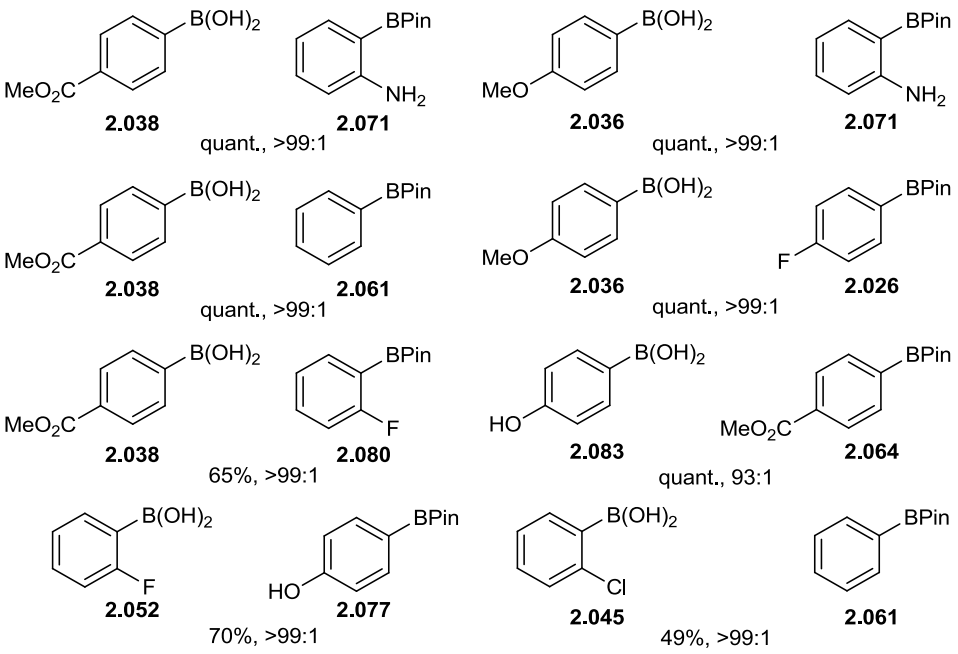


2.025



2.064

97%, >99:1

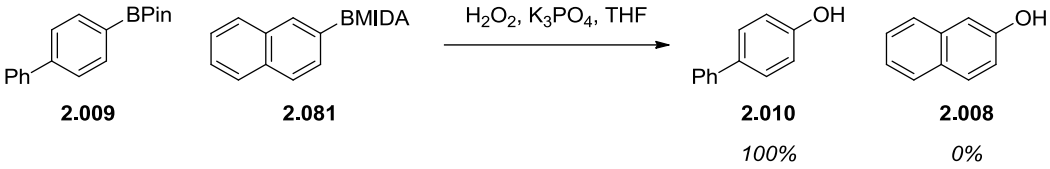


Scheme 2.16 Chemoselective oxidation of aryl diboron system: $B(OH)_2$ *vs.* BPin substrate scope. Ratio given for oxidation of boronic acid:pinacol ester. Determined by HPLC.

In summary, the optimal conditions developed for chemoselective oxidation are generally applicable to a wide variety of boronic acid and boronic ester substrates, regardless of the functionality they contain. The substitution pattern of the aromatic ring system can have an effect on the overall conversion to the desired phenolic product, but chemoselectivity remains high in all cases.

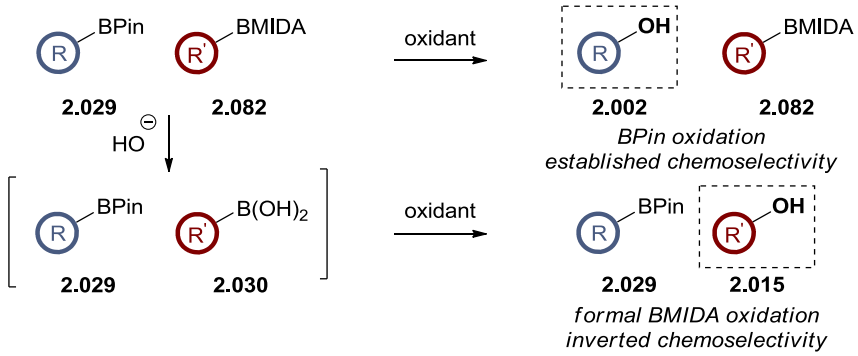
2.5 Inverting established chemoselectivity

Chemoselective oxidations of diboron systems have thus far followed traditional reactivity profiles; *i.e.*, boronic acids are preferentially oxidised in the presence of boronic esters. In line with this, when other boronic acid protecting groups are employed, such as *N*-methyliminodiacetic acid (MIDA) esters, which form stable tetrahedral boron species, boronic esters are oxidised preferentially (Scheme 2.17).



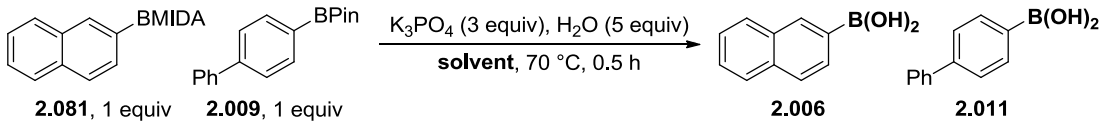
Scheme 2.17 Traditional oxidation selectivity.

However, BMIDA esters are labile in aqueous basic conditions; similar conditions to those in which the chemoselective oxidation is conducted.[118] Therefore, it was postulated that the traditional chemoselectivity profile observed above could be inverted by performing the speciation controlled hydrolysis of a MIDA ester, **2.082**, to generate boronic acid **2.030** *in situ* (Scheme 2.18). Subsequent addition of an oxidant to the reaction mixture would facilitate the chemoselective oxidation of boronic acid **2.030**, leaving boronic ester, **2.029**, untouched.



Scheme 2.18 Inverting established chemoselectivity: oxidation of a BMIDA ester in the presence of a BPin ester.

With chemoselective oxidation conditions already established, optimisation focussed on the hydrolysis component of the process. Ideally, both hydrolysis and oxidation stages of the reaction would proceed in the same solvent. To this end, initial investigations focussed on the reaction solvent, namely, hydrophobic solvents in which chemoselective oxidation was facilitated (Table 2.15). In order to achieve consistent conditions with the oxidation process the same base, tripotassium phosphate, and reaction temperature, 70 °C, were initially used.



entry	solvent	conversion[a]	**2.006**:**2.011**[a]
1	2-MeTHF	quant.	2:1
2	EtOAc	quant.	2:1
3	toluene	83%	4:1
4	CPME	quant.	5:1

[a]Determined by HPLC analysis using an internal standard.

Table 2.15 MIDA hydrolysis optimisation – solvent study.

Pleasingly, after stirring for 30 minutes, hydrolysis was facile in all solvents trialled, retuning quantitative yields in three cases; 2-MeTHF, CPME, and EtOAc (Table 2.15, entries 1, 2, and 4). However, speciation events were prevalent in all cases with CPME providing the highest level of chemoselectivity (entry 4). Combining this with the excellent conversion obtained, and with the knowledge that oxidation was highly chemoselective in CPME, the solvent was carried through the optimisation process.

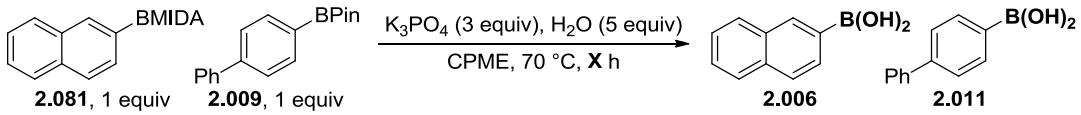
The observed chemoselectivity can be aligned with the water solubility of the solvent used (Table 2.16). 2-MeTHF and EtOAc are too hydrophilic which allows for quantitative conversion to the desired boronic acid, however no speciation control is observed, leading to poor chemoselectivity (entries 1 and 2). CPME appears to be in the so-called ‘sweet spot’ of properties; being not too hydrophobic or hydrophilic for MIDA hydrolysis while avoiding speciation (entry 3). Toluene is too hydrophobic for an efficient hydrolysis reaction to occur, leading to an incomplete reaction (entry 4).

entry	solvent	solubility in water (g/100 g)	dielectric constant	conversion[a]	**2.006**:**2.011**[a]
1	2-MeTHF	14.0	6.97	quant.	2:1
2	EtOAc	8.7	6.02	quant.	2:1
3	CPME	1.1	4.76	quant.	5:1
4	toluene	0.52	2.38	83%	4:1

[a]Determined by HPLC analysis using an internal standard.

Table 2.16 Properties of MIDA hydrolysis solvents.

One issue that must be addressed is the amount of speciation occurring in the hydrolysis process (Table 2.15). It was hypothesised that this was caused by a prolonged reaction time *i.e.*, clean hydrolysis was occurring only for speciation events to commence as the time progressed. In order to avoid this, the reaction time was shortened (Table 2.17). As expected, halving the reaction time to 15 minutes provided exquisite chemoselective hydrolysis selectivity, albeit with incomplete conversion (entry 1). Any increase in the reaction time decreased chemoselectivity dramatically although conversion increased, as expected (entries 2–6). Despite the increase in conversion, chemoselectivity is the key factor when performing a chemoselective oxidation procedure. Consequently, a 15 minute reaction time was progressed into further optimisation studies.

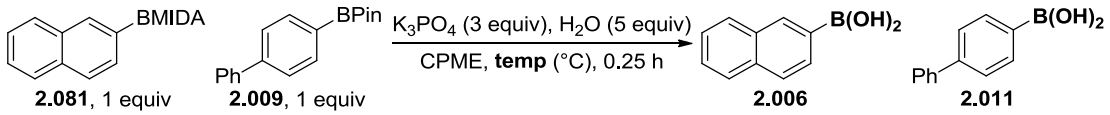


entry	time (h)	conversion[a]	**2.006**:**2.011**[a]
1	0.25	87%	86:1
2	0.5	quant.	5:1
3	0.75	quant.	2:1
4	1	quant.	2:1
5	1.25	quant.	2:1
6	1.5	quant.	2:1

[a]Determined by HPLC analysis using an internal standard.

Table 2.17 MIDA hydrolysis optimisation – time study.

Finally, a small temperature study revealed that a slight temperature increase to 80 °C provided smooth BMIDA hydrolysis while avoiding any speciation events (Table 2.18, entry 2). Any attempt to further increase the reaction temperature yielded uncontrolled speciation (entries 3–5).

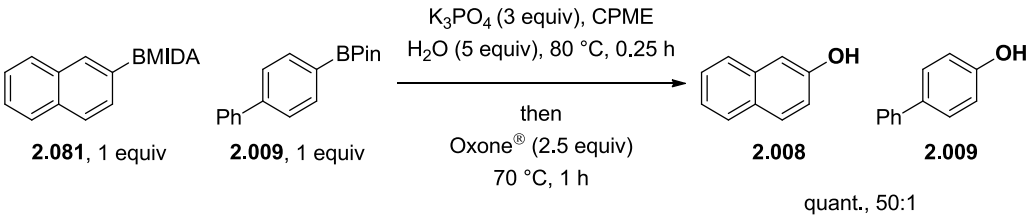


entry	temperature (°C)	conversion[a]	**2.006**:**2.011**[a]
1	70	87%	86:1
2	80	quant.	20:1
3	90	quant.	5:1
4	100	quant.	2:1
5	110	quant.	2:1

[a]Determined by HPLC analysis using an internal standard.

Table 2.18 MIDA hydrolysis optimisation – temperature study.

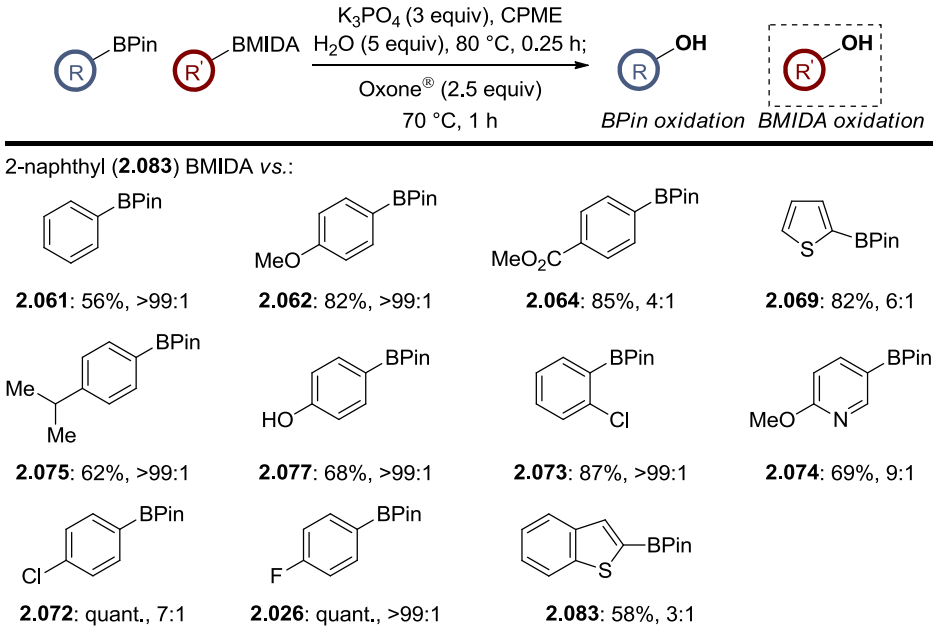
The optimised conditions were then combined with the chemoselective oxidation procedure and applied to the workhorse reaction system (Scheme 2.19). Gratifyingly, excellent conversion and chemoselectivity were observed.



Scheme 2.19 Inversion of traditional chemoselectivity.

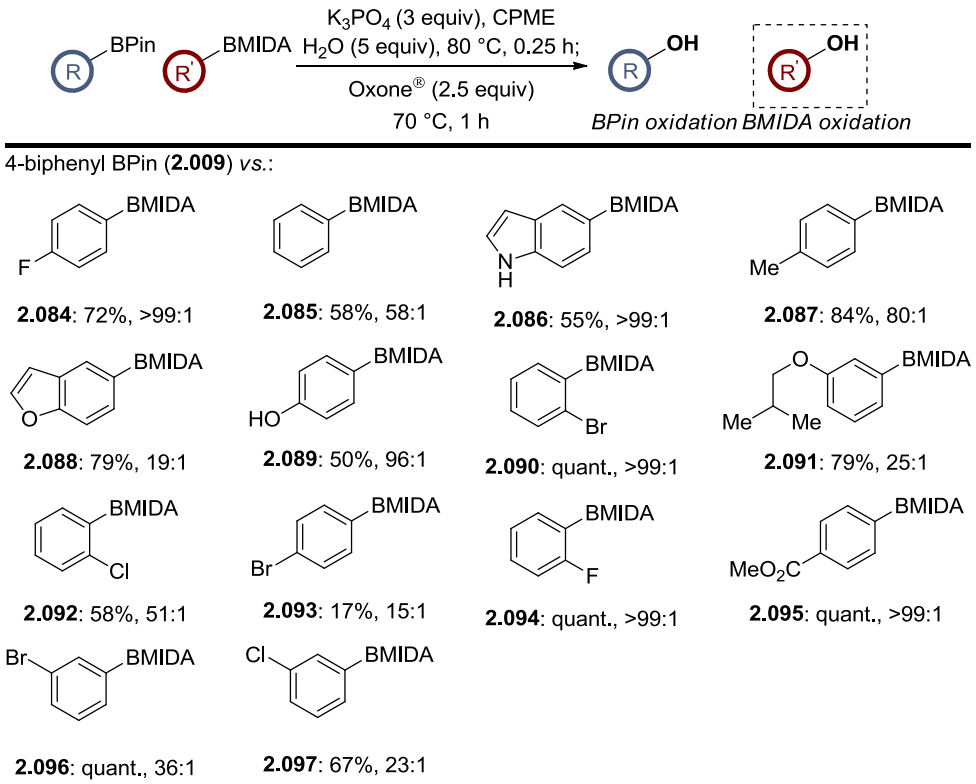
With general chemoselective conditions in hand, the substrate scope of the reaction was then explored. Initially, the pinacol ester derivative was altered while conserving the 2-naphthyl BMIDA species, **2.081** (Scheme 2.20). The reaction conditions were tolerable to a wide variety of functionality including ethers, **2.062**, esters, **2.064**, alcohols, **2.077**, and halogens, **2.073**, **2.072**, and **2.026**. The yields and

chemoselectivity remained high regardless of the electronic properties of the aryl group. Chemoselectivity was slightly diminished when heterocyclic derivatives were employed, **2.069**, **2.074**, and **2.083**, although conversion remained high. This reduced chemoselectivity could either be due to the inherent instability of the parent boronic ester, or to more subtle phase distribution effects.



Scheme 2.20 Chemoselective oxidation of aryl diboron system: BMIDA *vs.* BPin substrate scope. Ratio given for oxidation of boronic acid, MIDA ester:boronic acid, pinacol ester. Determined by HPLC.

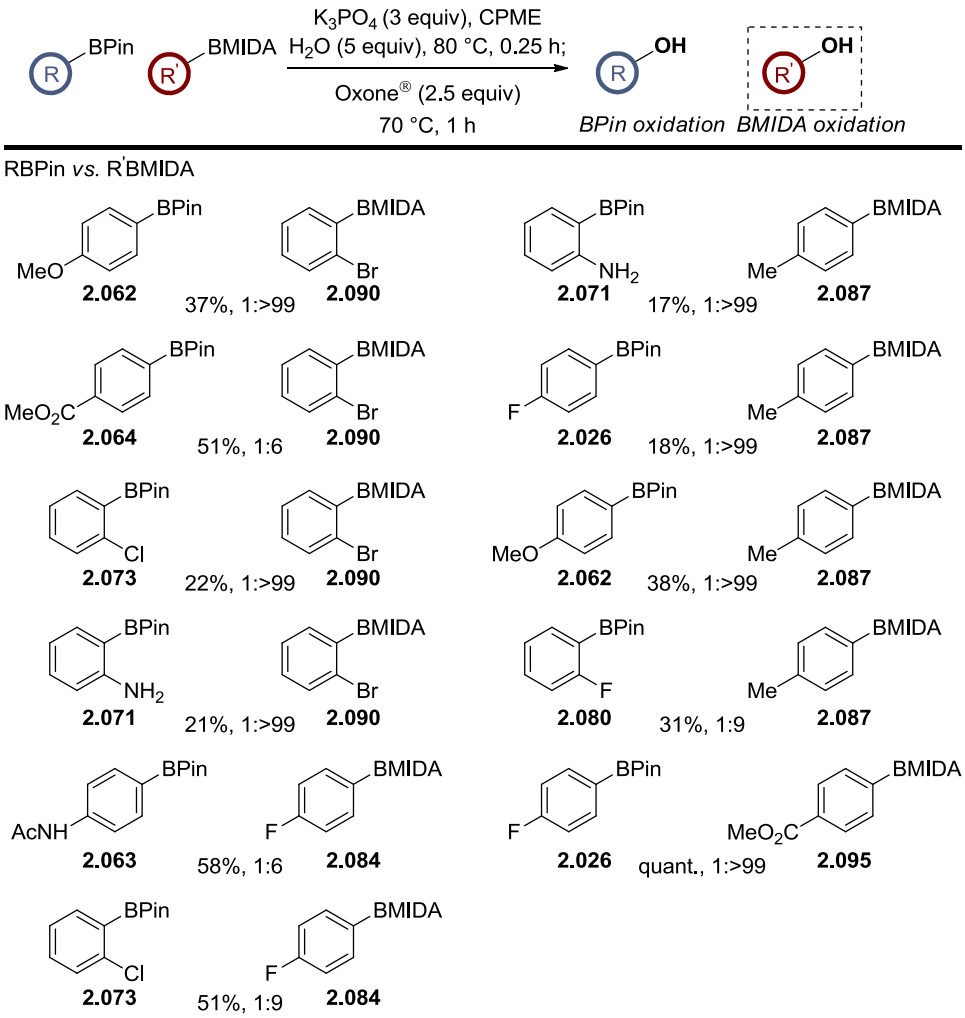
Subsequently, the BMIDA ester moiety was varied while maintaining the 4-biphenyl boronic ester substituent **2.009** (Scheme 2.21). The substitution of the pendant aryl unit had minimal effect on the chemoselectivity of the reaction: alcohols, **2.089**, ethers, **2.091**, esters, **2.095**, and halogens, **2.084**, **2.090**, **2.092**, **2.093**, **2.094**, **2.096**, and **2.097**, were all tolerated. Notably, a low yield was obtained with 4-bromophenylBMIDA, **2.093**, however, the chemoselectivity of the reaction remained excellent. The low yield was caused by incomplete hydrolysis of the MIDA ester leaving predominantly a protected boron species that could not be oxidised. A longer hydrolysis time for this substrate would improve the overall conversion.



Scheme 2.21 Chemoselective oxidation of aryl diboron system: BMIDA *vs.* BPin substrate scope. Ratio given for oxidation of boronic acid, MIDA ester, boronic acid, pinacol ester. Determined by HPLC.

Heterocycles were also tolerated as part of the MIDA ester with both indole, **2.086**, and benzofuran, **2.088**, performing well in the optimised reaction conditions. The substitution pattern of the aryl unit has minimal effect on the chemoselectivity of the reaction, *cf.*, arylbromides **2.090**, **2.093**, and **2.096**. However, the hydrolysis of the MIDA ester may be influenced as shown by quantitative conversion for both *ortho*- and *meta*-substituted arylbromides but only 17% conversion their *para*-substituted counterpart. This could be due to electronic, steric, or possibly solubility differences in the compounds.

With a thorough investigation into the applicability of this chemistry to a number of arylboron species complete, a number of arylboronic pinacol ester and arylBMIDA ester combinations were submitted to the optimised reaction conditions to further examine the substrate scope of the reaction (Scheme 2.22).

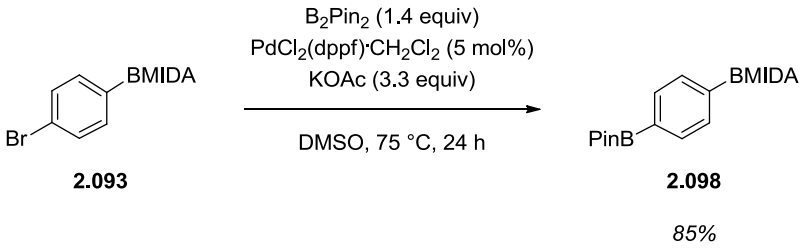


Scheme 2.22 Chemoselective oxidation of aryl diboron system: BMIDA *vs.* BPin substrate scope. Ratio given for oxidation of boronic acid, MIDA ester:boronic acid, pinacol ester. Determined by HPLC.

Excellent levels of chemoselectivity were maintained throughout the substrates screened, however, conversion was diminished in many cases. 2-BromophenylBMIDA ester, **2.090**, 4-fluorophenylBMIDA ester, **2.084**, and *p*-tolylBMIDA ester, **2.087**, were all hydrolysed and oxidised chemoselectively against a variety of boronic acid, pinacol esters, but overall conversion was poor to moderate. Significant amounts of MIDA ester starting materials can be observed by HPLC, contributing to a large proportion of the mass balance. A longer hydrolysis time is required to increase the conversion levels for these low-yielding substrates. On the other hand, (4-(methoxycarbonyl)phenyl)boronic acid, MIDA ester, **2.095**,

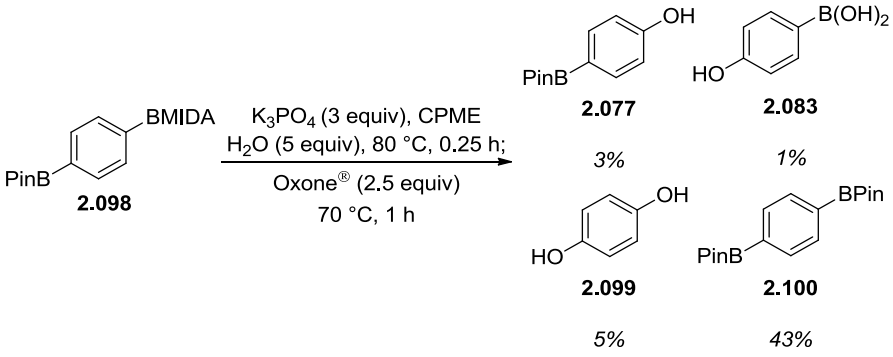
was oxidised in quantitative yield and with exquisite chemoselectivity in identical reaction conditions. This, combined with the poor hydrolysis of other substrates, points to the high substrate dependence of the hydrolysis reaction.

This BMIDA oxidation process provided the opportunity to further confirm the hypothesis of the requirement to physically separate the two boron residues in order to achieve chemoselectivity. Diboron compound **2.098**, where both boron residues were located on the same aryl unit, was synthesised via Miyaura borylation of 4-bromophenylboronic acid, MIDA ester in good 85% yield (Scheme 2.23).



Scheme 2.23 Miyaura borylation of 4-bromophenylboronic acid, MIDA ester.

Diboron compound **2.098** was a very poor substrate when subjected to optimised oxidation conditions, and delivered a mixture of the desired phenol **2.077** as well as **2.083** (the product of BPin oxidation and BMIDA hydrolysis), **2.099** (the product of global oxidation), but mainly **2.100** (the product of equilibration) (Scheme 2.24).



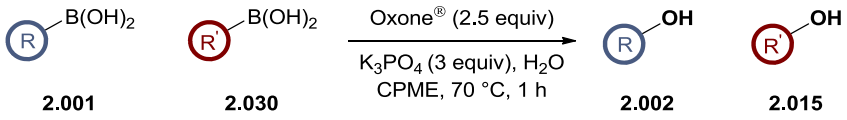
Scheme 2.24 Attempted chemoselective oxidation of diboron compound **2.098**. Determined by HPLC.

The fact that selective phase transfer is not possible with diboron system **2.098**, combined with the poor yield of desired product is further evidence for the phase splitting hypothesis described previously (sections 2.2 and 2.3).

2.6 Chemoselective oxidation of diboronic acid systems

Previously, chemoselectivity in diboron systems has been driven by competing boronate formation between chemically different organoboron compounds *i.e.*, boronic acid *vs.* boronic ester. However, the formation of aryl boronates is heavily influenced by the electronics of the aryl unit.[157] This, in turn, controls the propensity of the boron species to form its more water soluble boronate derivative. In particular, substitution on the aryl unit directly influences the Lewis-acidity of the boronic acid and can heavily effect the aqueous solubility.[13] Substitution on the aryl moiety also effects the rate of protodeboronation.[156] Consequently, the rate of protodeboronation in aqueous basic conditions must not be too fast in order to allow oxidation to occur.[156]

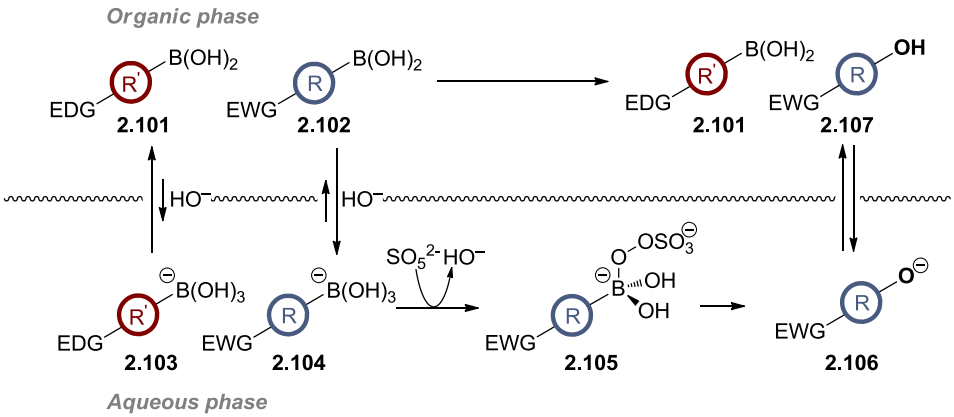
Using this rationale, investigations were carried out into whether chemoselective oxidation in a diboronic acid system could be achieved (Scheme 2.25). That is, could alcohol **2.002** be formed preferentially if R is more electron withdrawing than R'.



Scheme 2.25 Oxidation of diboronic acid systems.

If R is highly electron deficient, the boronic acid functionality becomes more Lewis-acidic and forms a boronate species more readily than the more electropositive boronic acid connected to aryl group R' (Scheme 2.26). Consequently, selective phase transfer of this boronate will occur, leaving predominantly R boronic acid in the aqueous phase and R' boronic acid in the organic phase. Oxidation, which only occurs in the aqueous phase, would then facilitate the formation of desired electron-deficient alkoxide species **2.104**. Protonation, either on return to the organic phase or

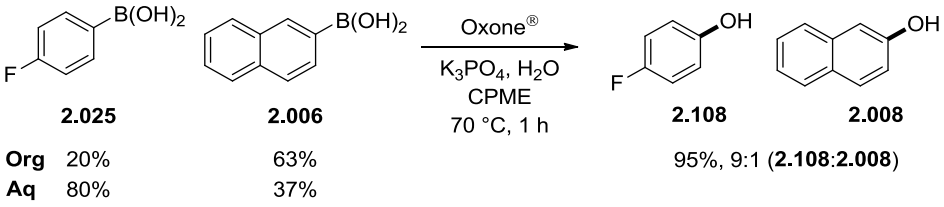
on work-up, generates the desired phenol **2.107** leaving the electron-rich arylboron species, theoretically, untouched. However, in practice, it is conceivable that excess base present in the reaction mixture could facilitate boronate formation of both boron species, resulting in poor chemoselectivity. The propensity for this to occur depends on the influence that the electronic effects of the aromatic system exert on the Lewis-acidity of the boron centre. This factor will vary dramatically between aromatic groups.



Scheme 2.26 Rationale for chemoselective boronic acid oxidation.

Previously, HPLC analysis of the biphasic reaction system was conducted in order to determine the relative phase distribution of boron species (Table 2.13). The same analysis could be undertaken with diboronic acid systems to determine the phase distribution of the arylboronic acids. This would give an indication into the relative electronic effects of the aryl groups on the electron density of boron and enable prediction of the chemoselectivity of the oxidation reaction.

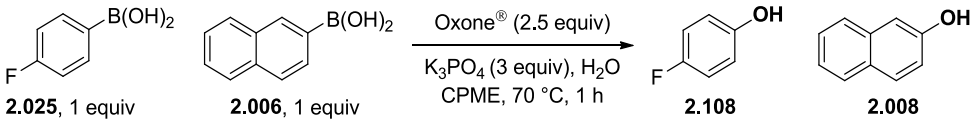
HPLC analysis was initially conducted on a diboronic acid system containing 4-fluorophenyl boronic acid **2.025** and 2-naphthyl boronic acid **2.006** (Scheme 2.27). The two boronic acids were chosen due to their different electronic properties which could lead to selective boronate formation and subsequent phase transfer of the more electron-deficient 4-fluorophenylboronic acid, **2.025**.



Scheme 2.27 Phase distribution and chemoselective oxidation of a diboronic acid system containing **2.025** and **2.006**. Determined by HPLC analysis using an internal standard.

Gratifyingly, fluorinated boronic acid **2.025** was found to distribute into the aqueous phase at a higher rate than naphthalene-2-boronic acid **2.006**. However, when the oxidant was added to the reaction mixture, the ratio of approximately 2:1 distribution of **2.025**:**2.006** in the aqueous phase did not correlate with the observed chemoselectivity; 9:1 in favour of **2.025**. Conversion to the oxidised product remained high (95%) due to the ability of the naked boronic acid species to form boronate species.

A small solvent screen was then conducted to ensure that CPME was the optimal reaction solvent for the diboronic acid system (Table 2.19). As previously observed, hydrophobic solvents provided good levels of chemoselectivity (entries 1–5) with CPME being the optimal solvent, providing near quantitative conversion and good chemoselectivity (entry 2).



entry	solvent	conversion[a]	**2.108**:**2.008**[a]
1	2-MeTHF	97%	6:1
2	CPME	95%	9:1
3	THF	quant	3:1
4	EtOAc	44%	5:1
5	$CHCl_3$	45%	6:1

[a]Determined by HPLC analysis using an internal standard.

Table 2.19 Competitive boronic acid oxidation optimisation – solvent study.

The observed chemoselectivity can be rationalized through a combination of the solubility of the solvent in water and the dielectric constant of the solvent (Table 2.20). The extent of phase splitting will be heavily influenced by the solubility of the solvent in water; the lower the solubility, the better the phase splitting, and consequently the better the observed chemoselectivity. The dielectric constant of a solvent heavily influences its ability to solvate compounds. In this case, the lower the dielectric constant, the poorer that solvent should be at dissolving polar boronate species, thus forcing them into the aqueous phase. THF is miscible with water which results in poor chemoselectivity but excellent conversion (entry 1). Evidence of a phase boundary is observed when 2-MeTHF and EtOAc are used as a co-solvent for the reaction. Their solubility in water is reduced (entries 2 and 3), which results in slightly enhanced chemoselectivity for the reaction. Chloroform (entry 4) is denser than water which may be why the observed chemoselectivity is similar to that of EtOAc and 2-MeTHF despite the low solubility in water and dielectric constants. The excess base and oxidant that collect at the bottom of the microwave vial may

influence the complex equilibria involved in the chemoselective reaction. CPME (entry 5) has a good balance of low solubility in water and dielectric constant and provides excellent chemoselectivity and conversion when diboronic acid systems are employed.

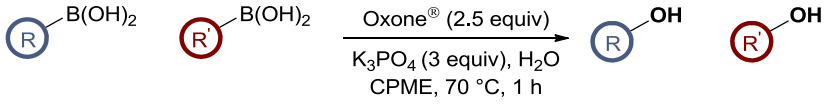
entry	solvent	solubility of solvent in water (g/100 g)	dielectric constant	**2.108**:**2.008**[a]
1	THF	∞	7.58	3:1
2	2-MeTHF	14.0	6.97	6:1
3	EtOAc	8.7	6.02	5:1
4	$CHCl_3$	0.8	4.81	6:1
5	CPME	1.1	4.76	9:1

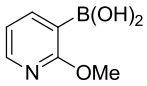
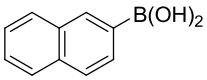
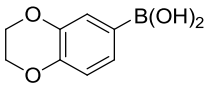
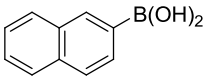
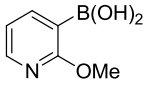
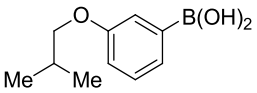
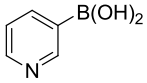
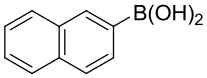
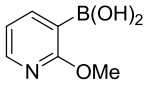
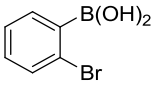
[a]Determined by HPLC analysis using an internal standard.

Table 2.20 Rationale for observed chemoselectivity.

Finally, a variety of diboron systems were screened using optimised reaction conditions (Table 2.21). Chemoselective oxidation of diboronic acid systems was found to be transferable across a range of substrates. Initially, electron-deficient (2-methoxypyridin-3-yl)boronic acid, **2.044**, is readily oxidised in the presence of naphthalen-2-boronic acid, **2.006** (entry 1). Surprisingly, the more electron-rich (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid, **2.046**, is oxidised preferentially over **2.006** in good yield and chemoselectivity (entry 2). Boronic acid **2.044** is again oxidised as part of a diboron system in moderate yield and chemoselectivity (entry 3). Pyridin-3-ylboronic acid is also more electron-deficient than **2.006** and is readily oxidised in good yield but with slightly diminished chemoselectivity (entry 4). The chemoselectivity is further lowered when two electron-deficient species are used in the reaction (entry 5).

Generally, the efficiencies and chemoselectivities of the process were not as pronounced as the more substantially differentiated diboron systems described previously (Schemes 2.14 and 2.15). However, this represents the first predictive chemoselective discrimination of two boronic acid species, based on subtle differences in the substitution of the pendant aryl unit.



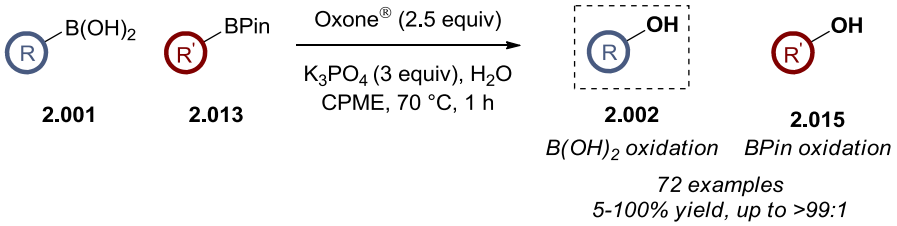
entry	$RB(OH)_2$	$R'B(OH)_2$	conversion[a]	oxidation (R:R')[a,b]
1	 **2.044**	 **2.006**	62%	3:1
2	 **2.046**	 **2.006**	86%	4:1
3	 **2.044**	 **2.050**	71%	3:1
4	 **2.109**	 **2.006**	85%	2:1
5	 **2.044**	 **2.048**	42%	2:1

[a]Determined by HPLC analysis using an internal standard. [b]Ratio given for oxidation of R-$B(OH)_2$: R'-$B(OH)_2$.

Table 2.21 Chemoselective oxidation of diboronic acid systems.

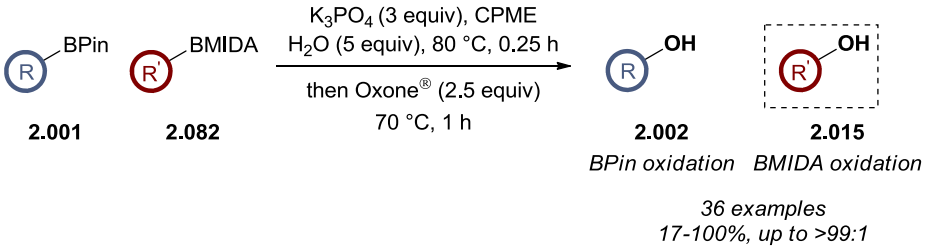
3 Conclusions

In conclusion, after extensive optimisation, the chemoselective oxidation of boronic acid and boronic ester diboron systems is readily achieved under basic biphasic reaction conditions (Scheme 2.28).



Scheme 2.28 Chemoselective oxidation in diboron systems.

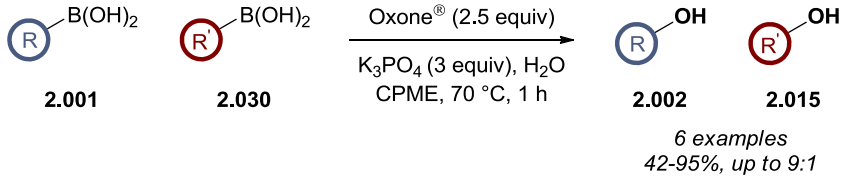
Conventional protecting group strategies can be overturned to allow oxidation of BMIDA compounds in the presence of a typically more reactive pinacol ester species (Scheme 2.29).



Scheme 2.29 Inversion of established chemoselectivity.

The mechanism by which chemoselectivity was leveraged was then investigated. Combined HPLC and NMR analysis revealed that chemoselectivity is derived from the selective phase transport of boronic acids to the aqueous phase under the aqueous basic reaction conditions, leaving primarily boronic ester in the organic phase. Oxone® solely resides in the aqueous phase and, consequently, boronic acids are chemoselectively oxidised. Initially, HPLC analysis showed the presence of boronic acids in the aqueous phase but the nature of the boron species was unknown, *i.e.*, neutral boronic acid or negatively charged boronate. Secondly, ^{11}B NMR analysis conclusively proved the existence of pure boronic acid boronate in the aqueous phase, whereas only neutral boronic acid pinacol ester was seen in the organic phase.

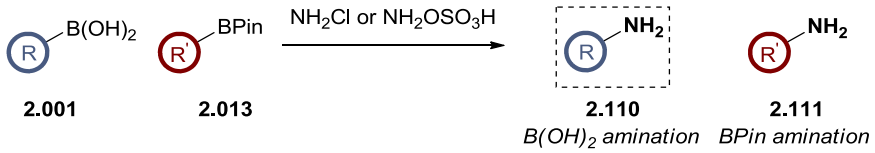
From the probing of the reaction mechanism it was also envisaged that electronically differentiated diboronic acid systems could be chemoselectively oxidised. Subsequently, it was shown that it is possible to chemoselectively oxidise a mixture of two boronic acids and predict the outcome of the reaction *a priori* by HPLC analysis of the reaction partners (Scheme 2.30).



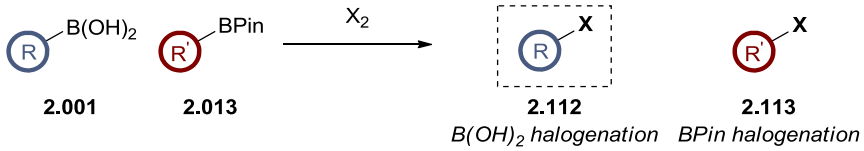
Scheme 2.30 Chemoselective oxidation of diboronic acid systems.

4 Future work

With conditions established for the chemoselective oxidation of diboron systems, the methodology could be expanded to facilitate other chemoselective transformations of boron species. For example, could chemoselective amination (Scheme 2.31) or halogenation (Scheme 2.32) be achieved using the same basic biphasic conditions?

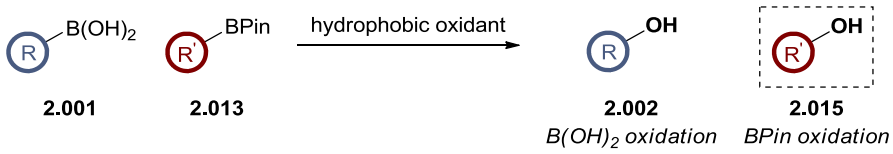


Scheme 2.31 Chemoselective amination reaction.



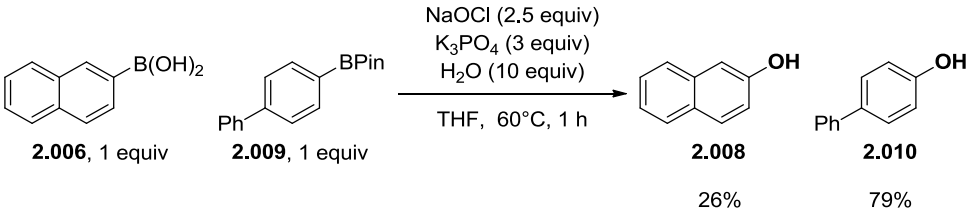
Scheme 2.32 Chemoselective halogenation reaction.

Furthermore, could chemoselectivity be inverted in oxidation reactions of diboron systems through changing the oxidant used (Scheme 2.33). Oxone® is insoluble in organic media, and as such, boronic acid oxidation is prevalent. However, with the use of a hydrophobic oxidant that is soluble in organic solvents, could chemoselective boronic ester oxidation occur?



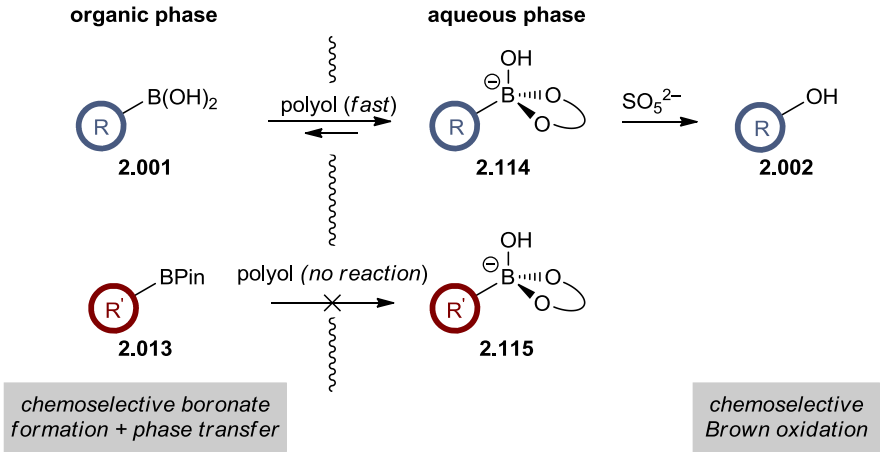
Scheme 2.33 Inverting oxidation chemoselectivity.

During the optimisation of the current chemoselective oxidation conditions, sodium hypochlorite was trialled as an oxidant for the process (Scheme 2.34). An inversion in chemoselectivity was observed with selective oxidation of boronic ester **2.009** in the presence of boronic acid **2.006**. The 3:1 ratio in favour of boronic ester oxidation could be further optimised to provide complete chemoselectivity.



Scheme 2.34 Inversion of established chemoselectivity using sodium hypochlorite. Determined by HPLC.

Finally, Hall and coworkers used polyols to perform pH-selective phase transfer of boronic acids in order to purify boron-containing compounds (Scheme 2.08).[150] The application of polyols to our system, and manipulation of the pH of the system, could lead to improved chemoselectivity in oxidation reactions of diboron systems (Scheme 2.35). Furthermore, this could be applied to diboronic acid systems to enhance the chemoselectivity leveraged in this process.



Scheme 2.35 Polyol-mediated chemoselective oxidation of diboron systems.

5 Experimental

5.1 General experimental

All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.[55]

5.1.1 Purification of solvents

Dry THF and toluene were obtained from a PureSolv SPS-400-5 solvent purification system. These solvents were transferred to and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves and purged with and stored under nitrogen. CH_2Cl_2, $CHCl_3$, CPME, 1,4-dioxane, DMF, Et_2O, EtOAc, IPA, MeCN, 2-MeTHF, and petroleum ether 40–60 °C for purification purposes were used as obtained from suppliers without further purification.

5.1.2 Drying of inorganic bases

Cesium carbonate, potassium carbonate, and tripotassium phosphate were dried in a Heraeus Vacutherm oven at 60 °C under vacuum for a minimum of 24 h before use.

5.1.3 Experimental details

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

MR 3004 safety, or Heidolph MR 3002. Reactions were stirred at stir rate of ~350 rpm unless otherwise stated.

5.1.4 Purification of products

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

5.1.5 Analysis of products

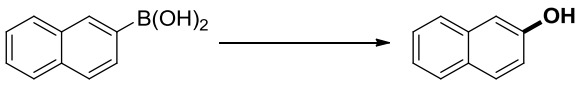
Fourier Transformed Infra-Red (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. ^{1}H and ^{13}C NMR spectra were obtained on either a Bruker AV 400 spectrometer (Oxford magnet) at 400 MHz and 101 MHz, respectively, or Bruker Ascend AV(III) HD 500 spectrometer at 500 MHz and 126 MHz, respectively. ^{11}B NMR spectra were obtained on a Bruker AV 400 spectrometer (Oxford magnet) at 128 MHz. ^{19}F NMR spectra were obtained on a Bruker AV 400 spectrometer (Oxford magnet) at 376 MHz. ^{11}B NMR were obtained in Norell® natural quartz 5 mm NMR tubes (500 MHz limit). Chemical shifts are reported in ppm and coupling constants are reported in Hz: $CDCl_3$ is referenced at 7.27 (^{1}H) and 77.0 (^{13}C), d_6-DMSO is referenced at 2.50 (^{1}H) and 39.5 (^{13}C). High-resolution mass spectra (HRMS) were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University or at the Mass Spectrometry Facility at Glasgow University. Reversed phase HPLC data was obtained on an Agilent 1200 series HPLC using a Machery-Nagel Nucleodur C18 column, which was maintained at a constant temperature of 40 °C. Analysis was performed using a gradient method, eluting with 5–80% MeCN/H_2O over 16 min at a flow rate of 2 mL/min. Samples for HPLC analysis were prepared through the addition of 2 mL of caffeine standard to the completed reaction mixture, the resulting solution was then stirred before the removal of a 200 µL aliquot. The aliquot was diluted to 1 mL with MeCN; a 0.20 mL aliquot of the diluted solution was then filtered and further diluted with 800 µL of

MeCN and 0.50 mL of H_2O for HPLC analysis against established conversion factors. Conversion factors were established as a 1:1 ratio caffeine:product. Reaction HPLC samples were stirred with a 1:4 ratio caffeine:product unless stated otherwise.

5.2 General experimental procedures

General procedure A: oxidation study of monoaryl boron systems (Table 2.01, Charts 2.01 and 2.02)

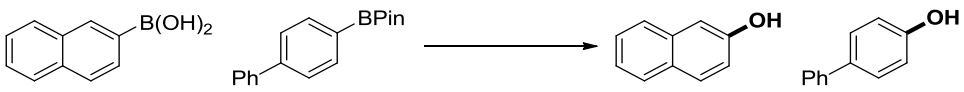
For example, oxidation of naphthalen-2-ylboronic acid, **2.006**



To an oven-dried 5 mL microwave vial was added naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv). THF (0.63 mL, 0.25 M) was then added followed by a slurry of Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) in water (1.28 mL). The reaction mixture was stirred at ambient temperature for 30 min. Sodium metabisulfite (0.12 g, 0.64 mmol, 4 equiv) was added and conversion to product was determined by HPLC against an internal standard (caffeine) indicating oxidation of the naphthalen-2-ylboronic acid (98%).

General procedure B: optimised reaction boronic acid *vs.* BPin ester or boronic acid (Schemes 2.04, 2.05, 2.14, 2.15, 2.16, 2.28, and 2.30)

For example, selective oxidation of naphthalen-2-ylboronic acid (**2.006**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**2.009**)

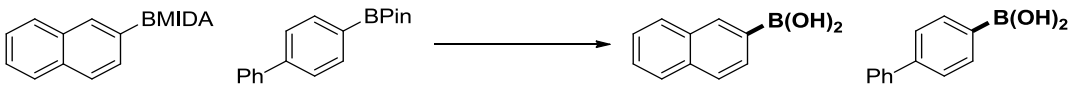


To an oven-dried 5 mL microwave vial was added naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), and tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv). CPME (0.63 mL, 0.25 M) was then added followed by a slurry of Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) in water (1.28 mL) and CPME (0.25 mL). The reaction mixture was then heated to 70 °C with stirring in a sand bath for 1 h. The reaction

was allowed to cool to ambient temperature before addition of sodium metabisulfite (0.12 g, 0.64 mmol, 4 equiv). Conversion to products was determined by HPLC against an internal standard (caffeine) indicating selective oxidation of the naphthalen-2-ylboronic acid (quant., >99:1 selectivity).

General procedure C: BMIDA hydrolysis optimisation (Tables 2.15, 2.17, and 2.18 and Schemes 2.24 and 2.29)

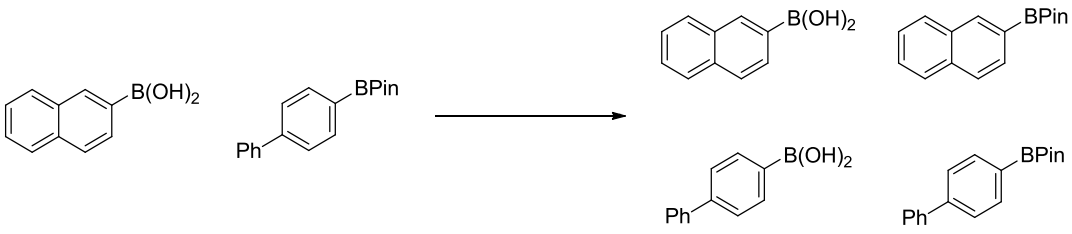
For example, selective hydrolysis of naphthalen-2-ylboronic acid, MIDA ester (**2.081**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**2.009**)



To an oven-dried 5 mL microwave vial was added naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), and tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv). The vial was then capped and purged with nitrogen before addition of CPME (0.63 mL, 0.25 M) and water (15 µL, 0.80 mmol, 5 equiv). The reaction mixture was then heated to 80 °C in a sand bath with stirring for 15 min. Conversion to products was determined by HPLC against an internal standard (caffeine) indicating selective hydrolysis of naphthalen-2-ylboronic acid, MIDA ester (87%, 86:1).

General procedure D: equilibration reaction (Scheme 2.06)

For example, equilibration of naphthalen-2-ylboronic acid (**2.006**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**2.009**)

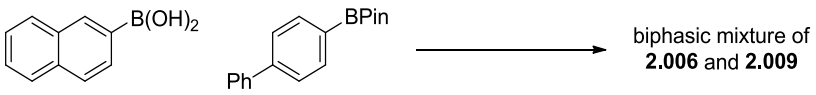


To an oven-dried 5 mL microwave vial was added [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), naphthalen-2-ylboronic acid (0.028 g,

0.16 mmol, 1 equiv), and tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv). A mixture of THF and water (10:1, 0.70 mL) was added and the reaction mixture was heated to 50 °C with stirring in a sand bath for 1 h. The reaction mixture was allowed to cool to ambient temperature and the conversion to products was determined by HPLC against an internal standard (caffeine) indicating a (1:1:1:1) mixture of products. **2.006**:**2.009**:**2.007**:**2.011**.

General procedure E: origin of chemoselectivity – HPLC analysis (Table 2.13)

For example, HPLC analysis of biphasic system for naphthalen-2-ylboronic acid (**2.006**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**2.009**)

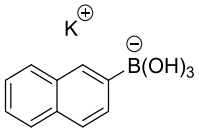


2.006 **2.009**

To an oven-dried 5 mL microwave vial was added naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), potassium bisulfate (0.027 g, 0.20 mmol, 1.25 equiv), and potassium sulfate (0.034 g, 0.20 mmol, 1.25 equiv). A mixture of water (1.28 mL) and CPME (0.88 mL) were then added, and the reaction mixture was heated to 70 °C with stirring in a sand bath for 10 min. The reaction mixture was removed from agitation and allowed to settle to form a biphase. A 0.20 mL aliquot was removed from each phase (aqueous and organic) and distribution of products was determined by HPLC against a known quantity of internal standard (caffeine) indicating selective phase transfer of naphthalen-2-ylboronic acid, **2.006**, 54:46 (organic/aqueous), **2.009**, >99:1 (organic/aqueous).

General procedure F: boronate formation of boron species (Schemes 2.10 and 2.11)

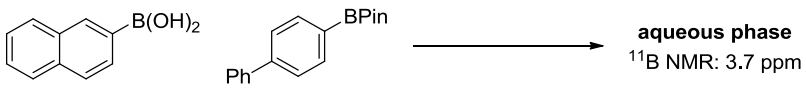
For example, synthesis of potassium trihydroxy(naphthalen-2-yl)borate, **2.022**



Naphthalen-2-ylboronic acid (0.006 g, 0.04 mmol, 1 equiv) and tripotassium phosphate (0.023 g, 0.11 mmol, 3 equiv) were weighed out into a vial. D_2O (0.75 ml) was added and the mixture was sonicated until a solution was formed. The solution was transferred to a quartz NMR tube and an ^{11}B NMR was recorded at 343 K. Potassium trihydroxy(naphthalen-2-yl)borate provided a signal at 3.7 ppm.

General procedure G: origin of chemoselectivity – NMR analysis (Schemes 2.10 and 2.11 and Figures 2.03, 2.04, 2.05, 2.06, and 2.07)

For example, NMR analysis of biphasic system for naphthalen-2-ylboronic acid (**2.006**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**2.009**)

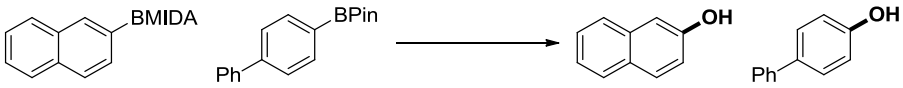


Naphthalen-2-ylboronic acid (0.017 g, 0.10 mmol, 1 equiv) and [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.028 g, 0.10 mmol, 1 equiv) were dissolved in CPME (0.40 mL, 0.25 M) and transferred to a quartz NMR tube (Tube A). Tripotassium phosphate (0.063 g, 0.30 mmol, 3 equiv), potassium bisulfate (0.017 g, 0.13 mmol, 1.25 equiv), and potassium sulfate (0.022 g, 0.13 mmol, 1.25 equiv) were weighed out into a vial (Vial A) and were dissolved in D_2O (0.80 mL) for later use. A D_2O blank (0.80 mL) NMR sample tube (Tube B) was prepared and used as a lock on the NMR machine. After locking (Tube B) was complete, Vial A containing inorganics was transferred slowly *via* syringe and long needle (needle must reach the bottom of the NMR tube) to Tube A to generate an aqueous biphasic system. The biphasic NMR sample (Tube A) was placed in the magnet and after shimming a data set was recorded every 5 min for 1 h at 293 K (128 scan per data set recording). After 1 h the

temperature was increased to 323 K and a data set was recorded every 5 min for 1 h. After 1 h the temperature was further increased to 343 K and a data set was recorded every 5 min for 1 h (no spinning was used in this NMR study).

General procedure H: optimised reaction BMIDA *vs.* BPin (Schemes 2.19, 2.20, 2.21, and 2.22)

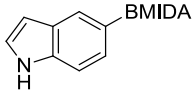
For example, selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (**2.081**) *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (**2.009**)



To an oven-dried 5 mL microwave vial was added naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), and tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv). The vial was then capped and purged with nitrogen before addition of CPME (0.63 mL, 0.25 M) and water (15 µL, 0.80 mmol, 5 equiv). The reaction mixture was then heated to 80 °C in a sand bath with stirring for 10 min. The vial was then decapped and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv), as a slurry in water (1.28 mL) and CPME (0.25 mL), was added. The reaction was heated to 70 °C with stirring in a sand bath for 1 h. The reaction was allowed to cool to ambient temperature before addition of sodium metabisulfite (0.12 g, 0.64 mmol, 4 equiv). Conversion to products was determined by HPLC against an internal standard (caffeine) indicating selective oxidation of the naphthalen-2-ylboronic acid, MIDA ester (quant., 50:1).

General procedure I: synthesis of MIDA esters from boronic acids

For example, for the preparation of (1*H*-indol-5-yl)boronic acid, MIDA ester, **2.086**



$C_{13}H_{13}BN_2O_4$

A mixture of (1*H*-indol-5-yl)boronic acid (2.00 g, 12.40 mmol, 1 equiv) *N*-methyliminodiacetic acid (1.90 g, 13.02 mmol, 1.05 equiv) in DMF (50 mL, 0.15 M)

was heated at 90 °C for 18 h. The reaction mixture was allowed to cool to ambient temperature and concentrated under vacuum to give an off-white slurry. EtOAc (100 mL) was added and the resulting precipitate was collected by filtration. The precipitate was washed with water (2 × 50 mL) and Et_2O (2 × 50 mL) before being dried under vacuum to give the desired product as a white crystalline solid (3.30 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1 H), 7.62 (s, 1 H), 7.37 (d, J = 8.2 Hz, 1 H), 7.30 (t, J = 2.7 Hz, 1 H), 7.14 (d, J = 8.2 Hz, 1 H), 6.41 (s, 1 H), 4.30 (d, J = 17.2 Hz, 2 H), 4.08 (d, J = 17.2 Hz, 2 H), 2.45 (s, 3 H); ^{11}B NMR ($CDCl_3$, 128 MHz) δ 12.52; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 136.5, 127.5, 124.9, 124.5, 110.8, 101.1, 61.6, 47.5, three coincident peaks and carbon bearing boron not observed; υ_{max} (solid)/cm^{-1} 3401, 3008, 2962, 1766, 1744, 1578, 1455, 1340, 1245, 1236; HRMS *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}BN_2O_4$ 273.1041; found 273.1045.

5.3 Oxidation of monoaryl boron systems – kinetic study

5.3.1 Oxidant study (Table 2.01 and Scheme 2.03)

Reactions were carried out according to General Procedure A using either naphthalen-2-ylboronic acid **2.006** (0.028 g, 0.16 mmol, 1 equiv), or naphthalen-2-ylboronic acid, pinacol ester **2.007** (0.041 g, 0.16 mmol, 1 equiv), **oxidant** (0.40 mmol, 2.5 equiv), water (1.28 mL), and THF (0.63 mL, 0.25 M). Reactions were stirred at ambient temperature for 30 min.

5.3.2 Time study (Chart 2.01)

Reactions were carried out according to General Procedure A using either naphthalen-2-ylboronic acid **2.006** (0.028 g, 0.16 mmol, 1 equiv), or naphthalen-2-ylboronic acid, pinacol ester **2.007** (0.041 g, 0.16 mmol, 1 equiv), Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and THF (0.63 mL, 0.25 M). Reactions were stirred at ambient temperature for **X** min.

entry	boron species	time (min)	conversion[a]
1	**2.006**	0*	39%
2	**2.006**	5	59%
3	**2.006**	10	80%
4	**2.006**	15	86%
5	**2.006**	20	89%
6	**2.006**	30	96%
7	**2.007**	0*	4%
8	**2.007**	5	9%
9	**2.007**	10	12%
10	**2.007**	15	17%
11	**2.007**	20	20%
12	**2.007**	30	23%

*Reactions were quenched after 10 seconds. [a]Determined by HPLC analysis using an internal standard.

5.4 Reaction optimisation data

5.4.1 Boronic acid selective oxidation

5.4.1.1 Base and water study (Table 2.02)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), with or without tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), THF (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry without or without water (1.28 mL) and THF (0.25 mL). Reactions were stirred at ambient temperature for 1 h.

entry	base	water	conversion[a]	**2.006**:**2.009**
1	---	---	0%	---
2	✓	---	0%	---
3	---	✓	95%	1.1:1
4	✓	✓	54%	14:1

[a]Determined by HPLC analysis using an internal standard.

5.4.1.2 Oxidant study (Table 2.02)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), **base** (0.48 mmol, 3 equiv), THF (0.63 mL, 0.25 M), and **oxidant** (0.40 mmol, 2.5 equiv). Reactions were stirred at ambient temperature for 1 h.

5.4.1.3 Water study (Table 2.03)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid,

pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), THF (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (**X** equiv), THF (0.25 mL), and acetone (0.25 mL). Reactions were stirred at 60 °C for 1 h.

5.4.1.4 Acetone study (Table 2.04)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), THF (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL), THF (0.25 mL), and acetone (**X** equiv). Reactions were stirred at 60 °C for 1 h.

5.4.1.5 Time Study (Table 2.05)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), THF (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and THF (0.25 mL). Reactions were stirred at 60 °C for **X** h.

5.4.1.6 Oxidant equivalents study (Table 2.06)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), THF (0.63 mL, 0.25 M), and Oxone® (**X** equiv) as a slurry in water (1.28 mL) and THF (0.25 mL). Reactions were stirred at 60 °C for 1 h.

5.4.1.7 Base study (Table 2.07)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), **base** (0.48 mmol, 3 equiv), THF (0.63

mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and THF (0.25 mL). Reactions were stirred at 60 °C for 1 h.

5.4.1.8 Base equivalents study (Table 2.09)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (**X** equiv), THF (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and THF (0.25 mL). Reactions were stirred at 60 °C for 1 h.

5.4.1.9 Temperature study (Table 2.10)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), THF (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and THF (0.25 mL). Reactions were stirred at **X** °C for 1 h.

5.4.1.10 Solvent study (Table 2.11)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), **solvent** (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and **solvent** (0.25 mL). Reactions were stirred at 70 °C for 1 h.

5.4.1.11 Reaction optimisation summary (Table 2.12)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), with or without tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), **solvent** (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40

mmol, 2.5 equiv) as a slurry in **solvent** (0.25 mL) with or without water (1.28 mL). Reactions were stirred at **X** °C for 1 h.

5.4.1.12 Oxidant study (Scheme 2.34)

Reactions were carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), THF (0.63 mL, 0.25 M), sodium hypochlorite (0.27 mL, 0.40 mmol, 2.5 equiv), water (1.28 mL), and THF (0.25 mL). Reactions were stirred at 60 °C for 1 h.

5.4.2 BMIDA selective oxidation

5.4.2.1 Hydrolysis solvent study (Table 2.15)

Reactions were carried out according to General Procedure C using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), **solvent** (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). Reactions were stirred at 90 °C for 30 min.

5.4.2.2 Hydrolysis time study (Table 2.17)

Reactions were carried out according to General Procedure C using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). Reactions were stirred at 90 °C for **X** h.

5.4.2.3 Hydrolysis temperature study (Table 2.18)

Reactions were carried out according to General Procedure C using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). Reactions were stirred at **X** °C for 30 min.

5.4.3 Boronic acid *vs.* boronic acid selective oxidation

5.4.3.1 Oxidation solvent study (Table 2.19 and Scheme 2.27)

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid (0.022 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), **solvent** (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 30 min.

5.5 Determination of the origin of chemoselectivity

5.5.1 Boronic acid and BPin ester equilibration investigation (Scheme 2.06)

Reactions were carried out according to General Procedure D using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), **base** (0.48 mmol, 3 equiv), and a mixture of THF and water (10:1, 0.7 mL). Reactions were stirred at 50 °C for 1 h.

entry	base (mass)	**2.006** (conversion)	**2.009** (conversion)	**2.007** (conversion)	**2.011** (conversion)
1	---	96%	93%	4%	7%
2	K_3PO_4 (0.10 g)	55%	46%	45%	54%
3	KOH (0.027 g)	47%	47%	53%	53%

[a]Determined by HPLC analysis using an internal standard.

5.5.2 Shearing effect investigation (Chart 2.02)

Reactions were carried out according to General Procedure A using [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv) and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and THF (0.63 mL, 0.25 M). Reactions were stirred at ambient temperature with stirring at **X** rpm for **X** min.

entry	stir rate (rpm)	time (min)	conversion[a]
1	900	0*	4%
2	900	5	42%
3	900	10	54%
4	900	15	69%
5	900	20	75%
6	900	30	89%
7	350	0*	4%
8	350	5	9%
9	350	10	12%
10	350	15	17%
11	350	20	20%
12	350	30	23%

*Reactions were quenched after 10 seconds. [a]Determined by HPLC analysis using an internal standard.

5.5.3 Determination of phase distribution – HPLC analysis (Table 2.13 and Scheme 2.27)

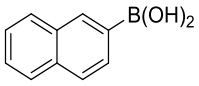
Reactions were carried out according to General Procedure E using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), and a mixture of water and CPME (1.28:0.88 mL). Reactions were stirred at **X** °C for 10 min using varying combinations of the following salts: tripotassium phosphate (0.10 g, 0.48 mmol, 3

equiv), potassium bisulfate (0.027 g, 0.20 mmol, 1.25 equiv), and potassium sulfate (0.034 g, 0.20 mmol, 1.25 equiv).

5.5.4 Determination of phase distribution – NMR analysis

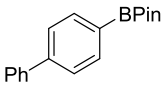
5.5.4.1 NMR analysis of monoaryl boron systems

NMR aqueous phase analysis of naphthalen-2-ylboronic acid, **2.006** (Scheme 2.10 and Figure 2.03)



The NMR experiment was prepared according to General Procedure G using naphthalen-2-ylboronic acid (0.017 g, 0.10 mmol, 1 equiv), tripotassium phosphate (0.063 g, 0.30 mmol, 3 equiv), potassium bisulfate (0.017 g, 0.13 mmol, 1.25 equiv), potassium sulfate (0.022 g, 0.13 mmol, 1.25 equiv), CPME (0.40 mL, 0.25 M), and D_2O (0.80 mL). An ^{11}B NMR was recorded (128 scans) at 293 K every 5 min for 1 h. This process was repeated with the same sample at both 323 K and 343 K.

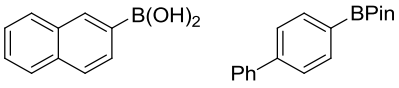
NMR aqueous phase analysis of [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009** (Scheme 2.10 and Figure 2.03)



The NMR experiment was prepared according to General Procedure G using [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.028 g, 0.10 mmol, 1 equiv), tripotassium phosphate (0.063 g, 0.30 mmol, 3 equiv), potassium bisulfate (0.017 g, 0.13 mmol, 1.25 equiv), potassium sulfate (0.022 g, 0.13 mmol, 1.25 equiv), CPME (0.40 mL, 0.25 M), and D_2O (0.80 mL). An ^{11}B NMR was recorded (128 scans) at 293 K every 5 min for 1 h. This process was repeated with the same sample at both 323 K and 343 K.

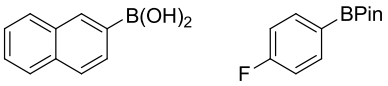
5.5.4.2 NMR analysis of diaryl boron systems (Schemes 2.10 and 2.11 and Figures 2.04 and 2.05)

NMR aqueous phase analysis of naphthalen-2-ylboronic acid, **2.006** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



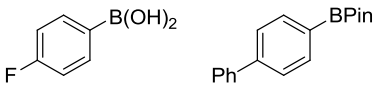
The NMR experiment was prepared according to General Procedure G using naphthalen-2-ylboronic acid (0.017 g, 0.10 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.028 g, 0.10 mmol, 1 equiv), tripotassium phosphate (0.063 g, 0.30 mmol, 3 equiv), potassium bisulfate (0.017 g, 0.13 mmol, 1.25 equiv), potassium sulfate (0.022 g, 0.13 mmol, 1.25 equiv), CPME (0.04 mL, 0.25 M), and D_2O (0.80 mL). An ^{11}B NMR was recorded (128 scans) at 293 K every 5 min for 1 h. This process was repeated with the same sample at both 323 K and 343 K.

NMR aqueous phase analysis of naphthalen-2-ylboronic acid, **2.006** *vs.* (4-fluorophenyl)boronic acid, pinacol ester, **2.026** (Scheme 2.11 and Figure 2.06)



The NMR experiment was prepared according to General Procedure G using naphthalen-2-ylboronic acid (0.017 g, 0.10 mmol, 1 equiv), (4-fluorophenyl)boronic acid, pinacol ester (0.022 g, 0.10 mmol, 1 equiv), tripotassium phosphate (0.063 g, 0.30 mmol, 3 equiv), potassium bisulfate (0.017 g, 0.13 mmol, 1.25 equiv), potassium sulfate (0.022 g, 0.13 mmol, 1.25 equiv), CPME (0.40 mL, 0.25 M), and D_2O (0.80 mL). An ^{11}B NMR was recorded (128 scans) at 293 K every 5 min for 1 h. This process was repeated with the same sample at both 323 K and 343 K. The overall process was repeated on a new sample for ^{19}F NMR (16 scans).

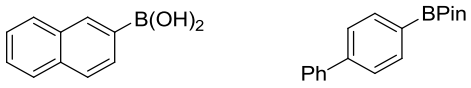
NMR aqueous phase analysis of (4-fluorophenyl)boronic acid, **2.025** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009** (Scheme 2.11 and Figure 2.07)



The NMR experiment was prepared according to General Procedure G using (4-fluorophenyl)boronic acid (0.014 g, 0.10 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.028 g, 0.10 mmol, 1 equiv), tripotassium phosphate (0.063 g, 0.30 mmol, 3 equiv), potassium bisulfate (0.017 g, 0.13 mmol, 1.25 equiv), potassium sulfate (0.022 g, 0.13 mmol, 1.25 equiv), CPME (0.40 mL, 0.25 M), and D_2O (0.80 mL). An ^{11}B NMR was recorded (128 scans) at 293 K every 5 min for 1 h. This process was repeated with the same sample at both 323 K and 343 K. The overall process was repeated on a new sample for ^{19}F NMR (16 scans).

5.6 Chemoselective oxidation - boronic acid *vs.* BPin (Schemes 2.04, 2.05, 2.14, 2.15, 2.16, and 2.28)

Naphthalen-2-ylboronic acid, **2.006** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

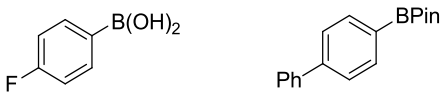


The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (quant., >99:1).

[1,1'-Biphenyl]-4-ylboronic acid, **2.011** *vs.* naphthalen-2-ylboronic acid, pinacol ester, **2.007**

The reaction was carried out according to General Procedure B [1,1'-biphenyl]-4-ylboronic acid (0.032 g, 0.16 mmol, 1 equiv), naphthalen-2-ylboronic acid, pinacol ester (0.041 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of [1,1'-biphenyl]-4-ylboronic acid (quant., >99:1).

(4-Fluorophenyl)boronic acid, **2.025** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

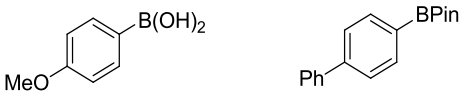


The reaction was carried out according to General Procedure B using (4-fluorophenyl)boronic acid (0.022 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-fluorophenyl)boronic acid (quant., >99:1).

Phenylboronic acid, **2.016** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

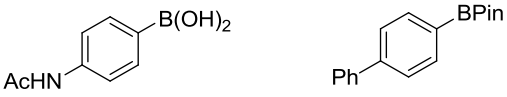
The reaction was carried out according to General Procedure B using phenylboronic acid (0.020 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of phenylboronic acid (quant., >99:1).

(4-Methoxyphenyl)boronic acid, **2.035** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure B using (4-methoxyphenyl)boronic acid (0.024 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-methoxyphenyl)boronic acid (quant., >99:1).

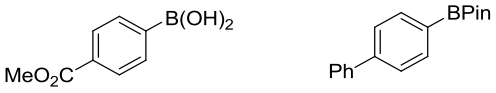
(4-Acetamidophenyl)boronic acid, **2.036** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure B using (4-acetamidophenyl)boronic acid (0.029 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as

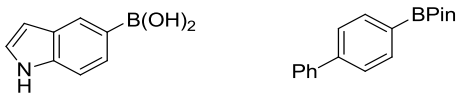
outlined in the general procedure indicating selective oxidation of (4-acetamidophenyl)boronic acid (64%, 60:1).

(4-(Methoxycarbonyl)phenyl)boronic acid, **2.037** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



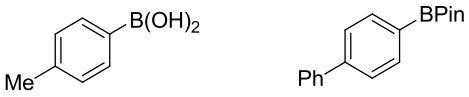
The reaction was carried out according to General Procedure B using (4-(methoxycarbonyl)phenyl)boronic acid (0.029 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-(methoxycarbonyl)phenyl)boronic acid (quant., >99:1).

(1*H*-Indol-5-yl)boronic acid, **2.038** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure B using (1*H*-indol-5-yl)boronic acid (0.026 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (1*H*-indol-5-yl)boronic acid (quant., >99:1).

(4-Methylphenyl)boronic acid, **2.039** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

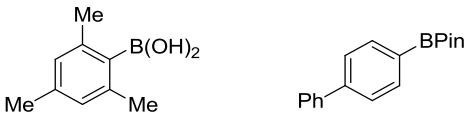


The reaction was carried out according to General Procedure B using (4-methylphenyl)boronic acid (0.022 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-methylphenyl)boronic acid (quant., >99:1).

(2-Nitrophenyl)boronic acid, **2.040** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

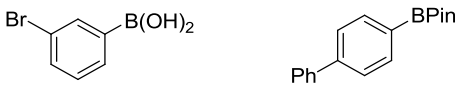
The reaction was carried out according to General Procedure B using (2-nitrophenyl)boronic acid (0.027 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-nitrophenyl)boronic acid (quant., >99:1).

Mesitylboronic acid, **2.041** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure B using mesitylboronic acid (0.026 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of mesitylboronic acid (62%, 15:1).

(3-Bromophenyl)boronic acid, **2.042** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure B using (3-bromophenyl)boronic acid (0.032 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (3-bromophenyl)boronic acid (quant., >99:1).

Benzofuran-5-ylboronic acid, **2.043** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

The reaction was carried out according to General Procedure B using benzofuran-5-ylboronic acid (0.026 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the

general procedure indicating selective oxidation of benzofuran-5-ylboronic acid (90%, 89:1).

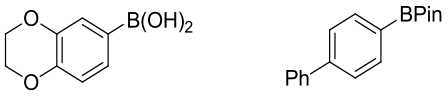
(2-Methoxypyridin-3-yl)boronic acid, **2.044** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

The reaction was carried out according to General Procedure B using (2-methoxypyridin-3-yl)boronic acid (0.024 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-methoxypyridin-3-yl)boronic acid (quant., >99:1).

(2-Chlorophenyl)boronic acid, **2.045** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

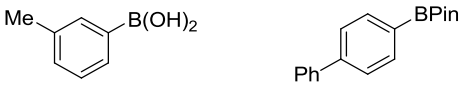
The reaction was carried out according to General Procedure B using (2-chlorophenyl)boronic acid (0.020 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-chlorophenyl)boronic acid (64%, >99:1).

(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid, **2.046** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure B using (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid (0.029 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid (44%, >99:1).

(3-Methylphenyl)boronic acid, **2.047** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

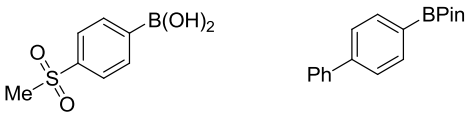


The reaction was carried out according to General Procedure B using (3-methylphenyl)boronic acid (0.022 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (3-methylphenyl)boronic acid (83%, 82:1).

(2-Bromophenyl)boronic acid, **2.048** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

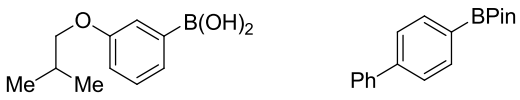
The reaction was carried out according to General Procedure B using (2-bromophenyl)boronic acid (0.032 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-bromophenyl)boronic acid (quant., >99:1).

(4-(Methylsulfonyl)phenyl)boronic acid, **2.049** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure B using (4-(methylsulfonyl)phenyl)boronic acid (0.032 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-(methylsulfonyl)phenyl)boronic acid (25%, >99:1).

(3-Isobutoxyphenyl)boronic acid, **2.050** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure B using (3-isobutoxyphenyl)boronic acid (0.031 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction

was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (3-isobutoxyphenyl)boronic acid (quant., 36:1).

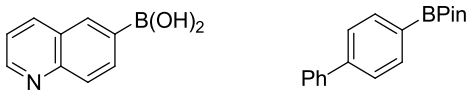
(2-Fluorophenyl)boronic acid, **2.051** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

The reaction was carried out according to General Procedure B using (2-fluorophenyl)boronic acid (0.022 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-fluorophenyl)boronic acid (quant., 43:1).

(3-Chlorophenyl)boronic acid, **2.052** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

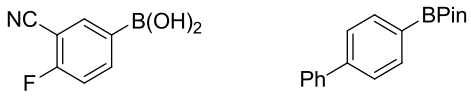
The reaction was carried out according to General Procedure B using (3-chlorophenyl) boronic acid (0.025 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (3-chlorophenyl)boronic acid (quant., 73:1).

Quinolin-6-ylboronic acid, **2.053** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure B using quinoline-6-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of quinoline-6-ylboronic acid (49%, >99:1).

(3-Cyano-4-fluorophenyl)boronic acid, **2.054** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

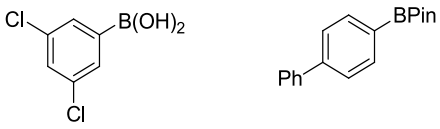


The reaction was carried out according to General Procedure B using (3-cyano-4-fluorophenyl)boronic acid (0.028 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (3-cyano-4-fluorophenyl)boronic acid (53%, >99:1).

(2-Methylphenyl)boronic acid, **2.055** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

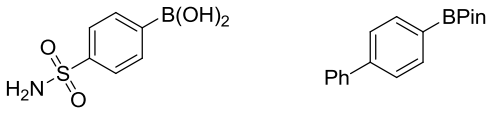
The reaction was carried out according to General Procedure B using (2-methylphenyl)boronic acid (0.022 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-methylphenyl)boronic acid (quant., >99:1).

(3,5-Dichlorophenyl)boronic acid, **2.056** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure B using (3,5-dichlorophenyl)boronic acid (0.030 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (3,5-dichlorophenyl)boronic acid (47%, 38:1).

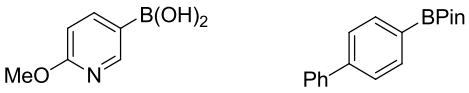
(4-Sulfamoylphenyl)boronic acid, **2.057** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure B using (4-sulfamoylphenyl)boronic acid (0.032 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40

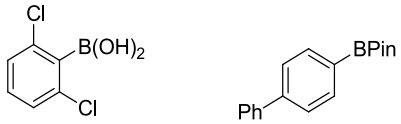
mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-sulfamoylphenyl)boronic acid (40%, >99:1).

(6-Methoxypyridin-3-yl)boronic acid, **2.058** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



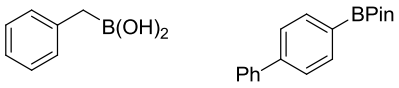
The reaction was carried out according to General Procedure B using (6-methoxypyridin-3-yl)boronic acid (0.025 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (6-methoxypyridin-3-yl)boronic acid (37%, 67:1).

(2,6-Dichlorophenyl)boronic acid, **2.059** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



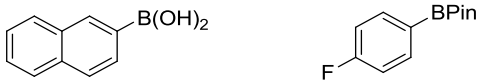
The reaction was carried out according to General Procedure B using (2,6-dichlorophenyl)boronic acid (0.030 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2,6-dichlorophenyl)boronic acid (5%, 44:1).

Benzylboronic acid, **2.060** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



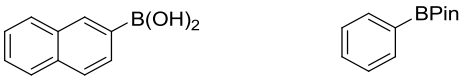
The reaction was carried out according to General Procedure B using benzylboronic acid (0.022 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of benzylboronic acid (9%, >99:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (4-fluorophenyl)boronic acid, pinacol ester, **2.026**



The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid, pinacol ester (0.036 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (quant., >99:1).

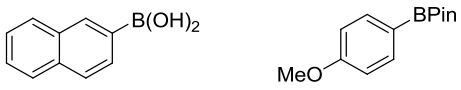
Naphthalen-2-ylboronic acid, **2.006** *vs.* phenylboronic acid, pinacol ester, **2.061**



The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), phenylboronic acid, pinacol ester (0.033 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in

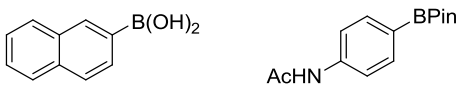
water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (79%, 75:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (4-methoxyphenyl)boronic acid, pinacol ester, **2.062**



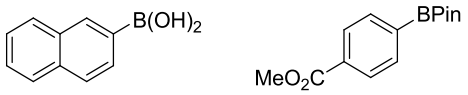
The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (4-methoxyphenyl)boronic acid, pinacol ester (0.037 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (90%, 85:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (4-acetamidophenyl)boronic acid, pinacol ester, **2.063**



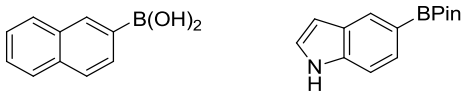
The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (4-acetamidophenyl)boronic acid, pinacol ester (0.042 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (87%, 13:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester, **2.064**



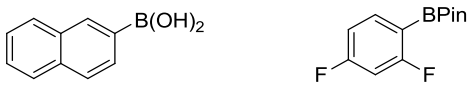
The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester (0.042 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (85%, 20:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (1*H*-indol-5-yl)boronic acid, pinacol ester, **2.065**



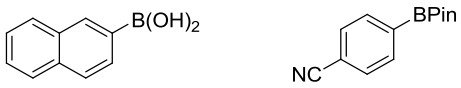
The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (1*H*-indol-5-yl)boronic acid, pinacol ester (0.039 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (quant., >99:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (2,4-difluorophenyl)boronic acid, pinacol ester, **2.066**



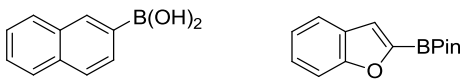
The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (2,4-difluorophenyl)boronic acid, pinacol ester (0.038 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (61%, 60:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (4-cyanophenyl)boronic acid, pinacol ester, **2.067**



The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (4-cyanophenyl)boronic acid, pinacol ester (0.037 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (85%, 14:1).

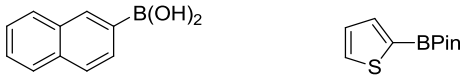
Naphthalen-2-ylboronic acid, **2.006** *vs.* (benzofuran-2-yl)boronic acid, pinacol ester, **2.068**



The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (benzofuran-2-yl)boronic acid, pinacol ester (0.042 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for

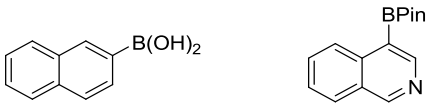
1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (56%, 55:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* thiophen-2-ylboronic acid, pinacol ester, **2.069**



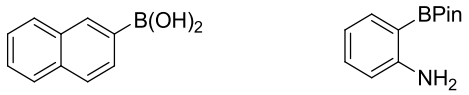
The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), thiophen-2-ylboronic acid, pinacol ester (0.034 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (66%, 65:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* isoquinolin-4-ylboronic acid, pinacol ester, **2.070**



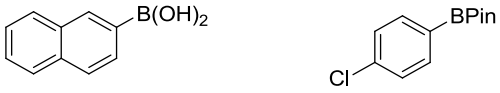
The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), isoquinolin-4-ylboronic acid, pinacol ester (0.041 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (quant., 50:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (2-aminophenyl)boronic acid, pinacol ester, **2.071**



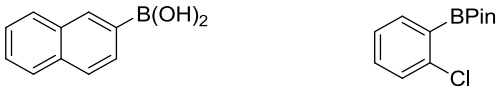
The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (2-aminophenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (76%, 75:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (4-chlorophenyl)boronic acid, pinacol ester, **2.072**



The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (4-chlorophenyl)boronic acid, pinacol ester (0.038 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (99%, 7:1).

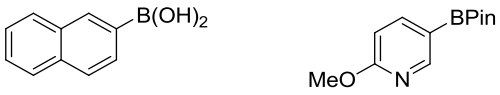
Naphthalen-2-ylboronic acid, **2.006** *vs.* (2-chlorophenyl)boronic acid, pinacol ester, **2.073**



The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (2-chlorophenyl)boronic acid, pinacol

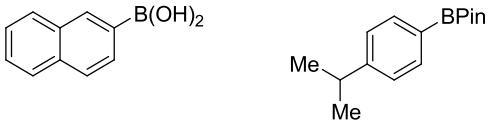
ester (0.038 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (quant., >99:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (6-methoxypyridin-3-yl)boronic acid, pinacol ester, **2.074**



The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (6-methoxypyridin-3-yl)boronic acid, pinacol ester (0.038 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (quant., 3:1).

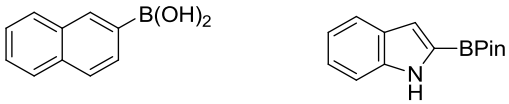
Naphthalen-2-ylboronic acid, **2.006** *vs.* (4-isopropylphenyl)boronic acid, pinacol ester, **2.075**



The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (4-isopropylphenyl)boronic acid, pinacol ester (0.039 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the

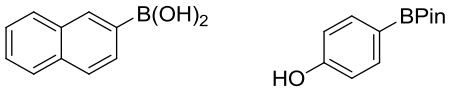
general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (quant., >99:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (1*H*-indol-2-yl)boronic acid, pinacol ester, **2.076**



The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (1*H*-indol-2-yl)boronic acid, pinacol ester (0.039 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (38%, >99:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (4-hydroxyphenyl)boronic acid, pinacol ester, **2.077**



The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (4-hydroxyphenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (48%, >99:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (3-methylphenyl)boronic acid, pinacol ester, **2.078**

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (3-methylphenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (93%, >99:1).

Naphthalen-2-ylboronic acid, **2.006** *vs.* (3-cyanophenyl)boronic acid, pinacol ester, **2.079**

The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (3-cyanophenyl)boronic acid, pinacol ester (0.037 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid (14%, >99:1).

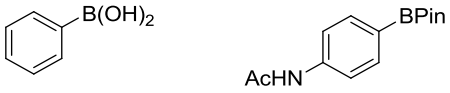
Phenylboronic acid, **2.016** *vs.* (4-hydroxyphenyl)boronic acid, pinacol ester, **2.077**

The reaction was carried out according to General Procedure B using phenylboronic acid (0.020 g, 0.16 mmol, 1 equiv), (4-hydroxyphenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of phenylboronic acid (98%, >99:1).

Phenylboronic acid, **2.016** *vs.* (2-aminophenyl)boronic acid, pinacol ester, **2.071**

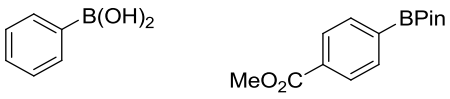
The reaction was carried out according to General Procedure B using phenylboronic acid (0.020 g, 0.16 mmol, 1 equiv), (2-aminophenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of phenylboronic acid (99%, >99:1).

Phenylboronic acid, **2.016** *vs.* (4-acetamidophenyl)boronic acid, pinacol ester, **2.063**



The reaction was carried out according to General Procedure B using phenylboronic acid (0.020 g, 0.16 mmol, 1 equiv), (4-acetamidophenyl)boronic acid, pinacol ester (0.042 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of phenylboronic acid (quant., 47:1).

Phenylboronic acid, **2.016** *vs.* (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester, **2.064**



The reaction was carried out according to General Procedure B using phenylboronic acid (0.020 g, 0.16 mmol, 1 equiv), (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester (0.042 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of phenylboronic acid (quant., >99:1).

Phenylboronic acid, **2.016** *vs.* (4-fluorophenyl)boronic acid, pinacol ester, **2.026**

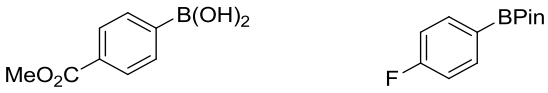
The reaction was carried out according to General Procedure B using phenylboronic acid (0.020 g, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid, pinacol ester (0.036 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of phenylboronic acid (93%, >99:1).

Phenylboronic acid, **2.016** *vs.* (2-chlorophenyl)boronic acid, pinacol ester, **2.073**

The reaction was carried out according to General Procedure B using phenylboronic acid (0.020 g, 0.16 mmol, 1 equiv), (2-chlorophenyl)boronic acid, pinacol ester (0.038 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv),

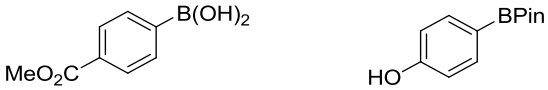
CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of phenylboronic acid (92%, >99:1).

(4-(Methoxycarbonyl)phenyl)boronic acid, **2.037** *vs.* (4-fluorophenyl)boronic acid, pinacol ester, **2.026**



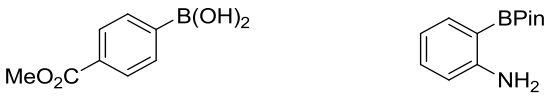
The reaction was carried out according to General Procedure B using (4-(methoxycarbonyl)phenyl)boronic acid (0.029 g, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid, pinacol ester (0.036 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-(methoxycarbonyl)phenyl)boronic acid (quant., >99:1).

(4-(Methoxycarbonyl)phenyl)boronic acid, **2.037** *vs.* (4-hydroxyphenyl)boronic acid, pinacol ester, **2.077**



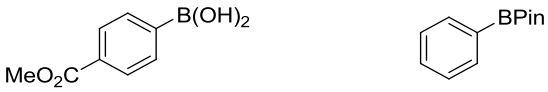
The reaction was carried out according to General Procedure B using (4-(methoxycarbonyl)phenyl)boronic acid (0.029 g, 0.16 mmol, 1 equiv), (4-hydroxyphenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-(methoxycarbonyl)phenyl)boronic acid (44%, >99:1).

(4-(Methoxycarbonyl)phenyl)boronic acid, **2.037** *vs.* (2-aminophenyl)boronic acid, pinacol ester, **2.071**



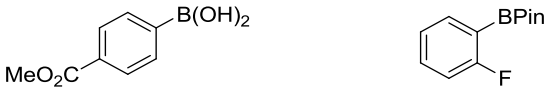
The reaction was carried out according to General Procedure B using (4-(methoxycarbonyl)phenyl)boronic acid (0.029 g, 0.16 mmol, 1 equiv), (2-aminophenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-(methoxycarbonyl)phenyl)boronic acid (quant., >99:1).

(4-(Methoxycarbonyl)phenyl)boronic acid, **2.037** *vs.* phenylboronic acid, pinacol ester, **2.061**



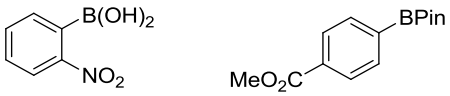
The reaction was carried out according to General Procedure B using (4-(methoxycarbonyl)phenyl)boronic acid (0.029 g, 0.16 mmol, 1 equiv), phenylboronic acid, pinacol ester (0.033 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-(methoxycarbonyl)phenyl)boronic acid (quant., >99:1).

(4-(Methoxycarbonyl)phenyl)boronic acid, **2.037** *vs.* (2-fluorophenyl)boronic acid, pinacol ester, **2.080**



The reaction was carried out according to General Procedure B using (4-(methoxycarbonyl)phenyl)boronic acid (0.029 g, 0.16 mmol, 1 equiv), (2-fluorophenyl)boronic acid, pinacol ester (0.036 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-(methoxycarbonyl)phenyl)boronic acid (65%, >99:1).

(2-Nitrophenyl)boronic acid, **2.040** *vs.* (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester, **2.064**



The reaction was carried out according to General Procedure B using (2-nitrophenyl)boronic acid (0.027 g, 0.16 mmol, 1 equiv), (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester (0.042 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-nitrophenyl)boronic acid (quant., 21:1).

(2-Nitrophenyl)boronic acid, **2.040** *vs.* (2-aminophenyl)boronic acid, pinacol ester, **2.071**

The reaction was carried out according to General Procedure B using (2-nitrophenyl)boronic acid (0.027 g, 0.16 mmol, 1 equiv), (2-aminophenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred

at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-nitrophenyl)boronic acid (quant., >99:1).

(2-Nitrophenyl)boronic acid, **2.040** *vs.* phenylboronic acid, pinacol ester, **2.061**

The reaction was carried out according to General Procedure B using (2-nitrophenyl)boronic acid (0.027 g, 0.16 mmol, 1 equiv), phenylboronic acid, pinacol ester (0.033 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-nitrophenyl)boronic acid (quant., >99:1).

(2-Nitrophenyl)boronic acid, **2.040** *vs.* (2-fluorophenyl)boronic acid, pinacol ester, **2.080**

The reaction was carried out according to General Procedure B using (2-nitrophenyl)boronic acid (0.027 g, 0.16 mmol, 1 equiv), (2-fluorophenyl)boronic acid, pinacol ester (0.036 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-nitrophenyl)boronic acid (quant., 8:1).

(2-Nitrophenyl)boronic acid, **2.040** *vs.* (2-methoxyphenyl)boronic acid, pinacol ester, **2.062**

The reaction was carried out according to General Procedure B using (2-nitrophenyl)boronic acid (0.027 g, 0.16 mmol, 1 equiv), (2-methoxyphenyl)boronic acid, pinacol ester (0.037 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-nitrophenyl)boronic acid (85%, >99:1).

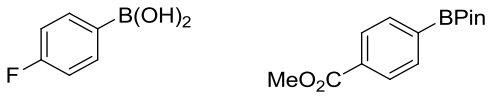
(2-Nitrophenyl)boronic acid, **2.040** *vs.* (4-hydroxyphenyl)boronic acid, pinacol ester, **2.077**

The reaction was carried out according to General Procedure B using (2-nitrophenyl)boronic acid (0.027 g, 0.16 mmol, 1 equiv), (4-hydroxyphenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-nitrophenyl)boronic acid (quant., >99:1).

(4-Fluorophenyl)boronic acid, **2.025** *vs.* (2-fluorophenyl)boronic acid, pinacol ester, **2.080**

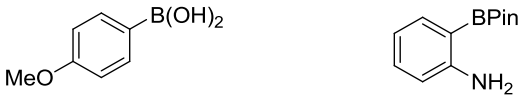
The reaction was carried out according to General Procedure B using (4-fluorophenyl)boronic acid (0.022 g, 0.16 mmol, 1 equiv), (2-fluorophenyl)boronic acid, pinacol ester (0.036 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-fluorophenyl)boronic acid (quant., 11:1).

(4-Fluorophenyl)boronic acid, **2.025** *vs.* (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester, **2.064**



The reaction was carried out according to General Procedure B using (4-fluorophenyl)boronic acid (0.022 g, 0.16 mmol, 1 equiv), (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester (0.042 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-fluorophenyl)boronic acid (97%, >99:1).

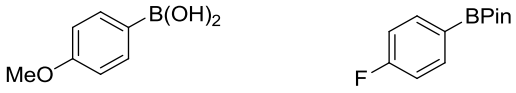
(4-Methoxyphenyl)boronic acid, **2.036** *vs.* (2-aminophenyl)boronic acid, pinacol ester, **2.071**



The reaction was carried out according to General Procedure B using (4-methoxyphenyl)boronic acid (0.037 g, 0.16 mmol, 1 equiv), (2-aminophenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred

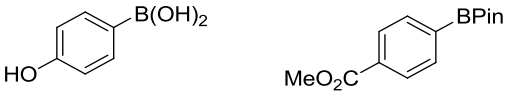
at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-methoxyphenyl)boronic acid (quant., >99:1).

(4-Methoxyphenyl)boronic acid, **2.036** *vs.* (4-fluorophenyl)boronic acid, pinacol ester, **2.026**



The reaction was carried out according to General Procedure B using (4-methoxyphenyl)boronic acid (0.037 g, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid, pinacol ester (0.036 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-methoxyphenyl)boronic acid (quant., >99:1).

(4-Hydroxyphenyl)boronic acid, **2.083** *vs.* (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester, **2.064**



The reaction was carried out according to General Procedure B using (4-hydroxyphenyl)boronic acid (0.033 g, 0.16 mmol, 1 equiv), (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester (0.042 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-hydoxyphenyl)boronic acid (quant., 93:1).

(2-Fluorophenyl)boronic acid, **2.052** *vs.* (4-hydroxyphenyl)boronic acid, pinacol ester, **2.077**

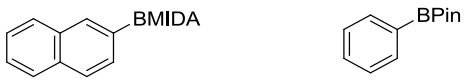
The reaction was carried out according to General Procedure B using (2-fluorophenyl)boronic acid (0.022 g, 0.16 mmol, 1 equiv), (4-hydroxyphenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.28 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-fluorophenyl)boronic acid (70%, >99:1).

(2-Chlorophenyl)boronic acid, **2.045** *vs.* phenylboronic acid, pinacol ester, **2.061**

The reaction was carried out according to General Procedure B using (2-chlorophenyl)boronic acid (0.025 g, 0.16 mmol, 1 equiv), phenylboronic acid, pinacol ester (0.033 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-chlorophenyl)boronic acid (49%, >99:1).

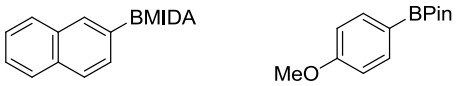
5.7 Chemoselective oxidation - BMIDA *vs.* BPin (Schemes 2.19, 2.20, 2.21, 2.22, and 2.29)

Naphthalen-2-ylboronic acid, MIDA ester, **2.081** *vs.* phenylboronic acid, pinacol ester, **2.061**



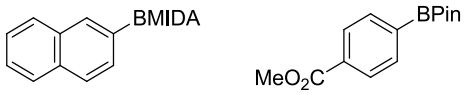
The reaction was carried out according to General Procedure H using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), phenylboronic acid, pinacol ester (0.033 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was then added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (56%, >99:1).

Naphthalen-2-ylboronic acid, MIDA ester, **2.081** *vs.* (4-methoxyphenyl)boronic acid, pinacol ester, **2.062**



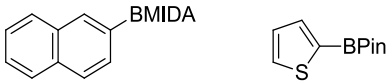
The reaction was carried out according to General Procedure H using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), (4-methoxyphenyl)boronic acid, pinacol ester (0.037 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (82%, >99:1).

Naphthalen-2-ylboronic acid, MIDA ester, **2.081** *vs.* (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester, **2.064**



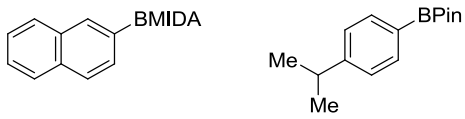
The reaction was carried out according to General Procedure H using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester (0.042 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (85%, 4:1).

Naphthalen-2-ylboronic acid, MIDA ester, **2.081** *vs.* thiophen-2-ylboronic acid, pinacol ester, **2.069**



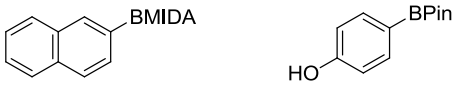
The reaction was carried out according to General Procedure H using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), thiophen-2-ylboronic acid, pinacol ester (0.034 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (82%, 6:1).

Naphthalen-2-ylboronic acid, MIDA ester, **2.081** *vs.* (4-isopropylphenyl)boronic acid, pinacol ester, **2.075**



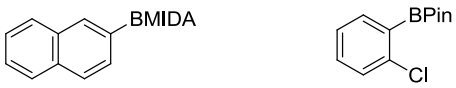
The reaction was carried out according to General Procedure H using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), (4-isopropylphenyl)boronic acid, pinacol ester (0.039 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (62%, >99:1).

Naphthalen-2-ylboronic acid, MIDA ester, **2.081** *vs.* (4-hydroxyphenyl)boronic acid, pinacol ester, **2.077**



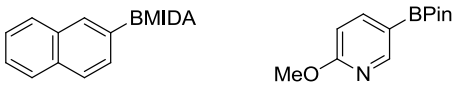
The reaction was carried out according to General Procedure H using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), (4-hydroxyphenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (68%, >99:1).

Naphthalen-2-ylboronic acid, MIDA ester, **2.081** *vs.* (2-chlorophenyl)boronic acid, pinacol ester, **2.073**



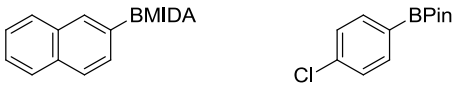
The reaction was carried out according to General Procedure H using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), (2-chlorophenyl)boronic acid, pinacol ester (0.038 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (87%, >99:1).

Naphthalen-2-ylboronic acid, MIDA ester, **2.081** *vs.* (6-methoxypyridin-3-yl)boronic acid, pinacol ester, **2.074**



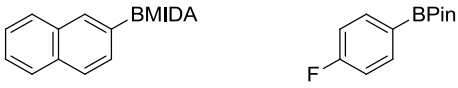
The reaction was carried out according to General Procedure H using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), (6-methoxypyridin-3-yl)boronic acid, pinacol ester (0.038 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (69%, 9:1).

Naphthalen-2-ylboronic acid, MIDA ester, **2.081** *vs.* (4-chlorophenyl)boronic acid, pinacol ester, **2.072**



The reaction was carried out according to General Procedure H using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), (4-chlorophenyl)boronic acid, pinacol ester (0.038 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (quant., 7:1).

Naphthalen-2-ylboronic acid, MIDA ester, **2.081** *vs.* (4-fluorophenyl)boronic acid, pinacol ester, **2.026**



The reaction was carried out according to General Procedure H using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid, pinacol ester (0.036 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (quant., >99:1).

Naphthalen-2-ylboronic acid, MIDA ester, **2.081** *vs.* benzo[*b*]thiophen-2-ylboronic acid, pinacol ester, **2.083**

The reaction was carried out according to General Procedure H using naphthalen-2-ylboronic acid, MIDA ester (0.045 g, 0.16 mmol, 1 equiv), benzo[*b*]thiophen-2-ylboronic acid, pinacol ester (0.042 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of naphthalen-2-ylboronic acid, MIDA ester (58%, 3:1).

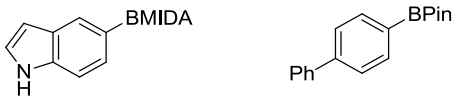
(4-Fluorophenyl)boronic acid, MIDA ester, **2.084** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

The reaction was carried out according to General Procedure H using (4-fluorophenyl)boronic acid, MIDA ester (0.040 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-fluorophenyl)boronic acid, MIDA ester (72%, >99:1).

Phenylboronic acid, MIDA ester, **2.085** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

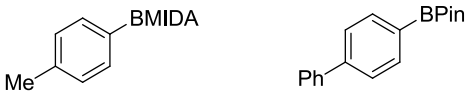
The reaction was carried out according to General Procedure H using phenylboronic acid, MIDA ester (0.037 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of phenylboronic acid, MIDA ester (58%, 58:1).

(1*H*-Indol-5-yl)boronic acid, MIDA ester, **2.086** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



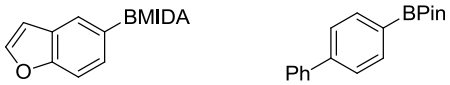
The reaction was carried out according to General Procedure H using (1*H*-indol-5-yl)boronic acid, MIDA ester (0.044 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (1*H*-indol-5-yl)boronic acid, MIDA ester (55%, >99:1).

(4-Methylphenyl)boronic acid, MIDA ester, **2.087** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



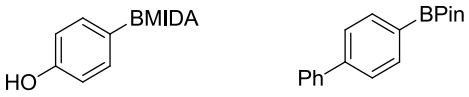
The reaction was carried out according to General Procedure H using (4-methylphenyl)boronic acid, MIDA ester (0.040 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-methylphenyl)boronic acid, MIDA ester (84%, 80:1).

Benzofuran-5-ylboronic acid, MIDA ester, **2.088** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure H using benzofuran-5-ylboronic acid, MIDA ester (0.044 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of benzofuran-5-ylboronic acid, MIDA ester (79%, 19:1).

(4-Hydroxyphenyl)boronic acid, MIDA ester, **2.089** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure H using (4-hydroxyphenyl)boronic acid, MIDA ester (0.040 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-hydroxyphenyl)boronic acid, MIDA ester (50%, 96:1).

(2-Bromophenyl)boronic acid, MIDA ester, **2.090** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

The reaction was carried out according to General Procedure H using (2-bromophenyl)boronic acid, MIDA ester (0.050 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-bromophenyl)boronic acid, MIDA ester (quant., >99:1).

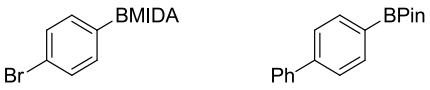
(3-Isobutoxyphenyl)boronic acid, MIDA ester, **2.091** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

The reaction was carried out according to General Procedure H using (3-isobutoxyphenyl)boronic acid, MIDA ester (0.031 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (3-isobutoxyphenyl)boronic acid, MIDA ester (79%, 25:1).

(2-Chlorophenyl)boronic acid, MIDA ester, **2.092** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

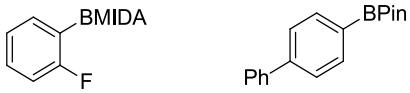
The reaction was carried out according to General Procedure H using (2-chlorophenyl)boronic acid, MIDA ester (0.043 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-chlorophenyl)boronic acid, MIDA ester (58%, 51:1).

(4-Bromophenyl)boronic acid, MIDA ester, **2.093** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure H using (4-bromophenyl)boronic acid, MIDA ester (0.050 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-bromophenyl)boronic acid, MIDA ester (17%, 15:1).

(2-Fluorophenyl)boronic acid, MIDA ester, **2.094** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

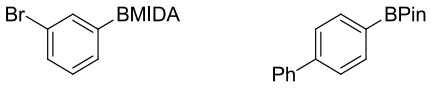


The reaction was carried out according to General Procedure H using (2-fluorophenyl)boronic acid, MIDA ester (0.040 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-fluorophenyl)boronic acid, MIDA ester (quant., >99:1).

(4-(Methoxycarbonyl)phenyl)boronic acid, MIDA ester, **2.095** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

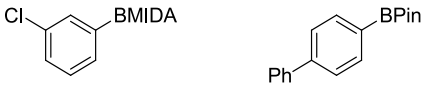
The reaction was carried out according to General Procedure H using (4-(methoxycarbonyl)phenyl)boronic acid, MIDA ester (0.047 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-(methoxycarbonyl)phenyl)boronic acid, MIDA ester (quant., >99:1).

(3-Bromophenyl)boronic acid, MIDA ester, **2.100** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**



The reaction was carried out according to General Procedure H using (3-bromophenyl)boronic acid, MIDA ester (0.043 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.050 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (3-bromophenyl)boronic acid, MIDA ester (quant., 36:1).

(3-Chlorophenyl)boronic acid, MIDA ester, **2.097** *vs.* [1,1'-biphenyl]-4-ylboronic acid, pinacol ester, **2.009**

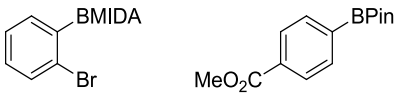


The reaction was carried out according to General Procedure H using (3-chlorophenyl)boronic acid, MIDA ester (0.043 g, 0.16 mmol, 1 equiv), [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.045 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (3-chlorophenyl)boronic acid, MIDA ester (67%, 23:1).

(2-Bromophenyl)boronic acid, MIDA ester, **2.090** *vs.* (4-methoxyphenyl)boronic acid, pinacol ester, **2.062**

The reaction was carried out according to General Procedure H using (2-bromophenyl)boronic acid, MIDA ester (0.050 g, 0.16 mmol, 1 equiv), (4-methoxyphenyl)boronic acid, pinacol ester (0.037 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-bromophenyl)boronic acid, MIDA ester (37%, >99:1).

(2-Bromophenyl)boronic acid, MIDA ester, **2.090** *vs.* (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester, **2.064**



The reaction was carried out according to General Procedure H using (2-bromophenyl)boronic acid, MIDA ester (0.050 g, 0.16 mmol, 1 equiv), (4-(methoxycarbonyl)phenyl)boronic acid, pinacol ester (0.042 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-bromophenyl)boronic acid, MIDA ester (51%, 6:1).

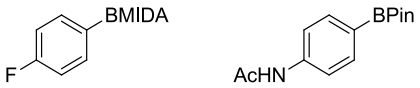
(2-Bromophenyl)boronic acid, MIDA ester, **2.090** *vs.* (2-chlorophenyl)boronic acid, pinacol ester, **2.073**

The reaction was carried out according to General Procedure H using (2-bromophenyl)boronic acid, MIDA ester (0.050 g, 0.16 mmol, 1 equiv), (2-chlorophenyl)boronic acid, pinacol ester (0.038 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-bromophenyl)boronic acid, MIDA ester (22%, >99:1).

(2-Bromophenyl)boronic acid, MIDA ester, **2.090** *vs.* (2-aminophenyl)boronic acid, pinacol ester, **2.071**

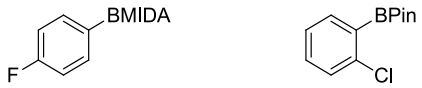
The reaction was carried out according to General Procedure H using (2-bromophenyl)boronic acid, MIDA ester (0.050 g, 0.16 mmol, 1 equiv), (2-aminophenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-bromophenyl)boronic acid, MIDA ester (21%, >99:1).

(4-Fluorophenyl)boronic acid, MIDA ester, **2.084** *vs.* (4-acetamidophenyl)boronic acid, pinacol ester, **2.063**



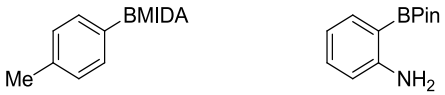
The reaction was carried out according to General Procedure H using (4-fluorophenyl)boronic acid, MIDA ester (0.040 g, 0.16 mmol, 1 equiv), (4-acetamidophenyl)boronic acid, pinacol ester (0.042 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-fluorophenyl)boronic acid, MIDA ester (58%, 6:1).

(4-Fluorophenyl)boronic acid, MIDA ester, **2.084** *vs.* (2-chlorophenyl)boronic acid, pinacol ester, **2.073**



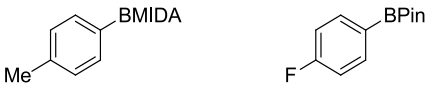
The reaction was carried out according to General Procedure H using (4-fluorophenyl)boronic acid, MIDA ester (0.040 g, 0.16 mmol, 1 equiv), (2-chlorophenyl)boronic acid, pinacol ester (0.038 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-fluorophenyl)boronic acid, MIDA ester (51%, 9:1).

(4-Methylphenyl)boronic acid, MIDA ester, **2.087** *vs.* (2-aminophenyl)boronic acid, pinacol ester, **2.071**



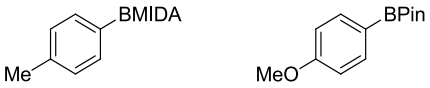
The reaction was carried out according to General Procedure H using (4-methylphenyl)boronic acid, MIDA ester (0.040 g, 0.16 mmol, 1 equiv), (2-aminophenyl)boronic acid, pinacol ester (0.035 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-methylphenyl)boronic acid, MIDA ester (17%, >99:1).

(4-Methylphenyl)boronic acid, MIDA ester, **2.087** *vs.* (4-fluorophenyl)boronic acid, pinacol ester, **2.026**



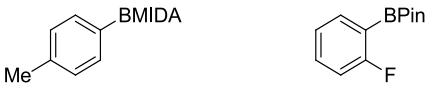
The reaction was carried out according to General Procedure H using (4-methylphenyl)boronic acid, MIDA ester (0.040 g, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid, pinacol ester (0.036 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-methylphenyl)boronic acid, MIDA ester (18%, >99:1).

(4-Methylphenyl)boronic acid, MIDA ester, **2.087** *vs.* (4-methoxyphenyl)boronic acid, pinacol ester, **2.062**



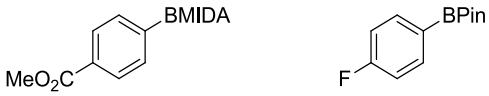
The reaction was carried out according to General Procedure H using (4-methylphenyl)boronic acid, MIDA ester (0.040 g, 0.16 mmol, 1 equiv), (4-methoxyphenyl)boronic acid, pinacol ester (0.037 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-methylphenyl)boronic acid, MIDA ester (38%, >99:1).

(4-Methylphenyl)boronic acid, MIDA ester, **2.087** *vs.* (2-fluorophenyl)boronic acid, pinacol ester, **2.080**



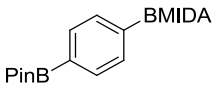
The reaction was carried out according to General Procedure H using (4-methylphenyl)boronic acid, MIDA ester (0.040 g, 0.16 mmol, 1 equiv), (2-fluorophenyl)boronic acid, pinacol ester (0.036 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-methylphenyl)boronic acid, MIDA ester (31%, 9:1).

(4-(Methoxycarbonyl)phenyl)boronic acid, MIDA ester, **2.095** *vs.* (4-fluorophenyl)boronic acid, pinacol ester, **2.026**



The reaction was carried out according to General Procedure H using (4-(methoxycarbonyl)phenyl)boronic acid, MIDA ester (0.042 g, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid, pinacol ester (0.040 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-(methoxycarbonyl)phenyl)boronic acid, MIDA ester (quant., >99:1).

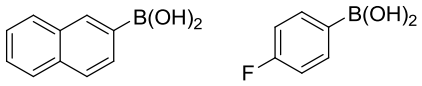
Benzene-1-boronic acid, pinacol ester-4-boronic acid, MIDA ester, **2.098** (Scheme 2.24)



The reaction was carried out according to General Procedure H using benzene-1-boronic acid, pinacol ester-4-boronic acid, MIDA ester, (0.057 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and water (15 µL, 0.80 mmol, 5 equiv). The reaction was stirred at 80 °C for 15 min. Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) was added as a slurry in water (1.60 mL) and CPME (0.25 mL) and the reaction was stirred at 70 °C for 1 h. Conversion to products was analysed by HPLC as outlined in the general procedure indicating unselective oxidation of benzene-1-boronic acid, pinacol ester-4-boronic acid, MIDA ester (3%).

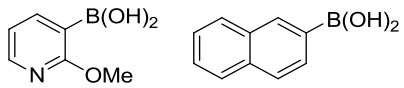
5.8 Chemoselective oxidation - boronic acid *vs.* boronic acid (Table 2.21 and Schemes 2.27 and 2.30)

Naphthalen-2-ylboronic acid, **2.006** *vs.* (4-fluorophenyl)boronic acid, **2.025**



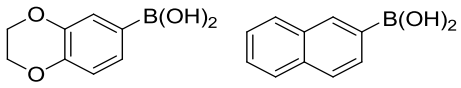
The reaction was carried out according to General Procedure B using naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), (4-fluorophenyl)boronic acid (0.022 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 30 min. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (4-fluorophenyl)boronic acid (95%, 9:1).

(2-Methoxypyridin-3-yl)boronic acid, **2.044** *vs.* naphthalen-2-ylboronic acid, **2.006**



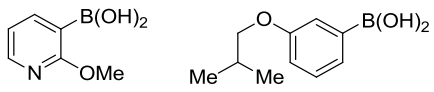
The reaction was carried out according to General Procedure B using (2-methoxypyridin-3-yl)boronic acid (0.024 g, 0.16 mmol, 1 equiv), naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 30 min. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-methoxypyridin-3-yl)boronic acid (62%, 3:1).

(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid, **2.046** *vs.* naphthalen-2-ylboronic acid, **2.006**



The reaction was carried out according to General Procedure B using (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid (0.029 g, 0.16 mmol, 1 equiv), naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 30 min. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid (86%, 4:1).

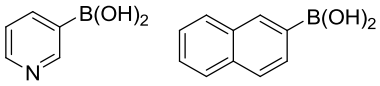
(2-Methoxypyridin-3-yl)boronic acid, **2.044** *vs.* (3-isobutoxyphenyl)boronic acid, **2.050**



The reaction was carried out according to General Procedure B using (2-methoxypyridin-3-yl)boronic acid (0.024 g, 0.16 mmol, 1 equiv), (3-isobutoxyphenyl)boronic acid (0.031 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction

was stirred at 70 °C for 30 min. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-methoxypyridin-3-yl)boronic acid (71%, 3:1).

Pyridin-3-ylboronic acid, **2.109** *vs.* naphthalen-2-ylboronic acid, **2.006**



The reaction was carried out according to General Procedure B using pyridin-3-ylboronic acid (0.020 g, 0.16 mmol, 1 equiv), naphthalen-2-ylboronic acid (0.028 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 g, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 30 min. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of pyridin-3-ylboronic acid (85%, 2:1).

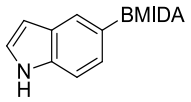
(2-Methoxypyridin-3-yl)boronic acid, **2.044** *vs.* (2-bromophenyl)boronic acid, **2.048**

The reaction was carried out according to General Procedure B using (2-methoxypyridin-3-yl)boronic acid (0.024 g, 0.16 mmol, 1 equiv), (2-bromophenyl)boronic acid (0.032 g, 0.16 mmol, 1 equiv), tripotassium phosphate (0.10 g, 0.48 mmol, 3 equiv), CPME (0.63 mL, 0.25 M), and Oxone® (0.13 mg, 0.40 mmol, 2.5 equiv) as a slurry in water (1.60 mL) and CPME (0.25 mL). The reaction was stirred at 70 °C for 30 min. Conversion to products was analysed by HPLC as outlined in the general procedure indicating selective oxidation of (2-methoxypyridin-3-yl)boronic acid (42%, 2:1).

5.9 Compound characterisation

5.9.1 Characterisation data for BMIDA intermediates

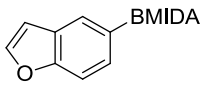
(1*H*-Indol-5-yl)boronic acid, MIDA ester, **2.086**



$C_{13}H_{13}BN_2O_4$

Prepared according to General Procedure I using (1*H*-indol-5-yl)boronic acid (2.00 g, 12.40 mmol, 1 equiv), *N*-methyliminodiacetic acid (1.90 g, 13.02 mmol, 1.05 equiv), and DMF (50 mL, 0.15 M) to afford the desired product as a white solid (3.30 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1 H), 7.62 (s, 1 H), 7.37 (d, J = 8.2 Hz, 1 H), 7.30 (t, J = 2.7 Hz, 1 H), 7.14 (d, J = 8.2 Hz, 1 H), 6.41 (s, 1 H), 4.30 (d, J = 17.2 Hz, 2 H), 4.08 (d, J = 17.2 Hz, 2 H), 2.45 (s, 3 H); ^{11}B NMR (128 MHz, $CDCl_3$) δ 12.52; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 136.5, 127.5, 124.9, 124.5, 110.8, 101.1, 61.6, 47.5, three coincident peaks and carbon bearing boron not observed; υ_{max} (solid)/cm^{-1} 3401, 3008, 2962, 1766, 1744, 1578, 1455, 1340, 1245, 1236; HRMS *m/z*: $[M+H]^+$ calcd for $C_{13}H_{13}BN_2O_4$ 273.1041; found 273.1045.

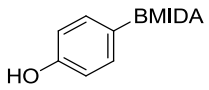
(Benzofuran-5-yl)boronic acid, MIDA ester, **2.088**



$C_{13}H_{12}BNO_5$

Prepared according to General Procedure I using (benzofuran-5-yl)boronic acid (0.20 g, 0.74 mmol, 1 equiv), *N*-methyliminodiacetic acid (0.11 g, 0.77 mmol, 1.05 equiv), and DMF (2 mL, 0.36 M) to afford desired product as a white solid (0.28 g, 85%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.96 (d, J = 2.1 Hz, 1 H), 7.72 (s, 1 H), 7.58–7.55 (m, 1 H), 7.37 (dd, J = 8.2, 1.2 Hz, 1 H), 6.96 (dd, J = 2.1, 0.9 Hz, 1 H), 4.34 (d, J = 17.4 Hz, 2 H), 4.12 (d, J = 17.1 Hz, 2 H), 2.48 (s, 3 H); ^{11}B NMR (128 MHz, d_6-DMSO) δ 11.72; ^{13}C NMR (101 MHz, d_6-DMSO) δ 169.4, 155.1, 145.6, 128.5, 126.9, 125.6, 110.5, 106.7, 61.7, 47.6, two coincident peaks and carbon bearing boron not observed; υ_{max} (solid)/cm^{-1} 3145, 3112, 2967, 1760, 1738, 1340, 1260; HRMS *m/z*: $[M+H]^+$ calcd for $C_{13}H_{13}BNO_5$ 274.0881; found 274.0886.

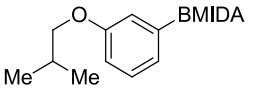
4-Hydroxyphenylboronic acid, MIDA ester, **2.089**



$C_{11}H_{12}BNO_5$

Prepared according to General Procedure I using 4-hydroxyphenylboronic acid (1.75 g, 12.70 mmol, 1 equiv), *N*-methyliminodiacetic acid (1.89 g, 12.80 mmol, 1.01 equiv), and DMF (160 mL, 0.04 M) to afford the desired product as a white solid (3.00 g, 95%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.39 (br. s, 1 H), 7.21 (d, J = 8.3 Hz, 2 H), 6.74 (d, J = 8.6 Hz, 2 H), 4.27 (d, J = 17.2 Hz, 2 H), 4.04 (d, J = 17.2 Hz, 2 H), 2.46 (s, 3 H); ^{11}B NMR (128 MHz, d_6-DMSO) δ 12.20; ^{13}C NMR (101 MHz, d_6-DMSO) δ 169.4, 158.1, 133.6, 114.7, 61.5, 47.4, four coincident peaks and carbon bearing boron not observed; υ_{max} (solid)/cm^{-1} 3361, 3010, 1740, 1610, 1584; HRMS *m/z*: [M-H]$^-$ calcd for $C_{11}H_{11}BNO_5$ 248.0736; found 248.0730.

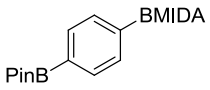
(3-Isobutoxyphenyl)boronic acid, MIDA ester, **2.091**



$C_{15}H_{20}BNO_5$

Prepared according to General Procedure I using (3-isobutoxyphenyl)boronic acid (0.60 g, 3.10 mmol, 1 equiv), *N*-methyliminodiacetic acid (0.48 g, 3.24 mmol, 1.05 equiv), and DMF (30 mL, 0.07 M) to afford the desired product as a white solid (0.90 g, 95%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.26 (t, J = 7.7 Hz, 1 H), 6.99–6.92 (m, 2 H), 6.91 (dd, J = 8.1, 2.6 Hz, 1 H), 4.31 (d, J = 17.2 Hz, 2 H), 4.10 (d, J = 17.2 Hz, 2 H), 3.73 (d, J = 6.5 Hz, 2 H), 2.51 (s, 3 H), 2.02–1.98 (m, 1 H), 0.98 (d, J = 6.7 Hz, 6 H); ^{11}B NMR (128 MHz, d_6-DMSO) δ 11.06; ^{13}C NMR (101 MHz, d_6-DMSO) δ 169.4, 158.3, 128.8, 124.4, 118.2, 114.7, 73.4, 61.8, 47.5, 27.8, 19.1, three coincident peaks and carbon bearing boron not observed; υ_{max} (solid)/cm^{-1} 3004, 2956, 2872, 1768, 1748, 1577, 1457, 1424, 1286, 1253; HRMS *m/z*: [M+H]$^+$ calcd for $C_{15}H_{21}BNO_5$ 305.1507; found 305.1513.

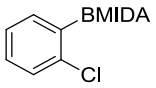
Benzene-1-boronic acid, pinacol ester-4-boronic acid, MIDA ester, **2.098** (Scheme 2.23)



$C_{17}H_{23}B_2NO_6$

(4-Bromophenyl)boronic acid, MIDA ester (0.08 g, 0.25 mmol, 1 equiv), bis(pinacolato)diboron (0.09 g, 0.36 mmol, 1.4 equiv), Pd(dppf)Cl_2·CH_2Cl_2 (0.01 g, 0.01 mmol, 5 mol%), and potassium acetate (0.08 g, 0.83 mmol, 3.3 equiv) were weighed out into an oven-dried 5 mL microwave vial. The vial was capped and purged with nitrogen. DMSO (2 mL, 0.13 M) was added *via* syringe and the reaction was heated to 75 °C in a sand bath with stirring for 24 h. The reaction was allowed to cool to ambient temperature and was vented, decapped, and poured into EtOAc (50 mL) after which water (40 mL) was added. The organic phase was separated and washed with water (2 x 40 mL). The aqueous layer was extracted with further EtOAc (25 mL) and the organic layers were combined, dried by passing through a hydrophobic frit, and concentrated under reduced pressure. Purification by normal phase column chromatography on silica, eluting with 10–70% acetone/Et_2O, afforded the *title compound* as a white crystalline solid (0.08 g, 85%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.66 (d, J = 8.0 Hz, 2 H), 7.45 (d, J = 8.0 Hz, 2 H), 4.34 (d, J = 17.2 Hz, 2 H), 4.10 (d, J = 17.2 Hz, 2 H), 2.46 (s, 3 H), 1.29 (s, 12 H); ^{11}B NMR (128 MHz, d_6-DMSO) δ 32.46, 11.78; ^{13}C NMR (101 MHz, d_6-DMSO) δ 169.3, 133.6, 131.8, 83.6, 61.8, 47.6, 24.7, eight coincident peaks and two carbons bearing boron not observed; υ_{max} (solid)/cm^{-1} 2978, 1761, 1748, 1517, 1457, 1362; HRMS *m/z*: [M-H]$^-$ calcd for $C_{17}H_{22}B_2NO_6$ 358.1639; found 358.1634.

(2-Chlorophenyl)boronic acid, MIDA ester, **2.092**

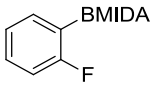


$C_{11}H_{11}BClO_4N$

Prepared according to General Procedure I using (2-fluorophenyl)boronic acid (0.25 g, 1.79 mmol, 1 equiv), *N*-methyliminodiacetic acid (0.24 g, 1.79 mmol, 1 equiv), and DMF (2 mL, 0.47 M) to afford the desired product as a white solid (0.37 g, 87%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.63–7.56 (m, 2 H), 7.43–7.31 (m, 2 H),

4.42 (d, *J* = 17.4 Hz, 2 H), 4.16 (d, *J* = 17.4 Hz, 2 H), 2.66 (s, 3 H); ^{13}C NMR (101 MHz, *d*$_6$-DMSO) δ 169.1, 137.7, 135.8, 131.1, 129.7, 126.5, 63.6, 48.1, two coincident peaks and carbon bearing boron not observed; υ_{max} (solid)/cm^{-1} 3070, 3018, 2977, 1765, 1740, 1342, 1309, 1279, 1200, 1126, 1020, 1002, 964, 854.

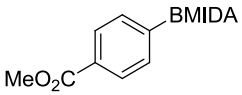
(2-Fluorophenyl)boronic acid, MIDA ester, **2.094**



$C_{11}H_{11}BFO_4N$

Prepared according to General Procedure I using (2-fluorophenyl)boronic acid (0.25 g, 1.79 mmol, 1 equiv), *N*-methyliminodiacetic acid (0.26 g, 1.79 mmol, 1 equiv), and DMF (2 mL, 0.50 M) to afford the desired product as a white solid (0.27 g, 60%). ^{1}H NMR (400 MHz, *d*$_6$-DMSO) δ 7.52–7.41 (m, 2 H), 7.22 (t, *J* = 7.3 Hz, 1 H), 7.16–7.10 (m, 1 H), 4.41 (d, *J* = 17.4 Hz, 2 H), 4.10 (d, *J* = 17.1 Hz, 2 H), 2.62 (s, 3 H); ^{13}C NMR (101 MHz, *d*$_6$-DMSO) δ 168.9, 134.7 (d, $^3J_{C\text{-}F}$ = 8.8 Hz), 131.7 (d, $^4J_{C\text{-}F}$ = 8.8 Hz), 124.1, 114.9 (d, $^2J_{C\text{-}F}$ = 24.9 Hz), 111.5, 62.4, 47.5, two coincident peaks and carbon bearing boron not observed; υ_{max} (solid)/cm^{-1} 3011, 2969, 1744, 1614, 1467, 1445, 1339, 1310, 1291, 1281, 1251, 1198, 1036, 998.

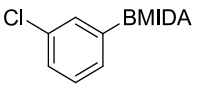
(4-(Methoxycarbonyl)phenyl)boronic acid, MIDA ester, **2.095**



$C_{13}H_{14}BO_6N$

Prepared according to General Procedure I using (4-(methoxycarbonyl)phenyl)boronic acid (0.25 g, 1.39 mmol, 1 equiv), *N*-methyliminodiacetic acid (0.20 g, 1.39 mmol, 1 equiv), and DMF (2 mL, 0.43 M) to afford the desired product as a white solid (0.32 g, 80%). ^{1}H NMR (400 MHz, *d*$_6$-DMSO) δ 7.96–7.92 (m, 2 H), 7.61–7.57 (m, 2 H), 4.36 (d, *J* = 17.1 Hz, 2 H), 4.14 (d, *J* = 17.1 Hz, 2 H), 3.86 (s, 3 H), 2.51 (s, 3 H); ^{13}C NMR (101 MHz, *d*$_6$-DMSO) δ 169.2, 166.4, 132.8, 130.0, 128.2, 61.9, 52.1, 47.6, four coincident peaks and carbon bearing boron not observed; υ_{max} (solid)/cm^{-1} 3028, 2958, 1770, 1746, 1699, 1334, 1290, 1275, 1245, 1035.

(3-Chlorophenyl)boronic acid, MIDA ester, **2.097**

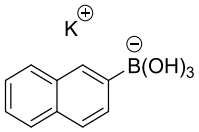


$C_{11}H_{11}BClO_4N$

Prepared according to General Procedure I using (3-chlorophenyl)boronic acid (0.25 g, 1.60 mmol, 1 equiv), *N*-methyliminodiacetic acid (0.24 g, 1.60 mmol, 1 equiv), and DMF (2 mL, 0.47 M) to afford the desired product as a white solid (0.35 g, 83%). ^{1}H NMR (400 MHZ, d_6-DMSO) δ 7.37–7.45 (m, 4 H), 4.34 (d, J = 17.1 Hz, 2 H), 4.14 (d, J = 17.1 Hz, 2 H), 2.54 (s, 3 H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 169.2, 132.9, 132.0, 131.0, 129.7, 128.8, 62.0, 47.7, two coincident peaks and carbon bearing boron not observed; υ_{max} (solid)/cm^{-1} 3013, 2968, 1775, 1760, 1285, 1235, 1206.

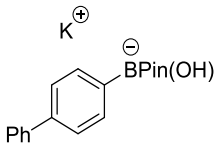
5.9.2 Characterisation data for NMR analysis

Potassium trihydroxy(naphthalen-2-yl)borate, **2.022**



Prepared according to General Procedure F using naphthalen-2-ylboronic acid (0.006 g, 0.04 mmol, 1 equiv), tripotassium phosphate (0.023 g, 0.11 mmol, 3 equiv), and D_2O (0.75 ml). The NMR sample was stirred at 343 K. ^{11}B NMR (128 MHz, D_2O, 343 K) δ 3.67.

Potassium [1,1'-biphenyl]-4-yltrihydroxyborate, pinacol ester, **2.023**

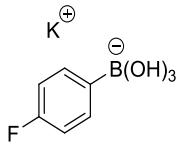


Prepared according to General Procedure F using [1,1'-biphenyl]-4-ylboronic acid, pinacol ester (0.010 g, 0.04 mmol, 1 equiv), **base** (0.11 mmol, 3 equiv), and D_2O (0.75 mL). The NMR sample was stirred at **X** K.

entry	base (mass)	temperature (K)	^{11}B signal
1[a]	K_3PO_4 (0.023 g)	293	---
2[a]	K_3PO_4 (0.023 g)	343	---
3	KOH (0.006 g)	293	6.00 ppm
4[b]	KOH (0.006 g)	343	3.57 ppm

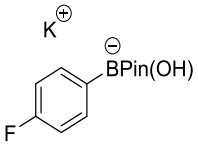
[a]Starting material did not form a solution to transfer into the NMR tube. [b]BPin boronate hydrolysis to the corresponding boronic acid boronate occurred.

Potassium (4-fluorophenyl)trihydroxyborate, **2.027**



Prepared according to General Procedure F using (4-fluorophenyl)boronic acid (0.005 g, 0.04 mmol, 1 equiv), tripotassium phosphate (0.023 g, 0.11 mmol, 3 equiv), and D_2O (0.75 ml). The NMR sample was stirred at 343 K. ^{11}B NMR (128 MHz, D_2O, 343 K) δ 3.49; ^{19}F NMR (376 MHz, D_2O, 343 K) δ –118.65.

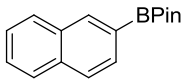
Potassium (4-fluorophenyl)trihydroxyborate, pinacol ester, **2.028**



Prepared according to General Procedure F using (4-fluorophenyl)boronic acid (0.005 g, 0.04 mmol, 1 equiv), tripotassium phosphate (0.023 g, 0.11 mmol, 3 equiv), and D_2O (0.75 ml). The NMR sample was stirred at 343 K. Hydrolysis of BPin boronate was seen by NMR (3.49 and –188.65 ppm for ^{11}B and ^{19}F NMR respectively). ^{11}B NMR (128 MHz, D_2O, 343 K) δ 6.24; ^{19}F NMR (376 MHz, D_2O, 343 K) δ –119.07.

5.9.3 Assay characterisation

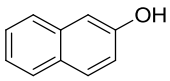
Naphthalen-2-ylboronic acid, pinacol ester,[56] **2.007**



$C_{16}H_{19}BO_2$

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1 H), 7.91–7.88 (m, 1 H), 7.86–7.82 (m, 3 H), 7.55–7.46 (m, 2 H), 1.41 (s, 12 H); υ_{max} (solid)/cm^{-1} 3052, 2978, 2971, 1629, 1599.

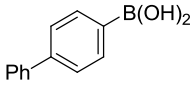
Naphthalen-2-ol,[57] **2.008**



$C_{10}H_8O$

^{1}H NMR (500 MHz, d_6-DMSO) δ 7.80–7.75 (m, 2 H), 7.69 (d, J = 8.2 Hz, 1 H), 7.44 (m, 1 H), 7.34 (m, 1 H), 7.16 (d, J = 2.4 Hz, 1 H), 7.11 (dd, J = 8.9, 2.4 Hz, 1 H), one exchangeable proton not observed; υ_{max} (solid)/cm^{-1} 3241, 3053, 3043, 1744, 1630.

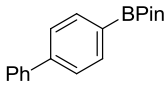
[1,1'-Biphenyl]-4-ylboronic acid,[58] **2.011**



$C_{12}H_{11}BO_2$

^{1}H NMR (500 MHz, d_6-DMSO) δ 8.07 (s, 2 H), 7.89 (d, J = 8.2 Hz, 2 H), 7.69 (d, J = 7.3 Hz, 2 H), 7.64 (d, J = 7.9 Hz, 2 H), 7.48 (t, J = 7.8 Hz, 2 H), 7.38 (t, J = 7.3 Hz, 1 H); υ_{max} (solid)/cm^{-1} 3344, 3054, 3034, 1608, 1552.

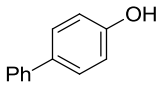
[1,1'-Biphenyl]-4-ylboronic acid, pinacol ester,[59] **2.009**



$C_{18}H_{21}BO_2$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.2 Hz, 2 H), 7.66–7.63 (m, 4 H), 7.49–7.45 (m, 2 H), 7.38 (m, 1 H), 1.39 (s, 12 H); υ_{max} (solid)/cm^{-1} 3034, 2976, 1612, 1400, 1361.

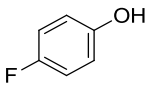
[1,1'-Biphenyl]-4-ol,[60] **2.010**



$C_{12}H_{10}O$

^{1}H NMR (500 MHz, d_6-DMSO) δ 9.51 (s, 1 H), 7.59–7.54 (m, 2 H), 7.50–7.46 (m, 2 H), 7.40 (t, J = 7.8 Hz, 2 H), 7.29–7.25 (m, 1 H), 6.87–6.82 (m, 2 H); υ_{max} (solid)/cm^{-1} 3378, 3036, 2921, 1610, 1597.

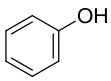
4-Fluorophenol,[61] **2.108**



C_6H_5FO

^{1}H NMR (500 MHz, d_6-DMSO) δ 6.97–6.90 (m, 2 H), 6.81–6.75 (m, 2 H), one exchangeable proton not observed; υ_{max} (solid)/cm^{-1} 3181, 2898, 2682, 1871, 1506, 1448.

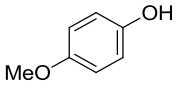
Phenol,[62] **2.112**



C_6H_6O

^{1}H NMR (500 MHz, d_6-DMSO) δ 7.27–7.23 (m, 2 H), 6.94 (m, 1 H), 6.86–6.83 (m, 2 H), one exchangeable proton not observed; υ_{max} (solid)/cm^{-1} 3211, 3045, 3023, 2960, 1595.

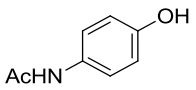
4-Methoxyphenol,[63] **2.113**



$C_7H_8O_2$

^{1}H NMR (500 MHz, d_6-DMSO) δ 6.82–6.76 (m, 4 H), 3.77 (s, 3 H), one exchangeable proton not observed; υ_{max} (solid)/cm^{-1} 3378, 3032, 3013, 2950, 2833, 1504, 1452, 1442.

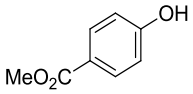
4-Acetamidophenol,[64] **2.114**



$C_8H_9NO_2$

^{1}H NMR (500 MHz, d_6-DMSO) δ 9.62 (s, 1 H), 9.10 (s, 1 H), 7.35–7.30 (m, 2 H), 6.69–6.64 (m, 2 H), 1.97 (s, 3 H); υ_{max} (solid)/cm^{-1} 3323, 3163, 3110, 1653, 1612, 1565, 1508.

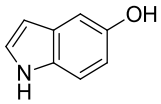
Methyl 4-hydroxybenzoate,[65] **2.115**



$C_8H_8O_3$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99–7.95 (m, 2 H), 6.89–6.85 (m, 2 H), 3.90 (s, 3 H), one exchangeable proton not observed; υ_{max} (solid)/cm^{-1} 3306, 2962, 1748, 1679, 1588.

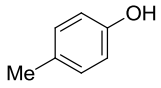
1*H*-Indol-5-ol,[66] **2.116**



C_8H_7NO

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71–7.64 (m, 2 H), 7.58–7.52 (m, 1 H), 7.50–7.44 (m, 2 H), two exchangeable protons not observed; υ_{max} (solid)/cm^{-1} 3330, 2954, 2922, 2852, 1467.

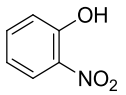
p-Cresol,[67] **2.117**



C_7H_8O

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06–7.03 (m, 2 H), 6.76–6.72 (m, 2 H), 2.28 (s, 3 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3333, 2967, 2960, 1613, 1600, 1509, 1500, 1223.

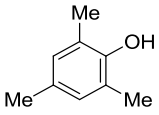
2-Nitrophenol,[68] **2.118**



$C_6H_5NO_3$

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.60 (s, 1 H), 8.13 (dd, J = 8.5, 1.5 Hz, 1 H), 7.62–7.57 (m, 1 H), 7.18 (dd, J = 8.5, 1.2 Hz, 1 H), 7.03–6.98 (m, 1 H); υ_{max} (solid)/cm^{-1} 3237, 3114, 3093, 1612, 1589, 1580, 1532, 1476, 1446.

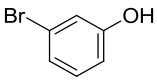
2,4,6-Trimethylphenol,[69] **2.119**



$C_9H_{12}O$

^{1}H NMR (500 MHz, d_6-DMSO) δ 6.80 (s, 2 H), 2.24–2.21 (m, 9 H), one exchangeable proton not observed; υ_{max} (solid)/cm^{-1} 3388, 3016, 2975, 2917, 2857, 1485.

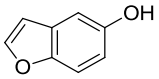
3-Bromophenol,[70] **2.120**



C_6H_5BrO

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13–7.06 (m, 2 H), 7.03 (t, J = 2.0 Hz, 1 H), 6.78 (m, 1 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3629, 3426, 1599, 1582, 1474, 1439, 1296.

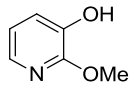
Benzofuran-5-ol,[71] **2.121**



$C_8H_6O_2$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 2.1 Hz, 1 H), 7.37 (d, J = 8.5 Hz, 1 H), 7.03 (d, J = 2.4 Hz, 1 H), 6.83 (dd, J = 8.9, 2.4 Hz, 1 H), 6.68 (dd, J = 2.1, 0.9 Hz, 1 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3315, 1621, 1597, 1465, 1454, 1191.

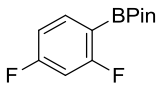
2-Methoxypyridin-3-ol,[72] **2.122**



$C_7H_7NO_2$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 4.9 Hz, 1 H), 7.14 (d, J = 7.9 Hz, 1 H), 6.83 (dd, J = 7.5, 5.0 Hz, 1 H), 4.05 (s, 3 H), one exchangeable proton not observed; υ_{max} (solid)/cm^{-1} 3049, 2963, 2889, 2839, 2683, 2660, 1602, 1498, 1455, 1429, 1264.

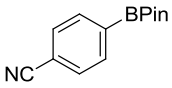
2,4-Difluorophenylboronic acid, pinacol ester,[73] **2.066**



$C_{12}H_{15}BF_2O_2$

^{1}H NMR (500 MHz, d_6-DMSO) δ 7.76–7.70 (m, 1 H), 6.90–6.85 (m, 1 H), 6.80–6.74 (m, 1 H), 1.36 (s, 12 H); υ_{max} (solid)/cm^{-1} 3075, 2980, 1617, 1595.

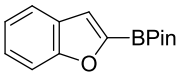
4-Cyanophenylboronic acid, pinacol ester,[74] **2.067**



$C_{13}H_{16}BNO_2$

^{1}H NMR (500 MHz, d_6-DMSO) δ 7.91–7.88 (m, 2 H), 7.66–7.63 (m, 2 H), 1.36 (m, 12 H); υ_{max} (solid)/cm^{-1} 3006, 2974, 2932, 2227, 1400, 1381, 1355.

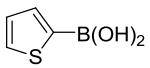
(Benzofuran-2-yl)boronic acid, pinacol ester,[75] **2.068**



$C_{14}H_{17}BO_3$

^{1}H NMR (500 MHz, d_6-DMSO) δ 7.64 (d, J = 7.9 Hz, 1 H), 7.58 (d, J = 8.2 Hz, 1 H), 7.41 (s, 1 H), 7.35 (td, J = 7.8, 1.2 Hz, 1 H), 7.22–7.26 (m, 1 H), 1.40 (s, 12 H); υ_{max} (solid)/cm^{-1} 3060, 2974, 2928, 1567, 1361, 1325.

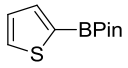
Thiophen-2-ylboronic acid,[76] **2.123**



$C_4H_5BO_2S$

^{1}H NMR (500 MHz, d_6-DMSO) δ 8.16 (s, 2 H), 7.74 (d, J = 4.9 Hz, 1 H), 7.68 (d, J = 3.1 Hz, 1 H), 7.18–7.15 (m, 1 H); υ_{max} (solid)/cm^{-1} 3215, 1521, 1424, 1359.

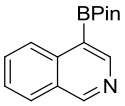
Thiophen-2-ylboronic acid, pinacol ester,[77] **2.069**



$C_{10}H_{15}BO_2S$

^{1}H NMR (500 MHz, d_6-DMSO) δ 7.59 (dd, J = 3.5, 0.8 Hz, 1 H), 7.57 (dd, J = 4.7, 0.8 Hz, 1 H), 7.20 (dd, J = 4.6, 3.4 Hz, 1 H), 1.36 (s, 12 H); υ_{max} (solid)/cm^{-1} 3101, 2978, 1523, 1426.

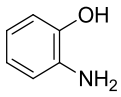
Isoquinolin-4-ylboronic acid, pinacol ester,[78] **2.070**



$C_{15}H_{18}BNO_2$

^{1}H NMR (500 MHz, d_6-DMSO) δ 9.51–9.48 (m, 1 H), 8.98 (d, J = 8.8 Hz, 1 H), 8.95 (s, 1 H), 8.30 (d, J = 8.2 Hz, 1 H), 8.19–8.15 (m, 1 H), 7.99–7.94 (m, 1 H), 1.45 (s, 12 H); υ_{max} (solid)/cm^{-1} 2980, 2930, 1630, 1498.

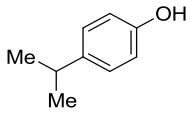
2-Aminophenol,[79] **2.124**



C_6H_7NO

^{1}H NMR (500 MHz, d_6-DMSO) δ 8.88 (br. s, 1 H), 6.64–6.60 (m, 1 H), 6.59–6.55 (m, 1 H), 6.52 (m, 1 H), 6.38 (m, 1 H), 4.44 (br. s, 2 H); υ_{max} (solid)/cm^{-1} 3372, 3300, 3049, 2709, 2584, 1600, 1511, 1461, 1403.

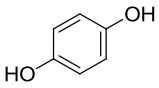
4-Isopropylphenol,[80] **2.125**



$C_9H_{12}O$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13–7.09 (m, 2 H), 6.79–6.75 (m, 2 H), 2.86 (sept, J = 7.0 Hz, 1 H), 1.23 (d, J = 6.7 Hz, 6 H), one exchangeable proton not observed; υ_{max} (solid)/cm^{-1} 3291, 3017, 2976, 2952, 1614, 1601, 1513.

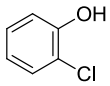
Hydroquinone,[81] **2.099**



$C_6H_6O_2$

^{1}H NMR (500 MHz, d_6-DMSO) δ 8.59 (s, 2 H), 6.55 (s, 4 H); υ_{max} (solid)/cm^{-1} 3136, 3028, 1515, 1463, 1353.

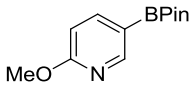
2-Chlorophenol,[82] **2.126**



C_6H_5ClO

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, J = 8.2, 1.5 Hz, 1 H), 7.22–7.16 (m, 1 H), 7.04 (dd, J = 8.2, 1.5 Hz, 1 H), 6.91–6.86 (m, 1 H), 5.56 (br. s, 1 H); υ_{max} (thin film)/cm^{-1} 3514, 3073, 3038, 1595, 1584, 1480, 1452.

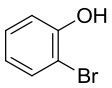
(6-Methoxypyridin-3-yl)boronic acid, pinacol ester,[83] **2.074**



$C_{12}H_{18}BNO_3$

^{1}H NMR (500 MHz, d_6-DMSO) δ 8.56 (d, J = 1.8 Hz, 1 H), 7.94 (d, J = 8.2 Hz, 1 H), 6.73 (d, J = 8.2 Hz, 1 H), 3.98 (s, 3 H), 1.35 (m, 12 H); υ_{max} (solid)/cm^{-1} 3010, 2973, 2948, 2846, 1599, 1563, 1355.

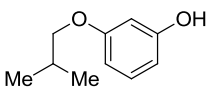
2-Bromophenol,[84] **2.127**



C_6H_5BrO

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.9, 1.5 Hz, 1 H), 7.25–7.21 (m, 1 H), 7.04 (dd, J = 8.2, 1.5 Hz, 1 H), 6.80–6.84 (m, 1 H), 5.52 (br. s, 1 H); υ_{max} (thin film)/cm^{-1} 3493, 3069, 1576, 1474, 1448.

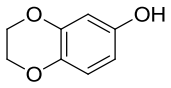
3-Isobutoxyphenol,[85] **2.128**



$C_{10}H_{14}O_2$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14–7.10 (m, 1 H), 6.52–6.48 (m, 1 H), 6.42–6.39 (m, 2 H), 3.70 (d, J = 6.5, Hz, 2 H), 2.08 (t, J = 6.5 Hz, 1 H), 1.02 (d, J = 6.5 Hz, 6 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3396, 2960, 2872, 1595, 1495, 1470, 1288, 1149.

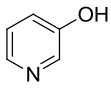
2,3-Dihydrobenzo[*b*][1,4]dioxin-6-ol,[86] **2.129**



$C_8H_8O_3$

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (d, J = 8.5 Hz, 1 H), 6.39 (d, J = 2.5 Hz, 1 H), 6.35–6.31 (m, 1 H), 4.26–4.22 (m, 2 H), 4.22–4.19 (m, 2 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3385, 2922, 2874, 1608, 1509, 1468, 1454, 1312.

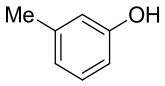
Pyridin-3-ol,[87] **2.130**



C_5H_5NO

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 2.7 Hz, 1 H), 8.08 (dd, J = 4.8, 1.2 Hz, 1 H), 7.40 (m, 1 H), 7.33 (dd, J = 8.4, 4.8 Hz, 1 H), 6.93 (s, 1 H); υ_{max} (thin film)/cm^{-1} 2422, 1790, 1573, 1478, 1374.

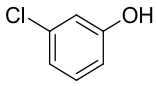
m-Cresol,[88] **2.131**



C_7H_8O

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (t, J = 7.8 Hz, 1 H), 6.76 (d, J = 7.3 Hz, 1 H), 6.68–6.63 (m, 2 H), 2.32 (s, 3 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3302, 3036, 2917, 2857, 1613, 1589, 1491, 1463, 1441, 1335, 1279, 1266, 1152.

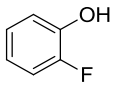
3-Chlorophenol,[89] **2.132**



C_6H_5ClO

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (t, J = 8.1 Hz, 1 H), 6.93 (ddd, J = 8.0, 1.9, 0.8 Hz, 1 H), 6.87 (t, J = 2.1 Hz, 1 H), 6.73 (ddd, J = 8.2, 2.4, 0.9 Hz, 1 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3365, 3060, 2950, 2919, 2850, 1705, 1593, 1567, 1465, 1377.

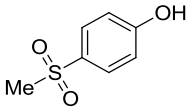
2-Fluorophenol,[90] **2.133**



C_6H_5FO

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11–7.05 (m, 1 H), 7.05–6.99 (m, 2 H), 6.89–6.83 (m, 1 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3346, 1615, 1599, 1513, 1500, 1461, 1359, 1262, 743.

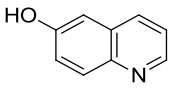
4-(Methylsulfonyl)phenol,[91] **2.134**



$C_7H_8O_3S$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85–7.81 (m, 2 H), 7.00–6.96 (m, 2 H), 3.05 (s, 3 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3556, 3497, 3367, 3069, 3010, 2926, 2822, 1640, 1586, 1504, 1455, 1383, 1283, 1264, 1141, 1089.

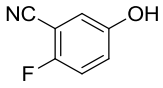
6-Hydroxyquinoline,[92] **2.135**



C_9H_7NO

^{1}H NMR (500 MHz, d_6-DMSO) δ 9.99 (s, 1 H), 8.66 (dd, J = 4.1, 1.4 Hz, 1 H), 8.14 (d, J = 8.2 Hz, 1 H), 7.86 (d, J = 9.2 Hz, 1 H), 7.40 (dd, J = 8.4, 4.1 Hz, 1 H), 7.34–7.30 (m, 1 H), 7.16–7.13 (m, 1 H); υ_{max} (thin film)/cm^{-1} 3013, 2966, 2872, 2774, 2677, 2603, 2538, 2350, 1638, 1578, 1500, 1463, 1435, 1416, 1377, 1318.

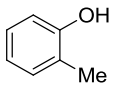
2-Fluoro-5-hydroxybenzonitrile,[93] **2.136**



C_7H_4FNO

^{1}H NMR (400 MHz, d_6-DMSO) δ 7.34–7.27 (m, 1 H), 7.08–7.14 (m, 2 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3307, 3073, 2980, 2255, 2238, 1667, 1591, 1504, 1470, 1455, 1299.

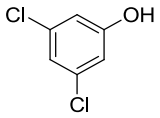
o-Cresol,[94] **2.137**



C_7H_8O

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15–7.07 (m, 2 H), 6.86 (t, J = 7.5 Hz, 1 H), 6.78 (d, J = 7.9 Hz, 1 H), 2.27 (s, 3 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3361, 3060, 3028, 2917, 2857, 1593, 1504, 1493, 1463, 1444, 1240, 1106.

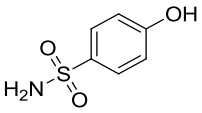
3,5-Dichlorophenol,[95] **2.138**



$C_6H_4Cl_2O$

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (t, J = 1.8 Hz, 1 H), 6.76 (d, J = 1.8 Hz, 2 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3211, 3051, 1600, 1574, 1495, 1485, 1465, 1387, 1368, 1290, 1245.

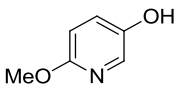
4-Hydroxybenzenesulfonamide,[96] **2.139**



$C_6H_7NO_3S$

^{1}H NMR (400 MHz, d_6-DMSO) δ 10.15 (br. s, 1 H), 7.66–7.61 (m, 2 H), 7.08 (br. s, 2 H), 6.89–6.85 (m, 2 H); υ_{max} (thin film)/cm^{-1} 3477, 3322, 3245, 1601, 1585, 1501, 1435, 1314, 1288, 1149, 1093, 832, 747.

6-Methoxypyridin-3-ol,[97] **2.140**

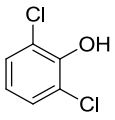


$C_6H_7NO_2$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 2.7 Hz, 1 H), 7.23 (dd, J = 8.9, 3.1 Hz, 1 H), 6.70 (d, J = 8.9 Hz, 1 H), 3.91 (s, 3 H), one exchangeable proton not observed;

υ_{max} (thin film)/cm^{-1} 3047, 3002, 2974, 2961, 2887, 2837, 2723, 2681, 2658, 1602, 1498, 1454, 1429, 1264.

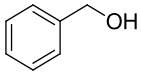
2,6-Dichlorophenol,[98] **2.141**



$C_6H_4Cl_2O$

^{1}H NMR (400 MHz, d_6-DMSO) δ 7.35 (d, J = 8.1 Hz, 2 H), 6.86 (t, J = 8.1 Hz, 1 H), one exchangeable peak not observed; υ_{max} (solid)/cm^{-1} 3435, 1578, 1463, 1448, 1335, 1240, 1175, 764, 711.

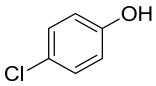
Benzyl alcohol,[99] **2.142**



C_7H_8O

^{1}H NMR (400 MHz, d_6-DMSO) δ 7.43–7.34 (m, 4 H), 7.31–7.25 (m, 1 H), 5.27–5.20 (m, 1 H), 4.62–4.54 (m, 2 H); υ_{max} (thin film)/cm^{-1} 3310, 1496, 1454, 1208, 1009, 732, 695.

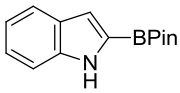
4-Chlorophenol,[100] **2.143**



C_6H_5ClO

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.18 (d, J = 2.7 Hz, 2 H), 6.80–6.75 (m, 2 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3251, 1591, 1493, 1442, 1435.

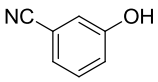
(1*H*-Indol-2-yl)boronic acid, pinacol ester,[101] **2.076**



$C_{14}H_{18}BNO_2$

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 1 H), 7.40 (d, J = 8.2 Hz, 1 H), 7.26–7.21 (m, 1 H), 7.13–7.08 (m, 2 H), 1.38 (s, 12 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3414, 3062, 2978, 1539, 1375, 1333.

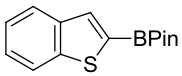
3-Cyanophenol,[102] **2.144**



C_7H_5NO

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 7.9 Hz, 1 H), 7.25 (d, J = 7.6 Hz, 1 H), 7.15–7.12 (m, 1 H), 7.11–7.07 (m, 1 H), one exchangeable proton not observed; υ_{max} (thin film)/cm^{-1} 3396, 3296, 2242, 1651, 1615, 1582, 1478, 1398.

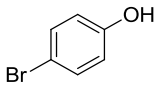
Benzo(*b*)thiophene-2-boronic acid, pinacol ester,[103] **2.083**



$C_{14}H_{17}BO_2S$

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.91 (m, 2 H), 7.88–7.86 (m, 1 H), 7.40–7.35 (m, 2 H), 1.40 (s, 12 H); υ_{max} (thin film)/cm^{-1} 2978, 1526, 1348, 1338, 1137.

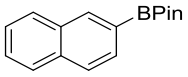
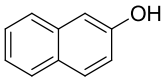
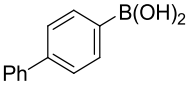
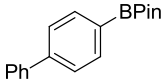
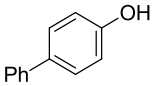
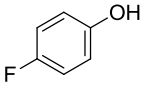
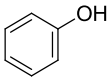
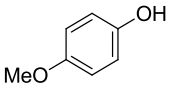
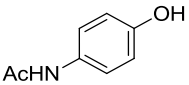
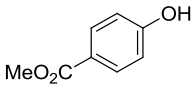
4-Bromophenol,[104] **2.145**

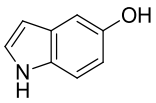
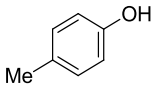
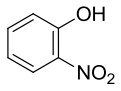
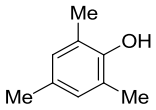
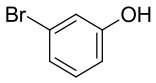
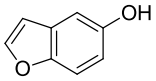
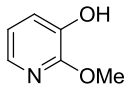
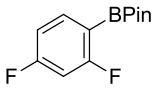
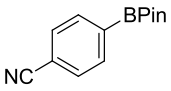
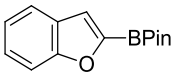
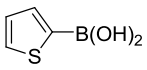
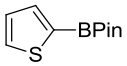


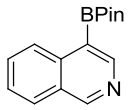
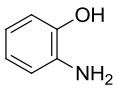
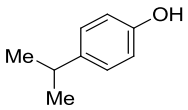
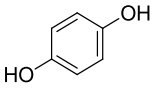
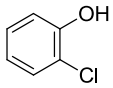
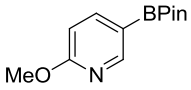
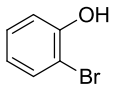
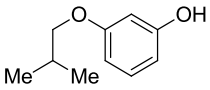
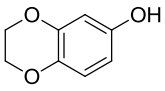
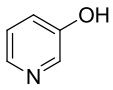
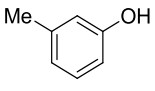
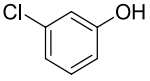
C_6H_5BrO

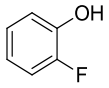
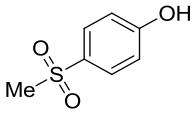
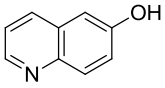
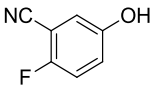
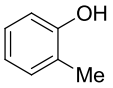
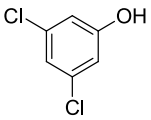
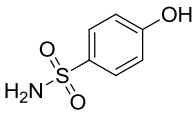
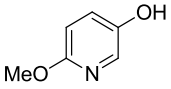
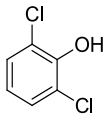
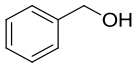
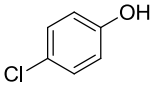
^{1}H NMR (400 MHz, d_6-DMSO) δ 9.67 (br. s, 1 H), 7.33–7.27 (m, 2 H), 6.75–6.69 (m, 2 H); υ_{max} (solid)/cm^{-1} 3332, 1590, 1488, 1434, 1241, 1217, 1174, 1069, 1006, 824.

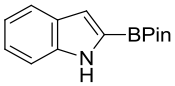
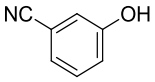
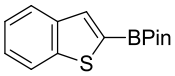
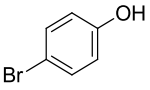
5.10 HPLC retention times and factors of products

compound	structure	retention time (min)[a]	conversion factor[a]
2.007		10.4	0.42
2.008		6.2	0.60
2.011		6.6	5.22
2.009		10.8	4.38
2.010		7.3	4.02
2.108		4.2	0.03
2.112		3.5	0.07
2.113		3.4	0.12
2.114		1.8	2.98
2.115		4.3	3.50

2.116		2.7	0.47
2.117		4.8	0.03
2.118		5.5	0.65
2.119		7.1	0.04
2.120		6.1	0.06
2.121		4.5	3.34
2.122		2.2	0.16
2.066		3.7	0.05
2.067		3.4	0.32
2.068		4.5	3.67
2.123		2.5	2.08
2.069		8.7	2.23

2.070		1.1	0.17
2.124		3.0	0.07
2.125		6.9	0.05
2.099		1.4	0.05
2.126		5.2	0.07
2.074		1.8	0.25
2.127		5.6	0.06
2.128		7.4	0.06
2.129		3.5	0.07
2.130		0.5	0.09
2.131		4.7	0.06
2.132		5.6	0.03

2.133		3.9	0.09
2.134		2.6	1.70
2.135		1.1	7.06
2.136		4.8	0.01
2.137		4.9	0.07
2.138		7.5	0.05
2.139		1.5	1.14
2.140		0.4	0.08
2.141		6.2	0.04
2.142		2.2	0.06
2.143		6.7	0.06

2.076		4.5	0.43
2.144		1.7	0.22
2.083		5.4	1.74
2.145		3.5	0.11

[a]HPLC analysis of compounds conducted using method described in section 5.1.5.

Chapter 2

Diversity orientated one-pot synthesis of substituted tetrahydropyridopyrimidines enabled by COware

1 Introduction

The field of chemical synthesis is advancing rapidly with a plethora of novel reactions and state-of-the-art technologies available.[158,159] The incorporation of these new practices into everyday chemistry is pivotal to the evolution of drug discovery and is a requirement for keeping up to date with the expanding needs of the population.

Within drug discovery, hydrogenation and carbonylation reactions are essential transformations in the synthetic chemists' toolbox. Hydrogen and carbon monoxide are versatile reagents in organic synthesis, required for a wide range of reactions of fundamental importance.[160,161] However, the flammability of hydrogen and the toxicity of carbon monoxide mean that there are significant safety issues associated with their use and storage.[162,163]

Skrydstrup and co-workers have recently introduced a two-chamber glassware system for the *in situ* generation and use of low molecular weight gases including hydrogen and carbon monoxide.[160,161] Commercialised by Sigma-Aldrich®, COware is capable of producing hydrogen or carbon monoxide *in situ* allowing transformations to be carried out in a more controlled manner.[164,165] Hydrogen can be generated through the reaction of zinc and hydrochloric acid in chamber B, which can then pass through to chamber A where it is consumed (Figure 3.01, Scheme 3.01).[160] Similarly, the COware system has also been used to generate carbon monoxide by the palladium-catalysed decarbonylation of pivaloyl chloride, allowing hydroxycarbonylation and aminocarbonylation reactions to be achieved (Scheme 3.02).[161]

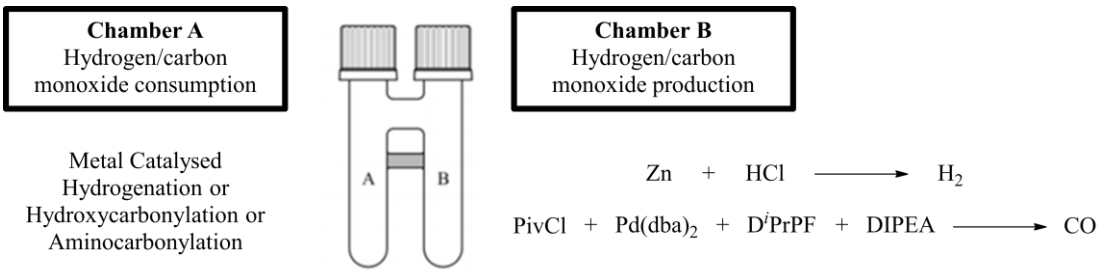
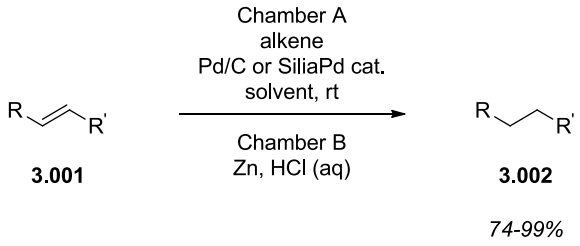
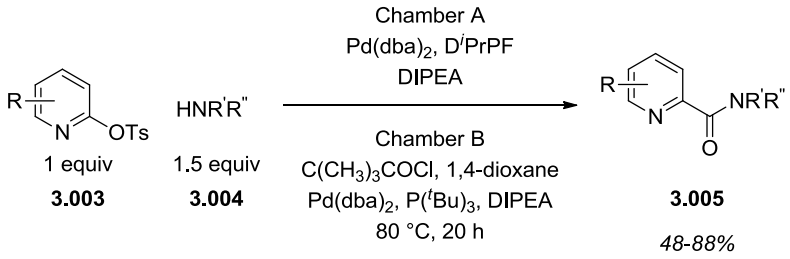


Figure 3.01 COware apparatus.[160]

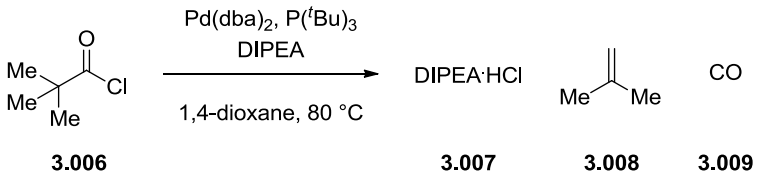


Scheme 3.01 Hydrogenation reactions performed in COware.[160]



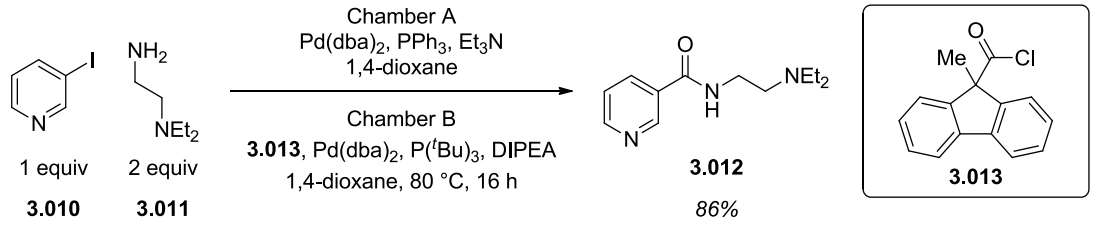
Scheme 3.02 Aminocarbonylation reactions performed in COware.[161]

Carbon monoxide was initially produced from palladium catalysed decomposition of pivaloyl chloride, generating isobutene gas as a by-product (Scheme 3.03).[161] The gaseous by-product proved to be problematic due to excess pressure build up inside the reaction vessel. Furthermore, the reactivity of the isobutene gas generated limited the substrates that could be used in the reaction. For example, isobutene is known to be involved in Prins condensations,[166] ene reactions,[167] and Friedel-Crafts alkylations[168] as well as being used to protect carboxylic acids[169] and alcohols[170] so careful choice of starting materials is required in order to avoid potential side-reactions.



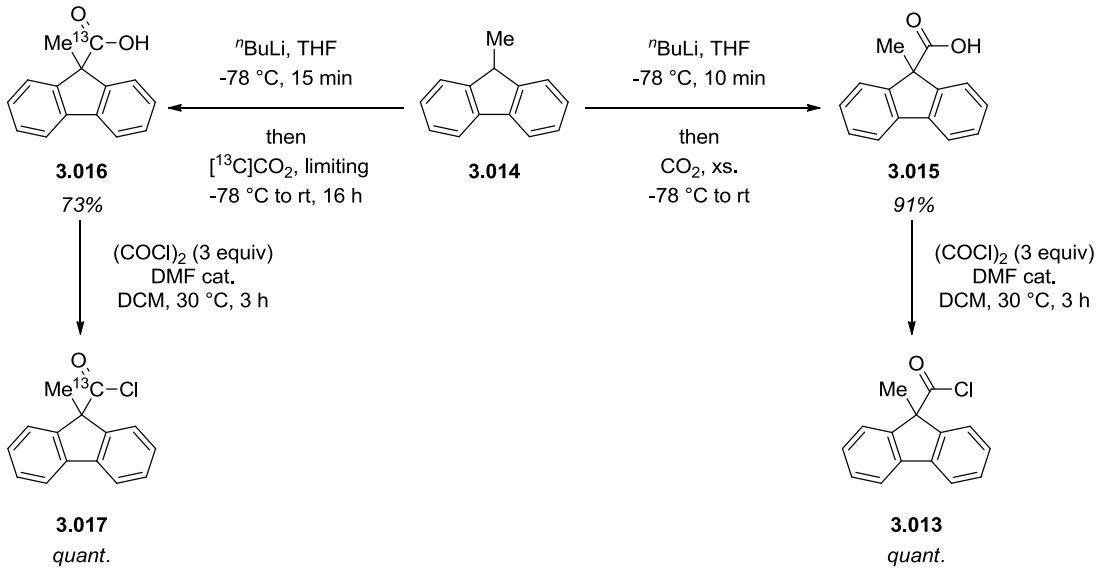
Scheme 3.03 Carbon monoxide generation from pivaloyl chloride.[161]

To circumvent this issue, Skrydstrup *et al.* generated carbon monoxide through the palladium-catalysed decarbonylation of acyl chloride **3.013** which also allowed for the incorporation of carbon isotopes into the carbon monoxide source (Schemes 3.04 and 3.05).[161]



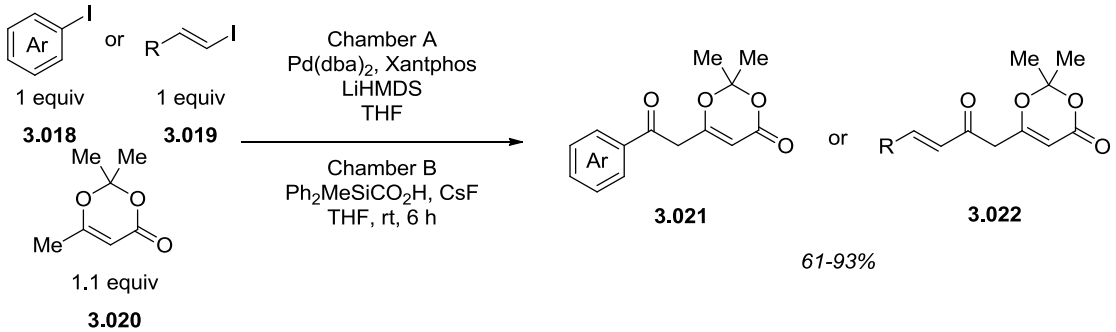
Scheme 3.04 The *in situ* generation and use of carbon monoxide from palladium catalysed decomposition of acid chloride **3.013**.[161]

Furthermore, acyl chloride **3.013** is a stable solid, it is easy to synthesise (Scheme 3.05), and the carbon monoxide precursor can be resynthesised from the alkene product generated from the release of carbon monoxide.[161] In addition, the ^{13}C labelled analogue can be easily synthesised in the same fashion through the use of $[^{13}C]CO_2$.[161]



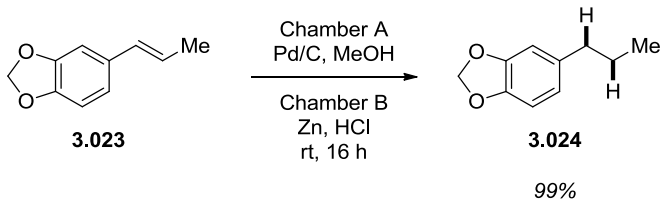
Scheme 3.05 Synthesis of bench-stable carbon monoxide precursor **3.013** and its ^{13}C labelled analogue, **3.017**.[161]

More recently, siliacarboxylic acids, specifically $Ph_2MeSiCO_2H$ (commercialised as SiliaCOgen) has been utilized as a bench stable, easy-to-handle, and metal-free carbon monoxide source (Scheme 3.06).[171,172] Treatment of the siliacarboxylic acid with a catalytic fluoride source, either potassium fluoride or cesium fluoride, has been shown to generate carbon monoxide.[171,172] This method of generating carbon monoxide *in situ* is particularly appealing, predominantly due to the absence of a transition metal catalyst. Transition metal-free reactions are beneficial as, generally, they are less air and moisture sensitive, avoid the use of often expensive and toxic catalyst-ligand systems, and eliminate the need to check for trace metals in pharmaceutical products.[173]



Scheme 3.06 Mild, metal-free carbon monoxide generation and reaction.[172]

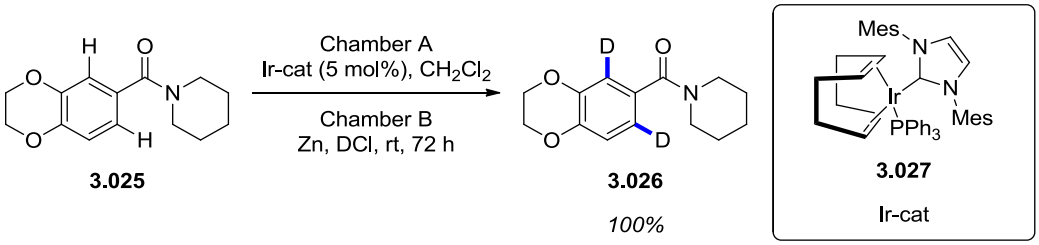
As stated previously, the two-chamber system has also been utilized for the *in situ* generation and use of hydrogen and deuterium.[160] This has been exemplified in performing conventional hydrogenation reactions (Scheme 3.07) and hydrogen-deuterium exchange (Scheme 3.08).



3.023 **3.024**

99%

Scheme 3.07 Example hydrogenation carried out using COware.[160]

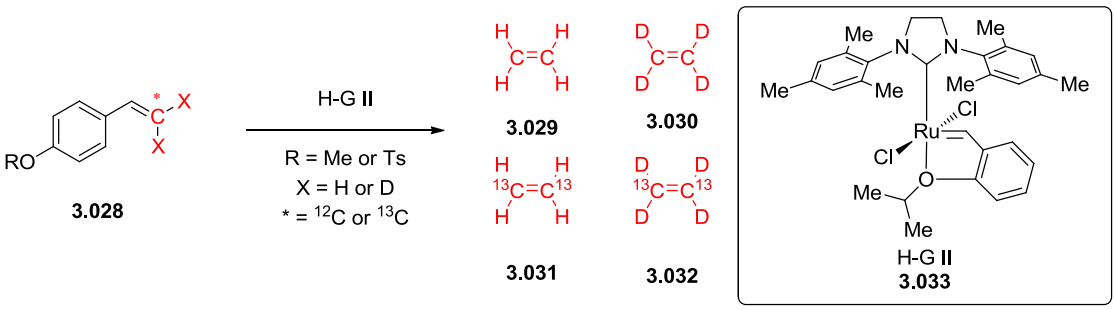


3.025 **3.026** **3.027**

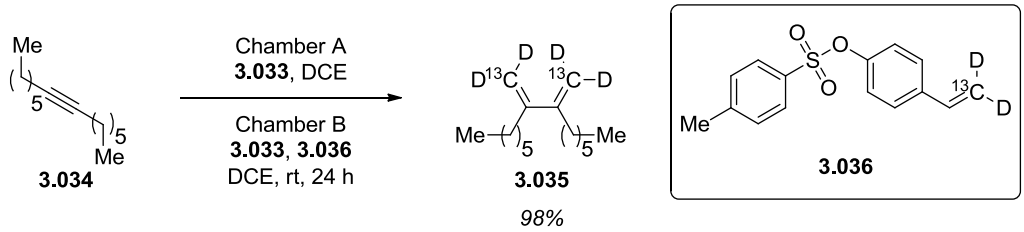
100% Ir-cat

Scheme 3.08 Deuterium-hydrogen isotope exchange using COware.[160]

COware has also been used to generate ethylene.[164] Even though it is the most commercially produced organic compound globally, isotopically-labelled ethylene is not easily accessed and the use of COware provides a simple solution to this issue (Scheme 3.09).[165] Ethylene is formed from the metathesis of labelled styrene derivatives which efficiently generate the desired isotopes **3.030**, **3.031**, and **3.032**. Once formed, ethylene can then be used in a number of transformations including, but not exclusively, metathesis reactions (Scheme 3.10).[165]



Scheme 3.09 Generation of ethylene in COware.[165]



Scheme 3.10 Use of ethylene in COware.[165]

The synthetic tractability of COware in hydrogenations has been demonstrated by Skrydstrup *et al.* performing olefin, acetylene, nitro, and ketone reductions with both hydrogen and deutertium.[160] Isotopes of hydrogen are generated in chamber B of the COware apparatus using a combination of zinc and either hydrochloric acid or deuterium chloride. The stoichiometric amount of hydrogen generated then diffuses into the reaction chamber A performing the desired reduction (Figure 3.01). The amount of gas generated can be tailored to the reaction system. If higher pressures are required then this can be achieved by using excess zinc and acid. Theoretically, if all the generated hydrogen reacts, there should be no hydrogen waste. However, in practice, this is not the case; therefore it is necessary to generate one additional equivalent of hydrogen to that which is required, in order to account for any seepage that may occur. The system has been pressure tested up to four bar so pressurised reactions can be performed in the glassware.[171]

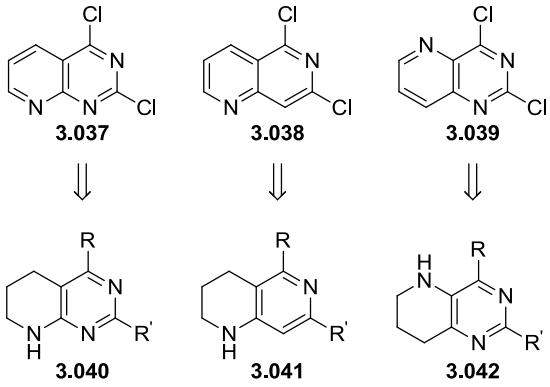
The benefits of using COware range from its ease of use, allowing the chemist to perform reactions in the fumehood without having to find an external source of hydrogen, to the elimination of the need for an auxiliary hydrogen generation or storage facility *i.e.*, expensive specialist equipment which is also a significant health

and safety hazard due to the flammability of hydrogen.[162] Furthermore, the use of COware avoids the need for hydrogen-filled balloons which are prone to bursting. This can rapidly release a large volume of hydrogen into a fume cupboard causing significant health and safety issues.

1.1 Aims

A more subtle advantage of COware is the potential to perform multi-step reactions using the glassware. Specifically, the ability to carry out a hydrogenation or carbonylation as one step in a multi-step process without the need for a solvent swap or change in reaction vessel.

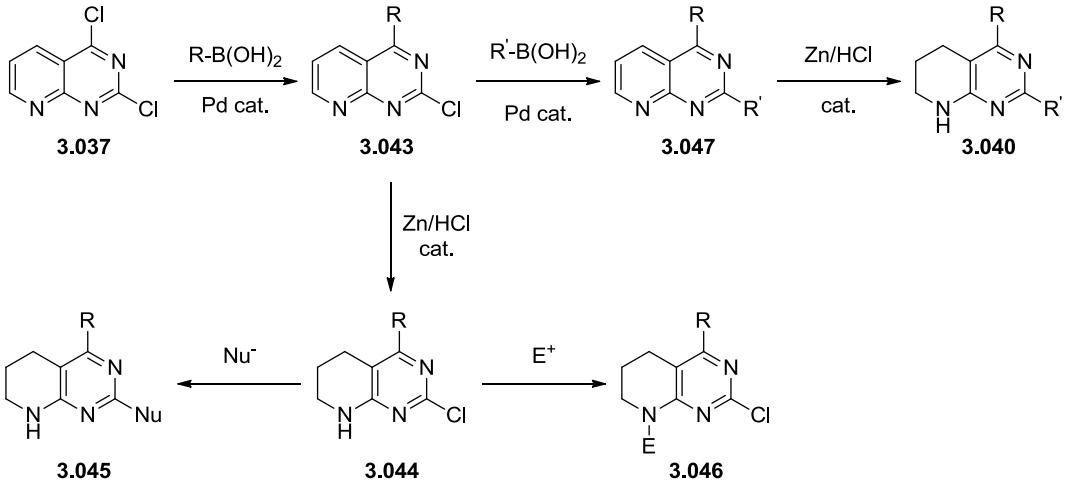
To exploit this potential, it was hypothesised that multiple reactions could be completed in one-pot before the hydrogenation of an unsaturated system using COware. Halogenated polyheteroaromatic compounds **3.037**, **3.038**, and **3.039** were identified as ideal targets for this chemistry due to their relevance in drug discovery and their perceived favourable reactivity in S_NAr, cross-coupling, and hydrogenation chemistries (Scheme 3.11).[174,175]



Scheme 3.11 Commercially-available halogenated polyheteroaromatic compounds and the potential semi-saturated drug-like targets that could be accessed in one-pot.

In particular, 2,4-dichloropyrido[2,3-*d*]pyrimidine **3.037** was recognized as a good starting compound that could be easily diversified at multiple positions to produce a vast array of structurally different, drug-like, compounds in a one-pot process (Scheme 3.12). A regioselective Suzuki-Miyaura reaction that is known to occur at

the 4-position would allow access to intermediate **3.043**.[176] Reduction of the intermediate arylchloride at this stage would form a series of tetrahydropyridopyrimidines (THPPs) of type **3.044**, containing two functional handles with complementary reactivity; an arylchloride which could be further reacted under cross-coupling or S_NAr conditions and a secondary amine which could react with a variety of electrophiles.



Scheme 3.12 Library of possible THPP core compounds.

However, if a second nucleophile is added into the COware apparatus before hydrogenation, then compounds of type **3.047** will be formed. Selective hydrogenation of the pyridopyrimidine system would then allow access to many desirable drug-like cores with structure **3.040** (Scheme 3.12). By using a variety of different boronic acid and ester nucleophiles, one can easily envisage access to a wide range of medicinally relevant structures in one vessel without the need for intermediate purification. This strategy could prove to be extremely valuable in the rapid synthesis of potential drug cores, especially when quick structure activity relationship (SAR) exploration is required.

The Suzuki-Miyaura reaction was chosen as the cross-coupling reaction to perform on the pyridopyrimidine core due to the relative inertness of boronic acid and ester species compared to other organometallic species, the commercial availability of boron species, mild reaction conditions used, and the low toxicity of boron.[3] Initially,

hydrogen would be generated after the addition of one nucleophile to the heterocyclic core. Drug-like cores of type **3.048** and **3.049** could then be easily synthesised in one-pot from simple starting materials (Figure 3.02).

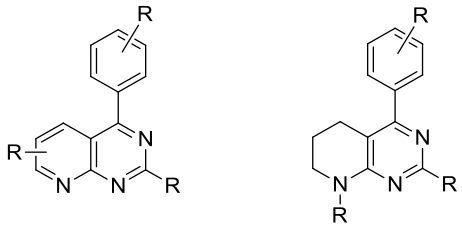


Figure 3.02 Drug-like cores that could be accessed in one-pot.

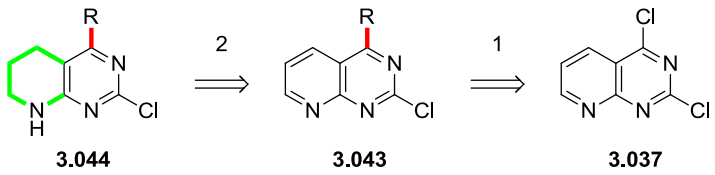
Therefore, the aims of the project were to: -

1) Develop a one-pot, Suzuki-Miyaura/hydrogenation procedure for expedient access to highly functionalised THPP cores.

2) Apply the optimised methodology to synthesise a series of semi-saturated inhibitors and compare their physicochemical properties to that of known, fully-saturated analogues.

2 Results and discussion

With the aims of the project clearly set out, the first port of call was to devise a strategy for the optimisation of the one-pot reaction. Clearly, the one-pot procedure can be broken down into two distinct steps: step one, a regioselective Suzuki-Miyaura reaction, and step two, a chemoselective hydrogenation reaction (Scheme 3.13). To generate an effective, high yielding one-pot reaction, each of the respective steps were individually optimised on a model substrate and then combined into COware apparatus.

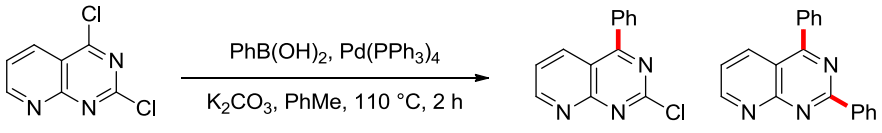


3.044 **3.043** **3.037**

Scheme 3.13 Reaction optimisation breakdown. 1: optimise the Suzuki-Miyaura cross-coupling reaction. 2: optimise the hydrogenation of cross-coupled product.

2.1 Suzuki-Miyaura reaction optimisation

Initially, the regioselective Suzuki-Miyaura reaction of phenylboronic acid with 2,4-dichloro[2,3-*d*]pyrimidine, **3.037**, was examined (Scheme 3.14). Phenylboronic acid was chosen as a simple boronic acid nucleophile with minimal functionality that could interfere with either the cross-coupling or hydrogenation steps of the process. Following literature conditions, moderate 23% conversion to the desired heterocycle, **3.050**, was observed (Scheme 3.14).[176] However, a small amount (2%) of overreaction at both 2- and 4-positions to form compound **3.051** was also observed by LCMS, but this compound was not isolated. The low isolated yield is probably due to the anhydrous reaction conditions employed. As discussed previously (Section 1.3.12), water is required for the catalytic cycle of the Suzuki-Miyaura reaction to progress. Most of the water present in the reaction mixture will be sourced from slightly wet solvent meaning that some cross-coupling can occur. Therefore, it is predicted that the literature conditions used wet solvent that enabled the reaction to progress to completion.

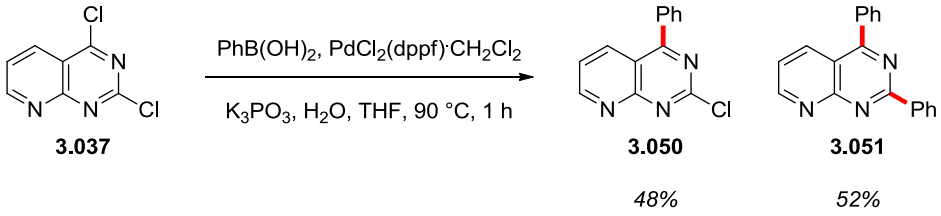


3.037 **3.050** **3.051**

	3.050	**3.051**
literature yield	*81%*	*0%*
repeat of literature	*23%*	*2%*

Scheme 3.14 Repeat of literature Suzuki-Miyaura reaction conditions.[176]

In-house Suzuki-Miyaura reaction conditions were then applied to the system due to the poor yield obtained when repeating the previous literature conditions (Scheme 3.15).[177]

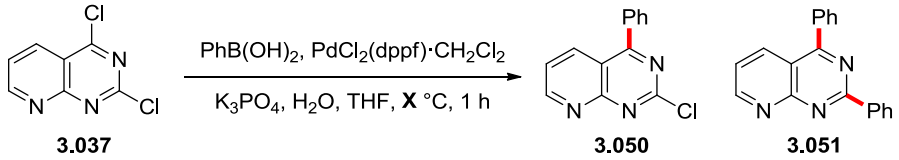


3.037 **3.050** **3.051**

48% *52%*

Scheme 3.15 In-house Suzuki-Miyaura reaction conditions. Performed using $PhB(OH)_2$ (1.5 equiv), $PdCl_2(dppf)\cdot CH_2Cl_2$ (4 mol%), K_3PO_4 (3 equiv), H_2O (5 equiv), and THF (0.25 M). Determined by HPLC analysis using an internal standard.

Altering the catalyst, base and solvent, combined with a decrease in reaction temperature and time gave an increased amount of desired product **3.050** plus a large quantity, 52%, of over-reacted side product **3.051**. Thorough analyses of the reaction conditions were then conducted in an attempt to avoid excessive formation of the side-product **3.051**. This was initially started through the lowering of the reaction temperature (Table 3.01).



3.037 **3.050** **3.051**

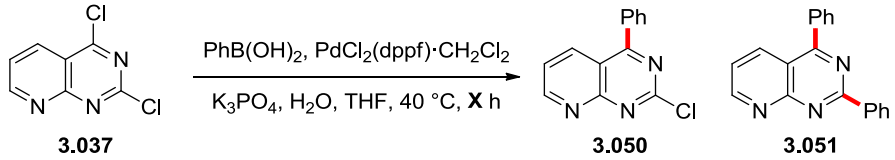
entry	temperature (°C)	conversion (%) (**3.037**:**3.050**:**3.051**)[a]	isolated yield in COware (%)
1	23	53:47:0	---
2	30	1:79:20	37
3	40	1:74:25	63
4	50	0:73:27	55
5	60	1:93:6	---
6	70	0:54:46	---
7	80	0:52:48	---

[a]Determined by HPLC analysis using an internal standard.

Table 3.01 Suzuki-Miyaura reaction temperature study.

Significantly decreasing the reaction temperature from 90 °C to ambient temperature resulted in poor conversion to the desired mono-coupled product **3.050**, leaving a large amount of starting material remaining (entry 1). Increasing the reaction temperature to 30 °C gave a large increase in conversion (entry 2); however, coupling at both arylchloride centers was occurring. Further increase in the temperature to 40 °C and then to 50 °C showed similar amounts of product formation (entries 3 and 4). Elevating the temperature to 60 °C provided excellent levels of desired product formation with minimal levels of overreaction and starting material present (entry 5). Any further increase in the reaction temperature produced a large amount of doubly cross-coupled product **3.051** (entries 6 and 7). A factor in this may

be the excess (1.5 equiv.) of boronic acid used in the reaction. With the optimal reaction temperature being 60 °C these conditions were trialed in COware apparatus. Disappointingly, a large amount of solvent was transferred between the two chambers when heating at 60 °C for one hour. This is due to the low boiling point (66 °C) of tetrahydrofuran (THF). Therefore, the reaction temperature had to be lowered in order to successfully achieve a one-pot transformation. The cross-coupling reaction was repeated in COware at 30, 40, and 50 °C, a process which determined that the highest practical temperature at which the reaction could take place without solvent transfer between chambers was 40 °C. The lack of solvent transfer was reflected in the isolated yield of product generated. Isolation was not attempted for the reaction at 60 °C due to the significant amount of solvent transfer observed. The reaction time was the next factor to be examined, as extending this factor may allow the reaction to progress to completion at diminished temperatures (Table 3.02).



3.037 **3.050** **3.051**

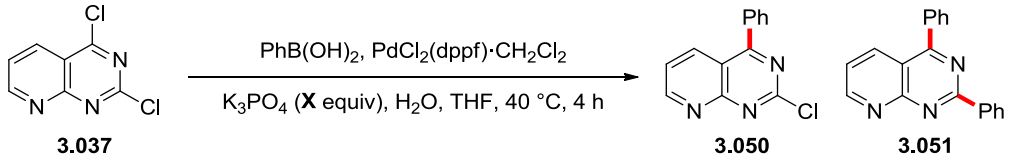
entry	time (h)	conversion (%) (**3.037**:**3.050**:**3.051**)[a]
1	1	36:60:4
2	2	15:79:6
3	4	1:86:13
4	6	1:81:15
5	8	1:83:15
6	16	0:78:22
7	24	0:52:48

[a]Determined by HPLC analysis using an internal standard.

Table 3.02 Suzuki-Miyaura reaction time study.

As expected, increasing the reaction time from one (entry 1) and decreasing the amount of boronic acid used to 1.05 equivalents improved conversion to the desired mono-coupled product **3.050** in most cases. Conversion was significantly enhanced when the reaction time was doubled to two hours (entry 2). This coincided with a reduction in the amount of starting material remaining. Further increasing the reaction time to four, six, and then eight hours facilitated similar levels of conversion to the desired product (entries 3, 4, and 5). Interestingly, on allowing the reaction to stir for more than two hours, the amount of remaining starting material was considerably diminished (entries 2 and 3). This outcome was incredibly promising, resulting in a minimal amount of both starting material and undesired over-reacted

product. Leaving the reaction to stir for 24 h resulted in a significant amount of undesired product **3.051** (entry 7). With high levels of conversion observed for a number of time points between two and 16 hours, the reaction was optimised over a four hour reaction time to allow for a rapid optimisation process. However, the reaction time could be increased to 16 hours with the knowledge that excess amounts of undesired product would not be formed. Attention then turned to examination of the amount of base present in the reaction mixture (Table 3.03).



3.037 **3.050** **3.051**

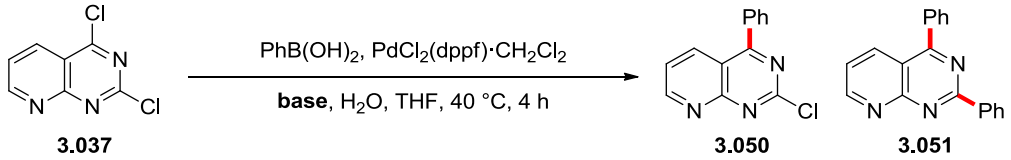
entry	base equivalents	conversion (%) (**3.037**:**3.050**:**3.051**)[a]
1	0	100:0:0
2	0.5	50:50:0
3	1	23:76:1
4	1.5	19:77:3
5	2	1:83:13
6	2.5	2:76:22
7	3	1:86:13

[a]Determined by HPLC analysis using an internal standard.

Table 3.03 Suzuki-Miyaura reaction base equivalents study.

Initially, tripotassium phosphate was completely removed from the reaction mixture which, as expected, resulted in no cross-coupling reaction occurring (entry 1). The addition of half an equivalent of base allowed for moderate levels of conversion to

the desired product, **3.050**, but a significant amount of starting material was still present (entry 2). When the amount of base was further elevated to one, one-and-a-half, and then two equivalents, conversion to the desired product reached good levels (entries 3, 4, and 5). Additional base, two and a half and three equivalents, gave similar conversion and levels of undesired product **3.051** and starting material (entries 6 and 7). Accordingly, the optimal amount of base to use in the reaction could be decreased to two equivalents, which still facilitated good conversion to the desired product, a small amount, 1%, of starting material remaining, and a limited amount of doubly cross-coupled product formed. Over the course of the base study it became apparent that the amount of base in the reaction mixture played a key role in ensuring that no overreaction occurred. A small number of bases were subsequently screened in order to determine if tripotassium phosphate was indeed the optimal base (Table 3.04).

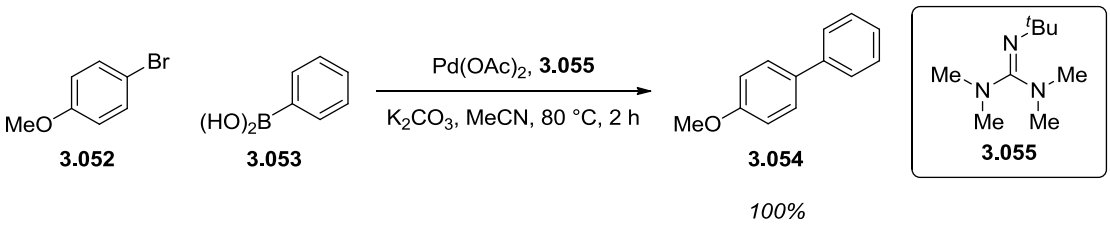


entry	base	conversion (%) (**3.037**:**3.050**:**3.051**)[a]
1	K_3PO_4	1:86:13
2	2-*tert*-butyl-1,1,3,3-tetramethylguanidine	0:0:10
3	KOAc	0:23:1
4	Na_2CO_3	67:14:0
5	K_2CO_3	62:4:23
6	Cs_2CO_3	1:61:31

[a]Determined by HPLC analysis using an internal standard.

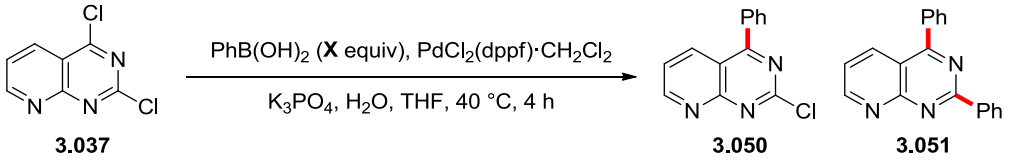
Table 3.04 Suzuki-Miyaura reaction base study.

Organobases such as guanidine have been employed successfully as bases in Suzuki-Miyaura cross-coupling reactions (Scheme 3.16).[178] In particular, the use of 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (TMG), **3.055**, has facilitated the cross-coupling of boronic acids with a wide range of arylhalides in good to excellent yields and high turnover numbers.[178]



Scheme 3.16 Organobase mediated Suzuki-Miyaura reaction.[178]

When this dibasic system was applied to the model reaction poor conversion was observed (entry 2). No starting material, **3.037**, or desired product **3.051** was detected, leading to the assumption that decomposition had occurred in the reaction mixture. The presence of wet base could also have facilitated facile S_NAr reaction of the pyridopyrimidine core. Other inorganic bases were then trialled in place of tripotassium phosphate, initially potassium acetate (entry 3). A low level of desired product formation was obtained with all starting material being consumed, possibly due to S_NAr reactions occurring between the nucleophilic acetate groups and the heteroaryl halide starting material. Another plausible side-reaction that could be taking place is S_NAr with any water present in the aqueous basic system. Carbonate bases provided mixed amounts of cross-coupling, with potassium carbonate providing the lowest, with only 4% product formation (entry 5). Changing the counterion to sodium and then to cesium contributed to a large increase in product formation (entries 4 and 6). However, these levels were still not as high as tripotassium phosphate and, as such, the same base was used in the following studies, starting with a boronic acid equivalents study (Table 3.05), which was conducted to determine if product formation could be improved without the formation of more undesired doubly cross-coupled product **3.051**.



3.037 **3.050** **3.051**

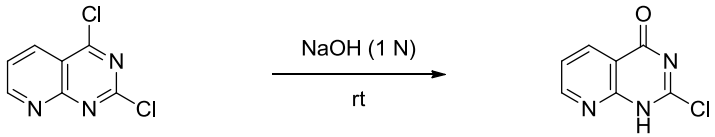
entry	boronic acid equivalents	conversion (%) (**3.037**:**3.050**:**3.051**)[a]
1	1.05	1:86:13
2	1.10	0:74:25
3	1.30	0:52:46
4	1.50	0:44:56

[a]Determined by HPLC analysis using an internal standard.

Table 3.05 Suzuki-Miyaura reaction boronic acid equivalents study.

Increasing the amount of boronic acid present in the reaction mixture from 1.05 to 1.10 equivalents showed an increase in conversion (entries 1 and 2). However, as expected, more undesired product, **3.051**, was also formed which was difficult to separate from the desired mono-coupled product, **3.050**. Further increasing the amount of boronic acid to 1.30 and 1.50 equivalents facilitated a large increase in by-product formation and lowered the amount of desired product formed (entries 3 and 4). From this study, it was determined that 1.05 equivalents of boronic acid were optimal for the reaction as it avoided a significant amount of by-product formation.

The amount of water present in Suzuki-Miyaura reactions can have a large effect on the outcome of the reaction.[177] This is particularly significant when halopyrimidine templates are involved in the reaction as S_NAr reactions readily transpire in aqueous basic conditions to yield pyrimidinone derivatives of type **3.056** (Scheme 3.17).[179]

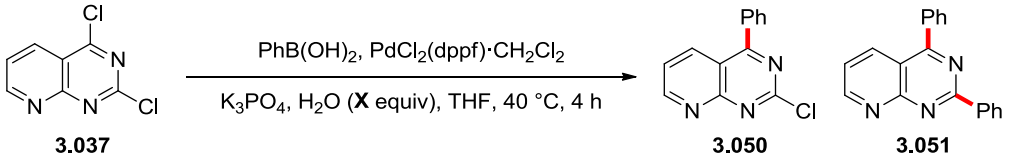


3.037 **3.056**

60%

Scheme 3.17 S_NAr reaction of 2,4-dichloro[2,3-*d*]pyrimidine under aqueous basic conditions.[179]

Therefore, analysis of the water content in the reaction system was investigated (Table 3.06). Moderate levels of conversion were observed when no additional water was added into the reaction mixture (entry 1). When the amount of water in the reaction mixture was doubled from five, as present in previous studies, to ten equivalents, conversion slightly decreased (entries 2 and 3). The addition of a further five equivalents of water afforded more by-product formation (entry 4) and increasing the amount of water to twenty equivalents showed no improvement on the original conditions (entry 5). Consequently, the amount of water in the reaction mixture was kept at five equivalents.



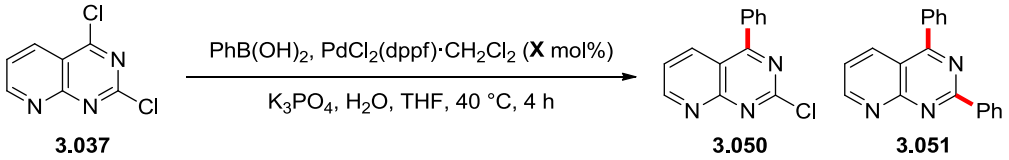
3.037 **3.050** **3.051**

entry	water equivalents	conversion (%) (**3.037**:**3.050**:**3.051**)[a]
1	0	33:66:1
2	5	1:86:13
3	10	1:82:16
4	15	0:81:18
5	20	1:85:12

[a]Determined by HPLC analysis using an internal standard.

Table 3.06 Suzuki-Miyaura reaction water equivalents study.

Next, the catalyst used in the reaction was explored. Initially the amount of catalyst present in the reaction mixture was lowered from 4 mol% to 1 mol% (Table 3.07). Incomplete conversion to the desired product was observed (entry 1). On increasing the amount of catalyst to 2.5 mol% (entry 2), conversion to the desired product vastly improved. Increasing the amount of catalyst to 5 mol% and then 7.5 mol% showed no significant improvement on the initial conditions used for the reaction (entries 4 and 5). The reaction was then scaled up to 0.1 g scale using 2.5 mol% of catalyst. This resulted in incomplete conversion to the desired product and, as such, 4 mol% of catalyst was used in all future reactions.



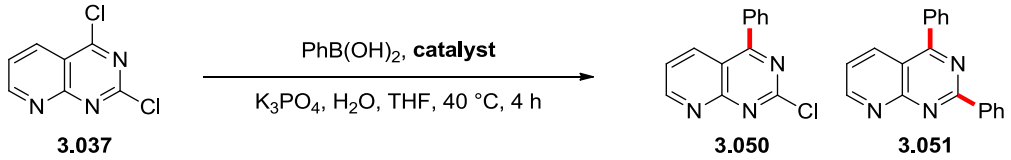
3.037 **3.050** **3.051**

entry	catalyst equivalents (mol%)	conversion (%) (**3.037**:**3.050**:**3.051**)[a]
1	1	35:65:0
2	2.5	1:80:15
3	4	1:86:13
4	5	0:90:9
5	7.5	0:88:11
6[b]	2.5	9:64:5[c]

[a]Determined by HPLC analysis using an internal standard. [b]0.10 g scale reaction. [c]Determined by LCMS analysis, 37% isolated yield.

Table 3.07 Suzuki-Miyaura reaction catalyst equivalents study.

With the quantity of catalyst required determined, attention then turned to the choice of catalyst (Table 3.08). Removal of the DCM adduct from the 1,1'-bis(diphenylphosphino)ferrocene (dppf) catalyst afforded similar levels of conversion (entries 1 and 2). However, changing ligands on the palladium(II) source to allyl, acetate, chloride, and acetonitrile resulted in no to poor levels of conversion to the desired product (entries 3, 4, 5, and 6). When PEPPSI^{TM}-IPr was used, good conversion to the desired product was observed with no starting material or over-reacted by-product detected (entry 7). $PdCl_2$(dppf) was chosen to conduct further studies due to the expensive price of the *N*-heterocyclic carbene PEPPSI^{TM} catalyst and removal of environmentally unfriendly DCM from the reaction system.[180]



3.037 **3.050** **3.051**

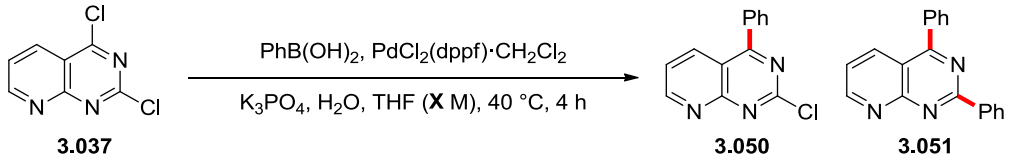
entry	catalyst	conversion (%) (**3.037**:**3.050**:**3.051**)[a]
1	$PdCl_2(dppf)\cdot CH_2Cl_2$	1:86:13
2	$PdCl_2(dppf)$	0:89:11
3	$[PdCl(allyl)]_2$	14:26:7
4	$Pd(OAc)_2$	1:3:16
5	$PdCl_2$	98:0:2
6	$PdCl_2(CH_3CN)_2$	100:0:0
7	PEPPSI™-IPr	0:98:2

[a]Determined by HPLC analysis using an internal standard.

Table 3.08 Suzuki-Miyaura reaction catalyst study.

The next reaction factor to be investigated was the concentration (Table 3.09). Concentration is a key factor in the Suzuki-Miyaura cross-coupling reaction as the relative rates of protodeboronation and transmetallation can be affected dramatically.[181] Lowering the concentration of the reaction from 0.25 M to 0.1 M resulted in a decrease in desired product formation (entries 3 and 2 respectively). Further dilution of the reaction mixture to 0.02 M gave minimal desired product formation (entry 1). Increasing the concentration to 0.5 M produced improved levels of product formation although the amount of solvent present was not sufficient to dissolve all of the reaction components (entry 4). The HPLC data generated was only a measure of conversion in solution. Resultantly, good conversion may be observed

in CPME but overall, there was still significant starting material remaining which was not dissolved in the solvent. This poor solubility meant that 0.5 M was not a feasible concentration at which to conduct the reaction and consequently, the previously employed concentration (0.25 M) was maintained.



3.037 **3.050** **3.051**

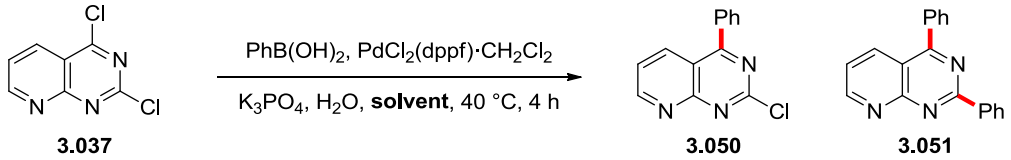
entry	concentration (M)	conversion (%) (**3.037**:**3.050**:**3.051**)[a]
1	0.02	99:1:0
2	0.1	1:97:2
3	0.25	1:86:13
4	0.5	0:92:8

[a]Determined by HPLC analysis using an internal standard.

Table 3.09 Suzuki-Miyaura reaction concentration study.

Finally, the reaction solvent was altered in an attempt to improve conversion of the reaction (Table 3.10). Originally, alcoholic solvents were trialled in the reaction as such solvents have been reported to give superior yields in Suzuki-Miyaura reactions.[25] *Tert*-butanol proved to be a good reaction solvent although not as proficient as THF (entries 1 and 2). Isopropanol also proved to be a good solvent but a significant amount of overreacted by-product **3.051** was formed (entry 3). Methanol and ethanol were very poor solvents as no desired product was formed due to a rapid S_NAr reaction occurring under the basic reaction conditions, with the solvent, or water, acting as a nucleophile (entries 4 and 5). Ethyl acetate (EtOAc) proved to be an excellent reaction solvent providing 88% conversion (entry 6). Other ethereal solvents 1,4-dioxane, cyclopentyl methyl ether (CPME), 2-MeTHF, and *tert*-

butyl methyl ether (TBME) were also generally good solvents for the cross-coupling reaction (entries 7, 8, 9, and 10).



3.037 **3.050** **3.051**

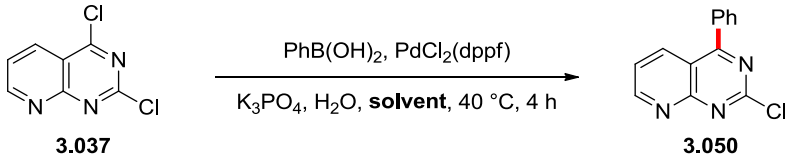
entry	solvent	conversion (%) (**3.037**:**3.050**:**3.051**)[a]
1	THF	1:86:13
2	^{t}BuOH	18:79:3
3	IPA	1:68:10
4	EtOH	7:0:24
5	MeOH	17:0:8
6	EtOAc	1:82:10
7	1,4-Dioxane	1:55:30
8	CPME	2:75:15
9	2-MeTHF	1:76:14
10	TBME	2:65:17

[a]Determined by HPLC analysis using an internal standard.

Table 3.10 Suzuki-Miyaura reaction solvent study.

With numerous solvents providing good levels of product formation the reaction was scaled-up in a number of solvents and isolated yields calculated (Table 3.11). THF and EtOAc produced good isolated yields with CPME also relatively high (Table

3.11, entries 1, 2, and 3). 2-MeTHF and TBME isolated yields were considerably lower than the HPLC conversion and, as such, were discarded (entries 4 and 5).



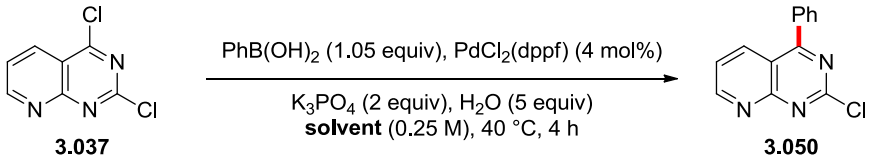
3.037 **3.050**

entry	solvent	yield (%)[a]
1	THF	73
2	EtOAc	75
3	CPME	72
4	2-MeTHF	43
5	TBME	40

[a]Isolated yields.

Table 3.11 Suzuki-Miyaura reaction solvent study – isolated yields.

As a result of the reaction study, optimised Suzuki-Miyaura conditions were established (Scheme 3.18). There was a choice of solvents that could be used for the reaction that produced good isolated yields. These solvents can be analysed in the hydrogenation step to see if a one-pot procedure is viable in any of these solvents. This flexibility in choice of reaction solvent could prove crucial in determining optimum conditions for the one-pot procedure.

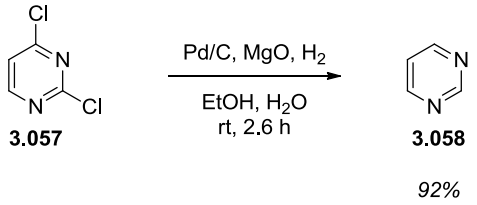


3.037 **3.050**

Scheme 3.18 Optimised regioselective Suzuki-Miyaura reaction conditions.

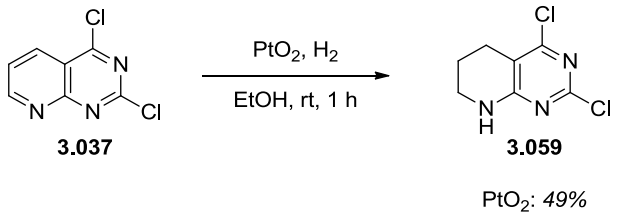
2.2 Hydrogenation optimisation

With optimised Suzuki-Miyaura reaction conditions in hand (Scheme 3.18); investigation began into the hydrogenation of the fused bicyclic system **3.050**. The major issue associated with heterocyclic reduction is the presence of a readily cleavable, arylchloride bond (Scheme 3.19).



Scheme 3.19 Hydrogenolysis of 2,4-dichloropyrimidine.

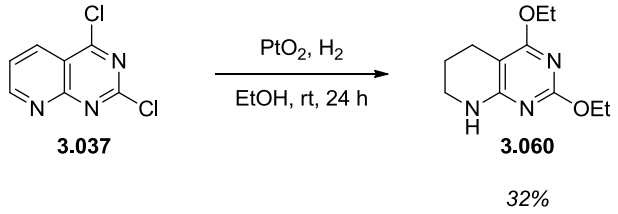
There have been relatively few investigations into the chemoselective reduction of such heterocycles, although one example from 1956 provided a solution to the chemoselectivity issue that could be envisaged; the use of Adams' catalyst, platinum(IV) oxide (Scheme 3.20).[182] The pyridine ring was reduced in moderate, 49% yield in ethanol. In fact, the authors had been attempting to reduce the arylhalide bonds and inadvertently discovered the chemoselective reduction. No follow-up work was performed by the authors to further explore this chemistry.



Scheme 3.20 Literature hydrogenation conditions.[182]

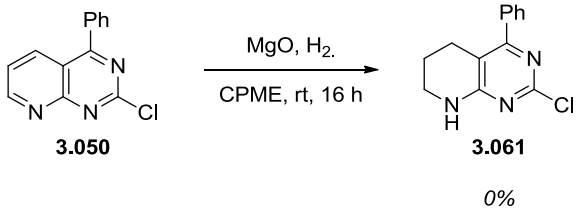
In a further attempt to reduce the arylchloride bonds, magnesium oxide was trialled by the authors which yielded the same compound, **3.059**, when the hydrogenation was carried out.[182] No comment on the reaction yield was made in the publication. Initial investigations focused on validating reduction conditions trialled in the literature (Scheme 3.20). Surprisingly, no hydrogenation was observed when

substrate **3.037** was treated with platinum(IV) oxide under an atmosphere of hydrogen in conventional hydrogenation apparatus (Scheme 3.21).



Scheme 3.21 Attempted validation of literature reduction conditions with platinum(IV) oxide.

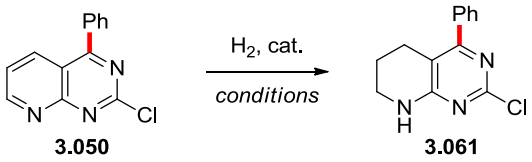
Instead, exclusive S_NAr reaction at both 2- and 4-arylhalide positions and hydrogenation was observed and isolated in poor 32% yield. Magnesium(II) oxide was also trialled in the hydrogenation reaction and 100% of the starting heterocycle, **3.050**, was recovered (Scheme 3.22).



Scheme 3.22 Attempted validation of literature reduction conditions with magnesium(II) oxide.

As such, to identify optimal reaction conditions in a concise manner, a number of catalysts and solvents were screened for the hydrogenation reaction of the cross-coupled ring system, **3.050**. A total of eight transition metal catalysts and six solvents were initially evaluated using catalyst screening technology (Table 3.12). The reactions were carried out in parallel in a CAT96 reactor (Figure 3.03). The CAT96 is a high-pressure screening unit that permits 96 simultaneous reactions to occur under the same pressure, temperature, and agitation conditions. The use of this technology allowed for the reactions to be stirred under an atmosphere of hydrogen (4 bar) and at the same temperature, in this case, ambient temperature. Conversion to the product was then determined by HPLC.

Figure 3.03 CAT96 reactor



entry	reaction conditions[a]	conversion (%)[b]
1	H_2, $Pd/BaSO_4$, CPME	9
2	H_2, $Pd/BaSO_4$, EtOAc	30
3	H_2, $Pd/BaSO_4$, EtOH	30
4	H_2, Pd/C, DMSO	12
5	H_2, Pd/C, EtOH	42
6	H_2, Pd/C, THF	78
7	H_2, Pd/Al_2O_3, CPME	71
8	H_2, Pd/Al_2O_3, EtOAc	55
9	H_2, Pd/Al_2O_3, THF	76
10	H_2, $RhCl(PPh_3)_3$, CPME	1
11	H_2, $RhCl(PPh_3)_3$, DMSO	0

12	H_2, $RhCl(PPh_3)_3$, EtOH	2
13	H_2, Rh/C, DMSO	54
14	H_2, Rh/C, EtOAc	7
15	H_2, Rh/C, PhMe	13
16	H_2, Ru/C, CPME	0
17	H_2, Ru/C, PhMe	0
18	H_2, Ru/C, THF	0
19	H_2, PtO_2, EtOAc	40
20	H_2, PtO_2, EtOH	21
21	H_2, PtO_2, PhMe	92
22	H_2, Pt/C, DMSO	8
23	H_2, Pt/C, PhMe	95
24	H_2, Pt/C, THF	95

[a]H_2 was applied at a pressure of 4 bar, 5 mol% of catalyst and 0.5 mL of solvent was used. The reactions were stirred for 16 h at ambient temperature. [b]Determined by HPLC analysis using an internal standard.

Table 3.12 Hydrogenation catalyst and solvent study.

Analysis of the data generated from the reaction screen was then performed. Preliminary investigations began with studying the conversion to product in various solvents (Chart 3.01). As observed previously, ethanol was a poor solvent for the reaction with a maximum conversion of 42% observed with palladium on carbon, presumably due to a large amount of S_NAr chemistry occurring or palladium-

catalysed protodehalogenation. DMSO and ethyl acetate were also poor solvents for the reduction with maximum conversion of 55% and 54% respectively. The best solvents, with multiple examples showing excellent (>90%) conversion, were toluene and THF. CPME also showed good conversion in one case, when palladium on alumina was used, although was arguably the worst solvent if this result is excluded. However, all catalyst-solvent combinations are not examined as a consequence of the screening technique used which could lead to the optimal conditions being overlooked. Specifically, excellent conversion was observed when platinum catalysts are used. Furthermore, there was no direct comparison between the ethereal solvents of THF and CPME. To ensure that optimal conditions were not overlooked, more detailed analysis of the data generated was conducted.

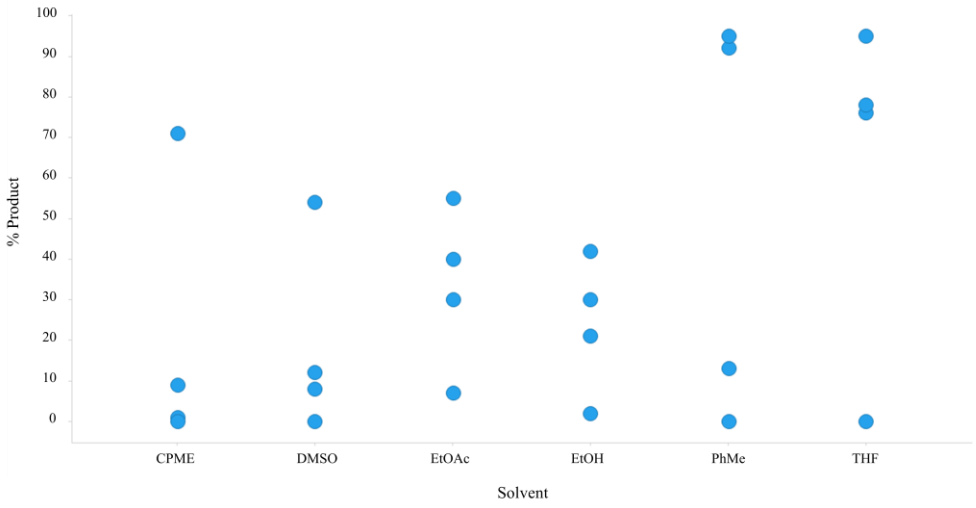


Chart 3.01 Conversion to product *vs*. solvent.

Examination of the proportion of remaining starting material would give an idea of the number of by-products forming when compared with the overall conversion chart above. A third variable, the reaction solvent, was added into the chart to allow for more extensive analysis (Chart 3.02).

Chart 3.02 Percentage of remaining starting material *vs*. catalyst.

Both Wilkinson's catalyst and ruthenium on carbon showed vast amounts of starting material present, irrespective of the solvent used. However, in all other cases, there was less than 20% starting material remaining meaning that there must be a significant number of reactive pathways occurring in the reaction mixture. In particular, rhodium on carbon provides low conversion to the desired product but significant impurities were formed. More conclusive data was then obtained in the form of plotting the conversion to product against the catalyst used in the reaction (Chart 3.03).

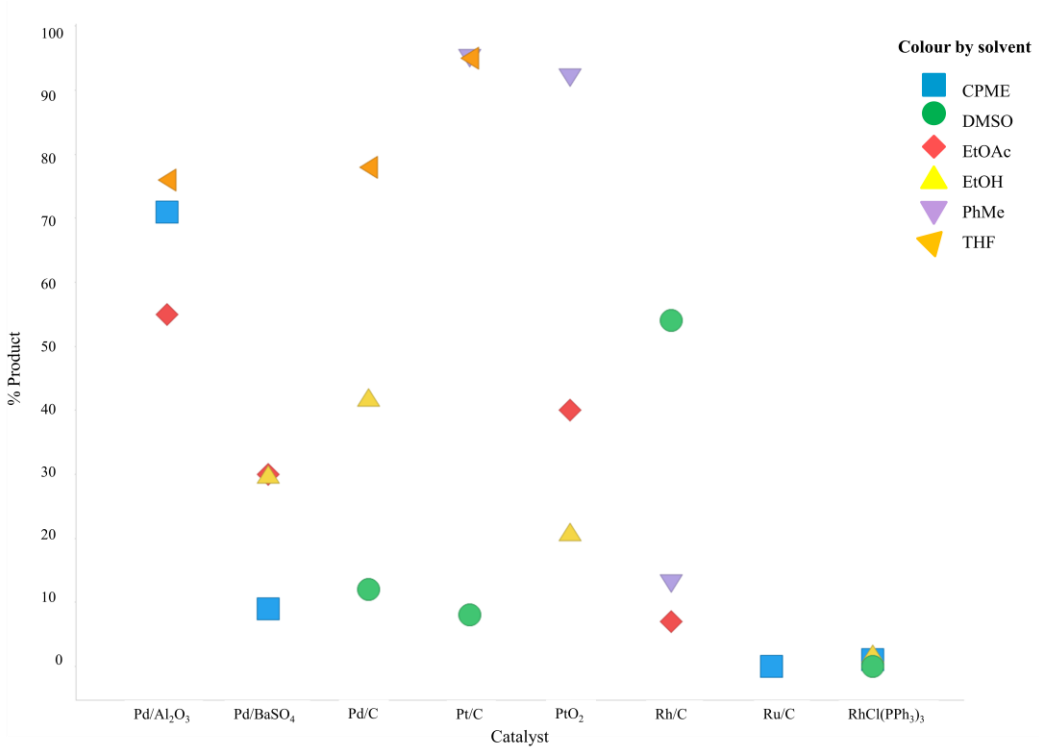
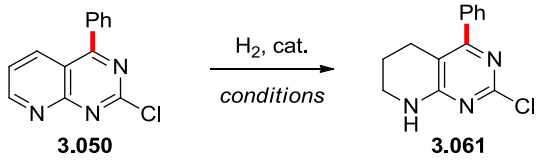


Chart 3.03 Percentage conversion to product *vs*. catalyst used.

As seen previously, Wilkinson's catalyst and ruthenium on carbon are extremely poor catalysts for the reaction giving no conversion to the desired product. Palladium on barium sulfate and rhodium on carbon are also relatively poor. However, palladium on alumina, palladium on carbon, platinum on carbon, and platinum(IV) oxide all show promising results, especially when combined with ethereal solvents THF or CPME. Despite the promising results obtained in the reaction screen, the one-pot procedure was not run at 4 bar of pressure, and was performed in totally different glassware (COware). The CAT96 was used in order to quickly screen a variety of catalyst and solvent combinations to quickly assess which systems would facilitate chemoselective pyridine reduction. As such, the best catalyst and solvent combinations were transferred into the COware reactor (Table 3.13).



3.050 **3.061**

entry	reaction conditions[a]	conversion[b] (**3.050**:**3.061**)	yield (%)[c]
1	H_2, Pd/Al_2O_3, THF	0:0	0
2	H_2, Pd/Al_2O_3, CPME	0:36	34
3	H_2, Pt/C, CPME	0:52	18
4	H_2, PtO_2, THF	0:51	39
5	H_2, PtO_2, CPME	0:89	96

[a]5 mol% of catalyst and 1 mL of solvent were used in COware. Zinc and aqueous hydrochloric acid were used to generate hydrogen. [b]Determined by LCMS analysis. [c]Isolated yields.

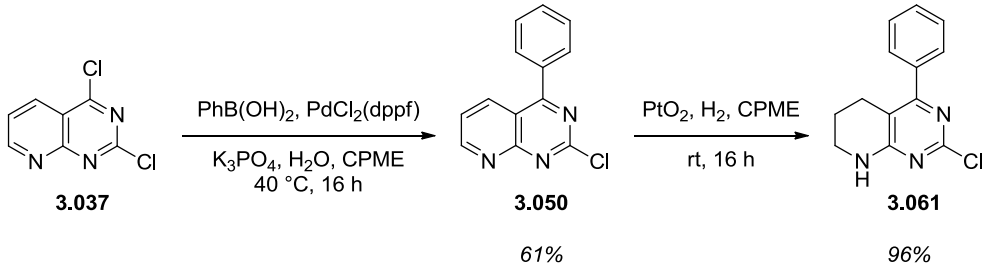
Table 3.13 Isolated yields of semi-saturated compound **3.050** when hydrogenation reaction performed in COware.

When five sets of optimal conditions from the catalyst screen were transferred to COware (Table 3.13) the results were conclusive as to which set of conditions were optimal for the one-pot procedure. No desired product was isolated when palladium on alumina in THF combination was used (entry 1). When the solvent was changed to CPME the desired reduced product was isolated in 34% yield (entry 2). A poor 18% yield was obtained when the solvent and catalyst were altered to platinum on carbon in CPME (entry 3). Using platinum(IV) oxide as the catalyst, an improved isolated yield of 39% was obtained (entry 4). Pleasingly, on changing the solvent to CPME, an excellent yield of pure product was accomplished (entry 5). These conditions were deemed optimal to take forward into the one-pot Suzuki-Miyaura/hydrogenation procedure. Pleasingly, both cross-coupling and

hydrogenation optimised procedures proceeded well in CPME, which avoided the need for a solvent swap (Scheme 3.18 and Table 3.13).

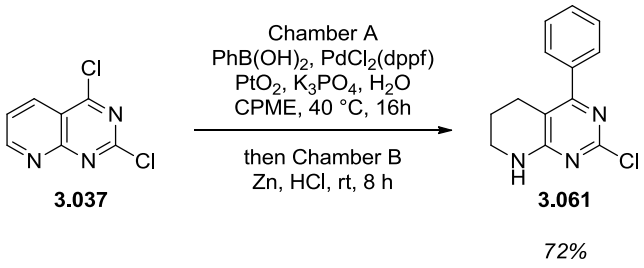
2.3 One-pot Suzuki-Miyaura/hydrogenation procedure

The potential for a one-pot procedure was next examined after optimal reaction conditions had been identified for both individual Suzuki-Miyaura and hydrogenation steps (Scheme 3.23).



Scheme 3.23 Optimal individual steps for the one-pot procedure.

Gratifyingly, when the two individual steps were performed in succession in COware, the desired cross-coupled and reduced substrate, **3.061**, was isolated in good yield over two steps (Scheme 3.25), corresponding to 87% conversion for each individual step. To further simplify the experimental procedure of the one-pot process, platinum(IV) oxide was added to the COware apparatus prior to the Suzuki-Miyaura reaction (Scheme 3.24).

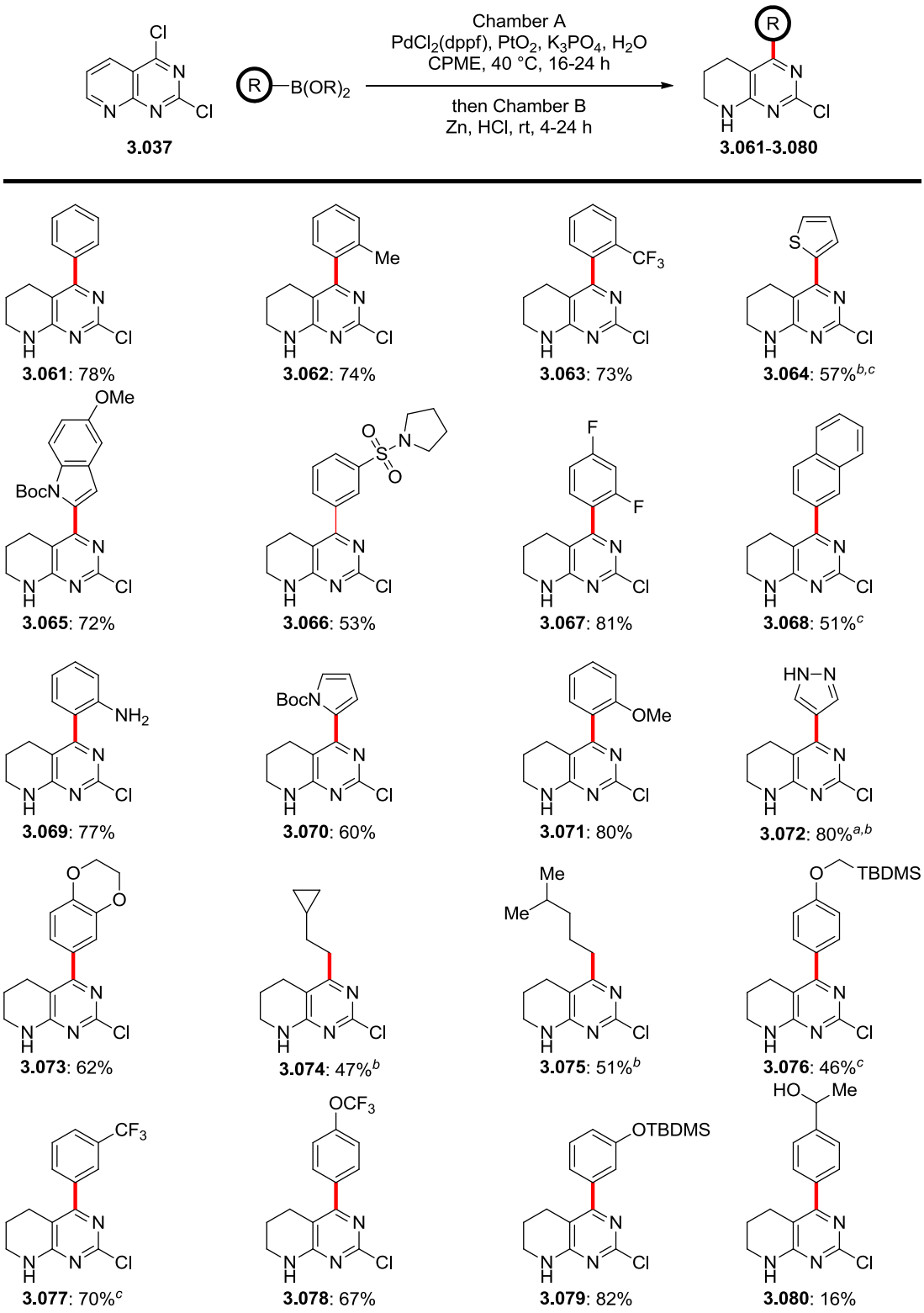


Scheme 3.24 Impact of platinum(IV) oxide on the Suzuki-Miyaura reaction.

The addition of platinum(IV) oxide to the reaction mixture was not shown to be detrimental to the process with the desired heterocycle **3.061** being isolated in good,

72% yield. The yield for the one-pot procedure (Scheme 3.24) was considerably greater than that of the two individual steps (Scheme 3.23).

Therefore, only the hydrogen-generating materials, zinc and hydrochloric acid, need to be added to chamber B after the completion of the Suzuki-Miyaura reaction. Subsequently, the boronic acid substrate scope was explored (Scheme 3.25).



Scheme 3.25 Nucleophile substrate scope of the one-pot Suzuki-Miyaura/hydrogenation procedure. [a]HCl (as a 3 M solution in CPME) was added to

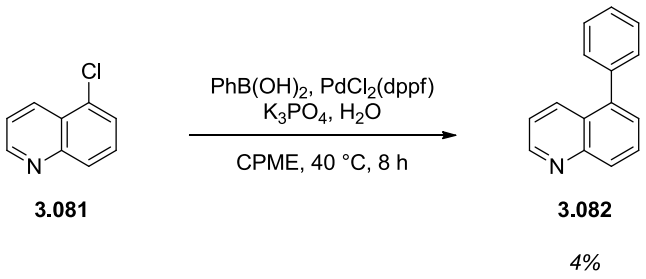
the reaction mixture after hydrogenation. [b]BPin ester was used. [c]AcOH was added to chamber A after completion of Suzuki-Miyaura reaction.

Initially, adding steric bulk around the boronic acid nucleophile diminished the yield slightly with the electronic nature of the *ortho*-substituent having a negligible effect on reactivity (**3.062** and **3.063**). The mild reaction conditions were tolerant of a wide variety of functionality, including a selection of heterocycles such as thiophene, indole, pyrrolidine, pyrrole, and pyrazole (**3.064**, **3.065**, **3.066**, **3.070**, and **3.072**). Interestingly, Boc-protected nitrogen-containing heteroaromatics can be successfully incorporated into the one-pot procedure (**3.065** and **3.070**). Furthermore, the protecting group can be easily removed by the addition of acid into the reaction mixture, effectively performing three reactions: a cross-coupling, hydrogenation, and deprotection, in one-pot as demonstrated by pyrrole **3.072**. Free heteroatoms are also tolerated in the process demonstrated by aniline, **3.069**.

Additionally, boronic esters can be incorporated into the Suzuki-Miyaura reaction by simply increasing the equivalents of water present in the reaction from five to twenty. This allows for efficient cross-coupling to occur, exemplified by the use of stable vinyl boronic esters in the cross-coupling reaction. The resulting olefin was also reduced when hydrogen was introduced into the reaction system, formally generating a Csp^2-Csp^3 bond in one-pot (**3.074** and **3.075**). Silyl groups are also legitimate protecting groups for the reductive procedure with the bulky *tert*-butyldimethylsilyl (TBDMS) group remaining intact throughout the reaction (**3.076** and **3.079**).

Interestingly, when a methyl ketone was present, the Suzuki-Miyaura step proceeded smoothly. However, on introduction of hydrogen into the system, both pyridine and ketone functionalities were successfully reduced, albeit in poor yield, **3.080**.

With the nucleophile substrate scope explored, attention then turned to the electrophilic partner in the cross-coupling reaction. Incomplete conversion to the desired bicycle was observed by LCMS when the optimal conditions from the previous dichlorinated heterocycle **3.037** were trialled on 5-chloroquinoline **3.081** (Scheme 3.26).

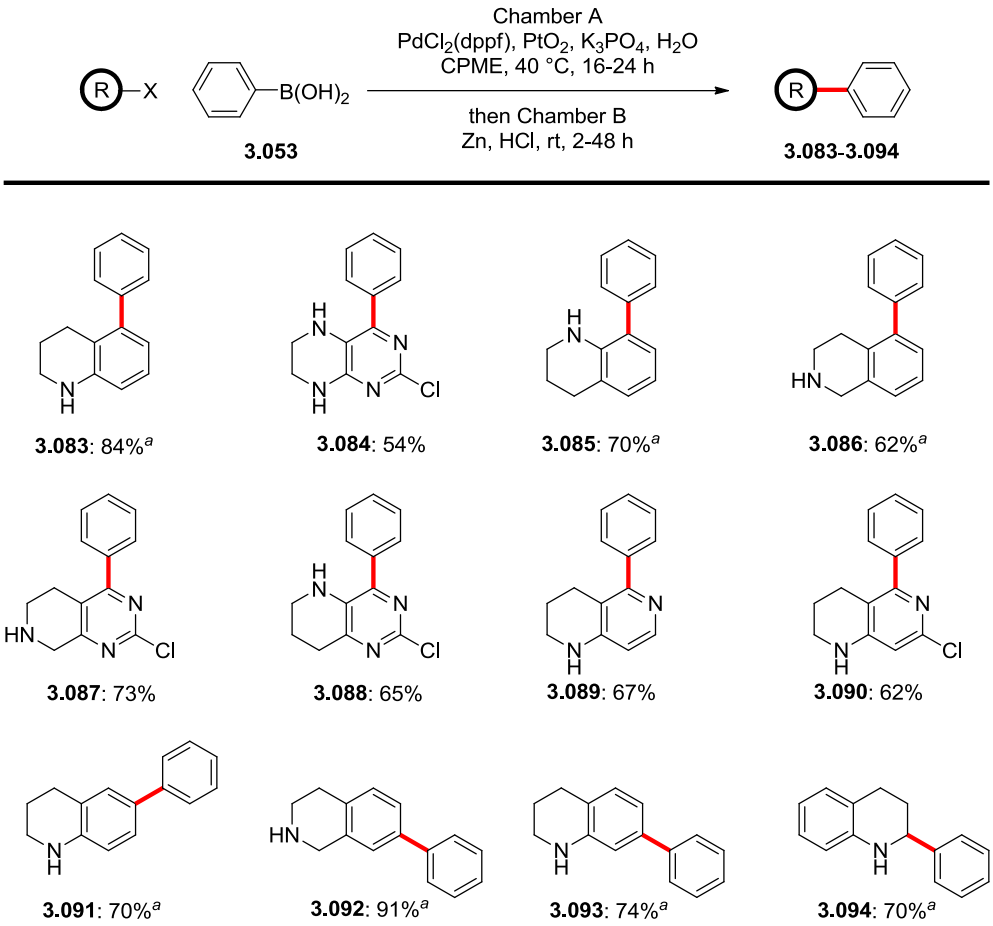


3.081 **3.082**

4%

Scheme 3.26 Trial Suzuki-Miyaura reaction on a chloroquinoline core. Conversion determined by LCMS.

It was vitally important to ensure that the reaction progressed to completion to aid purification of the reduced products; coelution was prevalent if the initial Suzuki-Miyaura reaction had not progressed to completion if overreaction had occurred. As such, brominated heterocycles were employed to aid oxidative addition.[183] This enhanced reactivity, coupled with the use of the more active palladium-ligand combination of palladium(II) acetate and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos), propagated the cross-coupling reactions to completion within 24 h. Accordingly, all substrates that did not proceed to completion with the original cross coupling conditions of $PdCl_2$(dppf) were run using the new catalyst-ligand combination (Scheme 3.27). The palladium(II) acetate conditions were not attempted with any dichlorinated heterocycles as significant amounts of cross-coupling at both arylhalide positions was observed.

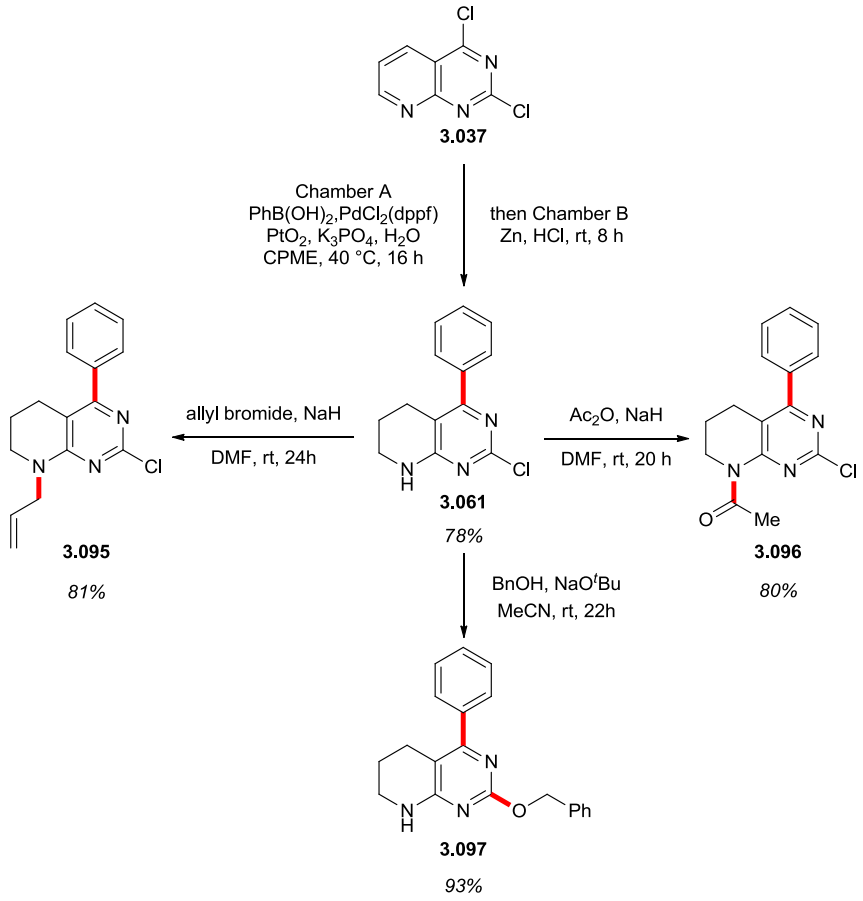


Scheme 3.27 Electrophile substrate scope of the one-pot Suzuki-Miyaura hydrogenation procedure. [a]$Pd(OAc)_2$ (4 mol%), XPhos (8 mol%) were used instead of $PdCl_2(dppf)$. 1.5 equivalents of $PhB(OH)_2$ was used.

A number of quinoline and isoquinoline derivatives were successful substrates in the one-pot procedure, generating secondary amine and anilinic functional handles which could undergo further functionalisation (Scheme 3.27, **3.083**, **3.085**, **3.086**, and **3.091**–**3.094**). 2,4-Dichloropteridine also underwent regioselective cross-coupling followed by facile hydrogenation to generate tetrahydropteridine **3.084** in moderate yield. The position of the nitrogen atom in the pyridine ring could also be altered, affording compounds **3.087** and **3.088** in good yield. Cross-coupling and hydrogenation could also be facilitated on the same ring, forming a racemic centre on reduction (compound **3.094**). Other heterocyclic variants were also successful in the one-pot procedure, specifically tetrahydronaphthyridine compounds **3.089** and **3.090**.

2.4 Functionalisation of THPP derivatives

One of the key properties of the products synthesised from the one-pot procedure is the presence of two complementary functional handles; namely a nucleophilic aniline and an electrophilic arylchloride. Their reactivity was investigated to show that they have the potential to be reacted further (Scheme 3.28).



Scheme 3.28 Functionalisation of THPP derivatives.

Initially, the aniline was reacted with allyl bromide under basic conditions. A strong base, sodium hydride, was required to ensure that the reaction progressed to completion, despite the inherent reactivity of the electrophile. In a similar fashion, acetamide formation was effected though treatment of the semi-saturated intermediate, **3.061**, with acetic anhydride and sodium hydride. The arylchloride moiety readily underwent S_NAr chemistry when treated with benzyl alcohol and sodium *tert*-butoxide. The desired disubstituted product was obtained in excellent

93% yield. Reaction with both nucleophilic and electrophilic functional handles was facile showing that the semi-saturated core, **3.061**, can be elaborated.

2.5 Synthesis of semi-saturated inhibitors

Substituted pyridopyrimidine derivatives have long been established as important scaffolds in the drug discovery literature due to their broad spectrum of biological activity including their antifolic,[184] antipyretic,[185] analgesic,[186] and antihistaminic properties,[187] as well as their use as phosphodiesterase 4 (PDE4) inhibitors,[188] adenosine kinase inhibitors (AKI), tyrosine kinase inhibitors (TKI),[189] and diuretics.[179,190] In particular, pyridopyrimidine derivatives were reported to exhibit antitumor activity,[191] which may be attributed to inhibition of cyclin-dependent kinase,[192,193] check point kinase, **3.098**,[194] or mammalian target of rapamycin (mTOR), **3.099** (Figure 3.04).[195]

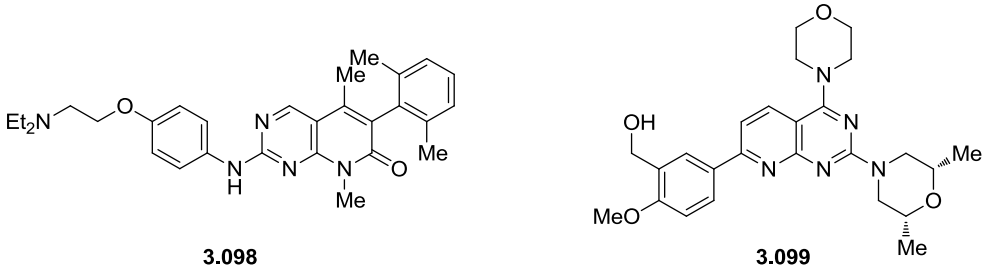
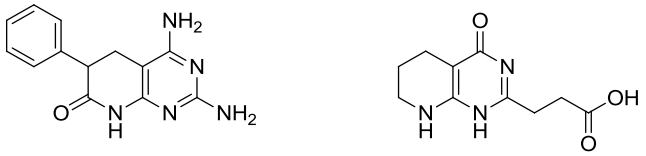


Figure 3.04 Check point kinase, **3.098**, and mTOR, **3.099**, inhibitors.

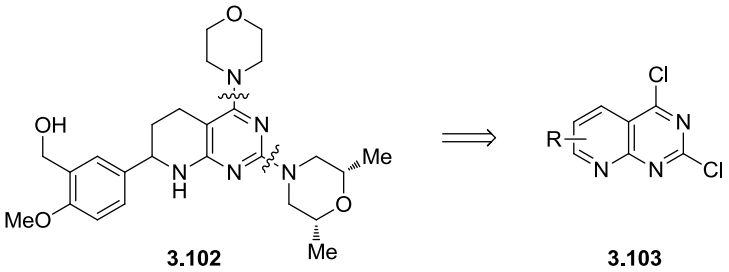
However, there has been relatively little research around the biological activity of the related semi-saturated THPP systems (Figure 3.05). The lack of exploration around this template is predominantly due to the difficulties in synthesis and, in particular, the often linear nature of analogue formation; namely that functionality must be introduced early in the synthesis. This leads to difficulties in SAR exploration of THPP and THPP-like templates.



3.100 **3.101**

Figure 3.05 Epidermal growth factor receptor, **3.100**, and tankyrase kinase, **3.101**, inhibitors.[196,197]

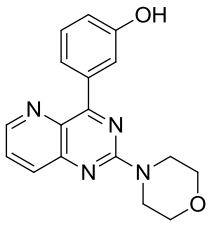
Therefore, we envisaged that access to novel heterocyclic cores in a one-pot procedure, through the combination of conventional Suzuki-Miyaura cross-coupling, nucleophilic aromatic substitution, and hydrogenation reactions utilising new COware technology, was possible (Figure 3.06).



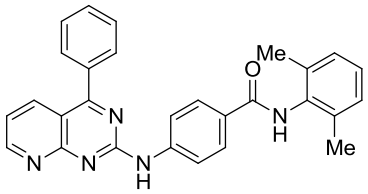
3.102 **3.103**

Figure 3.06 Reterosynthetic analysis of potential semi-saturated mTOR inhibitor **3.102** to a commercially available heterocycle.

Semi-saturated THPPs are attractive pharmacophores, as increasing the fraction of sp^3 (Fsp^3) hybridized carbon atoms that a compound contains has been shown to improve its physiochemical properties, in particular, decreasing melting point and increasing solubility.[198] Furthermore, a reduction in promiscuity and decrease in cytochrome P450 (CYP450) inhibition has also been publicised.[199] Consequently, both saturated and semi-saturated versions of inhibitors **3.104** and **3.105** will be synthesised in order to determine what impact saturation of the pyridopyrimidine system has on the physicochemical properties of the molecules (Figure 3.07).



3.104



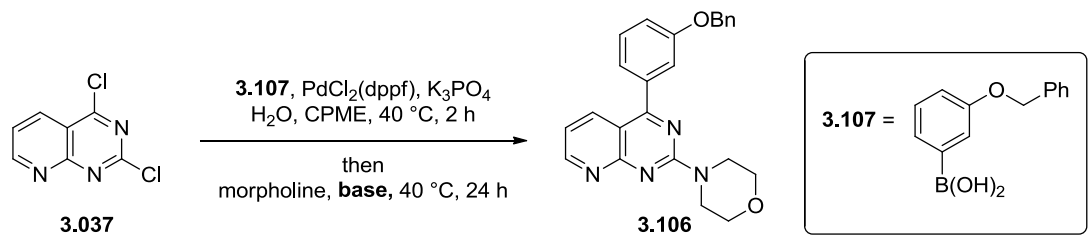
3.105

Figure 3.07 Unsaturated dual PI3K/mTOR, **3.104**, and hedgehog, **3.105**, inhibitors.[200]

With a regioselective Suzuki-Miyaura/hydrogenation procedure already established, unsaturated pyridopyrimidine inhibitors **3.104** and **3.105** were seen as ideal targets for the incorporation of a hydrogenated pyridine ring (Figure 3.07). No optimisation would have to be completed on the initial Suzuki-Miyaura reaction to install a phenyl derivative at the 4-position (*vide infra*). Furthermore, the chlorine atom is also not present when hydrogenation takes place, removing the need for such mild hydrogenation conditions and any potential regiochemical issues associated with the presence of an arylchloride bond.

2.5.1 Synthesis of unsaturated inhibitors

Initially, model substrate **3.037** was used to trial S_NAr reaction conditions. A small base study was initially conducted in order to determine the optimal base for the S_NAr reaction (Table 3.14). The equivalents of base used are pivotal in the preliminary Suzuki-Miyaura reaction to gain complete regioselectivity and avoid any overreaction. As such, extra base was added into the reaction mixture after completion of the cross-coupling step along with morpholine to facilitate the substitution reaction. Tripotassium phosphate, cesium carbonate, sodium bicarbonate, potassium acetate, potassium carbonate, sodium carbonate, and *N*,*N*-diisopropylethylamine (DIPEA) were all added into the reaction and complete conversion of the intermediate Suzuki coupled material to desired product **3.106** was observed in all cases.

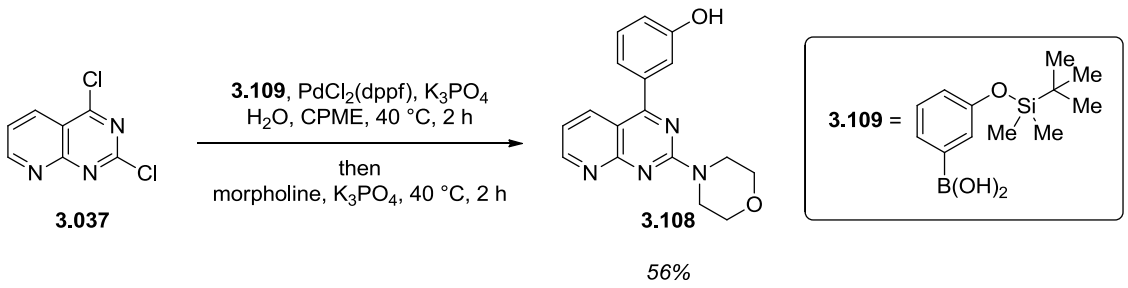


entry	base	conversion (%)[a]
1	Cs_2CO_3	46
2	$NaHCO_3$	65
3	KOAc	48
4	K_2CO_3	46
5	Na_2CO_3	46
6	K_3PO_4	59
7	DIPEA	52

[a]Determined by LCMS analysis.

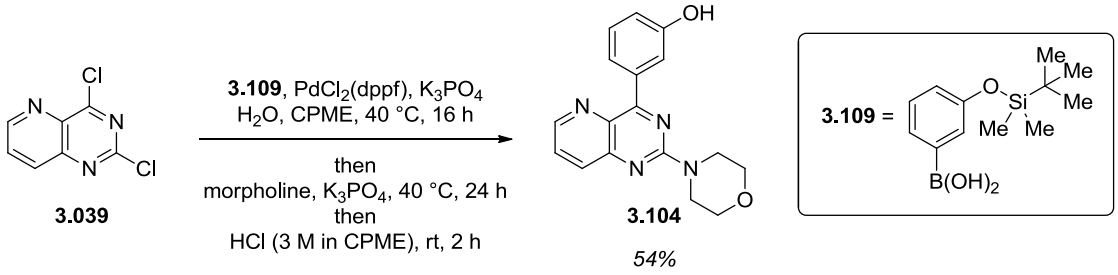
Table 3.14 Base study for one-pot Suzuki-Miyaura/S_NAr reaction.

Consequently, tripotassium phosphate was chosen in order to maintain consistency with the previous cross-coupling step. The optimal conditions were then applied to the model substrate **3.037** in order to determine if the three-reaction, one-pot procedure was possible (Scheme 3.29). Silyl protection of the alcohol was required to allow the Suzuki-Miyaura reaction to progress to completion. This change from the benzyl protecting group previously used (Table 3.14) was due to the ease of protecting group removal, *i.e.*, the silyl protecting group is more easily removed under less forcing conditions than a benzyl group. Gratifyingly, the desired product was obtained in good 56% yield over the two steps in one-pot. The silyl protecting group was removed on heating during the nucleophilic substitution step of the reaction, avoiding the need for a separate deprotection step.



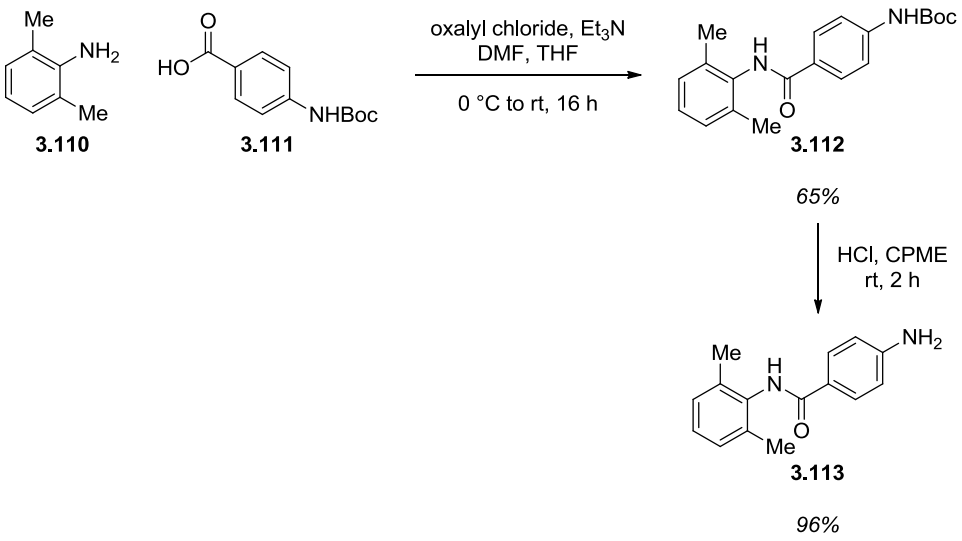
Scheme 3.29 One-pot synthesis of model substrate, **3.108**.

A published dual PI3K/mTOR inhibitor, **3.104**, was then synthesised in a similar fashion (Scheme 3.30).[200] The desired unsaturated inhibitor was obtained in 54% yield. In this case the silyl protecting group was not concomitantly removed in the final step and so excess acid was added to the reaction mixture which facilitated clean deprotection. In comparison, the published synthesis of the same inhibitor was completed over three steps with an overall isolated yield of 18%, considerably lower than the 54% yield derived from the one-pot procedure.



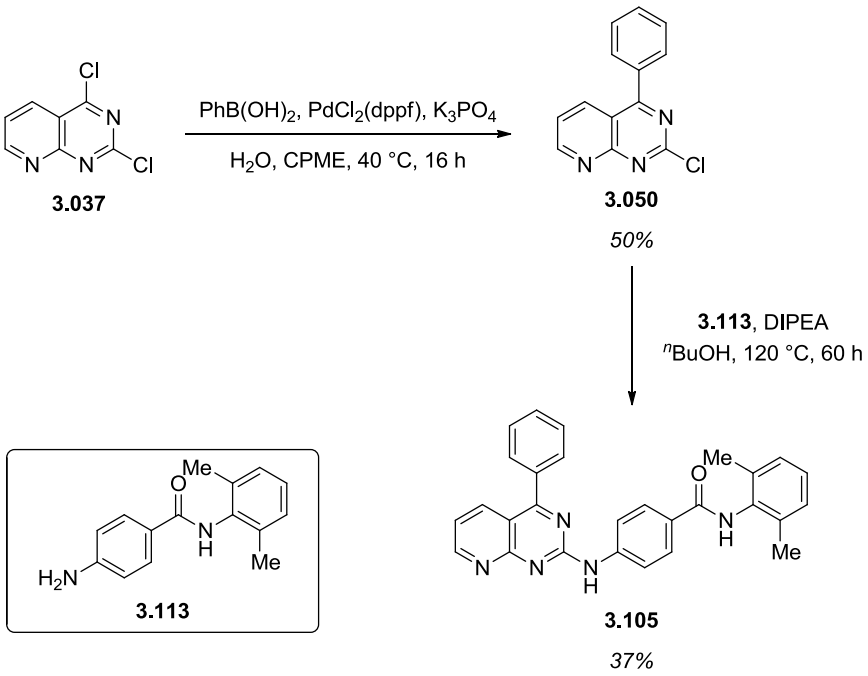
Scheme 3.30 One-pot synthesis of a saturated PI3K/mTOR inhibitor.

Attention turned next to the synthesis of the fully unsaturated hedgehog inhibitor **3.105**. Aniline **3.113** was synthesised in two steps from commercially available aniline, **3.110**, and carboxylic acid, **3.111** (Scheme 3.31). Initially oxalyl chloride mediated amine coupling furnished amide **3.112** in moderate yield. Boc removal using hydrochloric acid produced the free amine in excellent 96% yield.



Scheme 3.31 Synthesis of amine **3.113**.

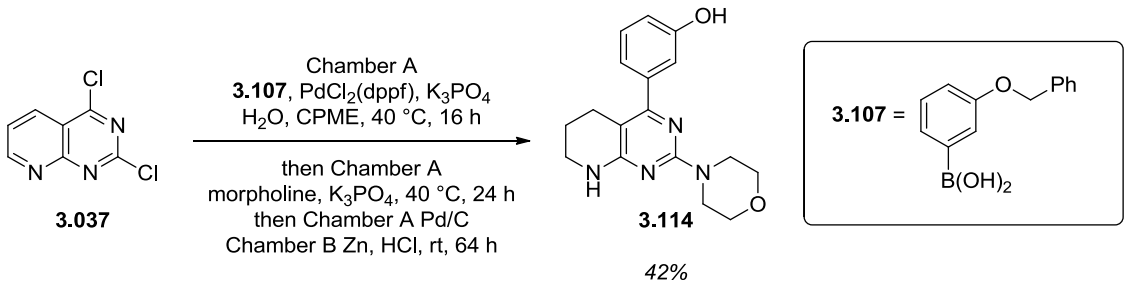
Due to the perceived difficulty of the second S_NAr reaction, the synthesis of **3.105** was completed in two separate reactions (Scheme 3.32). The regioselective Suzuki-Miyaura reaction proceeded smoothly, however, the subsequent S_NAr reaction was problematic due to significant amounts of butanol substitution, observable by LCMS, at the 2-position. Despite this drawback, the fully unsaturated product **3.105** was isolated in 37% yield. All three saturated inhibitors were then submitted for physicochemical property analysis.



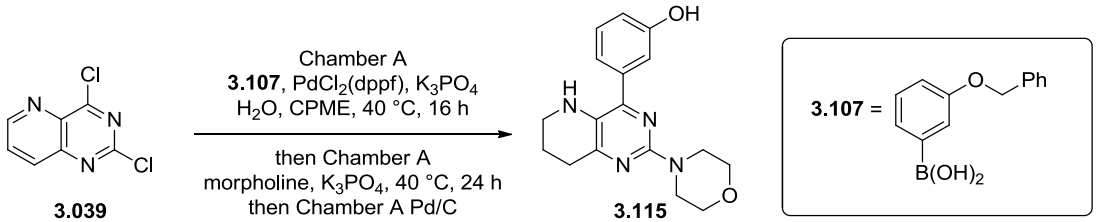
Scheme 3.32 Synthesis of a saturated hedgehog inhibitor.

2.5.2 Semi-saturated inhibitor synthesis

The semi-saturated versions of inhibitors **3.104**, **3.105** and **3.108** were then synthesised (Schemes 3.33, 3.34, and 3.35). The PI3K/mTOR inhibitors were then prepared initially, due to the enhanced nucleophilicity of morpholine relative to aniline **3.113** making the S_NAr reaction considerably simpler. Pleasingly, in both cases, the desired semi-saturated systems were isolated in good yield, corresponding to over 70% yield for each individual step (Schemes 3.33 and 3.34). In both cases the phenol was benzyl-protected. The benzyl group was then removed through hydrogenolysis at the same time that the pyridine ring was being reduced. The choice of a benzyl protecting group avoided the need for a separate step for protecting group removal. Furthermore, palladium on carbon was used for the reduction step as it gave a faster reaction time than platinum(IV) oxide and there are no other reducible groups in the material that could be affected.

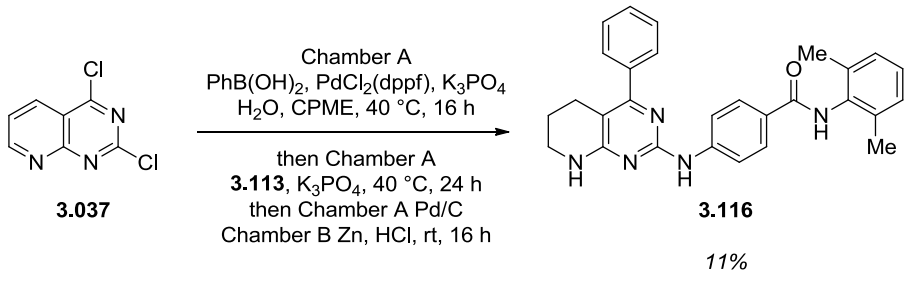


Scheme 3.33 One-pot synthesis of a model compound **3.114**.



Scheme 3.34 One-pot synthesis of a semi-saturated PI3K/mTOR inhibitor analogue.

The semi-saturated hedgehog inhibitor **3.116** was then synthesised (Scheme 3.35). The Suzuki-Miyaura reaction proceeded to completion, as determined by LCMS analysis. However, the anilinic nucleophile was poor, resulting in incomplete conversion in the S_NAr reaction, accounting for the low overall yield of desired compound **3.116**. Pyridine reduction progressed smoothly to generate the desired semi-saturated inhibitor in 11% overall yield, corresponding to an average yield of 48% per step.



Scheme 3.35 One-pot synthesis of a semi-saturated Hedgehog inhibitor analogue.

2.5.2 Physicochemical properties of medicinal chemistry templates from the literature

When model PI3K/mTOR pyridopyrimidine system **3.108** was hydrogenated to the semi-saturated THPP **3.114**, a considerable improvement in solubility, over 20 fold, was observed (Table 3.15). The property forecast index (PFI)[201] which is a measure of compound developability (PFI = $logD_{7.4}$ + number of aromatic rings), dropped primarily due to the removal of one aromatic ring. The free fraction of compound in human serum albumin also increased and a significant increase in permeability was also observed. As expected the fraction of sp^3 (fsp^3) hybridised carbon atoms increases, giving the compound more chance of success in the clinic through, in theory, decreasing promiscuity.[198,199]

Saturating the pyridine ring in Hedgehog inhibitor **3.105** had a significant impact on the physicochemical properties of the system (Table 3.15). Of particular interest was the marked increase, over ten fold, in the solubility of the semi-saturated compound **3.116** compared to the fully unsaturated analogue **3.105**. This trend correlates well with the previous example, **3.108** to **3.114**. Furthermore, a drop in PFI was also observed in moving to the semi-saturated analogue **3.116**. Also of interest, is the significant increase in permeability observed, from 375 nm/sec to 815 nm/sec. Finally, the fsp^3 hybridised carbons increases considerably from 0.07 to 0.18.

These date correlate well with the improved physicochemical properties when using the COware methodology to synthesise semi-saturated analogues of medicinal chemistry relevant templates in the literature.

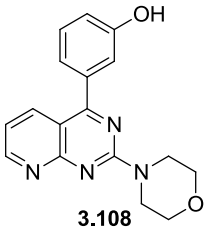
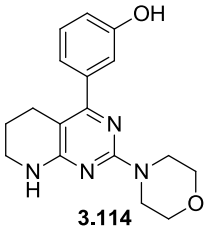
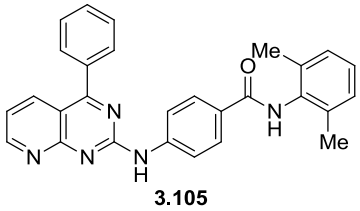
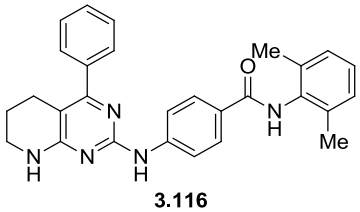
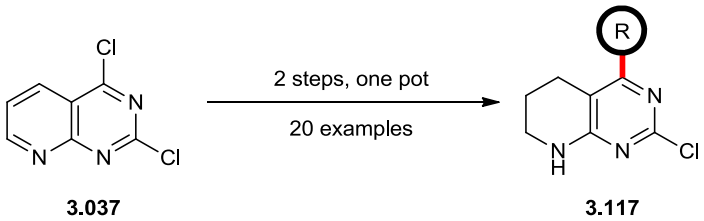
compound	fsp^3	solubility (μg/mL)	PFI	HSA	permeability (nm/sec)
 **3.108**	0.24	14	5.9	90.1	150
 **3.114**	0.41	308	5.5	89.2	395
 **3.105**	0.07	3	10.8	97.7	375
 **3.116**	0.18	31	9.7	93.3	815

Table 3.15 Physicochemical properties of saturated and semi-saturated PI3K/mTOR and Hedgehog inhibitors.

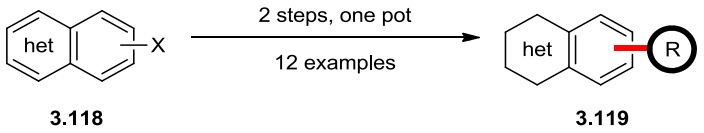
3 Conclusion

In summary, we have demonstrated the efficient synthesis of a number of 5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidinone derivatives through a one-pot sequential Suzuki-Miyaura/hydrogenation procedure utilising COware (Scheme 3.36).



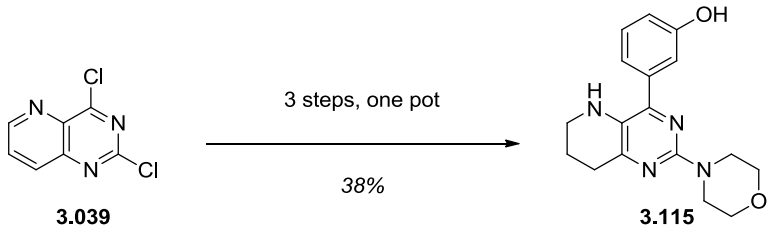
Scheme 3.36 General synthesis of THPP derivatives.

The mild conditions are tolerable to a range of aryl and vinyl borates. This methodology provides expedient access to highly functionalized, novel heterocyclic cores with further functional handles for elaboration. The electrophilic arylchloride and nucleophilic aniline residues have been further reacted, which demonstrates the synthetic utility of the process. The scope of the electrophilic heteroaromatic ring has also been explored with a variety of pyridine-containing heterocycles successfully cross-coupled and reduced (Scheme 3.37).



Scheme 3.37 Electrophile substrate scope of the one-pot process.

In addition, the synthesis of semi-saturated PI3K/mTOR and Hedgehog analogues have also been demonstrated (Scheme 3.38). These novel motifs show improved physicochemical properties compared to their fully unsaturated counterparts due to the increased fraction of sp^3 hybridized carbon atoms in the molecules.

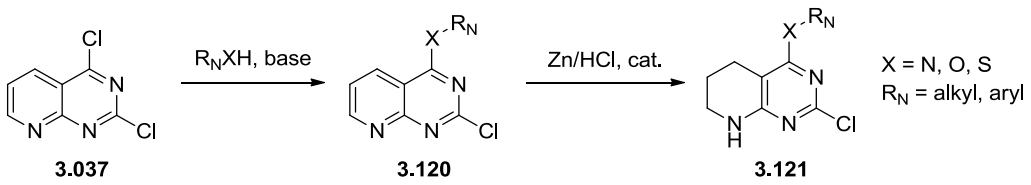


Scheme 3.38 One-pot synthesis of a semi-saturated PI3K/mTOR analogue, **3.115**.

In general, semi-saturation increased the solubility, permeability, and free fraction whilst at the same time reducing the PFI of the PI3K/mTOR and Hedgehog molecules. Overall, partial reduction of a pyridopyrimidine system in drug-like compounds leads to a favorable modification of physicochemical properties.

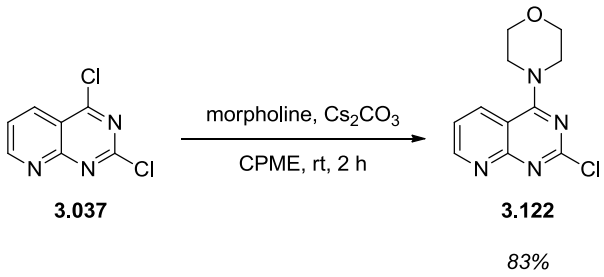
4 Future work

With optimal conditions for a one-pot cross-coupling/hydrogenation procedure established attention then turned to the use of other nucleophiles in the one-pot process. Regioselective S_NAr reactions are known to occur at the 4-position of the pyridopyrimidine ring in a similar fashion to cross-coupling reactions (Scheme 3.39).[202] Nucleophilic substitution could then be combined with the same hydrogenation conditions used previously to furnish a variety of drug-like cores of type **3.121**.



Scheme 3.39 Proposed S_NAr-hydrogenation reaction.

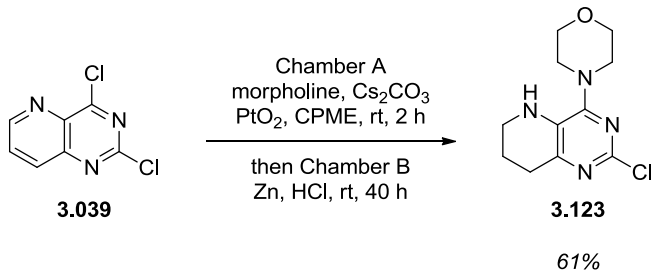
A quick reaction optimisation was completed using morpholine as nucleophile (Scheme 3.40). Optimal conditions were deemed to be using a slight excess of morpholine (1.05 equiv) and cesium carbonate as base in CPME at ambient temperature. The desired product, **3.122**, was isolated in 83% yield.



Scheme 3.40 Application of optimised S_NAr conditions to a nitrogen nucleophile.

The optimised S_NAr reaction conditions were then combined with the previously optimised reduction conditions to probe whether a one-pot S_NAr/hydrogenation reaction was possible (Scheme 3.41). Gratifyingly, the desired semi-saturated

compound was isolated in 61% overall yield meaning that a variety of carbon-heteroatom linkers could, in theory, be synthesised.



Scheme 3.41 Application of S_NAr/hydrogenation conditions to a pyridopyrimidine template.

The scope of the nucleophile could be expanded utilizing the optimised one-pot procedure. This would allow the synthesis of a variety of drug-like compounds to be synthesised. These could then be screened within the GSK enhanced cross-screen panel to look for any sign of activity at a variety of receptors. The nucleophiles chosen would be taken from a series of compounds put together by GSK that, once formed, will give desirable physiochemical properties to the final target compounds (Figure 3.08).[203]

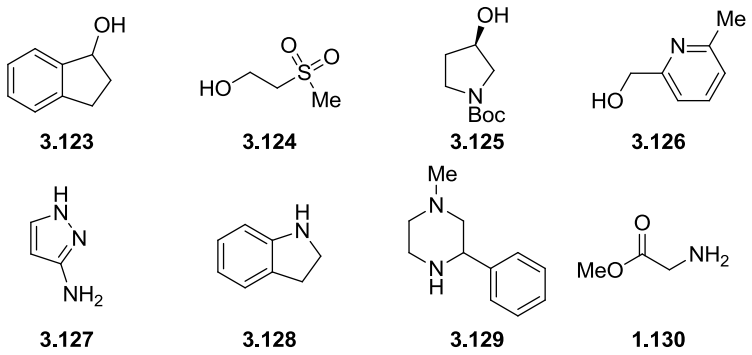
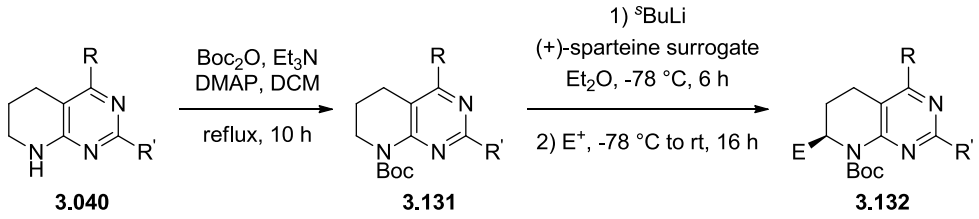


Figure 3.08 Example amine and alcohol nucleophiles from internal GSK set.[203]

Functionalisation could also be introduced through addition of electrophiles to the piperidine ring generated. Investigation into the *α*-functionalisation of piperidine rings through directed *ortho*-lithiation and subsequent quenching with an electrophile (Scheme 3.42).[204] This would enable the addition of functional groups which access

a novel vector. This could be important when considering drug analogue synthesis. Furthermore, the asymmetric nature of this reaction would allow for access to different vectors to those achieved in the original system, **3.040**, without the need for a chiral purification step.



Scheme 3.42 Asymmetric deprotonation of *N*-Boc dihydropiperidine derivative **3.131**.[204,205]

5 Experimental

5.1 General experimental

5.1.1 Solvents and reagent

Magnetic stirrer bars were stirred vigorously using stirrer hot plates. Unless otherwise stated, all reactions were carried out under an atmosphere of nitrogen using anhydrous solvent. Solvents and reagents were purchased from commercial suppliers and used as received unless otherwise stated. Tripotassium phosphate, sodium carbonate, potassium carbonate, and cesium carbonate were dried in a Heraeus Vacutherm oven at 40 °C under vacuum for a minimum of 24 hours before use. Reactions were monitored by TLC or LCMS. Heating was conducted using hotplates with DrySyn adaptors.

5.1.2 Chromatography

TLC was carried out using POLYGRAM®-backed 50 precoated silica plates (particle size 0.2 mm). Spots were visualised by ultraviolet (UV) light (λ_{max} = 254 nm or 365 nm) and then stained with potassium permanganate solution followed by gentle heating. Flash column chromatography was carried out using the Teledyne ISCO Combi*Flash*® *Rf*+ apparatus with Redi*Sep*® or Biotage® SNAP KP-NH cartridges.

5.1.3 Experimental details

Reactions were carried out using conventional glassware (preparation of intermediates), in capped 5 mL microwave vials (Suzuki-Miyaura reaction optimisation), using a CAT96 reactor (hydrogenation optimisation) or in capped 20 mL COware vessels (for all one-pot hydrogenation experiments). COware vessels were purchased from Sigma Aldrich (COware, screwable two-chamber glass system, catalogue number 744077). Microwave vials and magnetic stirrer bars were used as supplied in the Biotage Microwave 2–5 mL Reaction Kit (2–5 mL Biotage Microwave Reaction Kit, catalogue number 351521). The CAT96 was used as supplied by the HEL group. The glassware was purged with N_2 before use. Purging

refers to a vacuum/nitrogen-refilling procedure. Ambient temperature was generally 23 °C. Reactions carried out at elevated temperatures were completed in a sand bath using a temperature-regulated stirrer/hotplate. Temperature quoted is a measurement of the sand bath heating block. Temperature-regulated stirrer/hotplates employed over the course of this study were either of the following: an IKA® RCT basic or a Radleys Carousel Tech Stirring Hotplate.

5.1.4 Liquid chromatography mass spectrometry (LCMS)

LCMS analysis was carried out on an Waters Acquity ultra performance liquid chromatography instrument equipped with an ethylene bridged hybrid column (50 mm x 2.1 mm, 1.7 µm packing diameter) and Waters micromass ZQ mass spectrometer using alternate-scan positive and negative electrospray. Analytes were detected as a summed UV wavelength of 210–350 nm. Two liquid phase methods were used:

Method A - Formic - 40 °C, 1 mL/min flow rate. Gradient elution with the mobile phases as (A) H_2O containing 0.1% volume/volume (v/v) formic acid and (B) acetonitrile containing 0.1% v/v formic acid. Gradient conditions were initially 1% B, increasing linearly to 97% B over 1.5 min, remaining at 97% B for 0.4 min then increasing to 100% B over 0.1 min.

Method B - High pH - 40 °C, 1 mL/min flow rate. Gradient elution with the mobile phases as (A) 10 mM aqueous ammonium bicarbonate solution, adjusted to pH 10 with 0.88 M aqueous ammonia and (B) acetonitrile. Gradient conditions were initially 1% B, increasing linearly to 97% B over 1.5 min, remaining at 97% B for 0.4 min then increasing to 100% B over 0.1 min.

5.1.5 Nuclear magnetic resonance (NMR) spectroscopy

Proton (^{1}H), carbon (^{13}C), and fluorine (^{19}F) spectra were recorded in deuterated solvents at ambient temperature (unless otherwise stated) using standard pulse methods on any of the following spectrometers and signal frequencies: Bruker AV-400 (^{1}H = 400 MHz, ^{13}C = 101 MHz, ^{19}F = 376 MHz) and Bruker AV-500 (^{1}H = 500

MHz, ^{13}C = 126 MHz, ^{19}F = 470 MHz). Chemical shifts are reported in ppm and are referenced to tetramethylsilane or one of the following solvent peaks: $CDCl_3$ (^1H = 7.27 ppm, ^{13}C = 77.0 ppm), d_6-acetone (^1H = 2.05 ppm, ^{13}C = 206.7, 29.9 ppm), d_6-DMSO (^1H = 2.50 ppm, ^{13}C = 39.5 ppm), and MeOD (^1H = 3.31 ppm, ^{13}C = 49.0 ppm). Peak assignments were made on the basis of chemical shifts, integrations, and coupling constants, using COSY, DEPT, HMBC, HSQC, and NOESY where appropriate. Coupling constants are quoted to the nearest 0.1 Hz and multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sxt), septet (sept), broad (br.), and multiplet (m).

5.1.6 Infrared (IR) spectroscopy

Infrared spectra were recorded using a Perkin Elmer Spectrum 1 Fourier transform infrared spectrometer. Absorption maxima (υ_{max}) are reported in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w), and broad (br.).

5.1.7 High-resolution mass spectrometry (HRMS)

High-resolution mass spectra were recorded on a Micromass Q-Tof Ultima hybrid quadrupole time-of-flight mass spectrometer, with analytes separated on an Agilent 1100 Liquid Chromatography equipped with a Phenomenex Luna C18 (2) reversed phase column (100 mm x 2.1 mm, 3 µm packing diameter). Liquid chromatography conditions were 0.5 mL/min flow rate, 35 ºC, and injection volume 2–5 µL. Gradient elution with (A) H_2O containing 0.1% v/v formic acid and (B) acetonitrile containing 0.1% v/v formic acid. Gradient conditions were initially 5% B, increasing linearly to 100% B over six min, remaining at 100% B for 2.5 min then decreasing linearly to 5% B over one min followed by an equilibration period of 2.5 min prior to the next injection. Mass to charge ratios (*m/z*) are reported in atomic mass units.

5.1.8 Melting points

Melting points were recorded on Stuart SMP10 and Gallenkamp melting point apparatus.

5.1.9 Mass directed auto purification (MDAP)

Mass-directed automatic purification was carried out using a Waters ZQ mass spectrometer using alternate-scan positive and negative electrospray and a summed UV wavelength of 210–350 nm. Two liquid phase methods were used:

Formic – XSelect CSH C18 column (100 mm x 19 mm, 5 µm packing diameter, 20 mL/min flow rate) or XSelect CSH C18 column (150 mm x 30 mm, 5 µm packing diameter, 40 mL/min flow rate). Gradient elution at ambient temperature with the mobile phases as (A) H_2O containing 0.1% v/v formic acid and (B) acetonitrile containing 0.1% v/v formic acid.

High pH – XSelect CSH C18 column (100 mm x 19 mm, 5 µm packing diameter, 20 mL/min flow rate) or XSelect CSH C18 column (150 mm x 30 mm, 5 µm packing diameter, 40 mL/min flow rate). Gradient elution at ambient temperature with the mobile phases as (A) 10 mM aqueous ammonium bicarbonate solution, adjusted to pH 10 with 0.88 M aqueous ammonia and (B) acetonitrile.

5.1.10 CLND solubility

CLND solubility is a high throughput solubility determination from a 10 mM DMSO stock solution, using a chemiluminescence nitrogen detector (CLND) end point. The solubility range covered by the method is from 1 µM to 500 µM. This method is likely to overestimate a compound's true solubility, particularly if the compound is highly crystalline and/or has a high melting point. It also takes no account of the compound's thermodynamic stability or dissolution rate. The signal from CLND is directly proportional to the number of moles of the molecule/number of nitrogen. This makes it possible to quantify the solubility of the compounds using a calibration based on one single compound (for example caffeine). GSK in-house kinetic solubility assay conditions: 5 mL of 10 mM DMSO stock solution diluted to 100 mL with pH 7.4 phosphate buffered saline, equilibrated for 1 h at ambient temperature, and filtered through Millipore Multiscreen HTS-PCF filter plates. The eluent is quantified by suitably calibrated flow injection CLND.

5.1.11 ChromlogD

ChromlogD has been introduced to replace the octanol/water logD measurements and is applied together with solubility. ChromlogD is derived from the gradient retention time of the compound in reversed phase HPLC using three different pHs for starting mobile phases with acetonitrile gradient. The compound's lipophilicity is measured in acidic, neutral, and basic environments to reveal the acid/base character of the compound. The ChromlogD at three pHs is measured via fast gradient retention time using UPLC instruments. The retention time is converted to CHI (chromatographic hydrophobicity index). The CHI scale is projected onto a ChromlogD scale based on the linear regression of CHI values against ChromlogP values for several thousands of diverse project compounds. Both ChromlogD and CHIlogD are derived from CHI and can be inter-converted using the following formulae:

ChromlogD = 1.632 CHIlogD + 0.396
CHIlogD = 0.613 ChromlogD – 0.24

GSK in-house hydrophobicity assay conditions: 10 mL of 10 mM DMSO stock solution diluted to 750 mL with octanol saturated $pH_{7.4}$ phosphate buffer and 160 mL buffer saturated octanol in a 96 well deep well block. The block is sealed and inverted for three sets of 50 inversions, the centrifuged at 300 g for 20 min. Both phases are then quantified using generic gradient UV-HPLC.

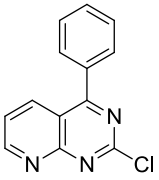
5.1.12 Permeability

Permeability is the ease with which molecules pass through a membrane. Two methods are used to measure permeability at GSK. The high throughput artificial membrane assay and the Madin Darby Canine Kidney (MDCK) assay, a cell based intestinal permeability assay.

5.2 General experimental procedures

General procedure A: Suzuki-Miyaura reaction of 2,4-dichloropyrido[2,3-*d*]pyrimidine (Schemes 3.15 and 3.18 and Tables 3.01, 3.02, 3.03, 3.04, 3.05, 3.06, 3.07, 3.08, 3.09, 3.10, and 3.11)

For example, synthesis of 2-chloro-4-phenylpyrido[2,3-*d*]pyrimidine, **3.050**[176]

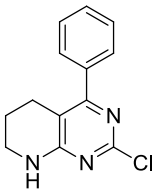


$C_{13}H_8ClN_3$

A microwave vial was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.159 g, 0.750 mmol, 3 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.05 equiv), and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.008 g, 0.001 mmol, 4 mol%). The reaction vessel was then purged with nitrogen after which water (0.023 mL, 0.125 mmol, 5 equiv) and THF (1 mL, 0.125 M) were added. The vial was sealed, heated to 90 °C, and was allowed to stir for 1 h. After cooling to ambient temperature, conversion to product was determined by HPLC against an internal standard (caffeine) indicating cross-coupling at the 4-position (51% yield).

General procedure B: Hydrogenation of 2-chloro-4-phenylpyrido[2,3-*d*]pyrimidine (Table 3.12)

For example, synthesis of 2-chloro-4-phenylpyrido[2,3-*d*]pyrimidine, **3.061**



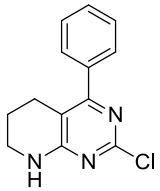
$C_{13}H_{12}ClN_3$

A HPLC vial was charged with 2-chloro-4-phenylpyrido[2,3-*d*]pyrimidine (0.020 g, 0.083 mmol, 1 equiv), palladium on carbon (0.009 g, 0.004 mmol, 5 mol%), and

DMSO (0.5 mL). The reaction vessel placed in a CAT 96 reactor which was then purged with nitrogen. The reaction was then stirred at ambient temperature under an atmosphere of hydrogen (4 bar) for 16 h. Conversion to product was determined by HPLC against an internal standard (caffeine) indicating selective pyridine hydrogenation (12% yield).

General procedure C: Hydrogenation of 2-chloro-4-phenylpyrido[2,3-*d*]pyrimidine (Table 3.13)

For example, synthesis of 2-chloro-4-phenyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.061**

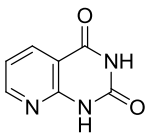


$C_{13}H_{12}ClN_3$

Chamber A of a two chamber COware apparatus was charged with 2-chloro-4-phenylpyrido[2,3-*d*]pyrimidine (0.050 g, 0.207 mmol, 1 equiv), platinum(IV) oxide (0.005 g, 0.022 mmol, 10 mol%), and CPME (2 mL, 0.104 M). Zinc (0.188 g, 2.88 mmol, 13.9 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 71.5 equiv, as a 7.4 M aqueous solution) were then added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 16 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% TBME/cyclohexane, afforded the *title compound* as a white solid (0.049 g, 96%).

5.3 Intermediate compound characterisation

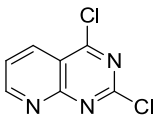
Pyrido[2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-dione



$C_7H_5N_3O_2$

Urea (4.40 g, 73.30 mmol) and 2-aminonicotinic acid (1.00 g, 7.24 mmol) were warmed to 150 °C and allowed to stir for 16 h. The reaction mixture was cooled to 100 °C and water (8 mL) was added. The reaction was allowed to sitr for 10 mins after which it was allowed to cool to ambient temperature. The reaction was filtered and sodium hydroxide (10 mL, as a 1 M solution) was added. The reaction mixture was allowed to stand for 1 h and acetic acid (5 mL) was added dropwise. The solid precipitate was filtered and dried under reduced pressure to afforded the title compound as a cream solid (1.032 g, 87%). m.p. >300 °C (above limit of machine); LCMS (Method B, UV, ESI) R_t = 0.34 min, $[M+H]^+$ = 162, 100% purity; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.59 (dd, J = 4.8, 1.8 Hz, 1 H), 8.25 (dd, J = 7.8, 2.0 Hz, 1 H), 7.23 (dd, J = 7.7, 4.8 Hz, 1 H), two exchangable protons not observed; ^{13}C NMR (101 MHz, d_6-DMSO) δ 162.4, 154.5, 152.6, 150.5, 136.3, 118.7, 109.9; υ_{max} (solid)/cm^{-1}; 3335, 3176, 3091, 3002, 2755, 1722, 1668, 1602, 1504, 1461, 1416, 1396, 1285, 1235, 781, 754; HRMS (ESI- Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_7H_6N_3O_2$ 164.0455; found 164.0457.

2,4-Dichloropyrido[2,3-*d*]pyrimidine

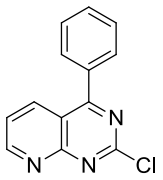


$C_7H_3Cl_2N_3$

Phosphorus oxychloride (3.00 mL, 32.20 mmol) was added to pyrido[2,3-*d*]pyrimidine-2,4-diol (0.025 g, 0.153 mmol) under an atmosphere of nitrogen at ambient temperature. The reaction mixture was warmed to 110 °C and allowed to stir for 18 h. The reaction mixture was cooled to ambient temperature and the solvent was removed under reduced pressure. Ice (0.50 g) was added to the resulting residue and the solution was extracted with chloroform (5 x 5 mL). The combined organic

extracts were washed with water (2 x 5 mL), dried by passing through a hydrophobic frit, and concentrated under reduced pressure to afforded the title compound as a cream solid (0.023 g, 75%). LCMS (Method B, UV, ESI) R_t = 0.49 min, $[M+H]^+$ = 196, 97% purity; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.56 (dd, J = 4.8, 1.8 Hz, 1 H), 8.23 (dd, J = 7.7, 1.9 Hz, 1 H), 7.20 (dd, J = 7.6, 4.8 Hz, 1 H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 162.8, 159.9, 154.5, 151.2, 136.3, 118.5, 110.0; υ_{max} (solid)/cm^{-1}; 3078, 2474, 1716, 1558, 1536, 1445, 1307, 1138, 982, 892, 856, 788; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_7H_4Cl_2N_3$ 199.9777; found 199.9774.

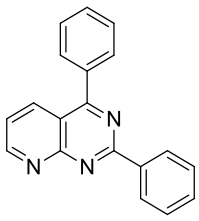
2-Chloro-4-phenylpyrido[2,3-*d*]pyrimidine, **3.050**[176] (Scheme 3.14)



$C_{13}H_8ClN_3$

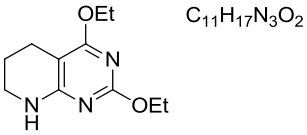
A microwave vial was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), potassium carbonate (0.052 g, 0.376 mmol, 1.5 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.05 equiv), and toluene (3 mL, 0.083 M). The reaction vessel was then purged with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (0.015 g, 0.013 mmol, 5 mol%) was then added and the vial was sealed, heated to 110 °C, and was allowed to stir for 2 h. After cooling, the reaction mixture was filtered through a Celite® pad, washing with EtOAc (10 mL) and the filtrate was concentrated under reduced pressure. Purification by MDAP afforded the title compound as a white solid (0.014 g, 23%). m.p. 147–149 °C (lit. 143–144 °C)[176]; LCMS (Method B, UV, ESI) R_t = 0.92 min, $[M+H]^+$ = 242, 92% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (dd, J = 4.0, 1.8 Hz, 1 H), 8.52 (dd, J = 8.3, 1.8 Hz, 1 H), 7.83–7.76 (m, 1 H), 7.72–7.52 (m, 4 H), 7.50–7.43 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.1, 173.1, 160.4, 160.3, 158.6, 136.9, 135.0, 133.1, 132.1, 132.0, 131.9, 131.3, 130.2, 129.0, 128.5, 128.4, 123.3, 116.5, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3089, 3050, 1597, 1556, 1529, 1466, 1115, 895, 796, 770, 712, 694; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{13}H_9ClN_3$ 242.0480; found ^{35}Cl 242.0475 and ^{37}Cl 244.0444.

2,4-Diphenylpyrido[2,3-*d*]pyrimidine, **3.051** (Scheme 3.14)



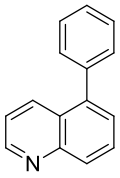
A vessel was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.500 g, 2.500 mmol, 1 equiv), tripotassium phosphate (2.412 g, 11.360 mmol, 4.5 equiv), phenylboronic acid (0.667 g, 5.470 mmol, 2.2 equiv), and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.186 g, 0.227 mmol, 9 mol%). The reaction was purged with nitrogen after which water (0.205 mL, 11.360 mmol, 4.5 equiv) and THF (9.5 mL, 0.239 M) were added, the reaction was warmed to 60 °C, and was allowed to stir for 18 h. After cooling, the reaction was filtered through a Celite® pad, washing with EtOAc (25 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (80 g), eluting with 0–75% EtOAc/cyclohexane, afforded the *title compound* as an off-white solid (0.521 g, 74%). m.p. 174–176 °C; LCMS (Method B, UV, ESI) R_t = 1.23 min, $[M+H]^+$ = 284, 99% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (dd, J = 4.2, 2.0 Hz, 1 H), 8.87–8.81 (m, 2 H), 8.51 (dd, J = 8.3, 2.0 Hz, 1 H), 7.92–7.86 (m, 2 H), 7.67–7.62 (m, 3 H), 7.59–7.49 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 163.5, 159.9, 157.6, 137.4, 136.7, 136.4, 131.3, 130.5, 130.2, 129.3, 128.8, 128.5, 122.4, 116.4, four equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3058, 1592, 1558, 1539, 1469, 1372, 1344, 1168, 1026, 971, 853, 780, 717, 684; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{14}N_3$ 284.1182; found 284.1177.

2,4-diethoxy-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine, **3.060** (Scheme 3.21)



2,4-Dichloropyrido[2,3-*d*]pyrimidine (0.103 g, 0.515 mmol, 1 equiv), as a solution in ethanol (3 mL, 0.172 M), was added to platinum(IV) oxide (0.013 g, 0.057 mmol, 11 mol%) under a hydrogen atmosphere at ambient temperature. The reaction mixture was allowed to stir for 1 h after which the reaction mixture was filtered through Celite®, washing with ethanol (20 mL), and concentrated under reduced pressure. Purification by MDAP method B afforded the *title compound* as a white solid (0.057 g, 50%). m.p. 118–120 °C; LCMS (Method B, UV, ESI) R_t = 1.11 min, $[M+H]^+$ = 224, 90% purity; ^{1}H NMR (400 MHz, d_6-DMSO) δ 6.90 (br. s, 1 H), 4.24 (q, J = 7.1 Hz, 2 H), 4.15 (q, J = 7.1 Hz, 2 H), 3.20–3.15 (m, 2 H), 2.37 (t, J = 6.4 Hz, 2 H), 1.71 (quin, J = 5.4 Hz, 2 H), 1.28–1.21 (m, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 162.6, 162.0, 88.3, 62.2, 61.6, 40.9, 21.1, 19.0, 14.7, 14.6; υ_{max} (thin film)/cm^{-1} 3228, 2978, 2854, 1608, 1580, 1424, 1377, 1340, 1318, 1222, 1196, 1152, 1066, 787; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{18}N_3O_2$ 224.1394; found 224.1390.

5-Phenylquinoline, **3.082**[206] (Scheme 3.26)

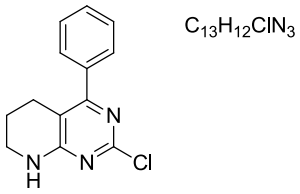


$C_{15}H_{11}N$

A microwave vial was charged with 5-bromoquinoline (0.100 g, 0.481 mmol, 1 equiv), tripotassium phosphate (0.306 g, 1.442 mmol, 3 equiv), phenylboronic acid (0.088 g, 0.721 mmol, 1.5 equiv), palladium(II) acetate (0.005 g, 0.024 mmol, 5 mol%), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane (0.023 g, 0.048 mmol, 10 mol%), water (0.043 mL, 2.403 mmol, 5 equiv), and THF (2 mL, 0.241 M). The reaction vessel was sealed and was allowed to stir at 40 °C for 18 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane, afforded the title compound as a brown solid (0.075 g, 76%). m.p. 81–83 °C (lit. 82–83 °C)[206]; LCMS (Method B, UV, ESI) R_t = 1.16 min,

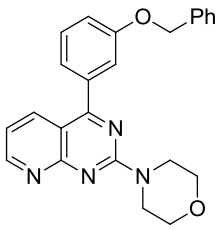
$[M+H]^+$ = 206, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (dd, J = 4.2, 1.5 Hz, 1 H), 8.18 (d, J = 8.6 Hz, 1 H), 8.07 (d, J = 8.6 Hz, 1 H), 7.83 (dd, J = 8.3, 7.3 Hz, 1 H), 7.58–7.49 (m, 7 H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 150.4, 148.0, 139.9, 138.7, 133.5, 129.7, 129.0, 128.6, 127.7, 127.1, 125.8, 121.6, three equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3036, 1592, 1568, 1502, 1466, 1442, 1405, 1390, 1203, 959, 829, 796, 764, 752, 704, 693, 666; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{12}N$ 206.0970; found 206.0972.

2-Chloro-4-phenyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.061** (Scheme 3.23)



Chamber A of a two chamber COware apparatus was charged with 2-chloro-4-phenylpyrido[2,3-*d*]pyrimidine (0.050 g, 0.207 mmol, 1 equiv), platinum(IV) oxide (0.005 g, 0.022 mmol, 11 mol%), and CPME (2 mL, 0.104 M). Zinc (0.188 g, 2.880 mmol, 13.9 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 71.5 equiv, as a 7.4 M aqueous solution) were then added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 16 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% TBME/cyclohexane, afforded the *title compound* as a white solid (0.049 g, 96%). m.p. 248–250 °C; LCMS (Method B, UV, ESI) R_t = 0.99 min, $[M+H]^+$ = 246, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.52 (m, 2 H), 7.47–7.40 (m, 3 H), 6.87 (br. s, 1 H), 3.56–3.50 (m, 2 H), 2.75 (t, J = 6.1 Hz, 2 H), 1.87 (quin, J = 5.9 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 162.3, 157.5, 137.2, 129.1, 128.8, 128.2, 108.5, 41.2, 24.2, 20.6, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3228, 3119, 2962, 2936, 2861, 1593, 1565, 1399, 1329, 1275, 1096, 1018, 846, 760, 694, 626; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{13}ClN_3$ 246.0793; found ^{35}Cl 246.0781 and ^{37}Cl 248.0759.

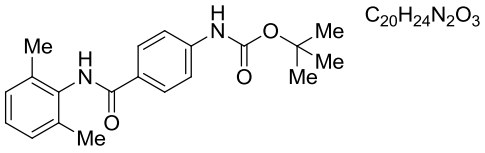
4-(4-(3-(Benzyloxy)phenyl)pyrido[2,3-*d*]pyrimidin-2-yl)morpholine, **3.106** (Table 3.14)



$C_{24}H_{22}N_4O_2$

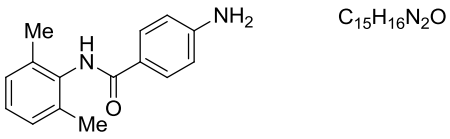
A microwave vial was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), (3-(benzyloxy)phenyl)boronic acid (0.060 g, 0.263 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (2 mL, 0.125 M). The reaction was warmed to 40 °C and allowed to stir for 8 h. After cooling, morpholine (0.026 mL, 0.300 mmol, 1.2 equiv) and tripotassium phosphate (0.064 g, 0.302 mmol, 1.2 equiv) were added to the reaction mixture. The reaction vessel was then sealed, warmed to 40 °C, and was allowed to stir for 16 h. After cooling, the reaction mixture was taken up in EtOAc (20 mL) which was then washed with water (20 mL) and brine (20 mL), was dried by passing through a hydrophobic frit, and was concentrated under reduced pressure. Purification by MDAP afforded the *title compound* as a yellow gum (0.058 g, 58%). LCMS (Method B, UV, ESI) R_t = 1.25 min, $[M+H]^+$ = 399, 100% purity; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.92 (dd, J = 4.4, 1.9 Hz, 1 H), 8.09 (dd, J = 8.2, 1.9 Hz, 1 H), 7.54–7.25 (m, 9 H), 7.23 (dd, J = 8.2, 4.4 Hz, 1 H), 5.22 (s, 2 H), 3.92–3.88 (m, 4 H), 3.74–3.69 (m, 4 H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 178.7, 170.2, 160.5, 159.7, 158.2, 157.4, 137.5, 136.9, 136.4, 129.8, 128.4, 127.8, 127.6, 122.2, 119.1, 117.1, 116.6, 115.8, 111.3, 69.3, 66.0, 44.1, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 2960, 2904, 2853, 1568, 1541, 1470, 1422, 1362, 1283, 1264, 1247, 1216, 1115, 876, 785; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{23}N_4O_2$ 399.1821; found 399.1817.

Tert-butyl (4-((2,6-dimethylphenyl)carbamoyl)phenyl)carbamate, **3.112** (Scheme 3.31)



Oxalyl chloride (0.443 mL, 5.060 mmol, 1.2 equiv), as a solution in THF (5 mL) was added to a stirred solution of 4-((*tert*-butoxycarbonyl)amino)benzoic acid (1.000 g, 4.210 mmol, 1 equiv) and DMF (0.2 mL) in THF (20 mL) at 0 °C. The reaction mixture was allowed to warm to ambient temperature over 3 h. After cooling to 0 °C, 2,6-dimethylaniline (0.623 mL, 5.060 mmol, 1.2 equiv) and triethylamine (1.175 mL, 8.430 mmol, 2 equiv) were added to the reaction mixture, which was allowed to warm to ambient temperature over 16 h. The solvent was removed under reduced pressure and the reaction mixture was taken up in EtOAc (50 mL) which was then washed with water (20 mL), $NaHCO_3$ (2 x 20 mL), and brine (20 mL). The organic phase was dried by passing through a hydrophobic frit and was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (80 g), eluting with 0–40% EtOAc/cyclohexane afforded the *title compound* as a white solid (0.933 g, 65%). m.p. 230–232 °C; LCMS (Method B, UV, ESI) R_t = 1.15 min, $[M+H]^+$ = 341, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.86 (m, 2 H), 7.54–7.47 (m, 2 H), 7.18–7.10 (m, 3 H), 6.66 (br. s, 1 H), 2.29 (s, 6 H), 1.55 (s, 9 H), one exchangeable proton not observed; ^{13}C NMR (101 MHz, d_6-DMSO) δ 164.4, 152.6, 142.5, 135.6, 135.5, 128.3, 127.6, 126.5, 117.2, 79.5, 28.1, 18.0, eight equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3322, 2976, 2919, 1695, 1646, 1589, 1515, 1487, 1406, 1369, 1316, 1240, 1150, 1056, 773; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{25}N_2O_3$ 341.1860; found 341.1844.

4-Amino-*N*-(2,6-dimethylphenyl)benzamide, **3.113**[207] (Scheme 3.31)



A solution of hydrochloric acid (as a 3 M solution in CPME) (4.406 mL, 13.220 mmol, 5 equiv) and *tert*-butyl (4-((2,6-dimethylphenyl)carbamoyl)phenyl)carbamate (0.900 g, 2.640 mmol, 1 equiv) was stirred at ambient temperature for 2 h. The reaction mixture was taken up in EtOAc (50 mL) which was then washed with water (20 mL), $NaHCO_3$ (2 x 20 mL), and brine (20 mL). The organic phase was dried by passing through a hydrophobic frit and was concentrated under reduced pressure to afford the title compound as a white solid (0.612 g, 96%). m.p. 213–215 °C (lit. 210–212 °C)[207]; LCMS (Method B, UV, ESI) R_t = 0.81 min, $[M+H]^+$ = 241, 91% purity; ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.24 (br. s, 1 H), 7.74–7.70 (m, 2 H), 7.09–7.07 (m, 3 H), 6.61–6.57 (m, 2 H), 5.65 (br. s, 2 H), 2.15 (s, 6 H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 164.9, 151.9, 136.0, 135.8, 129.1, 127.5, 126.2, 120.9, 112.6, 18.1, five equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3471, 3353, 3218, 3028, 2960, 2919, 1620, 1601, 1567, 1492, 1291, 1175, 837, 770; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}N_2O$ 241.1335; found 241.1331.

5.4 Reaction optimisation

5.4.1 Suzuki-Miyaura optimisation

5.4.1.1 Repeat of literature conditions (Scheme 3.14)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), potassium carbonate (0.052 g, 0.376 mmol, 1.5 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.05 equiv), tetrakis(triphenylphosphine)palladium(0) (0.015 g, 0.013 mmol, 5 mol%), and toluene (3 mL, 0.083 M). The vial was sealed, heated to 110 °C, and was allowed to stir for 2 h. After cooling, the reaction mixture was filtered through a Celite® pad, washing with EtOAc (10 mL) and the filtrate was concentrated under reduced pressure. Purification by MDAP afforded the *title compound* as a white solid (0.014 g, 23%).

5.4.1.2 In house Suzuki-Miyaura reaction conditions (Scheme 3.15)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.159 g, 0.750 mmol, 3 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.008 g, 0.001 mmol, 4 mol%), water (0.023 mL, 0.125 mmol, 5 equiv), and THF (1 mL, 0.25 M). The vial was sealed, heated to 90 °C, and was allowed to stir for 1 h. After cooling to ambient temperature, conversion to product was determined by HPLC against an internal standard (caffeine).

5.4.1.3 Temperature study (Table 3.01)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.025 g, 0.125 mmol, 1 equiv), tripotassium phosphate (0.080 g, 0.375 mmol, 3 equiv), phenylboronic acid (0.023 g, 0.188 mmol, 1.5 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.004 g, 0.005 mmol, 4 mol%), water (0.011 mL, 0.625 mmol, 5 equiv), and THF (0.5 mL, 0.25 M). The vial was sealed, heated to **X** °C, and was allowed to stir for 1 h. Conversion to product was determined by HPLC against an internal standard (caffeine).

5.4.1.4 Time study at set temperature (Table 3.02)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.025 g, 0.125 mmol, 1 equiv), tripotassium phosphate (0.080 g, 0.375 mmol, 3 equiv), phenylboronic acid (0.023 g, 0.188 mmol, 1.5 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.004 g, 0.005 mmol, 4 mol%), water (0.011 mL, 0.625 mmol, 5 equiv), and THF (0.5 mL, 0.25 M). The vial was sealed, heated to 40 °C, and was allowed to stir for **X** h. Conversion to product was determined by HPLC against an internal standard (caffeine).

5.4.1.5 Base equivalents study (Table 3.03)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.025 g, 0.125 mmol, 1 equiv), tripotassium phosphate (**X** equiv), phenylboronic acid (0.016 g, 0.131 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.004 g, 0.005 mmol, 4 mol%), water (0.011 mL, 0.625 mmol, 5 equiv), and THF (0.5 mL, 0.25 M). The vial was sealed, heated to 40 °C, and was allowed to stir for 4 h. Conversion to product was determined by HPLC against an internal standard (caffeine).

5.4.1.6 Base study (Table 3.04)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.025 g, 0.125 mmol, 1 equiv), **base** (0.25 mmol, 2 equiv), phenylboronic acid (0.016 g, 0.131 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.004 g, 0.005 mmol, 4 mol%), water (0.011 mL, 0.625 mmol, 5 equiv), and THF (0.5 mL, 0.25 M). The vial was sealed, heated to 40 °C, and was allowed to stir for 4 h. Conversion to product was determined by HPLC against an internal standard (caffeine).

5.4.1.7 Boronic acid equivalents study (Table 3.05)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.025 g, 0.125 mmol, 1 equiv), tripotassium phosphate (0.053 g, 0.250 mmol, 2 equiv), phenylboronic acid (**X** equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.004 g, 0.005 mmol, 4 mol%), water (0.011 mL, 0.625 mmol, 5 equiv), and THF (0.5 mL, 0.25 M). The vial was sealed, heated to 40 °C, and was allowed to stir for 4 h. Conversion to product was determined by HPLC against an internal standard (caffeine).

5.4.1.8 Water study (Table 3.06)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.025 g, 0.125 mmol, 1 equiv), tripotassium phosphate (0.053 g, 0.250 mmol, 2 equiv), phenylboronic acid (0.016 g, 0.131 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.004 g, 0.005 mmol, 4 mol%), water (**X** equiv), and THF (0.5 mL, 0.25 M). The vial was sealed, heated to 40 °C, and was allowed to stir for 4 h. Conversion to product was determined by HPLC against an internal standard (caffeine).

5.4.1.9 Catalyst equivalents study (Table 3.07)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.025 g, 0.125 mmol, 1 equiv), tripotassium phosphate (0.053 g, 0.250 mmol, 2 equiv), phenylboronic acid (0.016 g, 0.131 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (**X** mol%), water (0.011 mL, 0.625 mmol, 5 equiv), and THF (0.5 mL, 0.25 M). The vial was sealed, heated to 40 °C, and was allowed to stir for 4 h. Conversion to product was determined by HPLC against an internal standard (caffeine).

5.4.1.10 Catalyst study (Table 3.08)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.025 g, 0.125 mmol, 1 equiv), tripotassium phosphate (0.053 g, 0.250 mmol, 2 equiv), phenylboronic acid (0.016 g, 0.131 mmol, 1.05 equiv), **catalyst** (4 mol%), water (0.011 mL, 0.625 mmol, 5 equiv), and THF (0.5 mL, 0.25 M). The vial was sealed, heated to 40 °C, and was allowed to stir for 4 h. Conversion to product was determined by HPLC against an internal standard (caffeine).

5.4.1.11 Concentration study (Table 3.09)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.025 g, 0.125 mmol, 1 equiv), tripotassium phosphate (0.053 g, 0.250 mmol, 2 equiv), phenylboronic acid (0.016 g, 0.131 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.004 g, 0.005 mmol, 4 mol%), water (0.011 mL, 0.625 mmol, 5 equiv), and THF (**X** mL). The vial was sealed, heated to 40 °C, and was allowed to stir for 4 h. Conversion to product was determined by HPLC against an internal standard (caffeine).

5.4.1.12 Solvent study (Table 3.10)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.025 g, 0.125 mmol, 1 equiv), tripotassium phosphate (0.053 g, 0.250 mmol, 2 equiv), phenylboronic acid (0.016 g, 0.131 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.004 g, 0.005 mmol, 4 mol%), water (0.011 mL, 0.625 mmol, 5 equiv), and **solvent** (0.5 mL, 0.25 M). The vial was sealed, heated to 40 °C, and was allowed to stir for 4 h. Conversion to product was determined by HPLC against an internal standard (caffeine).

5.4.1.13 Isolation solvent study (Scheme 3.23 and Table 3.11)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.006 g, 0.010 mmol, 4 mol%), water (0.023 mL, 1.25 mmol, 5 equiv), and **solvent** (1 mL, 0.25 M). The vial was sealed, heated to 40 °C, and was allowed to stir for 4 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL). The solvent was then removed under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane, afforded the *title compound* as a white solid.

5.4.2 Hydrogenation optimisation (Table 3.12)

Reaction was carried out according to General Procedure B using with 2-chloro-4-phenylpyrido[2,3-*d*]pyrimidine (0.020 g, 0.083 mmol, 1 equiv), **catalyst** (4 mol%), and **solvent** (0.5 mL, 0.166 M). Conversion to product was determined by HPLC against an internal standard (caffeine).

5.4.3 Hydrogenation optimisation – isolation study (Scheme 3.22 and 3.23 and Table 3.13)

Reaction was carried out according to General Procedure C using with 2-chloro-4-phenylpyrido[2,3-*d*]pyrimidine (0.020 g, 0.083 mmol, 1 equiv), **catalyst** (4 mol%), and **solvent** (0.5 mL, 0.166 M). The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL). The solvent was then removed under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane, afforded the *title compound* as a white solid.

5.4.4 Impact of platinum(IV) oxide of the Suzuki-Miyaura reaction (Scheme 3.24)

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.05 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (1 mL, 0.25 M). The reaction vessel was sealed and then warmed to 40 °C and was allowed to stir for 20 h. After cooling, acetic acid (0.070 mL, 1.223 mmol, 4.9 equiv) was added to chamber A and zinc (0.479 g, 7.330 mmol, 29.3 equiv) and hydrochloric acid (2.0 mL, 14.80 mmol, 59.2 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was then sealed and was allowed to stir at ambient temperature for 8 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. The

reaction mixture was then taken up in EtOAc (20 mL) which was washed with water (20 mL) and brine (20 mL), was dried by passing through a hydrophobic frit, and concentrated under reduced pressure. Purification by MDAP afforded the *title compound* as a white solid (0.044 g, 72%).

5.4.5 Trial Suzuki-Miyaura reaction on a chloroquinoline core (Scheme 3.26)

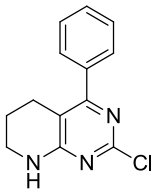
Reaction was carried out according to General Procedure A using 5-chloroquinoline (0.020 g, 0.122 mmol, 1 equiv), tripotassium phosphate (0.052 g, 0.245 mmol, 2 equiv), phenylboronic acid (0.016 g, 0.131 mmol, 1.07 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.004 g, 0.005 mmol, 5 mol%), water (0.011 mL, 0.611 mmol, 5 equiv), and CPME (0.5 mL, 0.244 M). The vial was sealed, heated to 40 °C, and was allowed to stir for 4 h. Conversion to product was determined by LCMS.

5.4.6 One-pot Suzuki-Miyaura/S_NAr base study (Table 3.14)

Reaction was carried out according to General Procedure A using 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.020 g, 0.100 mmol, 1 equiv), tripotassium phosphate (0.042 g, 0.198 mmol, 2 equiv), (3-(benzyloxy)phenyl)boronic acid (0.024 g, 0.105 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.003 g, 0.004 mmol, 4 mol%), water (0.009 mL, 0.500 mmol, 5 equiv), and CPME (1 mL, 0.1 M). The vial was sealed, heated to 40 °C, and was allowed to stir for 16 h. After cooling, morpholine (0.011 mL, 0.121 mmol, 1.2 equiv) and **base** (1.2 equiv) were added into the reaction mixture. The vial was sealed and allowed to stir at 40 °C for 24 h. Conversion to product was determined by LCMS.

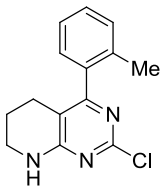
5.5 Compound characterisation data (Schemes 3.25, 3.27, 3.28, 3.29, 3.30, 3.31, 3.33, 3.34, 3.35, 3.38, 3.40, and 3.41)

2-Chloro-4-phenyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.061**



Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.047 g, 0.235 mmol, 1 equiv), tripotassium phosphate (0.100 g, 0.47 mmol, 2 equiv), phenylboronic acid (0.030 g, 0.246 mmol, 1.05 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.021 mL, 1.175 mmol, 5 equiv), and CPME (1 mL, 0.235 M). The reaction vessel was sealed, warmed to 40 °C, and was allowed to stir for 18 h. After cooling, zinc (0.213 g, 3.260 mmol, 13.9 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 63.0 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was then sealed and was allowed to stir at ambient temperature for 8 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane (+1% Et_3N), afforded the *title compound* as a white solid (0.045 g, 78%). m.p. 248–250 °C; LCMS (Method B, UV, ESI) R_t = 0.99 min, $[M+H]^+$ = 246, 95% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.53 (m, 2 H), 7.47–7.40 (m, 3 H), 6.42 (br. s, 1 H), 3.55–3.49 (m, 2 H), 2.75 (t, J = 6.1 Hz, 2 H), 1.87 (quin, J = 5.9 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 162.3, 157.5, 137.2, 129.1, 128.8, 128.2, 108.5, 41.2, 24.2, 20.6, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3231, 3118, 2965, 2941, 2863, 1590, 1563, 1399, 1328, 1274, 1188, 1092, 1017, 760, 692, 626; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{13}ClN_3$ 246.0793; found ^{35}Cl 246.0781 and ^{37}Cl 248.0757.

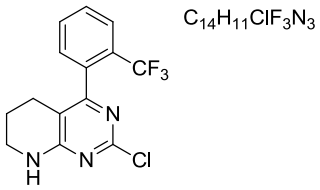
2-Chloro-4-(*o*-tolyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.062**



$C_{14}H_{14}ClN_3$

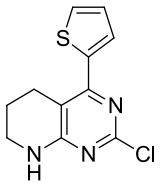
Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.049 g, 0.245 mmol, 1 equiv), tripotassium phosphate (0.104 g, 0.490 mmol, 2 equiv), *o*-tolylboronic acid (0.035 g, 0.257 mmol, 1.05 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.008 g, 0.011 mmol, 5 mol%), water (0.022 mL, 1.225 mmol, 5 equiv), and CPME (1 mL, 0.245 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.451 g, 6.900 mmol, 28.2 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 60.4 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 8 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane (+1% Et_3N), afforded the *title compound* as a white solid (0.047 g, 74%). m.p. 215–217 °C; LCMS (Method B, UV, ESI) R_t = 1.02 min, $[M+H]^+$ = 260, 94% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.20 (m, 3 H), 7.16–7.12 (m, 1 H), 6.80 (br. s, 1 H), 3.51 (td, J = 5.6, 2.7 Hz, 2 H), 2.40 (t, J = 6.0 Hz, 2 H), 2.20 (s, 3 H), 1.90–1.82 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 162.1, 157.3, 136.8, 135.3, 130.3, 128.7, 128.0, 125.7, 109.5, 41.2, 23.0, 20.4, 19.4; υ_{max} (solid)/cm^{-1} 3247, 3121, 2959, 2933, 2847, 1590, 1564, 1326, 1292, 1191, 1015, 853, 765; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{15}ClN_3$ 260.0949; found ^{35}Cl 260.0947 and ^{37}Cl 262.0923.

2-Chloro-4-(2-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.063**



Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), (2-(trifluoromethyl)phenyl)boronic acid (0.050 g, 0.263 mmol, 1.05 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (1 mL, 0.250 M). The reaction was warmed to 40 °C and allowed to stir for 4 h. After cooling, zinc (0.422 g, 6.450 mmol, 25.8 equiv) and hydrochloric acid (4.00 mL, 8.00 mmol, 32 equiv, as a 2 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 16 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–30% MeOH/DCM, afforded the *title compound* as a white solid (0.057 g, 73%). m.p. 204–206 °C; LCMS (Method B, UV, ESI) R_t = 1.06 min, $[M+H]^+$ = 314, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.8 Hz, 1 H), 7.61 (t, J = 7.6 Hz, 1 H), 7.53 (t, J = 7.6 Hz, 1 H), 7.30 (d, J = 7.3 Hz, 1 H), 6.92 (br. s, 1 H), 3.59–3.44 (m, 2 H), 2.41–2.26 (m, 2 H), 1.94–1.76 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 161.8, 156.8, 135.9 (q, $^4J_{C\text{-}F}$ = 1.5 Hz), 131.9, 129.8, 128.8, 128.1 (d, $^2J_{C\text{-}F}$ = 31.5 Hz), 126.5 (q, $^3J_{C\text{-}F}$ = 5.1 Hz), 123.8 (d, $^1J_{C\text{-}F}$ = 274 Hz), 110.0, 44.2, 23.0, 20.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –59.1 (s, 3 F); υ_{max} (solid)/cm^{-1} 3240, 3121, 2963, 2864, 1595, 1567, 1327, 1289, 1271, 1170, 1108, 1097, 1033, 1016, 771, 654; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{12}ClF_3N_3$ 314.0666; found ^{35}Cl 314.0666 and ^{37}Cl 316.0642.

2-Chloro-4-(thiophen-2-yl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.064**

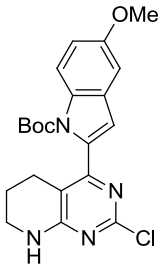


$C_{11}H_{10}ClN_3S$

Chamber A of a COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), 4,4,5,5-tetramethyl-2-(thiophen-2-yl)-1,3,2-dioxaborolane (0.055 g, 0.262 mmol, 1.05 equiv), water (0.090 mL, 5.000 mmol, 20 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.008 g, 0.012 mmol, 4 mol%), and CPME (1 mL, 0.250 M). The reaction was warmed to 40 °C and allowed to stir for 4 h. After cooling, acetic acid (0.070 mL, 1.223 mmol, 5 equiv) and platinum oxide (0.006 g, 0.026 mmol, 11 mol%) were then added to chamber A while zinc (0.448 g, 6.850 mmol, 27.4 equiv) and hydrochloric acid (1.00 mL, 8.00 mmol, 29.6 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 16 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (20 mL) and the filtrate was concentrated under reduced pressure. The brown solid was taken up in water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with a saturated solution of $NaHCO_3$ (2 x 20 mL), brine (20 mL), were dried by passing through a hydrophobic frit, and concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane afforded the *title compound* as a white solid (0.036 g, 57%). m.p. 208–210 °C; LCMS (Method B, UV, ESI) R_t = 1.03 min, $[M+H]^+$ = 252, 98% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.49 (m, 2 H), 7.14 (dd, J = 5.1, 3.7 Hz, 1 H), 6.79 (br. s, 1 H), 3.55–3.49 (m, 2 H), 2.94 (t, J = 6.4 Hz, 2 H), 2.03–1.94 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 157.2, 155.8, 141.3, 129.4, 129.3, 127.6, 106.7, 40.7, 24.3, 20.8; υ_{max} (solid)/cm^{-1} 3232, 3113, 2960, 2869, 1589, 1558, 1337, 1324, 1195, 1011, 775, 708; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}ClN_3S$ 252.0357; found ^{35}Cl 252.0348 and ^{37}Cl 254.0314.

Tert-butyl 2-(2-chloro-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-4-yl)-5-methoxy-1*H*-indole-1-carboxylate,

3.065

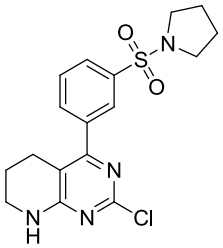


$C_{21}H_{23}ClN_4O_3$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.048 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.480 mmol, 2 equiv), (1-(*tert*-butoxycarbonyl)-5-methoxy-1*H*-indol-2-yl)boronic acid (0.073 g, 0.252 mmol, 1.05 equiv), platinum(IV) oxide (0.006 mg, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.022 mL, 1.200 mmol, 5 equiv), and CPME (1 mL, 0.240 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.451 g, 6.900 mmol, 28.7 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.7 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 4 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–25% EtOAc/cyclohexane (+1% Et_3N), afforded the *title compound* as a yellow solid (0.072 g, 72%). m.p. 208–210 °C; LCMS (Method B, UV, ESI) R_t = 1.27 min, $[M+H]^+$ = 415, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 9.0 Hz, 1 H), 7.03–6.96 (m, 2 H), 6.59 (s, 1 H), 6.31 (br. s, 1 H), 3.86 (s, 3 H), 3.53–3.48 (m, 2 H), 2.66 (t, J = 6.2 Hz, 2 H), 1.93–1.86 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 157.9, 157.1, 156.1, 149.3, 134.6, 131.8, 129.4, 116.2, 114.2, 111.1, 110.1, 103.3, 83.6, 55.7, 41.2, 27.8, 23.3, 20.4, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3247, 3121, 2969, 2938, 2837, 1730, 1581, 1478, 1354, 1326, 1160, 1121, 1085, 1068, 1016 807; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for

$C_{21}H_{24}ClN_4O_3$ 415.1531; found ^{35}Cl 415.1537 and ^{37}Cl 417.1508.

2-Chloro-4-(3-(pyrrolidin-1-ylsulfonyl)phenyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.066**

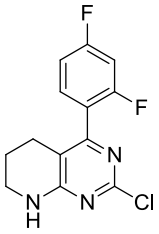


$C_{17}H_{19}ClN_4O_2S$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), (3-(pyrrolidin-1-ylsulfonyl)phenyl)boronic acid (0.067 g, 0.262 mmol, 1.05 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g 0.010 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (1 mL, 0.250 M). The reaction was warmed to 40 °C and allowed to stir for 20 h. After cooling, zinc (0.188 g, 2.880 mmol, 11.5 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 59.2 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 24 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane, afforded the *title compound* as a white solid (0.050 g, 53%). m.p. 228–230 °C; LCMS (Method B, UV, ESI) R_t = 1.01 min, $[M+H]^+$ = 379, 91% purity; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (t, J = 1.6 Hz, 1 H), 7.89 (dt, J = 7.8, 1.5 Hz, 1 H), 7.84 (dt, J = 7.9, 1.3 Hz, 1 H), 7.67–7.61 (m, 1 H), 6.02 (br. s, 1 H), 3.54–3.49 (m, 2 H), 3.29–3.24 (m, 4 H), 2.73 (t, J = 6.2 Hz, 2 H), 1.89 (quin, J = 5.9 Hz, 2 H), 1.82–1.76 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2, 161.5, 158.0, 138.2, 137.1, 133.1, 129.4, 128.0, 127.6, 108.9, 48.0, 41.2, 25.2, 23.9, 20.6, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3239, 3123, 2956, 2845, 1591, 1560, 1340,

1327, 1300, 1158, 1102, 1088, 1011, 774, 676, 628, 605; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{20}ClN_4O_2S$ 379.0990; found ^{35}Cl 379.0987 and ^{37}Cl 381.0956.

2-Chloro-4-(2,4-difluorophenyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.067**

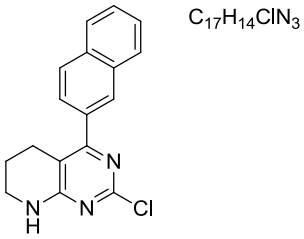


$C_{13}H_{10}ClF_2N_3$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), (2,4-difluorophenyl)boronic acid (0.041 g, 0.260 mmol, 1.04 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (1 mL, 0.250 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.233 g, 3.560 mmol, 14.3 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 59.2 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 24 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane (+1% Et_3N), afforded the *title compound* as a white solid (0.057 g, 81%). m.p. 241–243 °C; LCMS (Method B, UV, ESI) R_t = 1.02 min, $[M+H]^+$ = 282, 100% purity; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.44 (m, 1 H), 7.03–6.96 (m, 1 H), 6.92–6.85 (m, 1 H), 5.76 (br. s, 1 H), 3.53–3.47 (m, 2 H), 2.56 (t, J = 6.4 Hz, 2 H), 1.90 (quin, J = 5.8 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 161.8, 158.4, 157.9, 157.6, 132.2 (dd, $^3J_{C\text{-}F}$ = 10.3 Hz, $^3J_{C\text{-}F}$ = 5.1 Hz), 121.4 (dd, $^2J_{C\text{-}F}$ = 15.4 Hz, $^4J_{C\text{-}F}$ = 3.7 Hz), 111.9 (dd, $^2J_{C\text{-}F}$ = 21.3 Hz, $^4J_{C\text{-}F}$ = 3.7 Hz), 110.1, 104.0 (t, $^2J_{C\text{-}F}$ = 25.7 Hz), 41.2, 22.9, 20.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –107.9 (d, J = 10.4 Hz, 1 F), –109.2 (d, J = 10.4 Hz, 1 F); υ_{max} (solid)/cm^{-1} 3249, 3125, 2960, 2868, 1598, 1565, 1505, 1416, 1287, 1269, 1253, 1189, 1105, 840, 783; HRMS (ESI-Orbitrap)

m/z: $[M+H]^+$ calcd for $C_{13}H_{11}ClF_2N_3$ 282.0604; found ^{35}Cl 282.0602 and ^{37}Cl 284.0570.

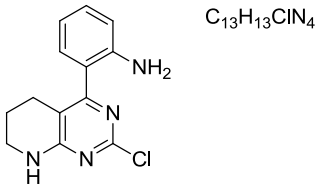
2-Chloro-4-(naphthalen-2-yl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.068**



Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.048 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.480 mmol, 2 equiv), naphthalen-2-ylboronic acid (0.045 g, 0.262 mmol, 1.09 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.008g, 0.011 mmol, 5 mol%), and CPME (1 mL, 0.240 M). The reaction was warmed to 40 °C and allowed to stir for 4 h. After cooling, acetic acid (0.070 mL, 1.223 mmol, 5.1 equiv) and platinum oxide (0.006 g, 0.026 mmol, 11 mol%) were then added to the same chamber while zinc (0.444 g, 6.790 mmol, 28.3 equiv) and hydrochloric acid (5.00 mL, 10.00 mmol, 41.7 equiv, as a 2 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 20 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (20 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–4% MeOH/DCM afforded the *title compound* as an off-white solid (0.036 g, 51%). m.p. 300 °C (decomposition); LCMS (Method B, UV, ESI) R_t = 1.19 min, $[M+H]^+$ = 296, 98% purity; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1 H), 7.94–7.86 (m, 3 H), 7.68 (dd, J = 8.3, 1.7 Hz, 1 H), 7.56–7.51 (m, 2 H), 5.65 (br. s, 1 H), 3.54–3.49 (m, 2 H), 2.83 (t, J = 6.2 Hz, 2 H), 1.93–1.87 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 162.0, 157.9, 134.5, 133.5, 132.8, 128.7, 128.5, 127.9, 127.7, 126.9, 126.4, 126.1, 108.7, 41.3, 24.3, 20.8; υ_{max} (solid)/cm^{-1} 3240, 3122, 2965, 1592, 1564, 1409, 1326,

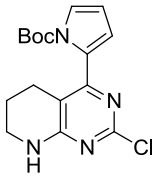
1299, 1193, 1166, 1094, 893, 863, 780; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{15}ClN_3$ 296.0949; found ^{35}Cl 296.0939 and ^{37}Cl 298.0908.

2-(2-Chloro-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-4-yl)aniline, **3.069**



Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.048 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.480 mmol, 2 equiv), (2-aminophenyl)boronic acid (0.035 g, 0.256 mmol, 1.07 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.022 mL, 1.200 mmol, 5 equiv), and CPME (1 mL, 0.240 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.423 g, 6.470 mmol, 27 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.7 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 4 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane (+1% Et_3N), afforded the *title compound* as a white solid (0.048 g, 77%). m.p. 194–196 °C; LCMS (Method B, UV, ESI) R_t = 1.03 min, $[M+H]^+$ = 261, 96% purity; ^1H NMR (400 MHz, d_6-DMSO) δ 8.17 (s, 1 H), 7.52 (dd, J = 8.6, 1.0 Hz, 2 H), 7.31–7.24 (m, 3 H), 7.02–6.69 (m, 1 H), 3.23 (dt, J = 6.8, 3.3 Hz, 2 H), 2.51 (t, J = 6.4 Hz, 2 H), 1.85–1.77 (m, 2 H); ^{13}C NMR (101 MHz, d_6-acetone) δ 162.2, 159.1, 157.6, 153.1, 141.3, 129.3, 123.3, 121.9, 121.8, 91.5, 41.1, 21.6, 20.8; υ_{max} (solid)/cm^{-1} 3242, 3121, 2847, 1607, 1569, 1495, 1436, 1400, 1333, 766, 744, 683; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}ClN_4$ 261.0902; found ^{35}Cl 261.0896 and ^{37}Cl 263.0864.

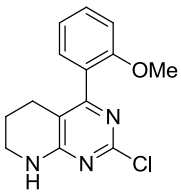
Tert-butyl 2-(2-chloro-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrrole-1 carboxylate, **3.070**



$C_{16}H_{19}ClN_4O_2$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.048 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.480 mmol, 2 equiv), (1-(*tert*-butoxycarbonyl)-1*H*-pyrrol-2-yl)boronic acid (0.055 g, 0.261 mmol, 1.09 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.022 mL, 1.200 mmol, 5 equiv), and CPME (1 mL, 0.240 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.208 g, 3.180 mmol, 13.3 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.7 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 4 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% TBME/cyclohexane, afforded the *title compound* as a white solid (0.048 g, 60%). m.p. 160–162 °C; LCMS (Method B, UV, ESI) R_t = 1.11 min, $[M+H]^+$ = 335, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 2.9, 1.5 Hz, 1 H), 6.67 (br. s, 1 H), 6.32 (dd, J = 3.1, 1.3 Hz, 1 H), 6.23 (t, J = 3.3 Hz, 1 H), 3.52–3.47 (m, 2 H), 2.60 (t, J = 6.2 Hz, 2 H), 1.92–1.84 (m, 2 H), 1.43 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 157.4, 156.7, 148.7, 128.7, 123.1, 115.8, 110.5, 110.1, 84.0, 41.1, 27.6, 23.3, 20.4, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3251, 3126, 2973, 2868, 1591, 1558, 1411, 1372, 1325, 1310, 1287, 1251, 1129, 1092, 733; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{20}ClN_4O_2$ 335.1269; found ^{35}Cl 335.1265 and ^{37}Cl 337.1241.

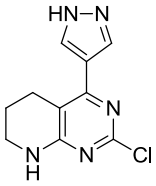
2-Chloro-4-(2-methoxyphenyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.071**



$C_{14}H_{14}ClN_3O$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), (2-methoxyphenyl)boronic acid (0.040 g, 0.263 mmol, 1.05 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (1 mL, 0.250 M). The reaction was warmed to 40 °C and allowed to stir for 20 h. After cooling, zinc (0.423 g, 6.470 mmol, 25.9 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 59.2 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 8 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane (+1% Et_3N), afforded the *title compound* as a white solid (0.055 g, 80%). m.p. 258–260 °C; LCMS (Method B, UV, ESI) R_t = 0.95 min, $[M+H]^+$ = 276, 100% purity; ^{1}H NMR (400 MHz, d_6-acetone) δ 7.41 (ddd, J = 8.4, 7.4, 1.8 Hz, 1 H), 7.24 (dd, J = 7.3, 1.7 Hz, 1 H), 7.09 (d, J = 8.3 Hz, 1 H), 7.03 (td, J = 7.5, 1.0 Hz, 1 H), 6.93 (br. s, 1 H), 3.81 (s, 3 H), 3.47–3.41 (m, 2 H), 2.83–2.74 (m, 2 H), 1.86–1.73 (m, 2 H); ^{13}C NMR (101 MHz, d_6-acetone) δ 162.8, 162.5, 158.3, 157.5, 131.1, 131.0, 128.0, 121.3, 112.0, 111.5, 55.9, 41.7, 23.9, 21.1; υ_{max} (solid)/cm^{-1} 3268, 2974, 2943, 1592, 1560, 1404, 1325, 1282, 1238, 1184, 1012, 745; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{15}ClN_3O$ 276.0898; found ^{35}Cl 276.0898 and ^{37}Cl 278.0865.

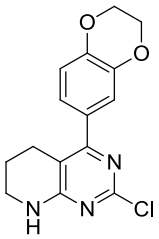
2-Chloro-4-(1*H*-pyrazol-4-yl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.072**



$C_{10}H_{10}ClN_5$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole-1-carboxylate (0.077 g, 0.262 mmol, 1.05 equiv), platinum(IV) oxide (0.006 mg, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.090 mL, 5.000 mmol, 20 equiv), and CPME (1 mL, 0.250 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.223 g, 3.410 mmol, 13.7 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 59.2 equiv, as a 7.4 M aqueous solution) were added to chamber B and hydrochloric acid (as a 3 M solution in CPME) (0.100 mL, 0.300 mmol, 1.2 equiv) was added to chamber A. The reaction vessel was sealed and was allowed to stir at ambient temperature for 4 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–100% EtOAc/cyclohexane followed by 0–20% MeOH/EtOAc (+1% Et_3N), afforded the *title compound* as a white solid (0.047 g, 80%). m.p. 300 °C (decomposition); LCMS (Method B, UV, ESI) R_t = 0.62 min, $[M+H]^+$ = 236, 100% purity; ^{1}H NMR (400 MHz, d_6-DMSO) δ 13.19 (br. s, 1 H), 8.05 (s, 2 H), 7.85 (s, 1 H), 3.30–3.25 (m, 2 H), 2.78–2.71 (m, 2 H), 1.85–1.78 (m, 2 H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 162.5, 157.2, 155.6, 151.9, 131.0, 119.1, 106.6, 40.1, 23.8, 20.7; υ_{max} (solid)/cm^{-1} 3243, 3146, 3120, 3002, 2960, 2852, 1577, 1331, 1117, 1025, 996, 928, 816, 774, 701; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{11}ClN_5$ 236.0698; found ^{35}Cl 236.0696 and ^{37}Cl 238.0664.

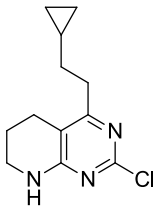
2-Chloro-4-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.073**



$C_{15}H_{14}ClN_3O_2$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.048 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.480 mmol, 2 equiv), (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid (0.045 g, 0.250 mmol, 1.04 equiv), platinum (IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.022 mL, 1.200 mmol, 5 equiv), and CPME (2 mL, 0.120 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.220 g, 3.360 mmol, 14 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.7 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 8 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane (+1% Et_3N), afforded the title compound as a white solid (0.045 g, 62%). m.p. 246–248 °C; LCMS (Method B, UV, ESI) R_t = 0.97 min, $[M+H]^+$ = 304, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.06 (m, 2 H), 6.96–6.90 (m, 1 H), 6.04 (br. s, 1 H), 4.34–4.26 (m, 4 H), 3.53–3.46 (m, 2 H), 2.81–2.73 (m, 2 H), 1.92–1.82 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 162.1, 157.6, 144.6, 143.2, 130.5, 122.4, 118.2, 117.0, 108.1, 64.6, 64.3, 41.2, 24.3, 20.8; υ_{max} (solid)/cm^{-1} 3241, 3122, 2972, 2944, 2931, 2918, 2868, 1559, 1507, 1399, 1281, 1253, 1192, 1094, 1063, 1020, 912, 884, 748; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{15}ClN_3O_2$ 304.0847; found ^{35}Cl 304.0842 and ^{37}Cl 306.0818.

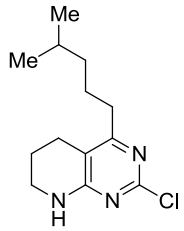
2-Chloro-4-(2-cyclopropylethyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.074**



$C_{12}H_{16}ClN_3$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.048 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.480 mmol, 2 equiv), (*E*)-2-(2-cyclopropylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.055 g, 0.283 mmol, 1.18 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.090 mL, 5.000 mmol, 20.8 equiv), and CPME (1 mL, 0.240 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.216 g, 3.300 mmol, 13.8 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.7 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 8 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane (+1% Et_3N), afforded the *title compound* as a white solid (0.027 g, 47%). m.p. 137–139 °C; LCMS (Method B, UV, ESI) R_t = 1.03 min, $[M+H]^+$ = 238, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (br. s, 1 H), 3.48–3.41 (m, 2 H), 2.71–2.62 (m, 4 H), 1.98–1.90 (m, 2 H), 1.59–1.52 (m, 2 H), 0.77–0.66 (m, 1 H), 0.46–0.40 (m, 2 H), 0.09–0.04 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 161.6, 157.3, 108.4, 40.9, 33.8, 33.3, 22.0, 20.6, 10.8, 4.5, one equivalent peak not observed; υ_{max} (solid)/cm^{-1} 3249, 3124, 2963, 2852, 1593, 1568, 1537, 1408, 1329, 1292, 1268, 1133, 1014, 992, 923, 893, 690; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{17}ClN_3$ 238.1106; found ^{35}Cl 238.1098 and ^{37}Cl 240.1065.

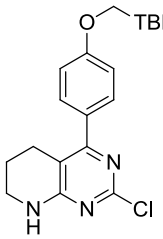
2-Chloro-4-(4-methylpentyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.075**



$C_{13}H_{20}ClN_3$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.048 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.480 mmol, 2 equiv), (*E*)-(4-methylpent-1-en-1-yl)boronic acid (0.032 g, 0.252 mmol, 1.05 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), palladium(II) acetate (0.002 g, 0.009 mmol, 4 mol%), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphane (0.009 g, 0.019 mmol, 8 mol%), water (0.022 mL, 1.200 mmol, 5 equiv), and CPME (2 mL, 0.120 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.223 g, 3.410 mmol, 14.2 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.7 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 24 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane (+1% Et_3N), afforded the title compound as a white solid (0.031 g, 51%). m.p. 112–114 °C; LCMS (Method B, UV, ESI) R_t = 1.22 min, $[M+H]^+$ = 254, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (br. s, 1 H), 3.48–3.42 (m, 2 H), 2.64 (t, J = 6.4 Hz, 2 H), 2.54–2.48 (m, 2 H), 1.97–1.90 (m, 2 H), 1.67–1.51 (m, 3 H), 1.28–1.20 (m, 2 H), 0.88 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 161.7, 157.3, 108.2, 40.9, 38.9, 34.2. 27.9, 26.2, 22.6, 22.0, 20.6, one equivalent peak not observed; υ_{max} (solid)/cm^{-1} 3242, 3125, 2955, 2865, 1593, 1574, 1408, 1326, 1272, 1155, 1132, 916; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{21}ClN_3$ 254.1419; found ^{35}Cl 254.1409 and ^{37}Cl 256.1376.

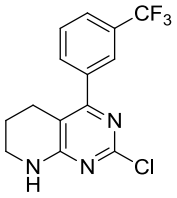
4-(4-((*Tert*-butyldimethylsilyl)methoxy)phenyl)-2-chloro-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.076**



$C_{20}H_{28}ClN_3OSi$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), (4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)boronic acid (0.070 g, 0.263 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.008 g, 0.011 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (1 mL, 0.250 M). The reaction was warmed to 40 °C and allowed to stir for 4 h. After cooling, acetic acid (0.070 mL, 1.223 mmol, 4.9 equiv) and platinum oxide (0.006 g, 0.026 mmol, 11 mol%) were then added to the same chamber while zinc (0.429 g, 6.560 mmol, 26.2 equiv) and hydrochloric acid (4.00 mL, 8.00 mmol, 32 equiv, as a 2 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 16 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (30 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–1.5% MeOH/DCM, afforded the *title compound* as white solid (0.045 g, 46%). m.p. 215–217 °C; LCMS (Method B, UV, ESI) R_t = 1.56 min, $[M+H]^+$ = 390, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.51 (m, 2 H), 7.42–7.37 (m, 2 H), 6.38 (br. s, 1 H), 4.79 (s, 2 H), 3.54–3.49 (m, 2 H), 2.76 (t, J = 6.2 Hz, 2 H), 1.90–1.83 (m, 2 H), 0.96 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 162.2, 157.6, 142.7, 135.7, 128.8, 125.7, 108.4, 64.7, 41.2, 25.9, 24.3, 20.7, 18.4, –5.2, five equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3241, 3126, 2930, 2854, 1595, 1565, 1415, 1332, 1305, 1283, 1097, 1041, 1020, 835, 775; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{29}ClN_3OSi$ 390.1763; found ^{35}Cl 390.1768 and ^{37}Cl 392.1739.

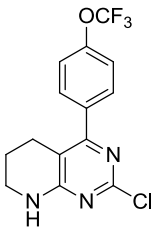
2-Chloro-4-(3-(trifluoromethyl)phenyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.077**



$C_{14}H_{11}ClF_3N_3$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.048 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.480 mmol, 2 equiv), (3-(trifluoromethyl)phenyl)boronic acid (0.500 g, 0.263 mmol, 1.10 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.022 mL, 1.200 mmol, 5 equiv), and CPME (2 mL, 0.120 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.210 g, 3.210 mmol, 13.4 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.7 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 24 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane (+1% Et_3N), afforded the *title compound* as a white solid (0.053 g, 70%). m.p. 203–205 °C; LCMS (Method B, UV, ESI) R_t = 1.17 min, $[M+H]^+$ = 314, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.80 (m, 1 H), 7.77–7.67 (m, 2 H), 7.61–7.55 (m, 1 H), 6.66 (br. s, 1 H), 3.57–3.52 (m, 2 H), 2.73 (t, J = 6.2 Hz, 2 H), 1.90 (quin, J = 5.9 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 161.6, 157.8, 137.9, 132.2, 130.8 (d, $^2J_{C\text{-}F}$ = 32.3 Hz), 128.8, 125.9 (q, $^3J_{C\text{-}F}$ = 3.7 Hz), 125.7 (q, $^3J_{C\text{-}F}$ = 3.9 Hz), 121.4 (d, $^1J_{C\text{-}F}$ = 224.3 Hz), 108.8, 41.2, 24.0, 20.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.6 (s, 3 F); υ_{max} (solid)/cm^{-1} 3250, 3125, 2969, 1599, 1572, 1326, 1317, 1162, 1118, 1099, 1073, 811, 711, 686; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{12}ClF_3N_3$ 314.0666; found ^{35}Cl 314.0654 and ^{37}Cl 316.0624.

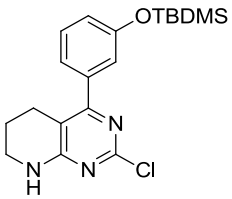
2-Chloro-4-(4-(trifluoromethoxy)phenyl)-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.078**



$C_{14}H_{11}ClF_3N_3O$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), (4-(trifluoromethoxy)phenyl)boronic acid (0.054 g, 0.262 mmol, 1.05 equiv), platinum (IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (2 mL, 0.125 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.237 g, 3.620 mmol, 14.5 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 59.2 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 24 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane (+1% Et_3N), afforded the *title compound* as a white solid (0.055 g, 67%). m.p. 300 °C (decomposition); LCMS (Method B, UV, ESI) R_t = 1.20 min, $[M+H]^+$ = 330, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.58 (m, 2 H), 7.31–7.28 (m, 2 H), 5.67 (br. s, 1 H), 3.53–3.47 (m, 2 H), 2.74 (t, J = 6.2 Hz, 2 H), 1.92–1.87 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.0, 158.0, 149.8, 135.7, 130.5, 124.8, 120.6, 119.4, 108.5, 41.2, 24.1, 20.6, two equivalent peaks not observed; ^{19}F NMR (376 MHz, $CDCl_3$) δ –57.8 (s, 3 F); υ_{max} (solid)/cm^{-1} 3242, 3128, 2967, 2859, 1597, 1567, 1326, 1251, 1194, 1161, 1097, 1017, 780; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{12}ClF_3N_3O$ 330.0616; found ^{35}Cl 330.0611 and ^{37}Cl 332.0586.

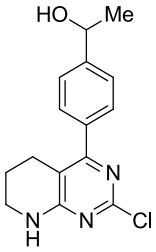
4-(3-((*Tert*-butyldimethylsilyl)oxy)phenyl)-2-chloro-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.079**



$C_{19}H_{26}ClN_3OSi$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.048 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.480 mmol, 2 equiv), (4-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)boronic acid (0.064 g, 0.254 mmol, 1.06 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.022 mL, 1.200 mmol, 5 equiv), and CPME (2 mL, 0.120 M). The reaction was warmed to 40 °C and allowed to stir for 20 h. After cooling, zinc (0.222 g, 3.400 mmol, 14.2 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.7 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 40 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–20% TBME/cyclohexane, afforded the *title compound* as a yellow oil (0.074 g, 82%). LCMS (Method B, UV, ESI) R_t = 1.55 min, $[M+H]^+$ = 376, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.8 Hz, 1 H), 7.13 (dt, J = 7.8, 1.3 Hz, 1 H), 7.00–6.97 (m, 1 H), 6.89 (ddd, J = 8.1, 2.3, 0.9 Hz, 1 H), 6.55 (br. s, 1 H), 3.54–3.49 (m, 2 H), 2.72 (t, J = 6.3 Hz, 2 H), 1.90–1.82 (m, 2 H), 1.00 (s, 9 H), 0.22 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 162.2, 157.5, 155.4, 138.5, 129.3, 121.9, 120.8, 120.5, 108.5, 41.2, 25.7, 24.2, 20.7, 18.2, –4.4, three equivalent peaks not observed; υ_{max} (thin film)/cm^{-1} 3250, 3127, 2930, 2858, 1594, 1563, 1327, 1299, 1270, 1254, 948, 853, 840, 779; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{27}ClN_3OSi$ 376.1606; found ^{35}Cl 376.1595 and ^{37}Cl 378.1573.

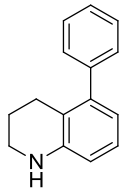
1-(4-(2-Chloro-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-4-yl)phenyl)ethanol, **3.080**



$C_{15}H_{16}ClN_3O$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.049 g, 0.245 mmol, 1 equiv), tripotassium phosphate (0.104 g, 0.490 mmol, 2 equiv), (4-acetylphenyl)boronic acid (0.042 g, 0.257 mmol, 1.05 equiv), platinum (IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.022 mL, 1.225 mmol, 5 equiv), and CPME (1 mL, 0.245 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.199 g, 3.040 mmol, 12.4 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 60.4 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 20 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane (+1% Et_3N), afforded the title compound as an off-white solid (0.011 g, 16%). m.p. 241–243 °C; LCMS (Method B, UV, ESI) R_t = 0.82 min, $[M+H]^+$ = 290, 100% purity; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.03 (br. s, 1 H), 7.52–7.39 (m, 4 H), 5.21 (d, J = 3.9 Hz, 1 H), 4.81–4.74 (m, 1 H), 3.32–3.27 (m, 2 H), 2.65 (t, J = 6.1 Hz, 2 H), 1.73–1.67 (m, 2 H), 1.35 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 162.0, 161.6, 156.9, 148.3, 135.2, 128.5, 124.9, 108.3, 67.8, 40.0, 25.8, 23.8, 20.0, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3242, 3120, 2963, 2928, 2862, 1591, 1564, 1411, 1326, 1303, 1286, 1249, 1190, 1093, 1016, 852, 841, 784; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{17}ClN_3O$ 290.1055; found ^{35}Cl 290.1042 and ^{37}Cl 292.1011.

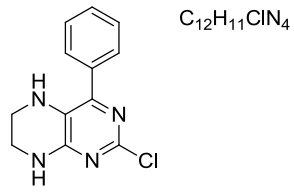
5-Phenyl-1,2,3,4-tetrahydroquinoline, **3.083**



$C_{15}H_{15}N$

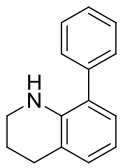
Chamber A of a two chamber COware apparatus was charged with 5-bromoquinoline (0.050 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.481 mmo1, 2 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.09 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), palladium(II) acetate (0.002 g, 0.009 mmol, 4 mol%), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (0.009 g 0.019 mmol, 8 mol%), water (0.020 mL, 1.200 mmol, 5 equiv), and CPME (1 mL, 0.241 M). The reaction was warmed to 40 °C and allowed to stir for 24 h. After cooling, zinc (0.189 g, 2.890 mmol, 12 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.6 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 24 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–20% TBME/cyclohexane, afforded the *title compound* as a colourless oil (0.042 g, 84%). LCMS (Method B, UV, ESI) R_t = 1.28 min, $[M+H]^+$ = 210, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.38 (m, 2 H), 7.36–7.30 (m, 3 H), 7.03 (t, J = 7.8 Hz, 1 H), 6.59 (dd, J = 7.3, 1.2 Hz, 1 H), 6.51 (dd, J = 7.9, 1.1 Hz, 1 H), 3.36–3.31 (m, 2 H), 2.63 (t, J = 6.4 Hz, 2 H), 1.90–1.82 (m, 2 H), one exchangeable proton not observed; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 142.6, 142.0, 129.1, 127.9, 126.6, 126.4, 118.9, 118.8, 113.4, 41.8, 25.8, 22.2, two equivalent peaks not observed; υ_{max} (thin film)/cm^{-1} 3408, 3054, 2925, 2839, 1586, 1487, 1462, 1346, 1301, 1244, 757, 722, 701; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}N$ 210.1277; found 210.1270.

2-Chloro-4-phenyl-5,6,7,8-tetrahydropteridine, **3.084**



Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropteridine (0.050 g, 0.249 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.497 mmol, 2 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.06 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.022 mL, 1.244 mmol, 5 equiv), and CPME (1 mL, 0.249 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.207 g, 3.170 mmol, 12.7 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 59.5 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 2 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% TBME/cyclohexane (+1% Et_3N) afforded the *title compound* as a white solid (0.033 g, 54%). m.p. 264–266 °C; LCMS (Method B, UV, ESI) R_t = 0.82 min, $[M+H]^+$ = 247, 100% purity; ^{1}H NMR (400 MHz, d_6-acetone) δ 7.73–7.68 (m, 2 H), 7.48–7.42 (m, 2 H), 7.41–7.37 (m, 1 H), 6.88 (br. s, 1 H), 5.08 (br. s, 1 H), 3.63–3.57 (m, 2 H), 3.35–3.31 (m, 2 H); ^{13}C NMR (101 MHz, d_6-acetone) δ 155.5, 149.4, 145.1, 137.5, 129.5, 129.4, 129.2, 123.7, 41.6, 40.2, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3338, 3227, 3125, 2964, 2857, 2376, 1590, 1568, 1532, 1455, 1358, 1338, 1273, 1226, 1204, 1096, 851, 760, 704, 624; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{12}ClN_4$ 247.0745; found ^{35}Cl 247.0738 and ^{37}Cl 249.0705.

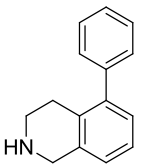
8-Phenyl-1,2,3,4-tetrahydroquinoline, **3.085**[208]



$C_{15}H_{15}N$

Chamber A of a two chamber COware apparatus was charged with 8-bromoquinoline (0.031 mL, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.481 mmol, 2 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.09 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), palladium(II) acetate (0.002 g, 0.009 mmol, 4 mol%), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (0.009 g, 0.019 mmol, 8 mol%), water (0.022 mL, 1.202 mmol, 5 equiv), and CPME (1 mL, 0.240 M). The reaction was warmed to 40 °C and allowed to stir for 20 h. After cooling, zinc (0.212 g, 3.240 mmol, 13.5 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.6 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 20 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–20% TBME/cyclohexane, afforded the title compound as a colourless gum (0.035 g, 70%). LCMS (Method B, UV, ESI) R_t = 1.37 min, $[M+H]^+$ = 210, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.43 (m, 4 H), 7.39–7.33 (m, 1 H), 7.01–6.93 (m, 2 H), 6.69 (t, J = 7.5 Hz, 1 H), 4.08 (br. s, 1 H), 3.30–3.25 (m, 2 H), 2.87 (t, J = 6.5 Hz, 2 H), 2.02–1.94 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 139.6, 129.4, 128.8, 128.8, 128.0, 127.0, 126.6, 121.2, 116.2, 42.0, 27.5, 22.0, two equivalent peaks not observed; υ_{max} (thin film)/cm^{-1} 3422, 3052, 2926, 2837, 1594, 1497, 1486, 1461, 1421, 1290, 1267, 754, 739, 701; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}N$ 210.1277; found 210.1279.

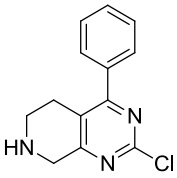
5-Phenyl-1,2,3,4-tetrahydroisoquinoline, **3.086**[209]



$C_{15}H_{15}N$

Chamber A of a two chamber COware apparatus was charged with 5-bromoisoquinoline (0.050 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.481 mmol, 2 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.09 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), palladium(II) acetate (0.002 g, 0.009 mmol, 4 mol%), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (0.009 g, 0.019 mmol, 8 mol%), water (0.022 mL, 1.202 mmol, 5 equiv), and CPME (1 mL, 0.240 M). The reaction was warmed to 40 °C and allowed to stir for 40 h. After cooling, zinc (0.231 g, 3.530 mmol, 14.7 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.6 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 28 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–100% TBME/cyclohexane followed by 0–20% MeOH/TBME (+1% Et_3N), afforded the title compound as a colourless gum (0.031 g, 62%). LCMS (Method B, UV, ESI) R_t = 1.09 min, $[M+H]^+$ = 210, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.39 (m, 2 H), 7.38–7.29 (m, 3 H), 7.21 (d, J = 7.6 Hz, 1 H), 7.10 (d, J = 7.1 Hz, 1 H), 7.05 (d, J = 7.6 Hz, 1 H), 4.12 (s, 2 H), 3.07 (t, J = 5.9 Hz, 2 H), 2.65 (t, J = 5.9 Hz, 2 H), 2.03 (br. s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 141.3, 135.9, 132.4, 129.1, 128.0, 127.5, 126.8, 125.5, 125.5, 48.7, 44.1, 28.3, two equivalent peaks not observed; υ_{max} (thin film)/cm^{-1} 3057, 3022, 2924, 2807, 1586, 1496, 1457, 1436, 1131, 953, 757, 700; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}N$ 210.1277; found 210.1270.

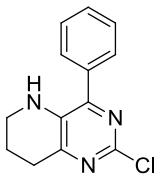
2-Chloro-4-phenyl-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidine, **3.087**



$C_{13}H_{12}ClN_3$

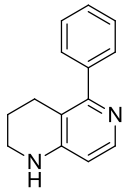
Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[3,4-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.05 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (1 mL, 0.250 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.222 g, 3.400 mmol, 13.6 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 59.2 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 20 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–100% EtOAc/cyclohexane followed by 0–20% MeOH/EtOAc (+1% Et_3N), afforded the *title compound* as a white solid (0.045 g, 73%). m.p. 300 °C (decomposition); LCMS (Method B, UV, ESI) R_t = 0.85 min, $[M+H]^+$ = 246, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.59 (m, 2 H), 7.51–7.47 (m, 3 H), 4.16–4.13 (m, 2 H), 3.49 (s, 1 H), 3.08 (t, J = 5.7 Hz, 2 H), 2.86–2.81 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 152.4, 144.9, 136.2, 130.0, 128.8, 128.5, 124.8, 50.7, 43.2, 26.9, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3327, 2926, 2847, 1533, 1435, 1332, 1262, 1025, 797, 758, 698, 627; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{13}ClN_3$ 246.0793; found ^{35}Cl 246.0797 and ^{37}Cl 248.0777.

2-Chloro-4-phenyl-5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidine, **3.088**



Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[3,2-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.50 mmol, 2 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.05 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g 0.010 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (1 mL, 0.250 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.202 g, 3.090 mmol, 12.4 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 59.2 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 24 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% TBME/cyclohexane (+1% Et_3N), afforded the *title compound* as a white solid (0.040 g, 65%). m.p. 87–89 °C; LCMS (Method B, UV, ESI) R_t = 1.04 min, $[M+H]^+$ = 246, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.67 (m, 2 H), 7.53–7.43 (m, 3 H), 4.33 (br. s, 1 H), 3.33–3.28 (m, 2 H), 2.97 (t, J = 6.6 Hz, 2 H), 2.10–2.02 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 151.1, 147.7, 135.5, 135.1, 129.7, 129.1, 128.2, 41.3, 30.1, 20.7, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3329, 2966, 2940, 2852, 1557, 1466, 1405, 1380, 1342, 1279, 1205, 1086, 902, 862, 698, 624; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{13}ClN_3$ 246.0793; found ^{35}Cl 246.0797 and ^{37}Cl 248.0767.

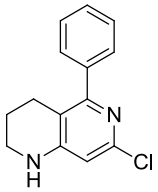
5-Phenyl-5,6,7,8-tetrahydro-1,6-naphthyridine, **3.089**[210]



$C_{14}H_{14}N_2$

Chamber A of a two chamber COware apparatus was charged with 5-chloro-1,6-naphthyridine (0.050 g, 0.304 mmol, 1 equiv), tripotassium phosphate (0.129 g, 0.608 mmol, 2 equiv), phenylboronic acid (0.039 g, 0.320 mmol, 1.05 equiv), platinum(IV) oxide (0.007 g, 0.031 mmol, 10 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.010 g, 0.012 mmol, 4 mol%), water (0.027 mL, 1.519 mmol, 5 equiv), and CPME (2 mL, 0.152 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.218 g, 3.330 mmol, 11 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 48.7 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 24 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–100% TBME/cyclohexane (+1% Et_3N) followed by 0–20% MeOH/TBME (+1% Et_3N), afforded the title compound as a white solid (0.043 g, 67%). m.p. 143–145 °C; LCMS (Method B, UV, ESI) R_t = 0.91 min, $[M+H]^+$ = 211, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 5.5 Hz, 1 H), 7.52–7.48 (m, 2 H), 7.44–7.32 (m, 3 H), 6.29 (d, J = 5.5 Hz, 1 H), 4.50 (br. s, 1 H), 3.37–3.32 (m, 2 H), 2.68 (t, J = 6.2 Hz, 2 H), 1.88–1.80 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 150.6, 146.9, 140.8, 128.9, 127.9, 127.5, 113.5, 107.3, 41.2, 25.1, 21.4, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3227, 3054, 2931, 2852, 1585, 1511, 1432, 1351, 1315, 1185, 1147, 1010, 810, 750, 699; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{15}N_2$ 211.1230; found 211.1226.

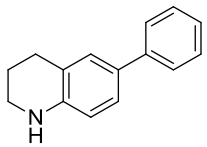
7-Chloro-5-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridine, **3.090**



$C_{14}H_{13}ClN_2$

Chamber A of a two chamber COware apparatus was charged with 5,7-dichloro-1,6-naphthyridine (0.050 g, 0.251 mmol, 1 equiv), tripotassium phosphate (0.107 g, 0.502 mmol, 2 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.05 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.023 mL, 1.256 mmol, 5 equiv), and CPME (2 mL, 0.126 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.197 g, 3.010 mmol, 12 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 58.9 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 24 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–50% TBME/cyclohexane, afforded the *title compound* as a white solid (0.038 g, 62%). m.p. 130–132 °C; LCMS (Method B, UV, ESI) R_t = 1.10 min, $[M+H]^+$ = 245, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.45 (m, 2 H), 7.43–7.33 (m, 3 H), 6.32 (s, 1 H), 4.68 (br. s, 1 H), 3.36–3.31 (m, 2 H), 2.64 (t, J = 6.2 Hz, 2 H), 1.85–1.77 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 152.6, 148.5, 139.5, 128.9, 128.0, 112.9, 105.6, 41.2, 24.8, 21.2, three equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3310, 3254, 3145, 3068, 2951, 2839, 1574, 1505, 1436, 1348, 1314, 1253, 1197, 1178, 1089, 1072, 1012, 907, 840, 831, 769, 701; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{14}ClN_2$ 245.0840; found 245.0838.

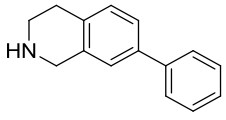
6-Phenyl-1,2,3,4-tetrahydroquinoline, **3.091**[211]



$C_{15}H_{15}N$

Chamber A of a two chamber COware apparatus was charged with 6-bromoquinoline (0.033 mL, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.481 mmol, 2 equiv), phenylboronic acid (0.044 g, 0.360 mmol, 1.5 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), palladium(II) acetate (0.002 g, 0.009 mmol, 4 mol%), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (0.009 g, 0.019 mmol, 8 mol%), water (0.022 mL, 1.202 mmol, 5 equiv), and CPME (2 mL, 0.120 M). The reaction was warmed to 40 °C and allowed to stir for 24 h. After cooling, zinc (0.212 g, 3.240 mmol, 13.5 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.6 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 24 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–20% TBME/cyclohexane, afforded the title compound as a yellow oil (0.035 g, 70%). LCMS (Method B, UV, ESI) R_t = 1.30 min, $[M+H]^+$ = 210, 99% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.51 (m, 2 H), 7.41–7.35 (m, 2 H), 7.27–7.22 (m, 4 H), 6.57–6.53 (m, 1 H), 3.38–3.33 (m, 2 H), 2.85 (t, J = 6.4 Hz, 2 H), 2.03–1.95 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 141.5, 130.0, 128.6, 128.2, 126.3, 125.9, 125.5, 121.6, 114.5, 42.0, 27.1, 22.2, two equivalent peaks not observed; υ_{max} (thin film)/cm^{-1} 3408, 3024, 2926, 2837, 1612, 1599, 1519, 1486, 1467, 1229, 815, 762, 696; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}N$ 210.1277; found 210.1269.

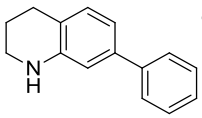
7-Phenyl-1,2,3,4-tetrahydroisoquinoline, **3.092**[212]



$C_{15}H_{15}N$

Chamber A of a two chamber COware apparatus was charged with 7-bromoisoquinoline (0.050 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.481 mmol, 2 equiv), phenylboronic acid (0.044 g, 0.360 mmol, 1.5 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), palladium(II) acetate (0.002 g, 0.009 mmol, 4 mol%), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (0.009 g, 0.019 mmol, 8 mol%), water (0.022 mL, 1.202 mmol, 5 equiv), and CPME (2 mL, 0.120 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, zinc (0.212 g, 3.240 mmol, 13.5 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.6 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 24 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–20% TBME/cyclohexane, afforded the title compound as a colourless oil (0.046 g, 92%). LCMS (Method B, UV, ESI) R_t = 1.09 min, $[M+H]^+$ = 210, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (br. s, 1 H), 7.57–7.28 (m, 7 H), 7.22 (d, J = 8.1 Hz, 1 H), 4.33–4.25 (m, 2 H), 3.42–3.34 (m, 2 H), 3.12–3.03 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 140.3, 140.0, 131.2, 130.0, 129.5, 128.8, 127.5, 127.0. 126.4, 125.2, 112.0, 44.7, 41.5, 25.8; υ_{max} (thin film)/cm^{-1} 3032, 2926, 2835, 1674, 1485, 1428, 1231, 1132, 761, 698; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}N$ 210.1277; found 210.1266.

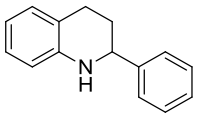
7-Phenyl-1,2,3,4-tetrahydroquinoline, **3.093**[212]



Chamber A of a two chamber COware apparatus was charged with 7-bromoquinoline (0.050 g, 0.240 mmol, 1 equiv), tripotassium phosphate (0.102 g, 0.481 mmol, 2 equiv), phenylboronic acid (0.031 g, 0.254 mmol, 1.06 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), palladium(II) acetate (0.002 g, 0.009 mmol, 4 mol%), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (0.009 g,

0.019 mmol, 8 mol%), water (0.022 mL, 1.202 mmol, 5 equiv), and CPME (2 mL, 0.120 M). The reaction was warmed to 40 °C and allowed to stir for 24 h. After cooling, zinc (0.212 g, 3.240 mmol, 13.5 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 61.6 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 16 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–5% TBME/cyclohexane, afforded the title compound as a colourless oil (0.037 g, 74%). LCMS (Method B, UV, ESI) R_t = 1.29 min, $[M+H]^+$ = 210, 89% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.53 (m, 2 H), 7.44–7.38 (m, 2 H), 7.34–7.29 (m, 2 H), 7.03 (d, J = 7.6 Hz, 1 H), 6.86 (dd, J = 7.7, 1.8 Hz, 1 H), 6.71 (d, J = 1.7 Hz, 1 H), 3.39–3.32 (m, 2 H), 2.82 (t, J = 6.4 Hz, 2 H), 2.03–1.95 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0, 141.7, 140.0, 129.9, 128.5, 127.0, 126.8, 120.7, 116.0, 112.8, 42.1, 26.7, 22.3, two equivalent peaks not observed; υ_{max} (thin film)/cm^{-1} 3405, 3025, 2924, 2837, 1612, 1566, 1485, 1467, 1449, 1336, 1312, 1227, 1006, 857, 757, 696; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}N$ 210.1277; found 210.1269.

2-Phenyl-1,2,3,4-tetrahydroquinoline, **3.094**[213]

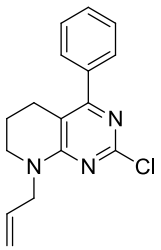


$C_{15}H_{15}N$

Chamber A of a two chamber COware apparatus was charged with 2-chloroquinoline (0.050 g, 0.306 mmol, 1 equiv), tripotassium phosphate (0.130 g, 0.611 mmol, 2 equiv), phenylboronic acid (0.039 g, 0.320 mmol, 1.05 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 9 mol%), palladium(II) acetate (0.003 g, 0.013 mmol, 4 mol%), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (0.012 g, 0.025 mmol, 8 mol%), water (0.028 mL, 1.528 mmol, 5 equiv), and CPME (2 mL, 0.153 M). The reaction was warmed to 40 °C and allowed to stir for 40 h. After cooling, zinc (0.198 g, 3.030 mmol, 9.9 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 48.4 equiv, as a 7.4 M aqueous solution) were added to chamber B. The

reaction vessel was sealed and was allowed to stir at ambient temperature for 28 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (12 g), eluting with 0–20% TBME/cyclohexane, afforded the title compound as a colourless oil (0.045 g, 70%). LCMS (Method B, UV, ESI) R_t = 1.33 min, $[M+H]^+$ = 210, 93% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.28 (m, 6 H), 7.05–6.99 (m, 2 H), 6.66 (td, J = 7.3, 1.0 Hz, 1 H), 6.58–6.53 (m, 1 H), 4.46 (dd, J = 9.3, 2.9 Hz, 1 H), 2.99–2.89 (m, 1 H), 2.79–2.71 (m, 1 H), 2.18–2.10 (m, 1 H), 2.07–1.95 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 144.7, 129.3, 128.6, 127.4, 126.9, 126.5, 120.9, 117.2, 114.0, 56.3, 31.0, 26.4, two equivalent peaks not observed; υ_{max} (thin film)/cm^{-1} 3406, 3058, 3032, 2924, 2845, 1607, 1481, 1310, 1274, 1252, 1110, 747, 700; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{16}N$ 210.1277; found 210.1269.

8-Allyl-2-chloro-4-phenyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.095**

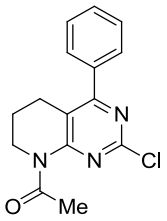


$C_{16}H_{16}ClN_3$

A microwave vial was charged with 2-chloro-4-phenyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (0.018 g, 0.073 mmol, 1 equiv), allyl bromide (0.008 mL, 0.092 mmol, 1.3 equiv), and DMF (1 mL, 0.073 M). The reaction mixture was cooled to 0 °C and was allowed to stir for 15 min, after which sodium hydride (0.004 g, 0.100 mmol, 1.4 equiv, as a 60% dispersion in mineral oil) was added. The reaction was allowed to warm to ambient temperature over 24 h. The reaction mixture was then cooled to 0 °C and was quenched with water (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with brine (10 mL), dried by passing through a hydrophobic frit, and concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (4 g), eluting with 0–25% EtOAc/cyclohexane, afforded the *title compound* as a

colourless oil (0.017 g, 81%). LCMS (Method B, UV, ESI) R_t = 1.32 min, $[M+H]^+$ = 286, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.49 (m, 2 H), 7.46–7.38 (m, 3 H), 5.87 (ddt, J = 17.6, 9.6, 5.8 Hz, 1 H), 5.26–5.23 (m, 1 H), 5.23–5.19 (m, 1 H), 4.30 (dt, J = 5.7, 1.3 Hz, 2 H), 3.44–3.39 (m, 2 H), 2.75–2.70 (m, 2 H), 1.89–1.80 (m, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 160.9, 158.0, 137.6, 132.5, 128.9, 128.8, 128.1, 117.4, 109.2, 51.0, 46.9, 24.7, 20.7, two equivalent peaks not observed; υ_{max} (thin film)/cm^{-1} 3088, 3062, 2955, 2928, 2850, 1583, 1559, 1516, 1321, 1240, 914, 764, 699; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{12}N_3S$ 286.1106; found ^{35}Cl 286.1107 and ^{37}Cl 288.1077.

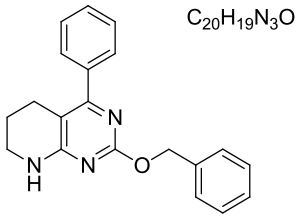
1-(2-Chloro-4-phenyl-6,7-dihydropyrido[2,3-*d*]pyrimidin-8(5*H*)-yl)ethanone, **3.096**



To a stirred solution of 2-chloro-4-phenyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (0.030 g, 0.122 mmol, 1 equiv), sodium hydride (0.006 g, 0.150 mmol, 1.229 equiv, as a 60% dispersion in mineral oil), and DMF (1 mL, 0.122 M), under a nitrogen atmosphere at ambient temperature, was added acetic anhydride (0.013 mL, 0.134 mmol, 1.1 equiv). The reaction mixture was allowed to stir for 21 h. After cooling, the reaction was taken up in EtOAc (20 mL) which was then washed with LiCl (2 x 20 mL, as a 5% aqueous solution). The organic phase was then washed with brine (20 mL), dried by passing through a hydrophobic frit, and concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (40 g), eluting with 0–50% TBME/cyclohexane, afforded the *title compound* as a colourless oil (0.028 g, 80%). LCMS (Method B, UV, ESI) R_t = 1.15 min, $[M+H]^+$ = 288, 97% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.53 (m, 2 H), 7.50–7.46 (m, 3 H), 3.93–3.88 (m, 2 H), 2.78 (t, J = 6.2 Hz, 2 H), 2.70 (s, 3 H), 1.88 (quin, J = 6.2 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 167.0, 160.1, 156.8, 136.7, 129.8, 128.9, 128.5, 115.9, 43.9, 27.6, 25.1, 21.8, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 2960, 2929, 1683, 1537, 1496, 1419, 1367, 1334, 1253,

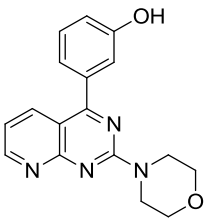
1187, 1106, 1016, 699; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{15}ClN_3O$ 288.0898; found ^{35}Cl 288.0899 and ^{37}Cl 290.0867.

2-(Benzyloxy)-4-phenyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine, **3.097**



To a stirred solution of 2-chloro-4-phenyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (0.046 g, 0.187 mmol, 1 equiv) in acetonitrile (3 mL, 0.062 M), under a nitrogen atmosphere at ambient temperature, was added sodium *tert*-butoxide (0.054 g, 0.562 mmol, 3 equiv) followed by benzyl alcohol (0.029 mL, 0.281 mmol, 1.5 equiv). The reaction mixture was then heated to reflux and allowed to stir for 26 h. After cooling, the reaction was taken up in water (20 mL) which was then washed with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried by passing through a hydrophobic frit, and concentrated under reduced pressure. Purification by normal phase column chromatography on Companion silica (40 g), eluting with 0–50% TBME/cyclohexane, afforded the *title compound* as a white solid (0.055 g, 93%). m.p. 212–214 °C; LCMS (Method B, UV, ESI) R_t = 1.25 min, $[M+H]^+$ = 318, 100% purity; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61–7.56 (m, 2 H), 7.50–7.25 (m, 8 H), 5.57 (br. s, 1 H), 5.39 (s, 2 H), 3.46–3.41 (m, 2 H), 2.72 (t, J = 6.1 Hz, 2 H), 1.84 (quin, J = 5.9 Hz, 2 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 163.0, 162.7, 162.4, 138.6, 137.6, 128.9, 128.7, 128.2, 128.0, 127.5, 104.1, 68.1, 41.2, 24.2, 21.5, four equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3230, 3118, 2939, 2859, 1606, 1571, 1393, 1340, 1261, 1210, 1046, 796, 739, 698; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{20}N_3O$ 318.1601; found 318.1599.

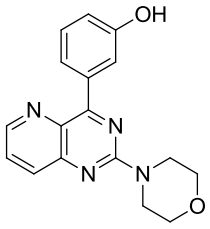
3-(2-Morpholinopyrido[2,3-*d*]pyrimidin-4-yl)phenol, **3.108**



$C_{17}H_{16}N_4O_2$

A microwave vial was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.200 g, 1.000 mmol, 1 equiv), tripotassium phosphate (0.424 g, 2.000 mmol, 2 equiv), (3-((*tert*-butyldimethylsilyl)oxy)phenyl)boronic acid (0.265 g, 1.050 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.029 g, 0.040 mmol, 4 mol%), water (0.090 mL, 5.000 mmol, 5 equiv), and CPME (10 mL, 0.100 M). The reaction was warmed to 40 °C and allowed to stir for 2 h. After cooling, morpholine (0.130 mL, 1.492 mmol, 1.5 equiv) and *N*,*N*-diisopropylethylamine (0.350 mL, 2.004 mmol, 2 equiv) were added to the reaction mixture. The reaction vessel was then sealed, warmed to 40 °C, and was allowed to stir for 10 h. After cooling, the reaction mixture was taken up in EtOAc (20 mL) which was then washed with water (20 mL) and brine (20 mL), was dried by passing through a hydrophobic frit, and was concentrated under reduced pressure. Purification by MDAP afforded the *title compound* as a yellow solid (0.172 g, 56%). m.p. 290 °C (decomposition); LCMS (Method B, UV, ESI) R_t = 0.81 min, $[M+H]^+$ = 309, 100% purity; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.91 (dd, J = 4.3, 1.8 Hz, 1 H), 8.51 (br. s, 1 H), 8.19 (dd, J = 8.1, 2.0 Hz, 1 H), 7.41–7.35 (m, 1 H), 7.26 (dd, J = 8.2, 4.3 Hz, 1 H), 7.14–7.09 (m, 2 H), 7.03–6.99 (m, 1 H), 3.92 (t, J = 4.8 Hz, 4 H), 3.72 (t, J = 4.8 Hz, 4 H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 170.5, 160.5, 159.7, 157.6, 157.3, 137.4, 136.5, 129.6, 120.3, 118.6, 117.3, 116.3, 111.3, 66.0, 44.1, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 2978, 2958, 2918, 2871, 2671, 1572, 1548, 1466, 1272, 1254, 1211, 1112, 782, 704; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{17}N_4O_2$ 309.1346; found 309.1332.

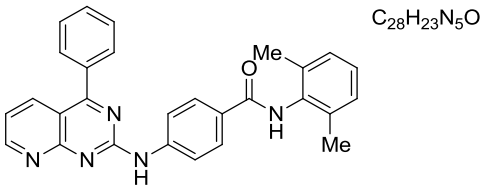
3-(2-Morpholinopyrido[3,2-*d*]pyrimidin-4-yl)phenol, **3.104**[200]



$C_{17}H_{16}N_4O_2$

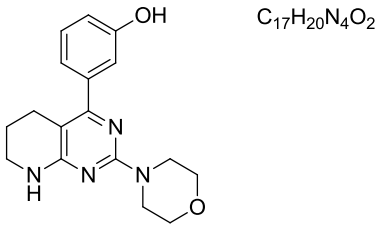
A microwave vial was charged with 2,4-dichloropyrido[3,2-*d*]pyrimidine (0.100 g, 0.500 mmol, 1 equiv), tripotassium phosphate (0.212 g, 1.000 mmol, 2 equiv), (3-((*tert*-butyldimethylsilyl)oxy)phenyl)boronic acid (0.132 g, 0.525 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.015 g, 0.020 mmol, 4 mol%), water (0.045 mL, 2.50 mmol, 5 equiv), and CPME (5 mL, 0.1 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, morpholine (0.070 mL, 0.803 mmol, 1.6 equiv) and tripotassium phosphate (0.159 mL, 0.750 mmol, 1.5 equiv) were added to the reaction mixture. The reaction vessel was then sealed, warmed to 40 °C, and was allowed to stir for 32 h. After cooling, the reaction mixture was taken up in EtOAc (20 mL) which was then washed with water (20 mL) and brine (20 mL), was dried by passing through a hydrophobic frit, and was concentrated under reduced pressure. Hydrochloric acid (5.00 mL, 15.00 mmol 30 equiv, as a 3 M solution in CPME), was then added to the crude residue which was allowed to stir at ambient temperature for 2 h. The solvent was removed under reduced pressure. Purification by MDAP afforded the title compound as a yellow solid (0.083 g, 54%). m.p. 113–115 °C; LCMS (Method B, UV, ESI) R_t = 0.95 min, $[M+H]^+$ = 309, 97% purity; ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.59 (s, 1 H), 8.67 (dd, J = 3.9, 1.7 Hz, 1 H), 7.95 (dd, J = 8.6, 1.5 Hz, 1 H), 7.74–7.68 (m, 2 H), 7.33 (t, J = 8.2 Hz, 1 H), 6.99–6.94 (m, 1 H), 3.90 (t, J = 4.8 Hz, 4 H), 3.73 (t, J = 4.8 Hz, 4 H), one exchangeable proton not observed; ^{13}C NMR (101 MHz, d_6-DMSO) δ 166.4, 157.6, 156.7, 149.1, 146.4, 137.5, 134.1, 133.8, 128.7, 128.3, 122.1, 118.0, 117.3, 66.0, 44.2, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3153, 2968, 2856, 1544, 1446, 1377, 1353, 1286, 1272, 1230, 1211, 1114, 987, 872, 792, 702, 623; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{17}N_4O_2$ 309.1346; found 309.1333.

N-(2,6-dimethylphenyl)-4-((4-phenylpyrido[2,3-*d*]pyrimidin-2-yl)amino)benzamide, **3.105**[214]



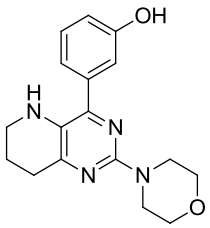
A microwave vial was charged with 2-chloro-4-phenylpyrido[2,3-*d*]pyrimidine (0.120 g, 0.497 mmol, 1 equiv), *N*-ethyl-*N*-isopropylpropan-2-amine (0.173 mL, 0.993 mmol, 2 equiv), 4-amino-*N*-(2,6-dimethylphenyl)benzamide (0.119 g, 0.497 mmol, 1 equiv), and 1-butanol (10 mL, 0.050 M). The reaction mixture was warmed to 120 °C and was allowed to stir for 61 h. After cooling, the reaction was diluted with EtOAc (20 mL) and was washed with water (20 mL) and brine (20 mL). The organic layer was dried by passing through a hydrophobic frit and concentrated under reduced pressure. Purification by MDAP afforded the title compound as a yellow solid (0.081 g, 37%). m.p. 178–180 °C; LCMS (Method B, UV, ESI) R_t = 1.06 min, $[M+H]^+$ = 446, 83% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (d, J = 4.4, 2.0 Hz, 1 H), 8.31 (dd, J = 8.2, 1.8 Hz, 1 H), 8.09 (d, J = 8.6 Hz, 2 H), 7.99 (d, J = 8.6 Hz, 2 H), 7.79–7.75 (m, 3 H), 7.66–7.61 (m, 3 H), 7.35 (br. s, 1 H), 7.32 (dd, J = 8.2, 4.3 Hz, 1 H), 7.17–7.13 (m, 3 H), 2.32 (s, 6 H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 171.1, 164.5, 159.9, 158.1, 157.5, 143.1, 136.5, 135.7, 135.7, 135.5, 130.3, 129.7, 128.6, 128.2, 127.6, 127.4, 126.5, 120.0, 118.3, 113.0, 18.1, seven equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3281, 3058, 2966, 1642, 1586, 1567, 1520, 1494, 1464, 1445, 1412, 1366, 1252, 763, 701; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{24}N_5O$ 446.1975; found 446.1991.

3-(2-Morpholino-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-4-yl)phenol, **3.114**



Chamber A of a COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), (3-(benzyloxy)phenyl)boronic acid (0.060 g, 0.263 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (2 mL, 0.125 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, morpholine (0.033 mL, 0.375 mmol, 1.5 equiv) and tripotassium phosphate (0.080 g, 0.375 mmol, 1.5 equiv) were added to chamber A. The reaction vessel was then sealed, warmed to 40 °C, and was allowed to stir for 8 h. After cooling, palladium on carbon (0.027 g, 0.025 mmol, 10 mol%) was added to chamber A and zinc (0.206 g, 3.150 mmol, 12.6 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 59.2 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was then sealed and the reaction mixture was allowed to stir for a further 64 h. The reaction mixture was then filtered through Celite®, washing with MeOH (15 mL). The filtrate was then concatenated under reduced pressure. Purification by MDAP afforded the *title compound* as a white solid (0.033 g, 42%). m.p. 244–246 °C; LCMS (Method B, UV, ESI) R_t = 0.90 min, $[M+H]^+$ = 313, 100% purity; ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.25 (s, 1 H), 7.19 (t, J = 8.1, 1 H), 6.97 (br. s, 1 H), 6.93–6.89 (m, 2 H), 6.76 (ddd, J = 8.1, 2.3, 1.1 Hz, 1 H), 3.63–3.54 (m, 8 H), 3.26–3.21 (m, 2 H), 2.52 (t, J = 6.1 Hz, 2 H), 1.70–1.63 (m, 2 H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 160.8, 160.7, 159.6, 156.9, 140.6, 128.6, 119.2, 115.5, 115.0, 99.4, 66.1, 44.1, 40.2, 23.9, 21.4, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3073, 2949, 2852, 1574, 1557, 1435, 1352, 1248, 1204, 1112, 993, 890, 785; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{21}N_4O_2$ 313.1659; found 313.1647.

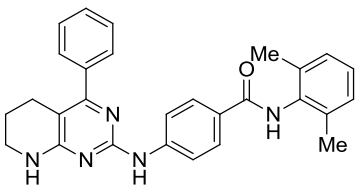
3-(2-Morpholino-5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidin-4-yl)phenol, **3.115**



$C_{17}H_{20}N_4O_2$

Chamber A of COware apparatus was charged with 2,4-dichloropyrido[3,2-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), (3-(benzyloxy)phenyl)boronic acid (0.060 g, 0.263 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (2 mL, 0.125 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, morpholine (0.033 mL, 0.375 mmol, 1.5 equiv) and tripotassium phosphate (0.080 g, 0.375 mmol, 1.5 equiv) were added to chamber A. The reaction vessel was then sealed, warmed to 40 °C, and was allowed to stir for 24 h. After cooling, palladium on carbon (0.027 g, 0.025 mmol, 10 mol%) was added to chamber A and zinc (0.196 g, 3.000 mmol, 12 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 59.2 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was then sealed and then the reaction mixture was allowed to stir for a further 48 h. The reaction mixture was then filtered through Celite®, washing with MeOH (15 mL). The filtrate was then concentrated under reduced pressure. Purification by MDAP afforded the *title compound* as a yellow gum (0.030 g, 38%). LCMS (Method B, UV, ESI) R_t = 0.93 min, $[M+H]^+$ = 313, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 2 H), 7.16 (s, 1 H), 6.87 (d, J = 7.3 Hz, 1 H), 3.82–3.76 (m, 4 H), 3.69–3.64 (m, 4 H), 3.21–3.17 (m, 2 H), 2.84 (t, J = 6.7 Hz, 2 H), 2.06–1.98 (m, 2 H), two exchangeable protons not observed; ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 155.8, 153.1, 150.2, 138.5, 129.9, 129.3, 120.3, 116.3, 115.5, 67.0, 45.4, 42.0, 30.3, 21.9, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 2960, 2844, 1614, 1559, 1441, 1330, 1286, 1259, 1220, 1183, 1114, 991; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{21}N_4O_2$ 313.1665; found 313.1660.

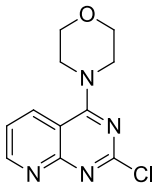
N-(2,6-dimethylphenyl)-4-((4-phenyl-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidin-2-yl)amino)benzamide, **3.116**



$C_{28}H_{27}N_5O$

Chamber A of COware apparatus was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), tripotassium phosphate (0.106 g, 0.500 mmol, 2 equiv), phenylboronic acid (0.032 g, 0.262 mmol, 1.05 equiv), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.007 g, 0.010 mmol, 4 mol%), water (0.023 mL, 1.250 mmol, 5 equiv), and CPME (2 mL, 0.125 M). The reaction was warmed to 40 °C and allowed to stir for 16 h. After cooling, 4-amino-*N*-(2,6-dimethylphenyl)benzamide (0.072 g, 0.300 mmol, 1.2 equiv) and tripotassium phosphate (0.080 g, 0.375 mmol, 1.5 equiv) were added to chamber A of COware. The reaction vessel was then sealed, warmed to 40 °C, and was allowed to stir for 24 h. After cooling, palladium on carbon (0.027 g, 0.025 mmol, 10 mol%) was added to chamber A of COware and zinc (0.208 g, 3.180 mmol, 12.7 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 59.2 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was then sealed and then the reaction mixture was allowed to stir for a further 16 h. The reaction mixture was then filtered through Celite®, washing with MeOH (15 mL). The filtrate was then concatenated under reduced pressure. Purification by MDAP afforded the *title compound* as a white solid (0.012 g, 11%). m.p. 250 °C (decomposition); LCMS (Method B, UV, ESI) R_t = 1.26 min, $[M+H]^+$ = 450, 100% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.5 Hz, 2 H), 7.77 (d, J = 8.5 Hz, 2 H), 7.61–7.57 (m, 2 H), 7.50–7.42 (m, 4 H), 7.14–7.11 (m, 2 H), 5.29 (br. s, 1 H), 3.51–3.46 (m, 2 H), 2.72 (t, J = 6.0 Hz, 2 H), 2.30 (s, 6 H), 1.92–1.84 (m, 2 H), two exchangeable protons not observed; ^{13}C NMR (101 MHz, d_6-DMSO) δ 178.8, 170.3, 161.4, 159.7, 151.3, 140.7, 137.8, 136.5, 130.1, 128.9, 128.4, 128.0, 127.6, 126.9, 119.1, 112.3, 104.8, 40.1, 23.8, 20.4, 18.3, seven equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3339, 3209, 2957, 1641, 1587, 1566, 1514, 1417, 1384, 1346, 1291, 1249, 1175, 1027, 767, 703; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{28}N_5O$ 450.2288; found 450.2271.

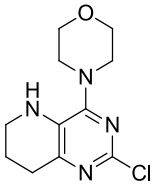
4-(2-Chloropyrido[2,3-*d*]pyrimidin-4-yl)morpholine, **3.122**[200]



$C_{11}H_{11}ClN_4O$

A microwave vial was charged with 2,4-dichloropyrido[2,3-*d*]pyrimidine (0.100 g, 0.500 mmol, 1 equiv), cesium carbonate (0.171 g, 0.525 mmol, 1.05 equiv), morpholine (0.046 mL, 0.525 mmol, 1.05 equiv), and CPME (1 mL, 0.500 M). The reaction was allowed to stir at ambient temperature for 2.5 h. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried by passing through a hydrophobic frit, and concentrated under reduced pressure to afford the title compound as a yellow solid (0.104 g, 83%). m.p. 171–173 °C; LCMS (Method B, UV, ESI) R_t = 0.65 min, $[M+H]^+$ = 251, 97% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (dd, J = 4.3, 1.8 Hz, 1 H), 8.22 (dd, J = 8.3, 1.7 Hz, 1 H), 7.37 (dd, J = 8.3, 4.2 Hz, 1 H), 3.98–3.93 (m, 4 H), 3.91–3.86 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 161.2, 159.5, 156.1, 134.3, 120.2, 108.7, 66.4, 49.7, two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 2959, 2909, 2871, 1593, 1563, 1520, 1435, 1417, 1293, 1256, 1105, 1020, 944, 794; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{12}ClN_4O$ 251.0694; found ^{35}Cl 251.0701 and ^{37}Cl 253.0664.

4-(2-Chloro-5,6,7,8-tetrahydropyrido[3,2-*d*]pyrimidin-4-yl)morpholine, **3.123**

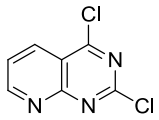
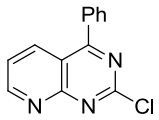
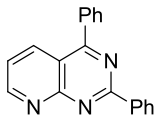
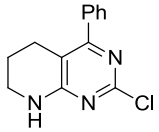


$C_{11}H_{15}ClN_4O$

Chamber A of a two chamber COware apparatus was charged with 2,4-dichloropyrido[3,2-*d*]pyrimidine (0.050 g, 0.250 mmol, 1 equiv), cesium carbonate (0.081 g, 0.250 mmol, 1 equiv), morpholine (0.022 mL, 0.250 mmol, 1 equiv), platinum(IV) oxide (0.006 g, 0.026 mmol, 11 mol%), and CPME (2 mL, 0.125 M). The reaction was warmed to 40 °C and allowed to stir for 2 h. After cooling, zinc (0.187 g, 2.860 mmol, 11.4 equiv) and hydrochloric acid (2.00 mL, 14.80 mmol, 59.2 equiv, as a 7.4 M aqueous solution) were added to chamber B. The reaction vessel was sealed and was allowed to stir at ambient temperature for 40 h. The reaction mixture was filtered through a Celite® pad, washing with MeOH (15 mL) and the filtrate was concentrated under reduced pressure. Purification by normal phase

column chromatography on Companion silica (12 g), eluting with 0–50% EtOAc/cyclohexane, afforded the title compound as a white solid (0.039 g, 61%). m.p. 168–170 °C; LCMS (Method B, UV, ESI) R_t = 0.83 min, $[M+H]^+$ = 255, 97% purity; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83–3.78 (m, 4 H), 3.35–3.31 (m, 4 H), 3.30–3.27 (m, 2 H), 2.84 (t, J = 6.6 Hz, 2 H), 2.06–1.98 (m, 2 H), one exchangeable proton not observed; ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 151.0, 147.5, 128.9, 66.7, 47.5, 41.6, 29.3, 21.3 two equivalent peaks not observed; υ_{max} (solid)/cm^{-1} 3344, 2960, 2891, 2854, 2834, 1574, 1474, 1439, 1333, 1281, 1246, 1113, 1103, 1068, 954, 901, 864, 683; HRMS (ESI-Orbitrap) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{16}ClN_4O$ 255.1020; found ^{35}Cl 255.1013 and ^{37}Cl 257.0992.

5.6 HPLC retention times and factors of products

compound	structure	retention time (min)	conversion factor
1		1.76	4.13
2		2.35	2.57
3		2.95	1.21
4		2.25	0.26

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Appendix