Transition Metal Catalysis for Novel Syntheses and Applications of Arylboronic Acids and their Derivatives

Volume 1 of 1
James Robert White
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University of Bath
Department of Chemistry
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Abstract

The research investigations presented herein are concerned with the syntheses and applications of arylboronic acids and their derivatives; with a particular focus on their accessibility or utility in certain of the most significant modern transition metal-catalysed reactions to involve organoborons.

Chapter 1 provides an introduction to the field of organoboron chemistry, from its roots employing borane and related highly reactive derivatives for uncatalysed hydroboration of olefins and acetylenes, to the modern classes of organoboron reagents of the greatest significance to the related contemporary transition metal-catalysed methodologies. Furthermore particular emphasis is placed on the discussion of arylboronic acids, their synthesis, and application to transition metal catalysis as a result of their propensity to undergo useful transmetallation events.

Chapter 2 details the use of a commercially available sulfonated monophosphine ligand in the rhodium-catalysed 1,2-addition reaction employing aryl aldehydes and arylboronic acids in aqueous media. The high and continued activity of the catalytic complex is demonstrated by it being successfully recycled five consecutive times in the arylation reaction of an aryl aldehyde; as well as being active for the arylations of more sterically demanding aryl methyl ketone substrates.

Chapter 3 details the design and synthesis of a novel bench-stable azidomethylene substituted arylboronate ester. The reactivity of this compound and a related analogue in both the copper-catalysed azide alkyne cycloaddition reaction and the Suzuki coupling reaction are detailed, culminating in the proof-of-concept use of such versatile synthetic building blocks in the synthesis of a drug-substance derivative.

Chapter 4 details alternative synthetic approaches to that used in Chapter 3 in order to access bifunctional azidomethylene substituted arylboronate esters. In particular the application of Miyaura borylation of arylhalides bearing benzylic azides is addressed as a means to rapidly access substrates which are otherwise shown to be incompatible with classical s-block synthetic intermediates.

Acknowledgements

First and foremost I would like to thank Chris and Gareth for all their help and advice over the years – I am truly lucky to have had two great supervisors. I would also like to say thanks to Steve Bull for all his encouragement.

The biggest thanks of all has to go to my Mum and Dad, without whom I would not have made it this far; so thank you. And yes, you told me so! I also have to say a big thanks to Rachel, Sarah, Emma, Mia and Fynn.

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Then there are all those who made my time at Bath extra special, including, but not limited to: Jez, Sam, Iwan, Halina, and of course Ai-Linh for all her support and lovingly cooked discount meals! And thank you Atomic.

There are too many people still left to mention, including many of the research, technical and support staff. However, Mary, Andy, Karen, Sheila, Sarah, Catrin and John deserve a special mention for everything from encouraging words and specialist advice, to very many enjoyable conversations.

How often people speak of art and science as though they were two entirely different things, with no interconnection. An artist is emotional, they think, and uses only his intuition; he sees all at once and has no need of reason. A scientist is cold, they think, and uses only his reason; he argues carefully step by step, and needs no imagination. That is all wrong. The true artist is quite rational as well as imaginative and knows what he is doing; if he does not, his art suffers. The true scientist is quite imaginative as well as rational, and sometimes leaps to solutions where reason can follow only slowly; if he does not, his science suffers.

Isaac Asimov

Table of Contents

Chapter 3 – Synthesis and Applications of a Novel Azidomethylene Substituted Aryl Pinacolboronate Ester

Chapter 5 – Experimental

Abbreviations

δ	Chemical shift in ppm
9-BBN	9-Borabicyclo[3.3.1]nonane
Ac	Acetyl
acac	Acetylacetonate
AIBN	Azobisisobutyronitrile
anhyd.	Anhydrous
app.	Apparent
aq.	Aqueous
Ar	Aryl
ATRP	Atom Transfer Radical Polymerisation
B_2Pin_2	Bis(pinacolato)diboron
$B(Ar_F)_4$	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
BDan	1,8-Diaminonaphthalene derived boronate
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-Bi(2-naphthol)
BMIDA	Methyliminodiacetic acid derived boronate
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BPin	Boron pinacolate ester
BPO	Benzoyl peroxide
br	Broad
Bu	Butyl
Bz	Benzoyl
COD	1,5-Cyclooctadiene
COE	Cyclooctene
Cp	Cyclopentadienyl
CuAAC	Copper-catalysed azide alkyne cycloaddition
Cy	Cyclohexyl
D	Deuterium, ^{2}H-
d	Doublet
d.e.	Diastereomeric excess

d.r.	Diastereomeric ratio
Dave-Phos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCB	1,2-Dichlorobenzene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzoquinone
DFT	Density Functional Theory
Diox. or Dioxane	1,4-Dioxane
DIPEA	*N*,*N*-Diisopropylethylamine
Distal	(Latin, literally: *to stand away from*)
DMA	*N*,*N*-dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DPEphos	Bis[(2-diphenylphosphino)phenyl] ether
DPPA	Diphenylphosphoryl azide
DPPB	1,4-Bis(diphenylphosphino)butane
DPPE	1,2-Bis(diphenylphosphino)ethane
DPPF	1,1’-Bis(diphenylphosphino)ferrocene
DPPM	Bis(diphenylphosphino)methane
DPPP	1,3-Bis(diphenylphosphino)propane
dtbpy	4,4'-Di-tert-butyl bipyridine
E	Entgegen (German, literally: *across from*)
e.e.	Enantiomeric excess
e.r.	Enantiomeric ratio
eq. or equiv.	Equivalents
ESI +/-	Electrospray ionisation (mass spectrometry)
Et	Ethyl
Fc	Ferrocene, or, in combination: Ferrocenyl
Fmoc	Fluorenylmethyloxycarbonyl
g	Gram(s)
GC	Gas Chromatography

Hal	Halogen
HBCat	Cathecholborane
HBPin	Pinacolborane
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
hr	Hour(s)
HTE	High-Throughput Experimentation
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IPA	*iso*-Propyl alcohol
Ipr	1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene
J	Coupling constant in Hz
John-Phos	2-(Dicyclohexylphosphino)biphenyl (Cyclohexyl JohnPhos)
Me	Methyl
Mes	Mesityl (2,4,6-Trimethylphenyl)
MHz	Megahertz
MIDA-H_2	Methyliminodiacetic acid
min	Minute(s)
mol	Mole(s)
Ms	Mesyl (Methansulfonyl)
MS	Mass spectroscopy
n-	Normal (primary)
Na-Asc	Sodium ascorbate
Nap	Naphthyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
Ns	Nosyl (Nitrobenzenesulfonyl)
OAc	Acetate
Ph	Phenyl
Pmc	2,2,5,7,8-Pentamethyl-chroman-6-sulfonyl

ppb	Parts per billion
ppm	Parts per million
Pr	Propyl
i-Pr	*iso*-Propyl
Proximal	(Latin, literally: *nearest*)
Pyr	Pyridine, or, in combination: Pyridyl
q	Quartet
r.t.	Room temperature
rac	Racemic, racemate
RuAAC	Ruthenium-catalysed azide alkyne cycloaddition
Ru-Phos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
s	Singlet
S-Phos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
^{s}S-Phos	Sodium 2′-dicyclohexylphosphino-2,6-dimethoxy-1,1′-biphenyl-3-sulfonate hydrate
t	Triplet
TBA	Tetrabuylammonium (anion)
TBAF	Tetrabuylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBTA	Tris[(1-benzyl-1,2,3-triazol-4-yl)methyl]amine
t-Bu	*tert*-Butyl
TEA	Triethylamine
Temp.	Temperature
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
TOF	Turnover frequency
Tol.	Toluene, or, in combination: Tolyl
TON	Turnover number
TPAP	Tetrapropylammonium perruthenate
TPPMS	Diphenyl(3-sulfonatophenyl)phosphane
TPPTS	Tris(3-sulfonatophenyl)phosphane trisodium salt
TREN	Tris(2-aminoethyl)amine
Trityl	Triphenylmethane

Ts	Tosyl (Toluenesulfonyl)
TXPTS	Tri(4,6-dimethyl-3-sulfonatophenyl)phosphine trisodium
Tz	1,2,3-Triazole, or, in combination: Triazolyl
X-Phos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
XRD	X-ray diffraction
xyl	Xylyl
Z	Zusammen (German, literally: *together*)

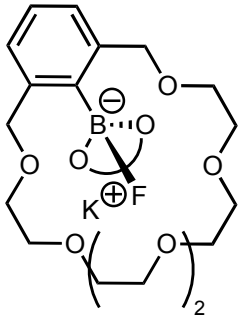
Chapter 1

1.1. Organoborons – Introduction & Context

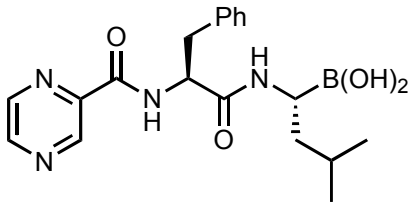
The term "organoboron" encompasses a very diverse and exceptionally important class of compounds – including, but not limited to, the alkylboranes; diborons; and arguably now one of the most important of all the contemporary organometallic reagents, the boronic acids and their related derivatives. And yet a little over half a century ago organoboron chemistry was merely a niche area of interest – holding only limited appeal even amongst the academic community.[1] However, organoboron chemistry has long since progressed from being driven merely by intellectual curiosity – the utility of organoborons now reaching far beyond the remit of synthetic organic chemistry alone. Indeed, various of the organoboron reagents find application across a broad range of scientific disciplines, employed so as to access physical products of very great real-world significance – such as is the case with the use of boronic acids in the manufacture of certain active pharmaceutical ingredients.[1-6]

While such work is at current more firmly rooted in the domain of academic research, rather than real-world application, boronic acids show promise as the core component for molecular-sensors – offering a minimal level of mechanical complexity that would otherwise be impossible to obtain with a macroscopic device. Significant demand exists for using such substrates in portable, ultra small-footprint and low-cost devices ideal for quantitative field analysis of various analyte classes. Proposed uses for such devices include as varied a scope of application as the determination of fluoride levels in drinking-water, to the rapid detection of atmospheric degradants formed by chemical weapons. Currently, a much further developed area of interest that advantageously employs the physical and chemical properties unique to boronic acids includes their use as separative agents, e.g. as a retentive functionality for chromatographic phases.[6] Indeed, many such applications arise as a result of boronic acids being able to interact with nucleophiles – as demonstrated by the catecholate ester **1.1** reported by Reetz and co-workers. **1.1** is able to act as a heterotopic host for KF, such that when KF is added to a solution of the host molecule in DCM, a stoichiometric quantity of otherwise insoluble KF is fully solvated after four hours. This is particularly dependant on the ability of **1.1** to interact with both the potassium cation and fluoride anion, whereas [18]-crown-6 – despite itself being selective for solvating potassium ions – fails to solvate any observable amount of potassium cation, even after several days under ultrasonication.[7]

Organoboron compounds may also display useful and interesting biological activities, with certain bacteria producing antibiotics containing boric acid derivatives or even organoboron functionalities.[8] More recently, and though currently a single example, bortezomib (**1.2**; *Velcade*®), a drug substance bearing an alkyl boronic acid moiety, was approved and licensed for use in the treatment of certain myeloma and lymphoma.[9]



1.1



Bortezomib (**1.2**)

Figure 1.1

Beyond their simple synthetic utility as organometallic reagents, then two factors have undoubtedly helped lead organoboron compounds to become as widely valued and ubiquitously employed as they are today. Namely, the relatively low toxicity and high stability typical of many contemporary organoborons – at least in juxtaposition with those corresponding features as exhibited by many other of the most important organometallic reagents. And whilst not every alternative class of organometallic reagent commonly employed does yield side products of significant concern with regards to the environment or operator safety, it is worth noting that many of the most useful modern organoboron reagents pose a particularly low risk in comparison. In the environment the B-C bond itself is oxidatively degraded, ultimately sequestering the boron centre as boric acid – a compound with a very low toxicity profile in mammals.[2]

Although the toxicity profile of organoborons should of course not be underemphasised, almost all of the commonly employed organoborons are significantly less toxic when considered alongside analogous and similarly versatile organometallic reagents, such as e.g. the organostannanes, organoleads and organomercurials.[8, 10] While organosilicon reagents are much more comparable to organoborons in respect to not having such high acute or chronic toxicities, nor in tending to require the very specialised and careful handling protocols that e.g. organomercurials do, they often do however require activation *via* the addition of potentially super-stoichiometric amounts of a fluoride source in order to exhibit the reactivities that are desired.[11]

Historically, the synthetic value and perceived utility of many of the most important organometallic reagents was intricately connected with their having a high reactivity profile. Consequently, due to their propensity for hydrolytic or oxidative degradation, many of the most ubiquitous classes of traditional organometallic substrates therefore have a rather lower tolerance for atmospheric exposure than is typical for the most significant of the contemporary main group organometallic reagents. In this regard then the synthetically valuable, but highly reactive, organolithiums and organomagnesiums are archetypal examples.[12, 13]

For the aforementioned reason, then investigations of the more stable main-group organosilicons and organoborons traditionally tended to focus on the more reactive examples of their types. It was only as the field of modern catalysis started to mature in the 1960s and 1970s in particular, that these reagents began to receive the level of attention they undoubtedly now deserve – instead of being constrained by their lack of spontaneous reactivity.[1, 12, 14, 15]

Indeed, it has became apparent that such organometallics are amenable to becoming involved in a range of catalytically-relevant events, which in turn has led to their use in an ever increasing range of catalysed reactions. And here their lack of reactivity in the absence of an appropriate catalyst becomes a very significant advantage: Higher stabilities and a lack of spontaneous reactivity improve not only the ease with which such organometallics may be employed, but also the selection of specific catalysts and reaction conditions can further mediate significant changes in their selectivity and reactivity profiles. Furthermore, as is more thoroughly detailed throughout this chapter, by having no significant uncatalysed reaction pathways with which to compete, this has contributed to certain of the contemporary organoborons becoming versatile reagents for a variety of important catalysed transformations – at times simultaneously exhibiting very high chemo-, regio- and stereo-selectivities, while themselves being compatible with modifications to other functional groups present in the same molecule.[16]

Though undoubtedly of great importance to inorganic, analytical, and supramolecular chemistry, as well as materials and biological sciences, it is the organometallic and organic chemistry of boron that will now be the focus of this review.

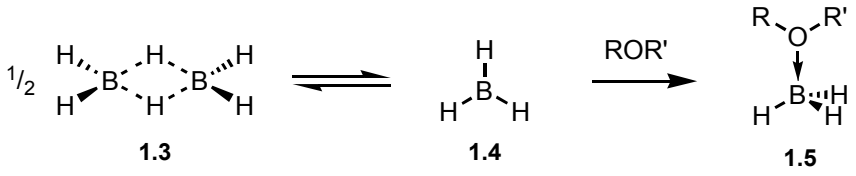
1.2. Boron as an Element

Boron is a metalloid element, atomic number 5, with an electron configuration of [He] $2s^2$ $2p^1$. With its three valence electrons boron typically forms trigonal planar compounds with three 2-electron 2-centre bonds; thus leaving a vacant p orbital. The dimensional accessibility of this orbital, combined with the deficiency of boron from a full electronic octet, results in the chemistry of boron compounds being dominated by the Lewis acidity of such trigonal planar compounds, and the resultant tetrahedral neutral or anionic species which are products of their interaction with Lewis bases or reaction with nucleophiles.[17] In the sp^2-hybridised state boron has an electronegativity value of 1.88, making it comparably less electronegative than either hydrogen or carbon (Table 1.1).[18]

Element	Electronegativity	Element	Electronegativity
H	2.17	N	2.93
B (sp^2)	1.88	O	3.61
C (sp^3)	2.45	F	4.14
C (sp^2)	2.69	Cl	3.05
C (sp)	3.17	Br	2.83

Table 1.1: Selected Mulliken electronegativity values.[18]

Borane **1.4** is a highly reactive gas, and exists predominantly in the dimeric diborane form (**1.3**), while in synthetic chemistry it is typically employed as the aforementioned adduct of, e.g., type **1.5**.[12]

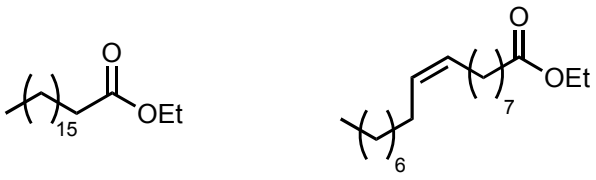


1.3 **1.4** **1.5**

Scheme 1.1

1.3. Organoboron Chemistry

Much of the work fundamental to the field of modern organoboron chemistry arose from the research studies performed by H.C. Brown over the course of his career. As well as his involvement in the development of borohydride reagents, it was Brown's work on organoborons and hydroboration that resulted in him being jointly awarded the 1979 Nobel Prize in Chemistry.[1]



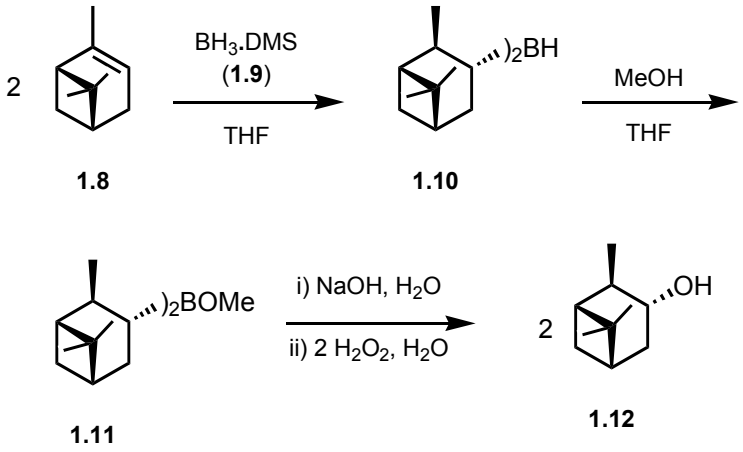
Ethyl stearate (**1.6**) Ethyl oleate (**1.7**)

Figure 1.2

During investigations of the relative reducing abilities of borohydride salts and borane reagents in the pursuit of selective reduction techniques, one of Brown's co-workers noted "*a minor anomaly*" which "*resulted in the discovery of hydroboration*". That anomaly was that during the aluminium chloride catalysed reductions of various esters with $NaBH_4$, more hydride was found to be consumed per equivalent of ethyl oleate **1.7**, than was consumed for ethyl stearate **1.6**.[1] It was later found that hydroboration of the olefin had occurred so as to yield an organoborane derivative. This discovery, and subsequent investigations prompted by it, ultimately resulted in the development of modern organoboron chemistry as it is understood today.

1.3.1. Hydroboration

In summary hydroboration involves the addition of H-B across a C-C multiple bond by reaction of the unsaturated substrate with, most typically, borane or an organoborane. Due to steric, as well as electronic effects relating to the aforementioned electrophilicities of boron and hydrogen, the boron atom of borane is comparatively more electrophilic and normally becomes bonded to the less-substituted carbon of the multiple bond. The hydroboration of alkenes involves a stereospecific *syn* addition of the B-H bond to the least hindered face of the olefin, proceeding *via* a four centred transition state with concerted formation of the C-B and C-H bonds. Hydroboration thus provides a powerful approach to the functionalisation of C-C multiple bonds, as the reactions typically proceed with a high level of regioselectivity to give products of *anti*-Markovnikov selectivity. Furthermore, the stereospecific hydroboration of alkenes yields products that may be derivatised at the B-C bond with retention of configuration in order to access alcohols, amines, carbonyl compounds and organohalides. The archetypal derivitisation protocol is undoubtedly the treatment of such products with peroxide, to elicit an overall hydroboration-oxidation sequence which yields the product alcohols in an *anti*-Markovnikov fashion. As such this makes the use of boranes in this context complementary to the (non-stereospecific) oxymercuration-reduction of alkenes that gives products of the opposing (i.e. Markovnikov) regioselectivity.[12]

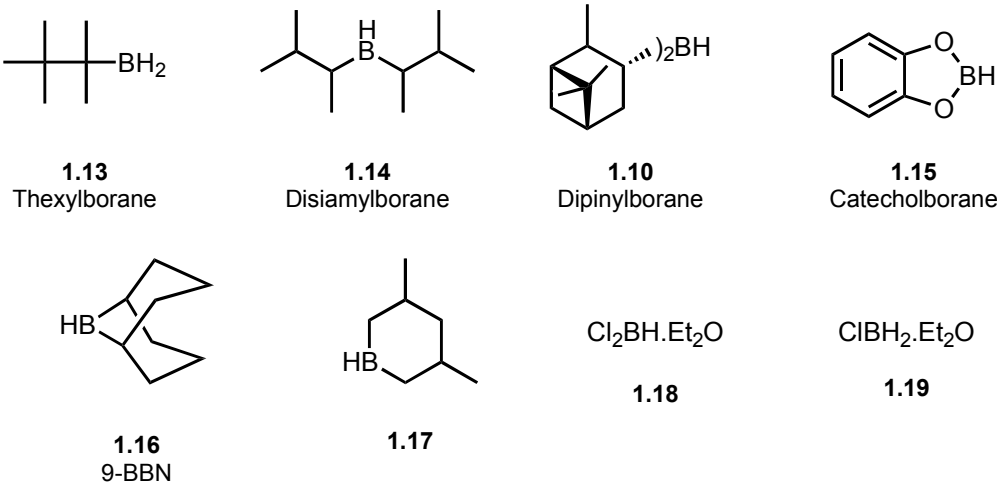


Scheme 1.2 [19]

Here bis-(isopinocamphenyl)borane **1.10** (otherwise known as dipinylborane or Ipc_2BH) proves ideal for discussion, as it demonstrates both the stereospecific nature of the hydroboration – prepared as an effectively enantiopure product from naturally available α-pinene – while itself being able to be converted to alcohol **1.12**, or used to induce enantioselective hydroborations of other alkene substrates.[12]

1.3.2. Borane Reagents for Hydroboration

Though Brown confirmed borane itself to be a useful hydroboration reagent – adding with a predictable regioselectivity across terminal olefins – it is often not nearly so discriminating when more elaborate internally-substituted substrates are involved. As a combination of its very high reactivity, exceptionally low initial steric restrictions, and the presence of three labile B-H bonds, then the use of borane can give rise to very complex mixtures of products in such cases. To circumvent the extreme activity and potentially super-stoichiometric reactivity borane possesses, the investigation of alternative hydroboration reagents was pursued. To this end were developed a number of archetypal reagents with more precisely defined levels of reactivity and selectivity, many of which resulted directly from Brown's own investigations.[1, 12]



1.13 Thexylborane

1.14 Disiamylborane

1.10 Dipinylborane

1.15 Catecholborane

1.16 9-BBN

1.17

1.18

1.19

Figure 1.3

The most noteworthy of such original borane reagents (as shown in Figure 1.3), along with their more recent analogues, can be loosely divided for convenience into the following groups – discussed in descending order of their typical reactivities, and conversely their increasing stabilities:

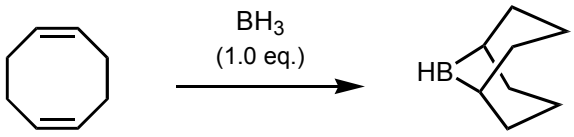
1.3.2.1. Borane and the Mono- and Di- Haloboranes

Borane, its Lewis base adducts such as borane-DMS **1.9**, and the halo- and dihalo- boranes such as **1.18** and **1.19**, are highly reactive towards alkenes. They are often complexed with a Lewis acid, in particular so as to improve stability and handling characteristics. These are also typically the most reactive boranes, although examples such as pyridine-borane complex can prove correspondingly much less so.[20] Overall the regioselectivities obtained with the haloboranes are often higher, while additionally the products they form can be derivatised with e.g. hydrides, thus allowing for controlled homologation by a sequential hydroboration approach.

1.3.2.2. Alkyl- and Dialkyl- Boranes

Examples include thexylborane **1.13**, 9-BBN **1.16**, and also those examples such as dipinylborane **1.10** that possess optically active hydrocarbon substituents. In terms of classical utility to the art of organic synthesis, then this is probably the most important of all the groups of borane derivatives. These reagents are accessed from certain readily available olefins that are also selected for structural characteristics that give rise to a high level of control over their reactivity with borane, and as such the corresponding monoalkyl- and dialkyl- boranes they generate are much more reliably produced in both good yields and with high regioselectivities – one of the best examples being 9-BBN, which is obtained *via* hydroboration of 1,5-cyclooctadiene **1.20** (Scheme 1.3). As well as giving improved

regioselectivities as a result of increased steric encumbrance, these reagents are also more stable and easy to handle than borane.[1]



1.20 **1.16**

Scheme 1.3

The alkyl and dialkyl boranes are important reagents in synthetic chemistry, however due to their high reactivity much of their utility is dominated by the uncatalysed hydroboration reactions they undergo,[21] as well as the corresponding reactions of their products. As such they will not be covered further.

1.3.2.3. Heteroatom Substituted Monoboranes

The final class of boranes are the heteroatom substituted monoboranes, the most notable of which are certain of the diol-derived cyclic di(alkoxy)boranes, such as catecholborane (HBCat, **1.15**). This class also includes the analogous heteroatom substituted borolidines which are typically of secondary importance.[2] In summary these reagents are often notably less reactive than are the alkylboranes, requiring increased reaction temperatures or the addition of a catalyst in order to elicit alkene hydroboration; as is discussed in more detail in Section 1.4.1.

1.3.3. Stability and Lewis Acidity of Organoborons

In the above series of borane derivatives there is a notable trend for reactivity to decrease as the hydrogen or halide substituents are sequentially replaced for hydrocarbon or heteroatom substituents. The disparity between the electronegativity of hydrogen and boron is much smaller than that between oxygen and boron. However, the effect of heteroatoms is to reduce the overall Lewis acidic character of the boron atom in such compounds. This is of particular significance to two of the most important classes of organoboron reagents, that along with the di(alkoxy)boranes are widely employed in modern synthetic chemistry as substrates in metal-catalysed reactions. Namely these are the tetraalkoxydiborons and boronic acids – containing either a single B-B or C-B bond, along with two heteroatom substituents at any sp^2-hybridised boron centre present. Consistent with the aforementioned trend they are typically much more stable compounds than even the di(alkoxy)boranes.[2] Due to their importance in contemporary transition metal-catalysed reactions these reagents will now be discussed further.

1.3.4. Tetraalkoxydiborons

Whilst other diboron compounds such as the diboron tetrahalides **1.21** and alternative heteroatom substituted diborons such as tetrakis(dimethylamino)diboron **1.22** are known, the tetraalkoxydiborons (e.g. **1.24**-**1.27**) are by far the most important class of these reagents in terms of their utility – and as such a small number are commercially available. This utility arises principally from the aforementioned stability imparted by the two alkoxide substituents bonded to each of the boron atoms through oxygen. Indeed, a comparison of the diboron tetrahalides and tetraalkoxydiborons demonstrates the stabilising effect of heteroatom substituents most readily of all: While bromine and chlorine are both rather electronegative they are less electronegative than oxygen, yet diboron tetrabromide **1.21a** and diboron tetrachloride **1.21b** are air sensitive and even unstable to disproportionation, reacting with C-C multiple bonds in the absence of a catalyst. In contrast bis(pinacolato)diboron (**1.24**, B_2Pin_2) is an air stable solid that can be stored at ambient temperatures and requires activation, most typically through application of a metal catalyst, in order to elicit reactions involving addition of the boron moiety to C-C or C-X multiple bonds.[22, 23]

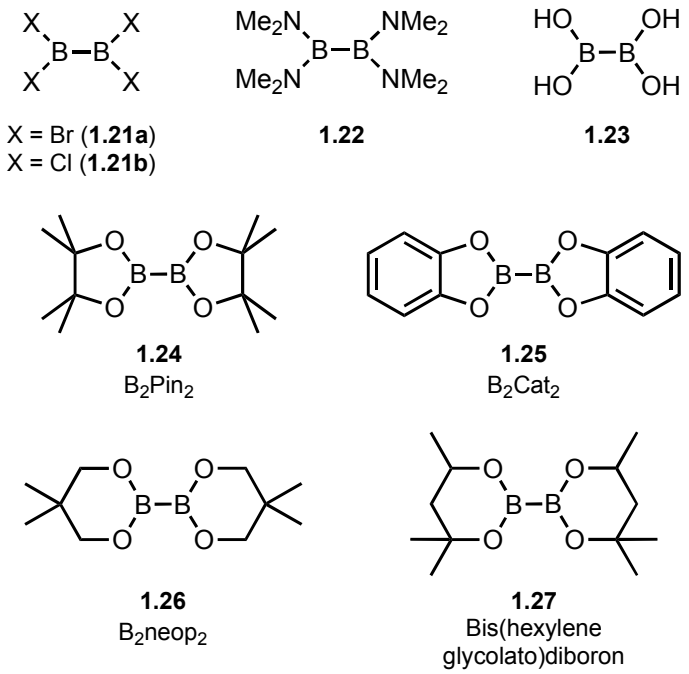
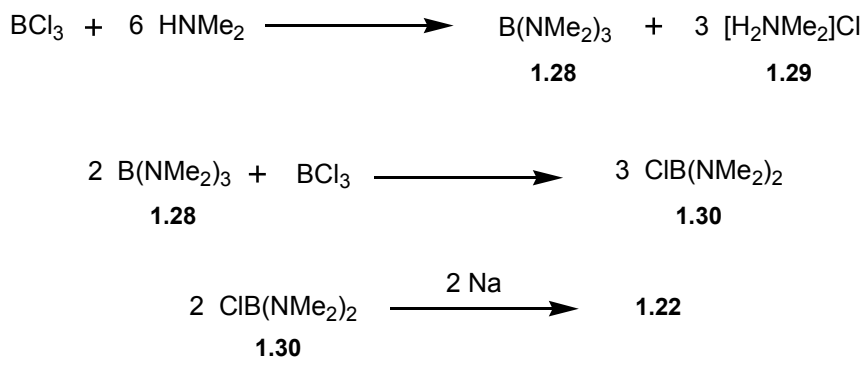


Figure 1.4

Tetraalkoxydiborons are prepared by reaction of the corresponding diols with tetrakis(dimethylamino)diboron **1.22** with loss of dimethylamine, while **1.22** may itself be prepared as follows:[24]



Scheme 1.4

1.3.5. The Boronic Acids and their Derivatives

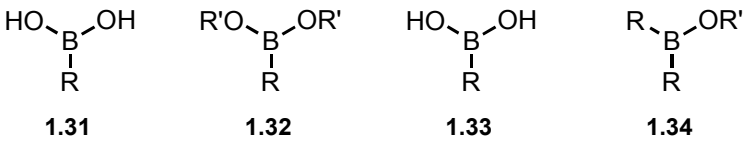


Figure 1.5

The importance of organoborane reagents to classical and contemporary synthetic organic chemistry is undeniable; and so too are the unique properties of boronic acids which make them of interest to a broad range of scientific disciplines.[2] However, in many respects it is the modern cross-coupling methodologies that have ultimately come to define the context within which organoboron chemistry has been of significant interest in synthetic circles over the last thirty years since the seminal publications by Suzuki and co-workers (see Section 1.5.1). Much interest in organoboron compounds now focuses on the use of boronic acids and their derivatives in such reactions, as well as routes to their preparation by means of other metal-catalysed procedures.[22, 25] Indeed such is their value that it was recently remarked that boronic acids look to be developing into a "*universal functional group*" which "*can be carried through a long synthesis and, at the end, exchanged for any commonly used atom on the periodic table under mild conditions for diversity exploration*".[26] As such the remaining discussions in this chapter will focus on the means to access these important reagents, including those metal-catalysed procedures which employ di(alkoxy)boranes and diborons, before discussing two of the most important reactions to employ boronic acid derivatives – the Suzuki coupling and rhodium-catalysed 1,4-addition reactions.

1.3.5.1. Classical Approaches to the Synthesis of Boronic Acids

The previously discussed hydroboration of alkynes and alkenes is a particularly important route commonly applied to the synthesis of alkenyl and alkyl boronic acids respectively. And

while such substrates are in addition often also amenable to being prepared by the approaches used for the preparation of arylboronic acids, with respect to hydroboration then the reverse is not true. As such, and in combination with the investigations detailed in future chapters focusing solely on the synthesis and applications of arylboronates and their derivatives, the following discussions in the remainder of this section will focus in particular on their preparation by means not covered in later discussions on modern metal-catalysed methodologies.

1.3.5.1.1. By Cycloaddition Reaction

The use of a cycloaddition reaction as a strategy to synthesise boronate esters has recently been reviewed.[27] While this approach is ultimately very much secondary to the main alternatives discussed below, it is becoming an increasingly important method for the construction of certain important substrates. In this area the work of the Harrity group is especially noteworthy,[28, 29] and the use of this approach is also briefly described in Chapters 3 and 4, where it is of particular relevance.

1.3.5.1.2. By Transmetallation of Other Main-Group Organometallics

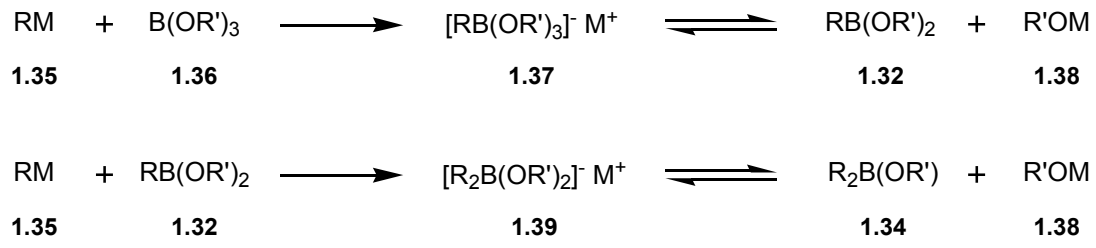
Organoborons, including arylboronic acids, can be synthesised *via* the transmetallation reaction of an appropriate organometallic reagent – most typically a stannane, silane or organomercurial – with a hard boron halide such as BBr_3. The major driving force for such reactions is likely thermodynamic in nature – the X-Hal and B-C bonds formed typically being favoured over the B-Hal and X-C ones they replace. Traditionally this approach was more widely employed than it is today, primarily as certain of the organometallic precursors provided a more straightforward means to access the corresponding organoborons, or allowed for the synthesis of examples not otherwise accessible. For example, organomercury reagents, and the protocols used for their formation, are much milder and more functional group tolerant than corresponding s-block variants, and transmetallation of such organometallics presented access to a greater variety of organoborons than did a reliance on the pivotal role of organomagnesium and organolithium intermediates in their syntheses.[2]

However, the use of such alternative organometallic precursors is often not without drawbacks. Organomercury and organotin reagents, though potentially allowing for milder conditions to be employed during a given synthesis, ultimately suffer from having much higher toxicity profiles when compared to many comparable organoboron and organosilicon reagents. Furthermore, and especially in the case of the organosilicon reagents, then there is also often a significant degree of overlap in the scope of those products already accessible *via* chemistry typical to the organoboranes.

In combination with advances in s-block metallation strategies, protecting group manipulations, and especially the recent developments in catalytic boration and borylation reactions (see relevant sections herein), these factors have together led to such transmetallation approaches typically being relegated to highly specific situational use in the syntheses of a small sub-set of organoborons – for example in the synthesis of otherwise troublesome to prepare vinylborane derivatives.[2, 30] In this context then the preparation of vinyl-MIDA boronates from the corresponding trimethylsilyl precursors is potentially the most noteworthy and recent case of relevance (see Section 1.3.7.2 for details). Moreover, it is now indeed as commonly the case that such an approach be applied in reverse – with readily prepared boronic acids and their derivatives being used as precursors for the synthesis of e.g. organolead compounds.[31]

1.3.5.1.3. *Via* s-Block Organometallics as Synthetic Intermediates

By far the most important of the traditional approaches towards the synthesis of arylboronic acids are those that involve the formation of a reactive s-block organometallic species **1.35** as a synthetic intermediate – the most notable being where these are an organomagnesium or organolithium species. Subsequent installation of the C-B bond can then be achieved at the C-M locus by trapping the reactive organometallic species with an electrophilic boron source, e.g. **1.36**, while subsequent chemoselective procedures to effect changes to the non-C-B bonds (in e.g. boronate ester **1.32**) may then be performed in order to yield the desired product.

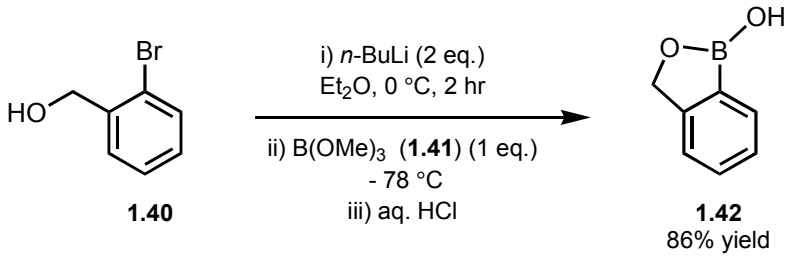


Scheme 1.5

Whilst there are a number of discrete metallation sub-types, each possessing certain mechanistic intricacies, these approaches are typified by the use of either an activated zero-valent metal or a preformed organometallic normally of very high-ionic character. As such, in the overall route to synthesising the target organoboron this necessitates the involvement of organometallic species that are strongly basic, strongly nucleophilic, or a combination of both. Thus, such protocols generally require rigourously dry conditions and the use of inert atmosphere techniques, while being broadly incompatible with ubiquitous electrophilic

functional groups and labile protons, e.g. carbonyl compounds and base epimerisable stereocentres. In order to ensure their safe execution, as well as good selectivities and yields, they also often require that a low temperature be consistently maintained over the portion of the reaction in which the s-block organometallic is involved.

The most noteworthy classes of such metallations are the metal-halogen exchange and directed-metallation reactions, the major advantages of these approaches being their substrate determined selectivities, which in turn are also well-documented in the chemical literature. As such they provide a reliable basis on which to design the synthetic route towards a target boronic acid. Furthermore they can be considered somewhat complementary: While a directing heterocyclic moiety may be a core component in the product, other typical directing groups – such as esters, ethers (and other masked or derivatised alcohols), amines or amides – may provide useful functional group handles in the target products. In the case of the metal-halogen exchange approach then aryl halides can offer a traceless point at which to functionalise the precursor, while e.g. dihaloarenes containing halides with differential reactivities towards the metallating agent may allow for orthogonal functionalisation of the substrate by means of sequential metallation steps. The drawbacks of these approaches are most often the requirement for an appropriately functionalised precursor, and also the associated cost of commercially sourcing or synthesising such substrates.[2, 12]



1.40 **1.42**
86% yield

Scheme 1.6

Due to the limitations inherent in the selection of compatible functionality that may safely be subjected to such metallation conditions, methods to circumvent the incompatibility of certain groups have been employed. For example, standard protecting group manipulations may be used to mask labile protons in alcohols and sufficiently acidic amines, or prevent the nucleophilic addition to carbonyls and their analogues. The use of differently coordinating solvents and additives such as metal salts, and organic amines or their salts, are often employed in Grignard and organolithium chemistry in order to effect modified activity or selectivity of a given organometallic species. Some of these modifications may render the s-block organometallic species less basic or nucleophilic in character, and can thus also be

used to address some of the shortcomings of such chemistry. Alternatively if the deprotonation of any sufficiently acidic protons does not lead to undesired epimerisation or dehydration, as is the case for benzylic alcohol **1.40**, then such labile protons may most easily be accounted for by using a stoichiometric excess of the metallating agent – which although procedurally straightforward, may not necessarily be cost effective for anything but small scale syntheses.[2, 12]

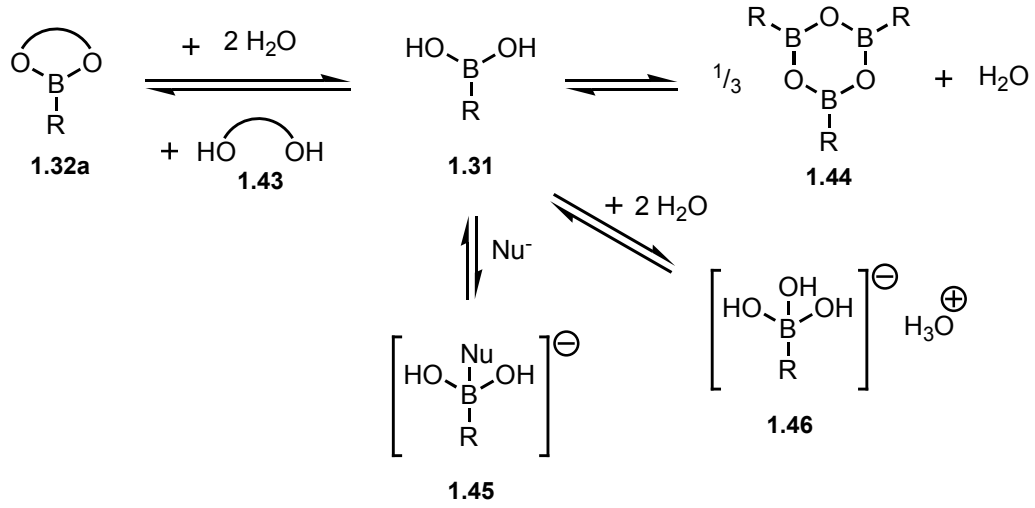
In the event that it is possible to access the organometallic precursor for a given target, the next step of the synthetic route involves either controlled addition of an electrophilic boron reagent to the organometallic species or, *vice versa*, the so-called "reverse addition" of the organometallic to the electrophile. Such electrophiles are typically the simple trialkylborates – derived from the dehydration reaction of boric acid with the corresponding alcohol – the simplest example therefore being $B(OMe)_3$ **1.41**, which is often a good choice on cost grounds. However, the selection of more sterically demanding alkyl groups is often particularly important in directing the desired formation of the boronic ester **1.32**, rather than allowing a mixture of products including the borinic ester **1.34** and potentially even the triorganoborane to form as a result of the borate reacting with multiple equivalents of the organometallic. As such, a reverse-addition procedure may also be employed, which may minimise the amounts of side products generated by maintaining a sufficient excess of borate relative to the organometallic species, while at low temperatures the initial tri(alkoxy)arylborate salt **1.37** that is formed may precipitate and disfavour equilibrium dissociation to a metal alkoxide **1.38** and the reactive boronic ester **1.32**.

In cases where the boronic ester of a diol is also the ultimate synthetic target then it may be desirable to use a more expensive or bespoke borate which already incorporates the cyclic boronate ester moiety. In this way separate isolation and esterification steps for the intermediate boronic acid may be avoided, and as some boronic acids are prone to rapid degradation while certain of their ester derivatives are not, this also provides a way in which to synthesise derivatives of what are otherwise prohibitively unstable boronic acids. The disadvantages of this approach are however the comparative costs of those borates compared to simple trialkylborates, and also the opportunity cost of not isolating the intermediate boronic acid: Being typically much more amphiphilic than the boronate ester derivatives, then the isolation of the free boronic acid can provide an ideal opportunity to remove any residual lipophilic contaminants, while the subsequent esterification step may further allow any residual hydrophilic contaminants to be removed too. Approaches such as reverse addition and the use of appropriate trialkylborates in order to directly form more

hydrolytically robust boronate esters, are also important in the synthesis of otherwise unstable 2-heteroatom substituted heteroaryl boronic acid derivatives.[2, 32]

1.3.5.2. Discussion of the Boronic Acids and Classical Derivatives

As mentioned above free boronic acids are quite often amphiphilic in character. While the organic substituent is, relatively speaking, typically quite lipophilic, the boronic acid moiety itself is rather polar and able to form hydrogen bonds. Furthermore, this is compounded as a result of the sp^2-hybridised boron centre often becoming involved in equilibrium formation of adducts in the presence of nucleophiles, including water, to yield varying amounts of borate ion **1.45** or related hydrate **1.46**. Isolated samples of otherwise pure boronic acids also exist as mixtures of oligomers in equilibrium with the free acid – the trimeric cyclic boroxines **1.44** being the most important of such species, their equilibrium formation involving the dehydration of three equivalents of boronic acid to yield one equivalent of boroxine and three equivalents of water. As such the position of this equilibrium may be heavily affected by both the parameters of the system in which the boronic acid is present, as well as the nature of the organic substituent itself, due to the direct effect it has on the electronics of the boron atom.[2]



Scheme 1.7

Furthermore, the varying amounts of boroxine which may be present in two otherwise identical samples of a given boronic acid, combined with the potential inhomogeneity of such materials, complicates determination of reaction stoichiometries and sample analyses (e.g. the melting point of a boronic acid might not be reliable due to dehydration[2]), and may impact upon the reliability of a synthetic route. Although this is not normally an issue of considerable importance in the context of small-scale protocols typically employed in a

research context, it may present a major challenge in the large-scale application of a boronic acid to the same chemistry.[4]

1.3.5.2.1. Boroxines

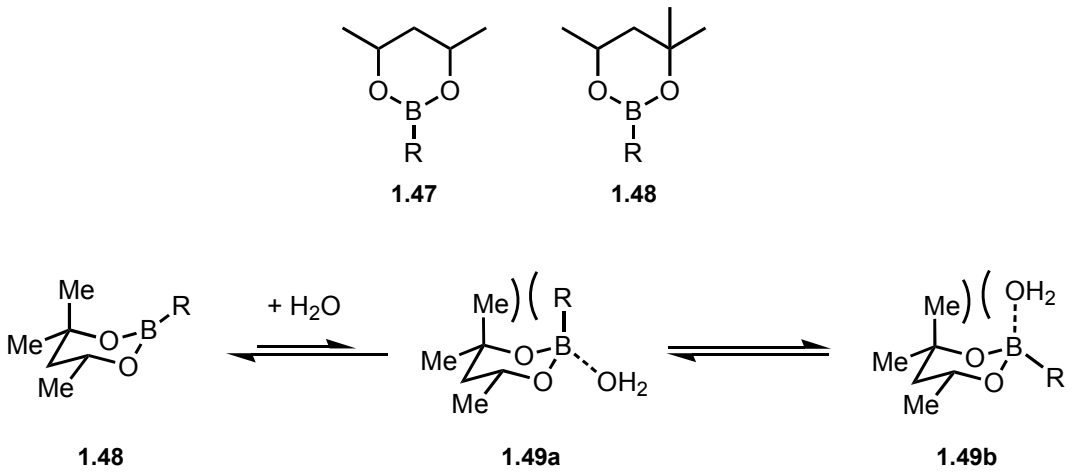
One solution to this problem is to drive dehydration of the boronic acid so as to specifically yield the boroxine **1.44** by employing azeotropic removal of water or through application of a suitable drying agent. In this way a boronate of known stoichiometry may be produced which can often be used directly in place of the free boronic acid. Additionally, when sensitivity of a reaction to water is an issue, then the use of the boroxine form can be advantageous, especially as they are often conveniently formed immediately prior to use without isolation, e.g. by *in situ* exposure of the boronic acid to molecular-sieves prior to commencing any moisture sensitive manipulations. However, while the utility of boroxines in certain instances is undeniable, there are significant limitations to their use. Firstly, the storage of "dry" boronic acid samples under an air atmosphere is known to result in their rapid decomposition in certain instances, with boroxines proposed as initiators of relevant autoxidation reactions. As such it is common for boronic acids to be purposefully stored with small amounts of water present so as to maintain their integrity over a longer period.[2] A reliance on the boroxine form to mask the reactivity of the parent boronic acid over the course of a synthetic route employing aqueous work-up as an isolation step, may also necessitate that multiple dehydration procedures be performed. Finally, the physical and chemical properties of the boroxines are directly linked to the identity of the parent boronic acid, and so are dominated by the steric and electronic characteristics of the single organic substituent of that parent monomer. This in turn means that if the synthesis of a given boroxine is low yielding, its solubility profile poor, or its reactivity insufficient for the intended application, then there are potentially very many fewer ways to address such issues.

1.3.5.2.2. Boronate Esters

While in the boroxine form the solubility and reactivity profiles of such organoborons are determined near exclusively by the electronic and steric character of the organic substituent, the overall character of the same organoboron reagents when integrated into typical "cyclic" boronic esters **1.32a** are often determined to a large degree by the identity of the ester moiety, rather than by the C-B substituent alone. Thus, the boronic esters of a given diol **1.43** may often exhibit a useful degree of commonality with one another, in both their physical properties and reactivity parameters. As such they can often be prepared, handled, and employed in a similar manner.

Akin to the boroxines, boronic esters are readily formed from the reversible condensation reaction between the boronic acid and an appropriate alcohol. While the esters of singular alcohols as well as less substituted diols are known, they are for many applications too easily hydrolysed during standard manipulations to make them of any great value as synthetic intermediates. The most important esters are thus derivatives of diols (which, where appropriate, are *cis*- isomers) possessing at least a moderate degree of steric bulk. As such the classical boronate esters of greatest utility, which have been known for over half a century, are the derivatives of the achiral diols pinacol and catechol.[2]

Steric bulk or a lack of conformational flexibility in such esters is important to their overall level of hydrolytic stability – as the formation of hydrates such as **1.46** (Scheme 1.7) are proposed to be key in the hydrolysis of boronate esters. The steric bulk of the ester inhibits coordination of nucleophilic species at the boron centre, while in conjunction the conformational rigidity of the diol backbone thermodynamically disfavours the borate adduct of type **1.45**.[33]



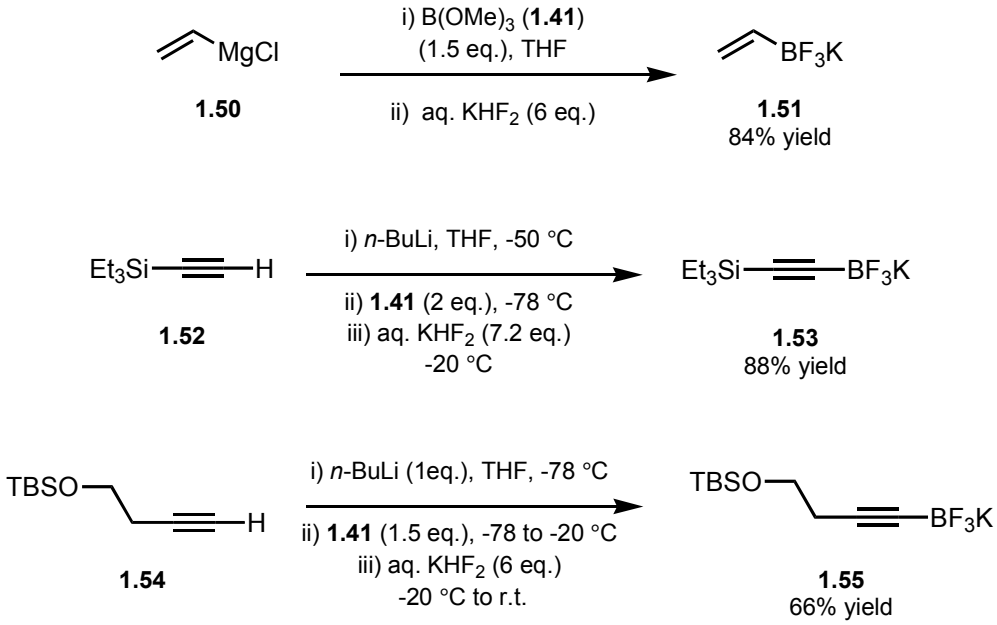
Scheme 1.8: Adapted from literature content.[2, 33]

As such the trimethyl substituted ester **1.48** is significantly more stable to hydrolysis than its equivalent dimethyl substituted analogue **1.47**.[33] Importantly this behaviour also extends to the resistance of the boronate moiety to other nucleophiles, making boronate esters important as protecting groups that can also much improve the lipophilicity of the parent boronic acids – both through a combination of the hydrophobicity of diol backbone and by disfavouring the approach of nucleophiles, so preventing formation of more the polar borate anion.

1.3.6. Modern Boronic Acid Derivatives: Reactive Towards Transmetallation

1.3.6.1. Potassium Organotrifluoroborate Salts

Although organotrifluoroborates had in fact been known since the 1940s at least, it was half a century before these important reagents began to see widespread application. The reason for this was that prior to 1995 the methods for synthesising organotrifluoroborate salts restricted both the ease and scope of their synthesis. The general methods used involved either the transmetallation of other main-group organometallics with highly reactive gaseous BF_3, or trapping of dihalo(organo)boronates – potentially unstable substrates to begin with – by treatment with aqueous solutions of KF. As such these procedures were extremely prohibitive in terms of their scope and ease of implementation, and so were not widely utilised.[13]



Scheme 1.9

In the 1960s Chambers and co-workers had shown that otherwise highly unstable trivalent perfluoroalkyl boronates could be prepared as stable potassium organotrifluoroborate salts by transmetallation of the corresponding stannanes with $BF_3.Et_2O$, followed by treatment with aqueous KF.[34] However, it was not until 1995 that Vedejs and co-workers reported that simply by treating boronic acids with methanolic aqueous KHF_2 the corresponding potassium organotrifluoroborate salts could be obtained in a much more straightforward, general and cost-effective manner.[35] Furthermore this approach can be combined with the standard methods used to prepare boronic acids – allowing telescoped syntheses such as are shown in Scheme 1.9. This methodology is also widely compatible with many functional

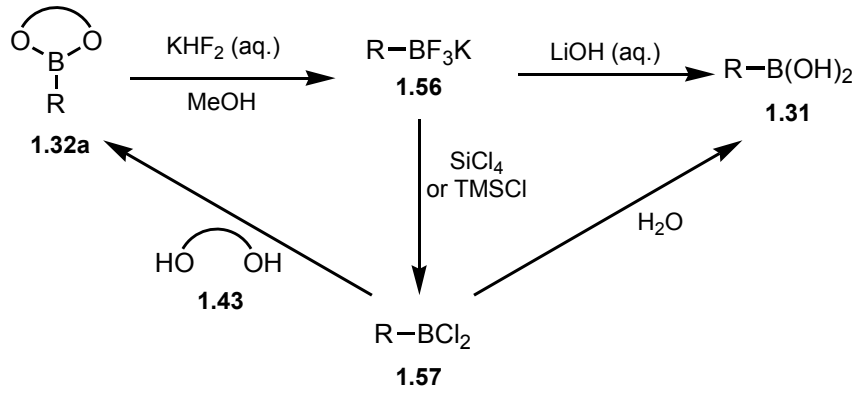
groups; for example trialkylsilyl groups at both carbon (*cf.* **1.52** and **1.53**)[36] and oxygen loci (*cf.* **1.54** and **1.55**)[37], though normally cleaved using a fluoride source, are not necessarily precluded from inclusion when using aqueous KHF_2.[13]

Potassium organotrifluoroborate salts are themselves typically stable and non-hygroscopic. The borate moiety is also much more electron donating than the sp^2-hybridised parent boronic acid, and with a less Lewis acidic boron centre and inhibited access to coordinating nucleophiles they are typically much more compatible with orthogonal functional group conversions using nucleophiles, bases or oxidants (e.g. TPAP/NMO, peroxides, IBX[38], and also NaN_3[39] as detailed further in Chapter 3),[13] while being remarkably inert to certain, for example, copper mediated reactions that otherwise consume the parent boronic acids.[40, 41] Furthermore, in some cases they are tolerant of strong nucleophiles to such an extent that substrates such as potassium 4-bromophenyltrifluoroborate can successfully be used in lithium-halogen exchange reactions employing *n*-BuLi.[38]

Specifically, isolated potassium organotrifluoroborate salts are often much more stable than the corresponding boronic acids (e.g. potassium vinyltrifluoroborate salt **1.51**)[36] and as such they have found significant utility as equivalents of important but otherwise rather unstable alkynyl, alkenyl, alkyl and vinyl boronic acids. For example, alkenyltrifluoroborates may be stable at ambient temperature for periods of several years, while the corresponding trivalent organoborons are not.[13] However, in contrast to the potassium analogues, alternative cations such as ammonium and barium render the organoboronates either less stable or extremely hygroscopic, respectively;[34] while Vedejs showed that treatment of potassium organotrifluoroborate salts with aqueous solutions of Li^+ or Mg^{2+} cations promotes their degradation to the corresponding boronic acids.[35]

Due to the high ionic character of the salts containing metal cations, these reagents exhibit "*insolubility or low solubility*" in many organic solvents, and while TBA salts have been prepared – allowing improved solubility in organic solvents that may translate into improvements in their reactivity – the comparative stability of such TBA salts has not been properly detailed.[13] However, this effect that the counterion identity has on stability may also be used advantageously, as potassium organotrifluoroborate salts provide not only a useful class of synthetic organometallic reagents, but also a useful intermediate for the synthesis or hydrolysis of boronate esters; this is especially useful with difficult to hydrolyse examples such as the pinanediol derivatives.[2] More recently Molander and co-workers have shown that potassium organotrifluoroborates can even be converted to the corresponding boronic acids simply by exposure to hydrated silica-gel.[42] Alternatively, treatment with tetrachlorosilane or

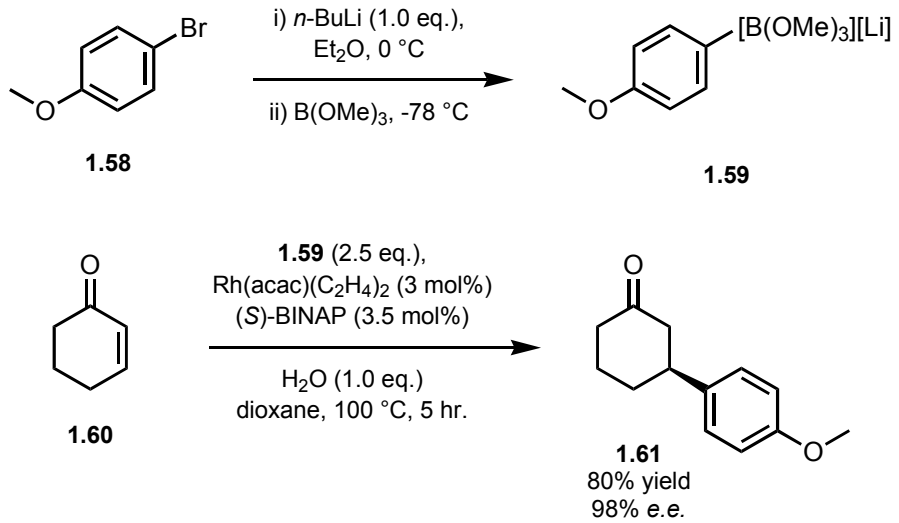
TMSCl allows access to the synthetically valuable intermediate dihalo-organoboranes such as **1.57**.



Scheme 1.10

1.3.6.2. Trialkoxyborates

In 1999 Hayashi and co-workers demonstrated the utility of *in situ* generated lithium trialkoxyborate salts in the rhodium-catalysed 1,4-addition reaction in place of boronic acids. The borates such as **1.59** were prepared by typical lithium-halogen exchange and subsequent transmetallation with $B(OMe)_3$, and instead of standard aqueous work-up were used un-isolated for subsequent rhodium-catalysed 1,4-addition reactions.[43]



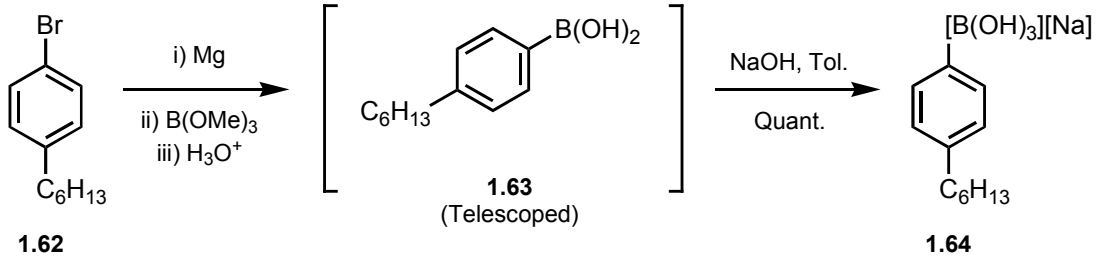
Scheme 1.11

The authors postulated that in the presence of water the $Li[ArB(OMe)_3]$ salts such as **1.59** were potentially generating methanol and activated organometallics of the type $Li[ArB(OMe)_2(OH)]$ or $ArB(OMe)(OLi)$ *in situ*, during the rhodium-catalysed 1,4-addition reactions. They proposed this after finding that $PhB(OMe)_2$ did not react under such

conditions until one equivalent of LiOH relative to the dimethyl boronate ester was added to the system. The trialkoxyborate salt **1.59** gave better results than did the corresponding boronic acid, albeit under separately optimised and base-free conditions.[44] Hayashi and co-workers attributed this improvement to the trialkoxyborate salts disfavouring protodeboronation – and so providing higher yields of conjugate addition products. However, while the enantioselectivities obtained from such reactions were not impacted by the amount of water added, the yields were heavily influenced. As such this suggests that hydrolytic release of the free boronic acid may have been an important factor not then apparent (for related discussions see Section 1.5.1.4).

1.3.6.3. Trihydroxyborates

Because of the issues in determining boronic acid stoichiometry, combined with the need for the reliable synthesis of reagents of known composition for application in synthesising drug substances, Cammidge *et al.* investigated the validity of isolating tetrahedral adducts of boronic acids formed upon their treatment with metal hydroxides.[45]



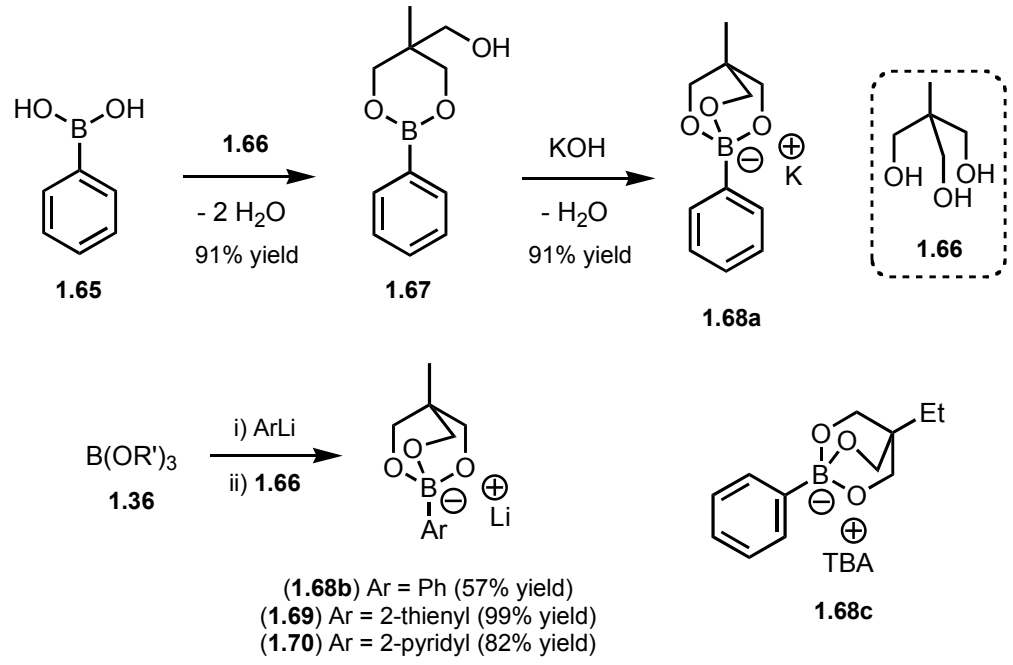
Scheme 1.12

Though such species had for many years prior to this been known to form in solution, the authors noted that they had rarely been isolated, and so wished to assess their physical and chemical properties. Typically, hydrophobic boronic acids such as **1.63** are waxy solids that exist as a mixture with the boroxine form. However, they can be derivatised in near quantitative yields by dropwise addition of concentrated aqueous sodium hydroxide to solutions of the boronate in toluene; with *p*-hexyl phenyl derivative **1.64** even isolated as a free flowing colourless powder. Hydrate forms of the borates from recrsytallisations performed in water could be converted to the anhydrous form by exposure to a desiccant, whilst potassium and barium salts also appeared to be comparable in terms of their physical and chemical properties – interestingly contrasting the related organotrifluoroborates, where only potassium salts are both significantly stable and non-hygroscopic.

Cammidge *et al.* found that various aryltrihydroxyborates underwent successful Suzuki coupling reactions without the need for additional base, which they attributed to trihydroxyborates being an "*activated*" form of the boronic acid. One example of successful achiral rhodium-catalysed 1,4-addition reaction to cyclohexene-2-one **1.60** was also reported. More recently Basu and co-workers have shown that trihydroxyborates can be used for on-water Suzuki coupling reactions with "ligand free" palladium, good results being obtained at ambient temperature using one equivalent of TBAB as an additive.[46]

1.3.6.4. Triolborates

In 2008 Miyaura and co-workers reported a novel class of borate formed using the triol 1,1,1-tris(hydroxymethyl)ethane (**1.66**). Potassium salts such as **1.68a** were obtained by reaction of isolated boronic acids and the triol, with corresponding azeotropic removal of water in order to form the intermediate boronate esters **1.67**; these intermediates were then quaternised by subsequent treatment with KOH. Alternatively the standard lithium-halogen exchange and trialkylborate transmetallation route to boronic acids could be intercepted at the point of the lithium trialkoxyborate by trapping with the triol so as to produce the corresponding lithium triolborate salts such as **1.68b**.[47]

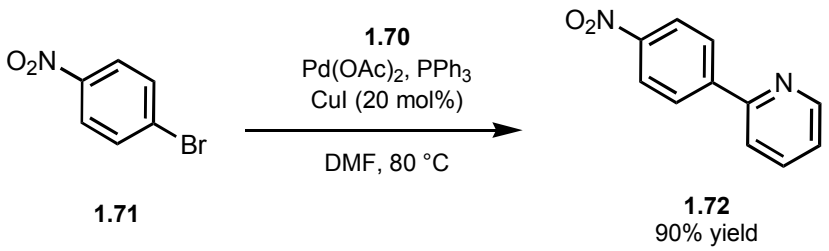


Scheme 1.13

In contrast to the organotrifluoroborate salt analogues, both of the metal hydroxide salts, as well as the hydrate of the TBAOH salt **1.68c** (synthesised for crystal structure determination), were noted as being air and water stable. Furthermore they possess greater solubility in most organic solvents than do their potassium organotrifluoroborate equivalents.

Most pleasingly, using the *in situ* quench avoids isolation of unstable 2-heteroaryl boronic acid intermediates, such that the stable triolborate salts **1.69** and **1.70** could be synthesised. In contrast to **1.70** the corresponding 2-pyridyl potassium trifluoroborate salt is actually less stable than even the parent boronic acid.[48]

While the *ortho*- heteroatom impacted the rate at which these substrates reacted in both Suzuki coupling and Chan-Evans-Lam reactions, they were nevertheless effective as coupling partners. For example, while aryl bromides such as **1.71** typically underwent Suzuki coupling with other triolborate substrates at ambient temperatures using only $Pd(OAc)_2$, the 2-pyridyl analogue **1.70** required additional phosphine ligand, CuI as additive, and an elevated reaction temperature (Scheme 1.14). Akin to the trialkoxy and trihydroxy borates, the triolborates are monomeric and no external source of base is required in order for their successful use in Suzuki coupling reactions.



Scheme 1.14

More recently aryl and heteroaryl[49] triolborates have been used in reactions such as the rhodium-catalysed 1,4-addition[50] and Chan-Evans-Lam reactions[51], while Miyaura has shown that pinacol boronate esters can even be transformed directly to their triolborate analogues.[52]

1.3.7. Modern Boronic Acid Derivatives: Unreactive Towards Transmetallation

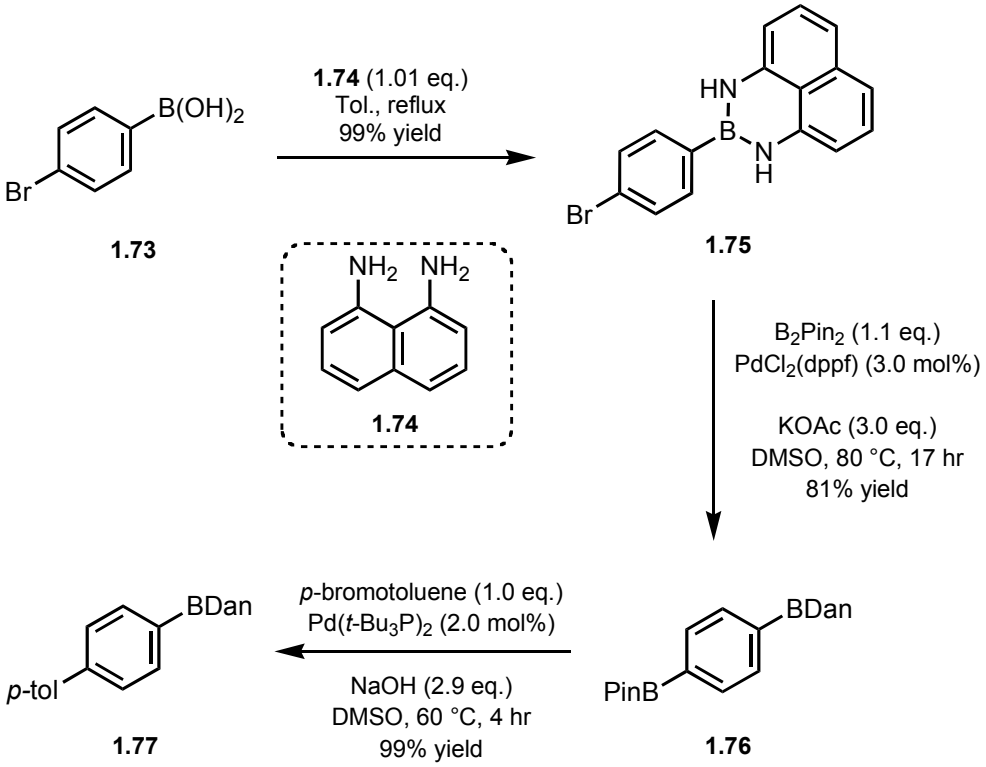
As synthetically valuable as any reactive functional group may prove to be, it is undoubtedly the case that the potential to mask such a reactivity profile by use of protecting groups is often of significant additional value, as in this way orthogonal chemoselective derivitisations of the corresponding masked and unmasked moieties may be achieved.[53]

As many boronic acids and their derivatives, most notably the trifluoroborates, are already compatible with a rather wide range of important synthetic transformations, the most important of their reactivities to mask is in many respects that for which they are now most valued – namely the reactivity they exhibit towards catalytically active transition metal

complexes, and most particularly in respect to transmetallation processes. To this end two notable boronic acid derivatives are worthy of discussion.

1.3.7.1. BDan-Boronates

As discussed in Sections 1.3.3 and 1.3.4, the Lewis acidity of boron in compounds of the type HBX_2 (X = hydrogen, halide or heteroatom substituent) is significantly affected by the identity of X. And as the Lewis acidity of the boron centre is an important factor in the reactivity of boronic acids towards transmetallation under Suzuki coupling conditions, Suginome and co-workers determined that the appropriate choice of diamine might allow the typical reactivity of arylboronic acids to be masked in the presence of otherwise active palladium catalysts.[54]



Scheme 1.15

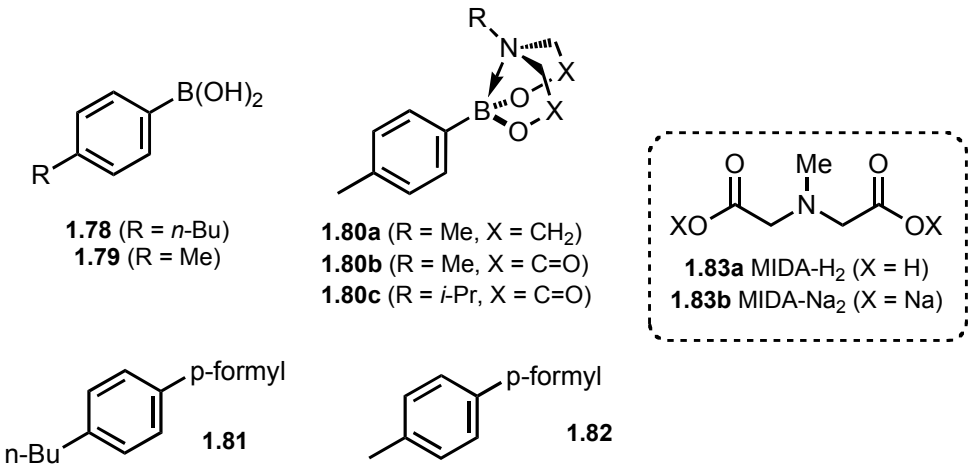
Boronic acids were esterified with 1,8-diaminonaphthalene **1.74**, with azeotropic removal of water to yield the corresponding diazaborinines such as **1.75**. In contrast to all the other diamine derivatives that Suginome and co-workers investigated, the 1,8-diaminonaphthalene derived boronates were stable to both aqueous work-up and silica-gel column chromatography. Furthermore, the BDan-arylboronates are effectively inactive to transmetallation in palladium-catalysed reactions such as Suzuki coupling and Miyaura borylation reactions[55], even when performed in basic media, allowing for the synthesis of

biaryl boronates such as **1.77** through sequential palladium-catalysed cross-coupling reactions. And whilst stable to hydrolysis under basic conditions, deprotection to the corresponding boronic acids can be achieved by treatment of the BDan-boronates with aqueous solutions of strong acids such as HCl and H_2SO_4 at room temperature.

Rather than their use in the context of typical synthetic organic chemistry, the Suginome group has instead focussed on using such arylboronate products in the synthesis of oligoarenes – important substrates in, e.g., materials science research.[5] Thus the breadth of functionality that has been demonstrated as compatible with their deprotection protocols is currently limited to such simple moieties as aryl methyl ethers.

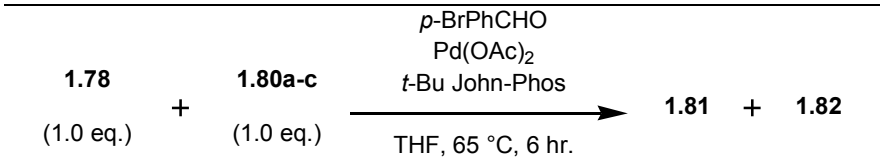
1.3.7.2. MIDA Boronates

The biosynthesis of complex molecules is often ultimately achieved by a reliance on readily accessible small-molecule bifunctional building blocks, which inspired the Burke group to develop *N*-methyliminodiacetic acid (MIDA) protected boronates such as **1.80b**, typically accessed by azeotropic removal of water from a system containing boronic acid and MIDA-di-acid **1.83a**.[56] Akin to the reasoning of Suginome detailed above, Burke and co-workers had targeted derivatives containing electron donating heteroatoms, but as the heteroatom bonds in tetrahedral adducts are comparatively weaker they surmised that this may also provide a more readily cleaved protecting group than an analogous cyclic ester unreactive to transmetallation. Although such MIDA boronates had originally been synthesised by Mancilla and co-workers in 1986,[57] and though the MIDA di-acid **1.83a** is in fact a low cost reagent available in bulk quantities, it was not until Burke and co-workers began to assess the compounds in their own work that the utility of the masking MIDA group was revealed.



Scheme 1.16

In order to determine the ability of different masking groups to inhibit the transmetallation event, Suzuki coupling reactions using a number of boronate esters were performed under anhydrous conditions developed by the Buchwald group[58]. While the *N*-isopropyl analogue **1.80c** gave a marginally increased degree of protection relative to the *N*-methyl substituent of the MIDA boronates, unlike MIDA di-acid **1.83a** the precursor acid of **1.80c** is not a commercially available reagent available in bulk quantities. The *N*-methyl diol analogue **1.80a** did not attenuate the boronate centre's propensity to transmetallate with the palladium catalyst, as unlike the MIDA adducts, such diethanolamine-type derivatives are not conformationally rigid.



Entry	R	X		1.81:1.82
1	–[a]		**(1.79)**	1.0:1
2	Me	CH_2	**(1.80a)**	1.0:1
3	Me	C=O	**(1.80b)**	24:1
4	*i*-Pr	C=O	**(1.80c)**	26:1

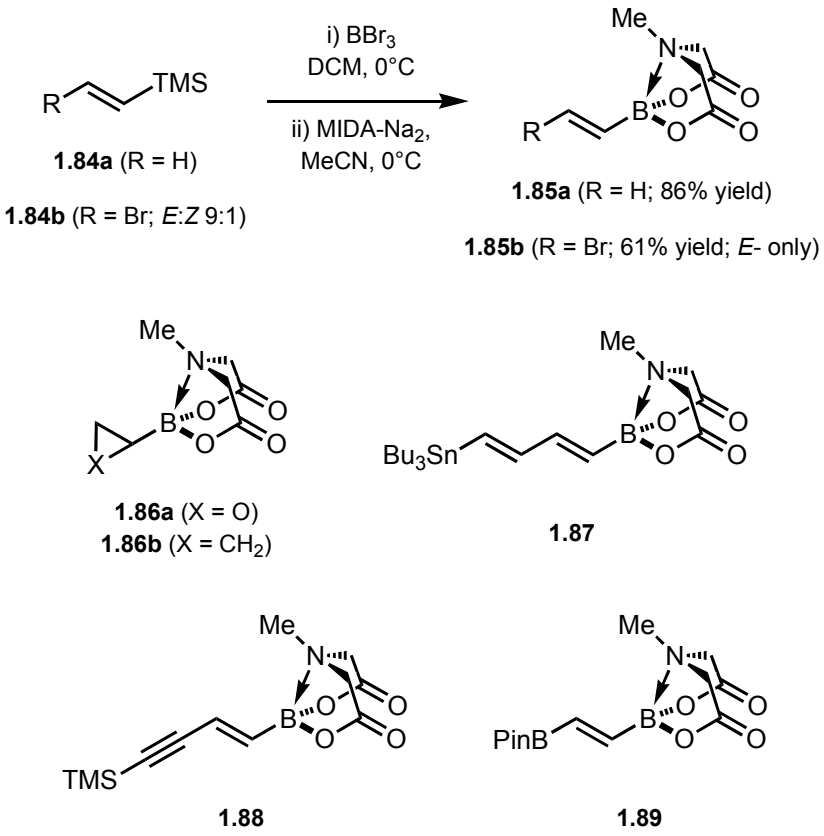
[a] Free boronic acid.

Table 1.2

Indeed, while MIDA boronates such as **1.80b** are stable to anhydrous Suzuki coupling conditions for 28 hours at 80 °C, 1 M NaOH(aq.)/THF can be used to deprotect them rapidly (i.e. 10 minutes) at room temperature, or under even milder conditions ($NaHCO_3$(aq.)/MeOH) over a longer period of time (6 hours). Suzuki coupling at an unprotected terminus and subsequent deprotection yields derivatised biaryl boronic acids in high yields. Also, despite the difference in the reactivity profiles of their parent boronic acids, the MIDA boronate proved an effective protecting group for aryl, heteroaryl, vinyl and alkyl boronates; which furthermore were all amenable to a standard deprotection protocol.

With the exception of reactions necessitating aqueous basic conditions then, much like the potassium organotrifluoroborates, MIDA boronates are themselves often extremely stable, while being compatible with an exceptionally broad range of synthetic transformations. For example the stable vinyl-MIDA boronate **1.85a**, accessed *via* transmetallation of vinyl-trimethylsilane **1.84a** with BBr_3 and subsequent treatment with di-sodium salt **1.83b**, is able to be used as a versatile boronate precursor – successfully derivatised by means of cross-

metathesis (Grubbs II), Heck or oxidative Heck, and epoxidation or cyclopropanation reactions at the vinylic carbons;[59] while (*E*)-(2-bromovinyl)-MIDA boronate **1.85b** can be functionalised under Sonogashira, Negishi, or Miyaura borylation conditions to yield the bifunctional products: TMS-protected enyne **1.88**, stannane **1.87**, and alkenyl 1,2-diboronate **1.89**, respectively.[60]



Scheme 1.17

The utility of MIDA boronates has been demonstrated in myriad applications including the synthesis of polyene natural products,[60] and as a solution to sensitive boronic acids[61] including notoriously unstable 2-heteroaryl substrates;[62] as such a large number of important MIDA boronates are now commercially available.[63]

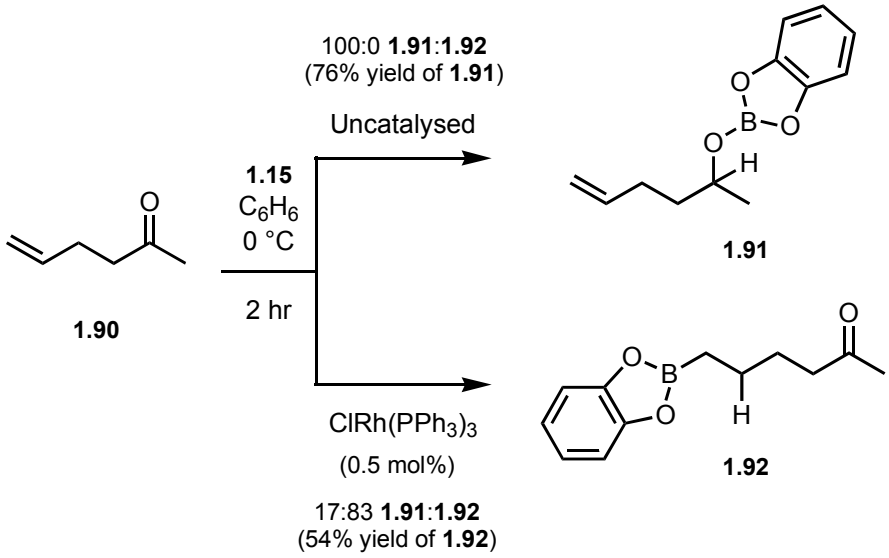
1.4. Metal-Catalysed Reactions for the Synthesis of Modern Organoborons

In this and the following section, a number of important methodological approaches are discussed for both the syntheses and applications of boronic acids and their contemporary derivatives. However, many areas of relevance have recently been reviewed in detail; e.g., the rhodium-catalysed 1,4-conjugate addition,[64] and metal-catalysed reactions involving an organoboron in a pivotal transmetallation event.[65] Furthermore a full review of the most notable of the remaining topics – the Suzuki coupling reaction – is beyond the scope of this review. As such the most relevant aspects are covered, with a particular emphasis on those details that allow for a broader understanding of the role of boronic acids and their derivatives in such catalytic protocols. In addition, discussion has also been devoted to some fundamental discoveries made in recent years on the nature of the species active towards transmetallation in reactions such as the Suzuki coupling; discussions which are also relevant to investigations detailed in later chapters.

1.4.1. Metal-Catalysed Hydroboration

In 1985 Mannig and Noth reported that Wilkinson's catalyst can elicit the catalytic hydroboration of both terminal and cyclic alkenes using catecholborane.[66] Although building on work earlier that decade by the groups of Sneddon (using cobalt,[67-69] iridium,[68] and palladium[70] complexes) and Hawthorne (using rhodium[71]), Mannig and Noth were the first to use "simple" boranes as opposed to carborane reagents.

Indeed, as was briefly mentioned in Section 1.3.2.3, such hydroboration reactions do not typically require a catalyst as the reaction between olefins or acetylenes and borane or alkylborane reagents is generally facile. However, due to the effect of the heteroatoms in the di(alkoxy)borane reagents the rates of their reactions with unsaturated C-C bonds are much reduced, such that the addition reaction is amenable to catalytic intervention. Thus while catecholborane **1.15** normally requires elevated reaction temperatures, e.g. 70 °C and 100 °C, in order to elicit the hydroboration of alkynes and alkenes, respectively, the reaction with **1.90** to yield ketone **1.92** proceeds at ambient temperature in the presence of a catalytic amount of Wilkinson's catalyst (Scheme 1.18).[66]



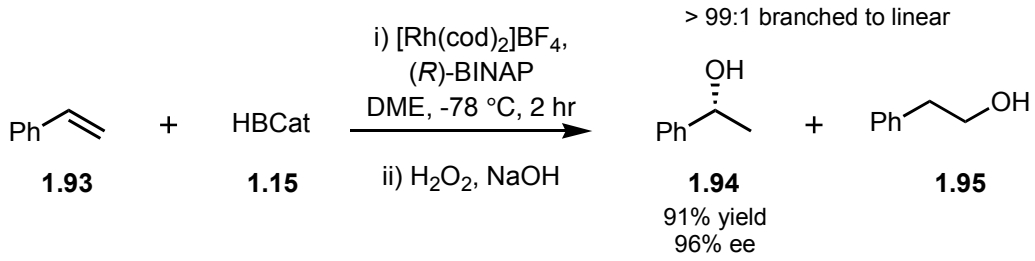
Scheme 1.18

Furthermore, the results obtained for the catalysed and un-catalysed reactions with **1.90** as substrate demonstrated the significant impact that the catalyst has on the chemoselectivity of the hydroboration reaction. Thus the product of hydroboration at the normally more reactive ketone carbonyl (**1.91**) was the minor component obtained in the presence of only 0.5 mol% rhodium complex. Unsurprisingly however, in the presence of a more reactive aldehyde functionality the corresponding reduction product was predominant even in the catalytic reaction.

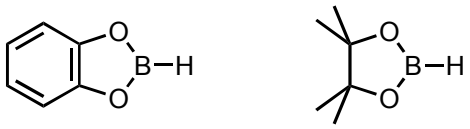
Whilst a number of rhodium complexes were effective, [$HRuCl(CO)(PPh_3)_3$] was much less active, while complexes of Pt, Pd, Ir, or Co were, at best, poor catalysts. Additionally, while an alternative di(alkoxy)borane proved comparably effective, diazaborolidine and dialkylborane reagents were not activated by the catalyst at all. The authors proposed that this behaviour was due to sufficient acidity of the borane being required in order for it to interact appropriately with the catalyst, and indeed Kono and co-workers had in 1975 reported that the same two di(alkoxy)boranes Mannig and Noth had employed were able to undergo oxidative addition to Wilkinson's catalyst or its bromide analogue.[72]

While Mannig and Noth concluded that this approach offered another option for chemoselective reductions to be performed, the true significance of this work was to widen the hydroboration reaction to catalytic protocols that allow for alternative regioselectivities to that of the un-catalysed reactions, or for chiral induction to be achieved by use of optically active complexes in the catalytic hydroborations of pro-chiral alkenes. Indeed much of the work in this area has focussed on the use of alkenes as substrates, as alkynes have in general not provided comparable results, while the hydroboration of alkenes using chiral ligands has

provided ready access to enantioenriched alkyl boronates of significant synthetic value[21] – the first of such protocols being developed by the Hayashi group four years after Mannig and Noth's original report (Scheme 1.19).[73] However, a full evaluation of this area is beyond the scope of this review, and as such the central features of this methodology will be briefly discussed – in part to address factors of relevance to the behaviour of such organoborons with transition metal complexes.



Scheme 1.19



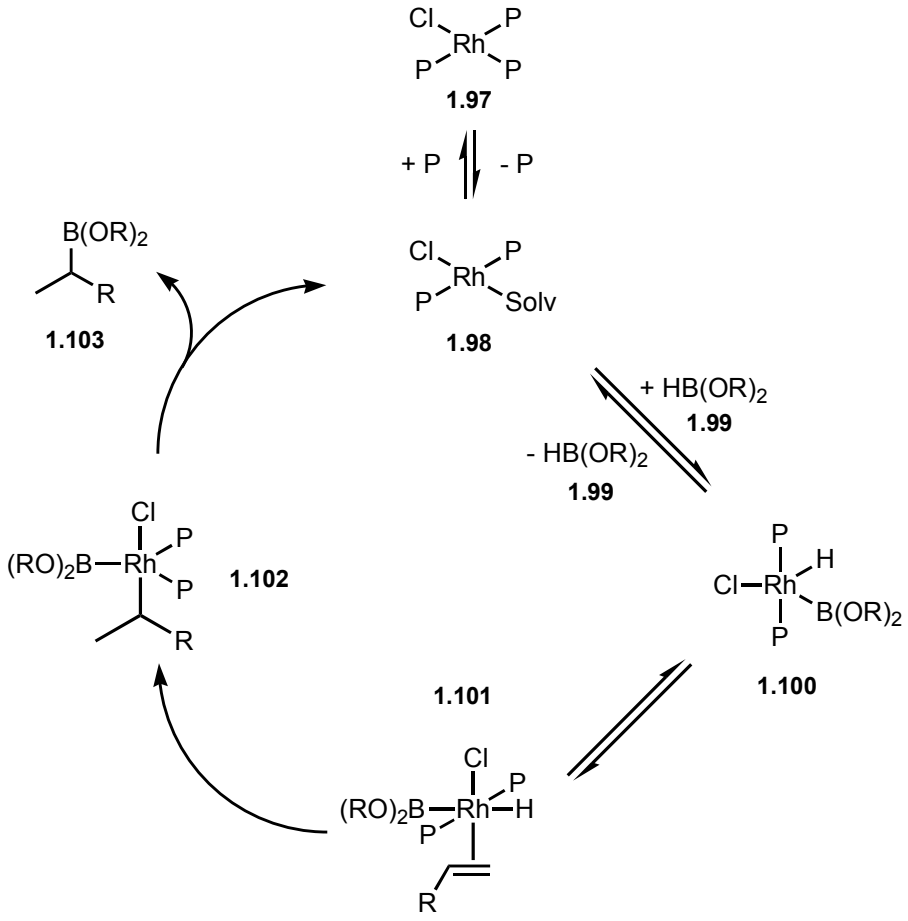
1.15 **1.96**

Figure 1.6

In terms of the choice of metal catalysts used for these reactions then rhodium complexes are still most noteworthy for their activity and so are most often employed; although iridium complexes have become increasingly used. Since its development in 1992 by Knochel and co-workers, pinacolborane (**1.96**)[74] has become the standard choice of di(alkoxy)borane reagent in many cases, primarily due to the greater steric bulk of the pinacolate moiety that in turn can influence the selectivity of such reactions. Overall the catalytic protocol can provide complementary selectivities to those of un-catalysed hydroboration, while allowing achiral boranes such as **1.15** and **1.96** to be employed in enantioselective hydroboration reactions – removing the need for optically active boranes such as dipinylborane (**1.10**) to be used in stoichiometric amounts.[21, 75]

The hydroboration reaction of alkenes proceeds by the aforementioned oxidative addition of the di(alkoxy)borane **1.99** to a rhodium(I) complex **1.98** in order to first yield, with respect to the hydride and boryl ligands, a *cis*- complex of type **1.100**. Reorganisation to the reactive *trans*- analogue then occurs,[76] followed by olefin complexation to generate the intermediate complex **1.101**. The olefin next inserts into the metal-hydride bond to give rhodium-alkyl

1.102, which undergoes reductive elimination to yield the boronate ester **1.103** and regenerate the active rhodium(I) complex **1.98**.[21]



Scheme 1.20: Simplified catalytic cycle for rhodium-catalysed olefin hydroboration employing Wilkinson's catalyst **1.97** (P = PPh_3).[21]

The factors that determine the selectivity of such reactions are both complex and numerous – and include the identities of the substrate, the di(alkoxy)borane and the active catalyst; as well as the degree to which any phosphine ligands have been oxidised upon storage or due to adventitious oxygen in the reaction media. Much of this potential for variation in product distribution arises through diversion from the catalytic cycle described above at the point at which complex **1.101** is generated. In summary however the catalysed reaction using rhodium-phosphine complexes, as typified by Wilkinson's catalyst, typically favours branched products, especially with catecholborane; while the greater steric bulk of pinacolborane can increase the amount of corresponding linear isomer produced. Although more reactive substrates such as terminal alkenes or cyclohexene derivatives are amenable to these protocols, less reactive hindered examples tend to give poor results. This is partly as a result of the ability of the rhodium complexes active for hydroboration also being efficient for hydrogenative pathways – the relevant rhodium-hydride complexes arising variously

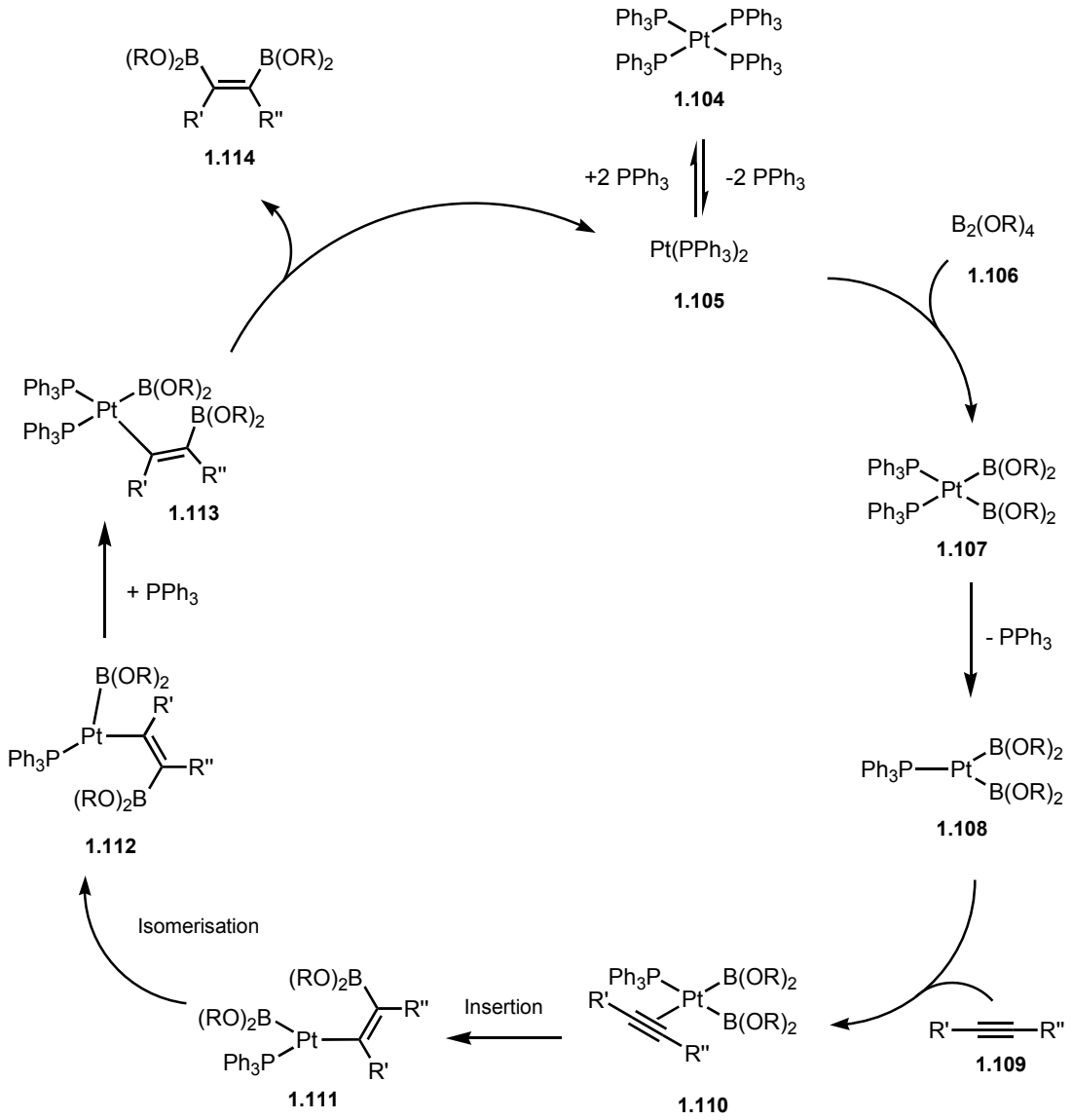
from dehydrogenative borylation or decomposition pathways of the di(alkoxy)boranes in the presence of phosphines.[21]

1.4.2. Metal-Catalysed Diboration and Related Reactions

As discussed earlier: While both dihaloboranes[12] and diboron tetrahalides[22] react spontaneously with C-C multiple bonds, the reactions of di(alkoxy)boranes are at the very least much slower,[66] while those of the corresponding tetraalkoxydiborons do not proceed under classical conditions, but instead require a catalyst.[22] Indeed, in an analogous fashion to that described above for the catalysed hydroboration reactions, the oxidative addition of a tetraalkoxydiboron reagent to a second or third row transition metal complex may yield a diboryl metal complex able to elicit diboration of unsaturated C-C bonds.[22, 25] As with the catalysed hydroboration, a detailed discussion of such reactions is beyond the scope of this review. In summary they, like the catalysed hydroboration reaction, provide an opportunity to employ chiral ligands with, e.g. cationic rhodium(I) complexes, in order to elicit potentially enantioselective additions of diborons across olefinic bonds; while platinum complexes related to $Pt(PPh_3)_4$ are important for the diboration of acetylenes.[25] More recently copper catalysts have become an important area of interest with respect to their ability to catalyse hydroboration and boration reactions.[77-80]

Most worthy of discussion here however is the lack of such activity exhibited by palladium complexes in the case of the diboration reactions. As, while palladium(0) complexes analogous to the highly active platinum analogues such as $Pt(PPh_3)_4$[25] are efficient catalysts for the cross-coupling borylations of C-X bonds (see Chapter 4), they fail to generate diboration products.

Morokuma *et al.* specifically addressed this issue by performing computational analyses of alkyne diboration reactions using $M(PH_3)_2$ complexes of platinum or palladium with $B_2(OH)_4$ as model components. Akin to studies of Suzuki coupling reactions with the classical choice of $Pd(PPh_3)_4$, it is expected that for activation of a phosphine ligated complex of type $L_4Pt(0)$, two ligands dissociate in order to generate a more reactive $L_2Pt(0)$ complex.[81]

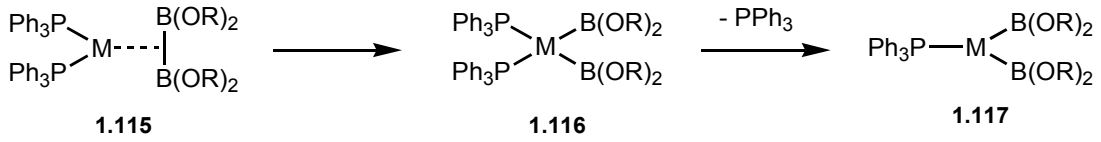


Scheme 1.21

The formation of the active $L_2M(0)$ complex for both metals is energetically comparable, after which the authors found that the palladium-catalysed reaction likely should proceed by a similar sequence of elementary steps. Namely: Coordination of the diboron to the metal centre leading to oxidative addition, dissociation of one phosphine ligand allowing coordination of the alkyne, insertion of the acetylene into a C-B bond, isomerisation and subsequent re-coordination of a phosphine ligand, and finally reductive elimination of the *cis* complex to yield the alkenyl diboron and regenerate the active catalyst.

From the complexes **1.115** containing the B-B bond weakly coordinating to the metal centre, of which the energy levels for the two metals are almost identical, in the case of the platinum complex the transition state energy for subsequent oxidative addition to yield **1.116** is +14.0 kcal/mol above **1.115**, while for Pd it is only +8.6 kcal/mol higher. However, the oxidative

addition adduct **1.116** for platinum lies 21.2 kcal/mol lower than the aforementioned transition state, making the overall oxidative addition exothermic with a value of -10.9 kcal/mol. And while the subsequent ligand dissociation from **1.116** is equally endothermic for both metal complexes (+18.8 kcal/mol), in contrast to the platinum system the oxidative addition adduct **1.116** for palladium is almost identical in energy to the aforementioned transition state. As such even in the model system then the oxidative addition adduct **1.116** for palladium significantly favours rapid reverse reductive elimination, rather than proceeding with the remaining steps of the catalytic cycle.

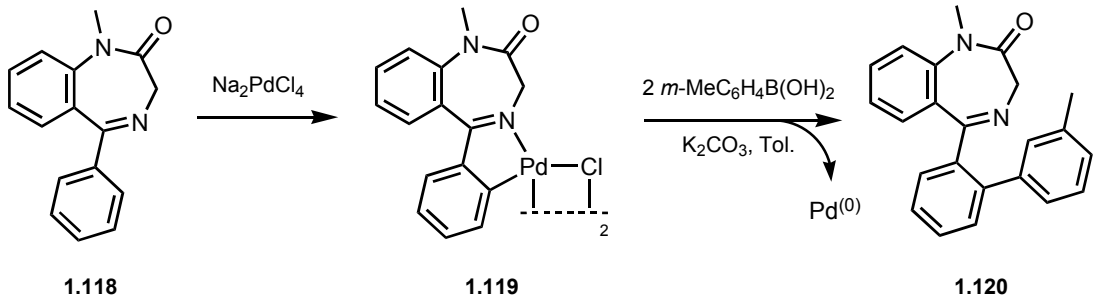


Scheme 1.22

So, while Pt(0), Rh(I), Ir(I) and Cp_2W complexes are able to undergo oxidative addition of tetraalkoxydiborons,[82] the corresponding process with palladium(0), though theoretically able to occur, may rapidly reverse by facile reductive elimination of the di(alkoxy)borane and palladium complex. In terms of experimental evidence this is consistent with the observation by Miyaura and co-workers during their elucidation of the catalytic cycle of the palladium-catalysed borylation of aryl halides with B_2Pin_2 (**1.24**) that incubation of the diboron with $Pd(PPh_3)_4$ did not produce any observable amount of diboryl palladium(II) complex as a result of oxidative addition (see Chapter 4 for further details).[83]

1.4.3. Transition Metal-Catalysed Borylation of C-H Bonds

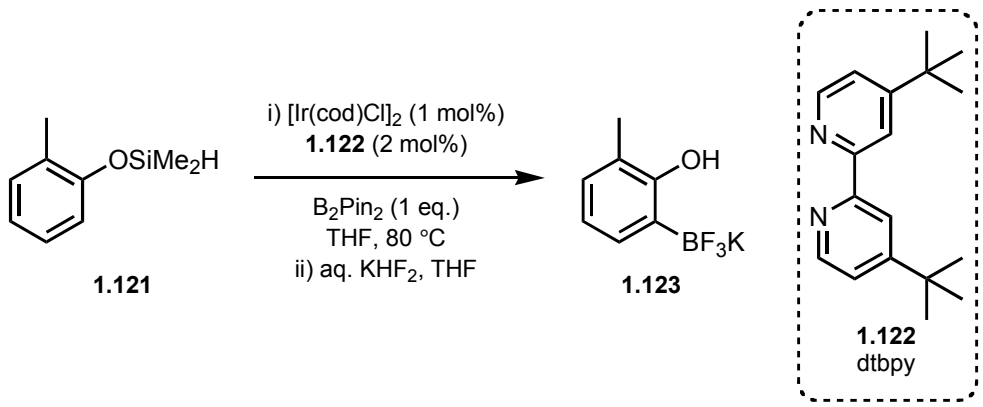
Chapter 4 details the palladium-catalysed borylation of aryl C-X bonds in some detail, and while the corresponding C-H borylation protocols are indeed worthy of attention, their discussion here can only be in passing.



Scheme 1.23

Principally it is worth noting that activation and functionalisation of C-H bonds has become an area of widespread and significant interest in recent years, offering the potential to circumvent the use of more valuable synthetic precursors by advantageously activating ubiquitous C-H functionalities. However these bonds are of course relatively "inert", both compared to C-X bonds traditionally targeted by analogous methodologies, as well as those bonds typically targeted in general synthetic chemistry.[84]

Despite this fact, directed C-H functionalisation has nonetheless been used as a foundation for generating both useful products and useful synthetic transformations. Examples such as palladacycle **1.119**, containing the benzodiazepine substructure, can be accessed by treatment of readily available precursors with palladium salts; i.e. in the case of **1.119** then simply stirring an ethanolic solution 1,4-benzodiazepine **1.118** in the presence of Na_2PdCl_4 results in a good yield of the metallacycle, as reported by Spencer and co-workers.[85, 86] In addition to representing useful synthetic intermediates in the derivitisation of important biologically active compounds – as is the case with **1.119** – palladacycles themselves provide interesting opportunities in terms of their behaviour as pre-catalysts. For example, in the broader context of C-H activation methodologies, then the investigations by Bedford and co-workers detailing aromatic C-H activation/halogenation *via* the generation of intermediate palladacycles – including a potentially very exciting new class of metallacycle – are indeed noteworthy.[87, 88] (For further discussion of palladacycles in the Suzuki coupling methodology, see Section 1.5.1.2)



Scheme 1.24

The C-H borylation itself was reported just over a decade ago by the groups of Hartwig [89-91] and M.R. Smith[92-95] who independently demonstrated that borylation of aliphatic and aromatic C-H bonds could be achieved with transition metal complexes, including catalytic reactions employing rhodium[91, 93, 94] and iridium[92, 95] complexes. In 2001 Marder and co-workers also reported the use of rhodium complexes in the C-H borylation of benzylic

substrates.[96] Currently the most important catalysts for the C-H borylation of alkanes are Cp*Rh type complexes, while iridium complexes containing bipyridine-based ligands are the primary catalysts for the C-H borylation of arenes.[97, 98]

The regioselectivity of such reactions is determined kinetically, such that the least hindered primary C-H bonds of alkanes and least sterically hindered C-H bonds of arenes are borylated. The exclusive regioselectivity of arene borylation for non-*ortho* positions, currently with only one notable exception – that of dialkyl hydrosilyl groups (e.g. as in **1.121**, Scheme 1.24) – is in contrast to the selectivity in the corresponding heteroarene borylation reactions (which are significantly determined by electronic factors[97]), and also the classical directed *ortho*-metallation/electrophilic quench approach to the synthesis of arylboronate esters.[97, 98] C-H activation protocols in the context of C-B bond forming reactions have recently been reviewed in depth by Hartwig, Marder and co-authors, and as such will not be discussed further.[98]

1.5. Applications of Modern Organoborons in Metal-Catalysed Reactions

For the di(alkoxy)boranes and diborons an overall combination of transmetallation and oxidative addition behaviours are seen that are important to their roles in such metal-catalysed reactions as have been discussed above.[99, 100] In contrast, with respect to their utility to contemporary synthetic organic chemistry, then the important metal-catalysed reactions involving boronic acids and their derivatives are almost exclusively those that involve the organoboron in a transmetallation event as part of the dominant catalytic process.

Partyka has recently reviewed the most important organoborons – those used as a source of unsaturated carbon nucleophiles – in the context of transition metal-catalysed C-X coupling reactions.[65] The following sections therefore focus on summarising the key features of two of the most versatile and important of such transformations, with a particular focus on mechanistic intricacies relevant to the chemistry of boronic acids in transmetallation events.

1.5.1. Suzuki-Miyaura Cross-Coupling Reaction

The Suzuki, or Suzuki-Miyaura, coupling reaction is undoubtedly one of the most important transition metal-catalysed cross-coupling reactions for the formation of C-C bonds in terms of utility and scope, a fact reflected both by the diversity of the disciplines in which it sees application, and the scales on which it is employed. Suzuki coupling protocols are of importance to manufacturing routes used for the development or production of pharmaceuticals,[4] in supramolecular and materials science,[5] as well as in flow-,[101] microwave-,[102, 103] and green chemistry;[104] including in-[105] or on-water[106] reactions. As a

result Professor Suzuki was named as a recipient of the 2010 Nobel Prize in Chemistry, jointly awarded with Professors Heck and Negishi, for contributions to the area of palladium-catalyzed cross couplings in organic synthesis.[15]

1.5.1.1. History and Context

The Suzuki coupling reaction involves the metal-catalysed cross-coupling of an organoboron and an organohalide or pseudo-halide (e.g. triflate or diazonium salt), in the presence of a base; the most important protocols being those involving a palladium catalyst and used in order to form biaryls through the coupling of arene or heteroarene halides with boronic acids or related derivatives.[14, 107]

Other transition metals have been reported as exhibiting activity in these reactions, most notably nickel complexes. However, despite the high relative cost of palladium, its dominance as the metal of choice in this context remains unchallenged for a number of reasons. Firstly, in contrast to their palladium counterparts, nickel species are as a rule notably more toxic, and show greater air and moisture sensitivity. Furthermore, while nickel complexes may be more reactive in the context cross-coupling reactions than palladium equivalents, they are also known to promote undesired homocoupling reactions, while being less tolerant of common functional groups; for example nickel-phosphine complexes are known to react with nitro moieties that would typically be inert to the corresponding catalytic protocols using palladium. Additionally, with nickel complexes being more sensitive, their higher initial activities may be more prone to attrition through contact with adventitious water or oxygen, and thus their continued catalytic activity may be compromised.[108] Many palladium pre-catalysts used in Suzuki coupling reactions are quite tolerant of oxygen and moisture, as even are some of the more active species they generate *in situ*, making palladium an extremely robust choice of metal in this respect. Furthermore, palladium salts are able to generate species so exceptionally active in these reactions that their ability to catalyse such reactions at loadings in the region of 50 ppb[109] have therefore been referred to as "*homeopathic*";[108, 110] while complete conversions are further documented as being obtainable at substrate to catalyst ratios of 1,000,000 to 1.[111]

With the volume of material reported each year in this area, and with the lack of significantly established alternatives to palladium catalysis, the following discussion focuses solely on the central concepts of the palladium-catalysed Suzuki coupling reactions, especially in the context of aryl halides and arylboronic acids – being that this combination of palladium and aryl substrates are also the most common of all types to be reported.

1.5.1.2. Modern Developments

Research efforts in the area over the last 15 years have focussed primarily on two core aspects of the methodology – namely, the development of more versatile boronic acid derivatives, and the development of more active and broadly applicable catalytic complexes and ligands. While many of the more germane points of discussion relating to the organoboron substrates are covered elsewhere, a synopsis covering notable features of relevant complexes and ligands now follows.

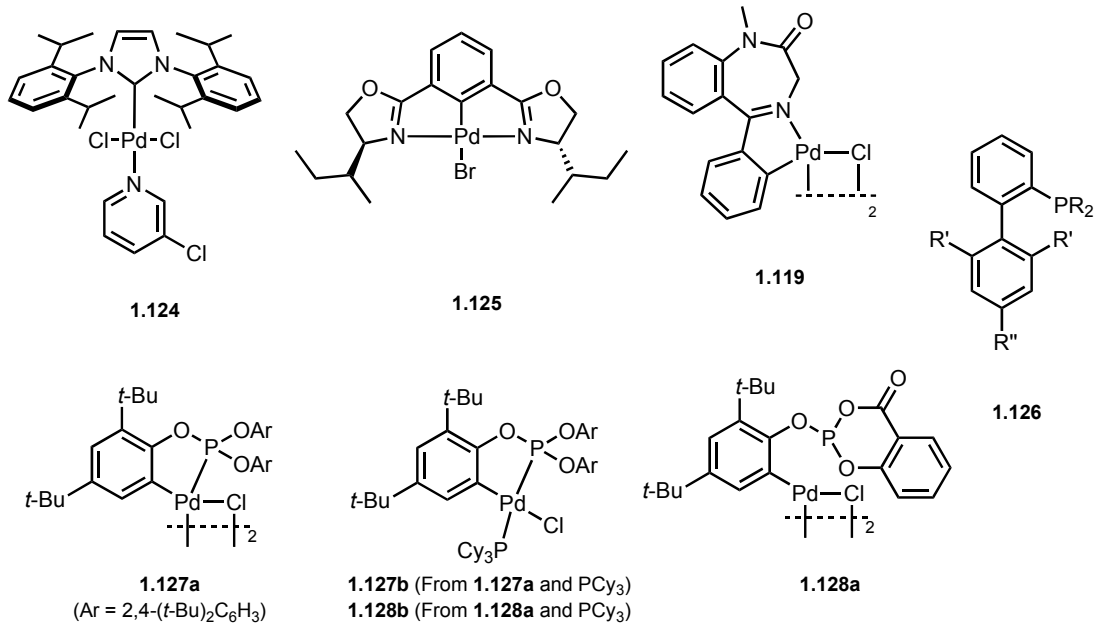
Prior to 1997 only a relatively small number of reports using classical catalysts for the Suzuki coupling of heteroaryl chlorides and boronic acids were detailed in the literature[112, 113] until Shen reported that, in combination with $PdCl_2$ as a pre-catalyst, PCy_3 was an effective choice of ligand – being able to form an active catalyst for the Suzuki coupling of aryl chlorides bearing electron withdrawing substituents.[114] Shen postulated that the greater steric bulk of the ligand might favour dissociation of a phosphine from L_2Pd to yield a more active coordinatively unsaturated LPd species, with the single remaining electron rich ligand still sufficiently able to activate the metal centre towards undergoing oxidative addition in the presence of the aryl chloride. These observations were further supported by the reports that other bulky and electron rich phosphine ligands such as P(*i*-Bu)$_3$ and P(*i*-Pr)$_3$ also performed well in the Suzuki cross-coupling reactions using activated aryl chlorides, while Fu and Littke demonstrated that P(*t*-Bu)$_3$ was a broadly effective choice of ligand for a range of aryl chlorides and arylboronic acids as substrates.[115]

Furthermore Fu and co-workers showed such ligands to be generally effective in other palladium-catalysed cross-coupling reactions such as Stille[116] and Heck[117] couplings, as well as the Sonogashira couplings of aryl bromides at ambient temperature.[118] In 2000 Fu *et al.* also reported that a palladium to phosphine ligand ratio of 1.0:1.5 was optimal in a Suzuki coupling protocol – further supporting the proposed high activity of monophosphine complexes.[119] Indeed this was later confirmed by the Hartwig group in 2002.[120]

In summation these reports, along with many others, have become the foundation for a revolution that has driven many of the most notable advances in the field of palladium-catalysed cross-coupling methodologies over the last decade. While the importance of concomitant advances such as the development of more versatile boronic acid derivatives (of which the potassium organotrifluoroborate salts are prime examples) cannot be ignored, the understanding that more active complexes are typically formed with bulky basic ligands such as PCy_3 and P(*t*-Bu)$_3$ has been central in the development of a number of important modern

ligand families with an increasingly rational approach afforded to their design. Indeed, such ligands and the complexes they form are today often used for standard substrate combinations, a number of active examples being commercially available that also demonstrate much improved stabilities and handling characteristics when compared with the classical choices of $Pd(PPh_3)_4$ or $Pd_2(dba)_3$ – known for exhibiting a relatively low tolerance for exposure to air, moisture, heat, and even light.[121, 122]

The most notable of the modern ligand classes are the commercially available biaryl monophosphines typified by those reported by the research group of Buchwald (of the type **1.126**, and which are variously discussed in greater detail throughout Chapters 2-4), the *N*-heterocyclic carbene (NHC) ligands, and palladacycles and the related pincer complexes.



1.124 **1.125** **1.119** **1.126**

1.127a (Ar = 2,4-(*t*-Bu)$_2$C$_6$H$_3$) **1.127b** (From **1.127a** and PCy_3) **1.128b** (From **1.128a** and PCy_3) **1.128a**

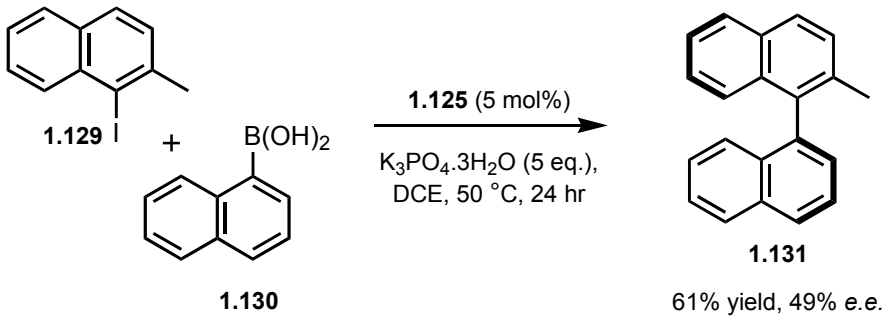
Figure 1.7

NHC ligands are both bulky and strongly electron donating, making them a good choice for Suzuki coupling reactions. Furthermore, in an analogous manner to employing stable pre-catalysts, the sensitive free carbene is often able to be generated *in situ* by exposure of a more stable salt form to a strong base.[123] Alternatively the commercially available PEPPSI catalyst **1.124** represents a bench-stable and readily employed palladium-NHC complex – activated *in situ* through loss of the chloropyridine ligand.[124, 125]

Palladacycles and the related pincer compounds have in recent years become an important class of complexes that are particularly noteworthy, primarily due to their potential for exhibiting exceptionally high catalytic activities. Phosphine and NHC ligating moieties may

also be present in the palladacycle ligand backbone, or present in adducts formed with additional ligands.[126-128] Schiff base and related motifs are also a common feature, as exemplified by the 1,4-benzodiazepine derived palladacycle **1.119**.[85] In regard to the catalytic applications of palladacycles, then the contributions of the groups and research associates of Bedford,[129, 130] Fairlamb,[131, 132] and Najera,[133, 134] are exemplary. In summary, investigations detailing palladacycles as pre-catalysts of complexes possessing exceptionally high and continued activities, as well as tolerance for atmospheric moisture and oxygen, have been disclosed.[135-137] Furthermore, such research groups as those named immediately above have demonstrated the pioneering reactivity profiles of palladacycles within not only the wider remit of palladium catalysis, but also their application in Suzuki coupling protocols.

The Bedford group's palladacycles are some of the most active Suzuki coupling catalysts known – with **1.127a** able to achieve TON's and TOF's at and close to 1,000,000, respectively, for the coupling of phenylboronic acid and aryl bromides.[129] Treatment of **1.127a** with PCy_3 yields monomeric complex **1.127b**, which is highly active for the coupling of aryl chlorides.[138, 139] Analogously the salicylate bridged version **1.128a** in combination with PCy_3 gives rise to **1.128b**, which is effective for the cross-coupling of particularly challenging deactivated, or sterically hindered, aryl chloride substrates.[140]



Scheme 1.25

The development of more selective optically active catalysts for the formation of enantioenriched atropisomeric biaryls in Suzuki coupling reactions, as well as the interest in related sp^3-sp^3 cross-coupling reactions (where there may be the potential for enantioinduction) has further increased the value of palladacycles and pincer complexes. For example Nishiyama *et al.* have reported that (*SS*,*SS*)-*s*-Bu-phebox complex **1.125** is able to allow moderate enantioselectivities to be obtained in the Suzuki coupling of 1-naphthyl substrates (Scheme 1.25).[141]

Notably however, many palladacycles are indirectly active, in that they often exhibit as highly stable pre-catalysts for exceptionally active species that are released *in situ*.[127, 142] Moreover the mechanistic intricacies of palladacycle catalysed Suzuki coupling reactions may be different to those typically observed, for example with evidence that palladium(II)/palladium(IV) pathways may be involved in some instances,[128, 143, 144] as opposed to the more usual palladium(0)/palladium(II) couple.

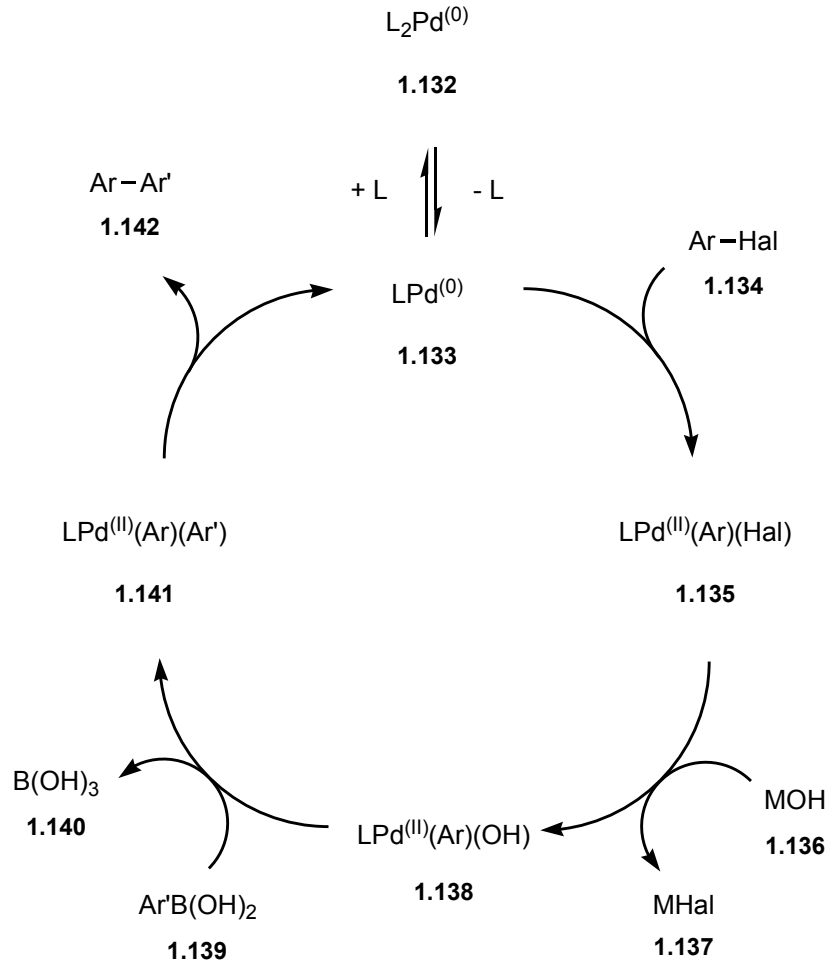
In summary, ligands and complexes such as those discussed have proven active in coupling extremely challenging combinations of substrates, and as such the bulky electron rich ligands, including S-Phos and P(*t*-Bu)$_3$, have been used for large scale reactions (≥ 100 mmol).[4] For example, S-Phos (0.6 mol%) was used in combination with $Pd_2(dba)_3$ (0.25 mol%) to yield 4.98 kg of a biaryl product.[145]

1.5.1.3. Catalytic Cycle

Although palladium(0) complexes, most notably $Pd(PPh_3)_4$ and later too $Pd_2(dba)_3$, were often used as the first choice of pre-catalyst for Suzuki coupling reactions, more recently it has become common practice to employ the contemporary ligands in combination with less sensitive palladium(II) pre-catalysts. More sensitive and active catalysts are therefore often able to be formed *in situ* from air-stable precursors, and thus there must occur one or more initial processes for the generation of active palladium(0) by overall reduction of palladium(II). While sacrificial oxidation of phosphine ligands has been suggested to account for this process, there is increasing evidence that in the presence of boronic acids a double transmetallation/reductive elimination pathway predominates.[144, 146] As such this better accounts for the efficiencies observed with certain ligands, especially when present in only equimolar amounts relative to the palladium(II) salts, and thus where sacrificial ligand oxidation would likely give more disparate reaction rates than are observed.

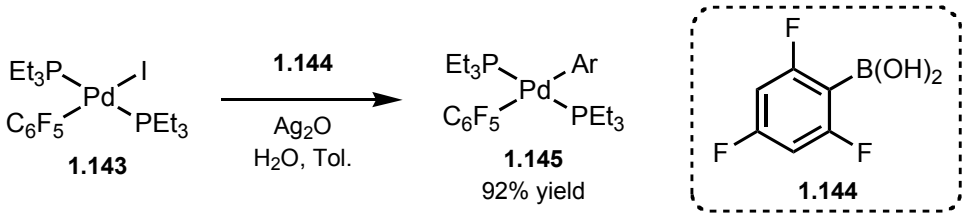
The palladium(0) species thus typically formed, generically represented as $L_nPd(0)$ (where, for monophosphine ligands, $2 \leq n \leq 4$), then undergoes ligand dissociation to yield a less stable, but more reactive, coordinatively unsaturated $L_{n-x}Pd(0)$ complex (where n-x = 1 or 2), which is necessary for the catalytic cycle to properly initiate. This occurs by oxidative addition, where the aryl halide and palladium complex can be considered respectively as an electrophilic electron acceptor and a nucleophilic electron provider.[144] In the case of many modern phosphine ligands which exhibit high activities, as exemplified by the Buchwald ligands, these reactive complexes often contain only one bulky and electron rich phosphine ligand. As such they are extremely reactive, being able to accommodate the incoming aryl halide, while still providing sufficient electron density to the metal centre.

The aryl halide, being a pseudo-electrophile, is also rendered more reactive by the presence of electron withdrawing substituents, especially when they are provided by moieties that do not contribute to steric crowding at the *ipso*- carbon. In relation to the carbon-halogen bond strengths the reactivity trend for comparable aryl halides towards oxidative addition is I>Br>Cl.[14]



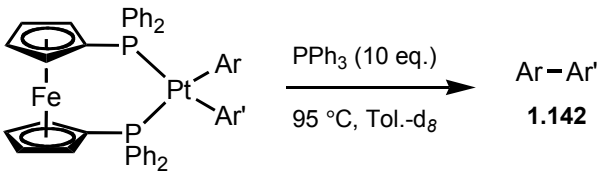
Scheme 1.26: Catalytic cycle for the Suzuki coupling reaction conducted in the presence of aqueous base and employing a bulky, electron rich, monophosphine ligand.

After formation of oxidative addition adduct **1.135** the catalytic reaction proceeds by a subsequent transmetallation event, further details of which are discussed separately in Section 1.5.1.4. The final step in the cycle then involves formation of the coupling product and regeneration of the active palladium(0) complex **1.133** *via* reductive elimination of biarylpalladium(II) complex **1.141**. Here it is worthwhile to note that reductive elimination is proposed to occur from the *cis*- rather than *trans*- diorganopalladium complexes,[65] as is supported by the extremely high stability exhibited by complex **1.145** towards reductive elimination, during both storage under air atmosphere and thermally whilst in solution.[147]



Scheme 1.27

While the *cis*-diorganopalladium analogues are typically too unstable to allow for an accurate and systematic study, Hartwig has detailed the rates at which various model DPPF ligated biarylplatinum complexes (such as those of type **1.146**) undergo reductive elimination. He notes that in the case of electron donating groups on the aryl rings the rate of reductive elimination is increased – but that the fastest rates are in fact obtained when one electron poor and one electron rich aryl moiety is involved (Scheme 1.28).[148]



1.146

Ar	Ar'	k_{rel}
p-$F_3CC_6H_4$	*p*-$F_3CC_6H_4$	1
p-$Me_2NC_6H_4$	*p*-$Me_2NC_6H_4$	23
p-$F_3CC_6H_4$	*p*-$Me_2NC_6H_4$	114

Scheme 1.28: Relative rates of reductive elimination (k_{rel}) for complexes **1.146**

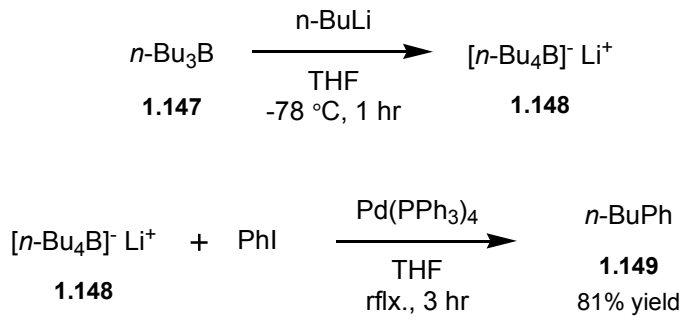
It is at this point worth noting again that while sp^3-hybridised alkylhalide substrates have been used successfully in Suzuki coupling reactions, they are typically both much less reactive to oxidative addition than the aryl and vinyl analogues,[144] the process also being characterised by a greater degree of S_N2 character,[149, 150] while the intricacies by which their adducts undergo reductive elimination differ too.[148]

1.5.1.4. Transmetallation

Over the last decade and a half in particular, the use of boronic acids and their derivatives in metal-catalysed cross-coupling reactions has been the target of significant and widespread interest, both in industrial and research quarters. However, until very recently there remained a distinct lack of consensus, or even general appreciation, as to how the quaternisation of sp^2-hybridised boronates impacts the rates and intricacies of the pathways for their transmetallation with catalytically relevant transition metal complexes. Indeed in the

literature there still broadly remains what could be termed a dichotomous stance on this issue – namely that while quaternised borates are often lauded for their stability towards undesired protodeboronation and actions of nucleophiles, they are often regarded as being more reactive than the parent boronates – a fact seemingly supported by the improved yields and selectivities elicited over boronic acids in certain situations.

Contextually, classical organometallic reagents of high utility to synthetic chemistry were most often those that possessed intimately connected and high levels of both reactivity and ionic character – allowing otherwise inaccessible reaction pathways by harnessing the nucleophilic "umpolung" character of their organic substituents.[151] And yet modern p-block organometallics such as the siloxanes and boronic acids are much more stable than the classical organometallic analogues, in part because of the high covalent character they possess. Notably in this context, the quaternisation of such sp^2 boron centres by nucleophiles is known to yield sp^3 borates of higher ionic character, and with correspondingly weaker C-B bond energies.[2] And indeed 1,2-alkyl migration reactions involving intramolecular transfer of nucleophilic organic substituents from boron to a neighbouring electrophilic centre are well documented for tetrasubstituted organoborates.[152] Furthermore, in their 1995 review of palladium-catalysed cross-coupling reactions of organoborons, Suzuki and Miyaura include the results of the palladium-catalysed reactions between iodobenzene and lithium borates such as **1.148** – formed by treatment of tributylborane **1.147** with organolithiums. Indeed both $Pd(PPh_3)_4$ and $PdCl_2(dppf)$ were able to effect the formation of the cross-coupling product **1.149** in the absence of base when using **1.148**.[14]

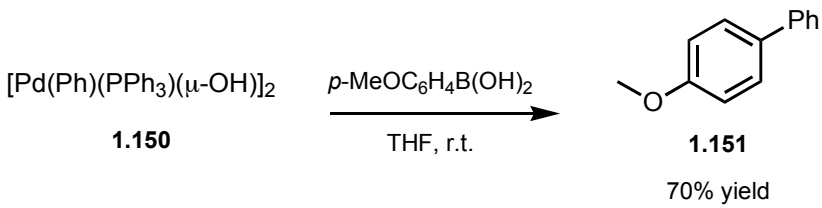


Scheme 1.29

As such the requirement for base in the Suzuki coupling reaction was able to be interpreted as being to "activate" the boronic acid in order to form a quaternised borate more easily able to undergo transmetallation. Indeed the rates of the Suzuki coupling reactions between arylboronic acids and aryl halides have been shown to be higher between a pH range of 9.5-11.0 than they are at a range of 7.0-8.5,[153] while the pK_a values of simple arylboronic acids

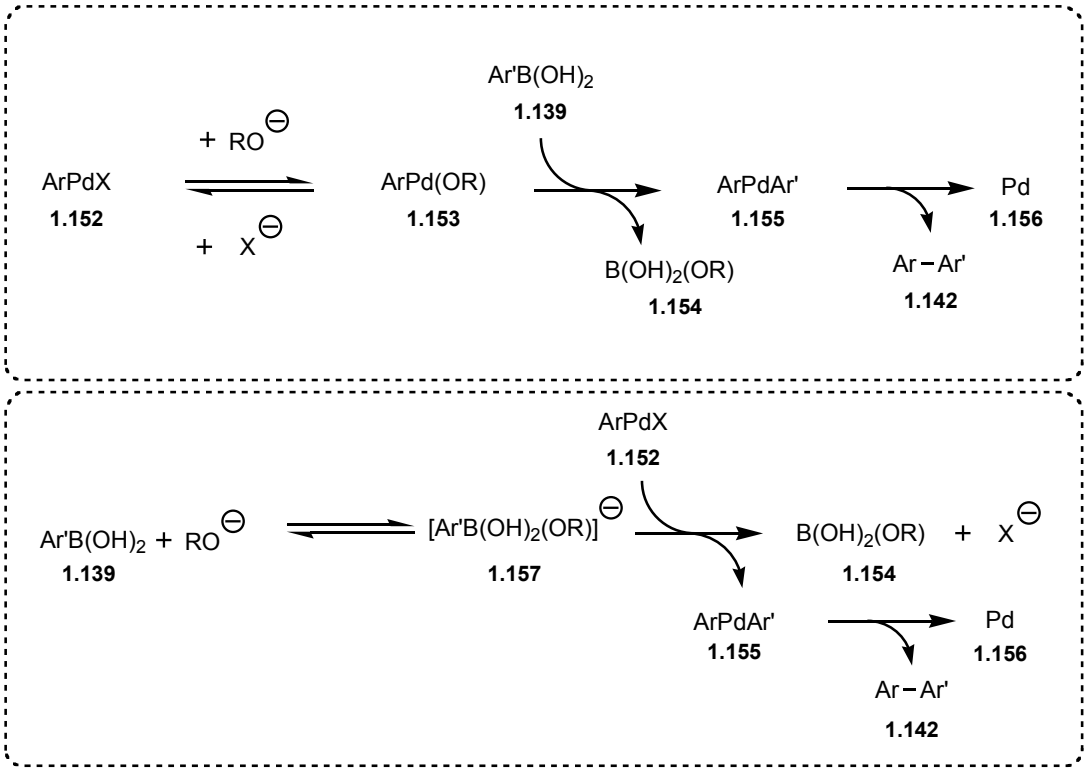
such as phenylboronic acid are typically around 9.[2] This view is also consistent with the fact that while the oxidative addition of aryl halides is able to occur in the absence of base, boronic acids do not react directly with complexes such as $PdCl_2(PPh_3)_n$ (n = 0 or 2) or $PhPdI(PPh_3)_2$.[14]

However, while noting that "*Although there is no direct evidence that the boronate anions, such as* $RB(OH)_3^-$*, are capable of effecting the transmetalation, it is quite reasonable to assume the similar effect of base for the transmetalation of organoboronic acids.*" Suzuki and Miyaura continued their discussion[14] of this issue by then detailing the behaviour of complexes such as **1.150** that are able to undergo the transmetallation with boronic acids in the absence of base, as was reported by Alper *et al.*[154] And thus they also stated that "*It is not yet obvious in many reactions which process*", i.e. transmetallation of the boronate with "Pd-OR", or the borate with "Pd-X", "*is predominant; however, the formation of alkoxo-, hydroxo-, or acetatopalladium(II) intermediate should be considered to be one of the crucial transmetalation processes in the base/palladium-induced cross-coupling reactions.*"



Scheme 1.30

However, the question as to what degree the boronate and borate forms each contribute to the overall rate of catalyst turnover in standard reaction protocols (as shown by the two alternative pathways in Scheme 1.31) was no doubt further complicated by the recent rise to prominence of pre-formed borate reagents, as exemplified by potassium organotrifluoroborate salts. And here there is a potential discontinuity between the stability and suggested reactivity of many such borates when compared to the analogous boronic acids – namely that while their B-C bonds are correspondingly weaker, their kinetic stability is generally higher. This is broadly true for boronic acids and related derivatives that are stable in isolation, as access by a nucleophilic species is typically necessary for their degradation to be effected.[2, 13]

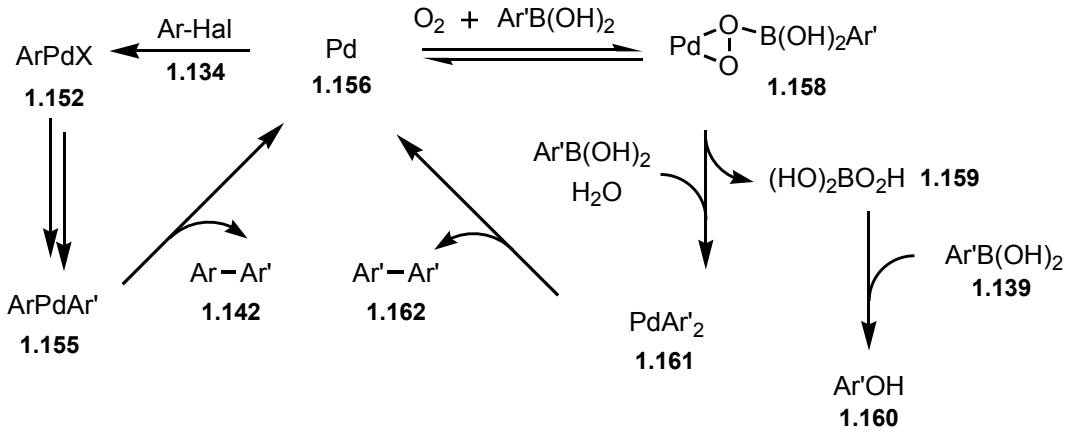


Scheme 1.31: Schematic pathways for the Suzuki coupling reaction involving either a boronic acid (top), or tetrahedral borate derivative (bottom), in the critical transmetallation event. Adapted from literature content.[144, 155]

Indeed, despite the aforementioned reactivities of palladium complexes such as **1.150** with boronic acids in the absence of base, as well as the corresponding precedence for the related hydroxorhodium complexes being highly active for transmetallation in the rhodium-catalysed 1,4-addition reactions detailed below, not until very recently has it become increasingly evident that the active species contributing most to the net rate of transmetallation in such reactions is the sp^2-hybridised boronate form, and not a corresponding borate anion derivative.

Interestingly despite fluoride salts being effective additives for Suzuki coupling of arylboronic acids,[14] in order for organotrifluoroborates to be reactive under Suzuki coupling conditions the addition of stoichiometric or super-stoichiometric amounts of base is widely known as being essential,[13] while in addition the use of a mixed aqueous/organic solvent system is also a necessity for reactions with standard substrates.[146] This led to the proposal that mixed borates of the type $[RBF_{3-n}(OH)_n]^-$ could be responsible for the overall activity of organotrifluoroborates in such reactions. In turn the mixed borates must therefore be much more active for transmetallation than the corresponding trihydroxyborates formed when boronic acids are present in basic aqueous media.

However, Lloyd-Jones and co-workers have instead recently reported that the active species for transmetallation in reactions employing organotrifluoroborate salts are actually the hydrolytically generated free boronic acids. Despite suggestions too that borates are more "active" than boronic acids, so as to account for their ability to provide cleaner reactions and higher yields, Lloyd-Jones and co-workers demonstrated that under comparable conditions, and although more by-products are generated with boronic acids, they do in fact give a higher rate of reaction than the corresponding organotrifluoroborate salts.[146]



Scheme 1.32

Although large amounts of homocoupled biaryl **1.162** are formed when model substrate *p*-fluorophenylboronic acid (**1.139**, where Ar' = *p*-FC_6H_4) is reacted under aerobic Suzuki coupling conditions with a simple aryl bromide (**1.134**, where Ar-Hal = 3,5-$(F_3C)C_6H_3Br$), the corresponding potassium organotrifluoroborate salt instead reacts cleanly (albeit indirectly) to give the expected cross-coupling product **1.142**. From such observations Lloyd-Jones and co-workers determined that this is a result of slow hydrolysis from the borate to the boronic acid disfavouring the process involving the palladium peroxo complex **1.158**, which itself catalyses both the formation of homocoupling product **1.162** and phenol **1.160**.[146, 156] This was further confirmed by performing a slow addition of the boronic acid to such an aerobic reaction mixture, whereupon a much lower ratio of homocoupling product **1.162** to Suzuki coupling product **1.142** formed. Thus, low concentrations of boronic acid generated *in situ* favour the palladium complex **1.156** undergoing oxidative addition with the aryl halide to form adduct **1.152**, rather than the peroxo process with the boronate to yield **1.158**.

Additionally, Lloyd-Jones and co-workers have shown that the populations of arylboronic acid (**1.139**) and corresponding borate (**1.163**) are close to parity under typical reaction conditions,[146] while Hartwig and Carrow have also concluded that the same is true for the

halide and hydroxide ligated palladium complexes such as **1.164** and **1.165** (Figure 1.8).[157] Furthermore, it was found that the rates of reaction between palladium hydroxo complexes and boronates (e.g. such as that between **1.150** and **1.166**, Scheme 1.33) are several orders of magnitude faster than the corresponding reactions of palladium halide complexes with trihydroxyborates (e.g. **1.168** and **1.169**). As such Hartwig and Carrow concluded that, although parameters such as ligand identity may have an unforeseen effect beyond the scope of their studies, in many instances the boronate is going to be responsible for the majority of the observed reactivity. Interestingly they found that boronate esters also react rapidly with palladium hydroxo complexes such as **1.150**, and although more sterically hindered boronate esters were slower to do so, it appears not to be a result of their hydrolysis being a prerequisite for transmetallation to subsequently occur.

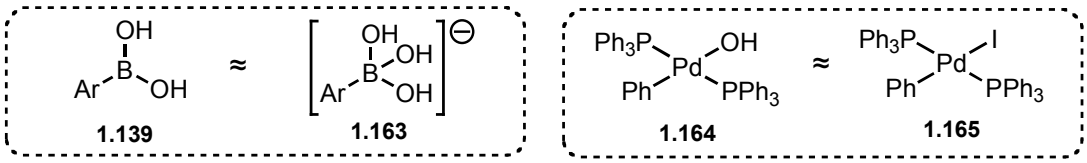
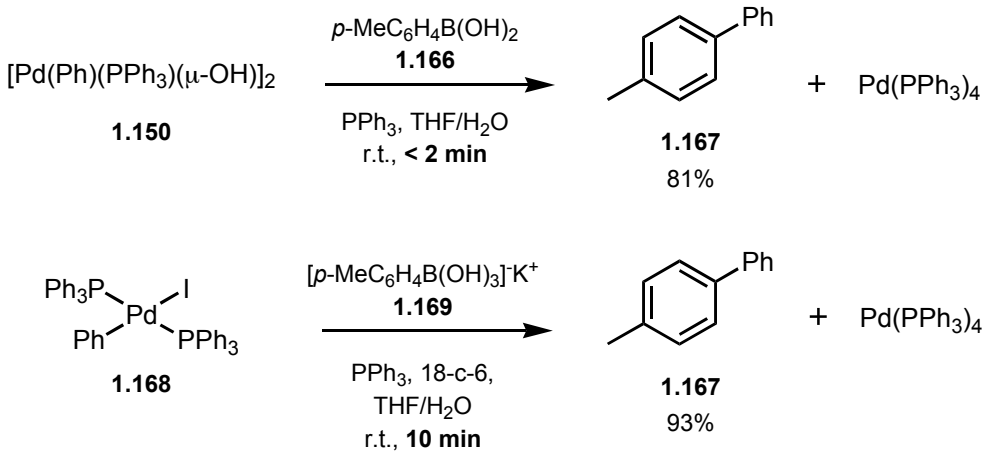


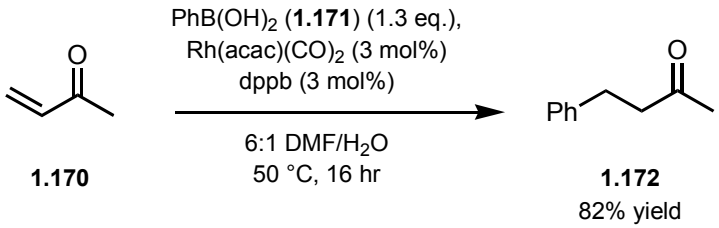
Figure 1.8



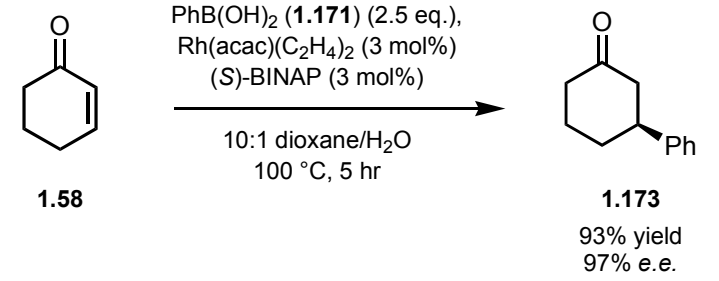
Scheme 1.33

This conclusion that boronates are the much more active species was confirmed most recently by Jutand *et al.* who reported an electrochemical analysis of the Suzuki coupling reaction. They were able to reveal that an optimal amount of base aided the formation of a palladium hydroxo complex, and also the reductive elimination of the biaryl. In contrast at higher loading base retarded the reaction by driving equilibrium formation of the less reactive trihydroxyborate.[155]

1.5.2. Rhodium-Catalysed 1,4-Conjugate Addition Reaction



Scheme 1.34

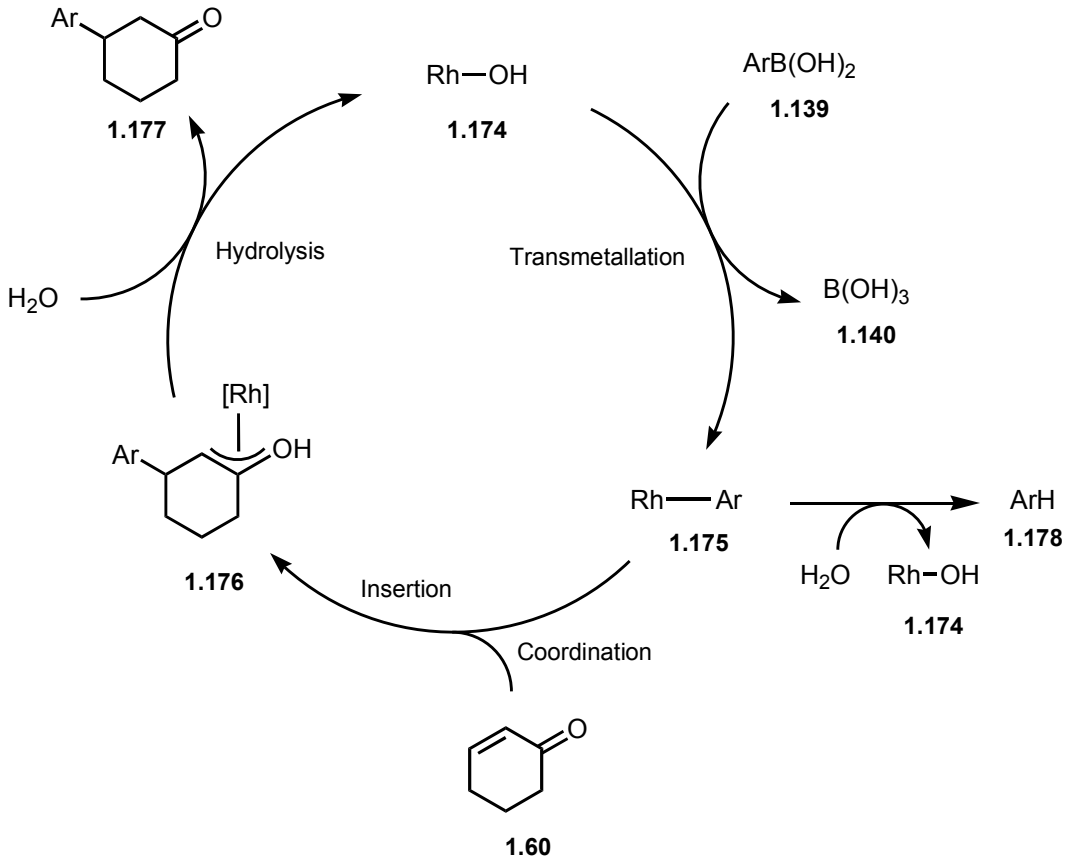


Scheme 1.35

In 1997 Miyaura and co-workers reported that rhodium(I) complexes were efficient catalysts for the 1,4-conjugate addition reaction of α,β-unsaturated carbonyl compounds with carbon nucleophiles arising from transmetallation of boronic acids (Scheme 1.34).[158] They noted that the choice of phosphine ligand was critical to achieving reasonable conversions, and for bidentate bisphosphines there appeared to be a correlation between increased bite angle and greater activity of the rhodium-phosphine complex formed, with the following activity trend observed: DPPE<DPPP<DPPB. The following year Miyaura, Hayashi and co-workers reported that the corresponding asymmetric addition reactions could be achieved with a high level of enantioselectivity elicited through use of (*S*)-BINAP in combination with $Rh(acac)(C_2H_4)_2$ (Scheme 1.35), which was found to more rapidly form the optically active bisphosphine complex *in situ* than did the $Rh(acac)(CO)_2$ pre-catalyst used in the original achiral protocol.[44, 159]

Whilst the copper-catalysed conjugate addition of organozinc and organomagnesium reagents, also being able to provide high levels of enantioselectivity, offers an important alternative to such rhodium-catalysed protocols employing boronic acids, the use of such organometallic reagents has the typical drawbacks. Notably the rhodium-catalysed addition of boronic acids allows for much more robust synthetic procedures, with reactions able to be performed at ambient or elevated temperatures and with a significant level of water tolerance. In contrast the copper-catalysed analogues often necessitate sub-ambient

temperatures and exclusion of moisture.[159] Indeed, not only are the rhodium-catalysed addition reactions of boronic acids tolerant of water, but they are typically accelerated in its presence, such that most protocols employ aqueous/organic co-solvent systems as is the case for the reactions shown above.

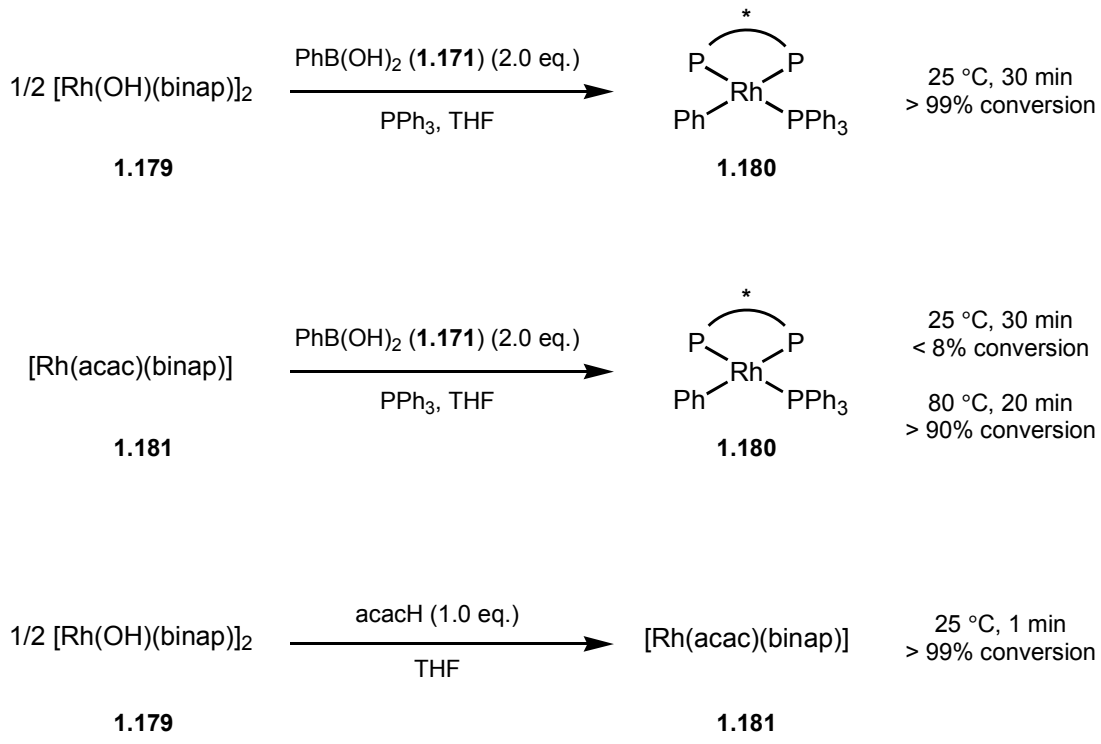


Scheme 1.36: Adapted from Frost *et al.*[64]

As both the applications[64] of the rhodium-catalysed 1,4-addition reaction (to substrates including acrylate esters and amides) and also the use of alternatives to the typically employed organoboron reagents[160] (the most noteworthy being the organozinc and organosilicon reagents) have recently been reviewed by members of our research group, then the remaining discussion here will instead focus on the mechanistic intricacies of relevance to other such discussions included throughout this work.

The proposed catalytic cycle for the rhodium(I) catalysed 1,4-addition reaction for cyclohexene-2-one and an arylboronic acid is shown in Scheme 1.36. The reaction is initiated first by formation of an active rhodium complex, most typically a hydroxorhodium complex **1.174** for which transmetallation with the boronic acid proceeds readily in order to yield an aryl rhodium complex **1.175**. This then coordinates the α,β-unsaturated substrate

before effecting carbometallation to yield an η^3-oxa-π-allyl rhodium complex **1.176**. Such species are normally very labile, and most especially in the presence of water then the subsequent hydrolysis to yield the arylated product **1.177** and regenerate the hydroxorhodium species **1.174** is extremely facile.[64, 159] Although both the arylboronic acids and aryl-rhodium species **1.175** are typically quite resistant to hydrolysis,[161] the boronic acid components are typically employed in excess in order to minimise the impact of any base-mediated, or metal-mediated (i.e. **1.175** to **1.178**), protodeboronation pathways on the overall yield of the addition product.



Scheme 1.37

The aqueous or aqueous-basic conditions typically employed in these reactions promote the formation of hydroxorhodium species, which have been shown to be highly active for the transmetallation reaction with boronic acids. During their investigations to elucidate the catalytic cycle, Hayashi and co-workers found that a hydroxorhodium complex **1.179** was readily derived from $[Rh(OH)(cod)]_2$ by displacement of the labile olefin ligands by the more strongly coordinating phosphine moieties of BINAP. Under base-free conditions, with or without an aqueous reaction media involved, $[Rh(OH)(binap)]_2$ **1.179** was found to undergo transmetallation with $PhB(OH)_2$ to yield aryl-rhodium **1.180** at a very high rate, even at ambient temperatures (Scheme 1.37). Similarly $Rh(acac)(C_2H_4)_2$ also reacts with BINAP with corresponding loss of the olefin ligands in order to yield the phosphine ligated Rh(acac)(binap) complex **1.181**. However, exposing complex **1.181** to $PhB(OH)_2$, under

identical conditions to those that with $[Rh(OH)(binap)]_2$ **1.179** resulted in complete conversion to transmetallation product **1.180**, led to less than 8% of the same phenyl-rhodium complex.

Indeed, only when the temperature is increased does the transmetallation reaction of the boronic acid occur at a significant rate with Rh(acac)(binap) **1.181**. In addition to the direct rate of transmetallation with the Rh(acac)(binap) complex being slow, the acac ligand is still available in solution, either in anionic or protonated acetylacetone form. Addition of one equivalent of acacH to $[Rh(OH)(binap)]_2$ **1.179** in THF at room temperature results in the exceptionally rapid and effectively quantitative formation of Rh(acac)(binap) **1.181** (> 99%, < 1 minute). Thus Rh(acac)(binap) **1.181** acts as a catalyst reservoir which contributes little to the direct catalytic activity of rhodium(I) species in such reactions, while $[Rh(OH)(cod)]_2$ is readily converted to an active phosphine ligated hydroxorhodium species.[162] As such the selection of appropriate pre-catalysts for these reactions is of significant importance in order to ensure high activities and rapid formation of the intended optically active phosphine adducts.[159]

In summary this methodology provides a functional group tolerant approach to the synthesis of a wide range of valuable products, both achiral, and even more importantly, with high levels of enantioselectivity. Such is the utility of this reaction that despite the costs associated with rhodium catalysts it has been employed even for multi-kilogram syntheses.[163]

1.6. Conclusions

This chapter has detailed some of the key characteristics, features, reactivities and applications of organoboron reagents, and of the more contemporary material to have been reviewed, then with a particular focus on what are arguably now the most widely important of all the modern organoboron reagents: The boronic acids and their related derivatives.

In combination, then such features as have been discussed have propelled organoboron chemistry from being the interest of only a very small number of curious academics – as was indeed the case when H.C. Brown began his career as a researcher – to the status it holds today as one of the central pillars of synthetic organic chemistry, and where it is undoubtedly of significance far beyond that single disciple. As further evidence of this, three recipients of the Nobel Prize in chemistry have so far been recognised for work relating to one facet or another of boron chemistry – namely, W.N. Lipscomb, Jr. (1976);[164] H.C. Brown (1979);[1] and most recently A. Suzuki (2011)[15].

Boronic acids and certain of their derivatives, as detailed in Sections 1.3.5-1.3.7, are very versatile and widely used reagents within, and also beyond, the field of synthetic organic chemistry. In this respect, and despite the incredible amount of interest over the last half century that has been focussed on investigating and developing such chemistry, it is still the case that significant progress is being made today – and not simply in the development of novel boronate and borate reagents – but also the wider area of those metal and non- metal-catalysed reactions employing organoborons.

More specifically, and with particular regards to boronic acids, then recent years have seen the development of the Chan-Evans-Lam[26] and Liebeskind-Srogl coupling reactions[165], while various examples of organocatalytic or metal-free reactions involving boronic acids or their equivalents – as either substrates,[166, 167] or catalysts,[168-170] – have been reported. Furthermore, such unprecedented reactivity in metal-free reactions is also increasingly being uncovered for other organoboron reagents – as exemplified by the report made by Hoveyda and co-workers detailing C-B bond forming conjugate addition reactions between bis(pinacolato)diboron and α,β-unsaturated carbonyl compounds, as catalysed by the combination of an *N*-heterocyclic carbene and an alkoxide base.

The following chapters detail and discuss research investigations made within the wider and ever expanding field of organoboron chemistry, with a particular focus on certain important

(and arguably, fundamentally rather similar) transition metal-catalysed reactions used either to access or employ substrates bearing the synthetically valuable arylboronic acid moiety.

In closing, the concluding remarks made by H.C. Brown in his 1979 Nobel lecture are worthy of contemplation for their relevance, foresight, and sentiment:

"*In 1938, when I received my Ph. D. degree, I felt that organic chemistry was a relatively mature science, with essentially all of the important reactions and structures known. There appeared to be little new to be done except the working out of reaction mechanisms and the improvement of reaction products. I now recognize that I was wrong. I have seen major new reactions discovered. Numerous new reagents are available to us. Many new structures are known to us. We have at hand many valuable new techniques.*

… I see no reason for believing that the next 40 years will not be as fruitful as in the past. I [previously] *quoted the poet: 'Tall oaks from little acorns grow.' But in this lecture I have started further back, to a time when the acorn was a mere grain of pollen. I have shown how that grain of pollen developed first into an acorn. Then the acorn became an oak. The oak tree became a forest. Now we are beginning to see the outlines of a continent. We have been moving rapidly over that continent, scouting out the major mountain ranges, river valleys, lakes, and coasts. But it is evident that we have only scratched the surface. It will require another generation of chemists to settle that continent and to utilize it for the good of mankind.*

But is there any reason to believe that this is the last continent of its kind? Surely not. It is entirely possible that all around us lie similar continents awaiting discovery by enthusiastic, optimistic explorers. … Good luck!"[1]

1.7. References

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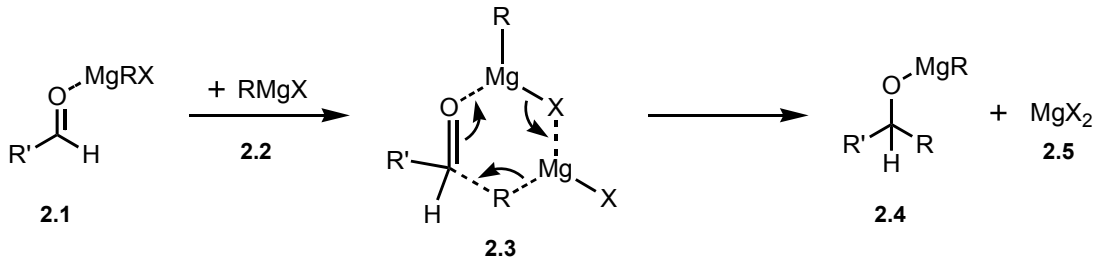
Chapter 2

This chapter details the use of a sulfonated Buchwald dialkylbiarylphosphine ligand (^{S}S-Phos) in the rhodium-catalysed 1,2-addition reactions between aryl aldehydes and arylboronic acids in aqueous basic media. The ligand allows the active complex to be recycled five times for the arylation reaction of *p*-tolualdehyde with *p*-tolylboronic acid, with high activity being maintained. Additionally, the activity of the system is such that it allows for the analogous arylation to be performed with trifluoromethyl ketones and aryl methyl ketones in high to moderate yields, respectively.

2.1. Nucleophilic Additions to Carbonyl Compounds

Nucleophilic additions performed to carbonyl compounds, forming new carbon-carbon bonds, exemplify one of the cornerstone-reactions in both synthetic organic and biological chemistry.[1] Undoubtedly one of the most important and versatile variants are the reactions that employ high-ionic character organometallics, as typified by the organomagnesiums and organolithiums.[2]

The addition reaction of a Grignard reagent to an aldehyde typically occurs so as to readily afford an alkoxide, which upon hydrolytic work up yields the corresponding secondary alcohol **2.4** (Scheme 2.1). The coordination of a carbonyl oxygen lone pair to a Lewis acidic species such as RMgX activates the carbonyl compound (adduct **2.1**), and also begins to pre-organise the system for the subsequent formation of a highly structured cyclic transition state (**2.3**).[3]



Scheme 2.1

The highly reactive s-block organometallics have already been discussed in Chapter 1, where it was noted that while being very useful synthetic reagents, they suffer from having a low tolerance for many of the most valuable and ubiquitous functional groups. Although that discussion was focussed ultimately on their use for the preparation of boronic acids, and though much is also relevant for their application to other synthetic transformations, certain details of are of particular relevance to the addition reactions with carbonyl compounds.

Firstly, while the identity of the organometallic reagent and the specific reaction conditions employed are relevant to determining the outcome of these reactions, the identity of the carbonyl substrate is of particular importance to its rates of reactions with nucleophiles.

Entry	Compound	$k \times 10^4$ M^{-1} s^{-1}	Relative rate
1	Ph_2CO	1.87	1.0
2	PhCOMe	2.05	1.1
3	Me_2CO	15.1	8.1
4	PhCHO	820[a]	439

[a] Calculated from data obtained at lower temperatures

Table 2.1: Kinetic data for the reaction of $NaBH_4$ with selected carbonyl compounds in IPA at 0 °C.[4]

While aldehyde carbonyls tend to react rapidly, the corresponding reactions with ketones and their derivatives are often much slower. This is predominantly due to the increased steric bulk around the ketone carbonyl, which not only hinders the approach of the incoming nucleophile, but also results in increased steric repulsion between substituents in both the transition state and the tetrahedral adduct which is then formed. As such this acts to dissuade nucleophilic attack at the carbonyl carbon of ketones, and when the addition reactions are reversible (e.g. cyanohydrin or hydrate formations), to shift the equilibrium back towards the sp^2-hybridised carbonyl compound.[3]

For example, the rates of reduction with sodium borohydride are very similar for benzophenone and acetophenone (Table 2.1, entries 1-2), while acetone (entry 3) is somewhat more reactive than either of the aryl ketones, because conjugative effects of aryl groups stabilise carbonyl bonds and so reduce their reactivity. However, this effect is relatively insignificant compared to that observed when changing the substrate to an aldehyde, with benzaldehyde being reduced at a rate approximately 50 times that of acetone, and 400 times that of the aryl ketones (Table 2.1, entry 4).

Though the dominance of steric over electronic effects is often particularly obvious in relation to carbonyl reactivity, electronic factors are still important, especially in determining the relative reactivity of otherwise comparable carbonyl compounds. Table 2.2 shows the equilibrium constants for the hydration of various carbonyl compounds, which is strongly correlated to reactivity in other addition reactions.[3]

Entry	R	R'	K^a
1	H	H	2.28×10^3
2	Me	H	1.06
3	Et	H	0.85
4	*i*-Pr	H	0.61
5	*t*-Bu	H	0.23
6	CF_3	H	2.9×10^4
7	Me	Me	1.4×10^{-3}
8	$ClCH_2$	Me	0.11
9	FCH_2	Me	0.11
10	CF_3	Me	35
11	CF_3	CF_3	1.2×10^6
12	Ph	H	8×10^{-3}
13	Ph	Me	9.3×10^{-6}
14	Ph	CF_3	78

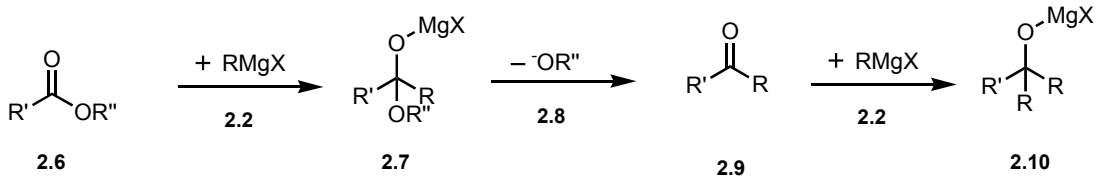
[a] K = [hydrate]/[carbonyl] = K_{eq} [H_2O] = 55.5 K_{eq}

Table 2.2: Equilibrium constants (K) for the hydration of selected carbonyl compounds (RC(O)R').[5, 6]

While formaldehyde (Table 2.2, entry 1) exists predominantly in its hydrated form, the introduction of a single alkyl substituent significantly affects the degree of hydration (entries 1-5). Although the presence rather than the exact nature of the alkyl group has the greatest impact, substituents that are more stabilising through hyperconjugation, and also with higher steric bulk, act to further disfavour the hydrated form (entries 2-5).

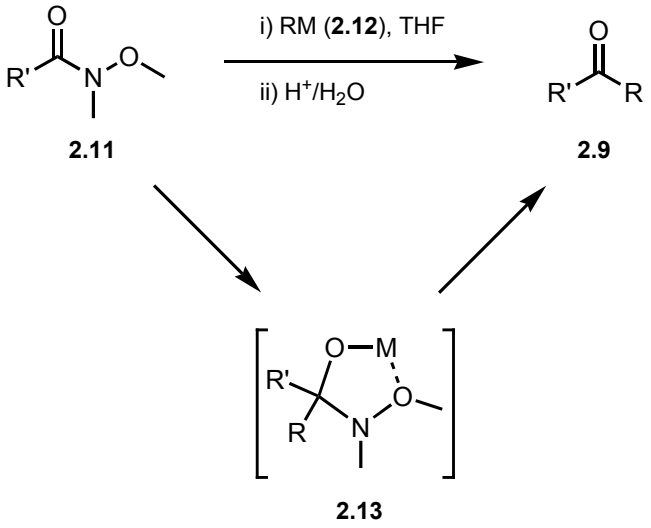
Upon changing to the ketone substrate, the introduction of the second alkyl substituent at the carbonyl carbon has an effect similar in magnitude to that of the first (Table 2.2 entries 1, 2, & 7). However, though the mono-halo methylene substituents (entries 8 & 9) are larger than the simple methyl substituent (entry 7), the halide acts to withdraw electron density from the carbonyl moiety, which results in a more electrophilic carbon atom. As a more extreme example of this, though the size of the CF_3 substituent is about intermediate between that of *i*-Pr and *t*-Bu,[7] the high electronegativity of fluorine in particular results in such an electron poor carbonyl carbon that hexafluoroacetone (entry 11) is hydrated significantly more than even formaldehyde (entry 1). Not only is α,α,α-trifluoromethyl acetophenone (entry 14) hydrated to a greater degree than acetophenone, but also benzaldehyde (entries 13 & 12, respectively).

Substituent electronics and sterics affect both the rate of the addition reaction, as well as the stability of the tetrahedral adduct which is formed. Thus, while aldehydes typically react with Grignard reagents at a facile rate to give the product of a single addition (e.g. as for acetaldehyde **2.21** in Scheme 2.5), the use of other carbonyl compounds may result in either sequential addition reactions or competing processes becoming favourable.



Scheme 2.2

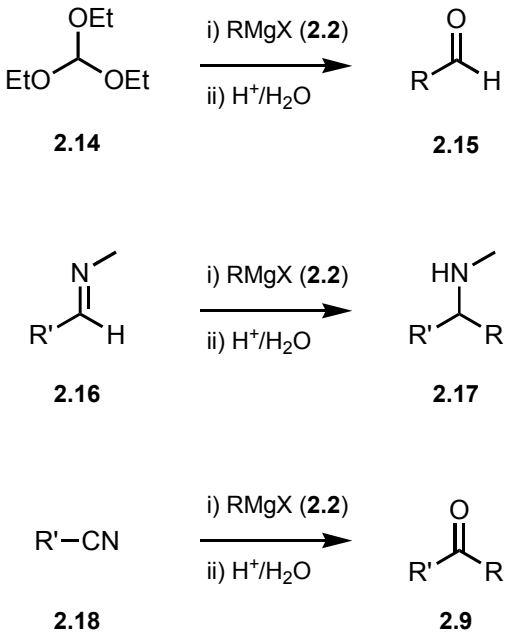
In the case where a good leaving group is present in the carbonyl compound, then the alkoxide species may break down to give a second carbonyl compound in the form of a ketone, which may then undergo addition with a second equivalent of Grignard reagent; in this way tertiary alcohols can be synthesised from esters. As the ketone that results from the breakdown of the ester adduct is more reactive than the ester itself, alternative carbonyl compounds are often employed to allow isolation of the ketone as the major product. Anhydrides and thioesters are examples of such substrates,[2] though the Weinreb amides **2.11** are widely applied for this transformation due to their ability to form chelation stabilised intermediates **2.13** that are not prone to elimination until intentionally hydrolysed.[8]



Scheme 2.3

It is not only C-O double bonds that prove reactive with the strongly nucleophilic s-block organometallics, as orthoformates (e.g. **2.14**), imines (e.g. **2.16**), and nitriles (**2.18**) are also

susceptible to such reactions, allowing access to aldehydes, amines and ketones, respectively.[2]

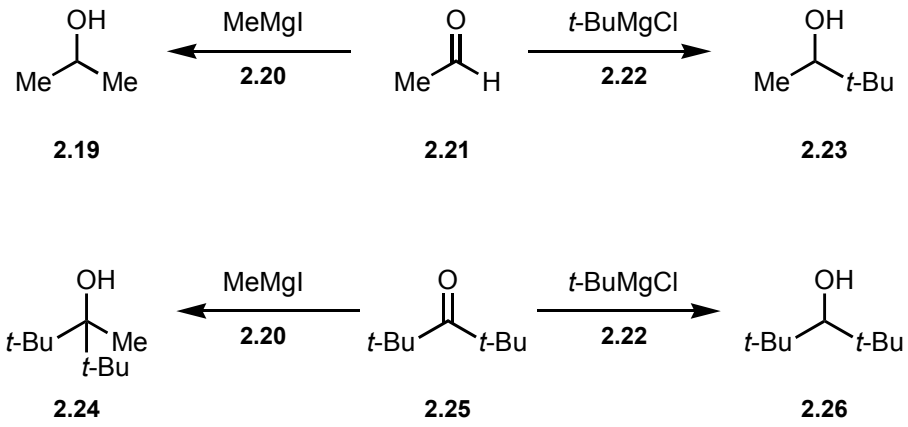


Scheme 2.4

While reactions such as those described above can be synthetically very useful, other side reactions are typically not so desirable. One of the most important factors to have an effect on the chemoselectivity of a reaction between a Grignard reagent and a carbonyl compound are the steric parameters of the reagents, especially when their combination results in a slow rate for the addition reaction.

Where steric hindrance inhibits the access of the Grignard reagent to the carbonyl then the basicity of the organometallic may become an issue, leading to enolisation, and potentially even aldol chemistry. As bulkier Grignard reagents are often also more basic, then this can compound the problem, and even when such deprotonation events are reversed upon hydrolytic work-up, they still act to consume the organometallic reagent at stoichiometric ratios.[2]

When both the carbonyl and Grignard reagent are sterically bulky, then reduction may also become a significant process. Whereas acetaldehyde **2.21** reacts to give mostly addition products (**2.19** and **2.23**) with both MeMgI **2.20** and *t*-BuMgBr **2.22** respectively, di-*tert*-butyl ketone **2.25** gives the addition product (**2.24**) with MeMgI, but large amounts of reduction product (**2.26**) when *t*-BuMgBr is the organometallic involved.[9]



Scheme 2.5

As previously detailed, the transition state approach of the nucleophile is mediated by Lewis-acidic interactions between the metal atom and the oxygen of the carbonyl group, activating the carbonyl and pre-organising the substrates ready for the transfer of the organic nucleophile in the transition state. However, in the case where **2.22** and **2.25** are involved then the approach and transfer of the *t*-Bu nucleophile itself is restricted to such a degree that an α-hydride is transferred to the carbonyl carbon in preference, thus resulting in reduction of the C=O bond. Where carbonyl reduction is a significant issue, then substitution of an organomagnesium reagent with the corresponding organolithium may sometimes improve selectivity for the desired 1,2-addition product.[2]

In cases employing α,β-unsaturated substrates with organomagnesium or organolithium reagents, then 1,2-addition typically dominates in preference to unmediated conjugate addition. Approaches taken to reverse this selectivity and so favour conjugate addition can include the use of Lewis acidic additives,[10] or *in situ* transmetallation to form "softer" organometallics.[2] Modification of the solvent composition can also have a significant effect – for example: HMPA is so highly coordinating that it acts to modify the Lewis acid character of the lithium ion and separate the organolithium ion-pair, which in combination favours increased levels of 1,4-addition.[11]

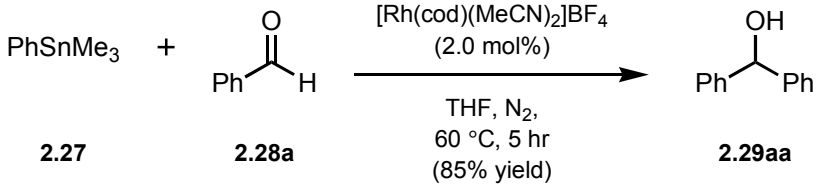
2.2. The Rhodium-Catalysed 1,2-Addition Reaction

Though undoubtedly very valuable for both lab-scale and industrial-scale processes, the high ionic character organometallic reagents suffer from drawbacks related to their handling, stability, and incompatibility with many ubiquitous functional groups (see also Chapter 1).[2, 12] As has been discussed above, these characteristics also extend to affect how such reagents behave in addition reactions with carbonyl compounds.

In contrast, boronic acids are an ideal example of main-group organometallic reagents that typically show much greater stability to moisture and oxygen.[13] Many of the reactions in which they are employed are also significantly more functional group tolerant than s-block organometallics will allow for. Again, though boronic acids do not lend themselves to reactions of an ionic nature, transmetallation circumvents this issue and allows them to be used as the source of a nucleophilic organic component in a number of important catalytic reactions. Indeed, just as rhodium complexes are able to catalyse the 1,4-conjugate addition of boronic acids with α,β-unsaturated carbonyl compounds (see Chapter 1), they are also able to effect the 1,2-addition to carbonyl compounds and their derivatives.

2.3. Precedent Using Arylstannanes

In 1997 the group of Oi and Inoue demonstrated that arylation of aldehydes could be achieved with arylstannanes under anhydrous conditions by the catalytic action of a cationic rhodium complex.[14]



Scheme 2.6

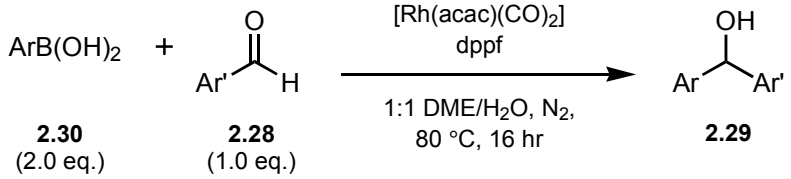
While the cationic rhodium complex $[Rh(cod)(MeCN)_2]BF_4$ was an efficient catalyst, neither the neutral rhodium complexes screened (namely Wilkinson's catalyst and $[RhCl(cod)]_2$), nor Lewis acids ($TiCl_4$ and $BF_3.Et_2O$), were effective at catalysing the arylation reaction. Five hours was sufficient time for the arylation of a number of electron poor aryl aldehydes to be obtained in > 90% yields (e.g. **2.29aa**). In contrast, electron rich aryl aldehydes required significantly longer times to achieve comparable yields, whilst aliphatic aldehydes gave only moderate yields even then. As well as being found to tolerate aromatic nitro and chloro substituents, the reaction was shown to be highly selective for aldehydes in preference to ketones. Acetophenone and heptan-2-one were not found to react under the optimised conditions, and though cyclohexanone did react, it did so much more slowly than the aldehyde substrates. Indeed, a competition reaction between one equivalent each of cyclohexanone, benzaldehyde, and trimethyl(phenyl)stannane resulted in only 4% of the arylated ketone, while diphenylmethanol was obtained in a 79% yield.

2.4. Application of Boronic Acids in the Rhodium-Catalysed 1,2-Addition Reaction

In the following year, building both on the work of Oi,[14] as well as their own work on the analogous rhodium-catalysed 1,4-conjugate addition reaction,[15] Miyaura *et al.* reported that the less toxic boronic acids could also be employed for the 1,2-addition reaction to aldehydes.[16]

2.4.1. Summary of the Central Features of the Original Reaction Protocol Employing Aryl Aldehydes

In contrast to addition reactions to aldehydes employing s-block organometallics, but akin to the use of stannanes, the reactions with boronic acids were found to be extremely tolerant of other synthetically valuable functional groups such as aromatic nitriles, halides, and esters. Though *p*-nitrobenzaldehyde was not able to be arylated under this original protocol, it too was recovered with the nitro moiety unchanged (Table 2.3, entry 9). One of the most interesting observations was that the reaction not only tolerated the presence of water, but was actually slower in its absence.



2.30 (2.0 eq.) **2.28** (1.0 eq.) **2.29**

Entry	Ar		Ar'		Yield (%)[a]
1	Ph	**2.30a**	Ph	**2.28a**	92
2	Ph	**2.30a**	*p*-$F_3CC_6H_4$	**2.28e**	97
3	Ph	**2.30a**	4-$MeCOC_6H_4$	**2.28b**	93
4	Ph	**2.30a**	4-MeC_6H_4	**2.28c**	48
5	4-MeC_6H_4	**2.30c**	4-NCC_6H_4	**2.28f**	99
6	Ph	**2.30a**	4-NCC_6H_4	**2.28f**	97
7	*p*-FC_6H_4	**2 30d**	4-NCC_6H_4	**2.28f**	52
8	4-$MeCOC_6H_4$	**2.30b**	4-NCC_6H_4	**2.28f**	< 1 [b]
9	Ph	**2.30a**	*p*-$O_2NC_6H_4$	**2.28g**	< 1 [b]

3.0 mol% rhodium complex and ligand, boronic acid (2.0 mmol), aldehyde (1.0 mmol), in 6.0 ml solvent.

[a] Isolated yields after silica-gel chromatography.

[b] Aldehyde was recovered unchanged.

Table 2.3

Analogous to the conceptual model of nucleophilic attack at the carbonyl carbon by an organometallic possessing high ionic character, it was found that the electronics of both "coupling" partners could be seen to have a noticeable effect on the rate and conversion of the reaction. So, whilst electron withdrawing groups on the aldehyde (Table 2.3, entries 1-3) and electron donating groups on the boronic acid (entry 5) both tended to result in higher yields, the reverse of that situation was detrimental – resulting in less electrophilic carbonyls, and less nucleophilic derivatives of the organometallic component (entries 4, 8 & 9).

Again consistent with this analogy, the reaction was noted to be selective for the more reactive aromatic aldehyde functionality in 4-acetyl benzaldehyde, with the aromatic ketone being unreactive (Table 2.3, entry 3). Indeed, though the majority of the aryl aldehydes were arylated in high yields, to ensure a comparable yield even with aliphatic aldehydes such as cyclohexanecarbaldehyde required an increase in the reaction temperature from 80 to 95 °C. The lower reactivity of aliphatic aldehydes was attributed to their lower electrophilicity at the carbonyl carbon.[16] The reaction also tolerated an *ortho*-methyl substituent on the arylboronic acid, although the mesityl analogue proved too bulky. Though arylboronic acids were the focus of the report, one example of the alkenylation of an aryl aldehyde was also reported, and with retention of the ene geometry.

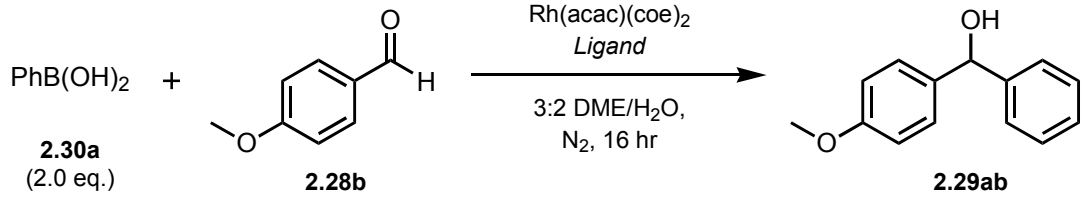
It was also noted that the choice of phosphine ligand was critical in achieving reasonable levels of conversion. For bidentate bisphosphines there appeared to be a correlation between increased bite angle and greater activity of the rhodium-phosphine complex formed, which was also noted in the corresponding 1,4-addition reaction.[15] Thus it was shown that DPPE<DPPP<DPPF, although DPPB proved to be an exception to this trend, being between the activities of the DPPE and DPPP ligated complexes.

2.4.2. Importance of Ligand Identity

Although the monodentate ligands screened in the original 1998 publication gave particularly poor results,[16] a later reinvestigation published by Miyaura's group in 2000 showed that both the electronic character of the ligand, as well as its stoichiometry relative to the metal centre were of great importance.[17]

While a ratio of 1:1 bidentate phosphine to rhodium had been employed throughout the initial publication, all monodentate phosphines had been used at a ratio of 3:1 with the rhodium pre-catalyst. It was subsequently shown that under the same reaction conditions as had been developed previously for the bisphosphines, the monodentate phosphines were indeed effective in forming highly active rhodium-phosphine complexes when employed at

lower stoichiometries. In particular, bulkier and more highly basic phosphines, as exemplified by *t*-Bu_3P, were then shown to out-compete the bidentate ligands for most substrate combinations – allowing for complete conversions to be obtained with many aryl aldehydes, even in reactions conducted at room temperature.



Entry	Ligand (eq.)[a]	Yield (%) at 50°C	Yield (%) at 80°C
1	DPPF (1)	20	85
2	Me_3P (1)	24	12
3	PPh_3 (1)	33	48
4	*i*-Pr_3P (1)	88	86
5	Cy_3P (1)	50	83
6	*t*-Bu_3P (1)	99 (99)[b]	79
7	*t*-Bu_3P (2)	67	77
8	*t*-Bu_3P (3)	57	-

[a] Equivalents of ligand given in parentheses are relative to the loading (3.0 mol%) of rhodium pre-catalyst.

[b] Reaction performed at room temperature.

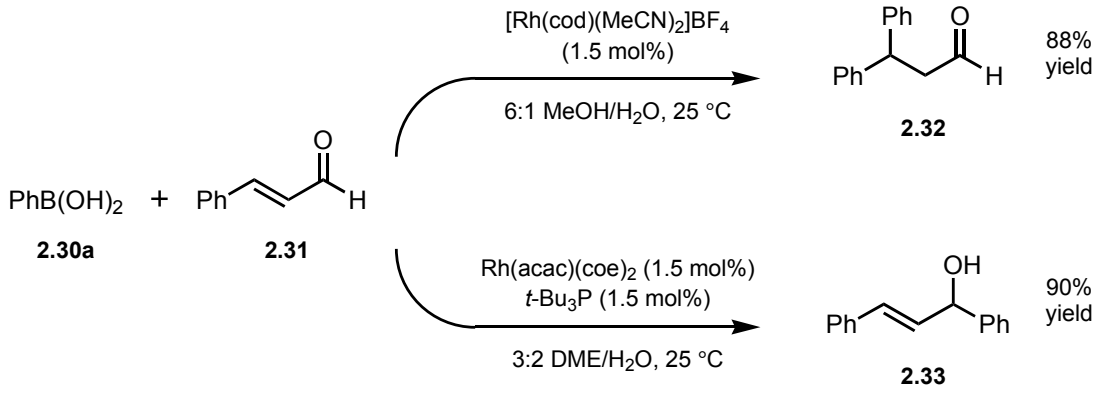
Table 2.4

Thus a 1:1 ratio of *t*-Bu_3P/Rh(acac)$(coe)_2$ was selected as the optimum system due to its high activity at ambient temperatures. Using this system even *p*-nitrobenzaldehyde, which had previously proved unreactive in the DPPF ligated system (Table 2.3, entry 9) was able to be arylated at room temperature in 94% yield. It is worth noting that certain of the monodentate phosphines, including *t*-Bu_3P, performed worse at 80°C than at lower temperatures, which was attributed to thermally induced degradation. For this reason *i*-Pr_3P was employed with less reactive substrate pairings that in turn required higher temperatures.

Miyaura noted that the reactions using monodentate phosphines seemed to be less significantly affected by electronic effects of the coupling partners. Though the reactions employing bisphosphines may simply have not reached completion in such cases, it was apparent that the use of bulky and more basic monophosphines at a ligand/pre-catalyst ratio of 1:1 was overall still more effective for the majority of substrates. From these observations and the results of the ligand screen it was postulated that the optimal choice of ligand should be electron rich enough so as to make the rhodium-carbon bond more labile, thus promoting

aryl transfer to the carbonyl carbon. However, such a ligand should also allow the rhodium centre to maintain sufficient Lewis-acidity such that the preceding step involving coordination of the aldehyde to the rhodium-aryl complex is itself not unfavourable. Bulky and electron rich monodentate phosphines were therefore suggested to allow for such increased nucleophilicity of the Rh-C substituent, but by employing them at an equimolar ratio to the rhodium centre it was also suggested that an appropriately balanced electronic environment could be maintained, in combination with a greater degree of coordinative unsaturation, so as to overall still favour coordination of the carbonyl compound.

To demonstrate how distinct the 1,2- and 1,4-addition reactions are in terms of electronic demands at the metal centre, cinnamaldehyde **2.31** was used to show that α,β-unsaturated aldehydes could be targeted for selective direct or conjugate addition, through modification of the reaction conditions (Scheme 2.7). Whilst the standard conditions using *t*-Bu_3P gave the 1,2-addition product **2.33** in 90% yield, in the absence of phosphine ligand the cationic rhodium complex $[Rh(cod)(MeCN)_2]BF_4$ was able to give 1,4-addition product **2.32** in a similar 88% yield.

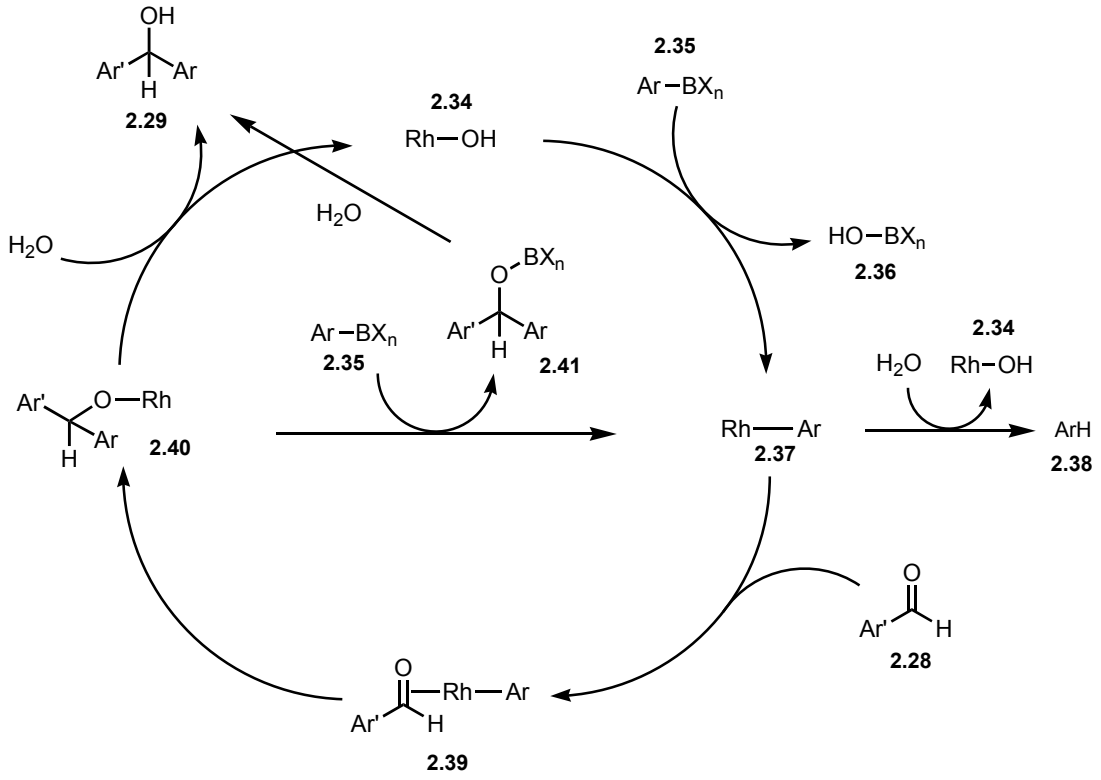


Scheme 2.7

2.4.3. Catalytic Cycle & Mechanistic Details

The proposed catalytic cycle for the rhodium(I) catalysed 1,2-addition reaction for an aldehyde and organoboronate or organoborate is shown in Scheme 2.8.[18, 19] In the presence of water a hydroxorhodium complex **2.34** undergoes transmetallation with a boronate (or analogous borate) **2.35** to yield the aryl-rhodium **2.37** and corresponding by-product, typically boric acid **2.36** ($BX_n = B(OH)_2$). At this point the coordination of the aldehyde is required for the continuation of the 1,2-addition catalytic cycle. For this to occur the aldehyde most likely displaces a labile solvato ligand, allowing ready access to a coordination site at the metal centre. This initial coordination occurs through one of the lone

pairs of the carbonyl oxygen, yielding a κ^1 σ-O-coordinated species. It is postulated that subsequent rearrangement to an η^2 π-C,O-coordinated species (depicted as **2.39**) is first necessary for the aryl migration step to take place.[19]

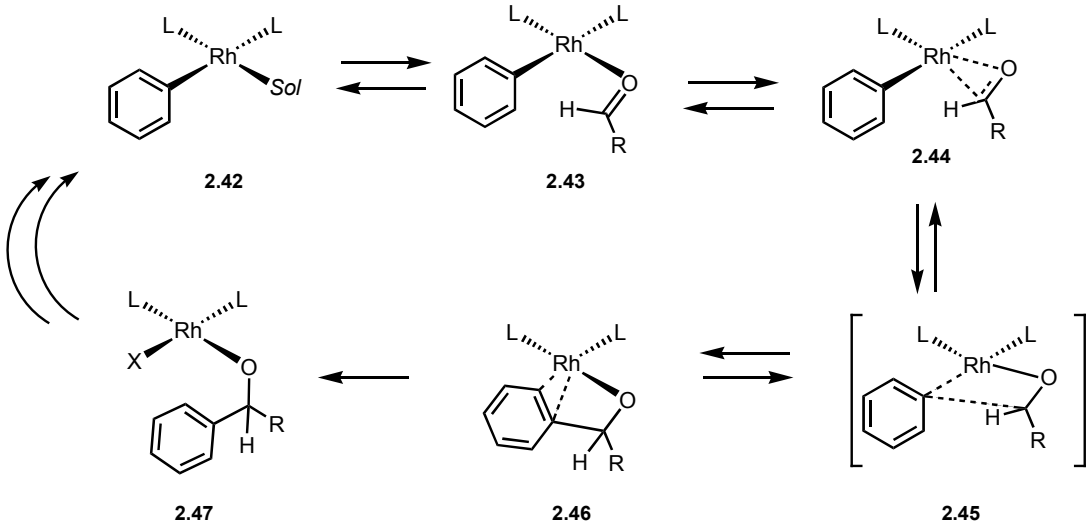


Scheme 2.8

It is worth noting that aryl-rhodium species of type **2.37** formed under such conditions are typically quite resistant to hydrolysis. However, although under basic reaction conditions the hydrolytic cleavage of the boronic acids themselves are a known source of protodeboronation product **2.38**, the rate of subsequent aldehyde coordination must still be high enough so as to avoid significant attrition of the organometallic coupling component through metal mediated hydrolytic processes, i.e. **2.37** to **2.38**.[13, 20]

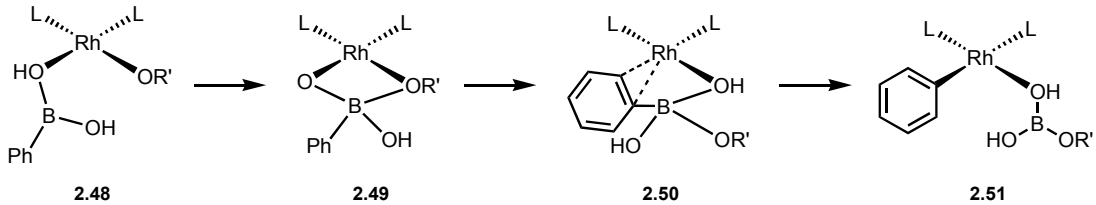
DFT analysis suggests that once coordination of the aldehyde has occurred, the aryl migration to the carbonyl carbon is then rate limiting, having a high kinetic free energy barrier relative to the rest of the catalytic cycle.[19] It is also suggested that the overall formation of the η^2-aryl coordinated alcoholate species (**2.46**) from the solvato-coordinated rhodium-aryl (**2.42**), though kinetically hindered, is reversible under coordinating reaction conditions according to the thermodynamic analysis (Scheme 2.9).[19] This has been demonstrated experimentally, with β-aryl eliminations from rhodium(I) alkoxides generating

rhodium-aryl and the corresponding ketone.[21] Thus, with aryl ketone substrates there is the potential for aryl scrambling to occur in these reactions.[22]



Scheme 2.9

However, such a process is disfavoured when either sufficient boronic acid or water are available for completion of the catalytic cycle, in which case substitution of the η^2-aryl moiety in **2.46** is readily achieved (forming the relevant variant of **2.47**). Under base free anhydrous conditions this proceeds with the coordination of the boronic acid, which in turn allows for an alcoholate migration to the electrophilic boron centre. This results in the formation of an activated borate (depicted as **2.49**), which being already coordinated to the metal centre, is then set up to undergo transmetallation (**2.49** to **2.51**, *via* **2.50**). Once this has occurred, ligand substitution with solvent liberates the borate ester and regenerates the rhodium-aryl species **2.42**, so bypassing the hydroxorhodium species **2.34** implicated in the presence of water.



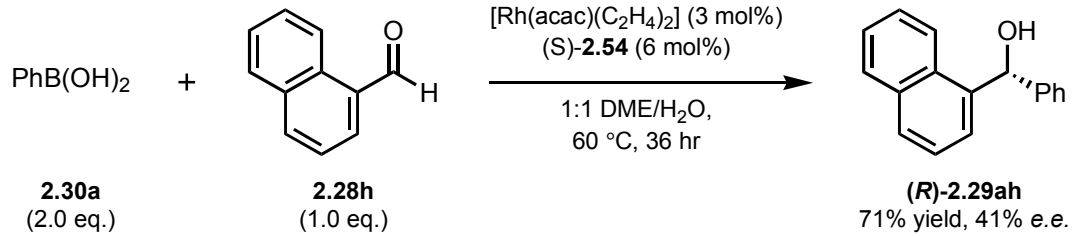
Scheme 2.10: Under base free anhydrous conditions for RCHO and phenylboronic acid then OR' = Ph(R)(H)CO; while for the analogous reaction in aqueous basic media then typically OR' = OH.

In contrast to the rhodium-aryl complex, rhodium alkoxide species of this type are much less stable,[20] and so in aqueous media the rhodium-alkoxide is readily hydrolysed to yield the free alcohol. Aqueous or aqueous-basic conditions promote the formation of

hydroxorhodium species, which have been shown to be highly active for the transmetallation process with boronic acids (as discussed in Chapter 1).[23]

2.4.4. Asymmetric Variants

Highly enantioenriched diarylmethanols are valuable substrates, being important moieties in many drug substances or their precursors.[24] Approaches to their synthesis include asymmetric additions of classical organometallics, or achiral additions followed by sequential redox manipulations such as asymmetric Noyori transfer-hydrogenation protocols.[24] However, these methods still suffer the restrictions imposed on substrate scope by the use of classical organometallics, or the use of additional synthetic manipulations to manipulate the stereocentre. Development of asymmetric 1,2-addition methodologies using boronic acids, to complement those involving classical organometallics, has therefore been a central focus in this field. Indeed, Miyaura's initial report very briefly detailed preliminary attempts to determine an appropriate optically active ligand for this reaction.



Scheme 2.11

Despite demonstrating high levels of enantioselectivity in the analogous rhodium-catalysed 1,4-addition reaction using enone substrates, (*S*)-BINAP (**2.52**) yielded only racemic diarylmethanol **2.29ah**, with the same being true when another bidentate phosphine (*S,S*)-diop **2.53** was employed. However, the monodentate phosphine (*S*)-MeO-MOP **2.54** was found to induce a modest enantioselectivity of 41% *e.e.* (Scheme 2.11). For much of the first decade after Miyaura's initial report, the literature detailing the asymmetric variant of this reaction employing aldehydes was dominated by reports of, at best, modest enantioselectivities, and with little scope for variation of the substrates in order to maintain such selectivities.[25, 26] However, a number of recent reports have exhibited enantioselective additions to multiple substrates, at levels of greater than 80% *e.e.*

One of the earliest reports of a system demonstrating such features was that reported in 2006 by Zhou and co-workers, who employed the spirocyclic monophosphite ShiP ligand **2.55a** with $[RhCl(C_2H_4)_2]_2$ as the rhodium source.[27] Under their optimised conditions they obtained yields of 90% or greater, with *e.e.*'s in the range of 62-87%. However, whilst electronic

factors seemed less important, they did note a general correlation between higher levels of enantioselectivity and steric bulk *ortho*- to the aldehyde substituent. The most apparent example of this effect being observed in the coupling of phenylboronic acid with 2- or 4-chloro benzaldehyde, which resulted in 82% *e.e.* and 62% *e.e.*, respectively.

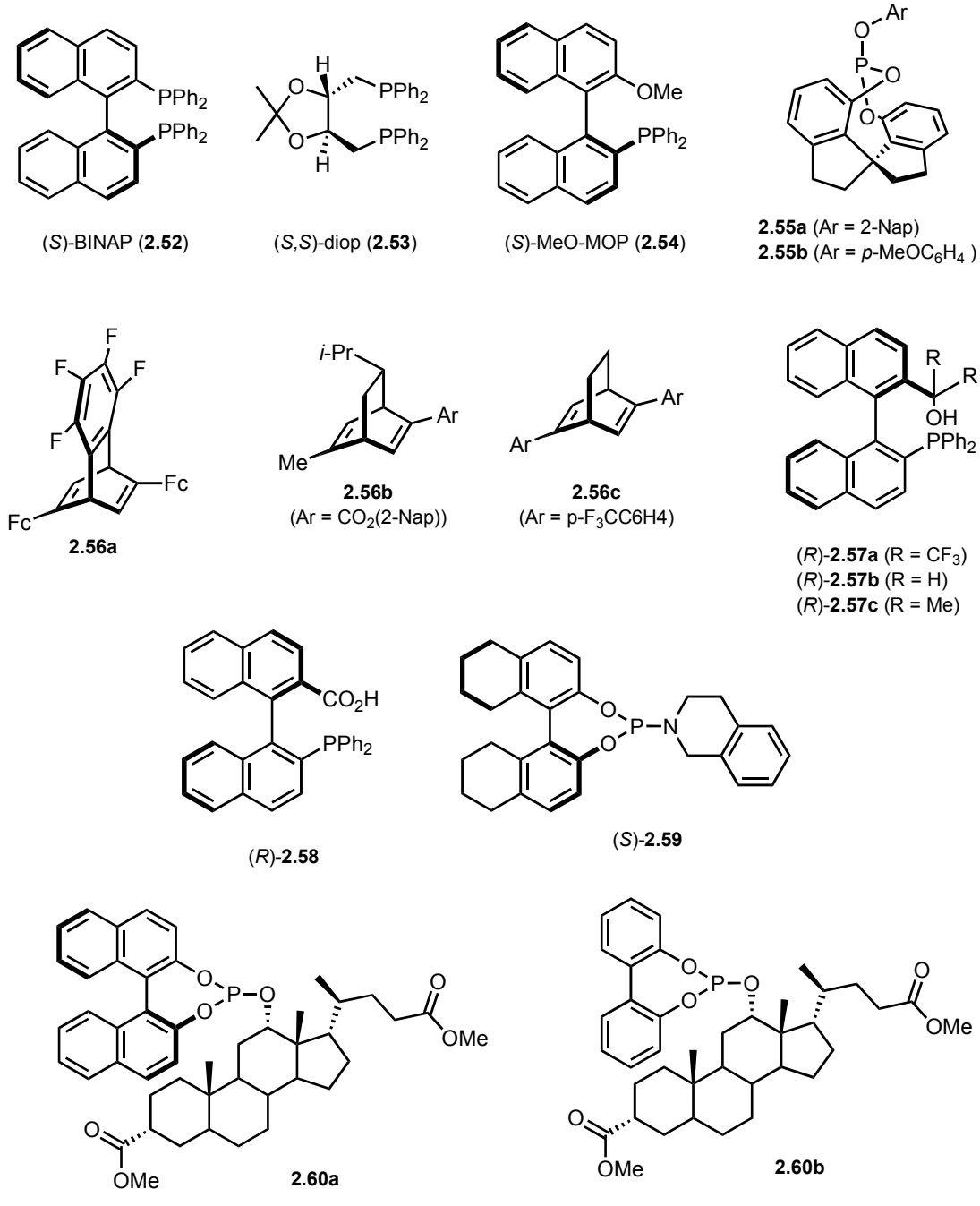
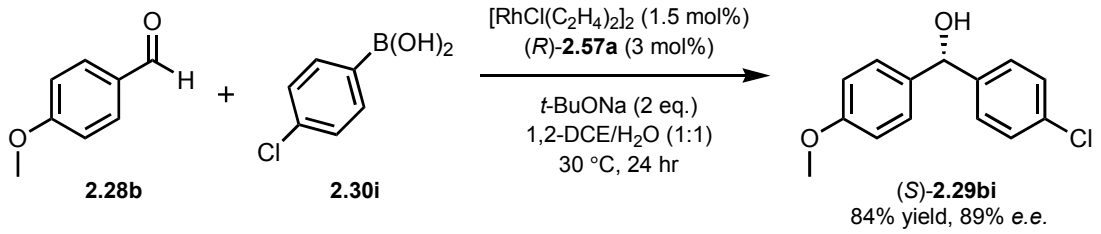


Figure 2.1

Hayashi *et al.* have reported the synthesis and application of various chiral diene ligands[28, 29] (chiral olefins as ligands in asymmetric catalysis have also been specifically reviewed[30]), including **2.56a**, which induces high enantioselectivities in the arylation reactions of aryl

aldehydes with boronic acids.[31] Again, steric bulk at the *ortho*- position of the aldehyde was important, though in contrast to the use of spirocyclic ligand **2.55a**, the best results were achieved when *ortho*- substituents were present on both components, resulting in *e.e.*'s in the range of 84-94%.

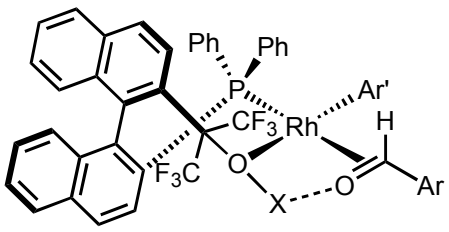
As far as the author is aware, at the time of writing the highest level of enantioselectivity obtained under the action of a chiral rhodium complex is that reported by Amii *et al.* Using a novel mono-phosphine binaphthyl ligand bearing a fluoro alcohol (**2.57a**) they were able to obtain moderate to good yields of diarylmethanols with consistently high *e.e.*'s (c. 80-90%) for a range of aryl aldehyde substrates. It was also noted that, unlike other recent reports – including those detailed above – there was no requirement for *ortho*- substituents on either of the aryl rings in order to maintain such high enantiodiscrimination (Scheme 2.12).[32]



2.28b **2.30i** (*S*)-**2.29bi**
84% yield, 89% *e.e.*

Scheme 2.12

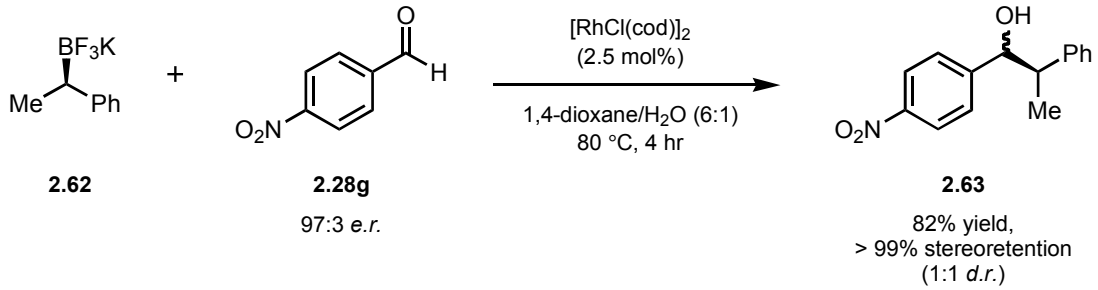
The fluoro alcohol moiety was found to be critical to the activity of the catalyst. For analogues where the moiety was replaced by either a non-fluorous primary alcohol (**2.57b**), tertiary dimethyl alcohol (**2.57c**), or carboxylic acid (**2.58**), significant or complete erosion of both the yields and enantioselectivities resulted. The authors propose that hydrogen bonding or Lewis acid activation between the "*weakly*" acidic fluoro alcohol proton (or sodium salt formed *in situ*) and the carbonyl oxygen, activates the aldehyde and organises the coordination environment such that the aryl transfer step occurs in a highly enantioselective manner (Figure 2.2).



2.61
(X = H or Na)

Figure 2.2

Finally, though the stereocentre is not generated during the rhodium-catalysed reaction, Aggarwal *et al.* have recently reported the elegant use of enantioenriched secondary benzylic trifluoroborate salts for the rhodium-catalysed 1,2-addition with aldehydes (Scheme 2.13).[33] The reactions employing the pinacolate ester involved the use of CsF, and a non-rhodium mediated addition pathway was observed to result, though with a significant degree of racemisation at the benzylic centre. In contrast, the trifluoroborate salts did not require additional base, and their rhodium-catalysed additions proceeded with very high levels of stereoretention.

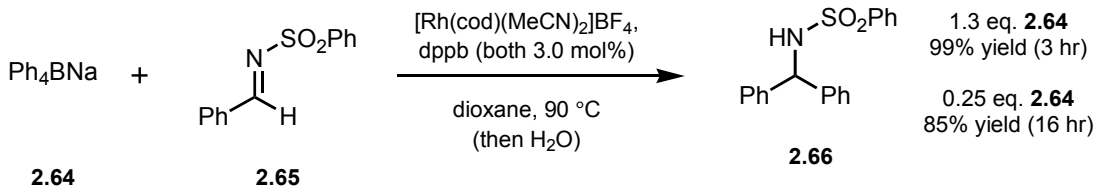


Scheme 2.13

2.5. Imine Substrates

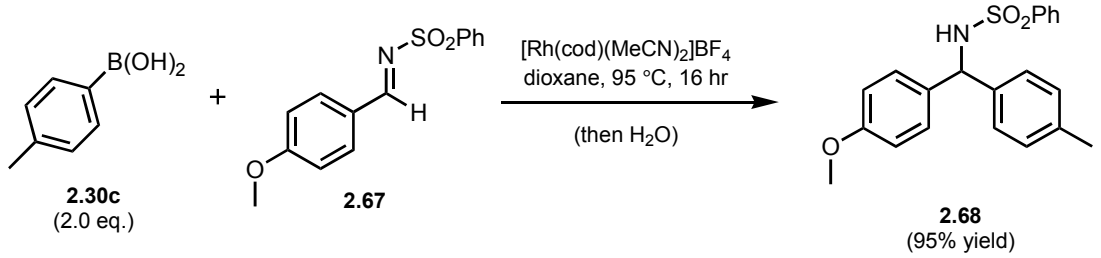
In 2000 Miyaura showed that akin to the corresponding addition reactions employing s-block organometallics, imines can also be arylated in the rhodium-catalysed 1,2-addition reaction. The initial report involved the use of sodium tetraphenylborate under anhydrous conditions, as attempts to employ boronic acids under similar conditions to those used for the aldehydes resulted in hydrolytic cleavage of the imine, and ultimately the arylated aldehyde was the major product.[34]

Although the reaction was confirmed to require the rhodium complex, no reaction occurring in its absence, $[Rh(cod)(MeCN)_2]BF_4$ was found to be active in the absence of additional phosphine ligands – though optimal results were obtained in combination with DPPB. The ability of tetraphenylborate to act as a viable source of up to four equivalents of the phenyl moiety was confirmed by the observation that, even at a loading of 0.25 equivalents of borate, the arylation product was still obtained in high yield – although an extended reaction time was necessary in such instances (Scheme 2.14).



Scheme 2.14

However, the lack of functionally diverse and commercially available tetraarylborates led Miyaura and co-workers to reassess the use of boronic acids in the reaction. They found that despite the ability for the boronic acid to form the corresponding boroxine and thus generate water *in situ*, by simply using anhydrous dioxane as the solvent system, arylation of the imine could be achieved in high yield and without generating any detectable by-products *via* the hydrolysis reaction (Scheme 2.15). Indeed, boronic acids were in fact found to react under anhydrous neutral conditions similar to those used for the tetraarylborates, while boronic esters required the addition of base to give correspondingly high yields, with NEt_3 proving the optimal choice. The labile boronic esters of 1,3-propanediol and 1,2-ethanediol proved to be most reactive, whilst the derivates of catechol, diethanolamine, and most especially pinacol, gave moderate to poor yields.



Scheme 2.15

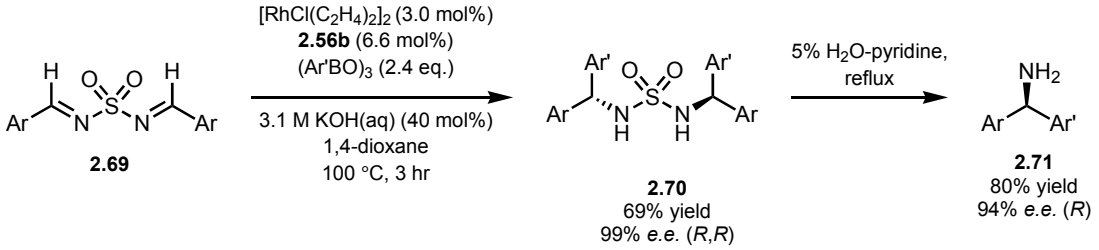
The nature of the *N*-substituent was also critical to high yields, with *N*-Bu, *N*-Ph and *N*-Bn all giving poor results. In contrast the more electron withdrawing *N*-benzoyl and *N*-sulfonyl groups typically gave high yields, with the electronic characteristics of the *N*-substituent dominant over those of the aryl aldehyde substituent. Again, both reports noted the same electronic effects as were seen with the aryl aldehydes, and similar to aliphatic aldehydes those imines derived from alkyl aldehydes gave particularly poor results, with no significant improvements resulting from an extension of the reaction time.

2.5.1. Asymmetric Variant Using Imines

Just as non-racemic diarylmethanols are of biological and pharmacological importance, so too are non-racemic diarylmethylamines. Catalytic asymmetric arylations of imines with

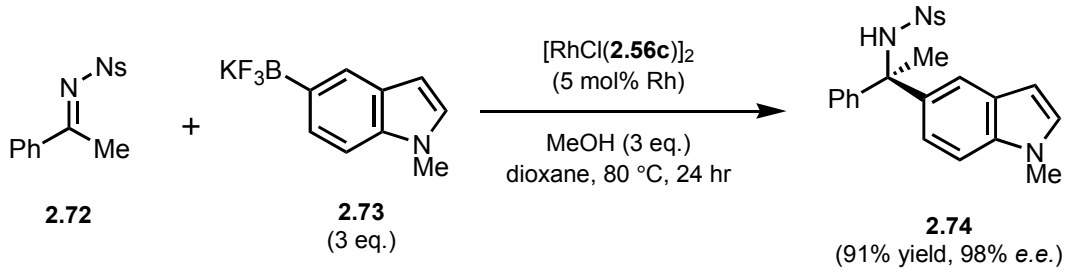
organoborons have recently been reviewed in detail,[35] and as such this section details only some of the more significant reports of relevance.

Woodward and co-workers have recently reported the use of one Hayashi's chiral dienes **2.56b** in the asymmetric double arylation of bis-sulfamyl imines **2.69** with boroxines.[36] Moderate to good yields were achieved using aryl boroxines, and while lithium trimethoxy(phenyl)borate gave a comparable result to the corresponding boroxine, the use of either boronic acid or trifluoroborate salt resulted in little or no conversion, respectively. High *e.e.*'s, typically > 99%, were recorded for the major diastereomer, with diastereoselectivities of ~ 10:1 to 32:1 (*rac*:*meso*).



Scheme 2.16: (Ar = Ph, Ar' = *p*-FC_6H_4)

One of the most notable features of this work is the use of the bis-sulfamyl imines themselves, which act as an easily cleaved, low molecular weight, *N*,*N'*-protecting group. Thus, in contrast to other *N*-protected imine derivatives typically employed, the double arylation potentially results in magnified stereoselectivities, as well as greater overall atom economy and broader functional group tolerance. Indeed, a number of product amines were isolated in moderate to excellent yields and *e.e.*'s generally in the range of 85-95%, by deprotection of the sulfamyl group using 5% H_2O-pyridine.



Scheme 2.17

The Hayashi group's chiral diene ligands have been successfully employed in the rhodium-catalysed 1,4- and 1,2-addition reactions (see Chapter 1 and discussions above, respectively), including the arylations of *N*-tosyl[37] and *N*-nosyl[38] aldimines using arylboroxines. More

recently Hayashi has disclosed the use of the chiral diene ligand **2.56c** for the arylation of *N*-tosyl ketimines using tetraarylborates,[39] and also the addition to both *N*-tosyl and *N*-nosyl ketimines using trifluoroborates.[40] Though trifluoroborates were initially found to give poor results in comparison to the tetraarylborates, relatively slight changes to the reaction conditions allowed comparable activities, typically with high yields and excellent enantioselectivities (e.g. Scheme 2.17). The use of trifluoroborate salts also allowed for the addition of an alkenyl moiety, while it was noted that efforts to synthesise the corresponding tetraalkenylborates failed. Finally, the *N*-nosyl group could also be deprotected under mild conditions with a high degree of stereoretention.

2.6. Substrate Scope Beyond Imines and Aldehydes

Though aryl aldehydes and aldimines in particular are now widely amenable to these protocols, progress on the rhodium-catalysed arylations of substrates such as aryl methyl ketones has so far been much slower. As with classical organometallics the addition to a more sterically demanding carbonyl carbon, with a concomitantly lower electrophilicity, makes such reactions more difficult.[41]

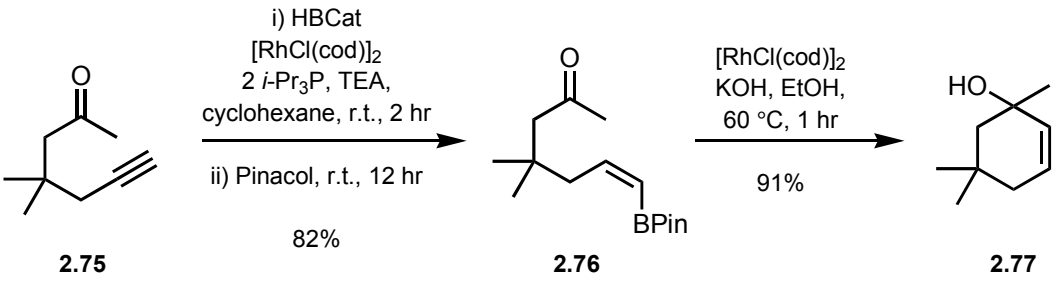
While Inoue and co-worker's original rhodium-catalysed 1,2-addition protocol employing arylstannanes showed a single example of a cyclic ketone being arylated in low yield after an extended reaction period (i.e. cyclohexanone, 29% yield), no reaction was reported to have occurred when acetophenone or heptan-2-one were employed.[14] Additionally, it has been discussed in a number of publications employing boronic acids (e.g. by the groups of Frost[42] and Furstner[43]), including Miyaura's original report,[16] that selective arylation of the aldehyde carbonyl was observed when acetyl substituted benzaldehyde was employed as a substrate. And though a relatively extreme example of a less reactive ketone in this context, it is noteworthy that Feringa *et al.* have reported the successful use of acetone as solvent for the 1,2-addition reactions involving such diverse substrates as aldimines,[44] isatins,[45] and trifluoromethyl ketones.[46]

Thus, many of the most demanding substrate types to have been successfully used in 1,2-additions of this kind are activated by strongly electron withdrawing substituents, conjugation with neighbouring systems, the release of ring-strain upon successful addition, or a combination of more than one of these factors.

2.6.1. Intramolecular Additions

The first report of the rhodium-catalysed 1,2-addition of a boronic acid derivative with a ketone was made by Miyaura in 2002, which involved the intramolecular addition of a

tethered boronic ester to a dialkyl ketone (**2.76** to **2.77**).[47] The tethered ketone substrates were prepared by a rhodium-catalysed hydroboration reaction of the precursor alkynes (**2.75**), making them particularly straightforward to synthesise. In comparison, the corresponding use of an aldehyde would require protecting group manipulations, whilst the ketone moiety is unaffected by such conditions.



Scheme 2.18

2.6.2. α-Dicarbonyl Compounds

One of the most common substrate classes to be employed for this reaction are the α-dicarbonyl compounds, which include 1,2-diketones **2.78**, α-keto esters **2.79**, oxalates **2.80**, and isatins **2.81**.

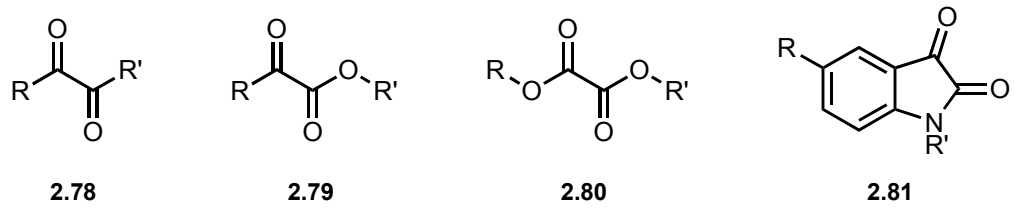
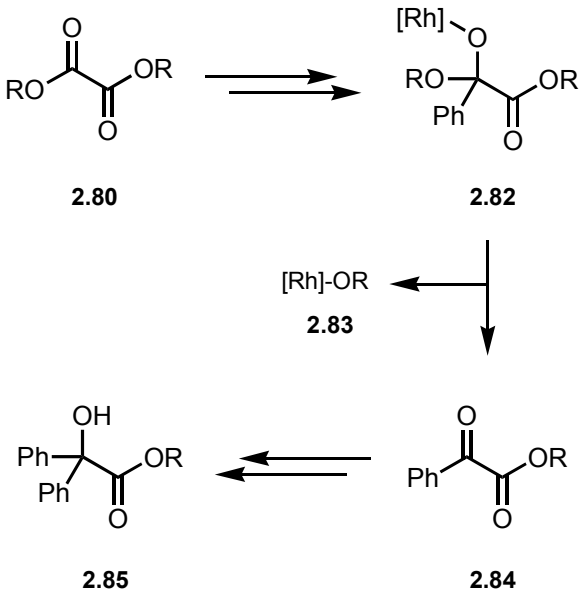


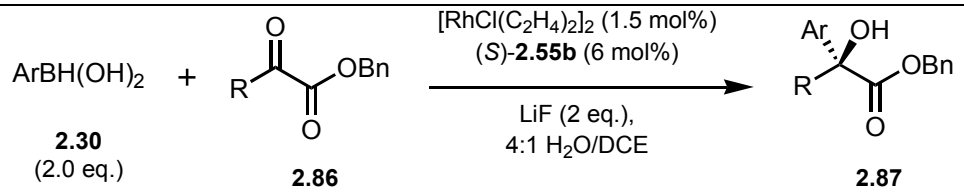
Figure 2.3

In 2007 Miura, Satoh, and co-workers reported the use of sodium tetraphenylborate for the diarylation of oxalates (**2.80**) in high boiling point non-polar solvents at reflux, with xylenes being the best of those screened.[48] The di-*tert*-butyl ester proved too bulky, though methyl, ethyl and *n*-butyl esters were amenable to the diarylation, yielding the corresponding α-hydroxydiarylacetates, **2.85**. They proposed that the first addition to the ester results in rhodium-alkoxide **2.82**, which then eliminates **2.83** (leaving it free to re-enter the catalytic cycle by undergoing a further transmetallation reaction) to give the α-keto ester **2.84**, which in turn undergoes a second arylation to yield **2.85**. Reactions performed directly on either a 1,2-diketone or α-keto ester (benzil – **2.78**, R = R' = Ph; or ethyl benzoylformate – **2.79**, R = Ph, R' = Et; respectively) both result in mono-arylation products analogous to the di-arylation product **2.85** observed with the oxalates. In addition this is akin to the

corresponding diarylations of esters using Grignard reagents, and indeed the corresponding reaction of diethyl oxalate with analogous organomagnesium reagents has been reported.[49]



Scheme 2.19



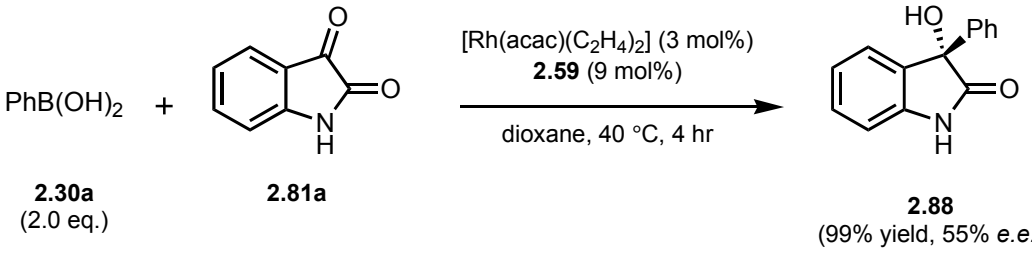
Entry	Ar	R	Time (hr)	Temp.	Yield% (*e.e.*%)
1	Ph	*p*-ClC_6H_4	12	r.t.	95 (84)
2	Ph	*p*-ClC_6H_4	48	0 °C	81 (90)
3	Ph	*p*-$F_3CC_6H_4$	48	0 °C	93 (91)
4	Ph	*p*-$MeOC_6H_4$	36	r.t.	93 (86)
5	*p*-MeC_6H_4	*E*-styryl	60	0 °C	77 (93)
6	*m*-MeC_6H_4	*E*-styryl	60	0 °C	75 (91)
7	*o*-MeC_6H_4	*E*-styryl	32	r.t.	92 (75)
8	*p*-$MeOC_6H_4$	*E*-styryl	60	0 °C	75 (90)
9	*p*-$F_3CC_6H_4$	*E*-styryl	32	r.t.	61 (90)

Table 2.5

In 2008 Zhou *et al.* demonstrated the addition of arylboronic acids to α-keto esters and β,γ-unsaturated α-keto esters (Table 2.5) using another of their spirocyclic monophosphite ShiP ligands, **2.55b**.[50] The benzyl ester was selected as it resulted in high *e.e.*'s without compromising the yields. Though the electronics had minimal impact on the *e.e.* (entries 2-3), analogous to the electronic effects observed in the arylation of aryl aldehydes the electron poor α-oxo(aryl)acetates are more reactive than their electron rich counterparts. Thus, the presence of electron withdrawing groups allow the reaction temperature to be reduced to 0 °C, and so give improved enantioselectivities (entries 1-4). *Ortho*- and *meta*- substituents were not tolerated on either **2.86** (R = Ph) or the boronic acid, with only trace amounts of product generated even after 48 hours at 40 °C. However, using the less hindered *E*-benzyl 2-oxo-4-phenylbut-3-enoate (**2.86**, R = *E*-styryl) did allow for the use of *ortho*- and *meta*-substituted arylboronic acids, though the *ortho*- derivatives still required the reaction to be run at room temperature, and impacted both the yields and *e.e.*'s (Table 2.5, entries 5-7). Again, though not important in determining the enantioselectivity of the reaction, the electronics of the boronic acid were important in determining the rate of reaction (entries 8-9).

The groups of Hayashi[51] and Feringa[45] independently reported the enantioselective 1,2-addition reaction of boronic acids with isatins **2.81**, which possess an activated α-keto moiety, so yielding 3-substituted 3-hydroxy-2-oxindoles.

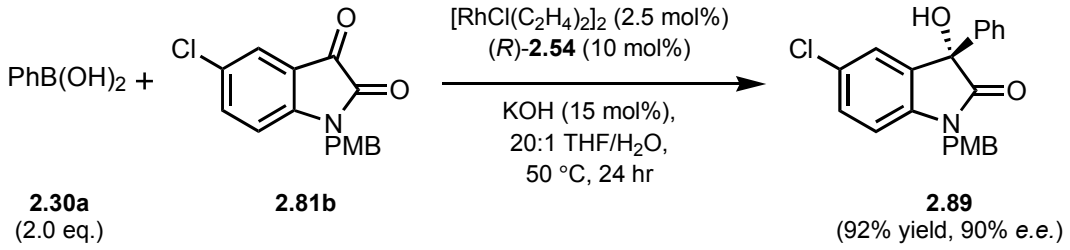
Having successfully demonstrated that triphenyl phosphite was an effective ligand for the achiral variant, Feringa *et al.* then employed the axially chiral phosphoramidite **2.59** under similar anhydrous and base free conditions, which allowed for the synthesis of 3-phenyl-3-hydroxyoxindole **2.88** in effectively quantitative yield and moderate *e.e.* (Scheme 2.20).



Scheme 2.20

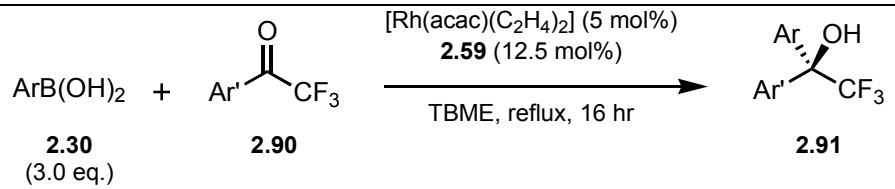
In contrast, Hayashi *et al.* employed aqueous basic conditions with *N*-substituted isatins which, in combination with MeO-MOP ligand ((*R*)-enantiomer of **2.54**; which was originally shown by Miyaura to be an effective ligand in asymmetric 1,2-additions[16]), allowed for

significantly higher *e.e.*'s to be obtained (Scheme 2.21). Alkenylboronic acids gave similarly high yields and enantioselectivities as arylboronic acids did, thus allowing for tertiary allylic alcohol 2-oxindole derivatives to be synthesised. Similar to the observations made by Zhou,[50] *ortho*- substituted arylboronic acids resulted in reduced *e.e.*'s, although in this instance no significant impact on the yield of the arylation reaction was noted.



Scheme 2.21

2.6.3. Trifluoromethyl Ketones



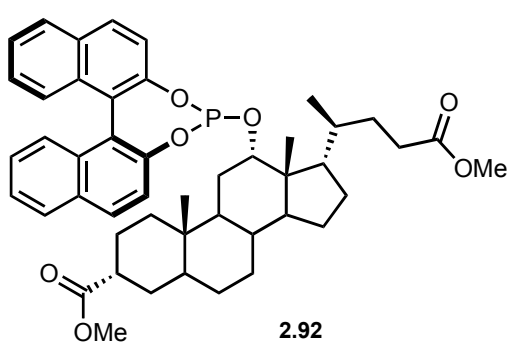
Entry	Ar	Ar'	Yield% (*e.e.*%)
1	*p*-ClC_6H_4	Ph	28 (72)
2	Ph	*p*-ClC_6H_4	90 (79)
3	*p*-$MeOC_6H_4$	Ph	50 (68)
4	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	96 (68)
5	*p*-Tolyl	*p*-ClC_6H_4	91 (83)
6	*m*-Tolyl	*p*-ClC_6H_4	91 (76)
7	*o*-Tolyl	*p*-ClC_6H_4	40 (50)
8	2-Nap	*p*-ClC_6H_4	69 (76)

Table 2.6

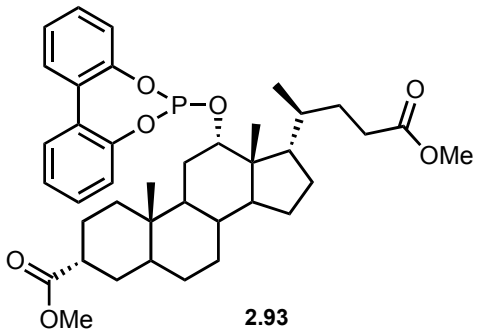
As discussed in Section 2.1, despite greater steric hindrance, due to the very high electronegativity of fluorine α,α,α-trifluoromethyl carbonyl compounds are significantly more electrophilic at the carbonyl carbon than are simple methyl analogues. In addition, the CF_3 moiety is a valuable bioisostere in drug design[52] (a bioisostere being a chemical moiety that is equivalent enough in terms of certain properties – e.g. size, charge, or hydrophobicity – such that it can substitute for another chemical moiety, not just in one compound, but

rather across a diverse range of compounds, and while simultaneously maintaining a variety of bioactivities associated with the moiety which it replaces[53]), and thus α,α,α-trifluoromethyl ketones are ideal as activated substrates with potential synthetic utility.

Feringa *et al.* reported that a rhodium complex formed with axially chiral phosphoramidite **2.59** is also effective for the arylation of trifluoromethyl ketones with arylboronic acids.[46] As with their work on isatins, these reactions were also conducted without base and under anhydrous conditions, though in this instance in refluxing TBME (b.p. 55 °C). It was especially important that the ketone was activated with at least the moderately electron withdrawing *p*-Cl substituent, which gave better yields than the unsubstituted phenyl trifluoromethyl ketone. Yet overall, the electronic parameters were found to be more important in determining the yield rather than the enantioselectivity (Table 2.6, e.g. compare entries 3 and 4). With the exception of *o*-tolylboronic acid, which resulted in low a yield and *e.e.* (entry 7), moderate to excellent yields and *e.e.*'s of 68-83% were obtained. *Meta*-substituents were however tolerated, as was the use of the bulky 2-naphthylboronic acid which, although it led to a good *e.e.*, gave a poor yield (entry 8).



2.92

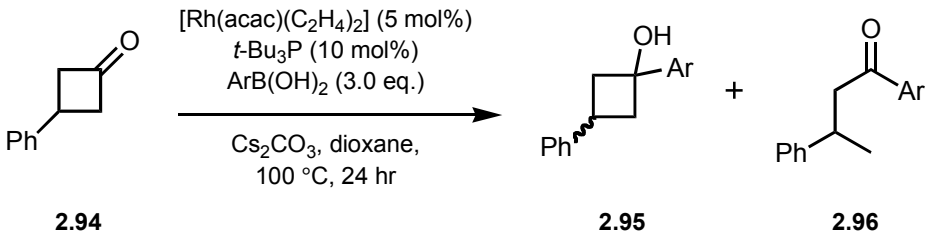


2.93

Figure 2.4

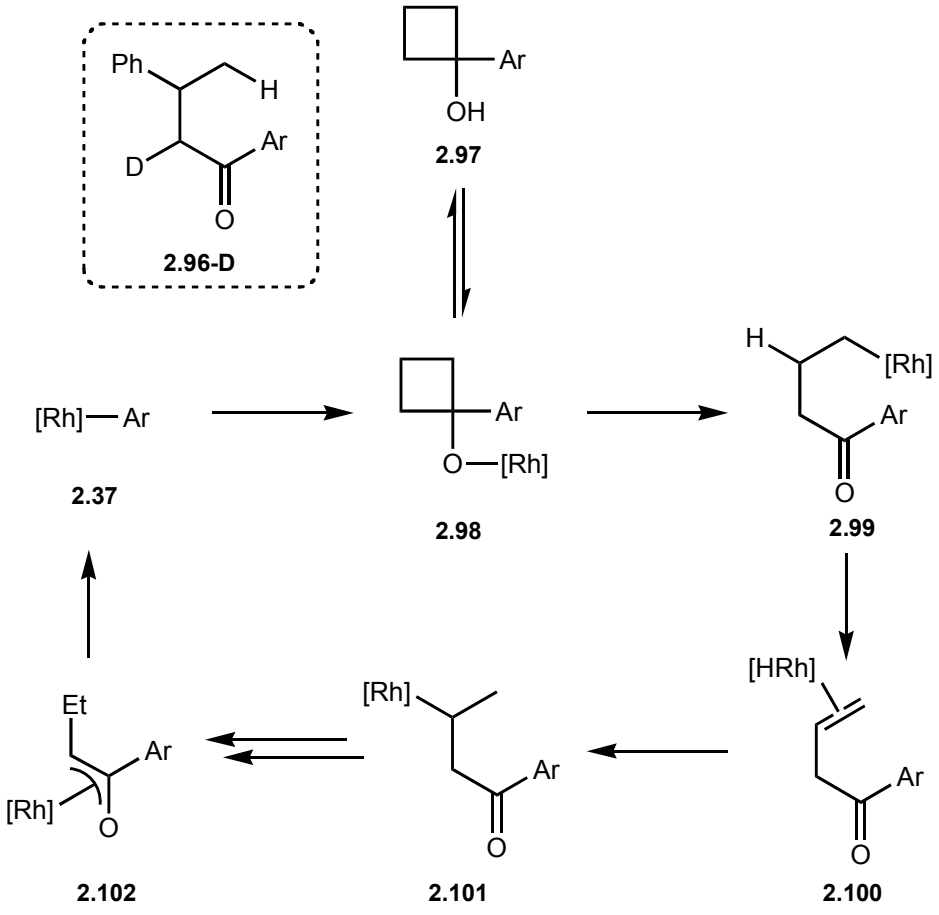
Iuliano *et al.* have used monodentate deoxycholic acid derived biphenylphosphite ligands (such as those in Figure 2.4) in asymmetric 1,4-addition and 1,2-addition reactions of arylboronic acids and cyclic enones (see also Section 2.6.4 below). When applied in an analogous manner to aryl aldehydes and trifluoromethyl ketones they found that those substrates also underwent facile arylation under the aqueous basic reaction conditions, though the enantioselectivities were moderate at best (11-54% *e.e.*). They did however note that the active catalyst was able to arylate the trifluoromethyl ketones at room temperature with comparatively short reaction times for such difficult substrates.[54]

2.6.4. Cyclic Ketones



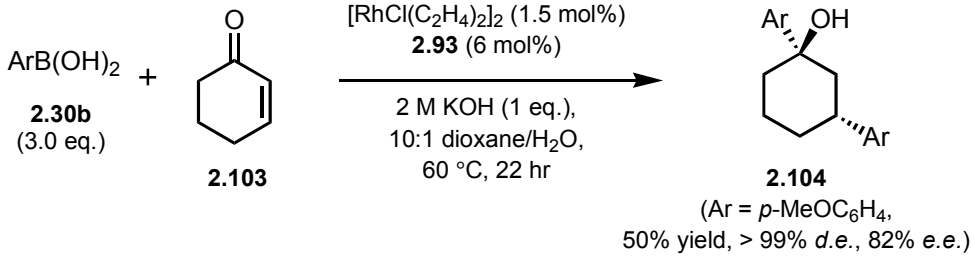
Scheme 2.22

In 2004 Murakami reported the rhodium-catalysed 1,2-addition/ring-opening reaction sequence with 2- and 3- monosubstituted cyclobutanones (e.g. **2.94**). The addition reaction proceeds first, with analysis of the reaction composition after three hours showing a 1:9 mixture of addition (**2.95**) to ring-opened product (**2.96**), which after 24 hours had completely converted to the ring-opened product. Heating the isolated addition product in the absence of rhodium resulted in no ring-opening, confirming that the rhodium catalyst was involved in both steps.



Scheme 2.23

It was proposed that 1,2-addition was followed by a β-elimination of the rhodium-alkoxide **2.98**, which in turn results in an alkyl-rhodium at the terminal γ-carbon (**2.99**). This in turn undergoes a sequence of β-hydride eliminations and reattachments so as to form the preferred rhodium enolate (**2.102**), which is ultimately hydrolysed. Evidence for this sequence of events was taken from deuterium labelling experiments, with deuterium being incorporated exclusively at the α-carbon (**2.96-D**) when the reaction was performed using the pinacolate ester in the presence of D_2O. 4-phenylcyclohexanone was not found to undergo the 1,2-addition reaction under identical conditions, confirming that the release of ring strain in the cyclobutanone substrates was a significant factor in their favouring the addition reaction.



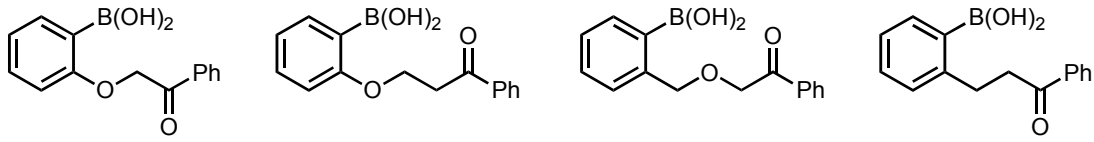
Scheme 2.24

As mentioned previously, Iuliano *et al.* have reported monodentate deoxycholic acid derived biphenylphosphite ligands in the asymmetric 1,4-addition reactions of arylboronic acids and cyclic enones. They noted that whilst a mono-ligated rhodium-phosphite complex was selective in promoting 1,4-addition, the related di-monophosphite-rhodium complex also catalysed the 1,2-addition pathway, such that it yielded diastereomerically pure 1,4-diarylcyclohexanols in good *e.e.*'s (Scheme 2.24). However, only the double addition reaction to cyclohexenone **2.103** was reported, with exclusive 1,4-addition occurring when cyclopentenone was employed.[55, 56]

2.7. Use of Alternative Transition Metal Catalysts

The focus of this review has been the rhodium-catalysed variant of the 1,2-addition reaction employing boronic acids and related organoborons. Indeed, this focus has mirrored that seen in the chemical literature, where rhodium catalysis remained dominant for much of the first decade after Miyaura's original publication. However, reports have been made detailing the successful application of a number of catalytically active transition metals, in both the achiral and asymmetric variants of this transformation, and as with rhodium, including examples employing less reactive carbonyl substrates.

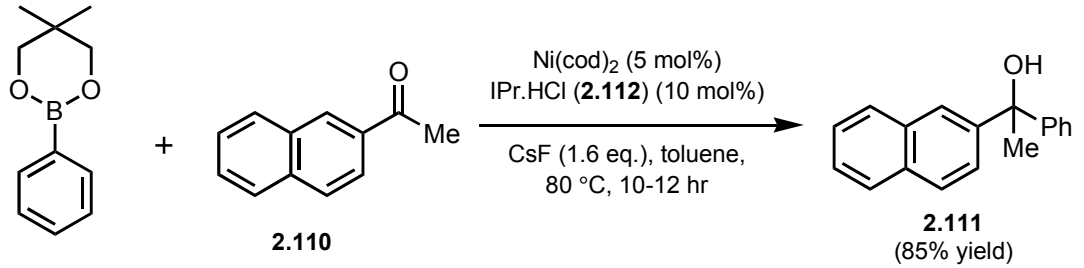
With the exception of rhodium, palladium has historically seen the greatest application to the 1,2-addition reaction employing both aldehydes and imines.[35, 57] Most notably, using a similar strategy to that used by Miyaura for the rhodium-catalysed intramolecular addition reaction,[47] Lu *et al.* have reported the palladium-catalysed intramolecular additions of tethered boronic acids to ketones.[58, 59] Whilst the asymmetric variant was reported, the synthetic routes to the tethered substrates involved the use of *n*-BuLi in a lithium-halogen exchange used to synthesise the aryl boronic acid moiety. Importantly, though reasonable yields could be obtained with *ortho*-ether substituted boronic acids such as **2.105** and **2.106** by simply using ligand free $Pd(OAc)_2$, altering the substrate so as to remove the exact *ortho*-ether moiety (**2.107** and **2.108**), resulted in a total loss of reactivity under such conditions.



2.105 **2.106** **2.107** **2.108**

Figure 2.5

A number of reports have now been made regarding the arylation of aryl aldehydes with nickel catalysts, including asymmetric variants.[60, 61] Most significantly Itami *et al.* reported the IPr ligated $[Ni(cod)_2]$ catalysed addition reactions to unactivated ketones using labile boronic esters (Scheme 2.25).[22] Initial attempts to induce asymmetric arylations by use of a chiral NHC ligand were reported to give, at best, only a poor 36% *e.e.* However, this publication is, to the best of the author's knowledge, currently that of the most active transition metal-catalysed system to have been reported for the 1,2-addition reaction of boronic acid derivatives with ketones.



2.109
(3.0 eq.)

2.110

2.111
(85% yield)

Scheme 2.25

Other transition metals to have been used for the 1,2-addition reaction to aldehydes employing boronic acids include copper[62] and iron[63], although the most notable recent

examples employing less widely used transition metals are undoubtedly the asymmetric variants reported by the groups of Miyaura[64] and Cheng[65] using ruthenium and cobalt, respectively.

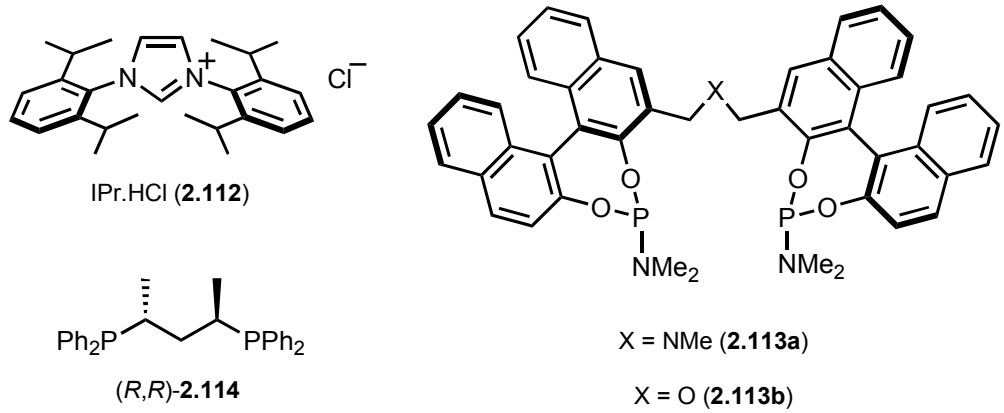
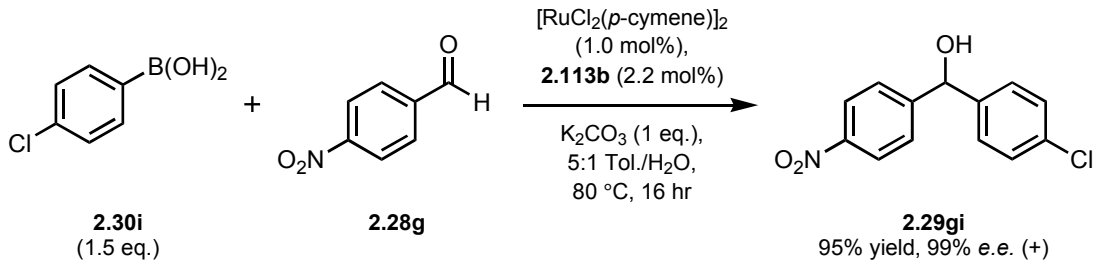


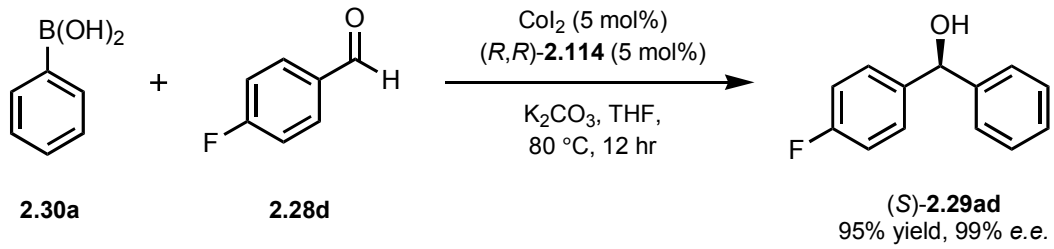
Figure 2.6



Scheme 2.26

Miyaura *et al.* developed the BIPAM ligand backbone, the *N*-Me-BIPAM variant **2.113a** having previously been applied to the successful rhodium-catalysed asymmetric arylation reaction of aldimines using boronic acids.[66] They subsequently reported the first use of ruthenium-catalysed arylation of aldehydes using Me-BIPAM **2.113b**, in typically very high yields and excellent enantioselectivities (Scheme 2.26), for a range of aryl and heteroaryl aldehydes.[64]

Cheng *et al.* reported the use of a cobalt catalyst formed from the precursor CoI_2 and commercially available ligand (*R*,*R*)-BDPP (**2.114**). Again, excellent yields and enantioselectivities were obtained for a range of aryl and heteroaryl aldehydes (Scheme 2.27).[65]



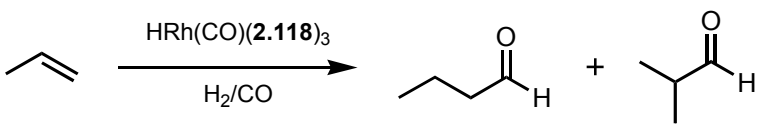
2.30a **2.28d** (*S*)-**2.29ad**
95% yield, 99% *e.e.*

Scheme 2.27

2.8. Hydrophilic Ligands in Transition Metal-Catalysed Reactions

Organometallic reagents are often stereotypically viewed as being incompatible with moisture, primarily due to associations made with the vigorous reactions that are indeed observed for the highly reactive s-block organometallics with water, and then sometimes erroneously extended to organometallics as a much broader class of compounds.[67] However, many transition metal to carbon bonds are in fact kinetically resistant to such reactions, and more specifically, neither boronic acids[13] nor organorhodium complexes[18, 20] are typically incompatible with water. Furthermore, in transition metal-catalysed reactions where the water content is high, then the use of hydrophilic ligands may be advantageous for a number of reasons.

For example, in an industrial context, whilst heterogeneous catalysis is still dominant,[68] homogeneous catalysts offer such significant improvements in activity and selectivity that they are employed for certain large-scale processes.[69] However, and although there are exceptions, to be cost-effective most of these processes require that the metal can be separated relatively easily from the organic components, either for ultimate re-use of the active catalyst, or to avoid contamination of synthetic products. Thus, the use of hydrophilic ligands in aqueous/organic biphasic systems, while still allowing for intimate contact between the catalyst and substrate during the reaction, may be one way to facilitate the eventual separation of the catalyst from the organic products. In addition, the use of an appropriate ligand may result in a hydrophilic complex that is not only readily recovered, but is also able to retain catalytic activity between applications.



2.115 **2.116** **2.117**

Scheme 2.28

Notably, the Ruhrchemie/Rhône-Poulenc hydroformylation process (Scheme 2.28) is an example of an industrial-scale procedure (nearly 1 megatonnes per annum, globally[70]) that employs a hydrophilic ligand to sequester a catalytically active rhodium complex in the water phase of an aqueous/organic biphasic system. The system is not only highly selective for producing aldehydes, but specifically linear butyraldehyde **2.116** as the major product (up to 98% selectivity).[71]

Factors including the extremely high cost of rhodium, long catalyst lifetime, and tolerance for relatively impure substrate, makes the Ruhrchemie/Rhône-Poulenc process a cost effective solution. Although not all homogeneous transition metal-catalysed reactions of industrial significance are likely to be quite so amenable to such an approach, research on the use of transition metal-catalysed reactions performed in aqueous media, with or without hydrophilic ligands, has also resulted in more active and selective systems being discovered for laboratory-scale syntheses.

One of the most notable examples of which is the CuAAC reaction, which has often been shown to be faster, cleaner, and more regioselective when performed in aqueous media (discussed in detail in Chapter 3). By using hydrophilic ligands, the recycling of catalytically active palladium complexes in reactions employing boronic acids has also been achieved.[72]

2.8.1. Literature Precedent for Hydrophilic Ligands in Rhodium-Catalysed 1,2-Addition Reactions Employing Boronic acids

As originally noted by Miyaura, the rhodium-catalysed 1,2-addition reaction of boronic acids and aryl aldehydes was not only tolerant of water, but accelerated in its presence. Although this effect may be rationalised predominantly by an understanding of the role water plays in the catalytic cycle, such reactions present an ideal opportunity to employ hydrophilic ligands for the benefits they can provide. In 2005 Shaughnessy and Huang reported that a rhodium complex formed *in situ* from $RhCl_3.3H_2O$ and *t*-Bu-Amphos **2.120** was able to catalyse the 1,2-addition of aryl and alkenyl boronic acids with aldehydes in an aqueous reaction media.[73]

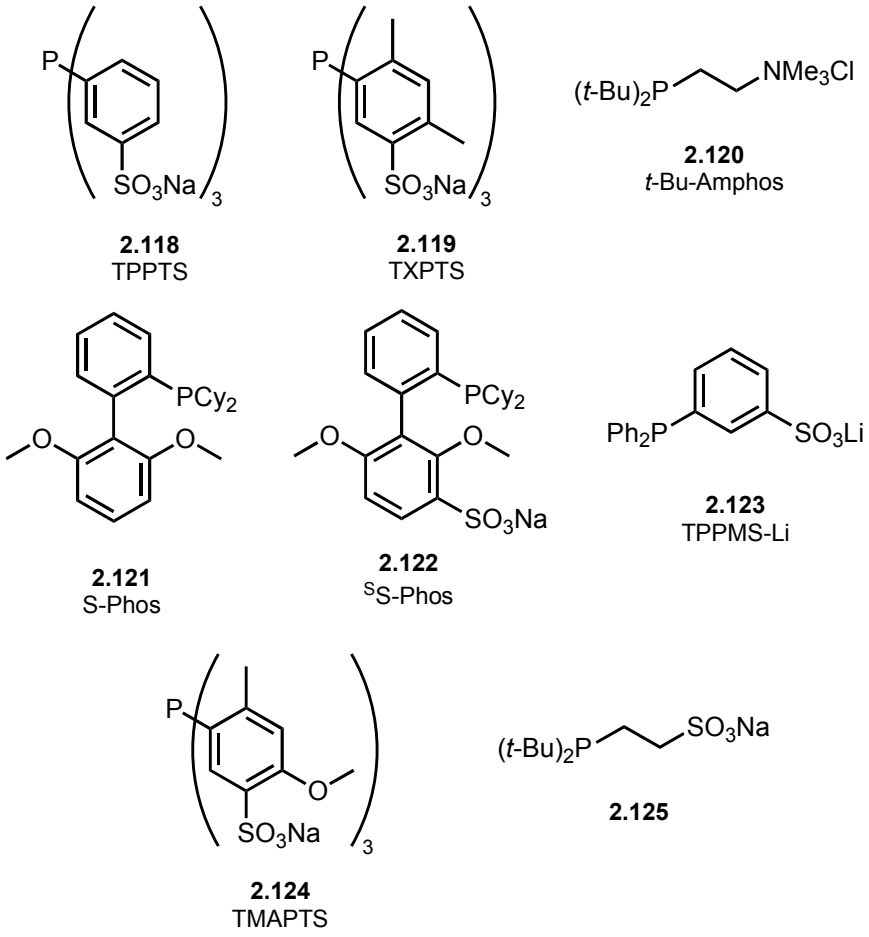
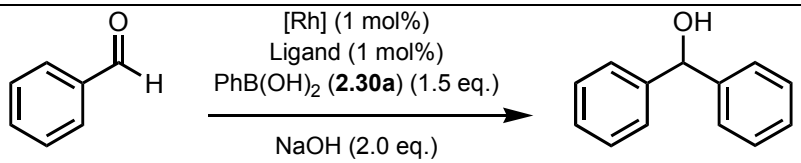


Figure 2.7

Whilst the reaction required a temperature of 80 °C and the addition of sodium hydroxide in order to proceed, the choice of rhodium source was less critical. Indeed, under the optimised conditions $[RhCl(cod)]_2$, $Rh(acac)(coe)_2$ and even $RhCl_3.3H_2O$ gave effectively identical results (Table 2.7, entries 5-7). Consistent with literature precedent a rhodium(I) species was believed to be the active catalyst, and it was suggested that $RhCl_3.3H_2O$ was in fact undergoing *in situ* reduction to rhodium(I) under the mediation of the boronic acid component (as discussed later). Thus $RhCl_3.3H_2O$ was selected for further use, being the most cost-effective rhodium source. In contrast to *t*-Bu-Amphos, use of the sulfonated triaryl phosphine ligands TPPTS **2.118** and TXPTS **2.119** (entries 2-3), typical of the type employed as hydrophilic ligands in industrial processes,[69, 70] were ineffective (as is discussed later).



2.28a **2.29aa**

Entry	Rh source	Ligand	Co-solvent	Yield (%)[b]
1	$RhCl_3.3H_2O$	*t*-Bu-Amphos (**2.120**)	MeCN/H_2O [a]	85
2	$RhCl_3.3H_2O$	TPPTS (**2.118**)	MeCN/H_2O [a]	0
3	$RhCl_3.3H_2O$	TXPTS (**2.119**)	MeCN/H_2O [a]	0
4	$RhCl_3.3H_2O$	**2.120**	Tol./H_2O [a]	84
5	$RhCl_3.3H_2O$	**2.120**	H_2O	90
6	$[RhCl(cod)]_2$	**2.120**	H_2O	88
7	$Rh(acac)(coe)_2$	**2.120**	H_2O	90
8	$RhCl_3.3H_2O$	**2.120**	MeCN/H_2O [a]	82[c]
9	$RhCl_3.3H_2O$	**2.120**	H_2O	78[c]

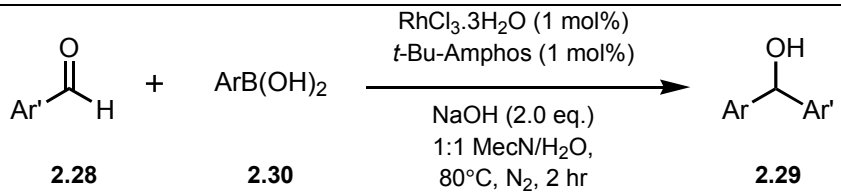
[a] 1:1 water/co-solvent used.

[b] GC yield.

[c] Isolated yield from 2 hour reaction.

Table 2.7

The rhodium/*t*-Bu-Amphos complex was highly active for the 1,2-addition reaction using either water alone, or in combination with miscible and immiscible co-solvents (MeCN and toluene, respectively; see Table 2.7). A range of aryl aldehydes and arylboronic acids were reacted in 1:1 MeCN/H_2O under the optimised conditions, with the commonly noted substituent electronic effects such that electron deficient boronic acids gave poor to moderate yields, with no significant increase in yield noted upon extension of the reaction time. Again, alkyl aldehydes were less reactive substrates, with pivaldehyde being notably unreactive. An alkenyl boronic acid also coupled to aryl aldehydes, though the use of an alkyl boronic acid was unsuccessful.



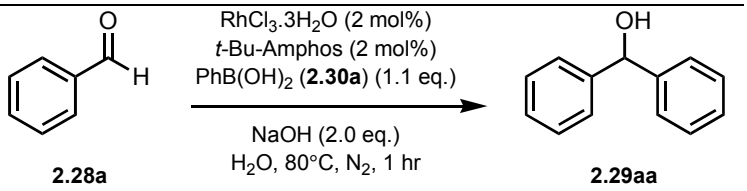
2.28 **2.30** **2.29**

Entry	Ar':		Ar:		Yield (%)[a]
1	*p*-FC_6H_4	**2.28d**	Ph	**2.30a**	78
2	*p*-$MeOC_6H_4$	**2.28b**	Ph	**2.30a**	59
8	Ph	**2.28a**	*p*-$MeOC_6H_4$	**2.30b**	79
9	Ph	**2.28a**	*p*-FC_6H_4	**2.30d**	55

[a] Isolated yield.

Table 2.8

Using a water-only reaction media for the arylation of benzaldehyde with phenylboronic acid allowed the hydrophilic character of *t*-Bu-Amphos to be used in an advantageous manner. Upon completion of the initial reaction, ethyl acetate was introduced and the organic-soluble components extracted, after which the aqueous phase still containing the active catalyst could be transferred *via* cannula into a separate reaction vessel charged with fresh aldehyde, boronic acid and base. In this way the catalytically active species could be recycled seven times with minimal difference in activity (Table 2.9).



2.28a **2.29aa**

Entry	Yield (%)[a]	Entry	Yield (%)[a]
1	79	6	90
2	83	7	86
3	90	8	74
4	85	9	76
5	90		

[a] GC yield.

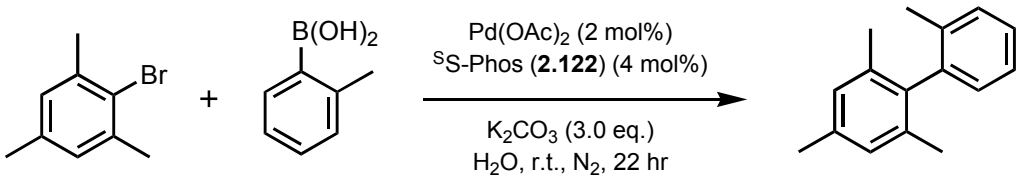
Table 2.9

2.8.2. Development of Sulfonated Buchwald Ligands

The Buchwald group's monophosphinobiaryl ligands have been shown to form exceptionally active catalysts for some of the key palladium-catalysed cross-coupling methodologies,[74, 75]

and in particular are able to efficiently promote the Suzuki coupling of less reactive aryl chlorides or sterically bulky substrates.[76]

Reports[77, 78] of active palladium complexes ligated with hydrophilic monophosphinobiaryl ligands for the Suzuki coupling in aqueous media led Buchwald's group to the development of sulfonated analogues of their own rationally designed biaryl ligands. In 2005 they reported that the sulfonated analogue (**2.122**) of one of the most active and widely utilised phosphines, S-Phos (**2.121**),[79] was able to form active catalysts for the facile Suzuki coupling reaction of challenging substrate combinations in aqueous media, even at ambient temperatures (Scheme 2.29).[80]



2.126 **2.30j** (1.2 eq.) **2.127**

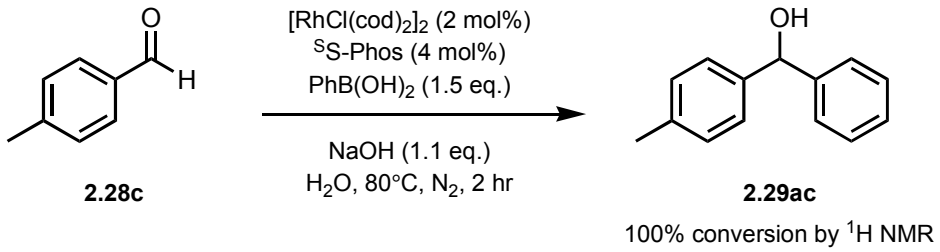
Scheme 2.29

Soon after the publication by Buchwald employing ^{S}S-Phos, the ligand was released commercially. Access to a hydrophilic ligand already reported to exhibit high activity in palladium-catalysed cross-coupling reactions led us to investigate whether it could be applied in the rhodium-catalysed 1,2-addition reaction of aryl aldehydes in aqueous media.

2.9. Results & Discussion

2.9.1. Initial Results for the Arylation of Aryl Aldehydes using ^{S}S-Phos

To determine whether ^{S}S-Phos was indeed an effective ligand for such a reaction we selected conditions similar to those employed by Shaughnessy.[73] Indeed, our initial investigations of the reaction between *p*-tolualdehyde **2.28c** and phenylboronic acid **2.30a** showed immediate promise, *p*-tolualdehyde being completely converted with our system to the diaryl carbinol product **2.29ac** in only two hours at 80 ºC (Scheme 2.30).



2.28c **2.29ac**

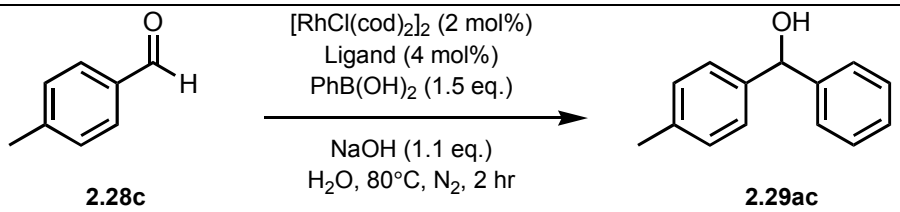
100% conversion by ^{1}H NMR

Scheme 2.30

2.9.2. Recycling of the Active Catalyst

Despite the very high activities in aqueous-phase Suzuki couplings of ^{S}S-Phos ligated palladium complexes as initially demonstrated by Buchwald and Anderson,[80] it was not reported whether the hydrophilic character of the ligand had been employed in an attempt to reuse the active catalyst.

Therefore, we next investigated whether the active catalyst formed in the presence of the hydrophilic ^{S}S-Phos ligand could be re-used for subsequent reaction cycles after extraction of the organic-soluble components. After allowing the arylation reaction of **2.28c** time to reach full conversion, the vessel was allowed to cool to room temperature. We found that by maintaining the system under an atmosphere of nitrogen, and then washing the aqueous phase sequentially with three portions of deoxygenated diethyl ether, extraction of the organic components was achieved. Once the final organic wash had been removed *via* cannula, the reaction vessel still containing the aqueous phase was then charged with further equivalents of fresh aldehyde and boronic acid, after which these substrates were again reacted at 80 °C for two hours. In this way we observed that a catalytically active species was retained in the aqueous phase, resulting in some continued conversion for the arylation of *p*-tolualdehyde upon the second and even third use of the aqueous phase containing the catalyst (Table 2.10, entries 1-3).



2.28c **2.29ac**

Entry	Ligand	Conv. (%)[a]
1	^{S}S-Phos (**2.122**)	100
2[b]	**2.122**	81
3[c]	**2.122**	66
4	TPPMS-Li (**2.123**)	83
5[b]	**2.123**	46
6[c]	**2.123**	Trace
7[d]	**2.122**	100

All reactions performed on 1.0 mmol of aldehyde in 1.5 ml water.

[a] As determined by ^{1}H NMR.

[b] Second run. Recycle *via* extraction of organic components, followed by addition of a further 1.0 eq. of aldehyde and 1.5 eq. boronic acid per cycle to the aqueous catalyst and designated ligand.

[c] Third run; catalyst recycled as above.

[d] Reaction performed at r.t. for a period of 48 hours.

Table 2.10

2.9.3. Comparison with a Prototypical Sulfonated Triarylphosphine

To determine how ^{S}S-Phos performed in contrast to the sulfonated triarylphosphine ligands more traditionally used in industrial processes, we employed TPPMS as the ligand under identical reaction conditions. Although TPPMS also gave an active and recyclable hydrophilic complex, the initial activity of that catalyst was lower than the corresponding species formed using ^{S}S-Phos as the ligand, and importantly the activity of the TPPMS system more rapidly subsided upon repeated use of the aqueous phase (Table 2.10, entries 4-6).

The sulfonated triarylphosphine backbone found in TPPMS is common to many industrially applied water-soluble phosphine ligands, primarily due to the relative ease and low cost with which they can be manufactured. However, it is known that sulfonated triaryl phosphine ligands can be much less effective in forming active catalysts than their non-sulfonated analogues.[81, 82] Though distinctly different reaction conditions may not allow for a simple comparison of these two forms, experimental measurements and computational analyses reveal two significant effects resulting from the incorporation of the sulfonate moiety.

Firstly, the introduction of one or more sulfonate groups on the aromatic rings directly connected to the coordinating phosphine removes electron density from the phosphine lone pair, and so results in lower donating ability to the metal centre. For example, comparison of the carbonyl stretches in complexes of *trans*-$L_2Rh(CO)Cl$ provides support for tris-sulfonated triarylphosphines being less donating (Table 2.11).

Entry	Phosphine	ν_{CO} (cm^{-1})[a]
1	TPPTS (**2.118**)[b]	1993
2	TXPTS (**2.119**)[b]	1993
3	TMAPTS (**2.124**)[b]	1993
4	PPh_3	1979
5	P(*o*-tol)$_3$	1972

[a] Measurements in DCM solution for complexes prepared *in situ*.

[b] Tris-tetrabutylammonium salts were used.

Table 2.11: Carbonyl stretching frequencies of *trans*-$Rh(L)_2(CO)Cl$ complexes.[83]

Secondly, the steric and ionic features of sulfonate groups also have an effect on the cone-angle of the ligand. This relationship is rather complex, and sulfonate groups could potentially result in reduced or increased cone angles, and depending on the specific species under investigation then computationally calculated and experimentally observed values even show variance between results obtained within the same experimental domain. And while the overall effect on the cone-angle is likely of less significance than the corresponding change in the electronic characteristics of the ligand, *meta*- sulfonate moieties have been shown to have a greater impact on the cone-angle than a sulfonate at either the *para*- position, or otherwise situated more remotely from the phosphine lone pair.[69]

As discussed in Chapter 1, investigations of Suzuki coupling reactions involving increasingly demanding substrate combinations have in turn led to a greater understanding of the optimal properties required of ligands, so as to allow more active catalysts to be developed. In the case of the Suzuki coupling reaction, electron rich and sterically demanding ligands are typically required to form more active catalysts. The more electron donating ligands increase the rate of oxidative addition with the less reactive aryl chlorides, while the steric bulk promotes the formation of the coordinatively unsaturated LPd(0) species from the $L_2Pd(0)$ resting state.[76, 82] Shaughnessy and co-workers have previously demonstrated that bulky and basic hydrophilic phosphine ligands are effective for Suzuki couplings performed in aqueous media, even allowing the catalytically active species to be recycled. In contrast, the phosphine lone pair in ligands such as TPPMS is affected both

electronically and sterically by the *meta*- sulfonate moiety, and thus they are poor ligands for such applications.[72, 84]

Although details of that catalytic process differ from the rhodium-catalysed 1,2-addition reaction, the requirement for a similar set of fundamental ligand characteristics has already been discussed. Specifically, Miyaura showed that increasing steric bulk and basicity of monophosphine ligands resulted in the following order of activity: PMe_3<PPh_3<PCy_3<*i*-Pr_3P<*t*-Bu_3P.[17] Indeed, Shaughnessy and co-workers noted in their report that while the more bulky and basic *t*-Bu-Amphos ligand performed well in the rhodium-catalysed arylation of aryl aldehydes, the use of the less electron rich tri-sulfonated triarylphosphines **2.118** and **2.119** resulted in no conversion to the diarylmethanol product whatsoever.[73]

In contrast, a remotely sited sulfonate group, insulated by either multiple methylene groups (as with *t*-Bu-Amphos),[85] or separated by a biphenyl bridge (as with ^{S}S-Phos),[86] insulates the phosphine from electronic effects typically resulting from the inclusion of the electron withdrawing sulfonate. Such is the effect that comparison of the CO stretches for $Ni(CO)_3PR_3$ complexes show that only two methylene spacers in **2.125** (Figure 2.7) insulate the phosphine to such a degree that it has a lower frequency CO stretch than even the *t*-Bu_3 analogue (Table 2.12, entries 1 and 3).

Entry	Phosphine	ν_{CO} (cm^{-1})[a]
1	**2.125**	2054.0
2	PCy_3	2056.4
3	*t*-Bu_3P	2056.1
4	*i*-Pr_3P	2059.2
5	PEt_3	2061.7
6	PPh_3	2068.9

[a] FTIR spectra recorded in DCM on CsF plates.

Table 2.12: Carbonyl stretching frequencies of $Ni(CO)_3PR_3$ complexes.[87]

Miyaura proposed that more donating ligands result in a more polarised Rh-Ar bond, and hence increase the nucleophilicity of the aryl group towards the electrophilic carbonyl carbon of the aldehyde.[17] As TPPTS is proposed to have a similar or slightly greater cone angle than PPh_3,[69] then TPPMS is likely very similar to PPh_3 in terms of steric parameters. In terms of its electronic character however, then TPPMS is less donating than PPh_3. And although the reaction conditions used by Miyaura[17] cannot be directly compared, it is likely that TPPMS is therefore a less efficient ligand for this reaction than PPh_3. In contrast, the

active ^{S}S-Phos ligated complex is likely to be electronically and structurally comparable with its non-sulfonated analogue, as the phosphine lone pair is sufficiently insulated from any significant electronic or steric effects due to the sulfonate moiety being located on the distal ring of the biaryl. This in turn makes ^{S}S-Phos more akin to the bulkier and donating ligands such as PCy_3 and *i*-Pr_3P, for which Miyaura demonstrated greater activity than PPh_3.

2.10. Optimisation of the Arylation of Aryl Methyl Ketones using ^{s}S-Phos

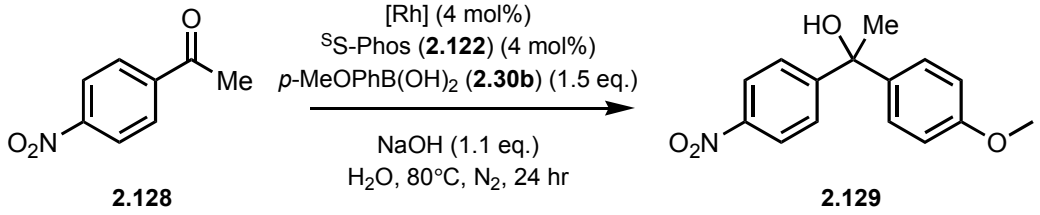
In addition to higher initial and continued conversions than were obtained with TPPMS, the room temperature activity of the ^{S}S-Phos system suggested that the active complex may possess a particularly high catalytic activity. As discussed in the literature review, progress on the analogous arylation reaction of ketones has been significantly slower than that for the aldehydes for steric and electronic reasons, while not only do the steric demands in such systems reduce their reactivity, but coordination of the substrate to the metal centre is also disfavoured further in comparison to analogous enone substrates.[18, 88, 89] Despite the limited precedent for the arylation of non-α-activated ketone substrates, we decided to assess whether the ^{S}S-Phos system could prove active enough to even allow for the arylation of such demanding substrates. Our initial exploratory investigations using aryl aldehydes had shown that greater conversions where obtained more rapidly with electron poor aldehydes and electron rich boronic acids, as consistent with the literature precedent discussed previously. We therefore selected *p*-nitroacetophenone **2.128** and *p*-methoxyphenyl boronic acid **2.30b** due to their correspondingly favourable electronic parameters.

2.10.1. Selection of Rhodium-Source

Despite being electron poor due to the *p*-nitro substituent, **2.128** is not α-activated, and thus it was encouraging to obtain a 41% conversion to the 1,1-diarylethanol **2.129** under our initial conditions (Table 2.13, entry 1). Furthermore, purification by column chromatography afforded **2.129** in a 39% yield, consistent with the conversion as had been determined by ^{1}H NMR. With a convenient model system therefore available we proceeded to further investigate the reaction parameters.

While the ^{S}S-Phos ligand was not required for catalytic activity, it was shown to accelerate the reaction, and appears to visibly increase the solubility of the rhodium complex in the aqueous phase (Table 2.13, entries 1 and 2). In contrast, when $[RhCl(cod)]_2$ was omitted from the reaction, then no conversion to the 1,1-diarylethanol product was observed (entry 4). Additionally, the screening of various rhodium sources showed that the selection of an appropriate pre-catalyst was essential. Both Rh(II) and Rh(III) sources (entries 5 & 6) were found to be ineffective at forming an active catalyst, as was the Rh(I) source

$Rh(acac)(C_2H_4)_2$ (entry 7). Our informed selection of $[RhCl(cod)]_2$ as the original pre-catalyst was therefore justified when we observed that $[Rh(OH)(cod)]_2$ (entry 8) was the only other rhodium-source of those screened to exhibit activity, giving an identical result to $[RhCl(cod)]_2$.



2.128 **2.129**

Entry	Rhodium source	Conv. (%)[a]
1	$[RhCl(cod)]_2$	41 (39)[b]
2	$[RhCl(cod)]_2$	43 (29)[c]
3	$[RhCl(cod)]_2$	40
4	(None)	0
5	$RhCl_3.3H_2O$	0
6	$Rh_2(tfa)_4$	0
7	$Rh(acac)(C_2H_4)_2$	0
8	$[Rh(OH)(cod)]_2$	40

All reactions performed on 0.125 mmol of ketone in 1.5 ml water, except entries 1-2 where 1.0 mmol of ketone was used in 3.0 ml water.

[a] As determined by ^1H NMR, isolated yields in parentheses.

[b] Reaction time of 2 hr.

[c] Without ligand, reaction time extended to 48 hr; purification was complicated by product colouration suggesting metal contamination.

Table 2.13

Under aqueous basic conditions, especially at elevated temperatures, then $[RhCl(cod)]_2$ is readily converted to $[Rh(OH)(cod)]_2$, or a corresponding derivative of that complex; and as discussed in Chapter 1 and Section 2.4.3 respectively: Hydroxorhodium complexes have been implicated in the catalytic cycles of both the rhodium-catalysed 1,4- and 1,2-addition reactions employing boronic acids, where it has been shown that hydroxide and alkoxide ligands accelerate the transmetallation event. However, it was also discussed that acac is able to act as a competitive ligand for hydroxide in such reactions, resulting in a "reservoir" for the active catalyst. As such the observed lack of catalytic activity for $Rh(acac)(C_2H_4)_2$ in our protocol may in part arise from the aqueous basic conditions disfavouring protonation of any freed acac, such that re-coordination to the rhodium complex is instead preferred. A potentially more significant effect might however be that the acac ligand is also acting to

competitively inhibit coordination of the less strongly ligating ketone with the rhodium-aryl complex – thus preventing turnover of the catalytic cycle, and so ultimately favouring hydrolysis of the rhodium-aryl complex.

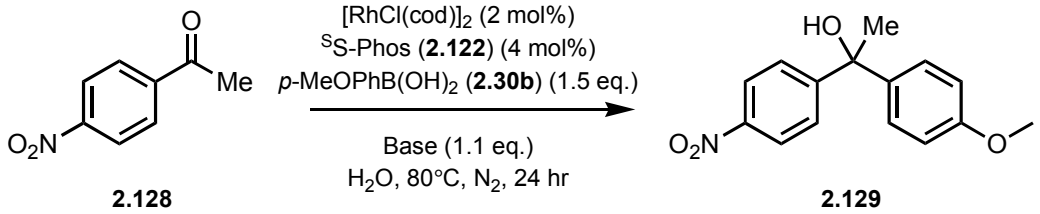
Interestingly, though $RhCl_3.3H_2O$ was successfully employed by Shaughnessy as a pre-catalyst with *t*-Bu-Amphos ligand and aqueous MeCN as the solvent system,[73] it proved ineffective as a source of an active rhodium(I) complex in our hands. Shaughnessy postulated the involvement of the boronic acid in the reduction of the $RhCl_3.3H_2O$, though no literature precedent was cited for this.

Although the direct sacrificial oxidation of phosphine ligands to generate $L_2Pd(0)$ from Pd(II) salts is known to occur,[90] it seems less likely that such a mechanism was at work in the case of the Rh(III) to Rh(I) reduction. As near identical results were obtained with rhodium(I) pre-catalysts, this process would require that the species generated by reduction of rhodium(III) would have an increased catalytic activity, such that with a lower ratio of unoxidised ligating phosphine remaining, it could still produce similar overall conversions. Our review of the literature then led us to the report by Zou *et al.* that $RhCl_3.3H_2O$ had been used as a rhodium source for the Rh(I) catalysed Heck-type coupling of aryl boronic acids and α,β-unsaturated esters. The reaction occurred in the presence of four equivalents of PPh_3 to rhodium, in a water/toluene solvent system and at elevated temperatures. The detection of biphenyl led them to postulate that it was the product of reductive elimination of a $Rh(III)Ph_2$ complex.[91] This is similar to the report by Lloyd-Jones *et al.*, who have also shown that arylboronic acids are consumed in producing the symmetrical homocoupled biaryl during a similar Pd(II) to Pd(0) reduction. This allows an active Pd(0) catalyst to be generated from Pd(II) pre-catalysts of the type typically used in Suzuki coupling reactions.[92]

Though our reaction conditions are somewhat similar to those employed by Shaughnessy, the presence of multiple equivalents of adequately coordinating ligands such as PPh_3, or MeCN in combination with *t*-Bu-Amphos, may be critical to such a process, hence potentially explaining why $RhCl_3.3H_2O$ was ineffective under our conditions.

2.10.2. Identity and Stoichiometry of Base

We next investigated the role of base in the reaction, with a brief base screen showing metal hydroxides to be most effective choice, there being no statistically significant difference observed when KOH was used in place of NaOH. However, the use of K_2CO_3 or NEt_3 proved to be less effective (Table 2.14).



2.128 **2.129**

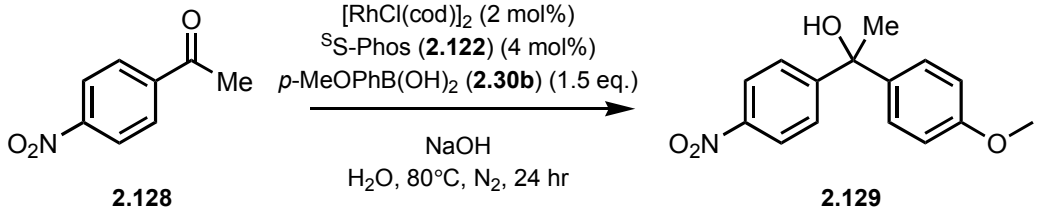
Entry	Base	Conv. (%)[a]
1	NaOH	40
2	K_2CO_3	17
3	NEt_3	30
4	KOH	41

All reactions performed on 0.125 mmol of ketone in 1.5 ml water.

[a] As determined by ^{1}H NMR.

Table 2.14

The basicity of the two metal hydroxides is not significantly different,[93] with both effectively being fully dissociated under our aqueous reaction conditions. Therefore, in combination with their similar ability to promote the reaction, it seems likely that they are simply more effective at generating an active hydroxorhodium species.



2.128 **2.129**

Entry	NaOH (eq.)	Conv. (%)[a]
1	(None)	21
2	0.1	27
3	0.5	33
4	1.1	40
5	2.0	<10
6	3.0	0

All reactions performed on 0.125 mmol of ketone in 1.5 ml water.

[a] As determined by ^{1}H NMR.

Table 2.15

Having selected NaOH as the base, we next assessed what effect the equivalency of hydroxide had on the reaction. Upon omission of base the reaction still proceeded (Table 2.15, entry 1), though with a much reduced conversion. This contrasts significantly with the

report made by Shaughnessy, in which it was noted that the addition of base was crucial to achieving catalytic activity in the arylation reactions employing the much more reactive aryl aldehydes.

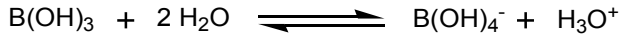
Under our conditions the conversion to the 1,1-diarylethanol product then improves as the equivalents of base increase, up to 1.1 equivalents of base, after which there is a rapid decline in the amount of arylation product (Table 2.15). At higher equivalencies (> 2.0) of base, rapid discolouration of the reaction mixture was noted, indicating that a rhodium complex of importance to the catalytic activity may be unstable in the presence of larger amounts of hydroxide ion. It therefore seems feasible that, at an optimal concentration, the base was acting to aid the generation of an active hydroxorhodium complex. We therefore reviewed the literature to help account for such improved activities when base was present at or below 1.1 equivalents.

Notably, Miyaura has shown that in the corresponding 1,4-addition reaction to α,β-unsaturated amides using $Rh(acac)(C_2H_4)_2$ in a 6:1 dioxane/water solvent mixture, the addition of catalytic amounts of strong Brønsted acids such as HCl completely inhibits the reaction. Upon further addition of base however, the reaction promptly re-starts, and thus they propose that catalytic quantities of acid are enough to reduce the availability of hydroxide to such a degree that formation of the more active hydroxorhodium species from the acac precursor is effectively prevented.[94]

Under hydrous 1,2-addition reaction conditions employing boronic acids such as ours, boric acid is generated as a by-product, as noted in the discussion of the catalytic cycle. Interestingly though, Miyaura demonstrated that at a stoichiometric level boric acid also promoted the aforementioned 1,4-addition reaction, though not to the degree that catalytic amounts of KOH did. Frost *et al.* have also used boric acid as an additive in the asymmetric 1,4-addition reaction of phenylboronic acid with acrylate esters in anhydrous dioxane as solvent. With 1.1 equivalents of boric acid present they noted a yield of 40%, which consistently rose with increasing amounts of boric acid, up to the point where 5.0 equivalents were used – after which no significant difference was encountered when compared to 10.0 equivalents.[95]

In contrast to such results, we noted that the addition of boric acid had a detrimental effect on the ketone arylation reaction. Therefore, it may be that the metal hydroxide bases are not merely more effective choices for forming the hydroxorhodium complex in this case. Over the course of the reaction boric acid will accumulate in the reaction media as the by-product

of the transmetallation event. While it is not a strong protic acid, at high concentrations it could affect the reaction pH by formation of the tetrahydroxyborate and hydroxonium ions through its reaction with water. However, the pK_a of boronic acid **2.30b** is 9.3, which is indeed very similar to that of boric acid, it being 9.24.[13] Thus, the high water content of our system may be a critical factor in explaining why boric acid has a negative impact on catalytic activity.



Scheme 2.31

Hartwig and Carrow have shown in a 1:1 acetone/water mixture, with K_2CO_3 present at levels typically employed in Suzuki coupling reactions, that an approximately equimolar mixture of *p*-fluorophenylboronic acid and the quaternised borate result. Although the exact ratio is dependent on the molarity of base, the respective ratios of boronic acid to borate range from 1:1 to 1:3 as the base is raised from 0.03 M to 0.15 M. They therefore concluded that "*the concentrations of boronic acid and trihydroxyborate are close to each other in organic media containing weak base and water*".[96]

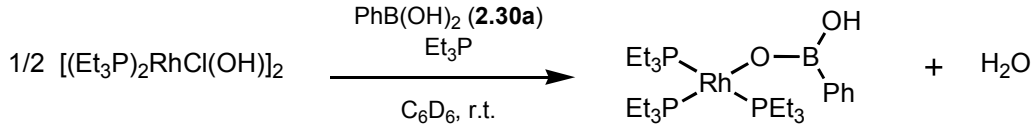
Lloyd-Jones and co-workers have also reported the effect that water-content and equivalents of base have on those same equilibrium concentrations of *p*-fluorophenylboronic acid and corresponding borate, which form from the aqueous basic hydrolysis of the parent potassium trifluoroborate salt. In THF/water mixtures with four equivalents of K_2CO_3 present, the amount of borate relative to boronic acid increases relatively linearly as the water content is increased – from ~ 0% borate in anhydrous THF, to ~100% borate in water alone. Additionally, comparison of the same ratio as a function of equivalents of K_2CO_3 was recorded in both 10:1 THF/water, and water: In the mixed THF/water solvent system no significant difference in the equilibrium concentration of the borate resulted, irrespective of whether no base, or even four equivalents (the maximum level assessed) was present. However, in the water-only system the amount of borate rapidly increased as the equivalents of base were raised, up until ~2 equivalents of base, after which the rate of quaternisation starts to decelerate, primarily because the majority of the boronic acid is already quaternised. Although those results were obtained with K_2CO_3, it was shown that Cs_2CO_3 and, most notably, KOH gave nearly identical results.[92]

Under our reaction conditions specifically, a concentration of approximately 0.1 M aqueous NaOH (Table 2.13, e.g. entries 1-2) or greater (e.g. entries 3-8) is used, which in isolation would give a pH of approximately 13. With 1.5 equivalents of boronic acid to 1.1

equivalents of base present at the start of the reaction then a significant amount of the boronic acid will be likely be quaternised. However, 2.0 equivalents of base were detrimental to the overall level of conversion under our reaction conditions (Table 2.15, entry 5), while at levels of base almost identical to that value, Lloyd-Jones and co-workers have shown that the borate form of *p*-fluorophenylboronic acid predominates in solvent systems with a high water content. As the pK_a of *p*-fluorophenylboronic acid (9.1) is only very slightly different to that of **2.30b** (9.3),[13] it could indicate that transmetallation is occurring most rapidly from the boronic acid in our system, while the trihydroxyborate is contributing significantly less to this process.

Indeed, studies on the Suzuki coupling reaction have shown that catalytically relevant palladium-hydroxide complexes show a preferential rate for transmetallation with the boronic acid, while palladium-halide complexes favour the borate for this process.[92 96] The rhodium-catalysed 1,4-addition reaction employing triolborate salts has been reported, and though it would appear that direct transmetallation from the quaternised borate is indeed occurring in that case, the rhodium source involved is cationic.[97] In comparison, if a neutral hydroxorhodium species is indeed the active complex undergoing the transmetallation event in this system, then it may favour the less polarised boronic acid.

Also, if the intermediates in the catalytic cycle are analogous to those calculated by DFT for the anhydrous catalytic cycle (discussed previously),[19] the sp^2-hybridised boronic acid may be converted to a tetrahedral borate intermediate *after* coordinating with the metal centre, as is shown in Scheme 2.10. In the anhydrous reaction this pathway accounts for the lysis of the rhodium-alkoxide bond by another equivalent of the boronic acid, and thus allows the anhydrous system to bypass the need for a hydroxorhodium species to effect the transmetallation event. Under conditions with aqueous base present the alkoxide will be cleaved rapidly without the need for the boronic acid to become involved in this way.[19] However, it has already been discussed that hydroxorhodium species are known to be highly reactive to transmetallation with boronic acids, whether under anhydrous or hydrous base-free conditions.[23] Under such base-free conditions the boronic acid will predominate over the borate, suggesting that the rapid transmetallation events observed in such cases involve a hydroxorhodium complex and boronic acid. The neutral sp^2-hybridised boronic acids may be more able to coordinate the metal centre in such cases, after which a similar process to that calculated for the anhydrous reaction would activate the boron centre while in the coordination sphere of the rhodium complex – effectively quaternising the boronic acid only at the moment that doing so is then favourable for weakening the B-C bond.

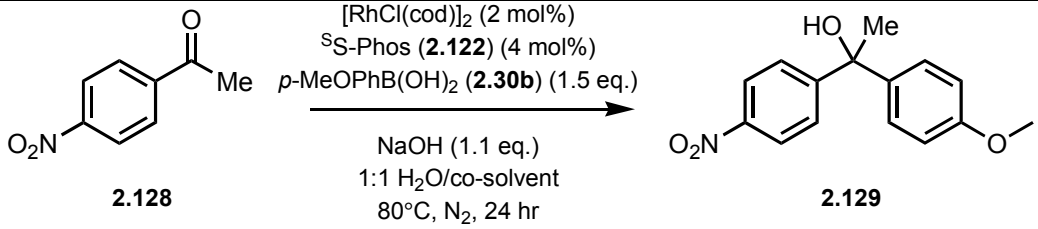


2.130 **2.131**

Scheme 2.32

Notably Hartwig and co-workers have demonstrated that direct transmetallation of the boronic acid does indeed occur to the neutral hydroxorhodium complex **2.130**, while it was specifically noted that no quaternised boronate species were detectable by NMR spectroscopic monitoring of this process.[98]

2.10.3. Effect of Solvent System and Temperature



2.128 **2.129**

Entry	Co-solvent	Conv. (%)[a]
1	(H_2O)	40
2	MeCN	5
3	DMSO	8
4	1,4-Dioxane	9
5	IPA	30
6	(None)	51

All reactions performed on 0.125 mmol of ketone in 0.75 ml water with 0.75 ml of co-solvent. Where no co-solvent was used the total volume of water remained at 0.75 ml.

[a] As determined by ^{1}H NMR.

Table 2.16

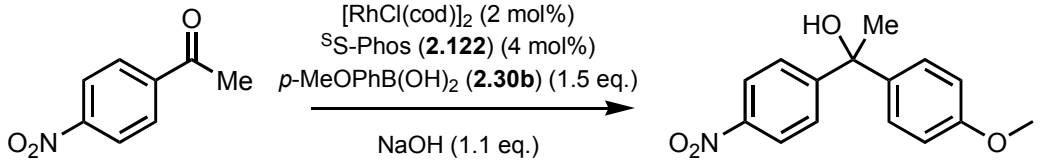
The arylation reactions proceed to give what visibly appears to be a biphasic heterogeneous system, which upon stirring contains droplets of the organic components dispersed in the volumetrically greater aqueous phase. We therefore investigated the use of water miscible co-solvents in order to discover whether a greater level of homogeneity would improve the results of the arylation reaction. However, no improvement was seen over the use of water alone, with polar aprotic solvents giving particularly poor results (Table 2.16, entries 2-4). We believe this could be due in part to the ability of those solvents to coordinate the metal centre, and so deactivate the catalyst. Although 1:1 MeCN/H_2O was as effective under the conditions employed by Shaughnessy as water alone,[73] and though it resulted in what

appeared to be homogenous mixing when employed in our system, the reaction exhibited a vivid deep purple colouration in contrast to a more typically observed yellow to orange colour. While the appearance of the reaction using either DMSO or 1,4-dioxane as co-solvent was not so obviously indicative of such complexation, the conversions were almost as low; and though IPA was an improvement on the polar aprotics, it still had a detrimental effect on the overall conversion (entry 5).

Interestingly, we found that the conversion could be increased to 51% by reducing the volume of water employed (Table 2.16, entry 6). The results from this solvent study suggest an "on water"[99] effect could be responsible, the majority of the organic reactants being dispersed within small water-immiscible droplets in the aqueous phase at any one time. Resultantly, such heterogeneous systems have both a very large surface area between the organic and aqueous phase, and also discreet "pockets" of highly concentrated organic phase containing a large proportion of the available hydrophobic reactants.

Significantly, whilst being hydrophilic, monosulfonated triarylphosphine ligands such as TPPMS are not in fact highly soluble in water.[69] Though the trisulfonated TPPTS ligand has a maximum water solubility of 1.9 M, the water solubility of the monosulfonated ligand TPPMS is only 0.2 M. Comparing the carbon-to-sulfonate group ratio for these ligands gives values of 6:1 and 18:1, respectively. Thus ^{S}S-Phos, with a ratio of 26:1 is likely to have a water solubility, at most, similar to that of TPPMS; and so in the region of 0.2 M. Additionally, low water solubility ligands such as TPPMS with their mixture of hydrophobic and hydrophilic regions, being somewhat akin to surfactants, are known to exhibit "surface activity". While TPPTS and TPPDS tend to behave as electrolytes and so dissolve the active catalyst into the aqueous phase of biphasic organic/water reactions, TPPMS tends to lead to the accumulation of the catalyst close to the phase boundary, and this surface activity can result in improved rates for certain reactions.[69 100]

Typically such behaviour is observed when the ligand is present at concentrations close to, or higher than, its critical micelle concentration. The critical micelle concentration for TPPMS is ~ 0.1 M, while ligands which possess additional molecular mass in the form of hydrophobic substituents have lower values. As such, ^{S}S-Phos, very likely being more hydrophobic than TPPMS, could be demonstrating surface activity, and at even lower concentrations. Thus, ^{S}S-Phos may not in fact be distributing the rhodium complex evenly throughout the aqueous layer, but localising much of it at the surface region of the hydrophobic organic droplets where the boronic acid, being amphiphilic in nature,[13] is also likely to accumulate, and so further accelerating the arylation reaction.



2.128 **2.129**

Entry	Temp. (°C)	Conv. (%)[a]
1	40	32
2	60	39
3	80	51
4	100	46

All reactions performed on 0.125 mmol of ketone in 0.75 ml.

[a] As determined by ^{1}H NMR.

Table 2.17

Finally we sought to determine whether altering the reaction temperature at this increased concentration could also be used to improve the conversion. However, both reducing and increasing the temperature failed in giving an increased conversion (Table 2.17; as discussed in Section 2.12).

2.11. Arylations Under Optimised Reaction Protocols

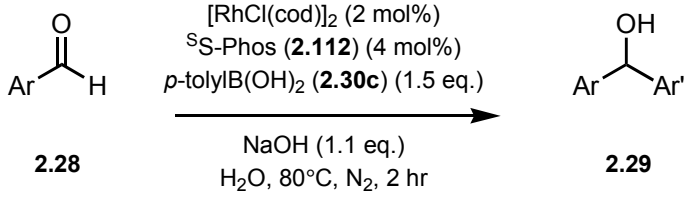
2.11.1. Electronic Effects in the Aryl Aldehyde Substrates

With reaction conditions optimised for use with the demanding aryl methyl ketones, we then re-investigated the arylation reactions with the more reactive aryl aldehydes. Although typical electronic effects were noted, with the more electron poor *p*-fluorobenzaldehyde undergoing arylation most readily (Table 2.18 entry 1), the system was active enough that high conversions were achieved even with the more electron rich *p*-methoxybenzaldehyde substrate (entry 2). We therefore focussed instead on improving the recyclability of the catalyst in the arylation of the relatively electron neutral coupling partners, *p*-tolualdehyde and *p*-tolylboronic acid.

2.11.2. Recycling Studies Employing Additional Base

After demonstrating the importance that the addition of base had for increasing the level of conversion in the arylation reaction employing the much more demanding *p*-nitroacetophenone substrate, we concluded that the addition of base in each reaction cycle should be of benefit. Following the same approach as before the reaction was maintained under an inert atmosphere while the organic components were extracted. To allow the

addition of further equivalents of base in reproducible stoichiometries whilst maintaining the reaction under an inert atmosphere, we added a small portion of deoxygenated concentrated aqueous NaOH to each of the subsequent cycles. We found that due to the build-up of salts over the course the recycling reactions this also acted to keep the aqueous phase more homogeneous. In contrast to previous results where only fresh aldehyde and boronic acid were charged into the vessel containing the retained aqueous layer, this approach allowed the high initial activity observed with the ^{S}S-Phos ligand present to be maintained for five cycles. Indeed, this activity was high enough that as such no discernable difference was apparent between the first and fifth uses of the catalyst (Table 2.18, entries 3 and 7).



2.28 **2.29**

Entry	Cycle	Ar		Product	Conv. (%)[a]
1	-	*p*-FC_6H_4	**2.28d**	**2.29cd**	100 (91)
2	-	*p*-$MeOC_6H_4$	**2.28b**	**2.29bc**	97[b]
3	1	*p*-MeC_6H_4	**2.28c**	**2.29cc**	>99 (96)
4	2[c]	*p*-MeC_6H_4	**2.28c**	**2.29cc**	>99
5	3[c]	*p*-MeC_6H_4	**2.28c**	**2.29cc**	>99
6	4[c]	*p*-MeC_6H_4	**2.28c**	**2.29cc**	>99
7	5[c]	*p*-MeC_6H_4	**2.28c**	**2.29cc**	>99 (97)

All reactions performed on 1.0 mmol of aldehyde in 1.5 ml water.

[a] As determined by ^{1}H NMR, isolated yields in parentheses

[b] Degradation, primarily to the diaryl ketone, occurred during purification.

[c] 1.0 eq. of aldehyde, 1.5 eq. boronic acid and 1.1 eq. of base added per cycle. Products removed after cooling *via* extraction with diethyl ether.

Table 2.18

This in turn indicated that the much more rapid loss of catalytic activity we had previously noted (Table 2.10, entries 1-3) was not due to degradation of the catalytically active species, but rather that the resultant build-up of boric acid somehow hinders the transmetallation step of subsequent reaction cycles. This would also account for the observation that, under our reaction conditions, boric acid as an additive acted to reduce the level of conversion in the arylation of ketone **2.128**.

Firstly, the boric acid formed as a by-product is moderately soluble in water, though its quaternised sodium tetrahydroxyborate salt should in turn be more soluble. Though base is

not required to generate the hydroxorhodium species when water is present, the basic aqueous conditions we have employed may serve to quaternise the boric acid that is generated as a by-product, and separate the majority of its salt into the aqueous layer. Although boric acid has a similar pK_a to the aryl boronic acids employed (*p*-$MeC_6H_4B(OH)_2$ 9.3; *p*-$MeOC_6H_4B(OH)_2$ 9.3),[13] neither the boronic acids or quaternised boronates are likely to be quite so water soluble due to the relative hydrophobicity of the aryl substituents. In the recycling experiments, extraction with three sequential portions of diethyl ether will most likely be enough to remove any residual boronic acid, including the portion that prior to introduction of the organic washes was in the quaternised borate form at equilibrium concentrations.

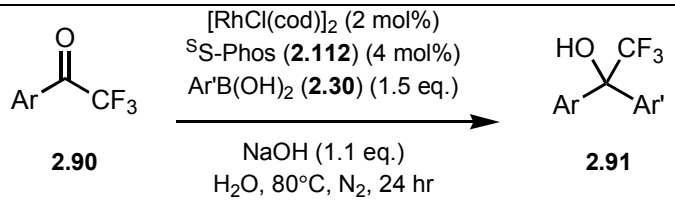
In contrast, boric acid and its sodium hydroxide salt will likely accumulate in the aqueous phase, not being as significantly soluble in diethyl ether. Thus, 1.1 equivalents of base per-cycle is apparently sufficient to maintain the pH at a level where any boric acid generated may be neutralised. This either prevents a reduction in the pH to a point at which it otherwise hinders the formation of the active hydroxorhodium complex, prevents boric acid from competitively inhibiting the metal centre, or acts as a combination of these two factors.

As mentioned above, Hartwig has reported that hydroxorhodium complex **2.130** reacts with phenylboronic acid with loss of water to generate the corresponding rhodium boronate complex **2.131** (Scheme 2.32). Thus, it is not unreasonable to expect that boric acid could also displace such hydroxide ligands. Additionally, enones bind more favourably to rhodium in 1,4-addition reactions than the corresponding carbonyl compounds do in 1,2-addition.[18, 88, 89] Thus boric acid may be reasonably effective at coordinating in place of the carbonyl compounds.

Such factors could be contributing to the observed effects of both solvent and base equivalency on the conversion of the arylation reactions. At higher equivalents of base (c. 2.0 equivalents) the boronic acid will exist predominantly in the quaternised form as demonstrated by Lloyd-Jones *et al.*, which may not favour transmetallation with a hydroxorhodium complex. The pK_a of the boronic acid is very similar to that of boric acid. However, the ionic character of the tetrahydroxyborate anion is more uniformly distributed than for the organoborate anion of an amphiphilic arylboronic acid.[13] As such, when both are present in a high water-content system, then quaternisation of boric acid should at least be somewhat more favourable due to the corresponding difference in solvation energy for the two species. While the borate by-products are therefore going to be preferentially diluted into the aqueous layer, higher concentrations of the amphiphilic boronic acids and

organoboronate salts should be found in the organic droplets, especially at, or close to, the phase boundary. As mentioned previously, ^{S}S-Phos is also likely to accumulate in this surface region too – hence potentially explaining why in combination these conditions yield such an active system.

2.11.3. Trifluoromethyl Ketones as Substrates



2.90 **2.91**

Entry	Ar		Ar'		Product	Yield (%)[a]
1	Ph	**2.90a**	Ph	**2.30a**	**2.91aa**	87
2	Ph	**2.90a**	*p*-MeC_6H_4	**2.30c**	**2.91ac**	90
3	Ph	**2.90a**	*p*-$MeOC_6H_4$	**2.30b**	**2.91ab**	89
4	2,4,6-Mes	**2.90c**	*p*-MeC_6H_4	**2.30c**	-	0[b]
5	*p*-ClC_6H_4	**2.90b**	Ph	**2.30a**	**2.91ab**	78
6	*p*-ClC_6H_4	**2.90b**	*p*-MeC_6H_4	**2.30c**	**2.91bc**	94
7	*p*-ClC_6H_4	**2.90b**	*m*-MeC_6H_4	**2.30k**	**2.91bk**	95
8	*p*-ClC_6H_4	**2.90b**	*o*-MeC_6H_4	**2.30j**	**2.91bj**	92
9	*p*-ClC_6H_4	**2.90b**	2-Nap	**2.30l**	**2.91bl**	93
10	*p*-ClC_6H_4	**2.90b**	*p*-$MeOC_6H_4$	**2.30b**	**2.91bb**	95
11	*p*-ClC_6H_4	**2.90b**	*m*-$MeOC_6H_4$	**2.30m**	**2.91bm**	96
12	*p*-ClC_6H_4	**2.90b**	*p*-ClC_6H_4	**2.30i**	**2.91bi**	87
13	*p*-ClC_6H_4	**2.90b**	*m*-ClC_6H_4	**2.30n**	**2.91bn**	82

All reactions performed on 1.0 mmol of ketone in 1.5 ml water.

[a] Isolated yields after column chromatography.

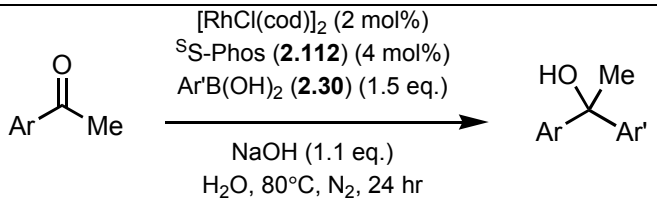
[b] The starting ketone was recovered quantitatively.

Table 2.19

While aryl methyl ketones are much less reactive than the corresponding aryl aldehydes, the use of electronically re-activated ketones in such reactions has already been discussed. Though mixtures of products are likely to be obtained for most of the 1,2-dicarbonyl substrates under the optimised reaction conditions, α,α,α-trifluoromethyl aryl ketones were selected for further investigation, being electronically activated yet still demanding substrates.

Rather pleasingly the arylation of **2.90a** and **2.90b** with a range of boronic acids gave the corresponding trifluoromethyl substituted diarylmethanols in consistently good yields (Table 2.19). Moving the *p*-methyl substituent to the *meta*- or *ortho*- position of the aryl ring of the boronic acid had no significant effect on the yields obtained (entries 6-8). Even including deactivating chloro substituents on the boronic acid was tolerated (entries 12-13). Indeed, and though rather unsurprising, the only substrate to not undergo facile arylation was the sterically demanding mesityl derivative **2.90c**, in which case the ketone was recovered unchanged in a quantitative yield (entry 4).

2.11.4. Aryl Methyl Ketones as Substrates



Entry	Ar		Ar'		Product	Conv. (%)[a]
1	*p*-$MeOC_6H_4$	**2.132**	*p*-$MeOC_6H_4$	**2.30b**	-	6
2	*p*-MeC_6H_4	**2.133**	*p*-$MeOC_6H_4$	**2.30b**	-	13
3	*p*-FC_6H_4	**2.134**	*p*-$MeOC_6H_4$	**2.30b**	-	19
4	*p*-$O_2NC_6H_4$	**2.128**	*p*-FC_6H_4	**2.30d**	-	41
5	*p*-$O_2NC_6H_4$	**2.128**	*p*-MeC_6H_4	**2.30c**	-	49
6	*p*-$O_2NC_6H_4$	**2.128**	*p*-$MeOC_6H_4$	**2.30b**	**2.129**	60
7	*p*-$O_2NC_6H_4$	**2.128**	*p*-$MeOC_6H_4$	**2.30b**	**2.129**	70 (68)[b]

All reactions performed on 1.0 mmol of ketone in 1.5 ml water.

[a] As determined by ^1H NMR, isolated yields in parentheses.

[b] Using 5.0 equivalents of boronic acid.

Table 2.20

Finally we investigated the reactivity of aryl methyl ketones under the optimised conditions, and found an electronic effect consistent with that typically observed in couplings of aryl aldehydes and arylboronic acids. Thus, reducing electron density at the carbonyl carbon (Table 2.20, entries 1-3), or correspondingly increasing electron density at the *ipso*- carbon of the boronic acid (entries 4-6), results in a higher conversion. It also appears that the electronic nature of the ketone substrate is of greater importance in determining the overall reactivity of the substrate pair, with only the *p*-nitroacetophenone substrate offering reasonable conversion to the corresponding products (entries 4-6).

2.12. Discussion of Protodeboronation as A Competing Pathway

The arylation of *p*-nitroacetophenone **2.128** with *p*-methoxyphenylboronic acid **2.30b** on a 1.0 mmol scale of the ketone resulted in a 60% conversion to the tertiary diaryl alcohol **2.129** (Table 2.20, entry 6). As has been mentioned previously, increasing the reaction temperature from 80 to 100 °C was shown to result in a marginally reduced conversion to the arylation product (Table 2.17, entries 3 & 4). Although this might be explained in a number of ways, it seems unlikely that degradation of the catalyst at the higher temperature was a significant factor, as the reaction still proceeded to give a similar result at 100 °C to that which was obtained at 80 °C. What is more likely is that, upon increasing the temperature from 80 °C to 100 °C, the rate of arylation is no longer increasing to the same degree as are the rates of other pathways that consume the boronic acid.

Such reactions may be broken down into either those that are mediated by the catalyst, or those that are not. Firstly, the reaction conditions involve the boronic acid being exposed to an aqueous reaction media, strong base, and elevated temperatures. Under such conditions, boronic acids are known to be susceptible to base-induced protodeboronation, yielding ArH. However, arylboronic acids, and especially those like *p*-methoxyphenylboronic acid (**2.30b**) which are also electron rich, are quite resistant to this process.[13] Alternatively, transmetallation to form the aryl-rhodium complex is known to be facile, while the arylation of ketone substrates is relatively slow.[20] Thus, the aryl-rhodium complex may undergo competitive side reactions that act to consume the boronic acid at a rate comparable to that at which the ketone is arylated. Under reaction conditions such as these then the major pathway available will very likely be hydrolysis of the rhodium-aryl bond to yield ArH.

In addition, the original ketone arylation reactions with and without added ^{S}S-Phos ligand (Table 2.13, entries 1 and 2) show that in the presence of ^{S}S-Phos after only two hours a 41% conversion is observed. In contrast, without the addition of ^{S}S-Phos the reaction using only $[RhCl(cod)]_2$ showed a 43% conversion after 48 hours. Though both reactions obtained a similar conversion, the reaction with ^{S}S-Phos was confirmed to be continuing beyond that period of time, while after 48 hours in the presence of $[RhCl(cod)]_2$ and aqueous base it is likely that the boronic acid will have been completely consumed. Thus, as is observed with electron rich phosphine ligands in arylation reactions of aryl aldehydes, ^{S}S-Phos appears to improve the ability of the rhodium centre to effect overall transfer of the aryl moiety to the carbonyl carbon of the ketone, but without reducing the Lewis-acidity of the rhodium centre to such a degree that the ketone is not first able to favourably coordinate.

Along with the result obtained from the use of only $[RhCl(cod)]_2$, the observation of increased conversion having occurred with a decreased volume of water employed suggests that the dominant pathway for the loss of boronic acid could well be through the hydrolysis of the rhodium-aryl bond. If the non-metal mediated pathway of base induced protodeboronation were dominant, then a more concentrated basic solution could be expected to accelerate this process and so potentially reduce the conversion overall, which was not found to be the case (Table 2.16, compare entries 1 and 6).

Whatever the relative contributions from these two pathways, the overall effect is to limit the maximum yield of arylation product that may be obtained. Therefore, further equivalents of boronic acid were employed, which did indeed allow the arylation product **2.129** to be obtained in a higher yield of 68% (Table 2.20, entry 7). Interestingly, no extra base was employed in this reaction (as too high an amount, e.g. 3.0 equivalents, was noted to result in an exotherm and rapid discolouration of the reaction media), and yet the improvement in conversion to the arylated product was only moderate. This could again suggest that the metal centre is involved in the dominant pathway responsible for the loss of the aryl component, *via* transmetallation of the boronic acid and subsequent hydrolysis of the rhodium-aryl bond.

2.13. Conclusions

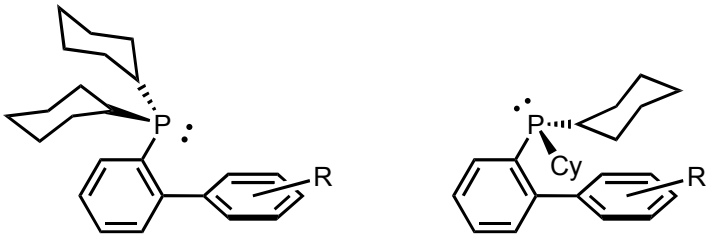
In conclusion we have shown ^{S}S-Phos to be a highly effective choice of ligand for the rhodium-catalysed 1,2-additions of arylboronic acids with a range of aryl carbonyl compounds in aqueous media. Classical sulfonated triarylphosphine ligands are often found to be less effective than their non-sulfonated analogues, especially for applications that require more strongly donating ligands. One of these such cases is the Suzuki cross-coupling of challenging substrates, where literature precedent demonstrates that the sulfonate moiety of ^{S}S-Phos, being remotely situated, does not impact the ligands ability to form very catalytically active palladium complexes that allow the reaction to proceed in aqueous media. We have subsequently shown that this ligand can also be applied to another important reaction class with a similarly high demand for electron rich phosphine ligands: The emerging rhodium-catalysed 1,2-addition reaction employing boronic acids.

The hydrophilic character of ^{S}S-Phos enabled the rhodium complex to be recycled in five successive aldehyde arylations affording quantitative conversions and 97% isolated yield of product **2.29cc** in the final run (Table 2.18). In contrast, the classical sulfonated triarylphosphine TPPMS, though of a similar hydrophilicity, produced not only a less

catalytically active complex, but was also less effective than ^{S}S-Phos for recycling purposes (Table 2.10).

Though both ^{S}S-Phos and TPPMS are monosulfonated ligands, and both may confer surface activity to the active catalyst, the phosphine environment within ^{S}S-Phos is more electron rich and sterically demanding, with such characteristics known to be prerequisite for high activity in the rhodium-catalysed 1,2-addition reaction employing boronic acids. Interestingly, computational and experimental studies on Buchwald monophosphine biaryl ligands have revealed a number of interesting features that are believed to be contributing factors in their high efficiencies for palladium-catalysed cross-coupling reactions.

Firstly, *ortho*- *ortho*'- substitution of the non-phosphine bearing aryl ring prevents the formation of palladacycles due to intramolecular C-H activation, which despite the high activity of the Herrmann-Beller catalyst and related complexes,[101] Buchwald and co-workers suggest may otherwise reduce the lifetime of active catalysts formed by ligands such as S-Phos.[102]



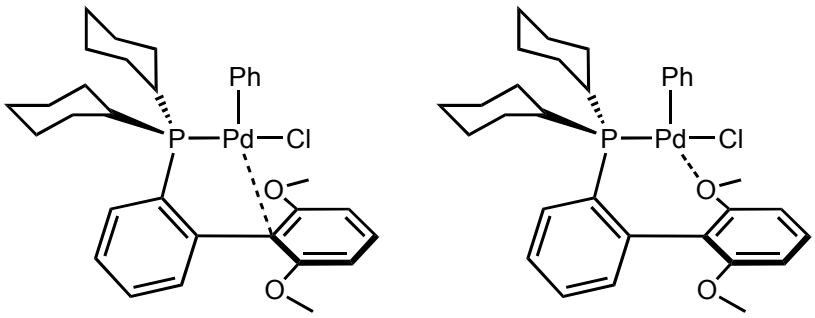
2.135 **2.136**

Figure 2.8

Secondly, all such ligands to so far have been structurally characterised by crystallographic analysis are known to exclusively adopt conformation **2.135**, where the non-biaryl substituents of the phosphine moiety are found to be sitting away from the neighbouring ring of the biphenyl backbone, rather than towards it as exemplified by conformation **2.136**. Computational analysis has ruled out inversion at the phosphine centre as being too energetically demanding, and as such the exact nature of the substituents involved determines the ease with which the system may move between these two conformers by means of rotation about to aryl-P bond. Despite the lower energy barrier for this process to occur with less hindered ligands such as S-Phos (in comparison to, e.g., X-Phos), ^{31}P NMR data confirms that even in solution the less sterically hindered analogues still adopt conformation **2.135**, as only a single phosphine resonance is observed.[103]

Importantly an *anti* conformation akin to **2.135** is also adopted by Pd(0) complexes containing one biarylphosphine ligand, such as [Pd(S-Phos)(dba)] **2.139**[102] and [Pd(X-Phos)(dba)][104]. Those complexes also exhibit η^1-arene interactions between the *ipso*- carbon of the neighbouring aryl ring and the Pd(0) centre (e.g. **2.139**, Figure 2.10). Coordinatively unsaturated complexes such as those derived from **2.139** are highly reactive, making them very active for the initial oxidative addition step of the Suzuki coupling catalytic cycle. This type of interaction is postulated to help increase complex stability, so avoiding degradation, but without coordinating the metal centre so strongly that it significantly affects the ease with which it is subsequently able to dissociate before insertion into even unactivated arylchloride bonds.

DFT analyses have revealed that these stabilising interactions do not appear to be of importance in the transition state structures calculated for the oxidative addition of PhCl and L•Pd (L = S-Phos, X-Phos). However, they do appear to stabilise both the highly active L•Pd complex and the oxidative addition adduct L•Pd(Ph)(Cl) in their ground states, helping to explain why biaryl ligands of this type form both very active, yet relatively stable, catalytic complexes.[104]

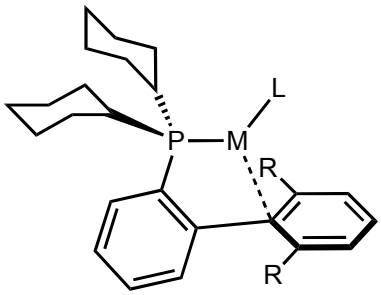


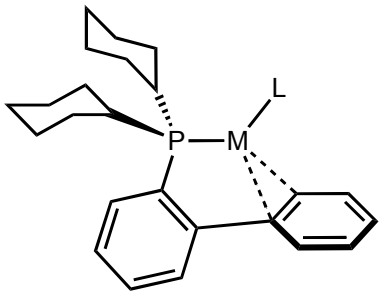
2.137 **2.138**

Figure 2.9

Specifically, the DFT analysis of S-Phos•Pd(Ph)(Cl) revealed that two complexes containing the chloride ligand *trans* to the phosphine were the most energetically favourable conformations, with the slightly higher energy one (**2.137**) exhibiting interaction between the palladium centre and the *ipso*-carbon, and the other (**2.138**) a Pd-O interaction with one of the methoxy ethers. Experimental support for this was obtained through variable temperature ^{31}P NMR of the oxidative addition adduct, which revealed two complexes in a ratio of approximately 3:1, which when extrapolated back closely agrees with the relative energies calculated by DFT.

Though the above studies were focussed on the relevance of the dialkylbiaryl monophosphine ligands in forming catalytically relevant palladium complexes, Goldberg *et al.* have recently shown that similar stabilising interactions can be found in their related rhodium(I) complexes.[105]





(**2.139**) M = Pd: L = DBA, R = OMe (XRD)

(**2.141**) [M] = [Rh][B(Ar_F)$_4$]: L = NBD (XRD)

(**2.140**) [M] = [Rh][B(Ar_F)$_4$]: L = NBD, R = O*i*-Pr (NMR)

Figure 2.10

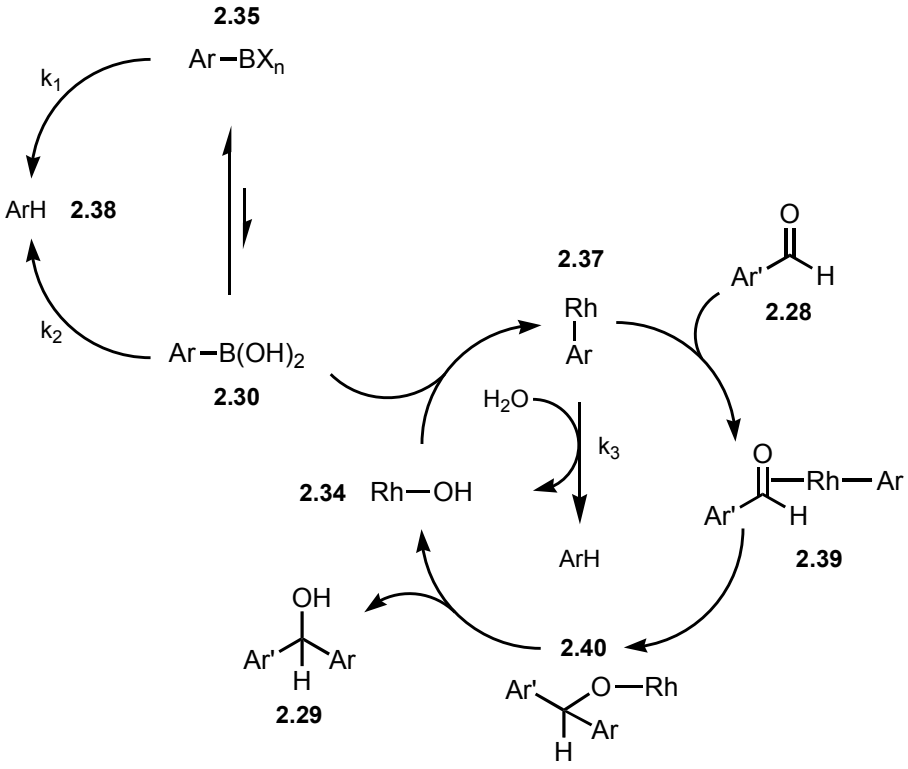
Treatment of $[RhCl(nbd)]_2$ with the appropriate biaryl ligand yielded [RhCl(phosphine)(nbd)], which underwent salt metathesis when treated with $NaB(Ar_F)_4$ to give cationic complexes, including **2.140** and **2.141**. The crystal structure of **2.141** reveals a square planar rhodium(I) complex (NBD ligand coordination mode is simplified in Figure 2.10, though coordinated as normal through both olefin moieties) exhibiting an η^2-arene coordination, and while the [Rh(Ru-Phos)(nbd)][B(Ar_F)4] complex **2.140** was not characterised by XRD, ^{13}C NMR analysis shows an upfield shifted *ipso*- carbon, also indicative of η^1-arene coordination analogous to that observed in the Pd(0)(S-Phos)(dba) complex **2.139**.[102]

Therefore ^{S}S-Phos, though somewhat electronically different to S-Phos at the non-phosphine aryl ring, could potentially also be offering similar stabilising interactions to a coordinatively unsaturated rhodium(I) complex active within our system. This could in turn be a contributory factor in the high activity maintained when using ^{S}S-Phos in recycling experiments.

2.14. Future Work

Future investigations could focus on better determining the hydrolytic stability of the boronic acids under aqueous basic conditions, in both the absence and presence of rhodium. Though staggered additions of sensitive boronic acids can result in better yields in e.g. Suzuki coupling reactions, such protocols are not as ideal as using reagents which slowly release the more sensitive species active for transmetallation.[106] Though some of these reagents would not be amenable to being used under these conditions (e.g. MIDA boronates, due to their sensitivity to aqueous base[107]), it may be possible to select a reagent class which is more resistant to both hydrolytic degradation and rapid hydrolytic activation.

For example, the use of certain diols or triols could yield boronate ester or borate derivatives that do not readily transmetallate with the metal centre, but which are hydrolysed at a slow rate to a species that does. As long as the alcohol freed on hydrolysis of the ester had no significant affinity for coordinating to the active catalyst, then this could allow for an initial charge of organoboron **2.35** to slowly release an active species such as the boronic acid (**2.30**), which then undergoes transmetallation to form a rhodium-aryl complex **2.37** (Scheme 2.33).



Scheme 2.33

However, this approach is only of significant utility if the majority of protodeboronation is base induced (k_1, but predominantly k_2), and not mediated by the metal centre (k_3). The rate-limiting step in Suzuki coupling reactions employing standard catalysts is often regarded as being oxidative addition, which precedes the transmetallation event (see discussions in Chapter 1). However, in the rhodium-catalysed 1,2-addition reaction even when employing aryl aldehydes it is generally accepted that coordination of the aldehyde to the organorhodium complex is rate limiting. With the less reactive ketones this process is likely even slower, and so if hydrolysis of the rhodium-aryl bond accounts for the majority of the protodeboronation by-product generated, then a slower release of the transmetallating agent should not have a significant impact on the overall yield of carbonyl arylation.

The potential already demonstrated by this early system is however still considerable – it already being a notable advance upon analogous protocols such as those detailed in the literature. In this respect specifically, then aryl methyl ketones have been uniformly avoided as substrates for rhodium-catalysed 1,2-addition reactions employing boronic acids – their involvement as functional groups having previously being limited to the role of a spectator moiety only otherwise present in certain aldehyde substrates, rather than being themselves the target for arylation. Furthermore, the ability to access trifluoromethyl substituted diarylmethanols by such protocols as the one we have developed, is also particularly significant given the value associated with the trifluoromethyl moiety within the context of medicinal chemistry.[52, 108] Future investigations would do well to focus on expanding the substrate scope so as to include provision for generating ketone and trifluoromethyl ketone arylated products, especially any which may otherwise be difficult to access by protocols employing organomagnesium or organolithium reagents.

The investigations detailed in this chapter have been published.[109]

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Chapter 3

This chapter details the synthesis of a novel azido-boronate ester possessing an extremely high level of bench-stability, and its application in sequential copper-catalysed azide-alkyne cycloaddition and Suzuki-Miyaura coupling reactions. The modular nature of such chemistry, combined with the potential modularity in respect to structural variations of the molecular core, make this a valuable approach for tackling a wide range of synthetic challenges across a diverse range of fields. Indeed, an initial proof-of-concept use demonstrates the utility and versatility offered by such privileged structures within the context of drug-discovery.

3.1. Click Chemistry

In 2001 Kolb, Finn and Sharpless detailed a new chemical philosophy they named "*click chemistry*" as an alternative approach for the expedient synthesis of drug-like molecules.[1] Central to that philosophy is the concept that molecular complexity is not necessarily an indicator of molecular utility; and while the syntheses of certain natural products remain significant as both synthetic achievements, and in terms of the methodological advances that they engendered, at times too much interest is focussed on attempting to mimic biochemical transformations. They state that while nature has had billions of years to perfect enzymatically mediated carbonyl chemistry of the aldol-type, that unless there is specific reason to do so, synthetic chemists would do better to concentrate on carbon-carbon bond forming reactions that they are more easily able to effect in a selective, facile, and straightforward manner.

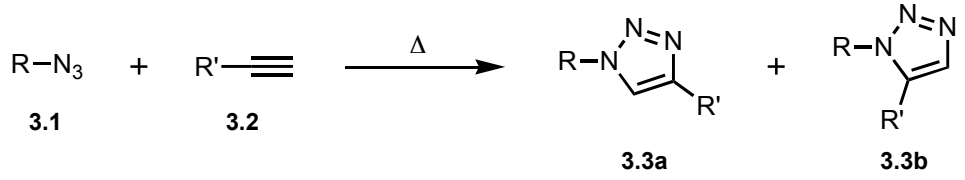
They then defined a number of parameters that a reaction should possess in order to be considered for primacy in such a context, naming such transformations "*click reactions*". In summary, click reactions are modular, scalable, wide in scope, reliable, high yielding, stereospecific, generate only inoffensive by-products, and involve simple synthetic protocols with straightforward isolation and purification steps. Although ultimately an idealised set of characteristics, a number of reactions with correspondingly high thermodynamic driving forces were named – including certain examples of nucleophilic ring-opening of strained heterocyclic rings (e.g. epoxides and aziridines), "*non-aldol*" carbonyl chemistry (e.g. Michael additions), and additions to carbon-carbon multiple bonds (e.g. oxidations and dihydroxylations).

Cycloadditions involving heteroatoms were noted to be one of the most ideal examples of a click reaction, especially the 1,3-dipolar cycloadditions. Of these, the authors famously cited the Huisgen 1,3-dipolar cycloaddition of azides and alkynes as "*the cream of the crop*".[1]

3.2. The Huisgen 1,3-Dipolar Cycloaddition

Reaction conditions typically involve that the organoazide and alkyne are reacted together in a high boiling point solvent, most often toluene or carbon tetrachloride, and heated at reflux for long periods – typically in the region of 10-48 hours; although strained and electronically activated alkynes may react more rapidly.[2, 3]

In their reactions with organic azides **3.1**, terminal alkynes **3.2** allow for the synthesis of disubstituted 1,2,3-triazoles (**3.3**), while internal alkynes yield the corresponding 1,4,5-trisubstituted analogues. The reaction proceeds *via* a concerted pathway, and as a result of the activation energies of the relevant intermediates typically being very similar, then the use of terminal alkynes generally results in the formation of a mixture of the 1,4- and 1,5-regioisomers (**3.3a** and **3.3b** respectively).



Scheme 3.1

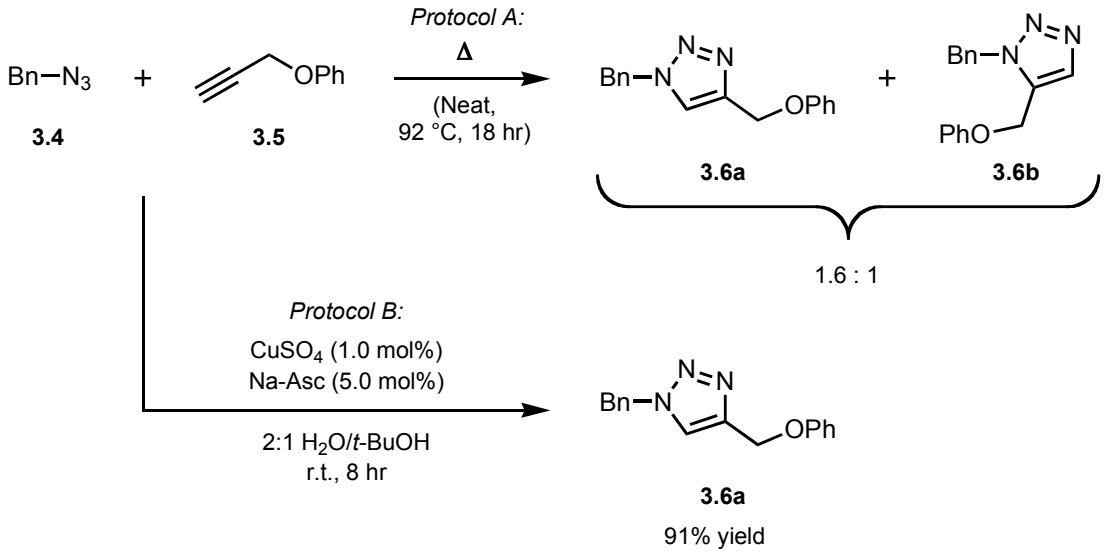
Converse to their high reactivity towards one another, both azides and alkynes are tolerant of many of the most common and useful synthetic manipulations, as well as atmospheric moisture and oxygen; allowing them to be easily carried through synthetic routes without the need for protecting group methodologies of the type that are so often a necessity when employing carbonyl chemistry in syntheses.[1] Despite the high synthetic utility of this cycloaddition reaction, Sharpless and co-workers noted that the reputation of azides as being unstable and potentially explosive had led them to being overlooked as the valuable synthetic intermediates they are.

3.3. The Copper-Catalysed Azide Alkyne Cycloaddition (CuAAC) Reaction

However, the year subsequent to the establishment of the click chemistry philosophy saw the publication of the seminal copper-catalysed variant of the Huisgen reaction, reported independently by the groups of Meldal[4] and Sharpless[5]. They both demonstrated that Cu(I) catalysts were highly active for the regioselective formation of 1,4-disubstituted 1,2,3-

triazoles from a range of organoazides and terminal alkynes, and that as such the requirement for refluxing azides at high temperatures – as is typically required for successful Huisgen cycloaddition – was negated.

Meldal and co-workers focussed on using resin-bound terminal alkynes, and as a result their protocols were somewhat limited in terms of scope. However, they did show that a range of azides could be coupled with the supported alkyne, while important functional groups relevant to solid-phase-synthesis such as Fmoc, Boc, Pmc and trityl groups were all tolerated.[4]



Scheme 3.2: Reaction conditions and product distribution for a thermal Huisgen 1,3-dipolar cycloaddition reaction (*Protocol A*), compared with Sharpless and co-worker's approach (*Protocol B*).

Though both of the original CuAAC reports noted a number of common and important features, the approach of Sharpless and co-workers proved to be a more general one (as exemplified by *Protocol B* of Scheme 3.2). In particular they noted excellent functional group tolerance and wide substrate scope for both the azide and alkyne components. The reaction protocol is operationally simple, with no need for special precautions so as to exclude oxygen or water. Indeed, the reactions were found to proceed more effectively when conducted in a solvent system containing water. They found that *in situ* reduction of Cu(II) to Cu(I) with sodium ascorbate (abbreviated in schemes as Na-Asc) yielded a highly active catalyst. Although Cu(I) sources also performed well, the use of $CuSO_4.5H_2O$ in combination with sodium ascorbate as a source of Cu(I) was more cost effective, more tolerant of adventitious oxygen, and noted to ultimately provide a purer source of active catalyst than did commercial Cu(I) sources. Such procedures allowed the reactions to be conducted in sealed vials, but with no other attempts to avoid exposure to atmospheric oxygen.[5]

In contrast to the thermally induced cycloaddition reaction between **3.4** and **3.5** (Scheme 3.2, *Protocol A*) which gave the 1,4- (**3.6a**) and 1,5- (**3.6b**) disubstituted triazole products in a ratio of 1.6:1, the copper-catalysed version (*Protocol B*) furnished exclusively the 1,4-regioisomer **3.6a** in high yield and purity, after a shorter reaction time, and without the need for heating. Sharpless and co-workers also noted that these reactions proceeded well between pH values in the approximate range of 4-12, and even in human plasma with proteins present.[5]

Overall the CuAAC reaction allows the coupling of diverse components to be achieved, linked by the thermally and hydrolytically stable 1,2,3-triazole moiety, in high yields and under myriad reaction conditions. As such, after the original publications by the groups of Meldal and Sharpless, the use of the CuAAC reaction rapidly crossed the disciplinary boundaries of the physical sciences, and now an extremely large number of reports are published every year on the application of this transformation in biology and biological chemistry,[6-8] as well as in materials, surface and polymer science.[9-11]

With such breadth for potential discussion, and so many recent reviews of these areas (*viz.*, each of the previous six references; in addition to a recent review,[12] as well as another very detailed, though nowhere near exhaustive review[13]) the focus of the remainder of this short introduction will be on briefly outlining those key aspects of the CuAAC reaction that are most applicable to organic synthesis, as well as to subsequent discussions of the research investigations presented herein.

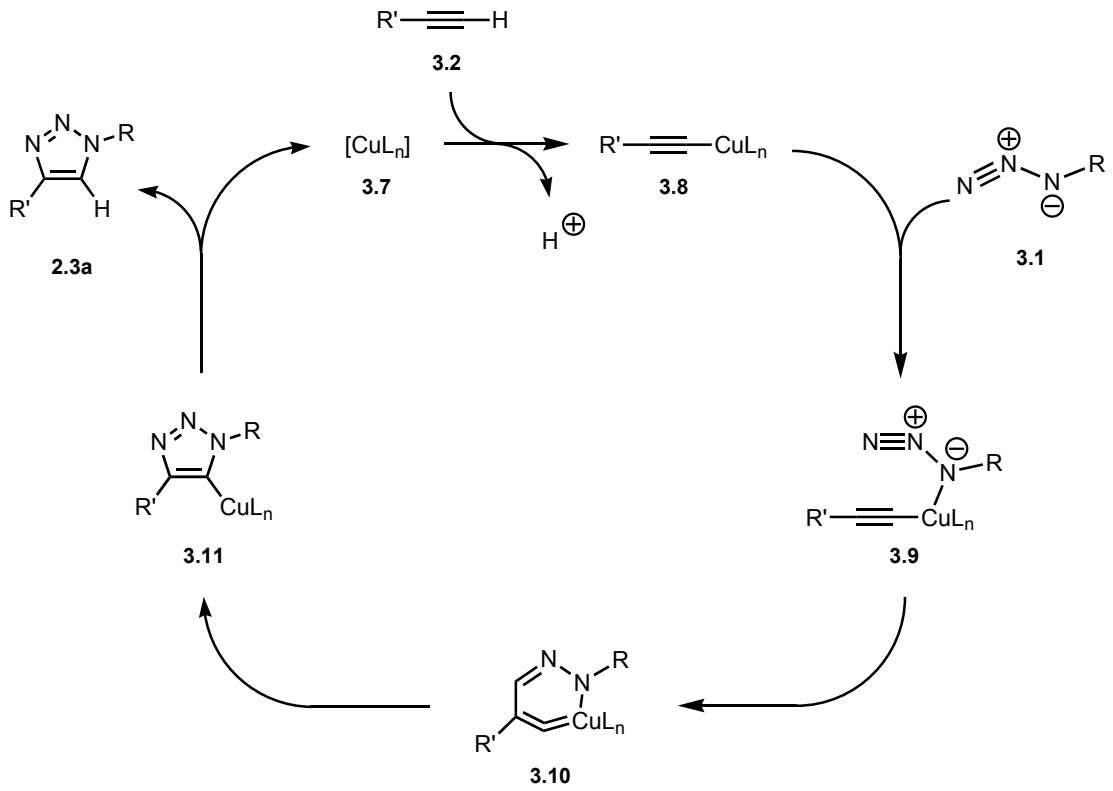
3.3.1. Mechanistic Details of the CuAAC

The concerted Huisgen cycloaddition reaction is highly exothermic (ΔH^0 of -50 to -65 kcal/mol), but has a correspondingly high activation barrier – calculated to be approximately 25 kcal/mol for the reaction between MeN_3 and propyne. In contrast, DFT analysis revealed that the copper-catalysed analogue proceeds by a stepwise sequence, with an overall rate of reaction approximately 10^7 times that of the thermal process.[14]

It is proposed that a π-alkyne copper complex is key in initiating the catalytic reaction by raising the acidity of the alkynyl proton – this in turn allows the exothermic formation of copper acetylide **3.8** to then proceed, even in the case of an acidic aqueous medium. Subsequent exchange of a spectator ligand allows coordination of the azide **3.1** at the metal centre to yield **3.9**, which results in activation of both the nucleophilic carbon of the alkyne and the electrophilic terminus of the azide. This allows for the formation of the first C-N bond

between N-3 and C-4 to occur, resulting in a strained six-membered Cu(III) metallacycle **3.10**. Although this step involving formation of **3.10** is calculated to be both endothermic and rate determining, the activation barrier of 18.7 kcal/mol (for L = H_2O) is notably lower than the activation barrier for the corresponding thermal 1,3-dipolar cycloaddition (25.7 and 26.0 kcal/mol), which accounts predominantly for the increased rate of the catalysed reaction.[14]

The subsequent transition state involved in the collapse of metallacycle **3.10** is very close in energy to this intermediate, and due to the high exothermicity of this pathway the process occurs rapidly, yielding the copper triazolide **3.11**. Finally, the copper triazolide is protonated, releasing the product triazole **2.3a** and regenerating the copper catalyst **3.7**.[14] The isolation of copper-triazolyl complexes containing sterically bulky substituents that act to disfavour the protonolysis step further supports this hypothesis.[15]

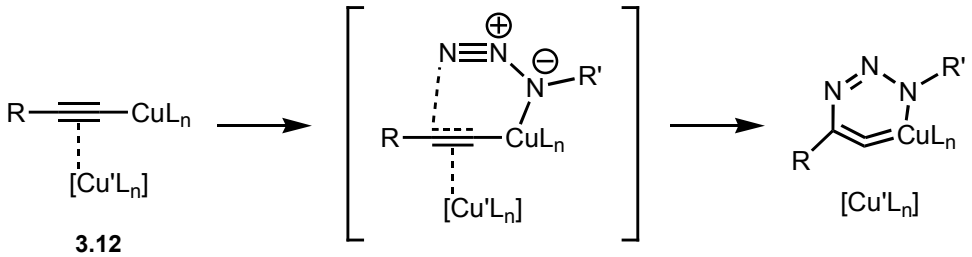


Scheme 3.3

Much of the above discussion on the intricacies of the CuAAC catalytic cycle are based on results from an early DFT analysis conducted by Sharpless, Fokin, Noodleman and co-workers.[14] Although the results of that analysis compared well with much of the experimental evidence available at that time to explain both the high regioselectivity and rate, further kinetic[16] and computational studies[17] suggest the involvement of dinuclear copper acetylides (such as those shown in Scheme 3.4). As such those species account for a further lowering of

the relevant activation barriers, including stabilisation of the unusual Cu(III) metallacycle **3.14** generated from **3.12** *via* **3.13** (*vs*. mononuclear analogue **3.10** formed from **3.9**), further increasing the rate of the catalytic reaction as calculated for their monomeric analogues.

Indeed, the CuAAC has now been shown to be much more complex even than that, as different species appear to be catalytically active during different stages throughout the progress of these reactions. This recently led Fokin to note that such exceptionally high and reliable catalytic activity for the selective formation of the 1,4-regioisomers is unique to copper(I), and that this may in part stem from its ability to interact with terminal alkynes in both π and σ coordination modes, as well being able to undergo rapid ligand substitution reactions, especially in aqueous media. As such the observed complexity in both the reaction kinetics and the coordination behaviour of Cu(I) are potentially intimately connected, and also critical to the unique ability of copper(I) to accelerate the reaction in this way.[12]



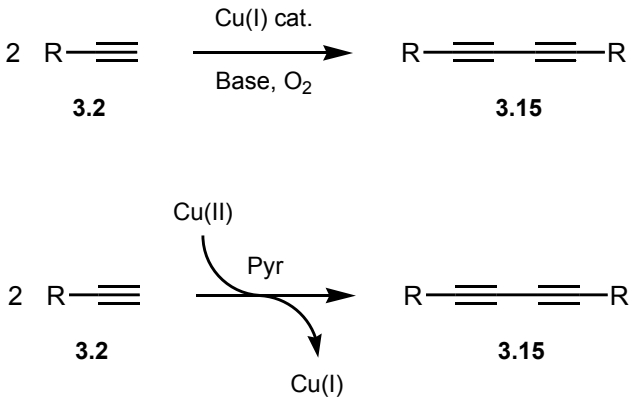
Scheme 3.4

3.3.2. Increasing the CuAAC Rate & Controlling Side Reactions

Cu(I) is the most thermodynamically unstable of the three most common copper oxidation states, Cu(0-II), and copper(I) used in organic solvent systems without exclusion of oxygen can promote oxidative homocoupling of terminal alkynes.[12] This behaviour also accounts for many of the limitations to the CuAAC system as reported originally by Meldal – primarily, that it was not possible to substitute the resin bound alkyne with an equivalent azide.[4] Furthermore the relative instability of Cu(I) was also what prompted Sharpless and co-workers to employ sodium ascorbate for the *in situ* reduction of $Cu(II)SO_4.5H_2O$, as using an excess of reducing agent relative to Cu(II) helps to ensure that any re-oxidation of Cu(I) to Cu(II) is reversed.[5]

Although reports citing active Cu(II) catalysts for the CuAAC reaction have been published, such claims are ultimately not accurate. Under such conditions as are required for the CuAAC reaction, a number of pathways are available that allow for the reduction of Cu(II) pre-

catalysts, resulting in the *in situ* formation of Cu(I) species possessing the corresponding catalytic activities which are ultimately what accounts for the observed results.[12] Most notably the Glaser coupling[18-20] and related Eglinton reaction[21] allow for the formation of Cu(I) from Cu(II) *via* oxidative homocoupling of terminal alkynes (Scheme 3.5). Thus, in the necessary presence of such substrates for the CuAAC reaction, then the generation of CuAAC active Cu(I) species through pathways such as these is very readily explained.



Scheme 3.5: Glaser coupling (top) and related Eglinton coupling (bottom).

Sharpless and co-workers originally noted that even copper(0) in the form of metal turnings was able to provide a sufficient amount of active Cu(I) catalyst (which arises from comproportionation of the Cu(II)/Cu(0) couple[14, 22]), although such reactions do proceed more slowly than those directly using either Cu(I), or Cu(II) in combination with a reductant such as sodium ascorbate.[5] More recently the CuAAC has been performed in flow-reactors, including examples where a metallic copper section of the reactor acts as the source of Cu(I).[23]

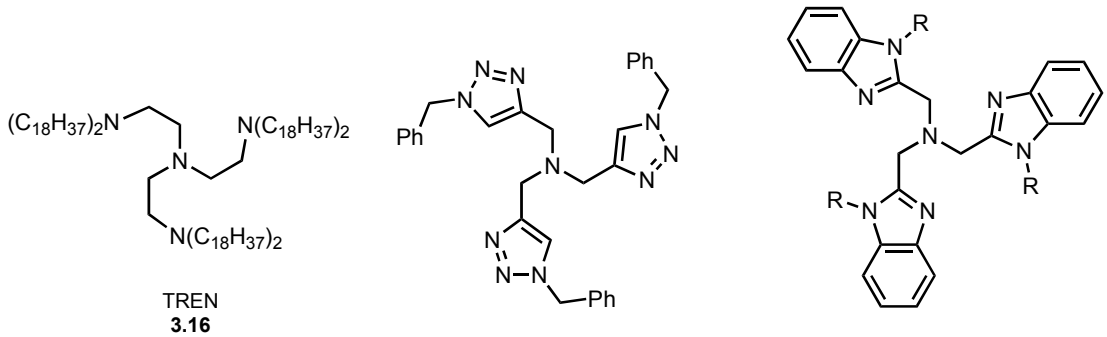


Figure 3.1

Although even simple catalyst systems such as that reported originally by Sharpless are highly active, numerous ligands and additives have been employed in different circumstances in order to increase the desired catalytic activity of various systems. As important as the

phosphine and NHC ligand classes are for many other transition metal-catalysed reactions, they are of less significance in the context of the CuAAC reaction. In contrast, amines and heterocyclic donor ligands (that in turn also typically include an amine moiety as part of the ligand backbone) see widespread application, as they are often particularly effective at preventing aggregation of the active Cu(I) species and also promote coordination of the azide to the relevant copper acetylide species.[12] Examples of amines include NEt_3 and DIPEA,[13] or TREN (**3.16**)[24]; while heterocyclic ligands include TBTA (**3.17**)[25] and tris(benzimidazole) amine derivatives of type **3.18**[26] – including water soluble variants substituted with hydrophilic sidearms.[26, 27]

In particular the multidentate ligands such as those in the TBTA (**3.17**) and tris(benzimidazole) amine (**3.18**) families may allow copper to be more completely removed from the products, and are often very effective at both stabilising the Cu(I) species and increasing the overall catalytic activity. For such reasons they are especially important in situations where overall copper concentrations must be kept low, while removal of dissolved oxygen from the system is not always feasible – for example in many bioconjugation protocols. These multidentate ligands may also bind more than one copper centre, and in combination with the findings that dinuclear copper acetylides are more active catalysts, this may also help to explain why they are so effective in catalysing an already remarkably facile reaction.[12]

3.4. The Ruthenium-Catalysed Azide Alkyne Cycloaddition (RuAAC) Reaction

Due to the involvement of a copper-acetylide in the CuAAC reaction, then the addition of internal alkynes with azides is not catalysed by the copper(I) centre. In contrast to this, and the 1,4-regioselectivity observed in the copper analogue, the use of ruthenium(II) complexes (most especially of the type [Cp*RuCl]) allow catalysed access to both 1,5-disubsituted (**3.6b**) and 1,4,5-trisubstituted 1,2,3-triazoles. Although the exceptional tolerance for deviation in almost every significant reaction parameter as exhibited by the CuAAC variant is, rather unsurprisingly, not closely matched, RuAAC reactions can still prove highly selective and high yielding.[28-30]

3.5. 1,2,3-Triazoles

The CuAAC, RuAAC and Huisgen reactions all allow for the synthesis of the thermally and hydrolytically stable 1,2,3-triazole moiety. Although this functional group is ideal for many conjugation and ligation strategies simply due to it forming what effectively is an inert bridging motif, the properties of these compounds mean that they have other important applications.

The original click chemistry philosophy was focussed in particular on accelerating the drug discovery process, and in this context both 1,2,3- and 1,2,4- triazoles are important structural features in a number of biologically active compounds. With recent advances in forming 1,2,3-triazoles, as have been detailed above, a significant increase in interest in using this motif for forming biologically active compounds has resulted.[31] Most notably in this respect a drug substance containing a 1,4-disubstituted 1,2,3-triazole was recently granted approval for the management of epileptic seizures (see Section 3.18). The importance of the 1,2,3-triazole moiety in this context is not simply as a result of it being accessible *via* a "click" reaction; indeed the 1,2,3-triazole itself is planar, has a strong dipole, and is able to form hydrogen bonds – both as an acceptor and donor – and thus typically imparts high levels of crystallinity. Furthermore, 1,2,3-triazoles can prove metabolically stable and may in some cases even mimic peptide bonds *in vivo* (as depicted in Figure 3.2), making the Huisgen, CuAAC and RuAAC reactions important ways to approach many potentially valuable functionalised 1,2,3-triazoles.[5, 8]

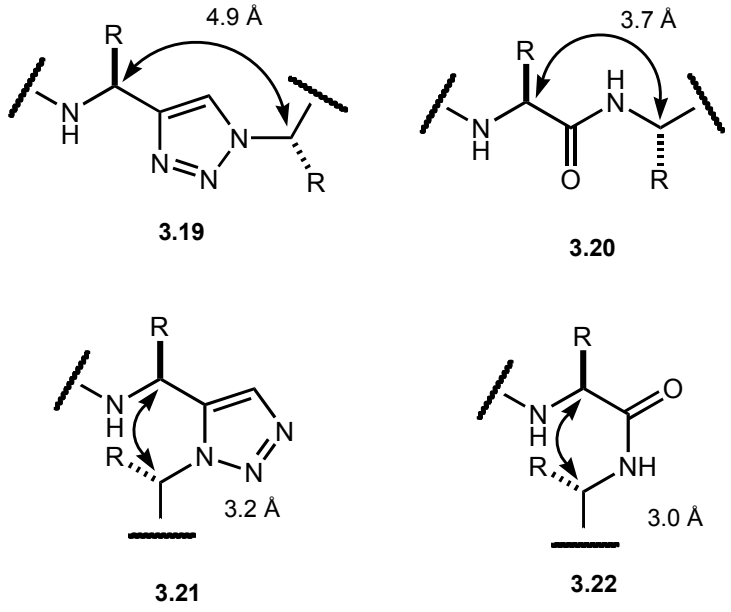
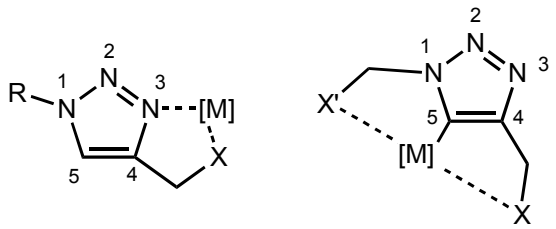


Figure 3.2: 3.19 and **3.21** are loose structural and electronic mimics for *trans*- and *cis*- peptide bonds **3.20** and **3.21** respectively.[8]

The utility resulting from such physical and chemical properties is not limited just to relevance in biochemical applications either. Indeed, such features also make the 1,2,3-triazole an interesting and potentially important metal ligating motif, especially in the N-3 (**3.23**) and metal-triazolyl type (**3.24**) coordination modes. Furthermore, the ease with which such derivatives can now be accessed has resulted in a much greater interest in their character as ligands.[32]



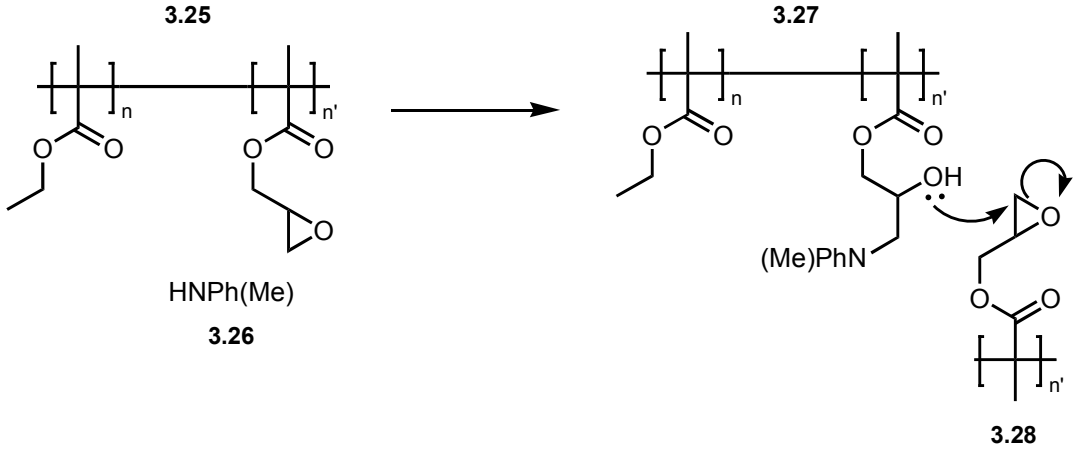
3.23 **3.24**

Figure 3.3 [32]

3.6. Results & Discussion – Aims

As has been discussed above, although the initial focus of the click chemistry philosophy was for increasing both synthetic efficiency and structural range in the investigations of chemical space containing drug-like structures, the same fundamental "click reaction" qualities are important to a much broader area of the physical sciences than just synthetic organic chemistry in the context of drug discovery.

The key features required of click reactions, such as reliability, reproducibility, broad substrate scope, and high selectivities are in fact equally important for reactions applied in such fields as macromolecular and supramolecular chemistry. Indeed, while a reaction may proceed at a facile rate and exactly as intended when employed in a homogeneous system with substrates typical of synthetic organic chemistry, the same may not be true when such small molecules are replaced by functionalised surfaces or polymers.[10, 23]



Scheme 3.6: Derivitisation of an atactic acrylate co-polymer.

During our own such attempts to translate what were otherwise straightforward synthetic organic protocols to both of the aforementioned substrate classes, we encountered various problems with poor levels of reactivity and selectivity. In addition, while isolation and

analysis of typical organic reaction products might be straightforward, the corresponding procedures with macromolecular substrates are generally much more time and resource intensive in this respect, and it is often a much more complex task to obtain even qualitative analytical data. For example, line-broadening due to diffusion effects and signal averaging, even in what are relatively low molecular-weight polymers, renders even as powerful a tool as ^{1}H NMR – frequently used in synthetic organic chemistry as a quantitative analytical technique – much less useful, and often qualitative at best.[33]

Indeed, even when we employed a click reaction – the nucleophilic opening of an epoxide with an amine – that proceeded as expected on a model organic substrate, when transferred to a functionalised polymer even such an elementary transformation was slow and we encountered problems specific to the polymer substrates – most significantly cross-linking *via* the resulting pendant alcohol (Scheme 3.6). This personally highlighted to us that although undoubtedly synthetically valuable in certain instances, pendant functionalities can prove problematic in others; therefore, reactions such as the CuAAC that incorporate only an inert motif into the synthetic product are often particularly valuable in such instances.

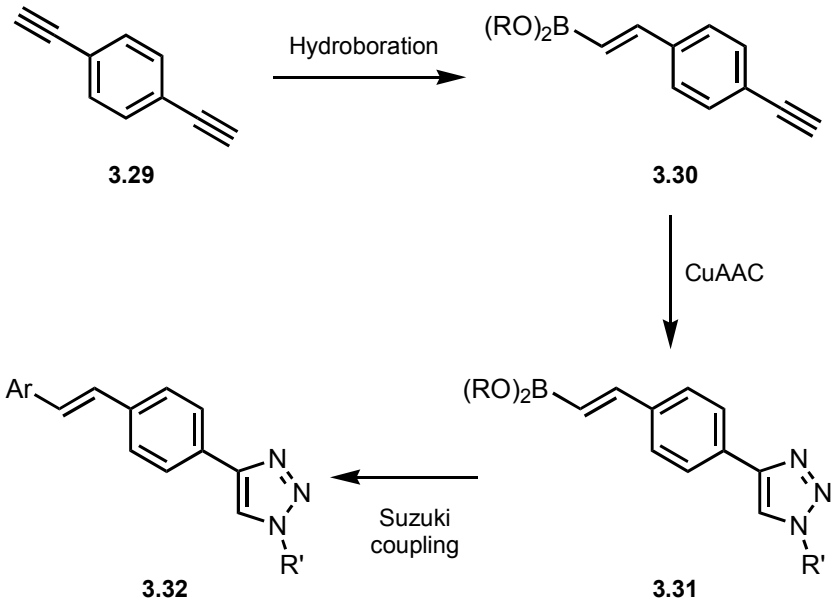
Although metal-catalysed cross-coupling reactions such as the Suzuki coupling reaction are not included in the click chemistry mandate, as has been discussed in Chapters 1 and 2 many of the key features that make the CuAAC reaction so popular are in fact common to the Suzuki-Miyaura coupling – water tolerance, robust and reliable reaction protocols, and wide substrate scope being the most important. Though traditionally high temperatures were required for Suzuki coupling reactions, more recent reports have demonstrated viable couplings at ambient temperature, and palladium has exhibited catalytic ability at exceptionally low loadings. Additionally, the organoboron derivatives employed frequently possess air and water stability at ambient temperatures, low toxicity when compared to other ubiquitous organometallics, and allow a range of other synthetic manipulations to be performed in their presence. Recent advances in the area have included reports of boronic acid derivatives with alternative physical and chemical characteristics, so allowing for improved outcomes in various generic or specific applications. Finally, boronic acid derivatives have also been demonstrated to be exceptionally versatile as modular building blocks (e.g. MIDA boronates) – modularity being one of the central features that has made click chemistry so important for a broad range of applications.

3.7. Initial Concept

We therefore envisaged that a modular linker containing “clickable” functionality in the form of either an azide or alkyne, in combination with a boronate moiety, would provide an ideal

molecular tether for various applications. This would ultimately allow a stable 1,2,3-triazole to be formed through the CuAAC reaction, while e.g. palladium-catalysed cross-coupling reactions of the boronate would prove traceless at the other functional terminus. For these reasons this methodology could be used to form either an inert molecular tether, or alternatively, by altering the substrate's core section, then useful chemical functionality or physical properties could potentially also be incorporated.

Our initial thoughts were that by using a diyne such as **3.29** we could ultimately access a substrate bearing an alkenyl boronate and a terminal alkyne, of the type **3.30**. However, a direct hydroboration protocol would provide mixtures of products in this case, and despite this not being an insurmountable problem we decided to further assess what structural and functional features we wished to include, and how best they could be incorporated, before undertaking the subsequent synthesis.



Scheme 3.7

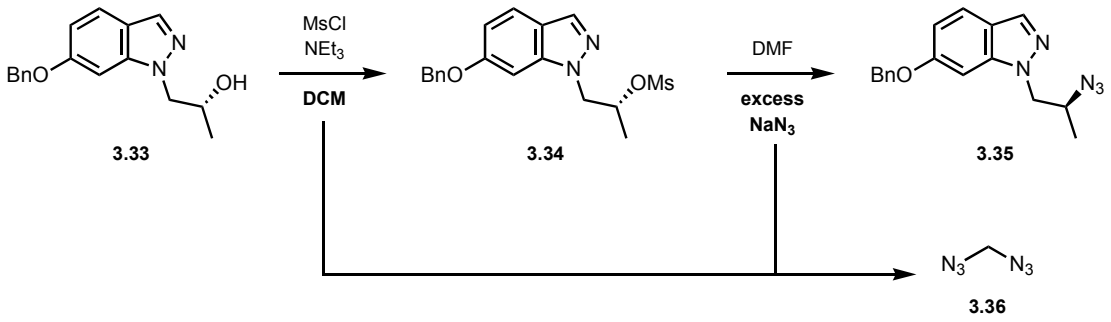
3.8. Specific Design Considerations

3.8.1. CuAAC Moiety

The first such consideration was whether either an azide or alkyne should be incorporated as the functionality to be employed in the CuAAC reaction. Sharpless and his co-authors highlighted in 2001 that despite the synthetic utility of organic azides there existed at that time a general reluctance by many synthetic chemists to make use of such substrates, a phenomenon that they termed "*azido-phobia*".[1] Importantly, while the widespread use and commercial availability of organic azides have both increased in recent years – undoubtedly

due to the popularity of the CuAAC reaction itself – in particular there still seems to be a hesitancy to synthesise such substrates.

However, Sharpless *et al.* specifically addressed this issue at the time, suggesting that typically a substrate containing any energetic functionalities should likely be stable if at least six carbon atoms (or similar) are present, per energetic moiety.[1] Accordingly, with only one such energetic functionality and more than to six carbon atoms or similar to compensate, literature azide **3.35** is indeed itself stable enough so that it was safe to prepare on a kilo scale by reaction of mesylate **3.34** with excess NaN_3. However, even after azeotropic removal employing DMF, DCM from the previous step was not fully removed and this allowed diazidomethane **3.36** to be produced from its reaction with the excess azide anion still present. With a corresponding ratio of 2:1, unsurprisingly, diazidomethane underwent (potentially shock-induced) explosive degradation.[34]



Scheme 3.8

However, azides were not the only such energetic functionality to be discussed by Sharpless and co-authors, with the same ratio also an indicator for stability of e.g. nitro compounds. While TNT for example is famously known as an explosive compound due to the high percentage of its total formula weight that is comprised of nitro groups (corresponding to a ratio of 3:7), we have noted that when azides and nitro compounds of similarly low-risk are being handled, then in comparison significantly more caution tends to be afforded to the azides.

We decided that including the azide function in a stable linker that could be isolated in high purity would be most desirable. This would limit the handling and use of azide source to the production of that single compound alone, avoiding potentially hazardous contamination of subsequent synthetic procedures, and potentially help demonstrate the benefits of using isolated organoazides. We reasoned that a benzyl azide would be synthetically simple to insert, their preparation easily achieved through procedurally simple nucleophilic substitution

reactions with azide salts, and in addition aliphatic azides are typically more stable than are equivalents located at aromatic, olefinic, or carbonyl carbons.[1]

3.8.2. Boronate Moiety

In contrast to the azide moiety, aryl boronates are typically more stable than their alkyl, alkenyl, or alkynyl counterparts, and we foresaw that an aryl boronic acid derivative could be more easily handled and stored without special precautions.

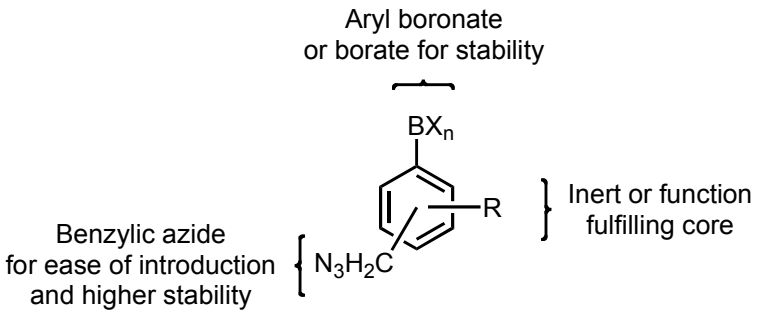
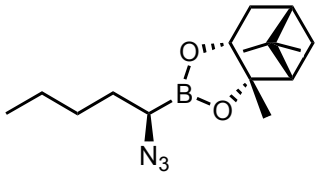


Figure 3.4: Summary of desirable design features targeted for inclusion in our proposed molecular linker.

3.9. Literature Precedent

Related azido-boronate substrates have in fact been known for much longer than the CuAAC reaction has, with the laboratory of D.S. Matteson having synthesised α-azido alkylboronic esters, including compound **3.37**, in the mid-1980s. Interestingly they noted that such substrates were surprisingly stable, such that they were unable to effect β-elimination of nitrogen.[35]



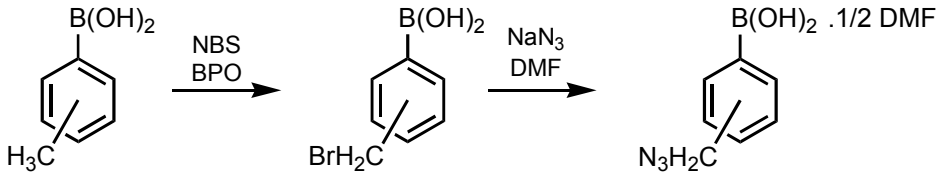
3.37

Figure 3.5

The remainder of this section now comprises a review detailing relevant azido-boronate substrates reported in the chemical literature. And while not technically comprehensive, it includes representative substrates from all publications to have consciously focussed on the application of azido-boronates as molecular building blocks, rather than simply detailing each and every report that happens to contain such substrates as isolated examples of coincidental synthetic intermediates.

3.9.1. Arylboronic Acid Substrates

In 2004 Fedorov and co-workers reported the synthesis of benzylazido-boronic acids in the form of all three positional isomers of **3.40**, which were synthesised by radical bromination of the corresponding boronic acid precursors (**3.38a-c**), followed by nucleophilic substitution of the benzylic bromine of intermediates **3.39a-c** with sodium azide in DMF.[36] This protocol yielded the products **3.40a-c** as viscous oils that formed as 2:1 boronic acid/DMF solvent adducts, the signal for the formamide proton of DMF in the ^{1}H NMR spectra being shifted significantly upfield (δH($CDCl_3$) 5.93, 5.86 and 5.77 ppm for **3.40a-c** respectively) in comparison to the formamide proton signal for free DMF (δH($CDCl_3$) 8.03 ppm). However, the ^{11}B NMR signals for the azide substrates (δB($CDCl_3$) 28.9 and 27.4 ppm for **3.40a-b** respectively; value for **3.40c** not reported), while broader than those of their respective bromobenzyl precursors (δB($CDCl_3$) 33.0 and 28.4 ppm for **3.39a-b** respectively; value for **3.39c** not reported), were at similar chemical shifts. Thus, although the ^{1}H NMR analyses suggested a strong interaction between the boronic acids and DMF, it was not possible to confirm whether the interaction involved coordination of solvent at boron, or hydrogen bonding of DMF with the OH moieties. Indeed, such was the strength of the interaction that attempts to remove DMF from these solvent adducts, either by repeated aqueous extractions, repeated precipitations in less coordinating solvents, or heating under reduced pressure, all failed. Furthermore, reactions to insert the azide moiety using alternative azide sources in solvents systems that are less coordinating (such as diethyl ether, THF, DCM or chloroform) were also unsuccessful.



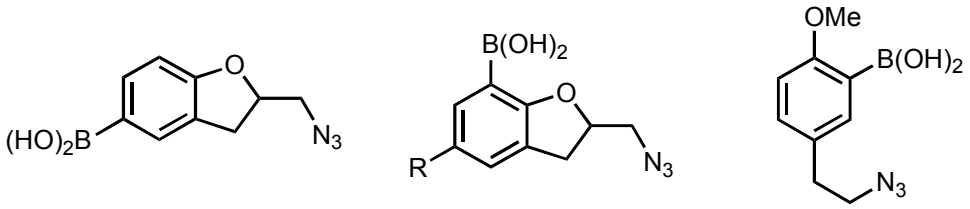
o- (**3.38a**)	*o*- (**3.39a**) (58%)	*o*- (**3.40a**) (46%) [27%]
m- (**3.38b**)	*m*- (**3.39b**) (37%)	*m*- (**3.40b**) (48%) [18%]
p- (**3.38c**)	*p*- (**3.39c**) (39%)	*p*- (**3.40c**) (49%) [19%]

Scheme 3.9: Synthesis of azidomethylene substituted phenyl boronic acids **3.40a-c**. (Individual yields are given in parentheses, while the two-step overall yields are in square brackets.)

The authors further determined the structural and electronic features of the three regioisomers by spectroscopic and computational methods, but did not investigate the synthetic applications of these reagents until the following year, when they reported employing the *ortho*- regioisomer **3.40a** for the synthesis of isoquinoline derivatives by use of the corresponding aryl lead reagents – synthesised *via* transmetallation of the boronic acid with

lead tetraacetate.[37] It was not until after we had initiated our own investigations that Fedorov and co-workers first demonstrated the use of these bifunctional reagents in sequential Suzuki coupling and CuAAC reactions.[38]

In 2006 Vasil'ev and co-workers reported the synthesis of 2-azidomethyldihydrobenzofurans **3.41**-**3.43** and 2-azidoethyl arylboronic acid **3.44** by a lithium halogen exchange route from the respective arylbromides, followed by electrophilic quench with trialkylborate and subsequent hydrolytic work-up to yield the boronic acid.[39] They then examined the reactivity of these compounds in the Suzuki coupling reaction with a number of aryl bromides in the presence of $Pd(PPh_3)_4$, with yields of the azidoalkyl-substituted biaryl products in the range of 68-86%. The coupling reaction of **3.42** with *p*-chloro anisole was also reported, and while $Pd(OAc)_2$ in combination with one of the Buchwald monophosphine biaryl ligands proved much more active than did the $Pd(PPh_3)_4$ system when used with the aryl chloride, the yield of the reaction was still only 34%.



3.41 **3.42** (R = H) **3.44**

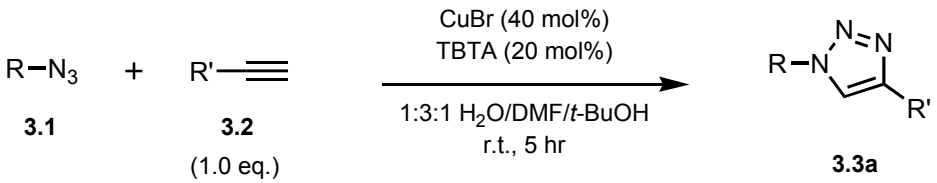
3.43 (R = Cl)

Figure 3.6

Very significantly they found that in cases employing the less reactive coupling partners, i.e. aryl chlorides or even just marginally less reactive aryl bromides, then the azide moiety was also converted to the corresponding nitrile compound. Thus, even with the most reactive arylbromides it was important to first incubate them with the palladium catalyst prior to addition of the azide, so as to ensure oxidative addition occurred prior to exposure of the azide moiety to a more reactive palladium complex. Further investigations were noted to have shown that the corresponding amine was also being formed in addition to the nitrile, and in a ratio of 1:2 (amine to nitrile), suggesting potential redox disproportionation in the presence of the palladium complex. However, further reactions (such as CuAAC) employing the intact azide motifs from relevant reactions were, rather surprisingly, not investigated.

One of the main reasons that both organoazides and boronic acids prove so synthetically useful is that they are compatible with a wide range of commonplace synthetic

transformations. As such they may remain unchanged while significant modifications are made elsewhere in a given substrate. It should be noted however that despite the different reactivity profiles of organoazides and boronic acids, there are undoubtedly situations when attempts to derivatise one will have a notable impact on the integrity of the other. Within the context of the discussions made in this chapter, then undoubtedly the most important point for consideration is the reactivity that boronic acids and their derivatives are known to exhibit towards copper complexes of relevance in CuAAC reactions.

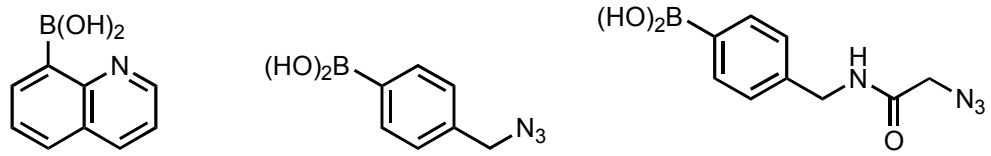


Scheme 3.10

During the course of our investigations Wang *et al.* published results of their studies on boronic acid tolerance to copper complexes of the type either required for direct catalytic CuAAC activity, or that may be indirectly generated under such reaction conditions. The group's standard CuAAC reaction protocol is shown in Scheme 3.10. (Here it is worth noting that due to the exceptional flexibility and robustness of the CuAAC reaction in terms of variation of almost all reaction parameters, then rather than being specific for a certain substrate or application, such conditions as are detailed in Scheme 3.10 can therefore be considered as typical as any others that are otherwise presented within this chapter.) Thus to ascertain the impact of such copper species on boronic acid integrity, Wang and co-workers exposed a range of structurally diverse boronic acids to the CuAAC reaction conditions, monitoring the change in sample composition over time by HPLC.[40]

As detailed previously, alkynes in particular interact in numerous and catalytically significant ways with Cu(I) complexes as part of the overall CuAAC catalytic cycle, and so Wang and co-workers initially omitted any *additional* azide or alkyne substrates – though, of the various boronic acids they screened a number incorporated either an organoazide or terminal alkyne moiety in addition to the boronate functionality. This initial limitation was no doubt imposed in the hope of elucidating the most significant and fundamental structural features involved in determining the stability profile of any given substrate. Despite this precaution the authors were however still unable to ascertain what factors determined stability of the boronic acids to the copper complex – with substrates such as **3.45** being almost unaffected (95% of the material being unchanged) after five hours of exposure to CuBr/TBTA (i.e. as per conditions in Scheme 3.10); while substrates such as **3.46** and **3.47** exhibited a much greater propensity

for attrition (76% and 79% of unchanged boronic acid remaining, respectively) – various unidentified by-products being generated as the boronic acids were consumed.



3.45 95% remaining

3.46 76% remaining (Not protected by F^-)

3.47 79% remaining (Protected by F^-)

Figure 3.7

Although a catalyst loading of 40 mol% CuBr could be considered rather high, it is not in fact unusual for sub-stoichiometric, or even stoichiometric amounts of copper salts to be used in CuAAC reactions. Furthermore TBTA (itself employed at 20 mol%) is a multidentate ligand with an affinity for copper, and known to be effective in stabilising Cu(I) so as to disfavour such ready oxidation to Cu(II). This is of specific note as Cu(II) is likely pivotal to the catalytic cycle of the Chan-Evans-Lam reactions – which is undoubtedly one of the more viable pathways by which the undesired conversion of boronic acids could result under CuAAC reaction conditions – and either by directly generating Chan-Evans-Lam products, or by initially generating reactive copper species that may be involved in other catalytic side-reactions.

Most importantly however Wang and co-workers demonstrated that with the addition of CsF to such reactions then some of the boronic acids less tolerant of the CuAAC reaction conditions, e.g. **3.47**, were then protected from degradation to a notable degree; an effect confirmed as being due to interaction of fluoride anion with the boron centre, rather than by means of a fluoride mediated change to the activity or selectivity of the copper catalyst. This protective effect was proposed to be due to quaternisation of the boronic acid with one or more fluoride ions, producing mixed borate species (such as are discussed in Chapter 1) which by computational analyses were determined to be thermodynamically less susceptible to insertion of Cu(I) into the C-B bond than was the case for the free boronic acid form. Notably however, some of the less copper-tolerant substrates – including **3.46** – were not amenable to such interventions, and the addition of CsF had no significant impact on their stability. Furthermore, the authors were unable to determine a correlation between the structural features of such boronic acids and the corresponding lack of protection that CsF offered.[40] Finally, it is worth noting that in the absence of fluoride then substrates including

3.47 demonstrate even *more rapid degradation* when the alkyne component is present too. As such this indicates that certain copper-acetylide species may indeed be acting as accelerants or as more effective catalysts for such degradation events.

3.9.2. Trifluoroborate Salts

In 2006 Molander and Ham reported the synthesis of various azido-functionalised organotrifluoroborates[41] (such as shown in Figure 3.8) by the nucleophilic substitution reactions of the corresponding halogen compounds[42] with NaN_3. Although the azide products could be isolated as crystalline solids, all reactions were performed only on a 0.1 mmol scale relative to the amount of halogen substrate. They then investigated the CuAAC reactions of these substrates with various terminal alkynes, either using the isolated azides, or by generating them *in situ* (again with NaN_3) prior to addition of the copper source and alkyne.

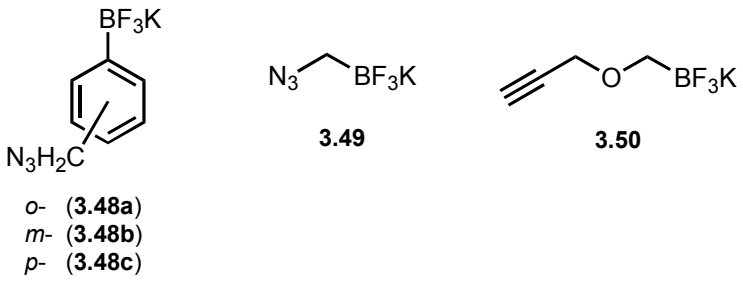
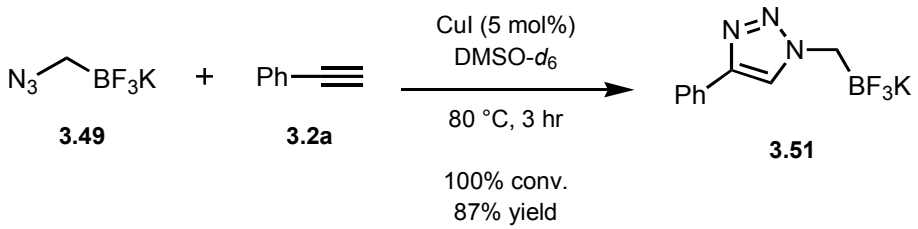


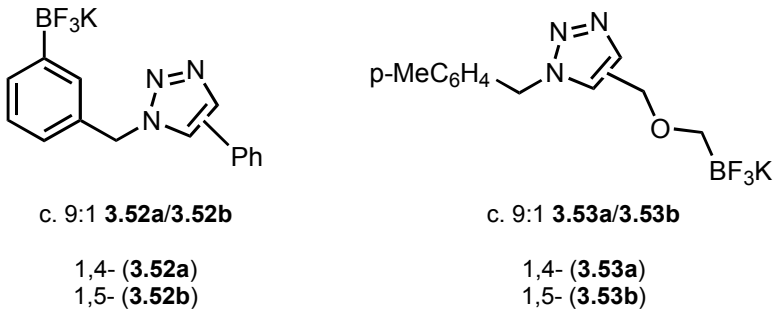
Figure 3.8

Of the copper salts screened for the CuAAC reaction CuI performed the best, with the reactions performed at 80 °C in DMSO-d_6 giving high yields of **3.51**. However, the reactions were extremely slow without heating, and DMSO-d_6 was the only suitable solvent – while the use of D_2O, MeCN-d_3, MeOD-d_4 or THF-d_8 all gave, at most, trace conversion to the product. This was proposed to be due to poor solubility of the copper salt in such solvents, but despite the addition of 10 mol% pyridine-d_5 in such a case, no improvement in catalytic activity was observed.



Scheme 3.11

Under the optimised conditions a range of azides and alkynes were reacted together, giving the corresponding products in high yields. The synthesis and CuAAC reactions of **3.50** – accessed by a similar nucleophilic substitution protocol, using the sodium salt of propargyl alcohol and bromomethyl potassium trifluoroborate salt – were also reported. Notably however azides **3.50** and **3.48b** gave rise to c. 9:1 mixtures of the 1,4- and 1,5- substituted triazoles in certain instances (Figure 3.9), despite CuAAC reactions on standard substrates such as these typically providing exclusively the 1,4-disubstituted 1,2,3-triazoles as products.



c. 9:1 **3.52a/3.52b**

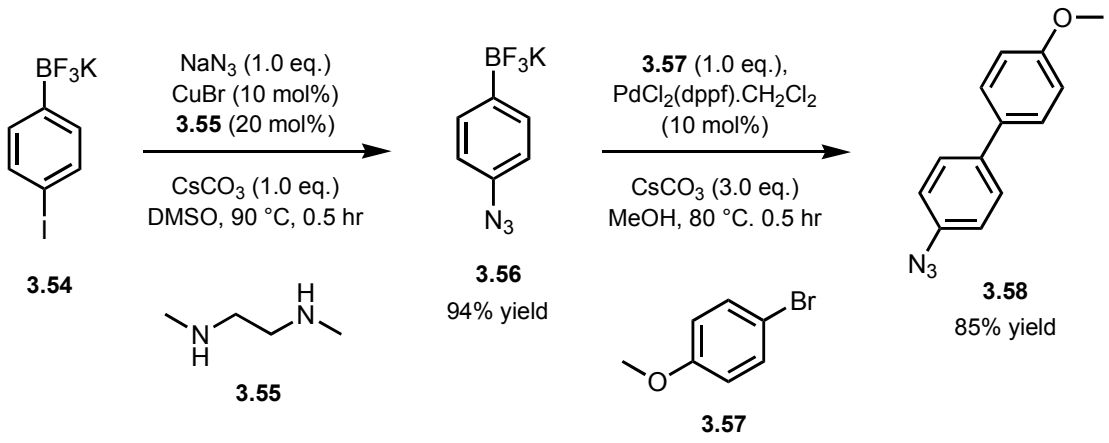
1,4- (**3.52a**)
1,5- (**3.52b**)

c. 9:1 **3.53a/3.53b**

1,4- (**3.53a**)
1,5- (**3.53b**)

Figure 3.9

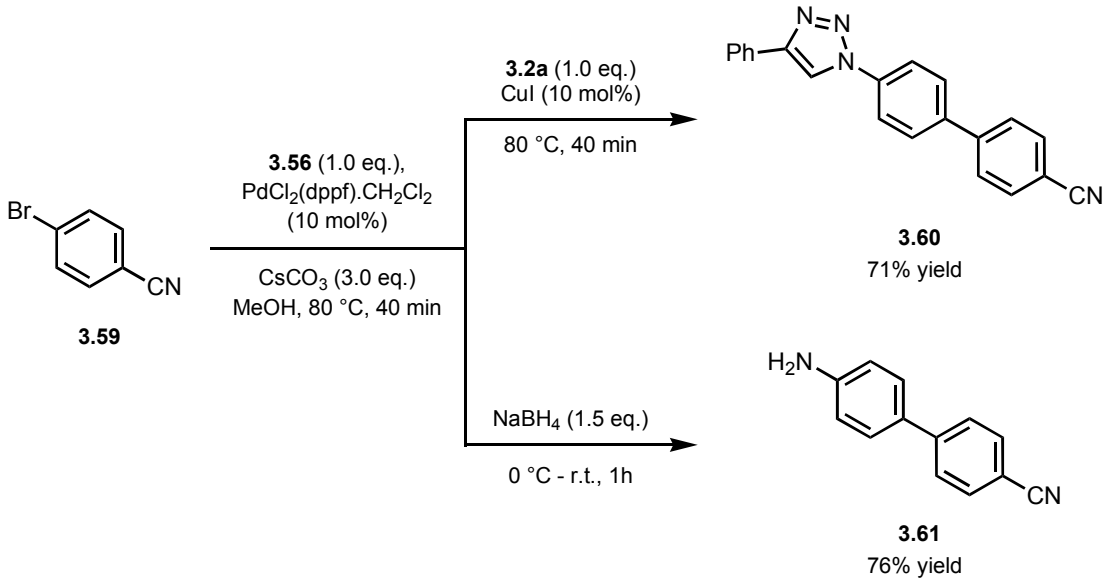
Despite numerous reports by Molander's group on the Suzuki coupling reactions employing potassium aryltrifluoroborate salts (as discussed in Chapter 1), in this case no further reactions involving the boronate moiety of the triazole functionalised trifluoroborate salts were reported. It was not until after we began our own studies on related substrates that a subsequent report was made by the authors involving aryl azide analogues in sequential Suzuki coupling and CuAAC reactions (Scheme 3.12). In this case aryl azides of the type **3.56** were synthesised by copper-catalysed coupling reaction of the corresponding aryl bromides or iodides (e.g. **3.54**) in the presence of NaN_3.[43]



Scheme 3.12

Suzuki coupling reactions employing **3.56** and aryl bromides gave the coupling products in good yields (although the use of 10 mol% palladium catalyst was required; Scheme 3.12). The use of aryl chlorides however required a higher reaction temperature and a more active catalyst (3 mol% $Pd(OAc)_2$, 6 mol% X-Phos, 100 °C), but even then only moderate yields were achieved at best.

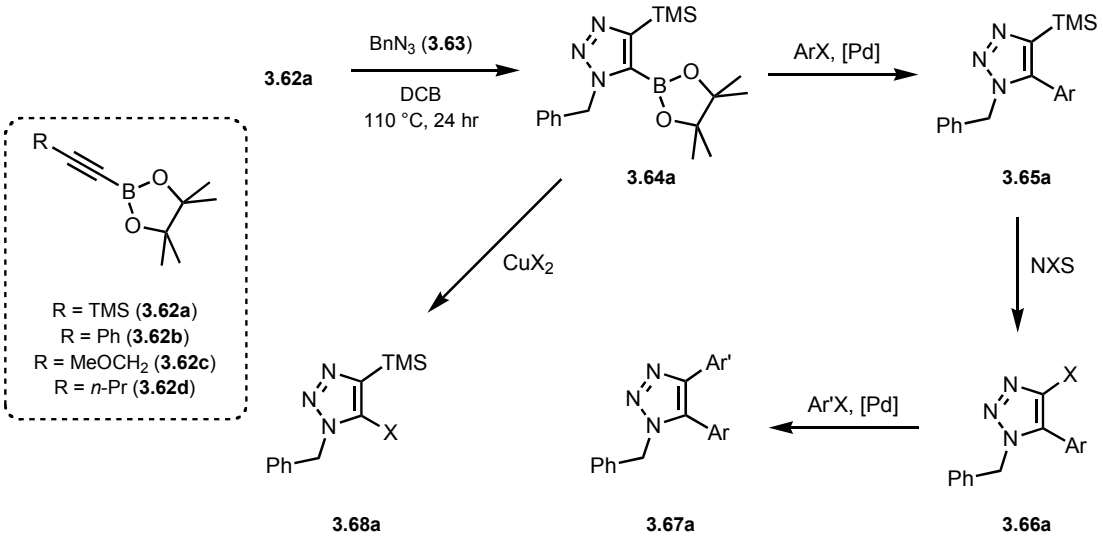
Finally they reported the one-pot Suzuki coupling reaction of **3.56** with *p*-bromobenzonitrile, followed by either subsequent CuAAC reaction to yield the biphenyl triazole derivative **3.60**, or alternatively, $NaBH_4$ reduction of the aryl azide to yield 4'-cyano biphenyl aniline **3.61**.



Scheme 3.13

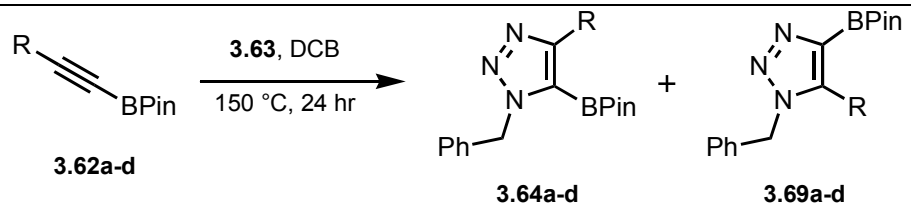
3.9.3. Boronate Esters

In 2009 Harrity and co-workers reported the formation of triazole boronic esters such as **3.64a** *via* the thermally promoted Huisgen 1,3-dipolar cycloaddition reaction between azides and the TMS substituted alkynyl boronate **3.32a**.[44] **3.64a** was obtained in an 84% yield, and surprisingly, as a single regioisomer (>98:2), though attempts to employ a RuAAC protocol in order to promote formation of the alternative regioisomer were unsuccessful.



Scheme 3.14

They were able to functionalise the boronate terminus of **3.64a** *via* Suzuki coupling reactions, although only aryl iodides were successful coupling partners; while Cu(II) halide reactions with the boronate also allowed them to form the chloro and bromo variants of product **3.68a**. Furthermore, under the action of NBS or NIS, the TMS terminus could also be halogenated to yield the bromo and iodo variants of **3.66a** respectively, and in this way orthogonal functionalisation by Suzuki coupling reactions could be achieved – with full positional control of such arylations (Scheme 3.14).



Entry	R		Selectivity 3.64/3.69	Conv. (%)
1[a]	TMS	(**3.62a**)	>98:2	(84%[b])
2	Ph	(**3.62b**)	2:3	(25%[b], 38%[c])
3	$MeOCH_2$	(**3.62c**)	3:2	99
4	*n*-Pr	(**3.62d**)	3:2	98

Regioselectivities and conversions determined by ^{1}H NMR analysis of the crude reaction mixtures with isolated yields given in parentheses.

[a] Reaction conducted at 110 °C.

[b] Yield for corresponding 5-boronate ester substituted triazole **3.64**.

[c] Yield for corresponding 4-boronate ester substituted triazole **3.69**.

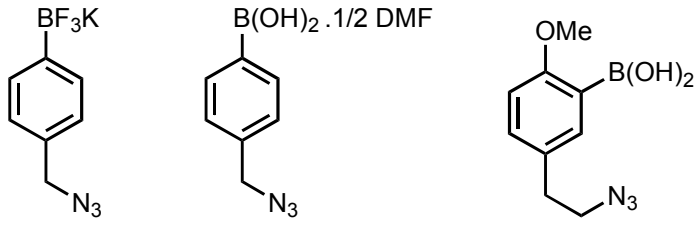
Table 3.1

While the TMS protected alkyne **3.62a** proved very reactive and gave high regioselectivities in the thermal cycloaddition reaction, when TMS was replaced by alternative substituents (**3.62b-d**) then higher temperatures were required to obtain the analogous triazoles, and in such cases the regioselectivities were only c. 3:2 (Table 3.1, compare entry 1 with entries 2-4). The crude product for the reaction of phenylacetylene derivative **3.62b** could be purified by column chromatography so as to separate the two regioisomers formed (**3.64b** and **3.69b**) (entry 2). However, although the analogous cyclisation reactions for alkynes **3.62c** and **3.62d** gave high conversions and clean crude reaction mixtures, the alkyl substituted products they formed were extremely unstable, and thus the regioisomeric mixtures could not be separated (entries 3-4).

Due to the pharmacological significance of the 1,2,3-triazole moiety the Harrity group subsequently used this approach to synthesise a small array of triazole boronic ester derivatives.[45] They found that by employing a one-pot sequential cycloaddition/Suzuki coupling protocol that good yields of the 1,4,5-trisubstituted 1,2,3-triazoles could be obtained, even with the unstable alkyl substituted substrates that had previously proved troublesome. However, they were still only able to obtain good regioselectivities for the cycloaddition reaction when using the alkynyl TMS substrate **3.62a**, while the c. 1:1 regioisomeric mixtures formed from other alkyl boronate esters were not always even separable by LC-MS.

3.10. Conclusions drawn from the Literature

Although at the time we began our investigations literature precedent existed for the synthesis of aryl boronates and borates bearing *para*-situated alkyl azides, as exemplified by the substrates in Figure 3.10, no such substrates had been employed in both the Suzuki coupling and CuAAC reactions. It should also be noted however that many of these such compounds also have issues associated with their synthesis, isolation and purification.



3.48c **3.40c** **3.44**

Figure 3.10

Despite the azide stability factors discussed above, **3.48c** and **3.40c** (as prepared by the groups of Molander[41] and Fedorov[36], respectively), had only been synthesised on, at most, a

0.5 mmol scale by nucleophilic substitution reaction of NaN_3 with the corresponding chloride and bromide, respectively.

Although the synthetic route to the *para*- substituted boronic acid **3.40c** involved only two steps – radical bromination and substitution of the benzylic bromine using the strongly nucleophilic azide anion – the overall yield from *p*-tolylboronic acid **3.38c** was a very poor 19% (Scheme 3.9). In addition, purification and handling was made difficult due to the substrate forming an adduct with DMF. While **3.44** was prepared on a much larger scale (c. 9 mmol isolated product) from the *in situ* derivitisation of the mesylate precursor by reaction with NaN_3, like **3.40c** it is also a viscous oil and was obtained in a very similar 20% overall yield from the commercial starting material (see Chapter 4 for further discussion).

The azido-substituted potassium trifluoroborate salts such as **3.48c** were typically formed and reacted *in situ*, and given the high polarity typical of trifluoroborate salts in general, we were unsure whether recrystallisation could efficiently and safely remove all traces of excess azide anion when such compounds were to be synthesised on the much larger preparative scale we envisioned.

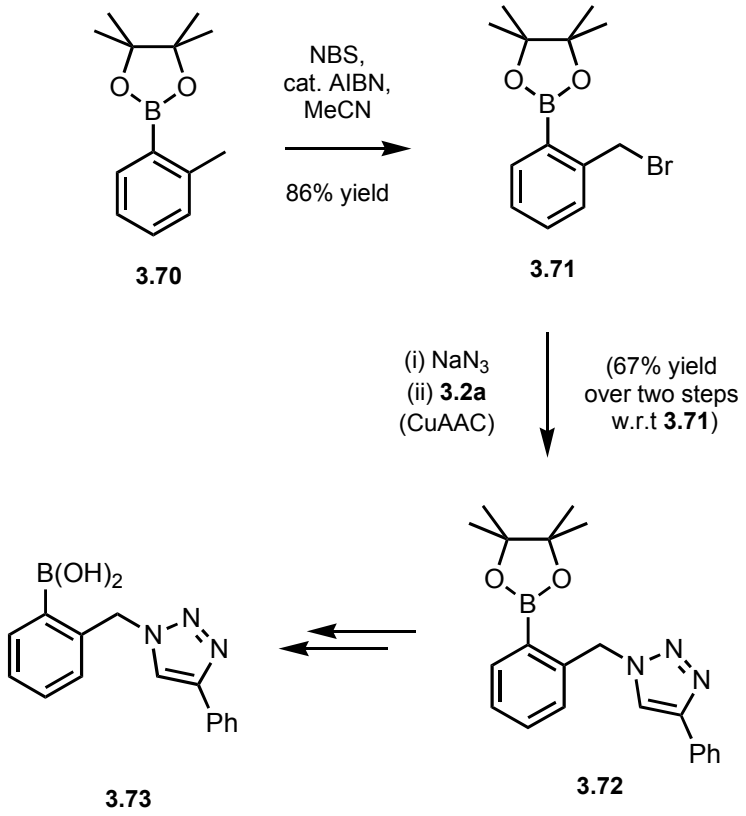
We therefore determined that an arylboronate should be more readily and safely purified after introduction of the azide function than could a corresponding quaternised arylborate. However, it was quite apparent that addressing the issue of coordination of nucleophiles, such as azide anion, at the boronic acid moiety was going to be critical to ensuring high yields and purities could be achieved for all synthetic intermediates involved in the synthesis of our linker substrate.

Indeed, coordination by azide anion and DMF at the boronic acid moieties in the three regioisomers of **3.40** (and precursors **3.39a-c**) was no doubt a very significant factor as to why the yields for their preparation were so poor. Better yields for both the bromination and substitution reactions were however obtained in the synthesis of *ortho*- regioisomer **3.40a**, while the *meta*- and *para*- analogues were prepared in very similar overall yields to each other (Scheme 3.9) (While Vasil'ev and co-workers had prepared *o*-methoxy ether substituted boronic acids such as **3.44** in higher yield, we wished to introduce the azide functionality after the boronate, so as to avoid any of the issues that may arise with this approach – for further discussion see Chapter 4).

Although this suggested that steric bulk *ortho* to the boronic acid moiety was beneficial in this context (i.e. radical bromination etc., rather than directed metallation), we specifically

wished to first target a *para*- substituted arylboronate, as more sterically demanding coupling partners often prove less reactive, especially in Suzuki coupling reactions. In doing so it would also maximise the potential for our linker to be of use for applications such as polymer derivitisation, where the bulk of the macromolecular substrate often has a severe impact on the rate and conversion of a reaction.[10, 23, 33, 46]

As it would be desirable to use a slight excess of azide ion to drive the substitution reaction to completion so as to avoid wasting the much more valuable boronate, we determined that a pinacolboronate ester would be an ideal partner due to the high lipophilicity, and inhibition of coordination by nucleophiles at the boron centre that it imparts.[40, 47] Most notably in this context, James and co-workers had recently reported the synthesis and application of the "*click-fluor*" molecular sensor **3.73**, which allows for fluorescence detection of saccharides.[48] It was reported that an *in situ* CuAAC reaction to directly form the *ortho*-benzyl triazole moiety of **3.72** was performed, with no note of having isolated the azide substrate in pure form. Thus, as with the substrates reported by Molander (e.g. **3.48**) and Fedorov (e.g. **3.40**), we were again unable to ascertain exactly how stable the azide moiety was in such a system.



Scheme 3.15

Importantly however, the yields of the radical bromination and azide substitution reactions in the case employing the pinacolate esters **3.70** and **3.71**, respectively, are notably higher than those reported by Fedorov for the case employing the free *ortho*- functionalised boronic acid **3.38a** as the precursor to **3.40a**. Indeed, the one-pot formation of triazole **3.72** from bromide **3.71** achieves a significantly higher yield for those *two* steps (i.e. 67%) than was reported for any of the straightforward substitution reactions involved in the formation of boronic acids **3.40a-c** from the corresponding benzyl bromides **3.39a-c**.

3.11. Synthesis of Bifunctional Linker 3.78

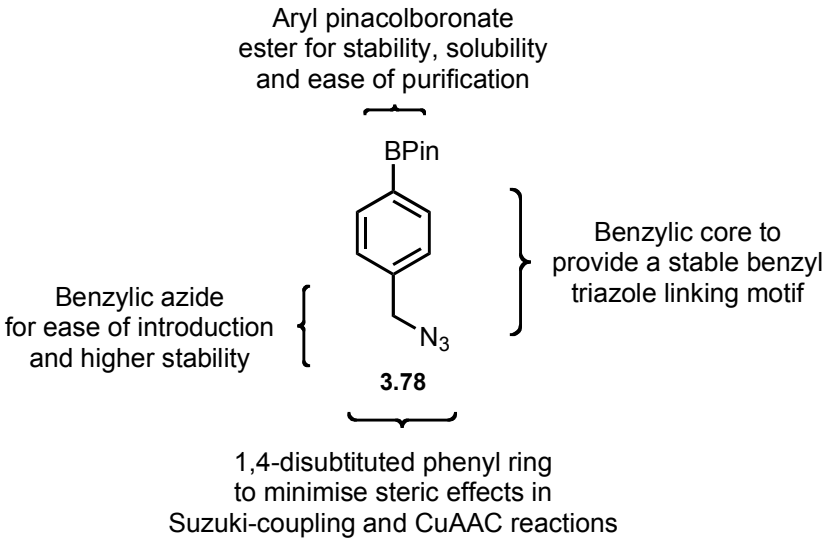
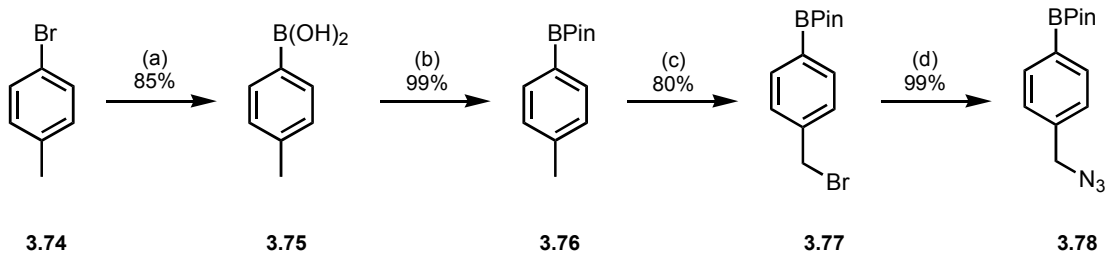


Figure 3.11

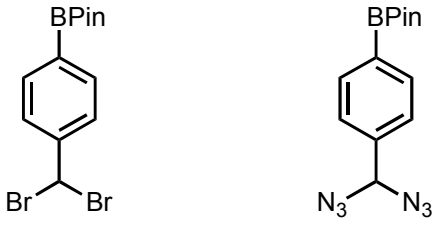
We therefore targeted **3.78** as an ideal candidate which could be accessed using a modification of the synthetic route employed by James *et al.* Although we later found a more cost-effective commercial source of boronic acid **3.75**, we initially synthesised it by means of a metal-halogen exchange reaction employing *p*-bromotoluene **3.74** and *n*-BuLi, subsequently trapping the generated aryllithium with triisopropylborate.



Scheme 3.16: Synthesis of **3.78** (values are for isolated yields after purification). Conditions: (a) (i) *n*-BuLi, THF, -78 °C. (ii) $(i\text{-PrO})_3B$, -78 °C to r.t. (iii) H_2O. (b) Pinacol, Et_2O, $MgSO_4$, r.t. (c) NBS, cat. AIBN, MeCN, 90 °C. (d) 1.1 eq. NaN_3, EtOH, r.t.

Introduction of the pinacolate ester through azeotropic removal of water *via* use of Dean-Stark apparatus was not necessary. In a more straightforward protocol we found that simply stirring a solution of **3.75** with a slight excess of pinacol in a solution of ether and the presence of $MgSO_4$, at ambient temperature overnight, resulted in full conversion to the ester **3.76**. Pleasingly the polarity of the boronate ester is much lower than that of the free acid, such that by dissolution in petroleum ether and subsequent passage through a plug of silica, any polar contaminants such as free pinacol or trace impurities remaining from the preparation of the boronic acid are readily separated. In this way **3.76** can be isolated in effectively quantitative yields from the boronic acid, and in such purity that when thoroughly dried it may be isolated as a crystalline solid.

In order to synthesise **3.77** we then submitted **3.76** to radical bromination under the protocol employed by James and co-workers (1.5 equivalents of NBS). Although this initially allowed us to obtain **3.77** in a reasonable 55% yield, there were significant problems associated with the practicality of this method. Most notably, at the end of the reaction a significant amount of excess elemental bromine or HBr was apparent in the system, which in turn made handling the crude material hazardous without first having removed much of the solvent under a flow of nitrogen in a well ventilated fume hood. Under such conditions with an excess of reactive bromine species remaining, the starting material was completely consumed, but in addition to the desired product, degradants were also formed.



3.79 **3.80**

Figure 3.12

"Over-bromination" of such substrates also leads to the formation of the geminal dibromo compounds, such as **3.79**. Unfortunately the physical properties of this impurity are such that it is very difficult to separate from **3.78** – indeed it tends to co-crystallise at fairly consistent concentrations with the monobromo compound. In particular the treatment of **3.79** with sodium azide would yield a potentially much more hazardous geminal diazide **3.80**.

We therefore quickly reviewed the literature and performed brief optimisation of the reaction conditions on a small scale in order to maximise the yield of **3.77** and simultaneously avoid

formation of **3.79** in more than trace amounts. Many literature procedures employ CCl_4,[49] which we wished to avoid if possible, while we found that in combination with MeCN that AIBN was a better choice of radical initiator than benzoyl peroxide.

Unfortunately, although we were able to obtain an almost perfectly clean conversion to the monobromo product on such a scale, when applied to the larger scale we required, this result did not translate. We subsequently found that a single equivalent of NBS was in fact sufficient, and rather surprisingly, by simply performing the reflux in a system open to the atmosphere, a much cleaner reaction and more operationally simple and safe protocol was achieved. Indeed this allowed a higher yield of **3.77** to be obtained, without significant contamination by **3.79**, and further solved the problems we had observed with residual bromine vapours. Furthermore, as with the precursor **3.76**, **3.77** is also soluble in petroleum ether, and so the succinimide by-product (as well as any other polar contaminants) present in the crude reaction mixture are easily removed by evaporation of acetonitrile and subsequent passage of the crude material through a plug of silica, using petroleum ether as the eluent. **3.77** is readily crystallised, and (although a small deviation is typically observed between batches) is isolated after recrystallisation in very high purity, with typically only small amounts of dibromo **3.79** or starting material **3.76** being present prior to recrystallisation.

Interestingly, we were later informed by a supplier of boronic acid **3.39c** that yields and purities of the commercial material were low, and that removal of residual solvent was not practicable. As such the purity of the commercial product **3.39c** was typically c. 70%, while other aryl boronic acids from the same supplier were of an extremely high quality – again highlighting the degree to which the pinacolate ester improves both the yield and ease of purification of **3.77**.

We then proceeded to incorporate the azide moiety by treating **3.77** with a small excess of NaN_3 in aqueous ethanol, followed by solvent extraction and isolation of the azide **3.78**. However, we found that discolouration of the organic components tended to occur during this process when water was used in the solvent system. Although the nature of the contaminant was not confirmed, the use of ethanol alone seemed to minimise its formation, and also allowed much of the inorganic salts to be filtered off prior to further handling of the organic products. Again **3.78** could be separated from any polar impurities by passage through a plug of silica (eluting with petroleum ether), including not only the very obviously polar excess azide salts, but also those species that caused the discolouration.

Despite monobromo **3.77** and dibromo **3.79** being so physically similar as to co-crystallise, the selection of boronate function has no real bearing on this fact. Thus, it is worth noting that our selection of the pinacolate ester proved to be highly advantageous not just to the yields when compared to those obtained for boronic acid **3.39c**, but also the ease with which intermediates in our synthetic route to **3.78** could be accessed and purified. Such are the solubilities of each of the products and major impurities from **3.75** through to **3.78** of our synthetic route, that as long as each of the reactions is allowed to reach high conversion, then removal of the major contaminants in the crude reaction mixtures, due to the differential in their polarities, is facile at each stage. In summary this synthetic route proved reproducible and scalable, with no column chromatography required for the purification of either the final product **3.78** or any of the synthetic intermediates. We were thus able to access multigram quantities of azide **3.78** in good overall yields from either *p*-bromotoluene **3.74** (> 65%, 4 steps) or the commercially available boronic acid **3.75** (> 75%, 3 steps).

3.12. Physical Properties of Linker 3.78:

Most pleasingly of all we found that **3.78** crystallized as a highly pure solid, ideal for easy handling, and stable when stored exposed to atmospheric oxygen and moisture. Indeed samples of **3.78** have remained unchanged over periods of greater than one year, even when stored in vials directly open to the air.

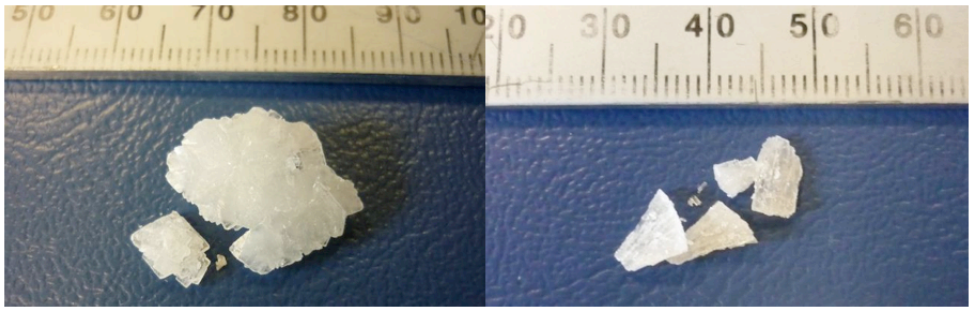


Figure 3.13: Crystals of **3.77** (left) and **3.78** (right).

In addition, the crystallinity of **3.78** (Figure 3.13, right) also allowed determination of the crystal structure (Figure 3.14). And while organoazides are known to exhibit photolytic behaviour,[50] we were surprised to find that deliberate attempts at inducing photodegradation of **3.78**, using equipment designed to monitor *in situ* solid-state photoinitiated changes (by exposure of sample crystals to high intensity UV-light) were unsuccessful. This level of stability was beyond what we expected, and though we saw a top-to-tail arrangement of azide groups in the unit cell of the crystal, the intermolecular azide-azide distance was not atypical.

We thus concluded that the stability profile of **3.78** should be a general feature of such compounds, which is discussed further in a later section of this chapter.

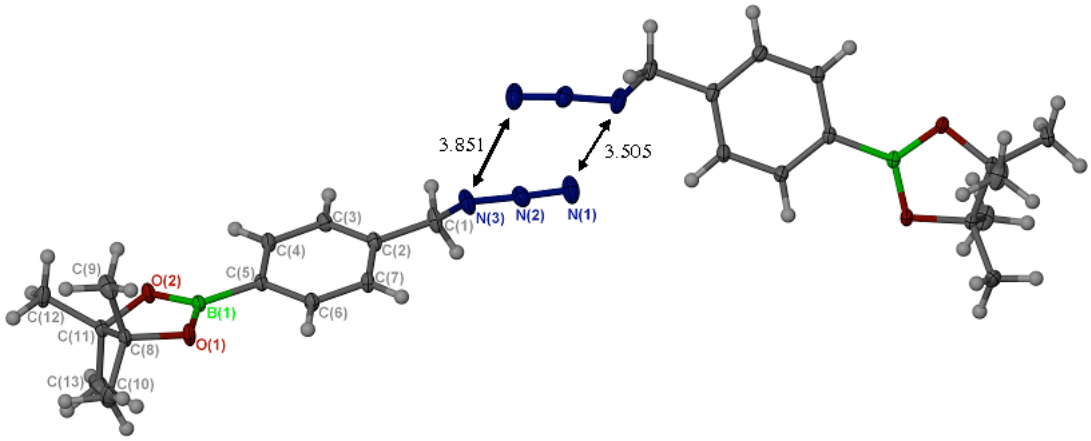


Figure 3.14

As inferred above, the solubility profile of **3.78** is also impressive, with the compound readily dissolving in organic solvents with such diverse polarities as petroleum ether and methanol. Indeed **3.78** even dissolves in mixed aqueous/organic solvent systems such as 1:1 *t*-BuOH/H_2O, as employed for reactions discussed later in this chapter. (Anecdotally, after mixed-hydrocarbons failed in securing a crystal of **3.78** in place for analysis by XRD due to the high solubility of the material in such solvents, the crystallographer then resorted to epoxy resin adhesive, and was surprised to note that even then care had to be taken as **3.78** still exhibited solubility in the adhesive.)

The extremely broad solubility profile of **3.78** is also of particular relevance given the significant increase in polarity when converting parent azides to the corresponding 1,2,3-triazoles, as discussed in the literature review above. Organic azide moieties such as that found in **3.78** are not especially polar, as supported in this instance by the ease with which the substrate is eluted from silica gel using only petroleum ether.

Given the often tight window for solvent selection, particularly in synthetic macromolecular disciplines, then the range of solvents compatible with **3.78** gives it potentially greater synthetic scope, especially when compared to compounds such as organotrifluoroborate salts which are already highly polar – prior even to the introduction of a triazole motif capable of hydrogen-bonding. Indeed, even simple aryl trifluoroborate salts are *normally* recrystallised from acetone with heating.[51]

3.13. Reactivity of 3.78 in the CuAAC Reaction

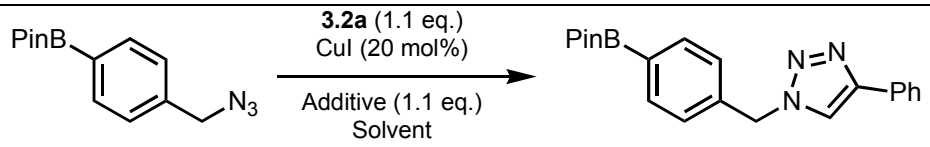
We decided that by first introducing the more stable 1,2,3-triazole moiety, higher overall yields should likely be obtained from the application of **3.78** in sequential CuAAC and Suzuki coupling reactions than if the azide was first exposed to a palladium catalyst. Indeed, although Vasil'ev *et al.* had at this time already demonstrated that Suzuki couplings could indeed be performed in the presence of an alkyl azide (e.g. as present in substrates **3.42** and **3.44**), as previously discussed such reactions were only viable with very simple aryl bromide substrates. Instead they obtained low yields and concomitant formation of nitrile by-product with the use of either aryl chlorides, or even simply less reactive examples of the aryl bromide coupling partners. Moreover, as reported in the chemical literature, the use of pinacolate esters in Suzuki couplings often involves that much more aggressive conditions are employed than for the corresponding reactions with boronic acids; although a recent study by Hartwig and Carrow highlights the fact that the lower reactivities of boronate esters are generally overemphasised.[52]

3.13.1. Initial CuAAC Reactions

We therefore first investigated the CuAAC reaction of **3.78** in the presence of CuI and different solvents, and using phenylacetylene **3.2a** as a model terminal alkyne – chosen for its lack of additional reactive functionality. By taking small aliquots the progress of these reactions, conducted initially at room temperature, was monitored by ^{1}H NMR – which showed that even after 18 hours, at most only trace amounts of the 1,2,3-triazole product **3.81a** had resulted in any of the three solvent systems assessed. To determine if an increase in temperature could effect a more facile CuAAC reaction, the reactions were subsequently allowed to continue for a further six hours at 60 °C. Although this did give much improved conversions relative to those obtained at room temperature, and despite the rather diverse range of character encompassed in only the three solvents screened, all of them ultimately gave poor results (Table 3.2, entries 1-3).

Notably, while James and co-workers had reported the successful use of CuI alone in the analogous CuAAC reaction of phenylacetylene and the azide derivative of **3.71**, this was in combination with DMSO as the solvent and a reaction temperature of 80 °C. Though this may also have been sufficient to generate a more reactive catalyst in our case, we particularly wished to avoid the use of DMSO as solvent if at all possible. It is feasible that, being more coordinating, DMSO acted to generate more discrete and solubilised Cu(I) species – indeed, Fokin has recently highlighted that CuI is particularly prone to forming aggregates that exhibit low catalytic activities. This is due to the ability of the iodide anion to become

involved as a bridging ligand between copper centres, such that polynuclear copper acetylide complexes with low catalytic potential may form – and even more readily than is otherwise normal under CuAAC reaction conditions.[12]



3.78 **3.81a**

Entry	Solvent	Additive	Conv. (%)[a]
1	H_2O	-	20[b]
2	Dioxane	-	20[b]
3	Ethanol	-	12[b]
4	H_2O	NEt_3	56[c]
5	H_2O	DIPEA	93[c]
6	1:1 *t*-BuOH/H_2O[d]	DIPEA	93[c]

All reactions performed in sealed tubes under air atmosphere using 0.50 mmol of **3.78** in 1.0 ml of solvent.

[a] Determined by ^{1}H NMR spectroscopy.

[b] Reaction run at r.t. for 18 hr, then at 60 °C for 6 hr.

[c] Reaction run at 60 °C for 1 hr.

[d] Used to aid mixing.

Table 3.2

A review of the literature led us to investigate the use of amines as additives to improve the conversions in our system, and as water had given an identical result to that obtained using dioxane we therefore screened the amines NEt_3 and DIPEA in an aqueous reaction media. Reassuringly the addition of either amine resulted in a much improved level of conversion to the 1,2,3-triazole after only a one hour reaction period, although DIPEA proved much better in this role than did NEt_3 (Table 3.2, entries 5 and 4, respectively). To improve the homogeneity of the reaction media – so that it was not necessary to periodically intervene and manually agitate the solution by handling the reaction vessel – we moved to the use of aqueous *t*-BuOH instead of water alone. This gave an otherwise identical result to that obtained with water, and indeed, did not require such interventions (entries 5 and 6).

3.13.2. Stability of 3.78 to Cu(I) in Combination with Atmospheric Oxygen

Irrespective of the poor results initially obtained in the CuAAC reaction in the absence of additives, the boronate moiety (as well as the azide group) of **3.78** demonstrated an exceptionally surprising level of tolerance for continued exposure to sub-stoichiometric

amounts of Cu(I) salt, even with prolonged heating and though, other than sealing the reaction vessel after charging with solvent and reagents, no particular attempts to exclude oxygen were made.

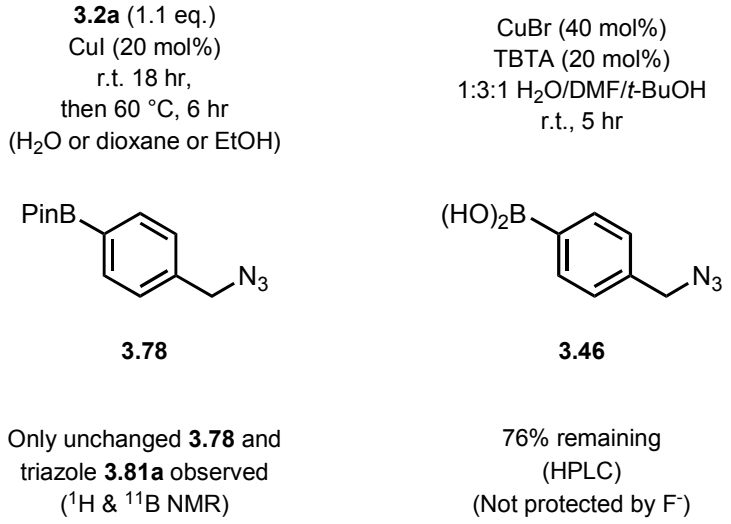


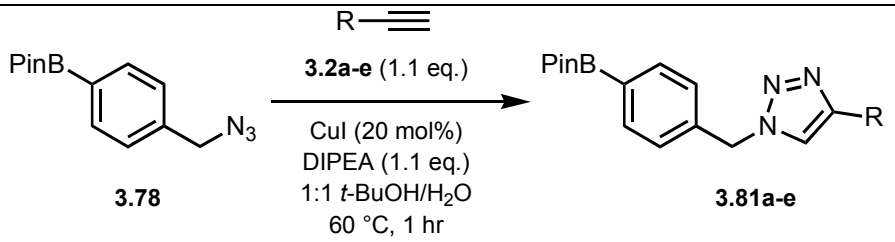
Figure 3.15: Summary of exposure to CuAAC reaction conditions and resulting impact on boronate integrity for **3.78** and analogous literature result for boronic acid **3.46**.

As has been discussed in the literature review of this chapter, Cu(I) is less thermodynamically stable than either the Cu(0) or Cu(II) oxidation states, and is well known for the ability to form Cu(II) under reaction conditions such as those that we employed. In turn Cu(II) is well documented to insert into C-B bonds of the type present in **3.78**, as is used advantageously in the case of the Chan-Evans-Lam coupling. Thus it was surprising that no such products were observed, especially in the presence of water or ethanol as the solvent. Even at a temperature of 60 °C, a basic aqueous reaction media (in the cases where the tertiary amines were present), and with what are reasonably high loadings of quite a sensitive Cu(I) salt, no observable vitiation of the boronate was observed (Table 3.2). As discussed above (Section 3.9.1), in contrast to this the free boronic acids typically undergo degradative side reactions under such conditions, and very significantly after five hours at room temperature 24% of **3.46** – the boronic acid directly analogous to **3.78** – was reported as having degraded (Figure 3.15). Although the amount of degradation quoted by Wang *et al.* for boronic acid **3.46** occurred in the presence of a higher loading of CuX salt (40 mol%, vs. 20 mol% in our system), their protocol also included using TBTA as the ligand. Such ligands are able to stabilise Cu(I), preventing it from being so readily oxidised to Cu(II), which in turn is the oxidation state required for catalytic activity in the Chan-Evans-Lam coupling.

3.13.3. CuAAC Under Optimised Conditions

With a suitable set of conditions for the CuAAC reaction thus obtained, we next proceeded to investigate the reactivity of **3.78** with a selection of representative terminal alkynes (Table 3.3). As originally noted by Sharpless and co-workers in their initial CuAAC report, the substrate scope for the reaction is extremely good, and under our optimised conditions quantitative conversion of **3.78** to the corresponding 1,2,3-triazoles **3.81a-e** is typically achieved after only one hour at 60 °C.

Much of the deviation observed in the isolated yields for 1,2,3-triazoles **3.81a-e** (Table 3.3) can be accounted for by the relative ease with which the products could be purified. Although discolouration indicating residual copper contaminants was a frequent problem, the crude reactions mixtures were often very clean by ^{1}H NMR, and the yields of such crude products were often found to be near quantitative when the original mass of copper salt was accounted for (this is discussed further in Section 3.17).



3.78 **3.81a-e**

Entry	R		Product	Yield (%)[a]
1	Ph	(**3.2a**)	**3.81a**	72
2	Ph	(**3.2a**)	**3.81a**	95[b]
3	EtO_2C	(**3.2b**)	**3.81b**	78
4	*n*-Pr	(**3.2c**)	**3.81c**	92
5	$Me_2C(OH)$	(**3.2d**)	**3.81d**	90
6	TMS	(**3.2e**)	**3.81e**	(30)[c]

All reactions performed in sealed tubes under air atmosphere using 1.0 mmol of **3.78** in 2.0 ml of 1:1 *t*-BuOH/H_2O as solvent.

[a] Determined by ^{1}H NMR spectroscopy.

[b] Performed on 3.0 mmol of **3.78** using 20 mol% $CuSO_4$/40 mol% sodium ascorbate (Na-Asc), 24 hr, r.t.

[c] Using 2.0 equiv. of **3.2e**, 2 hr, 60 °C. ^{1}H NMR spectroscopic analysis revealed a mixture containing unreacted **3.78** (45%), **3.81e** (30%) and **3.81f** (25%). See Scheme 3.18 below for further details.

Table 3.3

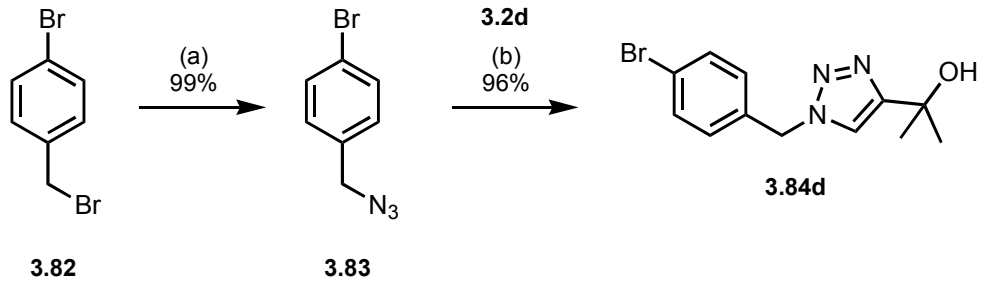
Though recrystallisation was an effective purification method, particularly for removing any organic impurities from the highly crystalline triazoles, it inherently impacted the yields

obtained on smaller scales. Although phenylacetylene tended to react more slowly under the standard conditions, it still gave high conversions; thus on a larger scale and using the $CuSO_4$/sodium ascorbate system for the *in situ* generation of Cu(I) reported by Sharpless and co-workers,[5] then a much higher yield of 95% was obtained (Table 3.3, entry 2).

Although **3.78** was the more valuable substrate in comparison to the commercially available alkynes, we specifically chose to use only a slight excess of the alkyne substrates in these CuAAC reactions. Our motive in this case was to confirm that **3.78** was amenable to use in situations where the alkyne moiety is available in limited quantities, such as in the functionalisation of polymers or surfaces bearing terminal alkynes. Indeed, we primarily employed the alkynes in slight excess only because certain examples are especially volatile – a situation that would not arise in the corresponding use of **3.78** for macromolecular applications.

3.14. Aryl Halide Analogue of 3.78

So as to determine how the bifunctional linker **3.78** compared to a simplified analogue we also synthesised the corresponding aryl bromide **3.83** by direct treatment of the commercially available precursor **3.82** with NaN_3 (Scheme 3.17).

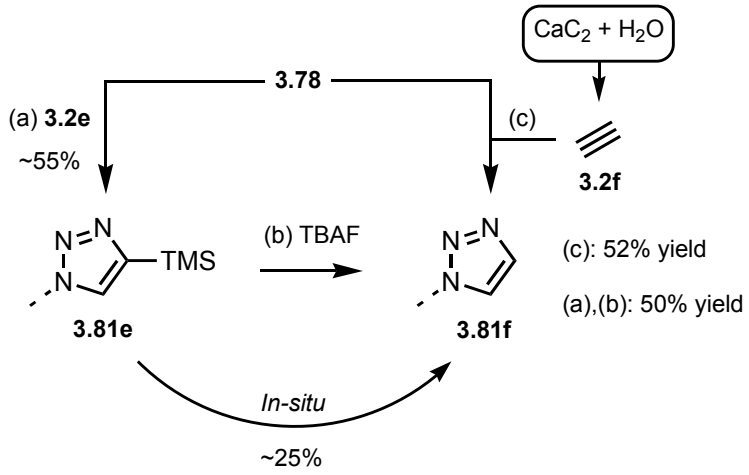


Scheme 3.17: (a) 1.1 eq. NaN_3, EtOH, r.t. (b) As for Table 3.3, entry 5.

While **3.82** took a similar time to completely convert to the azide **3.83** as was required for the corresponding formation of boronate **3.78** from **3.77** (further confirming that the pinacolate ester is effective at inhibiting nucleophiles such as the azide anion from interacting significantly with the boron centre), the rate at which **3.83** underwent the CuAAC reactions was found to be slightly greater. However, the overall difference in reactivity between the two benzylic azides was not of great significance, and as no undesired side reactions were noted to occur in the CuAAC reactions employing **3.78** anyway, simply allowing it to react for slightly longer periods than were otherwise required for **3.83** in the CuAAC reaction was sufficient to compensate for this.

3.15. Access to 4-H 1,2,3-Triazoles

The only alkyne that exhibited particularly low reactivity in the CuAAC reaction with **3.78** was trimethylsilylacetylene **3.2e** (Table 3.3, entry 6), which gave incomplete conversion to a mixture of **3.81e** and *in situ* de-silylated **3.81f**. The TMS group is known to be labile in the CuAAC reaction,[53] such that a mixture of the corresponding 4-TMS and 4-H 1,2,3-triazoles are the result of these reactions. Furthermore, **3.81e** exhibited much lower crystallinity when compared with all the other 1,2,3-triazoles synthesised, presumably due to the lipophilic character of the trimethylsilyl substituent, and as such it was not possible to separate from **3.78** by recrystallisation.

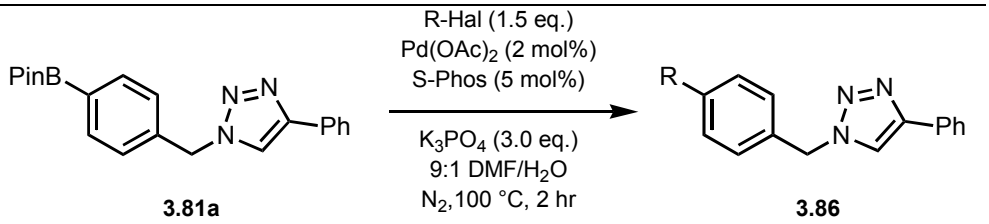


Scheme 3.18: (a) (See **Table 3.3**, **entry 6**); (b) TBAF, THF, r.t.; (c) twice reacted for 1 hr at 60 °C after purging with acetylene so as to saturate the reaction mixture; conditions otherwise as (a).

Given these factors we realized the potential that acetylene gas would have in giving direct access to 1-monosubstituted 1,2,3-triazoles such as **3.81f**, which could otherwise be produced *via* uneconomic silyl deprotection of **3.81e** (Scheme 3.18). Indeed Liang *et al.* have reported the use of acetylene gas (**3.2f**) sourced from pressurised cyclinders.[54] However, our approach was to generate discrete amounts of acetylene, formed in a separate reaction vessel upon contact of water with calcium carbide (CaC_2), and introduced into the CuAAC reaction solution *via* cannula. More recently reports have been made using water in the CuAAC solvent system, with calcium carbide then being added directly to the reaction vessel.[55, 56] However we chose not to do this for two reasons: Firstly the pinacolate ester could potentially have undergone partial or complete hydrolysis due to the resulting alkalinity caused by the $Ca(OH)_2$ by-product. Secondly, we allowed the generated acetylene to flow through the reaction media and headspace of the reaction vessel for a few minutes, employing a needle as an outlet for the excess gas. This method allowed us to ensure that the system was saturated as best as possible, and additionally, that once this had been achieved the vessel could then be

sealed without risk of explosion due to the generation of further equivalents of acetylene after that point. Despite this we found that re-saturation of the system, followed by a further period at elevated temperature, gave better results than a single saturation step – as has also been noted in the aforementioned literature reports. This is because the amount of acetylene able to dissolve in such solvent systems is not typically sufficient to completely convert the azides substrates to the corresponding 4-H triazoles. However, our use of this route to access 4-H 1,2,3-triazoles still proved to be more than competitive with that using trimethylsilyl-acetylene (Scheme 3.18).

3.16. Suzuki Coupling Reactions of Triazole Derivative 3.81a



3.81a **3.86**

Entry	Aryl halide		Product	Yield (%)
1	*p*-ClC_6H_4Me	**3.85a'**	**3.86a**	54[a]
2	*p*-ClC_6H_4Me	**3.85a'**	**3.86a**	81[b,c]
3	*p*-BrC_6H_4Me	**3.85a**	**3.86a**	89[c]
4	*o*-BrC_6H_4Me	**3.85b**	**3.86b**	99
5	*p*-BrC_6H_4OMe	**3.85c**	**3.86c**	99
6	3-bromopyridine	**3.85d**	**3.86d**	82[c]
7	2-bromothiophene	**3.85e**	**3.86e**	74[c]

All reactions performed using 0.5 mmol **3.81a**, 3.0 equiv. K_3PO_4 and 2.0 ml 9:1 DMF/H_2O.

[a] 32% of unchanged **3.81a** was also recovered, see Chapter 5 for discussion.

[b] Reaction run at 100°C for 5 hours.

[c] On this scale purification resulted in disproportionate attrition of the yield, though conversions were all complete by ^1H NMR; see Chapter 5 for details.

Table 3.4

As discussed in both Chapters 1 and 2, the biaryl monophosphine ligands reported by Buchwald and co-workers are able to form exceptionally active catalysts for palladium-catalysed cross coupling reactions. We therefore selected our reaction conditions based on those reported by the Buchwald group, who using S-Phos and $Pd(OAc)_2$ as pre-catalyst successfully demonstrated Suzuki coupling reactions of challenging substrates, including heteroaryl chlorides, with aryl pinacolboronate esters in mixed aqueous/organic media.[57] Pleasingly, under such conditions Suzuki couplings using **3.81a** as a model substrate with a range of aryl and heteroaryl bromides all gave complete conversion to the corresponding

products (Table 3.4, entries 3-7). Again, as was noted for the CuAAC reaction, the variations in product yields were due principally to differences in the ease with which purification could be achieved.

The use of the appropriate aryl chloride (Table 3.4, entry 1) in the synthesis of **3.86a** under the standard coupling conditions gave a lower yield than did the corresponding aryl bromide (entry 3), although the majority of the unreacted boronate was actually recovered intact, exhibiting remarkable stability. Consequently, by extending the reaction time to five hours, a comparable yield to the aryl bromide was achieved (entry 2).

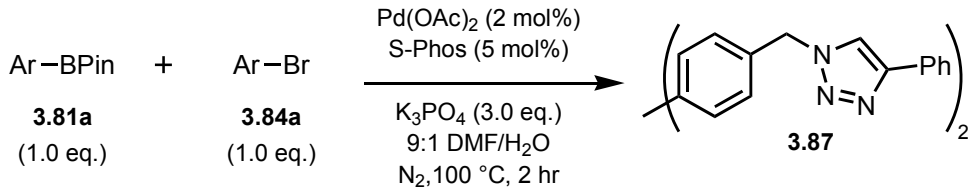
As discussed in Chapter 1, Suzuki coupling reactions involving boronate esters are almost universally regarded, either by inference or explicit statement, as necessitating aqueous basic reaction conditions in order to hydrolyse the ester moiety and release the free boronic acid, which equally is proposed (with or without prior quaternisation) as being a requirement for transmetallation to occur. Thus, while two hours was sufficient time to completely consume **3.81a** in the coupling reactions with aryl and heteroaryl bromides, after exposure to otherwise identical reaction conditions for the same amount of time but instead with the aryl chloride substrate **3.85a'**, the recovery of so much unhydrolysed boronic ester **3.81a** (i.e. 32% isolated yield after purification) is highly suggestive of a contribution of direct transmetallation involving the boronic ester.

This hypothesis is also consistent with results from the aforementioned study by Hartwig and Carrow regarding transmetallation of boronate esters with a phenylpalladium hydroxo complex in a solvent system comprising ≥ 25:1 THF/H_2O. They demonstrated that *p*-fluorophenylboronic acid, as well as its catecholate and neopentyl glycolate esters, react to consume > 95% of the phenylpalladium hydroxo complex in less than two minutes at -55 °C. Subsequent warming of such reaction mixtures to room temperature then results in the observed formation of the Suzuki coupling product, 4-fluorobiphenyl. Furthermore, and despite a lower rate of reaction, such that 1.5 hours was required to elicit the same > 95% consumption of the phenylpalladium hydroxo complex, the pinacolate ester of *p*-fluorophenylboronic acid also reacts at the same low temperature, and without any additional base or additives required. In combination then the observed reactivities for the four boronate analogues effectively rule out hydrolysis of boronate esters to the corresponding free boronic acid as being a prerequisite for transmetallation events – at least under any reaction conditions that allow even small amounts of such highly active palladium hydroxo species to be generated.[52] Indeed very many, if not the majority, of Suzuki coupling protocols do in

practice no doubt qualify in fulfilling this criteria – either primarily as a consequence of adventitious water or hydroxide base being present.

Furthermore, rationalising this observation requires too that the lower rate for oxidative addition of the aryl chloride under our reaction conditions is in fact the dominant factor in determining the yield of the desired cross-coupling product. Hence the relative rates of any undesirable side-reactions involving the boronate ester moiety are surprisingly low – potentially making **3.78** and its derivatives extremely useful in situations necessitating the use of highly demanding aryl halide substrates as coupling partners.

The Suzuki coupling products of the phenylacetylene derived triazole **3.81a** are all less soluble in non-polar solvents than the precursor boronic ester, some being quite difficult to dissolve. As a more extreme example of this, and although no more than a trace amount of either of the starting materials **3.81a** or **3.84a** (derived from CuAAC reaction of **3.83** with **3.2a**; see Chapter 5 for details) were recovered or could be observed by ^{1}H NMR analysis, the "dimeric" product **3.87** of the apparently successful coupling reaction (Scheme 3.19) was effectively insoluble even in DMSO-d_6.



Scheme 3.19

3.17. Removal of Residual Metal Catalysts from Product Triazoles

As discussed in the above literature review, 1,2,3-triazoles are effective ligands for binding metals such as copper and palladium, and as such have been used to synthesise new types of ligands.[32] Sharpless and co-workers noted in their original CuAAC publication that using copper turnings in place of discrete copper salts led to visibly lower levels of copper contamination in the organic products. The use of ligands such as TBTA are also important for CuAAC bioconjugation reactions, as they not only allow a lower loading of copper to be employed and stabilised in the Cu(I) oxidation state, but can also aid in removing copper contaminants from the products; for example when a cross-linked resin bearing an analogue of the ligand is employed.[12]

While we often obtained crude products from the CuAAC reactions in quantitative yield and ≥ 95% purity as determined by ^{1}H- and ^{11}B- NMR where appropriate, discolouration of these crude materials was frequently observed. Thus, due especially to the affinity of the 1,2,3-triazole for copper, subsequent purification was complicated, and normally resulted in disproportionate attrition of the yield on the scale we typically employed (as is representative of Table 3.3, entries 1 & 3-5). For example, **3.81a** was obtained in a 72% yield using the standard procedure (entry 1), compared to a 95% yield using the $CuSO_4$/sodium ascorbate system on a 3.0 mmol scale (entry 2). Notably, even at identical loadings of copper, then $CuSO_4$/sodium ascorbate tends to give less visible contamination of the product triazoles than does our optimised CuI system. Although interestingly, purified triazoles in the form of white powders can sometimes still slowly discolour over extended periods of time (e.g. days to weeks), suggesting that ultimately they are potentially very effective at retaining and stabilising residual Cu(I).

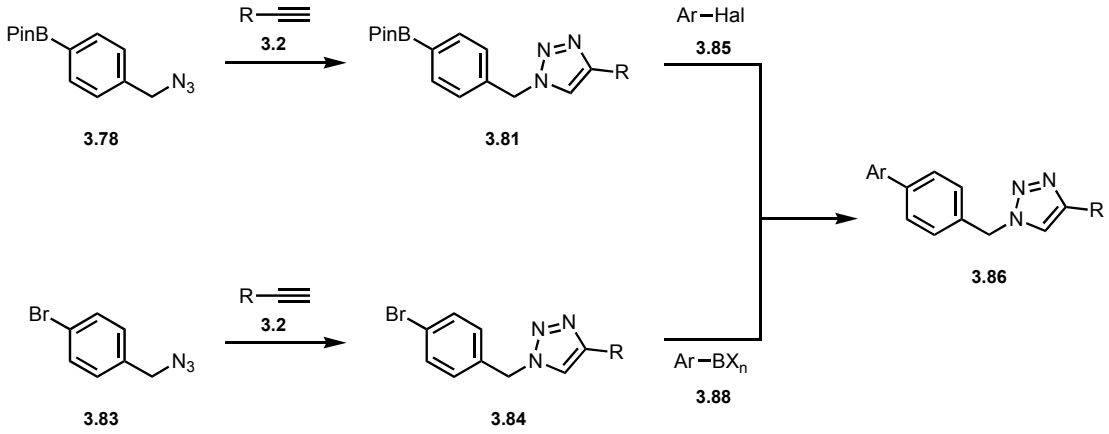
Our early attempts to remove copper contaminants from the products of the CuI catalysed CuAAC reactions involved the treatment of solutions of the triazoles with activated carbon, followed by silica gel chromatography. Interestingly Dowex Marathon resin, which is used in removal of Cu(I) from ATRP reactions,[58] was totally ineffective in this instance – highlighting the exceptional degree to which copper is retained by such 1,2,3-triazoles. We later found that Quadrapure TU resin was effective for this purpose, as noted by Ley and co-workers;[59] although long periods of incubation were still required to purify **3.81a** and the analogous triazoles, while even then not all copper contamination was observed to have been removed from our substrates. However, subsequent Suzuki couplings employing **3.81a** did not appear to be negatively impacted by such amounts of residual copper as remained after typical early purification procedures involving the use of activated carbon in warmed solvent, passage of the substrate through silica gel, and recrystallisation.

Similar metal contamination was observed as discoloration of the products **3.86a-e** from the Suzuki coupling reactions employing **3.81a**, although the affinity of 1,2,3-triazole for copper is particularly high,[16, 25] and we noted that discolouration due to palladium contamination was more rapidly and completely removed in comparison, especially when the QuadraPure TU resin was employed.

3.18. Potential Applications of Azido-Boronate Functionalised Linkers

The rapid and divergent nature of this chemistry gives it great potential for use in drug discovery work.[60-62] And here one of the most notable features of **3.78** is that it is obtained as a high purity solid, while in contrast **3.83** is a relatively viscous oil. As such removing solvent

from **3.83** to ensure correct stoichiometries is more difficult to achieve safely. **3.83** is also notably more light sensitive than **3.78**, and was typically kept in foiled containers, while during later investigations of these substrates it was further stored at low temperature so as to reduce its propensity to discolour upon prolonged storage.



Scheme 3.20

Importantly, although both **3.78** and **3.83** could ultimately be used to provide the same products of sequential CuAAC and Suzuki coupling reactions (Scheme 3.20), the use of the corresponding complementary coupling partners (**3.85** for the boronate; **3.88** for the arylbromide) would be necessary for the palladium-catalysed cross-coupling step. For this reason there is a significant advantage in employing **3.78** in place of aryl halide **3.83**. Namely, that in addition to being more straightforward than **3.83** to handle, **3.78** also has a greater synthetic utility, due in particular to the wide commercial availability of low-cost aryl and heteroaryl halides (**3.85**),[63, 64] thus allowing a much larger number of products to be obtained from a single stable dual-functional starting material bearing the boronate moiety.

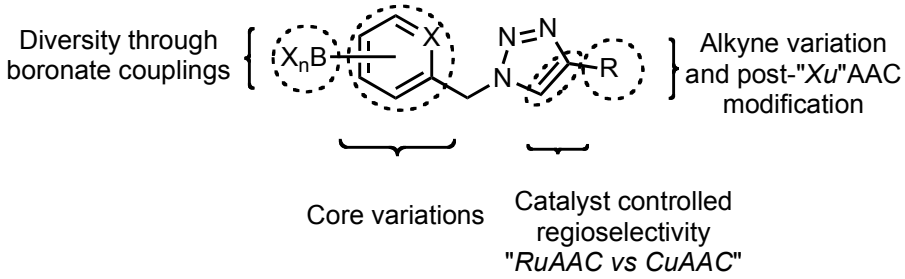
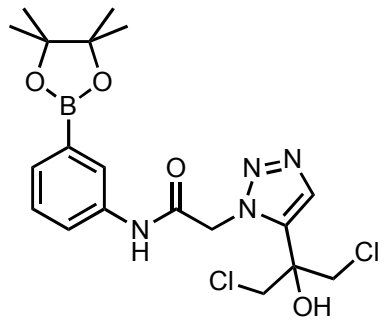


Figure 3.16

This concept is particularly relevant given the number of recent patents and publications detailing biological activity of compounds containing 1,2,3-triazoles,[31] and it can be envisaged that a small selection of linkers with varied cores could be used to build large

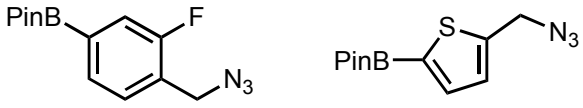
compound libraries simply by employing a selection of robust and cost-attractive transformations. For example, reactions including the Suzuki,[65] Chan-Evans-Lam,[66] and Heck or Heck-type cross-coupling methodologies involving organoborons,[67, 68] – as well as asymmetric rhodium-catalysed 1,4-conjugate addition and 1,2-addition reactions[69] – could all be employed for functionalising at the boronate terminus with a focus on increasing the diversity of products obtained. In addition to the CuAAC reaction providing 1,4-disubsituted 1,2,3-triazoles, the RuAAC variant could be used to produce the corresponding 1,5-regioisomers. Indeed Fokin and co-workers have shown that a similar substrate bearing a boron pinacolate ester can be coupled to a highly functionalised alkyne under RuAAC conditions to yield **3.89** in 76% yield on a 0.5 mmol scale with respect to the azide.[30]



3.89

Figure 3.17

Finally, and especially given the remarkable stability exhibited by **3.78**, variation of the benzyl triazole core could be used in order to access other potentially stable bifunctional linkers. Although a greater area of chemical space could be more rapidly accessed with an equivalent use of resources by derivatising the boronate and azide termini of one single linker synthesised using an analogous route to that detailed above for **3.78**, the appropriate choice of central motif would also provide very valuable starting materials for such an application.

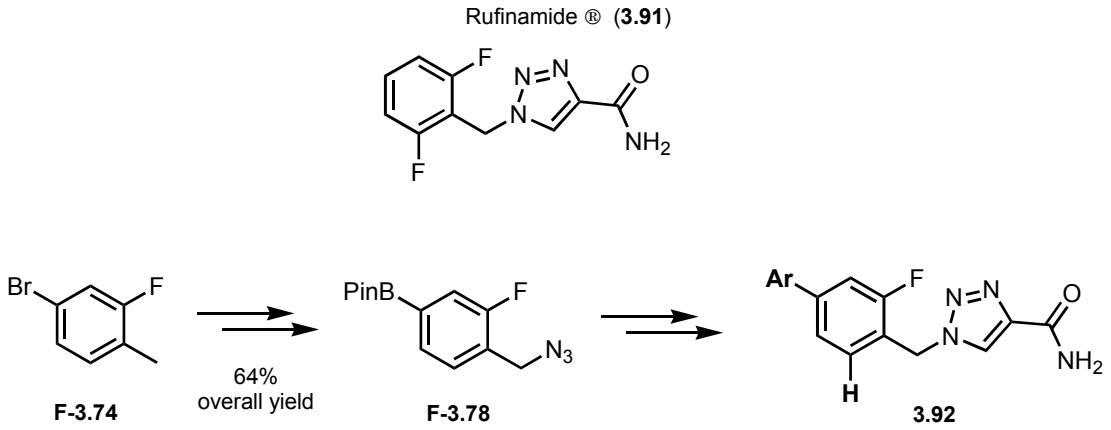


F-3.78 **3.90**

Figure 3.18

We therefore undertook the synthesis of two substrates analogous to **3.78**, with modified cores chosen for just such interesting structural qualities. However, our initial work to access thiophene **3.90** resulted in problems with selectivity issues in the radical bromination step,

with ring bromination and dibromination product mixtures observed by ^{1}H NMR. In addition 2-heteroaryl boronates are often much less stable than either aryl or alternatively substituted heteroaryl analogues. For simplicities sake we therefore chose to focus our subsequent efforts instead on **F-3.78**, as unlike the heteroaryl substrate, we expected that this could be synthesised in an identical manner to **3.78**, and should also possess a very similar stability and reactivity profile at both the azide and boronate termini. In addition to these practical considerations the recent approval of Rufinamide® **3.91** as an anti-epilepsy agent (which critically shares its benzyl-triazole core with triazole derivatives of **F-3.78**) made **F-3.78** a particularly interesting and relevant system to investigate – being a very valuable precursor from which a vast number of 5*H*-rufinamide derivatives could potentially be accessed.

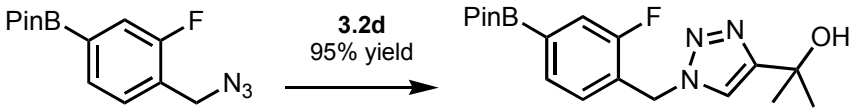


Scheme 3.21

Pleasingly we were able to synthesise **F-3.78** in a slightly higher overall yield than was obtained for **3.78**, again in multigram quantities from the relevant aryl bromide **F-3.74**, and without any need for purification of any synthetic intermediates by column chromatography. Additionally, unlike the targeted thiophene analogue **3.90**, all protocols used in the synthesis of **3.78** transferred directly to the fluoro analogue – most importantly the radical bromination, and pleasingly, despite the additional electron withdrawing moiety present in the benzyl bromide **F-3.77** the nucleophilic substitution reaction with NaN_3 also proceeded cleanly without any attrition of the ester.

3.18.1. Synthesis of 5*H*-Rufinamide Derivative

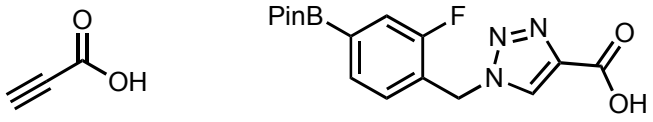
To first ascertain the CuAAC reactivity of **F-3.78** we subjected it to reaction with **3.2d**, and with a 95% yield obtained of **F-3.81d**, found it to be equally amenable to this type of chemistry (Compare Scheme 3.22 and **3.81d** which was obtained in a corresponding 90% yield by the analogous protocol; Table 3.3, entry 5).



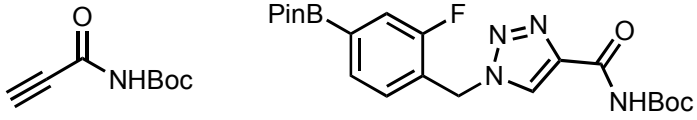
F-3.78 **F-3.81d**

Scheme 3.22

We initially set out to access 5*H*-1-(pinacolboronate ester)-*N*-Boc rufinamide **F-3.81h**, aiming to synthesise the protected secondary amide **3.2h** in parallel to **F-3.78**, so as to allow us to demonstrate the potential in further modifying the 4- substituent of the triazole, as well as being able to readily produce the hydrochloride salts of the Suzuki coupling products of type **3.92** (obtained from **F-3.81h**). However, and though not exhaustive, initial attempts to incorporate the *N*-Boc amide into either the alkyne (**3.2h** from **3.2g**) or triazole (**F-3.81h** from **F-3.81g**) were problematic and we therefore opted instead to incorporate a tertiary amide after the CuAAC reaction for ease.



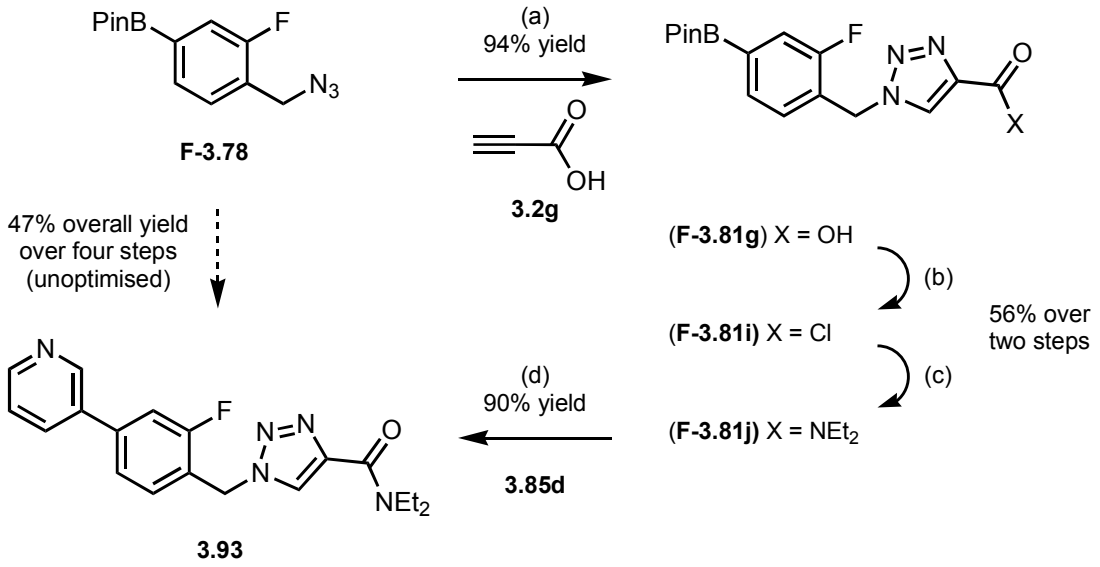
3.2g **F-3.81g**



3.2h **F-3.81h**

Figure 3.19

In this way, starting with the coupling of **F-3.78** with propiolic acid **3.2g**, the triazole-4-carboxylic acid **F-3.81g** was first synthesised in a very respectable 94% yield (Scheme 3.23). Subsequently, in an unoptimised one-pot procedure, **F-3.81g** was treated with oxalyl chloride, followed by trapping of the acid chloride **F-3.81i** with diethylamine, allowing us to obtain *N*,*N*-diethylamide **F-3.81j** in a 56% yield. With this final intermediate in hand we subjected it to reaction with **3.85d** under the same Suzuki coupling conditions as used previously for **3.78**; obtaining our target compound **3.93**, bearing a 3-pyridyl motif, in a respectable 90% yield. 5*H*-Rufinamide-derivative **3.93** was thus synthesised in a 47% overall yield in four unoptimised steps, starting from only 1.0 mmol of azido-boronate **F-3.78**.



Scheme 3.23: Reagents and conditions: (a) 1.2 equiv **3.2g**, 1:1 *t*-BuOH/H_2O (2.0 ml), 10 mol % $Cu(OAc)_2$, 20 mol% sodium ascorbate, 18 hr, r.t.; (b) oxalyl chloride, cat. DMF, DCM, 0 °C to r.t., 18 hr; then: (c) Et_2NH, DCM, 0–10 °C; (d) **F-3.81j** (0.44 mmol scale), otherwise as Table 3.4, entry 6.

3.19. Stability of F-3.78

Figure 3.20

Interestingly, and though still quite stable, relative to **3.78** the additional fluoro-substituent on the aryl ring of **F-3.78** does seem to result in a less stable substrate. This is observed by slow discolouration of the purified material, typically over a period of weeks, when stored in the dark at ambient temperatures and open to the atmosphere. We have not so far determined what this degradant or degradants may be, but as mentioned earlier the loss of material through such a process is very small. Given that the boronate esters of the corresponding methyl (**3.76** and **F-3.76**) and bromomethyl (**3.77** and **F-3.77**) substituted precursors of both **3.78** and **F-3.78** are not prone to any such discolouration, then it seems more likely that it involves the azide moiety.

Furthermore, the close proximity of the fluoro substituent to the proximal nitrogen of the benzylic azide moiety in **F-3.78** may explain why, while it by no means needs to be handled under an inert atmosphere, it is noticeably more prone to such discolouration than is **3.78**. Although a different situation, it is worth noting here observations made in Chapter 4, where

it is noted that a palladium(II) complex of type **3.95** (Figure 3.20) seems prohibitively stable towards further reactions. This most likely arises from an interaction between the metal centre and the proximal azide nitrogen. Thus it could be that in **F-3.78** the highly electronegative fluorine atom nearby to the azide moiety (as represented by **3.95**) acts to further polarise the azide bonds, either through space or *via* the aromatic system, so that they are more prone to reactions such as that which elicits the observed degradation.

Interestingly the discolouration appears to be localised to the surface of the solid samples of **3.78** and **F-3.78**, with larger crystals obtained *via* slower recrystallisation being notably more resistant to such changes – not having changed visibly or by NMR analysis after over a year of storage open to the air. Although such samples were stored in a laboratory cupboard, and therefore not typically exposed to significant amounts of light, it seems unlikely that the discolouration is caused by photolytic degradation. Primarily, as has previously been discussed, the crystal structure of **3.78** was identical after exposure to a UV source normally employed to elicit photolysis or photoinduced isomerisations in solid state samples. In addition, re-dissolution of any discoloured solid in petroleum ether, and subsequent passage through a plug of silica, readily removes such contaminants, and with an insignificant overall loss of material.

In comparison leaving samples of such azides, especially when impure, in solutions of organic solvents exposed to the air for much shorter periods of time also often results in such discolouration. For these reasons it appears that whatever process is occurring most probably involves a relatively reactive chemical species that it is causing the formation of a more polar impurity in only small amounts, and limited to the surface layer of the solid azide samples to which such species are directly accessible. As this effect is not observed with the boronate-only substrates, then it suggests that the azide is more reactive with a species present in the atmosphere. Given the rather slow rate of this process, even with fluoro-derivative **F-3.78**, then it could indicate that oxygen is involved in a radical mediated pathway, and indeed alkyl azides are known to be radical scavengers.[70]

3.20. Conclusions

In conclusion we have demonstrated that azido-boronate esters such as **3.78** have the potential to undergo sequential coupling reactions in high overall yield. We have added further evidence to the argument that organoazides can exhibit high levels of stability; a fact that we hope may help counter the common reluctance to make use of them. The perception sometimes encountered that these materials are always best used without intermediate isolation is in fact distinctly not the case for **3.78**. Its isolation makes positive improvements to process safety by eliminating contamination from the azide anion, which is dangerously incompatible with a wide range of common solvents, metal salts, and acids.[5, 71] The accessibility of triazole containing boronic acids, given the bioactivity both functional groups frequently exhibit, also warrants further investigation. Equally, the successful synthesis of **3.93** demonstrates the potential these substrates possess for diversity-oriented synthesis of drug-like molecules.

3.21. Future Work

Chapter 4 focuses on the continuation of the above investigations, with a specific emphasis on developing alternative synthetic routes to that presented herein – and in a way that allows for both much greater potential scope in terms of core structure, as well as offering more rapid access to such compounds from readily available commercial compounds.

The results of the investigations detailed within this chapter have also been published.[72]

3.22. References

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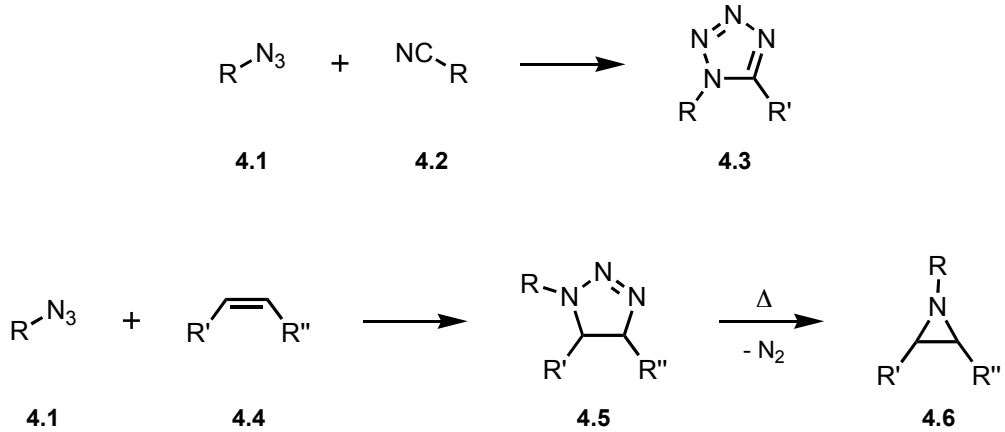
Chapter 4

Starting from commercially available aryl bromides, the synthetic route used to access azido-boronate ester **3.78** and analogue **F-3.78** presented in Chapter 3 gave extremely good overall yields of these products. However, while the optimised conditions for the radical bromination step transferred directly to the synthesis of the fluoro analogue, they did not transfer so directly to the synthesis of the desired target thiophene **3.94**, due both to over-bromination of the methyl moiety, and also halogenation of the heteroaryl system. This chapter details the development of an alternative methodology to that relying on a critical metal-halogen exchange step in order to synthesise such azido-boronate esters, with the focus on tolerance of the azide moiety such that it can be incorporated prior to the introduction of the boronate functionality. Here the palladium-catalysed borylation of aryl halides bearing benzylic azides is demonstrated as being useful in more rapidly accessing a potentially much wider range of core structures – further lending this approach and its products to applications in fields such as drug discovery.

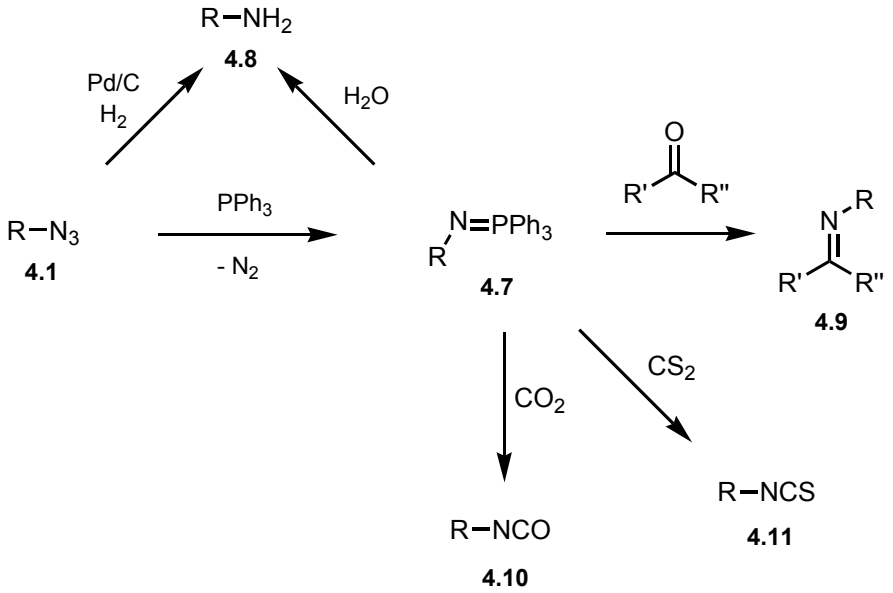
4.1. Applications of Organoazides

Although the widespread application of the CuAAC reaction has resulted in a significant increase in the level of attention organoazides have received as synthetically valuable substrates over the last decade, their utility in dipolar cycloaddition reactions is by no means limited solely to use in CuAAC or RuAAC reactions. For example, organoazides **4.1** react with other dipolarophiles, including nitriles **4.2** so as to form tetrazoles **4.3**, or alkenes **4.4** to give Δ^2-1,2,3-triazolines **4.5** – which in turn may undergo thermally induced loss of nitrogen to yield the corresponding aziridines **4.6**.[1]



Scheme 4.1

In the context of their utility as modular building blocks or molecular tethers, being simple alkyl azides, the azido-boronate esters of Chapter 3 are also amenable to a range of important transformations *via* aza-ylide intermediates, such as that exemplified by the iminophosphorane **4.7**, formed by the Staudinger reaction of an organoazide **4.1** with PPh_3.[1]

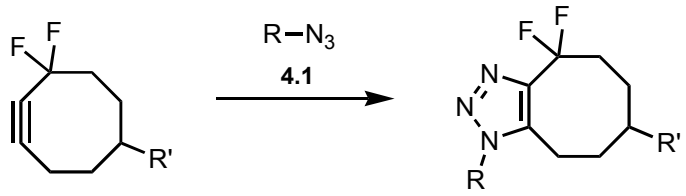


Scheme 4.2: (R = Aryl or alkyl)

Iminophosphoranes bearing synthetically valuable functionalities can be readily converted to primary amines **4.8** (Staudinger reduction) or imines **4.9** (aza-Wittig reaction), as well as being used as precursors to synthetically and biologically important substrates such as isocyanates **4.10** – allowing access to carbamates or ureas; or isothiocyanates **4.11** – which can be used to access thioureas.[1-3] Aza-ylides are also extremely important in bioconjugation reactions too, with the Staudinger ligation allowing amide bond forming reactions to be selectively achieved in the synthesis of peptides.[4] Furthermore, not only can azides be reduced *via* the aza-ylide intermediate, but also by other chemoselective methods in the presence of e.g. C=C bonds, which in part makes them an important alternative to protecting group manipulations of amines.[1] Finally, the utility of azides to form 1,2,3-triazoles in a click chemistry context is not limited to metal-catalysed variants of the reactions. The metal-free cycloaddition of azides and strained internal alkynes such as substituted difluorinated cyclooctynes **4.12** (Scheme 4.3) have been shown to have significant potential for use not only *in vitro*, but also *in vivo* where copper salts are too toxic to be employed.[4]

Additionally, arylboronate esters bearing either 1,2,3-triazoles[5] or alkyl azides[6, 7] can be derivatised to the corresponding potassium organotrifluoroborate salts by standard protocols employing aqueous KHF_2, as detailed in Chapter 1. As such the corresponding azide

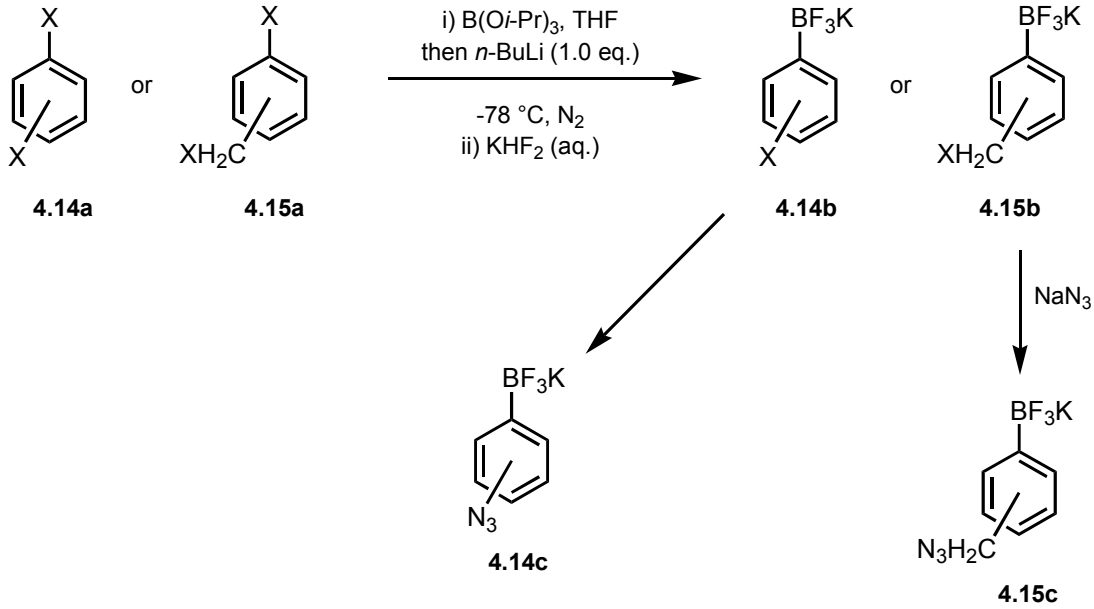
functionalised boronic acids should be readily accessible too – formation of the organotrifluoroborate salts as synthetic intermediates being undoubtedly one of the most reliable and mild methods available for the facile conversion of boronate esters into free boronic acids. This is also particularly noteworthy as both boronic acids and organoazides are important functional groups for a range of applications, including those relating to their biological utility.[1, 4] For all such reasons outlined above there is significant value in being able to access linkers of this sort rapidly, in a standardised fashion, and with the azide moiety already incorporated.



4.12 **4.13**

Scheme 4.3

4.2. Alternative Synthetic Approaches to Related Azide-Functionalised Organoborons

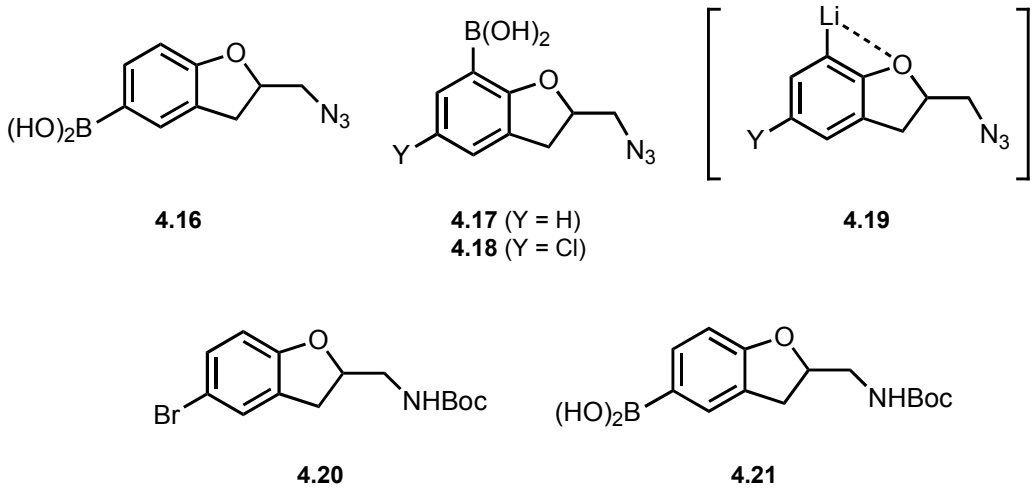


4.14a **4.15a** **4.14b** **4.15b** **4.14c** **4.15c**

Scheme 4.4

For the synthesis of both their original azidoalkyl linkers of type **4.15c**,[8] as well as their later azidoaryl ones of type **4.14c**,[9] Molander and co-workers employed a reverse-addition lithium-halogen exchange protocol. This allowed the intermediate aryllithiums to be rapidly trapped out as the acyclic diisopropyl boronic esters, which were then converted to the

corresponding trifluoroborate salts *in situ* with aqueous KHF_2 (Scheme 4.4). Finally, using NaN_3 the azide moieties were then incorporated, either by a standard nucleophilic substitution reaction for the alkyl and benzyl halide substrates such as **4.15b**, or by copper-assisted aromatic substitution reaction with CuBr and DMEDA for the aryl halides **4.14b** (as detailed in Chapter 3, Scheme 3.12). However, the latter approach for the synthesis of aryl azides is not generally applicable as a number of substrates employed gave rise to the corresponding aniline as the major product, and without the authors being able to ascertain what structural or electronic features where responsible for such a dramatic change in selectivity. Indeed, Helquist and co-workers have subsequently reported that the application of almost identical reaction conditions to those used by Molander and Ham do in fact provide a general and reliable method for the synthesis of anilines rather than aryl azides from the corresponding aryl iodides, bromides or even chlorides.[10]



4.16 **4.17** (Y = H) **4.18** (Y = Cl) **4.19**

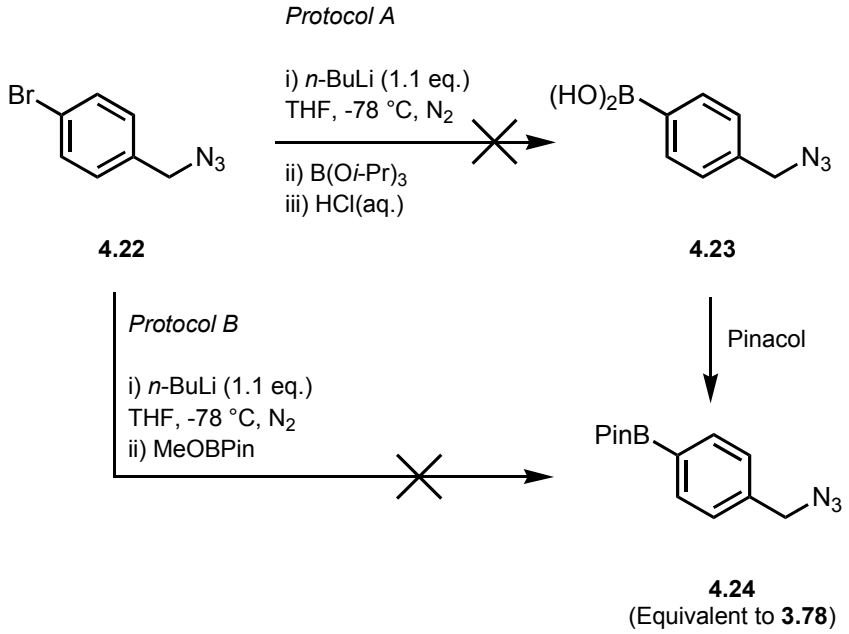
4.20 **4.21**

Figure 4.1

In contrast to the above approach Vasil'ev and co-workers employed a lithium-halogen exchange step after introduction of the azide moiety, and although this proved an effective means for synthesising linkers **4.17** and **4.18** (Figure 4.1), the same synthetic protocol could not be applied to **4.16**. This lack of generality was attributed to the lack of an appropriate *ortho*-directing group in order to maintain chemoselective reaction with *n*-BuLi so as to form a stabilised organolithium intermediate akin to **4.19**. As such the synthesis of **4.16** was not able to be achieved from the corresponding aryl bromide precursor, either by standard, or reverse addition, metallation/electrophilic trapping protocols – providing only ~ 10% yield of the desired boronic acid **4.16** in both cases. If however the azide moiety was first reduced and protected so as to yield Boc-protected amine **4.20**, then the standard protocol gave the corresponding *N*-Boc amine protected boronic acid **4.21** in good yield as expected, confirming that the presence of the azide moiety was what had resulted in the poor

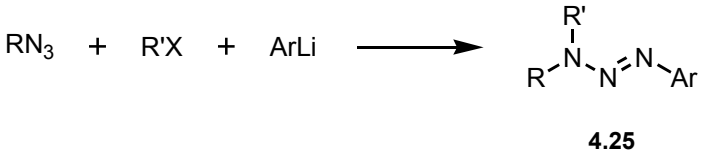
chemoselectivity obtained in the attempted synthesis of **4.16** under otherwise identical conditions.[11]

4.3. Investigation of the Synthesis of 4.24 *via* a Pivotal Metal-Halogen Exchange



Scheme 4.5: Attempted synthesis of **4.24** from **4.22** by a protocol analogous to that employed for the synthesis of boronic acid **3.75** from aryl bromide **3.74** – as detailed in Chapter 3.

Although literature precedent therefore suggested that **4.23** could likely not be accessed readily from aryl bromide **4.22** *via* a typical lithium-halogen exchange approach, we concluded that in this case a brief investigation was still merited due to the ease with which this precursor to **4.24** can be prepared from commercially available *p*-bromobenzyl bromide. However, and despite some of the desired boronic acid product apparently evident in the ^{1}H and ^{11}B NMR spectra of the crude reaction employing B(O*i*-Pr)$_3$ as the boron-source (Scheme 4.5, *Protocol A*), the crude mixture was effectively inseparable. Use of MeOBPin in this route (*Protocol B*), so as to yield the pinacol boronate ester directly, was also ineffective for improving the ease with which any of the desired product could be recovered.

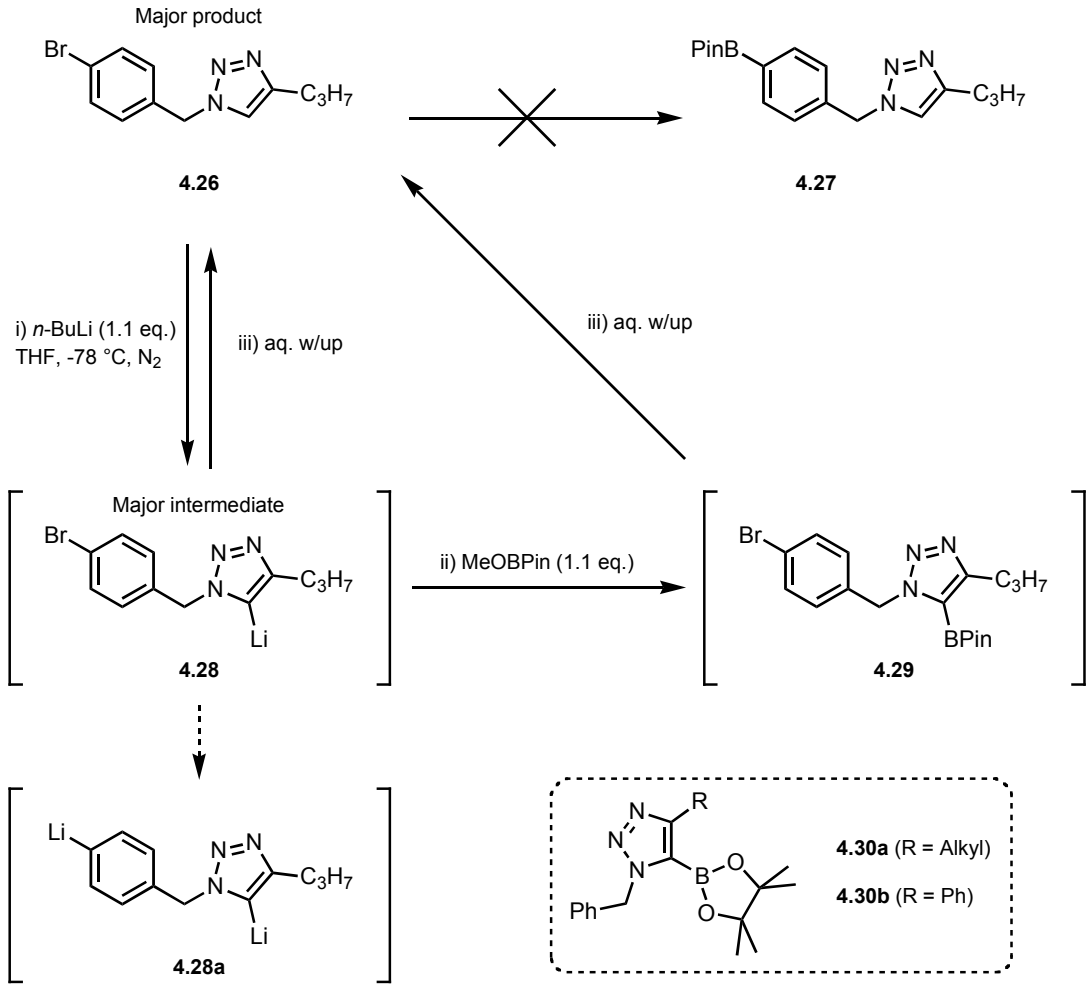


4.25

Scheme 4.6: A general route to the more stable aryl dialkyl triazenes.[12]

This behaviour can be attributed to the dipolar character of organoazides that makes them susceptible to attack by strong nucleophiles such as organolithium reagents, resulting in the

formation of triazenes **4.25** under such conditions (Scheme 4.6).[12] And although we considered that, e.g., using a less nucleophilic organometallic reagent might have been conducive to improving the chemoselectivity of such reactions at least to some degree, it seemed unlikely that such s-block metallation protocols would prove to be as tolerant of organoazide substrates in general terms as we desired from an alternative synthetic approach to analogues of **4.24**.



Scheme 4.7: Attempted synthesis of **4.27** from **4.26** by protocol analogous to that employed for the synthesis of **3.75** from **3.74** in Chapter 3.

Despite our aim being to determine alternative approaches that were tolerant of the azide moiety prior to it being derivatised, we also briefly investigated the synthesis of triazole **4.27** from aryl bromide **4.26** by this approach (Scheme 4.7). However, subjecting **4.26** to *Protocol B* (as detailed above in Scheme 4.5) yielded starting material as the major component observed in the crude reaction mixture. This can be explained by the fact that 5-H 1,2,3-triazoles are acidic enough such that a strong base like *n*-BuLi can be used to form the

triazolyl-lithium corresponding to **4.28**, which can in turn be quenched with typical electrophiles such as methyl iodide, elemental bromine or iodine, and D_2O.[13-15]

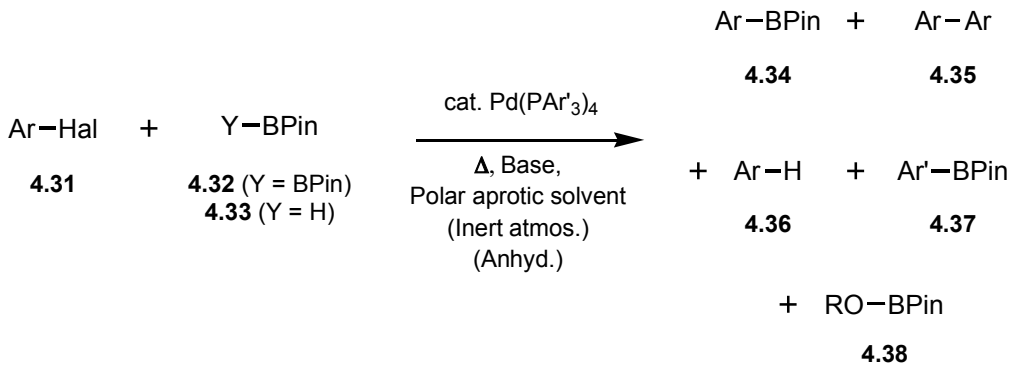
Interestingly, although triazole boronate ester **4.29** was likely to have formed upon the introduction of the trialkylborate, it should be noted that Harrity and co-workers were unable to purify either such substrates as **4.30a** bearing alkyl substituents at C-4, or the C-5 regioisomers with which they were generated with as part of inseparable mixtures – though as otherwise clean crude reaction products. Indeed, upon attempting purification the substrates were found to degrade (See also Chapter 3, Section 3.9.3). As they employed a thermally induced dipolar cycloaddition reaction in order to synthesise such compounds, and having specified that the stable aryl substituted analogues (e.g. **4.30b** and corresponding 1,5-disubstituted regioisomer) were purified by silica-gel chromatography, then it seems plausible that alkyl substituted triazole pinacolate esters such as **4.29** and **4.30a** are prone to protodeboronation under basic conditions. As such they are likely akin to labile 2-heteroaryl boronic acids and related organotrifluoroborate salts as detailed in previous chapters, and it is therefore unsurprising that the basic conditions we employed resulted in starting material **4.26** being the major component observed in the crude reaction mixture.

Again akin to previous discussions, such as those in Chapter 1, a stoichiometric excess of *n*-BuLi could be employed in order to drive the formation of a dilithiated species (represented by **4.28a**) by accounting for the acidic proton in the starting material. However, this seemed not to be an ideal approach for two reasons: Firstly, with aryl substituted triazoles especially, then the use of excess metallating agent may have given rise to mixtures of aryl and triazole boronate ester products upon introduction of the trialkylborate. More importantly however, we wished most to access the precursor azides, rather than the already formed triazoles. This would allow greater scope for derivitisation of such products after introduction of the boronate moiety. We therefore decided to investigate whether an alternative synthetic approach employing a palladium-catalysed C-X borylation reaction could provide a means for introducing the boronate ester moiety directly to organoazide bearing aryl halide substrates such as **4.22**, which although readily synthesised, are not yet derivatised at the synthetically versatile azide terminus – making their borylation products optimal for the purpose of subsequently introducing structural diversity.

4.4. Literature Review – Palladium-Catalysed C-X Borylation Reactions

In 1995 Miyaura and co-workers reported that under basic conditions palladium complexes catalysed the borylation of aryl bromides and iodides using bis(pinacolato)diboron (B_2Pin_2, **4.32**);[16] later reporting that aryl triflates,[17] aryl chlorides,[18] and related substrates such as 1-

alkenyl halides and triflates,[19] allyl acetates,[20] and benzyl halides[21] were also amenable to such protocols. In this way arylpinacolboronate esters (and thus also the corresponding arylboronic acids and related derivatives) can be accessed in an especially straightforward manner, without requiring the formation of s-block organometallics as is most typical in their syntheses. This suggested that this approach might be of particular value for the synthesis of any such substrates containing functionality or stereochemical information not otherwise well tolerated by procedures involving highly reactive organomagnesium or organolithium reagents. For example, in comparison to the standard protocols employing the s-block organometallics, the aforementioned 1-alkenyl substrates undergo such borylation reactions with a high level of stereoretention.[22]

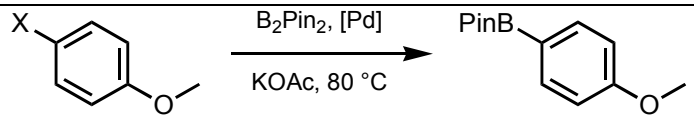


Scheme 4.8

Such reactions employing aryl halides (**4.31**) and diboron reagents (most typically bis(pinacolato)diboron – B_2Pin_2 – **4.32**) are now frequently referred to as Miyaura borylations, and typical reaction protocols involve the use of a palladium(II) pre-catalyst and phosphine ligand, appropriate inorganic base, elevated reaction temperature, and a polar aprotic solvent system. Furthermore, the reactions must be performed under anhydrous conditions and with maintenance of an inert atmosphere, so as to minimise the typical palladium-catalysed alternative processes of homo- and Suzuki cross-coupling. The choice of base in the reaction is also of particular importance in this respect, and while KOAc is almost always very effective at promoting the borylation reaction, the use of stronger bases such as K_3PO_4 or K_2CO_3 often results in significant amounts of biaryl products (**4.35**) being formed.

DPPF is typically used as the ligand for the borylation reactions of the more reactive electron-poor aryl bromide and iodide substrates, as the $PdCl_2$(dppf).DCM complex is commercially available, gives good results in such cases, and – unlike $Pd(PPh_3)_4$ – does not so readily yield phenyl pinacolboronate ester resulting from aryl-scrambling (by-product

4.37, Scheme 4.8, where Ar' = Ph) at the metal centre when using more electron rich aryl halides substrates.[16, 22] In terms of the aryl halide substrate (**4.31**), then the presence of electron donating groups on the aromatic ring typically results in lower rates of reaction, such that to compensate aryl iodides are generally used in place of less reactive bromides or triflates (Table 4.1). However, and as mentioned above, functional groups that are not so readily tolerated in the protocols employing s-block organometallic intermediates may be amenable to inclusion in palladium-catalysed borylation reactions, including substrates containing aryl- ester, ether, nitro and nitrile substituents.



4.39 **4.40**

Entry	X	Conditions[a]	Time (hr)	Yield (%)
1	I	A	2	82
2	Br	A	24	69
3	Br	B	7	81
4	Cl	B	48	78
5	OTf	B	2	83

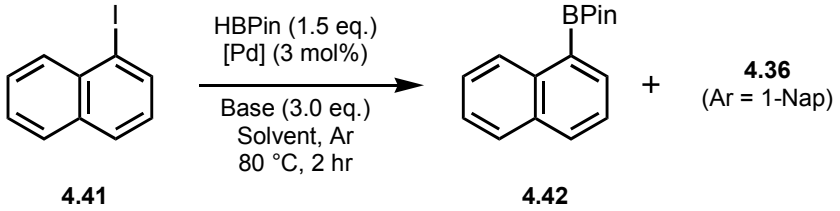
[a] A = $PdCl_2$(dppf), DMSO; B = $Pd(dba)_2$/2 PCy_3, dioxane.[16-18]

Table 4.1

Subsequent to the initial demonstrations made by Miyaura, the group of Masuda reported that a di(alkoxy)borane, namely pinacolborane (HBPin, **4.33**), could be used in place of bis(pinacolato)diboron (B_2Pin_2, **4.32**) for the borylation of aryl halides[23] and triflates[24]. These investigations were motivated by the poor atom-efficiency inherent when using B_2Pin_2 – as a result of the unproductive generation of one equivalent of boronate **4.38** as by-product – as well as the high cost and limited bulk availability of the diboron reagent at that time. Correspondingly, this C-X borylation approach is now sometimes referred to as Masuda borylation.

While KOAc was the most effective choice of base for Miyaura's protocol employing B_2Pin_2, in the presence of HBPin it led to a very small amount of the desired product **4.42** being produced, and instead the major product obtained in an 82% yield was hydrodehalogenated starting material (Table 4.2, entry 2). Indeed, the most important features of Masuda's system were the choice of appropriate reaction parameters in order to maximise the activity and selectivity of the borylation system, and so as to also minimise the

formation of the corresponding hydrodehalogenation product **4.36**. As such NEt_3 was chosen as the base, while dioxane proved to be a marginally better choice of solvent; although MeCN, toluene and 1,2-DCE also gave very similar results, all providing high yields of the desired borylation product with only small amounts (6-8%) of hydrodehalogenation product (entries 10-12). Most notably though DMF was found to result in both a poor level of reactivity and selectivity (entry 13), which is in stark contrast to the results in the corresponding systems employing diboron reagents where Miyaura reported that more polar solvents were more effective, such that DMSO ≥ DMF > dioxane > toluene. Masuda *et al.* attributed this effect in the HBPin system to tertiary amide induced decomposition of the dialkoxyborane to diborane, citing the report by Fu[25] that the hydroboration of olefins with catecholborane is catalysed by DMA *via* formation of species such as BH_3-DMA and B_2Cat_3. Thus, at least when issues such as the interaction between borane reagents and amide solvents are understood as being exceptions, then the Masuda borylation reaction appears to be much less sensitive towards choice of solvent than does the Miyaura borylation.



4.41 **4.42**

Entry	Catalyst	Base	Solvent	Yield (%)[a]
1	$PdCl_2(dppf)$	-	Dioxane	0 (3)
2	$PdCl_2(dppf)$	KOAc	Dioxane	6 (82)
3	$PdCl_2(dppf)$	DBU	Dioxane	3 (36)
4	$PdCl_2(dppf)$	Pyr.	Dioxane	12 (47)
5	$PdCl_2(dppf)$	DIPEA	Dioxane	64 (29)
6	$PdCl_2(dppf)$	NEt_3	Dioxane	89 (6)
7	$PdCl_2(PPh_3)_2$	NEt_3	Dioxane	75 (13)
8	$PdCl_2(PPh_3)_2/PPh_3$	NEt_3	Dioxane	0 (0)
9	$Pd(PPh_3)_4$	NEt_3	Dioxane	10 (1)
10	$PdCl_2(dppf)$	NEt_3	Toluene	79 (7)
11	$PdCl_2(dppf)$	NEt_3	1,2-DCE	81 (7)
12	$PdCl_2(dppf)$	NEt_3	MeCN	83 (8)
13	$PdCl_2(dppf)$	NEt_3	DMF	27 (23)

[a] Yields of **4.42** determined by GC; values for the hydrodehalogenation product **4.36** (where Ar = 1-Nap) are given in parentheses.

Table 4.2

Under their optimised conditions Masuda and co-workers were typically able to achieve moderate to good yields across a range of aryl halides and triflates. However, while the reactions of aryl iodides at 80 °C typically gave good yields and selectivities, the corresponding use of triflates, and most especially bromides, proved less successful. Indeed, while the triflates sometimes only required extended reaction times at the same temperature in order to achieve comparable results to the iodides, the aryl bromides were only reported to have been borylated at 100 °C, and typically also required much longer reaction times. Furthermore, due to the high degree of similarity to the reaction conditions used by Miyaura and co-workers, it is reasonable to demonstrate the comparative reactivity of bromobenzene in these two related borylation protocols: Thus, after two hours at 80 °C, bromobenzene was borylated in a 98% yield under Miyaura's protocol;[16] while the protocol developed by Masuda *et al.* gave only a 67% yield after a six hour reaction conducted at 100 °C.[24]

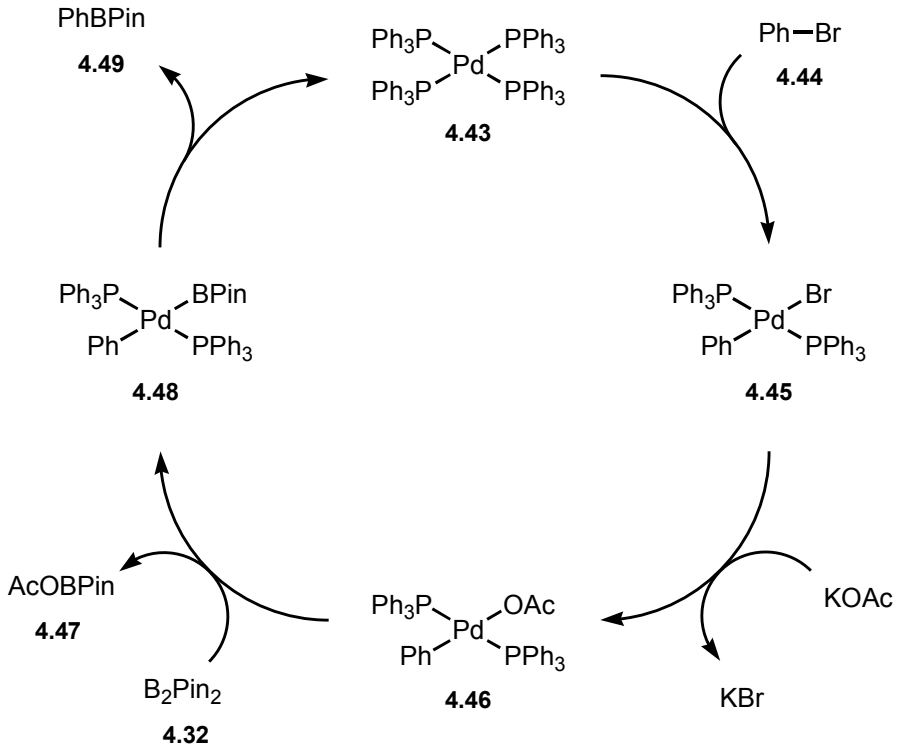
It should also be noted that the use of high temperatures and extended reaction times, in order to force the consumption of starting material in borylation reactions employing di(alkoxy)boranes, in turn often results in substantial amounts of hydrodehalogenated side-product being formed. However, Masuda and co-workers later reported the use of benzyl chlorides and bromides as substrates in these reactions, again under similar conditions, but with $PdCl_2(PPh_3)_2$ proving a much more effective choice of pre-catalyst. Interestingly though, the benzyl iodides were not reported as being amenable to this procedure, and while the chlorides proved more reactive than the corresponding bromides, in some cases the hydrodehalogenated product was still observed in significant amounts. Finally, the aryl halides were also shown to be less reactive than their benzylic equivalents, such that *p*-bromo benzyl bromide could be borylated selectively at the benzylic position to give the product in a 72% yield.[26]

4.4.1. Mechanistic Details and Catalytic Cycles of the Miyaura & Masuda Borylation Reactions

In Chapter 1 reactions involving the overall addition of B-B or B-X across C-C or C-X multiple bonds were discussed. The approaches to the formation of boronate esters detailed above – although there are mechanistic differences between them – are distinct from such addition reactions, in that they introduce the boron moiety by a metal-catalysed cross-coupling process of the organic substrate *via* a metal-boryl intermediate.[22, 27]

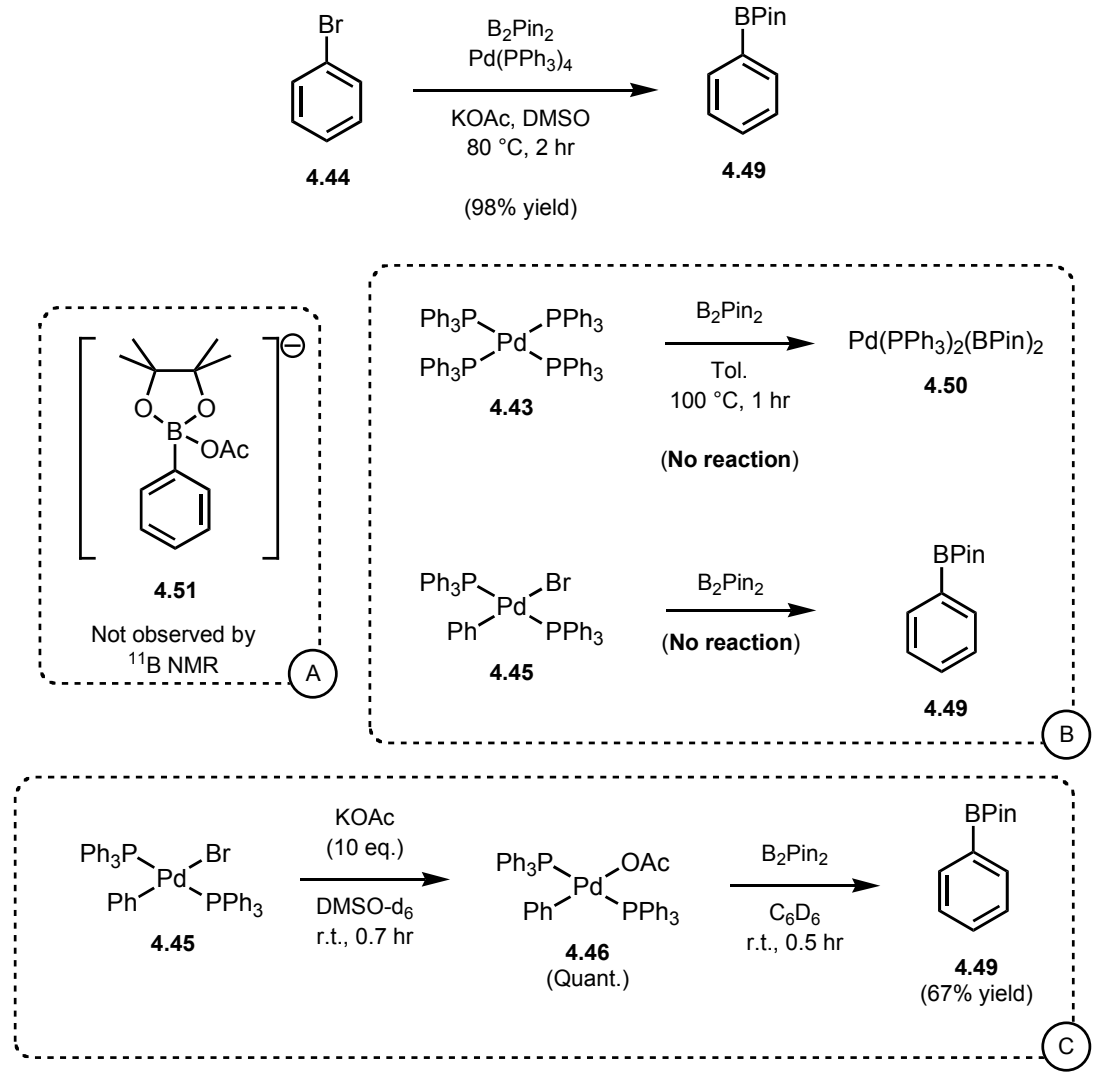
In the case of the palladium-catalysed borylation reactions employing B_2Pin_2 and HBPin, the initial step of the catalytic cycle involves oxidative addition of the aryl halide to yield an

arylpalladium(II) complex of type **4.45**, which is also a common intermediate in e.g. the Suzuki coupling reaction.



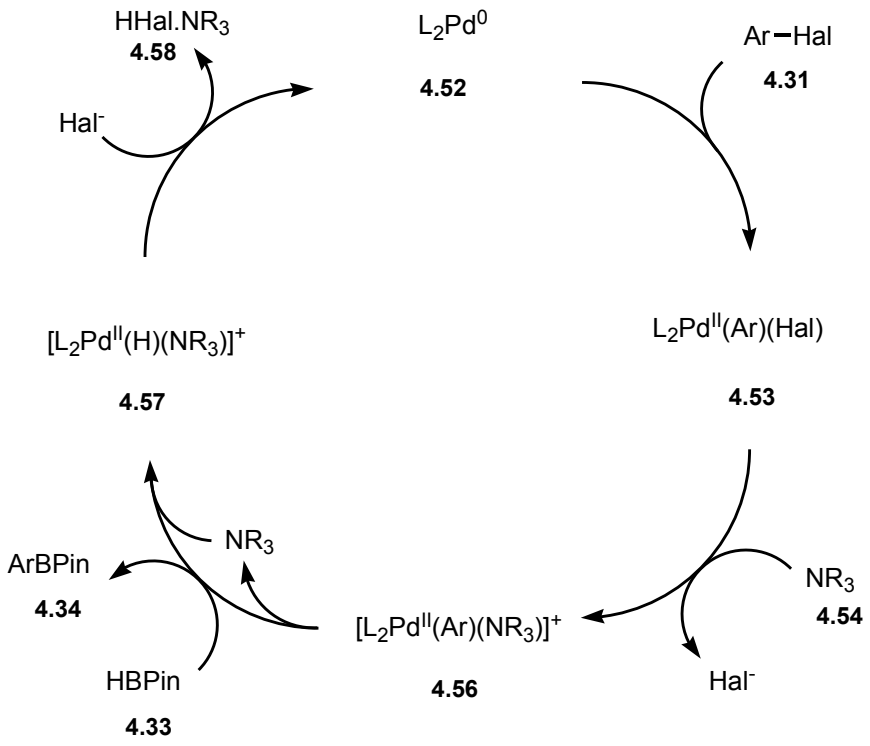
Scheme 4.9

Miyaura and co-workers concluded that in the presence of B_2Pin_2 and KOAc the catalytic cycle of the borylation reaction then proceeds *via* an anionic ligand exchange event, so as to yield an acetoxopalladium(II) complex **4.46**. This complex then undergoes transmetallation with B_2Pin_2 to yield **4.48**, which undergoes reductive elimination to give the product boronate ester **4.49**, with concomitant regeneration of the active palladium(0) complex **4.43**. This sequence of events was determined to occur as, despite potassium acetate selectively promoting a facile borylation reaction, B_2Pin_2 was not found to form borate **4.51** (Scheme 4.10, *Box A*) when treated separately with KOAc – thus implying that the role of acetate was not in activating the diboron reagent for transmetallation. Additionally, neither oxidative addition of B_2Pin_2 to $Pd(PPh_3)_4$ to yield **4.50**, nor transmetallation of B_2Pin_2 with arylpalladium bromide complex **4.45** in order to then yield product **4.49**, was shown to occur in isolation (*Box B*). However, treatment of oxidative addition product **4.45** with KOAc prior to B_2Pin_2 being introduced resulted in rapid anionic ligand exchange of the halide anion with acetate, yielding an acetoxopalladium(II) complex of the type **4.46** (*Box C*). In contrast to the oxidative addition adduct **4.45** formed by $Pd(PPh_3)_4$ and bromobenzene, complex **4.46** was found to be highly active for the transmetallation and reductive elimination steps when treated with B_2Pin_2 at room temperature, rapidly yielding the borylation product **4.49**.[16, 28]



Scheme 4.10

As such it seems that the role of acetate is to yield a more reactive complex for subsequent transmetallation with the diboron reagent, which is in turn attributed to the hard basic character of the acetate ligand that contrasts the soft acidic palladium centre, thus leading to a labile Pd-O interaction. Furthermore, the high oxophilicity of boron further compounds this, making formation of by-product **4.47** (Scheme 4.9) more favourable. Also, while the catalytic borylation of bromobenzene **4.44** requires a temperature of 80 °C in order to proceed, the studies of the ligand exchange step and subsequent transmetallation/reductive elimination sequence show these processes proceed readily at room temperature. Thus, as is typical of similar catalytic cross-coupling reactions – including the Suzuki coupling reaction[29] – oxidative addition of the aryl halide was therefore inferred to be the rate-limiting step of the catalytic cycle.

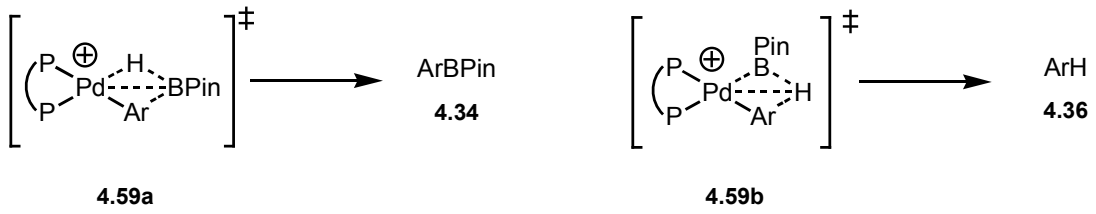


Scheme 4.11

In the case of Masuda borylation reactions with HBPin and amine bases, then the amine is proposed to be involved in an assisted-ionisation event with the oxidative addition adduct **4.53**, so as to yield the cationic complex **4.56**. Notably, the formation of this cationic complex is therefore promoted by use of a highly polar and appropriately basic solvent system, which in turn favours the formation, and subsequent stabilisation and solvation of such species.[30] The intermediate cationic complex **4.56** subsequently undergoes a metathesis reaction with HBPin **4.33** to form the borylation product **4.34** and palladium hydride **4.57**. Finally complex **4.57** undergoes reductive elimination to yield the trialkyl ammonium halide salt **4.58** and the active Pd(0) complex **4.52**, which is again free to continue the catalytic reaction by oxidative addition with aryl halide **4.31**. This catalytic process is analogous to the case involving transmetallation between the acetoxopalladium complex **4.46** and B_2Pin_2 **4.32**, in that neither catalytic cycle involves the formation of an anionic borate species by action of the corresponding base, but rather that the base is involved in activating the metal centre so as to promote the transmetallation event.[16, 30]

Borylation reactions employing di(alkoxy)borane reagents such as HBPin are known to give rise to notable amounts of the hydrodehalogenation product **4.37** in certain instances. Although the energy calculated for transition state **4.59a** is lower than that for transition state **4.59b** (20.9 kcal/mol compared with 25.8 kcal/mol, respectively, when Ar = Ph), potentially due to a more favourable charge matching in the case of $B^{\delta+}$–$Ar^{\delta-}$ and $Pd^{\delta+}$–$H^{\delta-}$, it is evident

that variations in the electronic and steric parameters of the aryl halide and active catalyst could therefore result in the varying ratios of borylation product **4.34** to hydrodehalogenation product **4.36** observed in such reactions.[30]



4.59a **4.59b**

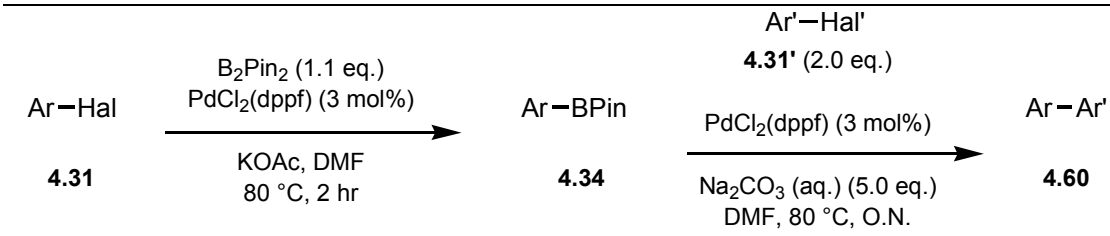
Scheme 4.12

4.4.2. Advances in the Palladium-Catalysed Aryl C-X Borylation Reactions

4.4.2.1. One-pot Sequential Borylation/Suzuki Coupling

As initially noted by Miyaura and co-workers, the use of KOAc in the diboron variant of the reaction was required as stronger bases typically employed in the Suzuki coupling reaction tended to result in significant quantities of "homocoupled" biaryl product **4.35**. By using an appropriate base, and maintaining more rigourously anhydrous conditions, this pathway can often be suppressed. However, this alternative activity of palladium complexes of the general type $L_nPd(0)$ (n = 1, 2) can also be used advantageously so as to perform one-pot borylation/Suzuki coupling reaction sequences.

In 1997 Prasit and co-workers reported that after employing Miyaura's standard borylation conditions with B_2Pin_2, the crude reaction mixture could then simply be temporarily cooled such that a second aryl halide, in addition to 2M Na_2CO_3 (aq.) and a second portion of $PdCl_2$(dppf), could be charged into the reaction vessel. In this way symmetrical or unsymmetrical biaryls **4.60** could be obtained directly from the corresponding aryl halides (**4.31** and an equivalent or inequivalent coupling partner **4.31'**; Table 4.3). Such reactions were typically more efficient when a more reactive aryl halide (e.g. iodo, and/or electron rich) was first borylated, then subsequently coupled with the less reactive component (e.g., compare entries 1 and 2). In the cases where both aryl halides were electron poor it was noted that substantial amounts of the homocoupling product from the second aryl halide were observed, irrespective of which of the two was added first. First performing the borylation of heteroaryl halides resulted in poor yields, which was attributed to a slow borylation reaction which allowed for competitive homocoupling.[31]



Entry	Ar	Hal	Ar'	Hal'	Yield (%)[a]
1	*p*-$MeOC_6H_4$	I	*p*-ClC_6H_4	Br	81
2	*p*-ClC_6H_4	Br	*p*-$MeOC_6H_4$	I	60
3	*p*-$HCOC_6H_4$	Br	*p*-ClC_6H_4	Br	43[b]
4	*p*-ClC_6H_4	Br	*p*-$HCOC_6H_4$	Br	50
5	*p*-NCC_6H_4	Br	*p*-ClC_6H_4	Br	41
6	*p*-$MeOC_6H_4$	I	(3-bromothiophene)		80
7	(3-bromothiophene)		*p*-$MeOC_6H_4$	I	34

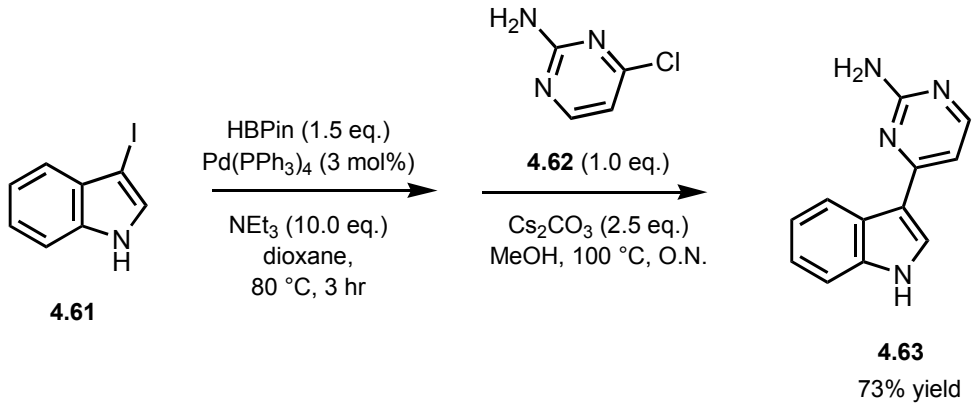
[a] Isolated yields.

[b] CsF (3.0 eq.) used in place of Na_2CO_3 (aq.).

Table 4.3

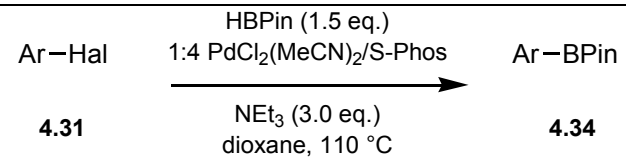
Subsequent reports in the chemical literature using B_2Pin_2 have demonstrated the use of "ligand-free" palladium catalysts,[32] symmetrical biaryl formation,[33] and more recently borylation of non-*ortho*-heteroatom substituted heteroaryl halides;[34] as well as the one-pot borylation/Suzuki coupling of aryl mesylates and tosylates, which provide a more stable alternative to aryl triflates.[35]

Analogous reactions have also been performed using HBPin protocols, with more demanding *ortho*-substituted aryl bromide and iodide substrates as reported by Baudoin *et al.*[36] using the Buchwald group's cyclohexyl John-Phos ligand,[37, 38] and alternatively by Colobert and co-workers who found DPEphos to be a more effective ligand in certain circumstances with such substrates.[39] Recently the one-pot borylation/Suzuki coupling protocol using HBPin was used to furnish meridianin G (**4.63**), although the *ortho*-heteroatom substituted aryl chloride component **4.62** was employed for the Suzuki coupling reaction and not as the borylation substrate where, as expected, a nitrogen atom in the heteroaryl system *ortho* to the halide prohibited successful synthesis of the corresponding borylation product.[40]



Scheme 4.13

4.4.2.2. Improvements in Substrate Scope



4.31 **4.34**

Entry	Ar	Hal	[Pd] (mol%)	Time (hr)	Yield (%)[a]
1	*p*-$MeOC_6H_4$	I	1.0	0.5	94
2	*p*-$MeOC_6H_4$	I	0.1	5	91
3	*p*-$MeOC_6H_4$	Br	1.0	1	97
4	*p*-$MeOC_6H_4$	Cl	3.0	24	96[b]
5	2,4,6-Mes	Br	2.0	4	90
6	*p*-(*n*-Bu)C_6H_4	Br	2.0	4	89
7	*p*-(*n*-Bu)C_6H_4	Cl	4.0	24	51[b]

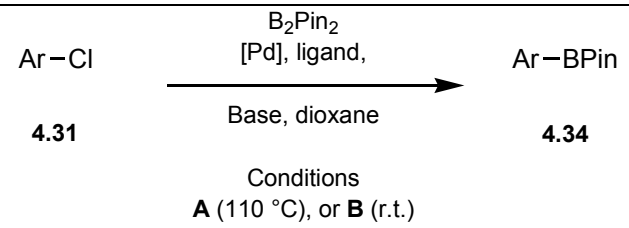
[a] Isolated yields.

[b] NEt_3 (1.0 ml/mmol halide) required as solvent in place of dioxane (0.6 ml/mmol halide) in order to obtain full conversion.

Table 4.4: Masuda borylation of aryl halides, as reported by Buchwald and Billingsley.

While the Miyaura borylation proved tolerant to a wide range of functional groups, including examples not normally compatible with the traditional s-block organometallic intermediates, certain products are still not readily accessible by the catalytic borylation reactions. Most notably such examples include those which also prove troublesome to prepare by traditional metallation protocols, such as the 2-heteroaryl boronates, and which is as a result of their instability towards the basic reaction conditions common to both such approaches.[28] As such many of the more important advances in this area have been the development of protocols that allow for the borylation of substrates that to begin with are simply less reactive, primarily to oxidative addition, such that more active complexes are required for their

effective borylation. For example, despite the common desire to demonstrate the successful use of aryl chlorides in palladium-catalysed cross-coupling reactions – due in particular to cost advantages – such substrates have typically proven rather unreactive in most systems.



Entry	Ar	Conditions	Pd (mol%)	Time (hr)	Yield (%)
1	*p*-$MeOC_6H_4$	A	2.0	(10 min)	97[a]
2	*p*-$MeOC_6H_4$	A	0.1	24	94
3	*p*-$MeOC_6H_4$	B	2.0	24	97
4	2,6-MeC_6H_3	A	4.0	5	62[b]
5	2,6-MeC_6H_3	B	2.0	48	86
6	*p*-Ph(H)NC(O)C_6H_4	A	0.5	0.5	96
7	*p*-HOC_6H_4	A	2.0	0.5	82
8	*m*-$H_2NC(O)C_6H_4$	A	2.0	0.5	89
9	*p*-(*n*-Bu)C_6H_4	B	2.0	48	91[c]

Values are for isolated yields of products. Conditions: (A): 1:2 $Pd(dba)_2$/X-Phos, B_2Pin_2 (1.2-3.0 eq.), KOAc (3.0 eq.), dioxane (2.0 ml/mmol halide), 110 °C; (B): 1:2.5 $Pd(OAc)_2$/S-Phos, B_2Pin_2 (3.0 eq.), K_3PO_4 (3.0 eq.), dioxane (2.0 ml/mmol halide), r.t.

[a] $Pd(OAc)_2$ used in place of $Pd(dba)_2$.

[b] 10:1 dioxane/H_2O used as solvent system.

[c] $K_3PO_4.H_2O$ as base.

Table 4.5: Miyaura borylation of aryl chlorides, as reported by Buchwald and co-workers.

However, as has been seen in both Chapters 1 and 2, the Buchwald group's monophosphine biaryl ligands have been shown to be highly active in many palladium-catalysed cross-coupling reaction methodologies (due in no small part to their complexes' exceptional activities towards undergoing oxidative addition with aryl halides). Indeed Buchwald and co-workers have reported an extremely active Masuda borylation protocol for use with aryl iodides and bromides, as well as unactivated aryl chlorides even at low palladium loadings. Using S-Phos as ligand gave the best results during optimisation, with it providing the highest conversion of starting material and correspondingly high GC yield (while some other of those ligands screened appear to have promoted side-reactions, as conversions are notably higher than GC yields). A lower reaction temperature of 80 °C was noted as being sufficient for aryl iodides and aryl bromides, with any less reactive examples being amenable to an

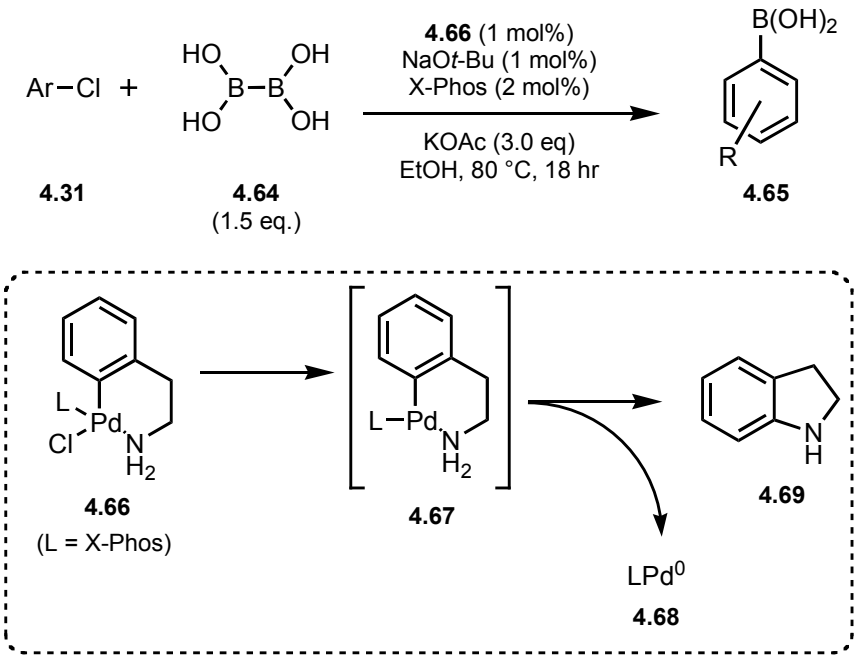
extension of the reaction time in order to improve the conversion. However, in order to ensure that the borylation reaction proceeded in those cases employing aryl chloride substrates, the higher reaction temperature of 110 °C was a requirement, as was the use of NEt_3 as solvent, rather than merely as an additive (Table 4.4).[41]

The Buchwald group have also reported using their monophosphine biaryl ligands successfully in the Miyaura borylation reaction, with X-Phos and S-Phos providing highly active palladium complexes for the borylation of aryl chlorides at elevated and ambient temperatures, respectively (Table 4.5).[42] Notably this protocol also allowed the use of substrates not disclosed in the group's subsequent publication on the Masuda borylations (discussed immediately above) such as phenols and primary amides (entries 7 and 8, respectively).

4.4.2.3. Alternative Boranes and Diborons

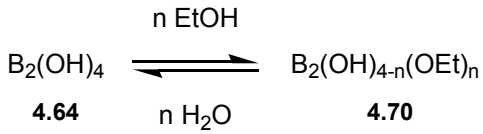
While modifications to the Masuda borylation protocol have been reported, including those employing alternative dialkoxyborane reagents that may even be formed *in situ*,[43-45] the results obtained in such cases are typically not as good as those resulting from the use of HBPin itself. And although differentially-reactive novel diboron reagents have recently been reported by Santos[46, 47] and Marder[27], as well as Suginome and co-workers[48] for the diboration of unsaturated C-C bonds so as to yield differentially protected boronate moieties, such reagents are not of significant importance to the Miyaura borylation.

However, Molander and co-workers have recently demonstrated that tetrahydroxydiboron **4.64** can be used in the borylation of aryl chlorides to directly yield aryl boronic acids **4.65**.[49] Reactions conditions were optimised by high-throughput experimentation techniques using *p*-chloroanisole as the substrate, which led to the selection of $Pd(OAc)_2$ as the pre-catalyst, in combination with X-Phos as the ligand, and at a palladium/ligand ratio of 1:3. However, when these conditions were translated to the preparative scale reactions they were not found to be at all as effective, which was determined to be due to the way in which the catalyst was charged to the reaction plates in the HTE screens – allowing the active phosphine ligated Pd(0) species to be formed prior to introduction of tetrahydroxydiboron **4.64**. Thus, scaled reactions were found to be better conducted by first pre-forming the active catalyst for one hour at 65 °C, or more simply the recently reported pre-catalyst **4.66**[50] developed by the Buchwald group could be used in place of $Pd(OAc)_2$. **4.66** rapidly eliminates indoline **4.69** under basic conditions to generate LPd(0) **4.68** (where L = X-Phos).



Scheme 4.14

It was also found that the palladium/ligand ratio, as well as the reaction concentration, was critical to achieving high yields. The reactions were also found to proceed best in alcohols, which gave improved solubility and reactivity parameters, with ethanol being the optimal choice. Under such conditions the authors note that tetrahydroxydiboron **4.64** will be in equilibrium with various ethyl esters **4.70**, as denoted in Scheme 4.15.

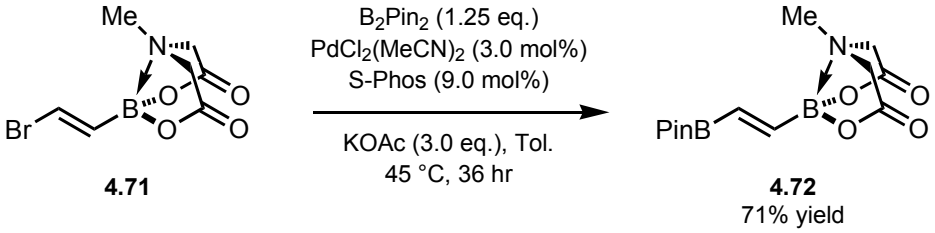


Scheme 4.15

The products could be isolated as the free boronic acids **4.65** simply by aqueous workup, followed by washing the crude solids with hexanes. Alternatively the boronic acid product could be trapped *in situ* to yield the corresponding boronate esters of pinacol, pinanediol, neopentyl glycol, and MIDA di-acid; or derivatised to the corresponding potassium organotrifluoroborate salt (see Chapter 1 for relevant protocols). Finally, the boronic acids could be reacted further by use of a one-pot borylation/Suzuki coupling protocol. Despite the good level of scope with aryl chloride substrates, neither the aryl bromides nor heteroaryl chlorides could reliably be employed in the reaction due to high levels of homocoupling and protodeboronation by-products being formed, respectively. Furthermore, in contrast to B_2Pin_2, tetrahydroxydiboron is not currently available in bulk quantities, and despite the

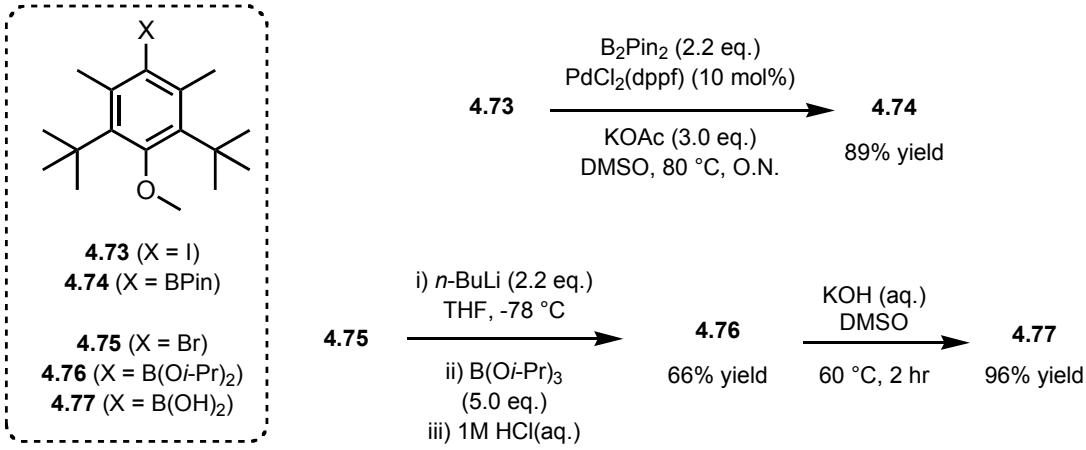
potential for improving atom-economy in the preparation of boronic acids, it is not currently a cost effective alternative to the alkoxydiboron reagents.

4.4.2.4. Notable Substrates



Scheme 4.16

Burke and co-workers have demonstrated that the borylation protocol is also compatible with their MIDA boronates, such that **4.71** (see Chapter 1 for synthesis and related discussions) could be borylated in high yield to give **4.72**. This substrate proved to be an invaluable component in the synthesis of polyene natural products due to the differential reactivity of the two boronate moieties.[51]

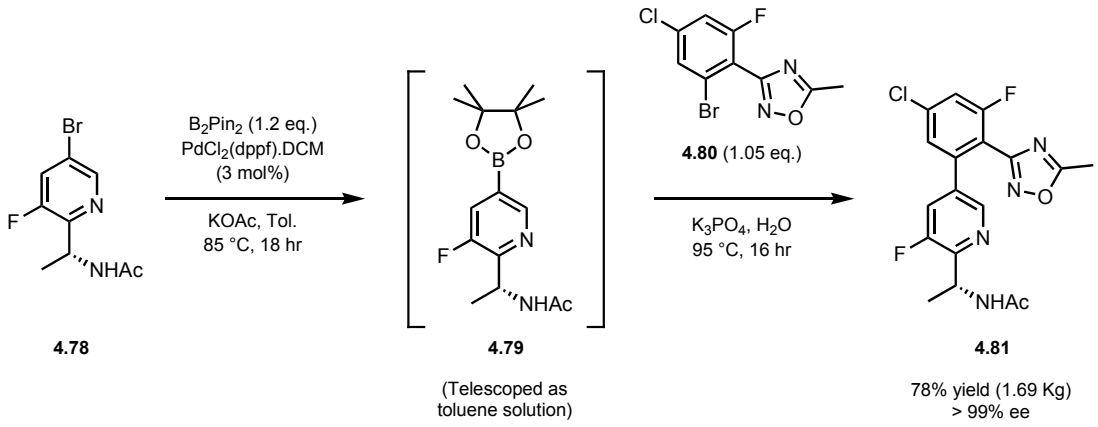


Scheme 4.17

Chaumeil and co-workers have demonstrated the utility of the Miyaura borylation in preparing extremely sterically hindered substrates such as **4.74** from the aryl iodide precursor **4.73** (Scheme 4.17). Most notably, when the corresponding aryl bromide **4.75** was subjected to classical lithiation conditions to produce the target boronic acid **4.77** directly, the steric bulk and conformational strain resulted in the acyclic diisopropyl borate ester **4.76** being so stable to hydrolysis that it was the only recovered product after standard hydrolytic work-up with 1M HCl(aq.), and was even found to be stable in air and to purification by column chromatography. The authors noted that acyclic esters are otherwise only reported in

the literature as isolable from such protocols when anhydrous HCl is employed. Overall the authors demonstrated that even such extremely sterically hindered and demanding substrates as **4.73** can be borylated, potentially allowing access to the products in better yields than even classical s-block metallation protocols are able to provide.[52]

The borylation protocol developed by Masuda was aimed at removing the need for diboron reagents in the borylation of aryl C-X bonds, as tetraalkoxydiborons not only necessitate the generation of one equivalent of boronate as by-product, but at that time were also very costly reagents of limited availability in bulk quantities. However, due no doubt to economies of scale as a result of the widespread use of B_2Pin_2 in particular, including use on large scales, this reagent is now available in bulk quantities (50-100 kg) and is much more competitively priced.[30, 53] Large scale borylation reactions, even those employing B_2Pin_2, are now becoming a common method for the synthesis of potential drug substance precursors by the pharmaceutical industry – as this approach allows straightforward access to custom boronate esters used for Suzuki coupling reactions – one of the pharmaceutical industry's most favoured methods for C-C aryl-aryl bond formation.[54]



Scheme 4.18

For example, to access **4.81**, the precursor to a kinin antagonist for pain and inflammation management, the preparation of the potassium organotrifluoroborate salt analogue of **4.79** by traditional means was investigated. However, although it allowed a boronate of known identity to be reliably synthesised, and one which underwent the targeted Suzuki coupling reaction, the concomitant generation of HF precluded the use of that intermediate on scale due to the resultant corrosion of stainless steel and glass reaction vessels. In contrast, the Miyaura borylation of **4.78** was used to prepare substituted 3-pyridyl pinacolboronate ester **4.79**, bearing a chiral benzylic *N*-acetyl substituent, which furthermore allowed the use of a

single charge of palladium catalyst at the start of the one-pot sequential borylation/Suzuki coupling reaction, ultimately yielding **4.81** on a multi-kilogram scale.[55]

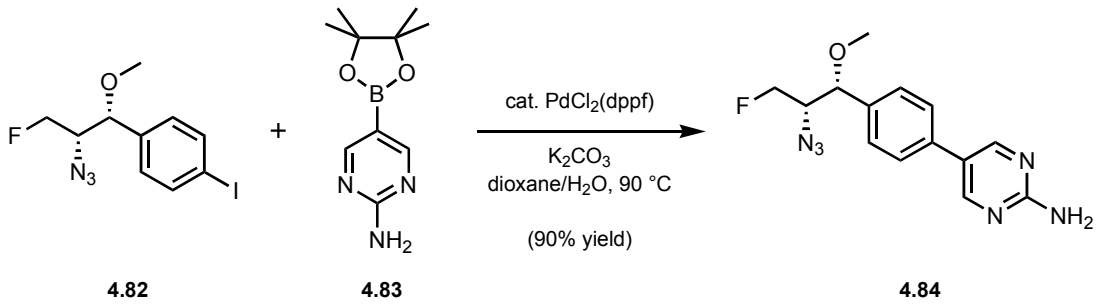
4.4.2.5. Summary

As discussed in Chapter 1, metals other than palladium are able to form catalytically active complexes that can effect C-X and C-H borylation *via* cross-coupling reactions involving diborons or boranes – including examples that may be used to generate products not otherwise accessible when using organolithium or organomagnesium reagents as synthetic intermediates. However – in part due to the tolerance for many important functional groups, including certain stereocentres (e.g. as demonstrated above in Scheme 4.18), high chemo- and regio- selectivity, and the ability to perform telescoped borylation/Suzuki coupling protocols – the Masuda, and most especially the Miyaura borylation protocol, are particularly noteworthy.

4.5. Organoazide Substrates in Suzuki Coupling and Borylation Reactions

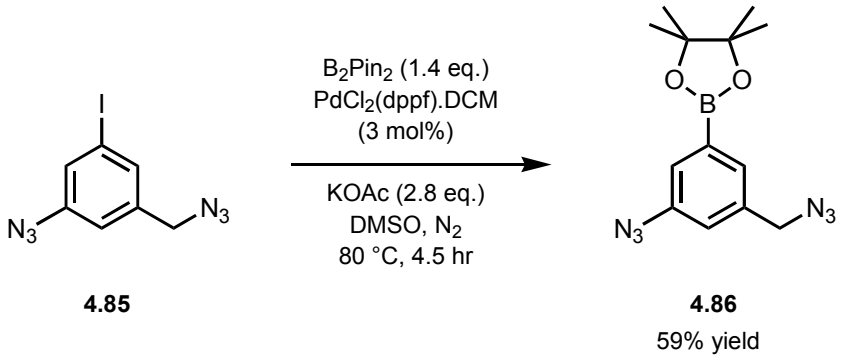
The reports made by the group of Vasil'ev[11] and those of Ham and Molander[9] (as detailed in Chapter 3) demonstrate that alkyl and aryl azides, respectively, are potentially tolerant of the conditions required for successful Suzuki coupling reactions.

Additionally, Hanselmann and co-workers recently detailed the drug-discovery route to **4.82**, a precursor to a novel clarithromycin derivative that shows promising activity as an antibiotic. Most importantly not only does precursor **4.82** contain an alkyl azide moiety, but one that it is located at a stereocentre, and this substrate is amenable to Suzuki coupling reaction with boronate ester **4.83** so as to access the later intermediate **4.84** in high yield and without epimerisation or loss of azide integrity – allowing **4.84** to be subsequently used in a CuAAC reaction with an alkynyl derivative of clarithromycin so as to link the two subunits through a stable 1,2,3-triazole moiety.[56]



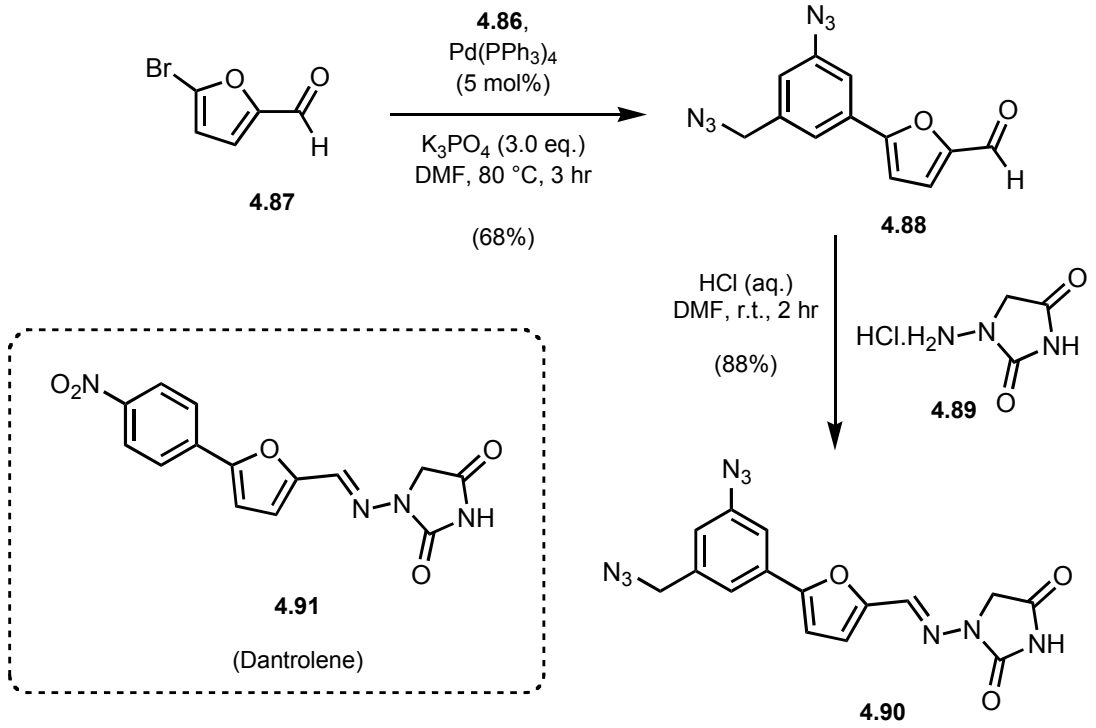
4.82 **4.83** **4.84**

Scheme 4.19



Scheme 4.20

Reports such as these demonstrate the compatibility of aryl and alkyl azides with Pd(0/II) catalysed reactions, of which the Miyaura and Masuda borylations are examples. Despite this, the only precedent we have found to date of an azide substituted aryl halide being used to access a synthetically valuable azido-boronate substrate, such as represented by our substrate **4.24** and analogous fluoro-derivative, was that reported by Hosoya *et al.* in 2009 (Scheme 4.20).[57]



Scheme 4.21

Using almost identical conditions to those used by Miyaura and co-workers in their original 1995 report, Hosoya and co-workers reported the synthesis of diazide **4.86** in 59% yield from aryl iodide **4.85**. They then used the isolated product in further Suzuki coupling reactions, including that detailed in Scheme 4.21 used to access derivatives of the drug

substance dantrolene (**4.91**), with the diazide subunit allowing **4.90** to be used as a photoaffinity probe. Despite **4.86** bearing both an aryl and benzyl azide substituent, only this single example of an aryl iodide was included in the aforementioned publication, with no discussion or optimisation of the borylation conditions, nor subsequent investigations of such reactions being reported since by the authors.

4.5.1. Access to Aryl Boronate Esters Bearing Unprotected Alkylamines

As demonstrated by the above discussions, substrates such as protected alkyl amines (e.g. **4.78**), unprotected indoles (e.g. meridianin G precursor **4.61**) and anilines such as the direct precursor to pyrimidine-2-ylamine boronate ester **4.83** (successfully produced on at least a multigram scale) have all been successfully borylated *via* the palladium-catalysed cross-coupling methodologies, with many more such examples having been reported.[56, 58]

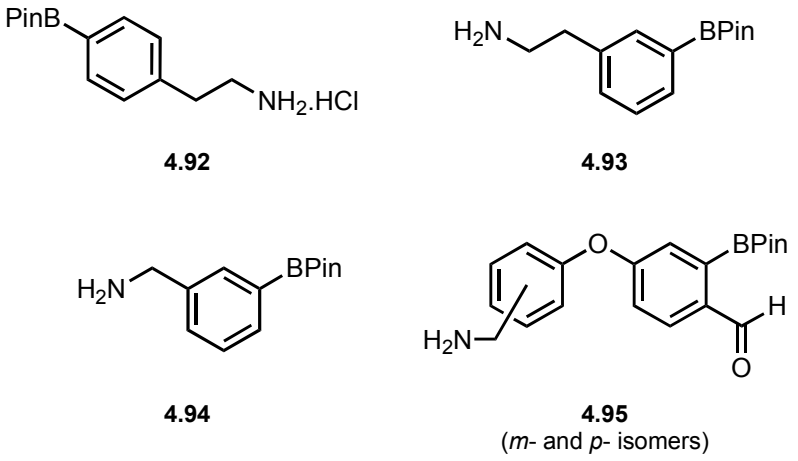
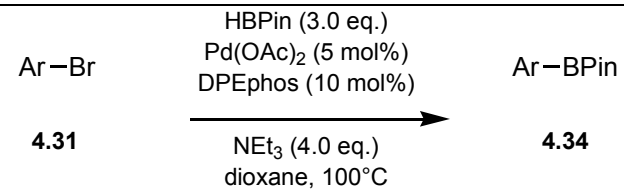


Figure 4.2

However, after an extensive search of the literature to determine whether substituted aryl halides had been used in the borylation reaction so as to access arylpinacolboronate esters bearing primary alkyl amines, we found only four potential candidates (Figure 4.2). Of these **4.92** was produced by borylation of the aryl bromide, at which point the amine was still protected as the Boc-amide.[59] The remaining three examples consist of two patents reporting the preparation of **4.93**[60] from the corresponding aryl bromide and **4.94**[61] from the aryl iodide, and one journal article reporting **4.95**[62], of which none detail the exact yields of these products. In addition, the journal article is unclear about whether the aryl bromide substituted amine precursors to the regioisomers **4.95** were Boc protected at the point that the borylation reaction was conducted, and a later step used to form the subsequent synthetic targets indeed involves the use of hydrogen chloride. All substrates were however borylated using generic borylation protocols derived from the chemical literature, with three substrates accessed by Miyaura borylation with B_2Pin_2, and one by Masuda borylation with HBPin.

Notably, with the ambiguity over regioisomers **4.95**, amine **4.93** is therefore the only documented aryl halide bearing a primary alkyl amine to have been formed by Miyaura borylation, and furthermore, for which a catalyst loading of 10 mol% palladium complex was employed.



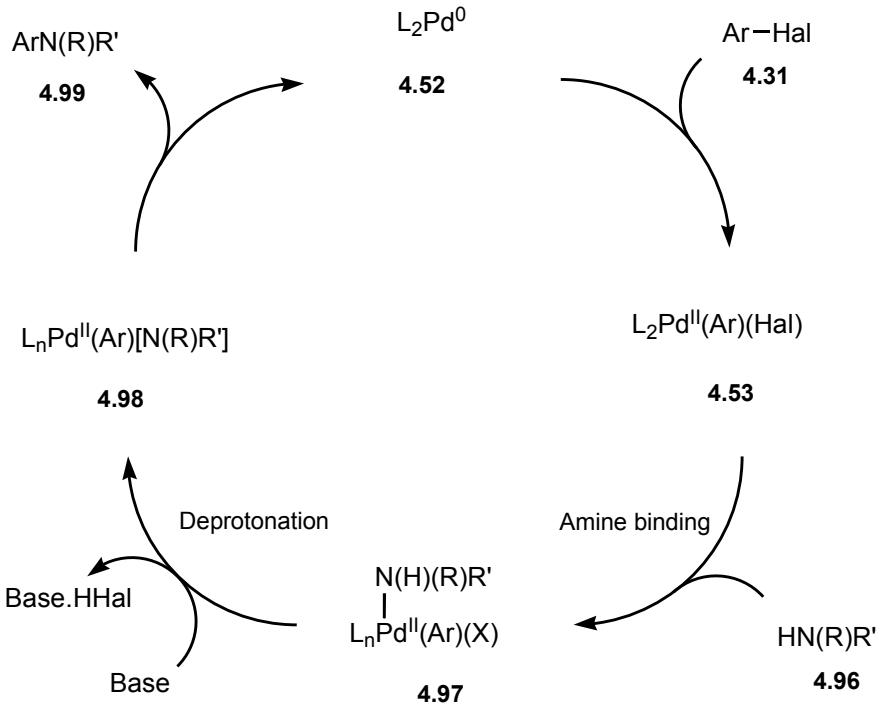
Entry	R	Time (hr)	Yield (%)[a]
1	*p*-$MeOC_6H_4$	4	99
2	*m*-$MeOC_6H_4$	20	27
3	*o*-$MeOC_6H_4$	4	78
4	*p*-$Me_2NC_6H_4$	3	96
5	*m*-$Me_2NC_6H_4$	4	63
6	*o*-$Me_2NC_6H_4$	20	0
7	*p*-$H_2NC_6H_4$	20	52
8	*m*-$H_2NC_6H_4$	20	29
9	*o*-$H_2NC_6H_4$	20	39
10	2,4,6-Mes	20	25
11	Ph	4	33
12	*p*-MeC_6H_4	4	36

[a] Isolated yield after column chromatography.

Table 4.6

Additionally, although anilines can be amenable to Masuda borylation protocols, they often give much poorer yields than substrates with corresponding steric and electronic characteristics provided by alternative aryl substituents. For example, the results reported by Colobert and co-workers for the borylation of aryl bromides with HBPin using $Pd(OAc)_2$ and DPEphos show that, with the exception of the *ortho*- regioisomer (Table 4.6, entry 6) – which is presumably due to steric or chelation effects during, or upon, formation of the oxidative addition adduct – dimethyl anilines (entries 4-5) give better yields than do the corresponding free anilines (entries 7-9). Comparison of entries 1 and 12 show the significant impact on yield that electron donation by conjugation has – yet despite the electronic effect of the NH_2 group, even the very sterically demanding mesityl bromide (entry 10) was found to provide a similar yield after the equally extended reaction time required for the free anilines.[39]

Finally, both the reaction conditions and catalytic cycle of these borylation reactions are fundamentally akin to those of the Buchwald-Hartwig amination (Scheme 4.22). Namely, typical oxidative addition of the aryl halide to the active palladium(0) complex to yield **4.53** is, in the case of the Buchwald-Hartwig amination, then followed by amine binding with **4.96** to generate complex **4.97**. Deprotonation then yields complex **4.98**, and finally reductive elimination of the arylated amine **4.99** regenerates the palladium(0) complex **4.52**. This may go some way further to explaining, in particular, the limitations with using primary alkylamines as substrates in such borylation reactions – as analogously it is noted that bearing no labile β-hydrogen atoms, primary anilines do not therefore make the formation of palladium-hydride complexes amenable under Buchwald-Hartwig amination conditions, so making them ideal substrates.[63]

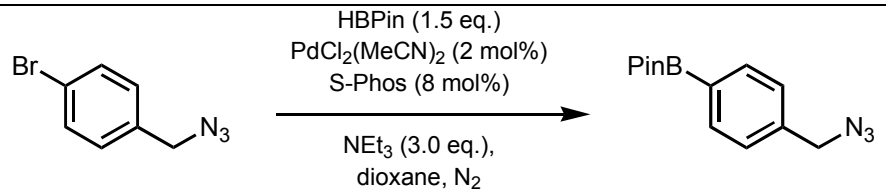


Scheme 4.22

Thus, neither the palladium-catalysed cross-coupling borylation reactions, nor the traditional s-block organometallic reagents (as discussed in Chapter 1) are overly compatible with free primary amines. In contrast an organoazide is a "*masked amine*"[64] that can readily be reduced in an atom-efficient manner by a metal-catalysed hydrogenation procedure or *via* the aza-ylide intermediate, as well as being used to access other valuable functional groups (as discussed previously in Section 4.1). Thus, not only would the development of a general borylation protocol tolerant of benzyl azides prove valuable to advance our own work, but it

should also be useful in advancing the scope of the borylation methodology in respect to the direct synthesis of boronate esters bearing alkyl amines.

4.6. Initial Masuda Borylation Reaction Results with 4.22



4.22 **4.24**

Entry	Temp. (°C)	Time (hr)	Yield (%)[a]
1	110	18	-[b]
2	70	1	30[c]

[a] Isolated yield after purification by column chromatography.

[b] Performed on a 0.5 mmol scale with respect to **4.22**; for which the starting material was converted to a complex mixture of products according to the crude ^{1}H NMR.

[c] Performed on a 1.0 mmol scale with respect to **4.22**.

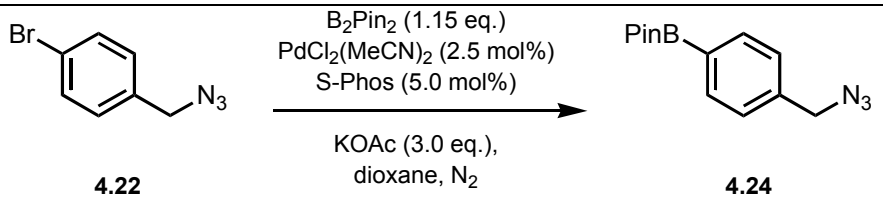
Table 4.7

We therefore set out to determine whether **4.24** could be produced by the borylation of the aryl bromide **4.22**, itself readily synthesised from commercially available *p*-bromo benzyl bromide as detailed in Chapter 3. Using the conditions reported by Buchwald and co-workers detailed in the literature review for the Masuda borylation of aryl halides,[41] we found that the starting material was completely consumed, while only trace product was evident in the crude reaction mixture by ^{1}H NMR (Table 4.7, entry 1). We surmised that lowering the reaction temperature would most likely aid in reducing the amount of side products generated, and indeed subsequent reaction at 70 °C for a much shorter reaction time of one hour allowed us to obtain **4.24** in a low, but still promising, 30% yield (entry 2).

4.7. Miyaura Borylation of Aryl Halides Bearing Benzylic Azides

4.7.1. Initial Reactivity of Aryl Bromide 4.22

As well as producing potentially significant amounts of hydrodehalogenated by-product, palladium complexes in combination with stoichiometric equivalents of hydride sources such as boranes or silanes are used for the catalytic reduction of certain ubiquitous functional groups, including organoazides (see Section 4.9.2 for further details). We therefore decided that higher yields of the desired product might be obtained by moving to Buchwald's reported Miyaura borylation system[42] in place of the Masuda variant,[41] especially given that azides are reduced by related palladium-hydride complexes.



4.22 **4.24**

Entry	Temp. (°C)	Time (hr)	4.22 (%)[a]	4.24 (%)[a]	By-Prod. (%)[a,b]	B_2Pin_2 conv. (%)[a]
1	90	4	0	c. 50	c. 50	115
2[c]	90	1.5	0	c. 80	c. 20	102
3	90	1.25	c. 20	c. 80	< 5	82
4[c]	80	2	0	92	5	99
5[c,d]	80	2	4	93 (84)	< 5	102

All reactions performed on a 0.5 mmol scale unless otherwise specified.

[a] Conversions determined by ^{1}H NMR of the crude reaction mixture; isolated yields in parentheses.

[b] Unidentified by-product.

[c] Using a stock solution of azide in dioxane.

[d] 1.0 mmol scale.

Table 4.8

We therefore subjected **4.22** to the borylation reaction using adapted literature conditions,[42] which showed that a temperature of 90 °C (Table 4.8, entry 1) was sufficient to completely consume the starting material and all 1.15 equivalents of B_2Pin_2 in four hours. Shorter reaction times at this same temperature (entries 2-3) demonstrate how time sensitive the reaction is, with the rate of side-reactions rapidly increasing as the borylation reaches high conversion. For this reason we found that reducing the temperature to 80 °C typically gave a cleaner reaction, while also allowing for greater leeway in the exact timing of the reaction. As such we were able to show higher reproducibility between reactions, such that conversion on a 0.5 and 1.0 mmol scale was almost identical after two hours, and allowing us to isolate **4.24** in 84% yield on the larger scale (entry 5).

4.7.2. Side Reactions

In addition to tabulating the amounts of starting material **4.22** and product **4.24**, Table 4.8 also notes the amount of side-products formed and amount of diboron consumed, as determined by analysis of the ^{1}H NMR spectra of the crude reaction mixtures.

Firstly, it is worth noting that in addition to the typical side-products arising from Miyaura borylation reactions as already discussed in the literature review of this chapter (namely

homo- and Suzuki coupling), metals including palladium are also known to be able to effect stoichiometric and catalytic reactions of organoazide substrates. Although a more full discussion of the origins of these side-reactions and the products they generate will be covered later in the chapter, the identity of the major impurity in the reaction of aryl bromide **4.22** appears to be an imine and corresponding aldehyde hydrolysis product. Most importantly however, it is apparent that during the early period of the reaction when the ratio of aryl bromide to palladium is high, then the rate of the borylation reaction is also high. As such, starting material **4.22** and borylation product **4.24** are the major components observed up until the point that a high conversion for the borylation reaction is achieved. However, upon near or complete consumption of the aryl bromide, the rates for other palladium-mediated processes then begin to become significant (e.g. compare Table 4.8, entries 1-3). Secondly, and before continuing, it is first worth detailing further the way in which B_2Pin_2 consumption value is calculated, and why it appears to be of particular significance in these reactions.

4.7.3. Consumption of the Diboron

During the isolation and purification of a boronate ester product by column chromatography for one of our later investigations, we recovered some of what appeared to be the excess diboron used in the reaction (see Chapter 5 for details). Certain reports in the literature have noted that B_2Pin_2 is quite stable, including that of Miyaura who showed (as already discussed) that in the presence $Pd(PPh_3)_4$ or oxidative addition adduct **4.45** no reaction with B_2Pin_2 occurred (Scheme 4.10). However, we were still surprised to find that any such amount of the diboron was able to be recovered, not just after exposure to the conditions of the catalytic reaction, but also contact with atmospheric oxygen in combination with the presence of palladium, followed too by aqueous basic conditions, and finally then also exposure to silica-gel.

We also noted that in the ^{1}H NMR spectra of the crude Miyaura-type borylation reactions of **4.22**, in addition to the pinacolate ester singlet of the product, that a singlet corresponding to the remaining B_2Pin_2 **4.32** was present as well (schematically represented in Figure 4.3). Again, rather surprisingly, when calculations were made to take into account the presence of 12 and 24 protons in the pinacol groups of the product (**4.24**) and B_2Pin_2 (**4.32**) respectively, and to correct for the use of 1.15 equivalents of diboron reagent, then analysis of the conversion value determined by consumption of the diboron reagent to form the boronate ester product proved extremely revealing. It should be noted that the other formal by-product of the catalytic cycle – AcOBPin (**4.47**) – under the protocol used to extract the reaction

products, appears to completely partition into the aqueous phase (or is rapidly converted to a derivative that is), such that it did not hamper these analyses in any observable way.

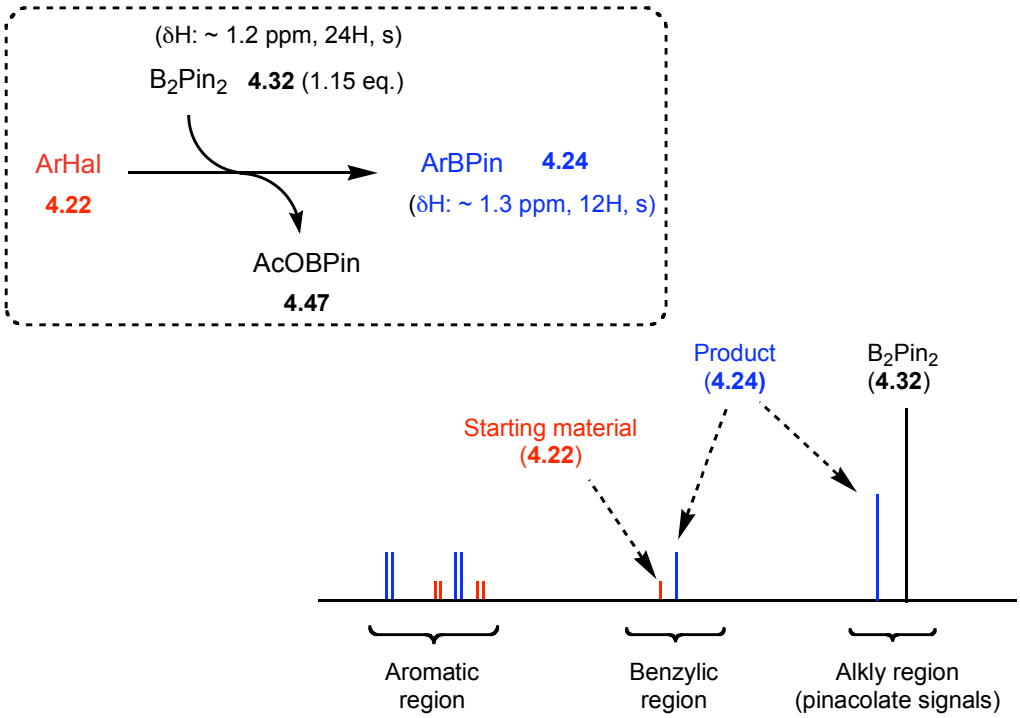
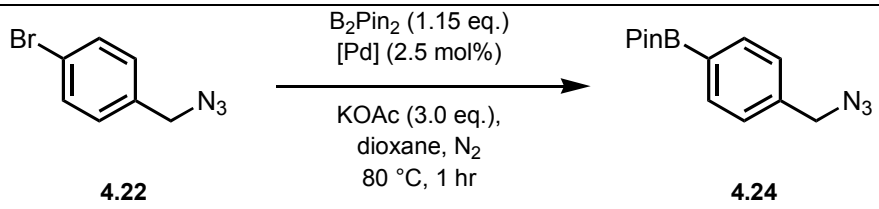


Figure 4.3

Figure 4.3 represents an incomplete conversion of **4.22** to **4.24** (i.e. <100% borylation) as determined by the relative ratios of the integrals for the arene or benzyl protons of the aryl halide starting material and the borylation product. By then separately calculating the conversion of the borylation reaction using the integrals of the pinacolate ester peaks in **4.24** and B_2Pin_2 **4.32**, a conversion value is obtained with respect to the consumption of the diboron and formation of ArBPin **4.24**. For many of the borylation reactions the two conversion values calculated in this way often correlate quite closely. Furthermore, when the conversion of the borylation reaction is high as determined by consumption of the starting material, corresponding formation of the product, and also consumption of B_2Pin_2, then the reactions of organoazide substrates such as **4.22** tend to be clean. However, if the reaction is allowed to continue after the aryl bromide has been consumed, then the diboron conversion value begins to increase beyond a level of c. 100%, and thus it appears that B_2Pin_2 may also be involved in certain later side reactions too. This is demonstrated by comparing entries 1 and 2 of Table 4.8 (above), which shows that as a second major impurity is generated, then correspondingly the amount of remaining B_2Pin_2 again starts to decrease.



4.22 **4.24**

Entry	[Pd]/L[a]	4.22 (%)[b]	4.24 (%)[b]	By-Prod. (%)[b,c]	B_2Pin_2 conv. (%)[b]
1	A	15	85	< 5	84
2	B	16	84	< 5	93
3	C	17	< 75[d]	8	37
4	D	33	67	< 5	65
5	E	41	59	< 5	56

All reactions performed on a 0.5 mmol scale.

[a] Catalyst and ligand as follows: (A) $PdCl_2(MeCN)_2$/S-Phos; (B) $PdCl_2$(dppf); (C) Complex **1.127a** (Chapter 1); (D) $Pd(OAc)_2$/S-Phos; (E) $PdCl_2(MeCN)_2$/X-Phos. S-Phos and X-Phos used at 5 mol% so as to give a Pd:L ratio of 1:2.

[b] Conversions determined by ^{1}H NMR of the crude reaction mixture.

[c] Unidentified by-product.

[d] Suzuki coupling by-product also present.

Table 4.9

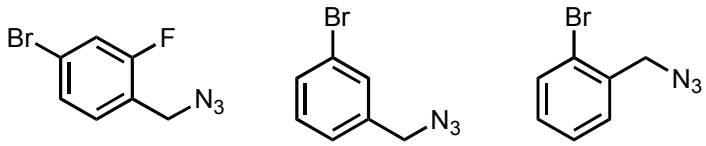
Although with appropriate timing of the reaction the S-Phos/$PdCl_2(MeCN)_2$ system was indeed effective in producing the desired product without generating large amounts of impurities, we also wished to quickly determine whether other ligands and palladium complexes gave similar or improved results.

We therefore screened a selection of catalysts in the borylation reaction under otherwise identical conditions to that used for S-Phos/$PdCl_2(MeCN)_2$ for a reduced reaction time of one hour (Table 4.9, entry 1). Commercially available $PdCl_2$(dppf), still the most commonly employed complex for such reactions in the literature, gave a very similar result (entry 2) to S-Phos/$PdCl_2(MeCN)_2$ in this instance, while the use of $Pd(OAc)_2$ in place of $PdCl_2(MeCN)_2$ was not beneficial (entry 4). X-Phos was chosen as it is also very active in many palladium-catalysed cross-coupling reactions, indeed S-Phos or X-Phos often prove the most generally effective of all the Buchwald group's ligands, and across even a very broad range of palladium-catalysed cross-coupling methodologies and also substrate classes (see also Chapters 1-3). However, X-Phos (entry 5) proved less effective than did S-Phos in this instance, potentially due to the increased level of steric bulk – which is the reverse of the observation by Buchwald using similar high temperature conditions for the borylation of aryl chlorides, where S-Phos proved to be marginally less effective.[42] Finally we assessed the activity of one of the Bedford group's palladacycle complexes (entry 3; see Chapter 1 for

details of this complex), which are known to be exceptionally active for the Suzuki coupling reaction. Thus it was rather unsurprising that in this case the borylation reaction did not proceed cleanly, with B_2Pin_2 consumption not at all in line with the amount of starting material remaining, as it appears that a much more sizable amount of C-C cross-coupling resulted in the presence of this complex.

4.7.4. Alternative Aryl Bromide Substrates

4.7.4.1. Synthesis

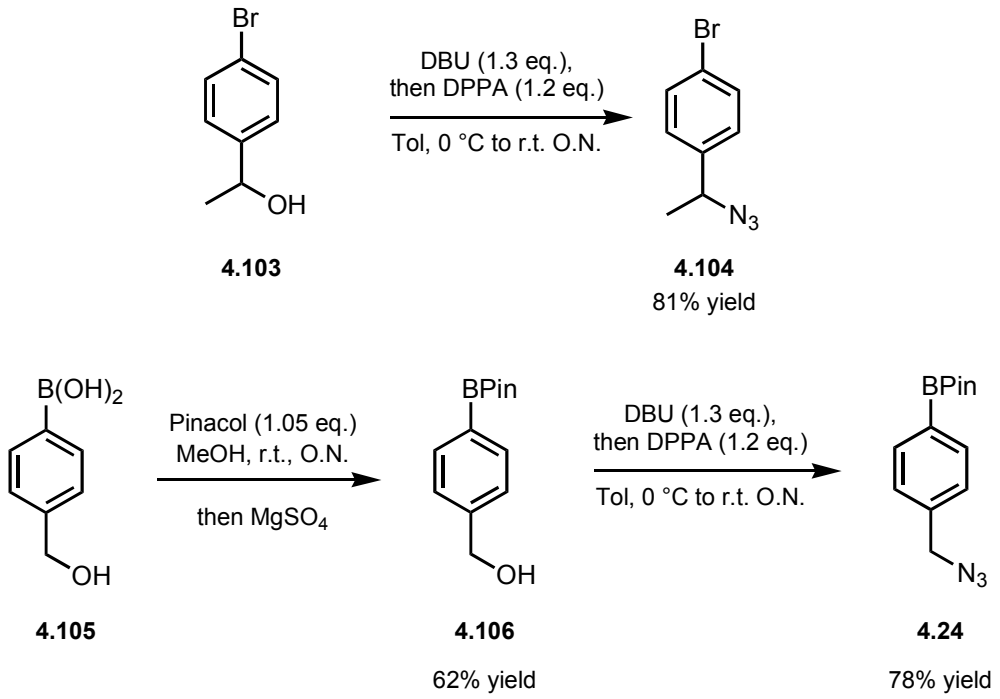


4.100 **4.101** **4.102**

Figure 4.4

We thus chose to retain the S-Phos system, especially as it offered the greatest potential chance for successfully borylating any less reactive substrates (including aryl chlorides) at a later juncture, and proceeded to use these conditions for the borylation of various aryl bromide substrates. The *meta*- and *ortho*-regioisomers of benzyl azide **4.22** (**4.101** and **4.102**, respectively), as well as the fluorosubstituted analogue **4.100** (which would allow us to access bifunctional linker **F-3.78**) were synthesised in an analogous way to **4.22** from the corresponding commercially available benzyl bromides by nucleophilic substitution reaction with NaN_3.

In addition, racemic secondary azide **4.104** was accessed by a Mitsunobu-type reaction of alcohol **4.103** with DPPA in the presence of DBU.[1] We also confirmed that this method could be used with the pinacol boronate ester **4.106**, readily obtained from the commercially available boronic acid **4.105**. Although this allowed us to access bifunctional linker **4.24** in greater than 45% yield over two steps, the cost of boronic acid **4.105** and purification procedures involved proved in general to be less straightforward than our optimised route as detailed in Chapter 3.



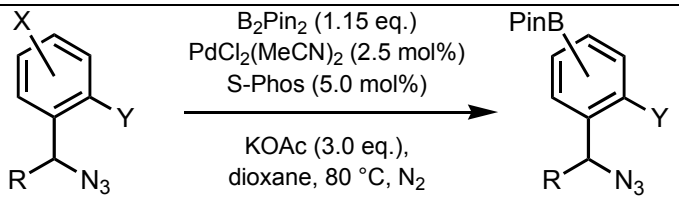
Scheme 4.23

4.7.4.2. Borylation Reactivities of the Aryl Bromide Substrates

Subsequent borylation reactions employing these substrates showed that the reactions of the *meta*- regioisomer **4.101**, fluorosubstituted analogue **4.100**, and secondary alkyl azide **4.104** all proceed at a similar overall rate to that of the *para*- regioisomer **4.22**, with a high yield of the products typically being obtained from the borylation reactions after two to three hours (Table 4.10, entries 3, 8, 11). In contrast to the other substrates, *ortho*- isomer **4.102** proved extremely slow to react (entries 4-6), while it appears that side reactions involving B_2Pin_2 might also be occurring at a slightly more favourable rate prior to consumption of the aryl bromide. As the azide moiety was not rapidly degraded, we postulate that the reaction of the *ortho*- regioisomer might have been slowed *subsequent* to the oxidative addition step, presumably due to interaction of the metal centre with, e.g. the most basic and proximal nitrogen, N_α, of the benzylic azide, such as is depicted by **4.107** in Scheme 4.24.

This is potentially consistent with the analogous observation by Ohno and co-workers that in the non-hydrogenative reduction of benzylic azides to benzonitriles catalysed by Pd/C, the presence of nearby polar functional groups led to much slower rates of reaction, and rather surprisingly vicinal diazides were not at all reactive under the reported protocol.[65] They attributed this to a bidentate coordination of such substrates to palladium(0) in such a way that an oxidative addition pathway, which could be visualised to arise from a complex of the type **4.109** and concomitant loss of N_2,[66] was no longer feasible due to the metal no longer interacting solely with the azide in an appropriate manner. Indeed, even the reduction of

geminal diazides with $Pd/C/H_2$ is not necessarily straightforward.[61] And despite the palladium centre being in such close proximity to the azide, the fact that the oxidative addition adduct akin to **4.107** does not rapidly give rise to azide degradation is also analogous to the palladium(II) complex reported by Thiel and co-workers, which only degraded slowly to the amine analogue when in solution, but was stable in the solid state (see Section 4.9.2 for full discussion and schemes).[67]



Entry	X[a]	R	Y	Time (hr)	ArBr (%)[b]	ArBPin (%)[b]	By-Prod. (%)[b,c]	B_2Pin_2 conv. (%)[b]
1	*m*-Br	H	H	1	42	54	< 5	54
2[d]	*m*-Br	H	H	2	Trace	96	< 5	96
3	*m*-Br	H	H	2	Trace	97 (82)	< 5	96
4	*o*-Br	H	H	1	≥ 95	Trace	Trace	<10
5[d]	*o*-Br	H	H	22	55	36	9	48
6[d,e]	*o*-Br	H	H	22	20	65	15	71
7	*p*-Br	H	F	1	43	57	< 5	57
8	*p*-Br	H	F	2	9	91 (59)	< 5	94
9	*p*-Br	Me	H	1	42	58	< 5	62
10	*p*-Br	Me	H	2	29	71	< 5	76
11	*p*-Br	Me	H	3	9	91 (76)	< 5	93

All reactions performed on a 1.0 mmol scale unless otherwise noted.

[a] Regioisomers as relative to the benzylic azide moiety.

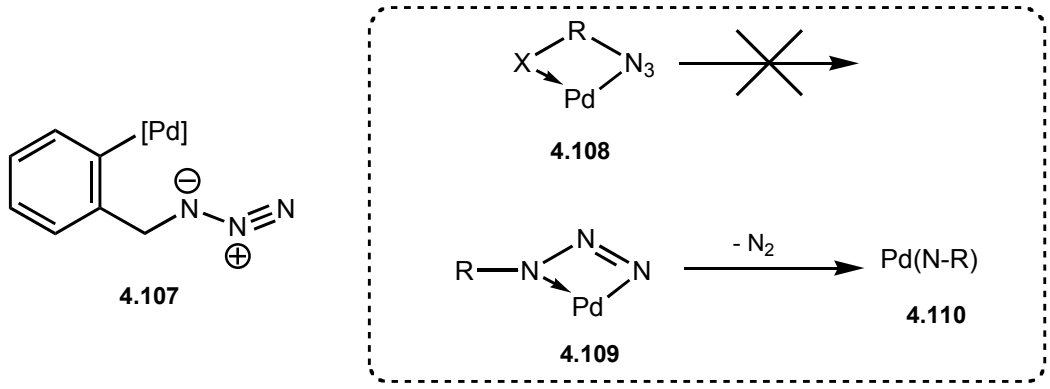
[b] Conversions determined by ^1H NMR of the crude reaction mixture; isolated yields in parentheses.

[c] Unidentified by-product.

[d] 0.5 mmol scale of aryl bromide.

[e] X-Phos (5 mol%) used as ligand in place of S-Phos.

Table 4.10



Scheme 4.24

Although a mixture of products still resulted prior to complete consumption of the *ortho*-azidomethyl aryl bromide (**4.102**), the use of the bulkier X-Phos ligand in this instance proved to be more effective (Table 4.10, entry 6), which may be due to the ligand's bulk reducing the degree to which the azide stabilises the oxidative addition adduct. In turn this improves the rate of the borylation reaction without having a significantly detrimental effect on the amounts of by-products generated (compare entries 5 & 6). Additionally, as dimeric palladacycles such as **4.111** and **4.112** are known, and although in solution and at high temperature the monomer is thought to predominate,[68] X-Phos may still help to act in breaking up any dimeric palladacycles akin to **4.113** as they form. Most importantly, in an analogous manner it may therefore disfavour any homo- or Suzuki coupling events from occurring, which even in trace amounts could possibly lead to an intermediate complex of the type **4.114**, which may very likely be slow to reductively eliminate, and so act as a reservoir for the active catalyst.

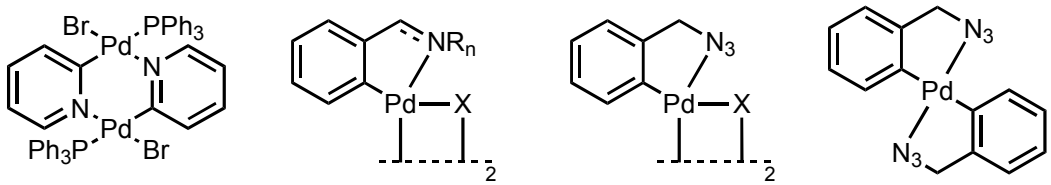
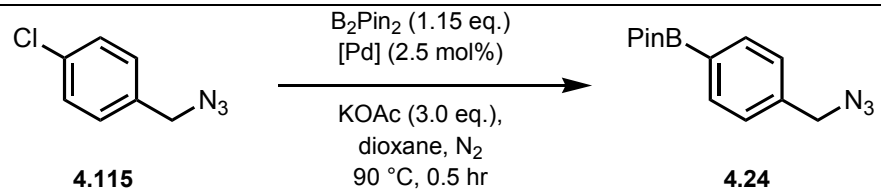


Figure 4.5

4.7.5. Synthesis & Reactivity of Aryl Chloride Analogue 4.115

We next proceeded to investigate the borylation reactions of the less reactive aryl chloride **4.115**, again synthesised from the commercially available benzyl halide precursor by reaction with NaN_3. However, while all five aryl bromides detailed above gave incomplete but quite straightforward conversion of starting material to corresponding borylation product after one hour at 80 °C, when aryl chloride **4.115** was reacted under identical conditions it

was immediately apparent that the borylation reaction was no longer facile, while the rate at which side-reactions were occurring was significantly greater (Table 4.11, entry 1).



4.115 **4.24**

Entry	[Pd]/L[a]	4.115 (%)[b]	4.24 (%)[b]	By-Prod. (%)[b,c]	B_2Pin_2 conv. (%)[b]
1[d]	A	< 5	27	68	28
2	A	29	41	30	42
3	C	Trace	< 20	> 75	<5
4	B	Trace	< 20	> 75	<5
5	E	Trace	< 20	> 75	8

All reactions performed on a 0.5 mmol scale.

[a] Catalyst and ligand as follows: (A) $PdCl_2(MeCN)_2$/S-Phos; (B) $PdCl_2$(dppf); (C) Complex **1.127a** of Chapter 1; (E) $PdCl_2(MeCN)_2$/X-Phos. S-Phos and X-Phos used at 5 mol% so as to give a Pd:L ratio of 1:2.

[b] Conversions determined by ^{1}H NMR of the crude reaction mixture.

[c] Unidentified by-product.

[d] 80 °C, 1 hr.

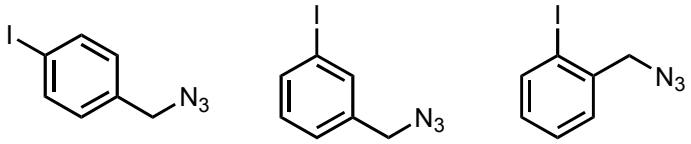
Table 4.11

From the results with the borylation of the aryl bromides we had concluded that the oxidative addition adduct did not appear to degrade the azide moiety, and being that aryl chlorides are less reactive towards oxidative addition we chose to shorten the reaction time, but simultaneously increase the temperature to 90 °C, to see if this favoured the desired borylation process. Indeed, and although the higher temperature for the borylation of aryl bromide **4.22** resulted in less clean conversions, in the case of the aryl chloride **4.115** this did give a slightly improved result overall (Table 4.11, compare entries 1 and 2), which would be consistent with an increased rate of oxidative addition. However, there also appeared to be a side-reaction occurring with an approximately equal amount of the starting material and borylation product involved; which suggests that the azide moiety is still involved in at least one significant side reaction, either pre- or post- borylation. Moreover, upon again screening various ligands and catalysts we found that the S-Phos system was in fact the most effective of those tested, with the other catalyst systems almost exclusively promoting conversion to the side product. Given that **4.115** represents the most straightforward of such aryl chloride substrates, the level of side product formation observed prompted us to continue our

investigations – using the conditions that had proved most effective for both the aryl bromides and the aryl chloride – with the corresponding aryl iodides instead.

4.7.6. Synthesis & Reactivity of Aryl Iodide Substrates

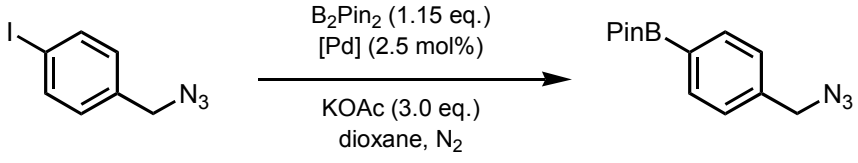
4.7.6.1. Initial Reactivity Under Conditions Optimised for the Aryl Bromides



4.116 **4.117** **4.118**

Figure 4.6

We therefore began by synthesising the three iodo benzyl azide regioisomers (Figure 4.6) by standard nucleophilic substitution reaction employing NaN_3 and the commercially sourced iodo substituted benzyl halides. As *p*-bromo benzyl azide **4.22** had proved a good model substrate we first subjected the corresponding, yet inherently more reactive, *p*-iodo analogue **4.116** to the same reaction conditions but for a reduced reaction time of 30 minutes. We had expected that this should be sufficient time to give, at the very least, a substantial conversion to the borylation product, and hopefully not so long that further reaction at the azide moiety was allowed to occur.



4.116 **4.24**

Entry	[Pd]/L[a]	Temp. (°C)	Time (hr)	4.116 (%)[b]	4.24 (%)[b]	By-Prod. "Y" (%)[b,c]	B_2Pin_2 conv. (%)[b]
1	A	80	0.5	> 95	< 5	Trace	< 5
2	A	90	1	80	12	8	20
3	B	80	0.5	> 95	< 5	Trace	< 5

All reactions performed on a 0.5 mmol scale.

[a] Catalyst and ligand as follows: (A) $PdCl_2(MeCN)_2$/S-Phos; (B) $PdCl_2$(dppf); S-Phos used at 5 mol% so as to give a Pd:L ratio of 1:2.

[b] Conversions determined by ^1H NMR of the crude reaction mixture.

[c] Unidentified by-product "**Y**".

Table 4.12

Despite large amounts of side products forming simultaneously, the analogous aryl chloride (**4.115**) proceeded to give a 27% conversion to the borylation product after one hour under otherwise identical conditions (Table 4.11, entry 1), while the supposedly much more reactive aryl iodide was predominantly unchanged (Table 4.12, entry 1). Even more interesting was that even upon doubling the reaction time and increasing the temperature to 90 °C, the starting aryl iodide was still the major component in the crude reaction mixture, while the increase in conversion to the product was minimal (entry 2). As $PdCl_2$(dppf) is most typically reported as the catalyst of choice in the chemical literature for Miyaura borylation of aryl iodides we next investigated whether this was somehow more effective than the S-Phos system. However, the effect of altering the pre-catalyst to $PdCl_2$(dppf) was not observed to be significant in terms of altering either the selectivity or conversion (compare entries 1 & 3).

It is unlikely that oxidative addition was not occurring rapidly in the reactions detailed in the above table employing aryl iodide **4.116** for two reasons: Firstly, in the chemical literature detailing palladium-catalysed cross-coupling reactions of aryl halide substrates it is clear that although there may not be so significant a difference between the reactivity of corresponding aryl iodides and aryl bromides with a given palladium(0) complex, it is quite consistently the case that aryl chlorides are noted to be the least reactive of the three substrate classes. Secondly, it has been concluded above that the borylation reaction of aryl bromide **4.22** proceeds cleanly until, due to a lack of the aryl halide, the catalytic cycle can no longer turnover, and as such the palladium complex begins to interact with the benzylic azide moiety in one or more ways.

4.7.7. Further Investigations with Non-Azide Functionalised Aryl Iodide Substrates

Although it seemed very unlikely that, for example, the oxidative addition adduct of aryl iodide **4.116** was somehow interacting with the azide moiety in a way not previously evident, we chose to confirm this hypothesis by investigating the borylation of simple aryl iodide substrates already reported to undergo this reaction. Thus we next reacted *p*-iodo anisole (**4.119**) at 90 °C for one hour under the standard conditions we had successfully used for the borylation of the aryl bromides, but obtained only a low conversion, with the major component being residual starting material (Table 4.13, entry 1). To be sure that this was not an isolated example we also employed *p*-iodo acetophenone (**4.120**) and again found it to be a poor choice of substrate (entry 2).

4.7.8. Selection and Discussion of Solvent System in the Chemical Literature

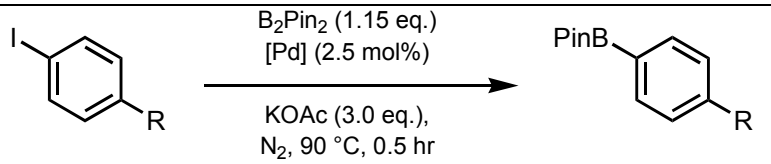
As discussed in the literature review of this chapter (Sections 4.4 & 4.4.1), DMF is known to be an inferior choice of solvent in Masuda-type borylation reactions for the very specific reason that it catalyses the degradation of di(alkoxy)boranes, and where dioxane is often used instead. In contrast, Miyaura specifically noted that for the borylation of aryl bromides and aryl iodides with B_2Pin_2, polar solvents accelerated the reaction, such that DMSO ≥ DMF > dioxane > toluene.[16] However, no quantitative data were reported, though they later stated that for aryl triflates then dioxane was a better choice of solvent than DMSO, for reasons of catalyst stability.[17] Additionally, dioxane was reported by Buchwald and co-workers as being the optimal solvent choice in both their publications on Miyaura-type borylations of aryl chlorides[42] and Masuda-type borylations of aryl halides[41] – but again no quantitative data, or even qualitative activity trends, were offered in support of that choice; or so as to give any insight whatsoever into the nature, scope or details of the optimisation processes themselves.

Interestingly, a review of the literature at this stage revealed that Miyaura and co-workers had briefly noted later that $Pd(dba)_2$/2.4 PCy_3 in dioxane was a more effective system for the borylation of aryl bromides than was $PdCl_2$(dppf) in DMSO. Overall however, the reactions of aryl iodides under the original protocol employing $PdCl_2$(dppf) and DMSO still gave faster rates of reaction and higher yields than even $Pd(dba)_2$/2.4 PCy_3 and dioxane could provide with the aryl bromides – although intriguingly the authors did not detail whether the aryl iodides were more, or even less reactive, under those newly optimised conditions.[18]

4.7.9. Accelerating Effect of DMF in the Borylation of Aryl Iodides

As both $PdCl_2$(dppf) and $PdCl_2(MeCN)_2$/S-Phos provide very active borylation catalysts, we therefore concluded that the choice of solvent might be more important to the success of the reactions employing aryl iodides than the identity of the catalyst and ligand, especially as we knew the rate-limiting step was unlikely to be oxidative addition, but instead anionic ligand exchange or transmetallation. Thus we repeated the borylation reaction with *p*-iodo acetophenone **4.120** under identical conditions to those that before had been ineffective, but for the choice of DMF as solvent in place of dioxane. Pleasingly this made a very notable difference, such that borylation product **4.120a** was formed in almost 50% conversion by ^{1}H NMR (Table 4.13, entry 3). However, the change of solvent system not only promoted the borylation reaction, but also resulted in a noticeable amount of Suzuki coupling product too – and this despite the fact that the reaction was not complete, with a large amount of starting material and B_2Pin_2 still remaining. Indeed, DMF and DMSO are used in conjunction with

catalysts of this type for one-pot sequential borylation/Suzuki coupling reactions.[69] Thus we next repeated the reaction using the standard literature choice of catalyst for aryl iodides, $PdCl_2$(dppf), to see if this gave any further improvement. Interestingly, and although the overall consumption of starting material was very similar, $PdCl_2$(dppf) seems to favour borylation of aryl iodides in DMF (entry 4), rather than promoting cross-coupling – which is not the case when using a combination of $PdCl_2(MeCN)_2$/S-Phos (entry 3).



4.119 (R = OMe)
4.120 (R = C(O)Me)

4.119a (R = OMe)
4.120a (R = C(O)Me)

Entry	R	[Pd]/L[a]	Solv.	ArHal (%)[b,c]	Prod. (%)[b,d]	Ar-Ar (%)[b,e]	B_2Pin_2 conv. (%)[b]
1[f]	*p*-MeO	A	Diox.	94	6	0	5
2	*p*-MeCO	A	Diox.	99	Trace	Trace	Trace
3	*p*-MeCO	A	DMF	42	48	10	52
4	*p*-MeCO	B	DMF	47	53	0	50

All reactions performed on a 0.5 mmol scale.

[a] Catalyst and ligand as follows: (A) $PdCl_2(MeCN)_2$/S-Phos; (B) $PdCl_2$(dppf). S-Phos used at 5 mol% so as to give a Pd:L ratio of 1:2.

[b] Conversions determined by ^{1}H NMR of the crude reaction mixture.

[c] Unchanged aryl halide starting material.

[d] Borylation product.

[e] Suzuki coupling by-product.

[f] 1 hour reaction.

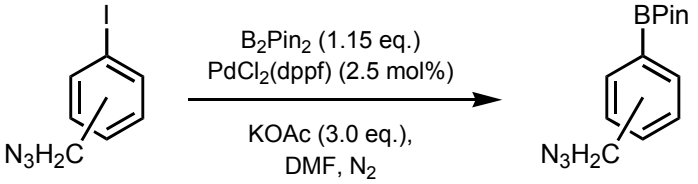
Table 4.13

4.7.10. Optimisation of the Borylation Conditions for Aryl Iodides

We therefore continued our investigations with the azide functionalised aryl iodide **4.116** using this alternative system. Interestingly however, we found that a non-exclusive pathway was available to the substrate at ≥ 80 °C (Table 4.14, entries 1-2), such that a second product (**Y**) was formed that was still capable of undergoing borylation.

Firstly, although the ratio of the desired borylation product **4.24** to starting material **4.116** increased from ~2.8:1 at 90 °C/0.5 hours (Table 4.14, entry 1), to ~3.5:1 at 80 °C/1.0 hours (entry 2), the ratios of product **4.24** to by-product **X** (~3.5:1) and starting material **4.116** to by-product **Y** (~2.3:1) both remained roughly constant despite a 10 °C change in temperature

and alteration of the reaction time between the two experiments. Additionally, the integrals for the coincident pinacol singlets corresponding to ArBPin correlate almost perfectly to the sum of product and by-product **X** (in summation they account for >99% of the pinacol ArBPin/Ar'BPin singlet). Finally, the ratio of **X** to **Y** at 90 °C was 1.8:1, while at 80 °C it was 2.4:1; however, when these ratios are used in combination with those of the product to starting material, this gives a value of (**P**/**SM**):(**X**/**Y**) of ~1.5 at both 80 and 90 °C.



Entry	ArHal	Temp. (°C)	Time (hr)	ArHal (%)[a,b]	Prod. (%)[a,c]	"Y" (%)[a,d]	B_2Pin_2 conv. (%)[b]
1	**4.116**	90	0.5	20	55	9 [16][e]	61
2	**4.116**	80	1	17	59	7 [17][e]	75
3	**4.116**	70	1	45	55	Trace	55
4	**4.116**	70	1.5	32	68	Trace	68
5[f]	**4.116**	70	6	5	95 (79)	Trace	97
6	**4.117**	70	6	Trace	96	4	99
7[f]	**4.117**	70	6	6	94 (76)	Trace	91
8	**4.118**	70	20	42	58	Trace	58
9[f,g]	**4.118**	70	20	19	81	Trace	77
10[f,h]	**4.118**	70	20	22	78 (67)	Trace	84

All reactions performed on a 0.5 mmol scale unless otherwise noted.

[a] Conversions determined by ^{1}H NMR of the crude reaction mixture; isolated yields in parentheses.

[b] Unchanged aryl halide starting material.

[c] Borylation product.

[d] Unidentified by-product "**Y**".

[e] Unidentified product "**X**".

[f] Reaction performed on a 1.0 mmol scale with respect to the aryl halide.

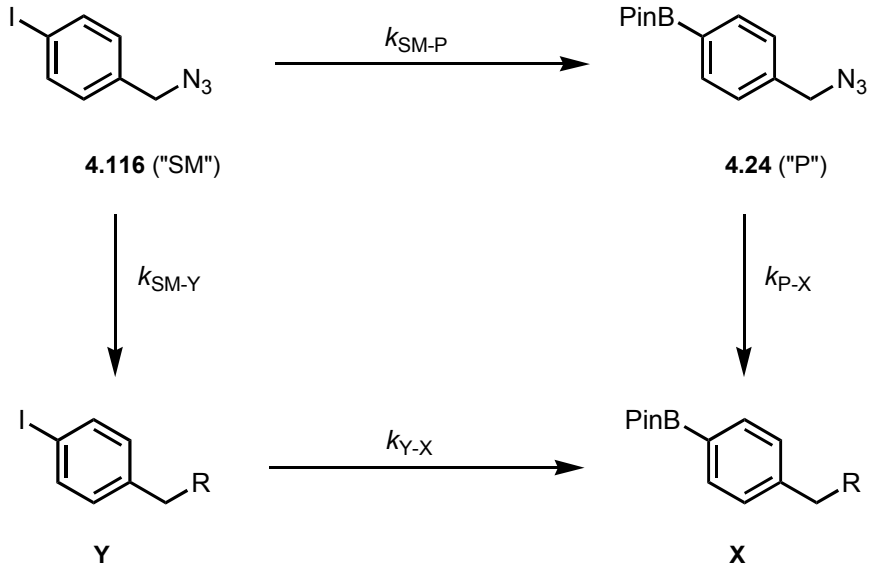
[g] 5.0 mol% $PdCl_2$(dppf) used.

[h] 9.0 mol% $PdCl_2$(dppf) used.

Table 4.14

Thus taken in combination, these facts suggest that the starting material undergoes two reactions at ≥ 80 °C, one of which is borylation of the aryl iodide starting material **4.116** ("**SM**") to yield borylation product **4.24** ("**P**"). The second being an independent process that converts **4.116** to **Y**, and **4.24** to **X**; with the resulting functional group transformation

having no impact on the relative rate at which by-product **Y** undergoes borylation to yield by-product **X**, compared to the rate at which **4.116** is borylated to give the desired product **4.24**; i.e. $k_{SM\text{-}P} \approx k_{Y\text{-}X}$, while $k_{SM\text{-}Y} \approx k_{P\text{-}X}$.



Scheme 4.25

However, the rate of this alternative and non-exclusive pathway is exceptionally slow at 70 °C, such that we were simply then able to increase the reaction time from an initial hour to six hours (Table 4.14, entries 3-5), in order to allow time for the borylation reaction to proceed so as to produce both the *para*- and *meta*- regioisomers (**4.24** and ***m*-4.24**) in good yields (entries 5 and 7, respectively). Under analogous conditions for an extended period of time ***o*-4.24** was also able to be formed cleanly (entry 8), and in contrast to the other regioisomers we chose to increase the loading of $PdCl_2$(dppf) rather than further extend the reaction time (entries 9-10). In this way we were able to obtain a high conversion and moderate yield of ***o*-4.24**, and additionally the use of a higher palladium loading did not result in any more by-product formation at this temperature.

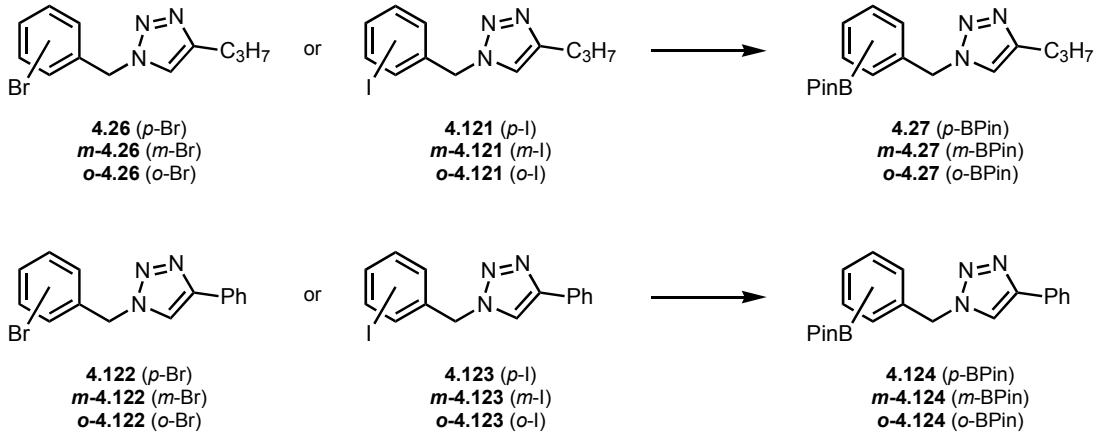
4.8. Miyaura Borylation of Aryl Halides Bearing Benzylic Triazoles

We next investigated the use of the CuAAC-derivatised triazole substrates to see how they compared to the corresponding azide precursors in the borylation reaction.

4.8.1. Reactivity of Methylene Triazole Substituted Aryl Bromides

We began with the aryl bromide substrate **4.26** and its regioisomers (derived from the reaction of the azide pre-cursors with 1-pentyne), using the higher reaction temperature of 90 °C that we had originally applied for the borylation of the *p*-bromo azide **4.22**. We chose this

higher temperature as the triazole moiety, though less reactive than the azide under such conditions, is also well known as a metal-binding motif, and is documented as a ligand for palladium complexes (see Chapter 3).



4.26 (*p*-Br)
***m*-4.26** (*m*-Br)
***o*-4.26** (*o*-Br)

4.121 (*p*-I)
***m*-4.121** (*m*-I)
***o*-4.121** (*o*-I)

4.27 (*p*-BPin)
***m*-4.27** (*m*-BPin)
***o*-4.27** (*o*-BPin)

4.122 (*p*-Br)
***m*-4.122** (*m*-Br)
***o*-4.122** (*o*-Br)

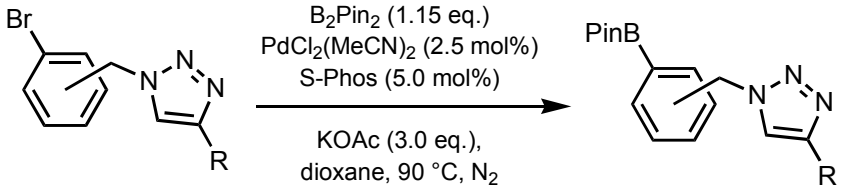
4.123 (*p*-I)
***m*-4.123** (*m*-I)
***o*-4.123** (*o*-I)

4.124 (*p*-BPin)
***m*-4.124** (*m*-BPin)
***o*-4.124** (*o*-BPin)

Figure 4.7

Ultimately the impact of the *p*-methylene triazole moiety of **4.26** on the rate of borylation is not too significant when compared with that of the corresponding parent azide **4.22** (compare Table 4.15, entries 1-2 with Table 4.8, entry 3), although the *meta*- regioisomer ***m*-4.26** is somewhat slower at reacting (Table 4.15, entry 6). Overall this still confirms that the active palladium complex formed under our reaction conditions particularly favours oxidative addition of the aryl halide, rather than any significant level of continued coordination to the triazole, and even less so to the azide moiety. However, with the *o*-methylene triazole substituent the borylation reaction is no longer favoured, and palladium-mediated intramolecular C-5 arylation of the triazole then becomes the dominant process (Table 4.15 entry 7; see also Section 4.9.1 for further discussion).

We later found that while the 1-pentyne derived triazoles gave good conversions in the borylation reactions, for both the aryl bromides and aryl iodides, purification of the *meta*- and *ortho*- borylation products was not as straightforward as for the *para*- regioisomer. As such we also employed the phenylacetylene triazole derivatives in both cases, which gave similar conversions and product distributions (e.g. Table 4.15, entries 2 & 5 *vs.* 8), but generated products that were purified more much more readily.



Entry	Regio-isomer	R	Time (hr)	ArHal (%)	Prod. (%)	Ar-Ar (%)	B_2Pin_2 conv. (%)
1[a]	*p*-	C_3H_7	1	42	58	0	58
2[a]	*p*-	C_3H_7	2	0	99	1	96
3[b,c,d]	*p*-	C_3H_7	16.5	43	57	0	53
4[b,c,e,f]	*p*-	C_3H_7	14.5	0	99 (96)	0	99
5[e]	*p*-	C_3H_7	2.5	0	99 (82)	1	105
6[e]	*m*-	C_3H_7	3.0	10	90	0	98
7[e]	*o*-	C_3H_7	3.5	32	4	[64][g]	<25
8	*p*-	Ph	2	0	99 (91)	0	96
9[e]	*m*-	Ph	3.0	20	80	0	79
10[e]	*o*-	Ph	3.5	25	6	[69][h]	<15

Unless otherwise stated the aryl halide (1.0 mmol) was reacted with B_2Pin_2 (1.15 equivalents) in the presence of KOAc (3.0 equivalents), $PdCl_2(MeCN)_2$ (2.5 mol%), S-Phos (5.0 mol%), and dioxane (6.0 ml/mmol aryl halide), at 90 °C for the indicated time. All conversion values were determined by ^{1}H NMR analysis of the crude reaction mixture, while isolated yields of the borylation product are given in parentheses.

[a] Reaction performed on 0.5 mmol scale based on the aryl halide.

[b] Dioxane (3.0 ml/mmol halide).

[c] $PdCl_2(MeCN)_2$ (1.25 mol%) and S-Phos (2.5 mol%).

[d] 0.55 equivalents of B_2Pin_2 relative to aryl halide.

[e] 1.05 equivalents of B_2Pin_2 relative to aryl halide.

[f] Reaction performed on 5.0 mmol scale based on the aryl halide.

[g] **4.127** is the major product (see Scheme 4.26).

[h] **4.128** is the major product (see Scheme 4.26).

Table 4.15

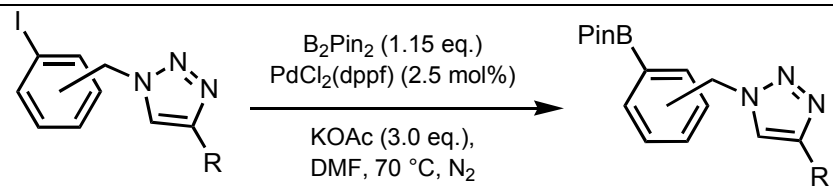
4.8.2. Effect of Diboron Stoichiometry on Product Distribution

Using ligand-free $Pd(OAc)_2$ for the Miyaura borylation of aryl halides, Zhang and co-workers determined that with 1.0 equivalent of B_2Pin_2 to *p*-bromoacetophenone, the aryl bromide was completely consumed after three hours under their reaction conditions to yield a 9:1 mixture of borylation product and biaryl. While the same reaction could be performed with an extended reaction time of 18 hours without any impact on this ratio, the use of only 0.5 equivalents of diboron with the same extended reaction time gave a ratio of 1:4 borylation product to biaryl. As such this confirmed that homocoupling was not a significant

pathway for the formation of the biaryl, and instead, Suzuki coupling of the borylation product and unreacted aryl bromide was.[32]

Thus, under similar conditions to those we employed, there is the potential for notable amounts of Suzuki coupling product to form when B_2Pin_2 is present in sub-stoichiometric amounts. Interestingly however, when we altered the reaction conditions such that the concentration of aryl bromide **4.26** was increased, while the equivalents of B_2Pin_2 were reduced to 0.55, no significant amount of biaryl was evident (Table 4.15, entry 3). Although the catalyst loading was also lower in this reaction, the analogous reaction at this concentration and catalyst loading, but instead with 1.05 equivalents of the diboron, gave complete consumption of the aryl bromide, and in a shorter period of time (entry 4) than was the case when the sub-stoichiometric loading of diboron was used. Thus it seems that the conditions used for the borylation of the aryl bromide substrates do not favour the Suzuki coupling reaction, which is also consistent with the results obtained for *p*-iodo acetophenone (Table 4.13, entries 2-3), which show that DMF seems to promote this reaction much more so than does dioxane.

4.8.3. Reactivity of Methylene Triazole Substituted Aryl Iodides



Entry	Sub.	R	Time (hr)	ArHal (%)	Prod. (%)	Ar-Ar (%)	B_2Pin_2 conv. (%)
1	*p*-	C_3H_7	24	0	95 (83)	5	104
2	*m*-	C_3H_7	24	0	97	3	99
3	*o*-	C_3H_7	24	0	90	10	107
4[a]	*p*-	Ph	20	< 5	(94)	0	98
5[a]	*m*-	Ph	20	< 5	(91)	0	94
6[a]	*o*-	Ph	24	27	61 (42)	12	86

Unless otherwise stated the aryl halide (1.0 mmol) was reacted with B_2Pin_2 (1.15 equivalents) in the presence of KOAc (3.0 equivalents), $PdCl_2(dppf)$ (2.5 mol%), and DMF (6ml/mmol aryl halide), at 70 °C for the indicated time. All conversion values were determined by ^1H NMR analysis of the crude reaction mixture, while isolated yields of the borylation product are given in parentheses.

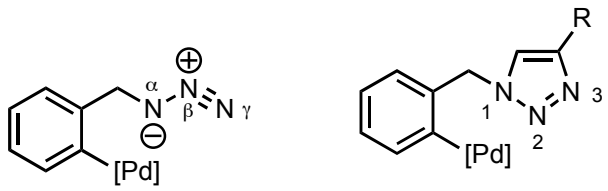
[a] 1.05 equivalents of B_2Pin_2 relative to the aryl halide.

Table 4.16

We then investigated the reactions of the analogous methylene triazole substituted aryl iodides under the conditions optimised for the borylation reactions of the parent azides, although in this case we retained the same reaction temperature of 70 °C, so as to be able to more directly compare their reactivities. The *para*-substituted iodoaryl azide took six hours to reach high conversion (Table 4.14, entry 5), and as we had already found that the triazole moiety did somewhat reduce the rate of borylation for the bromoaryl triazoles, we therefore began by increasing the reaction time to 24 hours. In this way the iodoaryl 1-pentyne derivatives all gave high conversion to the desired borylation products, although with varying amounts of biaryl as the minor product formed through homo- or Suzuki coupling (Table 4.16). In the case of the *para*- and *meta*- regioisomers of the phenylacetylene derived triazole we therefore reduced the reaction time to 20 hours, and then even employing only a slight excess of B_2Pin_2, found that the borylation product could be obtained in high yield without significant amounts of biaryl being generated (entries 4 and 5).

4.8.4. Comparison of the Aryl Bromide and Aryl Iodide Substrates

Very interestingly the borylation reactions of the bromo and iodo *o*-methylene azides (**4.102** and **4.118** respectively) were approximately an order of magnitude slower than their corresponding *para*- and *meta*- regioisomeric forms (For the aryl bromide substrates see Table 4.8, entry 4 and Table 4.10, entries 2 & 5. For the aryl iodide substrates see Table 4.14, entries 5, 7 & 10). In contrast to this, the rate at which the iodoaryl *o*-methylene triazoles are borylated is roughly comparable to the rates at which the other regioisomers are (i.e., compare Table 4.16, entries 1-3 or 4-6). While the corresponding results for the bromoaryl triazoles cannot be compared due to the high degree of intramolecular arylation (see Table 4.15), this might be explained by the change in basicity of the proximal nitrogen atoms between the azide and triazole substituents. So while the nitrogen atom closest to the palladium centre in the oxidative addition adduct **4.125** (Figure 4.8) is the most basic proximal N_α of the organoazide (with N_β being the least basic), the proximal N-1 of the triazole in oxidative addition adduct **4.126** is conversely the least basic (with the most basic being N-3). As such the comparative strength of the interaction with the palladium centre is likely to be weakened upon changing from the azide to the triazole. Additionally, the greater molecular torsion of the larger substituent is also likely to disrupt the interaction through rotation about the relevant C_{Ar}-C_{Bn} and C_{Bn}-N_{Tz} bonds, while neither N-2 nor N-3 is likely to be able to spatially orient so as to interact with the palladium centre as effectively as can N-1 (Figure 4.8).



4.125 **4.126**

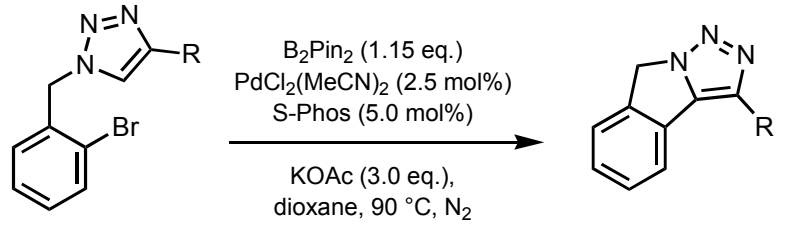
Figure 4.8

Finally, it should also be noted that in contrast to the bromoaryl *o*-methylene triazoles (Table 4.15, entries 7 & 10), the major product from the borylation of the iodoaryl *o*-methylene triazoles was the expected boronate ester (Table 4.16, entries 3 & 6), and not the intramolecular arylation products (Scheme 4.26).

4.9. Alternative Palladium-Mediated Pathways of Relevance to the Miyaura Borylation of Azido- or Triazolyl- Methylene Substituted Aryl Halides

4.9.1. Palladium-Mediated Arylation of Triazoles with Aryl Halides and Pseudo-Halides

Palladium-catalysed arylation of 1,2,3-triazoles at C-5 and C-4 with aryl halides, including the intramolecular variant that generates **4.127** and **4.128**, is documented in the chemical literature, with two recent reviews containing relevant discussion about such reactions.[13, 70]

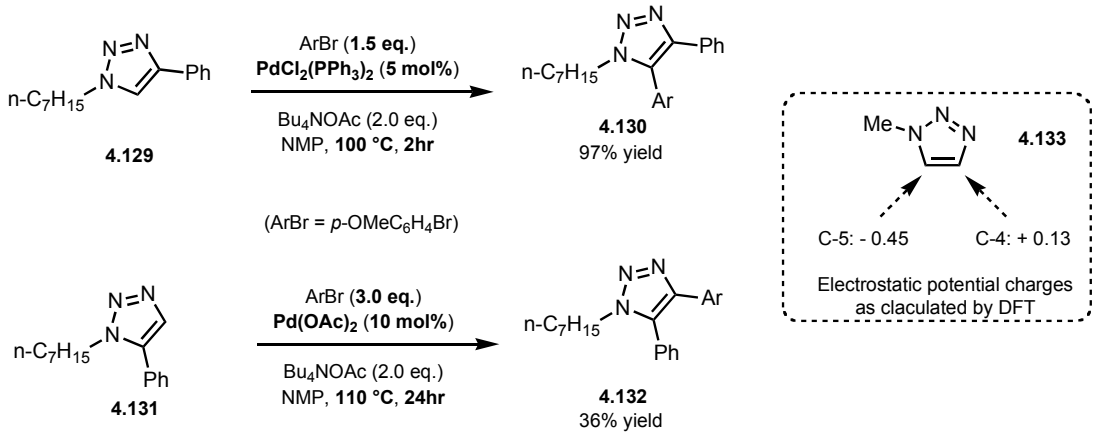


***o*-4.26** (R = C_3H_7)
***o*-4.122** (R = Ph)

4.127 (R = C_3H_7)
4.128 (R = Ph)
(Observed by ^{1}H NMR)

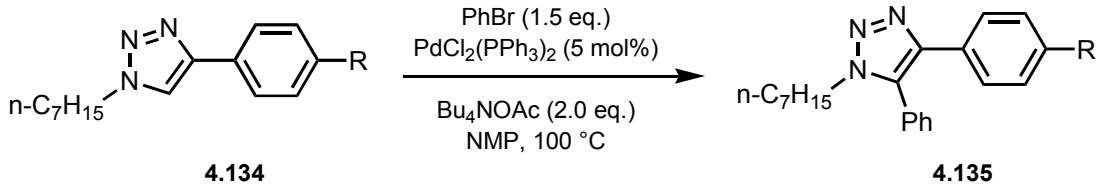
Scheme 4.26

Investigations made by Gevorgyan and co-workers concluded that, in conjunction with a suitable base, typical palladium(II) and palladium(0) pre-catalysts used in cross-coupling reactions such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3$ are able to effect C-5 or C-4 arylation of 1,2,3-triazoles using aryl bromides. They have also shown that, irrespective of substituent electronics for the aryl bromide substrates, the C-5 arylated product is strongly preferred – unless 1,5-disubstituted triazoles are employed as substrates, in which case the reactions to yield arylation at C-4 are in turn much slower (Scheme 4.27).[71]



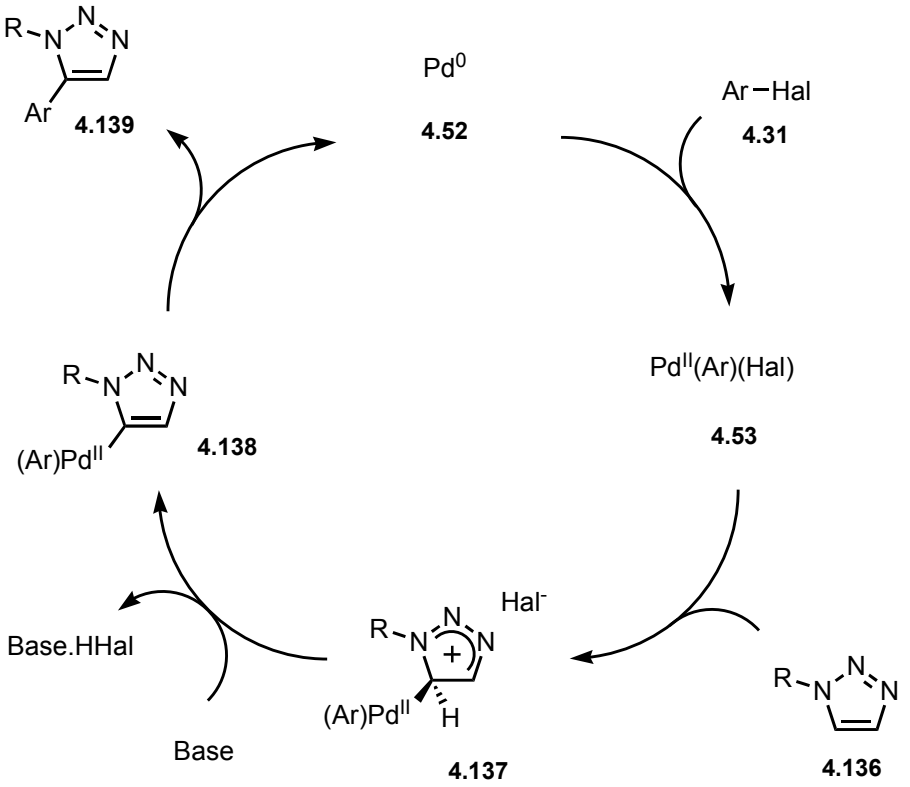
Scheme 4.27

DFT analysis using 1-methyl 1,2,3-triazole (**4.133**) as a model system determined that this preference for arylation at the C-5 position of 1,2,3-triazoles is a result of the greater degree of negative charge it bears in comparison to C-4. Kinetic studies of C-5 arylation using a 4-aryl substituted 1,2,3-triazole revealed no kinetic isotope effect (^{1}H vs. ^{2}H at C-5: $k_{H/D} = 1.0$). However, there was a positive correlation for the rate of C-5 arylation with increased electron density at the triazole ring resulting from a more electron rich 4-aryl substituent (Scheme 4.28). In combination with computational studies, the authors concluded that a palladium-mediated electrophilic substitution reaction was involved, rather than a C-H activation pathway.[71]



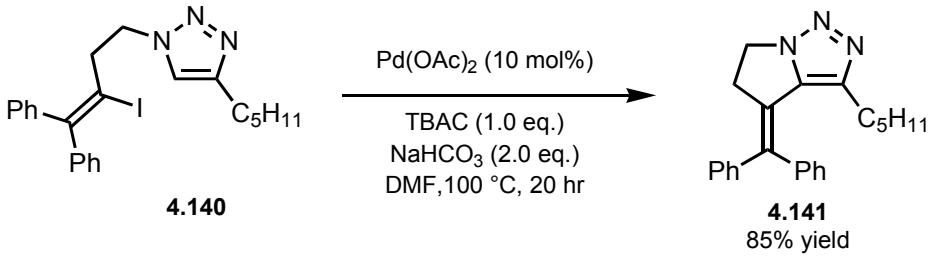
Entry	R	k_R/k_H
1	H	(1.0)
2	CO_2Et	1.0
3	OMe	1.3

Scheme 4.28



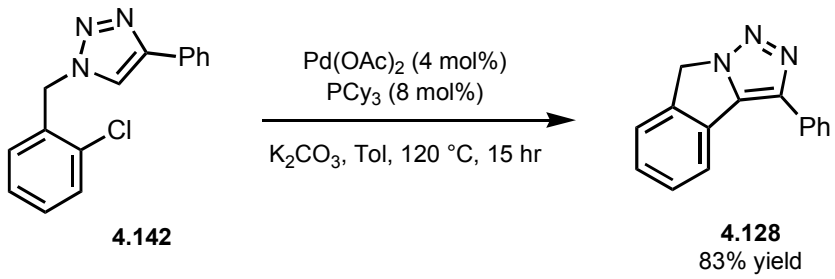
Scheme 4.29

As such the catalytic triazole arylation reaction is thought to proceed by oxidative addition of the aryl halide **4.31** to yield complex **4.53**, followed by electrophilic activation to yield intermediate **4.137**. After subsequent deprotonation of **4.137** to form **4.138**, reductive elimination is then able to occur so as to yield the arylated triazole **4.139** and simultaneously regenerate the active palladium(0) complex **4.52** (Scheme 4.29).[13, 71]



Scheme 4.30

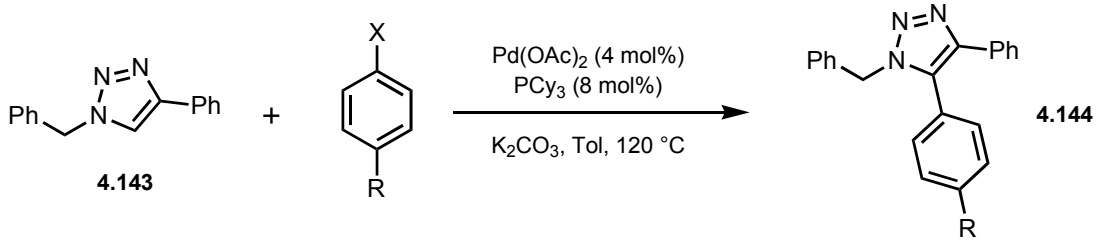
This methodology has been used to form cyclised products *via* intramolecular reactions, e.g. by Huang *et al.* who employed alkenyl iodides such as **4.140** to form **4.141**,[72] while Ackermann and co-workers have reported the corresponding intramolecular reaction using aryl chloride **4.142** to yield **4.128**.[73]



4.142 **4.128** 83% yield

Scheme 4.31

With intramolecular arylation available during the borylation of the *ortho*-methylene triazole substituted aryl halides, potentially further preferred due to the potential electrostatic interaction between the palladium centre and C-5 of the pendant triazole, it is unsurprising that **4.127** or **4.128** are formed. However, it is also possible to explain the much smaller amount of arylation product observed in the borylation reactions of the aryl iodides ***o*-4.121** and ***o*-4.123**, relative to the corresponding aryl bromides ***o*-4.26** and ***o*-4.122**.



4.143 **4.144**

Entry	R	X	Yield (%)
1	Cl	Br	73
2	Me	Cl	93
3	Me	Br	86
4	Me	I	0

Scheme 4.32

Interestingly Ackermann and co-workers have reported that the arylation reaction employing *p*-bromochlorobenzene is highly selective, so as to give 4-(*p*-chlorophenyl) substituted triazole **4.144** (R = Cl; Scheme 4.32, entry 1 of table therein), and as such they appear to have falsely concluded that aryl bromides are more reactive than aryl chlorides in the arylation reaction.[73] However, this is not consistent with another of their findings, namely that when the three *p*-halo toluenes are compared in the arylation of triazole **4.143**, the observed reactivity order is actually found to be Cl>Br>>I, with no reaction observed in the case of the aryl iodide (Scheme 4.32, entries 2-4 of table therein). Furthermore, the aforementioned report of intramolecular arylation of alkenyl iodides by Huang *et al.* (Scheme 4.30) was found to proceed best in the presence of TBAC, although as no data

relating to the optimisation process was reported or discussed it is impossible to gauge the absolute effect which can be attributed to the additive.

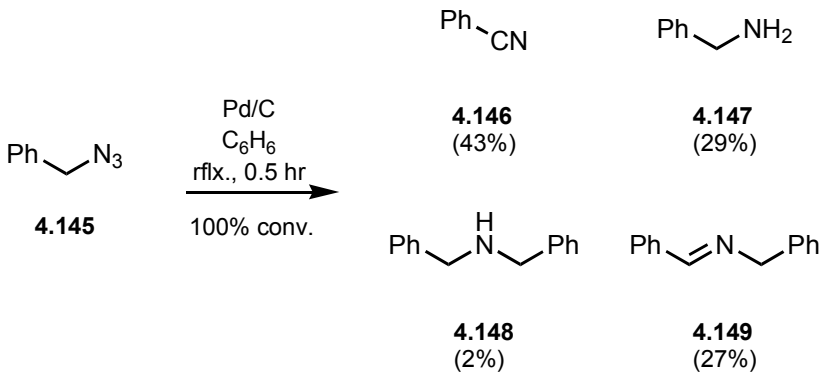
As such it is however apparent to us that although the rate of oxidative addition of the aryl halides indeed follows the expected trend of I>OTf>Br>>Cl,[29] the oxidative addition adducts derived from the aryl chlorides are overall more reactive in the catalytic arylation than are the aryl bromide adducts, which in turn are much more reactive than the corresponding aryl iodide analogues. Thus the rate of at least one subsequent step in the catalytic cycle appears to be very heavily influenced by the identity of the halide anion, with the iodide anion most disfavouring the arylation. As the halide is not likely to have any bearing on the rate of reductive elimination this suggests that the deprotonation, or more likely, the electrophilic activation step is responsible for the observed differences. Ackerman and co-workers also demonstrated that while S-Phos and PCy_3 were very effective choices of ligands for promoting the arylation reaction in combination with $Pd(OAc)_2$ at a Pd:ligand ratio of 1:2, DPPF and PPh_3 were not. Furthermore they also noted that dioxane and toluene were better solvents for the arylation reaction than much more polar solvents such as DMF, DMA and NMP.

As such we can conclude that the borylation of the *ortho*-methylene triazole substituted aryl iodides ***o*-4.121** and ***o*-4.123** results in much lower amounts of arylation products (**4.127** and **4.128** respectively) because neither iodide anion, nor DMF, nor DPPF favour the triazole arylation reaction. In direct contrast though, bromide anion, dioxane and S-Phos all individually favour an increased rate of arylation, and as such act in unison to generate the annulated triazoles **4.127** and **4.128** as the major products. Thus, even with a similar proportion of starting material consumed, then bromoaryl *o*-methylene triazole ***o*-4.122** gives rise to a c. 10:1 mixture of arylation and borylation products respectively, while the corresponding iodoaryl *o*-methylene triazole ***o*-4.123** instead generates a c. 5:1 ratio of the borylation and cross-coupling products (Table 4.15, entry 10 *vs.* Table 4.16, entry 6).

4.9.2. Palladium-Mediated Reactions of Organoazides

In addition to the potential formation of biaryls as is normal in the palladium-catalysed borylation reactions of aryl halides, it was mentioned earlier that palladium catalysts are also known to effect catalytic transformations of organoazides. For example, in 1976 Oka and co-workers reported that Pd/C or palladium black could be used to convert benzyl azide **4.145** to a mixture of benzonitrile **4.146**, benzylamine **4.147**, dibenzylamine **4.148** and *N*-benzyl imine **4.149** (Scheme 4.33). Additionally, through the addition of certain internal alkynes as

hydrogen-acceptors, higher selectivities for the nitrile products over the primary and secondary amines were observed for various benzylic azide substrates.[65]



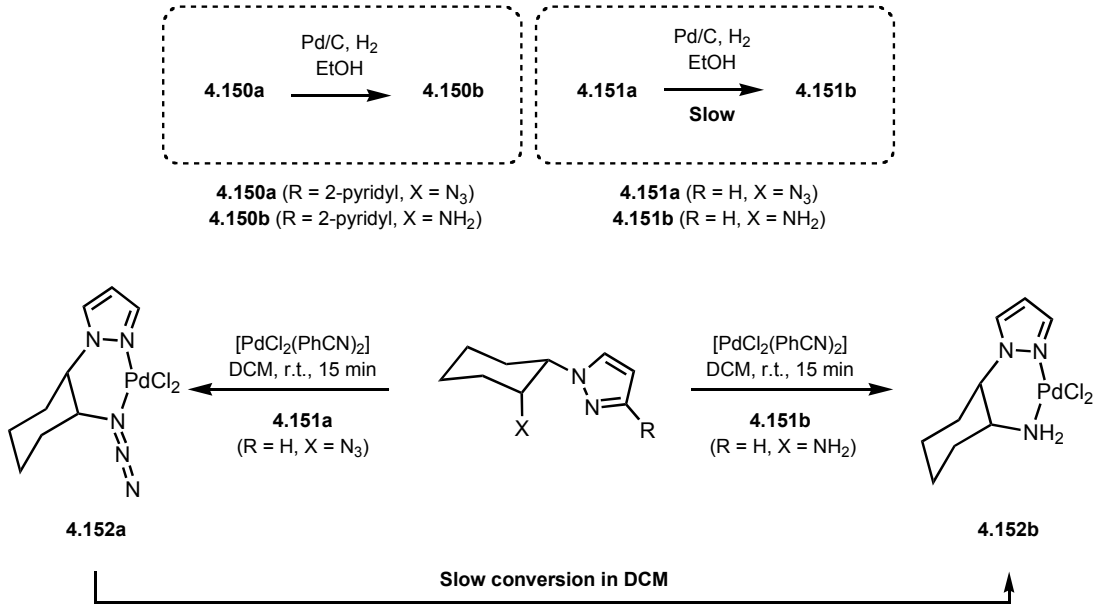
Scheme 4.33

More recently ruthenium complexes have been shown to catalyse transformations of benzylic azides to produce similar mixtures of products,[74, 75] while the groups of Kotsuki[76] and Yoon[77] have used Boc-anhydride and Pd/C catalysts in conjunction with silane and borane reductants, respectively, so as to form Boc-protected amines from organoazides by sequential palladium-catalysed reduction and resultant carbamate formation.

As such, although we have so far not made any specific attempts to generate or isolate any of the by-products formed in our reactions, their proposed identities are consistent with both the ^{1}H NMR analyses of the crude reaction mixtures, and also with the known products of palladium-catalysed organoazide degradation processes. Furthermore, the rates of these side reactions appear to be influenced variously by the identity of the substrate, choice of catalyst, ligand, solvent system, and even the reaction temperature employed. However, as starting material and borylation product are by far the major components present in the reaction mixtures prior to complete consumption of the aryl bromides and aryl iodides, this suggests that oxidative addition is both facile, and yields intermediates that are not significantly involved in generating substantial amounts of such side-products. In contrast, when little or no aryl iodide or aryl bromide remains, or when the less reactive aryl chloride is employed in the borylation reaction, then these alternative reaction pathways become comparatively accessible.

While attempting to synthesise multidentate ligands bearing an imine functionality, Thiel and co-workers subjected azides **4.150a** and **4.151a** to standard hydrogenation conditions using Pd/C in order to access amines **4.150b** and **4.151b** respectively (Scheme 4.34). However, although the 3-(2-pyridyl) pyrazolyl variant **4.150a** was readily reduced as

expected, the corresponding reduction of the mono-substituted pyrazolyl analogue **4.151a** was much slower. Upon treating azide **4.151a** and its reduction product **4.151b** with $PdCl_2(PhCN)_2$ the corresponding palladium(II) complexes **4.152a** and **4.152b** were obtained, which revealed the 1-substituted pyrazolyls to be acting as bidentate ligands as determined by crystallographic structural analysis. Although organoazide complex **4.152a** was stable in the solid state, even with exclusion of light it slowly degraded in solution to yield the amine analogue **4.152b**.[67]



Scheme 4.34

However, despite the proximal N_α in organoazides being the most basic, for metals that are not in high oxidation states (e.g. IV-VI), the coordination of simple monodentate organoazide substrates is most likely to involve the terminal N_γ atom for reasons of π-back bonding. Indeed, it is only the bidentate nature of ligands such as **4.151a** that favour metals such as palladium interacting with N_α in preference to N_γ in the resultant complex **4.152a**. This is especially noteworthy because **4.152a** is one of only a very small number of metal complexes with intact organoazides to have been characterised, as they are most often extremely reactive and rapidly react further, typically through loss of N_2 to generate a metal imido complex.[66]

Numerous reaction types are able to occur between metal complexes and organoazides, variously determined by the identity and character of the metal centre, its ligands, and the organoazide itself. These also include reactions of organoazides with other complexed

ligands – for as diverse a set as CO, hydride and phosphine – and by processes which are in turn often mediated by the metal centre in some manner.[66]

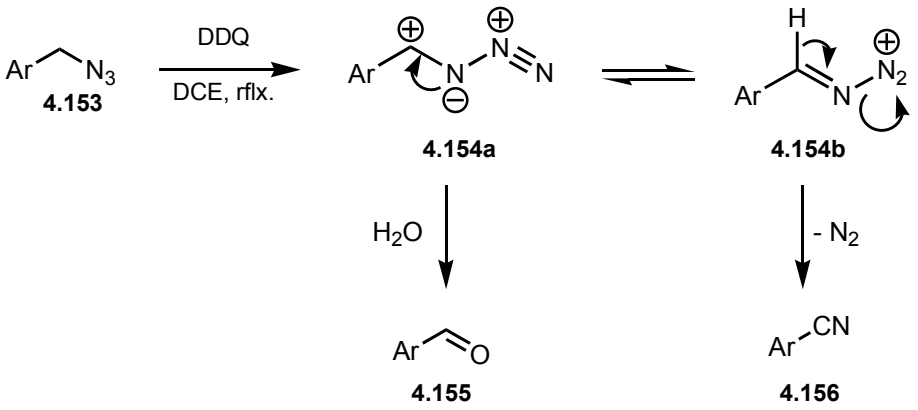
However, with the slow degradation of organoazide complex **4.152a** to yield amino complex **4.152b** continuing to proceed in solution despite the exclusion of light, it indicates that palladium-mediated degradation of the azide is involved, rather than photolytic generation of a nitrene intermediate.[1, 67] In conjunction with the lack of such behaviour in the solid state this suggests that a dissociative process could potentially be responsible for the transformation of the azide into the amine. Furthermore, the dissociation and generation of small amounts of palladium(0) is not unfeasible, originating from either ligated or dissociated palladium(II) intermediates, and could account for the slowly observed conversion of the azide to the amine that arises while complex **4.152a** is in solution.

Indeed, and although inconclusive, it is interesting to note that for the aforementioned reduction and Boc-protection of organoazides with triethylsilane and Pd/C, as reported by Kotsuki and co-workers,[76] the authors selected Pearlman's catalyst ($Pd(OH)_2/C$) rather than a standard supported palladium(0) substrate. Furthermore Seki *et al.* have shown that under appropriate conditions so as to allow reduction to palladium(0), that Pearlman's catalyst can then exhibit significantly higher activities in Fukuyama, Sonogashira and Suzuki coupling reactions than Pd(0)/C.[78] However, Kotsuki and co-workers noted that without Boc-anhydride present, then even the high activity of the active catalyst was inhibited by formation and accumulation of the free amine. As such this precedent might provide further support for highly active palladium(0) species, rather than palladium(II), being able to elicit transformations of organoazides, while concomitant formation of any amines generated may act as part of a negative feedback loop – preventing or masking, e.g., any autocatalytic behaviour.

Furthermore, to be consistent with literature precedent for the loss of N_2 and formation of a metal imido complex, then this event must be initiated by coordination of palladium at, or to, N_γ of the organoazide.[66] With said inclusion of the distal nitrogen in the ligating interaction then this process is favoured, while in contrast, that to the proximal N_α does not favour loss of N_2. As such this supports oxidative addition adduct of type **4.125** (Figure 4.8) being stable to loss of nitrogen despite the proximity of the palladium centre to the azide, as both the palladium(II) oxidation state and the interaction of the metal with N_α are demonstrably tolerated, at least in combination (e.g., as was reported to be the case with complex **4.152a**). In summation these facts are potentially also consistent with an oxidative addition event involving palladium(0) and the organoazide – yielding a palladium(II) imido complex and

N_2 – as the cause of azide degradation during the late stages of the borylation reactions. The fact that the interaction between palladium(0) and N_γ is likely fluxional and not strong, such that it does not often lead to formation of a reactive intermediate, would further support the observed lack of such a reaction prior to complete consumption of the aryl halide. Indeed, Thiel and co-workers noted that the Pd-N2 (pyrazole) bond of complex **4.152a** was "significantly shorter" (2.017 Å (3)) than that of the Pd-N_α (azide) bond (2.056 Å (3)). And yet N_α, being more basic than N_β or even N_γ, should provide the strongest interaction between the azide moiety and the Pd centre of those possible. So, as that interaction is therefore still relatively weak in nature, then this is again consistent with reaction of the azide moiety only being viable when other more favourable reactive pathways are no longer accessible for the palladium(0) complex to become involved with.

The reactivity of metal-organoazide complexes is sometimes different to that of organic azides in isolation from such complexes, such that while Δ^2-triazolines (**4.5**) are formed by thermal reactions of azides with alkenes, when metal catalysts are involved aziridines (**4.6**) or allylic amines are generated instead.[66] However, and despite the difference that the involvement of a metal-centre can make, Jiao and co-workers have reported the use of DDQ in the metal-free formation of aryl and alkenyl nitriles from benzylic and allylic azides, respectively; observing the generation of aldehydes in some cases, and for which they proposed the overall mechanism as shown in Scheme 4.35.[79] They also noted that electron withdrawing groups on the aryl ring of the benzylic azides **4.153** resulted in a much slower rate of reaction, and while it is again important to remember that an analogous metal-mediated reaction could proceed in a very different manner, this does however imply hydridic, and not acidic, character to the benzylic hydrogen atoms in such reactions.



Scheme 4.35

Interestingly this is also consistent with the fact that Molander and Ham employed aryl azides successfully in Suzuki coupling reactions, while specifically highlighting that they observed the formation of anilines as major products in certain of the copper-assisted aromatic substitution reactions used to form the aryl azide substrates (as discussed previously). However, they made no mention of aniline or nitrile by-products being generated during Suzuki coupling reactions involving the aryl azides, and despite noting too that the azide substituted aryl chlorides were ineffective as cross-coupling partners. This may mean that aryl azides are acting akin to primary anilines – which prove to be a good choice of substrate for Buchwald-Hartwig amination reactions – as neither have a labile α-hydrogen atom available, such that β-hydride elimination cannot occur by action of the palladium complex. Interestingly, if the above inference of hydridic character is in fact accurate, then this would mean that rather fortuitously the borylation products derived from azide substituted aryl halides are potentially even less prone to palladium-mediated organoazide reactions than are the starting materials, due to the rather significant amount of electron withdrawing character that the boronate ester moiety can exhibit.

4.10. Rationalisations for the Observed Effects of Solvent and Halide Identity on the Rate of Borylation

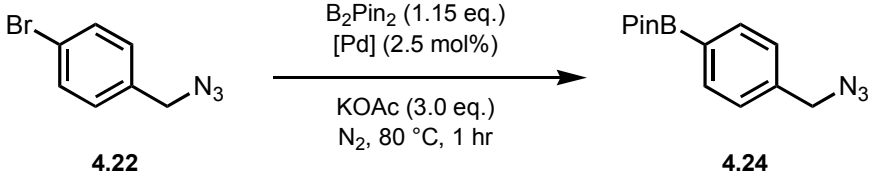
4.10.1. Conclusions from the Solvent Comparison Studies

The ultimate aim of these investigations was to determine whether conditions for the Miyaura borylation of aryl halides could be developed so as to tolerate substrates bearing benzylic azides. In this respect we have shown that although such azides are susceptible to alternative palladium-mediated reactions, when the oxidative addition step of the catalytic borylation reaction proceeds readily, then such undesirable reactions are suppressed. As such, in addition to the synthetic utility of the azido-boronate products that originally motivated us to develop these protocols, the azide moiety has simultaneously revealed certain details about the catalytic borylation reaction itself.

We began our investigations with aryl bromide **4.22** rather than aryl iodide **4.116** as we had concluded that if the azide moiety of an aryl bromide was tolerated in the borylation reaction, then it should effectively be guaranteed that the more reactive aryl iodides would give identical, if not potentially better results, and without concern that the azide moiety should behave any differently.

By monitoring the integrity of the azide moiety of aryl bromide **4.22** and aryl iodide **4.116** through the course of the borylation reactions we have been able to discern that oxidative

addition is facile with active catalysts such as those that are formed *in situ* by $PdCl_2$(dppf) or $PdCl_2(MeCN)_2$/S-Phos. In turn, the rate of borylation of the aryl iodides thus appears to be more dependent on the choice of DMF or dioxane as solvent than it does on the selection of those palladium complexes we assessed. Indeed, further investigations showed that the same solvent effect can act in reverse for aryl bromides, with dioxane proving to be a better choice of solvent than DMF for the borylation of **4.22** (Table 4.17).



4.22 **4.24**

Entry	[Pd]/L[a]	Solv.	4.22 (%)[b]	4.24 (%)[b]	By-Prod. (%)[b,c]	B_2Pin_2 conv. (%)[b]
1	A	Diox.	15	85	< 5	84
2	B	Diox.	16	84	< 5	93
3	A	DMF	45	55	< 5	50
4	B	DMF	56	44	< 5	49

All reactions performed on a 0.5 mmol scale.

[a] Catalyst and ligand as follows: (A) $PdCl_2(MeCN)_2$/S-Phos; (B) $PdCl_2$(dppf). S-Phos used at 5 mol% so as to give a Pd:L ratio of 1:2.

[b] Conversions determined by ^{1}H NMR of the crude reaction mixture.

[c] Unidentified by-product.

Table 4.17

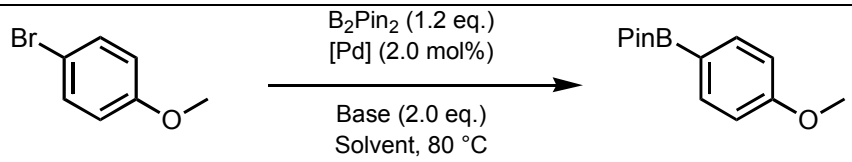
Although we have not investigated the aryl chloride substrate **4.115** so exhaustively, the preliminary results show that despite significant competition from other palladium-mediated processes, dioxane is indeed an effective choice of solvent for the borylation of such aryl chlorides. Furthermore, our reaction conditions were based on those developed by the Buchwald group specifically for the borylation of aryl chlorides, and despite no specific discussion of their optimisation process, dioxane was stated as being the optimal choice of solvent. Therefore it can be fairly presumed that aryl chlorides are likely to behave much akin to aryl bromides in these reactions.

4.10.2. Precedence for the Observed Solvent Effects in the Chemical Literature

As far as we are aware no reports in the literature detailing Miyaura borylation reactions make specific reference to the differential reactivity of aryl iodide substrates in comparison to their aryl bromide or aryl chloride analogues, as determined predominantly by the choice of solvent system rather than the palladium source or ligands.

4.10.2.1. Discussion on the Relative Rates of Oxidative Addition

The reactivity trend for the rate of oxidative addition of aryl halides with catalytically-relevant palladium(0) complexes is well known as being I>Br>Cl,[29] while in their initial report Miyaura and co-workers popularised the concept that the rate-limiting step of the borylation reaction was oxidative addition of the aryl halide.[16] As such, when optimising the borylation conditions for new palladium complexes – as is typical of such studies in the area of palladium-catalysed cross-coupling reactions – when researchers have employed more than a single halide identity then they have often focussed on transferring optimised conditions from a more reactive halide to a less reactive one.



Entry	[Pd][a]	Base	Solv.	Time (hr)	Yield (%)
1	A	Na_2CO_3	Dioxane	3	Trace
2	A	K_2CO_3	Dioxane	3	26
3	A	NaOAc	Dioxane	3	Trace
4	A	KOAc	Dioxane	1	79
5	A	KOAc	Dioxane	3	93
6	B	KOAc	Dioxane	3	93
7	C	KOAc	Dioxane	3	60
8	A	KOAc	Dioxane	6	93
9	A	KOAc	THF	3	89
10	A	KOAc	Toluene	3	77
11	A	KOAc	DMF	3	57
12	A	KOAc	DMSO	3	22

[a] Complexes employed: A **L-4.158** for which L = PCy_3; B **L-4.158** for which L = X-Phos; C **L-4.158** for which L = S-Phos.

Table 4.18

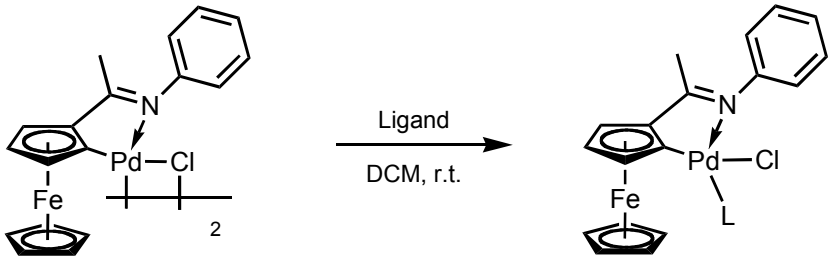
Because the solvent related discrepancy in reactivity for the aryl halides exists on moving from the iodides to the bromides, then any system optimised on a more reactive halide is very likely still going to produce results consistent with those expected for the less reactive halides. Furthermore, optimisation of reaction conditions with aryl chloride substrates could, due to their significantly lower reactivity, also yield a protocol that does not highlight the discrepancy for aryl iodides. Thus in cases reported in the chemical literature where a similar optimisation procedure has been performed on an aryl bromide substrate first, then the

researchers have subsequently continued to assess substrate scope for additional aryl bromide substrates, and at times for the less reactive aryl chlorides as well. And while other researchers may indeed have observed this discrepancy when transferring conditions optimised for an aryl bromide substrate to a corresponding aryl iodide one, they appear to have dismissed such findings as inconsistent with those originally made by Miyaura and co-workers – as is evidenced by a complete lack of any such conclusions being drawn and the rather telling omission of any such results for analogous aryl iodides.

Miyaura and co-workers stated that the optimised reaction conditions were determined using bromobenzene as a model substrate, however no quantitative data were included to justify the choice of solvent, only the fact that DMSO ≥ DMF > dioxane > toluene.[16] Furthermore, such reporting of generic trends, or simply just qualitative conclusions with very limited discussions being disclosed in favour of quantitative data, are all too common in the Miyaura borylation literature. In contrast, in-depth mechanistic studies of alternative catalytic borylation methodologies, including the Masuda borylation, have been expertly detailed by such researchers as Hartwig and Marder.[30, 80]

Despite the difficulty therefore in locating appropriate literature precedent to fully support our observations, our results are however consistent with those of Wu and co-workers. While they determined that palladacycles **L-4.158** (Scheme 4.36) are active pre-catalysts for the borylation of aryl bromides and aryl chlorides, no mention of employing aryl iodide substrates was made.[81] However, the authors conducted their detailed optimisation studies using *p*-bromo anisole as the model substrate, and importantly they also chose to include all such relevant quantitative data obtained during this process (Table 4.18). As such they demonstrate that dioxane is indeed the optimal choice of solvent for the aryl bromide, and demonstrate a trend which for the solvents DMSO, DMF and toluene is contrary to that originally stated as being the case by Miyaura and co-workers – who notably included no details of what the remaining reaction parameters where that resulted in them drawing such a conclusion.

Moreover, Wu *et al.* determined the palladacycles to be acting as pre-catalysts, because while the PCy_3 adduct was overall more active than the PPh_3 equivalent, they both displayed the same 20 minute induction period, after which the rate of borylation was observably faster in the case of the PCy_3 ligated adduct.[81] Serendipitously they also prepared ligand adducts with PPh_3, PCy_3, Dave-Phos, dicyclohexyl John-Phos, X-Phos, and S-Phos; and as such we know that S-Phos behaves very similarly under such reaction conditions as the more active PCy_3 pre-catalyst used for the full optimisation studies.



4.157 **L-4.158**

Scheme 4.36

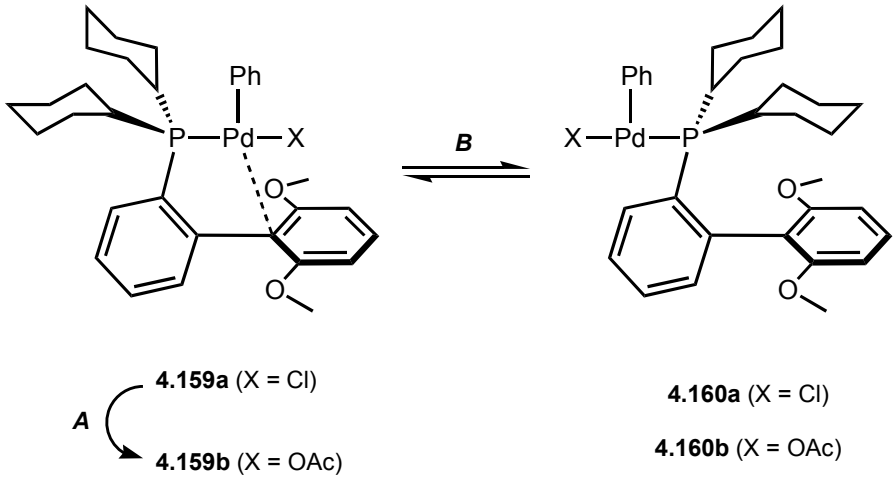
Here it should also be noted that despite the choice of $PdCl_2$(dppf) by Miyaura and co-workers as the optimal catalyst, the corresponding NMR studies of the mechanism of the catalytic borylation were conducted using $Pd(PPh_3)_4$ and its derivatives: *trans*-$PhPdX(PPh_3)_2$ (where X = Br or OAc).[16] As such the direct inference that oxidative addition was rate-limiting was not necessarily even true for the optimised system employing $PdCl_2$(dppf), and thus is even less likely to be true for such active complexes as are formed by Buchwald's monophosphine biaryl ligands – at least with certain not unreasonable solvent choices.

Indeed, in this respect the most important conclusion that may be drawn from our results, in combination with the literature precedent, is that with such modern pre-catalysts and ligands the rate of oxidative addition is very unlikely to be rate-limiting in the borylation of aryl bromides and aryl iodides. Indeed, Buchwald has shown that palladium-catalysed cross-coupling reactions of unactivated aryl chlorides can at times proceed even at ambient temperature when using such active complexes as are able to be formed by ligands including S-Phos and X-Phos; while reductive elimination of such palladium complexes is often facile too. As such the anionic ligand exchange or transmetallation events are very likely to become rate-limiting in such cases where the much more reactive aryl iodides and aryl bromides are involved, and therefore the choice of solvent must in turn be impacting at least one of these events in order to be responsible for the effects we have observed.

4.10.2.2. Buchwald Ligands in Borylation Reactions

Importantly, Buchwald and co-workers performed computational analyses to determine why S-Phos proved so effective a choice of ligand in the palladium-catalysed borylation of aryl chlorides with B_2Pin_2. Firstly they noted (as discussed in Chapter 2) that the lowest energy conformation of aryl halide oxidative addition adduct complexes such as **4.159a** are the ones where the palladium centre sits above the neighbouring aryl ring, while the distal complexes of type **4.160a**, accessed by rotation about the C_{aryl}-P bond, are higher in energy.[42] However,

they also expect transmetallation of B_2Pin_2 to occur while the complex is in fact in the higher energy distal conformation, due to the extreme steric crowding in the proximal conformers of such complexes and where the η^1 interaction between the non-phosphine containing aryl ring and palladium centre is also present. Furthermore, calculations suggest that while the rotation pathway for chloride complex **4.159a** is endothermic and has an activation energy of approximately 14 kcal/mol, not only is the activation energy for this rotation lower for the acetoxopalladium complex **4.159b**, but the process then also becomes marginally exothermic (Table 4.19 and related scheme). This is attributed to the ability of the acetate ligand in the distal conformer to bind and stabilise the palladium centre in a κ^2 manner, otherwise not possible with the halide ligand.



Entry	Process	X	$\Delta G^{\ddagger}$/kcal mol^{-1}	ΔG/kcal mol^{-1}
1	*A*	–	–	+ 9.2
2	*B*	Cl	~ 14	+ 3.8
3	*B*	OAc	10.5	- 0.6

Table 4.19

The authors conclude that the summation of these factors results in the S-Phos ligated acetoxopalladium oxidative addition adducts of type **4.159b** overall favouring rapid rotation to the distal conformer **4.160b**, which in turn frees a coordination site at the palladium centre and allows for the transmetallation event with B_2Pin_2 to occur, while finally, reductive elimination of such complexes is known to be facile. However, they also note that for chloride ion the anionic ligand exchange process (**4.159a** to **4.159b**) first required to occur is endothermic by +9.2 kcal mol^{-1} (see Table 4.19), and that precipitation of the KCl generated might act to drive the equilibrium formation of the corresponding acetoxopalladium(II) complex **4.159b**.

4.10.3. Concluding Remarks: Effect of Solvent Polarity on Anionic Ligand Exchange

As such it seems likely that one or more intricacies of the anionic ligand exchange process is responsible for the slow rates of the catalytic borylation of aryl iodides in dioxane, while the same reaction is much accelerated in DMF, and would also explain why the choice of solvent typically has a more dramatic effect than do the identity of the pre-catalyst and ligand. Indeed, comparing the polarities of these solvents (Table 4.20) reveals that the borylation of aryl iodides is favoured in highly polar solvents, while the aryl bromides favour the much less polar solvents.

Thus, the most likely explanation is that a major contribution to the solvent effect is in rendering the anionic ligand exchange process turnover-limiting by disfavouring formation of KHal, or favouring a reversible anionic ligand exchange such that an equilibrium exists between an oxidative addition adduct (e.g. **4.159a**) and an acetoxopalladium complex (e.g. **4.159b**); conversely this would in turn explain the dependency of the halide identity on such an effect too.

Entry	Solvent	μ^a	$\varepsilon_0{}^b$
1	Toluene	0.31	2.4
2	Dioxane	0.45	2.2
3	THF	1.75	7.6
4	DMF	3.24	36.7
5	DMSO	4.06	46.5

[a] Dipole moment in Debye.

[b] Dielectric constant.

Table 4.20: Dipole moments and dielectric constants for selected solvents.[82]

And here, critically, not only did Wu *et al.* determine that dioxane was a better choice of solvent than DMF or DMSO for the borylation of *p*-bromoanisole, but they also found a significant difference between the activity of the carbonate and acetate bases depending on whether the associated counterion was Na^+ or K^+ (Table 4.18, compare entries 1 & 2 and 3 & 4). As such this supports our hypothesis that, for the aryl iodide and aryl bromide substrates, the anionic ligand exchange step is in fact rate- or turnover- limiting; rather than the oxidative addition event, as is to be inferred from the results of the NMR studies presented by Miyaura and co-workers – which showed it to be the only step of the catalytic cycle to require an elevated temperature in order to proceed.

Potentially the choice of dioxane as solvent in the case of the aryl iodides disfavours the anionic ligand exchange process, due to the lower solvation energy for a more dissociated ion pair (i.e. KI) in a less polar solvent system; such that it becomes a turn-over limiting event. In contrast the results above for aryl bromide **4.22** (Table 4.17) may suggest that in dioxane the anionic ligand exchange is the rate-limiting step, as both S-Phos and DPPF gave similar results, and that with the less polar solvent system this process is more effectively rendered irreversible due to the precipitation of a less easily dissociated ion pair. In the case of the aryl bromide with DMF as the solvent, then the S-Phos complex performs notably better than the DPPF analogue. Buchwald and co-workers showed that chlorobenzene oxidative addition adduct **4.159a** undergoes anionic ligand exchange to form complex **4.159b**, then relatively readily undergoes rotation to form distal complex **4.160b** – stabilised by the acetate ligand. Although the enthalpy of formation for KBr is lower than that of KCl,[83] this is contrasted by the fact that Pd-Br bonds are weaker than their Pd-Cl counterparts.[84] Therefore the aryl bromide adduct will likely behave similarly, suggesting that the efficiency of S-Phos in the more polar DMF system might be related to the rotation process, such that equilibrium anionic ligand exchange becomes effectively irreversible, driven both by the rotation and subsequent transmetallation events.

4.11. Conclusions and Future Work

We have shown that despite their lack of compatibility with traditional s-block organometallic routes employed in the synthesis of boronic acids, azide functionalised aryl halides are in fact amenable to use in Masuda and Miyaura borylation protocols. As such the methodological developments detailed in this chapter should prove a useful tool for the rapid preparation of more diversely structured and functionalised azido-boronate esters, as exemplified by **4.24**. Within the context of expanding substrate scope, then future investigations would do well to first target heteroaryl examples of these compounds. In particular those heterocyclic systems seeing widespread application in the context of medicinal chemistry, such as indoles, would be an ideal starting point. Additionally, any specific boronate substituted heteroaryl substrates – selected for the additional utility with which an appended organoazide moiety synergistically infers them – are also very worthy of investigation.

During these investigations we have also determined that there is a significant difference in the behaviour of aryl iodides and aryl bromides in the Miyaura borylation reaction, and that this is related to the effect of solvent polarity on the intricacies of the anionic ligand exchange process involved in the catalytic cycle, rather than being a result of the relative rates at which the different aryl halides undergo oxidative addition.

Future work on this aspect would do well to focus first on eliciting, where possible, any further details relating to the anionic ligand exchange event and its overall place in the catalytic cycle of such reactions as the palladium-catalysed Miyaura borylation. Such information may help further the understanding of these reactions, allowing a more rational approach to be employed towards expanding substrate scope so as to include other synthetically valuable functional groups not currently well tolerated – or in developing more broadly effective combinations of borylation catalysts and reaction conditions, so as to best suit a targeted substrate class. Finally, organoazides are at current still considered almost purely for their reactivities in transition metal-catalysed reactions, and as such the potential to contribute towards the rather limited understanding and appreciation of organoazides as spectator functionalities in such situations is an important point worthy of consideration in determining the future direction of such studies. Transition metal-catalysed reactions which organoazide substrates are directly amenable to – or equally, those that they are tolerant of – will undoubtedly become areas of much greater interest in coming years than is true today.

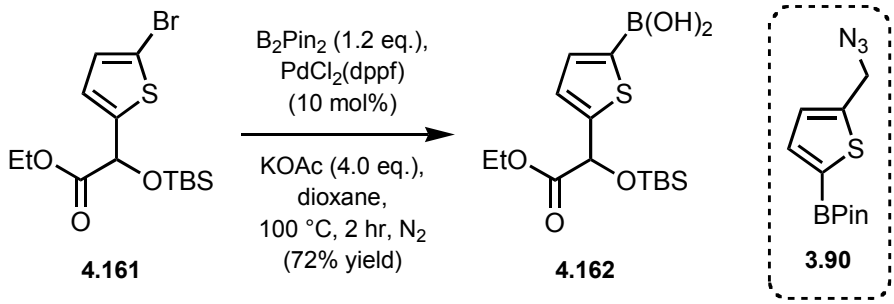
The research investigations detailed in this chapter are being prepared for publication.

4.12. Closing Remarks on Azido-Boronate Esters

Chapter 3 detailed the initial syntheses and applications of two azido-boronate esters, while this chapter has further advanced the chemistry of these privileged substrates in terms of viable and complementary approaches towards their synthesis. Our investigations have in combination demonstrated the significant potential for using such substrates as highly practical synthetic intermediates – able to be stored without special precautions, so allowing them to be kept at hand until the moment their use is required – at which point they are immediately amenable to use across a diverse range of applications.

Additionally, the organoazide and boronate moieties are themselves amenable to a wide range of important synthetic organic transformations, with a single azido-boronate ester presenting significant opportunities for chemical diversification. Furthermore, both functional groups are already widely employed *individually to one another* in chemical and biological ligation strategies.

We have already shown that **4.24** is able to be used to synthesise derivatives of relevance to drug-discovery, and as such the borylation methodology we have developed is particularly noteworthy, especially given the biological activity that both organoazide[1] and boronic acid[85] moieties can possess individually.



Scheme 4.37

Indeed, while certain 2- and 3- thienylboronic pinacolate esters are rendered susceptible to unavoidable hydrolysis of the boronate ester upon isolation as a result of substituent electronics – as is the case for substrates such as **4.161**[86] – usefully substituted halo-thiophenes are nonetheless amenable to both Miyaura[86] and Masuda[87] borylation protocols. As such, then the methodology we have developed could also provide access to azido-boronate functionalised heteroaryl substrates such as **3.90** that are not able to be straightforwardly synthesised (at least not without prior re-optimisation of various reaction parameters) by substitution of their precursors in place of the simple aryl equivalents used to access **3.78** (i.e. **4.24**) and **F-3.78** *via* the non-catalysis centric synthetic route detailed in Chapter 3.

Various borylation products derived from heteroaryl halide starting materials are included in a number of publications to have already been referenced in this chapter – including the Miyaura borylation protocol reported by Buchwald and co-workers which was successfully applied to heteroaryl chloride substrates such as 3-chlorothiophene and 3-chloropyridine,[42] or the preparation of pyrimidine-2-ylamine boronate ester **4.83** as reported by Hanselmann *et al*.[56] Furthermore, these are by no means isolated examples selected merely to support the premise that transition metal-catalysed borylation protocols are a powerful tool for accessing heteroaryl boronates – substrates which are themselves of importance to the synthesis of products having significant utility to such diverse fields as materials science,[80, 88] organic solar cell technologies,[89, 90] and of course, medicinal chemistry too.[54, 56, 91, 92]

Thus, in combination with the relevance of organoazides as important synthetic intermediates, and even as a functionality of relevance to the overall biological activity of various compounds,[1, 93, 94] then the chemistry and applications of such substrates as **4.24** particularly merits further investigation in order to capitalise on their status as privileged molecules of utility in tackling a range of contemporary synthetic challenges.

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Chapter 5

5.1. General Considerations

All solvents and reagents are commercially available and unless otherwise stated were used as received without prior purification. Sodium azide (≥ 99.99% trace metals basis), S-Phos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, 97%), 1,4-dioxane (anhydrous, 99.8%, Sure/Seal™ packaged), *N*,*N*-dimethylformamide (anhydrous, 99.8%, Sure/Seal™ packaged) and potassium acetate (≥ 99.0%) were obtained from Sigma Aldrich Ltd. Bis(pinacolato)diboron (99%) was purchased from Frontier Scientific Ltd. Sulfonated S-Phos (^{S}S-Phos; Sodium 6'-(dicyclohexylphosphino)-2,6-dimethoxybiphenyl-3-sulfonate) was obtained from Strem Chemicals UK, or Sigma-Aldrich Company Ltd. Palladium acetate (min. 98%, 99.9+%-Pd) was obtained from Strem Chemicals Inc. QuadraPure® TU resin was obtained from Sigma Aldrich Ltd. and used according to the manufacturer's instructions. *N*-bromosuccinimide was recrystallised from boiling water according to the procedure detailed in *Purification of Laboratory Chemicals*; Armarego, W. L. F.; Chai, C. L. L.; 5th Edn., Elsevier. The recrystallised material was subsequently stored at 0-5 °C. TPPMSLi was prepared according to literature procedure.[1] *p*-tolylboronic acid **3.75** was synthesised as described, or purchased from Frontier Scientific Ltd. All batches of this material were analysed prior to use by ^{1}H and ^{11}B NMR using $CDCl_3$ as solvent, and all data was found to be in accordance.

'Petrol' refers to the fraction of petroleum ether boiling in the range of 40-60 °C. Where specific ratios are specified for solvent mixtures, then their compositions are given as a function of individual solvent volumes prior to mixing. HPLC-grade solvents were dried by passage through an Innovative Technology *PureSolv* Solvent Purification System (SPS) and stored under an atmosphere of dry nitrogen prior to use. Solvents obtained in this way and used for palladium- or rhodium- catalysed reactions were first deoxygenated by sparging with nitrogen for a minimum of 15 minutes prior to use. All air-sensitive reactions were performed using standard Schlenk techniques.

Analytical thin layer chromatography (TLC) was performed using commercially available aluminium backed plates coated with Merck Kieselgel 60 0.20 mm (ALUGRAM® sil G/UV254) and visualised under ultra-violet light (at 254 nm) or by staining with either potassium permanganate, or for boronic acids and their derivatives, with curcumin. Flash column chromatography was carried out using Merck Kieselgel 60 H silica gel (63-100 μm). 'Celite' is a registered trademark and refers to diatomaceous earth.

NMR spectra were recorded on a Joel EX-400, Brüker DPX-300 or a Joel GX-270 spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm), with ^{1}H and ^{13}C shifts referenced relative to residual solvent. ^{19}F and ^{11}B shifts were referenced to external standards of neat $CFCl_3$ and 15% $BF_3.Et_2O$ in $CDCl_3$, respectively. Heteroaryl and aryl proton environments are labelled as Ar*H*; while Tz*H*, Bn*H* and Pin*H* refer to protons located on triazole, benzyl and pinacolate ester carbons, respectively. Chemical shifts for ^{13}C spectral data are recorded to one decimal place, except for derivatives of 2,2,2-trifluoro-1-phenylethanone and 1-(4-chlorophenyl)-2,2,2-trifluoroethanone, for which two decimal places are used. Despite repeat analyses of concentrated samples (such that all other ^{13}C signals were more than sufficiently intense and well resolved), all ^{13}C spectra detailed herein were recorded without ^{10}B or ^{11}B decoupling, and as such the signals corresponding to carbon nuclei involved in C-B bonding could not be clearly discerned for certain substrates. HRMS were performed on a Brüker micrOTOF (ESI-TOF) spectrometer.

5.1.1. Safe Preparation and Handling of Azides

All functional group manipulations employing organoazides detailed herein have been performed multiple times without incident. However, particular care was always taken when working with azides. It is widely recommended that any azide be first assessed for stability "on-paper"[2, 3] and if subsequently prepared, that the initial synthesis be performed on a small scale. This helps to ascertain both the stability of the material, and allows correct synthetic and handling procedures to be developed. As such, all organoazide substrates were initially synthesised on significantly smaller scales than may otherwise be detailed herein.

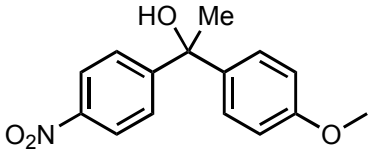
Suppliers' instructions for safe usage, handling, storage and disposal of azide salts should always be followed in full. Sodium azide is toxic and contact with acid liberates toxic HN_3 gas. Heating may cause an explosion. It is incompatible with a range of common solvents, reagents and metal salts due to the potential for formation of explosive derivatives. As such, reactions employing sodium azide were only conducted on materials of known composition, which were carefully dried to remove any halogenated solvents. In particular, and especially because of the degree to which they are otherwise so readily employed, then an awareness of the incompatibility of both DCM and chloroform with azide salts should be kept in mind.

5.2. Experimental Procedures for Chapter 2

5.2.1. Chapter Specific Considerations

For catalyst recycling experiments HPLC-grade diethyl ether was passed through an Innovative Technology Pure-Solv solvent purification system (SPS) and sparged with nitrogen for a minimum of 15 minutes prior to use. Solvents used in reactions, including deionised water and aqueous base solutions, were deoxygenated by sparging with nitrogen for a minimum of 15 minutes prior to use. All reactions were performed using standard Schlenk techniques.

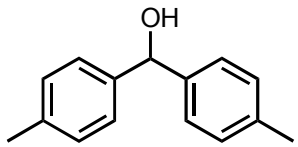
5.2.2. Optimisation of Reaction Conditions for the Rhodium-Catalysed 1,2-Addition Reaction of 4-methoxyphenylboronic acid and 1-(4-nitrophenyl)ethanone: Preparation of 1-(4-methoxyphenyl)-1-(4-nitrophenyl)ethanol (2.129); (Tables 2.13-2.17)



To a 24 mL screw-capped vial equipped with a rubber septum was charged 1-(4-nitrophenyl)ethanone (20.6 mg, 0.125 mmol), 4-methoxyphenylboronic acid (28.5 mg, 0.1875 mmol), $[RhCl(cod)]_2$ (1.23 mg, 2.5 μmol) and ^{S}S-Phos (2.56 mg, 5.0 μmol). The vessel was evacuated before being refilled with nitrogen. Co-solvent was added when indicated (0.75 mL). Nitrogen-sparged aqueous base solution (typically 1.50 mL; 0.75 mL for co-solvent screens) was then introduced with stirring, and the vessel was purged with nitrogen. The vessel was then placed on a preheated carousel plate at the designated temperature for 24 hours. The crude reaction mixture was then allowed to cool and the organic components taken up in diethyl ether (3 × 5.0 mL portions) dried ($MgSO_4$) and concentrated *in vacuo*.

Conversions were determined by ^{1}H NMR, using the ratio of the substituted-acetophenone methyl peak [δH (300 MHz; $CDCl_3$); 2.68 (3H, s, *Me*)], to diarylethanol methyl peak on the ethanolic carbon [δH (300 MHz; $CDCl_3$); 1.94 (3H, s, *Me*)]. Further data for the purified compound can be found in Section 5.2.4.2.

5.2.3. Optimisation Procedure for the Recycling of Rhodium/^{S}S-Phos Complex in the Preparation of di-*p*-tolylmethanol (2.29cc) (Table 2.18, entries 3-7)



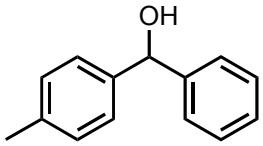
To a 24 mL screw-capped vial equipped with a rubber septum was charged *p*-tolylboronic acid (203.9 mg, 1.50 mmol), $[RhCl(cod)]_2$ (9.9 mg, 0.02 mmol) and ^{S}S-Phos (20.5 mg, 0.04 mmol). The vessel was evacuated before being refilled with nitrogen. Nitrogen-sparged aqueous sodium hydroxide solution (1.50 mL, 0.733 molar) was then introduced with stirring, and the vessel was purged with nitrogen before the addition of 4-methylbenzaldehyde (118 μL, 1.00 mmol). The vessel was then placed on a preheated carousel plate at 80 °C for 2 hours. The reaction mixture was then allowed to cool and the organic components taken up in nitrogen-sparged diethyl ether (3 × 1.0 mL portions) *via* use of a 5 mL syringe and needle, with all collected portions being removed simultaneously, thus ensuring preservation of a nitrogen atmosphere in the reaction vessel. The organic components were then dried ($MgSO_4$) and concentrated *in vacuo*. Prior to the next cycle, remaining traces of diethyl ether were removed *via* sequential evacuation and nitrogen refill, until no organic layer was left visible. Subsequent reactions were performed in the same vessel, with nitrogen atmosphere maintained, by charging *p*-tolylboronic acid (203.9 mg, 1.50 mmol), nitrogen-sparged aqueous sodium hydroxide solution (0.25 mL, 4.40 molar), and 4-methylbenzaldehyde (118 μL, 1.00 mmol) before placing on a preheated carousel plate at 80 °C for 2 hours.

Purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a white solid (Cycle 1: 203.5 mg, 96% yield; Cycle 5: 205.0 mg, 97% yield); δH (300 MHz; $CDCl_3$); 7.27 (4H, d, J = 7.9 Hz, Ar*H*), 7.17 (4H, d, J = 7.9 Hz, Ar*H*), 5.69 (1H, s, $(Ar)_2C(OH)H$), 2.98 (1H, br s, O*H*), 2.38 (6H, s, *Me*); δC (75.5 MHz; $CDCl_3$), 141.1, 136.7, 128.9, 126.3, 75.5, 20.9; Data in accordance with literature reference.[4]

5.2.4. Preparation of 1,1-Diaryl Alcohols *via* the 1,2-addition of Arylboronic Acids with Aryl Aldehydes, Aryl-Methyl Ketones, and 2,2,2-Trifluoroacetophenones (*General Procedure 2A*):

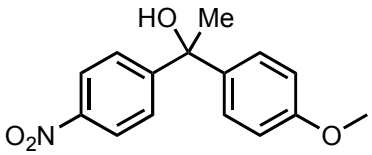
To a 24 mL screw-capped vial equipped with a rubber septum was charged the carbonyl compound (1.00 mmol), arylboronic acid (1.50 mmol), $[RhCl(cod)]_2$ (9.9 mg, 0.02 mmol) and ^{S}S-Phos (20.5 mg, 0.04 mmol). The vessel was evacuated before being refilled with nitrogen. Nitrogen-sparged aqueous sodium hydroxide solution (1.50 mL, 0.733 molar) was then introduced with stirring, and the vessel was purged with nitrogen before being placed on a preheated carousel plate at 80 °C for a period of 2 hours for aldehyde substrates, or 24 hours for ketone substrates. The reaction mixture was then allowed to cool and the organic components taken up in diethyl ether (3 × 5.0 mL portions), dried ($MgSO_4$), and concentrated *in vacuo*.

5.2.4.1. (*rac*)-phenyl(*p*-tolyl)methanol (2.29ac)



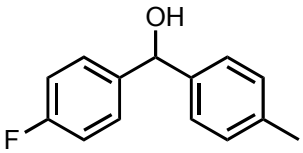
4-Methylbenzaldehyde (118 μL, 1.00 mmol) and phenylboronic acid (182.9 mg, 1.50 mmol), were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (171.1 mg, 86% yield); δH (300 MHz; $CDCl_3$); 7.43-7.33 (5H, m, Ar*H*), 7.31 (2H, d, J = 7.9 Hz, Ar*H*), 7.22 (2H, d, J = 7.9 Hz, Ar*H*), 5.77 (1H, s, (Ar)(Ar')C(OH)*H*), 2.93 (1H, br s, O*H*), 2.43 (3H, s, *Me*); δC (75.5 MHz; $CDCl_3$), 144.0, 141.0, 137.1, 129.1, 128.4, 127.4, 126.6, 126.5, 75.9, 21.2; Data in accordance with literature reference.[5]

5.2.4.2. (*rac*)-1-(4-methoxyphenyl)-1-(4-nitrophenyl)ethanol (2.129)



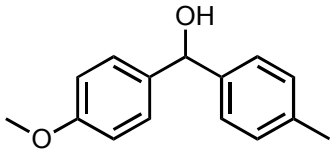
1-(4-Nitrophenyl)ethanone (165.2 mg, 1.00 mmol) and 4-methoxyphenylboronic acid (759.8 mg, 5.00 mmol), were reacted according to *general procedure 2A*, purification by column chromatography eluting at 4:1 petrol/diethyl ether generated the title compound as a pale-yellow solid (186.1 mg, 68% yield); δH (300 MHz; $CDCl_3$); 8.10 (2H, d, J = 9.0 Hz, Ar*H*), 7.56 (2H, d, J = 9.0 Hz, Ar*H*), 7.30 (2H, d, J = 9.0 Hz, Ar*H*), 6.84 (2H, d, J = 9.0 Hz, Ar*H*), 3.77 (3H, s, O*Me*), 2.63 (1H, s, O*H*), 1.94 (3H, s, *Me*); δC (75.5 MHz; $CDCl_3$), 158.8, 155.7, 146.5, 138.7, 127.1, 126.5, 123.2, 113.7, 75.5, 55.2, 30.5; ESI-HRMS (m/z): calcd for $C_{15}H_{15}NNaO_4$ $[M+Na]^+$ 296.0908, found: 296.0899.

5.2.4.3. (*rac*)-(4-fluorophenyl)(*p*-tolyl)methanol (2.29cd, Table 2.18, entry 1)



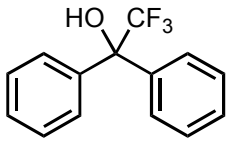
4-Fluorobenzaldehyde (107 μL, 1.00 mmol) and *p*-tolylboronic acid (203.9 mg, 1.50 mmol), were reacted according to *general procedure 2A*, purification by column chromatography eluting at 4:1 petrol/diethyl ether generated the title compound as a colourless oil (197.6 mg, 91% yield); δH (300 MHz; $CDCl_3$); 7.36-7.30 (2H, m, Ar*H*), 7.24 (2H, d, J_{H-H} = 8.3 Hz, Ar*H*), 7.17 (2H, d, J_{H-H} = 7.9 Hz, Ar*H*), 7.06-6.98 (2H, m, Ar*H*), 5.76 (1H, s, (Ar)(Ar')C(OH)*H*), 2.49 (1H, br s, O*H*), 2.36 (3H, s, *Me*); δC (75.5 MHz; $CDCl_3$), 140.8, 139.7, 137.4, 129.2, 128.1 (d, J_{C-F} = 8.1 Hz), 126.4, 115.3, 115.0, 75.3, 21.0; Data in accordance with literature reference.[6]

5.2.4.4. (*rac*)-(4-methoxyphenyl)(*p*-tolyl)methanol (2.29bc, Table 2.18, entry 2)



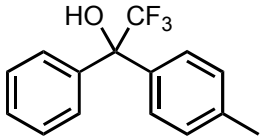
4-Methoxybenzaldehyde (122 μL, 1.00 mmol) and *p*-tolylboronic acid (203.9 mg, 1.50 mmol), were reacted according to *general procedure 2A*. Crude ^{1}H NMR data shows 97% conversion, and is consistent with literature data for product.[4] Purification attempts resulted in a complex mixture due to degradation, giving predominantly the oxidised product, (4-methoxyphenyl)(*p*-tolyl)methanone, and for which the ^{1}H NMR was also consistent with literature data.[7]

5.2.4.5. 2,2,2-trifluoro-1,1-diphenylethanol (2.91aa, Table 2.19, entry 1)



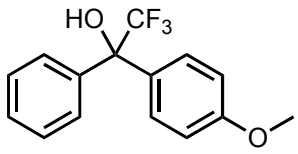
2,2,2-Trifluoro-1-phenylethanone (140 μL, 1.00 mmol) and phenylboronic acid (182.9 mg, 1.50 mmol) were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (218.1 mg, 87% yield); δH (300 MHz; $CDCl_3$), 7.61-7.55 (4H, m, Ar*H*), 7.45-7.39 (6H, m, Ar*H*), 3.05 (1H, s, O*H*); δC (75.5 MHz; $CDCl_3$), 139.31, 128.58, 128.20, 127.40, 125.31 (q, J_{C-F} = 286 Hz), 79.47 (q, J_{C-F} = 29 Hz); δF (376.5 MHz; $CDCl_3$), -74.21; Data in accordance with literature reference.[8]

5.2.4.6. (*rac*)-2,2,2-trifluoro-1-phenyl-1-*p*-tolylethanol (2.91ac, Table 2.19, entry 2)



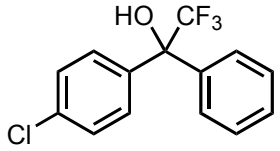
2,2,2-Trifluoro-1-phenylethanone (140 μL, 1.00 mmol) and *p*-tolylboronic acid (203.9 mg, 1.50 mmol) were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (239.0 mg, 90% yield); δH (300 MHz; $CDCl_3$), 7.44-7.40 (2H, m, Ar*H*), 7.31-7.25 (5H, m, Ar*H*), 7.10-7.07 (2H, m, Ar*H*), 2.88 (1H, s, O*H*), 2.27 (3H, m, *Me*); δC (75.5 MHz; $CDCl_3$), 139.43, 138.49, 136.50, 128.91, 128.49, 128.13, 127.38 (q, J_{C-F} = 1.86 Hz), 127.29 (q, J_{C-F} = 1.86 Hz), 125.37 (q, J_{C-F} = 286 Hz), 79.36 (q, J_{C-F} = 29 Hz), 20.90; δF (376.5 MHz; $CDCl_3$), -74.38; Data in accordance with literature reference.[8]

5.2.4.7. (*rac*)-2,2,2-trifluoro-1-(4-methoxyphenyl)-1-phenylethanol (2.91ab, Table 2.19, entry 3)



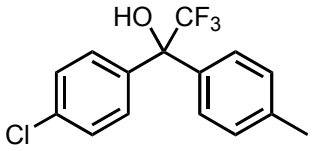
2,2,2-Trifluoro-1-phenylethanone (140 μL, 1.00 mmol) and 4-methoxyphenylboronic acid (227.9 mg, 1.50 mmol) were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (251.8 mg, 89% yield); δH (300 MHz; $CDCl_3$), 7.61-7.58 (2H, m, Ar*H*), 7.48 (2H, d, J_{H-H} = 8.7 Hz, Ar*H*), 7. 44-7.39 (3H, m, Ar*H*), 6.91 (2H, d, J_{H-H} = 8.7 Hz, Ar*H*), 3.79 (3H, s, O*Me*), 3.41 (1H, br s, O*H*); δC (75.5 MHz; $CDCl_3$), 139.54, 131.63, 128.75 (q, J_{C-F} = 1.86 Hz), 128.45, 128.09, 127.37 (q, J_{C-F} = 1.86 Hz), 125.40 (q, J_{C-F} = 287 Hz), 113.50, 79.12 (q, J_{C-F} = 29 Hz), 55.04; δF (376.5 MHz; $CDCl_3$), -74.39; Data in accordance with literature reference.[9]

5.2.4.8. (*rac*)-1-(4-chlorophenyl)-2,2,2-trifluoro-1-phenylethanol (2.91ba, Table 2.19, entry 5)



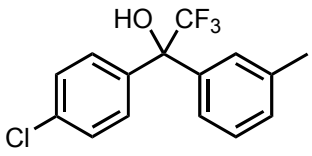
1-(4-Chlorophenyl)-2,2,2-trifluoroethanone (149 µL, 1.00 mmol) and phenylboronic acid (182.9 mg, 1.50 mmol) were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (224.2 mg, 78% yield); δH (300 MHz; $CDCl_3$), 7.55-7.34 (9H, m, Ar*H*), 3.05 (1H, s, O*H*); δC (75.5 MHz; $CDCl_3$), 138.98, 137.66, 134.75, 128.94 (q, J_{C-F} = 1.86 Hz), 128.88, 128.43, 128.38, 127.24 (q, J_{C-F} = 1.86 Hz), 125.11 (q, J_{C-F} = 286 Hz), 79.14 (q, J_{C-F} = 29 Hz); δF (376.5 MHz; $CDCl_3$), -74.18; Data in accordance with literature reference.[9]

5.2.4.9. (*rac*)-1-(4-chlorophenyl)-2,2,2-trifluoro-1-*p*-tolylethanol (2.91bc, Table 2.19, entry 6)



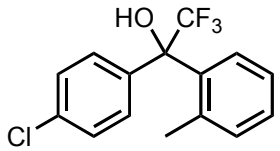
1-(4-Chlorophenyl)-2,2,2-trifluoroethanone (149 µL, 1.00 mmol) and *p*-tolylboronic acid (203.9 mg, 1.50 mmol) were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (282.3 mg, 94% yield); δH (300 MHz; $CDCl_3$), 7.48 (2H, d, J_{H-H} = 8.5 Hz, Ar*H*), 7.41 (2H, d, J_{H-H} = 8.5 Hz, Ar*H*), 7.36 (2H, d, J_{H-H} = 8.6 Hz, Ar*H*), 7.23 (2H, d, J_{H-H} = 8.6 Hz, Ar*H*), 3.04 (1H, s, O*H*), 2.41 (3H, s, *Me*); δC (75.5 MHz; $CDCl_3$), 139.00, 137.95, 136.30, 134.79, 129.29, 129.10 (app. d, J_{C-F} = 1.71 Hz), 128.45, 127.30 (q, J_{C-F} = 1.75 Hz), 125.30 (q, J_{C-F} = 286 Hz), 79.21 (q, J_{C-F} = 29 Hz), 21.12; δF (376.5 MHz; $CDCl_3$), -74.57; Data in accordance with literature reference.[9]

5.2.4.10. (*rac*)-1-(4-chlorophenyl)-2,2,2-trifluoro-1-*m*-tolylethanol (2.91bk, Table 2.19, entry 7)



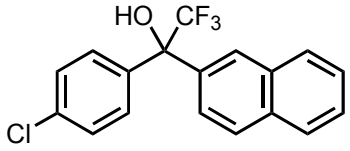
1-(4-Chlorophenyl)-2,2,2-trifluoroethanone (149 μL, 1.00 mmol) and *m*-tolylboronic acid (203.9 mg, 1.50 mmol) were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (284.4 mg, 95% yield); δH (300 MHz; $CDCl_3$), 7.52 (2H, d, J_{H-H} = 8.3 Hz, Ar*H*), 7.42-7.24 (6H, m, Ar*H*), 3.13 (1H, s, O*H*), 2.43 (3H, s, *Me*); δC (75.5 MHz; $CDCl_3$), 138.98, 138.25, 137.70, 134.66, 129.63, 128.94 (q, J_{C-F} = 1.86 Hz), 128.32, 128.29, 127.80 (q, J_{C-F} = 1.86 Hz), 125.10 (q, J_{C-F} = 287 Hz), 124.26 (q, J_{C-F} = 1.86 Hz), 79.12 (q, J_{C-F} = 29 Hz), 21.45 ; δF (376.5 MHz; $CDCl_3$), -74.40; Data in accordance with literature reference.[9]

5.2.4.11. (*rac*)-1-(4-chlorophenyl)-2,2,2-trifluoro-1-*o*-tolylethanol (2.91bj, Table 2.19, entry 8)



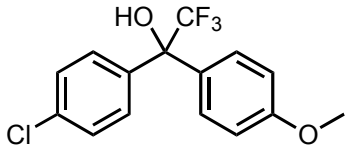
1-(4-Chlorophenyl)-2,2,2-trifluoroethanone (149 μL, 1.00 mmol) and *o*-tolylboronic acid (203.9 mg, 1.50 mmol) were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (274.5 mg, 92% yield); δH (300 MHz; $CDCl_3$), 7.86-7.81 (1H, m, Ar*H*), 7.49-7.37 (6H, m, Ar*H*), 7.30-7.27 (1H, m, Ar*H*), 3.21 (1H, s, O*H*), 2.09 (3H, s, *Me*); δC (75.5 MHz; $CDCl_3$), 138.57, 136.56, 136.51, 134.50, 133.43, 129.13, 129.09, 129.08, 128.10, 126.87 (q, J_{C-F} = 3.7 Hz), 125.39, 125.04 (q, J_{C-F} = 287 Hz), 79.99 (q, J_{C-F} = 27 Hz), 21.20; δF (376.5 MHz; $CDCl_3$), -74.29; Data in accordance with literature reference.[9]

5.2.4.12. (*rac*)-1-(4-chlorophenyl)-2,2,2-trifluoro-1-(naphthalen-2-yl)ethanol (2.91bl, Table 2.19, entry 9)



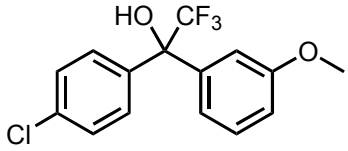
1-(4-Chlorophenyl)-2,2,2-trifluoroethanone (149 μL, 1.00 mmol) and 2-naphthaleneboronic acid (258.0 mg, 1.50 mmol) were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (312.2 mg, 93% yield); δH (300 MHz; $CDCl_3$), 8.07 (1H, br s, Ar*H*), 7.91-7.80 (3H, m, Ar*H*), 7.57-7.31 (7H, m, Ar*H*), 3.02 (1H, br s, O*H*); δC (75.5 MHz; $CDCl_3$), 137.46, 136.00, 134.81, 133.00, 132.50, 129.03 (q, J_{C-F} = 1.86 Hz), 128.61, 128.40, 127.50, 127.06, 126.64, 126.37 (q, J_{C-F} = 1.86 Hz), 125.16 (q, J_{C-F} = 287 Hz), 124.81 (q, J_{C-F} = 1.86 Hz), 79.33 (q, J_{C-F} = 29 Hz); δF (376.5 MHz; $CDCl_3$), -73.77; Data in accordance with literature reference.[9]

5.2.4.13. (*rac*)-1-(4-chlorophenyl)-2,2,2-trifluoro-1-(4-methoxyphenyl)ethanol (2.91bb, Table 2.19, entry 10)



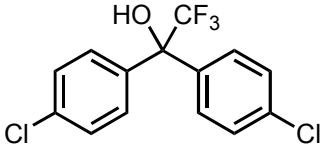
1-(4-Chlorophenyl)-2,2,2-trifluoroethanone (149 μL, 1.00 mmol) and 4-methoxyphenylboronic acid (227.9 mg, 1.50 mmol) were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (300.9 mg, 95% yield); δH (300 MHz; $CDCl_3$), 7.45 (2H, d, J_{H-H} = 8.5 Hz, Ar*H*), 7.39 (2H, d, J_{H-H} = 8.5 Hz, Ar*H*), 7.34 (2H, d, J_{H-H} = 8.9 Hz, Ar*H*), 6.87 (2H, d, J_{H-H} = 8.9 Hz, Ar*H*), 3.79 (3H, s, O*Me*), 3.21 (1H, br s, O*H*); δC (75.5 MHz; $CDCl_3$), 159.62, 137.92, 134.61, 131.24, 128.95 (q, J_{C-F} = 1.86 Hz), 128.66 (q, J_{C-F} = 1.86 Hz), 128.27, 125.18 (q, J_{C-F} = 287 Hz), 113.71, 78.87 (q, J_{C-F} = 29 Hz), 55.18; δF (376.5 MHz; $CDCl_3$), -74.64; Data in accordance with literature reference.[9]

5.2.4.14. (*rac*)-1-(4-chlorophenyl)-2,2,2-trifluoro-1-(3-methoxyphenyl)ethanol (2.91bm, Table 2.19, entry 11)



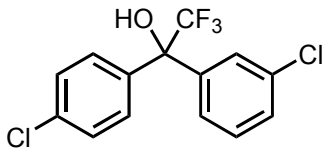
1-(4-Chlorophenyl)-2,2,2-trifluoroethanone (149 µL, 1.00 mmol) and 3-methoxyphenylboronic acid (227.9 mg, 1.50 mmol) were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (303.6 mg, 96% yield); δH (300 MHz; $CDCl_3$), 7.47 (2H, d, J_{H-H} = 8.3 Hz, Ar*H*), 7.36 (2H, d, J_{H-H} = 9.0 Hz, Ar*H*), 7.30 (1H, d, J_{H-H} = 8.3 Hz, Ar*H*), 7.10-7.06 (2H, m, Ar*H*), 6.92 (1H, ddd, J_{H-F} = 8.3, 2.6, 1.5 Hz), 3.80 (3H, s, O*Me*), 3.08 (1H, br s, O*H*); δC (75.5 MHz; $CDCl_3$), 159.46, 140.46, 137.51, 134.76, 129.45, 128.85 (q, J_{C-F} = 1.86 Hz), 128.37, 125.03 (q, J_{C-F} = 286 Hz), 119.52 (q, J_{C-F} = 1.86 Hz), 114.00, 113.50 (q, J_{C-F} = 1.86 Hz), 79.02 (q, J_{C-F} = 29 Hz), 55.26; δF (376.5 MHz; $CDCl_3$), -74.53; Data in accordance with literature reference.[9]

5.2.4.15. 1,1-bis(4-chlorophenyl)-2,2,2-trifluoroethanol (2.91bi, Table 2.19, entry 12)



1-(4-Chlorophenyl)-2,2,2-trifluoroethanone (149 µL, 1.00 mmol) and 4-chlorophenylboronic acid (234.6 mg, 1.50 mmol) were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (277.7 mg, 87% yield); δH (300 MHz; $CDCl_3$), 7.43 (4H, d, J_{H-H} = 8.3 Hz, Ar*H*), 7.36 (4H, d, J_{H-H} = 9.0 Hz, Ar*H*), 3.09 (1H, br s, O*H*); δC (75.5 MHz; $CDCl_3$), 137.28, 135.03, 128.79 (q, J_{C-F} = 1.86 Hz), 128.57, 124.87 (q, J_{C-F} = 287 Hz), 78.84 (q, J_{C-F} = 29 Hz); δF (376.5 MHz; $CDCl_3$), -74.67; Data in accordance with literature reference.[8]

5.2.4.16. (*rac*)-1-(3-chlorophenyl)-1-(4-chlorophenyl)-2,2,2-trifluoroethanol (2.91bn, Table 2.19, entry 13)



1-(4-Chlorophenyl)-2,2,2-trifluoroethanone (149 μL, 1.00 mmol) and 3-chlorophenylboronic acid (234.6 mg, 1.50 mmol) were reacted according to *general procedure 2A*, purification by column chromatography eluting at 9:1 petrol/diethyl ether generated the title compound as a colourless oil (263.2 mg, 82% yield); δH (300 MHz; $CDCl_3$), 7.64 (1H, br m, Ar*H*), 7.53 (2H, d, J_{H-H} = 8.3 Hz, Ar*H*) 7.48-7.35 (5H, m, Ar*H*), 3.17 (1H, s, O*H*); δC (75.5 MHz; $CDCl_3$), 140.69, 137.07, 135.11, 134.50, 129.63, 129.12, 128.75 (q, J_{C-F} = 1.86 Hz), 128.62, 127.56 (q, J_{C-F} = 1.86 Hz), 125.51 (q, J_{C-F} = 1.86 Hz), 124.80 (q, J_{C-F} = 287), 78.81 (q, J_{C-F} = 29 Hz); δF (376.5 MHz; $CDCl_3$), -74.60; Data in accordance with literature reference.[9]

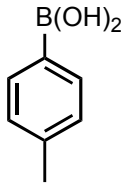
5.3. Experimental Procedures for Chapter 3

5.3.1. Chapter Specific Considerations

Attention is drawn to the safety notes on organoazides listed under the General Considerations at the start of this chapter. All air-sensitive reactions were performed using standard Schlenk techniques, while CuAAC reactions were performed in sealed reaction vessels, but with no other attempts to exclude oxygen.

5.3.2. Synthetic Route to Azido-Boronate 3.78

5.3.2.1. Preparation of *p*-tolylboronic acid (3.75)

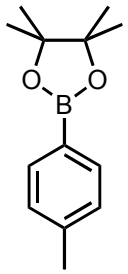


In a typical procedure an oven-dried 250 mL two-neck round bottomed flask with magnetic stirrer was equipped with a rubber septum and allowed to cool under a dry nitrogen atmosphere. Dry THF (125 mL) was then added *via* cannulation. 1-Bromo-4-methylbenzene (**3.74**), purified *via* passing neat through a short plug of neutral alumina (Brockmann I, 50-200 μm) prior to use (7.18 g, 5.17 mL, 42.0 mmol) was then injected into the flask, and the stirred solution was cooled to -78 °C. After 10 minutes a solution of *n*-butyllithium (16.8 mL, 2.5 M in hexanes, 42 mmol) was added dropwise over a period of 10 minutes. The solution was then allowed to warm slightly to ensure thorough mixing of the lithium salts, and stirred at -78 °C for a further 1.5 hours. Triisopropyl borate (9.70 mL, 42.0 mmol) was then added dropwise over 10 minutes, after which the solution was stirred for a further 1.5 hours before being allowed to warm to approximately 0 – 10 °C, whereupon water (10 mL) was added slowly. The resultant solution was then partitioned between water (100 mL), saturated aqueous NH_4Cl (15 mL), and diethyl ether (75 mL). The organic components were separated and the aqueous layer washed with further diethyl ether (3 × 50 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The resultant solid was further dried in a vacuum dessicator for 1-2 hours, to generate the title compound as a white to off-white powder (4.85 g, 85% yield), which was used without further purification.

δH (400 MHz; $CDCl_3$) 8.13 (2H, d, J = 7.7 Hz, Ar*H*), 7.32 (2H, d, J = 7.7 Hz, Ar*H*), 2.45 (3H, s, *Me*); δC (100.6 MHz; $CDCl_3$), 143.1, 135.9, 128.9, 22.1; δB (96.3 MHz; $CDCl_3$) 32.44; ESI-HRMS (m/z): calcd for $C_7H_8BO_2$ $[M]^-$ 135.0617, found: 135.0619.

Data for this compound was consistent with that recorded for the commercially sourced material (see general considerations).

5.3.2.2. Preparation of 4,4,5,5-tetramethyl-2-*p*-tolyl-1,3,2-dioxaborolane (3.76)

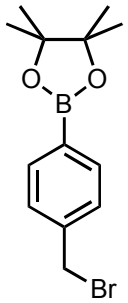


In a typical procedure, to a 100 mL round bottom flask fitted with a magnetic stirrer was added *p*-tolylboronic acid (**3.75**) (4.89 g, 36.0 mmol), anhydrous pinacol (4.68 g, 39.6 mmol), and diethyl ether (50 mL). After stirring for 5 minutes $MgSO_4$ (c. 5 g) was added and the flask sealed with a rubber septum. The reaction was stirred vigorously overnight at room-temperature, the solids were then removed by filtration, and washed with diethyl ether (3 × 25 mL). The crude filtrate was then concentrated *in vacuo* and redissolved in petrol, before being passed through a plug of silica slurried with petrol. The silica was washed with further portions of petrol and the resultant solution was concentrated *in vacuo* and thoroughly dried under vacuum to generate the title compound as a white crystalline solid (7.81 g, 99.5% yield) which was used without further purification. If necessary the product was forced to crystallise by cooling the flask briefly on a bed of dry-ice.

δH (300 MHz; $CDCl_3$) 7.76 (2H, d, J = 8.0 Hz, Ar*H*), 7.22 (2H, d, J = 8.2 Hz, J = 0.7 Hz, Ar*H*), 2.40 (3H, s, *Me*), 1.37 (12H, s, Pin*H*); δC (75.5 MHz; $CDCl_3$), 141.4, 134.9, 128.6, 83.7, 25.0, 21.8; δB (96.3 MHz; $CDCl_3$) 31.7; ESI-HRMS (m/z): calcd for $C_{13}H_{19}BNaO_2$ $[M+Na]^+$ 241.1376, found: 241.1352.

Data in accordance with literature reference.[10]

5.3.2.3. Preparation of 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.77)



This reaction should be performed in a well-ventilated fumehood. Acetone is incompatible with AIBN and thus glassware used was carefully dried before use. During the reflux step droplets of condensate should lose most of their colour over the course of the reaction, indicating minimal amounts of bromine remains. If the reaction is still reasonably brown in colour care should be taken to avoid exposure to any vapours.

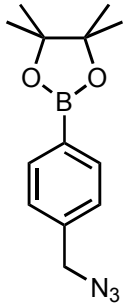
In a typical procedure, to a 500 mL round bottom flask fitted with a magnetic stirrer was added 4,4,5,5-tetramethyl-2-*p*-tolyl-1,3,2-dioxaborolane (**3.76**) (7.42 g, 34.0 mmol), *N*-bromosuccinimide (6.05 g, 34.0 mmol), and acetonitrile (250 mL). The solution was stirred for 5 minutes prior to the addition of AIBN (112 mg, 0.68 mmol, 2 mol%). A condensor was then fitted to the flask and the solution refluxed at 90 °C for 4 hours under an air atmosphere. After cooling to room temperature the solution was concentrated on a rotary evaporator, using two portions of ethyl acetate (c. 75 mL) to azeotropically remove the remaining acetonitrile. The crude material was then slurried with petrol (c. 25 mL) and filtered through a plug of silica, eluting with petrol. The resulting solution was then concentrated *in vacuo*, and dried under high vacuum if necessary. The crystalline product that formed was then washed with a small amount of petrol and recrystallised from minimal petrol to generate the title compound as large colourless crystals (7.17 g, 71% yield). Careful recrystallization of the retained mother-liquors and washes yielded further product upon concentration and cooling (0.92 g, 9% yield; total 80% yield).

δH (400 MHz; $CDCl_3$) 7.79 (2H, d, J = 8.2 Hz, Ar*H*) 7.39 (2H, d, J = 8.2 Hz, Ar*H*), 4.49 (2H, s, Bn*H*) 1.34 (12H, s, Pin*H*); δC (100.6 MHz; $CDCl_3$), 140.8, 135.4, 128.4, 84.0, 33.4,

25.0; δB (96.3 MHz; $CDCl_3$) 31.5; a satisfactory mass spectrum of this compound could not be obtained.

Data in accordance with literature reference.[11]

5.3.2.4. Preparation of 2-(4-(azidomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.78)



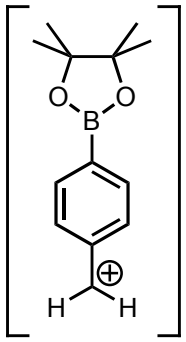
In a typical procedure, to a 250 mL round bottom flask fitted with a magnetic stirrer was added 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3.77**) (6.53 g, 22.0 mmol), ethanol (125 mL), the solution was briefly stirred and sodium azide (1.57 g, 24.2 mmol) was then added. After 5 minutes the flask was carefully sealed with a rubber septum and stirred vigorously at room temperature for 24 hours. The solvent was predominantly removed under a flow of nitrogen, petrol (c. 25 mL) was then added and the solution further evaporated. $MgSO_4$ (c. 2.5 g) and petrol (c. 25 mL) were added and the resultant solution was plugged through a pad of silica on celite, and washed through with petrol. The resulting solution was then **carefully** concentrated *in vacuo*, and if necessary any traces of remaining salts or discolouration were removed by a further plug step. Careful removal of remaining solvent under high vacuum resulted in a viscous colourless oil, which crystallised after standing or cooling to generate the title compound as, depending on the rate of crystallisation, either colourless crystals or a white crystalline solid (5.67 g, 99.5% yield).

δH (400 MHz; $CDCl_3$) 7.88 (2H, d, J = 8.0 Hz, Ar*H*), 7.32 (2H, d, J = 8.0 Hz, Ar*H*), 4.32 (2H, s, Bn*H*), 1.36 (12H, s, Pin*H*); δC (100.6 MHz; $CDCl_3$) 138.4, 135.4, 127.5, 83.9, 54.7, 24.9; δB (96.3 MHz; $CDCl_3$) 31.6;

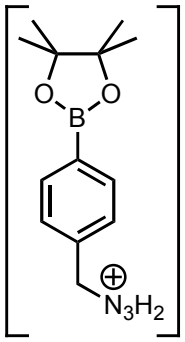
Though multiple ESI-HRMS analyses were performed on **3.78**, the parent-ion peak was not directly observed, as the following species seem to preferentially form *in situ*:

ESI-HRMS (m/z): calcd for $C_{13}H_{18}BO_2$ $[M]^+$ 217.1394, found: 217.1393

ESI-HRMS (m/z): calcd for $C_{13}H_{20}BN_3O_2$ $[M+H_2]^+$ 261.1643, found: 261.1654



$C_{13}H_{18}BO_2^+$
Exact Mass: 217.1394



$C_{13}H_{20}BN_3O_2^+$
Exact Mass: 261.1643

Crystal structure data for **3.78** can be obtained from the Cambridge Crystallographic Database Centre, entry number 747986.

5.3.2.4.1. Stability of 3.78:

During early syntheses of **3.78** it was observed that some improperly purified batches did discolour slightly on long-term storage. Therefore all material was subsequently purified by passage through a short plug of silica, eluting with petrol, concentrated *in vacuo*, and dried thoroughly under high vacuum. If necessary this step was repeated until it yielded a colourless liquid, from which was obtained either colourless crystals or a white crystalline solid (depending on the rate of crystallisation), at which point the material was suitable for long-term storage. It should also be noted that this procedure typically returned the product in effectively quantitative yield, and therefore the actual level of degradation occurring appears to be minimal.

Separately synthesised batches of **3.78** have been produced on varying scales; their spectral data, appearance, and stability to-date being in agreement. This includes material derived from commercially sourced **3.75**, and also that prepared using alternative batches of all other reagents and solvents.

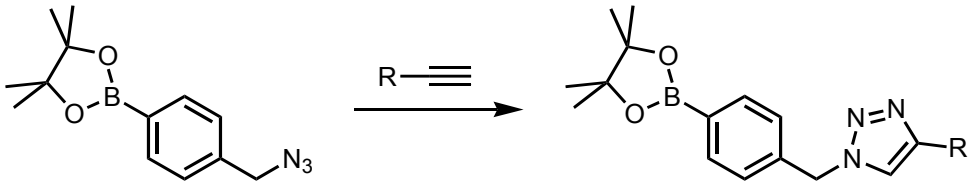
To test the stability of **3.78**, samples from two separately prepared batches were stored open to the air in un-capped glass sample vials in a laboratory cupboard, but with no intentional

precautions to protect against occasional exposure to light. Typical ambient temperature of the laboratory is c. 22-26 °C, and annual range is c. 18-28 °C. After a period of nine months the samples remained visibly unchanged. ^{1}H NMR analysis showed neither any noticeable appearance of new signals due to formation of degradants, nor a change in shift of the benzylic protons, suggesting the azide moiety was unchanged. ^{11}B NMR also confirmed the integrity of the boronate centre.

5.3.2.4.2. Initial CuAAC Reactivity of 3.78 with Phenylacetylene (3.2a) - (Table 3.2, entries 1-6)

In a procedure otherwise identical to *general procedure 3A* (see below), **3.78** (0.50 mmol) and **3.2a** (0.55 mmol), where reacted in the presence of the specified solvent (1.0 mL), copper (I) iodide (0.1 mmol), and where noted, additive (0.55 mmol). Entries 1-3 were periodically monitored by TLC, and after 18 hours at room temperature, conversion was also found to be minimal by ^{1}H NMR analysis. The reactions were then subjected to heating for a further 6 hours at 60°C, and analysed by ^{1}H and ^{11}B NMR spectroscopy. These experiments revealed a slow rate of reaction with **3.2a** in the absence of additive, though **3.78** appeared otherwise unaffected by extended exposure to sub-stoichiometric CuI, even when heated.

5.3.3. Preparation of 1-(4'-pinacolylboronate-benzyl)-4-substituted-1,2,3-triazoles (3.81a-e), *via* the Copper-Catalysed Azide Alkyne Cycloaddition (CuAAC) of 3.78 and Terminal Alkynes (3.2a-e) (Table 3.3) (*General Procedure 3A*):

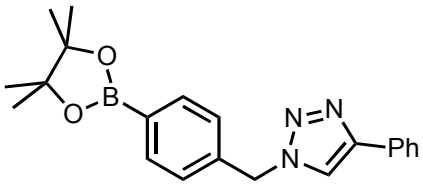


All reactions were performed under an air atmosphere, with no attempts made to preclude oxygen or moisture. To a 10 mL microwave tube equipped with a magnetic stirrer was charged **3.78** (259.1 mg, 1.0 mmol), alkyne (**3.2**) (1.1 mmol), *N*,*N*-diisopropylethylamine (0.19 mL, 1.1 mmol), and 1:1 tBuOH/water (2.0 mL). Rapid stirring was initiated, after which copper (I) iodide (38.1 mg, 0.2 mmol) was added and the vessel quickly sealed with a crimp-top Teflon® cap. The heterogeneous mixture was stirred for 5 minutes at room temperature then placed on a preheated carousel plate and vigorously stirred at 60 °C for 1 hour, unless otherwise stated. The reaction mixture was then allowed to cool, and the organic components extracted with ethyl acetate (3 × 15 mL), from water (20 mL) and saturated aqueous NH_4Cl (2.0 mL). The combined organic layers were dried ($MgSO_4$), filtered through celite, and concentrated *in vacuo* to yield the crude triazole. Unless otherwise stated the crude product was plugged through a short column of silica, eluting sequentially with 9:1 petrol/diethyl ether, ethyl acetate, and DCM. The products typically eluted in ethyl acetate and/or DCM fractions. They were further purified by careful recrystallisation from DCM layered with diethyl ether/petrol mixtures; the mother liquors yielding further material on concentration.

It should be noted that crude products were often obtained in quantitative yield and ≥ 95% purity by ^{1}H NMR. However, discolouration of the crude material was frequently observed as 1,2,3-triazoles are noted to have a high affinity for copper species.[12, 13] Therefore, subsequent purification was often difficult and normally resulted in disproportionate attrition of the yield on this scale. For example, **3.81a** was obtained in a 72% yield using the above procedure, compared to a 95% yield using an alternative method on a 3 mmol scale (see relevant compound for details).

During subsequent work on the Suzuki couplings of **3.81a** we found QuadraPure TU resin to be the best method of those tested for removing metal contaminants. However, by visually monitoring the degree of colouration over time, it still appeared to be less effective at removing residual copper than it was at removing residual palladium from any 1,2,3-triazole derivatives treated in this way.

5.3.3.1. 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-4-phenyl-1,2,3-triazole (3.81a)



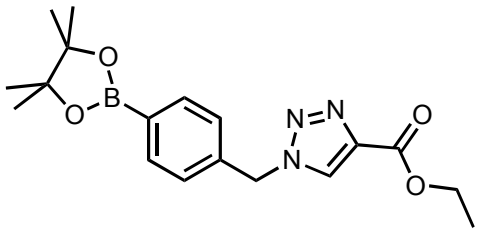
Phenylacetylene (**3.2a**) (121 μL, 1.1 mmol) was reacted with **3.78** using *general procedure 3A*, the crude material was recrystallised from DCM layered with diethyl ether, and the solid washed rapidly with cold diethyl ether. Further material was obtained on repeated concentration and recrystallisation of the mother liquors and washings, to generate the title compound as colourless crystals (259.7 mg, 72% total yield).

Alternatively, to a 24 mL screw-capped vial equipped with a magnetic stirrer and rubber septum was charged phenylacetylene (362 μL, 3.3 mmol), **3.78** (777.3 mg, 3.0 mmol), 1:1 *t*-BuOH/water (6.0 mL), and sodium ascorbate (238 mg, 1.2 mmol). The mixture was vigourously stirred for two minutes, after which $CuSO_4.5H_2O$ (150 mg, 0.6 mmol) was added rapidly and the vial sealed. The mixture was stirred vigourously for 24 hours at room temperature, at which point it had formed a bright yellow emulsion, to which was added water (50 mL), and the organic components extracted with ethyl acetate (3 × 25 mL), dried ($MgSO_4$), filtered through celite eluting with ethyl acetate, and concentrated *in vacuo*. The crude product was recrystallised as detailed above, to generate the title compound as colourless crystals (1.025 g, 95% yield).

δH (400 MHz; $CDCl_3$), 7.84-7.82 (2H, m, Ar*H*), 7.80-7.78 (2H, m, Ar*H*), 7.64 (1H, s, Tz*H*), 7.41-7.37 (2H, m, Ar*H*), 7.32-7.29 (3H, m, Ar*H*) 5.57 (2H, s, Bn*H*), 1.34 (12H, s, Pin*H*); δC (100.6 MHz; $CDCl_3$), 148.6, 137.8, 135.9, 130.8, 129.1, 128.5, 127.6, 126.0, 119.8, 84.3,

54.6, 25.2; δB (96.3 MHz; $CDCl_3$), 31.50; ESI-HRMS (m/z): calcd for $C_{21}H_{25}BN_3O_2$ $[M+H]^+$ 362.2040, found: 362.2026.

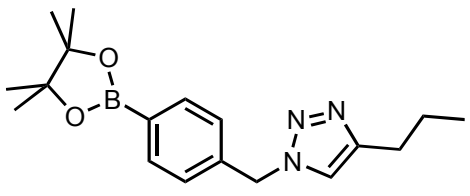
5.3.3.2. Ethyl 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,2,3-triazole-4-carboxylate (3.81b)



Ethyl propiolate (**3.2b**) (111 μL, 1.1 mmol) was reacted with **3.78** using *general procedure 3A*, and purified to generate the title compound as colourless crystals (278.5 mg, 78% yield).

δH (300 MHz; $CDCl_3$) 7.93 (1H, s, Tz*H*), 7.82 (2H, d, J = 8.2 Hz, Ar*H*), 7.27 (2H, d, J = 8.2 Hz, Ar*H*), 5.58 (2H, s, Bn*H*), 4.39 (2H, q, J = 7.1 Hz, OC*H*$_2$Me), 1.37 (3H, t, J = 7.1 Hz, OCH$_2$*Me*), 1.34 (12H, s, Pin*H*); δC (75.5 MHz; $CDCl_3$), 160.7, 136.5, 135.8, 127.6, 127.5, 127.4, 84.2, 61.5, 54.6, 25.0, 14.4; δB (96.3 MHz; $CDCl_3$) 33.7; ESI-HRMS (m/z): calcd for $C_{18}H_{24}BN_3NaO_4$ $[M+Na]^+$ 380.1758, found: 380.1764.

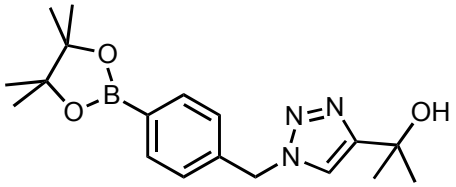
5.3.3.3. 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-4-propyl-1,2,3-triazole (3.81c)



1-Pentyne (**3.2c**) (108 μL, 1.1 mmol) was reacted with **3.78** using *general procedure 3A*, and purified to generate the title compound as colourless crystals (301.0 mg, 92% yield).

δH (300 MHz; $CDCl_3$) 7.73 (2H, d, J = 8.1 Hz, Ar*H*), 7.17 (2H, d, J = 8.1 Hz, Ar*H*), 7.14 (1H, s, Tz*H*), 5.42 (2H, s, Bn*H*), 2.58 (2H, t, J = 7.5 Hz, TzC$H_2$$CH_2$Me), 1.58 (2H, app. sextet, J = 7.4 Hz, $TzCH_2CH_2$Me), 1.26 (12H, s, Pin*H*), 0.86 (3H, t, J = 7.4 Hz, $TzCH_2CH_2$*Me*); δC (75.5 MHz; $CDCl_3$) 148.6, 137.8, 135.3, 127.1, 120.6, 83.9, 53.8, 27.6, 24.8, 22.5, 13.7; δB (96.3 MHz; $CDCl_3$) 31.5; ESI-HRMS (m/z): calcd for $C_{18}H_{27}BN_3O_2$ $[M+H]^+$ 328.2196, found: 328.2184.

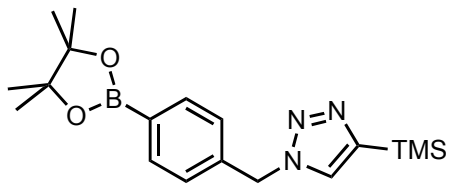
5.3.3.4. 2-(1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,2,3-triazol-4-yl)propan-2-ol (3.81d)



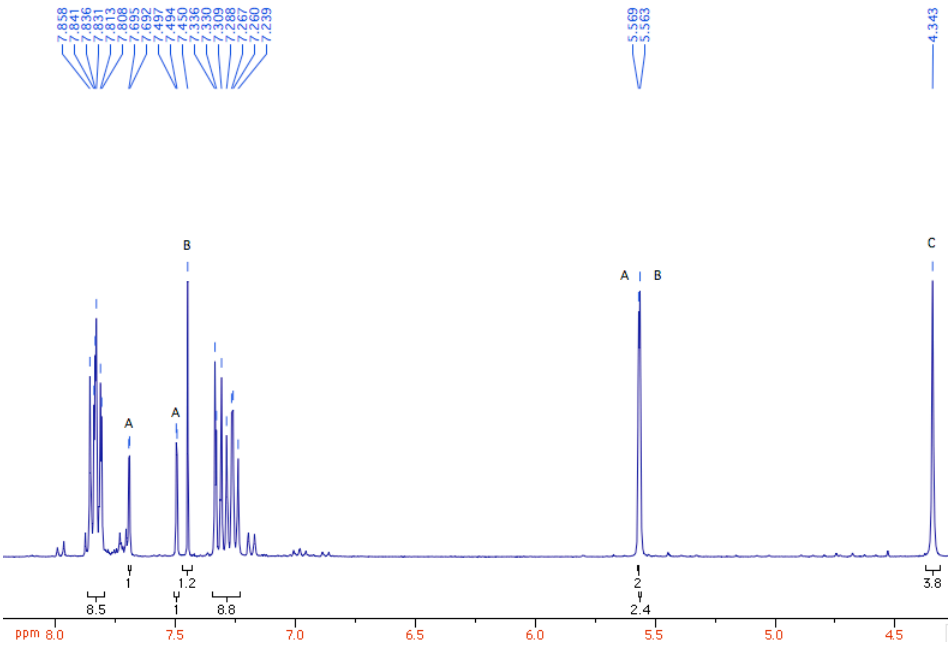
2-Methylbut-3-yn-2-ol (**3.2d**) (107 μL, 1.1 mmol) was reacted with **3.78** using *general procedure 3A*, and purified to generate the title compound as large colourless crystals (308.3 mg, 90% yield).

δH (300 MHz; $CDCl_3$) 7.75 (2H, d, J = 8.0 Hz, Ar*H*), 7.33 (1H, s, Tz*H*), 7.20 (2H, d, J = 8.0 Hz, Ar*H*), 5.42 (2H, s, Bn*H*), 3.34 (1H, s, RO*H*), 1.54 (6H, s, R(OH)Me_2), 1.23 (12H, s, Pin*H*); δC (75.5 MHz; $CDCl_3$), 156.2, 137.5, 135.4, 127.4, 119.2, 84.0, 68.4, 54.0, 30.4, 24.8; δB (96.3 MHz; $CDCl_3$), 31.5; ESI-HRMS (m/z): calcd for $C_{18}H_{26}BN_3NaO_3$ $[M+Na]^+$ 366.1965, found: 366.1969.

5.3.3.5. 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-4-(trimethylsilyl)-1,2,3-triazole (3.81e)



Trimethylsilylacetylene (**3.2e**) (283 µL, 2.0 mmol) was reacted with **3.78** for a period of 2 hours in a procedure otherwise identical to *general procedure 3A*. The crude material was analysed by NMR, which showed a c. 55% conversion to two major products, **3.81e** and **3.81f**:

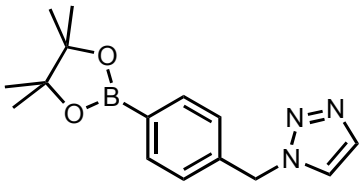


A) (**3.81f**) δH (300 MHz; $CDCl_3$), 7.70 (1.0H, d, J = 1.0 Hz, Tz*H*), 7.50 (1.0H, d, J = 1.0 Hz, Tz*H*), 5.57 (2.0H, s, Bn*H*); (c. 25%);
B) (**3.81e**) δH (300 MHz; $CDCl_3$), 7.45 (1.2H, s, TMS-Tz*H*), 5.56 (2.4H, s, Bn*H*); (c. 30%);
C) (**3.78**) δH (300 MHz; $CDCl_3$), 4.34 (3.8H, s, Bn*H*); (c. 45%);

δB (96.3 MHz; $CDCl_3$), 30.74; (Crude mixture – consistent with 4-(RCH_2)PhBPin); **3.81e**: ESI-HRMS (m/z): calcd for $C_{18}H_{29}BN_3O_2Si$ $[M+H]^+$ 358.2122, found: 358.2121

Initial attempts to separate **3.81e** and **3.81f** *via* silica-gel chromatography were unsuccessful and were not pursued further, as the TMS moiety is potentially labile and the products were shown to co-elute.

5.3.3.6. 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,2,3-triazole (3.81f)



To a dry 100 mL round bottom flask equipped with magnetic stirrer and rubber septum was charged 1.0 mmol equivalent of a crude **3.78**/**3.81f**/**3.81e** reaction mixture (composition as detailed above) in a small volume of dry DCM. The solvent was removed *in vacuo*, and the material dried under high vacuum for 1 minute, before the vessel was purged with nitrogen. This process was repeated three times, after which dry THF (20 mL) was added. The solution was stirred rapidly under a nitrogen atmosphere at room temperature, while TBAF solution (1.5 mL, 1.0 M in THF) was added dropwise over a period of 2 minutes. After a further 2 minutes the vessel was sealed and the solution stirred overnight at room temperature. The solvent was removed *in vacuo*, and the crude residues were purified by passage through a plug of silica, using a gradient elution with petrol and ethyl acetate mixtures. The clean fractions were concentrated *in vacuo*, and the resultant solid was recrystallised from diethyl ether and petrol to generate the title compound as colourless crystals (143.0 mg, 50% overall yield from **3.78**).

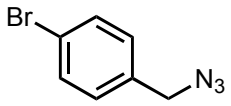
Alternatively, a vacuum-filtration adapter was fitted with a rubber septa on the top port, and Tygon® tubing connected to the T-joint. The end of the tubing was capped with an adapter and needle, followed by an empty 10 mL reaction vessel as a spacer, from which another set of tubing was attached so as to cannula acetylene gas into the reaction mixture. A dry 100 mL round bottom flask with magnetic stirrer was then charged with CaC_2 (c. 1-2 g; 0.3-1.0 mm granulated pieces, technical grade, ≥75% (gas-volumetric), Sigma Aldrich Ltd.) and the vacuum-filtration adapter was attached to the flask. A nitrogen inlet was then introduced through the rubber septa to maintain the CaC_2 under an inert atmosphere. All reagents except the alkyne were charged into a separate 10 mL reaction vessel and sealed, as detailed in *general procedure 3A*. The assembly containing the CaC_2 was then connected to the reaction vessel, and the whole system purged with nitrogen for 1-2 minutes. Water was **carefully** added **dropwise** to the dry stirred CaC_2, liberating acetylene gas, which was bubbled through the reaction mixture for c. 5 minutes (the nitrogen flow was stopped once a reliable flow of acetylene began to be generated). The cannula was then removed from the reaction vessel,

the septa covered with Parafilm®, and the reaction stirred at 60 °C for 1 hour. After which it was cooled and purged again with acetylene for another 5 minutes, before being allowed to react for a further hour at 60 °C. The crude mixture was extracted as detailed in *general procedure 3A*, and recrystallised from diethyl ether and petrol to generate the title compound as colourless crystals (147.0 mg, 52% yield).

δH (300 MHz; $CDCl_3$), 7.81 (2H, d, J = 8.2 Hz, Ar*H*), 7.70 (1H, d, J = 1.0 Hz, Tz*H*), 7.44 (1H, d, J = 1.0 Hz, Tz*H*), 7.25 (2H, d, J = 8.2 Hz, Ar*H*), 5.57 (2H, s, Bn*H*), 1.34 (12H, s, Pin*H*); δC (75.5 MHz; $CDCl_3$), 137.6, 135.6, 134.4, 127.4, 123.4, 84.2, 54.1, 25.0; δB (96.3 MHz; $CDCl_3$), 33.7; ESI-HRMS (m/z): calcd for $C_{15}H_{21}BN_3O_2$ $[M+H]^+$ 286.1721, found: 286.1725.

5.3.4. Preparation and CuAAC Derivitisations of 1-(azidomethyl)-4-bromobenzene (3.83)

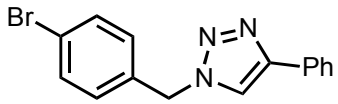
5.3.4.1. 1-(azidomethyl)-4-bromobenzene (3.83)



In a procedure otherwise identical to that used for the preparation and isolation of **3.78**, 1-bromo-4-(bromomethyl)benzene (2.499 g, 10.0 mmol) was dissolved in ethanol (50 mL), and reacted with sodium azide (0.715 g, 11.0 mmol), then purified to generate the title compound as a colourless oil (1.946 g, 92% yield).

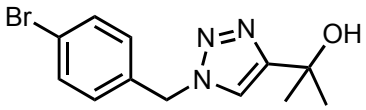
δH (300 MHz; $CDCl_3$), 7.48 (2H, d, J = 8.6 Hz, Ar*H*), 7.15 (2H, d, J = 8.6 Hz, Ar*H*), 4.25 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 134.2, 131.5, 129.4, 121.9, 53.6; Density at ambient temperature was determined to be c. 1.53 g/mL. Data in accordance with the literature reference.[14]

5.3.4.2. 1-(4-bromobenzyl)-4-phenyl-1,2,3-triazole (3.84a)



(This compound was synthesised according to *general procedure 4C* and is equivalent to **4.122**.)

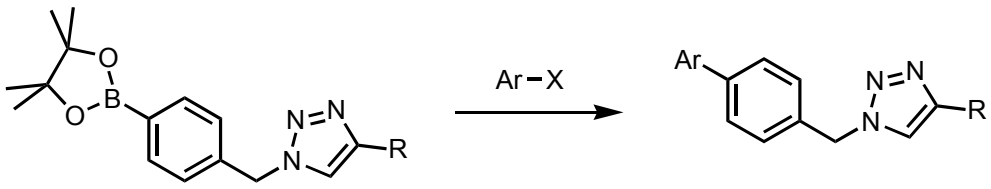
5.3.4.3. 2-(1-(4-bromobenzyl)-1,2,3-triazol-4-yl)propan-2-ol (3.84d)



In a procedure otherwise identical to that used for the preparation and isolation of **3.81d**, **3.83** (212.1 mg, 1.0 mmol), was reacted with 2-methylbut-3-yn-2-ol (**3.2d**) (107 μL, 1.1 mmol), to generate the title compound as colourless crystals (283.3 mg, 96% yield).

δH (300 MHz; $CDCl_3$) 7.50 (2H, d, J = 8.4 Hz, Ar*H*), 7.36 (1H, s, Tz*H*), 7.15 (2H, d, J = 8.4 Hz, Ar*H*), 5.44 (2H, s, Bn*H*), 2.46 (1H, s, RO*H*), 1.60 (6H, s, R(OH)Me_2); δC (75.5 MHz; $CDCl_3$), 151.2, 133.7, 132.4, 129.9, 123.0, 119.2, 68.7, 53.6, 30.6; ESI-HRMS (m/z): calcd for $C_{12}H_{14}BrN_3NaO$ $[M+Na]^+$ 318.0218, found: 318.0228.

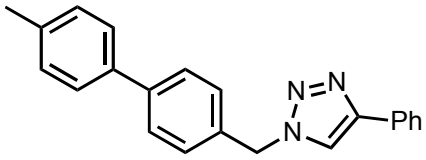
5.3.5. Preparation of 1-(4'-substituted-benzyl)-4-phenyl-1,2,3-triazoles (3.86a-e) *via* the Palladium-Catalysed Suzuki Coupling of 3.81a with Aryl and Heteroaryl Halides (3.85a-e) (Table 3.4) (*General Procedure 3B*):



To a 24 mL screw-capped vial equipped with a magnetic stirrer and rubber septum was charged **3.81a** (180.6 mg, 0.5 mmol), $Pd(OAc)_2$ (2.2 mg, 2.0 mol%), S-Phos (10.3 mg, 5.0 mol%), and K_3PO_4 (anhyd.) (318 mg, 1.5 mmol). The vessel was placed under vacuum and refilled with nitrogen, this process was repeated three times. Stirring was initiated and 9:1 DMF/H_2O (2.0 mL) was quickly injected through the septum. After 5 minutes the aryl or heteroaryl halide (0.75 mmol) was injected through the septum. The reaction was heated to 100 °C for 2 hours with rapid stirring. The reaction mixture was then allowed to cool to room temperature, and water (10 mL) was added to precipitate the product. The crude product was collected by filtration on a grade 3 porosity frit, washed with water (3 × 20 mL) and collected by dissolution in DCM (3 × 20 mL). The organics were dried ($MgSO_4$), filtered through celite and concentrated *in vacuo*.

If necessary the crude material was dissolved in DCM and gently stirred with QuaraPure TU resin until no change in colouration was visible. The material was subsequently plugged through silica, eluting sequentially with 9:1 petrol/diethyl ether, ethyl acetate, and DCM; products typically eluted in ethyl acetate and/or DCM. If necessary the silica was also flushed with methanol. The cleanest fractions were then concentrated *in vacuo*, and further purified by careful recrystallisation from DCM layered with diethyl ether/petrol mixtures; the mother liquors yielded further material on concentration.

5.3.5.1. 1-((4'-methylbiphenyl-4-yl)methyl)-4-phenyl-1,2,3-triazole (3.86a)



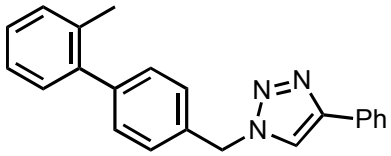
4-Bromotoluene (**3.85a**) (92 μL, 0.75 mmol) was reacted with **3.81a** using *general procedure 3B*, to generate the title compound as colourless crystals (144.9 mg, 89% yield).

Alternatively, 4-chlorotoluene (**3.85a'**) (89 μL, 0.75 mmol) was used in place of 4-bromotoluene, and reacted at 100°C for 5 hours in a procedure otherwise identical to *general procedure 3B*, to generate the title compound as colourless crystals (132.0 mg, 81% yield).

Running the reaction using **3.85a'** according to *general procedure 3B* for the standard 2 hours (which proved sufficient time for complete conversion of **3.81a** in all cases employing aryl and heteroaryl bromides) resulted in only a 54% yield (87.8 mg) of the desired cross-coupling product **3.86a**. However, an additional 32% isolated yield (57.9 mg) of unhydrolysed pinacolboronate ester **3.81a** was obtained after purification of the material recovered *via* ethyl acetate extraction of the combined aqueous phases and filtrate washings.

δH (300 MHz; $CDCl_3$), 7.83-7.79 (2H, m, Ar*H*), 7.70 (1H, s, Tz*H*), 7.62-7.58 (2H, m, Ar*H*), 7.50-7.46 (2H, m, Ar*H*), 7.43-7.24 (7H, m, Ar*H*), 5.61 (2H, s, Bn*H*), 2.40 (3H, s, *Me*); δC (75.5 MHz; $CDCl_3$), 148.4, 141.9, 137.7, 137.4, 133.4, 130.7, 129.7, 128.9, 128.7, 128.3, 127.8, 127.1, 125.8, 119.6, 54.1, 21.3; ESI-HRMS (m/z): calcd for $C_{22}H_{19}N_3Na$ $[M+Na]^+$ 348.1477, found: 348.1476.

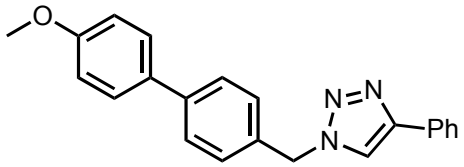
5.3.5.2. 1-((2'-methylbiphenyl-4-yl)methyl)-4-phenyl-1,2,3-triazole (3.86b)



2-Bromotoluene (**3.85b**) (90 μL, 0.75 mmol) was reacted with **3.81a** using *general procedure 3B*, to generate the title compound as colourless crystals (160.7 mg, 99% yield).

δH (300 MHz; $CDCl_3$), 7.77-7.73 (2H, m, Ar*H*), 7.68 (1H, s, Tz*H*), 7.35-7.09 (11H, m, Ar*H*), 5.53 (2H, s, Bn*H*), 2.17 (3H, s, *Me*); δC (75.5 MHz; $CDCl_3$), 148.3, 142.6, 141.0, 135.3, 133.3, 130.6, 130.5, 130.0, 129.8, 128.9, 128.3, 127.9, 127.7, 126.0, 125.8, 119.7, 54.0, 20.6; ESI-HRMS (m/z): calcd for $C_{22}H_{20}N_3$ $[M+H]^+$ 326.1657, found: 326.1656.

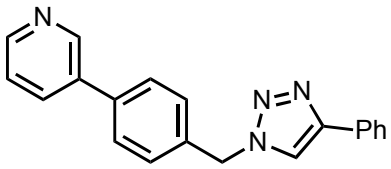
5.3.5.3. 1-((4'-methoxybiphenyl-4-yl)methyl)-4-phenyl-1,2,3-triazole (3.86c)



4-Bromoanisole (**3.85c**) (94 μL, 0.75 mmol) was reacted with **3.81a** using *general procedure 3B*, to generate the title compound as colourless crystals (169.0 mg, 99% yield).

δH (300 MHz; $CDCl_3$), 7.83-7.79 (2H, m, Ar*H*), 7.69 (1H, s, Tz*H*), 7.59-7.55 (2H, m, Ar*H*), 7.54-7.49 (2H, m, Ar*H*), 7.43-7.28 (5H, m, Ar*H*), 7.00-6.96 (2H, m, Ar*H*), 5.61 (2H, s, Bn*H*), 3.85 (3H, s, O*Me*); δC (75.5 MHz; $CDCl_3$), 159.6, 148.4, 141.6, 133.0, 132.8, 130.7, 128.9, 128.7, 128.3, 128.3, 127.5, 125.9, 119.6, 114.5, 55.5, 54.1; ESI-HRMS (m/z): calcd for $C_{22}H_{20}N_3O$ $[M+H]^+$ 342.1606, found: 342.1593.

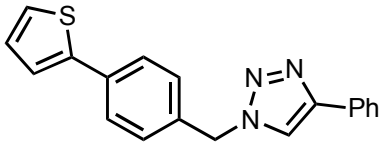
5.3.5.4. 3-(4-((4-phenyl-1,2,3-triazol-1-yl)methyl)phenyl)pyridine (3.86d)



3-Bromopyridine (**3.85d**) (72 μL, 0.75 mmol) was reacted with **3.81a** using *general procedure 3B*, to generate the title compound as colourless crystals (128.1 mg, 82% yield).

δH (300 MHz; $CDCl_3$), 8.81 (1H, br s, Ar*H*), 8.59 (1H, br s, Ar*H*), 7.84-7.78 (3H, m, Ar*H*), 7.73 (1H, s, Tz*H*), 7.56 (2H, d, J = 8.3 Hz, Ar*H*), 7.41-7.27 (6H, m, Ar*H*), 5.60 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 148.9, 148.4, 148.3, 138.4, 135.8, 134.7, 134.4, 130.5, 128.9, 128.8, 128.3, 127.9, 125.8, 123.7, 119.7, 53.8; ESI-HRMS (m/z): calcd for $C_{20}H_{17}N_4$ $[M+H]^+$ 313.1453, found: 313.1444.

5.3.5.5. 4-phenyl-1-(4-(thiophen-2-yl)benzyl)-1,2,3-triazole (3.86e)

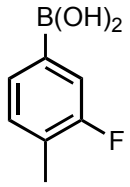


2-bromothiophene (**3.85e**) (73 μL, 0.75 mmol) was reacted with **3.81a** using *general procedure 3B*, to generate the title compound as colourless crystals (117.5 mg, 74% yield).

δH (300 MHz; $CDCl_3$), 7.82-7.78 (2H, m, Ar*H*), 7.69 (1H, s, Tz*H*), 7.65-7.61 (2H, m, Ar*H*), 7.43-7.37 (2H, m, Ar*H*), 7.35-7.29 (5H, m, Ar*H*), 7.10-7.07 (1H, m, Ar*H*), 5.59 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 148.4, 143.4, 135.1, 133.8, 130.6, 129.0, 128.8, 128.3, 128.3, 126.7, 125.8, 125.5, 123.8, 119.6, 54.0; ESI-HRMS (m/z): calcd for $C_{19}H_{16}N_3S$ $[M+H]^+$ 318.1065, found: 318.1063.

5.3.6. Synthetic Route to Azido-Boronate F-3.78

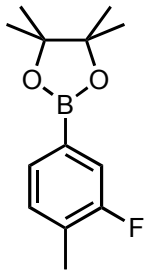
5.3.6.1. Preparation of 3-fluoro-4-methylphenylboronic acid (F-3.75)



In a procedure otherwise identical to that used for the preparation and isolation of **3.75**, 4-bromo-2-fluorotoluene (**F-3.74**) (3.17 mL, 25.0 mmol; Sigma-Aldrich, 99% assay grade, used as received), was dissolved in dry THF (125 mL). Sequential reaction at -78 °C with *n*-butyllithium (17.2 mL, 1.6 M in hexanes, 27.5 mmol) and triisopropyl borate (5.8 mL, 25.0 mmol), generated the title compound as a white powder (3.17 g, 82% yield), which was used without further purification.

δH (400 MHz; $CDCl_3$), 7.41-7.31 (2H, m, Ar*H*), 7.22-7.16 (1H, m, Ar*H*), 2.28 (3H, d, J = 1.3 Hz, *Me*); δC (100.6 MHz; $CDCl_3$), 161.4 (d, J = 244.9 Hz), 131.3 (d, J = 4.0 Hz), 128.8 (d, J = 3.1 Hz), 127.7 (d, J = 17.2 Hz), 119.6 (d, J = 20.2 Hz), 14.8 (d, J = 3.6 Hz); δB (96.3 MHz; $CDCl_3$), 31.2; δF (376.5 MHz; $CDCl_3$), -118.8 (t, $J_{H\text{-}F}$ = 7.0 Hz); ESI-HRMS (m/z): calcd for $C_7H_7BFO_2$ $[M]^-$ 153.0523, found: 153.0531

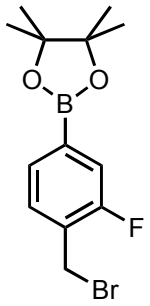
5.3.6.2. Preparation of 2-(3-fluoro-4-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (F-3.76)



In a procedure otherwise identical to that used for the preparation and isolation of **3.76**, **F-3.75** (2.00 g, 13.0 mmol), was reacted with anhydrous pinacol (1.69 g, 14.3 mmol), in diethyl ether (50 mL), to generate the title compound as a white solid (2.98 g, 97% yield), which was used without further purification.

δH (400 MHz; $CDCl_3$), 7.47-7.40 (2H, m, Ar*H*), 7.20-7.16 (1H, m, $J_{H\text{-}F}$ = 0.4 Hz, Ar*H*), 2.29 (3H, d, $J_{H\text{-}F}$ = 1.9 Hz, *Me*), 1.34 (12H, s, Pin*H*); δC (100.6 MHz; $CDCl_3$), 161.3 (d, J = 245.4 Hz), 131.2 (d, J = 4.4 Hz), 130.3 (d, J = 3.2 Hz), 128.4 (d, J = 16.9 Hz), 120.8 (d, J = 20.0 Hz), 84.1, 25.0, 14.9 (d, J = 4.0 Hz); δB (96.3 MHz; $CDCl_3$), 31.3; δF (376.5 MHz; $CDCl_3$), -119.0 (t, $J_{H\text{-}F}$ = 8.0 Hz); a satisfactory mass spectrum of this compound could not be obtained.

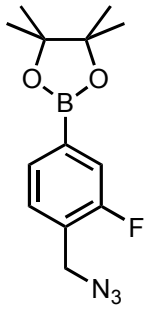
5.3.6.3. Preparation of 2-(4-(bromomethyl)-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (F-3.77)



In a procedure otherwise identical to that used for the preparation and isolation of **3.77**, **F-3.76** (2.79 g, 11.8 mmol), was dissolved in acetonitrile (100 mL), and reacted with *N*-bromosuccinimide (2.10 g, 11.8 mmol) and AIBN (39 mg, 2 mol%), to generate the title compound as large colourless crystals (2.81 g, 76% yield). Careful recrystallization of the retained mother-liquors and washes yielded further product upon concentration and cooling (0.20 g, 5% yield; total 81% yield).

δH (400 MHz; $CDCl_3$), 7.56-7.54 (1H, m, J_{H-F} = 1.0 Hz, Ar*H*), 7.50-7.46 (1H, m, J_{H-F} = 0.6 Hz, Ar*H*), 7.40-7.36 (1H, m, Ar*H*), 4.52 (2H, d, J_{H-F} = 0.6 Hz, Bn*H*), 1.34 (12H, s, Pin*H*); δC (100.6 MHz; $CDCl_3$), 160.4 (d, J_{C-F} = 251.0 Hz), 130.8 (m), 128.1 (d, J_{C-F} = 14.3 Hz), 121.6 (d, J_{C-F} = 19.7 Hz), 84.4, 25.7 (d, J_{C-F} = 5.0 Hz), 25.0; δB (96.3 MHz; $CDCl_3$), 31.1; δF (376.5 MHz; $CDCl_3$), -118.5 (t, J_{H-F} = 9.1 Hz); a satisfactory mass spectrum of this compound could not be obtained.

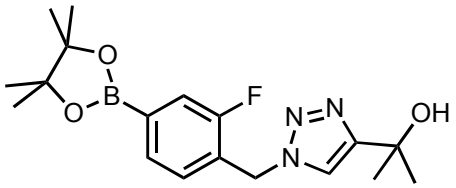
5.3.6.4. Preparation of 2-(4-(azidomethyl)-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (F-3.78)



In a procedure otherwise identical to that used for the preparation and isolation of **3.78**, **F-3.77** (0.945 g, 3.0 mmol), was dissolved in ethanol (30 mL), and reacted with sodium azide (0.215 g, 3.3 mmol), to generate the title compound as a white, to off-white powder (829.0 mg, 99.7% yield).

δH (400 MHz; $CDCl_3$), 7.60 (1H, d, J_{H-H} = 7.5 Hz, J_{H-F} = 0.9 Hz, Ar*H*), 7.52 (1H, d, J_{H-H} = 10.1 Hz, J_{H-F} = 0.6 Hz, Ar*H*), 7.34 (1H, t, J_{H-H} = 7.3 Hz, Ar*H*), 4.40 (2H, s, Bn*H*) 1.34 (12H, s, Pin*H*); δC (100.6 MHz; $CDCl_3$), 160.6 (d, J_{C-F} = 248.3 Hz), 130.8 (d, J_{C-F} = 3.6 Hz), 129.8 (d, J_{C-F} = 3.5 Hz), 125.6 (d, J_{C-F} = 15.3 Hz), 121.3 (d, J_{C-F} = 19.4 Hz), 84.3, 48.6 (d, J_{C-F} = 3.6 Hz), 25.0; δB (96.3 MHz; $CDCl_3$), 31.2; δF (376.5 MHz; $CDCl_3$), -119.4 (t, J_{H-F} = 8.9 Hz); a satisfactory mass spectrum of this compound could not be obtained.

5.3.7. CuAAC Reactivity of F-3.78: Preparation of 2-(1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,2,3-triazol-4-yl)propan-2-ol (F-3.81d)

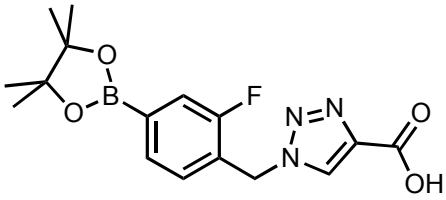


In a procedure otherwise identical to that used for the preparation and isolation of **3.81d**, **F-3.78** (277.1 mg, 1.0 mmol), was reacted with 2-methylbut-3-yn-2-ol (**3.2d**) (107 μL, 1.1 mmol), to generate the title compound as colourless crystals (343.0 mg, 95% yield).

δH (400 MHz; $CDCl_3$), 7.54 (1H, d, J_{H-H} = 7.6 Hz, Ar*H*), 7.51 (1H, d, J_{H-H} = 10.2 Hz, Ar*H*), 7.41 (1H, br s, Tz*H*), 7.24 (1H, t, J_{H-H} = 7.3 Hz, Ar*H*), 5.54 (2H, s, Bn*H*), 2.85 (1H, br s, O*H*), 1.58 (6H, s, R(OH)Me_2), 1.32 (12H, s, Pin*H*); δC (100.6 MHz; $CDCl_3$), 160.3 (d, J_{C-F} = 248.7 Hz), 156.2 (br), 131.1 (d, J_{C-F} = 3.5 Hz), 130.1 (d, J_{C-F} = 2.5 Hz), 124.6 (d, J_{C-F} = 14.7 Hz), 121.5 (d, J_{C-F} = 19.3 Hz), 119.3 (br), 84.4, 68.5 (m), 47.7 (d, J_{C-F} = 3.6 Hz), 30.5, 24.9; δB (96.3 MHz; $CDCl_3$), 31.1; δF (376.5 MHz; $CDCl_3$), -119.5 (t, J_{H-F} = 9.1 Hz); ESI-HRMS (m/z): calcd for $C_{18}H_{25}BFN_3NaO_3$ $[M+Na]^+$ 384.1871, found: 384.1870.

5.3.8. Synthetic Route to 5*H*-Rufinamide Derivative 3.93

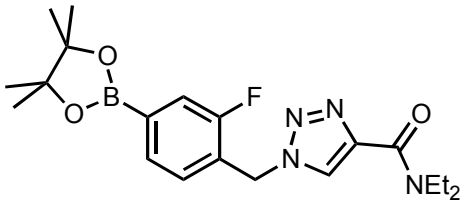
5.3.8.1. Preparation of 1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,2,3-triazole-4-carboxylic acid (F-3.81g)



Using a modification of the literature procedure,[15] to a 10 mL microwave tube equipped with a magnetic stirrer was charged **F-3.78** (277.1 mg, 1.0 mmol), propiolic acid (**3.2g**) (74 μL, 1.2 mmol), 1:1 *t*-BuOH/water (2.0 mL), $Cu(OAc)_2$ (18.2 mg, 10 mol%), and sodium ascorbate (39.6 mg, 20 mol%). The vessel was sealed with a crimp-top Teflon® cap and the heterogeneous mixture was stirred vigorously for 15 minutes at room-temperature, then sonicated (30 seconds) to aid mixing, before being stirred for a further 18 hours at room temperature. The isolation and purification protocol of the literature procedure was followed thereafter, to generate the title compound as colourless crystals (325.3 mg, 94% yield).

δH (400 MHz; $CDCl_3$), 9.46 (1H, br s, CO_2H), 8.14 (1H, s, Tz*H*), 7.59-7.52 (2H, m, Ar*H*), 7.30 (1H, t, J_{H-F} = 7.4 Hz, Ar*H*), 5.65 (2H, s, Bn*H*), 1.32 (12H, s, Pin*H*); δC (100.6 MHz; $CDCl_3$), 164.1 (br), 160.4 (d, J_{C-F} = 249.3 Hz), 155.5, 139.7 (br), 131.3 (d, J_{C-F} = 3.5 Hz), 130.3 (d, J_{C-F} = 2.1 Hz), 128.5 (m), 123.5 (d, J_{C-F} = 14.7 Hz), 121.8 (d, J_{C-F} = 19.2 Hz), 84.6, 48.5 (d, J_{C-F} = 4.0 Hz), 24.9; δB (96.3 MHz; $CDCl_3$), 33.5; δF (376.5 MHz; $CDCl_3$), -119.1 (t, J_{H-F} = 8.2 Hz); ESI-HRMS (m/z): calcd for $C_{16}H_{20}BFN_3O_4$ $[M+H]^+$ 348.1531, found: 348.1539.

5.3.8.2. Preparation of *N*,*N*-diethyl-1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-1,2,3-triazole-4-carboxamide (F-3.81j), *via* the Corresponding Acid Chloride (F-3.81i)

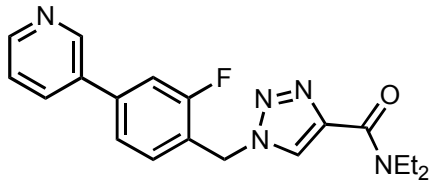


In an unoptimised one-pot procedure, to a dry 25 mL Schlenk tube equipped with magnetic stirrer and rubber septum under a nitrogen atmosphere was added **F-3.81g** (325.0 mg, 0.94 mmol). The material was further dried under vacuum for a few minutes, before the flask was purged with nitrogen. Dry DCM (6.0 mL) and dry DMF (1 drop!) were then added, stirring was initiated and the flask placed in an ice-bath. After 10 minutes to ensure complete cooling to 0 °C, oxalyl chloride (0.34 mL, 4.0 mmol) was added dropwise (connection to the nitrogen line of the manifold was maintained during this time). The ice-bath was replenished and the reaction was stirred overnight, during which time it was allowed to reach room temperature. The majority of the solvent was then removed under a stream of nitrogen, and the remaining volatiles removed *in vacuo*. The crude acid chloride (**F-3.81i**) was then redissolved in dry DCM (5.0 mL), before cooling again to 0 °C. A dry solution of diethylamine (0.42 mL, 4.0 mmol) in DCM (4.0 mL) was then slowly added dropwise (Care! HCl evolved) and the reaction stirred for a further 2 hours at 0 – 10 °C. The solvent was removed under a flow of nitrogen, and remaining volatiles removed *in vacuo*. The organics were extracted from saturated aqueous $NaHCO_3$ (25 mL) with ethyl acetate (3 × 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was precipitated with a small volume of diethyl ether and washed with two further small volumes of diethyl ether, before being recrystallised from DCM layered with ether, to generate the title compound as colourless crystals (201.1 mg). Upon standing the retained washings yielded further product (11.6 mg; 56% total yield).

δH (400 MHz; $CDCl_3$), 8.05 (1H, s, Tz*H*), 7.57-7.51 (2H, m, Ar*H*), 7.27 (1H, t, $J_{H\text{-}H}$ = 7.3 Hz, Ar*H*), 5.59 (2H, s, Bn*H*), 3.93 (2H, q, $J_{H\text{-}H}$ = 7.0 Hz, NCH_2Me), 3.51 (2H, q, $J_{H\text{-}H}$ = 7.1 Hz, NCH_2Me), 1.33 (12H, s, Pin*H*), 1.28 (3H, t, $J_{H\text{-}H}$ = 7.0 Hz, NCH$_2$*Me*), 1.20 (3H, t, $J_{H\text{-}H}$ = 7.1 Hz, NCH$_2$*Me*); δC (100.6 MHz; $CDCl_3$), 160.4 (d, $J_{C\text{-}F}$ = 249.5 Hz), 131.2 (d, $J_{C\text{-}F}$ = 3.7 Hz), 130.2 (d, $J_{C\text{-}F}$ = 2.4 Hz), 128.3 (br), 124.1 (d, $J_{C\text{-}F}$ = 15.0 Hz), 121.7 (d, $J_{C\text{-}F}$ = 19.2 Hz), 84.5, 48.1 (d, $J_{C\text{-}F}$ = 4.3 Hz), 43.2, 41.4, 25.0, 14.8, 12.9; δB (96.3 MHz; $CDCl_3$), 33.4; δF

(376.5 MHz; $CDCl_3$), -119.2 (t, J_{H-F} = 8.6 Hz); ESI-HRMS (m/z): calcd for $C_{20}H_{29}BFN_4O_3$ $[M+H]^+$ 403.2317, found: 403.2326.

5.3.8.3. Preparation of *N*,*N*-diethyl-1-(2-fluoro-4-(pyridin-3-yl)benzyl)-1,2,3-triazole-4-carboxamide (3.93)



In a procedure otherwise identical to *general procedure 3B*, **F-3.81j** (175.0 mg, 0.44 mmol) was reacted with 3-bromopyridine (**3.85d**) (63 μL, 0.65 mmol), $Pd(OAc)_2$ (2.0 mg, 2.0 mol%), S-Phos (9.0 mg, 5.0 mol%), and K_3PO_4 (anhyd.) (278 mg, 1.3 mmol). The plugged product thus obtained was precipitated *via* addition of diethyl ether and triturated using a glass rod. The solid material was further recrystallised from ethyl acetate and petrol, to generate the title compound as a white powder (138.2 mg, 90% yield).

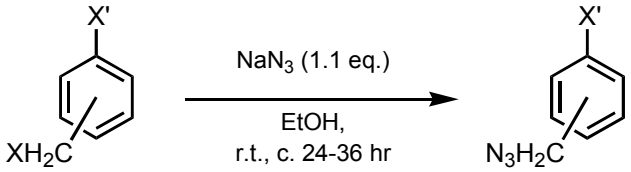
δH (400 MHz; $CDCl_3$), 8.78 (1H, br s, Ar*H*), 8.61 (1H, br d, J_{H-H} = 3.8 Hz, Ar*H*), 8.10 (1H, s, Tz*H*), 7.81 (1H, dt, J_{H-H} = 7.9 Hz, J_{H-H} = 2.0 Hz, Ar*H*), 7.41-7.30 (4H, m, Ar*H*), 5.62 (2H, s, Bn*H*), 3.92 (2H, q, J_{H-H} = 7.0 Hz, NCH_2Me), 3.49 (2H, q, J_{H-H} = 7.1 Hz, NCH_2Me), 1.27 (3H, t, J_{H-H} = 7.0 Hz, NCH_2*Me*), 1.18 (3H, t, J_{H-H} = 7.1 Hz, NCH_2*Me*); δC (100.6 MHz; $CDCl_3$), 161.0 (d, J_{C-F} = 249.5 Hz), 160.4, 149.4, 148.1, 145.4, 141.3 (d, J_{C-F} = 8.0 Hz), 134.7 (br), 134.4, 131.5 (d, J_{C-F} = 3.7 Hz), 128.2 (d, J_{C-F} = 4.3 Hz), 123.8 (br), 123.6 (d, J_{C-F} = 3.4 Hz), 121.1 (d, J_{C-F} = 14.8 Hz), 114.7 (d, J_{C-F} = 22.1 Hz), 47.6 (d, J_{C-F} = 4.0 Hz), 43.1, 41.3, 14.7, 12.8; δF (376.5 MHz; $CDCl_3$), -116.7 (t, J_{H-F} = 8.7 Hz); ESI-HRMS (m/z): calcd for $C_{19}H_{20}FN_5NaO$ $[M+Na]^+$ 376.1550, found: 376.1542.

5.4. Experimental Procedures for Chapter 4

5.4.1. Chapter Specific Considerations

(See those for Chapter 3 – Section 5.3.1)

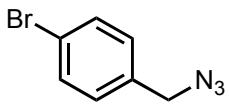
5.4.2. Preparation of Azidomethylene-Substituted Aryl Halides from the Corresponding Halomethylene-Substituted Precursors (*General Procedure 4A*):



To a 25 mL round bottom flask equipped with a magnetic stirrer bar and containing a stirred solution of halomethylene-substituted aryl halide (10.0 mmol, 1.0 equiv.) dissolved in ethanol (10 mL) was added sodium azide (715 mg, 11.0 mmol, 1.1 equiv.). The reaction mixture was allowed to stir for a few minutes, after which the flask was loosely sealed with a rubber septum and, unless otherwise stated, allowed to react with vigorous stirring at room temperature for a period of 24-36 hours, or until a small aliquot of the supernatant demonstrated complete conversion as determined by ^{1}H NMR analysis. (Note: To minimise contact between chlorinated solvents and azide anion, stirring of the reaction mixture was suspended and the salts were first allowed to settle. A small volume of supernatant was then removed, dried under a stream of nitrogen, diluted with diethyl ether, filtered through a small plug of celite and prepared for analysis by ^{1}H NMR using $CDCl_3$ as solvent.)

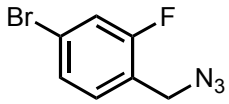
The crude reaction mixture was concentrated under a flow of nitrogen, petrol (c. 15 mL) was added, and the solution was again evaporated. $MgSO_4$ (c. 1-2 g) and petrol (c. 15 mL) were added and the resultant mixture was plugged through a pad of silica on celite, eluting with petrol (in the case of the more polar substrates, typically those with *ortho*- or iodo-substituents, then a mixture of petrol and diethyl ether was used in order to ensure elution of the organoazide). The resulting filtrate was carefully concentrated *in vacuo* (newly synthesised azides were always prepared on small scales, and in that case dried under nitrogen in order to further ascertain their stability), and if necessary any remaining salts or discolouration were removed by a further plug step. The resulting materials were carefully dried under high vacuum, with those that are solids then recrystallised, to yield the corresponding analytically pure azidomethylene substituted aryl halides.

5.4.2.1. 1-(azidomethyl)-4-bromobenzene (4.22)



(This compound is equivalent to **3.83** and was synthesised as detailed above in Section 5.3.4.1.)

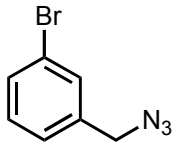
5.4.2.2. 1-(azidomethyl)-4-bromo-2-fluorobenzene (4.100)



4-Bromo-1-(bromomethyl)-2-fluorobenzene (2.679 g, 10.0 mmol) was reacted with NaN_3 and purified according to *general procedure 4A* to generate the title compound as a colourless oil (2.159g, 94% yield).

δH (300 MHz; $CDCl_3$), 7.34-7.20 (3H, m, Ar*H*), 4.37 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 160.6 (d, J_{C-F} = 252.3 Hz), 131.5 (d, J_{C-F} = 4.4 Hz), 128.0 (d, J_{C-F} = 3.7 Hz), 122.8 (d, J_{C-F} = 9.7 Hz), 122.0 (d, J_{C-F} = 15.1 Hz), 119.5 (d, J_{C-F} = 24.3 Hz), 48.1 (d, J_{C-F} = 2.9 Hz); δF (376.5 MHz; $CDCl_3$), -115.0 (t, J_{H-F} = 8.4 Hz); density at ambient temperature was determined to be c. 1.63 g/mL.

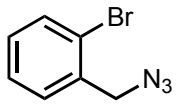
5.4.2.3. 1-(azidomethyl)-3-bromobenzene (4.101)



1-Bromo-3-(bromomethyl)benzene (2.499 g, 10.0 mmol) was reacted with NaN_3 and purified according to *general procedure 4A* to generate the title compound as a colourless oil (1.756 g, 83% yield).

δH (300 MHz; $CDCl_3$), 7.47-7.41 (2H, m, Ar*H*), 7.24-7.20 (2H, m, Ar*H*), 4.30 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 137.8, 131.5, 131.2, 130.5, 126.7, 123.0, 54.1; density at ambient temperature was determined to be c. 1.51 g/mL. Data in accordance with the literature reference.[16]

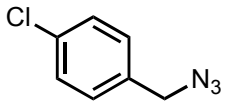
5.4.2.4. 1-(azidomethyl)-2-bromobenzene (4.102)



1-Bromo-2-(bromomethyl)benzene (2.499 g, 10.0 mmol) was reacted with NaN_3 and purified according to *general procedure 4A*, eluting from silica with petrol and diethyl ether, to generate the title compound as a colourless oil (1.871 g, 88% yield).

δH (300 MHz; $CDCl_3$), 7.61 (1H, app dd, J = 7.9 Hz, J = 1.2 Hz, Ar*H*), 7.42-7.32 (2H, m, Ar*H*), 7.21 (1H, app td, J = 7.6 Hz, J = 1.9 Hz, Ar*H*), 4.50 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 135.1, 133.2, 130.1, 129.9, 127.9, 123.8, 54.7; density at ambient temperature was determined to be c. 1.51 g/mL. Data in accordance with the literature reference.[17]

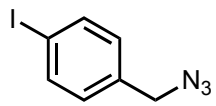
5.4.2.5. 1-(azidomethyl)-4-chlorobenzene (4.115)



1-Chloro-4-(chloromethyl)benzene (1.610 g, 10.0 mmol) was reacted with NaN_3 according to *general procedure 4A* at a temperature of 50 °C for a period of 72 hours, and purified to generate the title compound as a colourless oil (1.562 g, 93% yield).

δH (300 MHz; $CDCl_3$), 7.36 (2H, d, J = 8.6 Hz, Ar*H*), 7.25 (2H, d, J = 8.6 Hz, Ar*H*), 4.32 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 134.3, 134.0, 129.6, 129.1, 54.1; density at ambient temperature was determined to be c. 1.22 g/mL. Data in accordance with the literature reference.[18]

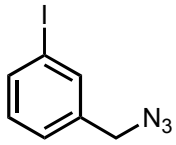
5.4.2.6. 1-(azidomethyl)-4-iodobenzene (4.116)



1-(Bromomethyl)-4-iodobenzene (2.969 g, 10.0 mmol) was reacted with NaN_3 and purified according to *general procedure 4A* to generate the title compound as, depending on the rate of crystallisation, a white powder or colourless crystals (2.456 g, 95% yield).

δH (300 MHz; $CDCl_3$), 7.72 (2H, d, J = 8.4 Hz, Ar*H*), 7.06 (2H, d, J = 8.4 Hz, Ar*H*), 4.29 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 138.0, 135.1, 130.1, 94.0, 54.2. Data in accordance with the literature reference.[19]

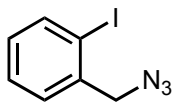
5.4.2.7. 1-(azidomethyl)-3-iodobenzene (4.117)



1-(Bromomethyl)-3-iodobenzene (2.969 g, 10.0 mmol) was reacted with NaN_3 and purified according to *general procedure 4A* to generate the title compound as a colourless oil (1.866 g, 72% yield).

δH (300 MHz; $CDCl_3$), 7.70-7.66 (2H, m, Ar*H*), 7.31-7.27 (1H, m, Ar*H*), 7.15-7.10 (1H, m, Ar*H*), 4.30 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 137.8, 137.5, 137.1, 130.6, 127.4, 94.7, 54.0; density at ambient temperature was determined to be c. 1.77 g/mL. Data in accordance with the literature reference.[20]

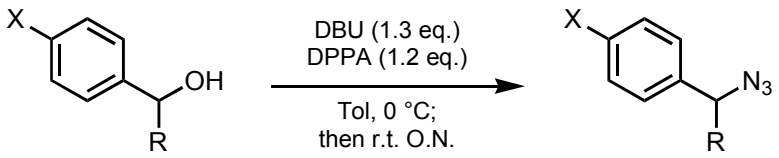
5.4.2.8. 1-(azidomethyl)-2-iodobenzene (4.118)



1-(Bromomethyl)-2-iodobenzene (1.485 g, 5.0 mmol, 1.0 equiv.) was dissolved in ethanol (5.0 mL), reacted with NaN_3 (358 mg, 5.5 mmol, 1.1 equiv.) at a temperature of 40 °C for a period of 36 hours, and purified according to *general procedure 4A* to generate the title compound as a colourless oil (1.013 g, 78% yield).

δH (300 MHz; $CDCl_3$), 7.88 (1H, d, J = 7.8 Hz, Ar*H*), 7.42-7.35 (2H, m, Ar*H*), 7.08-7.00 (1H, m, Ar*H*), 4.46 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 139.9, 138.2, 130.1, 129.6, 128.8, 99.1, 59.1; density at ambient temperature was determined to be c. 1.81 g/mL. Data in accordance with the literature reference.[21]

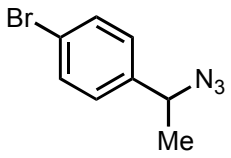
5.4.3. Preparation of Azidomethylene-Substituted Arenes from the Corresponding Hydroxymethylene-Substituted Precursors (*General Procedure 4B*):



(*Caution! DPPA may react with water to form hydrazoic acid (HN_3), a toxic and explosive gas. In addition, care was taken to avoid contamination with e.g. incompatible solvents.*)

Benzylic alcohols were converted to azides by treatment with DPPA according to a modification of the literature procedure:[22] To a dry round bottom flask maintained under an atmosphere of nitrogen and fitted with a magnetic stirrer and rubber septa were charged benzylic alcohol (1.0 equiv.) and dry toluene (1.25 mL/mmol alcohol). Stirring was initiated, DBU (1.3 equiv.) was added, the reaction vessel was placed in an ice-bath, and the resulting solution allowed sufficient time to thoroughly cool to 0 °C before proceeding. A vent needle was then introduced into the septa and, while still maintaining a low positive pressure of nitrogen, DPPA (1.2 equiv.) was carefully added *dropwise* over a period of 10 minutes. The reaction mixture was maintained at 0 °C for a further 30 minutes before being allowed to warm to room temperature, then stirred overnight. The crude materials were isolated in accordance with the literature procedure, namely by aqueous work-up with NH_4Cl(aq.), the organic components being extracted three times with ethyl acetate, combined, dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*. The crude azides so obtained were purified by silica-gel column chromatography.

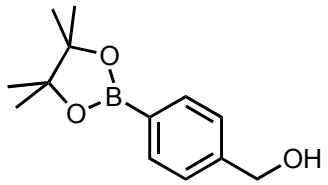
5.4.3.1. (*rac*)-1-(1-azidoethyl)-4-bromobenzene (4.104)



According to *general procedure 4B*, a solution of (*rac*)-1-(4-bromophenyl)ethanol (1.38 mL, 10.0 mmol, 1.0 equiv.) and DBU (1.94 mL, 13.0 mmol, 1.3 equiv.) in dry toluene (12.5 mL) was reacted with DPPA (2.59 mL, 12.0 mmol, 1.2 equiv.). The crude material so obtained was pre-absorbed onto silica and purified by silica-gel column chromatography using 20:1 petrol/ethyl acetate as the eluent to generate the title compound as a colourless oil (1.839 g, 81% yield).

δH (300 MHz; $CDCl_3$), 7.51 (2H, d, J = 8.5 Hz, Ar*H*), 7.21 (2H, d, J = 8.5 Hz, Ar*H*), 4.59 (1H, q, J = 6.8 Hz, Bn*H*), 1.51 (3H, d, J = 6.8 Hz, Bn*Me*); δC (75.5 MHz; $CDCl_3$), 140.0, 132.0, 128.2, 122.1, 60.5, 21.7; density at ambient temperature was determined to be c. 1.44 g/mL.

5.4.3.2. (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (4.106)



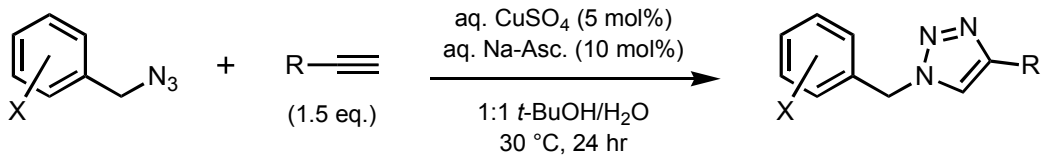
In a procedure analogous to that used for the preparation of **3.76** (Section 5.3.2.2), to a 100 mL round bottom flask equipped with a magnetic stirrer bar was charged commercially available 4-(hydroxymethyl)phenylboronic acid (5.00 g, 32.9 mmol, 1.0 equiv.), pinacol (4.08 g, 34.6 mmol, 1.05 equiv.), and methanol (c. 50 mL). The resulting solution was stirred at room temperature overnight, after which $MgSO_4$ (c. 2.5 g) was added, and the resulting suspension stirred for a further 30 minutes. The solids were removed by filtration and the filtrate concentrated *in vacuo*, re-dissolved in a small amount of diethyl ether and purified by passage through a plug of silica, eluting with diethyl ether. The solvent was removed *in vacuo* to yield the crude product, which was carefully recrystallised from hot petrol, the discoloured supernatant being removed, to leave the title compound as a white crystalline solid (4.79 g, 20.4 mmol, 62% yield).

δH (300 MHz; $CDCl_3$), 7.78 (2H, d, J = 7.8 Hz, Ar*H*), 7.33 (2H, d, J = 7.8 Hz, Ar*H*), 4.66 (2H, s, Bn*H*), 2.44 (1H, s, BnO*H*), 1.34 (12H, s, Pin*H*); δC (75.5 MHz; $CDCl_3$), 144.2, 135.1, 126.1, 83.9, 65.1, 24.9; δB (96.3 MHz; $CDCl_3$), 33.9. Data in accordance with the literature reference.[23]

5.4.3.2.1. Preparation of 4.24 by Reaction of 4.106 with DPPA

A solution of recrystallised **4.106** (4.68 g, 20.0 mmol, 1 equiv.) and DBU (3.89 mL, 26.0 mmol, 1.3 equiv.) in dry toluene (25 mL) was reacted with DPPA (5.17 mL, 24.0 mmol, 1.2 equiv.) according to *general procedure 4B*. The crude material so obtained was purified by silica-gel column chromatography using 19:1 petrol/ethyl acetate as the eluent to generate **4.24** as a white crystalline solid (4.056 g, 78% yield), for which the analytical data obtained was in accordance with that of the material synthesised by the standard route (i.e. **3.78**, Section 5.3.2.4).

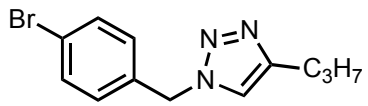
5.4.4. Preparation of 1,2,3-Triazole Substrates by CuAAC Reaction Employing $CuSO_4$ and Sodium Ascorbate (*General Procedure 4C*):



To a 24 mL screw-capped vial equipped with a magnetic stirrer and rubber septum were charged organoazide (2.0 mmol, 1.0 equiv.), terminal alkyne (3.0 mmol, 1.5 equiv.) and 1:1 *t*-BuOH/H_2O (1.7 mL; 0.85 mL/mmol azide) under an air atmosphere. Rapid stirring was initiated, $CuSO_4.5H_2O$(aq.) (0.15 mL of a 0.667 M solution, 5.0 mol% [Cu]/azide) was added, the vial was sealed and *freshly prepared* aqueous sodium ascorbate (0.15 mL of a 1.333 M solution, 10 mol% sodium ascorbate/azide) was added dropwise *via* syringe. Vigorous stirring was maintained and the reaction was heated at 30 °C for 24 hours, or until analysis of a reaction aliquot by ^{1}H NMR demonstrated complete conversion, whereupon the reaction mixture was cooled, water (c. 5 mL/mmol azide) was added and the organic components extracted with ethyl acetate (3 × c. 2.5 mL/mmol azide). The organic layers were combined, dried ($MgSO_4$), filtered through celite eluting with ethyl acetate, and the solvent removed *in vacuo* to yield the crude triazole.

To aid in removing residual copper salts, the crude product was typically re-dissolved in a small volume of diethyl ether to which was then added sodium ascorbate (c. 100 mg). The ethereal solution was then *carefully* warmed and the solid materials gently agitated in order to assist in reducing any residual copper – typically exhibiting upon reduction as an insoluble brown-orange residue. The solution was then allowed to cool and purified by passage through a short column of silica eluting with diethyl ether, or for more polar triazoles a gradient elution with increasing amounts of chloroform, up to c. 90:10 chloroform/methanol. The solvent was removed *in vacuo* to yield the product triazole, which was further purified by recrystallisation (less polar triazoles were recrystallised from diethyl ether using petrol as an anti-solvent, while for more polar examples diethyl ether and chloroform, or neat chloroform were employed).

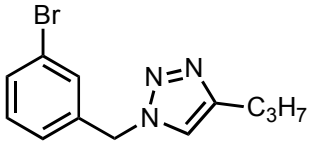
5.4.4.1. 1-(4-bromobenzyl)-4-propyl-1,2,3-triazole (4.26)



1-(Azidomethyl)-4-bromobenzene **4.22** (424.1 mg, 2.0 mmol, 1.0 equiv.) was reacted with 1-pentyne (296 µL, 3.0 mmol, 1.5 eqiuv.) and purified according to *general procedure 4C* to generate the title compound as, depending on the rate of crystallisation, a white powder or colourless crystals (506.4 mg, 90% yield).

δH (300 MHz; $CDCl_3$), 7.48 (2H, d, J = 8.5 Hz, Ar*H*), 7.18 (1H, br s, Tz*H*), 7.11 (2H, d, J = 8.5 Hz, Ar*H*), 5.43 (2H, s, Bn*H*), 2.66 (2H, t, J = 7.6 Hz, Tz*CH*$_2$CH$_2$Me), 1.66 (2H, app. sextet, J = 7.5 Hz, TzCH$_2$*CH*$_2$Me), 0.93 (3H, t, J = 7.4 Hz, TzCH$_2$CH$_2$*Me*); δC (75.5 MHz; $CDCl_3$), 149.0 (br), 134.2, 132.3, 129.7, 122.8, 120.6 (br), 53.4, 27.8, 22.8, 13.9; ESI-HRMS (m/z): calcd for $C_{12}H_{14}BrN_3Na$ $[M+Na]^+$ 302.0269, found: 302.0257.

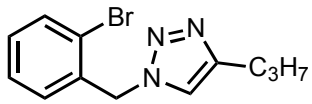
5.4.4.2. 1-(3-bromobenzyl)-4-propyl-1,2,3-triazole (*m*-4.26)



1-(Azidomethyl)-3-bromobenzene **4.101** (424.1 mg, 2.0 mmol, 1.0 equiv.) was reacted with 1-pentyne (296 µL, 3.0 mmol, 1.5 equiv.) and purified according to *general procedure 4C* to generate the title compound as, depending on the rate of crystallisation, a white powder or colourless crystals (530.7 mg, 95% yield).

δH (300 MHz; $CDCl_3$), 7.42-7.37 (1H, m, Ar*H*), 7.34-7.33 (1H, m, Ar*H*), 7.24 (1H, br s, Tz*H*), 7.19-7.09 (2H, m, Ar*H*), 5.41 (2H, s, Bn*H*), 2.62 (2H, t, J = 7.6 Hz, Tz*CH*$_2$CH$_2$Me), 1.62 (2H, app. sextet, J = 7.4 Hz, TzCH$_2$*CH*$_2$Me), 0.89 (3H, t, J = 7.4 Hz, TzCH$_2$CH$_2$*Me*); δC (75.5 MHz; $CDCl_3$), 148.9 (br), 137.3, 131.6, 130.8, 130.6, 126.4, 122.9, 120.8 (br), 53.1, 27.7, 22.6, 13.7; ESI-HRMS (m/z): calcd for $C_{12}H_{14}BrN_3Na$ $[M+Na]^+$ 302.0269, found: 302.0252.

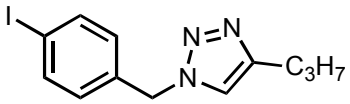
5.4.4.3. 1-(2-bromobenzyl)-4-propyl-1,2,3-triazole (*o*-4.26)



1-(Azidomethyl)-2-bromobenzene **4.102** (424.1 mg, 2.0 mmol, 1.0 equiv.) was reacted with 1-pentyne (296 µL, 3.0 mmol, 1.5 equiv.) according to *general procedure 4C* and purified to generate the title compound as a viscous clear yellow oil (544.4 mg, 97% yield).

δH (300 MHz; $CDCl_3$), 7.54 (1H, app. dd, J = 7.9 Hz, J = 1.4 Hz, Ar*H*), 7.30 (1H, br s, Tz*H*), 7.26-7.12 (2H, m, Ar*H*), 7.03 (1H, app. dd, J = 7.5, J = 1.8, Ar*H*), 5.56 (2H, s, Bn*H*), 2.63 (2H, t, J = 7.5 Hz, Tz$CH_2$$CH_2$Me), 1.64 (2H, app. sextet, J = 7.4 Hz, TzCH$_2$$CH_2$Me), 0.90 (3H, t, J = 7.3 Hz, TzCH$_2$CH$_2$*Me*); δC (75.5 MHz; $CDCl_3$), 148.8 (br), 134.5, 133.1, 130.1, 130.0, 128.1, 123.2, 121.1 (br), 53.6, 27.7, 22.6, 13.8; ESI-HRMS (m/z): calcd for $C_{12}H_{14}BrN_3Na$ $[M+Na]^+$ 302.0269, found: 302.0257.

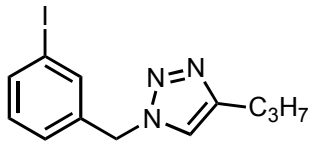
5.4.4.4. 1-(4-iodobenzyl)-4-propyl-1,2,3-triazole (4.121)



1-(Azidomethyl)-4-iodobenzene **4.116** (518.1 mg, 2.0 mmol, 1.0 equiv.) was reacted with 1-pentyne (296 µL, 3.0 mmol, 1.5 equiv.) and purified according to *general procedure 4C* to generate the title compound as, depending on the rate of crystallisation, a white powder or colourless crystals (582.0 mg, 89% yield).

δH (300 MHz; $CDCl_3$), 7.68 (2H, d, J = 8.4 Hz, Ar*H*), 7.21 (1H, s, Tz*H*), 6.98 (2H, d, J = 8.4 Hz, Ar*H*), 5.42 (2H, s, Bn*H*), 2.65 (2H, t, J = 7.5 Hz, Tz$CH_2$$CH_2$Me), 1.66 (2H, app. sextet, J = 7.3 Hz, TzCH$_2$$CH_2$Me), 0.93 (3H, t, J = 7.3 Hz, TzCH$_2$CH$_2$*Me*); δC (75.5 MHz; $CDCl_3$), 148.9, 138.1, 134.7, 129.7, 120.7, 94.4, 53.3, 27.7, 22.7, 13.8; ESI-HRMS (m/z): calcd for $C_{12}H_{14}IN_3Na$ $[M+Na]^+$ 350.0130, found: 350.0127.

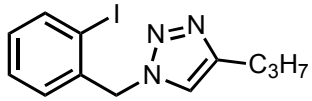
5.4.4.5. 1-(3-iodobenzyl)-4-propyl-1,2,3-triazole (*m*-4.121)



1-(Azidomethyl)-3-iodobenzene **4.117** (518.1 mg, 2.0 mmol, 1.0 equiv.) was reacted with 1-pentyne (296 µL, 3.0 mmol, 1.5 equiv.) and purified according to *general procedure 4C* to generate the title compound as, depending on the rate of crystallisation, a white powder or colourless crystals (602.2 mg, 92% yield).

δH (300 MHz; $CDCl_3$), 7.68-7.64 (1H, m, Ar*H*), 7.60-7.59 (1H, m, Ar*H*), 7.24 (1H, s, Tz*H*), 7.21-7.18 (1H, m, Ar*H*), 7.08 (1H, t, J = 7.8 Hz, Ar*H*), 5.42 (2H, s, Bn*H*), 2.66 (2H, t, J = 7.5 Hz, Tz$CH_2$$CH_2$Me), 1.67 (2H, app. sextet, J = 7.4 Hz, TzCH$_2$$CH_2$Me), 0.94 (3H, t, J = 7.3 Hz, TzCH$_2$CH$_2$*Me*); δC (75.5 MHz; $CDCl_3$), 148.9, 137.7, 137.3, 136.7, 130.8, 127.1, 120.7, 94.7, 53.1, 27.7, 22.7, 13.8; ESI-HRMS (m/z): calcd for $C_{12}H_{14}IN_3Na$ $[M+Na]^+$ 350.0130, found: 350.0133.

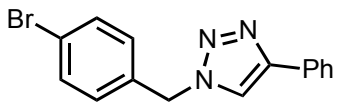
5.4.4.6. 1-(2-iodobenzyl)-4-propyl-1,2,3-triazole (*o*-4.121)



1-(Azidomethyl)-2-iodobenzene **4.118** (518.1 mg, 2.0 mmol, 1.0 equiv.) was reacted with 1-pentyne (296 µL, 3.0 mmol, 1.5 equiv.) and purified according to *general procedure 4C* to generate the title compound as a viscous clear pale yellow oil (615.6 mg, 94% yield).

δH (300 MHz; $CDCl_3$), 7.86 (1H, dd, J = 1.3 Hz, Ar*H*), 7.32-7.27 (2H, m, Ar*H* & Tz*H*), 7.04-6.98 (2H, m, Ar*H*), 5.55 (2H, s, Bn*H*), 2.67 (2H, t, J = 7.6 Hz, Tz$CH_2$$CH_2$Me), 1.66 (2H, app. sextet, J = 7.4 Hz, TzCH$_2$$CH_2$Me), 0.93 (3H, t, J = 7.4 Hz, TzCH$_2$CH$_2$*Me*); δC (75.5 MHz; $CDCl_3$), 148.7 (br), 139.9, 137.7, 130.3, 129.5, 129.1, 121.2 (br), 98.6, 58.3, 27.8, 22.7, 13.8; ESI-HRMS (m/z): calcd for $C_{12}H_{14}IN_3Na$ $[M+Na]^+$ 350.0130, found: 350.0120.

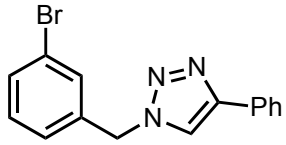
5.4.4.7. 1-(4-bromobenzyl)-4-phenyl-1,2,3-triazole (4.122)



1-(Azidomethyl)-4-bromobenzene **4.22** (424.1 mg, 2.0 mmol, 1.0 equiv.) was reacted with phenylacetylene (329 µL, 3.0 mmol, 1.5 equiv.) and purified according to *general procedure 4C* to generate the title compound as, depending on the rate of crystallisation, a white powder or colourless crystals (561.9 mg, 89% yield).

δH (300 MHz; $CDCl_3$), 7.81-7.78 (2H, m, Ar*H*), 7.66 (1H, s, Tz*H*), 7.52 (2H, d, J = 8.5 Hz, Ar*H*), 7.44-7.29 (3H, m, Ar*H*), 7.18 (2H, d, J = 8.5 Hz, Ar*H*), 5.53 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 148.6, 133.9, 132.5, 130.5, 129.8, 129.0, 128.4, 125.9, 123.1, 119.5, 53.7. Data in accordance with the literature reference.[24]

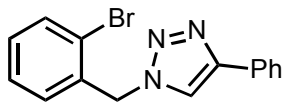
5.4.4.8. 1-(3-bromobenzyl)-4-phenyl-1,2,3-triazole (*m*-4.122)



1-(Azidomethyl)-3-bromobenzene **4.101** (424.1 mg, 2.0 mmol, 1.0 equiv.) was reacted with phenylacetylene (329 µL, 3.0 mmol, 1.5 equiv.) and purified according to *general procedure 4C* to generate the title compound as a white powder (574.5 mg, 91% yield).

δH (300 MHz; $CDCl_3$), 7.82-7.80 (2H, m, Ar*H*), 7.72 (1H, s, Tz*H*), 7.50-7.20 (7H, m, Ar*H*), 5.53 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 148.6, 137.0, 132.1, 131.1, 130.9, 130.4, 129.0, 128.4, 126.7, 125.9, 123.3, 119.6, 53.6. Data in accordance with the literature reference.[24]

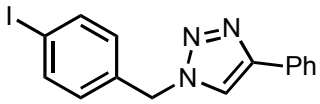
5.4.4.9. 1-(2-bromobenzyl)-4-phenyl-1,2,3-triazole (*o*-4.122)



1-(Azidomethyl)-2-bromobenzene **4.102** (424.1 mg, 2.0 mmol, 1.0 equiv.) was reacted with phenylacetylene (329 µL, 3.0 mmol, 1.5 equiv.) at 40 °C according to *general procedure 4C*, and the resulting material purified to generate the title compound as a white powder (596.4 mg, 95% yield).

δH (300 MHz; $CDCl_3$), 7.84-7.79 (3H, m, Ar*H* & Tz*H*), 7.63 (1H, app. dd, J = 7.8 Hz, J = 1.4 Hz, Ar*H*), 7.44-7.17 (6H, m, Ar*H*), 5.71 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 148.3, 134.4, 133.3, 130.5, 130.4, 129.0, 128.4, 128.4, 125.8, 123.5, 120.0, 54.0. Data in accordance with the literature reference.[24]

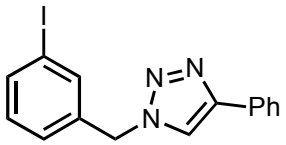
5.4.4.10. 1-(4-iodobenzyl)-4-phenyl-1,2,3-triazole (4.123)



1-(Azidomethyl)-4-iodobenzene **4.116** (518.1 mg, 2.0 mmol, 1.0 equiv.) was reacted with phenylacetylene (329 µL, 3.0 mmol, 1.5 equiv.) and purified according to *general procedure 4C* to generate the title compound as a white crystalline powder (696.9 mg, 96% yield).

δH (300 MHz; $CDCl_3$), 7.81-7.77 (2H, m, Ar*H*), 7.71 (2H, d, J = 8.4 Hz, Ar*H*), 7.67 (1H, s, Tz*H*), 7.43-7.29 (3H, m, Ar*H*), 7.04 (2H, d, J = 8.4 Hz, Ar*H*), 5.50 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 148.5, 138.4, 134.4, 130.4, 129.9, 129.0, 128.4, 125.8, 119.6, 94.7, 53.7. Data in accordance with the literature reference.[25]

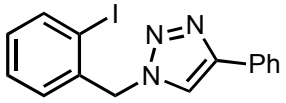
5.4.4.11. 1-(3-iodobenzyl)-4-phenyl-1,2,3-triazole (*m*-4.123)



1-(Azidomethyl)-3-iodobenzene **4.117** (518.1 mg, 2.0 mmol, 1.0 equiv.) was reacted with phenylacetylene (329 µL, 3.0 mmol, 1.5 equiv.) and purified according to *general procedure 4C* to generate the title compound as, depending on the rate of crystallisation, a white powder or colourless crystals (679.3 mg, 94% yield).

δH (300 MHz; $CDCl_3$), 7.81-7.77 (2H, m, Ar*H*), 7.71 (1H, s, Tz*H*), 7.68-7.65 (2H, m, Ar*H*), 7.42-7.21 (4H, m, Ar*H*), 7.07 (1H, t, J = 7.8 Hz, Ar*H*), 5.47 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 148.4, 137.9, 136.9, 136.8, 130.8, 130.4, 128.9, 128.3, 127.2, 125.7, 119.7, 94.8, 53.3. Data in accordance with the literature reference.[26]

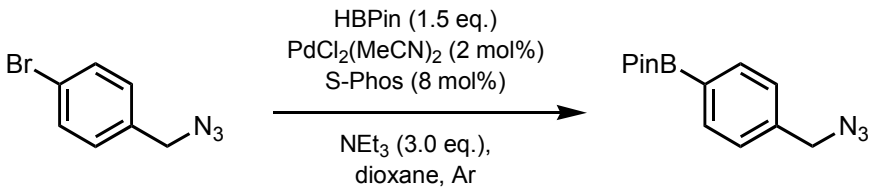
5.4.4.12. 1-(2-iodobenzyl)-4-phenyl-1,2,3-triazole (*o*-4.123)



1-(Azidomethyl)-2-iodobenzene **4.118** (518.1 mg, 2.0 mmol, 1.0 equiv.) was reacted with phenylacetylene (329 µL, 3.0 mmol, 1.5 equiv.) at 40 °C according to *general procedure 4C*, and the resulting material purified to generate the title compound as a white powder (556.8 mg, 77% yield).

δH (300 MHz; $CDCl_3$), 7.90 (1H, dd, J = 7.9 Hz, J = 1.2 Hz, Ar*H*), 7.84-7.80 (2H, m, Ar*H*), 7.77 (1H, s, Tz*H*), 7.44-7.29 (4H, m, Ar*H*), 7.13 (1H, dd, J = 7.7 Hz, J = 1.6 Hz, Ar*H*), 7.06 (1H, dt, J = 7.6 Hz, J = 1.7 Hz, Ar*H*), 5.66 (2H, s, Bn*H*); δC (75.5 MHz; $CDCl_3$), 148.3, 140.0, 137.5, 130.6, 129.7, 129.2, 128.9, 128.3, 125.9, 120.0, 98.7, 58.6. Data in accordance with the literature reference.[26]

5.4.5. Preparation of 4.24 by Masuda Borylation of 4.22 with Pinacolborane:



Using a modification of the literature procedure,[27] to an oven-dried 25 mL Schlenk tube equipped with a magnetic stirrer and rubber septum was charged $PdCl_2(MeCN)_2$ (2.0 mol%) and S-Phos (8.0 mol%). The vessel was placed under vacuum and refilled with argon; this process was repeated three times. The appropriate volume of dry dioxane (0.6 or 1.0 mL/mmol azide) was then added *via* syringe, followed by 1-(azidomethyl)-4-bromobenzene **4.22** (1.0 equiv.), dry triethylamine (3.0 equiv.) and pinacolborane (1.5 equiv.). The rubber septum was replaced with a gas-tight screw-thread ground-glass stopper, and the reaction was rapidly evacuated and immediately backfilled with argon, after which the vessel was sealed and heated* to the designated temperature and reacted for the time specified in **Table 4.7**. The reaction was then allowed to cool to room temperature, ethyl acetate was added, and the resulting mixture was filtered through a small plug of celite, eluting with ethyl acetate. The crude reaction mixture was then concentrated *in vacuo* and analysed by ^{1}H and ^{11}B NMR.

For **Table 4.7**, **entry 2**: 1-(azidomethyl)-4-bromobenzene (139 μL, 1.0 mmol, 1.0 equiv.) was reacted under the above protocol in dry dioxane (1.0 mL) for one hour at 70 °C. The crude product was purified by silica-gel column chromatography, using 20:1 petrol/ethyl acetate as the eluent to generate **4.24** (77.7 mg, 30% yield), for which the analytical data obtained was in accordance with that of the material synthesised by the standard route (see **3.78**).

* For standard aryl halide substrates the literature procedure recommends the use of a blast shield in the event that the solvent is heated to, or above, its boiling point. As organoazides themselves are potentially explosive, then extra care should be taken.

5.4.6. General Protocol for the Miyaura Borylation of Azidomethylene or Triazolylmethylene Substituted Aryl Halides (G*eneral Procedure 4D*):

To an oven-dried Schlenk tube equipped with a magnetic stirrer, rubber septum, and maintained under an argon atmosphere was quickly charged KOAc* (3.0 equiv.). The vessel was placed under vacuum and refilled with argon; this process was repeated three times. The base was then dried under high vacuum by careful heating of the reaction vessel walls with a warm-air gun (c. 40-60 °C) for a period of c. 3 minutes, after which the vessel was allowed to cool then refilled with argon; this process was repeated three times.

Bis(pinacolato)diboron (1.15 equiv.), palladium complex (2.5 mol%), and – where specified – phosphine ligand (5.0 mol%), were then added. The combined solid reagents were dried under high vacuum at ambient temperature for a further 5 minutes, after which the vessel was backfilled with argon; this process was repeated three times. Dry solvent (DMF or dioxane, 6.0 mL/mmol aryl halide) was added and the resulting suspension was stirred for 10 minutes at ambient temperature before the aryl halide (1.0 equiv.) was added *via* syringe through the septum.** The rubber septum was replaced with a gas-tight screw-thread ground-glass stopper, the vessel rapidly evacuated and backfilled with argon, then sealed. The reaction mixture was allowed to stir for a further 10 minutes at ambient temperature, after which the vessel was placed in a pre-heated oil-bath at the appropriate temperature.

After the specified time the reaction was allowed to cool to room temperature and quenched by addition of water and ethyl acetate. The crude mixture was partitioned between water and ethyl acetate (c. 25-50 mL each per mmol aryl halide – sufficient for the volume of hydrophilic solvent present), the organic soluble components extracted with three portions of ethyl acetate, combined, washed three times with water then once with brine, dried ($MgSO_4$), and filtered through a small plug of celite, eluting with ethyl acetate. The solvent was removed *in vacuo* to yield the crude product.

Where specified the crude azide functionalised boronate esters were isolated by silica-gel column chromatography employing 20:1 petrol/ethyl acetate as the eluent to yield the corresponding analytically pure products. The crude triazole functionalised boronate ester products were purified by silica-gel column chromatography by gradient elution analogous to that detailed in *general procedure 3A*.

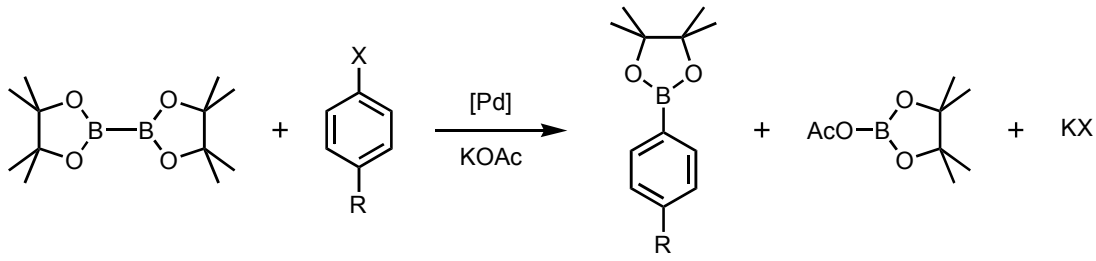
* KOAc is extremely hygroscopic. Samples were weighed out shortly before being charged into dry reaction vessels, using tared glass vials that were kept sealed whenever possible. ** Substrates that were oils were

deoxygenated by sequential vacuum/argon cycles prior to being introduced into the reaction vessel. Those that were solids were added at the same stage as the diboron.

5.4.6.1. Calculation of Conversion Values in the Borylation Reaction

Standard conversion values were determined by ^{1}H NMR *via* comparison of the benzylic peak of the aryl halide and that of the aryl boronate ester (where the aromatic signals were well enough resolved they were also included in the calculations).

"Diboron conversion values" were also determined by comparison of the integrals for the unreacted diboron and the aryl boronate ester product. Typically the aryl halide (1.0 equiv.) is reacted with an excess of diboron (1.15 equiv.). The following example is therefore used to illustrate the conversion value as determined by consumption of the diboron reagent through analysis of the two pinacolate ester peaks seen in the crude ^{1}H NMR spectrum:



At 0% conversion there is no pinacol peak for the product, while the aromatic protons of the aryl halide integrate to 4, and the pinacol peak for the diboron integrates to 27.6 protons (i.e. 1.15 × 24).

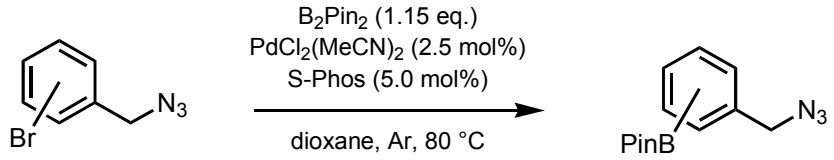
Using the same total values for the integrals: At 50% conversion the aromatic protons of the aryl halide integrate to 2. The aromatic protons of the arylboron pinacolate ester also integrate to 2, while the pinacolate ester singlet integrates to 6. In addition there remains 0.65 equivalents of the diboron (i.e. 1.15 initial - 0.5 consumed), for which the singlet associated with it integrates to 15.6 (i.e. 0.65 × 24).

As the other product of the reaction containing pinacol (which would otherwise also integrate to 6) is not retained in the organic phase then it can be ignored in the crude ^{1}H NMR. However, the total integration for the three components in the system bearing pinacol moieties prior to work-up and at a 50% conversion of aryl halide to arylboronate ester is still: 6 + 6 + 15.6 = 27.6

By accounting for the fact that the diboron is a dimer, then the conversion of product from diboron is equivalent to 6.0:7.8; i.e. 6:(15.6/2).

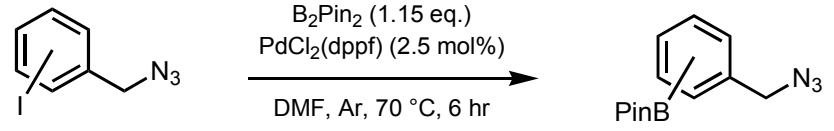
In percentage terms this corresponds to: 6/(6+7.8) × 100 = c. 43.5%, however to account for the excess of diboron this value is multiplied by 1.15; thus 43.5% × 1.15 = 50% conversion.

5.4.7. Optimised Reaction Conditions for the Miyaura Borylations of Aryl Bromides bearing Benzylic Azides (*General Procedure 4E*):



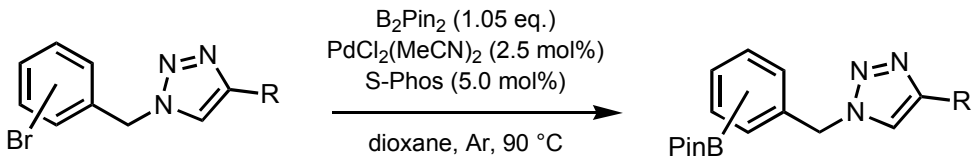
Unless otherwise specified: Azidomethylene-substituted aryl bromides (1.0 equiv.) were reacted with bis(pinacolato)diboron (1.15 equiv.) according to *general procedure 4D*, in the presence of $PdCl_2(MeCN)_2$ (2.5 mol%), S-Phos (5.0 mol%) and dry dioxane (6.0 mL/mmol aryl bromide) at a reaction temperature of 80 °C for the indicated time.

5.4.8. Optimised Reaction Conditions for the Miyaura Borylations of Aryl Iodides bearing Benzylic Azides (*General Procedure 4F*):



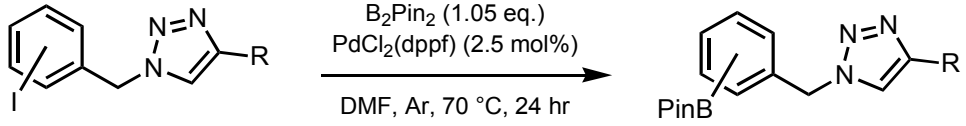
Unless otherwise specified: Azidomethylene-substituted aryl iodides (1.0 equiv.) were reacted with bis(pinacolato)diboron (1.15 equiv.) according to *general procedure 4D*, in the presence of $PdCl_2(dppf)$ (2.5 mol%), dry DMF (6.0 mL/mmol aryl iodide), but without any additional phosphine ligand, at a reaction temperature of 70 °C for a period of 6 hours.

5.4.9. Optimised Reaction Conditions for the Miyaura Borylations of Aryl Bromides bearing 4'-Substituted 1,2,3-Triazoles (*General Procedure 4G*):



Unless otherwise specified: Triazole-substituted aryl bromides (1.0 equiv.) were reacted with bis(pinacolato)diboron (1.05 equiv.) according to *general procedure 4D*, in the presence of $PdCl_2(MeCN)_2$ (2.5 mol%), S-Phos (5.0 mol%) and dry dioxane (6.0 mL/mmol aryl bromide) at a reaction temperature of 90 °C for the indicated time.

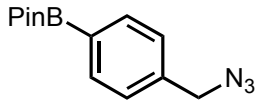
5.4.10. Optimised Reaction Conditions for the Miyaura Borylations of Aryl Iodides bearing 4'-Substituted 1,2,3-Triazoles (*General Procedure 4H*):



Unless otherwise specified: Triazole-substituted aryl iodides (1.0 equiv.) were reacted with bis(pinacolato)diboron (1.05 equiv.) according to *general procedure 4D*, in the presence of $PdCl_2(dppf)$ (2.5 mol%), dry DMF (6.0 mL/mmol aryl iodide), but without any additional phosphine ligand, at a reaction temperature of 70 °C for 24 hours.

5.4.11. Preparation of Azidomethylene Substituted Aryl Pinacol Boronate Esters by Miyaura Borylation of Azidomethylene Substituted Aryl Halides:

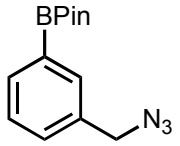
5.4.11.1. 2-(4-(azidomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.24)



1-(Azidomethyl)-4-bromobenzene **4.22** (139 µL, 1.0 mmol, 1.0 equiv.) was reacted with bis(pinacolato)diboron (292 mg, 1.15 mmol, 1.15 equiv.) according to *general procedure 4E* for a period of two hours, and the crude product purified to generate the title compound (218.1 mg, 84% yield), for which the analytical data obtained was in accordance with that of the material synthesised by the standard route (see **3.78** – Section 5.3.2.4).

Alternatively, 1-(azidomethyl)-4-iodobenzene **4.116** (259.1 mg, 1.0 mmol, 1.0 equiv.) was reacted with bis(pinacolato)diboron (292 mg, 1.15 mmol, 1.15 equiv.) according to *general procedure 4F*, and the crude product purified to generate the title compound (205.3 mg, 79% yield), for which the analytical data obtained was in accordance with that of the material synthesised by the standard route (see **3.78** – Section 5.3.2.4).

5.4.11.2. 2-(3-(azidomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*m*-4.24)

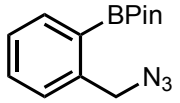


1-(Azidomethyl)-3-bromobenzene **4.101** (140 µL, 1.0 mmol, 1.0 equiv.) was reacted with bis(pinacolato)diboron (292 mg, 1.15 mmol, 1.15 equiv.) according to *general procedure 4E* for a period of two hours, and the crude product purified to generate the title compound (213.3 mg, 82% yield).

Alternatively, 1-(azidomethyl)-3-iodobenzene **4.117** (146 µL, 1.0 mmol) was reacted with bis(pinacolato)diboron (292 mg, 1.15 mmol, 1.15 equiv.) according to *general procedure 4F* and the crude product purified to generate the title compound (196.1 mg, 76% yield).

Appearance: Colourless oil; δH (300 MHz; $CDCl_3$), 7.82-7.77 (2H, m, Ar*H*), 7.45-7.37 (2H, m, Ar*H*), 4.35 (2H, s, Bn*H*), 1.36 (12H, s, Pin*H*); δC (75.5 MHz; $CDCl_3$), 134.8, 134.8, 134.7, 131.2, 128.3, 84.1, 54.8, 25.0; δB (96.3 MHz; $CDCl_3$), 33.85; ESI-HRMS (m/z): calcd for $C_{13}H_{18}BN_3NaO_2$ $[M+Na]^+$ 282.1390, found: 282.1367.

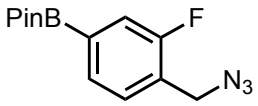
5.4.11.3. 2-(2-(azidomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*o*-4.24)



1-(Azidomethyl)-2-iodobenzene **4.118** (143 μL, 1.0 mmol) was reacted with bis(pinacolato)diboron (292 mg, 1.15 mmol, 1.15 equiv.) according to *general procedure 4F* in the presence of $PdCl_2$(dppf) (73.5 mg, 9.0 mol%) for a period of 20 hours and the crude product purified to generate the title compound as a colourless oil (173.8 mg, 67% yield).

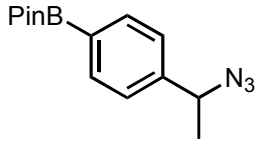
δH (300 MHz; $CDCl_3$), 7.90-7.87 (1H, m, Ar*H*), 7.47-7.44 (1H, m, Ar*H*), 7.37-7.31 (2H, m, Ar*H*), 4.67 (2H, s, Bn*H*), 1.37 (12H, s, Pin*H*); δC (75.5 MHz; $CDCl_3$), 141.7, 136.6, 131.6, 129.3, 127.6, 84.1, 54.3, 25.0; δB (96.3 MHz; $CDCl_3$), 33.94; ESI-HRMS (m/z): calcd for $C_{13}H_{18}BN_3NaO_2$ $[M+Na]^+$ 282.1390, found: 282.1372.

5.4.11.4. 2-(4-(azidomethyl)-3-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (F-4.24)



1-(Azidomethyl)-4-bromo-2-fluorobenzene **4.100** (141 μL, 1.0 mmol, 1.0 equiv.) was reacted with bis(pinacolato)diboron (292 mg, 1.15 mmol, 1.15 equiv.) according to *general procedure 4E* for a period of two hours, and the crude product purified to generate the title compound (164.7 mg, 59% yield), for which the analytical data obtained was in accordance with that of the material synthesised by the standard route (see **F-3.78** – Section 5.3.6.4).

5.4.11.5. (*rac*)-2-(4-(1-azidoethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 4.10, entries 9-11)

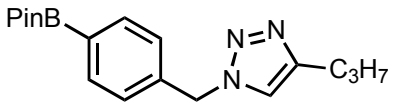


(*rac*)-1-(1-azidoethyl)-4-bromobenzene **4.104** (157 µL, 1.0 mmol, 1.0 equiv.) was reacted with bis(pinacolato)diboron (292 mg, 1.15 mmol, 1.15 equiv.) according to *general procedure 4E* for a period of three hours, and the crude product purified to generate the title compound as, depending on the rate of crystallisation, a white crystalline solid or colourless crystals (207.1mg, 76% yield).

δH (300 MHz; $CDCl_3$), 7.84 (2H, d, J = 8.0 Hz, Ar*H*), 7.34 (2H, d, J = 8.0 Hz, Ar*H*), 4.63 (1H, q, J = 6.8 Hz, Bn*H*), 1.52 (3H, d, J = 6.8 Hz, Bn*Me*), 1.35 (12H, s, Pin*H*); δC (75.5 MHz; $CDCl_3$), 144.0, 135.4, 125.8, 84.0, 61.2, 25.0, 21.7; δB (96.3 MHz; $CDCl_3$) 33.8; ESI-HRMS (m/z): calcd for $C_{14}H_{20}BN_3NaO_2$ $[M+Na]^+$ 296.1546, found: 296.1521.

5.4.12. Preparation of Triazolylmethylene Substituted Aryl Pinacol Boronate Esters by Miyaura Borylation of Triazolylmethylene Substituted Aryl Halides:

5.4.12.1. 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-4-propyl-1,2,3-triazole (4.27)

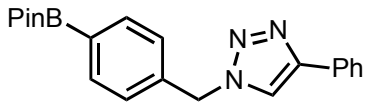


1-(4-Bromobenzyl)-4-propyl-1,2,3-triazole **4.26** (280.2 mg, 1.0 mmol, 1.0 equiv.) was reacted with bis(pinacolato)diboron (267 mg, 1.05 mmol, 1.05 equiv.) according to *general procedure 4G* for a period of 2.5 hours, and purified to generate the title compound (269.7 mg, 82% yield), for which the analytical data obtained was in accordance with that of the material synthesised by the standard route (see **3.81c** – Section 5.3.3.3).

The above procedure was performed on a larger scale using a lower loading of catalyst and ligand: 1-(4-Bromobenzyl)-4-propyl-1,2,3-triazole **4.26** (1.401 g, 5.0 mmol, 1.0 equiv.) was reacted with bis(pinacolato)diboron (1.333 g, 5.25 mmol, 1.05 equiv.) in the presence of $PdCl_2(MeCN)_2$ (16.2 mg, 1.25 mol%), S-Phos (51.3 mg, 2.5 mol%), KOAc (1.472 g, 15.0 mmol, 3.0 equiv.) and dry dioxane (15.0 mL) for a period of 14.5 hours, but otherwise according to *general procedure 4G* to generate the title compound (1.569 g, 96% yield).

Alternatively, 1-(4-iodobenzyl)-4-propyl-1,2,3-triazole **4.121** (327.2 mg, 1.0 mmol, 1.0 equiv.) was reacted with bis(pinacolato)diboron (292 mg, 1.15 mmol, 1.15 equiv.) according to *general procedure 4H* and purified to generate the title compound (271.2 mg, 83% yield).

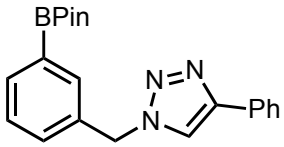
5.4.12.2. 1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-4-phenyl-1,2,3-triazole (4.124)



1-(4-Bromobenzyl)-4-phenyl-1,2,3-triazole **4.122** (314.2 mg, 1.0 mmol, 1.0 equiv.) was reacted with bis(pinacolato)diboron (267 mg, 1.05 mmol, 1.05 equiv.) according to *general procedure 4G* for a period of 2.5 hours, and purified to generate the title compound (328.3 mg, 91% yield), for which the analytical data obtained was in accordance with that of the material synthesised by the standard route (see **3.81a** – Section 5.3.3.1).

Alternatively, 1-(4-iodobenzyl)-4-phenyl-1,2,3-triazole **4.123** (361.2 mg, 1.0 mmol, 1.0 equiv.) was reacted with bis(pinacolato)diboron (267 mg, 1.05 mmol) according to *general procedure 4H* for a period of 20 hours, and purified to generate the title compound (340.7 mg, 94% yield).

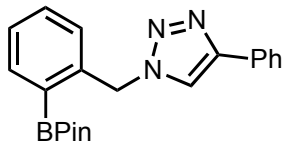
5.4.12.3. 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-4-phenyl-1,2,3-triazole (*m*-4.124)



1-(3-Iodobenzyl)-4-phenyl-1,2,3-triazole ***m*-4.123** (361.2 mg, 1.0 mmol, 1.0 equiv.) was reacted with bis(pinacolato)diboron (267 mg, 1.05 mmol, 1.05 equiv.) according to *general procedure 4H* for a period of 20 hours, and purified to generate the title compound as colourless crystals (329.6 mg, 91% yield).

δH (300 MHz; $CDCl_3$), 7.83-7.76 (4H, m, Ar*H*), 7.64 (1H, s, Tz*H*), 7.41-7.35 (4H, m, Ar*H*), 7.32-7.28 (1H, m, Ar*H*), 5.55 (2H, s, Bn*H*), 1.35 (12H, s, Pin*H*); δC (75.5 MHz; $CDCl_3$), 148.2, 135.3, 134.6, 134.0, 131.2, 130.7, 129.2, 128.9, 128.7, 128.1, 125.8, 119.6, 84.2, 54.3, 25.0; δB (96.3 MHz; $CDCl_3$), 33.76; ESI-HRMS (m/z): calcd for $C_{21}H_{24}BN_3NaO_2$ $[M+Na]^+$ 384.1859, found: 384.1872.

5.4.12.4. 1-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-4-phenyl-1,2,3-triazole (*o*-4.124)



1-(2-Iodobenzyl)-4-phenyl-1,2,3-triazole ***o*-4.123** (361.2 mg, 1.0 mmol, 1.0 equiv.) was reacted with bis(pinacolato)diboron (267 mg, 1.05 mmol, 1.05 equiv.) according to *general procedure 4H* and purified to generate the title compound as, depending on the rate of crystallisation, a white microcrystalline solid or colourless crystals (153.4 mg, 42% yield).

δH (300 MHz; $CDCl_3$), 7.94-7.90 (1H, m, Ar*H*), 7.80-7.75 (2H, m, Ar*H*), 7.74 (1H, s, Tz*H*), 7.48-7.27 (6H, m, Ar*H*), 5.91 (2H, s, Bn*H*), 1.36 (12H, s, Pin*H*); δC (75.5 MHz; $CDCl_3$), 147.7, 140.9, 136.9, 132.1, 130.9, 129.4, 128.9, 128.1, 128.1, 125.7, 120.0, 84.3, 53.6, 25.1; δB (96.3 MHz; $CDCl_3$), 33.96; ESI-HRMS (m/z): calcd for $C_{21}H_{24}BN_3NaO_2$ $[M+Na]^+$ 384.1859, found: 384.1897.

A small amount (c. 10 mg) of a white crystalline solid (crystallised from chloroform) was recovered during the purification of this compound in the early column fractions. This material was not evidenced by exposure of the TLC plates to a UV source, however visualisation was achieved by staining with curcumin, for which the typical colour change indicative of boron was observed. Data obtained for this material: δH (300 MHz; $CDCl_3$), 1.25 (24H, s, Pin*H*); δB (96.3 MHz; $CDCl_3$), 33.49. These analyses are consistent with the material being recovered bis(pinacolato)diboron.

Data of commercial bis(pinacolato)diboron: δH (300 MHz; $CDCl_3$), 1.26 (24H, s, Pin*H*); δB (96.3 MHz; $CDCl_3$), 33.46.

5.5. References

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