IMPROVING THE SCOPE AND UNDERSTANDING OF THE SYMMETRIC AND ASYMMETRIC SUZUKI COUPLING REACTION

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Preface

The research described in this thesis is, to the best of my knowledge, original and my own work, except where due reference has been made.

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Norwich, September 2012

Abstract

Investigations into the Symmetric and Asymmetric Suzuki cross-coupling reaction have been described. A new reaction protocol has been developed in which isolated pre-activated sodium trihydroxyarylborate salts were employed as the organoboron coupling partner, resulting in a more convenient and stoichiometrically efficient process. This alternative protocol has been applied to symmetric Suzuki reactions employing simple electron-rich and electron-poor aryl halide partners, and to sterically challenging Suzuki reactions employing bulkier substrates. Asymmetric (atroposelective) Suzuki coupling reactions were also successfully performed using sodium trihydroxyarylborate salts as coupling substrates. The versatility of these species as general organoboron reagents was also demonstrated by their successful application in a rhodium-catalysed 1,4-addition reaction.

Experimental studies of asymmetric Suzuki cross-couplings towards axially chiral biaryl products have also been detailed. Model reactions towards configurationally stable biaryl products were found to undergo a successful chiral induction with the use of chiral ferrocenyl ligand (*R*)-(*S*)-PPFA **180**, with high enantiomeric excesses achieved in some cases. Investigations into the possible influences on the asymmetric induction process exerted by the electronic and steric properties of the coupling partners were carried out, involving repeat asymmetric reactions towards the biaryl product 1-(2'-nitrophenyl)-2-phenylnaphthalene **179**. In these reactions, changes to the reacting moiety of the coupling substrates were tested, with an additional reaction carried out involving the reversal of the organic group borne by each substrate.

To Gary and Zoë

Acknowledgements

I would firstly like to sincerely thank Prof. Andrew N. Cammidge for the opportunity to work on this project. His support and advice has been invaluable to me, not only during academic discussions but during the difficult times I have faced following the birth of my daughter and through my ill health. Without his continued help and encouragement the completion of this work could not have been achieved.

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Additional thanks go Dr Ben Sutton and Dr Chris Schubert for collaborative work on the investigation of sodium trihydroxyarylborate salts, and to all friends and colleagues of lab 3.17 who have assisted me along the way. Special thanks go to Dr Abdessamad Arbaoui for all his time and help trialling the use of a glove-box protocol, and also to Dr Carl Redshaw for permitting the use of this equipment. I am also deeply indebted to Mr David Day for the carrying out of the chiral HPLC separations at UEA, without which I could not have achieved the vital analyses required of my final product samples.

Lastly, my heartfelt thanks go to my husband Gary and my daughter Zoë for all of their patience and support during the completion of this project. I am also very grateful to the help and encouragement received from my parents and Gary's parents during this time.

Abbreviations

Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
ATR	attenuated total reflectance
BINAP	2,2’-bis(diphenylphosphino)-1,1-binaphthyl
BINOL	2,2’-dihydroxy-1,1’-binaphthyl
BIPHEMP	2,2’-bis(diphenylphosphino)-6,6’-dimethyl-1,1’-biphenyl
Bu	butyl
n-Bu	*normal*-butyl
t-Bu	*tertiary*-butyl
Bn	benzyl
cat.	catalyst
CI	chemical ionisation
cm	centimetre(s)
cod	1,5-cyclooctadiene
compd	compound
Cy	cyclohexyl
δ	chemical shift in parts per million
Δ	heating
d	doublet
dba	dibenzylideneacetone
DCM	dichloromethane
de	diastereomeric excess
decomp.	decomposed
DFT	density functional theory
DMA	dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane

dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1’-bis(diphenylphosphino)ferrocene
DPPFA	*N*,*N*-dimethyl-1-[1’,2-bis(diphenylphosphino)ferrocenyl]ethylamine
dppp	1,3-bis(diphenylphosphino)propane
E	energy
ee	enantiomeric excess
EI	electron impact
equiv.	equivalent(s)
Et	ethyl
FTIR	Fourier Transform infrared
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared
J	coupling constant in NMR spectroscopy
kcal	kilocalorie(s)
KenPhos	2-dicyclohexylphosphino-2'-dimethylamine-1,1'-binaphthyl
L	ligand
m	multiplet
M	metal or molarity of solution
Me	methyl
meo-mop	2-(diphenylphosphino)-2’-methoxy-1,1’-binaphthyl
MHz	megahertz
min	minute(s)
mL	millilitre(s)
μm	micrometre(s)
mmol	millimole(s)
mol	mole(s)
MOP	2-(diphenylphosphino)-2’-methoxy-1,1’-binaphthyl
m.p.	melting point
m/z	mass to charge ratio
υ_{max}	absorption maxima

NAPHOS	2,2’-bis(diphenylphosphino)methyl-1,1’-binaphthyl
NBS	*N*-bromosuccinimide
nm	nanometre(s)
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Nu	nucleophile
pet.	petroleum
Ph	phenyl
PPFA	*N*,*N*-dimethyl-1-[2-(diphenylphosphino)ferrocenyl]ethylamine
PPFOEt	2-[(diphenylphosphino)ferrocenyl]ethoxyethane
PPFOMe	2-[(diphenylphosphino)ferrocenyl]methoxyethane
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
R	hydrogen or alkyl group
ref.	reference
R_f	retention factor
rt	room temperature
s	singlet or second(s)
sat.	saturated
soln.	solution
SLR	standard lab reagent
SPhos	2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
t	triplet
Tf	trifluoromethylsulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
tol	tolyl
TolBINAP	2,2’-bis(di-*p*-tolylphosphino)-1,1’-binaphthyl
t_R	retention time
tt	triplet of triplets
UV	ultraviolet
v/v	volume to volume ratio
X	halide

Contents

CHAPTER 1

Introduction

INTRODUCTION

1.1 Background: The Suzuki cross-coupling reaction

Reactions in which new carbon-carbon bonds are created are vital steps in organic synthesis. Many significant products (drugs, materials, polymers, optical devices, etc.) require the use of such reactions at some stage of their construction.

During the past 50 years, transition-metal mediated cross-coupling reactions have revolutionised this area of organic synthesis. They have become an important class of carbon-carbon bond forming reactions that have been modified and optimised over the years to give reliable, efficient results often using mild protocols. A few examples of the more well-known and utilised of these include the Heck,[1-5] Kumada,[6,7] Stille,[8-10] and Suzuki[11-23] coupling reactions.

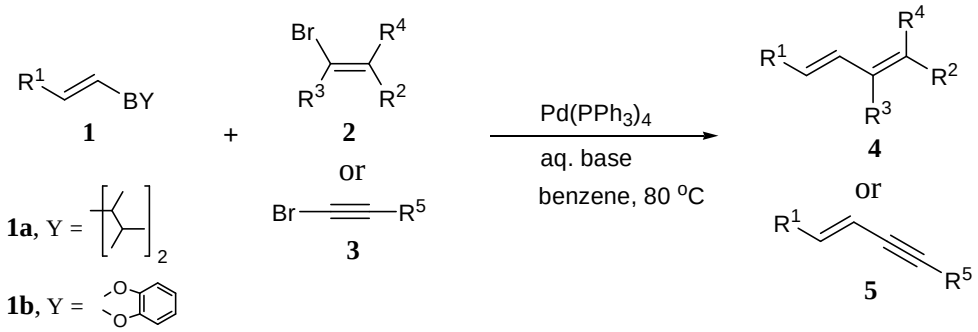
Prior to the discovery of these, the Ullmann reaction[24-26] – in which aryl halides are coupled in the presence of finely divided copper – was generally a routine method. Although its use in present times has somewhat dwindled, it is still of value and is still called upon on occasion. The scope of this reaction, however, is restricted by a number of inherent limitations. As the reaction usually requires elevated temperatures (in the region of 130 – 200 °C) conditions as harsh as these automatically rule out the use of more thermally sensitive substrates. Also, stoichiometric or quasi stoichiometric quantities of copper are required resulting in large amounts of metal waste, which is costly in both economic and environmental terms. Lastly, when the Ullmann reaction is applied to the synthesis of symmetrical biaryl products, respectable results are usually achieved, but when unsymmetrical couplings are attempted between two unactivated aryl halides, three biaryl products are produced in approximately equal amounts.[24] So, in light of these drawbacks, the need arose for an alternative, more selective cross-coupling protocol.

Given its widespread popularity and extensive utilisation in both academic and industrial settings, it can be argued that these needs have been best fulfilled by the Suzuki coupling reaction.[19] Exponential numbers of papers have been published on

the Suzuki reaction since its discovery, and it has often become the method of choice for carbon-carbon bond construction in many synthetic strategies.

1.1.1 Early Suzuki cross-coupling reactions

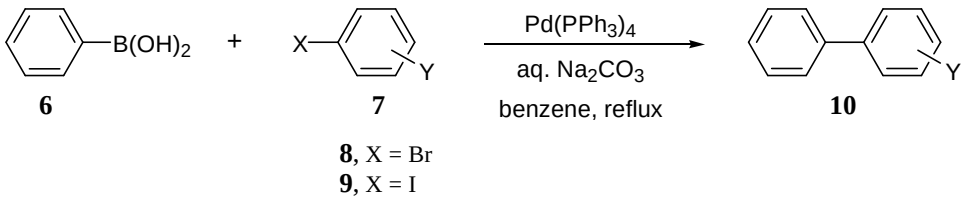
The first successful cross-coupling protocol employed by Suzuki and co-workers in 1979[11] coupled alkenyl boranes **1** together with alkenyl halides **2** or alkynyl halides **3** in the presence of a palladium catalyst and base to give conjugated dienes **4** or enynes **5**:



Scheme 1.1 First Suzuki cross-coupling reaction of (*E*)-1-alkenylboranes with 1-alkenyl or 1-alkynyl bromides.

Despite being initially performed with alkenyl and alkynyl reagents, its scope was rapidly extended to include the coupling of carbons in aryl,[12,20] alkyl[21-23] and heteroaryl[27,28] groups under a wide variety of conditions.

The first method towards the preparation of biaryls **10** was reported by Suzuki and Miyaura in 1981[20] and used the conditions shown below:



Scheme 1.2 First Suzuki cross-coupling reaction towards biaryl products.

The reaction was carried out under homogeneous conditions, using aqueous Na_2CO_3 base. Good yields were also obtained under heterogeneous conditions.

A wide range of standard bases were subsequently tested and used in the Suzuki reaction, namely K_2CO_3,[21,29] Cs_2CO_3,[30,31] Tl_2CO_3[32] and K_3PO_4[21,31,33] and all gave the desired coupled products in high yields. Other alternative bases have also been tested, with good results achieved for more sterically challenging biaryl cross-couplings with use of NaOH,[31] $Ba(OH)_2$,[31,34,35] and TlOH[36,37] to give just a few examples. Use of milder conditions such as those employing CsF, KF and Bu_4NF[38] have enabled the synthesis of biaryls containing base-sensitive functional groups.

1.1.2 Advantages of using the Suzuki coupling reaction

Throughout its development it has emerged that the Suzuki coupling reaction holds many advantages over other related methods.[19,39] These advantages are summarised as follows:

- Under conditions appropriate to the substrates, the Suzuki reaction typically demonstrates good reproducibility together with high yields and selectivity.[15-19]
- It can perform both symmetrical and unsymmetrical cross-coupling reactions equally well.[15-19,23]
- It displays a wide tolerance for a variety of functional groups (present on either the electrophile or the organometallic partner) and this adds to its synthetic flexibility. This has important advantages in terms of more convergent synthetic routes and improved overall yields.[32,34,35,40]
- The stability of the organoboron reagent (e.g. boronic acid) is a significant benefit as they are generally thermally stable and inert to water and oxygen, enabling ease of handling without special precautions.[41] This also entails a prolonged shelf-life without degradation and allows convenience of storage.
- Boronic acids and boronate esters are non-toxic so do not pose a hazard to human health or the environment.[41] The inorganic boron salt by-product is also non-toxic and can easily be removed from the reaction mixture.[19,39]
- Many boronic acids and esters are now commercially available.
- Mild experimental conditions can be employed, with reactions often performed at ambient temperatures.[37,42,43]
- The reaction of simple substrates is largely unaffected by the presence of water, in fact water has even been used as a solvent in some cases.[44-48]

- Very low quantities of palladium catalyst have been shown to catalyse the reaction efficiently, with[49-51] or without ligands.[48,52,53]
- Heterogeneous catalysts such as palladium on carbon[54,55] and polymer-supported palladium[56,57] can be used, facilitating their removal and enabling them to be recycled for further use.
- Aryl chlorides can now be used in some instances in place of generally more expensive aryl bromides or iodides.[43,49-51,55,58-65]
- Aryl fluorides have now been successfully employed as the aryl halide substrate in some select couplings.[66,67]

1.1.3 Limitations of the Suzuki coupling reaction

There are a small number of features associated with the Suzuki coupling reaction that are considered unfavourable:[19,39]

- The starting boronic acid can be difficult to purify, containing mixtures of trimeric anhydrides or 'boroxines'.[68-72] Although these have been shown to participate in the coupling reaction in the same way as the free boronic acid,[70] the presence of these species makes accurate calculations of stoichiometric amounts difficult.
- Aryl-aryl exchange between the palladium centre and phosphine ligands (ligand scrambling) in the palladium(II) species can occur.[73-75] Contamination of the desired coupled product with an alternate coupled species containing the aryl group originating from the phosphine ligand can result.
- Hydrolytic/protolytic deboronation side-reaction can pose problems especially with highly hindered substrates.[31,76-80]
- The Suzuki coupling of highly hindered partners bearing three or four *ortho* substituents is often problematic, although significant progress has been made in recent years.[81-86]

As can be seen from all the aforementioned advantages, the benefits of this reaction far outweigh the limitations, and so therefore it is unsurprising that the Suzuki coupling reaction has gained so much attention since its first conception. It has

become an attractive method not just in the laboratory but for industrial processes also and is now widely used in large-scale processes.[87,88]

Notable applications of the Suzuki coupling reaction include use in the synthesis of natural products such as michellamine,[35] vancomycin,[40] and ellipticine[89] as well in the construction of ligands[90,91] and polymers.[92,93]

1.2 Mechanism/catalytic cycle of the Suzuki reaction

1.2.1 General catalytic cycle

As in other transition-metal promoted coupling reactions, the generally accepted mechanism consists of a catalytic cycle.[15,17-19,94,95] This is thought to involve a sequence of steps; (i) oxidative addition, (ii) transmetallation, and (iii) reductive elimination. A simplified catalytic cycle for the Suzuki cross-coupling reaction towards biaryl products is summarised below (with ligands omitted for clarity):

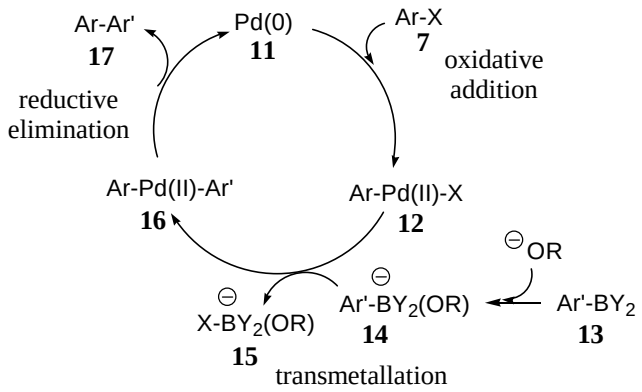
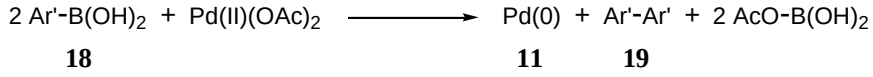


Figure 1.1 General catalytic cycle for the Suzuki cross-coupling reaction.

Oxidative addition of an aryl halide **7** to the palladium(0) species **11** occurs in the first step to form the arylpalladium(II) halide complex **12**, followed by transmetallation of the aryl group from the borate anion **14** to give the diarylpalladium complex **16**. This then undergoes reductive elimination to form the new C-C bond giving the coupled product **17**, with regeneration of the catalyst.

In many instances, oxidative addition forms the rate-limiting step,[12,15,19,23,96] although numerous synthetic and mechanistic studies have shown that any one of the other steps in the cycle may also determine the rate, depending on the conditions and substrates employed.[67,95,97,98]

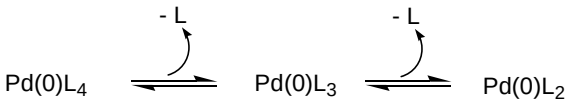
Reduction of a Pd(II) precursor to form the catalytically active Pd(0) species **11** is thought to occur in a separate process prior to the start of the cycle. The exact manner in which this reduction takes place remains unclear, but has been shown to occur in the presence of a phosphine such as triphenylphosphine,[97,99] hydroxide ions,[100] or as a result of a side-reaction involving homocoupling of the boronic acid substrate.[87,101] A simplified scheme of the reduction via boronic acid homocoupling is outlined below:



18 **11** **19**

Scheme 1.3 Formation of a Pd(0) species via boronic acid homocoupling reaction.

In the case of stable $Pd(0)L_4$ catalyst precursors (such as $Pd(PPh_3)_4$), formation of the catalytically active species is thought to occur as a result of the spontaneous (and reversible) dissociation of two ligands:[95,97,102]



Scheme 1.4 Formation of Pd(0) species via spontaneous deligation.

These coordinatively unsaturated Pd(0) species are then present in the reaction media (albeit as a transient species) and are thus able to initiate the catalytic cycle.

1.2.2 Alternative catalytic cycle

An alternative catalytic cycle has also been proposed,[13] in which the oxidative addition step is followed by direct displacement of the coordinated halide ion by the anionic base species to form an (oxo)palladium(II) complex **20** (figure 1.2); sometimes referred to as a 'metathetical' displacement.

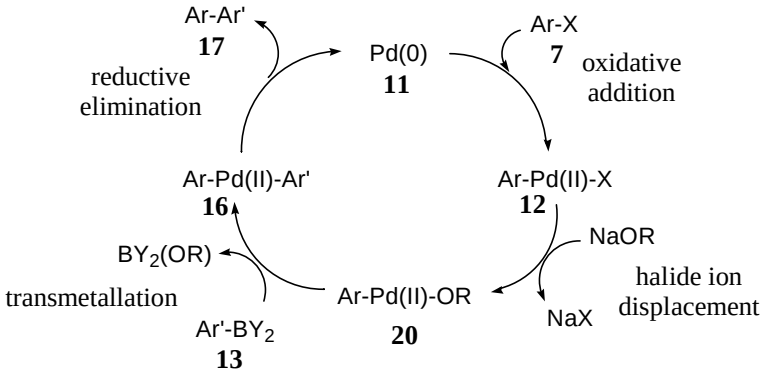


Figure 1.2 Alternative catalytic cycle for the Suzuki cross-coupling reaction.

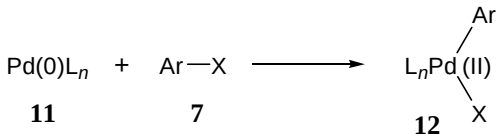
In this version of the catalytic cycle, a neutral arylboronic acid/borane reagent **13** is speculated to react with the (oxo)palladium(II) complex **20** in the transmetallation step.[13,103] Various stable (Ar-Pd(II)-OR) complexes have been successfully isolated and characterised.[100,104-107] Evidence supporting this alternative catalytic cycle has been gained from experiments involving isolated complexes such as these, in which they were shown to react with neutral organoboron species in the absence of base.[14,108]

In another variation of the catalytic cycle shown above, an arylborate anion **14** is postulated to react with the (oxo)palladium(II) complex **20** in the transmetallation step, with the overall process requiring two equivalents of base.[17-19]

The precise mechanisms of oxidative addition[66,67,97,102,109-113] and reductive elimination[114-124] have been studied to a large degree, and are relatively well understood. Although the transmetallation step has been studied to a lesser extent, recent investigations carried out by the groups of Maseras[125-128] Goossen[129,130] and Hartwig[108] have been successful in providing further insights into the nature of this process (see section **1.2.4**).

1.2.3 Oxidative addition

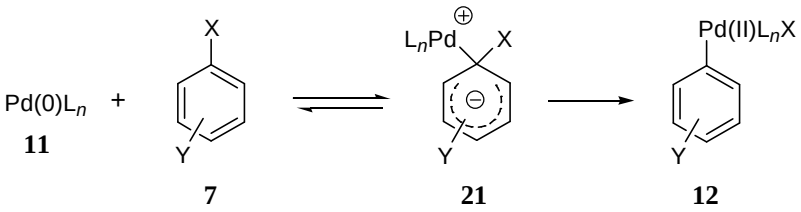
This step corresponds to the insertion of a transition metal, in this case palladium, into the Ar-X bond with subsequent cleavage of the σ bond and formation of two new σ bonds.[131-133]



Scheme 1.5 Oxidative addition of palladium into an Ar-X bond.

This process is named as such on account of the increase in oxidation state of the metal, which is raised by two. This is accompanied by an increase in the coordination number, with the new coordinated species arranged in a *cis* configuration.[97,127,129] Therefore, in order for oxidative addition to take place, the preliminary metal complex is required to be in a low oxidation state and coordinatively unsaturated, with *n* usually equal to either 2 or 1.[102] The oxidative addition step is also known to be facilitated by a higher electron density at the metal centre, with σ-donor ligands such as tertiary phosphines proven to increase this electron density.[102,134]

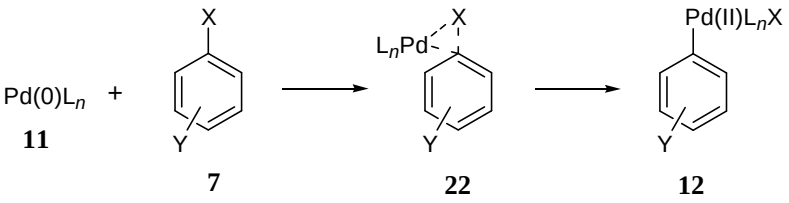
The exact mechanism is thought to differ slightly according to the nature of the organohalide substrate, and has been postulated to proceed via one of two different processes:[66,67,102,110,111] The first example of a mechanism (shown below) can be compared to a nucleophilic aromatic substitution reaction, in which the metal acts as the nucleophile.[102]



Scheme 1.6 S_NAr-type mechanism of oxidative addition.

Data gathered from some select studies[67,135] were found to fit this mechanism, with the cleavage of the aryl halide bond on the carbanion intermediate **21** thought to form the rate-determining step. This would agree with the observed reactivity of the aryl halides towards oxidative addition, in which the reactivity decreases with increasing strength of the Ar-X bond. The rate of oxidative addition has been shown to be particularly enhanced by the presence of electron-withdrawing groups on the aromatic ring; a feature also characteristic of S_NAr-type reactions.

The second possible mechanism involves the formation of a three-centred transition state **22**, in which the attack of the metal at the Ar-X bond happens as a direct, concerted process (scheme 1.7).[102,110]

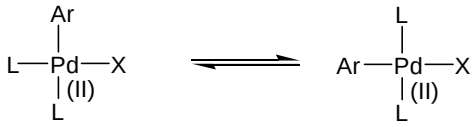


11 **7** **22** **12**

Scheme 1.7 Concerted mechanism of oxidative addition.

This mechanism was found to be consistent with the majority of data collected from investigations into the oxidative addition step.[66,83,97,102,111,127]

In the case of oxidative additions involving Pd(0)L_2 species, the direct formation of a *trans* configured oxidative adduct is generally accepted as symmetry forbidden.[136] This has been recently proven by theoretical studies, in which the formation of *trans* complexes directly from diphosphine palladium(0) species was confirmed as an unfeasible process.[127,129] Therefore, the resulting four-coordinate square-planar complex is initially arranged in a *cis* configuration **23**. Isomerisation to its *trans* isomer **24** is expected to occur rapidly:



23 **24**

Scheme 1.8 Isomerisation of an oxidative adduct from *cis* to *trans* geometry.

This isomerisation proceeds readily as the *trans* isomer is thermodynamically more stable[97,137] and is confirmed by the fact that *trans* palladium(II) complexes are commonly observed and isolated from this step,[128,132,134,137] unlike the *cis* complexes.[138,139]

Three potential mechanisms were proposed for this isomerisation; (i) direct rearrangement via a quasi-tetrahedral transition state arising from the distortion of the

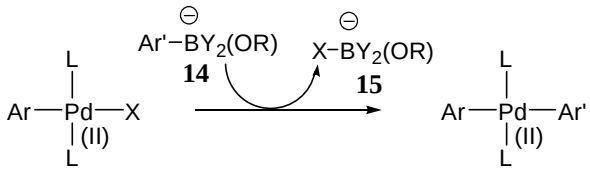
four-coordinate complex, (ii) ligand dissociation with rearrangement of the resulting three-coordinate species followed by subsequent re-association of a ligand, and (iii) initial incorporation of an additional ligand to the palladium coordination sphere to form a five-coordinate intermediate followed by pseudorotation and then loss of a ligand. In theoretical studies conducted by Maseras et al. the first mechanism was found to possess a high energy barrier associated with the unfavourable formation of the quasi-tetrahedral transition state.[127] The second mechanism possessed a significantly lower energy barrier, and thus appeared to be more favourable. A smooth energy profile was also obtained for the third mechanism, and so the formation of a five-coordinate species as an intermediate could not be ruled out. However, conflicting results were obtained in calculations performed by Goossen et al. in which no stable five-coordinate intermediates could be produced.[140] Results from experimental studies[139] agreed with the second mechanism as a more probable description, although kinetic data were complicated by the formation of dimeric species in the media as well as the effects of coordinating solvents.

Isomerisation to the *trans* configuration is usually considered to be a necessary requirement prior to transmetallation, although this commonly held belief has been challenged in some computational studies in which the transmetallation step was found to progress equally smoothly beginning with the *cis* isomer.[127,130]

1.2.4 Transmetallation and the role of the base

Transmetallation is the process by which an organometallic species reacts with the oxidative adduct from the previous step resulting in the transfer of a second organic group onto the palladium complex.[15,103,108,125-128] This step is regarded as a key feature of the Suzuki cross-coupling reaction.

According to the original model of the catalytic cycle (figure 1.1), this process occurs between an ‘activated’ arylborate anion **14** and the *trans* oxidative adduct **24**, giving the *trans*-diarylpalladium(II) complex **25** with formation of an inorganic borate salt by-product **15** (scheme 1.9).

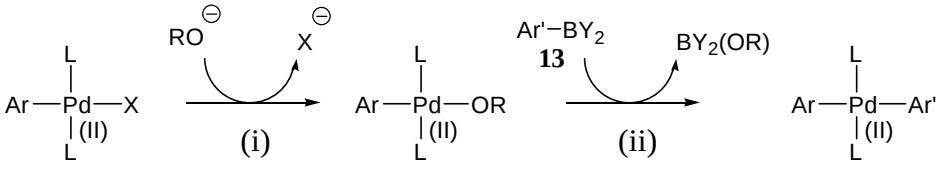


24 **25**

Scheme 1.9 Transmetallation step involving a negatively charged arylborate ion.

In this version of the process, the role of the base is that of forming the negatively charged arylborate ion **14**. Formation of this quaternary 'ate' species is believed to increase the nucleophilicity i.e. carbanionic nature of the organic group on the boron atom, thus enabling the transfer of the organic group onto the palladium centre.[17]

In the alternative version of the catalytic cycle (as depicted in figure 1.2), displacement of the halide ion on the oxidative adduct **24** by the base (RO^-) is thought to occur before transmetallation takes place.



24 **26** **25**

Scheme 1.10 Alternative pathway proposed for the transmetallation step.

Displacement of the halide ion (i) is followed by transfer of the aryl group from the neutral arylboron substrate **13** to the (oxo)palladium(II) complex **26** (ii). In this alternative process, the role of the added base is that of facilitating the formation of the (oxo)palladium(II) complex **26**, rather than formation of a quaternary borate anion **14**. These (oxo)palladium(II) complexes are believed to be more reactive towards transmetallation than arylpalladium(II) halide complexes, on account of the increased polarity of the Pd-O bond which renders the palladium centre more electrophilic.[18]

Recent computational studies into the intricate mechanisms of the catalytic cycle have been carried out by Maseras and co-workers.[125-128] During investigations

focused on the transmetallation step, their DFT calculations revealed that a 'control' reaction between neutral phenylboronic acid **6** and a phenylpalladium(II) bromide complex **27** (in the absence of base) possessed too high an energy barrier for the process to be viable.[126]

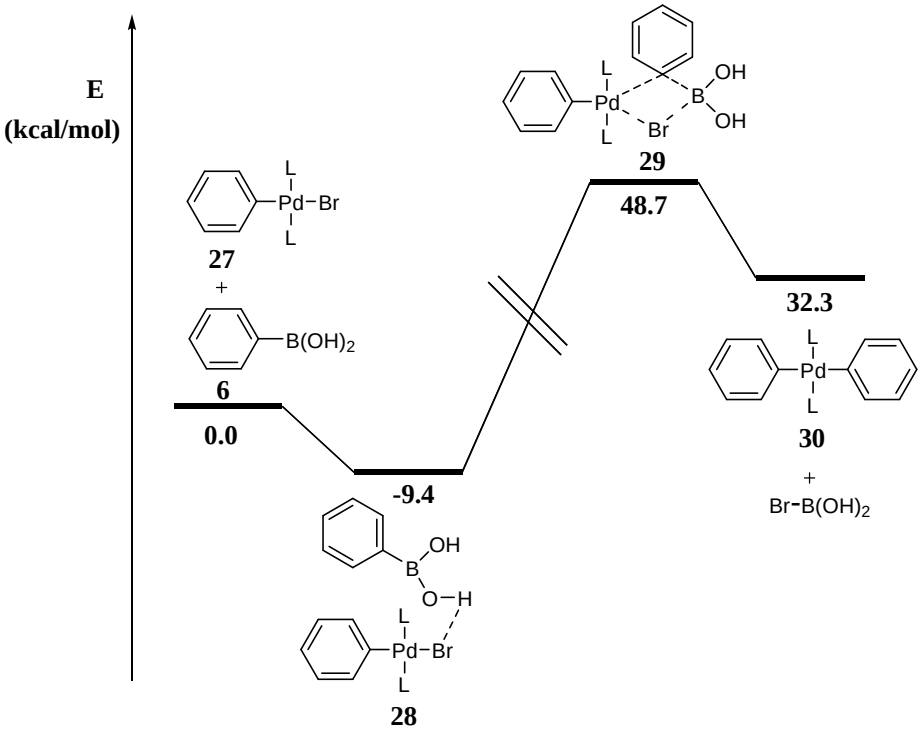
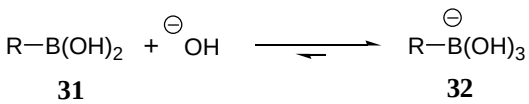


Figure 1.3 Theoretical energy profile for transmetallation between phenylboronic acid **6** and phenylpalladium(II) bromide complex **27** (where L = PH_3).

This profile indicated that the transmetallation was energetically unfeasible, with the overall reaction endothermic by 32.3 kcal/mol. This is in direct agreement with observations from the earliest experiments carried out by Suzuki[11] in which analogous Suzuki couplings did not proceed in the absence of base.

Additional calculations also revealed that the formation of an organoborate ion **32** from the coordination of a base (OH^-) with an organoboronic acid **31** was an extremely favourable process with virtually no energy barrier.[125,126]



31 **32**

Scheme 1.11 Formation of an organoborate species **32** from an organoboronic acid **31** and base.

Therefore the theoretical transmetallation reaction between phenylborate ion **33** and phenylpalladium(II) bromide complex **27** was calculated. It was found to be an energetically favourable process, with the likely intermediates identified as below.[126]

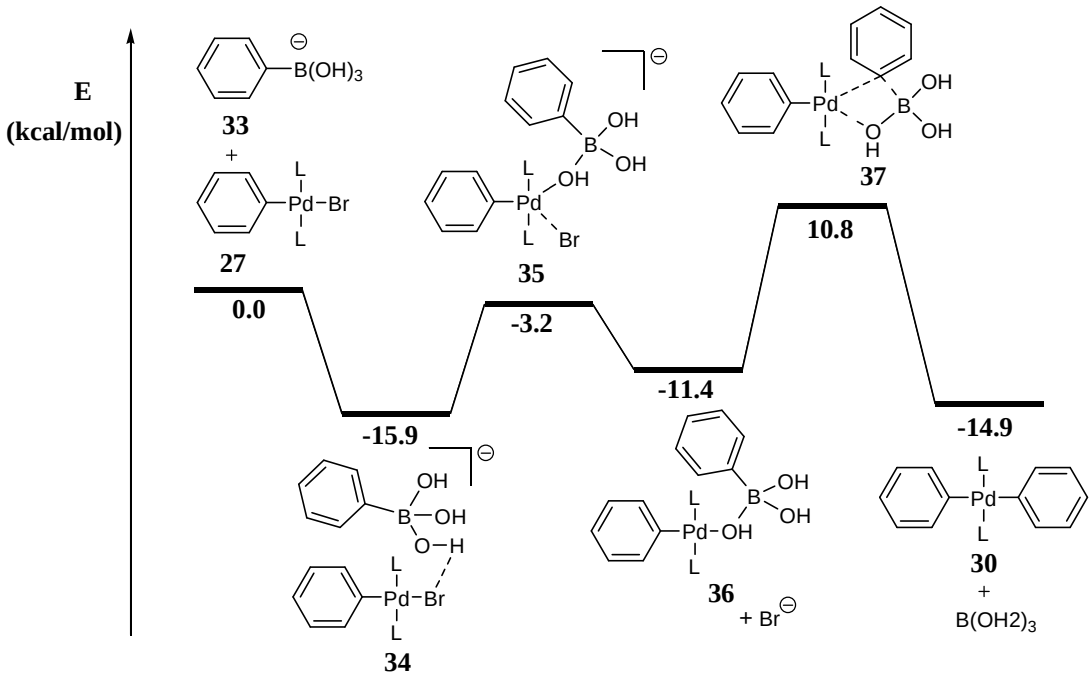


Figure 1.4 Theoretical energy profile for transmetallation between phenylborate ion **33** and phenylpalladium(II) bromide complex **27** (where L = PH_3).

In the first step, the phenylborate anion **33** approaches the palladium(II) complex **27** to form the hydrogen-bonded intermediate **34**. Coordination of the organoborate group to the palladium centre then occurs through the oxygen atom of one of its hydroxyl groups, giving transition state **35**. Displacement of the bromide ion leads to the intermediate **36**. In the next stage, the transmetallation itself takes place, through a 4-centred transition state **37** (a model also proposed by Matos and Soderquist[141]). In this transition state the base occupies a bridging coordination between the two metal atoms. The migration of the phenyl group from the boron atom to the palladium centre happens as a concerted process, resulting in the formation of the *trans*-diphenylpalladium(II) complex **30** and $B(OH)_3$.

When the theoretical transmetallation reaction between neutral phenylboronic acid **6** and a 'pre-prepared' (hydroxo)palladium(II) complex **38** was calculated, it was also found to be a viable process with few energy barriers (figure 1.5).

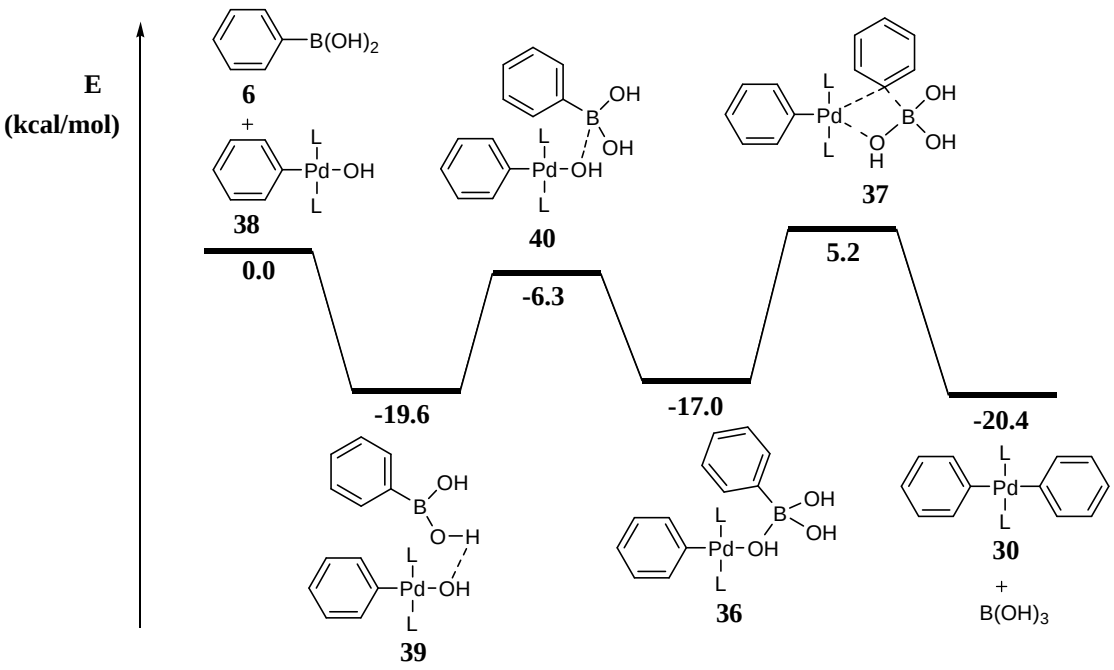


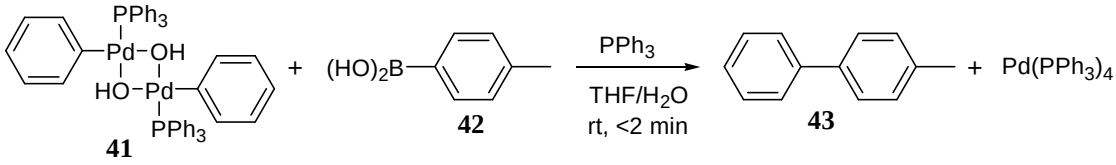
Figure 1.5 Theoretical energy profile for transmetallation between 'pre-prepared' (hydroxo)palladium(II) complex **38** and neutral phenylboronic acid **6** (where L = PH_3).

In the initial step a hydrogen-bonded intermediate **39** is formed, followed by coordination of the boron atom to the hydroxyl group of the palladium(II) complex via transition state **40**. The resulting intermediate **36** is essentially the same as the one seen in the previous energy profile (for phenylborate ion **33** with phenylpalladium(II) bromide **27**), with the 4-centred transition state **37** also equivalent to the one calculated previously.

As mentioned previously, experimental data have shown that isolated (oxo)palladium(II) complexes such as **38** are indeed able to react successfully with neutral organoboron compounds.[14] These results are often presented as persuasive evidence in favour of the alternative mode of transmetallation.

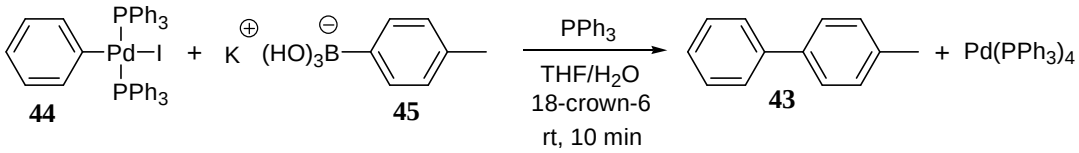
In a recent experimental study carried out by Carrow and Hartwig,[108] two contrasting reactions were performed in order to examine the main pathways proposed for transmetallation. The first reaction was carried out with a stoichiometric quantity

of the isolated dimeric (hydroxo)palladium(II) complex **41** and 4-methylphenylboronic acid **42**.



Scheme 1.12 Reaction of isolated dimeric (hydroxo)palladium(II) complex **41** with 4-methylphenylboronic acid **42**.

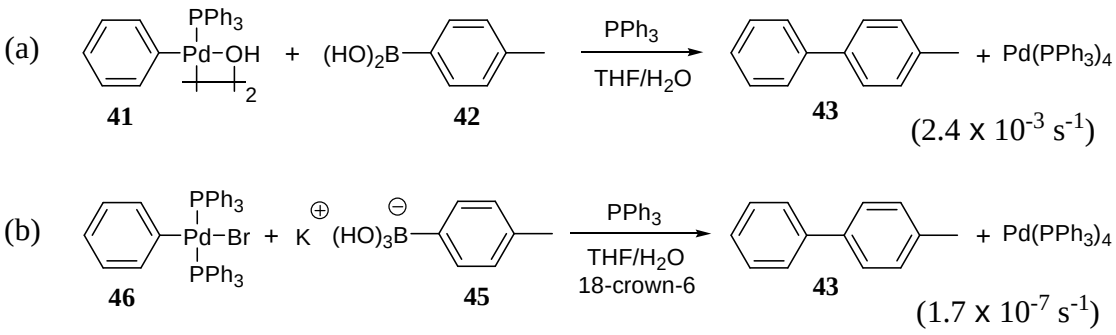
High yields of the cross-coupled product **43** were observed (81%) within minutes of the start of the reaction. The second reaction was performed with an isolated arylpalladium(II) iodide complex **44** and a pre-prepared potassium trihydroxyarylborate salt **45**.



Scheme 1.13 Reaction of isolated phenylpalladium(II) iodide complex **44** with potassium trihydroxy(4-methylphenyl)borate salt **45**.

This reaction also produced high yields of the coupled product **43** (93%) in a short period of time.

The rates of two reactions shown below (scheme 1.14) were then compared, with reaction (a) identical to scheme 1.12 and reaction (b) analogous to scheme 1.13 using an arylpalladium(II) bromide complex. It was found that the observed rate constant for the reaction between the (hydroxo)palladium(II) complex **41** and boronic acid **42** (at −40 °C) was orders of magnitude greater than the estimated rate constant for the reaction between the arylpalladium(II) bromide complex **46** with the potassium trihydroxyarylborate salt **45** (at −40 °C).



Scheme 1.14 Comparison of the rates of reaction between reactions (a) and (b).

This marked difference in the rate constants, despite being derived from an approximated value of the rate constant for reaction (b) and despite the seemingly conflicting data obtained from experimentally determined equilibrium constants for the species present in the reaction media, led the authors to propose that reaction (a) was the process most likely to represent the main transmetallation step of the catalytic cycle, under these conditions.

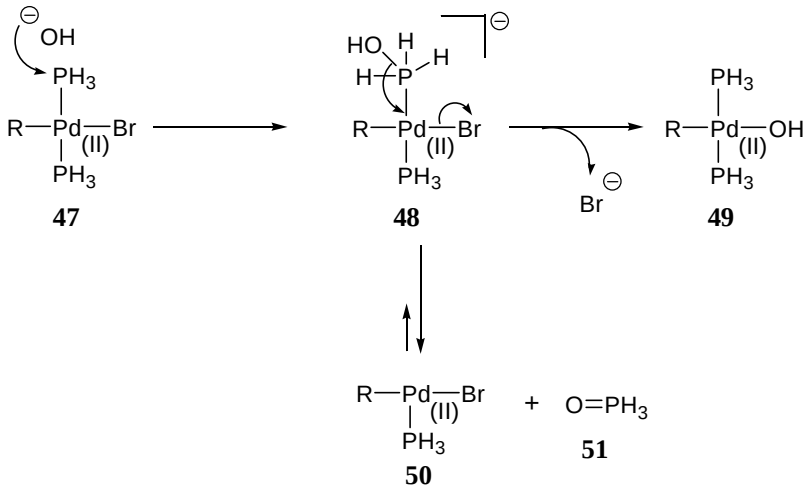
There were, however, several caveats imposed by the authors, and also a number of additional inconsistencies that arose as a result of the direct comparison between the two reactions. For example, important properties intrinsic to the dimeric form of the hydroxo complex **41** - that would have undoubtedly exerted a pronounced influence on the rate of reaction - were not taken into account. Firstly, as compared to its mononuclear form, the dimeric complex **41** is more 'phosphine deficient',[105] as each palladium atom in either half of the complex bears only one phosphine ligand. This would effectively reduce the electron density at the palladium centres, and so enhance reactivity towards transmetallation. With the palladium atoms bonded by two hydroxo bridges (as opposed to a single hydroxyl group) this would also further increase the electrophilic nature of the palladium centres. Additionally, a less sterically hindered approach for the incoming arylboron species would also result from the absence of second phosphine ligand. Therefore it is likely that the dimer is markedly more reactive than the mononuclear form $ArPdL_2(OH)$, and reacts preferentially. As the mononuclear form $ArPdL_2(OH)$ is the species usually depicted in schemes of the alternative transmetallation pathway[13,14,55,103] and is the species used to model computational pathways (e.g. figure 1.5), then it follows that a reaction in which the dimeric species participates cannot be considered as analogous to the postulated process occurring in the alternative pathway.

Although use of a mononuclear (hydroxo)palladium(II) complex $ArPdL_2(OH)$ in reaction (a) could have potentially produced both a closer representation of the suggested alternative transmetallation pathway and a more accurate comparison between the two reactions, it has been reported that dimerisation of these complexes occurs rapidly upon dissolution with the resulting equilibrium favoured towards the dimer.[105]

Lastly, as the reactions were performed under carefully selected conditions using stoichiometric amounts of the isolated palladium(II) complexes, this by its very nature entails that neither reaction can be claimed to be truly representative of a step within a catalytic process.

In fact, the presence of either (hydroxo)- or (alkoxo)palladium(II) complexes under catalytic reaction conditions was questioned in an earlier study conducted by Aliprantis and Canary.[94] It was reported that, from the direct analysis of intermediates in an active Suzuki coupling reaction (performed under standard conditions using aqueous base) no indication of the formation of such (oxo)palladium(II) complexes could be observed. This appeared to strongly challenge the alternative transmetallation mechanism as a feasible pathway, although by the authors' own admission; 'the absence of peaks corresponding to intermediates does not prove that such intermediates are absent.'

Returning to the investigations conducted by Maseras et al.[125,126] it was found that, despite best efforts to model an energetically and chemically feasible transition state for the direct replacement of the halide ion by the base, involving a low-energy approach of the OH^- ion, none could be achieved. As a result, it was deduced that the anionic base species was theoretically unable to displace the bromide ligand from the organopalladium(II) bromide complex in a direct manner. An alternative computationally feasible pathway was proposed, in which the base could possibly react via initial nucleophilic attack on the phosphorus atom of one of the phosphine ligands. This would be followed by migration onto the palladium centre, releasing the bromide ion and thus producing the (hydroxo)palladium(II) complex **49** (scheme 1.15).



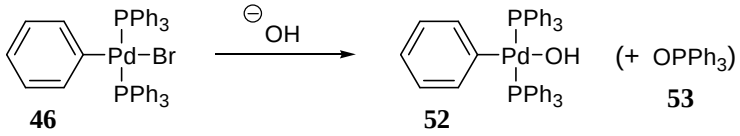
Scheme 1.15 Indirect substitution of the halide ion by the base.

This route would adequately account for the formation of the hydroxo complex **49**, although it could also lead to a side-reaction involving formation of phosphine oxide **51** and eventually to catalyst destruction. This led the authors to argue that a process in which oxidation of one of the phosphine ligands is implied cannot be claimed to represent the main transmetallation pathway in the catalytic cycle, because of its inherent links to catalyst degradation. All the same it must be borne in mind that, as with experimentally deduced results, computationally derived results also include limitations which have to taken into consideration. Therefore, as this pathway was calculated from the probable interactions of species reacting in the gas phase in which solvent and entropic effects are neglected, it cannot be taken as a definitive account of the halide displacement process.

It would certainly appear from a number of experimental reports into the preparation of (oxo)palladium(II) complexes from organopalladium(II) halide complexes that the direct replacement of the halide ion by the base species is implicit, as the process appears to occur rapidly and cleanly.[104,106,107] As a consequence, the apparent ease with which these (oxo)palladium(II) complexes are formed seems to contradict the findings from the DFT calculations, and yet the precise mechanism of this displacement (under the conditions of a Suzuki reaction) still remains unknown.

There are, however some reports in which the production of phosphine oxide is noted during the preparation,[100,141] which would suggest that there may be some

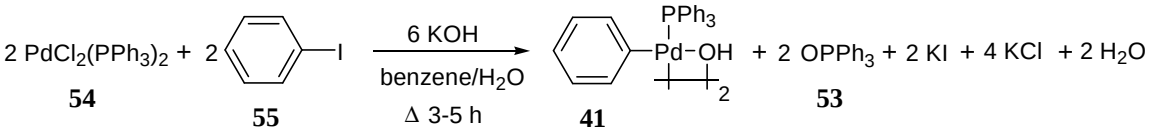
experimental evidence to support the indirect mechanism of halide displacement postulated by Maseras et al.[125,126] In work carried out by Matos and Soderquist[141] for example they observed that addition of base to *trans*-palladium(II) bromide complex **46** produced the hydroxo species **52** with a significant amount of triphenylphosphine oxide **53**:



46 **52** **53**

Scheme 1.16 Preparation of (hydroxo)palladium(II) complex **52** with formation of triphenylphosphine oxide **53**.

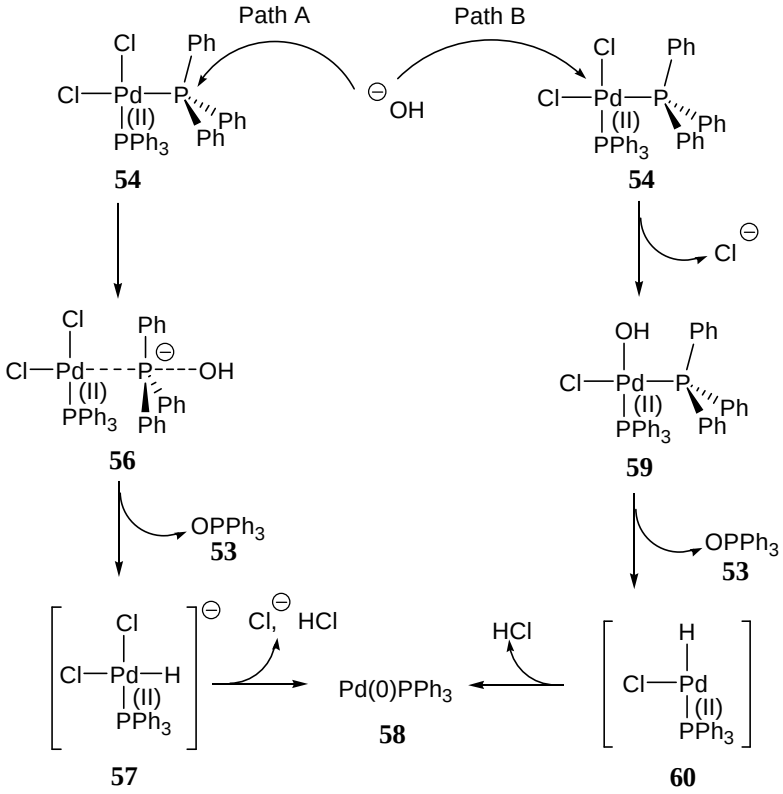
The presence of triphenylphosphine oxide **53** was also noted by Grushin and Alper[100] during their reported synthesis of the dimeric (hydroxo)palladium(II) complex **41**:



54 **55** **41** **53**

Scheme 1.17 'One-pot' preparation of (hydroxo)palladium(II) dimer **41**.

This could initially appear to support the indirect mechanism of halide displacement, if it is assumed that oxidative addition of iodobenzene **55** to a palladium(0) species occurs first, followed by attack of the base on the oxidative adduct (in the manner depicted in scheme 1.15) to form the (hydroxo)palladium(II) complex **41**. In this particular case (scheme 1.17), the formation of triphenylphosphine oxide **53** was postulated by the authors to result from the reduction of the palladium(II) chloride complex **54** by base; in a reaction occurring independently to oxidative addition. This reaction was predicted to result in a palladium(0) species **58** (scheme 1.18) with formation of triphenylphosphine oxide **53** as a by-product, deduced from experiments conducted with palladium(II) chloride complex **54** and base in the absence of iodobenzene **55**. Two possible pathways for this reduction reaction were put forward (scheme 1.18).



Scheme 1.18 Possible pathways for the reaction of base with bis(triphenylphosphine)palladium(II) chloride **54**.

In path A, nucleophilic attack of the hydroxide ion on the phosphorus atom of a ligand occurs, followed by loss of triphenylphosphine oxide **53** and eventual formation of a palladium(0) species **58**. It is interesting to note that this pathway closely resembles the side-reaction proposed by Maseras et al. (scheme 1.15). In path B, the base directly displaces a chloride ligand to form a hydroxo complex **59**, in a manner resembling the first step of the alternative transmetallation mechanism (scheme 1.10). Subsequent reductive elimination of triphenylphosphine oxide **53** from complex **59** occurs.

When this reaction was repeated using a palladium(II) complex bearing chiral phosphine ligands, the process was found to occur with retention of configuration at the phosphorus atom, with the stereochemistry of the phosphine oxide by-product confirmed by its optical rotation. This provided strong evidence to effectively rule out path A, as this mechanism would have led to inversion of configuration. Path B was thus suggested to be the most likely mechanism for this reaction, although no further

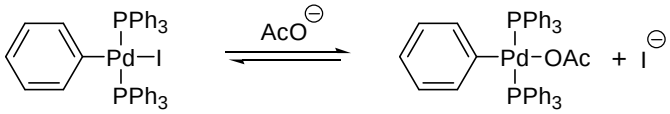
details regarding the exact nature of the chloride ion displacement that occurs at the beginning were elucidated.

Although analogies could be drawn between the results of this reaction and that of the palladium(II) oxidative adduct with base, unfortunately this is not necessarily the case. This is because of the differing nature of the ligands present on the palladium(II) complex, with complex **54** bearing an extra chloride ligand as opposed to an aryl group. This difference would most certainly influence the electronic (e.g. the *trans* effect) and steric properties in a way that may on one hand allow the direct displacement of a chloride ion from complex **54**; but on the other hand disallow the same process for an arylpalladium(II) oxidative adduct. In fact, even within this particular example (scheme 1.18) it was observed that there was a noticeable change in the rate of substitution of the chloride ligand according to which isomer of complex **54** was used; with the *cis* isomer reacting faster rather than the *trans* form. This was attributed to the stronger *trans* influence of a phosphine ligand as compared to a chloride ligand.

Another example of this sensitivity could be seen in the work of Otsuka et al.[107] in which it was noted that the success of preparing *trans*-[PdR(OMe)(PPh_3)$_2$] complexes from the corresponding chloride complex with base (NaOMe) was highly dependent on the nature of the *trans* ligand. It was observed that when the complex [Pd(CH=CCl_2)Cl(PPh_3)$_2$] was treated with NaOMe, the expected (methoxo)palladium(II) complex was not achieved. However, when the *trans* ligand R was either C_6F_5 or CCl=CCl_2, displacement of the chloride ligand by the base occurred rapidly to give the desired *trans*-[PdR(OMe)(PPh_3)$_2$] complex.

An additional issue brought to light was whether the identity of the halide ion on the palladium(II) oxidative adduct bears any influence on the transmetallation step. It would appear that, unlike the well-documented effects of a change in halide on the oxidative addition step[12,15,102,133,142] only a few reports address this related issue.[95,143,144]

In one report, Amatore and co-workers[144] examined the displacement of iodide from *trans*-PhPdI(PPh_3)$_2$ **44** by acetate ions and deduced that the reaction was in equilibrium:

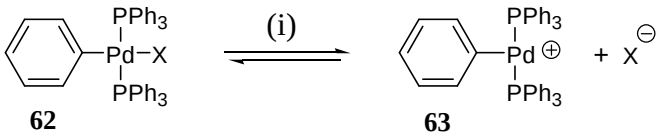


44 **61**

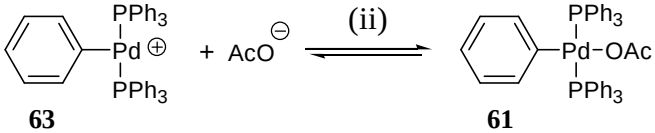
Scheme 1.19 Displacement of iodide ion from complex **44** by an acetate ion.

This reaction was found be general to other halides, with the addition of chloride ions to the reaction resulting in the formation of some *trans*-PhPdCl(PPh_3)$_2$. However, when the equilibrium constants were calculated for the substitution of different halides from the corresponding palladium(II) complexes it was found that the ease of substitution decreased in the order of I > Br > Cl. The rate of exchange was found to be enhanced in this case by the use of THF as the solvent. (Interestingly it was also noted that a detectable amount of triphenylphosphine oxide **53** was produced during this reaction).

The reaction was suggested to proceed via an S_N1 mechanism, in which heterolytic dissociation forming cationic intermediate **63** occurs as a first step, followed by association of the acetate ion:



62 **63**



63 **61**

Scheme 1.20 S_N1 mechanism proposed for the substitution of a halide ion.

In separate work by Smith et al.[95] the validity of this dissociative mechanism within the context of a real Suzuki coupling reaction was questioned. During their mechanistic study of a Suzuki reaction it was found that the rate-determining step changed according to which aryl halide was used. Kinetic runs revealed that the use of an aryl bromide substrate resulted in slow oxidative addition whereas use of an aryl

iodide resulted in slow transmetallation. This seemed to imply that, in the case of a decreased energy barrier for oxidative addition, the displacement of the halide ion from the oxidative adduct during the transmetallation step could become a rate-determining process (under the conditions used). When the rate constants for the transmetallation step were calculated using the kinetic data in mathematical models, the reactivities of the bromide and iodide complexes were found to be the same. Therefore a mechanism involving the formation of a cationic intermediate (from dissociation of the halide ion) was ruled out, as a difference in the ease of dissociation would have led to a difference in the rate of transmetallation between halides. (Other more recent theoretical studies have also disputed this cationic mechanism).[127]

An additional important observation from the work by Smith et al.[95] was that the transmetallation step appeared to be surprisingly sensitive to steric crowding on the palladium(II) oxidative adduct, with a ligated *ortho*-substituted aryl group acting to considerably slow the process.

Lastly, in other notable work conducted by the groups of Goossen[129,130] and Jutand[145,146] alternative transmetallation pathways have been proposed involving the participation of anionic intermediates, in which halide or acetate ions play an integral role. These alternative pathways have been postulated to include either three-coordinate palladium(II) species or five-coordinate palladium(II) species, with the feasibility of these modes investigated by computational methods. During experiments in which the reactive species were both generated and monitored by electrochemical methods, Amatore and Jutand[144,145] concluded that the influence of the extra anion (released from either reduction of the palladium catalyst precursor or from the aryl halide during the reaction) was not limited to just the oxidative addition step, as the reactivity of a five-coordinate palladium(II) oxidative adduct towards nucleophiles was also dependent on the type of anion ligated to the palladium complex.

Goossen and co-workers[129] could not find any evidence for the existence of such five-coordinate palladium(II) intermediates however, as all attempted calculations led to unfeasibly high energy systems. This mirrored their findings from previous investigations into *cis-trans* isomerisation mechanisms of the oxidative adduct. The participation of a three-coordinate intermediate was determined to be

more feasible, with a mono-phosphine palladium(II) complex found to be a very favourable starting point for transmetallation. Despite being obtained from theoretical reactions modelled on phenylboronic acid and acetic anhydride substrates, this result implied that transmetallation may, in general, be favoured by prior dissociation of a phosphine ligand, as this would not only enhance the electrophilicity of the palladium centre but also serve to decrease the steric crowding around the complex.

In summary, it has not yet been determined outright which postulated mechanism (scheme 1.9 or 1.10) represents the most accurate mode of transmetallation, as each method of analysis (theoretical or experimental) carries its own associated limitations. What can be established nevertheless is that transmetallation is a complex process in which the precise pathway is dictated by the nature of the substrates and reaction conditions employed. Theoretical and mechanistic studies are consequently hampered by this complexity, with real reaction systems containing a variety of different species; all of which may play a role in this step. Therefore, the search for a single universal mechanism to describe all transmetallation processes is perhaps an unrealistic endeavour, as it would seem that no one single model could possibly encompass all the possible variations in the reaction media.

In spite of the conflicting arguments that arise, several conclusions *can* be drawn from all the investigations carried out into this step. These are:

- Transmetallation is a multi-step process that occurs through a number of intermediates.[125-127]
- The precise pathway is highly dependant on the specific nature of the substrates and reaction conditions used.[103,127]
- From this, it follows that accurate parallels cannot be drawn between either isolated stoichiometric reactions or model reactions with an actual transmetallation step in a catalytic cycle, because of its sensitivity to the type of species and their presence (or absence) in the reaction media.[145,146]
- However it can be predicted with a reasonable degree of certainty that couplings in which the formation of a borate ion is favoured are likely to proceed via the

original scheme proposed, whereas couplings employing weakly Lewis acidic organoboron reagents are more likely to proceed via the alternative pathway.[141]

- In either scenario, the addition of a base is necessary in order to facilitate the transmetallation step.[13]
- The displacement of the halide ion from the palladium(II) oxidative adduct is a fundamental feature of the transmetallation process. If the exact manner in which this displacement occurs is elucidated, then this would unravel many uncertainties regarding the mechanism of transmetallation.
- The two main pathways proposed (figures 1.4 and 1.5) represent discrete examples in a number of possible interlinked pathways.[129,130,141]
- These mechanisms may not necessarily be mutually exclusive, with the strong possibility that both (or more) may be operative at the same time within the same reaction.
- It is also highly likely that rather than functioning in one specific role over another, the base performs multiple roles throughout the catalytic cycle, simultaneously.[141]

Inevitably, investigations into the mechanism of transmetallation are on-going as the intricacies of this step continue to be a source of interest. The benefits of an improved understanding are clearly evident, as this could lead to better design and optimisation of reaction conditions. It would seem that in order to elucidate the exact details of a transmetallation mechanism operating within a particular experimental system, studies involving meticulous attention to the exact nature of all variables e.g. substrates, ligands, solvent, etc. are essential.

1.2.5 Reductive elimination

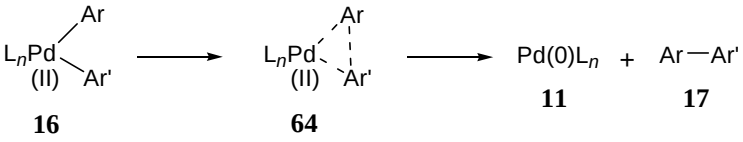
In simple terms, reductive elimination can be considered as a unimolecular process, in which palladium(II) is reduced back to palladium(0) with simultaneous elimination of the coupled biaryl product **17**.[15,131]

16 **11** **17**

Scheme 1.21 General ‘text-book’ description of the reductive elimination step.

The regenerated palladium(0) species **11** is then able to repeat the oxidative addition step to complete the catalytic cycle. This process can only take place through the *cis* configuration of the diorganopalladium(II) complex **16**, and is favoured by a reduced electron density at the palladium centre together with an increased steric bulk around the metal. It has been claimed that, in theory, if bulky, less electron-rich phosphine ligands are employed then the barriers for oxidative addition are expected to increase whereas those on the other hand for reductive elimination would be expected to decrease.[129]

The actual C-C bond formation is thought to proceed via a concerted process involving a three-centred transition state **64**:[123,124]



16 **64** **11** **17**

Scheme 1.22 Concerted process of C-C bond formation.

In the case of aryl groups, it has been suggested that reductive elimination is further enhanced by the participation of the π-orbitals during the formation of the C-C bond.[15,123,130]

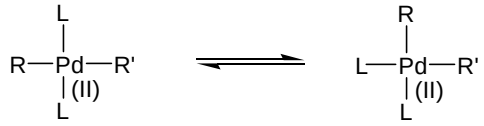
65 **11** **17**

Scheme 1.23 Participation of π-orbitals during reductive elimination.

The resulting perpendicular orientation of the aryl groups with respect to the coordination plane is thought to present a stereoelectronically favourable conformation for reductive elimination.[123]

Other important insights into the nature of reductive elimination have been gained from studies into the thermal decomposition of diorganopalladium(II) complexes.[115,116,122] Whilst investigating the decomposition of *cis*- and *trans*-dialkylpalladium(II) complexes, Yamamoto and co-workers found that both species

decomposed rapidly to produce a coupled alkane product with precipitation of palladium metal.[115] Isolated diarylpalladium(II) complexes were found to be more stable, but also decomposed readily upon dissolution to give a biaryl product and metallic palladium.[116] As this process was found to occur equally well for both *cis*- and *trans*-diorganopalladium(II) complexes, isomerisation of the *trans* complexes was deduced to take place prior to the process.



25 **66**

Scheme 1.24 Isomerisation of the *trans* isomer to the *cis* isomer.

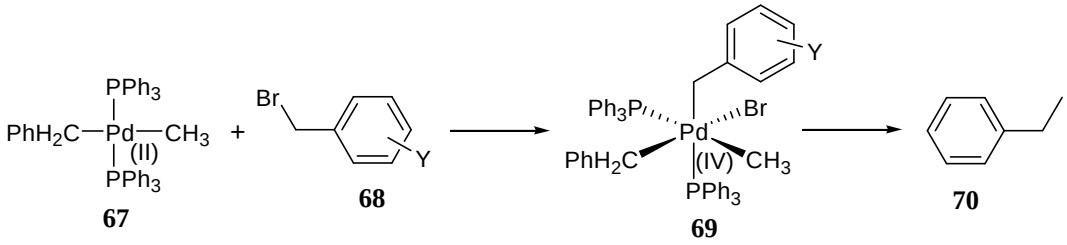
As with the isomerisation that follows oxidative addition, this isomerisation was also speculated to proceed via three possible processes; (i) distortion of the square planar complex into a quasi-tetrahedral transition state or (ii) initial loss of a phosphine ligand to form a three-coordinate species followed by rearrangement and re-association of a ligand, or (iii) coordination of an additional ligand to give a five-coordinate species followed by pseudorotation and dissociation of a ligand.[114,115,127,136] Computation of the energy profiles for these processes revealed that the dissociation of a ligand to give a three-coordinate species was the most feasible, with the others possessing high energy barriers. The formation of a five-coordinate intermediate was determined to be especially unfavourable, as the occupation of the apical position by an unsaturated organic group was found to exert a strongly destabilising influence in this partially antibonding position.[127] (A fourth possible process involving an extra oxidative addition to the diorganopalladium(II) complex was also proposed; see below).[8,114,118]

This isomerisation was also found to be enhanced by the use of polar, coordinating solvents, which at first was thought to infer a mechanism involving the five-coordinate transition state[114] but was later rationalised in terms of possible stabilisation of the three-coordinate species by a coordinating solvent molecule.

Although generally applicable to most reductive elimination processes,[123] the unimolecular mechanism depicted in scheme 1.21 was challenged by a number of

studies in which experimentally derived observations could not be adequately explained by this simplistic model.[8,114,117-119,147,148] The concept of stimulation of reductive elimination by an incoming organohalide substrate molecule, for example, was alluded to as early as 1976 in studies by Kumada and co-workers.[7] During examination of the catalytic cycle of nickel-catalysed coupling reactions they suggested that the reductive elimination of two organic ligands bound to the nickel complex L_2NiR_2 could possibly be stimulated by the addition of an extra molecule of organohalide, with the formation of a five-coordinate intermediate.

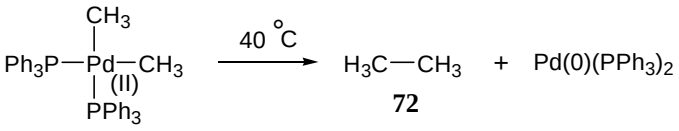
Later investigations by Milstein and Stille[8,118] into the mechanism behind palladium-catalysed couplings of either organotin or Grignard reagents with organohalides also included the supposition that reductive elimination was preceded by an interaction with the diorganopalladium(II) complex by another molecule of organohalide. Further oxidative addition to give a six-coordinate palladium(IV) intermediate was proposed to occur, with observations from preliminary studies in apparent support of this. For example, the rate of reductive elimination from palladium(II) complex **67** was found to be accelerated by the addition of an organohalide substrate **68**.[118]



Scheme 1.25 Reductive elimination promoted by addition of organohalide **68**.

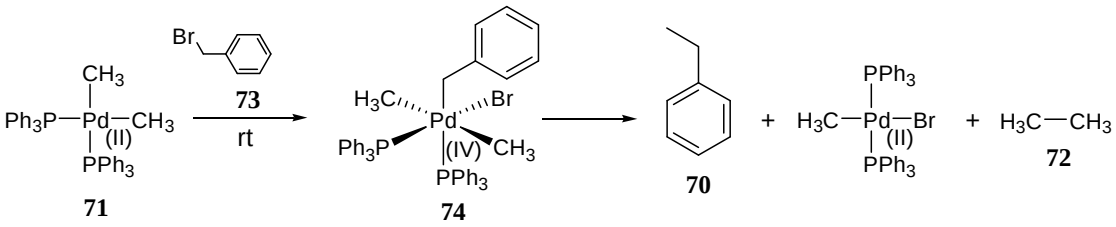
The enhanced rate was attributed to the resultant *cis* positioning of the organic groups as well as the increased desire of the palladium centre to return to a lower oxidation state.

The facile decomposition-type reaction of *cis*-palladium(II) complex **71** with resulting reductive elimination of ethane **72** was also monitored.[117,118] Evolution of ethane **72** was observed at 40 °C at a steady rate (scheme 1.26).



Scheme 1.26 Reductive elimination of ethane **72** from complex **71**.

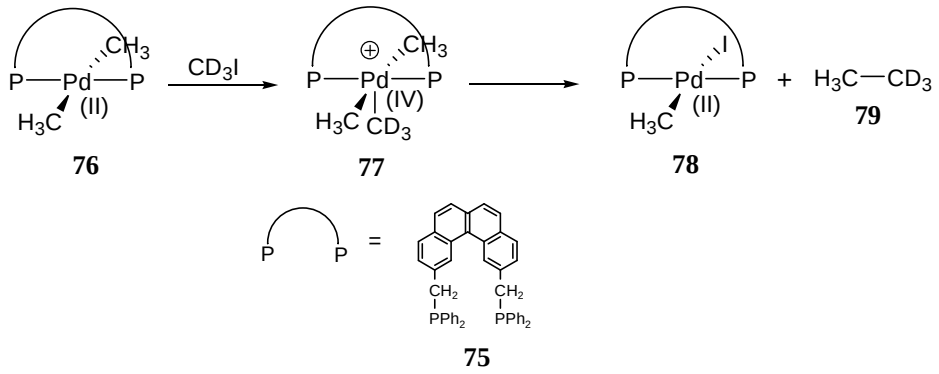
When benzyl bromide **73** was added however, reductive elimination proceeded rapidly at room temperature giving rise to a small amount of ethane **72** together with an alternative coupled product, ethylbenzene **70**:



Scheme 1.27 Rapid reductive elimination of ethylbenzene **70**.

As this process occurred at a lower temperature and at an increased rate it was deduced that the addition of the extra bromide resulted in the facilitation of reductive elimination, with resulting preferential elimination of coupled product **70**. The formation of this alternative coupled product was interpreted as proof of the participation of the postulated six-coordinate palladium(IV) intermediate **74**.

Further evidence supporting the involvement of a palladium(IV) intermediate was gained from the study of *trans*-dimethylpalladium(II) complex **76**, in which the *trans* configuration was fixed by the use of a bridging bidentate phosphine ligand 'TRANSPHOS' **75** (scheme 1.28).[117] It was noted that despite the fixed configuration preventing isomerisation to the *cis* geometry, rapid reductive elimination occurred after addition of methyl iodide, with evolution of ethane **72**. Use of trideuteriomethyl iodide provided further confirmation, as trideuterioethane **79** was the only product eliminated (scheme 1.28).



Scheme 1.28 Reductive elimination through postulated palladium(IV) intermediate **77**.

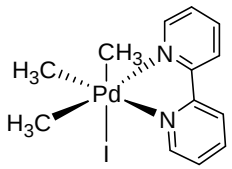
The involvement of palladium(IV) intermediates as part of the general catalytic cycle was also put forward as a possible explanation as to why overall rates of cross-coupling reactions have often found to be faster than the isolated reductive elimination step.

An alternative reductive elimination mechanism was also suggested in work carried out by our own research group.[147] In these studies, the Suzuki coupling of two sterically hindered aryl substrates was investigated, with the rate-determining step thought to be reductive elimination. Stimulation of reductive elimination was proposed to occur through the possible formation of an octahedral transition state. However, the feasibility of the formation of a transition state of this kind would strongly depend upon the ability of a second incoming organohalide molecule to overcome the significant steric barrier posed by the coordinated ligands already present. The high steric bulk of the organic ligands coordinated to the diorganopalladium(II) complex would suggest that the formation of such a highly congested species is unlikely. Studies have shown that square-planar four-coordinate palladium(II) species possessing large ligands display a marked preference for this form, with the formation of higher coordinated species energetically unfavourable due to strong repulsive steric interactions.[143]

Arguments against the alternative reductive elimination mechanism proposed by Stille et al. claim that the outcomes of reactions such as those previously described (schemes 1.22, 1.24 and 1.25) are the result of intermolecular processes, in which exchange of organic groups occurs between a diorganopalladium(II) complex and a

trans-organopalladium(II) halide complex (formed in situ) through a dimeric bridged intermediate.[120-122] It has also been claimed that if the postulated reductive elimination mechanism involving a six-coordinate palladium(IV) intermediate was operating universally then significant amounts of scrambled homocoupled products would be regularly observed,[122,148] which is not usually the case. Other points in contention include the fact that palladium(IV) complexes are rarely observed or isolated,[149,150] unlike the equivalent platinum(IV) complexes which are well documented.[136] There are also no reports of the direct observation of such a species within an actual catalytic Suzuki reaction, despite in-depth analyses utilising NMR spectroscopy[120] and electrochemical methods.[145,146]

In an exceptional case the preparation and isolation of a stable octahedral palladium(IV) complex **80** was achieved, with its structure confirmed by X-ray crystallography.[149]



80

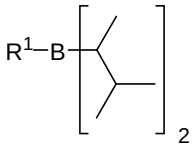
Figure 1.6 Isolation of octahedral palladium(IV) complex **80**.

Both the formation of **80** via oxidative addition of methyl iodide to a pre-prepared palladium(II) complex together with its subsequent decomposition through reductive elimination of ethane **72** were clearly observed by NMR spectroscopy.[149] The relative stability of this type of complex was found to be strongly dependent on both the nature of the ligands present and their positioning, with those disfavouring dissociation to a five-coordinate species greatly enhancing the stability.[150]

Consequently, it has been demonstrated that although palladium(IV) complexes are indeed viable and can even be isolated, it remains to be determined whether they represent an actual participating species in the reductive elimination step of a Suzuki coupling reaction.

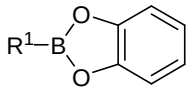
1.3 Coupling reagents: The organoboron substrate

Historically, early Suzuki coupling reactions utilised organoboranes and boronates, synthesised from hydroboration of their alkene or alkyne counterparts.[11,12] The first organoborane species used in these couplings were **81** and **82**:



81

and

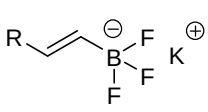


82

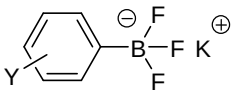
Figure 1.7 Organoboron species first employed in Suzuki coupling reactions.

Use of the catechol boronate or 'benzodioxaborole' substrate **82** was found to give the best yields as compared to alkylboranes **81**. This prompted the continued use of this substrate and other boronate esters, which subsequently led to the use of boronic acids. When they were tested as the organoboron substrate they were found to couple successfully in the presence of base. They displayed a higher reactivity than their boronate ester analogues and so rapidly became the organoboron reagents of preference. However boronate esters remained useful when employed in couplings where deboronation was a problem (see section **1.3.2**).[31]

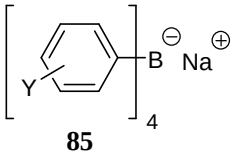
Other organoboron species have since been tested in Suzuki coupling reactions; specific examples include trifluoroborate salts **83** and **84**[151-153] and tetraarylborate salts **85**:[47,48,154]



83



84

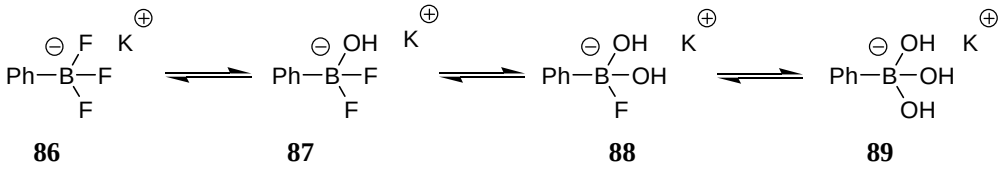


85

Figure 1.8 Other alternative organoboron coupling substrates.

Potassium vinyltrifluoroborate salts **83** were first used by Genêt et al.[151] in a Suzuki-type coupling reaction with arenediazonium salts to give a vinylated coupled product. This type of reaction was then extended to include the use of potassium aryltrifluoroborate salts **84** as substrates,[152] although subsequent studies by Molander et al.[153] and Lloyd-Jones et al.[155,156] have questioned the mode of participation of these

trifluoroborate species in the catalytic cycle. It was observed from ^{11}B and ^{19}F NMR analysis of test reactions that addition of base to potassium phenyltrifluoroborate salt **86** in methanol led to the displacement of fluoride, resulting in a different 'ate' complex bearing no fluorine substituents.[153] It was deduced that under these conditions the complete substitution of fluoride by hydroxyl groups occurred.



86 **87** **88** **89**

Scheme 1.29 Substitution of fluoride by hydroxyl groups.

Although the completely substituted species **89** was found to be the most predominant, the possibility of mono- **88**, di- **87** or trifluorinated **86** species participating in the catalytic cycle could not be ruled out. Calculations of the transmetallation energy profiles for all four species revealed that the trihydroxyborate species **89** was the most reactive.[155] The presence of the free boronic acid species **6** was also observed, and was found to be in rapid equilibrium with the borate species **89**. Under conditions in which the concentration of water in the reaction solvent was reduced, the equilibrium shifted dramatically in favour of the boronic acid species. Further investigations proposed that in such systems the trifluoroborate salt could act as an in situ 'slow-release' source of boronic acid, enabling smooth cross-coupling with inhibition of side-reactions such as deboronation.[156]

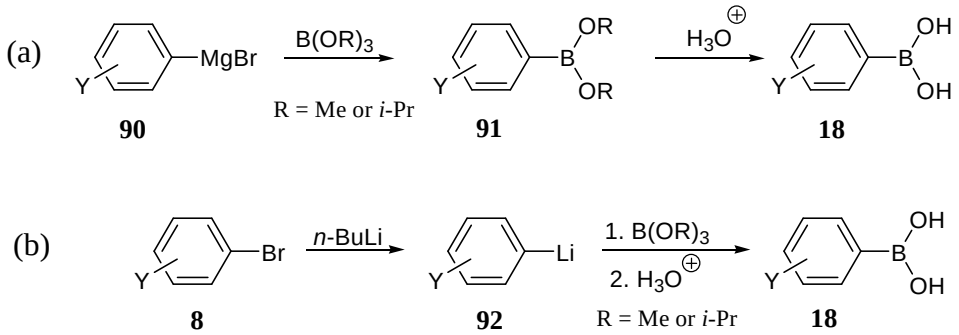
In 1992, sodium tetraarylborate salts **85** were first used in Suzuki coupling reactions with vinyl and aryl triflates by Ortar and co-workers.[154] The tetraarylborate species was speculated to surrender two of its aryl groups readily during successive transmetallation processes, with the transfer of a third aryl moiety less effective but also feasible. The addition of base was a necessary requirement, despite the quaternary nature of the initial species. Bumagin et al.[47] later reported the successful coupling of sodium tetraarylborate salts **85** with aryl halides **7**, carried out in aqueous media using 'ligandless' palladium catalysts. The scope of this reaction was extended to include the use of aryl chlorides as substrates. In more recent work, Xu and co-workers[48] also utilised sodium tetraarylborate salts **85** in Suzuki couplings, performed

under similar aqueous conditions in which it was also noted that the presence of a base was vital for the success of the reaction. The catalytic cycle proposed was essentially the same as the general catalytic cycle (see scheme 1.1) except for the involvement of successive alternative transmetallation steps allowing for the complete consumption of all aryl groups present on the starting substrate **85**.

1.3.1 Preparation of organoboron substrates

1.3.1.1 Preparation of arylboronic acids

Syntheses of arylboronic acids **18** employing Grignard reagents **90** or organolithium reagents **92** are generally considered the standard approaches for preparing such compounds:[41,72,157-159]



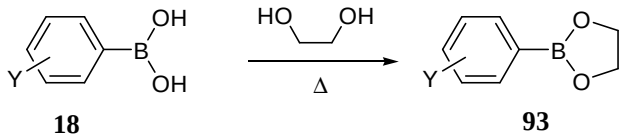
Scheme 1.30 Preparation of arylboronic acids via organometallic reagents.

The original protocol established by Bean and Johnson[157] was that of method (a) in which a Grignard reagent **90** is prepared from its aryl bromide **8** and then added to a solution of trialkylborate, followed by hydrolysis of the resulting boronic ester **91** to give the free acid **18**. This method is still commonly used although it is restricted to substrates that are compatible with the Grignard reagent. A later variant illustrated in method (b) utilised an organolithium reagent **92** which is reacted with trialkylborate in a similar manner followed by hydrolysis under acidic conditions.[158,159]

1.3.1.2 Preparation of arylboronate esters

Arylboronate esters of the type **91** are usually unstable and are prone to hydrolysis at room temperature by atmospheric moisture.[72] Cyclic boronate esters **93**

on the other hand are thermally stable and can be obtained from arylboronic acids **18** by a condensation reaction with diols under dehydrating conditions.[41]

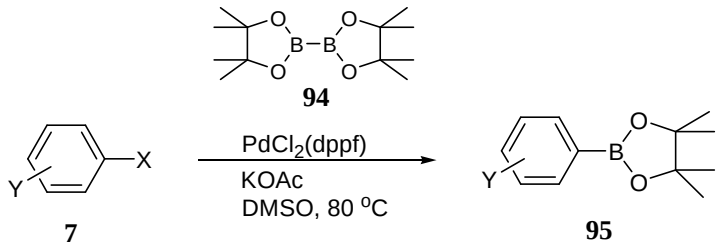


18 **93**

Scheme 1.31 Preparation of cyclic boronate esters from arylboronic acids.

In this example ethylene glycol is used but alternative boronate esters can be formed from diols such as pinacol and 1,3-propanediol. They typically form waxy solids and can usually withstand purification by column chromatography.

Arylboronate esters **95** have also been obtained directly from aryl halides **7** via the coupling of an alkoxydiboron **94**:



94

7 **95**

Scheme 1.32 Alternative route towards boronate esters.

This reaction is often referred to as the 'Miyaura borylation' and is useful as it tolerates a variety of functional groups such as esters, nitrile, nitro, and acyl groups.[160,161] It can also be utilised in 'one pot' strategies in which the boronate ester is formed in situ and then reacted directly with an aryl halide in a Suzuki coupling reaction.[162]

1.3.2 Reactivity of arylboron substrates

As discussed previously, boronic acid substrates remain unreactive in the Suzuki coupling reaction until a base is added.[11,17] The addition of base was found to be crucial to the success of the reaction, and is generally attributed to the formation of a quaternary 'ate' species. This is believed to be the reactive species that partakes in

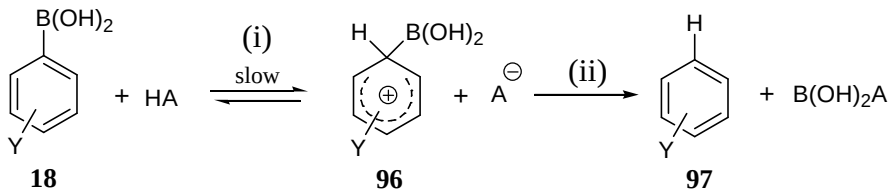
the transmetallation step of the catalytic cycle, although other modes of activation caused by the presence of the base have been proposed (see section **1.2.4**).

When employed in simple unhindered Suzuki coupling reactions, arylboronic acids are generally more reactive than their arylboronate ester analogues. However, when sterically hindered arylboronic acids are used, it has been noted that the rate of the coupling reaction drops significantly, with lower yields of product obtained.[31] In these reactions the deboronation side-reaction becomes more prominent and adversely consumes the organoboron starting reagent (see following section). Although the use of a stronger base was found to accelerate the rate of the coupling reaction, other measures taken to prevent the deboronation side-reaction were also beneficial. Such measures included the use of anhydrous, aprotic conditions, requiring the use of cyclic boronate esters such as **93** and **95** on account of their inability to act as a proton source and ease of drying. Therefore, in reactions such as these the use of boronate esters is usually preferential to that of boronic acids.

1.3.3 Deboronation side-reaction of arylboron substrates

The deboronation side-reaction of arylboronic acids **18** in Suzuki coupling reactions has been speculated to proceed by a variety of different pathways. Comprehensive studies conducted by Kuivila et al. revealed that deboronation of arylboronic acids can occur under both acidic and basic conditions,[76-79] as well as being catalysed by the presence of metal ions.[80,163]

A number of different mechanisms were initially postulated. In the case of acid-catalysed deboronation, results obtained from kinetic experiments revealed that the mechanistic pathway which correlated best with the observed data was that of the A-S_E2 mechanism.



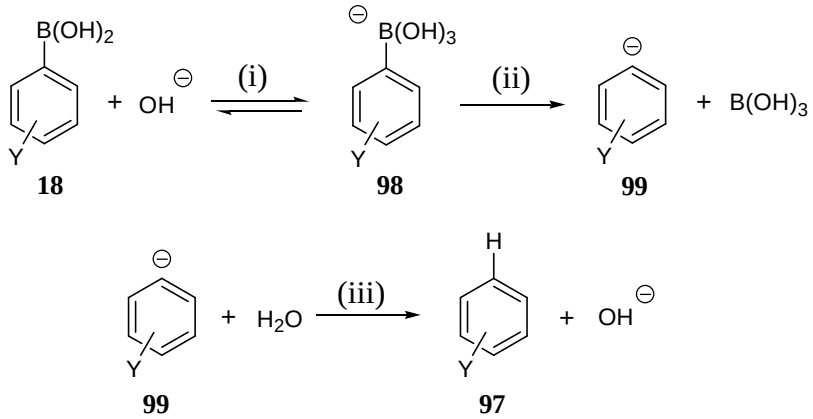
18 **96** **97**

Scheme 1.33 A-S_E2 mechanism of acid catalysed deboronation of arylboronic acids.

This simple two-step mechanism favoured by Kresge and Chiang[164] exemplifies 'general acid catalysis' in which the acid species is represented by 'HA'. The acid-catalysed deboronation reaction of arylboronic acids was found to fit this model as it was not specifically catalysed by H_3O^+ ions only. The first step involving proton transfer from an acid to form an arenium ion **96** (i) was found to be the rate determining step.[77] Cleavage of the C-B bond then occurs with the boronic acid moiety lost from the ring (ii), with hydrogen thus replacing the group in the *ipso* position. The main driving force behind the reaction is thought to be the formation of the new C-H bond which is stronger than the C-B bond. In this example of an aromatic substitution the proton acts as the electrophile, which explains why the reaction is often referred to as 'protolytic deboronation' or 'proto-deboronation'.

Although this mechanism can be considered to account for most acid-catalysed deboronation reactions, it cannot be applied to all cases. Further kinetic experiments on reactions carried out in highly concentrated acidic media gave results which deviated from those predicted using the A-S_E2 mechanism.[78] Other observations made from the acid-catalysed reactions revealed that arylboronic acids **18** with substituents in the *ortho* position were found to show a marked increase in the rate of deboronation.

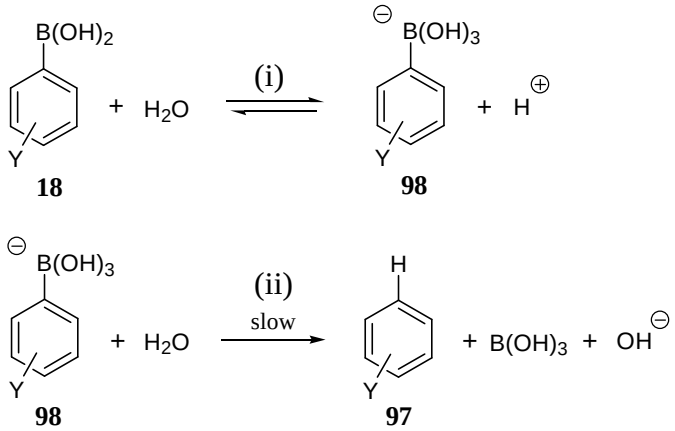
The mechanism of base-catalysed deboronation is less well-understood. Studies carried out revealed that data obtained from kinetic experiments did not fit the predicted pathway which was that of an S_E1 type mechanism:[79]



Scheme 1.34 Predicted aromatic S_E1 type mechanism for base-catalysed deboronation.

In this postulated mechanism, preliminary coordination by a hydroxide ion to the boronic acid group to form a borate anion **98** (i) was expected to occur, followed by loss of the group to form the intermediate carbanion **99** (ii). Protonation of the carbanion **99** by water was thought to form the last step (iii). However, this mechanism was ruled out on account of the observed experimental data, which was not in agreement with the formation of a negatively charged intermediate such as **99**.[79]

It was discovered that this reaction did not follow 'general base catalysis' and perhaps somewhat surprisingly, the mechanism found to fit the observed data best was as shown below:



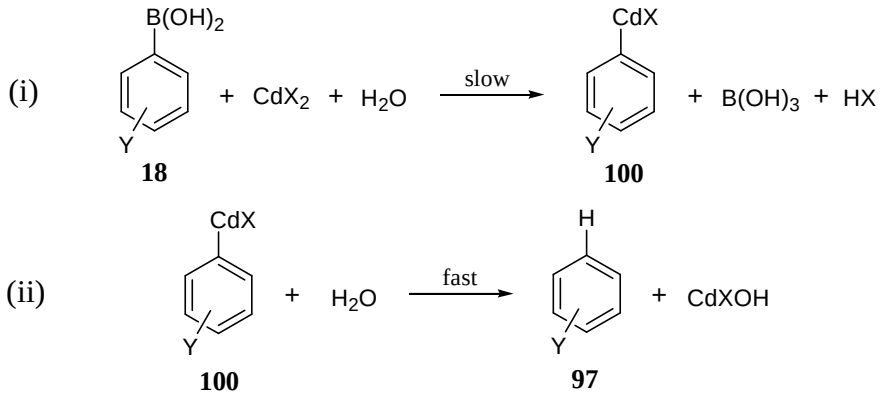
Scheme 1.35 Observed deboronation mechanism in aqueous basic media.

In this mechanism, the first step involves the reversible coordination of water to form the arylborate ion **98** (i) which then serves to activate the *ipso* position on the ring towards electrophilic attack by another water molecule in the second step (ii), with subsequent loss of the boronate group. Data obtained from kinetic experiments deduced the second step as being rate-determining, and also pointed towards the formation of a slightly positively charged intermediate.[79] Although observation of a positively charged intermediate served to confirm the mechanism as that of an electrophilic aromatic substitution, the small magnitude of the charge was unusual for such reactions. This was attributed to the presence of the negative charge on the borate group, which would effectively offset any positive charge gained from the addition of an electrophile.

This proposed mechanism could not be proven with absolute certainty, but was supported to some extent by the fact that deboronation of arylboronic acids **18** has been shown to occur in water alone, albeit at high temperature and pressure.[163] More recent deboronation experiments carried out by Frohn et al. on polyfluorinated arylboronic acids[165] revealed spectroscopic data that was also in agreement with the formation of a quaternary arylborate ion **98** during the base-catalysed reaction, but could not confirm the mechanism outright.

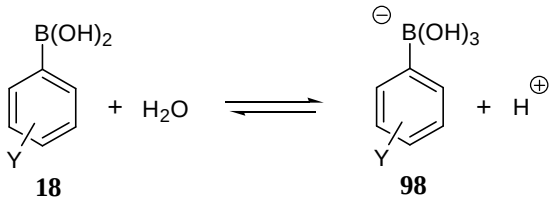
The effects of substituents on the rate of reaction were also investigated.[79] As observed in the acid-catalysed reaction, it was found that arylboronic acids **18** with substituents in the *ortho* position also displayed an increased tendency towards deboronation as compared to substituents in *meta* and *para* positions. It was also revealed that both electron-withdrawing and electron-donating groups served to accelerate the rate of reaction.

In the case of the metal-ion catalysed reaction, it has long been established that metallic salts such as those of mercury, cadmium, zinc and silver function as catalysts for the deboronation of arylboronic acids **18**.[72,80,163,166] Early studies conducted by Ainley and Challenger[163] suggested that the mechanism involved the formation of organometallic intermediates which were then easily hydrolysed in the presence of water. This mechanism was corroborated by Kuivila et al.[80] who carried out kinetic experiments on the cadmium ion catalysed reaction (shown below).



Scheme 1.36 Deboronation of an arylboronic acid catalysed by a cadmium salt.

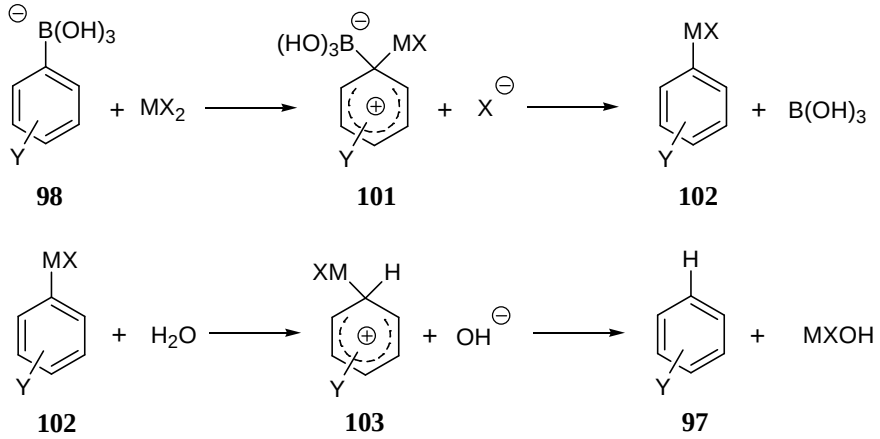
The data from these studies provided evidence in favour of the formation of a borate ion **98** prior to electrophilic attack on the *ipso* position by the metal ion.



18 **98**

Scheme 1.37 Formation of borate ion **98** prior to metal-catalysed deboronation.

The data also identified the probable formation of a positively charged intermediate, which as before, confirmed the mechanism as being an overall electrophilic aromatic substitution.



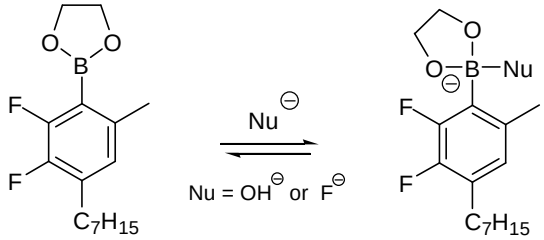
Scheme 1.38 Possible mechanism of deboronation catalysed by a metal salt.

It was discovered that in this mode of the deboronation, the rate-determining step was not the proton transfer, implying that the formation of organometallic intermediate **102** facilitates this step, thus increasing the overall rate. (The presence of *ortho* substituent groups on the aromatic ring also acted to further increase the rate of reaction).

In a test experiment, the phenylboronic acid was found to be stable towards dilute hydrochloric acid, which indicated that the deboronation was not due to acid formed from hydrolytic dissociation of the metal salt. This proposed mode of deboronation was further supported by the successful isolation of the mercuric chloride and bromide analogues of intermediate **102** from the equivalent reactions.[163]

In a similar manner, the acceleration of deboronation has also been found to occur in the presence of a palladium species. During investigations conducted by our

own research group, the deboronation of a sterically hindered boronate ester **104** was investigated.[147] It was discovered that the combination of both a base and a palladium species resulted in rapid deboronation, whereas the process was slower in media containing either just the base or the palladium catalyst. This implied that the formation of the 'ate' species was an important step prior to the palladium-promoted loss of the boron moiety.



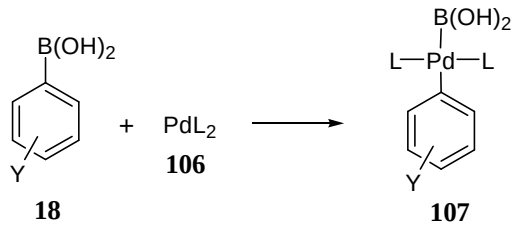
104 **105**

Scheme 1.39 Formation of an 'ate' species prior to deboronation.

An analogous mechanism to the one described by Kuivila et al. could then ensue; easily conceivable if palladium(II) chloride salt was used as the catalyst precursor. During the Suzuki coupling of substrate **104**, it was suggested that the observed deboronation could be due to hydrolysis of the diarylpalladium(II) species produced in the catalytic cycle following transmetallation. This could be possible, provided the electronic properties of this species are favourable. This process is less likely to constitute a main deboronation pathway however, as hydrolysis of the diarylpalladium(II) species could just as easily lead to protonation of the aryl moiety donated by the aryl halide substrate, with subsequent consumption of the aryl halide (again dependant on the electronic properties). Dehalogenated side-products are occasionally observed, although this is less common. On the whole, deboronation can be considered as a separate reaction that occurs alongside the catalytic cycle. Nevertheless the two processes are inherently linked, as a slow catalytic turnover may result in catalyst decomposition thus providing a palladium species able to accelerate deboronation.

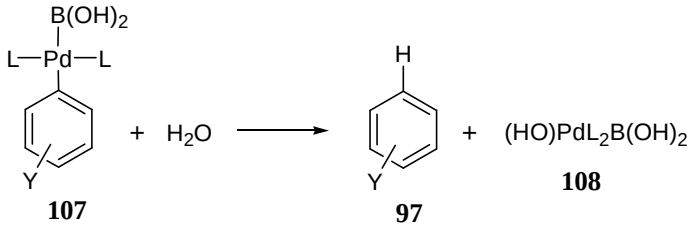
Studies by Moreno-Mañas[101] in which the mechanism of boronic acid homocoupling was explored have proposed the possibility that, in the absence of

competing processes, a $Pd(0)L_2$ species is able to insert into the C-B bond in a manner resembling that of oxidative addition (scheme 1.40).



Scheme 1.40 Insertion of palladium into a C-B bond.

Aside from the route leading to catalytic homocoupling, this could also be conceivably followed by proton transfer, resulting in deboronation.



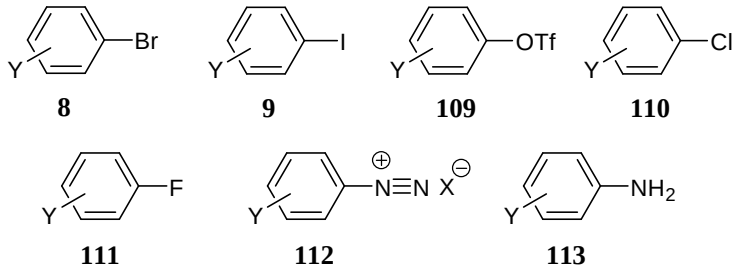
Scheme 1.41 Deboronation following palladium insertion.

Palladium(II) chloride, palladium(II) acetate, palladium on carbon and elemental palladium have all been shown to catalyse deboronation, with or without the presence of base.[41,80,147] Inhibition of this process has become an important goal in the optimisation of Suzuki coupling reactions, especially those employing sterically hindered substrates. The presence of water in reaction media is well-known to exacerbate the problem, as it can evidently assist both the formation of the borate ion and the subsequent protonation. Therefore the exclusion of water and other proton sources from hindered Suzuki coupling reactions has often become routine practice.[31,32,84,147,167-169]

1.4 Coupling reagents: The organohalide substrate

The Suzuki coupling reaction is typically carried out with aryl bromides **8** and aryl iodides **9**.[15-19] Less reactive aryl chlorides **110**[43,49-51,55,58-65] and even aryl fluorides **111**[66,67] have been successfully employed as the organohalide substrate. Aryl triflates

109 are also commonly used, under both palladium- and nickel-catalysed conditions.[96,135,154,170-176] Recently, arenediazonium salts **112**[151,152,177,178] and anilines **113**[179] have been effectively used as coupling substrates in cross-coupling reactions. In the case of anilines **113**, they were used by Wang et al.[179] as precursors to arenediazonium salts **112** in a 'one-pot' strategy, in which the salts were prepared in situ and then reacted with arylboronic acids in a Suzuki-type coupling reaction.



8 **9** **109** **110**

111 **112** **113**

Figure 1.9 Aryl halides and other species used as electrophiles in the Suzuki coupling reaction.

1.4.1 Reactivity of aryl halide substrates

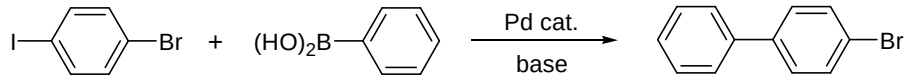
The relative reactivity of aryl halides and triflates was found to follow the order:[62,142,171,172]

$$I > Br > OTf > Cl > F$$

Figure 1.10 General order of reactivity of halides and pseudo-halides in the Suzuki coupling reaction.

This order (in the case of halide substrates in particular) is in direct correlation with the increasing strength of the Ar-X bond[142] and was confirmed in trends observed from many general Suzuki coupling reactions.

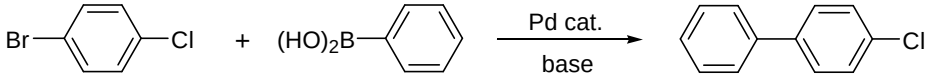
Competition reactions in which dihalogenated aryls were used as coupling substrates also provided additional confirmation. When 4-bromo-iodobenezene **114** was used, for example, the coupled product formed was found to be 4-bromobiphenyl **115** (scheme 1.42).[18]



114 **6** **115**

Scheme 1.42 Reactivity of iodide vs. bromide in a Suzuki coupling reaction.

Exclusive formation of biaryl product **115** provided verification that the iodo group was more reactive than the bromo group. When 4-bromo-chlorobenzene **116** was used, 4-chlorobiphenyl **117** was the only product:[19]



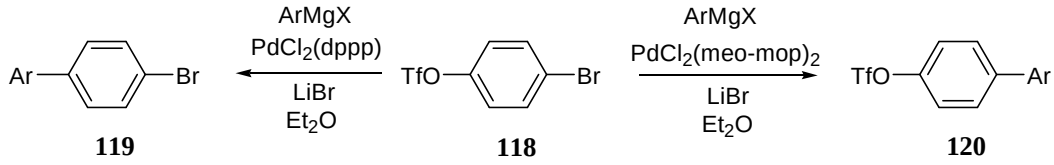
116 **6** **117**

Scheme 1.43 Reactivity of bromide vs. chloride in a Suzuki coupling reaction.

And so in this manner the order of reactivity of the halides was established. This observed order of reactivity allowed the manipulation of dihalogenated substrates such as the ones shown above (**114** and **116**) to afford useful chemoselective transformations.

Aryl triflates **109** were shown by Huth and co-workers[170] in 1989 to couple with arylboronic acids **18** under Suzuki conditions. They were observed to be less reactive than aryl bromides **8**. This trend was also noted by the groups of Snieckus[171] and Suzuki[172] who independently carried out competition reactions in an analogous fashion to those illustrated above.

The usual reactivity order of aryl bromides **8** and aryl triflates **109** could be reversed however, with the use of alternative reaction conditions. Mechanistic and kinetic studies performed by Jutand et al.[135] revealed that when DMF was used as the reaction solvent (with $Pd(PPh_3)_4$ as catalyst), aryl triflates **109** displayed a marginally higher reactivity than aryl bromides **8**. Hayashi also reported that the reactive site of 4-bromophenyl triflate **118** in a palladium-catalysed cross-coupling with a Grignard reagent could be controlled with remarkable efficiency depending on which specific ligand was used (scheme 1.44).[176]



Scheme 1.44 Control of reactive site by the use of specific ligands.

These findings were confirmed in related studies by Brown and co-workers[96] who noted the same chemoselectivity, and elaborated upon previous work by extending this method of control to other palladium-catalysed transformations.

Further investigations into the use of triflates as substrates in Suzuki coupling reactions revealed that yields could be increased by the addition of a metal halide salt such as lithium chloride or lithium bromide, as this seemed to prevent decomposition of the palladium catalyst.[15,16,18] The use of powdered K_3PO_4 suspended in THF or dioxane was also found to accelerate the coupling of triflates with boronic acids or esters.[172] The utilisation of triflates as coupling substrates presented an instant advantage in that they are easily accessible from phenols; a wide variety of which are commercially available. They are, however thermally labile thus requiring mild reaction conditions, and are prone to hydrolysis.[16,18,19]

Under the original Suzuki-Miyaura reaction protocols, aryl chlorides **110** were found to be unreactive and were generally considered to be inert to such coupling reactions. Mitchell and Wallbank later demonstrated that electron-deficient heteroaryl chlorides could be made to react satisfactorily when $Pd(dppb)Cl_2$, was used as the catalyst.[180] Other work carried out by the groups of Beller[58] and Shen[59] also revealed that aryl chlorides could be made to react when activated by the presence of one or more electron-withdrawing groups in *ortho* and/or *para* positions on the aromatic ring. In the reactions investigated by Shen,[59] the use of a more electron-rich ligand, tricyclohexylphosphine (PCy_3), was found to be beneficial. In studies carried out by Beller et al.[58] the use of a palladacyclic catalyst was found to facilitate the successful coupling of their substrates.

The use of unactivated aryl chlorides in Suzuki coupling reactions still presented a challenge however. This remained so until the groups of Fu[61-63] and

Buchwald[49,50,60,83] independently developed highly active ligand/catalyst systems that promoted the coupling of these difficult substrates. In the case of the catalyst systems developed by Fu[62] they were so successful at activating the C-Cl bond towards oxidative addition that they reversed the usual order of reactivity, with aryl chlorides **110** showing a higher reactivity under their conditions than aryl triflates **109**. Interestingly, aryl iodides **9** were found to be less reactive than their aryl bromide **8** counterparts under the same conditions. Other research groups also managed to achieve successful Suzuki coupling reactions with unactivated aryl chlorides, using similarly bulky, electron-rich ligands.[64,65] Overall, these new systems have led to more efficient reactions with lower catalyst loadings, higher coupling rates, and have enabled reactions to be carried out at ambient temperatures. Sterically hindered di-*ortho* substituted aryl chlorides have even been coupled with good results.[43,50,55]

This development has meant that the highly desirable use of aryl chlorides as starting materials has become a viable possibility. This is advantageous for industrial processes as aryl chlorides are much more readily available and less costly.

More recent advances have seen the successful coupling of aryl fluorides **111**. In 2003, Widdowson and Wilhelm[66] reported the coupling of electron-deficient aryl fluorides such as 2,4-dinitrofluorobenzene with various arylboronic acids, catalysed by $Pd_2(dba)_3$ with Me_3P as ligand. Control experiments confirmed that the reactions were indeed proceeding via palladium catalysis, in the manner typically expected for a Suzuki coupling reaction. Surprisingly, when 4-chlorophenylboronic acid was used as a coupling substrate, the C-Cl bond remained intact with oxidative addition occurring exclusively at the C-F bond. This result was further proof of the ability of a specific set of conditions to effect a reversal in the usual order of reactivity of the electrophilic partner. In this particular set of reactions it was found that the presence of a nitro group *ortho* to the fluoro- position was essential for the success of the reaction. Other electron-withdrawing groups such as trifluoromethyl in the *ortho* position did not result in the formation of coupled product. In related studies, Kim and Yu[67] achieved similar successful couplings of electron-deficient arylfluorides with arylboronic acids using $Pd(PPh_3)_4$ in DMF. Aryl fluorides with a nitro group in the *ortho* position and a second electron-withdrawing group in the *para* position were found to give the best yields of coupled product.

Finally, although not formally included in the general order featured above (see figure 1.10), arenediazonium salts **112** have been shown to be highly reactive coupling substrates in Suzuki coupling reactions. Competition reactions carried out by Genêt and co-workers[151,177] revealed that, under their conditions, the reactivity of the diazonium functional group surpassed that of triflates and of bromides. Fast conversion was observed even at ambient temperatures. The same high reactivity was also noted in experiments conducted by Sengupta et al.[178] As a result, it is highly probable that their utilisation as coupling partners will continue to generate interest in future developments.

In summary, the reactivity of aryl halides and pseudo-halides has been shown to usually follow the order illustrated in figure 1.10. However, when certain reaction conditions/catalysts are used, the order can be altered. The reactivity of aryl halides can generally be increased by the presence of electron-withdrawing groups in *ortho* positions.[23,142]

1.5 Catalysts and ligands

A vast array of catalysts and ligands have been used in Suzuki coupling reactions.[21-23,27,28,42-46,49-67,81-86,180] These reactions are typically performed with a palladium catalyst, although in some instances nickel catalysts have been used in 'Suzuki-type' couplings.[181-184] Homogeneous catalysts are usually employed, i.e. those that are soluble in the organic reaction solvent. They can exist as either Pd(0) catalysts or Pd(II) 'pre-catalysts' which are readily reduced to the active Pd(0) species in the reaction media. The facile redox interchange between Pd(II) and Pd(0) oxidation states has often been cited as a key characteristic responsible for the catalytic efficiency of palladium species during the catalytic cycle.[39]

Heterogeneous catalysts also exist and are attractive for use in industry as they are more easily separated from the end mixture, and can even be recycled.[16,19,39,88] Biphasic aqueous solvent systems are often implemented for these reactions,[44,55] or in other cases water alone is employed as the solvent.[45-48] Palladium catalysts with hydrophilic/water soluble ligands can be used,[44] or solid-supported catalysts such as

palladium on carbon (Pd/C) are also used.[48,55] The use of Pd/C without ligands[48,54,176,178] (in water or other solvent systems) has become a popular option, as it is readily separated from the mixture and contamination of the product by ligand species is avoided.[88] Other catalyst systems such as polmer-[56,57] or resin-supported palladium[45] have also gained interest.

Phosphine-free and 'ligandless' conditions have become established procedures and offer an instant advantage in that side-reactions relating to 'ligand scrambling' are prevented from occurring. The purification step involving removal of phosphine/phosphine oxide residues from the product is also eliminated. One of the first phosphine-free protocols was reported by Wallow and Novak[29] in which $Pd(OAc)_2$, $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and $Pd_2(dba)_3{\cdot}C_6H_6$ were tested as catalysts in couplings towards biaryl products. High yields were obtained at low catalyst loadings for all three catalysts.

Further work by other research groups extended the use of $Pd(OAc)_2$ as a phosphine-free catalyst for a variety of different substrates, including polysubstituted aryls,[89] heteroaryl ring systems,[52] potassium aryltrifluoroborate salts,[152] arenediazonium salts[151,177,178] and tetraarylborate salts.[47] In some investigations the use of a copper salt additive was found to be beneficial.[89,185,186] The use of 'ligandless' $PdCl_2$ has also been reported.[47,53,187] The exact mechanistic details and nature of the catalytic species generated in these ligand-free reactions remains unclear, although it has been suggested that catalysis occurs via either a heterogeneous process involving colloidal palladium particles[29,52] or by the formation of palladium complexes ligated by oxygen-containing species.[47] The term 'ligandless' is therefore used loosely for these reactions, as it has been shown in cross-couplings with other organometallic substrates under these conditions that weakly donating ligand species (such as polar solvent molecules) exist in the reaction media to stabilise the catalytic palladium(0) complexes.[188]

Palladacycle catalysts have also been investigated in Suzuki coupling reactions. It was initially reported by Beller and co-workers[58] that a palladacyclic catalyst **121** was able to facilitate the cross-coupling of aryl chlorides with arylboronic acids with remarkable efficiency. Later work by Bedford and co-workers also saw the

development of palladacyclic complex **122** which was able to catalyse coupling reactions at very low Pd concentrations.[189]

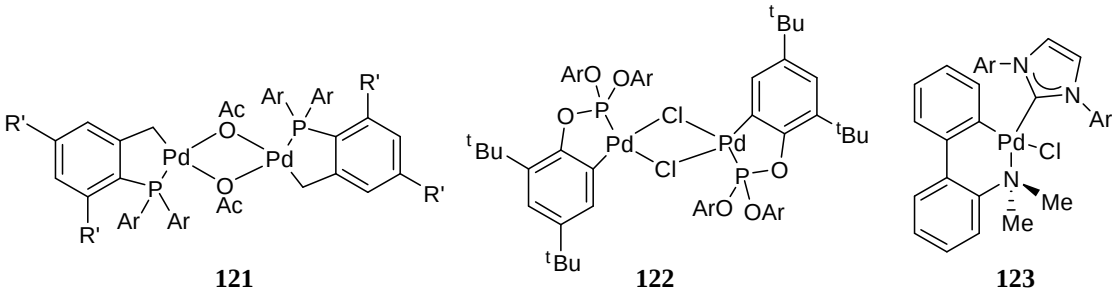


Figure 1.11 Examples of palladacyclic catalysts.

More recently, palladacyclic catalysts **123** bearing an *N*-heterocyclic carbene ligand have been demonstrated by Nolan et al. to efficiently catalyse the coupling of aryl chlorides with arylboronic acids at room temperature.[43] Less common substrates such as (organo)trifluoroborate salts **83** and **84**, and arenediazonium salts **112** have even been coupled successfully using a palladacyclic catalyst.[151,152]

It has been proposed that in palladacycles, oxidation states II and 0 of Pd are stabilised to a greater extent than in conventional catalytic species.[39] This would result in a more facile interchange between oxidation states and thus enhance the catalytic activity of the palladacyclic species, explaining their unusual efficiency. Other speculations surrounding the mechanism of palladacyclic catalysis have suggested that they act as catalytic precursors in which they provide a 'slow-release' source of colloidal Pd particles.[190] Pd(II)/Pd(IV) oxidation states have also been suggested to be involved, although this theory has been discounted in recent reviews.[190,191]

These alternative catalytic systems have all been shown to present their own unique set of advantages and benefits, however as they lie beyond the scope of this study, they will not be explored further. Several comprehensive reviews can be consulted for further details on these systems.[19,39,63,88,190-192]

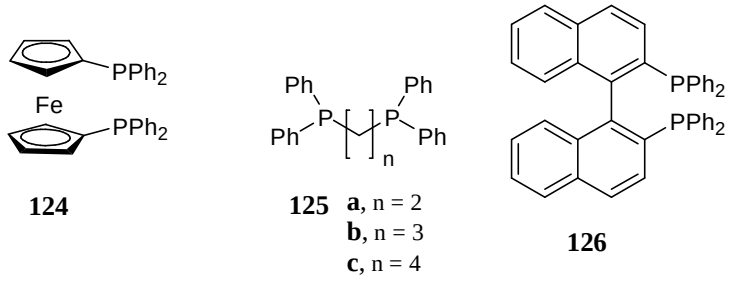
1.5.1 Palladium catalysts with phosphine ligands

1.5.1.1 General palladium/phosphine catalysts

In the very first Suzuki coupling reactions, the catalyst employed was tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$.[11,12,20] Throughout subsequent studies it became the catalyst most frequently used. It is still commonly employed to this day and is often regarded as a 'work-horse' catalyst, although it is usually reserved for relatively simple substrates and standard conditions.

A slight disadvantage encountered when using $Pd(PPh_3)_4$ is that it displays a marginally greater propensity towards 'ligand scrambling' in which the phenyl group from PPh_3 becomes incorporated in the coupled product. This drawback has been overcome to some extent by the use of alternative bulky ligands such as P(*o*-$MeOC_6H_4)_3$, which were found to restrict this type of side-reaction.[19] On the whole, phosphine-based palladium catalysts have remained popular, as they are stable at high temperatures and can thus withstand prolonged heating.

Many other phosphine-based catalysts have since emerged and have been shown to display high activity in Suzuki coupling reactions. A few examples include $PdCl_2(dppf)$,[21] $Pd(dppf)(OAc)_2$,[28] and $Pd(dppb)Cl_2$.[180] As a result, bidentate ligands such as dppf **124,** dppe **125a**, dppp **125b**, dppb **125c**, and BINAP **126** have become routine choices in aryl-aryl Suzuki coupling reactions:[21,22,42,180]



124 **125** **a**, n = 2 **b**, n = 3 **c**, n = 4 **126**

Figure 1.12 Commonly used phosphine ligands in Suzuki coupling reactions.

$Pd(OAc)_2$, $PdCl_2$, and $Pd_2(dba)_3$ used in conjunction with various other phosphine ligands have also become frequently used catalytic systems. Each individual catalyst/ligand combination has been discovered to present its own unique

set of electronic and steric properties, and as a result, systems such as these have been able to be tailored to meet the needs of specific types of substrates and reaction conditions. It has been frequently observed that the reaction conditions and types of substrates used show a high sensitivity towards the nature of the catalytic species, and vice versa. Predicting the exact performance of a catalyst/ligand combination in a specific set of conditions is difficult however, and usually the most feasible option towards identifying optimal catalyst systems is that of screening protocols.

An early example of this sensitivity could be seen in the work of Thompson et al.[28] Their investigations centred on the coupling of substituted pyrazine bromide/chloride substrates with aryl/heteroaryl boronic acids, using DMF as solvent and Et_3N as base. Initial attempts at the coupling reactions utilised $Pd(PPh_3)_4$ as the catalyst, which resulted in only traces of the coupled product. Using $Pd[P(o\text{-}tol)_3]_2(OAc)_2$ as an alternative was also met with limited success. It was only when $Pd(dppf)(OAc)_2$ was used as the catalyst that the desired coupled product was obtained in good yield.

In related work carried out by Mitchell and Wallbank,[180] heteroaryl chlorides also failed to couple with aryl/heteroaryl boronic acids in the presence of $Pd(PPh_3)_4$. But when $Pd(dppb)Cl_2$ was used, successful coupling was achieved with reasonable to good yields of the products formed.

Conversely, when Anderson et al. investigated the coupling of sterically hindered mesitylboronic acid with iodobenzene **55** at ambient temperature[42] it was found that $Pd(PPh_3)_4$, as well as the combination of $Pd_2(dba)_3$ with PPh_3, gave near quantitative yields of coupled product. The use of $Pd_2(dba)_3$ with dppf **124** as ligand resulted in no product formation at all. In these particular reactions dimethylacetamide (DMA) was used as solvent with TlOH as base.

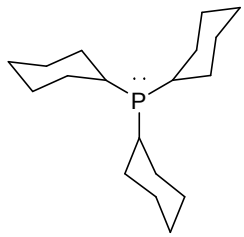
In similar studies conducted by Griffiths and Leadbeater[183] the coupling of di-*ortho* substituted aryl bromides such as 2,6-dimethylbromobenzene with phenylboronic acid **6** were investigated. Dioxane was chosen as the solvent, with K_3PO_4 as base. Ligand screening reactions revealed that the use of $Pd_2(dba)_3$ with

$P(OMe)_3$ gave the best yields, whereas $Pd_2(dba)_3$ with PPh_3 or dppf **124** resulted in no coupled product.

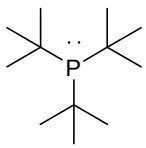
Therefore, as can be seen in the examples of studies discussed above, the efficiency of the catalytic system is clearly dependant on the reaction conditions and substrates employed.

1.5.1.2 Palladium/phosphine catalysts capable of activating aryl chloride substrates

In connection to the first two examples mentioned above, it can perhaps be claimed that one of the most significant advances in this area has been the discovery of catalytic systems able to activate the C-Cl bond towards oxidative addition. The use of bulky electron-rich phosphine ligands has been proven to especially enhance this activation. As mentioned previously (section **1.5.1.1**), numerous research groups have discovered new palladium catalyst systems able to facilitate the coupling of aryl chlorides, including those incorporating *N*-heterocyclic carbenes,[43,84] 'pincer-type' aminophosphine ligands,[51] ferrocenylphosphine ligands,[64,65] and ruthenocenylphosphine ligands.[85,86] Prominent examples have exploited the use of monophosphine ligands such as tri(cyclohexyl)phosphine PCy_3 **127** and tri(*t*-butyl)phosphine P(*t*-Bu)$_3$ **128**:



127



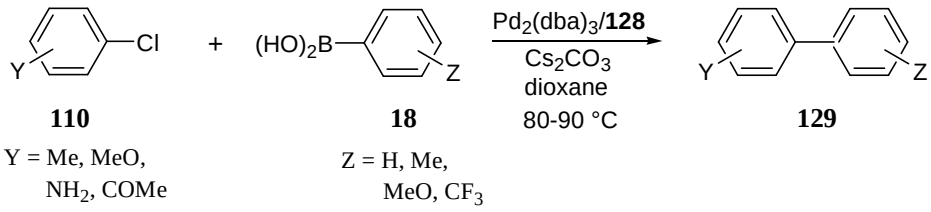
128

Figure 1.13 Electron-rich bulky phosphine ligands.

In a preliminary report by Shen, the coupling of arylboronic acids with aryl chloride substrates bearing two strongly electron-withdrawing groups were achieved using the standard catalysts $Pd(PPh_3)_4$ and $Pd(PPh_3)_2Cl_2$ (with NMP as solvent and CsF as base).[59] Aryl chlorides bearing only one electron-withdrawing group on the other hand were found to require the use of $Pd(PCy_3)_2Cl_2$ (Pd/**127**) or $Pd(OAc)_2$/dppp

(Pd/**125b**) catalysts; use of the former catalysts failed to provide any coupled product. In this particular study, aryl chlorides without electron-withdrawing groups did not react at all under either set of conditions.

Littke and Fu then developed the use of catalytic systems such as $Pd_2(dba)_3$ with P(*t*-Bu)$_3$ **128** to successfully couple a variety of aryl chlorides **110**, including 'unactivated' electron-neutral and electron-rich chlorides:[61]



110 Y = Me, MeO, NH_2, COMe

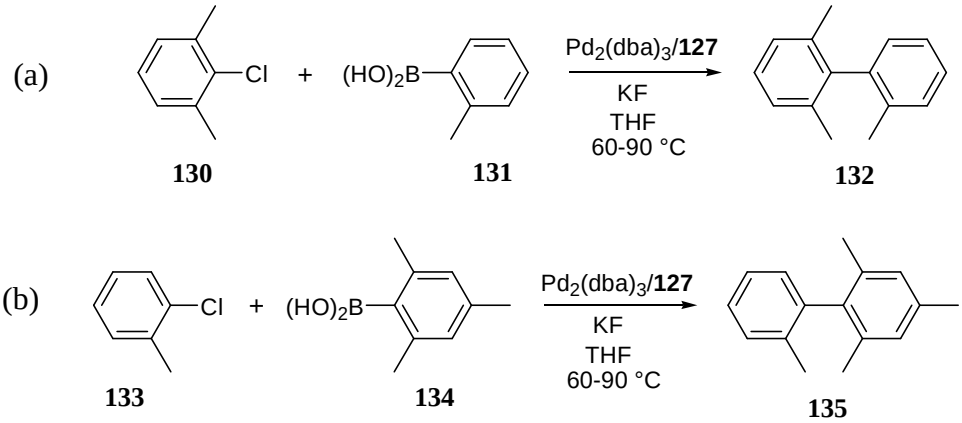
18 Z = H, Me, MeO, CF_3

129

Scheme 1.45 Suzuki coupling of unactivated aryl chlorides.

The combination of $Pd_2(dba)_3$ with PCy_3 **127** also gave good results but did not match the yields obtained with $Pd_2(dba)_3$/P(*t*-Bu)$_3$ in this set of reactions. Conditions used for these initial experiments were dioxane as solvent with Cs_2CO_3 as base.

Later modifications to these conditions by the same group[62] led to the successful coupling of sterically hindered unactivated aryl chlorides such as **130** and **133** with hindered arylboronic acids **131** and **134**, using KF as base, THF as solvent and $Pd_2(dba)_3$/ PCy_3.



130 **131** **132**

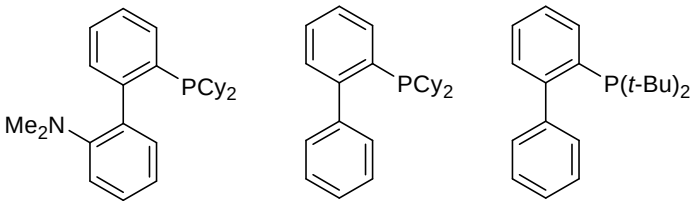
133 **134** **135**

Scheme 1.46 Suzuki coupling of sterically hindered unactivated aryl chlorides.

Exceptionally high yields were obtained for biaryl products **132** and **135**, in the region of 89-93%. This was a remarkable feat considering that aryl chloride substrates were previously deemed unreactive.

The high activity of systems such as $Pd_2(dba)_3$/ PCy_3 and $Pd_2(dba)_3$/ P(*t*-Bu)$_3$ was attributed to both steric bulk and electron-richness. These attributes were speculated to enhance the activation of the C-Cl bond towards oxidative addition and also favour the formation of a coordinatively unsaturated palladium complex, believed to be the highly reactive catalytic species. One minor drawback encountered with the catalytic system of $Pd_2(dba)_3$/ P(*t*-Bu)$_3$ was the pyrophoric nature of the ligand P(*t*-Bu)$_3$ **128**, which required special precautions while handling. This problem was later resolved when it was demonstrated that an air-stable phosphonium salt precursor, [P(*t*-Bu)$_3$H]BF_4 could be used to generate the desired ligand species in situ.[193]

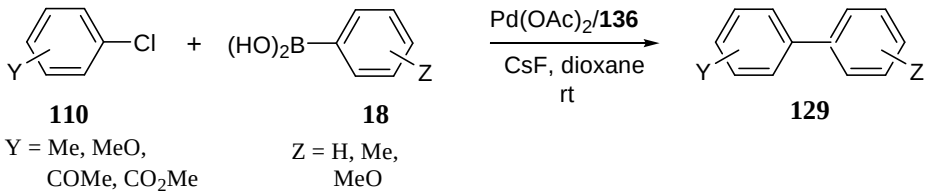
In studies conducted around the same time, Buchwald and co-workers developed biphenyl-type phosphine ligands that were also able to facilitate the coupling of unactivated aryl chlorides.[60] The first of these ligands was 2-(dimethylamino)-2'-dicyclohexylphospinobiphenyl or 'NMe_2-Phos' **136**:



136 **137** **138**

Figure 1.14 Electron-rich biphenyl-type phosphine ligands.

This ligand **136**, when used in conjunction with either $Pd(OAc)_2$ or $Pd_2(dba)_3$ (under conditions of dioxane as solvent and CsF as base) enabled the room temperature coupling of unactivated aryl chlorides **110** with boronic acids **18** in good yields (scheme 1.47).[60]



110
Y = Me, MeO, COMe, CO_2Me

18
Z = H, Me, MeO

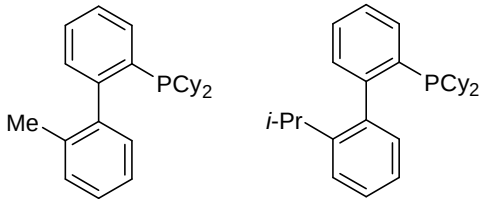
129

Scheme 1.47 Suzuki coupling of unactivated aryl chlorides using ligand **136**.

It was initially unclear as to whether **136** was acting as a monodentate or bidentate ligand (with the possibility of its efficacy being dependent on the presence of the amino group), so the catalytic efficiency of ligands *o*-(dicylohexylphosphino)biphenyl **137** and *o*-(di-*tert*-butylphosphino)biphenyl **138** were examined.[49] Ligand **138** was found to be equally effective in the room-temperature coupling of aryl chlorides, and tolerated the presence of a variety of different functional groups. Although ligand **138** gave better results at lower temperatures, ligand **137** was found to be more effective for Suzuki coupling reactions carried out with lower catalyst loadings at 100 °C.

These results indicated that the presence of the amino group on the second phenyl ring was not crucial to the catalytic activity of the ligand. The correct combination of solvent and base, on the other hand, was discovered to be essential for the success of the reactions. Bases KF and CsF were found to be the most effective, with THF or dioxane as solvent. The base K_3PO_4 was found to be useful in reactions run at very low catalyst loadings at 100 °C, but only when toluene was used as solvent.[50]

In these reactions it was noted that coupling substrates bearing one or more *ortho* substituents displayed a decreased reactivity, and so alternative ligands derived from the structure of **137** were investigated with the aim of improving the syntheses of hindered biaryl compounds. This led to the development of ligands **139** and **140** (figure 1.15).



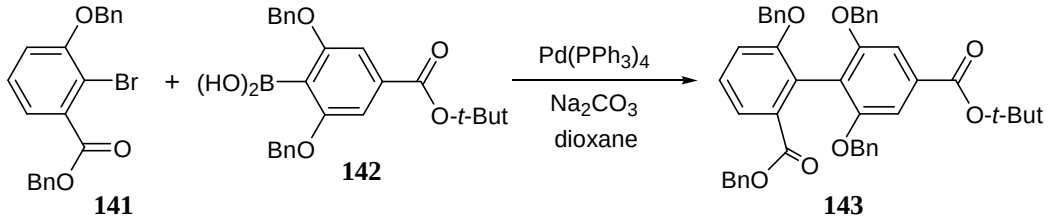
139 **140**

Figure 1.15 Biphenyl-type phosphine ligands for the coupling of hindered substrates.

In coupling reactions carried out between 2,6-dimethylphenyl chloride **130** and 2-methylphenylboronic acid **131**, catalyst systems employing ligands **137** and **140** were found to give the best results (at 100 °C). For coupling reactions carried out with a more hindered boronic acid, 2,6-dimethylphenylboronic acid, aryl bromides rather than chlorides were required in order to enable a successful reaction, and were coupled most successfully using ligands **136** and **138** (at 80-100 °C).[50]

1.5.1.3 Palladium/phosphine catalysts in the synthesis of tetra-*ortho* substituted biaryls

Following on from the successful coupling of unactivated aryl chlorides, perhaps the next significant hurdle to be overcome in the development of the Suzuki reaction has been the synthesis of tetra-*ortho* substituted biaryls. Prior to the discoveries of Buchwald's and Fu's highly active catalytic systems, the synthesis of such sterically hindered compounds was considered highly unfeasible, and there existed only one isolated report of the successful synthesis of a tetra-*ortho* substituted biaryl via the Suzuki coupling reaction. This was described in work carried out by Johnson and Foglesong:[81]

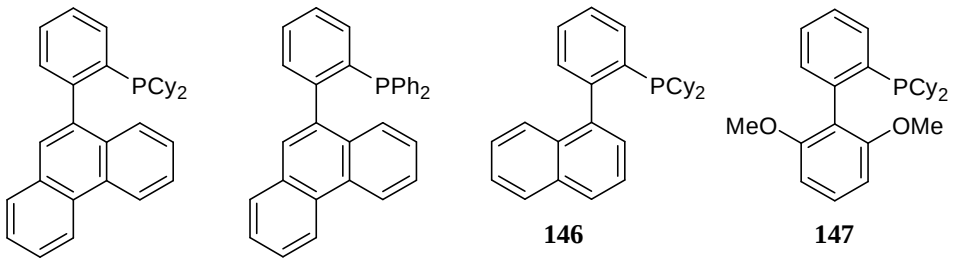


Scheme 1.48 Preparation of a tetra-*ortho* substituted biaryl via Suzuki coupling.

The conditions employed were fairly standard, with $Pd(PPh_3)_4$ as catalyst, Na_2CO_3 as base and dioxane as solvent. The yield of product **143** obtained however

was a lowly 12%, which could not be improved upon by either a change of base or by use of the aryl iodide.

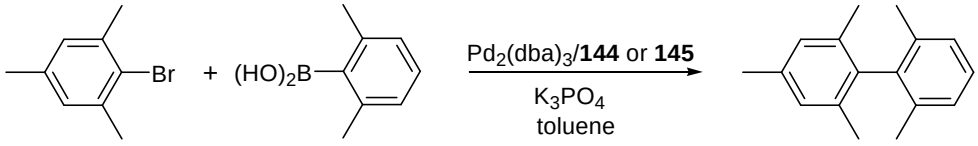
Later work carried out by Buchwald et al. on the synthesis of further analogues of ligand **137** led to the identification of other highly active ligand/catalyst systems able to catalyse the coupling of sterically hindered substrates.[82,83] These new systems utilised the following ligands (figure 1.16).



144 **145** **146** **147**

Figure 1.16 Bulky biaryl-based phosphine ligands.

Phenanthrene-based ligands **144** and **145** were found to be especially active in the coupling of substrates bearing *ortho* methyl substituents:[82]



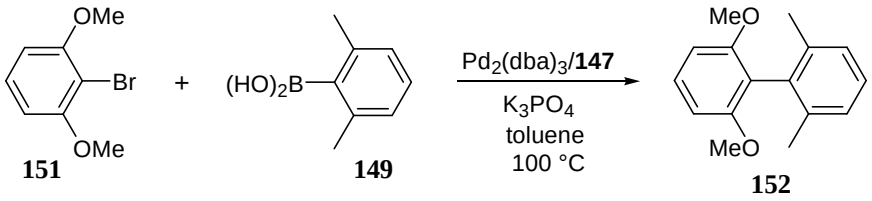
148 **149** **150**

Scheme 1.49 Suzuki coupling towards a tetra-*ortho* substituted biaryl.

Various combinations of *ortho* methyl and *ortho* methoxy groups on either substrate were also tolerated. Isolated yields of the coupled product were as high as 82%. The presence of an *ortho* electron-withdrawing group on the aryl halide however resulted in no product formation.

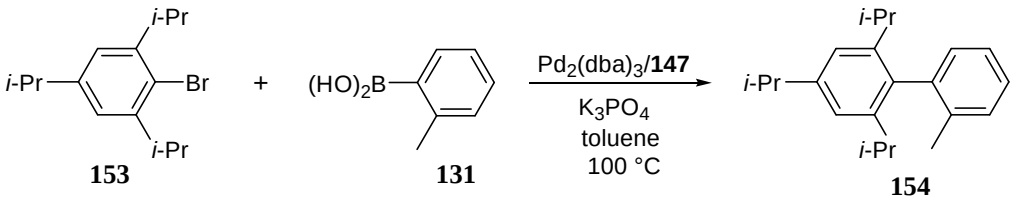
Use of the alkoxy-substituted biphenyl-derived ligand 'SPhos' **147** presented an immediate advantage in that it could be readily prepared using a 'one-pot' strategy.[83] This ligand also displayed excellent activity in couplings towards tetra-*ortho* substituted biaryls, giving equally high yields (82%) when used in reactions

such as the one illustrated in scheme 1.49, and similarly high yields in reactions in which di-*ortho* methoxy substituted aryl bromides were employed (scheme 1.50).



Scheme 1.50 Suzuki coupling towards a tetra-*ortho* substituted biaryl.

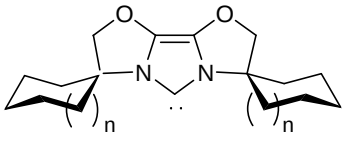
Another advantage gained from the use of 'SPhos' **147** was that it required only 3-4 mol% Pd whereas phenanthrene-based ligand **144** required 10% Pd. 'SPhos' **147** was also found to show superior activity when used in couplings employing extremely hindered aryl bromides bearing large *ortho* substituents:



Scheme 1.51 Suzuki coupling employing an extremely hindered aryl bromide.

In this example the coupled product **154** was achieved in an impressive 95% yield using only 0.1 mol% Pd. However, Suzuki couplings attempted with this catalyst system employing 2,6-dimethylphenylboronic acid **149** and aryl bromide **153** as partners were unsuccessful.

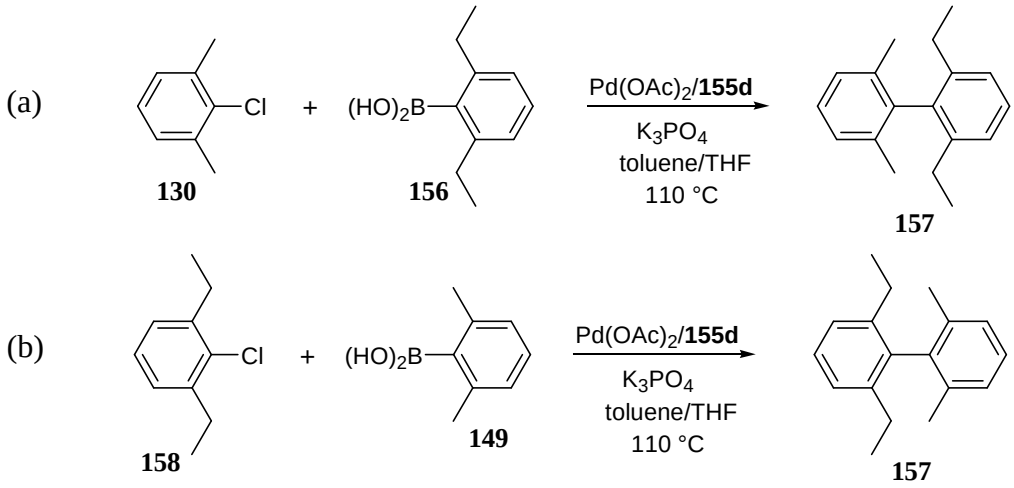
In recent work carried out by Würtz and Glorius,[84] exceptionally challenging coupling reactions were achieved using *N*-heterocyclic carbene ligands; specifically, the group of bioxazoline-derived 'IBiox' ligands:



155 a, n = 1 'IBiox6'
b, n = 2 'IBiox7'
c, n = 3 'IBiox8'
d, n = 7 'IBiox12'

Figure 1.17 *N*-heterocyclic carbene ligands.

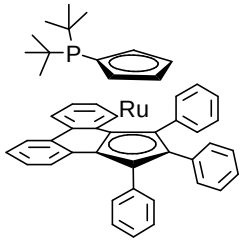
This series of monodentate carbene ligands was obtained by altering the size of the cycloalkyl ring substituents on each analogue. These ligands were then tested in sterically demanding Suzuki coupling reactions, with best results achieved with 'IBiox12' **155d**. Incredibly, this catalyst system enabled the coupling of di-*ortho* substituted aryl chlorides with di-*ortho* substituted arylboronic acids, tolerating di-*ortho* ethyl substituents on both the arylboronic acid **156** and the aryl chloride **158** partner.



Scheme 1.52 Suzuki coupling reactions towards tetra-*ortho* substituted biaryls employing an *N*-heterocyclic carbene ligand.

Yields of coupled product were high, in the region of 75-96%. These results represent the only reactions reported so far that have successfully employed aryl chlorides to give products bearing 4 *ortho* substituents comprising of methyl groups or larger.[84]

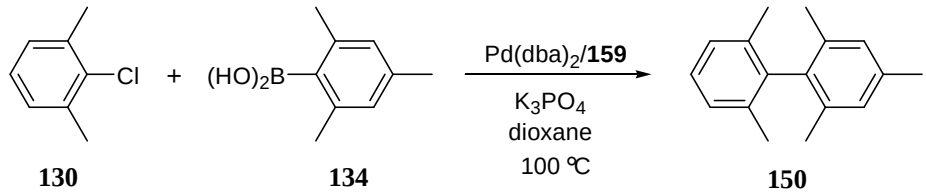
Finally, recent reports by Hoshi and co-workers[85,86] have demonstrated the efficiency of a biphenylene-substituted ruthenocenylphosphine ligand 'R-Phos' **159** in couplings towards tetra-*ortho* substituted biphenyl compounds:



159

Figure 1.18 Ruthenocenylphosphine 'R-Phos' ligand.

This ligand **159** was also shown to facilitate the efficient coupling of hindered aryl chloride substrates with hindered arylboronic acids, to give coupled biaryls in yields of up to 94%.[85]



130 **134** **150**

Scheme 1.53 Suzuki coupling towards a tetra-*ortho* substituted biaryl employing 'R-Phos' ligand.

The scope of this ligand was extended to include the coupling of extremely hindered aryl bromides such as **153** with *ortho* substituted boronic acids such as 2-methylphenylboronic acid **131** in an analogous procedure to that in scheme 1.51.[86] Yields matched those obtained with 'SPhos' **147**.

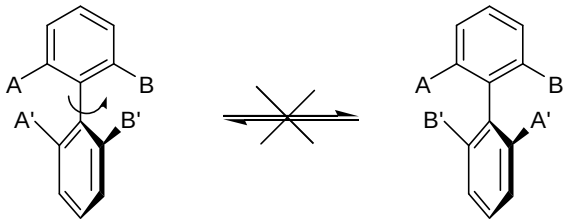
To conclude, it has been shown that by using modified ligand/catalyst systems tetra-*ortho* substituted biaryls can be prepared in very good yields,[82,83] even utilising aryl chlorides as coupling partners.[84,85] It is believed that the high activity of these types of ligands is due to a combination of electronic and steric effects, both of which exert a significant influence on the nature of the catalytic palladium species.[98,194] The electron-donating character of the ligand increases the electron density at the metal and so favours oxidative addition. This character may also help to stabilise other intermediates in the catalytic cycle.[195] The large steric bulk - as well as providing electron density - also facilitates the formation of a monoligated palladium species '$L_1Pd(0)$'. This is thought to be the species responsible for the high catalytic activity as, perhaps somewhat ironically, it provides a less crowded approach for incoming substrate molecules, as oppose to a '$L_2Pd(0)$' species.[194]

1.6 Axial chirality

Early investigations by Christie and Kenner[196] into the optical activity of tetra-*ortho* substituted 6,6'-dinitro-2,2'-diphenic acid gave rise to the first intimations of axial chirality. Their observations led to the reasoning that the two aryl rings were

linked by a common axis, but that the rings did not lie in the same plane. Later studies established the nature of this form of chirality more precisely,[197] with the steric hindrance produced by the *ortho* substituents on both aryl rings confirmed as the cause of restricted rotation around the aryl-aryl axis. Both the energy barrier to rotation and the dihedral angle between the planes of the two aryl rings were primarily dependent on the size and number of the *ortho* substituents. Contributions from 'buttressing' effects of *meta* substituents and electronic effects from *para* substituents were also observed, although they played a far less significant role.[198,199]

Axial chirality in biaryl compounds, known as atropisomerism, can thus be defined as a phenomenon in which the restricted rotation of the aryl-aryl bond gives rise to two separate atropisomers, provided that A ≠ B and A' ≠ B'. If A = A' and B = B', the molecule has C_2 symmetry, but is still chiral. Depending on the degree of steric hindrance, a minimum of three bulky substituents in *ortho* positions is usually required to produce a sufficient barrier to rotation.[197,200]



160 **161**

Figure 1.19 Restricted rotation around an axial C-C bond leading to separate atropisomers **160** and **161**.

The axial configuration of biaryls possessing fewer than three *ortho* substituents is not usually resistant to heat, with racemisation often occurring rapidly at room temperature.[200,201]

In more conventional terms, biphenyls **160** and **161** can be considered as enantiomers, as each one possesses a defined sense of chirality. The configuration of axially chiral molecules can be defined as *R* or *S* in accordance with the Cahn-Ingold-Prelog rules; sometimes prefixed with an '*a*' to denote axial chirality, as in *aR* or *aS*. Alternatively, *M* and *P* are used if considered as helices.

Assignment of the absolute axial configuration of a molecule can be achieved if viewed along the biaryl axis, in the form of a Newman projection.[202] Beginning with the *ortho* substituent of highest priority on the proximal ring (in this example A), the shortest 90° path to the ortho substituent of highest priority on the distal ring (A') is found.

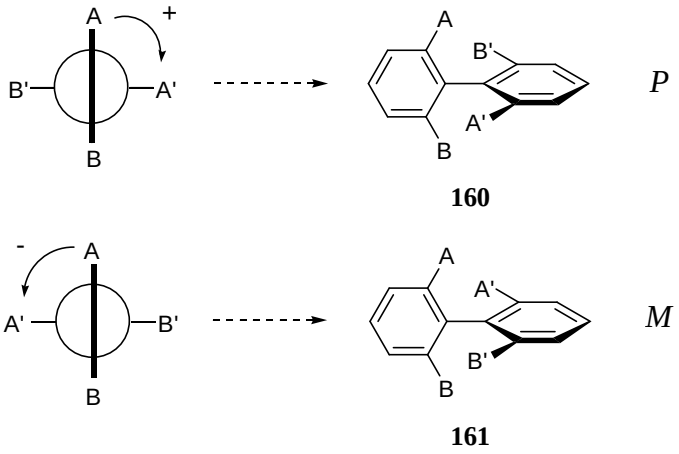


Figure 1.20 Assignment of absolute configuration in chiral biaryls **162** and **163**.

If the turn is clockwise as in **160**, the configuration is *P* (for plus). If the turn is anti-clockwise as in **161**, the configuration is determined as *M* (for minus). (It should be borne in mind that this denotation bears no relation to the direction in which the molecule rotates plane-polarised light).

1.6.1 The importance of axially chiral biaryls

Axially chiral biaryls are common structural motifs in many natural products, many of which display remarkable bioactivities. Notable examples of natural compounds incorporating a hindered biaryl unit include vancomycin,[40] michellamine,[35] steganacin[203] and knipholone.[204] It has only recently been recognised that natural products possessing a rotationally hindered biaryl axis are far more widespread and structurally diverse than previously assumed[202,205] and in many cases, the biological activity of the compound is dependent on the absolute axial configuration, with properties restricted to one atropisomeric form. Consequently, atroposelective syntheses of such compounds have become highly desirable.

Aside from pharmacologically active compounds, the interesting properties of axially chiral biaryls have led to their exploitation in other wide-ranging applications. They have for instance found common usage as chiral ligands in asymmetric catalysis[206-210] (exemplified by the well-known ligands BINAP **126**, BINOL and MOP) as well as being utilised in the cores of chiral liquid crystals[211] and more recently as molecular switches in nanoscience applications.[212]

Classical resolution methods employed in the separation of racemic atropisomeric mixtures typically suffer from low overall yields and often employ laborious procedures.[208,213] In view of this, and together with the growing number of applications of chiral biaryls, there has been considerable interest in the development of efficient protocols that produce enantiomerically enriched chiral biaryl products.

1.7 Methods of inducing asymmetry in axially chiral compounds

To date, a wide variety of different synthetic procedures enabling the control of axial chirality in biaryl compounds have been reported,[167-169,175,214-236] some of which have been applied in targeted syntheses.[219-222,234-236]

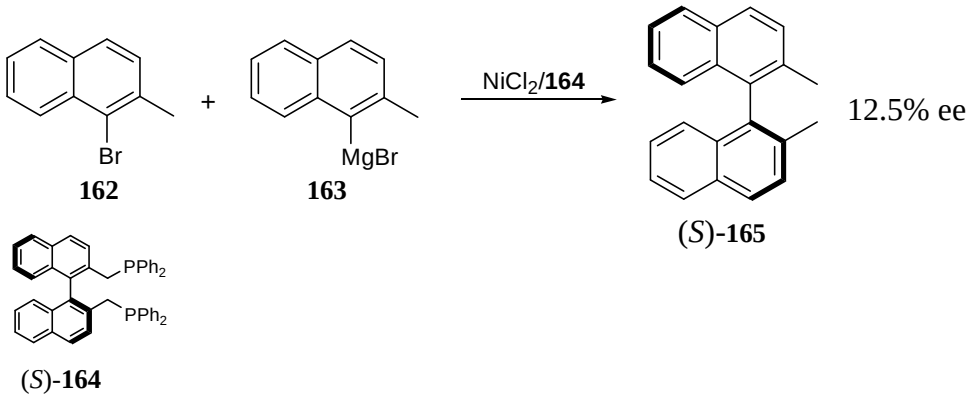
These procedures can usually be classified under one of three fundamentally different methods. The first method involves the direct intermolecular coupling in which the asymmetric configuration is generated during the formation of the aryl-aryl bond. The second method involves the atroposelective transformation of a (previously stereochemically undefined) biaryl system through a desymmetrisation process. The third involves the induction of asymmetry during the construction of an aromatic ring system.

Of the methods described above, the first involving the direct atroposelective coupling of two aryl substrates has arguably received the most attention,[203,214-217,220-223,226,229-231] and has since become an attractive method of chiral induction on account of its expedient nature. One of the main drawbacks associated with this method is the inherently challenging nature of coupling sterically crowded *ortho*-substituted biaryls, although significant improvements continue to be made in this area.

A number of procedures also fall under the description of the second and third methods, with exceptional results produced in some notable examples.[219,224,227] Although of value, these types of procedures lie beyond the context of this study and so will not be elaborated upon further.

1.7.1 Direct atroposelective cross-coupling reactions

The first atroposelective transition-metal catalysed cross-coupling was reported by Kumada and co-workers in 1977 in which the nickel-catalysed coupling of an aryl halide substrate with an aryl Grignard reagent was carried out.[214] In this reaction, two naphthyl halves were coupled in the presence of chiral binaphthyl phosphine ligand (*S*)-NAPHOS **164** to give an enantiomerically enriched product, (*S*)-2,2'-dimethyl-1,1'-binaphthalene **165**.

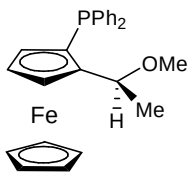


162 **163** (*S*)-**165** (*S*)-**164**

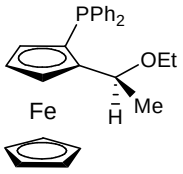
Scheme 1.54 Asymmetric nickel-catalysed coupling towards binaphthyl product (*S*)-**165**.

Although only a modest ee of 12.5% was achieved, the effect of the chiral ligand observed in this reaction was of particular significance. It presented strong evidence to suggest that the presence of a chiral species in such transition-metal catalysed coupling reactions could exert an influence over the stereochemistry of the final coupled product.

Subsequent work by Hayashi et al. proved this to be the case,[215] with axially chiral binaphthyls successfully synthesised in high enantioselectivity using chiral ferrocenylphosphine ligands (*S*)-(*R*)-PPFOMe **166** and (*S*)-(*R*)-PPFOEt **167** (figure 1.21).



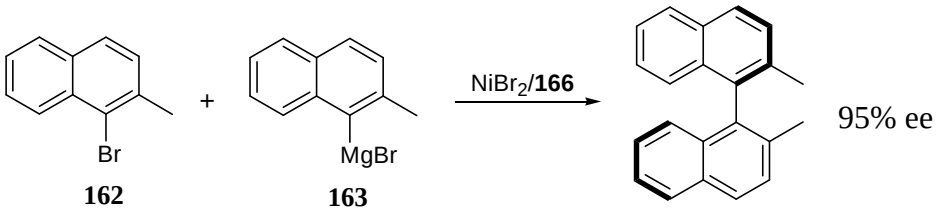
166



167

Figure 1.21 Chiral ferrocenylphosphine ligands (*S*)-(*R*)-PPFOMe **166** and (*S*)-(*R*)-PPFOEt **167**.

Best selectivities were achieved using ligand **166**, with coupled binaphthyl products such as (*R*)-2,2'-dimethyl-1,1'-binaphthalene **165** produced in high enantiomeric excess.

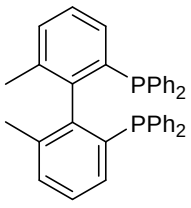


162 **163** (*R*)-**165**

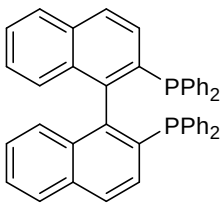
Scheme 1.55 Asymmetric nickel-catalysed coupling towards binaphthyl product **165**.

Use of a ferrocenyl ligand bearing opposite chirality ((*R*)-(*S*)-PPFOMe) led to the formation of the opposite atropisomer (*S*)-2,2'-dimethyl-1,1'-binaphthalene **165**, in a similarly high enantiomeric excess of 80%.

The scope of the asymmetric reaction between these substrates was extended by Frejd and Klingstedt[216] who tested the use of other chiral catalyst species. Axially chiral ligands (+)- and (−)-BIPHEMP **168** and (*R*)- and (*S*)-BINAP **126** were employed, this time using a palladium salt as the transition-metal catalyst precursor.



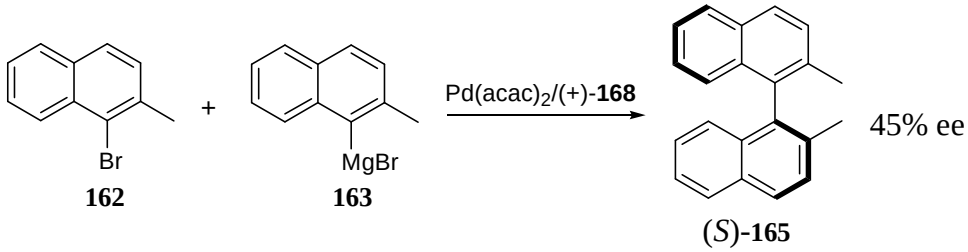
(+)- or (−)-**168**



(*R*)- or (*S*)-**126**

Figure 1.22 Axially chiral phosphine ligands (±)-BIPHEMP **168** and (*R*)- and (*S*)-BINAP **126**.

Use of the ligand (+)-BIPHEMP **168** was found to give the best ee values in these reactions.



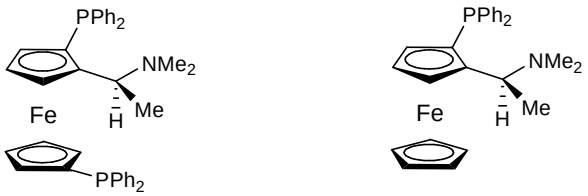
162 **163** (*S*)-**165**

Scheme 1.56 Asymmetric palladium-catalysed coupling towards **165**.

Although the enantiomeric excesses were not as high as those achieved by Hayashi et al.[215] the use of a chiral ligand nevertheless resulted in an enantiomerically enriched product. The same trend as in previous work was also observed, whereby use of a ligand of opposite chirality gave rise to the opposite atropisomeric product.

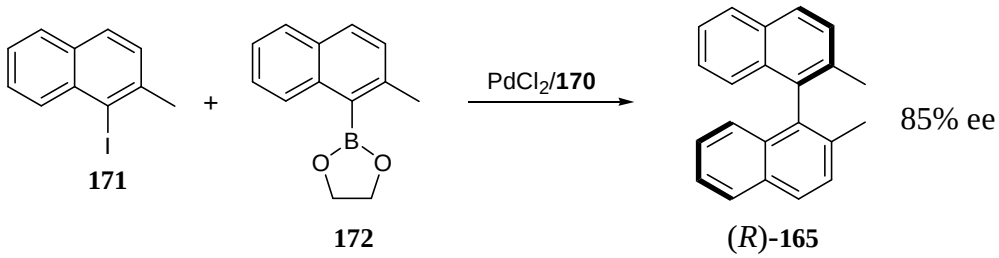
1.8 The Asymmetric Suzuki coupling reaction

The first asymmetric palladium-catalysed cross-coupling of an aryl halide with an arylboronic acid or boronate ester was achieved by our group in 2000.[167] Axially chiral *ortho*-substituted binaphthyl derivatives such as **165** were synthesised, with the atroposelectivity induced through the use of a chiral phosphine ligand. In these reactions, use of the ligands (*S*)-(*R*)-PPFOMe **166**, (*R*)-BINAP **126** and (*S*)-(*R*)-DPPFA **169** led to low to moderate ee values, whereas use of the chiral monophosphine ferrocenyl ligand (*S*)-(*R*)-PPFA **170** resulted in good selectivity, with a high ee of 85% produced.



169 **170**

Figure 1.23 Chiral ferrocenylphosphine ligands (*S*)-(*R*)-DPPFA **169** and (*S*)-(*R*)-PPFA **170**.

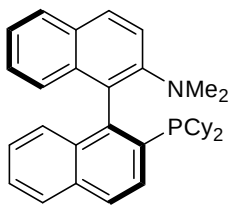


171 **172** (*R*)-**165**

Scheme 1.57 Asymmetric Suzuki coupling towards binaphthyl (*R*)-**165**.

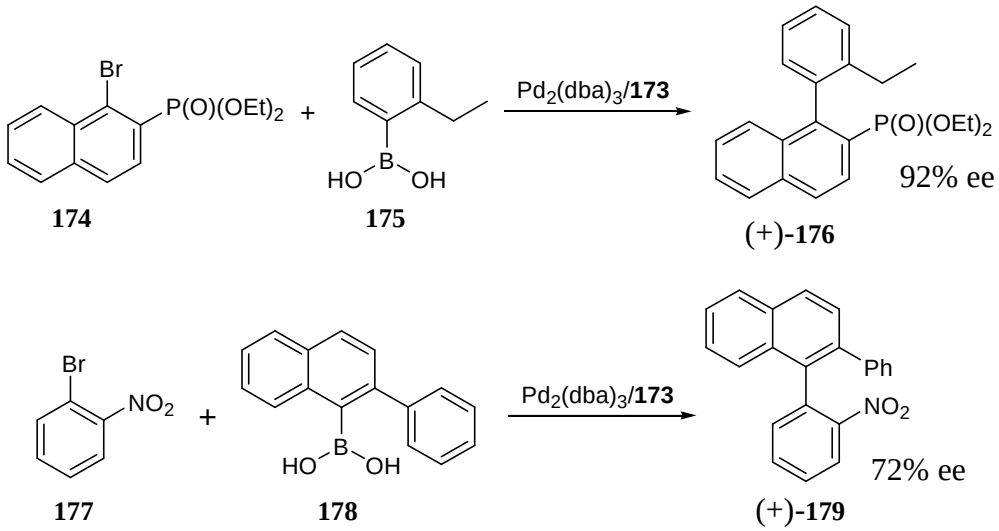
Despite this reaction incorporating the advantages generally associated with Suzuki reactions (such as the ease of handling of the organoboron substrate) high yields of product from these asymmetric coupling reactions were unfortunately difficult to achieve. This was due to the hindered nature of the coupling reaction, with competing deboronation a particular problem. During reactions towards **165** utilising (*R*)-BINAP **126**, a change in the boronate ester moiety from an ethylene glycol ester **172** to a bulkier pinacol ester led to the formation of the opposite atropisomer. This raised fundamental questions about the nature of the asymmetric induction, and implicated the transmetallation step in the catalytic cycle as a key moment in this process. From this result it was inferred that in these reactions the process of asymmetric induction was operating under kinetic control.[169]

Buchwald and Yin[168] subsequently reported the synthesis of axially chiral biaryl compounds also via an asymmetric Suzuki coupling reaction. Their reactions were primarily aimed towards the synthesis of naphthyl derivatives bearing *ortho*-phosphonate groups, with best enantiomeric excesses achieved using the monophosphine binaphthyl-derived ligand 'KenPhos' **173**. This chiral ligand was a structural analogue of the ligand NMe_2-Phos **136** (previously developed for use in Suzuki couplings employing unactivated aryl chloride substrates and sterically crowded *ortho*-substituted aryl substrates) in this case featuring a binaphthyl backbone.[50,60]



(*S*)-**173**

Figure 1.24 Chiral binaphthyl ligand (*S*)-KenPhos **173**.

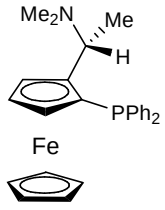


Scheme 1.58 Examples of asymmetric Suzuki couplings utilising chiral ligand (*S*)-KenPhos **173**.

Bidentate ligands such as BINAP **126** were found to give poor overall yields with low atroposelectivity, indicating that only one phosphinyl coordinating group was necessary for optimal performance. In addition, the presence of the dimethylamino group on (*S*)-KenPhos **173** was discovered to be essential for successful chiral induction, as the replacement of this group with alternative groups such as *n*-butyl or trimethylsilyl led to significant reductions in selectivity. This mirrored findings from our own studies[167] in which the use of a monophosphine ligand (*S*)-(*R*)-PPFA **170** gave superior results as compared to diphosphine ligands (*R*)-BINAP **126** and (*S*)-(*R*)-DPPFA **169**, with the necessity for a dimethylamino group also reflected in the lower selectivity resulting from use of a ligand bearing an alternative ether group (*S*)-(*R*)-PPFOMe **166**.

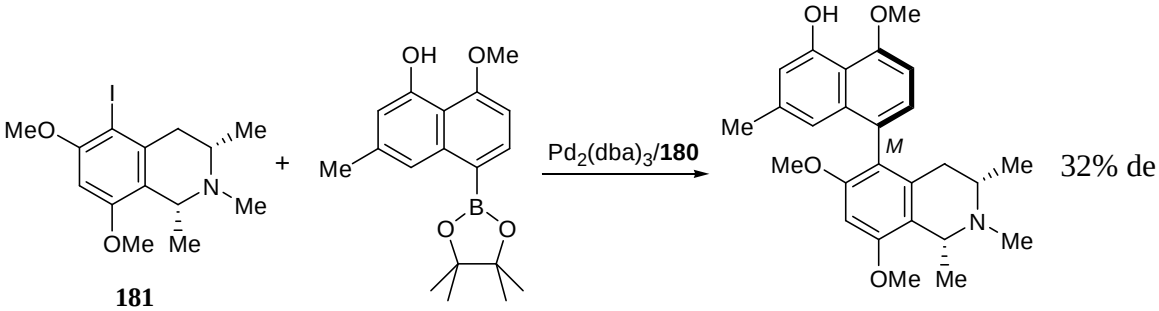
Since the publication of these findings, the asymmetric Suzuki reaction has been applied as a key step in the synthesis of a small number of pharmacologically important chiral biaryl compounds, including ancistrotanzanine B and 5-*epi*-4'-*O*-demethylancistrobertsonine C **183** reported by Bringmann et al.[235,236] (see scheme 1.59), as well as an analogue of (−)-rhazinilam reported by Baudoin and co workers.[234]

In the synthesis of 5-*epi*-4'-*O*-demethylancistrobertsonine C, use of the ligand (*R*)-(*S*)-PPFA **180** (figure 1.25) was found to give the best atropo-diastereomeric excess of all the ligands tested, with good conversion (85%).[236]



180

Figure 1.25 Chiral ferrocenylphosphine ligand (*R*)-(*S*)-PPFA **180**.



181 **182** (*M*)-**183**

Scheme 1.59 Atroposelective synthesis of (*M*)-**183** using ligand **180**.

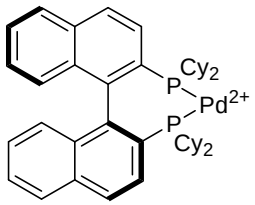
It was found that the use of a ligand bearing the opposite chirality (*S*)-(*R*)-PPFA **170** did not result in the formation of the opposite atropo-diastereomeric product (*P*)-**183** in an equal excess. Instead, an almost 1:1 ratio of the two atropo-diastereomers was produced, in a reduced overall conversion. This mirrored findings in their previous work towards the synthesis of ancistrotanzanine B, in which the use of ligand **182** gave the best diastereomeric excess with good conversion, whereas use of the opposite ligand **172** led to a 1:1 diastereomeric ratio in low yield.[235]

In subsequent studies on the asymmetric Suzuki coupling reaction, a variety of different variations to the reaction conditions have been reported, typically involving modifications to the catalyst and/or ligand species. For example, a group of alternative monophosphine ferrocenyl ligands bearing a sole element of planar chirality have been synthesised and tested by Jensen and Johannsen.[237] Although couplings towards binaphthyl product (*R*)-**165** achieved reasonable conversions, the

ee values did not improve upon those obtained by our group. It was noted during their studies that a decrease in the Pd:ligand ratio from 1:2 to 1:1.2 resulted in an increase in the catalytic turnover frequency, and was attributed to the possible high activity of a monophosphine palladium species.

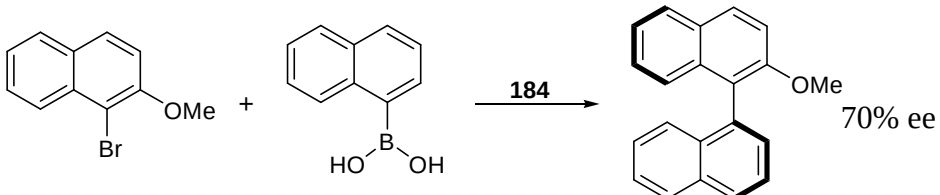
In a related study by Colobert and co-workers,[238] atroposelective couplings towards 2,2'-dimethoxy-1,1'-binaphthalene were found to be sensitive to the Pd:ligand ratio. Despite changes to the identity of the palladium salt, a Pd:ligand ratio of 1:1.1 or higher (where the ligand employed was either (*R*)-BINAP **126** or (*R*)-TolBINAP) consistently gave the (+) product, whereas a ratio of 1:0.97 or lower led to inversion of the stereochemistry. These findings were rationalised in terms of the different catalytic species that may form as a result of the differing proportions of palladium and ligand present in the reaction mixture.

Use of a cationic palladium(II) complex bearing a chiral cyclohexyl-BINAP derivative (figure 1.26) was reported by Mikami et al. to lead to reduced reaction times and improved yields with reasonable selectivity.[239]



184

Figure 1.26 Chiral cationic palladium(II) complex **184**.



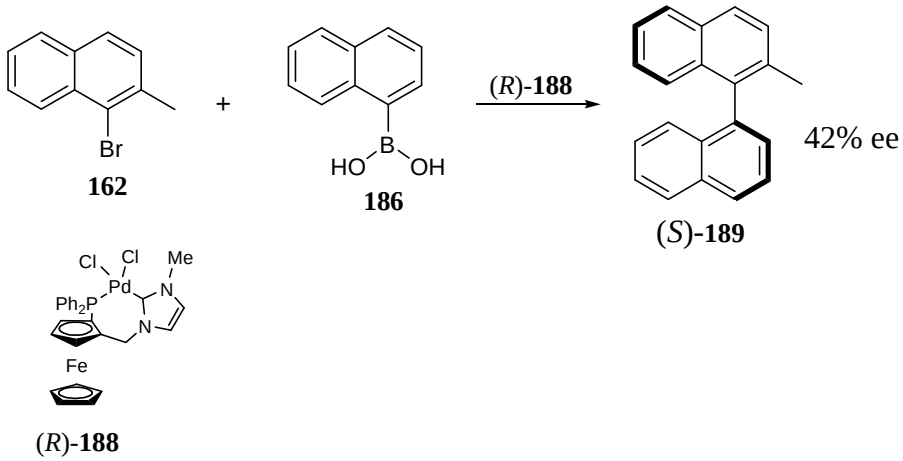
185 **186** (*S*)-**187**

Scheme 1.60 Cationic Pd^{2+} catalysed asymmetric Suzuki coupling reaction.

A maximum conversion of 92% with 70% ee was achieved in the synthesis of (*S*)-**187**; however the scope of the reaction was limited to binaphthyl products bearing one *ortho* group only.

Palladium nanoparticles have also been shown to effectively catalyse the asymmetric Suzuki coupling of naphthyl substrates at 25 °C when combined with chiral bisphosphine ligands (such as (*S*)-BINAP **126**) producing ee's of up to 74%.[240] However, as in the work of Mikami et al., the tolerance towards steric hindrance was limited to mono-*ortho* substituted binaphthyl products e.g. (*R*)-**187**.

Labande and co-workers recently reported the synthesis of planar chiral ferrocenyl phosphine ligands furnished with an *N*-heterocyclic carbene moiety that, after complexation with palladium, were able to catalyse asymmetric Suzuki couplings towards binaphthyl derivatives.[241]



Scheme 1.61 Asymmetric Suzuki coupling reaction towards (*S*)-**189** using catalyst (*R*)-**188**.

Good conversion was achieved in reactions towards binaphthyl product **189** (88%), with moderate ee values obtained. The scope of the reaction was also limited to the synthesis of mono-*ortho* substituted binaphthyls, with the arylboron coupling partner required to be the less hindered substrate. An attempted coupling using the 'reversed' substrates 2-methylnaphth-1-ylboronic acid and 1-bromonaphthalene resulted in no product formation.

1.8.1 Speculated mechanisms of chiral induction

Despite the intense interest surrounding the asymmetric variant of the Suzuki reaction together with the rapidly expanding range of alternative substrates and

conditions available for its protocol, very few studies have been conducted with the aim of elucidation of the mode of chiral induction.[242-244]

In the earliest attempts towards the rationalisation of this phenomenon, the highest selectivities achieved during asymmetric cross-couplings performed with an aryl Grignard reagent were speculated to be due to the presence of an ether group on the ligand employed, in which coordination of the magnesium atom of the Grignard substrate with the oxygen atom of the ether group was postulated to occur.[215] The transmetallation step was therefore tentatively proposed as the key step in the chiral induction, in which the delivery of the incoming organometallic partner at a particular orientation, facilitated by this coordination, was considered to be the determining factor behind the overall stereochemical outcome of the coupled product.

As mentioned previously, the transmetallation step of the catalytic cycle was also implicated as the key step in chiral induction during studies conducted by our own research group.[169] The apparent change in the stereochemistry of the coupled product resulting from a simple change in the boronate ester functionality strongly indicated this to the case, particularly considering the absence of other coordinating groups appended on the substrate molecule. It was similarly proposed that the presence of the chiral amino group on the ligand served to deliver the organoboron substrate in a manner analogous to that proposed for a Grignard reagent with an ether group, thus effecting a favoured orientation during this step.

Very recently during the completion of this investigation, a study was published by Buchwald et al. in which the mode of chiral induction was examined using computational methods modelled on substrates employed in previous experimental studies.[244] The results from these DFT calculations indicated that the stereoselectivity was induced from the combination of weak hydrogen-bonding interactions (and steric interactions) between the substrate groups and the ligand during the reductive elimination step. These hydrogen-bonding interactions arose as a direct result of the presence of oxygen-containing *ortho* groups on the organohalide substrate (such as phosphonates and amides) and were speculated to act as ‘anchor points’ preventing twisting of the organic portions during the reductive elimination process. Although beneficial towards the elucidation of the possible stereochemical

influences during asymmetric Suzuki reactions employing these substrates, the results from this study could not be extended to rationalise the mode of chiral induction operating between substrates lacking polar ‘anchoring’ substituent groups.

In light of these recent investigations, and given the great substrate dependency of the Suzuki coupling reaction, it is quite possible that the use of different coupling substrates could give rise to different mechanisms of stereochemical control.

1.9 Aims of this study

The primary aim of this study was to investigate the atroposelective version of the Suzuki reaction, in which coupling reactions utilising hindered aryl units to produce axially chiral biaryl compounds were studied. The goal was to perform carefully selected reactions (either novel or previously reported) in which the intricate relationship between the steric and electronic properties of the substrate species and the chiral catalyst species could be observed; with the ultimate aim of uncovering further details regarding the mode of asymmetric induction.

Attention was also directed towards the Suzuki coupling reaction of simple aryl substrates, in which investigations into the use of an alternative ‘activated’ quaternary organoboron species as a reagent were carried out. These studies were performed in order to extend the scope of the general Suzuki reaction and to enable the possible development of a more efficient protocol. An improved understanding into the fundamental steps of the general catalytic cycle was also the motivation behind these additional experiments.

1.10 References for Introduction

(1) R. F. Heck and J. P. Nolley Jr., *J. Org. Chem.* **1972**, *37*, 2320.

(2) H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.* **1974**, *96*, 1133.

(3) C. B. Ziegler Jr. and R. F. Heck, *J. Org. Chem.* **1978**, *43*, 2941.

(4) W. Cabri and I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2.

(5) F. Alonso, I. Beletskaya and M. Jus, *Tetrahedron* **2005**, *61*, 11771.

(6) K. Tamao, K. Sumitani and M. Kumada, *J. Am. Chem. Soc.* **1972**, *94*, 4374.

(7) K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato, M. Kumada, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958.

(8) D. Milstein and J. K. Stille, *J. Am. Chem. Soc.* **1979**, *101*, 4992.

(9) J. K. Stille, *Angew. Chem. Int. Ed.* **1986**, *25*, 508.

(10) T. N. Mitchell, *Synthesis* **1992**, 803.

(11) N. Miyaura, K. Yamada and A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437.

(12) N. Miyaura and A. Suzuki, *Chem. Commun.* **1979**, 866.

(13) N. Miyaura, K. Yamada, H. Suginome and A. Suzuki, *J. Am. Chem. Soc.* **1985**, *107*, 972.

(14) T. Moriya, N. Miyaura and A. Suzuki, *Synlett* **1994**, 149.

(15) N. Miyaura and A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457 and references therein.

(16) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147.

(17) A. Suzuki, *Chem. Commun.* **2005**, 4759.

(18) A. R. Martin and Y. Yang, *Acta Chem. Scand.* **1993**, *47*, 221.

(19) S. Kotha, K. Lahiri and D. Kashinath, *Tetrahedron* **2002**, *58*, 9633.

(20) N. Miyaura, T. Yanagi and A. Suzuki, *Synth. Commun.* **1981**, *11*, 513.

(21) N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh and A. Suzuki, *J. Am. Chem. Soc.* **1989**, *111*, 314.

(22) M. R. Netherton, C. Dai, K. Neuschütz and G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 10099.

(23) S. R. Chemler, D. Trauner and S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.

(24) P. E. Fanta, *Chem. Rev.* **1964**, *64*, 613.

(25) P. E. Fanta, *Synthesis*, **1974**, 9.

(26) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359.

(27) W. J. Thompson and J. Gaudino, *J. Org. Chem.* **1984**, *49*, 5237.

(28) W. J. Thompson, J. H. Jones, P. A. Lyle and J. E. Thies, *J. Org. Chem.* **1988**, *53*, 2052.

(29) T. I. Wallow and B. M. Novak, *J. Org. Chem.* **1994**, *59*, 5034.

(30) H. E. Katz, *J. Org. Chem.* **1987**, *52*, 3932.

(31) T. Watanabe, N. Miyaura and A. Suzuki, *Synlett* **1992**, 207.

(32) Y. Hoshino, N. Miyaura and A. Suzuki, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008.

(33) R. S. Coleman and E. B. Grant, *Tetrahedron Lett.* **1993**, *34*, 2225.

(34) P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron Lett.* **1993**, *34*, 2937.

(35) T. R. Kelly, A. Garcia, F. Lang, J. J. Walsh, K. V. Bhaskar, M. R. Boyd, R. Götz, P. A. Keller, R. Walter and G. Bringmann, *Tetrahedron Lett.* **1994**, *35*, 7621.

(36) J.-I. Uenishi, J.-M. Beau, R. W. Armstrong and Y. Kishi, *J. Am. Chem. Soc.* **1987**, *109*, 4756.

(37) J. C. Anderson and H. Namli, *Synlett.* **1995**, 765.

(38) S. W. Wright, D. L. Hageman and L. D. McClure, *J. Org. Chem.* **1994**, *59*, 6095.

(39) J. P. Corbet and G. Mignani, *Chem. Rev.* **2006**, *106*, 2651 and references therein.

(40) K. C. Nicolaou, J. M. Ramanjulu, S. Natarajan, S. Bräse, H. Li, C. N. C. Boddy and F. Rübsam, *Chem. Commun.* **1997**, 1899.

(41) D. G. Hall, *Structure, Properties, and Preparation of Boronic Acid Derivatives. Overview of Their Reactions and Applications*, Wiley-VCH GmbH, Weinheim, **2005**.

(42) J. C. Anderson, H. Namli and C. A. Roberts, *Tetrahedron* **1997**, *53*, 15123.

(43) O. Navarro, R. A. Kelly and S. P. Nolan, *J. Am. Chem. Soc.* **2003**, *125*, 16194.

(44) A. L. Casalnuovo and J. C. Calabrese, *J. Am. Chem. Soc.* **1990**, *112*, 4324.

(45) Y. Uozumi, H. Danjo and T. Hayashi, *J. Org. Chem.* **1999**, *64*, 3384.

(46) M. Ueda, M. Nishimura and N. Miyaura, *Synlett* **2000**, 856.

(47) N. A. Bumagin and V. V. Bykov, *Tetrahedron* **1997**, *53*, 14437.

(48) G. Lu, R. Franzén, Q. Zhang and Y. Xu, *Tetrahedron Lett.* **2005**, *46*, 4255.

(49) J. P. Wolfe and S. L. Buchwald, *Angew. Chem. Int. Ed.* **1999**, *38*, 2413.

(50) J. P. Wolfe, R. A. Singer, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(51) J. L. Bolliger, O. Blacque and C. M. Frech, *Angew. Chem. Int. Ed.* **2007**, *46*, 6514.

(52) E. M. Campi, W. R. Jackson, S. M. Marcuccio and C. G. M. Naeslund, *J. Chem. Soc., Chem. Commun.* **1994**, 2395.

(53) X. Tao, Y. Zhao and D. Shen, *Synlett* **2004**, 359.

(54) G. Marck, A. Villiger and R. Buchecker, *Tetrahedron Lett.* **1994**, *35*, 3277.

(55) J. P. Simeone and J. R. Sowa Jr., *Tetrahedron* **2007**, *63*, 12646.

(56) S.-B. Jang, *Tetrahedron Lett.* **1997**, *38*, 1793.

(57) I. Fenger and C. Le Drian, *Tetrahedron Lett.* **1998**, 39, 4287.

(58) M. Beller, H. Fischer, W. A. Herrmann, K. Öfele and C. Brossmer, *Angew. Chem. Int. Ed.* **1995**, *34*, 1848.

(59) W. Shen, *Tetrahedron Lett.* **1997**, *38*, 5575.

(60) D. W. Old, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722.

(61) A. F. Littke and G. C. Fu, *Angew. Chem. Int. Ed.* **1998**, *37*, 3387.

(62) A. F. Littke, C. Dai and G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(63) A. F. Littke and G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

(64) T. E. Pickett, F. X. Roca and C. J. Richards, *J. Org. Chem.* **2003**, *68*, 2592.

(65) S.-B. Yu, X.-P. Hu, J. Deng, J.-D. Huang, D.-Y. Wang, Z.-C. Duan and Z. Zheng, *Tetrahedron Lett.* **2008**, *49*, 1253.

(66) D. A. Widdowson and R. Wilhelm, *Chem. Commun.* **2003**, 578.

(67) Y. M. Kim and S. Yu, *J. Am. Chem. Soc.* **2003**, *125*, 1696.

(68) C. R. Kinney and D. F. Pontz, *J. Am. Chem. Soc.* **1936**, *58*, 197.

(69) H. R. Snyder, J. A. Kuck and J. R. Johnson, *J. Am. Chem. Soc.* **1938**, *60*, 105.

(70) Z. Z. Song and H. N. C. Wong, *J. Org. Chem.* **1994,** *59*, 33.

(71) M. Mastalerz, *Angew. Chem. Int. Ed.* **2008**, *47*, 445.

(72) M. F. Lappert, *Chem. Rev.* **1956**, *56*, 959.

(73) K.-C. Kong and C.-H. Cheng, *J. Am. Chem. Soc.* **1991**, *113*, 6313.

(74) D. F. O'Keefe, M. C. Dannock and S. M. Marcuccio, *Tetrahedron Lett.* **1992**, *33*, 6679.

(75) F. Y. Kwong and K. S. Chan, *Chem. Commun.* **2000**, 1069.

(76) H. G. Kuivila and K. V. Nahabedian, *J. Am. Chem. Soc.* **1961**, *83*, 2159.

(77) H. G. Kuivila and K. V. Nahabedian, *J. Am. Chem. Soc.* **1961**, *83*, 2164.

(78) K. V. Nahabedian and H. G. Kuivila, *J. Am. Chem. Soc.* **1961**, *83*, 2167.

(79) H. G. Kuivila, J. F. Reuwer Jr. and J. A. Mangravite, *Can. J. Chem.* **1963**, *41*, 3081.

(80) H. G. Kuivila, J. F. Reuwer Jr. and J. A. Mangravite, *J. Am. Chem. Soc.* **1964**, *86*, 2666.

(81) M. G. Johnson and R. J. Foglesong, *Tetrahedron Lett.* **1997**, *38*, 7001.

(82) J. Yin, M. P. Rainka, X.-X. Zhang and S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1162.

(83) T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685.

(84) S. Würtz and F. Glorius, *Acc. Chem. Res.* **2008**, *41*, 1523.

(85) T. Hoshi, T. Nakazawa, I. Saitoh, A. Mori, T. Suzuki, J.-I. Sakai and H. Hagiwara, *Org. Lett.* **2008**, *10*, 2063.

(86) T. Hoshi, I. Saitoh, T. Nakazawa, T. Suzuki, J.-I. Sakai and H. Hagiwara, *J. Org. Chem.* **2009**, *74*, 4013.

(87) Y. Urawa, H. Naka, M. Miyazawa, S. Souda and K. Ogura, *J. Organomet. Chem.* **2002**, *653*, 269.

(88) J. Magano and J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177.

(89) T. Konakahara, Y. B. Kiran, Y. Okuno, R. Ikeda and N. Sakai, *Tetrahedron Lett.* **2010**, *51*, 2335.

(90) S. Kaye, J. M. Fox, F. A. Hicks and S. L. Buchwald, *Adv. Synth. Catal.* **2001**, *343*, 789.

(91) C. Baillie, W. Chen and J. Xiao, *Tetrahedron Lett.* **2001**, *42*, 9085.

(92) W.-L. Yu, J. Pei, W. Huang and A. J. Heeger, *Chem. Commun.* **2000**, 681.

(93) M. Kertesz, C. H. Choi and S. Yang, *Chem. Rev.* **2005**, *105*, 3448.

(94) A. O. Aliprantis and J. W. Canary, *J. Am. Chem. Soc.* **1994**, *116*, 6985.

(95) G. B. Smith, G. C. Dezeny, D. L. Hughes, A. O. King and T. R. Verhoeven, *J. Org. Chem.* **1994**, *59*, 8151.

(96) G. Espino, A. Kurbangalieva and J. M. Brown, *Chem. Commun.* **2007**, 1742.

(97) C. Amatore, A. Jutand and A. Suarez, *J. Am. Chem. Soc.* **1993**, *115*, 9531 and references therein.

(98) D. H. Valentine Jr. and J. H. Hillhouse, *Synthesis* **2003**, 2437.

(99) C. Amatore, A. Jutand and M. A. M'Barki, *Organometallics* **1992**, *11*, 3009.
(100) V. V. Grushin and H. Alper, *Organometallics* **1993**, *12*, 1890.
(101) M. Moreno-Mañas, M. Pérez and R. Pleixats, *J. Org. Chem.* **1996**, *61*, 2346.
(102) J. K. Stille and K. S. Y. Lau, *Acc. Chem. Res.* **1977**, *10*, 434.
(103) N. Miyaura, *J. Organomet. Chem.* **2002**, *653*, 54.
(104) V. V. Grushin and H. Alper, *J. Am. Chem. Soc.* **1995**, *117*, 4305.
(105) V. V. Grushin and H. Alper, *Organometallics* **1996**, *15*, 5242.
(106) M. S. Driver and J. F. Hartwig, *Organometallics* **1997**, *16*, 5706.
(107) T. Yoshida, T. Okano and S. Otsuka, *J. Chem. Soc., Dalton Trans.* **1976**, 993.
(108) B. P. Carrow and J. F. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 2116.
(109) K. J. Klabunde and J. Y. F. Low, *J. Am. Chem. Soc.* **1974**, *96*, 7674.
(110) M. F. Semmelhack and L. Ryono, *Tetrahedron Lett.* **1973**, *14*, 2967.
(111) C. Amatore and F. Pflüger, *Organometallics* **1990**, *9*, 2276.
(112) C. Amatore, E. Carré, A. Jutand and M. A. M'Barki, *Organometallics* **1995**, *14*, 1818.
(113) C. Amatore, G. Broecker, A. Jutand and F. Khalil, *J. Am. Chem. Soc.* **1997**, *117*, 5176.
(114) A. Gillie and J. K. Stille, *J. Am. Chem. Soc.* **1980**, *102*, 4933.
(115) F. Ozawa, T. Ito, Y. Nakamura and A. Yamamoto, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1868.
(116) G. W. Parshall, *J. Am. Chem. Soc.* **1974**, *96*, 2360.
(117) A. Moravskiy and J. K. Stille, *J. Am. Chem. Soc.* **1981**, *103*, 4182.
(118) D. Milstein and J. K. Stille, *J. Am. Chem. Soc.* **1979**, *101*, 4981.
(119) H. Kurosawa, M. Emoto and A. Urabe, *J. Chem. Soc., Chem. Commun.* **1984**, 968.
(120) F. Ozawa, M. Fujimori, T. Yamamoto and A. Yamamoto, *Organometallics* **1986**, *5*, 2144.
(121) F. Ozawa, T. Hidaka, T. Yamamoto and A. Yamamoto, *J. Organomet. Chem.* **1987**, *330*, 253.
(122) F. Ozawa, K. Kurihara, M. Fujimori, T. Hidaka, T. Toyoshima and A. Yamamoto, *Organometallics* **1989**, *8*, 180.
(123) P. S. Braterman, R. J. Cross and G. B. Young, *J. Chem. Soc., Dalton Trans.* **1977**, 1892.

(124) E. Zuidema, P. W. N. M. van Leeuwen and C. Bo, *Organometallics* **2005**, *24*, 3703.

(125) A. A. C. Braga, N. H. Morgon, G. Ujaque and F. Maseras, *J. Am. Chem. Soc.* **2005**, *127*, 9298.

(126) A. A. C. Braga, N. H. Morgon, G. Ujaque, A. Lledós and F. Maseras, *J. Organomet. Chem.* **2006**, *691*, 4459.

(127) A. A. C. Braga, G. Ujaque and F. Maseras, *Organometallics* **2006**, *25*, 3647.

(128) C. Sicre, A. A. C. Braga, F. Maseras and M. M. Cid, *Tetrahedron* **2008**, *64*, 7437.

(129) L. J. Goossen, D. Koley, H. L. Hermann and W. Thiel, *J. Am. Chem. Soc.* **2005**, *127*, 11102.

(130) L. J. Goossen, D. Koley, H. L. Hermann and W. Thiel, *Organometallics* **2006**, *25*, 54.

(131) F. J. McQuillin, D. G. Parker and G. R. Stephenson, *Transition Metal Organometallics for Organic Synthesis*, Cambridge University Press, Cambridge, **1991**.

(132) P. Fitton, M. P. Johnson and J. E. McKeon, *Chem. Commun.* **1968**, 6.

(133) P. Fitton and E. A. Rick, *J. Organomet. Chem.* **1971**, *28*, 287.

(134) G. Calvin and G. E. Coates, *J. Chem. Soc.* **1960**, 2008.

(135) A. Jutand and A. Mosleh, *Organometallics* **1995**, *14*, 1810.

(136) G. K. Anderson and R. J. Cross, *Chem. Soc. Rev.* **1980**, *9*, 185.

(137) P. Fitton and J. E. Mckeon, *Chem. Commun.* **1968**, 4.

(138) H. Urata, M. Tanaka and T. Fuchikami, *Chem. Lett.* **1987**, 751.

(139) A. L. Casado and P. Espinet, *Organometallics* **1998**, *17*, 954.

(140) L. J. Goossen, D. Koley, H. L. Hermann and W. Thiel, *Organometallics* **2005**, *24*, 2398.

(141) K. Matos and J. A. Soderquist, *J. Org. Chem.* **1998**, *63*, 461.

(142) V. V. Grushin and H. Alper, *Chem. Rev.* **1994**, *94*, 1047.

(143) K. Fagnou and M. Lautens, *Angew. Chem. Int. Ed.* **2002**, *41*, 26.

(144) C. Amatore, E. Carré, A. Jutand, M. A. M'Barki and G. Meyer, *Organometallics* **1995**, *14*, 5605.

(145) C. Amatore and A. Jutand, *J. Organomet. Chem.* **1999**, *576*, 254.

(146) C. Amatore and A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 314.

(147) A. N. Cammidge and K. V. L. Crépy, *J. Org. Chem.* **2003**, *68*, 6832.

(148) D. G. Morrell and J. K. Kochi, *J. Am. Chem. Soc.* **1975**, *97*, 7262.

(149) P. K. Byers, A. J. Canty, B. W. Skelton and A. H. White, *J. Chem. Soc., Chem. Commun.* **1986**, 1722.

(150) A. Bayler, A. J. Canty, P. G. Edwards, B. W. Skelton and A. H. White, *J. Chem. Soc., Dalton Trans.* **2000**, 3325.

(151) S. Darses, G. Michaud and J.-P. Genêt, *Tetrahedron Lett.* **1998**, *39*, 5045.

(152) S. Darses and J.-P. Genêt, *Eur. J. Org. Chem.* **2003**, 4313.

(153) G. A. Molander and B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302.

(154) P. G. Ciattini, E. Morera and G. Ortar, *Tetrahedron Lett.* **1992**, *33*, 4815.

(155) M. Butters, J. N. Harvey, J. Jover, A. J. J. Lennox, G. C. Lloyd-Jones and P. M. Murray, *Angew. Chem., Int. Ed.* **2010**, *49*, 5156.

(156) A. J. J. Lennox and G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2012**, *134*, 7431.

(157) F. R. Bean and J. R. Johnson, *J. Am. Chem. Soc.* **1932**, *54*, 4415.

(158) D. S. Matteson, *Tetrahedron* **1989**, *45*, 1859.

(159) P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron* **1993**, *49*, 49.

(160) T. Ishiyama, M. Murata and N. Miyaura, *J. Org. Chem.* **1995**, *60*, 7508.

(161) T. Ishiyama, K. Ishida and N. Miyaura, *Tetrahedron* **2001**, *57*, 9813.

(162) A. Giroux, Y. Han and P. Prasit, *Tetrahedron Lett.* **1997**, *38*, 3841.

(163) A. D. Ainley and F. Challenger, *J. Chem. Soc.* **1930**, 2171.

(164) A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.* **1959**, *81*, 5509.

(165) H.-J. Frohn, N. Y. Adonin, V. V. Bardin and V. F. Starichenko, *Z. Anorg. Allg. Chem.* **2002**, *628*, 2834.

(166) H. R. Snyder and F. W. Wyman, *J. Am. Chem. Soc.* **1948**, *70*, 234.

(167) A. N. Cammidge and K. V. L. Crépy, *Chem. Commun.* **2000**, 1723.

(168) J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12051.

(169) A. N. Cammidge and K. V. L. Crépy, *Tetrahedron* **2004**, *60*, 4377.

(170) A. Huth, I. Beetz and I. Schumann, *Tetrahedron* **1989**, *45*, 6679.

(171) J.-M. Fu and V. Snieckus, *Tetrahedron Lett.* **1990**, *31*, 1665.

(172) T. Oh-e, N. Miyaura and A. Suzuki, *Synlett* **1990**, 221.

(173) W.-C. Shieh and J. A. Carlson, *J. Org. Chem.* **1992**, *57*, 379.

(174) K. Ritter, *Synthesis* **1993**, 735.

(175) T. Hayashi, S. Niizuma, T. Kamikawa, N. Suzuki and Y. Uozumi, *J. Am. Chem. Soc.* **1995**, *117*, 9101.

(176) T. Kamikawa and T. Hayashi, *Tetrahedron Lett.* **1997**, *38*, 7087.

(177) S. Darses, T. Jeffery, J.-P. Genêt, J.-L. Brayer and J.-P. Demoute, *Tetrahedron Lett.* **1996**, *37*, 3857.

(178) S. Sengupta and S. Bhattacharyya, *J. Org. Chem.* **1997**, *62*, 3405.

(179) F. Mo, D. Qiu, Y. Jiang, Y. Zhang and J. Wang, *Tetrahedron Lett.* **2011**, *52*, 518.

(180) M. B. Mitchell and P. J. Wallbank, *Tetrahedron Lett.* **1991**, *32*, 2273.

(181) A. F. Indolese, *Tetrahedron Lett.* **1997**, *38*, 3513.

(182) S. Saito, S. Oh-tani, N. Miyaura, *J. Org. Chem.* **1997**, *62*, 8024.

(183) C. Griffiths and N. E. Leadbeater, *Tetrahedron Lett.* **2000**, *41*, 2487.

(184) D. Zim, V. R. Lando, J. Dupont and A. L. Monteiro, *Org. Lett.* **2001**, *3*, 3049.

(185) P. Gros, A. Doudouh and Y. Fort, *Tetrahedron Lett.* **2004**, *45*, 6239.

(186) X.-X. Liu and M.-Z. Deng, *Chem. Commun.* **2002**, 622.

(187) Y. Deng, L. Gong, A. Mi, H. Liu and Y. Jiang, *Synthesis* **2003**, 337.

(188) I. P. Beletskaya, *J. Organomet. Chem.* **1983**, *250*, 551.

(189) D. A. Albisson, R. B. Bedford, S. E. Lawrence and P. N. Scully, *Chem. Commun.* **1998**, 2095.

(190) R. B. Bedford, *Chem. Commun.* **2003**, 1787.

(191) J. Dupont, C. S. Consorti and J. Spencer, *Chem. Rev.* **2005**, *105*, 2527.

(192) F. Bellina, A. Carpita and R. Rossi, *Synthesis* **2004**, 2419.

(193) M. R. Netherton and G. C. Fu, *Org. Lett.* **2001**, *3*, 4295.

(194) R. Martin and S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.

(195) P. Kočovský, *J. Organomet. Chem.* **2003**, *687*, 256.

(196) G. H. Christie and J. Kenner, *J. Chem. Soc., Trans.* **1922**, *121*, 614.

(197) R. Adams and H. C. Yuan, *Chem. Rev.* **1933**, *12*, 261.

(198) M. Rieger and F. H. Westheimer, *J. Am. Chem. Soc.* **1950**, *72*, 19.

(199) G. Bott, L. D. Field and S. Sternell, *J. Am. Chem. Soc.* **1980**, 102, 5618.

(200) P. Lloyd-Williams and E. Giralt, *Chem. Soc. Rev.* **2001**, *30*, 145.

(201) A. S. Cooke and M. M. Harris, *J. Chem. Soc.* **1963**, 2365.

(202) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner and M. Breuning, *Angew. Chem. Int. Ed.* **2005**, *44*, 5384.

(203) O. Baudoin, *Eur. J. Org. Chem.* **2005**, 4223.

(204) J. Mutanyatta, M. Bezabih, B. M. Abegaz, M. Dreyer, R. Brun, N. Kocher and G. Bringmann, *Tetrahedron* **2005**, *61*, 8475.

(205) G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.* **2011**, *111*, 563.

(206) L. Pu, *Chem. Rev.* **1998**, *98*, 2405.

(207) C. Rosini, L. Franzini, A. Raffaelli and P. Salvadori, *Synthesis* **1992**, 503.

(208) A. C. Spivey, F. Zhu, M. B. Mitchell, S. G. Davey and R. L. Jarvest, *J. Org. Chem.* **2003**, *68*, 7379.

(209) J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857.

(210) A. Chieffi, K. Kamikawa, J. Åhman, J. M. Fox and S. L. Buchwald, *Org. Lett.* **2001**, *3*, 1897.

(211) G. Solladié, P. Hugelé, R. Bartsch and A. Skoulios, *Angew. Chem. Int. Ed.* **1996**, *35*, 1533.

(212) D. Zehm, W. Fudickar, M. Hans, U. Schilde, A. Kelling and T. Linker, *Chem. - Eur. J.* **2008**, *14*, 11429.

(213) N. Maigrot and J.-P. Mazaleyrat, *Synthesis* **1985**, 317.

(214) K. Tamao, H. Yamamoto, H. Matsumoto, N. Miyake, T. Hayashi and M. Kumada, *Tetrahedron Lett.* **1977**, *18*, 1389.

(215) T. Hayashi, K. Hayashizaki, T. Kiyoi and Y. Ito, *J. Am. Chem. Soc.* **1988**, *110*, 8153.

(216) T. Frejd and T. Klingstedt, *Acta Chem. Scand.* **1989**, *43*, 670.

(217) T. Shimada, Y.-H. Cho and T. Hayashi, *J. Am. Chem. Soc.* **2002**, *124*, 13396.

(218) A. I. Meyers and K. A. Lutomski, *J. Am. Chem. Soc.* **1982**, *104*, 879.

(219) G.-Q. Lin and M. Zhong, *Tetrahedron Lett.* **1997**, *38*, 1087.

(220) T. Watanabe and M. Uemura, *Chem. Commun.* **1998**, 871.

(221) K. Kamikawa, T. Watanabe, A. Daimon and M. Uemura, *Tetrahedron* **2000**, *56*, 2325.

(222) T. Watanabe, Y. Tanaka, R. Shoda, R. Sakamoto, K. Kamikawa and M. Uemura, *J. Org. Chem.* **2004**, *69*, 4152.

(223) K. Kamikawa, T. Sakamoto, Y. Tanaka and M. Uemura, *J. Org. Chem.* **2003**, *68*, 9356.

(224) J. Clayden, P. M. Kubinski, F. Sammiceli, M. Helliwell and L. Diorazio, *Tetrahedron* **2004**, *60*, 4387.

(225) T. Hattori, M. Date, K. Sakurai, N. Morohashi, H. Kosugi and S. Miyano, *Tetrahedron Lett.* **2001**, *42*, 8035.

(226) T. Hayashi, *J. Organomet. Chem.* **2002**, *653*, 41.

(227) G. Bringmann, M. Breuning, R.-M. Pfeifer, W. A. Schenk, K. Kamikawa and M. Uemura, *J. Organomet. Chem.* **2002**, *661*, 31.

(228) A. V. Vorogushin, W. D. Wulff and H.-J. Hansen, *J. Org. Chem.* **2003**, *68*, 9618.

(229) X. Li, J. B. Hewgley, C. A. Mulrooney, J. Yang and M. C. Kozlowski, *J. Org. Chem.* **2003**, *68*, 5500.

(230) P.-E. Broutin and F. Colobert, *Org. Lett.* **2003**, *5*, 3281.

(231) F. Colobert, V. Valdivia, S. Choppin, F. R. Leroux, I. Fernández, E. Álvarez and N. Khiar, *Org. Lett.* **2009**, *11*, 5130.

(232) M. C. Willis, L. H. W. Powell, C. K. Claverie and S. J. Watson, *Angew. Chem. Int. Ed.* **2004**, *43*, 1249.

(233) P.-E. Broutin and F. Colobert, *Org. Lett.* **2005**, *7*, 3737.

(234) A. Herrbach, A. Marinetti, O. Baudoin, D. Guénard and F. Guéritte, *J. Org. Chem.* **2003**, *68*, 4897.

(235) G. Bringmann, A. Hamm and M. Schraut, *Org. Lett.* **2003**, *5*, 2805.

(236) G. Bringmann, S. Rüdenauer, T. Bruhn, L. Benson and R. Brun, *Tetrahedron* **2008**, *64*, 5563.

(237) J. F. Jensen and M. Johannsen, *Org. Lett.* **2003**, *5*, 3025.

(238) A.-S. Castanet, F. Colobert, P.-E. Broutin and M. Obringer, *Tetrahedron: Asymmetry*, **2002**, *13*, 659.

(239) K. Mikami, T. Miyamoto and M. Hatano, *Chem. Commun.* **2004**, 2082.

(240) K. Sawai, R. Tatumi, T. Nakahodo and H. Fujihara, *Angew. Chem. Int. Ed.* **2008**, *47*, 6917.

(241) N. Debono, A. Labande, E. Manoury, J.-C. Daran and R. Poli, *Organometallics* **2010**, *29*, 1879.

(242) A. Joncour, A. Décor, J.-M. Liu, M.-E. Tran Huu Dau and O. Baudoin, *Chem. -Eur. J.* **2007**, *13*, 5450.

(243) A. Bermejo, A. Ros, R. Fernández and J. M. Lassaletta, *J. Am. Chem. Soc.* **2008**, *130*, 15798.

(244) X. Shen, G. O. Jones, D. A. Watson, B. Bhayana and S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 11278.

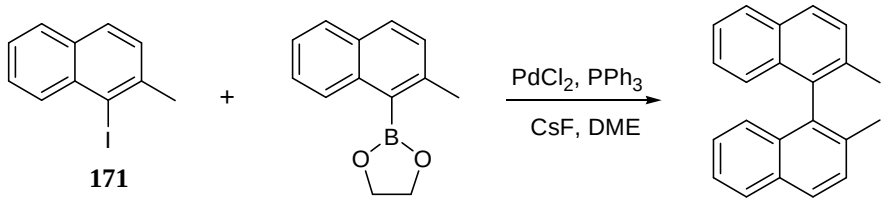
CHAPTER 2

Results and Discussion

RESULTS AND DISCUSSION

2.1 The re-examination of a known hindered Suzuki coupling: Synthesis of 2,2'-dimethyl-1,1'-binaphthalene

It was considered important from the outset to gain an immediate direct experience into the challenging nature of sterically hindered Suzuki couplings. Therefore, the re-examination of a known Suzuki coupling of this type was thought to present a beneficial first exercise, in which a coupling towards a highly hindered *ortho*-substituted biaryl would be repeated. The hindered coupling towards racemic binaphthyl **165** (scheme 2.1) originally described by our group[1-3] was thus chosen as a suitable starting point.



171 **172** **165**

Scheme 2.1 Suzuki coupling towards racemic 2,2'-dimethyl-1,1'-binaphthalene **165**.

This coupling reaction had been found to be particularly challenging, on account of its sterically demanding substrates. The presence of *ortho* methyl substituents on both naphthyl partners tested the uppermost limits of the tolerance of the Suzuki coupling towards steric bulk, and consequently a reaction protocol employing rigorously anhydrous conditions was discovered to be essential for the achievement of respectable yields. Prior to the development of this reaction, a small number of earlier studies had also reported the improved success of hindered Suzuki couplings with the use of non-aqueous conditions.[4-6] To date, the exclusion of water is still an often used measure to facilitate the coupling of bulky or precious substrates.[7,8]

In this protocol, significant efforts were made towards the minimisation of factors leading to the promotion of deboronation side-reaction. Therefore the use of boronate esters as opposed to boronic acids was tested and found to be advantageous,

as was the use of DME as the reaction solvent. (The beneficial use of this aprotic polar coordinating solvent in Suzuki couplings was originally described by Gronowitz).[9] The use of an iodide substrate was also found to give superior yields as compared to the bromide equivalent; an observation also reported in previous work.[10] Cesium fluoride was found to give best results in this reaction compared to other bases.

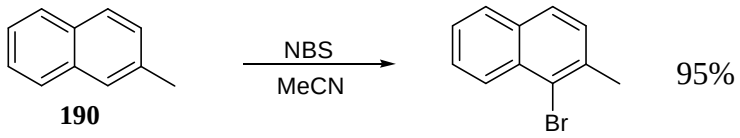
The use of this base has been described as a good choice for these reactions on account of the high affinity of the fluoride ion towards the boron atom of the organoboron substrate.[11] The potential for base-catalysed deboronation (which has been tentatively speculated in some reports to be accelerated by an increase in the concentration of hydroxide ions)[12] is decreased, as is the potential for catalyst destruction on account of the weak affinity of fluoride towards palladium. (The mild nature of cesium fluoride has also been found to be advantageous in the coupling of substrates bearing base-sensitive functional groups). The highly hygroscopic nature of this base on the other hand presents a slight drawback, in that atmospheric moisture can inadvertently be introduced into the reaction media.

2.1.1 Synthesis of 2,2'-dimethyl-1,1'-binaphthalene : Preparation of coupling substrates

Synthesis of the coupling substrates **171** and **172** was necessary prior to the undertaking of the coupling reaction outlined in scheme 2.1. In general, the preparation of these substrates was successfully achieved following the previously reported procedures,[1,3] although on some occasions the procedures were modified in order to optimise conversions or to give more expedient routes (see experimental).

2.1.1.1 Initial preparation of 1-bromo-2-methylnaphthalene

Synthesis of 1-bromo-2-methylnaphthalene **162** was achieved by the addition of a slight excess of *N*-bromosuccinimide to a solution of 2-methylnaphthalene **190** in acetonitrile at room temperature (scheme 2.2). (The mixture was kept covered and away from direct sources of light throughout the procedure).



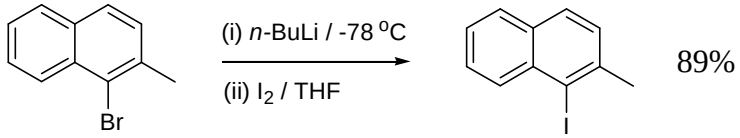
190 **162**

Scheme 2.2 Preparation of 1-bromo-2-methylnaphthalene **162**.

The yellow oil that remained was analysed by ^{1}H NMR spectroscopy and was found to contain the desired brominated product **162**. A substantial amount of unreacted 2-methylnaphthalene starting material **190** was also present, comprising approximately 10% of the mixture (calculated from ^{1}H NMR peak integrals). This impurity could not be removed by column chromatography or by any other methods attempted. (In previous studies, purification by distillation was found to be unsuccessful and so was not attempted here). The reaction was repeated, and allowed to stir for a greater length of time to encourage the reaction to go to completion. This did not improve the yield as the observed ratio of product to unreacted starting material remained the same after the extended length of time. Commercially available 1-bromo-2-methylnaphthalene **162**, despite containing the same impurity, was found to be of a higher purity and so was used in all subsequent syntheses.

2.1.1.2 Preparation of 1-iodo-2-methylnaphthalene coupling substrate

1-Iodo-2-methylnaphthalene **171** was prepared according to the procedure described by Crépy[1] via a metal-halogen exchange reaction using 1-bromo-2-methylnaphthalene **162**:



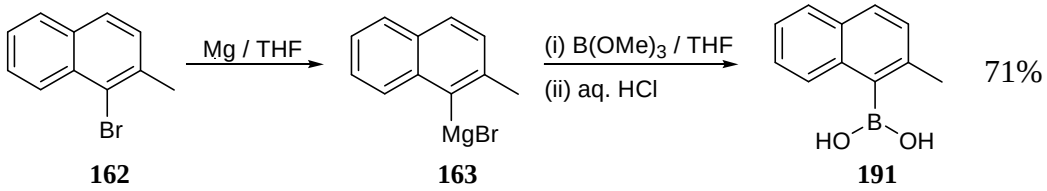
162 **171**

Scheme 2.3 Preparation of 1-iodo-2-methylnaphthalene coupling substrate **171**.

The product **171** was isolated as a pale yellow oil which was dried under vacuum and kept under an inert atmosphere until required for use.

2.1.1.3 Preparation of 2-methylnaphth-1-yl(ethylene glycol)boronate ester coupling substrate

Preparation of the (ethylene glycol)boronate ester substrate **172** was then undertaken, with the initial synthesis of the parent boronic acid **191** achieved via conversion of 1-bromo-2-methylnaphthalene **162** to its Grignard reagent **163**.

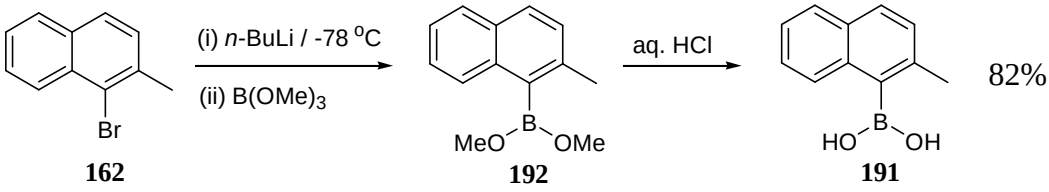


162 **163** **191**

Scheme 2.4 Preparation of 2-methylnaphth-1-yl boronic acid **191** via Grignard reagent **163**.

The Grignard reagent **163** was added to a cooled solution of trimethyl borate and the resulting ester hydrolysed under aqueous acidic conditions to give the free boronic acid **191**. On each occasion, this method produced satisfactory yields of boronic acid in the region of 60 – 70%. However, the step in the procedure involving addition of the Grignard reagent to the trimethyl borate solution was often fraught with problems. Upon preparation, the Grignard reagent **163** frequently crystallised out of solution despite continued heating and vigorous stirring. Transferral of this mixture to the cooled trimethyl borate solution via canula was also difficult due to the viscosity of the mixture. In addition, immediate solidification of the Grignard reagent **163** on addition to the cooled trimethyl borate solution resulted in a large solid mass that often prevented efficient stirring of the mixture. Consequently, yields of product obtained were lower than expected.

An alternative protocol for the synthesis of boronic acid **191** was thus considered, and achieved by metal-halogen exchange using *n*-butyllithium (originally described by Brown and Cole).[13]

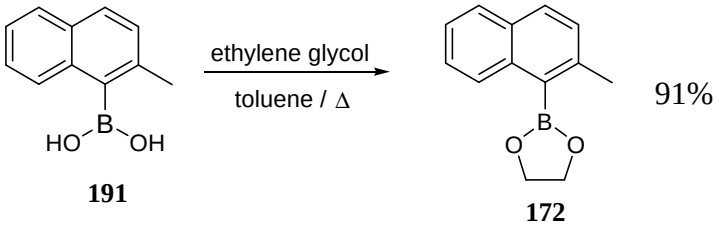


162 **192** **191**

Scheme 2.5 Alternative route towards synthesis of 2-methylnaphthylboronic acid **191**.

This method gave improved yields of the product **191** in a smooth and less arduous manner, and so was used preferentially for all subsequent boronic acid syntheses.

The boronic acid **191** was then converted to its (ethylene glycol)boronate ester analogue **172** by treatment with anhydrous ethylene glycol under heating:



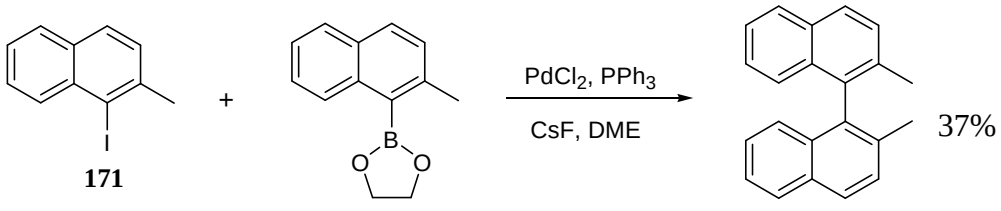
191 **172**

Scheme 2.6 Preparation of 2-methylnaphth-1-yl(ethylene glycol)boronate ester **172**.

Simple reflux conditions were found to be adequate as the reaction proceeded readily to give the product **172** in 91% yield. Any excess ethylene glycol starting reagent was effectively removed during the aqueous work-up. The product obtained was initially a viscous oil that solidified after refrigeration at 5 °C. ^{1}H NMR spectroscopic analysis of the pale yellow waxy solid confirmed the structure and purity.

2.1.2 Symmetric Suzuki coupling towards 2,2'-dimethyl-1,1'-binaphthalene

In this test experiment, the aim of the coupling reaction was to achieve the successful repeat preparation of the hindered biaryl product **165** in its simple racemic form. Therefore, the conventionally employed ligand triphenylphosphine was employed.



171 **172** **165**

Scheme 2.7 Suzuki coupling towards binaphthalene product **165** as a racemate.

Care was taken to ensure that the reaction conditions were completely anhydrous, in accordance with the original protocol.[1,3] To this end, the reaction vessel and condenser were flame-dried prior to use, and the iodide **171** and boronate ester **172** reagents dried and stored under vacuum prior to use. Following the addition of each solid reagent the reaction vessel was evacuated and purged with argon, with the liquid iodide starting material **171** added via syringe. Freshly distilled solvent was added, and the mixture heated to reflux for 6 days with addition of extra catalyst and ligand every 24 h. The system was kept under a positive pressure of argon throughout this period of time.

The first attempt at this Suzuki coupling resulted in only a very small amount of the product **165**. The probable cause was speculated to be moisture from atmospheric air entering the system through the ground glass joints. Using this particular set-up (round-bottom flask with Liebig condenser) entailed that this was always a possibility. The opportunity for atmospheric moisture to enter the system during the addition of fresh catalyst and ligand was also unavoidable, although care was taken to maintain a positive pressure of argon throughout this process.

The second attempt resulted in greater success with the product **165** clearly identifiable by its prominent peaks in the ^{1}H NMR spectrum. Unreacted iodide starting material **171** was also identified together with deboronated side-product (2-methylnaphthalene **190**). Isolation from the crude mixture proved difficult as the deboronated side-product eluted closely to the product; however successful separation was achieved using a gradient solvent system. The isolated coupled product was obtained in a 37% yield as a viscous pale yellow oil, with NMR data in agreement with previous reports.[1]

The accomplishment of this reaction served to provide a useful insight into the sensitive nature of this type of reaction, and confirmed that stringent measures during the preparation and undertaking of the reaction were indeed vital in order to ensure maximum success.

In the consideration of Suzuki coupling reactions suitable for asymmetric investigations, it was decided that this particular coupling reaction could not be taken

further. In previous studies it was discovered that an unfortunate characteristic of the two atropisomeric forms of the product was their inadequate separation via chiral HPLC methods. The use of chiral HPLC separation of isomers for the calculation of enantiomeric excesses is on the whole considered an accurate method; however a good baseline separation of peaks is required particularly in the calculation of large excesses. (An inadequate baseline separation leads to the merging of peaks which consequently results in imprecise calculations of the enantiomeric excess).

An additional inherent drawback to this particular reaction arose from the fact that the homocoupled product has an identical structure to the cross-coupled product. The formation of this side-product could also lead to an inaccurate determination of the enantiomeric excess achieved. As a result, alternative model reactions towards rotationally restricted biaryl products fulfilling all necessary criteria were sought.

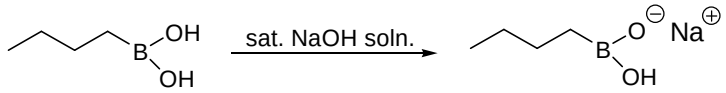
2.2 Investigations into the use of sodium trihydroxyarylborate salts as alternative organoboron substrates

During the course of this investigation, it became apparent from a discovery within our own research group that a previously unreported class of organic trihydroxyborate salts could be synthesised and isolated from the treatment of boronic acids with strong base.

A search through the historical literature revealed that the existence of quaternary borate species has been acknowledged for a number of years.[13,14,15] The formation of quaternary borate ions from boric acid was postulated in early work by Ainley and Challenger[14] and was attributed to the desire of the boron atom to complete its octet of electrons. Subsequent work by Edwards et al.[15] observed the presence of a $B(OH)_4^-$ ion in an aqueous solution of boric acid with potassium hydroxide from the analysis of Raman spectra. The combination of their data led the authors to conclude that the identity of the ion was indeed that of $B(OH)_4^-$ and that the structure of this ion displayed tetrahedral symmetry. In more recent times, the presence of organoborate species in alkaline aqueous media has been confirmed by

NMR spectroscopy[12,16,17] and are known to exist in equilibrium with their neutral boronic acid forms.

Early investigations into the chemical properties of boronic acids revealed the tendency of boronic acids to behave as Lewis acids.[18,19] However, preliminary tests conducted by Snyder et al.[18] involving the treatment of boronic acids with saturated aqueous sodium hydroxide solution led to the erroneous deduction that the precipitated salt product was composed of the structure shown below.



193 **194**

Scheme 2.8 Initial structure suggested for a borate salt product.

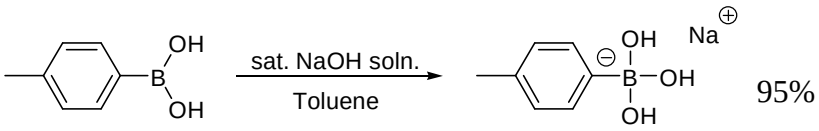
Since these early findings there exists (to the best of our knowledge) no other attempted isolation of organotrihydroxyborate salt species, despite their implicated presence in aqueous alkaline media. There have however been a number of studies which have documented the preparation and isolation of organotrifluoroborate salts[17,20-23] and also tetraarylborate salts[24] with application in Suzuki-type coupling reactions.

In the context of a Suzuki coupling reaction, it has been commonly proposed that it is a quaternary borate species that participates in the transmetallation step of the catalytic cycle.[25] Therefore the availability of a procedure enabling the preparation and isolation of these 'pre-activated' species held promising implications regarding their potential use in Suzuki coupling reactions, with the intention of the possible improvement (and widening of the scope) of the existing protocol.

Therefore, attention was immediately turned towards investigation and preparation of these compounds. The aim was to test these alternative species in simple Suzuki coupling reactions in order to establish their reactivity and feasibility as possible coupling substrates. For this purpose, structurally simple, readily available boronic acids were selected as initial candidates for the preparation of these compounds.

2.2.1 Preparation of sodium trihydroxyarylborate salts from simple boronic acids

The first synthesis of this type of compound was attempted using the structurally simple boronic acid 4-methylphenylboronic acid **42**.



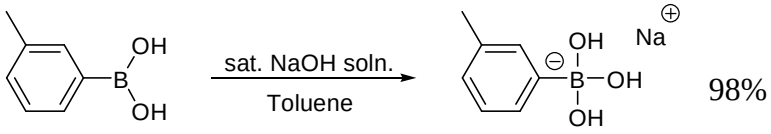
42 **195**

Scheme 2.9 Preparation of sodium 4-methylphenylborate salt **195**.

4-Methylphenylboronic acid **42** was added to a portion of hot toluene under stirring. The boronic acid was found to be only sparingly soluble, so an extra portion of toluene was added and the mixture heated further. Upon complete dissolution, aqueous saturated sodium hydroxide solution was added dropwise. On addition, a creamy white precipitate formed instantly. After continued addition precipitation eventually ceased. The suspension was left to cool under stirring and then filtered. The white solid that remained was washed with cold toluene under suction and transferred to a flask for drying. The white solid product was dried under high vacuum with the resulting solid crushed to a fine powder and stored in a desiccator. The final yield of product **195** was 95%.

The solid product was analysed by ^{1}H NMR spectroscopy, using D_2O as solvent with a couple of drops of anhydrous acetonitrile added as a reference. The spectrum observed was consistent with that expected for the product, as the peaks resembled those of the starting material except at a lower chemical shift as a result of the increased shielding effect of the negative charge present on the boron atom. A ^{13}C NMR was obtained for further verification and also a ^{11}B NMR spectrum to confirm the quaternary nature of the boron species (see work by Schubert).[26] This data indicated the formation of a negatively charged, quaternary 'ate' species. Determination of the melting point for borate salt **195** was attempted; however the white solid did not melt despite being heated to the uppermost limit of the melting point apparatus (over 300 °C).

Other readily available boronic acids were obtained and their borate salt analogues prepared and isolated. 3-Methylphenylboronic acid **196** for example was converted to borate salt **197**.

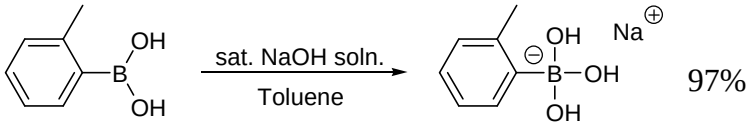


196 **197**

Scheme 2.10 Preparation of sodium 3-methylphenylborate salt **197**.

Observations were the same as those for 4-methylphenylboronic acid **42**. The boronic acid **196** was only sparingly soluble in toluene, therefore complete dissolution only occurred with strong heating and addition of an extra quantity of solvent. The white solid precipitate was then filtered and dried under high vacuum. The product **197** was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy.

The next boronic acid to be converted to its borate salt analogue was 2-methylphenylboronic acid **131**:

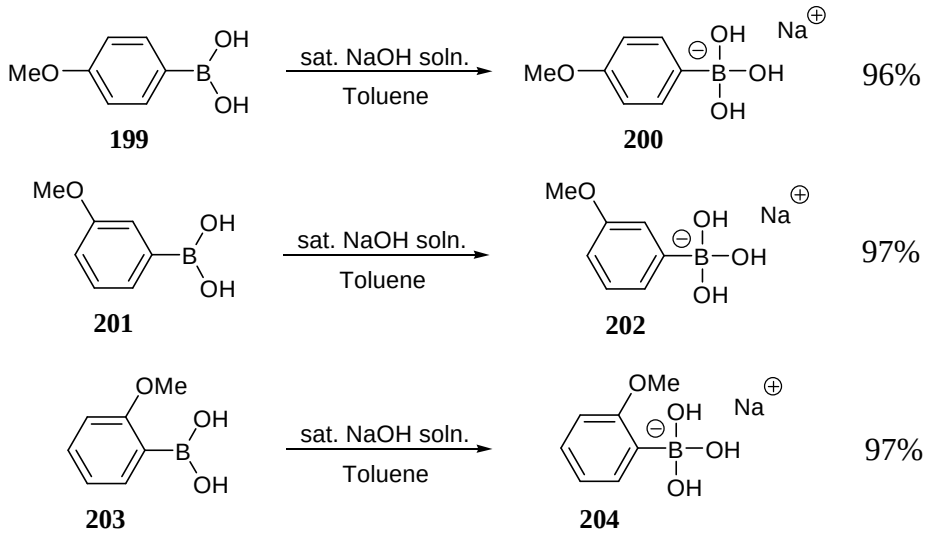


131 **198**

Scheme 2.11 Preparation of sodium 2-methylphenylborate salt **198**.

Observations from this procedure were the same as those noted in previous preparations. A white precipitate formed immediately after addition of saturated aqueous sodium hydroxide solution, which was filtered and dried. The white solid was confirmed as the borate salt product **198** in 97% yield.

Other simple phenylboronic acids bearing a methoxy group on alternative positions on the ring were converted to their sodium trihydroxyarylborate salts (scheme 2.12).



Scheme 2.12 Preparation of sodium methoxyphenylborate salts **200**, **202** and **204**.

These were prepared in the same manner as before. The increased polarity of the boronic acids arising from the presence of the methoxy group appeared to render them even less soluble in toluene. All boronic acids eventually dissolved however, allowing subsequent addition of saturated sodium hydroxide solution to give characteristic white precipitates. After filtration and drying the borate salts were obtained in similarly quantitative yields.

X-ray crystallography data was obtained for sodium 4-methoxyphenylborate salt **200**, which revealed conclusively the quaternary structure of the borate group.[27]

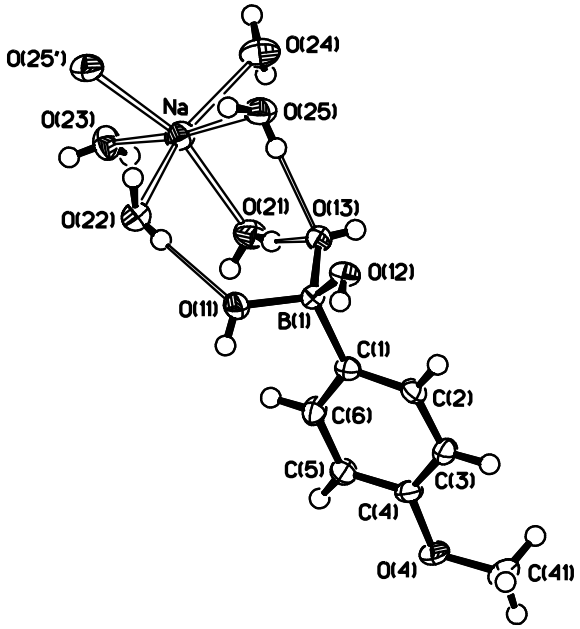
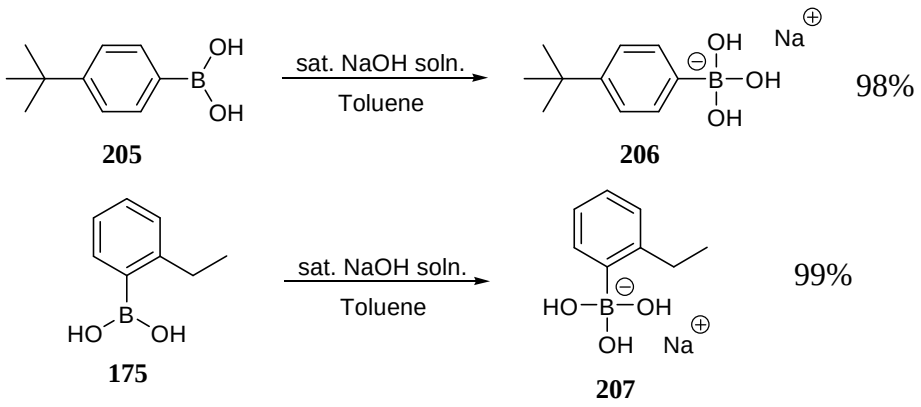


Figure 2.1 X-ray crystal structure of sodium 4-methoxyphenylborate salt **200**.

The borate salt was shown to be a hydrate, with 6 coordinated water molecules surrounding the sodium atom. This relatively high degree of hydration could have resulted from the growth of the crystal used for the X-ray analysis in aqueous media, or could have been a simple consequence of the nature of the preparation of the salt using aqueous base.

The following boronic acids to be converted to their borate salts were 4-*tert*-butylphenylboronic acid **205** and 2-ethylphenylboronic acid **175**.



Scheme 2.13 Preparation of sodium 4-*tert*-butylphenylborate salt **206** and 2-ethylphenylborate salt **207**.

Observations during preparation of these borate salts did not differ significantly to ones noted previously, with the exception of these particular boronic acids dissolving more readily in toluene most likely due to the presence of their non-polar aliphatic substituent groups. Borate salts **206** and **207** were isolated as white solids in quantitative yields, with structures confirmed by the standard analytical methods.

In summary, these compounds have been found to be relatively straightforward to prepare and are easily isolable solids that can be handled without special precautions. Although hygroscopic, they appear to be able to be stored for long periods of time at ambient temperature if kept in an air-tight container.

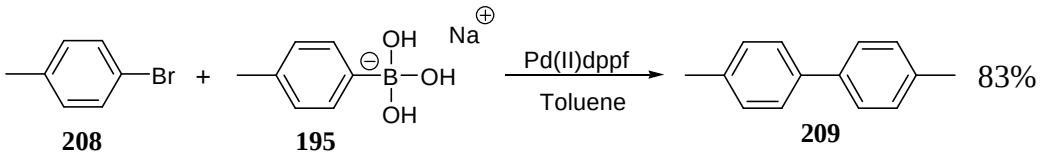
As discussed previously, trihydroxyarylborate salts could have considerable potential for use as coupling substrates in Suzuki coupling reactions, as these salts

exist in a pre-activated form. It is conceivable that an increased rate of coupling reaction could be achieved by the use of these borate salts, which in turn could possibly lessen the effects of deboronation side-reaction. Therefore, a series of test Suzuki couplings reactions employing these isolated salts were investigated.

2.2.2 Test Suzuki coupling reactions using sodium borate salts as organoboron substrates with a simple unhindered aryl bromide

A structurally simple, readily available bromide, 4-bromotoluene **208** was chosen as the halide reagent with which to perform the first test Suzuki coupling reactions. For these basic test reactions, a bromide substrate as opposed to an iodide was chosen, as in simple couplings using unhindered substrates bromides perform equally well (and are on the whole less costly if to be purchased from commercial sources).

Sodium 4-methylphenylborate salt **195** was chosen as the first borate salt to test as an alternative organoboron coupling partner:



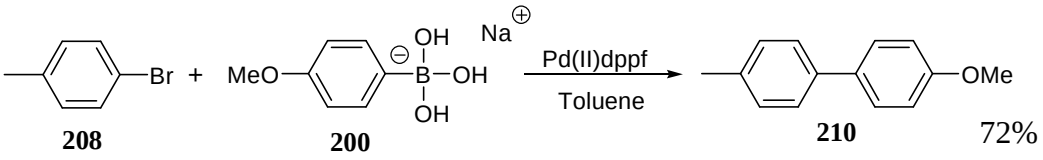
Scheme 2.14 Test Suzuki coupling employing sodium 4-methylphenylborate salt **195**.

The dried borate salt **195** was added to the reaction vessel followed by the bromide coupling partner **208** and catalyst. The reaction solvent was added and the mixture heated to reflux for 24 h. During this time the mixture underwent a gradual change of colour from a pale red solution to a black suspension, which was an indication of the formation of 'palladium black' and thus a sign of completion. The mixture was allowed to cool to room temperature and worked up according to standard protocol (see experimental). ^{1}H NMR spectroscopic data obtained of the crude material revealed peaks attributable to the desired coupled product in high yield. All of the bromide starting material **208** appeared to have been consumed as there were no traces seen in the ^{1}H NMR spectrum. The crude material was passed through

a short column of silica and the pure product **209** was isolated as a white solid in a yield of 83%. Data collected from NMR analyses were consistent with literature data.

The success of this test reaction provided evidence to suggest that the borate salt had participated in the catalytic cycle, affording the desired coupled product with no apparent detrimental effects. The reaction appeared to proceed smoothly and cleanly to give a comparable yield of coupled product. This result implied that other boronic acids could also be effectively replaced by their borate salt counterparts, and so further test coupling reactions were attempted.

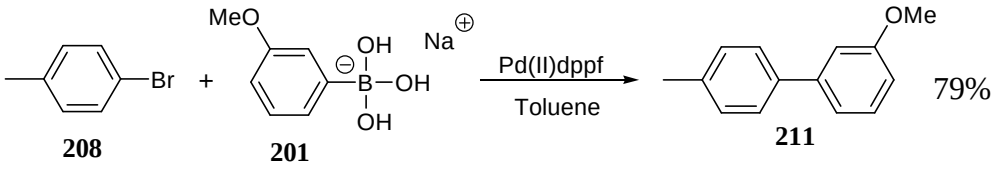
The second test Suzuki coupling reaction employed sodium 4-methoxyphenylborate salt **200** as the organoboron reagent with 4-bromotoluene **208** as the halide reagent following the same procedure:



Scheme 2.15 Test Suzuki coupling using sodium borate salt **200** as the organoboron coupling partner.

The borate salt **200** and 4-bromotoluene **208** were added to the reaction vessel followed by the catalyst. The solvent was added and the mixture heated to reflux for 24 h. After this period of time the pale red solution had become a black suspension, and so the mixture was allowed to cool and subjected to the same work-up procedure as before. The crude material was analysed by ^{1}H NMR spectroscopy which identified the coupled product **210** in good yield. The crude mixture was purified through a short column of silica to give the product **210** as an off-white solid. The presence of an electron-donating methoxy group on the borate salt **200** did not appear to adversely affect the reaction in any manner as it progressed smoothly and cleanly to give a respectable yield of the coupled product.

The following test Suzuki coupling reaction employed sodium 3-methoxyphenylborate salt **201** with the same bromide **208**:



Scheme 2.16 Test Suzuki coupling using sodium borate salt **201** with bromide **208**.

The borate salt **201**, bromide **208** and catalyst were heated to reflux in toluene for 24 h. Analysis of the crude material by ^{1}H NMR spectroscopy revealed peaks attributable to those of the coupled product **211**, with characteristic singlet peaks occurring at 2.39 and 3.85 ppm corresponding to those of the product methyl and methoxy groups respectively. The pure product **211** was isolated as a colourless oil in a yield of 79%.

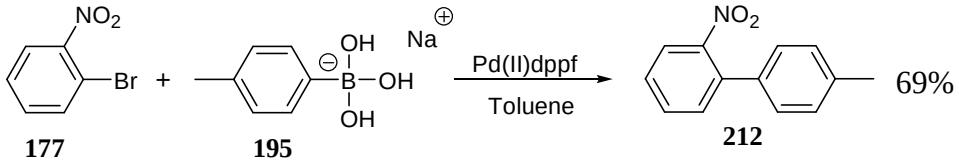
The success achieved with these reactions provided clear evidence to suggest that these species participate readily and effectively in the catalytic cycle of the Suzuki coupling, and demonstrated that they can be used in place of the commonly employed boronic acids. An immediate advantage gained from the use of these isolated borate salts was that the addition of a base to the reaction was not necessary, as the correct stoichiometric amount of base was in effect already present within the 'ate' species. It follows from this that a more accurate calculation of the stoichiometric amount of the organoboron coupling substrate could be achieved, in contrast to that of boronic acids in which anhydride impurities cause this calculation to be imprecise.

These results prompted the undertaking of further investigations, with the aim of establishing the limits (and any possible latent problems) of the use of these borate salts as alternative coupling substrates.

2.2.3 Test Suzuki coupling reactions employing sodium borate salts with an electron-deficient aryl halide

In the following Suzuki reactions an alternative bromide coupling partner, 1-bromo-2-nitrobenzene **177**, was chosen. This reagent was selected on account of its electron-deficient nature, resulting from the presence of the electron-withdrawing *ortho*-nitro group. The use of this bromide could determine whether these reactions - which have so far been seen to proceed successfully using the comparatively electron-rich bromide 4-bromotoluene **208** - would be affected by the use of an electron-deficient halide coupling partner.

The first test Suzuki coupling employing 1-bromo-2-nitrobenzene **177** was performed with sodium 4-methylphenylborate salt **195** as the organoboron reagent:

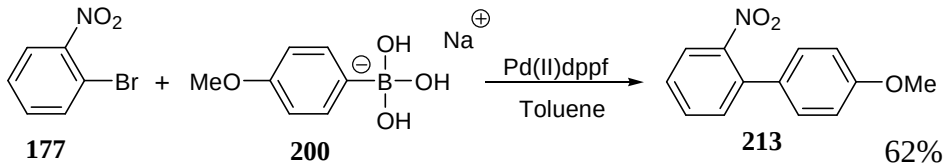


177 **195** **212**

Scheme 2.17 Test Suzuki coupling using 1-bromo-2-nitrobenzene **177** as halide.

Coupling partners borate salt **195** and bromide **177** were added to the reaction vessel, followed by the catalyst. Following the same protocol as before, toluene was added and the mixture heated to reflux for 24 h. Analysis of the crude mixture by ^{1}H NMR spectroscopy confirmed the presence of the desired coupled product **212**. Purification by column chromatography isolated the product **212** as a yellow oil in 69% yield.

The next Suzuki coupling employing 1-bromo-2-nitrobenzene **177** was carried out with sodium 4-methoxyphenylborate salt **200**.

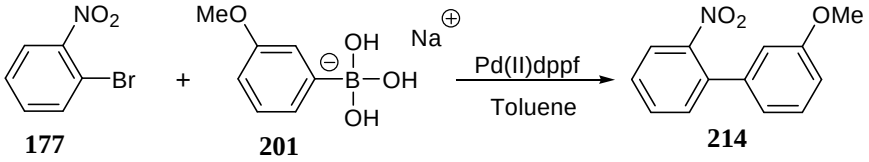


177 **200** **213**

Scheme 2.18 Suzuki coupling using 1-bromo-2-nitrobenzene **177** with borate salt **200**.

The same procedure was followed and after work-up the crude material was analysed by ^{1}H NMR spectroscopy. The spectrum revealed a distinct singlet at 3.85 ppm attributable to the methoxy group present in the coupled product **213**, together with other peaks corresponding to traces of impurities, including possible homocoupled product. The mixture was separated by column chromatography to give the pure product **213** as a yellow oil.

The final test Suzuki coupling employing 1-bromo-2-nitrobenzene **177** was performed with sodium 3-methoxyphenylborate salt **201** as the organoboron reagent:



177 **201** **214**

Scheme 2.19 Test Suzuki coupling using 1-bromo-2-nitrobenzene **177** as halide with borate salt **201**.

After the reaction was performed, the ^{1}H NMR spectroscopic analysis of the crude material revealed peaks corresponding to the desired coupled product **214**, specifically a prominent singlet at 3.82 ppm due to the methoxy group. The mixture was purified by column chromatography to give the isolated product **214** as a crystalline yellow solid.

When the results from all test coupling reactions were collated (see table 2.1) it could be seen that all reactions proceeded successfully to give reasonable yields of coupled product. When an electron-poor aryl bromide was used (**177**), the observed yields of product were slightly lower than those of reactions with an electron-rich bromide (**208**).

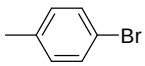
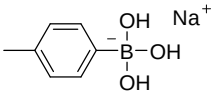
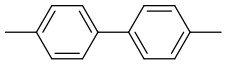
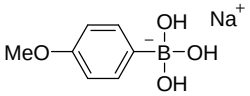
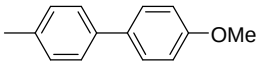
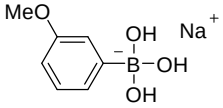
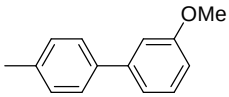
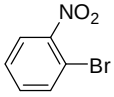
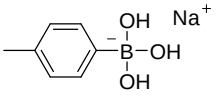
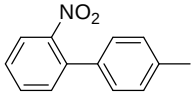
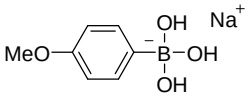
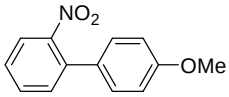
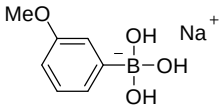
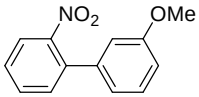
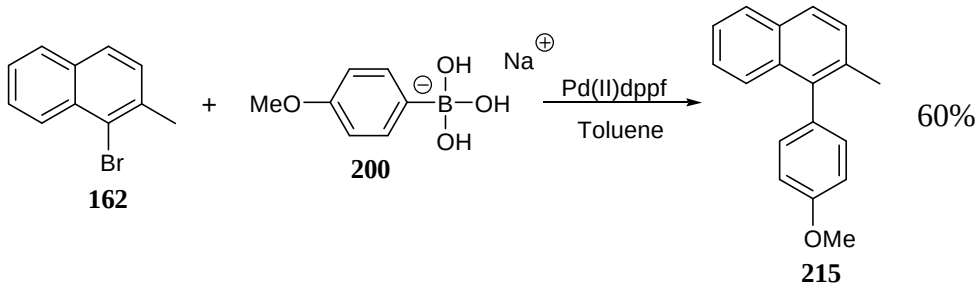
Entry	Aryl bromide	Trihydroxyarylborate salt	product	Isolated yield (%)
1	 **208**	 **195**	 **209**	83
2		 **200**	 **210**	72
3		 **201**	 **211**	79
4	 **177**	 **195**	 **212**	69
5		 **200**	 **213**	62
6		 **201**	 **214**	53

Table 2.1 Table summarising simple test Suzuki coupling reactions performed with sodium trihydroxyarylborate salt substrates

2.2.4 Test Suzuki coupling reactions using sodium borate salts with a sterically hindered naphthyl halide

Following the success of the use of sodium trihydroxyarylborate salts in simple unhindered Suzuki coupling reactions, it was considered a logical next step to test some further Suzuki reactions using a more challenging sterically hindered naphthyl halide substrate. 1-Bromo-2-methylnaphthalene **162** was chosen, with sodium borate salts **200**, **204**, **195** and **198** selected as organoboron coupling partners.

The first Suzuki coupling reaction employing the sterically crowded bromide 1-bromo-2-methylnaphthalene **162** was performed with sodium 4-methoxyphenylborate salt **200** as organoboron substrate (scheme 2.20).

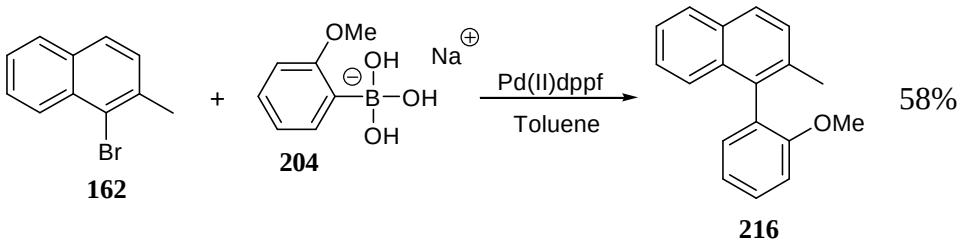


162 **200** **215**

Scheme 2.20 Suzuki reaction using 1-bromo-2-methylnaphthalene **162** and borate salt **200**.

The reaction was heated for 24 h, after which the black suspension was allowed to cool and worked-up as before. The ^{1}H NMR spectrum of the crude material revealed peaks attributable to the desired coupled product **215**, together with traces of unreacted bromide **162**. Purification of the crude material gave the isolated product **215** as an off-white crystalline solid in a yield of 60%. Although this was a slightly lower than expected yield it was nevertheless an encouraging result as it demonstrated the tolerance of the borate salt towards the bulkier bromide partner **162**. The presence of unreacted bromide in the crude material accounted for the lower product yield, as it indicated that the reaction had not proceeded to completion.

The second experiment employing the sterically hindered bromide **162** was performed with an electron-rich *ortho*-substituted sodium borate salt **204**:



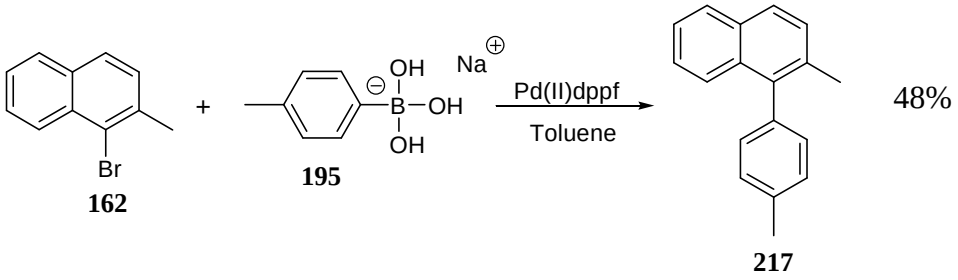
162 **204** **216**

Scheme 2.21 Suzuki reaction using 1-bromo-2-methylnaphthalene **162** and borate salt **204**.

This reaction was expected to present a greater challenge as the borate salt coupling partner **204** featured an *ortho* group. After 24 h the crude material was analysed by ^{1}H NMR spectroscopy. The spectrum displayed peaks corresponding to the coupled product **216**, as well as unreacted bromide **162**. The mixture was purified by column chromatography to give the isolated product **216** as a viscous colourless

oil. The outcome of this reaction was comparable to that of the previous reaction, although in this case there appeared to be a greater quantity of unreacted bromide **162** present in the crude mixture after work-up. As seen previously, this implied that the reaction had not reached completion, and hinted at a decreased rate of reaction possibly resulting from the increased steric hindrance of the *ortho*-substituted substrates.

The next Suzuki coupling was performed using sodium 4-methylphenylborate salt **195**:



162 **195** **217**

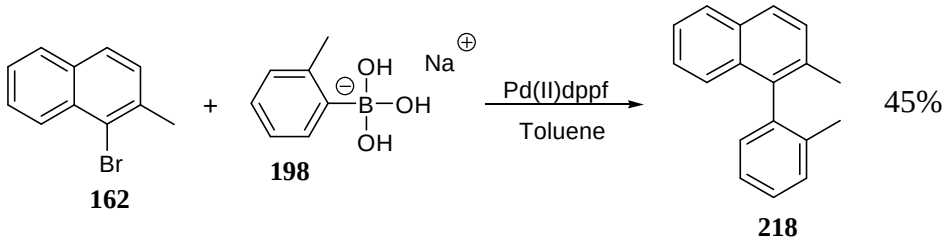
Scheme 2.22 Suzuki reaction using 1-bromo-2-methylnaphthalene **162** and borate salt **195**.

Borate salt **195** was successfully coupled with bromide **162** to give the product **217** which was isolated as a colourless oil in a yield of 48%. This was lower than expected, and examination of the crude material revealed the presence of small amounts of unreacted bromide **162**. This was, as before, an indication that the coupling reaction had not gone to completion. With the use of this particular sodium borate salt **195** it was impossible to determine whether a competing deboronation side-reaction had consumed an amount of the organoboron starting material, as the by-product from such a process would have been toluene. It is possible that consumption of the organoboron species in this way could have occurred, although it is possible that catalyst degradation could have also prevented completion. The difficulty in achieving efficient purification of the crude mixture was also a contributing factor to the modest isolated yield.

This reaction was repeated, and on the second attempt the progress of the reaction was monitored at regular intervals by ^{1}H NMR spectroscopy. Aliquots of the reaction mixture were removed and analysed at 1 h intervals after the start of the reaction. After 6 h, the next aliquot was withdrawn at 24 h and a final one at 48 h.

Analysis revealed that the reaction appeared to have almost proceeded to completion after just one hour, with only a small amount of bromide **162** present. After 24 h the bromide starting material had been virtually all consumed, but traces were still visible. After 48 h no traces of bromide starting material were observed. From calculations of the NMR integrals it could be deduced that the reaction had gone to completion with an estimated yield of coupled product of 98%. Therefore, extending the reaction time for an additional 24 h was found to be beneficial to the final yield of product.

A final Suzuki coupling using hindered naphthyl bromide **162** was performed with sodium 2-methylphenylborate salt **198**:



162 **198** **218**

Scheme 2.23 Suzuki reaction using 1-bromo-2-methylnaphthalene **162** and borate salt **198**.

This reaction proceeded satisfactorily to give the coupled product **218** as a viscous colourless oil in a 45% isolated yield. There were no traces of bromide **162** in the ^{1}H NMR spectrum of the crude mixture. A calculated yield from the spectral integrals gave a figure of around 85%. Only small amounts of minor impurities could be observed, identifiable as 2-methylnaphthalene **190**, an impurity known to be present in the 1-bromo-2-methylnaphthalene **162** starting material, and possible homocoupled product. As experienced previously the crude mixture proved exceptionally difficult to separate. Column chromatography was performed eluting for the whole duration with a non-polar solvent (hexane) in order to achieve maximum separation. This was successful in isolating the majority of coupled product; however loss of the product nevertheless occurred with the disposal of mixed fractions. This was a major factor contributing to the low isolated yield.

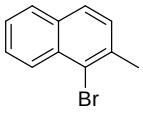
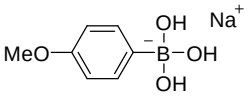
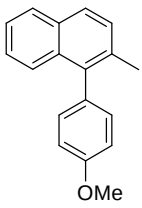
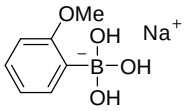
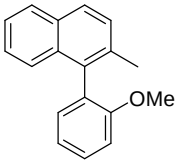
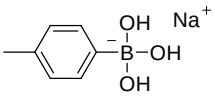
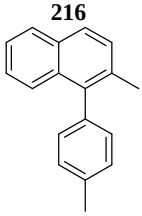
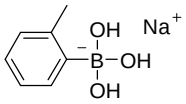
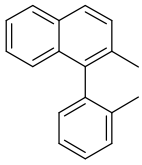
Entry	Aryl bromide	Trihydroxyaryl borate salt	product	Isolated yield (%)
1	 **162**	 **200**	 **215**	60
2		 **204**	 **216**	58
3		 **195**	 **217**	48
4		 **198**	 **218**	45

Table 2.2 Table summarising test Suzuki coupling reactions performed with sodium trihydroxyarylborate salt substrates and a sterically hindered halide.

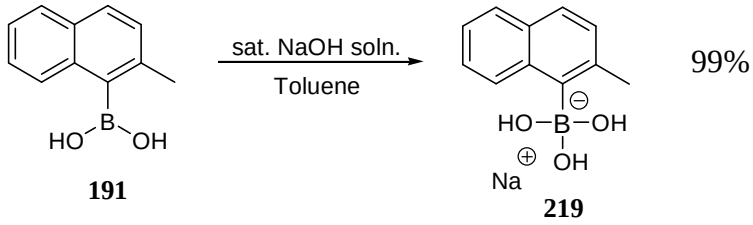
2.2.5 Test Suzuki coupling reaction using a sterically hindered naphthylborate salt with a hindered naphthyl halide

Following on from the successful outcomes of all test reactions carried out so far, it was considered worthwhile to perform a final test reaction employing a sterically hindered arylborate salt together with an equally bulky aryl halide. The results from this would serve as a useful comparison against the conditions employed previously (see scheme 2.7) and would highlight any advantages or limitations of the use of borate salts in hindered couplings.

Therefore the final test coupling reaction was aimed towards the synthesis of 2,2'-dimethyl-1,1'-binaphthalene **165**, in order to determine whether the exceptionally

challenging nature of this coupling could be overcome by the use of an activated borate salt substrate. Having already examined this coupling reaction and previously deemed it unsuitable for further asymmetric investigations, the purpose of carrying out this following reaction was solely to determine the limits of borate salts as coupling substrates.

The desired sodium borate salt **219** was thus prepared from 2-methylnaphth-1-ylboronic acid **191** in an analogous fashion to all previous borate salt preparations.

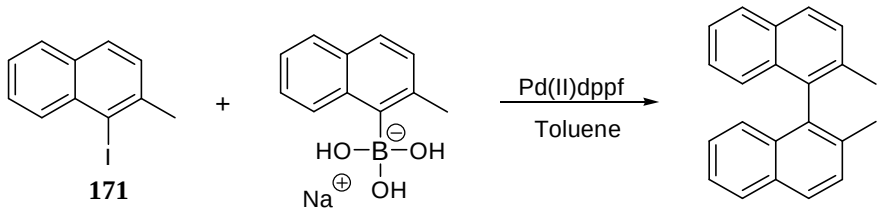


191 **219**

Scheme 2.24 Preparation of sodium 2-methylnaphth-1-ylborate salt **219**.

The preparation of this new borate salt proceeded smoothly and gave the product **219** as an off-white solid in quantitative yield. This was dried under high vacuum and stored in a desiccator prior to use.

The highly hindered Suzuki coupling reaction was then attempted using borate salt **219** as the organoboron partner with 1-iodo-2-methylnaphthalene **171**.



171 **219** **165**

Scheme 2.25 Attempted Suzuki coupling towards racemic 2,2'-dimethyl-1,1'-binaphthalene **165** using sodium borate salt coupling substrate **219**.

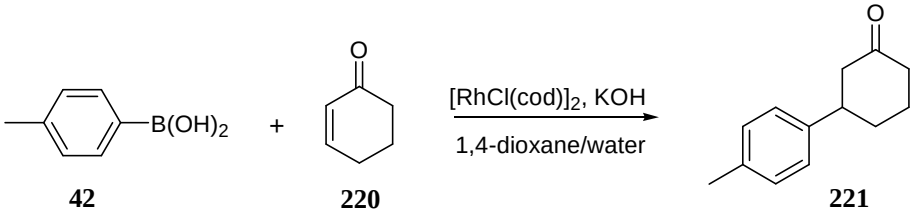
The catalyst 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) was chosen as it had performed well in all previous test reactions. This catalyst also presented an added advantage in that addition of a separate ligand was not required. As toluene had been the solvent of choice in all previous test coupling reactions it was also used for this experiment. However, as a precautionary measure, freshly dried and distilled toluene was used.

The dried starting reagents together with catalyst were heated to reflux in toluene for 48 h, after which the standard work-up protocol was carried out. The crude material obtained was analysed by ^{1}H NMR spectroscopy which revealed prominent peaks belonging to the iodide **171** and deboronated material, 2-methylnaphthalene **190**. Only traces of the binaphthalene product **165** could be observed. It was evident that on this occasion the desired coupling reaction had not proceeded satisfactorily. It can be deduced that the sodium borate salt **219** was predominantly consumed by a deboronation side-reaction.

On this occasion it appeared as though (unlike in previous test reactions) the presence of coordinated water within the borate salt could have been detrimental to the coupling reaction. The exclusion of water is known to have a beneficial effect in hindered couplings due to the inhibition of deboronation;[3-8] and yet it could not be predicted with certainty prior to performing this reaction whether the coordinated water in the borate salt would lead to a deleterious effect. It appears that it does, and so despite an anticipated accelerated rate of reaction resulting from the use of a 'pre-activated' organoboron substrate, competing deboronation negated any advantages gained from this increased reactivity.

2.2.6 Investigation into the use of a sodium trihydroxyarylborate salt in a rhodium-catalysed 1,4-addition reaction

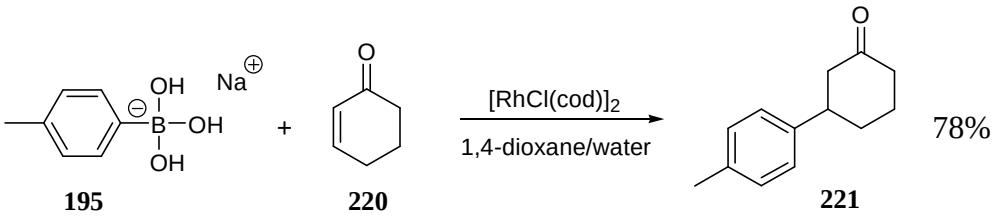
In order to test the wider scope of arylborate salts as alternative organoboron reagents, a rhodium-catalysed 1,4-addition reaction described by Miyaura and co-workers[28] was examined. In the original protocol, a boronic acid with base was used to effect the conjugate addition with an α,*β*-unsaturated carbonyl compound; with the addition of a base found to significantly accelerate the process.



42 **220** **221**

Scheme 2.26 Original conditions for the 1,4-addition of a boronic acid **42** to an α,β-unsaturated ketone **220**.

In this reaction, the use of a boronic acid with a separate base was considered suitable for substitution with a borate salt.



195 **220** **221**

Scheme 2.27 Use of sodium trihydroxyarylborate salt **195** in the 1,4-addition to α,*β*-unsaturated ketone **220**.

When the borate salt **195** was employed in this version, the reaction proceeded smoothly at room temperature to give the desired product in good yield. A slightly modified procedure was found to give best results, in which the aqueous reaction solvent was degassed thoroughly with argon prior to addition of the reagents.

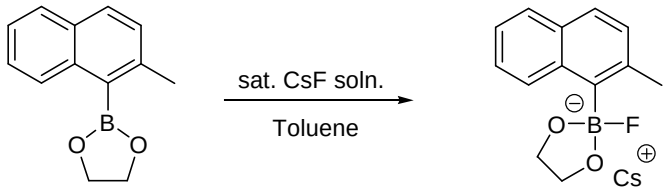
2.2.7 Summary of the results from test Suzuki coupling reactions performed using sodium trihydroxyarylborate salts

In summary, the test reactions performed have demonstrated the successful application of borate salts in reactions in place of boronic acids and base. These borate salts displayed versatility in that they reacted successfully with an electron-rich halide, an electron-deficient halide and a sterically hindered halide partner. The use of these borate salts enabled a simplified protocol in which the separate addition of a stoichiometric amount of base was not required. However, use in a highly hindered coupling (scheme 2.25) was not met with success. It was believed that the presence of coordinated water in the borate salt promoted competing deboronation, thus consuming all the borate salt starting material. The successful employment of a borate salt in a rhodium-catalysed 1,4-addition also demonstrated their potential for use in broader applications.

2.3 Attempted synthesis of alternative ‘activated’ arylborate salts

With the successful preparation and application of the sodium trihydroxyarylborate salts in hand, it was speculated as to whether an equivalent

activated borate salt species could be generated and isolated using a boronate ester with a fluoride base. Selecting cesium fluoride to begin with, a saturated aqueous solution was prepared and added dropwise to a hot solution of the (ethylene glycol)boronate ester **172** in a similar fashion to the preparation of sodium trihydroxyarylborate salts.

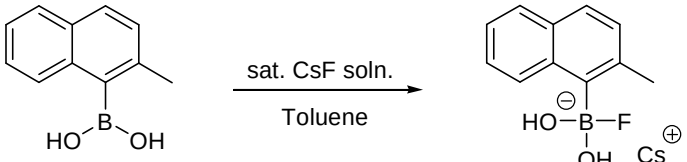


172 **222**

Scheme 2.28 Attempted preparation and isolation of activated boronate species **222**.

No precipitation was observed after this addition, so the mixture was left to stir for a further 30 min. No solid product precipitated after this time and so the mixture was allowed to cool to room temperature. The solution of boronate ester appeared to remain unchanged, with an immiscible layer comprising the aqueous salt solution observed at the bottom of the flask. This was confirmed by extraction of the organic layer, removal of solvent and analysis of the solid residue. The ^{1}H NMR spectrum confirmed the presence of unreacted (ethylene glycol)boronate ester **172**. Therefore it could be deduced that the preparation of the desired borate salt had not been successful.

In a similar attempt, a solution of the parent boronic acid **191** was treated with a saturated aqueous solution of the same base.

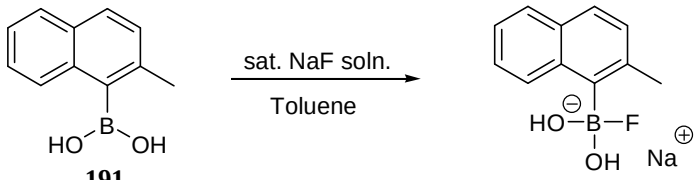


191 **223**

Scheme 2.29 Attempted preparation of alternative borate salt species **223**.

No immediate precipitation occurred upon addition of the base solution so the mixture was left to stir for an additional period of time and subsequently allowed to cool to room temperature. This did not result in the formation of any solid precipitate, with two separate immiscible layers visible in the flask. Therefore the preparation of this borate salt species was also deemed unsuccessful.

In a final attempt, a saturated aqueous solution of sodium fluoride was prepared and used instead of cesium fluoride, to determine whether use of an alternative base would result in precipitation.



191 **224**

Scheme 2.30 Attempted preparation of alternative borate salt species **224**.

Preparation of a concentrated saturated solution of sodium fluoride was not possible on account of the reduced solubility of this salt; nevertheless the dilute solution obtained was added dropwise to a hot solution of the boronic acid **191** in toluene. No precipitate formed either upon addition of base or after being left to stir at room temperature. As observed before, two separate layers remained in the flask consisting of dissolved boronic acid in toluene and aqueous sodium fluoride solution. No further steps were carried out and the reaction was deemed unsuccessful.

2.4 Investigations into symmetric and asymmetric Suzuki coupling reaction towards axially chiral biaryls

Attention was focussed back to the original aim of this project, which was the investigation of symmetric Suzuki coupling reactions and their asymmetric versions towards axially chiral biaryl products. The intention was to develop a suitable model reaction in which both a symmetric and an asymmetric version could be achieved successfully. Following this, the asymmetric version towards an enantiomerically enriched product would be probed further by investigations into the effects of changes in the steric and electronic properties of the coupling partners, with the aim of uncovering finer details surrounding the exact mode of chiral induction.

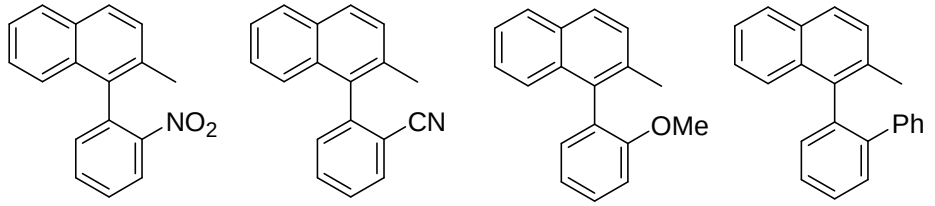
This would necessitate the undertaking of multiple asymmetric Suzuki couplings towards the same structurally identical biaryl product, in which each version would feature an altered coupling substrate possessing a differing functionality (e.g. a boronate ester or borate salt). A change in the identity of the halide in the opposing partner (e.g. bromide or iodide) would also be tested. Any

effects on either the value of the enantiomeric excess or the preference for a particular atropisomer arising from the use of a particular substrate would be examined.

An asymmetric reaction towards the same product but using 'reversed' coupling partners (i.e. in which the identities of the organic groups on each coupling substrate are, in effect, swapped over) was also considered an important experiment to perform. If successful, this reaction could also provide an insight into possible influences on the catalytic cycle - and associated mechanism of chiral induction - arising from the nature of the organic groups on each partner. Investigations of this type have been performed in previous work by Wallow and Novak[10] and Anderson et al.[29] on the determination of the aforementioned effects within the simple symmetric coupling (usually for the purposes of optimisation), and yet, to date, no investigations of this kind have been carried out towards the elucidation of similar influences affecting the asymmetric version of the reaction.

In order to for these investigations to achieve success the biaryl product was required to be sufficiently hindered in order to possess axial chirality, and to be resistant to racemisation at the elevated temperatures used during the coupling reaction. Furthermore, as the determination of the enantiomeric excess was to be achieved using chiral HPLC separation of the atropisomers, the biaryl product was also required to display good separation via this method.

Biaryl compounds considered to meet these criteria were thus chosen, with the next targets for coupling reactions shown below. These compounds comprised an *ortho*-substituted naphthyl top portion with an *ortho*-substituted phenyl ring on the lower half. The presence of *ortho* groups on both halves of the molecule was an intentional feature designed to create a sufficiently high barrier to rotation resulting in the existence of atropisomers.



225 **226** **216** **227**

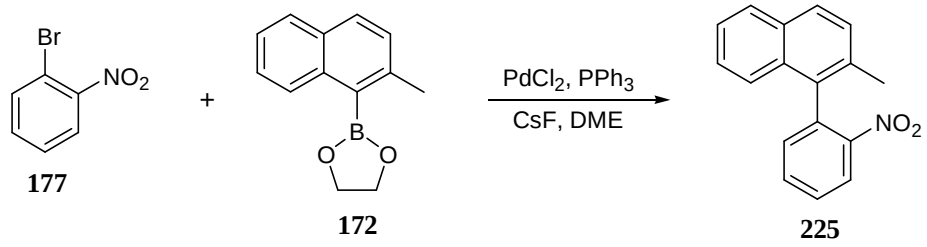
Figure 2.2 Targeted axially chiral biaryl compounds **225**, **226**, **216** and **227**.

Another characteristic intentionally incorporated into the structures of these target biaryl compounds was the presence of differing *ortho* substituents on the two halves of the molecule. This characteristic was included in order to act as a possible aid to separation of the atropisomers during chiral HPLC analysis. It was hoped that the contrasting properties (e.g. polarity) of the *ortho* substituents would enable the chiral stationary phase to acquire a better resolution of isomers thus leading to an improved baseline separation of peaks. Another advantage of the unsymmetrical nature of the two halves was that any homocoupled product formed would be able to be easily distinguished from the cross-coupled product.

Investigations therefore began with symmetric couplings towards these products. Following a successful outcome, the reaction was considered for repetition under asymmetric conditions (utilising a chiral ligand).

2.5 Symmetric Suzuki coupling reactions towards 1-(2'-nitrophenyl)-2-methylnaphthalene

Efforts were firstly focussed on Suzuki couplings towards 1-(2'-nitrophenyl)-2-methylnaphthalene **225**. The conditions chosen for an initial coupling towards the racemic product were as illustrated below. Boronate ester **172** and 1-bromo-2-nitrobenzene **177** were employed with palladium chloride/ triphenylphosphine as the catalyst and DME as the solvent. Cesium fluoride was used as base. (These reaction conditions reflected those used in the original conditions described by Crépy).[1-3]



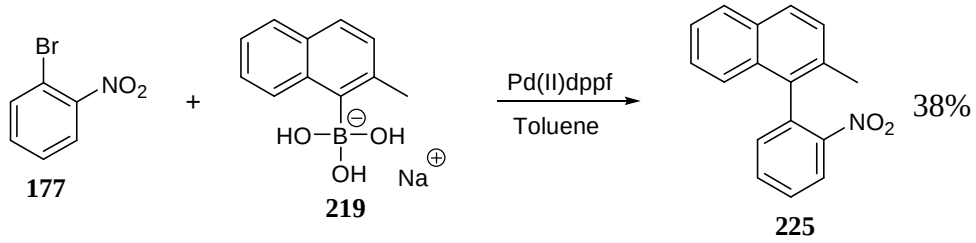
177 **172** **225**

Scheme 2.31 Symmetric Suzuki coupling towards 1-(2'-nitrophenyl)-2-methylnaphthalene **225** using (ethylene glycol)boronate ester **172**.

The reaction was carried out, and the crude material obtained from work-up analysed by ^{1}H NMR spectroscopy. There appeared to be a large amount of

deboronated material (2-methylnaphthalene **190**) with no peaks corresponding to the coupled product **225**.

As the first attempt using the conditions shown above was unsuccessful, the coupling was attempted again but under different conditions. Previously prepared sodium borate salt **219** and 1-bromo-2-nitrobenzene **177** were chosen as the coupling partners, with 1,1' bis(diphenylphosphino)ferrocene dichloropalladium(II) as the catalyst and toluene as solvent.



177 **219** **225**

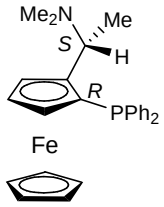
Scheme 2.32 Symmetric Suzuki coupling towards 1-(2'-nitrophenyl)-2-methylnaphthalene **225** using sodium borate salt **219**.

After the reaction mixture was heated for 24 h at 90 °C, the crude material obtained after work-up was found to display peaks in the ^{1}H NMR spectrum attributable to the coupled product **225**. Isolation of the coupled product **225** was achieved to give an orange oil in 38% yield.

As the coupling reaction towards 1-(2'-nitrophenyl)-2-methylnaphthalene **225** employing the borate salt **219** was successful, this was taken forward as a potential model reaction for investigations into the asymmetric variant.

2.6 Asymmetric Suzuki coupling reactions towards 1-(2'-nitrophenyl)-2-methylnaphthalene

The chiral ferrocenyl ligand *R*-(−)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino) ferrocenyl]ethylamine **180** (figure 2.3), originally developed by Ugi et al.,[30] was selected for use in the asymmetric Suzuki couplings. (Since their original conception, the application of this type of ferrocenyl ligand in catalysis has become widespread).[31]

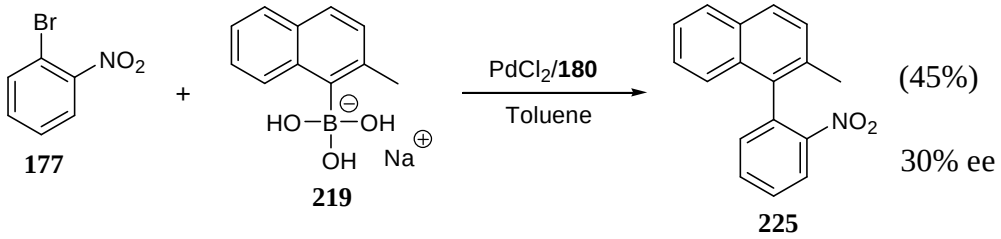


180

Figure 2.3 Chiral ferrocenyl ligand (*R*)-(*S*)-PPFA **180**.

This ligand was chosen on account of the high enantiomeric excesses achieved with the use of its analogue of opposite chirality, (*S*)-(*R*)-PPFA **170**, in previous studies into the asymmetric Suzuki reaction.[1-3] Unfortunately, ligand **170** was no longer available from commercial sources and so (*R*)-(*S*)-PPFA **180** was considered the best alternative.

The coupling partners employed in the asymmetric Suzuki coupling towards **225** were the same as those towards the racemic product (scheme 2.32), i.e. borate salt **219** and 1-bromo-2-nitrobenzene **177**. The chiral ligand (*R*)-(*S*)-PPFA **180** was used with palladium chloride as the catalyst (scheme 2.33).



Scheme 2.33 Asymmetric Suzuki coupling reaction towards 1-(2'-nitrophenyl)-2-methylnaphthalene **225** utilising chiral ligand **180**.

In this experiment, an alternative protocol was developed in order to reduce the possibility for atmospheric moisture to enter the system. A thick-walled pressure tube sealed with a Teflon® screwcap was chosen as the reaction vessel and thoroughly flame-dried and purged with argon before use. After the addition of each reagent the atmosphere was evacuated and refreshed with argon. Upon addition of all the reagents and freshly distilled solvent, the mixture was heated to 90 °C for 24 h. After work-up the crude brown mixture was analysed and found to contain deboronated side-product

190 together with the coupled product **225**. After purification the product **225** was isolated as a yellow crystalline solid in 45% yield.

Samples of the product obtained from the coupling reaction towards the racemic product (scheme 2.32) and from this asymmetric version (scheme 2.33) were analysed by chiral HPLC. In the trace obtained for the racemic product (figure 2.4), the presence of two separate peaks confirmed the existence of two discrete atropisomeric forms. It was also apparent that although resolution of the two atropisomers had been achieved via this method (see experimental for conditions), the peaks occurred close together.

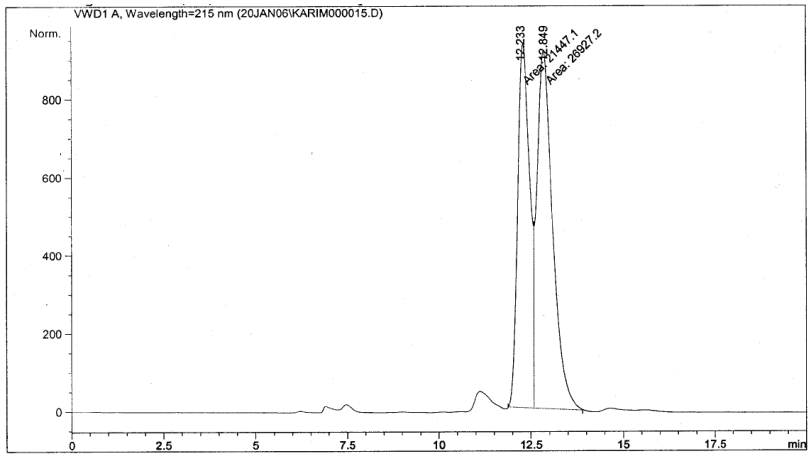


Figure 2.4 Chiral HPLC separation of 1-(2'-nitrophenyl)-2-methylnaphthalene **225** obtained from the symmetric coupling reaction.

From the calculated ratio of the areas under the peaks the product was confirmed as an approximately 50:50 mixture of isomers (i.e. a racemic mixture) which was the outcome expected for this symmetric coupling.

In the chiral HPLC trace for the product of the asymmetric coupling (figure 2.5), it was evident from the intensity of the two peaks that it did not comprise a racemic mixture of isomers. From the calculation of the ratio of the areas under each peak it was determined that one atropisomer has been produced in an excess of 30%.

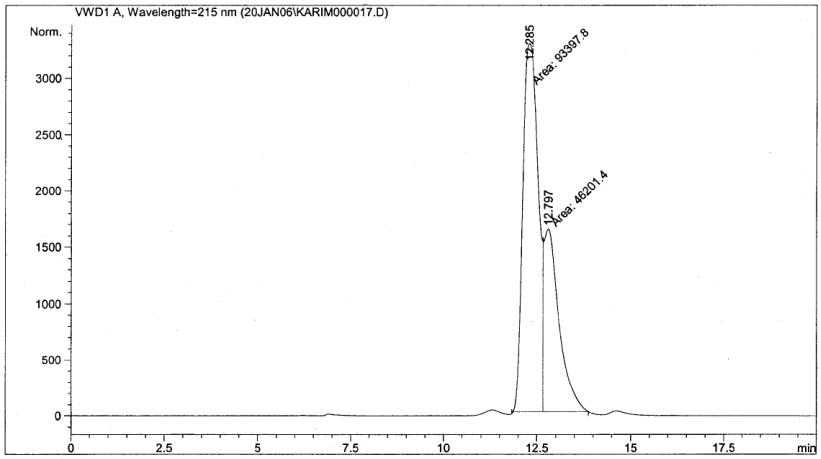


Figure 2.5 Chiral HPLC separation of 1-(2'-nitrophenyl)-2-methylnaphthalene **225** obtained from the asymmetric coupling reaction.

This result was able to be seen with greater clarity when the traces were overlaid (figure 2.6). The second isomer eluting at the later retention time is clearly diminished in the product synthesised using the chiral ligand. This, together with the calculated ratio, confirmed that an asymmetric induction had been achieved with successful production of a reasonable enantiomeric excess.

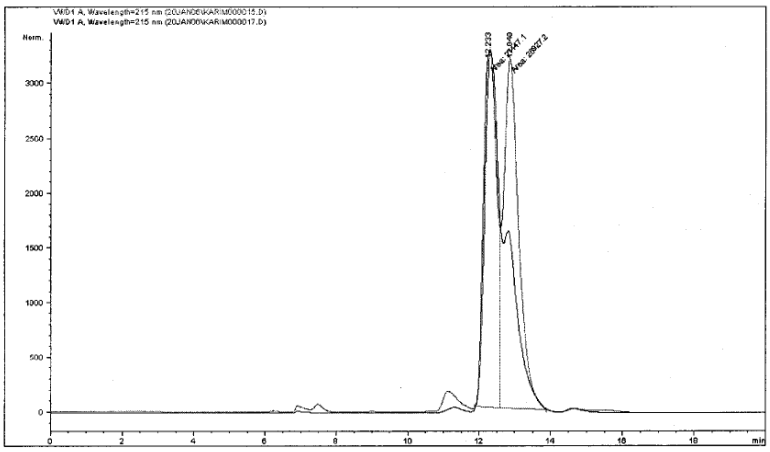


Figure 2.6 Overlay of chiral HPLC traces for product **225** obtained from symmetric and asymmetric reactions.

Although this reaction represented an additional example of the ability of a chiral ligand to effect an asymmetric induction in a Suzuki coupling, and was in this respect an encouraging result, the two atropisomeric forms were unfortunately not resolved to an adequate enough degree during the separation. The atropisomers eluted

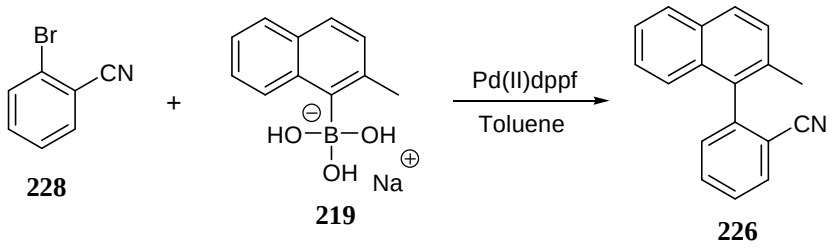
too closely and it could be envisaged that had a greater enantiomeric excess been achieved then the second later peak would have formed an indistinct ‘shoulder’ on the side of the first. This would have made calculation of the area under this peak difficult, resulting in an inaccurate value for the enantiomeric excess.

Therefore, coupling reactions towards the next axially chiral biaryl compound were undertaken, with the aim of achieving a better separation of isomers.

2.7 Symmetric Suzuki couplings towards 1-(2’-cyanophenyl)-2-methylnaphthalene

The rotationally restricted biaryl chosen as the next target of Suzuki couplings was 1-(2’-cyanophenyl)-2-methylnaphthalene **226**; this time possessing an *ortho*-nitrile group on the lower phenyl portion of the molecule.

The first attempt at the coupling reaction towards the racemic product utilised sodium borate salt **219** as the organoboron substrate, 2-bromobenzonitrile **228** as the halide substrate and 1,1’-bis(diphenylphosphino)ferrocene dichloropalladium(II) as the catalyst.

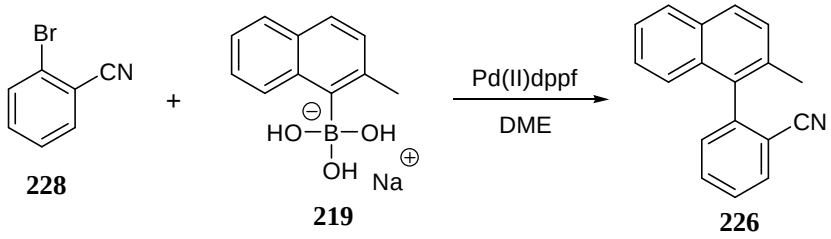


228 **219** **226**

Scheme 2.34 Symmetric Suzuki coupling towards 1-(2’-cyanophenyl)-2-methylnaphthalene **226** using sodium borate salt **219**.

The reaction was performed in a sealed pressure tube with the mixture heated to 90 °C for 48 h. The brown oil obtained after work-up contained deboronated side-product (2-methylnaphthalene **190**) and a small amount of coupled product **226**. An approximate yield of the product was calculated as 10%, taken from the ratio of integrals in the ^{1}H NMR spectrum. As this was a poor yield no further purification steps were carried out.

The second attempt towards this coupled species used the same coupling partners and catalyst but with a different solvent.

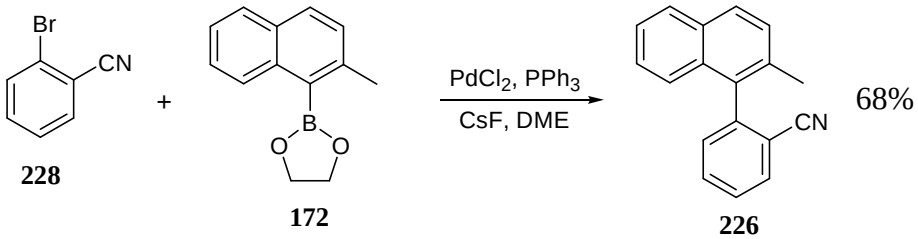


228 **219** **226**

Scheme 2.35 Symmetric Suzuki coupling towards 1-(2'-cyanophenyl)-2-methylnaphthalene **226** using DME as solvent.

In this attempt, DME was chosen as the reaction solvent on account of its reported ability to encourage inorganic substances such as bases to become 'drawn' into solution.[11] It was hoped that this solvent would exert the same beneficial effect towards the otherwise insoluble borate salt. Therefore, a pressure tube containing all the solid reagents was charged with DME and heated at the appropriate temperature for the required time. The crude material was then analysed, with the ^{1}H NMR spectrum displaying peaks attributable to deboronated side-product (2-methylnaphthalene **190**) and coupled product **226**. The yield of product calculated from the ^{1}H NMR integrals was approximately 20%, which was again a lower than expected yield and so no purification steps were carried out.

As deboronation side-reaction appeared to be especially deleterious in this reaction, the coupling was attempted again but under the original aprotic conditions described by Crépy.[1-3] Therefore, the use of (ethylene glycol)boronate ester **172** and 2-bromobenzonitrile **228** with cesium fluoride and palladium chloride/ triphenylphosphine was tested.



228 **172** **226**

Scheme 2.36 Symmetric Suzuki coupling towards 1-(2'-cyanophenyl)-2-methylnaphthalene **226** using (ethylene glycol)boronate ester **172**.

A sealed pressure tube containing the reaction mixture was heated to 80 °C for 24 h, after which the crude material remaining after work-up was analysed by ^{1}H NMR spectroscopy. Peaks were identified as the coupled product **226** together with small amounts of unreacted boronate ester **172** and deboronated side-product (2-methylnaphthalene **190**). After purification the product **226** was obtained as an off-white solid in a yield of 68%.

As the coupling reaction carried out under these conditions led to a much improved yield, a sample of the pure product was analysed by chiral HPLC (figure 2.7). (On this occasion the degree of separation of the two atropisomers in the racemic product was determined in advance of the undertaking of any asymmetric Suzuki couplings).

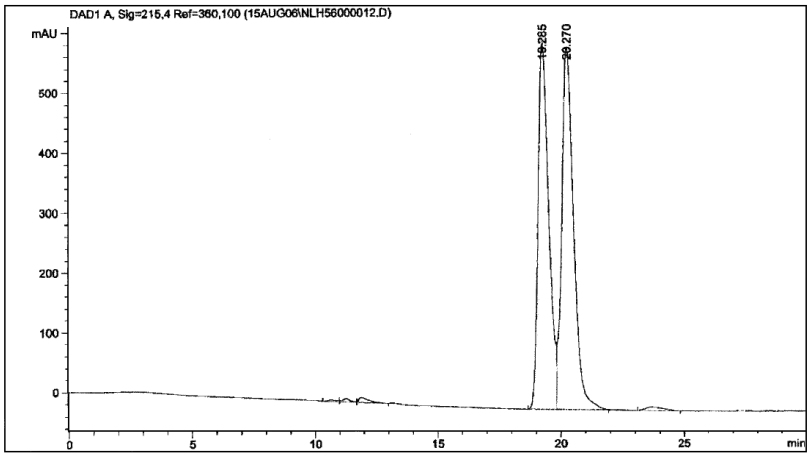


Figure 2.7 Chiral HPLC separation of 1-(2'-cyanophenyl)-2-methylnaphthalene **226** obtained from a symmetric coupling reaction.

Separation of the two atropisomeric forms was achieved and the product was found to consist of a racemic mixture as expected. There was not, however, a great enough degree of baseline separation, and so as a result, the corresponding asymmetric coupling reaction utilising a chiral ligand was not performed. Investigations utilising this biaryl product were not taken further and so the next alternative axially chiral biaryl product **216** was targeted.

2.8 Investigations into Suzuki coupled product 1-(2'-methoxyphenyl)-2-methylnaphthalene

The next targeted sterically hindered biaryl compound was 1-(2'-methoxyphenyl)-2-methylnaphthalene **216**. As a successful symmetric Suzuki coupling towards this product had already been performed in these studies (scheme 2.21) a sample of the product from this reaction was analysed by chiral HPLC.

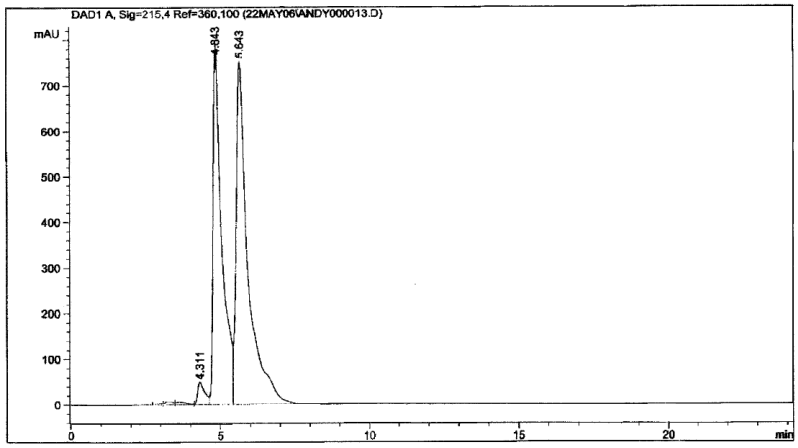


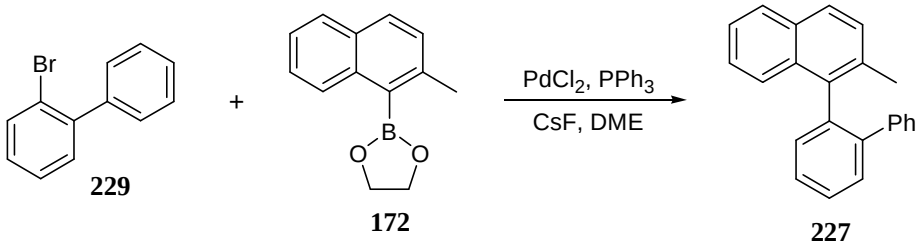
Figure 2.8 Chiral HPLC separation of 1-(2'-methoxyphenyl)-2-methylnaphthalene **216** obtained from a symmetric coupling reaction.

The percentages of each atropisomer correlated to an approximately 50:50 mixture as anticipated. Although separation was achieved, the two atropisomeric forms of this coupled product did not display the degree of baseline separation required for asymmetric investigations, and so no further reactions towards this product were performed.

2.9 Symmetric Suzuki coupling reactions towards 1-(2'-biphenyl)-2-methylnaphthalene

Subsequent coupling reactions were aimed towards the construction of axially chiral biaryl 1-(2'-biphenyl)-2-methylnaphthalene **227**.

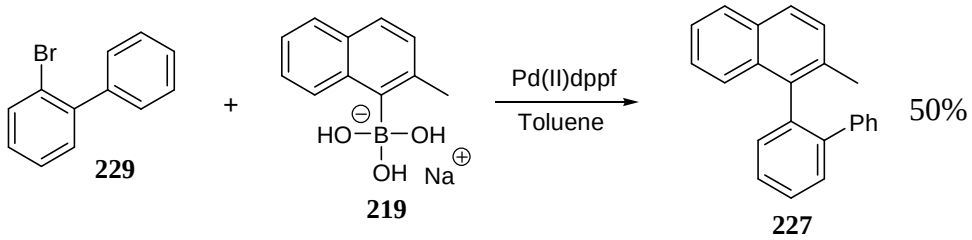
An initial attempt towards **227** as a racemic product utilised (ethylene glycol)boronate ester **172** with 2-bromobiphenyl **229**, cesium fluoride as the base and palladium chloride/triphenylphosphine as the catalyst. Anhydrous DME was used as the solvent.



Scheme 2.37 Symmetric Suzuki coupling towards 1-(2'-biphenyl)-2-methylnaphthalene **227**.

All the solid reagents were added to a pressure tube followed by 2-bromobiphenyl **229** via syringe. Freshly distilled solvent was used and the mixture heated at 80 °C for 24 h. The ^{1}H NMR spectrum of the crude material revealed peaks attributable to (ethylene glycol)boronate ester **172** and bromide **229** starting materials, with only small amounts of the coupled product **227**. An estimated yield calculated from the integrals gave a figure of around 20%; therefore no further steps towards purification were performed.

The next attempt used sodium borate salt **219** and bromide **229** as coupling partners with 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) as catalyst and toluene as solvent.

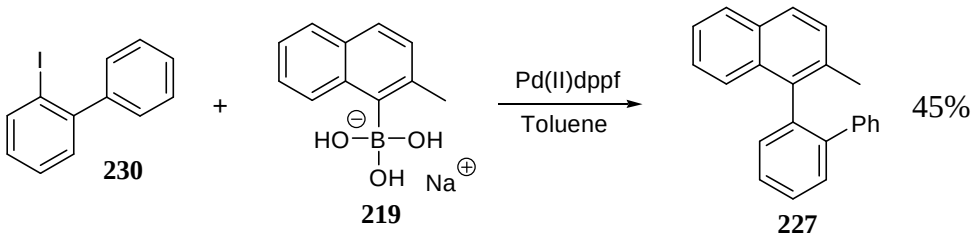


Scheme 2.38 Symmetric Suzuki coupling towards 1-(2'-biphenyl)-2-methylnaphthalene **227** using borate salt **219**.

The sodium borate salt **219** and catalyst were added to a pressure tube, followed by the liquid bromide reagent **229** via syringe. Upon addition of solvent the mixture was heated to 90 °C for 48 h, after which the crude mixture was analysed by

the standard methods. There appeared to be a greater quantity of coupled product **227** present and so the mixture was purified to give the product as a viscous colourless oil in 50% yield.

Despite achieving an improved yield using the conditions shown above it was speculated as to whether the use of an iodide coupling partner would result in an even greater improvement in yield. Therefore the reaction was repeated using iodide **230**.



230 + **219** → **227**

Scheme 2.39 Symmetric Suzuki coupling towards 1-(2'-biphenyl)-2-methylnaphthalene **227** employing iodide **230**.

Following the same protocol, the crude material was found to contain the desired coupled product. After purification the product **227** was isolated as a viscous colourless oil in a yield of 45%.

It was surprising to observe that the yield was not greater in this reaction, as it is generally known that iodides display a higher reactivity than bromides in Suzuki coupling reactions,[25] with this effect usually more noticeable in hindered couplings.[1-3,10] This implied that oxidative addition was not the rate-determining step in this instance, and that transmetallation of the bulky naphthylborate substrate was most likely to be the slow step and thus the probable cause of the low yields. As the use of an iodide did not lead to an improvement in this reaction, use of the bromide **229** as the halide coupling partner was resumed for subsequent reactions towards this product.

A sample of the product **227** obtained from the symmetric coupling reaction using the bromide **229** (scheme 2.38) was analysed by chiral HPLC (figure 2.9).

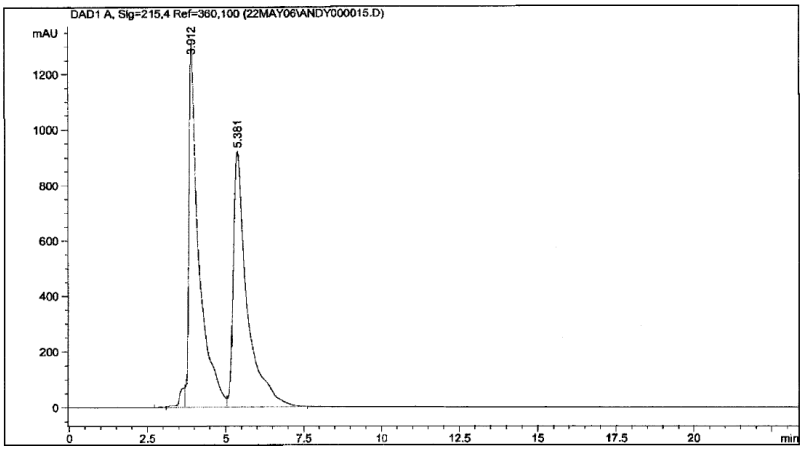
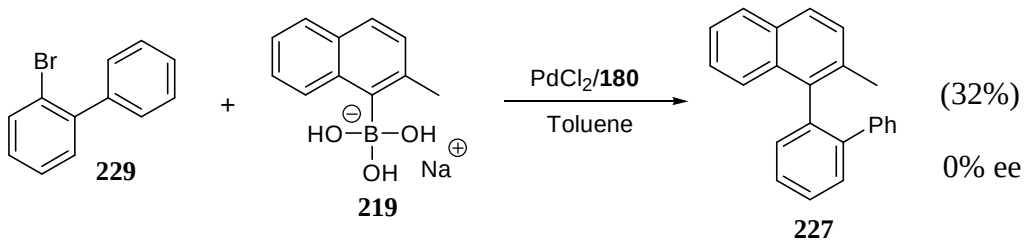


Figure 2.9 Chiral HPLC separation of 1-(2'-biphenyl)-2-methylnaphthalene **227** obtained from the symmetric coupling reaction.

The two atropisomers were found to be present in racemic proportions as expected. The two peaks displayed a reasonable baseline separation, greater than those achieved for all previous biaryl products. Due to this improved degree of separation, the corresponding asymmetric version of the reaction was subsequently performed.

2.10 Asymmetric Suzuki coupling reactions towards 1-(2'-biphenyl)-2-methylnaphthalene

As the reaction conditions employing the borate salt **219** and bromide **229** were found to give the best yield of the racemic product **227** (scheme 2.38) the same conditions were used for the first attempt at the asymmetric coupling reaction.



Scheme 2.40 Asymmetric Suzuki coupling towards 1-(2'-biphenyl)-2-methylnaphthalene **227**.

The reaction was performed, with the crude mixture found to contain the desired coupled product **227** together with deboronated side-product (2-

methylnaphthalene **190**). After purification the pure product was isolated as a viscous colourless oil and a sample analysed by chiral HPLC (figure 2.10).

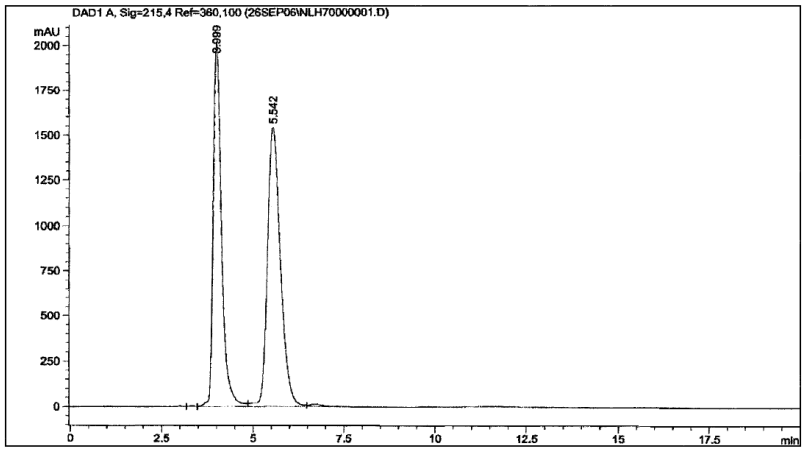


Figure 2.10 Chiral HPLC trace of product **227** obtained from asymmetric coupling reaction.

It could be seen that once again a reasonable degree of baseline separation had been achieved. However, calculation of the ratio of atropisomers revealed that an approximately equal amount of each had resulted, i.e. a racemic mixture, and so it appeared as though asymmetric induction had not been achieved.

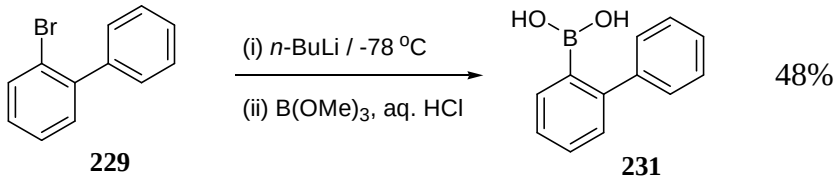
It was initially unclear as to whether this outcome had resulted from an unsuccessful chiral induction arising from the use of these particular substrates, or whether the coupled product simply racemised under the elevated temperatures. Therefore, for clarification purposes, it was considered worthwhile to attempt the asymmetric reaction again using alternative coupling substrates so as to rule out the first possibility.

In the second attempt, alternative coupling substrates were prepared in order to carry out the asymmetric coupling reaction.

2.10.1 Preparation of alternative coupling substrates

In the next attempt at the asymmetric Suzuki coupling towards biaryl **227**, the lower biphenyl portion of the coupled product was to originate from the organoboron coupling substrate. As sodium 2-biphenylborate salt was chosen as the organoboron

coupling species, its preparation required the initial synthesis of the parent boronic acid **231** from the corresponding bromide **229**.

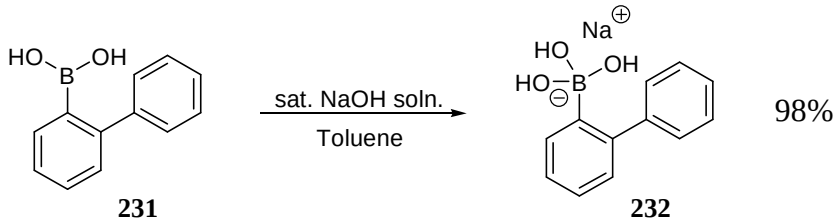


229 **231**

Scheme 2.41 Preparation of 2-biphenylboronic acid **231** from 2-bromobiphenyl **229**.

This was achieved via metal-halogen exchange using *n*-butyllithium and subsequent treatment with trimethylborate. Following acidic work-up, the oily residue obtained was triturated with hexane to give the boronic acid as a white solid.

Sodium 2-biphenylborate salt **232** was then prepared from boronic acid **231** via the usual procedure:



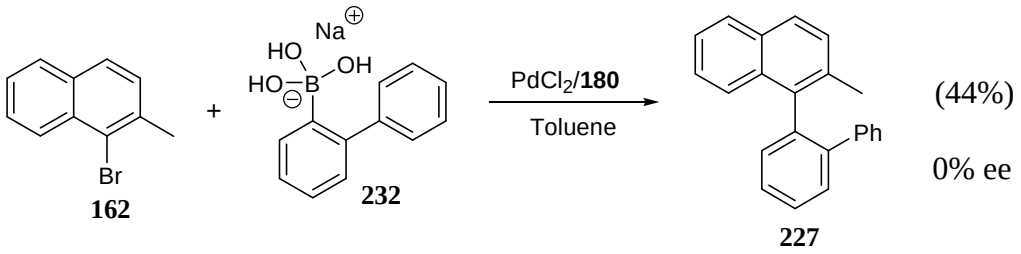
231 **232**

Scheme 2.42 Preparation of sodium 2-biphenylborate **232** from boronic acid **231**.

The borate salt product **232** precipitated out readily from the treatment of the boronic acid solution with saturated aqueous sodium hydroxide and was isolated in near quantitative yield. The white solid was dried under vacuum.

2.10.2 Asymmetric Suzuki coupling towards 1-(2'-biphenyl)-2-methylnaphthalene using alternative 'reversed' coupling substrates

With the borate salt partner in hand, the asymmetric Suzuki coupling towards 1-(2'-biphenyl)-2-methylnaphthalene **227** was attempted using 1-bromo-2-methylnaphthalene **162** (scheme 2.43).



162 **232** **227**

Scheme 2.43 Alternative Asymmetric Suzuki coupling towards 1-(2'-biphenyl)-2-methylnaphthalene **227** using borate salt **232** and bromide **162**.

The Suzuki coupling reaction was performed and the crude material analysed. The ^{1}H NMR of the mixture revealed peaks attributable to the coupled product **227** and unreacted bromide **162**. Purification isolated the product as a viscous colourless oil in 44% yield and a sample was analysed by chiral HPLC (figure 2.11).

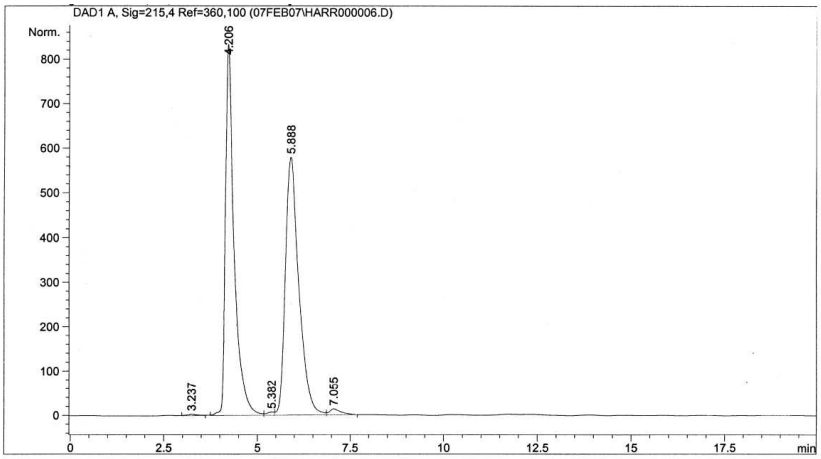


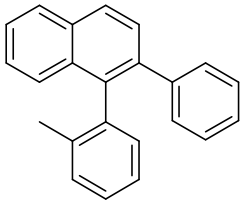
Figure 2.11 Chiral HPLC trace of 1-(2'-biphenyl)-2-methylnaphthalene **227** obtained from asymmetric Suzuki coupling performed with borate salt **232** and bromide **162**.

The observed ratio of the two atropisomers was again found to correspond to a racemic mixture. This result and that of the previous reaction (scheme 2.40) strongly indicated that the coupled product racemised under the reaction conditions. It is possible that the chiral ligand could have exerted an asymmetric influence; however the barrier to rotation around the newly formed C-C bond was evidently overcome by the elevated reaction temperature resulting in racemisation of the coupled product.

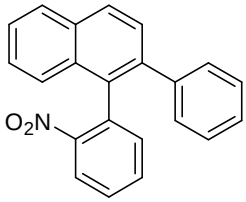
Further investigations into Suzuki coupling reactions to produce this particular biaryl compound were abandoned, with subsequent efforts focussed on Suzuki coupling reactions towards other rotationally stable chiral biaryl compounds.

2.11 Investigations into alternative targets for symmetric and asymmetric Suzuki coupling reactions

The next candidates deemed suitable for the necessary investigations were biaryl compounds **233** and **179**:



233



179

Figure 2.12 Alternative axially chiral compounds **233** and **179**.

Compound **233** was first selected, as it bore a structural resemblance to compound **227** synthesised in previous reactions. This previous compound had displayed the best separation on chiral HPLC so far, possibly due to the nature of the substituent groups present. Although this product had undergone racemisation, it was not possible to determine conclusively which specific point of steric clash had been overcome, i.e. that occurring between the *ortho*-methyl and the *ortho*-phenyl group, or that between the *ortho*-phenyl group and the hydrogen on position 8 of the naphthyl portion. If solely the latter, then racemisation could theoretically be prevented if a different, bulkier *ortho*-group than phenyl was present on the lower half. Therefore, the next target **233** was chosen, bearing the same substituent groups but on different halves of the molecule. The good separation of isomers observed in the previous compound **227** was the motivation behind the examination of this structurally similar compound, as the resolution achieved was a possible effect of these particular substituents.

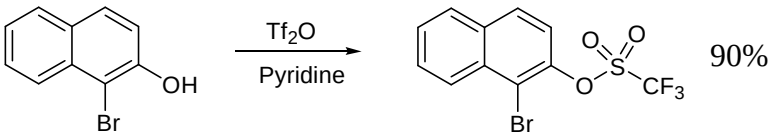
Biaryl **179** was chosen on account of its favourable properties and attributes described in previous studies conducted by Buchwald and Yin.[32] In these preliminary studies on the asymmetric version of the Suzuki reaction, this compound was successfully synthesised in high enantiomeric excess and was reported as being resistant to racemisation. In addition, separation of its two atropisomeric forms via

chiral HPLC had been reported and was demonstrated as displaying reasonable resolution.

2.11.1 Preparation of coupling substrates for Suzuki coupling reactions

Before Suzuki coupling reactions towards either compound could be performed, syntheses of starting reagents were required as they were not available from commercial sources.

In the first step towards preparation of the bromide coupling partner, the conversion of 1-bromonaphthol **234** to its triflate analogue **235** was undertaken.

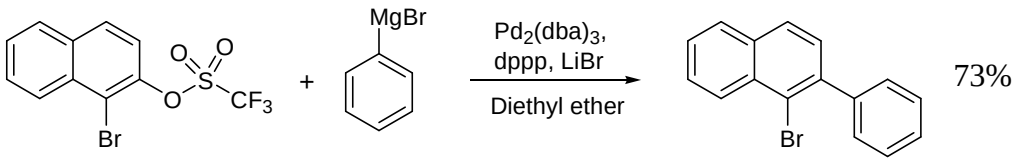


234 **235**

Scheme 2.44 Preparation of 1-bromo-2-naphthyltriflate **235**.

Following the experimental procedure described in the literature,[32] dropwise addition of triflic anhydride to a cooled solution of 1-bromo-2-naphthol in anhydrous pyridine was performed, followed by an acidic work up and neutralisation with aqueous sodium hydrogen carbonate. Purification was achieved to give the pure product **235** as a pale yellow crystalline solid in 90% yield.

The palladium-catalysed coupling of 1-bromo-2-naphthyltriflate **235** with phenylmagnesium bromide **236** was then performed in order to replace the triflate group with a phenyl group.



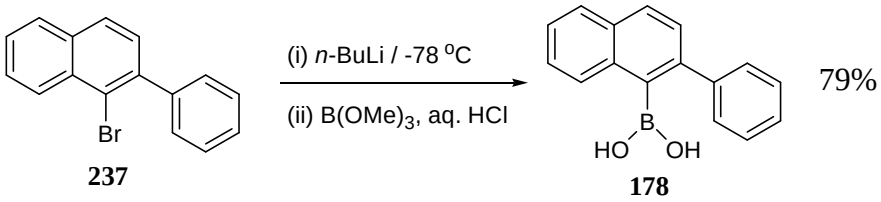
235 **236** **237**

Scheme 2.45 Preparation of 1-bromo-2-phenylnaphthalene **237**.

The inclusion of the lithium bromide salt additive in this literature procedure[32] was undoubtedly due to the reported benefits of these salts in coupling reactions

employing triflates, in which they were found to help prevent catalyst decomposition.[9,25,33] The reaction proceeded accordingly to give the desired product in reasonable yield. The crude product was not sufficiently pure for direct use and so column chromatography was performed. The pure product was isolated as a pale yellow crystalline solid.

Using the pure bromide **237**, boronic acid **178** was subsequently prepared following the favoured protocol:[34]

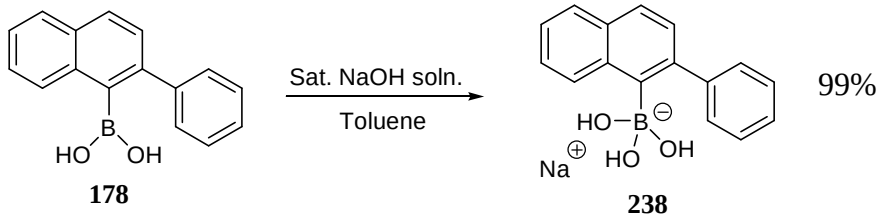


237 **178**

Scheme 2.46 Preparation of 2-phenylnaphth-1-ylboronic acid **178**.

A solution of the bromide **237** in anhydrous THF was cooled to −78 °C and treated with *n*-butyllithium. Trimethylborate was added in one portion, and then the mixture subjected to an acidic work up. The resulting oily substance was triturated with hexane to give boronic acid **178** as an off-white powder in 79% yield.

The sodium borate salt **238** was then prepared from the boronic acid **178** by the standard method:

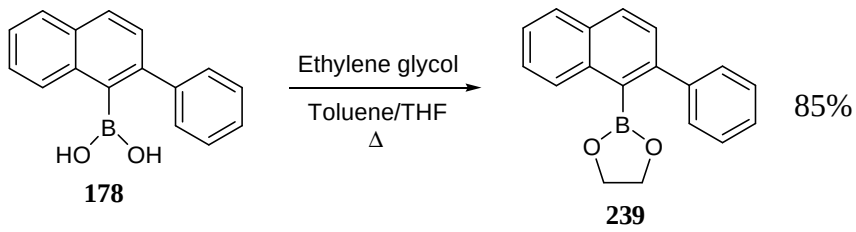


178 **238**

Scheme 2.47 Preparation of sodium 2-phenylnaphth-1-ylborate salt **238**.

Sodium borate salt **238** precipitated out as a white solid in near quantitative yield. This was dried under vacuum and stored in a desiccator.

Boronic acid **178** was also converted to its (ethylene glycol)boronate ester analogue **239**, via a slightly modified protocol employing a solvent mixture of 1:4 toluene/THF (scheme 2.48).

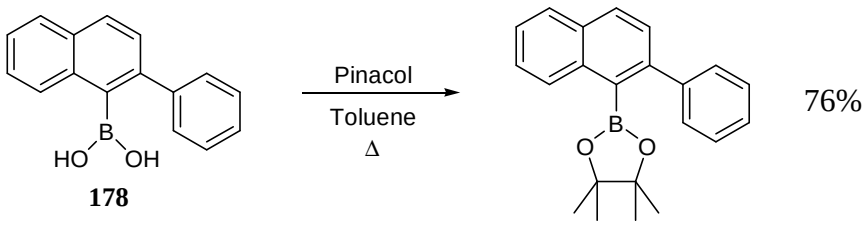


178 **239**

Scheme 2.48 Preparation of 2-phenylnaphth-1-yl(ethylene glycol)boronate ester **239**.

An initial attempt following the original procedure (in which neat toluene is used as the solvent) was not met with success. After 20 h of heating under reflux no detectable amount of product **239** was present, with drops of unreacted ethylene glycol visible on the walls of the flask. Sustained heating under reflux for an extended period of time was not found to be beneficial. Therefore the reaction was repeated (as shown above) using a more polar solvent mixture in which the ethylene glycol reagent was soluble. After heating under reflux for 48 h, the product **239** was isolated initially as a viscous pale yellow oil which solidified upon standing to give an off-white waxy solid in good yield.

Preparation of the (pinacol)boronate ester **240** was also undertaken, with a successful conversion of the boronic acid **180** achieved under the standard reaction conditions.



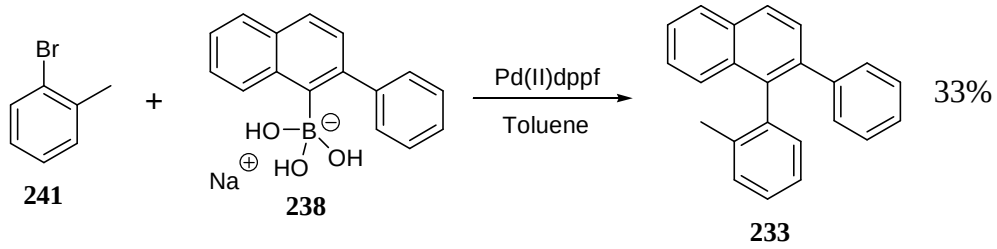
178 **240**

Scheme 2.49 Preparation of 2-phenylnaphth-1-yl(pinacol)boronate ester **240**.

After the reaction mixture was heated under reflux for 24 h, the boronate ester product **240** was isolated from extractions with DCM as an off-white waxy solid.

2.12 Symmetric Suzuki coupling reactions towards 1-(2'-methylphenyl)-2-phenylnaphthalene

The first attempt towards hindered biaryl product **233** as a racemate utilised the prepared borate salt **238** as the organoboron partner with commercially available 1-bromo-2-methylbenzene **241**.



241 **238** **233**

Scheme 2.50 Symmetric Suzuki coupling towards 1-(2'-methylphenyl)-2-phenylnaphthalene **233**.

The solid reagents (borate salt **238** and catalyst) were added to a dried pressure tube, followed by 1-bromo-2-methylbenzene **241** via syringe. Anhydrous toluene was added and the mixture heated at 90 °C for 24 h. After this time the reaction mixture yielded a dark red oil after work-up which was analysed by the standard methods. The desired coupled product **233** was found to be present, together with deboronated side-product, 2-phenylnaphthalene. Purification by column chromatography afforded the product **233** as a white solid. A sample was then analysed by chiral HPLC (figure 2.13).

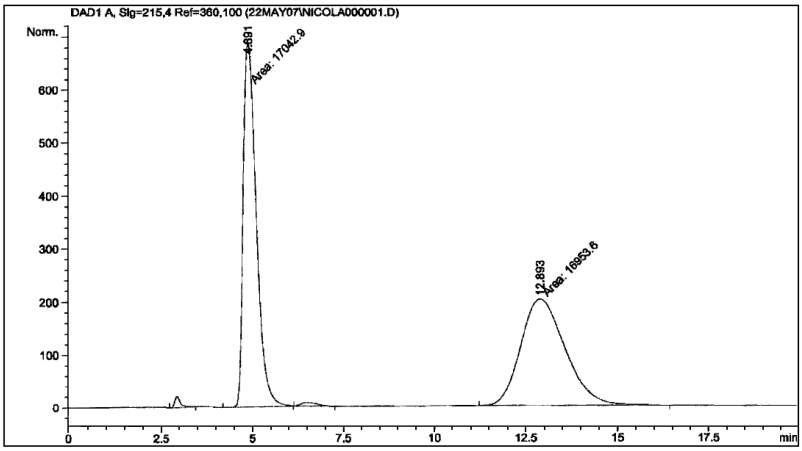
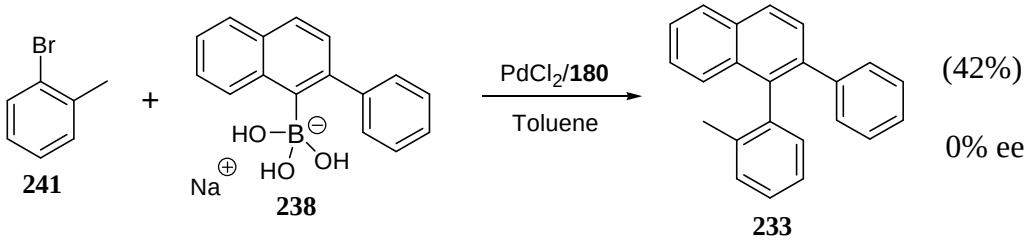


Figure 2.13 Chiral HPLC trace of 1-(2'-methylphenyl)-2-phenylnaphthalene **233** obtained from symmetric coupling reaction.

It can be seen that an exceptional separation of atropisomers had been achieved for this coupled product. The ratio of the areas under the peaks revealed it as being a racemic mixture, as predicted for this symmetric coupling.

2.13 Asymmetric Suzuki coupling reaction towards 1-(2'-methylphenyl)-2-phenylnaphthalene

The reaction towards **233** was thus repeated using the same coupling partners, this time using palladium(II) chloride with chiral ligand **180**.



241 **238** **233**

Scheme 2.51 Asymmetric Suzuki coupling towards 1-(2'-methylphenyl)-2-phenylnaphthalene **233**.

As before, all the solid reagents were initially added to a dried pressure tube followed by the liquid bromide **241** and the solvent. After heating at the specified temperature for the required time the crude mixture was found to contain the coupled product **233** together with deboronated side-product (2-phenylnaphthalene). A sample of the purified product was subsequently analysed by chiral HPLC (figure 2.14).

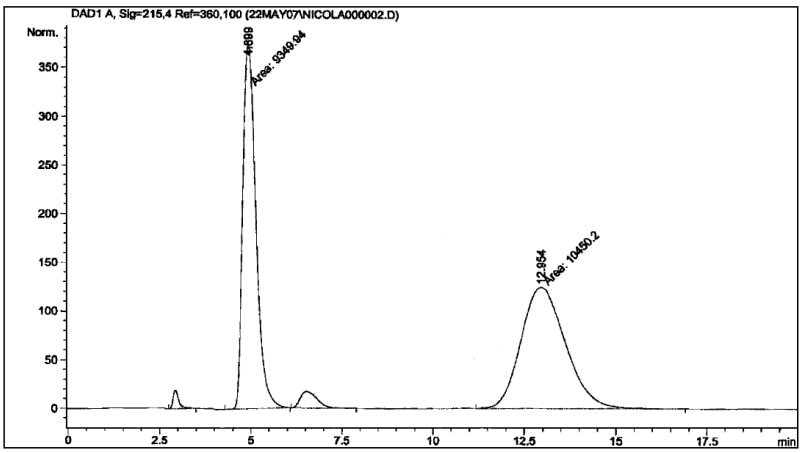


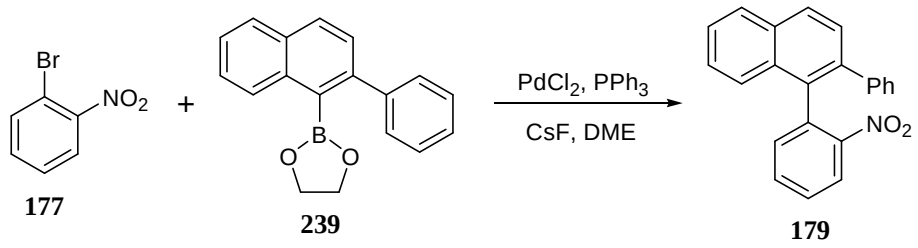
Figure 2.14 Chiral HPLC trace of 1-(2'-methylphenyl)-2-phenylnaphthalene **233** obtained from asymmetric coupling reaction.

Once again a very good baseline separation of peaks had resulted, however an enantiomeric excess had not been achieved as the ratio of the areas under the peaks reflected a racemic mixture. It can be concluded from this result that coupled product 1-(2'-methylphenyl)-2-phenylnaphthalene **233** also racemises under the reaction conditions. The barrier to rotation is evidently overcome as a direct result of the combination of these two particular *ortho*-substituent groups; also seen in the previous compound 1-(2'-biphenyl)-2-methylnaphthalene **227**.

Attention was therefore directed towards the next hindered biaryl compound **179**. (This compound was one of the coupled products originally featured in the report by Buchwald and Yin on the asymmetric Suzuki reaction).[32]

2.14 Symmetric Suzuki coupling reactions towards 1-(2'-nitrophenyl)-2-phenylnaphthalene

The first Suzuki coupling towards the racemic product **179** was carried out using (ethylene glycol)boronate ester **239** and 1-bromo-2-nitrobenzene **177**.



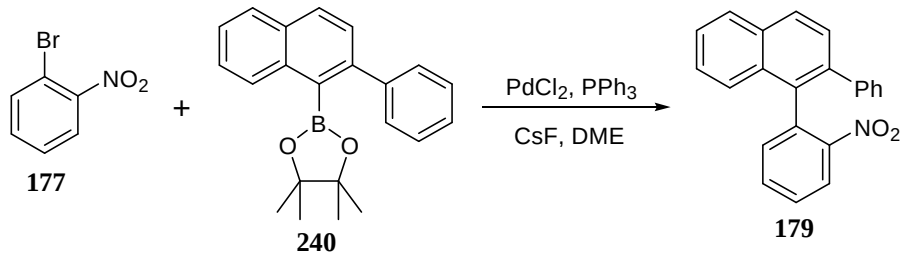
177 **239** **179**

Scheme 2.52 Attempted symmetric Suzuki coupling towards 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** using (ethylene glycol) boronate ester **239**.

A slightly modified procedure was carried out for this reaction, in which the cesium fluoride base was added to a dried pressure tube prior to the addition of the other reagents, and thoroughly flame-dried under vacuum. (This precautionary measure of flame-drying the base prior to use has been reported as giving improved results).[8] The dried base was allowed to cool to room temperature under an atmosphere of argon, with the tube subsequently charged with the rest of the solid reagents. The required volume of freshly distilled solvent was then added, and the mixture heated for 24 h at 80 °C. After this time the crude material obtained after

work-up was found to contain unreacted boronate ester **239**, deboronated side-product (2-phenylnaphthalene) and 1-bromo-2-nitrobenzene starting material **177**. There were no peaks observed in the ^{1}H NMR spectrum that corresponded to the coupled product **179**.

The following symmetric Suzuki reaction towards biaryl **179** was attempted using the (pinacol)boronate ester coupling partner **240**.

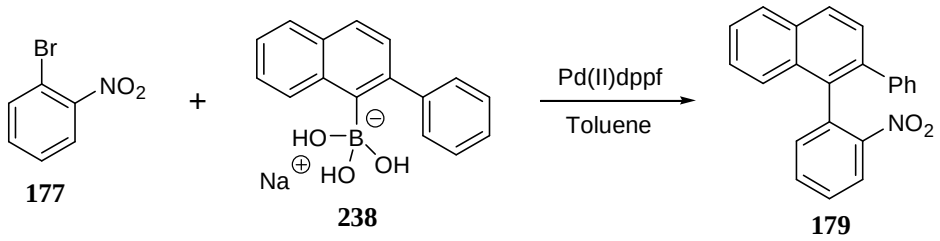


Scheme 2.53 Attempted symmetric Suzuki coupling towards 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** using (pinacol)boronate ester **240**.

The same protocol as above was carried out in which the cesium fluoride base was thoroughly flame-dried in the pressure tube prior to use. After addition of the rest of the reagents and solvent, the mixture was heated at the specified temperature for the required time, after which the crude material was analysed. This was found to contain unreacted (pinacol)boronate ester **240** and 1-bromo-2-nitrobenzene **177** with no traces of coupled product **179**.

The presence of unreacted coupling reagents in this reaction (and deboronated material in the one described previously - scheme 2.52) suggested that the rate of the coupling reaction was slow, possibly due to the use of the less reactive boronate ester organoboron partner. It appears that the (pinacol)boronate ester is more resistant to deboronation than the ethylene glycol analogue, and yet it fails to participate in the coupling reaction as a probable result of its increased steric bulk.

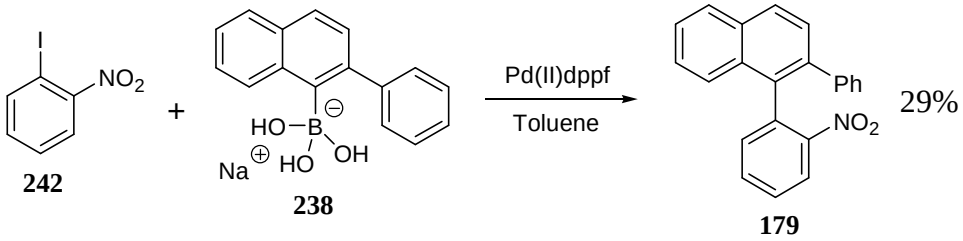
Therefore the next Suzuki coupling towards the same racemic product was performed with the more reactive sodium borate salt **238**. The conditions used for this reaction (employing 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) as catalyst with toluene as solvent) reflected those used in previous couplings employing borate salts.



Scheme 2.54 Attempted symmetric Suzuki coupling towards 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** using borate salt **238**.

The reaction was carried out following the standard procedure employing a sealed pressure tube, with the crude mixture obtained found to contain deboronated material (2-phenylnaphthalene) and unreacted 1-bromo-2-nitrobenzene **177**. On this occasion all of the organoboron coupling substrate had been consumed by deboronation side-reaction, and although peaks were observed in the ^{1}H NMR spectrum that could be assigned to the desired coupled product **179**, the low intensity indicated that only traces had been produced. (A repeat of this reaction using palladium chloride and triphenylphosphine as the catalyst and ligand failed to give any traces of coupled product).

A subsequent Suzuki coupling towards the racemic product was performed using the same borate salt **238** but with 1-iodo-2-nitrobenzene **242** as the halide partner.



Scheme 2.55 Symmetric Suzuki coupling towards 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** using 1-iodo-2-nitrobenzene **242**.

Using the same protocol, the mixture obtained after work-up was found to contain peaks in the ^{1}H NMR spectrum corresponding to deboronated material (2-phenylnaphthalene) and unreacted 1-iodo-2-nitrobenzene **242**. There were however also significant peaks present that matched those for the coupled product[32] and so purification was performed towards the isolation of coupled product **179**. An initial yield calculated for the yellow crystalline solid obtained was 29%.

In this reaction it could be clearly seen that the use of an iodide coupling partner produced a much improved result. This would seem to suggest that, with the use of a more reactive organoboron substrate, the rate-determining step was now oxidative addition. The presence of deboronated material revealed however that an unfortunate consequence of the increased reactivity of the borate salt was also its increased propensity towards deboronation. Despite using an excess of this substrate, consumption by this side-reaction prevented complete conversion, evident from the presence of unreacted iodide **242**. It was also possible that catalyst degradation could have occurred over the period of time allowed for the reaction.

The product obtained from this reaction was analysed by ^{1}H NMR spectroscopy and revealed to contain an unknown impurity. Repeated attempts at purification failed to remove this impurity, as it eluted at the same time as the coupled product. Close inspection of the ^{1}H NMR spectrum of the commercially obtained 1-iodo-2-nitrobenzene **242** revealed that it was not pure, with additional peaks attributable to an impurity that could be a regioisomer e.g. 1-iodo-3-nitrobenzene or 1-iodo-4-nitrobenzene. This impurity could have conceivably participated in an analogous concurrent coupling reaction to give an alternative coupled product. As the unknown impurity in the product **179** possessed very similar physical and spectroscopic properties this could serve as a possible explanation.

A sample of the impure product was nonetheless analysed by chiral HPLC.

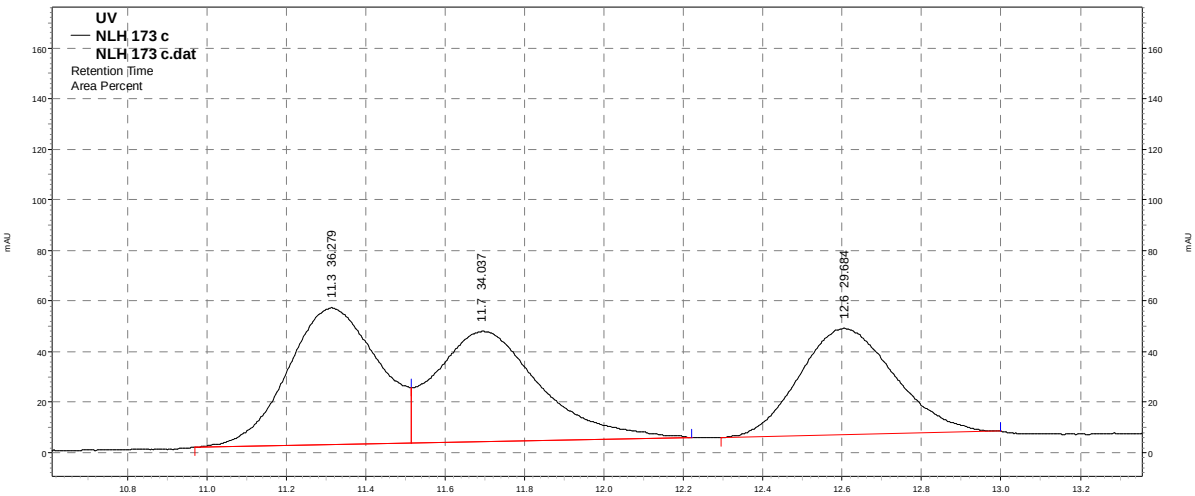
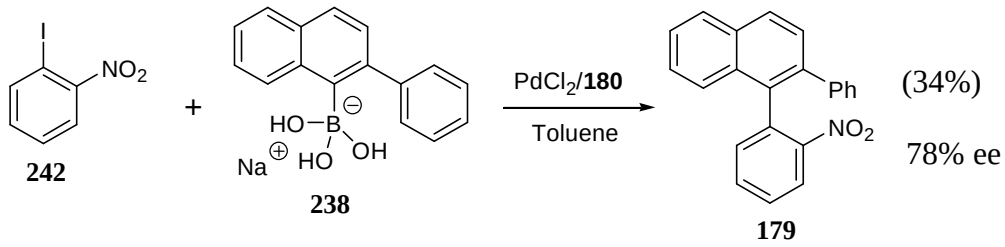


Figure 2.15 Chiral HPLC trace of 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** obtained from the symmetric coupling reaction using 1-iodo-2-nitrobenzene **242**.

Using a different chiral HPLC system (see Experimental for details) the two atropisomeric forms of coupled product **179** were separated and identified as the first and last peaks. An approximate calculation revealed that they were present in racemic proportions which was expected for this symmetric coupling. Unfortunately, the unknown impurity eluted at a similar time, appearing as a peak in between the two atropisomers. Repeated column chromatography (as mentioned above) was unsuccessful in removing this impurity. Despite this, the observed retention times for the peaks of the two atropisomers provided a useful reference for comparison with other samples of the same product synthesised under different conditions.

2.15 Asymmetric Suzuki coupling reactions towards 1-(2'-nitrophenyl)-2-phenylnaphthalene

The first asymmetric Suzuki reaction towards biaryl **179** was performed with the substrates found to perform best in the symmetric version, i.e. 1-iodo-2-nitrobenzene **242** and sodium borate salt **238**.



Scheme 2.56 Asymmetric Suzuki coupling towards 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** using 1-iodo-2-nitrobenzene **242** and sodium borate salt **238**.

The reaction was carried out employing the standard sealed tube protocol, with the desired coupled product **179** identified in the crude worked-up material by ^{1}H NMR spectroscopy together with unreacted 1-iodo-2-nitrobenzene **242** and deboronated side-product (2-phenylnaphthalene). Successful isolation was achieved via column chromatography, to give the pure product as a yellow crystalline solid in 34% yield. (Use of a different source of 1-iodo-2-nitrobenzene **242** resulted in a pure product). A sample of the product was analysed by chiral HPLC (figure 2.16).

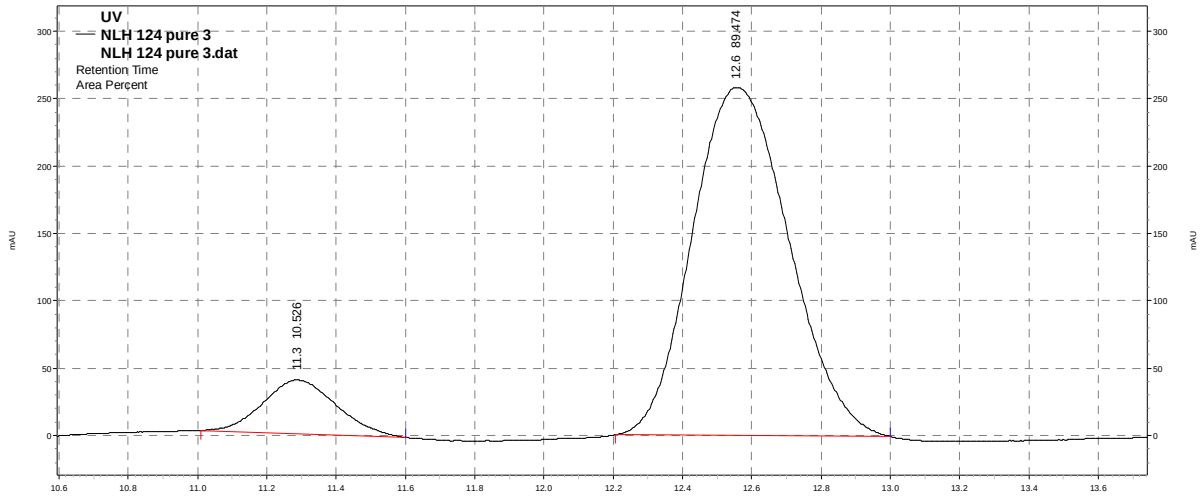
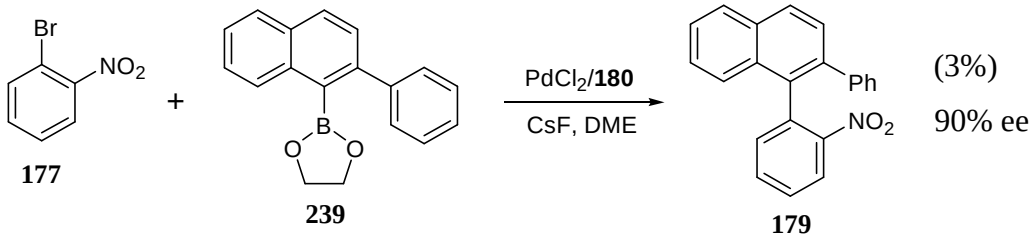


Figure 2.16 Chiral HPLC trace of 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** obtained from asymmetric coupling reaction using 1-iodo-2-nitrobenzene **242**.

The retention times of the peaks corresponding to the two atropisomers were found to match those seen in the trace for the racemic product (figure 2.15). From the ratio of the areas under the peaks it was calculated that an enantiomeric excess of 78% had been achieved. The intensity of the peaks and the difference in areas indicated a clear preference for the formation of the atropisomer that elutes at the later time. This was an encouraging result in which a successful asymmetric induction had clearly been achieved. This prompted the undertaking of further asymmetric reactions towards this product employing, to begin with, different organoboron substrates.

The next asymmetric Suzuki reaction carried out towards this product employed 1-bromo-2-nitrobenzene **177** as the halide with (ethylene glycol)boronate ester **239** as the organoboron substrate (scheme 2.57). This reaction had been previously attempted as a symmetric version (scheme 2.52) but was not met with success. The first attempts towards this asymmetric version were also unsuccessful, with no traces of product observed.



Scheme 2.57 Asymmetric Suzuki coupling towards 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** using (ethylene glycol)boronate ester **239** and bromide **177**.

As it was considered important to gain the maximum amount of information possible from the comparison of analogous asymmetric reactions, continued efforts were made towards a successful outcome for this reaction. The data obtained was intended to be directly compared to that from the same reaction employing the pinacol ester **240** (and possibly a reaction employing 'reversed' substrates). Therefore efforts towards optimisation were restricted, as in order to gain meaningful data from the comparison of this reaction with others, variables other than the change in coupling substrate had to be kept constant or as close to constant as reasonably possible. As a result, optimisation was limited to minor adjustments in the reaction procedure.

Best results in which isolable amounts of biaryl **179** were produced involved the inclusion of flame-dried molecular sieves in the reaction vessel (dried together with the base) and degassing of the reaction solvent both prior to use and following addition of the boronate **239** and bromide **177** substrates. After the addition of the ligand **180** and palladium salt the mixture was heated for 24 h and worked-up according to the standard protocol. The crude mixture was found to contain unreacted boronate ester **239** and a small amount of the coupled product **179**. An approximate yield was calculated as 3% (from the ratio of integrals in the ^{1}H NMR spectrum).

In this reaction it appeared as though degassing the solvent with argon before and after the addition of the coupling substrates was crucial to the success of the reaction. Attempts in which the solvent was only degassed prior to addition did not achieve even traces of the coupled product. This inferred that the reactive catalyst species was sensitive to the presence of oxygen, which can be 'trapped' within the solid reagent and thus introduced into the system. The detrimental effects of oxygen in the reaction system have also been reported in other studies, with the degassing of the reaction solvent found to be beneficial[35,36] or in some cases essential[37] in the prevention of catalyst degradation (and/or homocoupling), leading to improved yields. Overall, the rate of the coupling reaction was evidently very slow from the poor conversion observed, likely due to the less reactive nature of the boronate ester substrate.

A small amount of the product was successfully isolated from the best attempt, and was duly analysed by chiral HPLC (figure 2.17).

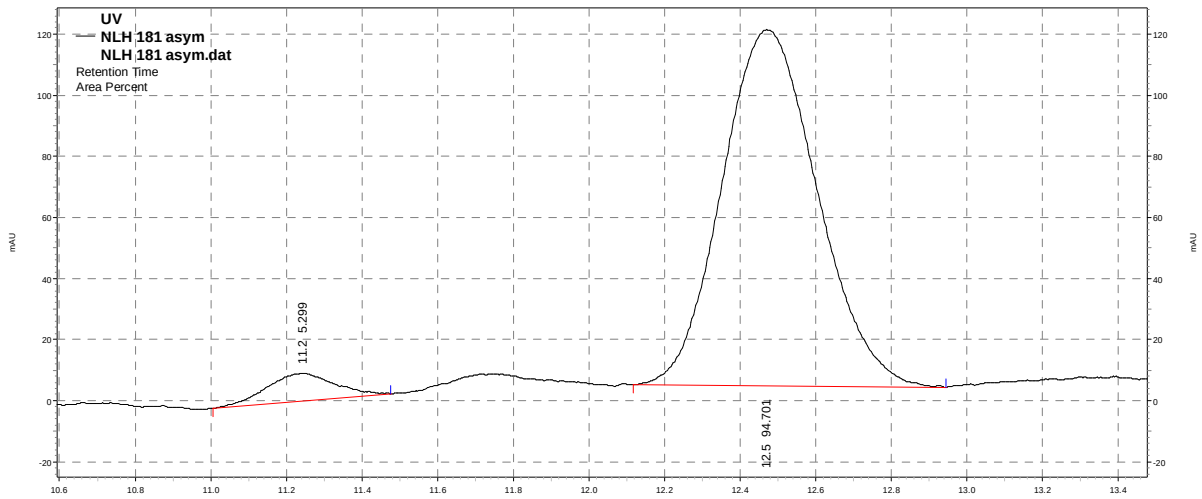
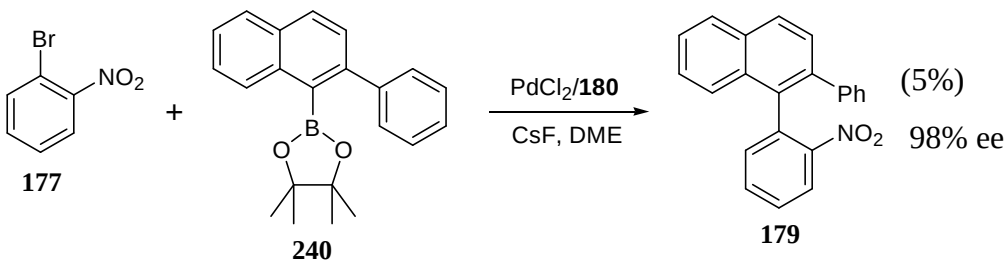


Figure 2.17 Chiral HPLC trace of 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** obtained from asymmetric coupling reaction using (ethylene glycol)boronate ester **239**.

It could be observed that a successful asymmetric induction had been achieved, and, despite a change in the reaction conditions and substrates, the preferred atropisomeric form resulting from this version of the asymmetric reaction was still that eluting at the later time. Calculation of the difference in the areas under the peaks revealed an enantiomeric excess of 90%. This was a very pleasing result, and efforts were next focussed upon the equivalent reaction employing the (pinacol)boronate ester **240**.

In this reaction, as in the previous, multiple attempts towards a successful coupling initially failed under the standard procedure. Utilising a similarly modified procedure was found to improve the success of the reaction, in that a small isolable amount of product was observed as opposed to none.



Scheme 2.58 Asymmetric Suzuki coupling towards 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** using (pinacol)boronate ester **240** and bromide **177**.

The procedure found to produce the best results involved the inclusion of flame-dried molecular sieves in the reaction vessel (dried together with the base) and degassing of the reaction solvent. On this occasion, degassing of the mixture of solvent and added coupling substrates was not found to be necessary. However, a noticeable improvement was observed when the (pinacol)boronate ester **240** was added to the reaction vessel as a final step, once all the other reagents and solvent had already been added. Despite these additional measures a very poor conversion was observed, with a calculated yield from the ratio of integrals in the ^{1}H NMR spectrum in the best attempt found to be approximately 5%.

Purification by column chromatography successfully isolated the coupled product, which was analysed by chiral HPLC.

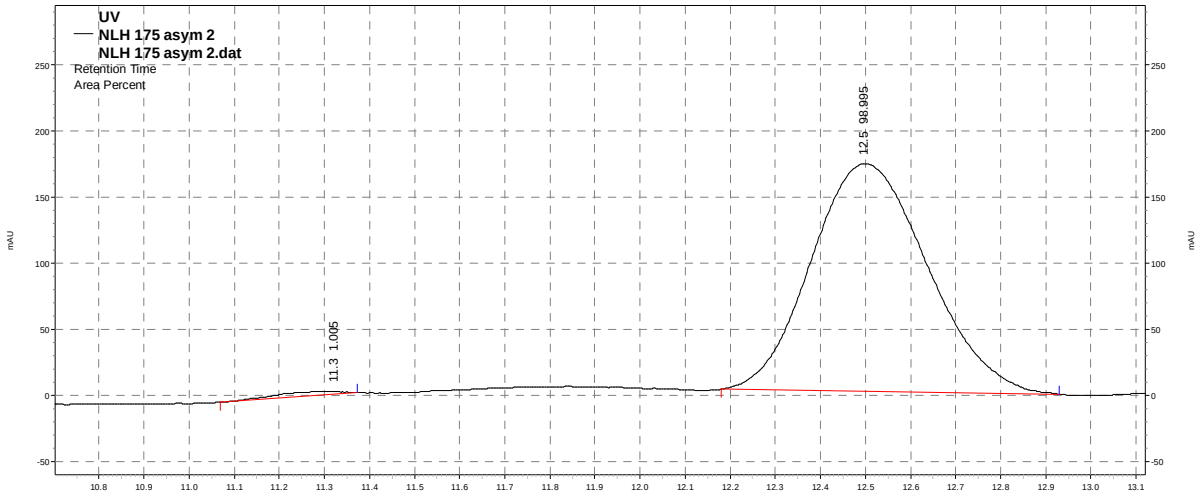
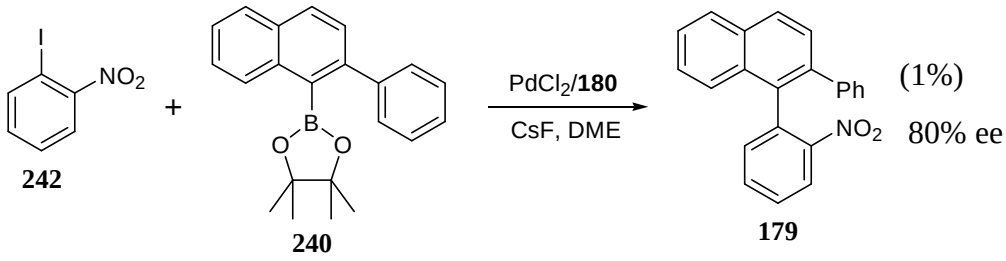


Figure 2.18 Chiral HPLC trace of 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** obtained from asymmetric coupling reaction using (pinacol)boronate ester **240** and bromide **177**.

This reaction was found to have produced an impressive enantiomeric excess of 98%, the highest reported value for this particular compound.[32] As before, the atropisomer eluting at the later time was formed preferentially, and so on this occasion a change in the boronate ester moiety did not result in the formation of the opposite atropisomer (as seen in earlier reported studies).[1-3] The increased steric bulk of the (pinacol)boronate ester group appeared to improve the selectivity, although at a very poor conversion rate.

The last asymmetric reaction carried out in this series was performed with a change in the halide coupling partner, utilising 1-iodo-2-nitrobenzene **242** instead of bromide **177** with the hindered (pinacol)boronate ester **240**.



Scheme 2.59 Asymmetric Suzuki coupling towards 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** using (pinacol)boronate ester **240** and iodide **242**.

The same modifications to the procedure as in the previous reaction were applied, in that flame-dried molecular sieves were used, with the reaction solvent degassed prior to use. Addition of the (pinacol)boronate ester **240** to the pressure tube also formed the final step before the mixture was heated for 24 h. After this time, analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to unreacted boronate ester **240** and iodide **242** and an unidentified impurity.

As can be seen in this reaction, a change in the halide substrate to iodide **242** did not result in an improved yield, which strongly indicated that the oxidative addition step was not rate-determining. It was clear from the significant amounts of unreacted boronate ester material that the transmetallation of this hindered compound was very slow. The lack of deboronated material also indicated that this substrate was particularly stable towards deboronation. This extra stability could possibly be an associated factor contributing to its decreased reactivity in the catalytic cycle.

A sample of product **179** was nevertheless obtained from this reaction, which unfortunately contained the same unknown impurity as that observed in the symmetric reaction towards the racemic product (figure 2.15). This strongly implicated the iodide reagent **242** as the source of this impurity, as the same batch was used to perform this reaction. (Unfortunately, due to time constraints, repeat attempts towards this and the symmetric reaction using a purer source of iodide were not able to be carried out).

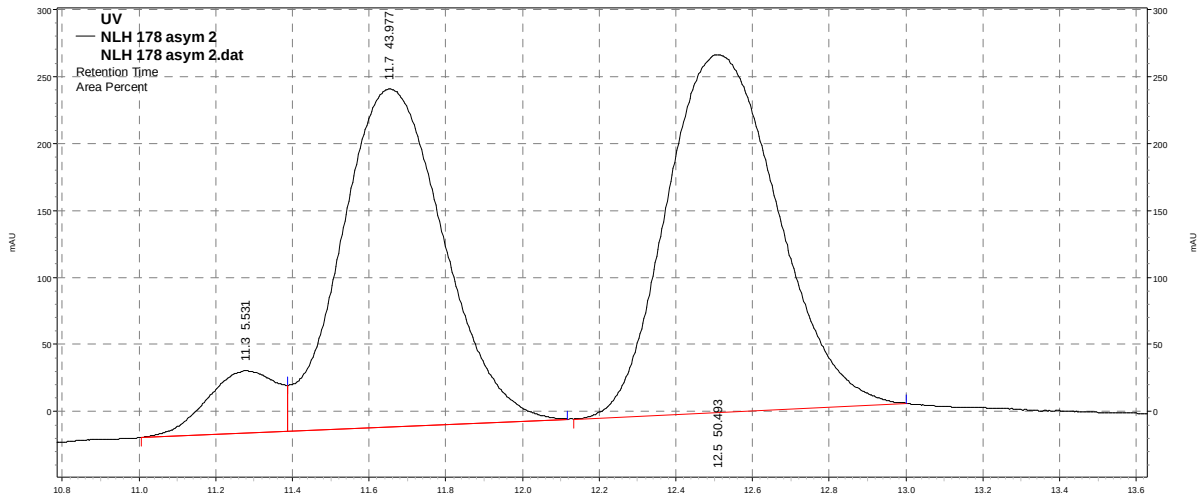


Figure 2.19 Chiral HPLC trace of 1-(2'-nitrophenyl)-2-phenylnaphthalene **179** obtained from asymmetric coupling reaction using (pinacol)boronate ester **240** and iodide **242**.

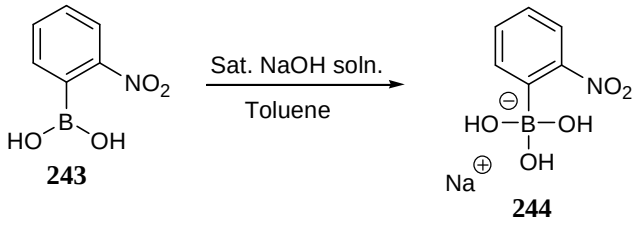
An approximate calculation of the enantiomeric excess achieved in this reaction was 80%, although it had to be borne in mind that this was not an accurate figure on account of the presence of the impurity peak occurring at 11.7 minutes. The retention times of the other two peaks matched those for the atropisomers seen in the trace of the racemic product and in subsequent traces. Comparison of this reaction with the analogous reaction performed with the bromide **177** (scheme 2.58) revealed that a lower enantiomeric excess had resulted from the use of iodide **242** as the halide coupling partner.

2.16 Asymmetric Suzuki coupling reactions towards 1-(2'-nitrophenyl)-2-phenylnaphthalene using 'reversed' coupling partners

The next investigations were aimed towards the undertaking of equivalent asymmetric reactions employing 'reversed' substrates, in order to analyse any possible changes in the stereochemical outcome. Preparation of alternative organoboron coupling partners bearing the *ortho*-nitrophenyl organic portion was therefore necessary.

2.16.1 Preparation of alternative organoboron coupling partners from 2-nitrophenylboronic acid

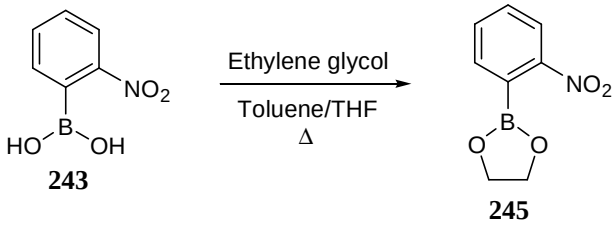
The first synthesis attempted was that towards the sodium borate salt **244** using commercially available 2-nitrophenylboronic acid **243**. This organoboron substrate was intended to be employed in an asymmetric reaction mirroring that of scheme 2.56 but with the substrates bearing opposite organic groups. The reaction towards **244** was performed in the same manner as all other borate salt preparations.



Scheme 2.60 Attempted preparation of sodium 2-nitrophenylborate salt **244**.

Dissolution of the boronic acid **243** in hot toluene occurred readily, with the resulting pale yellow solution treated with saturated sodium hydroxide solution. No precipitation was observed and so the mixture was left to stir for a continued period of time. This did not result in the formation of any solid product, and so the organic layer was extracted and found to contain unreacted boronic acid **243**. Repeated attempts at this synthesis failed to produce the desired sodium borate salt **244**. In light of the unsuccessful preparation of this borate salt substrate, the preparation of the iodide analogue of 1-bromo-2-phenylnaphthalene **237** - also intended for use in the same asymmetric reaction as a coupling partner - was not performed.

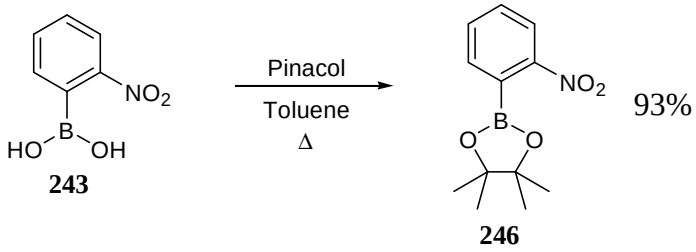
The next synthesis was aimed towards the preparation of 2-nitrophenyl(ethylene glycol)boronate ester **245** from the parent boronic acid **243**. This was intended for use in an opposite asymmetric coupling analogous to that of scheme 2.57.



Scheme 2.61 Attempted preparation of boronate ester **245**.

The standard protocol was initially employed in which the boronic acid was heated to reflux in toluene with ethylene glycol. The first attempt was unsuccessful, with unreacted boronic acid **243** present after heating for 24 h. A second attempt was performed using Dean-Stark apparatus as a precautionary measure, to aid the removal of water from the mixture. After heating for 5 h there appeared to be no water left in the reaction mixture and so work-up was performed. As before, analysis of the yellow solid obtained revealed it to be unreacted boronic acid **243**. A final attempt was performed using a solvent mixture of 1:4 toluene/THF as this had enabled the successful preparation of (ethylene glycol)boronate ester **239**. Organic extractions resulted in the isolation of a yellow solid which was found to be 2-nitrophenylboronic acid starting material **243**. As a result, no further efforts were made towards the preparation of this organoboron substrate.

The final preparation was towards the (pinacol)boronate ester **246**, for use in an asymmetric coupling reaction resembling that illustrated in scheme 2.58 but with opposite coupling partners.



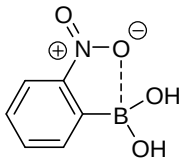
243 **246**

Scheme 2.62 Preparation of 2-nitrophenyl(pinacol)boronate ester **246**.

Unlike the attempted synthesis of boronate ester **245**, the preparation of 2-nitrophenyl(pinacol)boronate ester **246** proceeded smoothly under the standard conditions in which the boronic acid **243** was treated with pinacol and heated to reflux in toluene. After 48 h the mixture was extracted, with the successful isolation of the product **246** as a waxy yellow solid in good yield. As the ^{1}H NMR spectrum of this product appeared to be free of impurities, no further purification was performed.

It was unclear as to why this reaction should proceed smoothly and not the reaction toward the (ethylene glycol)boronate ester **245**. It was postulated that the *ortho*-nitro group could possibly coordinate weakly to the boron atom through one of

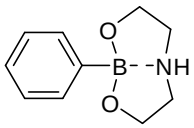
the oxygen atoms, and so prevent any incoming nucleophiles from occupying the vacant coordination site on the boron atom.



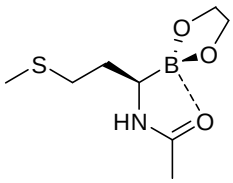
243

Figure 2.20 Possible intramolecular coordination of a nitro group oxygen atom with the boron centre.

This suggested interaction occurring in boronic acid **243** was also alluded to in literature accounts,[38] with examples of this type of intramolecular coordination having already been confirmed in the structures of some boronic acid derivatives by X-ray crystallography analysis.



247



248

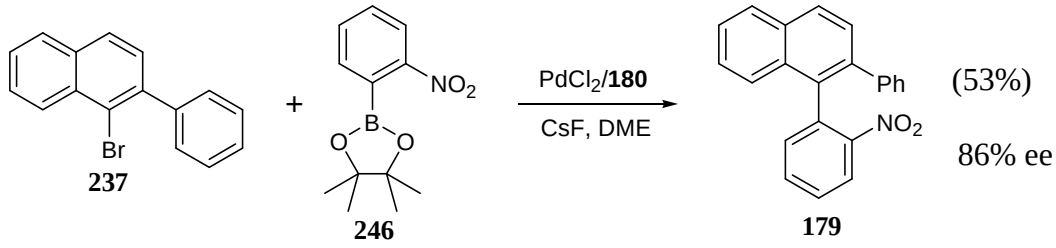
Figure 2.21 Examples of boronic acid derivatives found to possess intramolecular coordination with the boron atom.

This may be used to rationalise the failure of the attempted preparations towards substrates **244** and **245** - in that the intended coordination site on the boron atom is effectively 'blocked' - but does not explain the successful preparation of pinacol boronate ester **246**. It could be possible that the increased electron density provided by the tertiary carbon centres within the pinacol reagent serves to enhance its nucleophilic properties to a degree that enables the initial barrier posed by any intramolecular coordination to be overcome.

2.16.2 Asymmetric Suzuki coupling carried out with 'reversed' coupling partners

As a result of the unsuccessful preparation of alternative organoboron substrates **244** and **245**, the only asymmetric Suzuki coupling able to be carried out

using reversed coupling substrates was that shown below, employing 2-nitrophenyl(pinacol)boronate ester **246** and bromide **237**. The outcome of this asymmetric reaction was to be compared against that achieved for the asymmetric reaction shown in scheme 2.58.



Scheme 2.63 Asymmetric Suzuki coupling towards **179** employing 'reversed' coupling substrates 1-bromo-2-phenylnaphthalene **237** and 2-nitrophenyl(pinacol) boronate ester **246**.

On this occasion, a successful outcome was achieved without the need for additional measures such as the inclusion of sieves or the degassing of solvent. A much improved yield was obtained for this coupling reaction, which could be directly attributed to the use of the alternative coupling substrates. The oxidative addition step clearly tolerated the increased steric bulk of the halide substrate, with an evident improvement in transmetallation resulting from the presence of the relatively less bulky nitrophenyl group. Reductive elimination could also be deduced as having proceeded smoothly.

This result (when compared to that of the reaction shown in scheme 2.58) indicated that the transmetallation step was sensitive to the steric bulk of the organic group on the organoboron coupling partner. The particular reactivity displayed by the organoboron substrate **246** was especially surprising in light of the remaining steric bulk from the (pinacol)boronate ester group and the presence of the strongly withdrawing *ortho*-nitro group. (Transmetallation is generally considered to be favoured by an increase in nucleophilicity of the organic group attached to the boron atom).[39] Moreover, the use of an organoboron substrate such as **246** bearing a strongly electron-withdrawing *ortho*-substituent was highly anticipated to result in rapid competing deboronation, as the susceptibility of these types of organoboron substrates towards deboronation has been well-documented.[40,41]

The observation of the general sensitivity of the transmetallation step to steric hindrance has been reported in many studies.[6,39,42-46] In most cases the yield was found to be significantly reduced if the organoboron partner was the substrate bearing the greater steric bulk. It was also observed in one study that a high degree of steric bulk already present on the palladium species following oxidative addition also resulted in a slow transmetallation step.[29] In the reaction above however, the high steric bulk of the naphthyl group ligated to the oxidative adduct did not appear to cause any major adverse effects during transmetallation.

A sample of the product obtained from this reaction was analysed by chiral HPLC (figure 2.22).

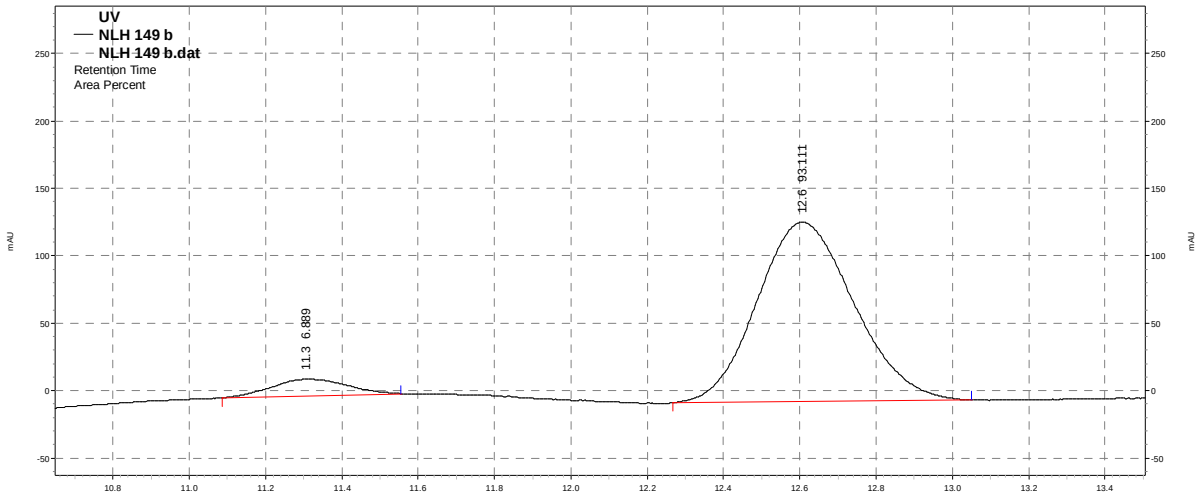


Figure 2.22 Chiral HPLC trace for the coupled product **179** isolated from asymmetric reaction using 'reversed' substrates 1-bromo-2-phenylnaphthalene **237** and 2-nitrophenyl(pinacol)boronate ester **246**.

The chiral HPLC separation of the two atropisomers revealed that this opposite asymmetric coupling had produced an enantiomeric excess of 86%. The same preference towards the atropisomer eluting at the later time was observed.

It was apparent that despite a slightly decreased enantiomeric excess achieved in this reaction compared to its opposite analogue (scheme 2.58) on the whole a change in the organic groups on each substrate did not alter the stereochemical outcome. Perhaps most significant was the greatly improved yield of product arising from the use of these coupling substrates.

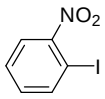
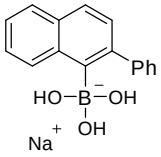
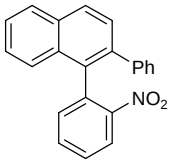
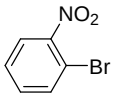
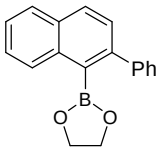
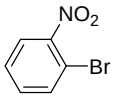
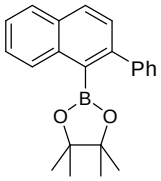
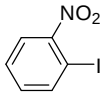
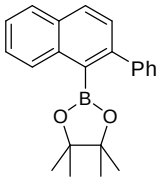
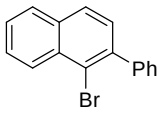
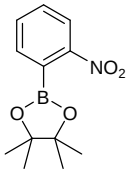
Entry	Aryl halide	Organoboron partner	product	yield(%)	ee (%)
1	 **242**	 **238**	 **179**	34	78
2	 **177**	 **239**		3	90
3	 **177**	 **240**		5	98
4	 **242**	 **240**		1	80
5	 **237**	 **246**		53	86

Table 2.3 Table of results summarising all asymmetric reactions towards biaryl **179**.

2.17 Summary of results

Upon examination of the results obtained for these asymmetric Suzuki coupling reactions, it can be deduced with a reasonable degree of certainty that the rate-determining step for entries 2, 3 and 4 is transmetallation. Comparison of entries 3 and 4 supports this, as a change to the more reactive iodide substrate **242** did not result in any improvement in yield. It is a little surprising however that the use of the less bulky (ethylene glycol)boronate ester **239** did not achieve a better conversion than the use of the (pinacol)boronate ester **240**, which implied that these substrates were approximately equal in their general reactivity towards transmetallation.

The striking difference in yield obtained from the asymmetric reaction performed with the substrates bearing opposite organic groups (entry 5) strongly indicated that the transmetallation step was sensitive towards steric hindrance exerted by the organic group appended on the organoboron substrate, as the reaction proceeded more rapidly with a comparatively less bulky organic group. This was despite the relatively unfavourable electronic properties of organoboron substrate **246**, in which the presence of the electron-withdrawing *ortho*-nitro group has been commonly reported as having a deactivating effect during transmetallation.[40] It would appear that any negative electronic effects exerted by this substrate were effectively overridden by the advantages gained from the reduction in steric bulk. The high yield of this reaction also implicated a relatively facile oxidative addition for bromide substrate **237**, which was also an unexpected outcome considering its hindered nature.

The unexpected success of this reaction served as an additional example of the unpredictable nature of the Suzuki reaction, with its inherent sensitivity towards the fine balance of electronic and steric influences exerted by the reacting substrates. It has often been shown that, despite applying well-proven theories and generally observed trends to predict the outcome of Suzuki couplings, an alternative and sometimes surprising outcome can often result. This would suggest that, until more precise theoretical models are developed for the Suzuki coupling reaction, reaction screening retains its value as a practice for the determination of optimal reaction conditions for a given target compound.

With regards to the implications towards asymmetric induction, there appears to be a general trend in which, despite changes to the nature of the coupling substrates and dramatic differences in conversions, the same preference for the later eluting atropisomer results in all cases, with enantiomeric excesses consistently falling between the region of 78 - 98%. Differences in enantiomeric excesses between reactions were relatively slight, and so accurate conclusions regarding the possible effect of a change in a certain substrate on the asymmetric induction process could not be drawn.

By far the most significant result was that obtained for the asymmetric coupling reaction employing coupling partners bearing opposite organic groups (entry

5). In this reaction, it was observed that the same dominant enantiomer was produced in the same enantiomeric excess. This could indicate that, once a common reactive intermediate species has been reached, i.e. the diorganopalladium(II) species, then the same atropisomeric form is produced in the same excess, regardless of the identities (and hence properties) of the reacting moieties used to deploy the organic portions, and irrespective of the order in which the organic portions are installed onto the diorganopalladium(II) complex. If this were the case, then it could be speculated that equilibration of the organic portions prior to reductive elimination was the key moment in chiral induction, with the presence of the chiral ligands (or ligand) serving to control this equilibration in favour of a particular enantiomer. However, in order for this to be confirmed, a much more extensive series of experiments would need to be undertaken, perhaps with more robust substrates.

In conclusion, the chiral environment created by the ferrocenyl ligands (or ligand) in the final intermediate controls the outcome and enantiomeric excess in these asymmetric Suzuki reactions. Although the rates and efficiency of each step (oxidative addition, transmetallation etc.) affect the overall yield and usefulness of the reactions, the enantiomeric excess cannot at the moment be controlled by substrate choice. This work concludes that improvements in the asymmetric Suzuki reaction are likely to come mostly from inspired ligand design, and indeed focus has been rightly placed in this aspect to date.[31,45,47,48] These results indicate that chemists can chose coupling partners to facilitate reaction rate and yield without fear of compromising the enantiomeric excesses of these challenging reactions.

2.18 References for Results and Discussion

(1) K. V. L. Crépy, PhD thesis, University of East Anglia, **2001**, 63.

(2) A. N. Cammidge and K. V. L. Crépy, *Chem. Commun.* **2000**, 1723.

(3) A. N. Cammidge and K. V. L. Crépy, *Tetrahedron* **2004**, *60*, 4377.

(4) W. J. Thompson and J. Gaudino, *J. Org. Chem.* **1984**, *49*, 5237.

(5) Y. Hoshino, N. Miyaura and A. Suzuki, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008.

(6) T. Watanabe, N. Miyaura and A. Suzuki, *Synlett* **1992**, 207.

(7) J. F. Payack, E. Vazquez, L. Matty, M. H. Kress and J. McNamara, *J. Org. Chem.* **2005**, *70*, 175.

(8) S. Würtz and F. Glorius, *Acc. Chem. Res.* **2008**, *41*, 1523.

(9) A. R. Martin and Y. Yang, *Acta Chem. Scand.* **1993**, *47*, 221 and references therein.

(10) T. I. Wallow and B. M. Novak, *J. Org. Chem.* **1994**, *59*, 5034.

(11) S. W. Wright, D. L. Hageman and L. D. McClure, *J. Org. Chem.* **1994**, *59*, 6095.

(12) H.-J. Frohn, N. Y. Adonin, V. V. Bardin and V. F. Starichenko, *Z. Anorg. Allg. Chem.* **2002**, *628*, 2834.

(13) H. C. Brown and T. E. Cole, *Organometallics* **1983**, *2*, 1316.

(14) A. D. Ainley and F. Challenger, *J. Chem. Soc.* **1930**, 2171.

(15) J. O. Edwards, G. C. Morrison, V. F. Ross and J. W. Schultz, *J. Am. Chem. Soc.* **1955**, *77*, 266.

(16) J. C. Norrild and H. Eggert, *J. Am. Chem. Soc.* **1995**, *117*, 1479.

(17) G. A. Molander and B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302.

(18) H. R. Snyder, J. A. Kuck and J. R. Johnson, *J. Am. Chem. Soc.* **1938**, *60*, 105.

(19) M. F. Lappert, *Chem. Rev.* **1956**, *56*, 959.

(20) D. L. Fowler and C. A. Kraus, *J. Am. Chem. Soc.* **1940**, *62*, 1143.

(21) S. L. Stafford, *Can. J. Chem.* **1963**, *41*, 807.

(22) S. Darses, G. Michaud and J.-P. Genêt, *Tetrahedron Lett.* **1998**, *39*, 5045.

(23) S. Darses and J.-P. Genêt, *Eur. J. Org. Chem.* **2003**, 4313.

(24) P. G. Ciattini, E. Morera and G. Ortar, *Tetrahedron Lett.* **1992**, *33*, 4815.

(25) N. Miyaura and A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457 and references therein.

(26) C. J. Schubert, MChem dissertation, University of East Anglia, **2005**.

(27) A. N. Cammidge, V. H. M. Goddard, H. Gopee, N. L. Harrison, D. L. Hughes, C. J. Schubert, B. M. Sutton, G. L. Watts and A. J. Whitehead, *Org. Lett.* **2006**, *8*, 4071.

(28) R. Itooka, Y. Iguchi and N. Miyaura, *J. Org. Chem.* **2003**, *68*, 6000.

(29) J. C. Anderson, H. Namli and C. A. Roberts, *Tetrahedron* **1997**, *53*, 15123.

(30) D. Marquarding, H. Klusacek, G. Gokel, P. Hoffmann and I. Ugi, *J. Am. Chem. Soc.* **1970**, *92*, 5389.

(31) R. C. J. Atkinson, V. C. Gibson and N. J. Long, *Chem. Soc. Rev.* **2004**, *33*, 313.

(32) J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12051.

(33) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147 and references therein.

(34) D. S. Matteson, *Tetrahedron* **1989**, *45*, 1859.

(35) A.-S. Castanet, F. Colobert, P.-E. Broutin and M. Obringer, *Tetrahedron: Asymmetry*, **2002**, *13*, 659.

(36) J. Magano and J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177.

(37) E. M. Campi, W. R. Jackson, S. M. Marcuccio and C. G. M. Naeslund, *J. Chem. Soc., Chem. Commun.* **1994**, 2395.

(38) D. G. Hall, *Structure, Properties, and Preparation of Boronic Acid Derivatives. Overview of Their Reactions and Applications*, Wiley-VCH GmbH, Weinheim, **2005**.

(39) A. Suzuki, *Chem. Commun.* **2005**, 4759.

(40) R. R. González, L. Liguori, A. M. Carrillo and H.-R. Bjørsvik, *J. Org. Chem.* **2005**, *70*, 9591.

(41) Y. Urawa, H. Naka, M. Miyazawa, S. Souda and K. Ogura, *J. Organomet. Chem.* **2002**, *653*, 269.

(42) D. A. Widdowson and Y.-Z. Zhang, *Tetrahedron,* **1986**, *42*, 2111.

(43) G. B. Smith, G. C. Dezeny, D. L. Hughes, A. O. King and T. R. Verhoeven, *J. Org. Chem.* **1994**, *59*, 8151.

(44) S. Saito, S. Oh-tani, N. Miyaura, *J. Org. Chem.* **1997**, *62*, 8024.

(45) S.-B. Yu, X.-P. Hu, J. Deng, J.-D. Huang, D.-Y. Wang, Z.-C. Duan and Z. Zheng, *Tetrahedron Lett.* **2008**, *49*, 1253.

(46) T. Konakahara, Y. B. Kiran, Y. Okuno, R. Ikeda and N. Sakai, *Tetrahedron Lett.* **2010**, *51*, 2335.

(47) J. F. Jensen and M. Johannsen, *Org. Lett.* **2003**, *5*, 3025.

(48) N. Debono, A. Labande, E. Manoury, J.-C. Daran and R. Poli, *Organometallics* **2010**, *29*, 1879.

CHAPTER 3

Experimental

EXPERIMENTAL

3.1 General Methods

3.1.1 Physical measurements

^{1}H NMR spectra were recorded at 400 MHz on a Varian 400 spectrometer, and ^{13}C NMR spectra were recorded at either 75 MHz or 100 MHz on a Varian 300 or Varian 400 spectrometer respectively. Signals are quoted in ppm as δ downfield from tetramethylsilane (δ 0.00) as the internal standard, unless otherwise stated. Coupling constants *J* are quoted in hertz. Solvents used to dissolve NMR samples were either $CDCl_3$ with tetramethylsilane as the reference, or D_2O with acetonitrile as the internal reference (δ_H 2.06, δ_C 1.47).[1] All NMR spectra were run at ambient temperature.

Infrared spectra were recorded on a Perkin-Elmer Spectrum BX FTIR system with SensIR DuraSampl*IR* II ATR attachment as either liquid films or as solids.

Low resolution mass spectra (EI (electron impact) and CI (chemical ionisation)) and high resolution mass spectra (HRMS) were obtained via the EPSRC National Mass Spectrometry Service Centre at the University of Wales in Swansea.

Melting points were recorded using a Reichert Thermovar hot-stage melting point apparatus.

Column chromatography was performed at ambient temperature using Fluka silica gel 60 with solvent ratios stated as v/v. TLC analyses were carried out on Merck aluminium-backed silica gel 60 F_{254} coated plates with compounds viewed under a UV lamp at 254 nm.

Enantiomeric excesses were determined by chiral HPLC resolution of isomers. Chiral HPLC analyses were performed using either (i) a Hewlett-Packard 1100 Agilent HPLC system (GlaxoSmithKline, UK) or (ii) a Hitachi Elite LaChrom system with L2400 UV detector (University of East Anglia, UK) using the appropriate chiral columns and HPLC-grade solvents. Compounds were detected by integrated UV

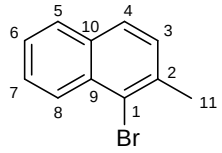
detectors at 215 and 230 nm respectively. The flow rate (0.3, 0.5 or 1.0 mL/min) and the ratio of solvents used as eluent (v/v) are as stated. All chiral HPLC analyses were performed at room temperature.

3.1.2 Reagents, solvents and reaction conditions

Unless otherwise mentioned, chemicals were purchased from commercial sources and were used without further purification. Where indicated, solvents were freshly distilled, and glassware either oven- or flame-dried prior to use. DME and THF were distilled over sodium metal with benzophenone as the indicator. Toluene was distilled over calcium hydride. Other solvents used were SLR grade and were not dried prior to use unless otherwise stated. Distilled deionised water was used throughout. Brine refers to a saturated aqueous solution of sodium chloride. Organic extractions were dried over anhydrous sodium sulfate. Solvents were removed under reduced pressure using a Büchi rotary evaporator. Solid products were dried either on a vacuum line or under vacuum in a desiccator over silica.

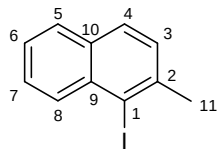
3.2 Preparation of coupling partners for Suzuki reactions

Preparation of 1-bromo-2-methylnaphthalene 162



Following the experimental procedure described by Crépy[2] for the synthesis of the title compound, *N*-bromosuccinimide (13.78 g, 77.4 mmol, 1.1 equiv.) was added to a solution of 2-methylnaphthalene **190** (10.0 g, 70.3 mmol, 1 equiv.) in anhydrous acetonitrile (160 mL) at room temperature under stirring. The reaction mixture was allowed to stir for 18 h at room temperature in the dark. After this time, the solvent was removed under vacuum leaving a yellow solid residue. Water (80 mL) was added to the residue, and the mixture was extracted with hexane (80 mL). The aqueous layer was further extracted with hexane (2 x 40 mL) and the organic layers combined and dried over sodium sulfate. This was filtered and removed of solvent to give a yellow oil (14.72 g, 95%). Spectroscopic data confirmed that it comprised a mixture of the product **162** and starting material **190**. No further purification steps were performed. δ_H (400 MHz, $CDCl_3$) (peaks belonging to **162** only) 8.31 (1H, d, *J* 8.4), 7.81 (1H, d, *J* 8.4), 7.71 (1H, d, *J* 8.4), 7.59 (1H, t, *J* 7.6), 7.49 (1H, t, *J* 7.6), 7.35 (1H, d, *J* 8.4, H-3), 2.65 (3H, s, H_3-11); δ_C (100 MHz, $CDCl_3$) 136.22, 133.25, 132.76, 128.93, 128.26, 127.52, 127.50, 127.17, 125.88, 124.28, 24.42 (C-11).

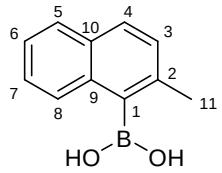
Preparation of 1-iodo-2-methylnaphthalene 171



Following the experimental procedure described by Crépy,[2] a solution of 1-bromo-2-methylnaphthalene **162** (4.0 g, 18.09 mmol, and 1 equiv.) in freshly distilled THF (200 mL) was prepared, and cooled to −78 °C under argon. *n*-Butyllithium (2.5 M in hexane, 8 mL, 19.9 mmol, 1.1 equiv.) was added dropwise to the solution, and the mixture stirred at −78 °C for 1 h, during which the solution turned from a

colourless solution to an orange colour. A solution of iodine (6.0 g, 23.52 mmol, 1.2 equiv.) in dry THF (80 mL) was prepared and cooled to −78 °C, and then added dropwise to the reaction mixture. The dark brown mixture was allowed to warm gradually to room temperature under stirring, after which water (150 mL) was added. The mixture was extracted with DCM (2 x 100 mL). The combined organic layers were washed with aqueous sodium metabisulfite (10%, 2 x 100 mL), dried, and the solution filtered and solvent removed. The resulting brown oil was passed through a short column of silica to give the product **171** as a clear yellow oil (4.3 g, 89%). δ_H (400 MHz, $CDCl_3$) 8.30 (1H, d, *J* 8.4), 7.77 (1H, d, *J* 8.0), 7.72 (1H, d, *J* 8.4), 7.59 (1H, t, *J* 7.6), 7.49 (1H, t, *J* 6.8), 7.36 (1H, d, *J* 8.0), 2.73 (3H, s, H_3-11); δ_C (100 MHz, $CDCl_3$) 141.01, 135.43, 132.711, 132.56, 128.73, 128.52, 128.29, 128.02, 126.04, 106.15, 30.73 (C-11).

Preparation of 2-methylnaphth-1-ylboronic acid 191



(i) Via synthesis of the Grignard reagent;

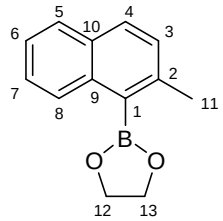
The experimental procedure described by Crépy[2] was followed, with initial synthesis of the Grignard reagent **163**: A solution of 1-bromo-2-methylnaphthalene **162** (10 g, 45.2 mmol, 1 equiv.) in freshly distilled THF (20 mL) was prepared, and in a separate vessel, dry magnesium turnings (1.1 g, 45.2 mmol, 1 equiv.) and a crystal of iodine were heated under stirring whilst under an inert atmosphere. The bromide solution was added in small portions to the turnings until the reaction had begun, after which the solution was added at a rate so as to maintain a gentle reflux. The mixture was heated under gentle reflux for 2 h and then allowed to cool to room temperature. A solution of trimethyl borate (10.3 mL, 90.4 mmol, 2 equiv.) in dry THF (20 mL) was cooled to −78 °C, and the prepared Grignard reagent **163** transferred into it in small portions. The resulting mixture was allowed to gradually warm to room temperature, and stirred overnight. Dilute hydrochloric acid (2 M, 40 mL) was added to the reaction mixture and stirred for 30 minutes. This was extracted with diethyl

ether (3 x 50 mL) and the combined organic layers were dried, filtered, and the solvent removed. The off-white solid was recrystallised from toluene to give 2-methylnaphth-1-ylboronic acid **191** as an off-white powder (6.20 g, 71%). M.p. 91-93 °C; δ_H (400 MHz, $CDCl_3$) 7.83-7.73 (3H, m), 7.47- 7.38 (2H, m), 7.29 (1H, d, *J* 8.8), 4.94 (2H, bs, 2 x OH), 2.55 (3H, s, H_3-11); δ_C (100 MHz, $CDCl_3$) (C-1 is not observed), 138.36, 135.28, 131.52, 129.14, 128.55, 128.51, 127.63, 126.51, 125.22, 22.59 (C-11).

(ii) Via alternative method using n-*butyllithium;*

Adapting the procedure described by Gray et al.[3] a solution of 1-bromo-2-methylnaphthalene **162** (4.42 g, 20 mmol, 1 equiv.) in freshly distilled THF (40 mL) was prepared and cooled to −78 °C under argon. *n*-Butyllithium (2.5 M in hexane, 8.8 mL, 22 mmol, 1.1 equiv.) was added dropwise to the solution and the mixture stirred for 1 h at −78 °C. This was then transferred dropwise via canula to a separate flask containing anhydrous trimethyl borate (4.16 g, 40 mmol, 2 equiv.) at −78 °C, and stirred for 1 h. After this time the mixture was allowed to gradually warm to room temperature overnight. Dilute hydrochloric acid (2 M, 20 mL) was added to the mixture, and stirred for 30 minutes. This was then extracted with diethyl ether (4 x 30 mL) and the combined organic layers dried, filtered and removed of solvent. The off-white solid was recrystallised from toluene to give 2-methylnaphth-1ylboronic acid **191** (3.04 g, 82%). (Data as above).

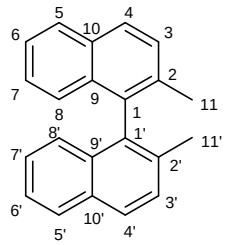
Preparation of 2-methylnaphth-1-yl(ethylene glycol)boronate ester 172



Adapting the procedure described by Cammidge and Crépy[4] for the synthesis of the title compound, a solution of 2-methylnaphth-1-ylboronic acid **191** (2.0 g, 10.76 mmol, 1 equiv.) in dry toluene (25 mL) was prepared, and ethylene glycol (0.74 g, 11.84 mmol, 1.1 equiv.) added to it. The mixture was heated under reflux for 2 h, after which the mixture was allowed to cool to room temperature and left to stir

overnight. The solvent was removed under vacuum and DCM (20 mL) added to the residue. Water (20 mL) was then added and the layers separated. The aqueous layer was extracted with DCM (2 x 20 mL), and the organic layers combined and dried. The solution was filtered and removed of solvent, leaving a yellow oil. After leaving at 5 °C overnight the oil solidified giving the boronate ester product **172** as an off-white solid (2.01 g, 91%). M.p. 51 °C; R_f 0.4 (DCM); δ_H (400 MHz, $CDCl_3$) 8.13 (1H, d, *J* 8.4), 7.77 (2H, d, *J* 8.4), 7.46-7.36 (2H, m), 7.30 (1H, d, *J* 8.4), 4.54 (4H, s, H_2-12 and H_2-13), 2.63 (3H, s, H_3-11); δ_C (100 MHz, $CDCl_3$) (C-1 is not observed) 142.34, 136.95, 131.64, 130.22, 128.87, 128.45, 128.09, 126.38, 125.00, 66.13 (C-12 and C-13), 23.28 (C-11).

3.3 Symmetric Suzuki coupling reactions towards 2,2'-dimethyl-1,1'-binaphthalene



(i) Using conditions described by Crépy;[2]

All of the solid reagents, 2-methylnaphth-1-yl(ethylene glycol)boronate ester **172** (0.26 g, 1.24 mmol, 1.5 equiv.), palladium chloride (3.5 mg, 0.02 mmol, 3 mol%), triphenylphosphine (10.5 mg, 0.04 mmol, 6 mol%) and cesium fluoride (0.35 g, 2.28 mmol, 1.5 equiv.) were placed in a flame-dried flask, under an atmosphere of argon. A solution of 1-iodo-2-methylnaphthalene **171** (0.22 g, 0.83 mmol, 1 equiv.) in freshly distilled DME (10 mL) was prepared separately, and injected into the flask containing the dry reagents. The mixture was then heated to reflux under argon for 6 days (adding fresh Pd-catalyst every 24 h). After this time the mixture was allowed to cool to room temperature, and DCM (30 mL) added. This was transferred to a separating funnel and shaken with water (30 mL). The layers were separated and the aqueous layer extracted with further portions of DCM (2 x 30 mL). The combined organic layers were washed with a final portion of water (30 mL) and dried. The solution was filtered, and the solvent removed. Purification by column

chromatography on silica eluting with 10:1 hexane/DCM isolated racemic 2,2'-dimethyl-1,1'-binaphthalene **165** as a viscous pale yellow oil[2] (0.05 g, 37%). R_f 0.4 (10:1 hexane/DCM); δ_H (400 MHz, $CDCl_3$) 7.91-7.86 (4H, m), 7.52 (2H, d, *J* 8.4), 7.40 (2H, t, *J* 7.4), 7.21 (2H, t, *J* 7.6), 7.06 (2H, d, *J* 8.4, H-3 and H-3'), 2.04 (6H, s, H_3-11 and H_3-11'); δ_C (75 MHz, $CDCl_3$) 135.37, 134.52, 133.01, 132.46, 128.94, 128.15, 127.65, 126.30, 125.86, 125.10, 20.05 (C-11 and C-11').

(ii) Via alternative conditions using sodium 2-methylnaphth-1-ylborate salt **219***, 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) and toluene as solvent;*

Sodium 2-methylnaphth-1-ylborate salt **219** (1.09 g, 4.8 mmol, 1.6 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (95 mg, 0.116 mmol, 4 mol%) were placed in a flame-dried flask, and freshly distilled toluene (40 mL) added. 1-Iodo-2-methylnaphthalene **171** (0.78 g, 2.9 mmol, 1 equiv.) was injected into the mixture, which was then heated to reflux for 48 h under an atmosphere of argon. After this time the black mixture was allowed to cool to room temperature, and diluted with DCM (50 mL). This was transferred to a separating funnel and water (50 mL) added. The two layers were separated and the aqueous layer extracted further with DCM (2 x 50 mL). The organic layers were combined, washed with a final portion of water (50 mL), separated, and dried. The solution was filtered and removed of solvent to give a brown oil. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to unreacted iodide starting material **171** and deboronated side-product (2-methylnaphthalene **190**) with only traces of coupled product **165**.

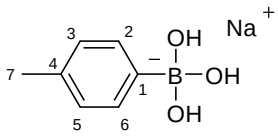
3.4 Preparation of sodium trihydroxyarylborate salts

General procedure[5]

The corresponding arylboronic acid was dissolved in a minimum amount of hot toluene (~100 mL) under stirring. Once completely dissolved, saturated aqueous sodium hydroxide solution (~12 mL) was added dropwise to the hot solution until no further precipitation was observed. The mixture was allowed to stir for 30 minutes after which the white precipitate was filtered and washed with toluene. The solid was

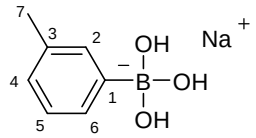
firstly placed under high vacuum for 48 h, then crushed to a fine powder and dried in a desiccator over silica. The remaining white solid was used without further purification.

Preparation of sodium 4-methylphenylborate salt 195



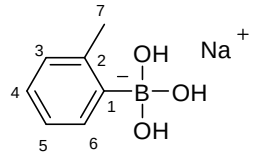
Sodium 4-methylphenylborate salt **195** was prepared from 4-methylphenylboronic acid **42** (2.04 g, 15 mmol) following the general procedure (2.51 g, 95%). (M.p. above 300 °C). δ_H (400 MHz, D_2O ref. CH_3CN) 7.47 (2H, d, *J* 7.6, H-2, H-6) 7.15 (2H, d, *J* 7.6, H-3, H-5), 2.29 (3H, s, H_3-7); δ_C (75 MHz, D_2O ref. CH_3CN) (C-1 is not observed) 135.91, 132.16, 128.61, 20.86 (C-7).

Preparation of sodium 3-methylphenylborate salt 197



Sodium 3-methylphenylborate salt **197** was prepared from 3-methylphenylboronic acid **196** (2.04 g, 15 mmol) following the general procedure (2.56 g, 98%). δ_H (400 MHz, D_2O ref. CH_3CN) 7.39 (1H, s, H-2), 7.35 (1H, d, *J* 7.2, H-6), 7.21 (1H, t, *J* 7.2, H-5), 7.05 (1H, d, *J* 7.2, H-4), 2.30 (3H, s, H_3-7); δ_C (75 MHz, D_2O ref. CH_3CN) (C-1 is not observed) 137.54, 132.75, 129.00, 128.24, 127.12, 21.57 (C-7).

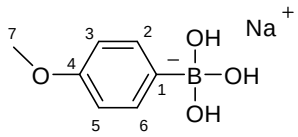
Preparation of sodium 2-methylphenylborate salt 198



Sodium 2-methylphenylborate salt **198** was prepared from 2-methylphenylboronic acid **131** (2.04 g, 15 mmol) following the general procedure

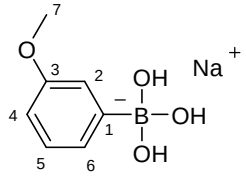
(2.55 g, 97%). δ_H (400 MHz, D_2O ref. CH_3CN) 7.54 (1H, d, *J* 5.2, H-6), 7.13 (3H, m, H-3, H-4 and H-5), 2.45 (3H, s, H_3-7); δ_C (75 MHz, D_2O ref. CH_3CN) (C-1 is not observed) 142.02, 132.54, 130.29, 126.73, 124.99, 22.43 (C-7).

Preparation of sodium 4-methoxyphenylborate salt 200



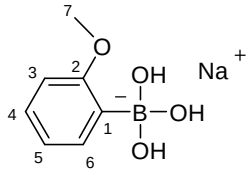
Sodium 4-methoxyphenylborate salt **200** was prepared from 4-methoxyphenylboronic acid **199** (2.00 g, 13 mmol) following the general procedure (2.41 g, 96%). δ_H (400 MHz, D_2O ref. CH_3CN) 7.50 (2H, d, *J* 8.4), 6.92 (2H, d, *J* 8.4), 3.82 (3H, s, H_3-7); δ_C (75 MHz, D_2O ref. CH_3CN) (C-1 is not observed) 157.76, 133.24, 113.56, 55.86 (C-7).

Preparation of sodium 3-methoxyphenylborate salt 202



Sodium 3-methoxyphenylborate salt **202** was prepared from 3-methoxyphenylboronic acid **201** (2.00 g, 13 mmol) following the general procedure (2.43 g, 97%). δ_H (400 MHz, D_2O ref. CH_3CN) 7.27 (1H, t, *J* 7.6, H-5), 7.19 (1H, d, *J* 7.6, H-6) 7.16 (1H, s, H-2) 6.82 (1H, d, *J* 7.6, H-4) 3.84 (3H, s, H_3-7); δ_C (75 MHz, D_2O ref. CH_3CN) (C-1 is not observed) 158.72, 129.32, 125.10, 117.31, 111.83, 55.83 (C-7).

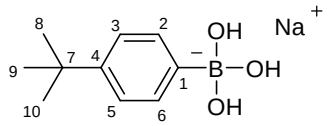
Preparation of sodium 2-methoxyphenylborate salt 204



Sodium 2-methoxyphenylborate salt **204** was prepared from 2-methoxyphenylboronic acid **203** (2.00 g, 13 mmol) following the general procedure

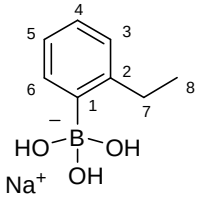
(2.42 g, 97%). δ_H (400 MHz, D_2O ref. CH_3CN) 7.46 (1H, d, *J* 6.8, H-6), 7.25 (1H, t, *J* 7.6, H-4), 6.98-6.94 (2H, m, H-3 and H-5), 3.82 (3H, s, H_3-7); δ_C (75 MHz, D_2O ref. CH_3CN) (C-1 is not observed) 162.75, 133.36, 128.18, 121.33, 110.90, 55.73 (C-7).

Preparation of sodium 4-*tert*-butylphenylborate salt 206



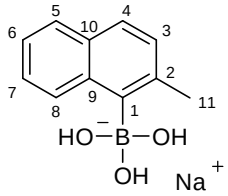
Sodium 4-*tert*-butylphenylborate salt **206** was prepared from 4-*tert*-butylphenylboronic acid **205** (2.31 g, 13 mmol) following the general procedure (2.76 g, 98%). δ_H (400 MHz, D_2O ref. CH_3CN) 7.53 (2H, d, *J* 8.0, H-2 and H-6), 7.40 (2H, d, *J* 8.0, H-3 and H-5), 1.30 (9H, s, H_3-8, H_3-9 and H_3-10); δ_C (75 MHz, D_2O ref. CH_3CN) (C-1 is not observed) 149.58, 132.16, 124.81, 34.29, 31.29 (C-8, C-9 and C-10).

Preparation of sodium 2-ethylphenylborate salt 207



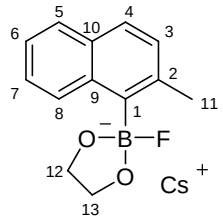
Sodium 2-ethylphenylborate salt **207** was prepared from 2-ethylphenylboronic acid **175** (2.0 g, 13.3 mmol) following the general procedure (2.52 g, 99%). δ_H (400 MHz, D_2O ref. CH_3CN) 7.44 (1H, d, *J* 7.2, H-6), 7.12-7.04 (2H, m), 6.99 (1H, t, *J* 7.2), 2.76 (2H, q, *J* 7.6, H_2-7), 1.10 (3H, t, *J* 7.6, H_3-8); δ_C (75 MHz, D_2O ref. CH_3CN) (C-1 is not observed) 147.51, 131.85, 127.30, 125.76, 123.89, 27.15 (C-7), 15.67 (C-8).

Preparation of sodium 2-methylnaphth-1-ylborate salt 219



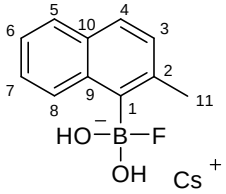
Sodium 2-methylnaphth-1-ylborate salt **219** was prepared from 2-methylnaphth-1-ylboronic acid **191** (2.00 g, 10.7 mmol) following the general procedure (2.39 g, 99%). δ_H (400 MHz, D_2O ref. CH_3CN) 7.92 (1H, d, *J* 8.0, H-8), 7.87 (1H, d, *J* 8.0, H-5), 7.75 (1H, d, *J* 8.4, H-4), 7.54-7.44 (2H, m), 7.39 (1H, d, *J* 8.4, H-3), 2.53 (3H, s, H_3-11); δ_C (75 MHz, D_2O ref. CH_3CN) (C-1 is not observed) 136.92, 135.66, 131.66, 129.61, 129.17, 128.61, 126.92, 126.15, 125.26, 22.67 (C-11).

Attempted preparation and isolation of cesium fluoro(ethylene glycol)-2-methylnaphth-1-ylboronate salt 222



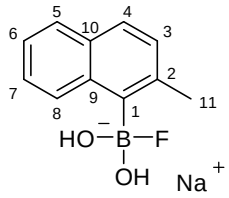
2-Methylnaphth-1-yl(ethylene glycol)boronate ester **172** (0.5 g, 2.36 mmol) was dissolved in hot toluene (30 mL) under stirring. Once completely dissolved, saturated aqueous cesium fluoride solution (2.5 mL) was added dropwise to the hot solution. The mixture was allowed to stir for 1 h however after this time no precipitate had formed.

Attempted preparation and isolation of cesium fluorodihydroxy-2-methylnaphth-1-ylborate salt 223



2-Methylnaphth-1-ylboronic acid **191** (0.5 g, 2.69 mmol) was dissolved in hot toluene (30 mL) under stirring. Once completely dissolved, saturated aqueous cesium fluoride solution (2.5 mL) was added dropwise to the hot solution. The mixture was allowed to stir for 1 h however after this time no precipitate had formed.

Attempted preparation and isolation of sodium fluorodihydroxy-2-methylnaphth-1-ylborate salt 224



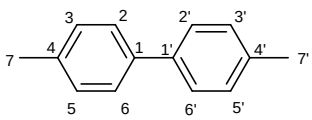
2-Methylnaphth-1-ylboronic acid **191** (0.5 g, 2.69 mmol) was dissolved in hot toluene (30 mL) under stirring. Once completely dissolved, saturated aqueous sodium fluoride solution (3 mL) was added dropwise to the hot solution. The mixture was allowed to stir for 1 h however after this time no precipitate had formed.

3.5 Suzuki coupling reactions using sodium trihydroxyarylborate salts as the organoboron coupling partner

General procedure[5]

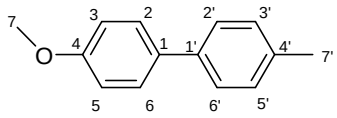
The sodium trihydroxyarylborate salt (2 equiv.), aryl halide (1 equiv.) and palladium catalyst, 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (4 mol%) were added to a flask equipped with a stirrer bar and Liebig condenser. Freshly distilled toluene (30 mL) was added and the mixture heated to reflux under nitrogen for 24 h (or for 48 h where indicated). After this time the reaction mixture was allowed to cool to room temperature and diluted with DCM (50 mL). This was transferred to a separating funnel and water (50 mL) added. The two layers were separated and the aqueous layer extracted further with DCM (2 x 50 mL). The organic layers were combined, washed with a final portion of water (50 mL), separated, and dried over Na_2SO_4. The solution was then filtered, removed of solvent under reduced pressure and purified by column chromatography over silica.

Suzuki coupling to give 4,4'-dimethylbiphenyl 209



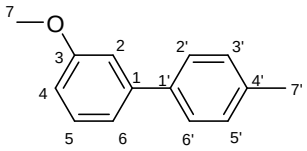
Sodium 4-methylphenylborate salt **195** (1.02 g, 5.8 mmol, 2 equiv.), 4-bromotoluene **208** (0.5 g, 2.9 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (95 mg, 0.116 mmol, 4 mol%) were heated to reflux in toluene (30 mL) for 24 h according to the general procedure. After work-up the crude material was passed through a short column of silica to isolate 4,4'-dimethylbiphenyl **209** as a white crystalline solid (0.44 g, 83%) with spectral data consistent with literature values.[6] M.p. 119 °C; R_f 0.76 (10:1 pet. ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.48 (4H, d, *J* 8.0, H-2, H-2', H-6 and H-6'), 7.24 (4H, d, *J* 8.0, H-3, H-3', H-5 and H-5'), 2.39 (6H, s, H_3-7 and H_3-7'); δ_C (100 MHz, $CDCl_3$) 138.50, 136.93, 129.66, 127.04, 21.32 (C-7 and C-7').

Suzuki coupling to give 4-methoxy-4'-methylbiphenyl 210



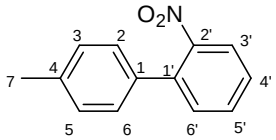
Sodium 4-methoxyphenylborate salt **200** (1.11 g, 5.8 mmol, 2 equiv.), 4-bromotoluene **208** (0.5 g, 2.9 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (95 mg, 0.116 mmol, 4 mol%) were heated to reflux in toluene (30 mL) for 24 h according to the general procedure. After work-up purification was achieved by passing the crude mixture through a short column of silica to give 4-methoxy-4'-methylbiphenyl **210** as an off-white crystalline solid (0.41 g, 72%). Spectral data were consistent with literature values.[7] M.p. 104-106 °C; R_f 0.56 (10:1 pet. ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.52 (2H, d, *J* 8.8, H-2 and H-6), 7.46 (2H, d, *J* 8.0, H-2' and H-6'), 7.24 (2H, d, *J* 8.0, H-3' and H-5'), 6.98 (2H, d, *J* 8.8, H-3 and H-5), 3.85 (3H, s, H_3-7), 2.39 (3H, s, H_3-7'); δ_C (100 MHz, $CDCl_3$) 159.13, 138.17, 136.58, 133.96, 129.65, 128.17, 126.81, 114.37, 55.57 (C-7), 21.28 (C-7').

Suzuki coupling to give 3-methoxy-4'-methylbiphenyl 211



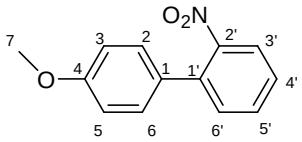
Sodium 3-methoxyphenylborate salt **201** (1.11 g, 5.8 mmol, 2 equiv.), 4-bromotoluene **208** (0.5 g, 2.9 mmol, 1 equiv.), and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (95 mg, 0.116 mmol, 4 mol%) were heated to reflux in toluene (30 mL) for 24 h according to the general procedure. After work-up purification by column chromatography on silica eluting with 10:1 hexane/DCM gave 3-methoxy-4'-methylbiphenyl **211** as a colourless oil (0.45 g, 79%). Spectral data were in agreement with literature values.[8] R_f 0.57 (10:1 pet. ether/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.49 (2H, d, *J* 8.0, H-2' and H-6'), 7.34 (1H, t, *J* 7.6, H-5), 7.24 (2H, d, *J* 7.6, H-3' and H-5'), 7.17 (1H, d, *J* 8.0, H-6) 7.11 (1H, s, H-2), 6.87 (1H, d, *J* 8.0, H-4), 3.85 (3H, s, H_3-7), 2.39 (3H, s, H_3-7'); δ_C (100 MHz, $CDCl_3$) 160.13, 142.92, 138.43, 137.45, 129.93, 129.68, 127.26, 119.74, 112.93, 112.60, 55.51 (C-7), 21.35 (C-7').

Suzuki coupling to give 4-methyl-2'-nitrobiphenyl 212



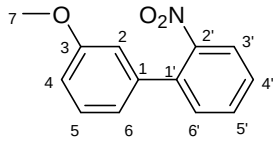
Sodium 4-methylphenylborate salt **195** (1.02 g, 5.8 mmol, 2 equiv.), 1-bromo-2-nitrobenzene **177** (0.59 g, 2.9 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (95 mg, 0.116 mmol, 4 mol%) were heated to reflux in toluene (30 mL) for 24 h according to the general procedure. After work-up purification by column chromatography on silica eluting with 8:1 hexane/DCM isolated 4-methyl-2'-nitrobiphenyl **212** as a yellow oil (0.40 g, 69%). R_f 0.13 (8:1 hexane/DCM); υ_{max} (ATR)/cm^{-1} 1518 and 1351 (nitro); δ_H (400 MHz, $CDCl_3$) 7.83 (1H, d, *J* 8.0, H-3'), 7.61 (1H, t, *J* 7.6, H-5'), 7.49-7.43 (2H, m, H-4' and H-6'), 7.27-7.21 (4H, m, H-2, H-3, H-5 and H-6), 2.41 (3H, s, H_3-7); δ_C (100 MHz, $CDCl_3$) (C-2' is not observed) 138.40, 136.49, 134.61, 132.43, 132.16, 129.69, 128.14, 127.97, 124.25, 21.48 (C-7); *m/z* (CI) 231 ($M+NH_4^+$, 100%); HRMS (CI): Found: 231.1130. $C_{13}H_{15}O_2N_2$ ($M+NH_4^+$) Requires 231.1128.

Suzuki coupling to give 4-methoxy-2'-nitrobiphenyl 213



Sodium 4-methoxyphenylborate salt **200** (1.11 g, 5.8 mmol, 2 equiv.), 1-bromo-2-nitrobenzene **177** (0.59 g, 2.9 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (95 mg, 0.116 mmol, 4 mol%) were heated to reflux in toluene (30 mL) for 24 h according to the general procedure. After work-up purification by column chromatography on silica eluting with 2:1 hexane/DCM isolated the 4-methoxy-2'-nitrobiphenyl **213** as a yellow oil (0.41 g, 62%). R_f 0.34 (1:1 hexane/DCM); υ_{max} (ATR)/cm^{-1} 1518 and 1354 (nitro), 1244 and 1034 (aryl ether); δ_H (400 MHz, $CDCl_3$) 7.81 (1H, d, *J* 8.0, H-3'), 7.59 (1H, t, *J* 7.6, H-5'), 7.47-7.43 (2H, m, H-4' and H-6') 7.28-7.24 (2H, m), 6.96 (2H, d, *J* 7.6), 3.85 (3H, s, H_3-7); δ_C (100 MHz, $CDCl_3$) 159.90, 149.62, 136.07, 132.37, 132.14, 129.70, 129.34, 127.95, 124.23, 114.44, 55.53 (C-7); *m/z* (EI) 229 (M^+, 58%), 139 (100); HRMS (CI): Found: 247.1076. $C_{13}H_{15}O_3N_2$ ($M+NH_4^+$) Requires 247.1077.

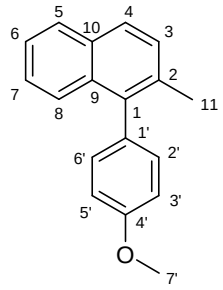
Suzuki coupling to give 3-methoxy-2'-nitrobiphenyl 214



Sodium 3-methoxyphenylborate salt **201** (1.11 g, 5.8 mmol, 2 equiv.), 1-bromo-2-nitrobenzene **177** (0.59 g, 2.9 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (95 mg, 0.116 mmol, 4 mol%) were heated to reflux in toluene (30 mL) for 24 h according to the general procedure. After work-up purification by column chromatography on silica eluting with 4:1 hexane/DCM isolated the product **214** as a crystalline yellow solid (0.35 g, 53%). M.p. 65-68 °C; R_f 0.30 (2:1 hexane/DCM); υ_{max} (ATR)/cm^{-1} 1521 and 1351 (nitro), 1220 and 1021 (aryl ether); δ_H (400 MHz, $CDCl_3$) 7.84 (1H, d, *J* 8.0, H-3'), 7.60 (1H, t, *J* 7.6, H-5'), 7.50-7.43 (2H, m, H-4' and H-6'), 7.33 (1H, t, *J* 8.0, H-5), 6.94 (1H, d, *J* 8.0, H-6), 6.89 (1H, d, *J* 8.0, H-4), 6.86 (1H, s, H-2) 3.83 (3H, s, H_3-7); δ_C (75 MHz, $CDCl_3$) 160.39, 150.02, 139.32, 136.79, 132.80, 132.46, 130.36, 128.83, 124.57,

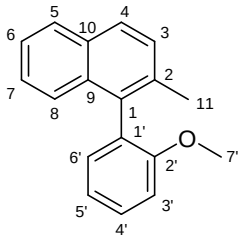
120.90, 114.36, 114.27, 55.78 (C-7); *m/z* (CI) 247 ($M+NH_4^+$, 100%); HRMS (CI): Found: 247.1078. $C_{13}H_{15}O_3N_2$ ($M+NH_4^+$) Requires 247.1077.

Suzuki coupling to give 1-(4'-methoxyphenyl)-2-methylnaphthalene 215



Sodium 4-methoxyphenylborate salt **200** (1.11 g, 5.8 mmol, 2 equiv.), 1-bromo-2-methylnaphthalene **162** (0.64 g, 2.9 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (95 mg, 0.116 mmol, 4 mol%) were heated to reflux in toluene (30 mL) for 24 h according to the general procedure. The brown solid remaining after work-up contained the coupled product **215** and traces of unreacted bromide starting material **162**. Purification by column chromatography over silica eluting with 10:1 hexane/DCM isolated 1-(4'-methoxyphenyl)-2-methylnaphthalene **215** as a crystalline off-white solid (0.43 g, 60%). Spectral data were in agreement with literature values.[9] M.p. 96-98 °C; R_f 0.44 (2:1 hexane/DCM); υ_{max} (ATR)/cm^{-1} 1239 and 1031 (aryl ether); δ_H (400 MHz, $CDCl_3$) 7.83 (1H, d, *J* 8.0, H-8), 7.76 (1H, d, *J* 8.0, H-5), 7.46-7.29 (4H, m, H-3, H-4, H-6 and H-7), 7.19 (2H, d, *J* 8.0, H-2'and H-6'), 7.04 (2H, d, *J* 8.0, H-3'and H-5'), 3.90 (3H, s, H_3-7'), 2.25 (3H, s, H_3-11); δ_C (100 MHz, $CDCl_3$) 158.81, 138.06, 133.72, 133.51, 132.20, 132.14, 131.42, 128.85, 127.96, 127.29, 126.41, 125.96, 124.91, 114.02, 55.52 (C-7'), 21.12 (C-11); *m/z* (EI) 248 (M^+, 100%); HRMS (EI): Found: 248.1195. $C_{18}H_{16}O$ (M^+) Requires 248.1196.

Suzuki coupling to give 1-(2'-methoxyphenyl)-2-methylnaphthalene 216



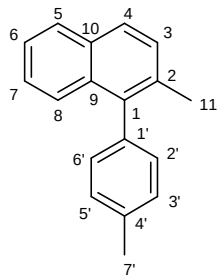
Sodium 2-methoxyphenylborate salt **204** (1.11 g, 5.8 mmol, 2 equiv.), 1-bromo-2-methylnaphthalene **162** (0.64 g, 2.9 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (95 mg, 0.116 mmol, 4 mol%) were heated to reflux in toluene (30 mL) for 24 h according to the general procedure. The brown oil that remained after work-up contained the title compound **216** and unreacted bromide starting material **162**. Purification by column chromatography over silica eluting with 5:1 hexane/DCM gave 1-(2'-methoxyphenyl)-2-methylnaphthalene **216** as a viscous colourless oil (0.42 g, 58%). Spectral data were consistent with literature values.[10] R_f 0.2 (3:1 hexane/DCM); υ_{max} (ATR)/cm^{-1} 1245 and 1024 (aryl ether); δ_H (400 MHz, $CDCl_3$) 7.82 (1H, d, *J* 8.0, H-8), 7.77 (1H, d, *J* 8.4, H-5), 7.45-7.27 (5H, m), 7.15-7.03 (3H, m), 3.67 (3H, s, H_3-7'), 2.21 (3H, s, H_3-11); δ_C (100 MHz, $CDCl_3$) 157.59, 134.89, 134.17, 133.17, 132.23, 132.06, 129.07, 128.78, 128.48, 128.08, 127.48, 126.16, 125.93, 124.85, 120.92, 111.35, 55.80 (C-7'), 20.78 (C-11); *m/z* (EI) 248 (M^+, 100%); HRMS (CI): Found: 266.1538. $C_{18}H_{20}NO$ ($M+NH_4^+$) Requires 266.1539.

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Heptane/EtOH	Flowrate (mL/min)	t_R of 1st isomer[b] (min)	t_R of 2nd isomer[b] (min)	Ratio of isomers
216	OJ[a]	70/30	0.5	4.8	5.6	44:56

[a] Chiralcel OJ column by Daicel Chemical Ind., Ltd. [b] Detected at 215 nm.

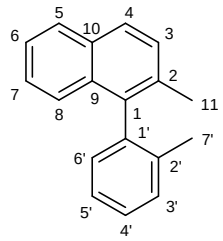
Suzuki coupling to give 1-(4'-methylphenyl)-2-methylnaphthalene 217



Sodium 4-methylphenylborate salt **195** (0.77 g, 4.37 mmol, 2 equiv.), 1-bromo-2-methylnaphthalene **162** (0.48 g, 2.18 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (71 mg, 0.087 mmol, 4 mol%)

were heated to reflux in toluene (30 mL) for 24 h according to the general procedure. The brown oil that remained after work-up contained the title product **217** and traces of unreacted bromide starting material **162**. Purification by column chromatography over silica eluting with neat hexane gave the product **217** as colourless oil (0.24 g, 48%). Spectral data were in agreement with literature values.[11] R_f 0.46 (10:1 hexane/DCM); δ_H (400 MHz, $CDCl_3$) 7.83 (1H, d, *J* 8.0, H-8), 7.77 (1H, d, *J* 8.0, H-5), 7.45-7.37 (3H, m), 7.34-7.30 (3H, m), 7.16 (2H, d, *J* 8.0, H-3' and H-5'), 2.47 (3H, s, H_3-7'), 2.25 (3H, s, H_3-11); δ_C (75 MHz, $CDCl_3$) 138.97, 137.51, 137.26, 133.93, 133.89, 132.77, 130.78 (C-3', C-5'), 129.85 (C-2', C-6'), 129.36, 128.48 (C-8), 127.84 (C-5), 126.98, 126.46, 125.43, 21.86 (C-7'), 21.41 (C-11); *m/z* (EI) 232 (M^+, 100%).

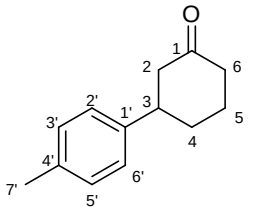
Suzuki coupling to give 1-(2'-methylphenyl)-2-methylnaphthalene 218



Sodium 2-methylphenylborate salt **198** (1.02 g, 5.8 mmol, 2 equiv.), 1-bromo-2-methylnaphthalene **162** (0.64 g, 2.9 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (95 mg, 0.116 mmol, 4 mol%) were heated to reflux in toluene (30 mL) for 48 h according to the general procedure. Purification of the brown oil obtained after work-up was achieved by column chromatography over silica eluting with neat hexane. 1-(2'-Methylphenyl)-2-methylnaphthalene **218** was isolated as a colourless oil (0.30 g, 45%). Spectral data were consistent with literature values.[12] R_f 0.3 (8:1 hexane/DCM); δ_H (400 MHz, $CDCl_3$) 7.83 (1H, d, *J* 8.0, H-8), 7.78 (1H, d, *J* 8.4, H-5), 7.44-7.21 (7H, m), 7.12 (1H, d, *J* 7.6, H-3'), 2.16 (3H, s, H_3-11), 1.91 (3H, s, H_3-7'); δ_C (100 MHz, $CDCl_3$) 139.45, 137.74, 137.05, 133.31, 132.81, 132.25, 130.27, 130.21, 128.81, 128.04, 127.62, 127.32, 126.16, 126.10, 125.95, 124.96, 20.33 (C-11), 19.55 (C-7').

3.6 Rhodium-catalysed 1,4-addition reaction

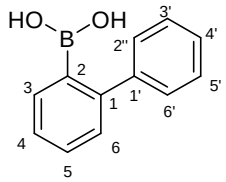
1,4-Addition to give 3-(4-methylphenyl)cyclohexanone 221



Adapting the experimental procedure described by Miyaura et al. for synthesis of the title compound,[13] the reaction solvent 1,4-dioxane/water (12:2 mL) was firstly degassed with argon for ca. 30 minutes, then sodium 4-methylphenylborate salt **195** (0.74 g, 4.2 mmol, 1.5 equiv.) and chloro(1,5-cyclooctadiene)rhodium(I) dimer (40 mg, 0.08 mmol, 3 mol%) added. The mixture was allowed to stir for 20 minutes at room temperature after which 2-cyclohexenone **220** (0.27 g, 2.8 mmol, 1 equiv.) was added dropwise to the flask. The mixture was left to stir at room temperature for a further 16 h. After this time dilute hydrochloric acid (1 M, 10 mL) was added to the reaction mixture which was then extracted with toluene (2 x 20 mL). The combined organic layers were combined, dried, filtered and removed of solvent to give the product **221** as an orange oil (0.412 g, 78%). No further purification steps were performed as the spectral data were consistent with literature values.[13] δ_H (400 MHz, $CDCl_3$) 7.16-7.10 (4H, m, H-2', H-3', H-5' and H-6'), 2.98 (1H, tt, *J* 11.2 and 4.4, H-3), 2.62-2.35 (4H, m, H_2-2 and H_2-6), 2.33 (3H, s, H_3-7') 2.19-2.02 (2H, m, H_2-4), 1.89-1.70 (2H, m, H_2-5); δ_C (100 MHz, $CDCl_3$) 211.14, 141.29, 136.11, 129.20, 126.31, 48.97, 44.26, 41.08, 32.77, 25.43, 20.86.

3.7 Preparation of additional organoboron reagents

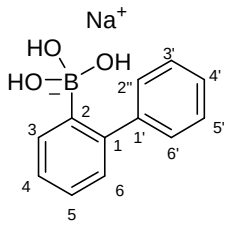
Synthesis of 2-biphenylboronic acid 231



A solution of 2-bromobiphenyl **229** (2.10 g, 9.0 mmol, 1 equiv.) in dry THF (20 mL) was prepared and cooled to −78 °C under argon. *n*-Butyllithium (2.5 M in

hexane, 4.0 mL, 9.9 mmol, 1.1 equiv.) was added dropwise to the solution, and the mixture stirred at −78 °C for 15 minutes. After this time, trimethylborate (1.88 g, 18.0 mmol, 2 equiv.) was added in one portion to the flask, and stirred for 1 h at −78 °C. The mixture was then allowed to warm gradually to room temperature overnight. Dilute hydrochloric acid (2 M, 20 mL) was added and the mixture stirred for 30 minutes. This was then extracted with diethyl ether (3 x 20 mL) and the combined organic layers were dried, filtered, and removed of solvent. Addition of hexane (10 mL) to the oily residue resulted in the formation of a solid precipitate which was filtered and washed with ice-cold hexane. This was dried to give the pure product **231** as a white solid (0.85 g, 48%). Spectral data were in agreement with literature values.[14] M.p. 123-125 °C; δ_H (400 MHz, $CDCl_3$) 7.93 (1H, d, *J* 7.2), 7.52-7.38 (7H, m), 7.31 (1H, d, *J* 7.2), 4.34 (2H, s, 2 x OH); δ_C (75 MHz, $CDCl_3$) (C-2 is not observed) 147.56, 142.98, 135.37, 130.69, 129.63, 129.35, 129.08, 128.22, 127.22.

Synthesis of sodium 2-biphenylborate salt 232



2-Biphenylboronic acid **231** (0.62 g, 3.13 mmol) was dissolved in a minimum amount of hot toluene (40 mL) under stirring. Once completely dissolved, saturated aqueous sodium hydroxide solution (~6 mL) was added dropwise to the hot solution. The mixture was allowed to stir for 30 minutes after which the white precipitate was filtered off using a sintered glass funnel and washed with cold toluene. The solid was dried under vacuum and confirmed as the borate salt product **232** (0.76 g, 98%). δ_H (400 MHz, D_2O ref. CH_3CN) 7.73 (1H, d, *J* 6.4), 7.52-7.40 (5H, m), 7.36-7.12 (3H, m); δ_C (75 MHz, D_2O ref. CH_3CN) (C-1, C-1' and C-2 are not observed) 132.31, 128.59, 128.40, 127.91, 126.37, 125.91, 125.25.

3.8 Symmetric and asymmetric Suzuki reactions towards axially chiral biaryl compounds

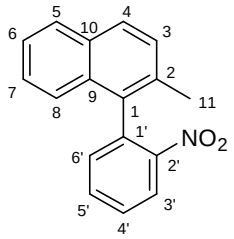
Original procedure:

To an oven-dried round-bottom flask capped with a rubber septum was added the base, organoboron reagent, ligand and catalyst, followed by the organohalide. (The flask was evacuated and purged with argon after each addition). Freshly distilled solvent was added, and the flask equipped with a Liebig condenser. The mixture was heated to reflux for the specified amount of time under argon. After this the crude reaction mixture was allowed to cool to room temperature, diluted with DCM (30 mL), and shaken with water (30 mL). The layers were separated, and the aqueous layer extracted with further portions of DCM (2 x 30 mL). The organic layers were combined, dried over sodium sulfate, filtered, and removed of solvent. The crude material was purified by column chromatography over silica.

Alternative protocol using a sealed pressure tube:

A thick-walled Ace® pressure tube was equipped with a stirrer bar, capped with a rubber septum, flame-dried and allowed to relax under argon. The solid reagents i.e. boronate ester or sodium borate salt, palladium chloride, ligand (and base, if required) were added, with the tube evacuated and backfilled with argon after each addition. Any liquid reagents such as organohalide were added via syringe, followed by freshly distilled solvent. The tube was then sealed tightly with a Teflon® screw-cap and heated in a pre-heated oil bath at the indicated temperature for the required time (24-48 h) under stirring. After this time the crude reaction mixture was allowed to cool to room temperature, and worked-up according to the standard protocol described above.

Symmetric Suzuki couplings towards 1-(2'-nitrophenyl)-2-methylnaphthalene 225



(i) Using boronate ester **172** *as the organoboron coupling partner;*

Cesium fluoride (0.37 g, 2.49 mmol, 3 equiv.) was added to an oven-dried round-bottom flask, followed by 2-methylnaphth-1-yl(ethylene glycol)boronate ester **172** (0.26 g, 1.24 mmol, 1.5 equiv.) triphenylphosphine (10.5 mg, 0.04 mmol, 6 mol%) and palladium chloride (3.5 mg, 0.02 mmol, 3 mol%). 1-Bromo-2-nitrobenzene **177** (0.17 g, 0.83 mmol, 1 equiv.) was added, followed by freshly distilled DME (10 mL). The flask was equipped with a Liebig condenser and the mixture heated to reflux for 48 h under argon. After this time the mixture was allowed to cool to room temperature, and worked-up according to the standard protocol. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to deboronated side-product (2-methylnaphthalene **190**). There were no peaks corresponding to the coupled product **225**.

(ii) Using sodium 2-methylnaphth-1-ylborate salt **219** *as the organoboron coupling partner;*

Sodium 2-methylnaphth-1-ylborate salt **219** (1.31 g, 5.8 mmol, 2 equiv.), 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (95 mg, 0.116 mmol, 4 mol%) and 1-bromo-2-nitrobenzene **177** (0.59 g, 2.9 mmol, 1 equiv.) were added to a dried round-bottom flask under argon. Freshly distilled toluene (30 mL) was added and the mixture heated to reflux for 24 h under stirring. After this time the black mixture was allowed to cool to room temperature, and worked-up according to the standard protocol. The brown oil that remained was purified by column chromatography over silica eluting with 10:1 hexane/DCM to give the product **225** as an orange oil (0.29 g, 38%). Spectral data were consistent with literature values.[15] R_f 0.3 (2:1 hexane/DCM); υ_{max} (ATR)/cm^{-1} 1520 and 1345 (nitro); δ_H (400 MHz, $CDCl_3$) 8.14

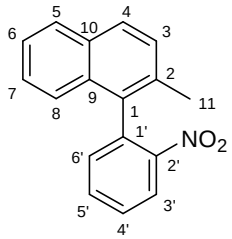
(1H, d, *J* 8.0), 7.86-7.79 (2H, m), 7.73 (1H, t, *J* 7.6), 7.63 (1H, t, *J* 8.0), 7.42-7.30 (4H, m), 7.14 (1H, d, *J* 8.0), 2.19 (3H, s, H_3-11); δ_C (100 MHz, $CDCl_3$) (C-2' not observed) 150.08, 134.98, 133.59, 133.25, 133.19, 132.43, 132.13, 128.89, 128.66, 128.33, 128.29, 126.58, 125.23, 125.09, 124.61, 20.53 (C-11); *m/z* (EI) 263 (M^+, 95%), 215 (100); HRMS (CI): Found: 281.1285. $C_{17}H_{17}O_2N_2$ ($M+NH_4^+$) Requires 281.1285.

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Heptane/EtOH	Flowrate (mL/min)	t_R of 1st isomer[b] (min)	t_R of 2nd isomer[b] (min)	Ratio of isomers
225	AS[a]	98/2	0.5	12.2	12.8	44:56

[a] Chiralpak AS column by Daicel Chemical Ind., Ltd. [b] Detected at 215 nm.

Asymmetric Suzuki coupling towards 1-(2'-nitrophenyl)-2-methylnaphthalene 225



Following the alternative protocol, sodium 2-methylnaphth-1-ylborate salt **219** (0.68 g, 3.0 mmol, 2 equiv.), 1-bromo-2-nitrobenzene **177** (0.30 g, 1.5 mmol, 1 equiv.), palladium chloride (8.0 mg, 0.045 mmol, 3 mol%) and *R*-(−)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine **180** (40 mg, 0.09 mmol, 6 mol%) were added to a flame-dried pressure tube. Freshly distilled toluene (15 mL) was added and the tube sealed and heated to 90 °C for 24 h, under stirring. After this time the mixture was allowed to cool to room temperature and worked-up according to the standard protocol. Analysis by ^{1}H NMR spectroscopy revealed significant peaks attributable to the coupled product **225**.[15] Purification of the crude mixture by column chromatography over silica eluting with 5:1 hexane/DCM gave the product **225** as a yellow crystalline solid (0.34 g, 45%). M.p. 84-89 °C; R_f 0.3 (2:1 hexane/DCM); υ_{max} (ATR)/cm^{-1} 1520 and 1345 (nitro); δ_H (400 MHz, $CDCl_3$) 8.14 (1H, d, *J* 8.0, H-3'),

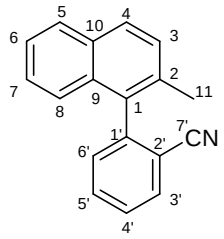
7.86-7.79 (2H, m, H-8, H-5), 7.73 (1H, t, *J* 7.6, H-5'), 7.63 (1H, t, *J* 8.0, H-4'), 7.42-7.30 (4H, m, H-4, H-6, H-7, H-6'), 7.14 (1H, d, *J* 8.0, H-3), 2.19 (3H, s, CH_3-11); δ_C (75 MHz, $CDCl_3$) (C-2' is not observed) 150.08, 135.00, 133.59, 133.25, 133.20, 132.43, 132.12, 128.88, 128.66, 128.34, 128.30, 126.58, 125.24, 125.09, 124.61, 20.53 (C-11); ee 34% (determined from chiral HPLC data).

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Heptane/EtOH	Flowrate (mL/min)	t_R of 1st isomer[b] (min)	t_R of 2nd isomer[b] (min)	Ratio of isomers
225	AS[a]	98/2	0.5	12.2	12.8	67:33

[a] Chiralpak AS column by Daicel Chemical Ind., Ltd. [b] Detected at 215 nm.

Symmetric Suzuki couplings towards 1-(2'-cyanophenyl)-2-methylnaphthalene 226



(i) Using sodium 2-methylnaphth-1-ylborate salt **219** *as the organoboron coupling partner and toluene as solvent;*

Following the alternative protocol, sodium 2-methylnaphth-1-ylborate salt **219** (0.68 g, 3.00 mmol, 2 equiv.), 2-bromobenzonitrile **228** (0.27 g, 1.50 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (50 mg, 0.06 mmol, 4 mol%) were added to a flame-dried pressure tube. Freshly distilled toluene (15 mL) was added and the tube sealed and heated to 90 °C for 48 h, under stirring. After this time the mixture was allowed to cool to room temperature and worked-up according to the standard protocol. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to deboronated side-product (2-methylnaphthalene **190**) and only a very small amount of coupled product **226**. No further purification steps were carried out.

(ii) Using sodium 2-methylnaphth-1-ylborate salt **219** *and DME as solvent;*

Following the alternative protocol, sodium 2-methylnaphth-1-ylborate salt **219** (0.68 g, 3.00 mmol, 2 equiv.), 2-bromobenzonitrile **228** (0.27 g, 1.50 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (50 mg, 0.06 mmol, 4 mol%) were added to a flame-dried pressure tube. Freshly distilled DME (15 mL) was added and the tube sealed and heated to 80 °C for 24 h, under stirring. After this time the mixture was allowed to cool to room temperature and worked-up according to the standard protocol. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to deboronated side-product (2-methylnaphthalene **190**) and only a small amount of coupled product **226**. No further purification steps were carried out.

(iii) Using 2-methylnaphth-1-yl(ethylene glycol)boronate ester **172** *as the organoboron coupling partner;*

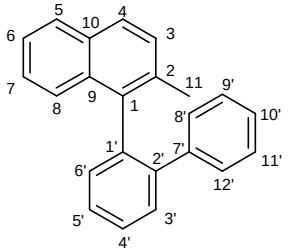
Following the alternative protocol, 2-methylnaphth-1-yl(ethylene glycol)boronate ester **172** (0.42 g, 2 mmol, 1.5 equiv.), 2-bromobenzonitrile **228** (0.24 g, 1.3 mmol, 1 equiv.), palladium chloride (9 mg, 0.05 mmol, 4 mol%), triphenylphosphine (26 mg, 0.1 mmol, 8 mol%) and cesium fluoride (0.61 g, 4 mmol, 3 equiv.) were added to a flame-dried pressure tube. Freshly distilled DME (15 mL) was added and the tube sealed and heated to 80 °C for 24 h, under stirring. After this time the mixture was allowed to cool to room temperature and worked-up according to the standard protocol. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed significant peaks attributable to the desired coupled product **226** and traces of deboronated side-product (2-methylnaphthalene **190**). Purification by column chromatography over silica eluting with 10:1→ 3:1 hexane/DCM gave the title product **226** as a white solid[16] (0.21 g, 68%). M.p. 88-92 °C; R_f 0.4 (5:1 pet. ether/ethyl acetate); υ_{max} (ATR)/cm^{-1} 2224 (nitrile); δ_H (400 MHz, $CDCl_3$) 7.88-7.84 (3H, m), 7.73 (1H, dt, *J* 7.6 and 1.2), 7.56 (1H, dt, *J* 7.6 and 1.2), 7.46-7.33 (4H, m) 7.15 (1H, d, *J* 8.8), 2.24 (3H, s, H_3-11); δ_C (100 MHz, $CDCl_3$) 144.26, 134.09, 134.04, 133.33, 132.99, 132.57, 132.21, 131.63, 128.96, 128.75, 128.33, 128.12, 126.67, 125.34, 125.20, 117.95, 114.32, 20.56 (C-11); *m/z* (EI) 243 (M^+, 100%); HRMS (CI): Found: 261.1387. $C_{18}H_{17}N_2$ ($M+NH_4^+$) Requires 261.1386

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Heptane/EtOH	Flowrate (mL/min)	t_R of 1st isomer[b] (min)	t_R of 2nd isomer[b] (min)	Ratio of isomers
226	AD[a]	98/2	0.3	19.2	20.2	48:52

[a] Chiralpak AD column by Daicel Chemical Ind., Ltd. [b] Detected at 215 nm.

Symmetric Suzuki couplings towards 1-(2'-biphenyl)-2-methylnaphthalene 227



(i) Using 2-methylnaphth-1-yl(ethylene glycol)boronate ester **172** *and 2-bromobiphenyl* **229***;*

2-Methylnaphth-1-yl(ethylene glycol)boronate ester **172** (0.42 g, 2 mmol, 1.5 equiv.), triphenylphosphine (26 mg, 0.1 mmol, 8 mol%), palladium chloride (9 mg, 0.05 mmol, 4 mol%) and cesium fluoride (0.61 g, 4 mmol, 3 equiv.) were added to a flame-dried pressure tube followed by 2-bromobiphenyl **229** (0.31 g, 1.3 mmol, 1 equiv.) via syringe. Freshly distilled DME (15 mL) was added and the tube sealed and heated to 80 °C for 24 h, under stirring. After this time the mixture was allowed to cool to room temperature and worked-up according to the standard protocol. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to boronate ester starting material **172**, 2-bromobiphenyl starting material **229** and only a small amount of coupled product **227**.

(ii) Using sodium 2-methylnaphth-1-ylborate salt **219** *and 2-bromobiphenyl* **229***;*

Sodium 2-methylnaphth-1-ylborate salt **219** (0.68 g, 3.00 mmol, 2 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (50 mg, 0.06 mmol, 4 mol%) were added to a flame-dried pressure tube followed by 2-bromobiphenyl **229** (0.35 g, 1.50 mmol, 1 equiv.) via syringe. Freshly distilled toluene (15 mL) was added

and the tube sealed and heated to 90 °C for 48 h, under stirring. After this time the mixture was allowed to cool to room temperature and worked-up according to the standard protocol. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to the coupled product **227**. Purification by column chromatography over silica eluting with hexane→15:1 hexane/DCM gave 1-(2'-biphenyl)-2-methylnaphthalene **227** as a viscous colourless oil (0.22 g, 50%). Spectral data were consistent with literature values.[17] R_f 0.14 (hexane); δ_H (400 MHz, $CDCl_3$) 7.76 (1H, d, *J* 7.6), 7.65 (1H, d, *J* 8.4), 7.54-7.41 (4H, m), 7.38-7.30 (2H, m), 7.25 (1H, d, *J* 7.6), 7.17 (1H, d, *J* 8.4), 7.02-6.93 (5H, m), 1.97 (3H, s, H_3-11); δ_C (100 MHz, $CDCl_3$) 142.43, 141.53, 138.09, 137.45, 133.69, 133.64, 132.07, 131.69, 130.49, 128.92, 128.69, 128.13, 128.05, 127.81, 127.49, 127.40, 126.78, 126.53, 126.15, 124.85, 20.88 (C-11); *m/z* (EI) 294 (M^+, 100%); HRMS (CI): Found: 312.1750. $C_{23}H_{22}N$ ($M+NH_4^+$) Requires 312.1747.

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Heptane/EtOH	Flowrate (mL/min)	t_R of 1st isomer[b] (min)	t_R of 2nd isomer[b] (min)	Ratio of isomers
227	OJ[a]	70/30	1.0	3.9	5.3	51:49

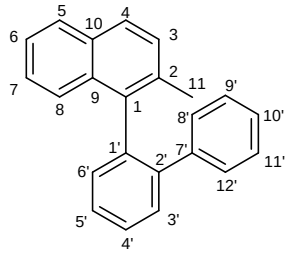
[a] Chiralcel OJ column by Daicel Chemical Ind., Ltd. [b] Detected at 215 nm.

(iii) Using sodium 2-methylnaphth-1-ylborate salt **219** *and 2-iodobiphenyl* **230***;*

Sodium 2-methylnaphth-1-ylborate salt **219** (0.68 g, 3.00 mmol, 2 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (50 mg, 0.06 mmol, 4 mol%) were added to a flame-dried pressure tube followed by 2-iodobiphenyl **230** (0.42 g, 1.50 mmol, 1 equiv.) via syringe. Freshly distilled toluene (15 mL) was added and the tube sealed and heated to 90 °C for 48 h, under stirring. After this time the mixture was allowed to cool to room temperature and worked-up according to the general protocol. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to the coupled product **227**. Purification by column chromatography over silica eluting with hexane→15:1 hexane/DCM gave 1-(2'-biphenyl)-2-

methylnaphthalene **227** as a viscous colourless oil (0.20 g, 45%). Spectral data were consistent with literature values.[17] (See above for data).

Asymmetric Suzuki couplings towards 1-(2'-biphenyl)-2-methylnaphthalene 227



(i) Using sodium 2-methylnaphth-1-ylborate salt **219** *and 2-bromobiphenyl* **229***;*

Sodium 2-methylnaphth-1-ylborate salt **219** (0.51 g, 2.25 mmol, 1.5 equiv.), palladium chloride (11 mg, 0.06 mmol, 4 mol%) and *R*-(−)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine **180** (53 mg, 0.12 mmol, 8 mol%) were added to a flame-dried pressure tube followed by 2-bromobiphenyl **229** (0.35 g, 1.5 mmol, 1 equiv.) via syringe. Freshly distilled toluene (15 mL) was added and the tube sealed and heated to 90 °C for 48 h, under stirring. After this time the mixture was allowed to cool to room temperature and worked-up according to the general protocol. Purification by column chromatography over silica eluting with hexane→15:1 hexane/DCM isolated the product **227** as a viscous colourless oil (0.14 g, 32%). (See above for spectral data). An enantiomeric excess was not achieved as the ratio of isomers corresponded to an approximately racemic mixture:

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Heptane/EtOH	Flowrate (mL/min)	t_R of 1st isomer[b] (min)	t_R of 2nd isomer[b] (min)	Ratio of isomers
227	OJ[a]	70/30	1.0	3.9	5.5	46:54

[a] Chiralcel OJ column by Daicel Chemical Ind., Ltd. [b] Detected at 215 nm.

(ii) Using 'reversed' coupling partners 1-bromo-2-methylnaphthalene **162** *and sodium 2-biphenylborate salt* **232***;*

Sodium 2-biphenylborate salt **232** (0.74 g, 3 mmol, 1.5 equiv.), palladium chloride (14 mg, 0.08 mmol, 4 mol%) and *R*-(−)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine **180** (70 mg, 0.16 mmol, 8 mol%) were added to a flame-dried pressure tube followed by 1-bromo-2-methylnaphthalene **162** (0.50 g, 2 mmol, 1 equiv.) via syringe. Freshly distilled toluene (15 mL) was added and the tube sealed and heated to 90 °C for 48 h, under stirring. After this time the mixture was allowed to cool to room temperature and worked-up according to the general procedure. Purification by column chromatography over silica eluting with hexane gave the product **227** as a colourless oil[17] (0.26 g, 44%). (Data as above). An enantiomeric excess was not achieved as the ratio of isomers corresponded to a roughly racemic mixture mixture:

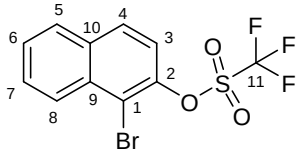
Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Heptane/EtOH	Flowrate (mL/min)	t_R of 1st isomer[b] (min)	t_R of 2nd isomer[b] (min)	Ratio of isomers
227	OJ[a]	70/30	1.0	4.2	5.8	48:52

[a] Chiralcel OJ column by Daicel Chemical Ind., Ltd. [b] Detected at 215 nm.

3.9 Preparation of organoboron and organohalide coupling partners for further Suzuki reactions

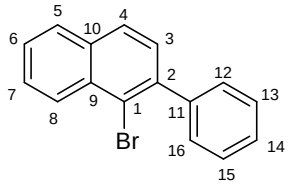
Synthesis of 1-bromonaphth-2-yl triflate 235



Following the procedure described by Buchwald and Yin,[18] a solution of 1-bromo-2-naphthol **234** 8.30 g, 37.2 mmol, 1 equiv.) in dry pyridine (37 mL) was prepared and cooled to −5 °C under argon. Trifluoromethanesulfonic anhydride (7.15

mL, 40.85 mmol, 1.1 equiv.) was added dropwise to the solution via syringe. The mixture was stirred at −5 °C for 30 minutes and then allowed to warm to room temperature and stirred for a further 18 h. The resulting mixture was taken up in diethyl ether (100 mL) and dilute hydrochloric acid (3 M, 100 mL) added. The aqueous layer was extracted with diethyl ether (50 mL) and the combined organic layers washed with hydrochloric acid (3 M, 2 x 50 mL), saturated $NaHCO_3$ solution (50 mL), brine (50 mL) and then dried and removed of solvent. The remaining oil was purified by column chromatography on silica eluting with hexane to give 1-bromonaphth-2-yl triflate **235** as a pale yellow crystalline solid (11.94 g, 90%). M.p. 24-26 °C; R_f 0.5 (5:1 pet. ether/ethyl acetate); δ_H (300 MHz, $CDCl_3$) 8.30 (1H, d, *J* 8.1, H-8), 7.88 (2H, d, *J* 9.0), 7.72-7.58 (2H, m), 7.43 (1H, d, *J* 9.0, H-3); δ_C (75 MHz, $CDCl_3$) 145.33, 133.28, 132.95, 129.96, 129.03, 128.59, 128.01, 127.96, 120.14, 118.98 (1C, q, *J* 319, C-11), 116.38.

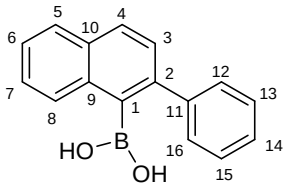
Synthesis of 1-bromo-2-phenylnaphthalene 237



Following the procedure described by Buchwald and Yin,[18] 1-bromonaphth-2-yl triflate **235** (3.56 g, 10.0 mmol, 1 equiv.), tris(dibenzylideneacetone)dipalladium(0) (0.138 g, 0.15 mmol, 3 mol% Pd), 1,3-bis(diphenylphosphino)propane (0.124 mg, 0.30 mmol, 3 mol%), lithium bromide (0.87 g, 10.0 mmol, 1.0 equiv.) and diethyl ether (15 mL) were added to a dried flask equipped with a Liebig condenser and stirrer bar. The mixture was stirred at room temperature for 5 minutes, and then phenylmagnesium bromide **236** (3 M, 4.0 mL, 12.0 mmol, 1.2 equiv) added in one portion (a water bath at room temperature was used to cool the exothermic reaction). The mixture was stirred at room temperature for 6 h, and then quenched with methanol (2 mL). Water (20 mL) was added and the mixture extracted with diethyl ether (3 x 30 mL). The organic layers were combined, dried, and removed of solvent. The product **237** was isolated by column chromatography over silica eluting with hexane, and then further purified by recrystallisation with DCM/ethanol to give a white crystalline solid (2.07 g, 73%). M.p. 63-65 °C; R_f 0.3 (hexane); δ_H (400 MHz,

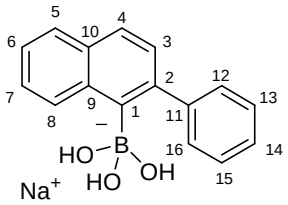
$CDCl_3$) 8.41 (1H, d, *J* 8.4, H-8), 7.86 (2H, m), 7.64 (1H, t, *J* 8.4, H-7) 7.55 (1H, t, *J* 8.4, H-6), 7.49-7.42 (6H, m); δ_C (75 MHz, $CDCl_3$) 142.60, 141.06, 133.88, 132.78, 129.90, 128.75, 128.34, 128.23, 128.20, 127.94, 127.78, 127.73, 126.80, 122.77.

Synthesis of 2-phenylnaphth-1-ylboronic acid 178



Following the procedure described by Buchwald and Yin,[18] a solution of 1-bromo-2-phenylnaphthalene **237** (1.5 g, 5.29 mmol, 1 equiv.) in freshly distilled THF (20 mL) was prepared, and cooled to −78 °C under argon. *n*-Butyllithium (2.5 M in hexane, 2.34 mL, 5.8 mmol, 1.1 equiv.) was added dropwise to the solution and stirred for 15 minutes. Trimethyl borate (1.10 g, 10.6 mmol, 2 equiv.) was added to the mixture in one portion, and stirred for 30 minutes. After this time the mixture was allowed to warm to room temperature and left to stir overnight. The resulting mixture was quenched with dilute hydrochloric acid (2 M, 20 mL) allowed to stir for 30 minutes and then extracted with diethyl ether (3 x 20 mL). The organic layers were dried and removed of solvent to give an oily residue. Addition of hexane resulted in precipitation of a white solid which was filtered, washed with ice-cold hexane and dried to give the pure boronic acid **178**. Spectral data were in agreement with literature values.[18] (1.03 g, 79%). M.p. 280 °C (decomp.); δ_H (400 MHz, $CDCl_3$) 8.14 (1H, d, *J* 8.0, H-8), 7.94-7.87 (2H, m), 7.58-7.40 (8H, m), 4.63 (2H, s, 2 x OH); δ_C (75 MHz, $CDCl_3$) (C-1 is not observed) 143.82, 143.51, 135.43, 132.29, 129.64, 128.97, 128.96, 128.59, 128.44, 127.84, 127.44, 126.89, 126.08.

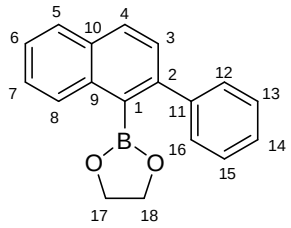
Synthesis of sodium 2-phenylnaphth-1-ylborate salt 238



Following the general procedure for the synthesis of sodium trihydroxyarylborate salts,[5] 2-phenylnaphth-1-ylboronic acid **178** (4.0 g, 16.1 mmol)

was dissolved in a minimum amount of hot toluene (100 mL) under stirring. Once completely dissolved, saturated aqueous sodium hydroxide solution (15 mL) was added dropwise to the hot solution. The mixture was allowed to stir for a further 30 min until cooled to room temperature, after which the solid precipitate was filtered, washed with cold toluene and dried under vacuum. The solid was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy as the borate salt product **238** (4.70 g, 99%). δ_H (400 MHz, D_2O ref. CH_3CN) 8.00 (1H, d, *J* 8.0), 7.82-7.73 (2H, m), 7.58 (2H, d, *J* 7.6), 7.46-7.34 (5H, m), 7.29 (1H, t, *J* 7.6); δ_C (75 MHz, D_2O ref. CH_3CN) (C-1 is not observed) 181.51, 144.40, 140.49, 135.08, 131.70, 129.54, 128.78, 128.58, 127.97, 127.27, 126.93, 125.86, 125.57.

Synthesis of 2-phenylnaphth-1-yl(ethylene glycol)boronate ester 239



(i) Using toluene as solvent:

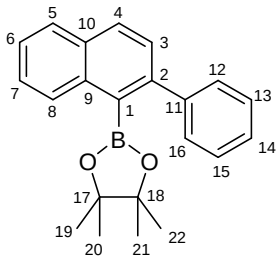
2-Phenylnaphth-1-ylboronic acid **178** (4.0 g, 16.1 mmol, 1 equiv.) was dissolved in toluene (100 mL) under stirring and heating, then ethylene glycol (1.10 g, 17.71 mmol, 1.1 equiv.) added via syringe and the mixture heated to reflux for 20 h. After this time no product formation was observed by TLC so an additional portion of ethylene glycol (0.5 mL) was added and the mixture heated for a further 24 h. After this time the solvent was removed, with only starting materials boronic acid **178** and ethylene glycol found to be present (as determined by ^{1}H NMR spectroscopy).

(ii) Using a solvent mixture of THF and toluene:

2-Phenylnaphth-1-ylboronic acid **178** (4.0 g, 16.1 mmol, 1 equiv.) was dissolved in a mixture of THF and toluene (4:1, 100 mL) under stirring and heating. Ethylene glycol (1.10 g, 17.71 mmol, 1.1 equiv.) was added to the solution via syringe. The mixture was heated to reflux for 48 h, after which the mixture was allowed to cool to room temperature. The solvent was removed under vacuum and

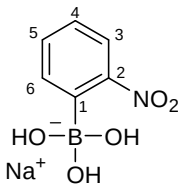
DCM (50 mL) added to the residue. This was shaken with water (50 mL) and the layers separated. The aqueous layer was extracted with DCM (50 mL) and the organic layers combined, dried, filtered, and removed of solvent to leave a yellow oil. On standing the oil solidified to an off-white solid which was confirmed as the pure product **239** (3.75 g, 85%). M.p. 109 °C; R_f 0.3 (3:1 hexane/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.05 (1H, d, *J* 8.0), 7.92 (1H, d, *J* 8.4), 7.85 (1H, d, *J* 8.4), 7.60-7.40 (7H, m), 7.36 (1H, t, *J* 7.2) 4.28 (4H, s, H_2-17 and H_2-18); δ_C (100 MHz, $CDCl_3$) (C-1 is not observed) 145.43, 143.94, 136.12, 131.93, 129.69, 128.65, 128.35, 128.29, 128.22,127.20, 127.07, 126.40, 125.64, 66.07 (C-17 and C-18); *m/z* (CI) 275 (M+1, 100%); HRMS (CI): Found: 275.1240. $C_{18}H_{16}BO_2$ ($M+H^+$) Requires 275.1238.

Synthesis of 2-phenylnaphth-1-yl(pinacol)boronate ester 240



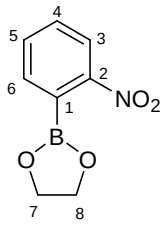
2-Phenylnaphth-1-ylboronic acid **178** (1.84 g, 7.41 mmol, 1 equiv.) and pinacol (0.96 g, 8.15 mmol, 1.1 equiv.) were heated in toluene (50 mL) under reflux for 24 h, after which the reaction mixture was allowed to cool to room temperature. The mixture was diluted with DCM (50 mL) and water added (50 mL). The layers were separated and the aqueous layer extracted with further portions of DCM (2 x 50 mL). The organic layers were combined, dried, and filtered. The solvent was removed leaving a viscous oil. After allowing to dry under vacuum for two days solidification occurred resulting in an off-white waxy solid. This was confirmed as the product **240** (1.86 g, 76%). No further purification was performed as spectral data were in accordance with literature values.[19] M.p. 47 °C; R_f 0.3 (5:1 hexane/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.10 (1H, d, *J* 8.0), 7.85 (2H, t, *J* 8.4), 7.56-7.32 (8H, m), 1.24 (12H, s, H_3-19, H_3-20, H_3-21 and H_3-22); δ_C (75 MHz, $CDCl_3$) (C-1 is not observed) 145.42, 143.93, 136.16, 131.97, 129.42, 129.26, 128.32, 128.13, 127.90, 127.28, 127.13, 126.37, 125.49, 84.06 (C-17 and C-18), 24.88 (C-19, C-20, C-21 and C-22); *m/z* (CI) 331 (M+1, 100%); HRMS (CI): Found: 331.1864. $C_{22}H_{24}BO_2$ ($M+H^+$) Requires 331.1870.

Attempted synthesis of sodium 2-nitrophenylborate salt 244



2-Nitrophenylboronic acid **243** (0.5 g, 3.0 mmol) was dissolved in hot toluene (40 mL). Once fully dissolved, saturated sodium hydroxide solution (6 mL) was added dropwise to the hot solution. The mixture was allowed to cool to room temperature and left to stir for 30 minutes, however no precipitation of any solid product occurred.

Attempted synthesis of 2-nitrophenyl(ethylene glycol)boronate ester 245



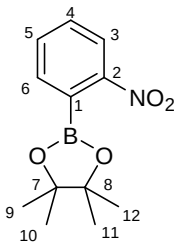
(i) Using toluene as solvent:

2-Nitrophenylboronic acid **243** (1.0 g, 6 mmol, 1 equiv.) was dissolved in freshly distilled toluene (30 mL) and anhydrous ethylene glycol (0.41 g, 6.6 mmol, 1.1 equiv.) added via syringe. The mixture was heated to reflux for 5 h with azeotropic removal of water using Dean-Stark apparatus. After this time the mixture was allowed to cool to room temperature, removed of solvent, and DCM (20 mL) added to the residue. Water (20 mL) was added and the layers separated. The aqueous layer was extracted with DCM (2 x 20 mL), and the organic layers combined and dried. The solution was filtered and removed of solvent, leaving only a very small amount of yellow residue. Re-extraction of the aqueous layer with diethyl ether recovered a substantial amount of yellow solid which was confirmed by ^{1}H NMR spectroscopy to be 2-nitrophenylboronic acid starting material **243**.

(ii) Using a solvent mixture of THF and toluene:

2-Nitrophenylboronic acid **243** (4.0 g, 23.96 mmol, 1 equiv.) was dissolved in a mixture of THF and toluene (4:1, 100 mL) under stirring and heating, with anhydrous ethylene glycol (1.64 g, 26.36 mmol, 1.1 equiv.) added via syringe. The mixture was heated to reflux for 64 h, and then allowed to cool to room temperature and removed of solvent. DCM (60 mL) was added to the residue, and then shaken with water (60 mL). The layers were separated, and the aqueous layer extracted with DCM (2 x 60 mL). The organic layers were combined, dried, filtered and removed of solvent to leave a yellow solid which was found to be 2-nitrophenylboronic acid starting material **243** (analysis by ^{1}H NMR spectroscopy).

Synthesis of 2-nitrophenyl(pinacol)boronate ester 246



2-Nitrophenylboronic acid **243** (2.0 g, 11.98 mmol, 1 equiv.) and pinacol (1.5 g, 13.18 mmol, 1.1 equiv.) were heated in toluene (50 mL) under reflux for 48 h. After this time the reaction mixture was allowed to cool then diluted with DCM (50 mL). Water (50 mL) was added and the layers separated. The aqueous layer was extracted with DCM (2 x 50 mL), and the organic layers combined and dried. The solution was filtered and removed of solvent to give the boronate ester product **246** as a waxy yellow solid (2.77 g, 93%). No further purification was performed as spectral data were consistent with literature values.[20] M.p. 40 °C; R_f 0.5 (5:1 hexane/ethyl acetate); δ_H (400 MHz, $CDCl_3$) 8.13 (1H, d, *J* 8.0, H-3), 7.64 (1H, t, *J* 7.6), 7.55-7.47 (2H, m), 1.40 (12H, s, H_3-9, H_3-10, H_3-11 and H_3-12); δ_C (75 MHz, $CDCl_3$) (C-1 is not observed) 133.80, 132.87, 130.10, 123.02, 84.60 (C-7 and C-8), 24.59 (C-9, C-10, C-11 and C-12).

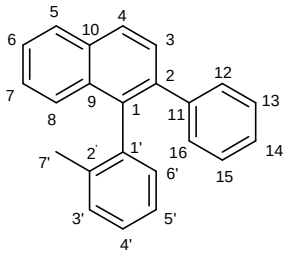
3.10 Symmetric and asymmetric Suzuki coupling reactions towards alternative axially chiral biaryl compounds

In the following set of Suzuki coupling reactions, the procedure employing a sealed pressure tube (as described previously) was modified slightly for those reactions in which the use of a base was necessary. This modification was to enable the rigorous drying of the base prior to its use in the reaction. In addition, solid organoboron and organohalide reagents were ground to a fine powder and placed under high vacuum for a minimum of 4 h prior to use.

General procedure

A thick-walled Ace® pressure tube was equipped with a stirrer bar, capped with a rubber septum, flame-dried and allowed to relax under argon. If the use of a base (such as cesium fluoride) was necessary, the required amount was added to the tube, rigorously flame-dried under vacuum and allowed to cool to room temperature under argon. Once completely cooled the remaining solid reagents i.e. organoboron reagent, organohalide reagent, catalyst and ligand were subsequently added. The tube was evacuated and backfilled with argon after each addition. Freshly distilled solvent was added via syringe. The tube was then sealed tightly with a Teflon® screw-cap and heated in a pre-heated oil bath at the indicated temperature for the required time (24-48 h) under stirring. After this time the crude reaction mixture was allowed to cool to room temperature, diluted with DCM (30 mL), and shaken with water (30 mL). The layers were separated, and the aqueous layer extracted with further portions of DCM (2 x 30 mL). The organic layers were combined, dried over sodium sulfate, filtered, and removed of solvent. The crude material was purified by column chromatography over silica.

Symmetric Suzuki coupling towards 1-(2'-methylphenyl)-2-phenylnaphthalene 233



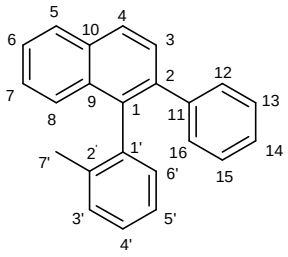
Sodium 2-phenylnaphth-1-ylborate salt **238** (0.57 g, 2.0 mmol, 2 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (11.4 mg, 0.014 mmol, 2 mol%) were added to a flame-dried pressure tube under argon. 1-Bromo-2-methylbenzene **241** (0.17 g, 1.0 mmol, 1 equiv.) was added to the tube via syringe, followed by anhydrous toluene (15 mL). The tube was sealed and the mixture heated to 90 °C under stirring for 24 h. After this time the mixture was allowed to cool and worked-up according to the general procedure. The combined organic layers were dried, filtered and removed of solvent to leave a dark red oil. Analysis of this crude mixture (by ^{1}H NMR spectroscopy) revealed peaks attributable to the coupled product **233** together with deboronated material (2-phenylnaphthalene). Purification by column chromatography over silica eluting with neat heptane isolated 1-(2'-methylphenyl)-2-phenylnaphthalene **233** as a white crystalline solid (0.10 g, 33%). Spectral data were in agreement with literature values.[21] M.p. 115 °C; δ_H (400 MHz, $CDCl_3$) 7.94 (2H, t, *J* 7.8), 7.58 (1H, d, *J* 8.4), 7.47 (1H, t, *J* 7.2), 7.43-7.35 (2H, m), 7.27-7.10 (9H, m), 1.86 (3H, s, H_3-7'); δ_C (100 MHz, $CDCl_3$) 141.89, 138.46, 138.18, 137.15, 136.92, 132.73, 132.53, 131.64, 129.74, 129.66, 128.27, 127.91, 127.60, 127.56, 127.29, 126.64, 126.34, 126.28, 125.68, 125.22, 19.97 (C-7'); *m/z* (CI) 295 (M+1, 100%); HRMS (CI): Found: 295.1483. $C_{23}H_{19}$ (M+H$^+$) Requires 295.1481.

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Heptane/EtOH	Flowrate (mL/min)	t_R of 1st isomer[b] (min)	t_R of 2nd isomer[b] (min)	Ratio of isomers
233	OJ[a]	70/30	1.0	4.9	12.9	50:50

[a] Chiralcel OJ column by Daicel Chemical Ind., Ltd. [b] Detected at 215 nm.

Asymmetric Suzuki coupling towards 1-(2'-methylphenyl)-2-phenylnaphthalene 233



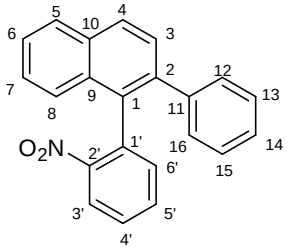
Sodium 2-phenylnaphth-1-ylborate salt **238** (0.57 g, 2.0 mmol, 2 equiv.), palladium chloride (4.6 mg, 0.026 mmol, 2 mol%) and *R*-(−)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine **180** (22.9 mg, 0.052 mmol, 4 mol%) were added to a flame-dried pressure tube under argon, equipped with a stirrer bar. 1-Bromo-2-methylbenzene **241** (0.17 g, 1.0 mmol, 1 equiv.) was added to the tube via syringe, followed by anhydrous toluene (15 mL). The tube was sealed and the mixture heated to 90 °C under stirring for 24 h. After this time the mixture was allowed to cool and then worked-up according to the general procedure. The pale red oil obtained after work-up was analysed by ^{1}H NMR spectroscopy which revealed peaks belonging to those of the coupled product **233**. Purification by column chromatography over silica eluting with neat heptane isolated 1-(2'-methylphenyl)-2-phenylnaphthalene **233** as a white crystalline solid[21] (0.12 g, 42%). M.p. 115 °C. (Spectral data as above). An enantiomeric excess was not achieved as the ratio of isomers corresponded to an approximately racemic mixture:

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Heptane/EtOH	Flowrate (mL/min)	t_R of 1st isomer[b] (min)	t_R of 2nd isomer[b] (min)	Ratio of isomers
233	OJ[a]	70/30	1.0	4.9	12.9	47:53

[a] Chiralcel OJ column by Daicel Chemical Ind., Ltd. [b] Detected at 215 nm.

Symmetric Suzuki couplings towards 1-(2'-nitrophenyl)-2-phenylnaphthalene 179



(i) Using 2-phenylnaphth-1-yl(ethylene glycol)boronate ester **239**, *1-bromo-2-nitrobenzene* **177**, *palladium chloride and triphenylphosphine;*

To a dried pressure tube was added cesium fluoride (0.55 g, 3.6 mmol, 3 equiv.), which was thoroughly flame-dried under vacuum and allowed to cool under an atmosphere of argon. 2-Phenylnaphth-1-yl(ethylene glycol)boronate ester **239** (0.49 g, 1.8 mmol, 1.5 equiv.), 1-bromo-2-nitrobenzene **177** (0.24 g, 1.2 mmol, 1 equiv.), triphenylphosphine (6.3 mg, 0.024 mmol, 2 mol%) and palladium chloride (2.1 mg, 0.012 mmol, 1 mol%) were added, followed by freshly distilled DME (15 mL) via syringe. The tube was sealed and heated to 80 °C for 24 h under stirring. After this time the mixture was allowed to cool and then worked-up according to the general procedure. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to boronate ester starting material **239**, deboronated side-product (2-phenylnaphthalene) and 1-bromo-2-nitrobenzene starting material **177** only.

(ii) Using 2-phenylnaphth-1-yl(pinacol)boronate ester **240**, *1-bromo-2-nitrobenzene* **177**, *palladium chloride and triphenylphosphine;*

To a dried pressure tube was added cesium fluoride (0.674 g, 4.44 mmol, 3 equiv.), which was thoroughly flame-dried under vacuum and allowed to cool under an atmosphere of argon. 2-Phenylnaphth-1-yl(pinacol)boronate ester **240** (0.73 g, 2.22 mmol, 1.5 equiv.), 1-bromo-2-nitrobenzene **177** (0.30 g, 1.48 mmol, 1 equiv.), triphenylphosphine (31.0 mg, 0.1184 mmol, 8 mol%) and palladium chloride (10.5 mg, 0.0592 mmol, 4 mol%) were subsequently added, followed by freshly distilled DME (18 mL) via syringe. The tube was sealed and heated to 80 °C for 24 h under stirring. After this time the mixture was allowed to cool and worked-up according to the general procedure. Analysis of the crude mixture by ^{1}H NMR spectroscopy

revealed peaks attributable to unreacted boronate ester starting material **240** and unreacted bromide starting material **177**. No other peaks were observed.

(iii) Using sodium 2-phenylnaphth-1-ylborate salt **238**, *1-bromo-2-nitrobenzene* **177** *and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II);*

Sodium 2-phenylnaphth-1-ylborate salt **238** (0.57 g, 2.0 mmol, 2 equiv.), 1-bromo-2-nitrobenzene **177** (0.20 g, 1.0 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (16.3 mg, 0.02 mmol, 2 mol%) were added to a flame-dried pressure tube under argon. Anhydrous toluene (18 mL) was added via syringe and the tube sealed and heated to 90 °C for 24 h. After this time the mixture was allowed to cool and worked-up according to the general procedure. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to deboronated side-product (2-phenylnaphthalene) and 1-bromo-2-nitrobenzene starting material **177**. Only traces of the coupled product **179** were observed.

(iv) Using sodium 2-phenylnaphth-1-ylborate salt **238**, *1-bromo-2-nitrobenzene* **177**, *palladium chloride and triphenylphosphine;*

Sodium 2-phenylnaphth-1-ylborate salt **238** (0.52 g, 1.8 mmol, 1.5 equiv.), 1-bromo-2-nitrobenzene **177** (0.24g, 1.2 mmol, 1 equiv.), triphenylphosphine (6.3 mg, 0.024 mmol, 2 mol%) and palladium chloride (2.1 mg, 0.012 mmol, 1 mol%) were added to a flame-dried pressure tube under argon. Anhydrous toluene (15 mL) was added via syringe and the tube sealed and heated to 90 °C for 24 h. After this time the mixture was allowed to cool and worked-up according to the general procedure. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to deboronated side-product (2-phenylnaphthalene) and 1-bromo-2-nitrobenzene starting material **177**. No other peaks were observed.

(v) Using sodium 2-phenylnaphth-1-ylborate salt **238**, *1-iodo-2-nitrobenzene* **242** *and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II);*

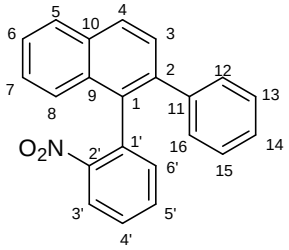
Sodium 2-phenylnaphth-1-ylborate salt **238** (0.57 g, 2.0 mmol, 2 equiv.), 1-iodo-2-nitrobenzene **242** (0.25 g, 1.0 mmol, 1 equiv.) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (16.3 mg, 0.02 mmol, 2 mol%) were added to a flame-dried pressure tube under argon. Anhydrous toluene (18 mL) was added via syringe and the tube sealed and heated to 90 °C for 24 h. After this time the mixture was allowed to cool and worked-up according to the general procedure. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to deboronated side product (2-phenylnaphthalene), unreacted iodide starting material **242,** a small amount of an unknown impurity, and the desired coupled product **179**. Purification of the crude mixture by column chromatography over silica eluting with neat hexane → 9:1 hexane/DCM successfully removed unreacted iodide **242** and deboronated material. A crystalline yellow solid was isolated (0.094 g, 29%), however spectral data revealed that the solid consisted of a mixture of the coupled product **179** and the unidentified impurity, which could not be removed by further attempts at purification (repeated column chromatography). Peaks observed for the product **179** in the ^{1}H NMR spectrum were in agreement with literature values.[18] R_f 0.07 (5:1 hexane/DCM); δ_H (400 MHz, $CDCl_3$) 8.01-7.92 (3H, m), 7.58-7.34 (6H, m), 7.29 (1H, dd, *J* 7.6 and 1.6), 7.20-7.13 (5H, m); δ_C (100 MHz, $CDCl_3$) 149.10, 140.20, 137.05, 133.62, 133.20, 132.70, 131.60, 131.53, 130.67, 128.47, 127.35, 127.33, 127.27, 127.03, 126.83, 125.84, 125.75, 124.91, 124.20, 123.31.

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Hexane/^{i}PrOH	Flowrate (mL/min)	t_R of 1st isomer^b (min)	t_R of 2nd isomer^b (min)	Ratio of isomers
179	01^a	90/10	0.5	11.3	12.6	55:45

^{a} 5μm particle size Eurocel column by Knauer, GmbH. ^{b} Detected at 230 nm.

Asymmetric Suzuki couplings towards 1-(2'-nitrophenyl)-2-phenylnaphthalene 179



(i) Using sodium 2-phenylnaphth-1-ylborate salt **238** *and 1-iodo-2-nitrobenzene* **242***;*

Sodium 2-phenylnaphth-1-ylborate salt **238** (0.57 g, 2.0 mmol, 2 equiv.), 1-iodo-2-nitrobenzene **242** (0.25 g, 1.0 mmol, 1 equiv.), palladium chloride (4.6 mg, 0.026 mmol, 2 mol%) and *R*-(−)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine **180** (22.9 mg, 0.052 mmol, 4 mol%) were added to a flame-dried pressure tube under argon. Anhydrous toluene (15 mL) was added via syringe, the tube sealed tightly and the mixture heated to 90 °C for 24 h. After this time the mixture was allowed to cool and worked-up according to the general procedure. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to the desired coupled product **179** together with unreacted iodide starting material **242** and deboronated side-product (2-phenylnaphthalene). Purification by column chromatography over silica eluting with neat hexane → 8:1 hexane/DCM isolated the pure coupled product **179** as a yellow crystalline solid (0.11 g, 34%). M.p. 149 °C. Spectral data were as above and were in agreement with literature values.[18] ee 78% (determined from chiral HPLC data).

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Hexane/^{i}PrOH	Flowrate (mL/min)	t_R of 1st isomer^{b} (min)	t_R of 2nd isomer^{b} (min)	Ratio of isomers
179	01^{a}	90/10	0.5	11.3	12.6	11:89

^{a} 5μm particle size Eurocel column by Knauer, GmbH. ^{b} Detected at 230 nm.

(ii) Using 2-phenylnaphth-1-yl(ethylene glycol)boronate ester **239** *and 1-bromo-2-nitrobenzene* **177***;*

Using a slightly modified procedure, the reaction solvent (DME) was distilled then collected and degassed (with argon) in a separate flask for 1 h before use. Molecular sieves (3 Å) were added to the pressure tube and flame-dried under vacuum. Cesium fluoride (0.46 g, 3.0 mmol, 3 equiv.) was added to the tube and thoroughly flame-dried under vacuum. After cooling to room temperature under argon, 1-bromo-2-nitrobenzene **177** (0.20 g, 1.0 mmol, 1 equiv.) and 2-phenylnaphth-1-yl(ethylene glycol)boronate ester **239** (0.41 g, 1.5 mmol, 1.5 equiv.) were added, followed by distilled and degassed DME (15 mL) via syringe. The mixture was degassed further in situ for 1 h after which *R*-(−)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine **180** (35 mg, 0.08 mmol, 8 mol%) and palladium chloride (7.1 mg, 0.04 mmol, 4 mol%) were added. The tube was sealed and heated to 80 °C for 24 h. After this time the mixture was allowed to cool and worked-up according to the general procedure. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to unreacted boronate ester **239** starting material and a small amount of the coupled product **179**. An approximate yield was calculated as 3% (from the ratio of integrals in the ^{1}H NMR spectrum). A small sample of the pure coupled product **179** was successfully isolated by column chromatography over silica eluting with neat hexane → 9:1 hexane/DCM. Spectral data were as above and were in agreement with literature values.[18] ee 90% (determined from chiral HPLC data).

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Hexane/^{i}PrOH	Flowrate (mL/min)	t_R of 1st isomer^{b} (min)	t_R of 2nd isomer^{b} (min)	Ratio of isomers
179	01^{a}	90/10	0.5	11.3	12.6	5:95

^{a} 5μm particle size Eurocel column by Knauer, GmbH. ^{b} Detected at 230 nm.

(iii) Using 2-phenylnaphth-1-yl(pinacol)boronate ester **240** *and 1-bromo-2-nitrobenzene* **177***;*

Using a slightly modified procedure, the reaction solvent (DME) was firstly distilled, then collected and degassed for 1 h (with argon) in a separate flask before use. Molecular sieves (3 Å) were added to the pressure tube and flame-dried under vacuum. Cesium fluoride (0.46 g, 3.0 mmol, 3 equiv.) was next added to the tube and thoroughly flame-dried under vacuum. After cooling to room temperature under argon, 1-bromo-2-nitrobenzene **177** (0.20 g, 1.0 mmol, 1 equiv.), *R*-(−)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine **180** (35 mg, 0.08 mmol, 8 mol%) and palladium chloride (7.1 mg, 0.04 mmol, 4 mol%) were added, followed by the distilled and degassed DME (15 mL) via syringe. 2-Phenylnaphth-1-yl(pinacol)boronate ester **240** (0.5 g, 1.5 mmol, 1.5 equiv.) was added, and the tube sealed and heated to 80 °C for 24 h under stirring. After this time the mixture was allowed to cool and worked-up according to the general procedure. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to unreacted boronate ester starting material **240**, unreacted bromide starting material **177** and small amounts of the coupled product **179**. (The yield calculated from the ratio of integrals in the ^{1}H NMR spectrum was approximately 5%). The crude mixture was purified by column chromatography over silica eluting with neat hexane → 9:1 hexane/DCM to give the isolated product **179** as a crystalline yellow solid (6 mg, 1%). Spectral data were as above and were in agreement with literature values.[18] ee 98% (determined from chiral HPLC data).

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Hexane/^{i}PrOH	Flowrate (mL/min)	t_R of 1st isomer^{b} (min)	t_R of 2nd isomer^{b} (min)	Ratio of isomers
179	01^{a}	90/10	0.5	11.3	12.6	1:99

^{a} 5μm particle size Eurocel column by Knauer, GmbH. ^{b} Detected at 230 nm.

(iv) Using 2-phenylnaphth-1-yl(pinacol)boronate ester **240** *and 1-iodo-2-nitrobenzene* **242***;*

Cesium fluoride (0.55 g, 3.6 mmol, 3 equiv.) was added to a dried pressure tube, thoroughly flame-dried and allowed to cool to room temperature under argon. 1-Iodo-2-nitrobenzene **242** (0.3 g, 1.2 mmol, 1 equiv.), *R*-(−)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine **180** (42 mg, 0.096 mmol, 8 mol%) and palladium chloride (17 mg, 0.048 mmol, 4 mol%) were added, followed by freshly distilled DME (15 mL). 2-Phenylnaphth-1-yl(pinacol)boronate ester **240** (0.6 g, 1.8 mmol, 1.5 equiv.) was added and the tube sealed and heated at 80 °C for 24 h. After this time the mixture was allowed to cool and worked-up according to the general procedure. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to boronate ester starting material **240**, iodide starting material **242** and an unidentified impurity. A very small amount of coupled product **179** was present, which was successfully isolated by column chromatography over silica eluting with neat hexane → 9:1 hexane/DCM. Analysis of the yellow solid by ^{1}H NMR spectroscopy revealed a mixture of the coupled product **179** and an unidentified impurity. The estimated yield was calculated as ~1% from the ratio of integrals in the ^{1}H NMR spectrum. Spectral data were as above and were in agreement with literature values.[18] (The retention times of the isomers matched those of previous samples of product **179**). ee ~ 80% (determined from chiral HPLC data).

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Hexane/^{i}PrOH	Flowrate (mL/min)	t_R of 1st isomer^{b} (min)	t_R of 2nd isomer^{b} (min)	Ratio of isomers
179	01^{a}	90/10	0.5	11.3	12.6	10:90

^{a} 5μm particle size Eurocel column by Knauer, GmbH. ^{b} Detected at 230 nm.

(v) Using 'reversed' coupling partners 2-nitrophenyl(pinacol)boronate ester **246** *and 1-bromo-2-phenylnaphthalene* **237***;*

Cesium fluoride (0.91 g, 6.0 mmol, 3 equiv.) was added to a dried pressure tube, thoroughly flame-dried and allowed to cool to room temperature under argon. 1-Bromo-2-phenylnaphthalene **237** (0.57 g, 2.0 mmol, 1 equiv.), 2-nitrophenyl(pinacol)boronate ester **246** (1.0 g, 4.01 mmol, 2 equiv.), palladium chloride (14 mg, 0.08 mmol, 4 mol%) and *R*-(−)-*N*,*N*-dimethyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine **180** (70 mg, 0.16 mmol, 8 mol%) were added to the tube. Freshly distilled DME (18 mL) was then added and the tube sealed and heated to 90 °C for 24 h under stirring. After this time the tube was allowed to cool to room temperature and the crude mixture worked-up according to the general procedure. Analysis of the crude mixture by ^{1}H NMR spectroscopy revealed peaks attributable to the desired coupled product **179** as well as unreacted bromide starting material **237** and deboronated side-product (nitrobenzene). Purification by column chromatography over silica eluting with neat hexane → 8:1 hexane/DCM isolated the pure coupled product **179** as a yellow crystalline solid (0.35 g, 53%). M.p. 149 °C. Spectral data were as above and were in agreement with literature values.[18] ee 86% (determined from chiral HPLC data).

Chiral HPLC separation conditions and retention times of isomers:

Compd	Column	Eluent: Hexane/^{i}PrOH	Flowrate (mL/min)	t_R of 1st isomer^{b} (min)	t_R of 2nd isomer^{b} (min)	Ratio of isomers
179	01^{a}	90/10	0.5	11.3	12.6	7:93

^{a} 5μm particle size Eurocel column by Knauer, GmbH. ^{b} Detected at 230 nm.

3.11 References for Experimental

(1) H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512.

(2) K. V. L. Crépy, Ph.D. thesis, University of East Anglia, **2001**.

(3) G. W. Gray, M. Hird, D. Lacey and K. J. Toyne, *J. Chem. Soc. Perkin Trans. II*, **1989**, 2041.

(4) A. N. Cammidge and K. V. L. Crépy, *Tetrahedron*, **2004**, *60*, 4377.

(5) A. N. Cammidge, V. H. M. Goddard, H. Gopee, N. L. Harrison, D. L. Hughes, C. J. Schubert, B. M. Sutton, G. L. Watts and A. J. Whitehead, *Org. Lett.* **2006**, *8*, 4071.

(6) T. Mino, Y. Shirae, M. Sakamoto and T. Fujita, *J. Org. Chem.* **2005**, *70*, 2191.

(7) M. L. N. Rao, D. Banerjee and R. J. Dhanorkar, *Tetrahedron Lett.* **2010**, *51*, 6101.

(8) W. K. Chow, C. M. So, C. P. Lau and F. Y. Kwong, *J. Org. Chem.* **2010**, *75*, 5109.

(9) G. Ren, X. Cui and Y. Wu, *Eur. J. Org. Chem.* **2010**, 2372.

(10) A. C. Glass, B. B. Morris, L. N. Zakharov and S.-Y. Liu, *Org. Lett.* **2008**, *10*, 4855.

(11) Z. Jin, S.-X. Guo, X.-P. Gu, L.-L. Qiu, H.-B. Song and J.-X. Fang, *Adv. Synth. Catal.* **2009**, *351*, 1575.

(12) W. Su, S. Urgaonkar, P. A. McLaughlin and J. G. Verkade, *J. Am. Chem. Soc.* **2004**, *126*, 16433.

(13) R. Itooka, Y. Iguchi and N. Miyaura, *J. Org. Chem.* **2003**, *68*, 6000.

(14) M. Filthaus, I. M. Oppel and H. F. Bettinger, *Org. Biomol. Chem.* **2008**, *6*, 1201.

(15) Y. Uozumi, Y. Matsuura, T. Arakawa and Y. M. A. Yamada, *Angew. Chem. Int. Ed.* **2009**, *48*, 2708.

(16) Synthesis of 1-(2'-cyanophenyl)-2-methylnaphthalene **226** is reported but the corresponding NMR data are not provided; L. Benesch, P. Bury, D. Guillaneux, S. Houldsworth, X. Wang and V. Snieckus, *Tetrahedron Lett.* **1998**, *39*, 961.

(17) A. Bermejo, A. Ros, R. Fernández and J. M. Lassaletta, *J. Am. Chem. Soc.* **2008**, *130*, 15798.

(18) Synthetic procedures are described for 1-bromonapth-2-yl triflate **235** and 1-bromo-2-phenylnaphthalene **237** but the corresponding NMR data are not provided; J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12051.

(19) A. C. Spivey, F. Zhu, M. B. Mitchell, S. G. Davey and R. L. Jarvest, *J. Org. Chem.* **2003**, *68*, 7379.

(20) O. Baudoin, D. Guénard and F. Guérrite, *J. Org. Chem.* **2000**, *65*, 9268.

(21) Synthesis of 1-(2'-methylphenyl)-2-phenylnaphthalene **233** is reported but the corresponding NMR data are not provided; M. Ciclosi, J. Lloret, F. Estevan, P. Lahuerta, M. Sanaú and J. Pérez-Prieto, *Angew. Chem. Int. Ed.* **2006**, *45*, 6741.