The University Of Sheffield.

Transition Metal Mediated Transformations of Alkylboronic Esters

Francesca Dennis

Supervisor:

Dr. Benjamin Partridge

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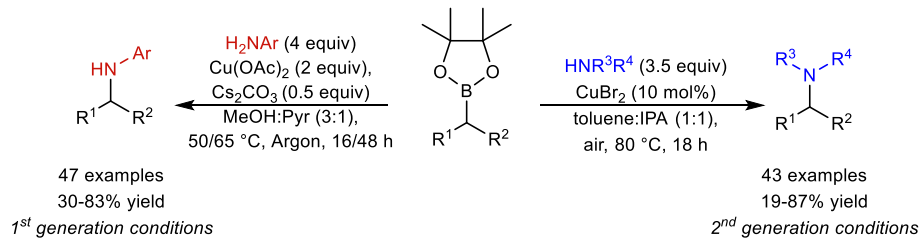
1. Abstract

Alkylboron reagents while possessing much potential have not been applied in synthesis as widely as their arylboron analogues. In particular, catalytic transformations of alkylboronic esters are underdeveloped. For instance, the Chan-Lam reaction for C-N bond formation with arylboronic acids has been widely investigated. However, reported methods using the corresponding alkylboronic ester counterparts are limited. Successful development of an alkyl variant of the Chan-Lam reaction would provide a useful tool to produce alkylamines, complementary to existing synthetic methods.

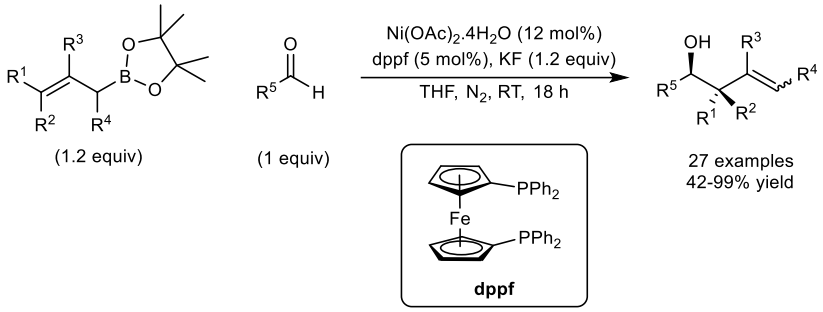
This thesis outlines two divergent strategies which have been developed for the oxidative coupling of alkyl pinacol boronic esters with anilines and aliphatic amines respectively. The first generation alkyl Chan-Lam conditions from the Partridge group involve the coupling of anilines with benzylic and allylic boronic esters. The method employs stoichiometric quantities of $Cu(OAc)_2$ under an inert atmosphere, which was required to minimise oxidation side-products. The scope of reaction was found to be functional group tolerant, with mono-alkylation of 1° anilines observed. However, the conditions were low yielding using either 2° aliphatic amines or non-benzylic boronic esters, and no reaction occurred when using 1° alkylamines.

Cu-catalysed conditions for the coupling of 1° and 2° alkylamines with benzylic boronic esters have been subsequently developed. These second generation conditions require only 10 mol% $CuBr_2$, with O_2 from air used as the terminal oxidant. Low conversions with sterically demanding 1° and 2° amines highlight limitations of the methodology. Initial mechanistic studies for both methods indicate that transmetalation of boronic ester occurs through a single electron process.



In addition, mild and operationally simple conditions for the nickel-catalysed allylboration of aldehydes have been developed. Both 1° and 2° allylboronic esters react to give homoallylic alcohol products in high yields and diastereoselectivity. The diastereoselective outcomes are

consistent with allylboration occurring through a well-defined 6-membered transition state, with the Ni-catalyst acting as a Lewis acid.



2. Acknowledgements

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Finally, thank you to my parents for your constant encouragement, support and for always believing in me.

3. Abbreviations

1°	Primary
2°	Secondary
3°	Tertiary
9-BBN	9-Borabicyclo[3.3.1]nonane
Ar	Aryl
BINAP	(2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl)
bipy	2,2'-Bipyridine
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
br	Broad
br. d	Broad Doublet
br. s	Broad Singlet
Bu	Butyl
Cb	*N,N*-Diisopropylcarbamoyl
COD	cyclooctadiene
Cy	Cyclohexane
d	Doublet
DABCO	(1,4-diazabicyclo[2.2.2]octane)
dba	dibenzylideneacetone
dbu	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
dd	doublet doublet
ddd	doublet doublet doublet
DFT	Density Functional Theory
DG	Directing group
DMAP	Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppb	1,4-Bis(diphenyl-phosphino)butane
dppBz	1,2-Bis(diphenylphosphino)benzene
dppf	1,1'Bis(diphenyl-phosphino)ferrocene
d.r.	Diastereomeric Ratio
dt	doublet triplet
DTBM	3,5-Di-*tert*-butyl-4-methoxyphenyl
dtbpy	4,4'-Di-*tert*-butyl-2,2'-bypyridine
DTBP	Di-*tert*-butyl peroxide
Equiv	Equivalents
e.r.	Enantiomeric Ratio
ESI	Electrospray Ionisation
GC-MS	Gas Chromatography – Mass Spectrometry
HMBC	Heteronuclear Multiple Bond Coherence
HPLC	High-Performance Liquid Correlation spectroscopy
HRMS	High Resolution Mass Chromatography spectrometry
HSQC	Heteronuclear Single Quantum Coherence
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazolinium chloride
IPA	Isopropyl alcohol
IPr	1,3-Bis(2,6-diisopropyl-phenyl)imidazolium chloride
^{i}Pr	Isopropyl
J	Coupling Constant (NMR)
LA	Lewis acid
m	meta
m	Multiplet
M	Molar concentration
MHz	Megahertz
mp	Melting point
MS	Molecular sieves
m/z	Mass/charge ratio
ND	Not determined
NHC	*N*-Heterocyclic Carbene
NMO	*N*-methymorpholine *N*-oxide
NMR	Nuclear magnetic resonance
o	ortho
p	para
p	pentet
Ph	Phenyl
pin	pinacol
pyr	pyridine
q	quartet
Q-TOF	Quadrupole Time Of Flight
RBF	Round-bottom flask

rr	Regiomeric Ratio
RT	Room temperature
s	singlet
t	tert
t	triplet
td	triplet doublet
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatograph
TM	Transition Metal
TMEDA	*N,N,N‘,N‘*-Tetramethylethyldiamine
Ts	Tosyl
TS	Transition State
δ	Chemical shift

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1. Introduction

Research on the synthesis of boronic acids, their derivatives and subsequently their transformations has expanded greatly in the past fifty years.[1] These organoboron derivatives are now ubiquitous in synthesis, namely in the Suzuki-Miyaura cross coupling reaction.[2,3] Organoboron reagents are now commonplace in pharmaceutical and agrochemical development due to their orthogonal reactivity to many other functional groups.[3]

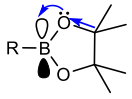


Figure 1: π-backbonding and electron density donation from oxygen to boron.

The nature of trivalent (sp^2 hybridised) boron stability and subsequent practicality in synthesis is derived from the Lewis acidity of the vacant *p*-orbital. The reactivity and properties of these organoboron reagents are affected by the attached alkyl or hydroxyl substituents.[1] Increased oxygen coordination decreases the Lewis acidity of the vacant *p*-orbital (Figure 1). This is a consequence of the increased B-O bond strength compared to C-B bonds, due to the conjugation of the oxygen lone pair into the empty *p*-orbital of boron. Triorganoboranes are prone to atmospheric oxidation to borinic acids, which can undergo further oxidation to boronic acids. Reduced Lewis acidity is displayed for the analogous borinic and boronic esters. The additional carbon enables σ-donation to oxygen, increasing the electron density available for π-back-donation, reducing the polarisation of the C-B bond as a result. These borinic and boronic esters are more robust but less reactive than their acid counterparts, enabling easy purification and further manipulation. Their increased stability originates from the additional ligand increasing steric bulk around boron.[4]

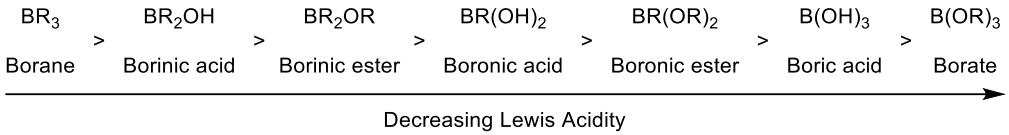
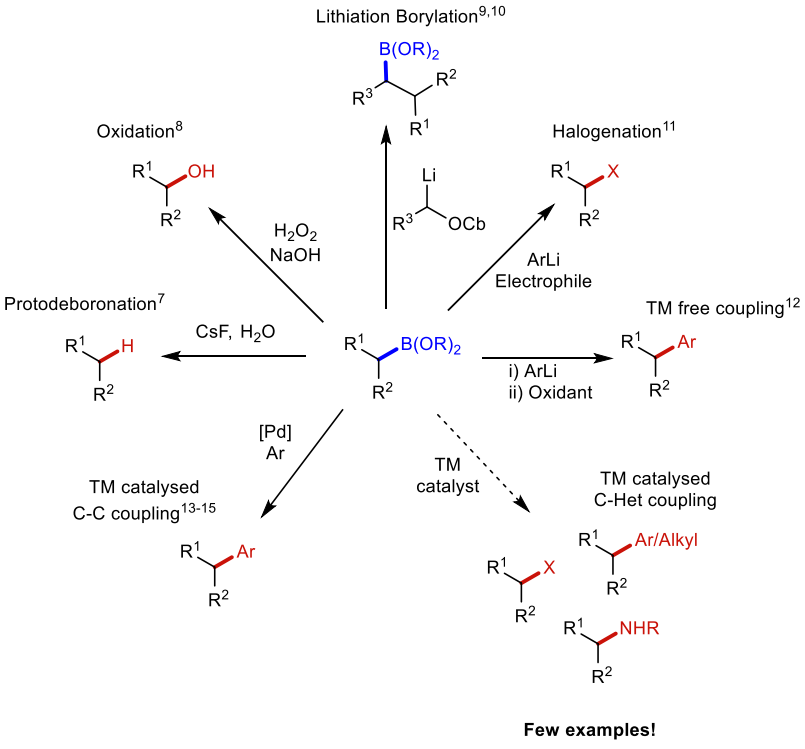


Figure 2: Organoboron reagents with decreasing Lewis acidity related to increasing electron density on boron.

Catalytic transformations of arylboronic acids and esters have been extensively researched and well reported. Investigations into the analogous onwards transformations of alkylboronic acids and esters are underdeveloped. This is in part due to enhanced reactivity of arylboronic acids and esters towards transmetalation. Once transmetalation has taken place aryl metal species cannot undergo β-hydride elimination, which alkyl metal species can be susceptible to. In addition, the expansion of methods to synthesise arylboronic acids and esters

consequently enabled research growth into their transformations. Arylboronic acids and esters are now widely commercially available.[3] This has supported large developments in the use of arylboronic acids and esters in C-C and C-heteroatom bond forming reactions.[4]

While there are now a growing number of methods to synthesise alkylboronic esters, their onwards transformations using transition metal catalysts have not been widely explored. Difficulties remain due to a relatively reduced rate of transmetalation and the resulting alkyl metal propensity for β-hydride elimination. Whilst there have been a number of reported stoichiometric transformations of alkylboronic esters in C-C and C-heteroatom bond formations, these strategies often employ harsh reaction conditions and subsequently suffer from lack of functional group compatibility (Scheme 1).[5] Consequently, development of complimentary transformation under mild and catalytic conditions could negate these issues and expand the scope of the reactions. In particular, methods for the metal-mediated formation of C-C bonds using alkylboron reagents are scarce, with even fewer reports for C-heteroatom bond formation (Scheme 1).[6]



Scheme 1: Examples of transformations of alkylboronic esters.[7–15]

1.1 Methods of Alkylboronic Ester Synthesis

Transformations of alkylboron reagents could provide access to functionalised C-sp^3 centres for synthetic applications in medicinal and biological fields. The potential for their onwards transformations has promoted research into alkylboronic ester synthesis. Preparation of 2° and 3° alkylboronic esters can now be achieved easily through numerous procedures, with asymmetric borylation strategies available.[16–20] Discussed below are a relevant selection of borylation methods to prepare 2° and 3° boronic esters.

1.1.1 Borylation of Organic Halides

Traditional methods to synthesise organoboronic acids or esters utilise reactions of organolithium or Grignard reagents. The organometallic reagents are formed from aryl, alkenyl and alkyl halides, subsequently reacting with an electrophilic boron source, producing the organoboron reagent (Figure 3). This form of electrophilic borylation has several limitations due to the basic carbon nucleophiles produced, including functional group tolerance, air and moisture sensitivity.[21] Overalkylation can also occur due to the high reactivity of the organometallic reagents, forming bis and trialkylboranes.[22] This can be mitigated through the use of sterically bulky triisopropyl borates and reaction temperatures of -78 °C.[22,23] Methodologies have been subsequently developed to utilise pinacolborane under Grignard or Barbier conditions to effectively synthesise alkyl and arylboronic esters.[24] These procedures do minimise the propensity for overalkylation but do not negate issues associated with functional group tolerance.

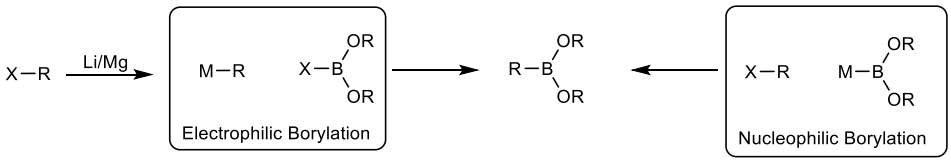
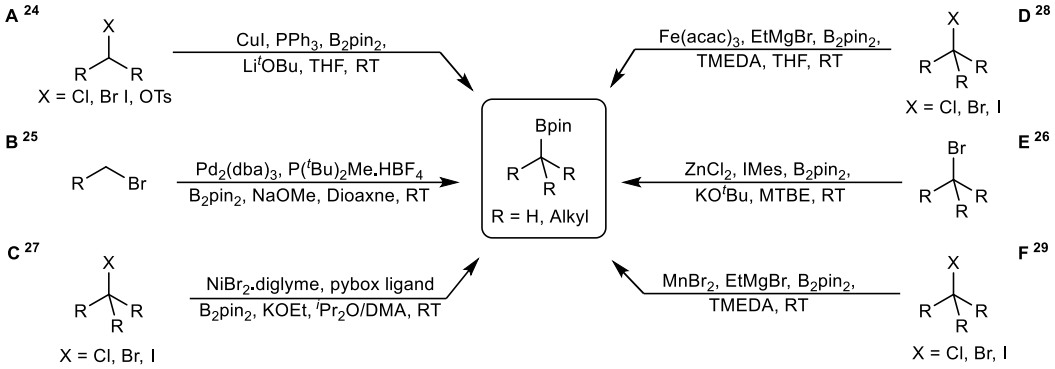


Figure 3: Electrophilic and nucleophilic borylation strategies.

Although useful for simple organoboron synthesis with limited functionality, the requirement for specific reaction conditions and propensity to overalkylation led to investigations into transition metal mediated borylations of organohalides. These nucleophilic borylations of organohalides can be mediated by numerous transition metals including Cu, Pd, Ni, Fe, Zn and Mn (Scheme 2).



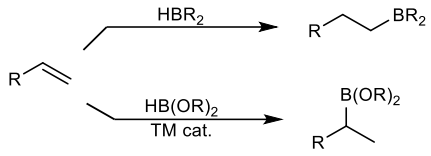
Scheme 2: Transition metal mediated nucleophilic borylations of alkyl halides.

Using various transition metal and ligand combinations 1°, 2° and 3° alkyl substituents with Cl, Br, I and OTs moieties can be coupled. Although a large number of systems exist, limitations related to substrate generality persist. Copper can be used to mediate the coupling of 1° alkyl halides, whilst 2° substrates are limited to the use of alkyl bromides and iodides (Scheme 2, A).[25] The Pd catalysed transformation only functions with 1° bromides (Scheme 2, B).[26] Utilising Zn facilitated the coupling with 1°, 2° and only one reported 3° alkyl bromide (Scheme 2, E).[27] The use of Ni, Fe and Mn mediated borylations enabled the most general strategies to access 1°, 2° and 3° boronic esters (Scheme 2, C, D, F).[28–30] The mild and functional group tolerant conditions of transition metal mediated nucleophilic borylation allow access to a wide range of boronic esters.[25–33]

1.1.2 Hydroboration

Hydroboration of alkenes and alkynes in a regioselective manner has become widespread in boronic ester synthesis since it was first reported by Brown (Scheme 3).[34] The hydroboration can be performed without a catalyst when employing highly reactive boranes. The uncatalysed hydroboration of unsymmetrical alkenes usually proceeds in an anti-Markovnikov fashion.[35] The addition of pinacolborane to unsaturated hydrocarbons largely requires the use of a catalyst due to the reduced electrophilicity of boron.[36] Transition metal catalysed reactions have since emerged allowing control over the chemo-, regio- and stereoselective outcomes of hydroboration. The divergent products are thought to originate from different reaction mechanisms. The regioselectivity of both catalysed and uncatalysed reactions can be influenced by substrate sterics and electronics.[35] The first reported metal catalysed hydroboration employed Wilkinson's catalyst in the addition of pinacolborane to alkenes.[37] This methodology delivered the same regioselectivity as uncatalysed hydroborations, forming

the 1° alkylboronic ester. Rh(I) catalysed hydroborations provided an additional benefit, in the presence of a ketone hydroboration would proceed chemoselectively at the alkene.



Scheme 3: Generalised reaction outcomes of uncatalysed hydroboration forming anti-Markovnikov products and catalysed hydroboration forming Markovnikov products.

Interest in rhodium catalysed hydroborations provided wide-ranging reports employing a number of diphosphine ligands.[18] Complimentary to uncatalysed reactions a switch in regioselectivity was detected with the use of cationic rhodium complexes, forming the Markovnikov product.[18] Investigation into the mechanism of both processes highlighted differences when altering the rhodium catalyst (Figure 4). The proposed mechanisms both proceed via an oxidative addition/insertion/reductive elimination pathway. Importantly, when using the cationic rhodium process an η^3-benzylrhodium complex **1** is formed, determining the regioselective outcome of the reaction. Due to steric factors forming the Rh complex **2** the neutral pathway forms the 1° product.

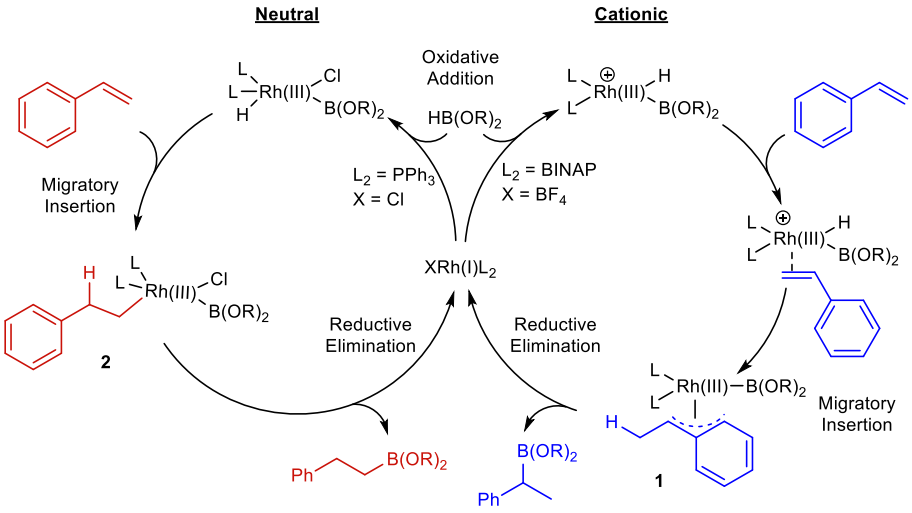
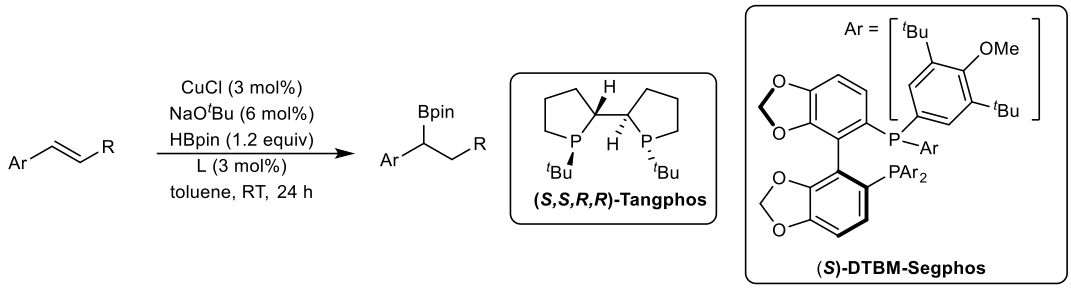


Figure 4: Simplified neutral and cationic Rh catalysed hydroboration cycles.

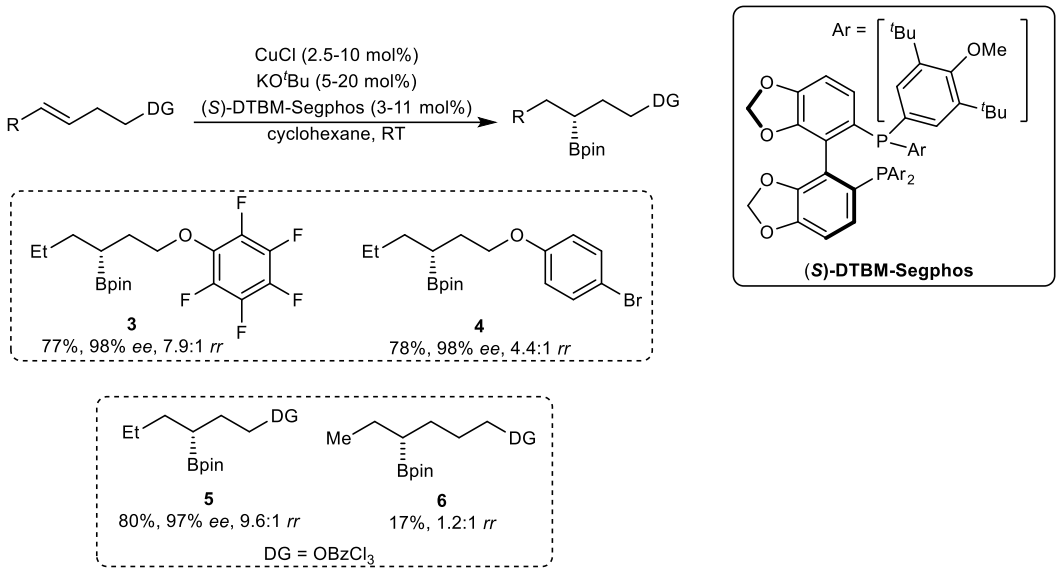
Research has since expanded, focusing on the more abundant first row transition metals, reports of catalysed hydroborations employing Fe, Co, and Cu have emerged. A Cu(I) catalysed hydroboration of styrenes with pinacolborane, employing bisphosphine ligand Tangphos was reported by Yun and co-workers (Scheme 4).[38] Although the scope remained limited to

styrenes, the group later utilised (*S*)-DTBM-Segphos as a ligand in their methodology, giving products with excellent enantioselectivities.[39]



Scheme 4: Cu-catalysed hydroboration of styrenes.[38,39]

Hartwig and co-workers further expanded substrate compatibility of Cu-catalysed hydroborations to internal alkenes (Scheme 5).[40] Using a directing group (DG) strategy and (*S*)-DTBM-Segphos, hydroborations could be performed with high regio- and enantioselectivity. Regioselectivity was greater for substituents bearing more electron-withdrawing moieties, **3** when compared to less electron-withdrawing groups **4**. Proximal polar groups are able to stabilise negative charge accumulation created at carbon during formation of the Cu-C bond.[40,41] Regioselectivity was also diminished when the distance between the olefin and DG is increased, from a 5-membered, **5** to an increased 6 membered-ring Cu-DG chelate, **6**.



Scheme 5: Cu-catalysed hydroboration of unactivated alkenes.[40,41]

Yun proposed a mechanism for the formation of the benzylic boronic ester products from the hydroboration of styrenes.[38] Mechanistic investigations relating to the hydroboration of unactivated alkenes were also subsequently performed by Hartwig and co-workers.[40,41] Both

mechanistic proposals of Cu-catalysed hydroborations were generally in agreement (Figure 5). Initially transmetalation of a Cu(I) complex with pinacolborane, forms Cu-hydride **7**. Alkene insertion into the Cu-H bond generates Cu-alkyl **8**, which can undergo transmetalation with pinacolborane forming **9**. Formation of the desired benzylic boronic ester and regeneration of Cu-hydride **7** is then achieved.

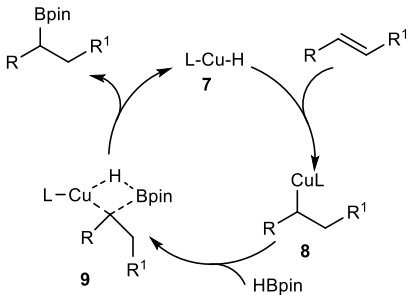
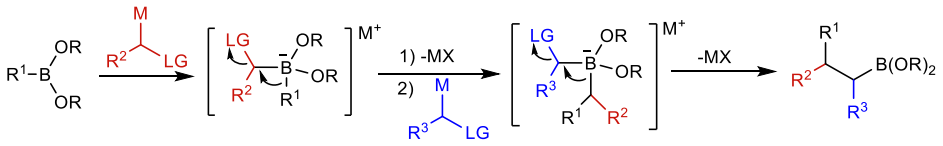


Figure 5: Proposed mechanism for Cu-catalysed hydroboration of alkenes.[38,40,41]

1.1.3 1,2-Metallate Rearrangements

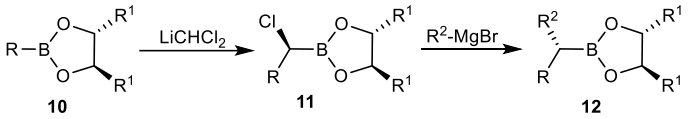
A boronate 1,2-metallate rearrangement encompasses boron bound to an R group migrating to an α-carbon (Scheme 6). Upon migration, loss of a leaving group from the α-carbon forms a new C-C bond.[17] The process can be repeated in a sequential manner, extending the carbon chain. The rearrangement proceeds only when an anti-periplanar alignment of the migrating and leaving groups is achieved. The migration is therefore stereospecific with inversion occurring at the α-carbon.[42] Non-racemic homologation can be accomplished via substrate control, utilising a chiral auxiliary on the boronic ester component. Alternatively, enantioselectivity can be imparted with reagent control by use of an enantioenriched carbenoid.



Scheme 6: Iterative 1,2-metallate rearrangements of a boronic ester.

Displacement of halogens from α-haloalkane boronic esters by nucleophiles was first noted by Matteson and Mah.[43] General utility of this homologation method was halted due to difficulty synthesising the α-haloalkane boronic ester precursors.[44] The potential importance of the onwards homologation was noted, resulting in reports of synthetically useful procedures to access α-haloalkane boronic esters.[45] Matteson first reported the use of dichloromethyl lithium

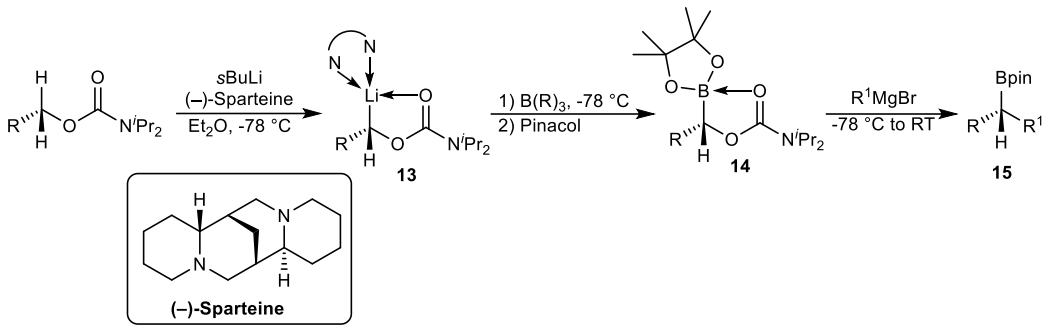
in the synthesis of α-chloroalkylboronic esters.[46,47] Extending this work Matteson described a 1,2-metallate rearrangement with a chiral-diol ligated boronic ester, exploiting substrate controlled homologation (Scheme 7).[48,49] The method proceeds in a sequential two-step reaction, initially with addition of dichloromethyl lithium to the boronic ester **10**, forming an enantioenriched α-alkylboronic ester **11**. Subsequent addition of a nucleophile, frequently a Grignard reagent delivered boronic ester **12** with excellent diastereoselectivity. Subsequent reports highlighted the use of zinc chloride to improve stereoselectivity of the boronic ester products and promote 1,2 metallate rearrangement.[50]



Scheme 7: Matteson's sequential substrate-controlled homologation.

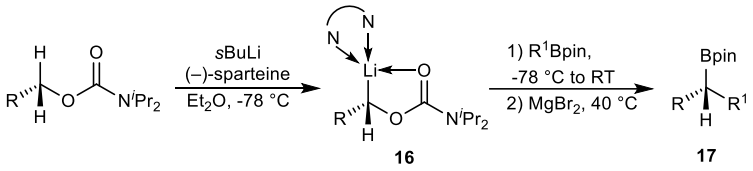
Substrate controlled homologation whilst powerful, is problematic, as stereochemical outcomes are dependent on the stereochemistry of the boronic ester. If a switch in stereoisomer is required a non-trivial replacement of the chiral auxiliary is necessary.[51] Reagent controlled homologation provides advantageous access to the desired enantiomer by easily selecting the appropriate stereochemical reagent.

Reagent controlled homologation was first reported by Hoppe (Scheme 8).[52,53] Lithiated chiral carbamates were utilised in the asymmetric synthesis of boronic esters. The methodology presented followed the stepwise Matteson-type homologation. Retentive stereochemical deprotonation of alkylcarbamates in the presence of *s*-BuLi and **(−)**-sparteine, produced enantioenriched lithiated carbamates **13**. Trapping with a borane and subsequent transesterification produced boronic ester **14** with retentive stereochemical configuration. Access to the 1,2-metallate rearranged product **15** is achieved with addition of a Grignard reagent. The carbamate, alongside being able to provide an activated leaving group to fulfil 1,2-metalate rearrangement requirements also provides several stabilising effects throughout the reaction. Lithiation is directed alpha to the carbamate due to coordination of the carbonyl oxygen. The carbamate stabilises the lithiated intermediate, avoiding decomposition of the carbenoid intermediate. The resulting boronic esters are likewise thought to be stabilised by electron density donation from the carbonyl into the empty p-orbital on boron.



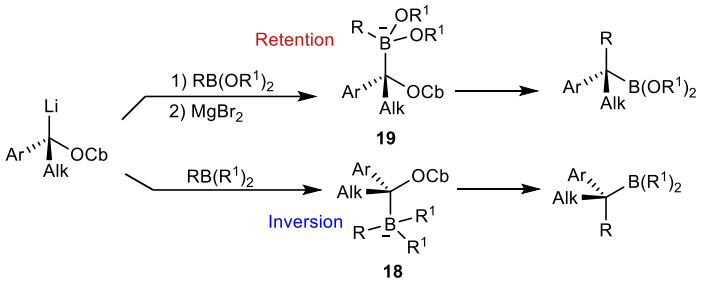
Scheme 8: Hoppe carbamate lithiation in boronic ester homologation.[52,53]

Aggarwal and co-workers simplified the methodology using carbamates reporting a one-step lithation borylation (Scheme 9).[54] The strategy built on the same principles as Hoppe's homologation. Reagent controlled carbamate lithiation products **16** were stereoretentively reacted with boronic esters, forming the boronate complex that can undergo steroinvertive 1,2-metallate rearrangement to give boronic ester **17**. This methodology negated the use of a Grignard reagent to induce homologation by directly using the boronic ester. The 1,2-metallate rearrangement is slower for boronic ester substrates than for boranes.[55,56] In agreement with Matteson's observations the addition of Lewis acids, specifically magnesium bromide enhanced the ate rearrangement in these cases.[50,54]



Scheme 9: Aggarwal's lithiation borylation methodolodgy.[54]

Aggarwal was able to expand the homologation reaction to access 3° borane or boronic esters (Scheme 10).[57–61] Interestingly, when using these 2° carbamates the stereochemical outcome is dependent on the boron reagent. Inversion of stereochemistry is observed when using boranes **18** and a retention of stereochemistry **19** is detected when using boronic esters.[62] This outcome is thought to be due to the ester moiety present in boronic esters. The oxygen in the ester can coordinate with the lithiated carbamate, delivering the boronic ester to the same face as the metal. Lacking oxygen, boranes are unable to complex and react on the opposite face to the metal. This is due to avoidance of the buildup of electron density around the metal caused by the flattened nature of the benzylic carbamate. The structure of the boron only influences stereochemical outcomes when benzylic carbamates are employed, due to its influence on electron density. Consequently, when using alkyl carbamates all substrates proceed with stereochemical retention.



Scheme 10: Stereochemical outcomes of lithiation borylations of 2° carbamates with boronic esters or boranes.

1.2 Methods to Prepare C-N Bonds

Carbon-nitrogen bonds are prevalent in many pharmaceuticals, agrochemicals and dyes (Figure 6).[1,63] During an analysis of synthetic methodologies used in medicinal chemistry it was found that 'many C-N bond forming reactions occur'.[64] The synthesis of C-N bonds is still a challenging process as common methods show poor selectivity, use of expensive catalysts, and/or require harsh reaction conditions.[65] The development of new methods to form C-N bonds, with high functional group tolerance and mild reaction conditions, is therefore highly desirable.

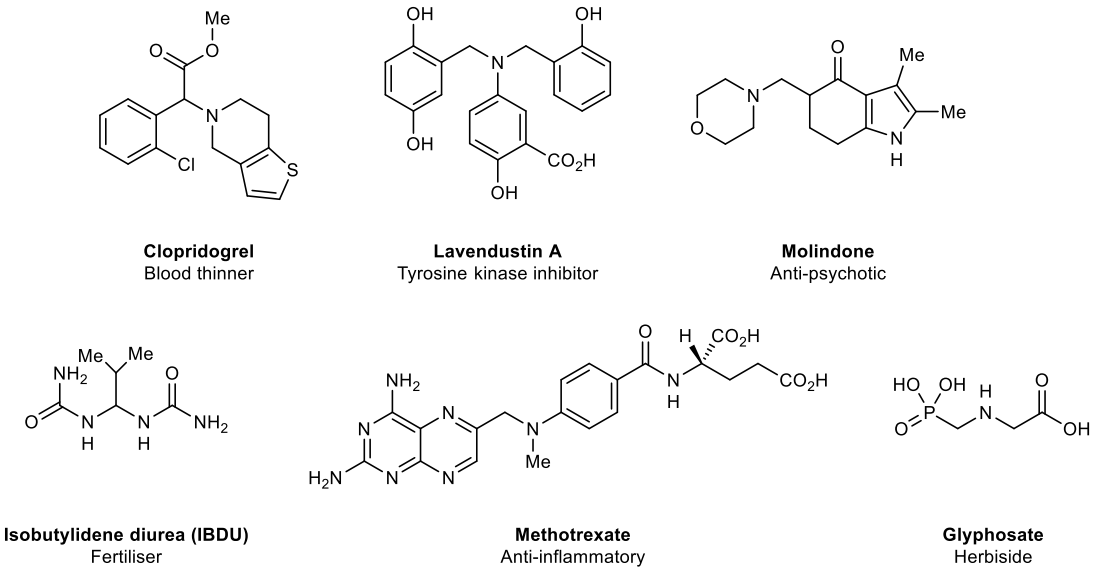
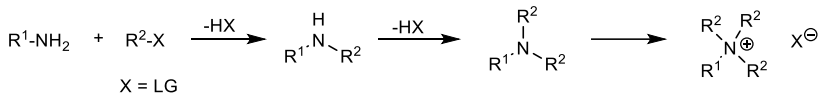


Figure 6: Examples of carbon-nitrogen bonds present in pharmaceuticals and agrochemicals.

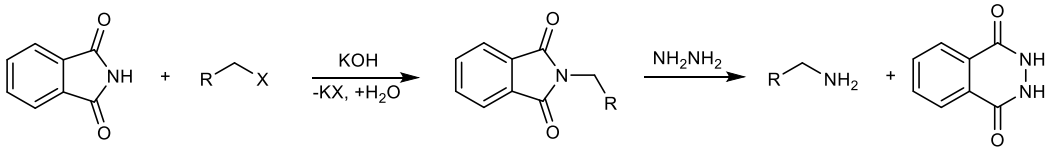
1.2.1 Nucleophilic Substitution

One such method to form a new C-N bond is the nucleophilic substitution of a nitrogen nucleophile and alkylating agent (Scheme 11). The propensity for overalkylation to occur is high, due to the increase in nucleophilicity of the products. This often results in further substitution reactions occurring, eventually leading to the formation of quaternary ammonium salts. The selectivity of the reaction is therefore often limited, and a mixture of substituted amines is generally produced. Formation of 2° amines can sometimes be controlled by using an excess amount of amine. This is consequently an unrealistic strategy for use in large scale syntheses or when using a costly amine.



Scheme 11: Nucleophilic substitution of amines resulting in overalkylation.

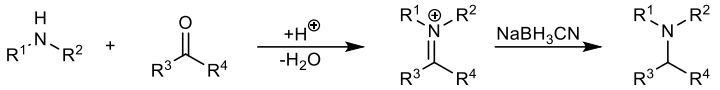
An alternative protecting group strategy can be employed, such as in the Gabriel synthesis to form 1° amines (Scheme 12).[66] However, protecting group strategies require extra steps to install and remove the protecting group, reducing the efficiency and atom economy of the overall process.



Scheme 12: Gabriel synthesis of 1° amines.

1.2.2 Reductive Amination

Another more versatile methodology to control amine formation is reductive amination. This relies on condensing an amine with an aldehyde or ketone to form an iminium ion. The second step is reduction of the iminium ion with a weak reducing agent (Scheme 13). This process can be carried out as two single steps. Alternatively, the reduction can be performed *in situ* if a selective reducing agent is chosen that will not reduce the carbonyl precursors e.g. sodium cyanoborohydride and sodium triacetoxyborohydride (STAB).



Scheme 13: Reductive amination of aldehydes or ketones, reduced with a weak reducing agent.

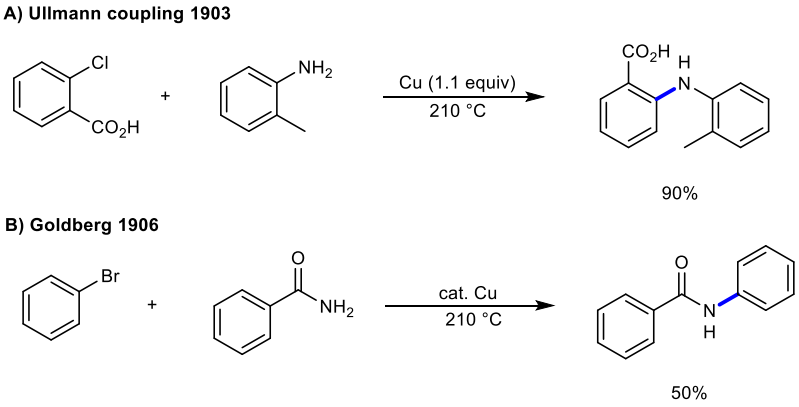
Reductive amination is an advantageous alkylation method as installation of the alkyl groups can be controlled. Sequential reductive aminations can be employed to form 3° amines. The protocol is generally highly functional group tolerant and high yielding, with minimal side products when only one carbonyl is employed. However, this method is limited to the formation of Csp^3-N compounds.

1.3 Transition metal mediated cross coupling reactions in the formation of C-N bonds

1.3.1 Ullmann Coupling

Transition metal mediated cross-couplings offer an alternative method for the synthesis of C-N bonds. These methods were introduced to overcome issues associated with previous C-N bond formation and allowed access to arylamines.

Initially there were two established methods for the transition metal catalysed formation of C-N bonds, Ullmann-Goldberg and Buchwald-Hartwig coupling. Ullmann reported in 1903 the copper mediated coupling of aryl halides and amines to form a new C-N bond (Scheme 14, A).[67] Goldberg reported shortly afterwards a similar Cu catalysed coupling of amides (Scheme 14, B).[68] These reactions despite the use of cheap Cu were limited by the range of scope, low yields and harsh conditions.[69] Excess Cu was often essential due to its poor solubility.[70]



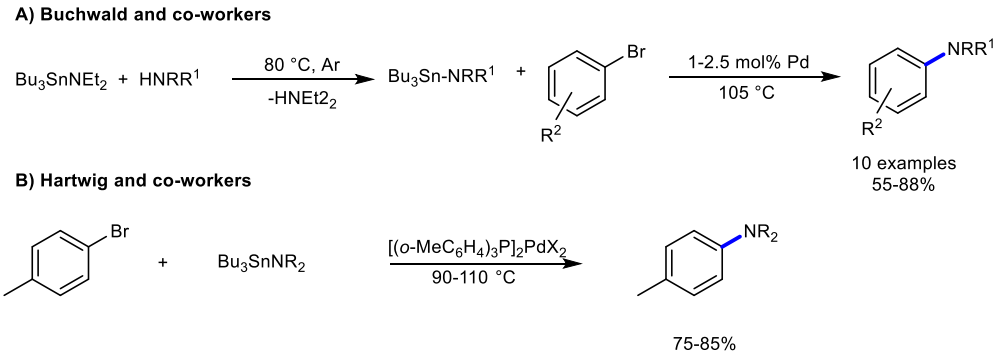
Scheme 14: Cu-mediated couplings to form C-N bonds.

Initial reports of Ullmann-Goldberg couplings did not include ligands.[69] It was proposed that some ketones and esters could promote the reaction, mainly attributed to improved solubility of Cu.[71] Liebeskind and Buchwald reported the addition of thiophene carboxylate and naphthoic acid respectively to give improved yield.[72,73] These additives were each initially attributed to differing roles, either aiding oxidative addition or enhancing solubility. Subsequently, Buchwald and co-workers employed stoichiometric phenanthroline and dibenzylideneacetone as an additive.[74] This prompted studies on further bidentate ligands, which appear more active than monodentate ligands.[75] Most commonly *N*- and *O*-based ligands are used in Ullmann couplings.[69] The use of ligands allowed the reduction of reaction temperatures and sub-stoichiometric amounts of Cu, resulting in milder reaction conditions.[69] Taillefer and co-workers investigated the reaction mechanism using cyclic voltammetry and SAR.[76–79] Buchwald and co-workers also performed mechanistic studies using kinetics.[80,81] Whilst these mechanistic probes have been undertaken, the role of the ligand is still underexplored.[82]

Several reviews on the Ullmann coupling have been reported.[69,83]

1.3.2 Buchwald Hartwig Coupling

Buchwald and co-workers later developed a palladium catalysed cross coupling, utilising in situ generated organostannanes (Scheme 15, A).[84] Independently Hartwig and co-workers reported similar cross-coupling conditions to form a new C-N bond (Scheme 15, B).[85] These reaction conditions also suffered drawbacks, the use of expensive Pd and the toxicity of Sn, as well as high reaction temperatures and strong bases. The avoidance of Sn was later overcome after studies into the reaction mechanism by Hartwig and co-workers.[86]



Scheme 15: Pd-catalysed Buchwald-Hartwig cross couplings.

The use of bulky P(*o*-tolyl)$_3$ was common in initial reports and is often referred to as a 'first generation' catalyst. However, coupling of 1° amines could not be effectively undertaken due to the competitive β-hydride elimination.[87] Evolution of the reaction to avoid harsh conditions, expand scope and improve selectivity was controlled by ligand design.[88]

Aims to generalise the reaction were aided by so called 'second generation' ligands. These were aromatic bisphosphine ligands defined by their chelating nature. BINAP and dppf ligands were primarily utilised (Figure 7). Chelation of the ligands to the metal centre supressed β-hydride elimination, promoting reductive elimination and therefore increasing yield.[87] Despite improvement, the amination of aryl chlorides were limited and high reaction temperatures were required.

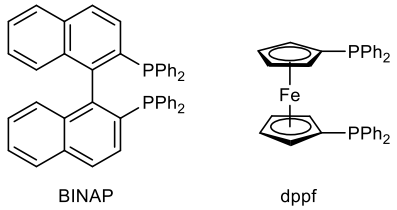


Figure 7: BINAP and dppf 'second generation' aromatic bisphosphine ligands.

Focus shifted to the use of biaryl monophosphine ligands in a more active 'third generation' catalyst. The most developed ligands often had bulky alkyl groups at phosphorus.[88] DavePhos, JohnPhos, XPhos, BrettPhos, SPhos and RuPhos have enhanced the reactivity of aryl chlorides under mild conditions (Figure 8).

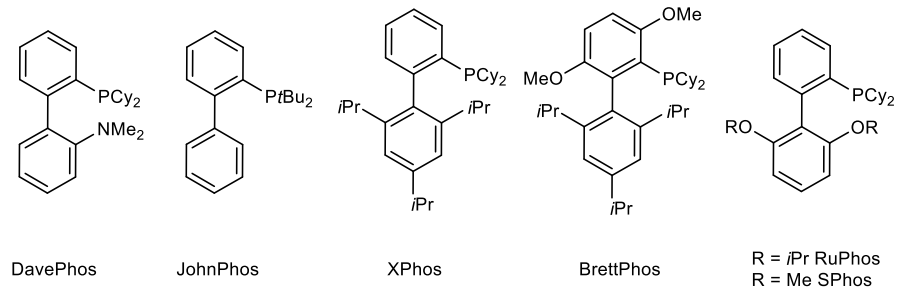
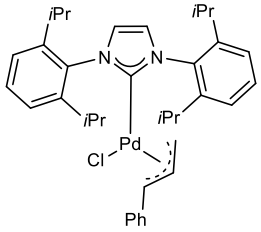


Figure 8: Biaryl monophosphine ligands used in 'third generation' Buchwald-Hartwig catalysts.

Alongside this, *N*-heterocyclic carbenes encompassing strong electron donating and sterically hindered components were developed for the coupling of aryl halides and heteroatom nucleophiles.[87,89] Due to their robustness and tunability a number of Pd-NHC catalyst

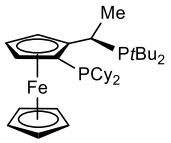
precursors were reported.[90] The coupling of aryl chlorides at room temperature could be mediated by the use of **20**, which had been modified to include a cinnamyl ligand (Figure 9).[91]



20

Figure 9: Pd(II) NHC complex with tuned cinnamyl ligand.

Despite increased reaction scope, these catalysts still suffered with selectivity issues, often producing mixtures of mono- and diarylation products and regularly required increased loadings of palladium.[89] An extremely hindered, electron donating and air-stable JosiPhos-type ligand **21** was used by Hartwig and co-workers to overcome key issues with previous catalysts (Figure 10).[89] The use of ligand **21** enabled the coupling of heteroaryl or aryl chlorides with 1° amines, including ammonia to selectively produce the monoarylated product. Thiols could also be coupled with haloarenes to form aryl thioethers. Whilst there has been considerable development towards generality, no ligand is superior for all substrates.[87]



21

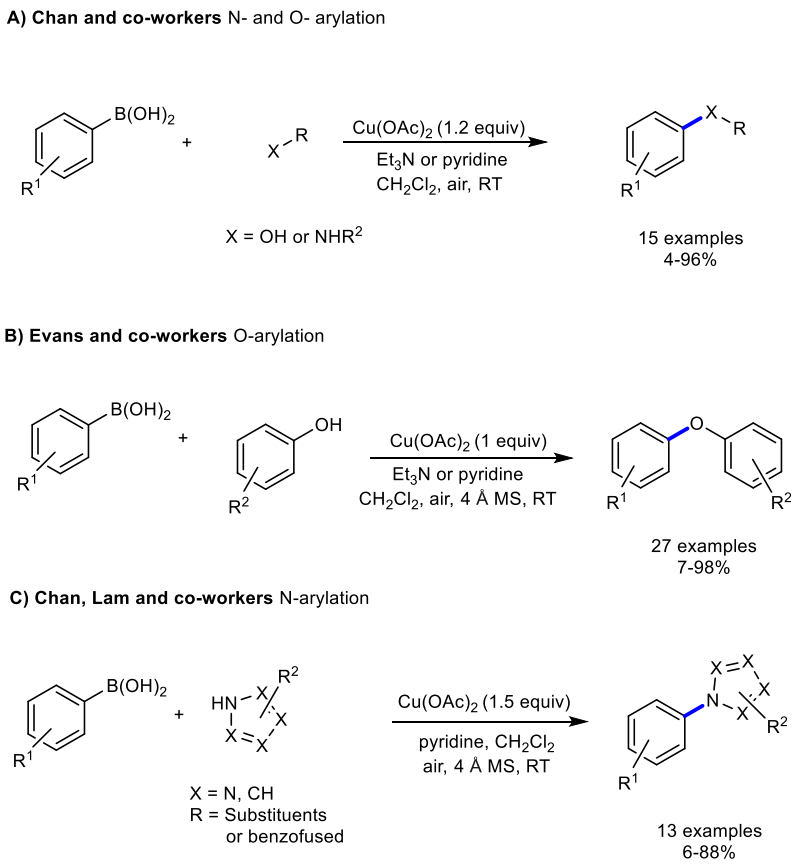
Figure 10: JosiPhos CyPF*t*Bu 'fourth generation' ligand.

Buchwald-Hartwig couplings to form Csp^3-N bonds are limited, although stoichiometric[92–94] and catalytic examples have been reported.[95,96] This is due to the challenging reductive elimination of alkyl-Pd-NR_2 complexes to form alkylamines. The formation of these alkylamines is highly desirable due to their use in pharmaceuticals, therefore the advancement of methodology to reliably form Csp^3-N is required.[97]

Several reviews on the Buchwald Hartwig coupling[87,98,99] and its applications have been reported.[100]

1.3.3 Chan-Lam Coupling

A further breakthrough came in 1998, when a copper-mediated oxidative coupling of boronic acids and heteroatom-based nucleophiles was reported to form new C-N and C-O bonds. Chan and co-workers published the coupling of arylboronic acids with alcohols and amines mediated by copper acetate (Scheme 16, A).[101] Evans and co-workers independently reported the copper acetate mediated coupling of arylboronic acids and phenols to form ethers (Scheme 16, B).[102] Another report by Chan, Lam and co-workers came on the coupling of arylboronic acids and heteroaryl compounds to form new C-N bonds also mediated by copper acetate (Scheme 16, C).[103]



Scheme 16: Chan, Evans and Lam's reports of copper-mediated coupling of boronic acids and heteroatoms.

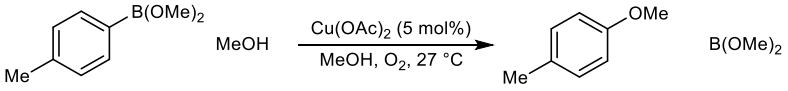
These simultaneous reports of copper-mediated cross couplings of boronic acids and heteroatom-based nucleophiles had a number of similarities in method, which are frequently referred to as "classical" conditions[101–103] and led to the establishment of the Chan-Lam reaction. Early publications often used $Cu(OAc)_2$ as the copper source, triethylamine as a base, DCM as the solvent, requiring no ligand or additive at room temperature. In general, the Chan-

Lam coupling has been found to be functional group tolerant and have a broad reaction scope. An additional benefit is that the copper acetate catalyst employed is cheaper than the palladium catalysts required for Buchwald-Hartwig amination.

1.3.4 General Mechanistic Insight of the Chan-Lam Reaction

To give background to the discussion of substrate scope and reaction variables consideration needs to be given to the mechanism of the Chan-Lam coupling. A number of studies into the mechanism have been undertaken.[102,104–111] Despite this there remain key holes in knowledge, due in part to the complex role of copper, the formation of by-products and the alteration of variables which could impact the kinetics and pathway.

The Stahl group investigated the mechanism of the Chan-Lam etherification reaction.[107,108] The group aimed to elucidate information surrounding the catalyst resting state, the turnover-limiting step and the copper mediation of a two-electron oxidative coupling. The investigation was based upon a model system, coupling *p*-tolylboronic acid dimethyl ester with methanol under catalytic copper conditions (Scheme 17). They performed a number of gas uptake measurements and kinetic EPR studies.



Scheme 17: Model system used in mechanistic insights into Chan-Lam etherification.

Their first study was able to confirm a number of mechanistic insights, such that the group were able to offer a proposed a mechanism for the Chan-Lam etherification (Figure 11).[108] The mechanism begins with an undefined Cu(II) species **22**. Lewis pairing of **22** with the organoboron compound leads to Cu(II) complex **23**. This species **23** then undergoes the turnover limiting transmetalation to form Cu(II) complex **24**. Disproportionation with another Cu(II) species forms Cu(III) species **25**, which undergoes reductive elimination with methanol to release the desired coupled product and a Cu(I) complex **26**. Oxidative turnover of Cu(I) **26** with O_2, HX and the by-product of transmetalation reforms the Cu(II) species **22**.

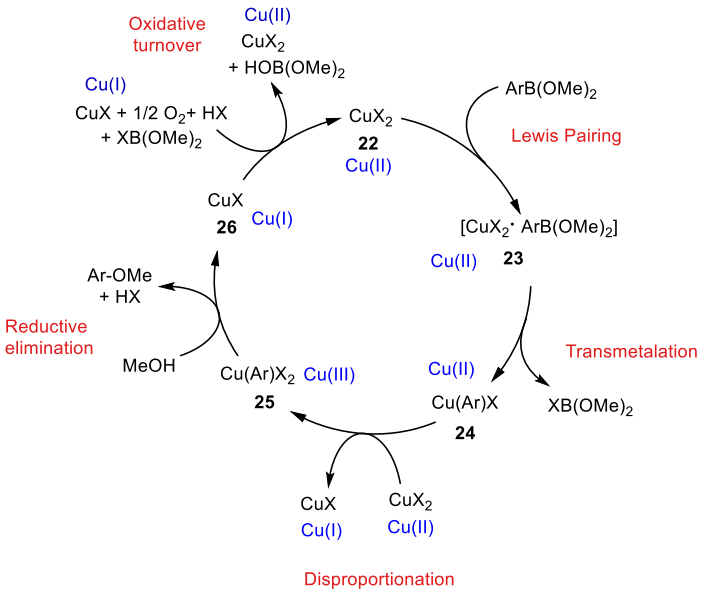


Figure 11: Proposed mechanism of Chan-Lam etherification.

The groups experimental findings informed and solidified their proposed reaction mechanism. The relative stoichiometry of Cu(II):product was determined to be 2:1, supporting the need for a second equivalent of Cu(II) for disproportionation. The reaction proceeds without O_2 present, therefore Cu(II) can act as an oxidant, which also supports the idea of disproportionation. From kinetic studies it was found there was a first order dependence on $[Cu(OAc)_2]$, saturation dependence on $[ArB(OMe)_2]$ and zero order with respect to $[O_2]$. These dependencies suggest that Cu(I) re-oxidation is quicker than initial substrate oxidation. Consequently, the turnover limiting step is proposed to be the transmetalation of the aryl group to Cu. During EPR studies it was found almost all Cu in solution was Cu(II), which lacked strong donor ligands, reinforcing the hypothesis that transmetalation is the turnover limiting step.

Stahl's second study undertook further kinetic and spectroscopic investigations into Chan-Lam etherifications, focusing on inhibitory effects and a proposal of the mechanism of transmetalation.[107] The addition of AcOH or AcO^- was found to have an inhibitory effect on the reaction when using $Cu(OAc)_2$ as a catalyst. Substituting $Cu(OAc)_2$ for $Cu(ClO_4)$ rendered the reaction inactive. Reactivity could be reinstated with the addition of AcO^-, highlighting its importance. Activity when using $Cu(ClO_4)$ could also be enhanced with the addition of MeO^-. From these findings they were able to suggest resting states prior to transmetalation (Figure 12). The inactive copper paddlewheel **27** enables formation of acetate bridged heterobimetallic Cu(II)/boron species **28**. Upon loss of acetate, complex **28** can undergo rearrangement to

methoxide bridged species **29**, where transmetalation can then occur. These insights offered a foundation for future mechanistic studies into Chan-Lam couplings.

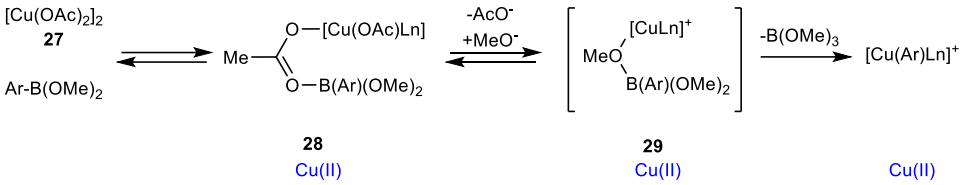


Figure 12: Proposal of catalyst resting states prior to transmetalation.

Building on the work of the Stahl group the Watson group explored spectroscopically the reaction of arylboronic acids and esters with alkyl and arylamines.[109] After extensive work the group proposed the following reaction mechanism (Figure 13). $Cu(OAc)_2$, which generally exists in solution as a paddlewheel dimer **30**, is denucleated to an active mononuclear Cu(II) species **31** by the amine. This Cu(II) species **31** is also in equilibrium with its dimer **32** and tetramer **33**. A Lewis pairing event occurs between the hydroxy group on copper and the organoboron species to form **34**. This species allows transmetalation delivering the aryl copper complex **35**. Disproportionation with a second Cu(II) complex give Cu(III) intermediate **36**. Reductive elimination can then occur, to form the coupled product and a Cu(I) species **37**. The Cu(I) species **37** is then oxidised back to the reactive Cu(II) **31** complex by oxygen, completing the cycle. If the oxidative turnover is inefficient, products from protodeboronation, oxidation, and oxidative homocoupling can occur.

Catalyst deactivation can be promoted by both acetic acid and pinacol, resulting in a detrimental effect on the yield of the Chan-Lam reaction. The paddlewheel dimer **30** can be reformed by AcO^-, preventing the formation of the active catalyst **31**. AcOH in the system prevents denucleation via protonation of the amine and can subsequently form the hexa-acetate paddlewheel **38**. The use of pinacol boronic esters is thought to be troublesome in Chan-Lam reactions due to catalyst inhibition through coordination of pinacol, formed as a by-product of transmetallation, to give complex **39**.

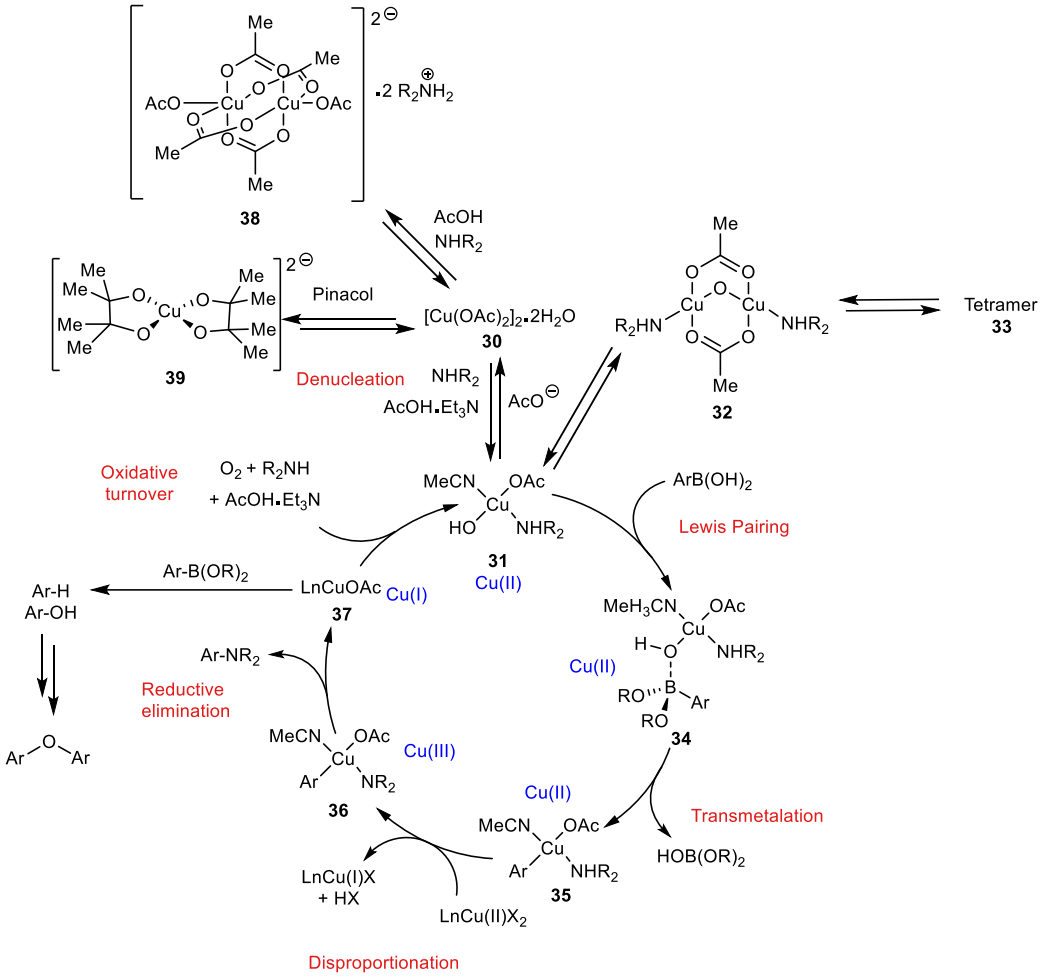


Figure 13: Mechanism for the Chan-Lam amination suggested by Watson and co-workers.

The formation of by-products in the Chan-Lam reaction is commonplace. Their production is often derived from the degradation of the organoboron reagent, or as a consequence of further reactions of the organoboron reagent with its degradants (Figure 14).[109,112] Alongside the desired C-heteroatom bond formation, oxidation, oxidative homocoupling and protodeboronation all frequently occur.[112] Less commonly observed is the reductive homocoupling product[109,110] for which the mechanism for its formation uncertain.[113] The oxidation of the boronic acid allows the formation of phenol, which in turn can react in a Chan-Lam etherification with the boronic acid to form the diaryl ether by-product.[109] Lam reported that the oxidation product forms from water present in the reaction,[104] therefore the use of anhydrous reaction conditions and molecular sieves can reduce the formation of phenol, and subsequently the etherification product.[112,114] Organoboron protodeboronation using Cu(II) has been documented since 1930,[115,116] and can occur when no other pathway is present.[109]

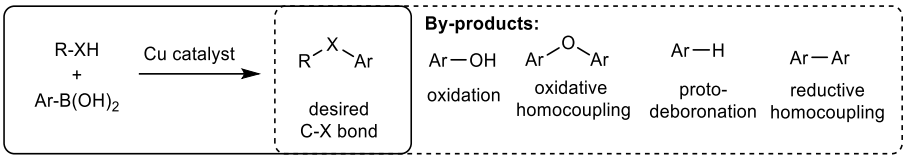


Figure 14: By-product formation during Chan-Lam reactions.

Typical Chan-Lam conditions are relatively similar across most reports, though challenging substrates often require further reaction optimisation. Some common features include:

1. An excess of the boron reagent is often used, due to the formation of by-products originating from the organoboron reagent.[112]
2. The copper source used in these reactions is usually $Cu(OAc)_2$, with early examples employing super-stochiometric loadings.[101–103] Copper acetate is relatively inexpensive, making it a practical choice. The reaction requires two equivalents of Cu(II) per C-X bond formed.[107–111,117] Where sub-stoichiometric loadings of copper are used, oxygen or another oxidant is required for catalyst turnover. Some solid oxidants, such as TEMPO and pyridine-*N*-oxide have been used in Chan-Lam couplings, but increase complexity and cost-efficiency.[118–120]
3. The solubility of copper is critical and therefore solvent choice is significant. The use of DCM is most prevalent in Chan-Lam couplings.[112] Alcoholic solvent additives can be used to improve solubility, however, their use can result in competing etherification.[112]
4. The majority of Chan-Lam reactions do not employ a ligand, a more limited number include them or add a preformed Cu-ligand complex.[112] If included, the ligands often have a bis-nitrogen structure.[106,121–128] Reports of pre-formed complexes include $[Cu(OH)\cdot TMEDA]_2Cl_2$,[105,106] $[Cu(DMAP)_4I]I$[129] and Schaper's tailored complexes.[110,117]
5. Many of the reactions do not require an additive. The addition of boric acid has been shown to enable the effective coupling of arylboronic esters by preventing pinacol inhibition of the catalyst.[109]
6. An equivalent of HX is produced in the disproportionation step, therefore addition of a base in some systems is required to prevent protonation of the amine coupling partner, which would inhibit denucleation. Initial Chan-Lam couplings reported the addition of a base enhanced reaction yield.[101–103] Subsequent reports have often used weak organic bases,

namely triethylamine and pyridine.[112] Despite this a number of base-free couplings have been documented.[109,122,130–134] The amine could realise the role of the base in this instance.

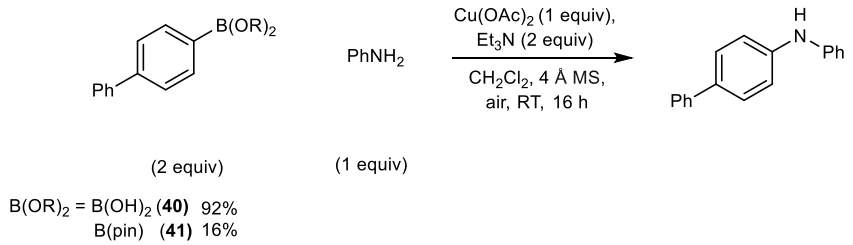
7. Chan-Lam couplings are often performed at room temperature, with some substrates requiring heating. Increased temperature has been used to improve efficiency or promote solubility of the copper source.[112]
8. The organoboron substrate scope of initial reports of Chan-Lam couplings was limited primarily to arylboronic acids. The use of alkylboronic acids was less frequent. The analogous boronic esters use is limited due to the copper inhibition by pinacol.[109] Work to increase substrate scope of the organoboron reagent and the coupling partner has been ongoing since the discovery of the reaction.

1.3.5 Substrate variation of the Chan-Lam Reaction

Method development has expanded the substrate scope of the organoboron reagent to include boronic esters, trifluoroborates, boroxines and triolboronates.[112] Arylboronic acids are still the predominant boron substrate used for Chan-Lam couplings. However, the use of boronic esters in Chan-Lam couplings would be advantageous due to their increased stability.[1]

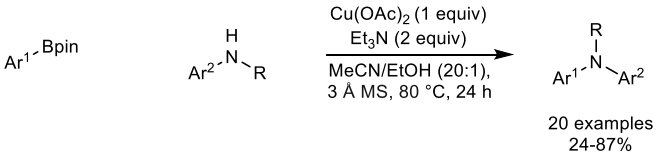
1.3.5.1 Arylboronic Acids and Esters

There has been reported difficulty in utilising boronic esters under classical Chan-Lam reaction conditions (Scheme 18).[109] It is thought that reduced yields for reactions of pinacol boronic ester are due to the release of pinacol after transmetalation, which can inhibit the copper catalyst.[109] Diols such as pinacol are known to form complexes with Cu(II) sources, therefore causing immediate slowing of reaction rate.[135,136] Boronic esters also have a lower general reactivity when compared to boronic acids, this consequently leads to lower yields in the Chan-Lam reaction.[137] Highlighted in a study by Watson and co-workers arylboronic acid **40** produced coupled product in good yield when compared to arylboronic ester **41**.[109]



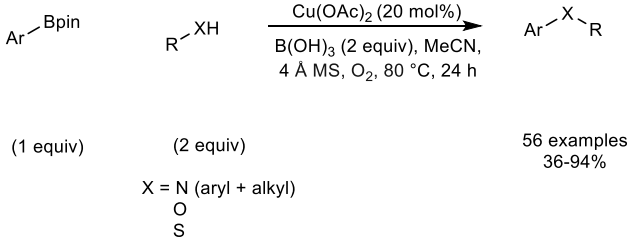
Scheme 18: Comparison of the yields of a boronic acid and boronic ester in a Chan-Lam reaction.[109]

Watson and co-workers explored methods to overcome this difficulty when using boronic esters in Chan-Lam couplings.[138] The group developed a mixed solvent method in the coupling of arylboronic esters with arylamines (Scheme 19). The use of the solvent system in a ratio of 20:1, acetonitrile to ethanol, minimised the formation of the etherification product. The reaction could not be performed using sub-stoichiometric loadings of $Cu(OAc)_2$, due to pinacol inhibition. Therefore stoichiometric quantities are thought to aid reactions when using boronic esters.[138] Many functional groups are tolerated under these reaction conditions. However, when performing the reaction with alkylamines the addition of ethanol was not required.



Scheme 19: Mixed solvent method in the coupling of arylboronic esters and amines.

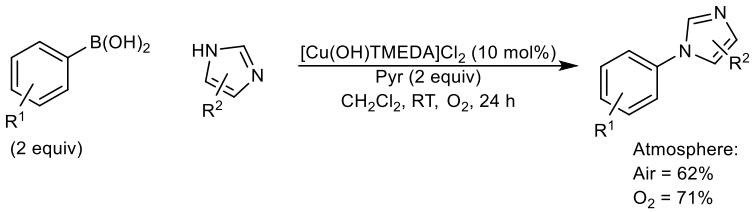
Watson and co-workers later discovered that boric acid can sequester pinacol during the reaction, reducing inhibition of the copper catalyst (Scheme 20).[109] The substitution of triethylamine for boric acid as an additive also promotes oxidation of Cu(I) to Cu(II), enabling turnover.[109] The reaction conditions were found to be suitable for coupling of alkyl and arylamines, phenols, and thiols.



Scheme 20: Boric acid promoted Chan-Lam coupling of arylboronic acids.[109]

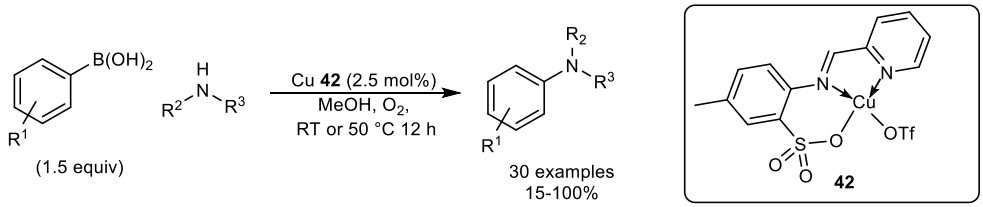
Chan-Lam couplings do not generally employ the use of a ligand or preformed Cu complex. Despite this Collman reported the use of $[Cu(OH)TMEDA]_2Cl_2$ as a preformed

catalyst (Scheme 21).[105] The preformed catalyst had been previously used in aerobic oxidations, with O_2 regenerating the catalyst.[139,140] The catalyst was able to mediate the coupling of arylboronic acids and imidazoles. Lower conversions were reported using ambient air rather than O_2, highlighting the importance of efficient re-oxidation.



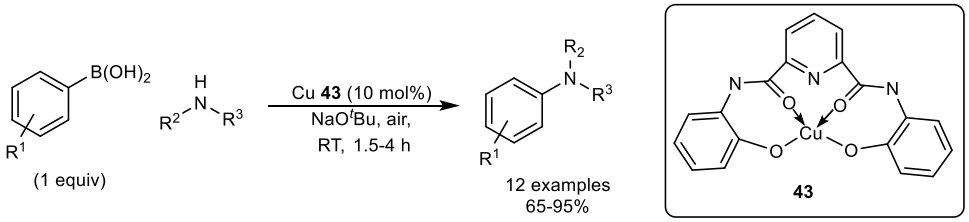
Scheme 21: Imidazole coupling with a preformed complex under O_2.[105]

Cu-complexes have since been reported to promote the coupling of arylboronic acids with aryl and alkylamines. Nitrogen, oxygen and sulfur bi-, tetra- and multidentate ligands have been reported to enable a wider scope of coupling partner under mild and catalytic conditions. Schaper and co-workers reported a pyridylamino arylsulfonate complex efficiently coupling boronic acids with varied nucleophiles including sterically demanding *tert*-butylamine (Scheme 22).[110] Common oxidation and degradation by-products were not observed when using complex **42**.



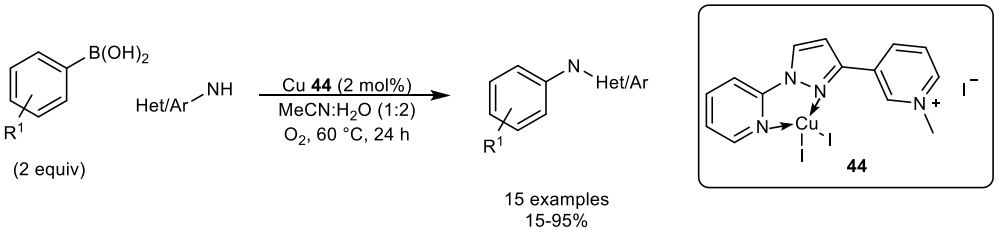
Scheme 22: Coupling boronic acids with a pyridylamino arylsulfonate complex **42**.[110]

Aberi and co-workers have reported a solvent free, polydentate pyridyl Cu complex facilitating coupling of boronic acids and heteroaromatics (Scheme 23).[141] The heterogenous Cu complex **43** can be reused for seven cycles with minimal reduction in efficiency.



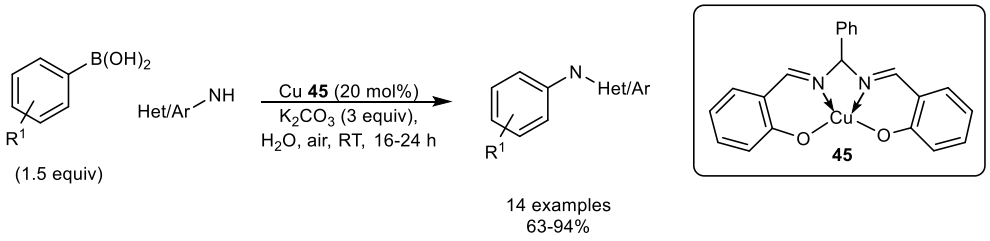
Scheme 23: Polydentate Cu complex mediated coupling.[141]

Lang and co-workers sought to develop a homogenous, green, water-soluble Chan-Lam catalyst (Scheme 24).[142] Incorporation of hydrophilic moieties into the catalyst such as imidazolium salts and ammonium groups could achieve this. Cationic bi-dentate ligand forming **44** could catalyse the coupling of arylboronic acids with imidazoles and aniline in aqueous media.



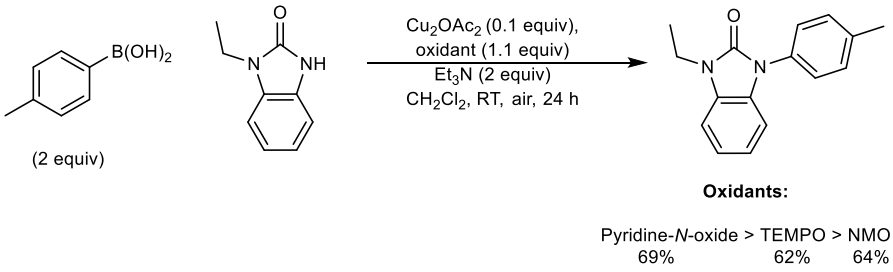
Scheme 24: Chan-Lam coupling employing bi-dentate Cu complex in aqueous media.[142]

Bora and co-workers also reported the use of Cu-Salen complex **45** in water to efficiently couple anilines and imidazoles with arylboronic acids (Scheme 25).[143] Arylboronic acids are stable in aqueous media, enabling enhanced solubility for bases to activate the boronic acid. In-situ generated catalysts produced significantly decreased yields when compared to the use of preformed catalysts. This difference in yield was suggested to be due to slow formation of the active complex **45** in situ.



Scheme 25: Tetradentate Cu-complex mediated Chan-Lam coupling.[143]

The use of oxidants to facilitate and provide efficient conversion from Cu(II) to Cu(III) when using Cu as a catalyst was investigated by Lam and co-workers (Scheme 26).[118] Mild oxidants were tested, aiming to improve upon substrate scope reported by Colmann (see Scheme 21). A number of oxidants were screened, with the three highest performing being, pyridine-*N*-oxide, TEMPO and *N*-methymorpholine-*N*-oxide. When oxidant systems were extended to a variety of substrates no single system could be generally applicable.

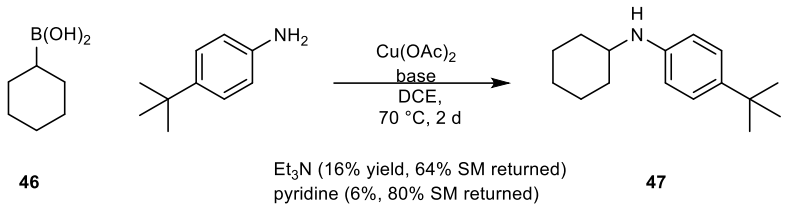


Scheme 27: Test of oxidants in the Chan-Lam coupling of an amide.[118]

1.3.5.2 Alkylboronic Acids and Esters

Despite continued explorations and improved methodology, alkylboronic acids and esters are not widely employed in Chan-Lam couplings and are often limited to privileged structures, including cyclopropyl and benzylboronic acids and esters.[112] Utilising alkylboron substituents would allow for the formation of Csp^3-N bond formation. Such bonds are prevalent in pharmaceutical and agrochemical synthesis, therefore, development of new methodology for their construction is highly desired.[97,144–146]

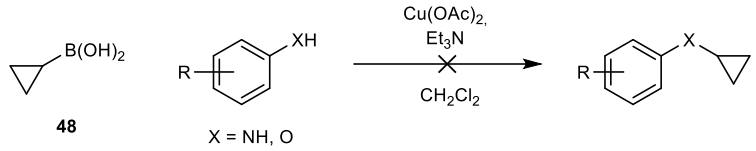
Lam and co-workers initially explored in unpublished work the coupling of cyclohexylboronic acid **46** with *p-tert*-butyl aniline to produce coupled product **47** (Scheme 28).[147] Alteration of the organic base from triethylamine to pyridine offered no yield improvement. Notwithstanding the modest yield, the proof of concept was promising for future method development of alkylboron moieties in Chan-Lam couplings.



Scheme 28: Cyclohexyl boronic acid Chan-Lam coupling with an arylamine.[147]

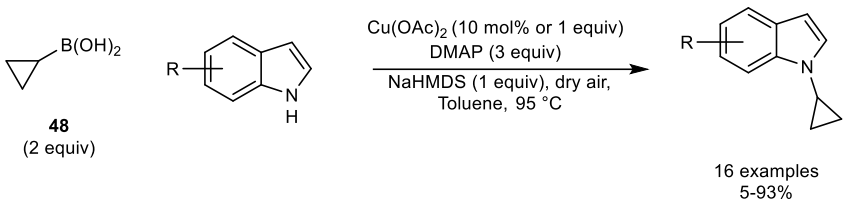
Cyclopropylamines are common motifs in pharmaceutical and agrochemical substrates.[146] New methods for the formation of this functional group is therefore desirable. Cyclopropyl reagents generally have increased reactivity due to the strained ring system, giving the CH bonds more sp^2 hybridised character.[148] Utilisation of this cyclopropyl boron motif in Chan-Lam coupling is therefore slightly easier than with other alkylboron reagents.

Despite this an unsuccessful attempt at the Chan-Lam coupling of cyclopropylboronic acid **48** with anilines and phenols, utilising classical conditions[101-103] was reported by Wallace and Chen (Scheme 29).[149]



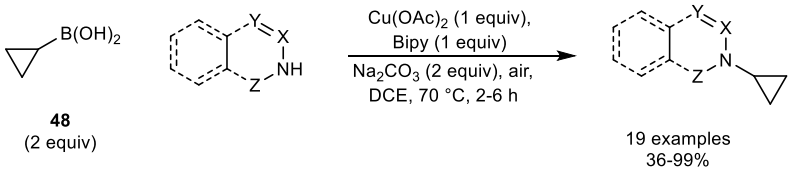
Scheme 29: Attempt at the Chan-Lam coupling of cyclopropyl boronic acid with phenols and anilines.[149]

A number of successful Chan-Lam couplings of cyclopropylboronic acids were later reported after optimisation of the reaction conditions. Tsuritani and co-workers first reported the coupling of cyclopropylboronic acid **48** with indoles and cyclic amides in good yield (Scheme 30).[150] The reactions were performed both with stoichiometric and sub-stoichiometric loadings of $Cu(OAc)_2$. All reactions gave a higher yield with stoichiometric quantities of Cu with the exception of electron donating substrates.



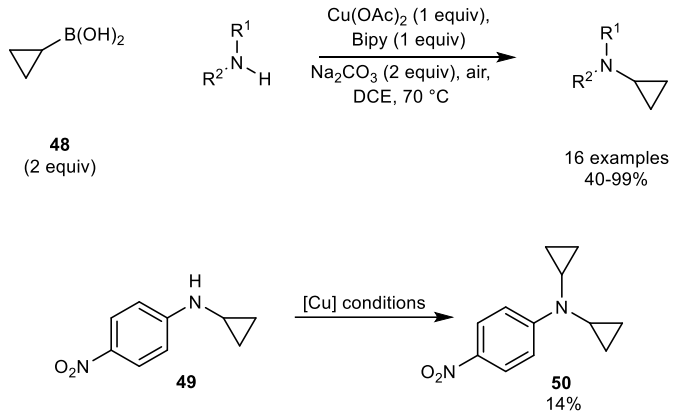
Scheme 30: Chan-Lam coupling of cyclopropyl boronic acid with indoles and cyclic amides.[150]

Subsequently, Zhu and co-workers published the coupling of cyclopropylboronic acid **48** with heterocycles, amides and sulphonamides in good yield (Scheme 31).[151] Excess boronic acid was required to minimise the impact of oxidation side-products. Addition of a ligand and base was beneficial to the yield of coupled amine products. However, reduced yields were reported for the coupling with alkylamines and carbamates. Coupling with anilines were not attempted under these reaction conditions.



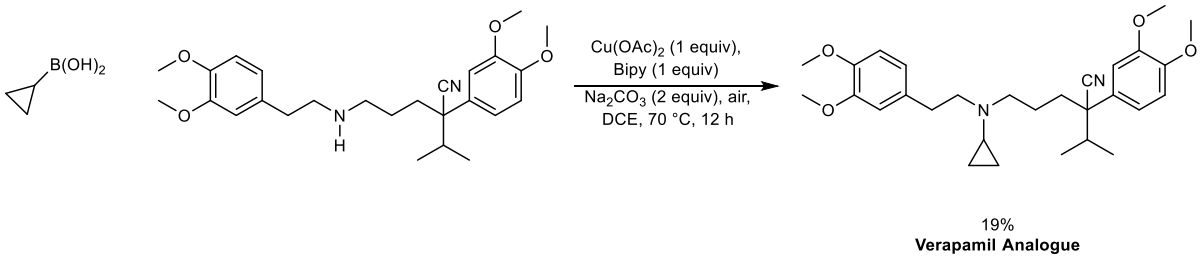
Scheme 31: Chan-Lam coupling of cyclopropyl boronic acid with heterocycles, amides and sulphonamides.[151]

The same group further reported a more general Chan-Lam scope, coupling cyclopropylboronic acid with 1° and 2° aliphatic amines and anilines in good yields (Scheme 32).[152] The group employed the same reaction conditions reported in their previous paper (see Scheme 31). The reaction did proceed with sub-stoichiometric loadings of $Cu(OAc)_2$, however the yield was much decreased. Using the method by Tsuritani and co-workers (see Scheme 30) on some of their substrates failed to produce the cyclopropylated compounds.[150] Only after resubmission of product **49** to the reaction conditions was the dialkylation product **50** observed.



Scheme 32: Further substrate expansion employing the same reaction conditions from Scheme 31.[152]

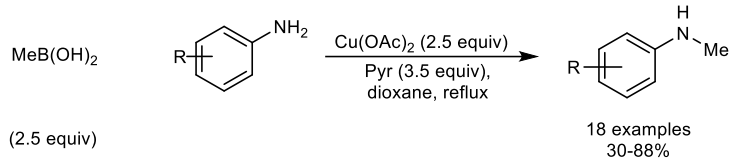
The reaction conditions reported by the Zhu group[151,152] have now been used in the total synthesis of analogues of a tuberculosis drug (Verapamil) to investigate the SAR (Scheme 33).[153]



Scheme 33: SAR investigation using a Chan-Lam coupling reaction to produce analogues of Verapamil.[153]

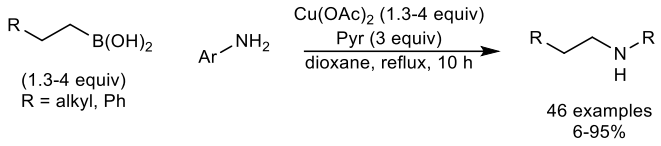
Cruces and co-workers reported the first coupling of a 1° alkylboronic acid and anilines (Scheme 34).[154] The group tried to employ palladium chemistry for the transformation, this afforded no methylated product. Using 'classical' Chan-Lam conditions formed the desired product in only a 4% yield after 3 d. Optimisation using DoE highlighted the importance of the order of addition. The coupling required an incubation period of 15 minutes mixing the copper and aniline substrate prior to the addition of the methylboronic acid to proceed. The

corresponding dimethylated product was observed when reaction times were extended or greater equivalents of boronic acid or Cu were employed. Ketones and esters, often challenging substrates in reductive amination reactions due to their own reduction were tolerated under these conditions. Pudlo and co-workers implemented this methodology in the synthesis of hit molecules for the treatment of Alzhiemer's disease.[155]



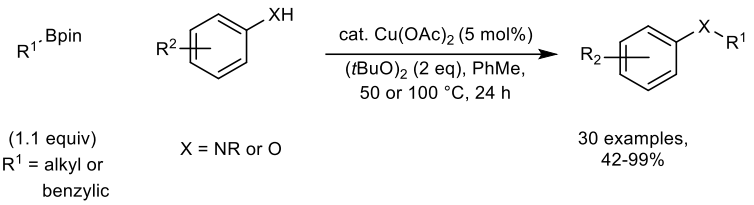
Scheme 34: Coupling of a 1° alkylboronic acids with anilines to form a new C-N bond.[154]

The group were able to further expand the scope of the alkylboronic acids with substrate dependent alteration of boronic acid and Cu stoichiometries (Scheme 35).[156] Longer chain alkylboronic acids could be coupled in good yield. However, large reagent excess and increased reaction times are required for electron poor anilines. Yields were also substrate dependent, performing best with electron-donating groups. Reaction conversion was again reliant on on the order of addition. Following the same pattern as their previous report, boronic acid is required to be added as the final step.[154]



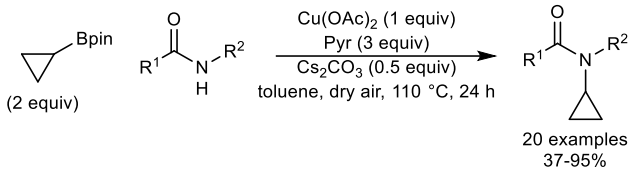
Scheme 35: Extended scope of coupling alkylboronic acids and anilines.[156]

Kuninobu and Sueki reported an expansion to the reaction scope to include alkylboronic esters (Scheme 36).[157] 1° and 2° alkyl and benzylboronic esters could be coupled with anilines and phenols in good yield. However, aliphatic amines were not tolerated and the scope of the boronic esters reported is limited. The coupling with morpholine and butylamine were unsuccessful. The use of the strong oxidant, di-*tert*-butyl peroxide is also undesirable. Dialkylated product could be formed preferentially if the equivalency of boronic ester was increased to two.



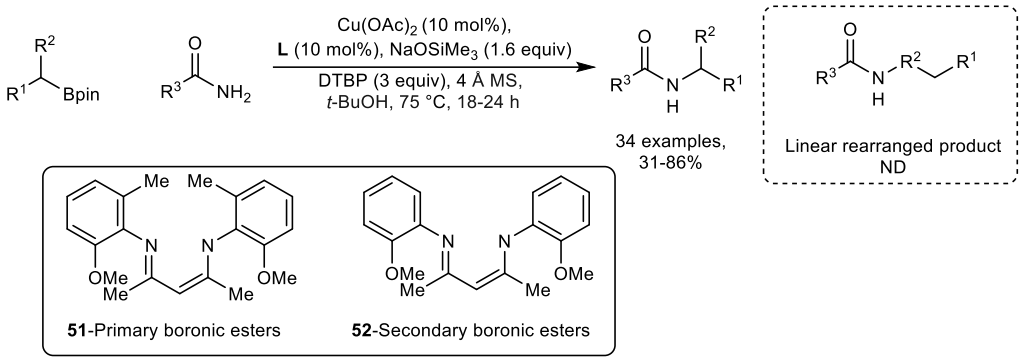
Scheme 36: Alkyl or benzylic boronic esters catalytically coupled with anilines or phenols.[157]

Alkylboronic esters could also be utilised in couplings with amides. Taillefer and co-workers developed the coupling of 2° cyclic and acyclic amides tolerating alkyl and aryl groups forming 3° acyclic amides (Scheme 37).[158] Other oxidants were tested in the reaction such as pyridine *N*-oxide, however no improvement in yield was observed when compared to dry air.



Scheme 37: Amide coupling with cyclopropyl boronic ester.[158]

Watson and co-workers later reported the use of diketimine (NacNac) ligands to promote the coupling of 1° and 2° alkylboronic esters with 1° amides (Scheme 38).[159] Ligands usually employed in aromatic Chan-Lam reactions (2,6-bipyridine, 1,10-phenanthroline, and 2,2',2"-tripyridine) gave low yielding results.[160] Ligand **51** could be used for the coupling of 1° boronic esters. The use of alternative ligand **52** for the coupling of 2° boronic esters limited the formation of the linear rearranged product, providing high regioselectivity. The methoxy groups present in both ligands are thought to aid metal chelation.

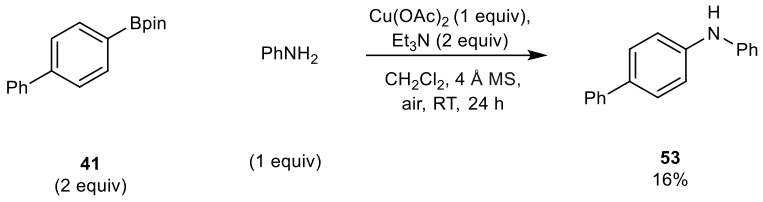


Scheme 38: Chan-Lam coupling of 1° and 2°alkylboronic esters with amides.[159]

Whilst the scope of the boronic ester has increased to include aryl, benzylic and 1° and 2° alkyl compounds it is clear there is some work required to expand further the use of alkylboronic esters and improve reaction generality in these Chan-Lam reactions.

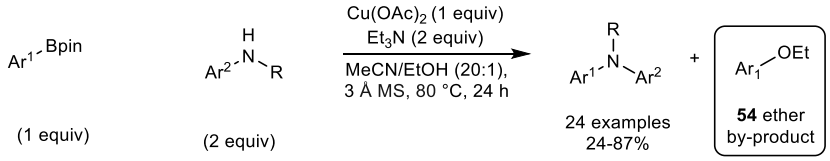
1.3.5.3 Arylamines

Arylamines are a common substrate for coupling with boronic acids in Chan-Lam reactions. However, diminished yields are often reported for the corresponding coupling with arylboronic esters.[138] Watson and co-workers reported a 16% yield when coupling arylboronic ester **41** with aniline under classical Chan-Lam conditions to give coupled product **53** (Scheme 39).[138]



Scheme 39: Low-yielding Chan-Lam coupling of arylboronic esters and anilines.[161]

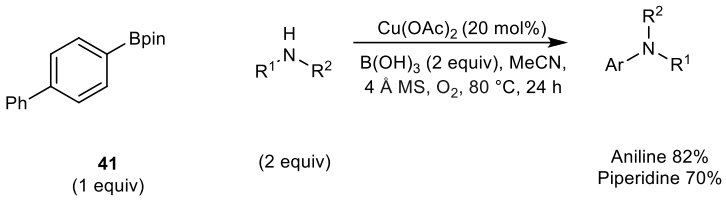
The group performed reaction optimisation to overcome this arylamine coupling problem. The addition of ethanol increased the yield of the desired product to 43%, although by-product formation, namely the ether coupling product **54** increased significantly (Scheme 40). The improved yield is thought to arise from the alcohol aiding formation of the active mononuclear Cu(II) from the paddlewheel complex. The use of a mixed solvent system of MeCN:EtOH (20:1) minimised the formation of the ether by-product, and allowed amination in good yield. The reaction conditions were found to show broad functional tolerance across both coupling partners (Scheme 40).



Scheme 40: Conditions for the coupling of arylboronic esters and anilines.

A mechanistic investigation from the same group was able to further explain the associated issues with the use of arylamines compared to alkylamines in Chan-Lam couplings.[109] EPR studies highlighted that the dissociation of the copper paddlewheel dimer was slower with aniline than with piperidine. This dissociation event is vital in starting the

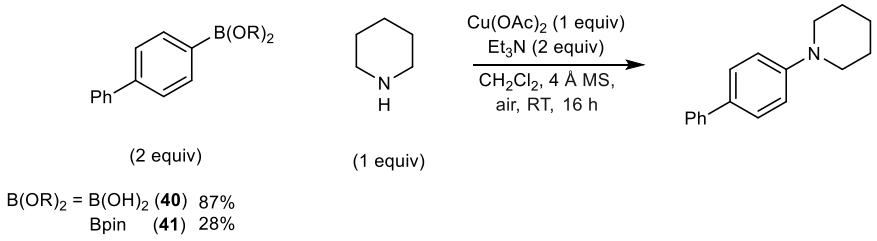
mechanistic cycle as the paddlewheel complex is unreactive (See Figure 13).[109,112] This event is therefore dependent on the Lewis basicity of the amine, increasing the amine concentration could force forward this dissociation. UV-Vis spectroscopy studies also uncovered another issue when using anilines in Chan-Lam reactions. The oxidation of Cu(I) to Cu(II) is generally quicker with piperidine than aniline, this key step is required to complete the catalytic cycle. To overcome these issues they proposed the use of boric acid as an additive and an increase in the amine stoichiometry, a reversal from standard conditions, would be beneficial. The addition of boric acid was seen to promote the oxidation from Cu(I) to Cu(II) aiding turnover of the catalytic cycle. The alteration of aniline stoichiometry would help promote the oxidation step, but would also encourage denucleation of the copper paddlewheel to the active complex. Employing these optimised reaction conditions with boronic ester **41** yielded comparable results with aniline and piperidine (Scheme 41).



Scheme 41: Mechanistic insight allowing optimisation of the coupling of arylboronic esters and anilines.[109]

1.3.5.4 Alkylamines

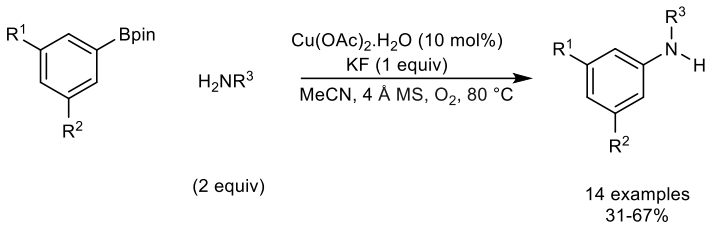
1° and 2° alkylamines are common substrates in Chan-Lam couplings. They are often coupled with arylboronic acids, but Chan-Lam coupling with the analogous boronic esters are less explored. Watson and co-workers reported decreased yields when using boronic ester **41** to couple with piperidine versus boronic acid **40** under classical conditions (Scheme 42).[109]



Scheme 42: Coupling of boronic acid or ester with piperidine with differing yields.[109]

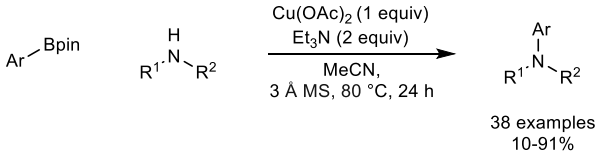
There have now been a number of reports of Chan-Lam couplings with arylboronic esters and alkylamines. Hartwig and co-workers first described the use of a boronic ester in a Chan-Lam coupling with 1° amines (Scheme 43).[162] Previous conditions for the coupling of

arylboronic esters reported by Batey and Quach did not produce the desired product with both alkyl and arylamines.[122] An excess of amine and the inclusion of potassium fluoride, thought to aid transmetalation, provided the coupled products in moderate yield.



Scheme 43: First reported Chan-Lam coupling of a boronic ester with 1° amines.[162]

Watson and co-workers reported the coupling of arylboronic esters with 1° and 2° amines (Scheme 44).[138] 'Classical' Chan-Lam coupling did not afford product. These conditions can be altered with the addition of ethanol to allow coupling with anilines (see Scheme 40). This highlights reaction conditions for Chan-Lam couplings are not general, they still require optimisation for the alteration of substrates.



Scheme 44: Chan-Lam coupling of arylboronic esters with alkylamines.[138]

Whilst there is a large scope of arylboron-arylamine and arylboron-alkylamine Chan-Lam couplings there are limited reports of alkylboron-alkylamine couplings. The report by Zhu and co-workers (see Scheme 32) to the best of our knowledge is the only account describing a Chan-Lam coupling between an alkylboronic acid and alkylamines.[152] This methodology is limited to the use of the privileged cyclopropylboronic acid.

2. 1st Generation Alkyl Chan-Lam Reaction – Coupling of Anilines

2.1 Aims

Chan-Lam reactions reporting the use of alkylboronic acids are often limited to privileged structures, namely cyclopropylboronic acids (see Section 1.3.5.2, Scheme 30, Scheme 31, Scheme 32, Scheme 37). The analogous alkylboronic esters are underdeveloped for use in amination reactions. Limited examples detail the coupling of cyclopropylboronic esters and to the best of our knowledge only one reports the use of alkylboronic acid coupling with alkylamines (Scheme 32).[152,157–159] While some of the reactions can be performed catalytically this necessitates the use of harsh terminal oxidants such as di-*tert*-butyl peroxide. Scope with respect to both coupling partners is often limited. Reaction conditions are unpredictable and are frequently substrate dependent with reaction generality yet unattainable.

The aim of this project was to improve the scope of the Chan-Lam reaction by investigating the coupling of anilines with 2° benzylboronic esters. These boronic esters were targeted as we hypothesised that transmetalation could be promoted through charge stabilisation of the intermediate organocuprate by the aryl ring. In addition, it was planned to determine if the reaction is stereoselective when using chiral non-racemic boronic esters.

Once conditions are developed, we planned to apply the method to the reaction of 3° boronic esters and allylboronic esters will also be investigated. These substrates, to our knowledge, have not been reported as coupling partners in Chan-Lam reactions. In particular, the coupling of 3° boronic esters would enable access to 3° amines, which cannot be formed through reductive amination.

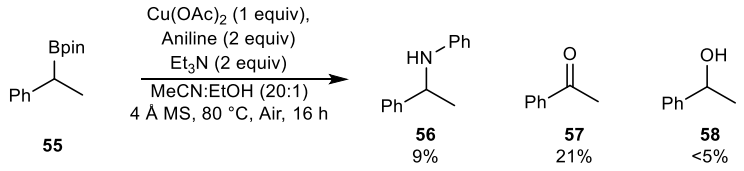
2.2 Results and Discussion: Aryl Amination of Alkylboronic Esters

2.2.1 Method Development for the Amination of Boronic Ester 55

Optimisation reactions were carried out by Dr James D Grayson. In order to give background to the discussion and further optimisation work undertaken, included in this section are select optimisation reactions for method development. For a complete overview of reaction

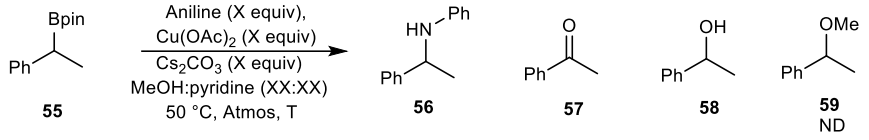
optimisation please refer to Dr James D Grayson's thesis.[163] All reactions and tables completed by James Grayson are denoted with 'JDG'.

For optimisation, the reaction of 2° benzylboronic ester **55** coupling with aniline was explored, using Watson and co-workers' classical Chan-Lam conditions as a starting point (Scheme 45).[161] Promisingly amine **56** was produced, albeit in low yield. Alongside this, oxidation by-products ketone **57** and alcohol **58** were identified.[164] The incomplete mass balance is thought to be due to protodeboronation of **55** to give ethylbenzene, which is volatile and so not detected after work up.



Scheme 45: Amination of boronic ester **55** using Watson and co-workers' conditions.[161] JDG.

Through a systematic alteration of conditions, the yield of amine **56** was increased which coincided with a reduction of oxidation by-products **57** and **58** noted from earlier work conducted within the group and previous Chan-Lam couplings. [112,164] An overview of selected optimisation results towards the Chan-Lam coupling of alkylboronic esters with aniline is shown in Table 1.[165] Throughout this study the alkylboronic ester was the limiting reagent partner as they are regarded as the more valuable reagent when compared to many anilines. In contrast, many reported Chan-Lam couplings employ an excess of the boron reagent to diminish side-products often originating from this coupling partner.[112] Consequently, method development was focused on the reduction of side-products from the boronic ester component (see Scheme 45).



Entry	Cu equiv	Aniline equiv	MeOH:Pyr	Cs_2CO_3 equiv	Atmos	Time (h)	Yield (%) 55	56	57	58
1	2	2	3:2	2	Air	4	0	16	34	48
2	2	2	3:2	0.5	Air	4	0	30	32	5
3	2	2	3:2	-	Air	4	0	6	60	<5
4	2	2	3:2	0.5	Ar	4	0	39	6	6
5	2	4	3:2	0.5	Ar	4	23	48	<5	6
6	2	4	3:1	0.5	Ar	4	51	38	<5	<5
7[a]	2	4	3:1	0.5	Ar	16	ND	73	ND	ND
8[a]	1	2	3:1	0.5	Ar	16	ND	36	ND	ND
9[a]	1.5	3	3:1	0.5	Ar	16	ND	67	ND	ND
10[a]	2	1	3:1	0.5	Ar	16	ND	46	ND	ND
11	0	4	3:1	0.5	Ar	16	ND	0	<5	33
12	2	4	1:0	0.5	Ar	16	45	37	<5	0

Table 1: Overview of the optimisation of the amination of boronic ester **55** with aniline. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. a) Reactions conducted on a 0.5 mmol scale of **55**, yield of isolated material. JDG.

$Cu(OAc)_2$ is the most widely used Cu source for Chan-Lam couplings.[112] For the coupling of boronic ester **55** with aniline the only Cu source to produce amine **56** was $Cu(OAc)_2$. Performing the reaction under air (Table 1, Entry 1, 2, and 3) whilst forming amine **56** in moderate yield also produced large quantities of oxidation by-products **57** and **58**.[108,109,112,164,166] Decreasing the equivalents of Cs_2CO_3 (Entry 2) increased the yield of amine **56** and decreased the formation of alcohol **58**. The use of an inert atmosphere (Entry 4) decreased the formation of by-products **57** and **58**, which is consistent with O_2 being involved in their formation.[164] Consequently without the use of air or an external chemical oxidant, stoichiometric loadings of $Cu(OAc)_2$ are required. Two equivalents of Cu were found to give a consistently high yield of the corresponding amine product. Increasing the aniline equivalent to provide a 2:1 ratio of aniline:$Cu(OAc)_2$ (Entry 5) provided a boost in amine **56** production. Lowering of the pyridine content to a 3:1 ratio gave a better overall mass balance (Entry 6). This could be due to decreased protodeboronation occurring under these conditions. The use of an alcoholic solvent medium in aryl Chan-Lam reactions may sometimes provide the corresponding etherification product.[108,109] During optimisation and assessing the scope of the reaction no etherification by-product **59** was observed. Increasing the reaction time to 16 h (Entry 7, 8 and 9) allowed the boronic ester to be fully consumed, producing good yields of amine **56**. Attempts to decrease Cu loading and amine equivalency provided lower amine **56** yield (Entry 8 and 9). Due to the low cost of $Cu(OAc)_2$ and often low costs of the coupling partner amine, 2 equivalents of $Cu(OAc)_2$ and 4 equivalents of amine were used as the

optimised reaction conditions (Entry 7). An inverse of the stoichiometry of reagents was tested (Entry 10). With only one equivalent of aniline a moderate yield of amine **56** was still obtained, allowing a reduction in the amine coupling partner if this were the more valuable reagent.

In control reactions, Cu was required to produce any coupled product **56** (Entry 11). This suggests the reaction proceeds via a metal-mediated process. The removal of pyridine from the reaction conditions reduced amine **56** yield (Entry 12). Pyridine could be working to break up aggregates of $Cu(OAc)_2$, allowing a larger portion of active catalyst to be present.[109]

2.3 Scope of the Reaction for the Amination of Alkylboronic Esters

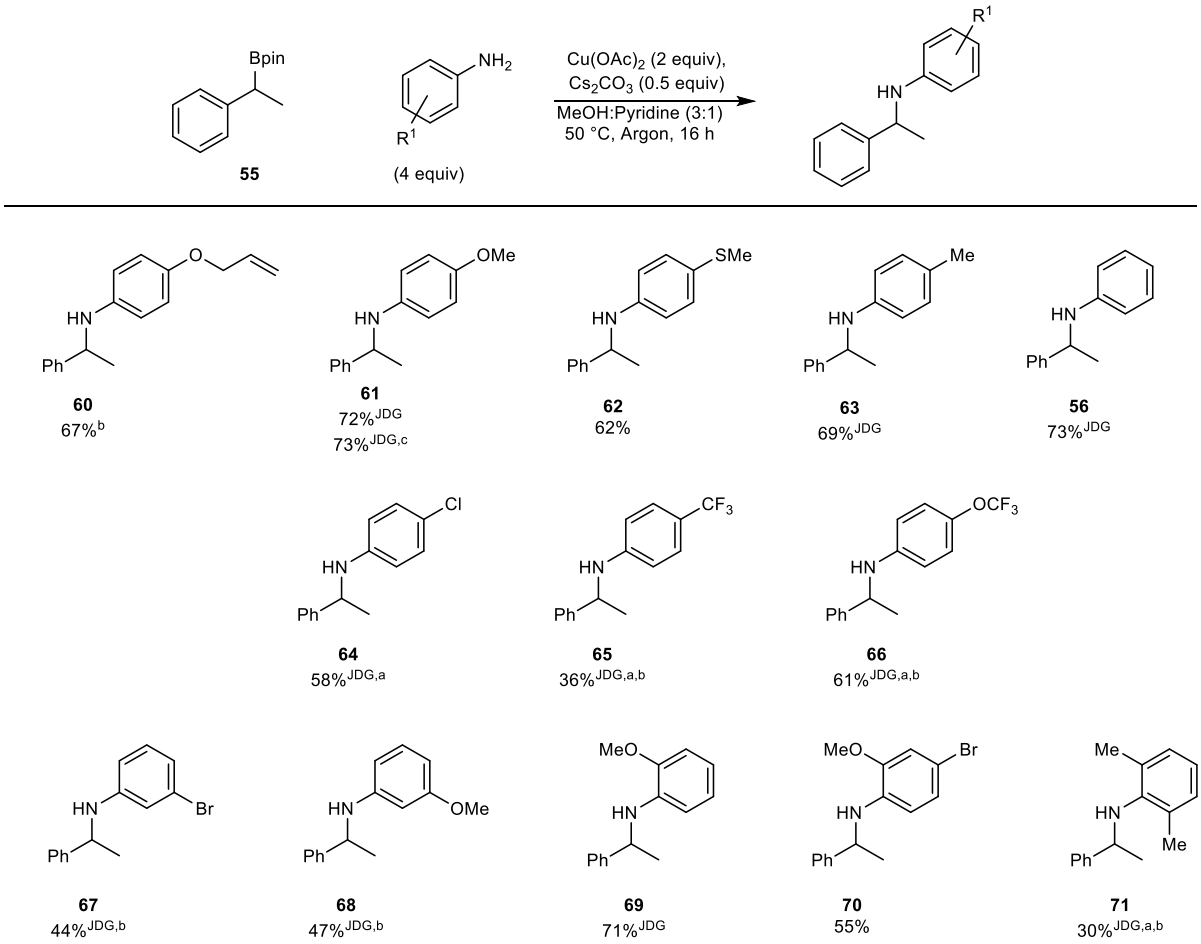
2.3.1 Aniline Scope

The work in this section was completed in collaboration with James Grayson. The reaction was frequently performed in duplicate by both James Grayson and myself. The reactions performed by James Grayson are included to allow a full overview and complete discussion of this project.

Using the optimised reaction conditions, the scope of the amination reaction was tested. A number of 1° and 2° amines were coupled with a range of 2° and 3° boronic esters. During optimisation, reactions were carried out on a 0.05 mmol scale with the yield determined by ^{1}H-NMR analysis. Once the reaction scale was increased to 0.5 mmol consideration needed to be given to the work-up procedure to remove Cu salts. Extraction with ammonium hydroxide facilitated the removal of the majority of Cu salts to improve purification. In some instances, during column chromatography purification co-elution of the amine product and unreacted boronic ester occurred. In this case, oxidation of the remaining boronic ester to the corresponding alcohol was carried out using sodium perborate, allowing better separation and therefore purification of the amine product. The yields of compounds that required the additional oxidation step were comparable to the corresponding NMR yield from the crude reaction mixture, suggesting minimal loss of material during the oxidation.

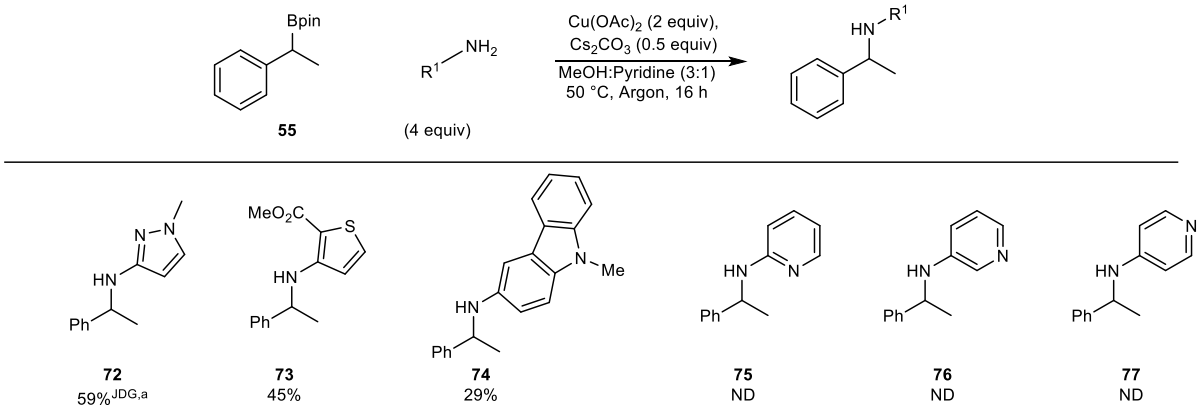
Boronic ester **55** was coupled with a range of 1° anilines (Scheme 46). Both electron donating and withdrawing substituents on the aniline were tolerated. However, electron poor anilines generally required more forcing conditions, including higher temperatures and increased reaction times to obtain a good yield. A wide range of functional groups are tolerated including alkenes **60**, sulfides **62** and trifluoromethyl **65**. A reduced yield was obtained for

sterically hindered 2,2-dimethyl aniline **71** despite increased temperature and reaction time. This is comparable to other Chan-Lam couplings of arylboronic acids, which have been reported to be sensitive to the sterics surrounding the amine.[117] The electronic properties of methoxy substituted anilines appear to impact reactivity more so than their steric interactions. Comparable yields are achieved for reaction of *p*-anisidine **61** and the sterically more congested *o*-anisidine **69**. Whereas *m*-anisidine **68** only reacted in a modest yield even after an increased reaction time. The electronic effect of an additional *p*-bromo substituent in **70** detrimentally impacts the yield when compared *o*-anisidine, likely due to its electron-withdrawing properties. The reaction can also be scaled up to 1 g with no impact on the yield of **61**. No Ullmann coupling products from aryl halides were observed. Bromine-substituted anilines tended to result in a reduced yield of coupling product **67** and **70**. In all cases, no dialkylation products were observed.



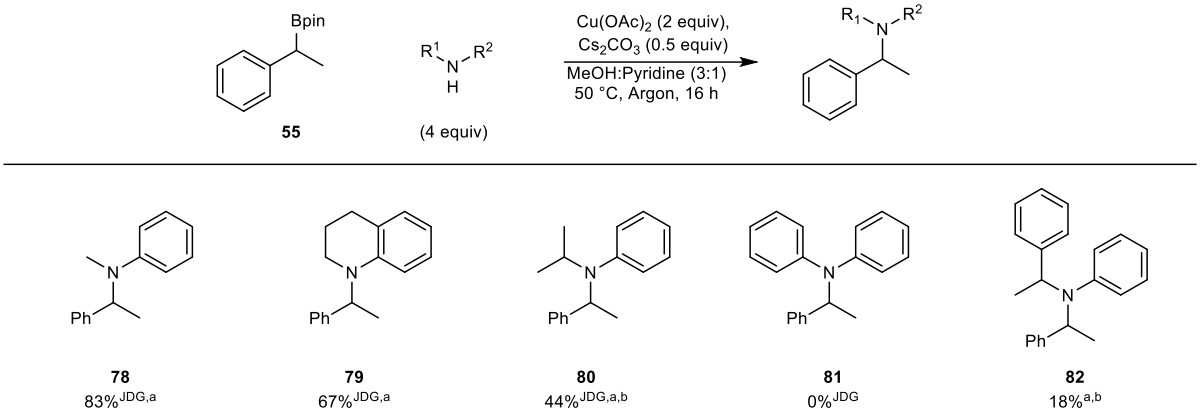
Scheme 46: Scope of anilines with boronic ester **55**. Yields are of the isolated material. Reactions performed on a 0.5 mmol scale of **55**. a) Reaction temperature of 65 °C. b) Reaction time of 48 h. c) Reaction performed on 1 g scale of **55**.

Heteroaromatic and carbazole derived anilines produced the amination products **72, 73** and **74** in moderate yield (Scheme 47). Conversely, when coupling pyridine-derived anilines purification became an issue, despite the corresponding products being observed by NMR analysis and mass spectrometry of the crude reaction mixture. Isolation was therefore not possible, presumably due to the compounds apparent water solubility and incompatibility with purification. Lam and co-workers also reported diminished yields of *N*-arylated products when using amino-pyridine substrates.[147,167] This could be due to the coordinating nature of these compounds.



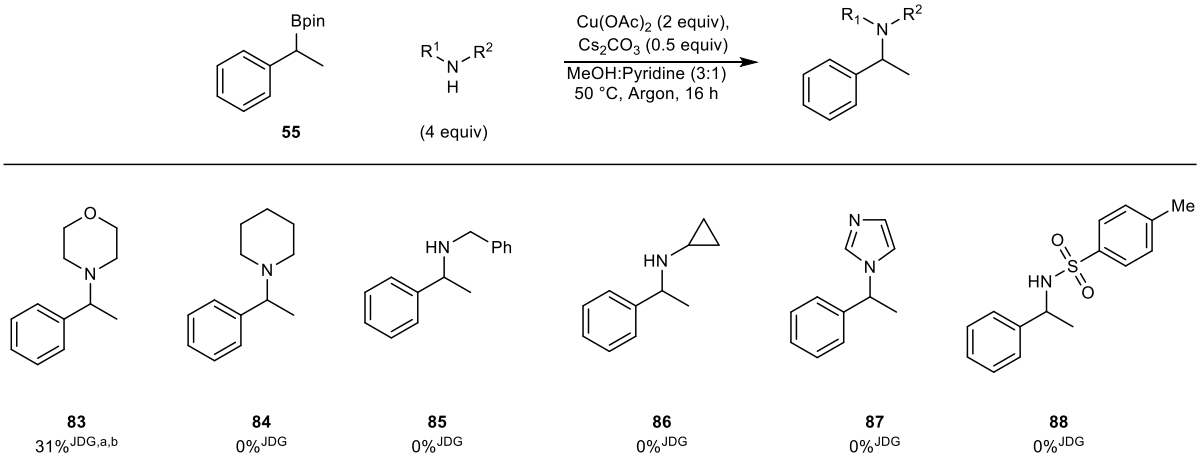
Scheme 47: Scope of heteroaryl amines with boronic ester **55**. Yields are of the isolated material. Reactions performed on a 0.5 mmol scale of **55**. a) Reaction temperature of 65 °C.

A number of 2° anilines are tolerated, with the corresponding products formed in good yield (Scheme 48). However, with increased steric hindrance of the amine, the reactivity decreases. *N*-Methyl aniline **78** and tetrahydroquinoline **79** only required an increase in reaction temperature to 65 °C to produce good yields. The more sterically demanding *N*-isopropyl aniline required both increased temperature and reaction time to produce a moderate yield of **80**, whilst diphenyl aniline **81** did not undergo alkylation. When amination product **56** was re-subjected to the reaction conditions, further coupling did occur in low yield to give amine **82**. This modest dialkylation suggests that whilst possible it is challenging, potentially explaining why generally dialkylation products were not detected.



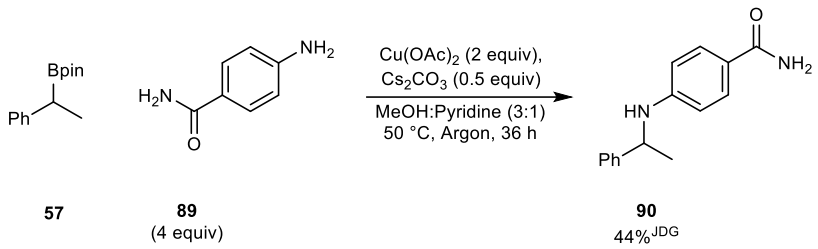
Scheme 48: Scope of 2° amines with boronic ester **55**. Yields are of the isolated material. Reactions performed on a 0.5 mmol scale of **55**. a) Reaction temperature of 65 °C. b) Reaction time of 48 h.

The generality of the reaction was tested further with a wider class of amines (Scheme 49). Morpholine was coupled in a moderate yield (**83**), however piperidine did not undergo reaction (**84**). Benzylamine and cyclopropylamine (leading to **85** and **86**), imidazole **87** and tosylamine **88** were not tolerated under these reaction conditions. The incompatibility of alkylamines, imidazole and sulphonamides shows potential for further optimisation of the current reaction conditions to expand the reaction's generality.



Scheme 49: Scope of wider amines with boronic ester **55**. Yields are of the isolated material. Reactions performed on a 0.5 mmol scale of **55**. a) Reaction temperature of 65 °C. b) Reaction time of 48 h.

The chemoselectivity of the reaction was tested with difunctional aniline **89** (Scheme 50). Coupling was solely observed at the amine position. The alternative amide coupling was not detected by either NMR analysis or mass spectrometry. The moderate yield of **90** is presumably due to the electron-withdrawing properties of the amide group reducing the reactivity of the aniline. The chemoselectivity of this reaction is complementary to amide coupling reports of Watson and co-workers.[168,159]

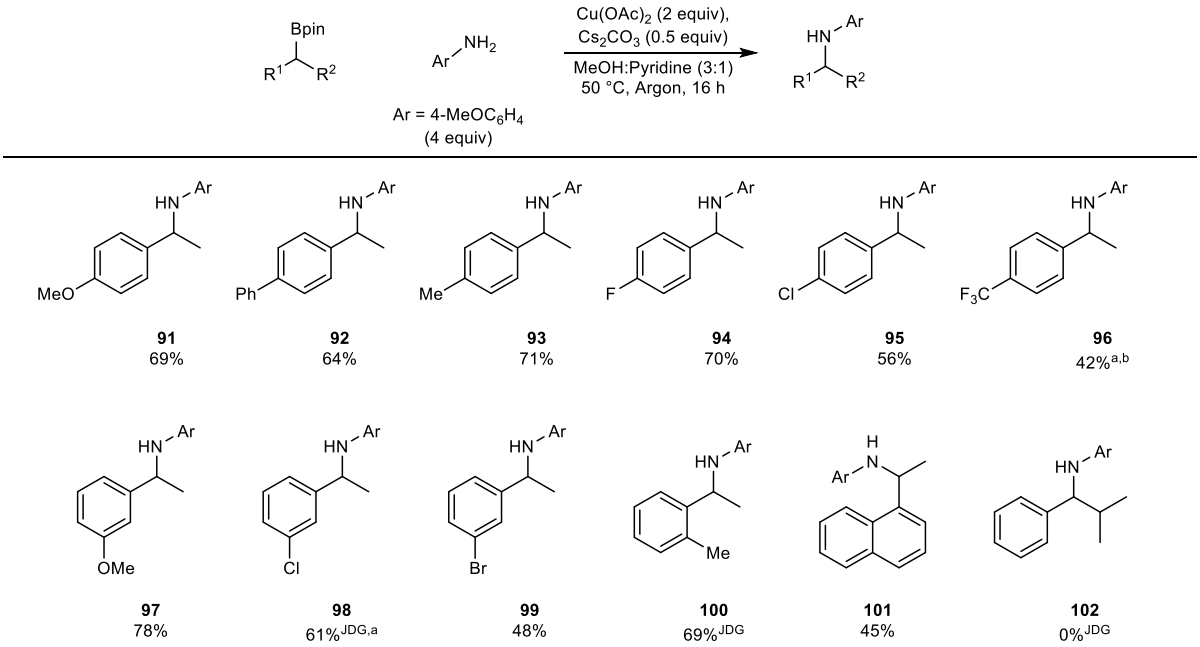


57 **89** (4 equiv) **90** 44%[JDG]

Scheme 50: Chemoselectivity of amine or amide. Yields are of the isolated material. Reactions performed on a 0.5 mmol scale of **55**.

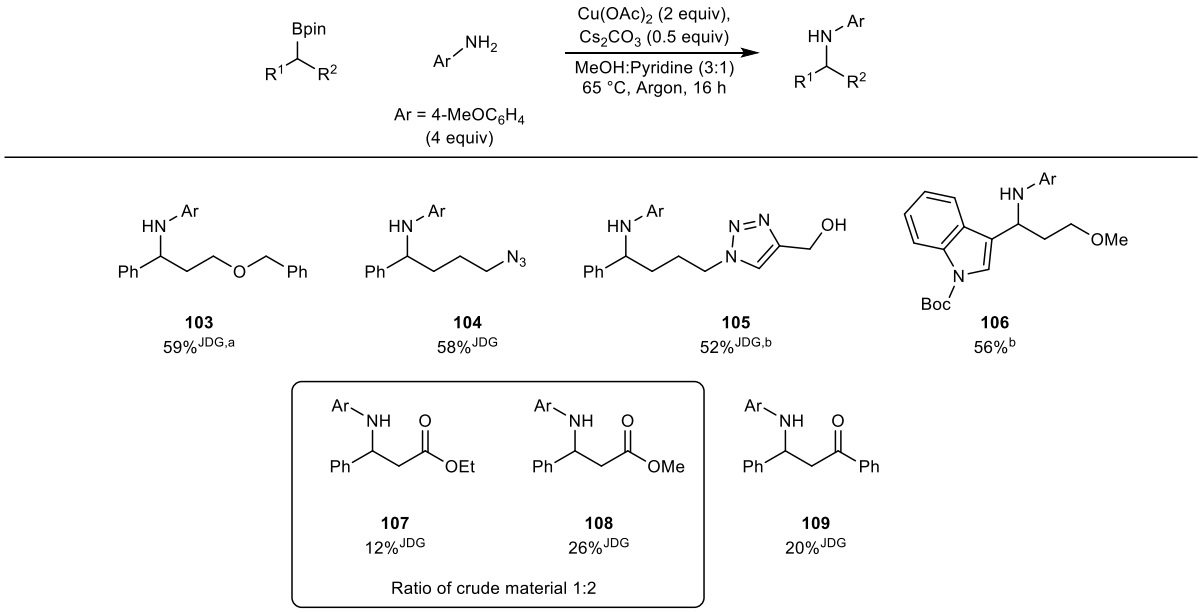
2.3.2 Boronic Ester Scope

The scope of 2° boronic esters was next investigated (Scheme 51). All boronic esters presented in the scope were prepared using known literature methods. In some instances, when using aniline as the coupling partner co-elution of the product and the boronic ester starting material occurred during silica chromatography. To aid purification and avoid co-elution, *p*-anisidine was used as the coupling partner for all boronic esters tested. This negated the need for an additional oxidative work-up step. Both electron-donating and withdrawing aryl substituents on the 2° benzylic boronic esters were compatible with the reaction conditions. However, increased reaction times and temperatures were required for the more electron poor boronic ester (**96**). Sterically demanding *o*-methyl-substituted benzylic boronic ester (**100**) reacted in comparable yield to *p*-methyl-substituted boronic ester (**93**). Increasing steric hindrance using 1-naphthyl-substituted boronic ester led to a slight reduction in yield of amine **101**. No coupling product was observed when using a boronic ester with additional steric hindrance of an isopropyl group alpha to boron (**102**). Aryl halide substituted boronic esters **94**, **95**, **98** and **99** are compatible, producing no observable Ullmann coupling products.



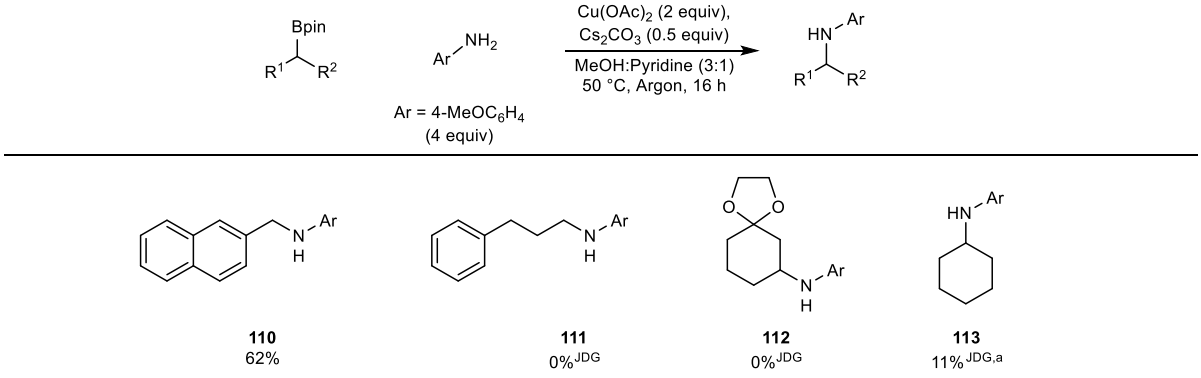
Scheme 51: Scope of the amination of 2° benzylic boronic esters. Yields are of the isolated material. Reactions performed on a 0.5 mmol scale of boronic ester. a) Reaction temperature of 65 °C. b) Reaction time of 48 h.

The amination reaction was next tested with 2° benzylic boronic esters with extended α-alkyl chain length (Scheme 52). Compared to α-methylboronic esters, a modest decrease in reactivity was typically observed. Subsequently, an increased temperature of 65 °C was necessary, with longer reaction time required for some examples (**103**, **105** and **106**). Functional groups tolerated include azide **104**, ketones **109** and an unprotected alcohol **105**. Heteroaromatic boronic ester **106** was also compatible. β-ester boronic ester formed an inseparable mix of amine **107**, as well as the corresponding transesterification methyl ester-product **108** in a ratio of 1:2. Both β-ester and β-ketoboronic esters react to form amines **107** and **109** respectively, albeit in diminished yield. This could be attributed to product decomposition through a retro-Mannich reaction.



Scheme 52: Scope of the amination of 2° alkyl substituted benzylic boronic esters. Yields are of the isolated material. Reactions performed on a 0.5 mmol scale of boronic ester. a) Reaction time of 32 h. b) Reaction time of 48 h.

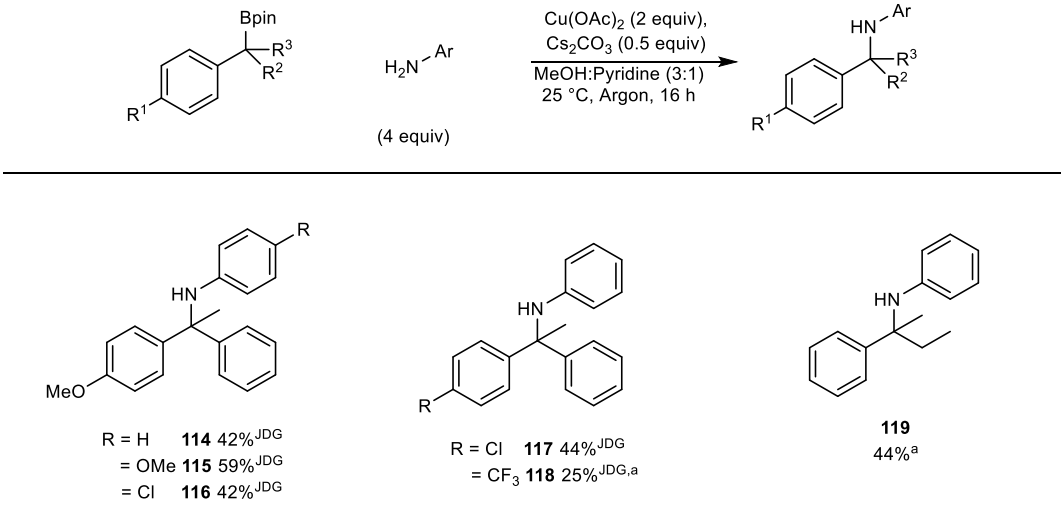
1° benzylic and non-benzylic boronic esters were tested to further explore the generality of the amination reaction (Scheme 53). 1° naphthyl benzylic boronic ester was coupled effectively to produce amine **110** in good yield. No dialkylation of **110** was observed, which is contrary to some examples reported by Kuninobu and co-workers.[157] Conversely, both 1° and 2° alkylboronic esters displayed reduced reactivity. Formation of amines **111** and **112** were not tolerated under the current amination procedure. Cyclohexylboronic ester was coupled to produce amine **113**, albeit in a low yield. The increased reactivity of benzylic boronic esters is presumably due to stabilisation of a benzyl Cu intermediate by the aryl ring.



Scheme 53: Amination scope of 1° benzylic, 1° and 2° alkylboronic esters. Yields are of the isolated material. Reactions performed on a 0.5 mmol scale of boronic ester. a) Reaction temperature of 65 °C.

2.3.3 Aryl Amination of 3° Boronic Esters

Transformations of 3° boronic esters under transition metal meditated conditions are limited. Chan-Lam couplings of 3° boronic esters to our knowledge have not been previously reported. Coupling of both diaryl and dialkyl 3° boronic esters was investigated (Scheme 54). During reaction optimisation for the coupling of 3° boronic esters a number of unidentified by-products were formed. Alongside this, protodeboronated and alcohol side-products were formed. The alcohol side-product had been observed after several days to undergo dehydration to form an alkene. Reactions performed best at room temperature, presumably due to increased stabilisation provided by a tertiary intermediate, promoting transmetalation even at reduced temperatures. Coupling an aniline with an electron donating group formed amine **115** in higher yield than with an electron withdrawing group **116**. No Ullmann coupling products were observed when coupling *p*-chloro aniline. Boronic esters with electron withdrawing substituents could be coupled to produce amine **117** and **118**. When using a *p*-trifluoromethyl group an increase in reaction temperature was required to promote coupling. Coupling with dialkyl 3° boronic ester also required an increased reaction temperature for full consumption of starting material to produce amine **119** in moderate yield.

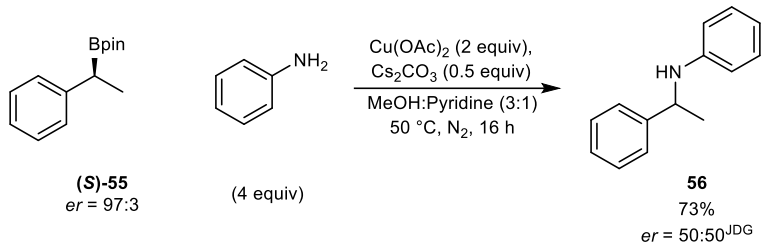


Scheme 54: Coupling of 3° boronic esters. Yields are of the isolated material. Reactions performed on a 0.5 mmol scale of boronic ester. a) Reaction temperature of 50 °C.

2.3.4 Mechanistic Insight into the Reaction

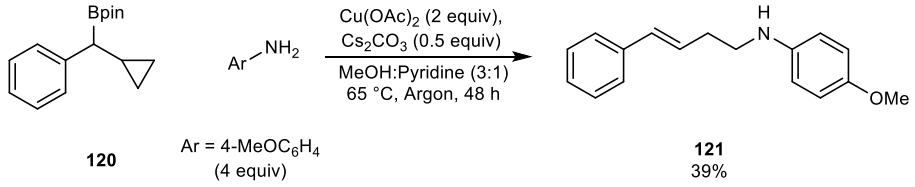
The amination of enantiomerically enriched boronic ester **(*S*)-55** was undertaken in order to explore if the amination reaction proceeded stereoselectively (Scheme 55). The amine **56**

was formed in high yield, however, only as a racemate. This complete loss of stereochemical information could be due to the formation of a radical intermediate during transmetalation. Another possible explanation could be attributed to the configurational instability of an organocuprate intermediate. Knochel and co-workers have previously reported that 2° alkyl Cu(I) species epimerise above −30 °C.[169]



Scheme 55: Amination and subsequent racemisation of enantioenriched boronic ester **(*S*)-55**. Yields are of the isolated material. Reactions performed on a 0.5 mmol scale of **(*S*)-55**.

In order to gain further mechanistic insight a radical clock experiment was proposed. Cyclopropylboronic ester **120** was subjected to amination conditions to explore if an alkyl radical is forming (Scheme 56). If the cyclopropane ring remains intact, this implies transmetalation occurs via a two-electron process. Alternatively, if ring-opening of the cyclopropyl is observed, this suggests a radical intermediate is likely to have formed. This radical intermediate could form in two ways, by H atom abstraction alpha to boron or by homolytic C-B bond cleavage. Amination of **120** provided solely the ring opened product **121**. This is presumably due to the reaction proceeding through a radical intermediate.

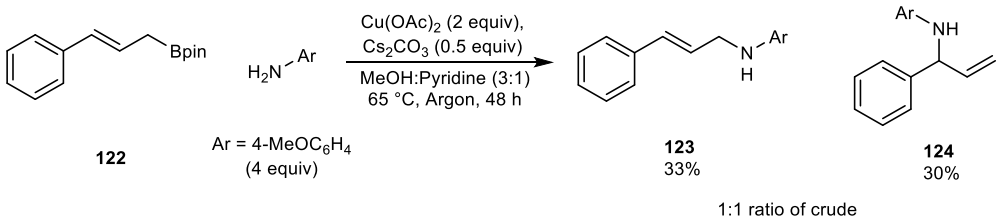


Scheme 56: Amination of cyclopropylboronic ester **120** to form the ring opened product **121**. Yields are of the isolated material. Reactions performed on a 0.5 mmol scale of **120**.

2.3.5 Amination of Allylboronic Esters

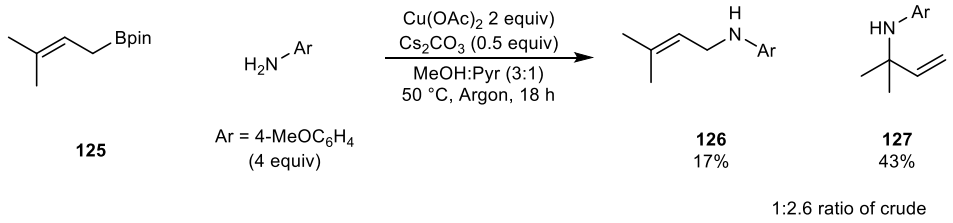
To expand the scope of boronic esters, allylboronic esters were tested under the amination conditions. To the best of our knowledge no allylboronic esters have been used as coupling partners in Chan-Lam couplings. Unsymmetrical boronic ester **122** formed both linear **123** and branched product **124** in a 1:1 ratio (Scheme 57). An explanation for formation of both regioisomers in this ratio is currently unknown. Transmetalation could occur at both the α and

γ positions, providing a mixture of products. Alternatively, 1,3 allylic transposition of the allyl-Cu linear isomer could occur prior to reductive elimination.[170] Good yields were obtained for all couplings with allylboronic esters, suggesting the allylic position provides similar stabilisation to that of benzylic boronic esters.



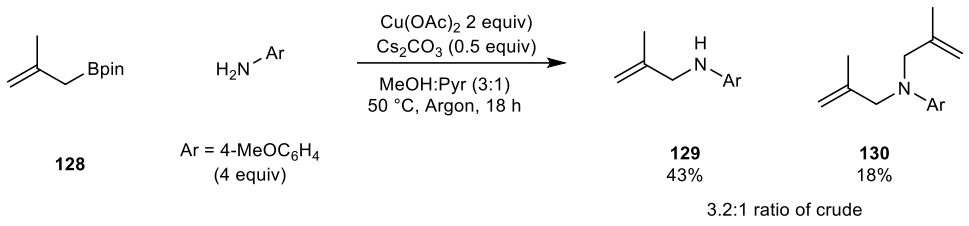
Scheme 57: Amination of boronic ester **122** with *p*-Anisidine.

Another non-symmetrical allylboronic ester **125** was submitted to the reaction conditions to further test the regiomeric outcome (Scheme 58). In this case a 1:2.5 ratio of linear amine **126** to rearranged isomer **127** was isolated, matching the ratio in the crude material. Cu-catalysed allylic substitutions with organometallic nucleophiles typically form γ-substituted products, though the substitution pattern depends on a number of factors including reaction solvent, temperature and both coupling species.[171] The increased formation of amine **127** could be attributed to formation of a more stable 3° allyl-Cu or radical intermediate.



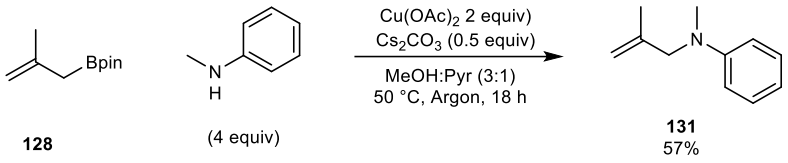
Scheme 58: Amination of boronic ester **125** with *p*-Anisidine.

Next, the coupling of a symmetrical allylboronic ester **128** was tested (Scheme 59). A 2.4:1 ratio of amine **129** was produced in moderate yield alongside dialkylated amine **130**. This was the only example of dialkylation during this investigation (except when resubmitting a product back to reaction conditions, see Scheme 48). Presumably, this could be due to the less sterically demanding nature of the allylboronic ester **128** compared to benzylic boronic esters.



Scheme 59: Amination of boronic ester **128** with *p*-Anisidine.

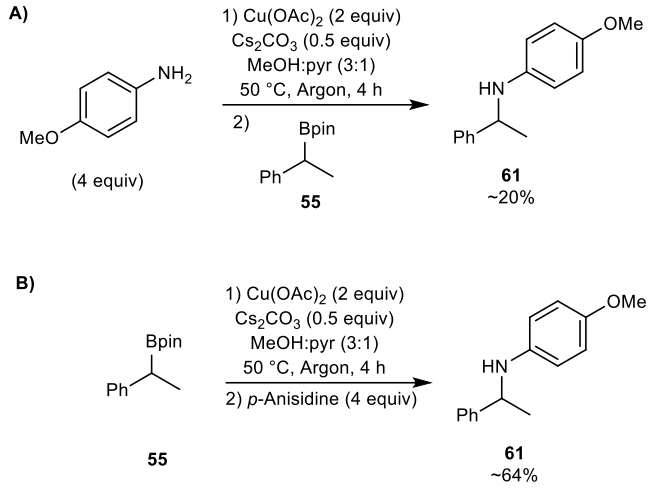
The use of *N*-methyl amine was employed in the coupling with boronic ester **128** (Scheme 60). This amine was chosen to avoid dialkylation and enable a test of steric tolerance when coupling allylboronic esters. A good yield of amine **131** was achieved when compared to the coupling with benzylic boronic ester requiring the use of forced reaction conditions (see Scheme 48, **78**).



Scheme 60: Amination of boronic ester **128** with *N*-methyl amine.

2.3.6 Initial Kinetic Studies

Preliminary kinetic investigations were performed under standard reaction conditions. This work was completed in collaboration with the Centre for Rapid Online Analysis of Reactions (ROAR) at Imperial College, London. Data on the rate of production of amine **61** and consumption of starting material boronic ester **55** was collected using ReactIR and LCMS analysis of aliquots of the reaction mixture. During initial data collection the order of addition of reagents had a large impact on yield of amine **61**. The standard methodology developed comprised a simple 'one pot' addition of all reagents to the reaction vessel prior to addition of solvent. For the kinetic studies the reaction needed to be initiated by addition of a key reagent at 50 °C to control and monitor the starting point of the reaction. Initial attempts to incubate Cu, base and amine at 50 °C for 30 mins prior to the addition of boronic ester **55** produced a significantly reduced yield of 20% of amine **61** after 4 h (Scheme 61, A). The reduction in yield suggests a Cu-complex formed from *p*-anisidine and $Cu(OAc)_2$ is inactive for the coupling. Changing the order of addition to incubate Cu, base and boronic ester **55** with subsequent addition of a solution of amine resulted in amine **61** being produced in comparable yield to the 'one pot' methodology (Scheme 61, B).



Scheme 61: Order of addition tests of aniline and boronic ester **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.5 mmol scale of **55**. Reaction concentration of 0.38 M.

Utilising this methodology, ReactIR data was collected for the formation of amine **61** and consumption of *p*-anisidine (Figure 15). Aliquots of the reaction mixture were also taken and analysed by LCMS to evaluate the concentration of amine **61** (Figure 16). A correlation was observed between the LCMS and ReactIR results for the formation of amine **61**. This suggests ReactIR could provide a method to suitably monitor the reaction. Amine **61** was produced in approximately 60% yield after 4 h from LCMS analysis. This result is comparable to reaction optimisation data, using ^{1}H NMR analysis producing a 55% yield after 4 h.[163] Unfortunately, due to the COVID-19 pandemic, plans for further investigation of the reaction mechanism at ROAR were not able to be carried out.

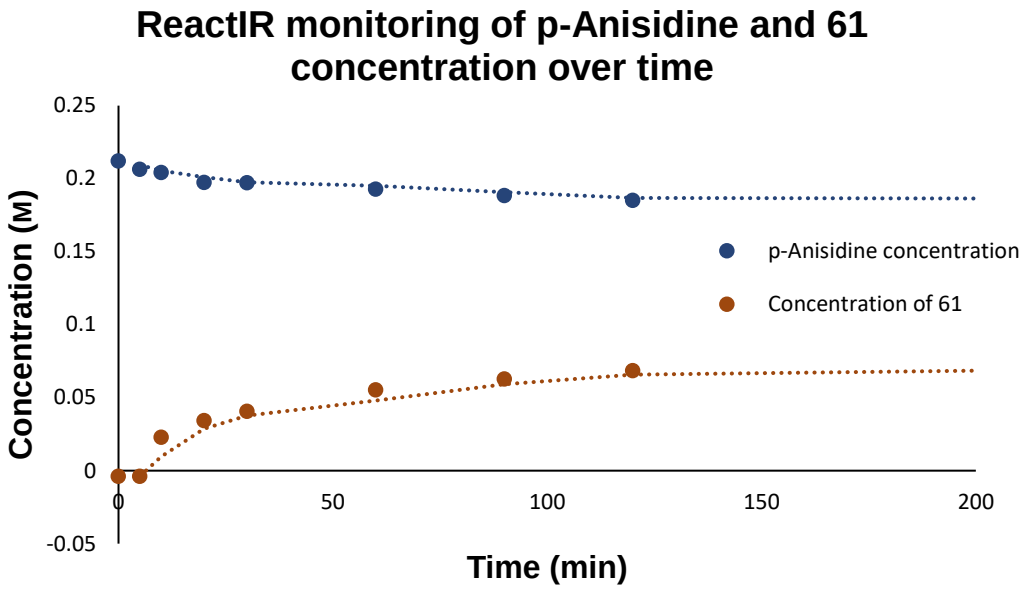


Figure 15: Concentration change of *p*-Anisidine (blue) and amine **61** (orange) over time determined by ReactIR.

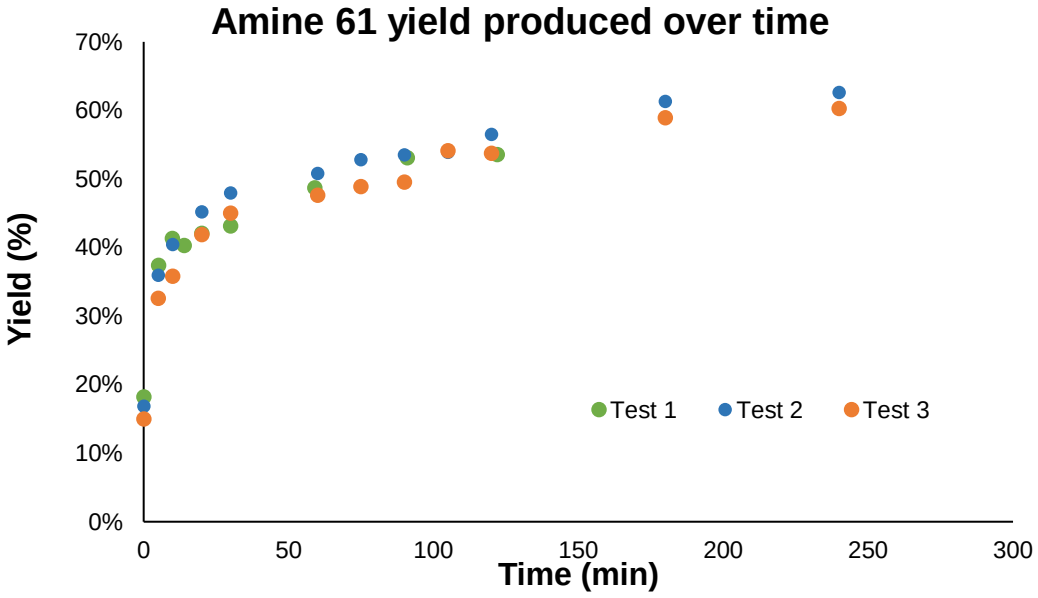
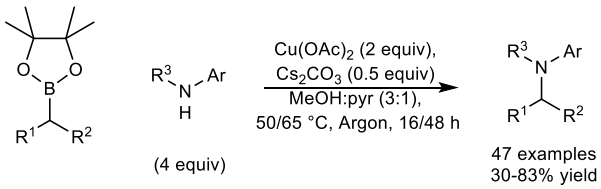


Figure 16: Change in concentration of amine **61** formation over time. Yields determined by LCMS analysis, using biphenyl as an internal standard.

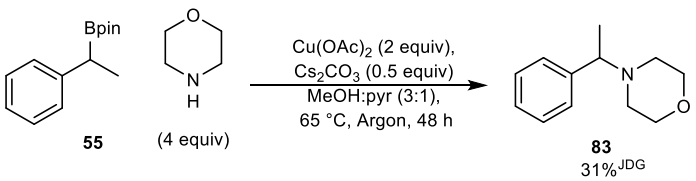
2.4 Conclusions and Future Work

Work was focused on the expansion of the substrate scope under established conditions for the amination of alkylboronic esters and anilines. Deviating from arylamine coupling partners to incorporate alkylamines resulted in reduced yields. Several noteworthy products were synthesised that merit further investigation.



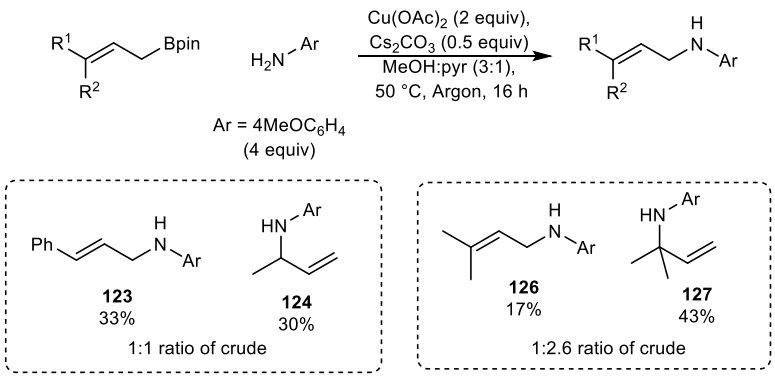
Scheme 62: Overview of the amination of alkylboronic esters with anilines.

Coupling of alkylboronic esters and alkylamines is underdeveloped and to our knowledge has only been reported when utilising cyclopropylboronic acid.[152] Consequently, the *N*-alkylation of non-cyclic boronic ester **55** and morpholine provides a valuable proof of concept, albeit in moderate yield under forced conditions.



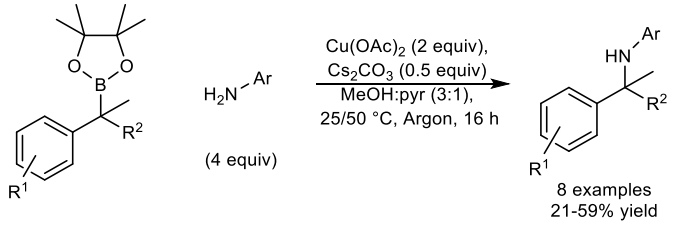
Scheme 63: Successful coupling of an alkylboronic ester and alkylamine.

Chan-Lam couplings with allylboronic esters, to our knowledge have not been previously reported. *N*-Alkylations with unsymmetrical allylboronic esters proceed successfully. However, reasoning for the regioisomeric ratio formed is still unknown.



Scheme 64: Regiomeric outcomes from the amination of unsymmetrical allylboronic esters.

3° boronic esters were also shown to be viable coupling partners. These substrates have also, to our knowledge not been reported in Chan-Lam couplings. These investigations, while modest, provide access to 3° amines which are synthetically challenging to form. The formation of a large number of side-products when utilising these substrates highlights a limitation to the methodology.



Scheme 65: Overview of the amination of 3° alkylboronic esters.

Future work would look to develop divergent reaction conditions to enable the coupling of alkylboronic esters and alkylamines. Further optimisation work could look to develop the reaction conditions by reviewing the use of ligands and additives. The use of coordinating groups or ligands could also enable stabilisation of allyl Cu intermediates to influence regiomeric outcomes.

Although the transfer of stereochemistry was not achieved under current conditions the development of an asymmetric amination methodology would deliver a powerful synthetic procedure. Initial mechanistic studies suggest the formation of a radical intermediate. This accounts for the radical clock ring-opening product and loss of stereochemistry. Development of reaction conditions to tolerate chiral ligands could be investigated to access an asymmetric amination reaction.

3. 2nd Generation Alkyl Chan-Lam Reaction – Coupling of Alkylamines

3.1 Aims

The focus of this project was to develop conditions to extend the scope of the reaction to the amination of alkylboronic esters with alkylamines. This would provide a complimentary approach to the coupling of alkylboronic esters and anilines. Currently to our knowledge, there is only one reported example of alkylboronic acid and alkylamine coupling by Zhu and co-workers.[152] This report is limited to the use of privileged cyclopropylboronic acid.

Intentions to use mild reaction conditions with the avoidance of unfavourable terminal oxidants would be beneficial in producing another practical Chan-Lam coupling method. An asymmetric variant of the coupling will be investigated through the use of either an enantioenriched alkylboronic ester or through the use of chiral ligated Cu complexes. Efforts to expand the scope to include the coupling of 3° boronic esters will be undertaken.

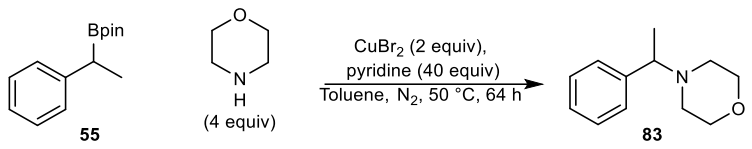
3.2 Results and Discussion: Development of an Alkyl Amination of Alkylboronic Esters

This section of work was done in collaboration with Dr Antonio Romero-Arenas, and built on initial results from MChem student Jonathan Andrews (denoted by 'JA'). Optimisation tables and amine substrates produced by Antonio Romero-Arenas are denoted by 'ARA'. These results are included to allow a complete discussion of the method development.

3.2.1 Method Development for the Alkyl Amination of Boronic Ester 55

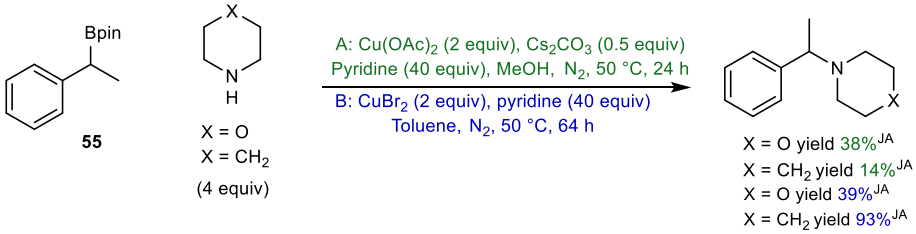
Initial investigations were focused on the reaction of 2° benzylic boronic ester **55** and morpholine in the presence of Cu salts based on inherited conditions (Scheme 66). 2° Benzylic boronic esters were initially used, due to our previous results for the coupling of anilines (Chapter 2). These showed that transmetalation of the benzylic boronic esters was promoted, presumably due to charge stabilisation from the aryl group of the resulting benzyl copper species. Optimisation reactions were performed on a 0.05 mmol scale, unless otherwise stated, with yields determined through ^{1}H-NMR analysis of the crude material using 1,3,5-trimethoxybezene internal standard. The observed formation of amine **83** (and other side-products) were confirmed through comparison of data from an authentic sample, and

subsequent doping and comparison of NMR samples. It has been assumed that throughout optimisation any incomplete mass balance is due to protodeboronation, to give ethyl benzene, which is presumably lost during work up due to its low boiling point. Optimisation was completed with morpholine as the coupling partner, as the product **83** has an indicative benzylic proton, distinct from any residual solvent peaks, facilitating accurate quantification of reaction yields through ^{1}H NMR analysis.



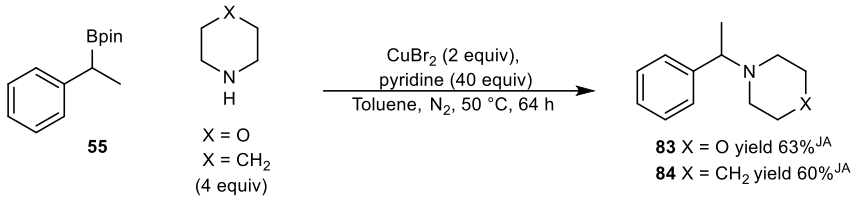
Scheme 66: Inherited alkylamine coupling conditions. JA.

Initial results had been previously performed in the group by Jonathan Andrews on 2° benzylic boronic ester **55** with morpholine and piperidine as coupling partners (Scheme 67). Yields using conditions A, developed for the coupling of anilines and 2° boronic esters (see Section 2.2.1), were modest but demonstrated proof of concept for the coupling of aliphatic amines. After systematically adjusting the conditions Jonathan was able to increase the yields of the coupling products by using 2 equivalents of $CuBr_2$, pyridine in 40 equivalents in toluene at 50 °C. However, in order to achieve these increased yields an extended 64 h reaction time was required.



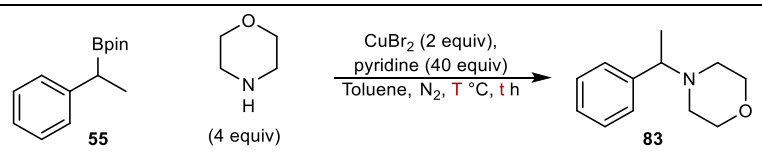
Scheme 67: Alkylamine Chan-Lam coupling with A) aniline optimised conditions and B) previously optimised conditions by JA. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.1 M.

Using these conditions, Jonathan performed the coupling of boronic ester **55** with morpholine and piperidine on larger scale (Scheme 68). Amine products **83** and **84** were isolated in good yield and showed promise for the expansion of alkyl coupling partners with boronic ester **55**. These initial results were irreproducible and further reaction optimisation was therefore undertaken.



Scheme 68: Coupling of boronic ester **55** with morpholine and piperidine. JA.

To increase the practicality of the reaction conditions, both reducing reaction time and aiming to decrease catalyst loading, further method development was undertaken. Utilising these inherited conditions, temperature and time frames were first investigated (Table 2). Reaction temperatures of 50 °C, over both timeframes formed amine **83** in poor yield (Table 2, Entry 1 and 2). An increased temperature of 80 °C and a reduced time frame of 16 h gave comparable yields of amine **83** to those recorded by JA (Entry 4). Further elevated temperatures were tested. Increased temperatures decreased product formation and lowered the amount of unreacted starting material **55**, presumably due to an increase in protodeboronation (Entry 5 and 6).

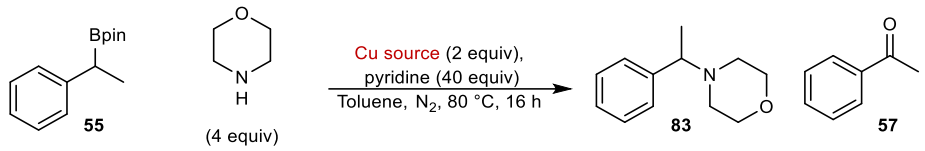


Entry	Time (h)	Temperature (°C)	Yield (%)	
			83	**55**
1	40	50	21	76
2	16	50	25	50
3	40	80	36	58
4	16	80	46	51
5	16	90	25	61
6	16	100	24	39

Table 2: Effect on the temperature and time on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.1 M.

The copper source was next investigated with a range of Cu(I) and Cu(II) sources trialled (Table 3). Cu(I) sources were generally poor in producing amine **83**, with the exception of CuBr (Table 3, Entry 1). This is potentially due to the ease of oxidation of CuBr to $CuBr_2$. Most Cu(II) sources tested also failed to form the desired amine product **83**. Using $CuCl_2$ (Entry 5) produced some amine **83**, however, less starting material remained when compared to $CuBr_2$ (Table 2, Entry 4). Acetate counterions are often preferable over halogenated ions in Chan-Lam couplings.[109] Previously reported yields when employing these Cu-halogen catalysts are often low, including coupling alkylboronic acids and alkylamines.[151,152,172] However, it has

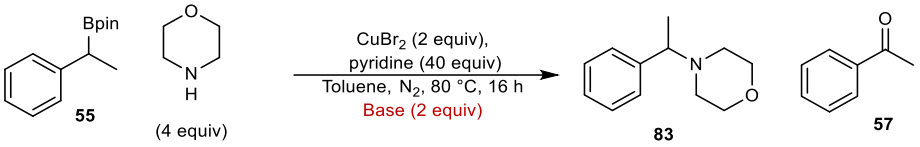
been proposed that the halide could be promoting the reaction by acting as a Lewis base activator of the boronic ester.[173]



		Yield (%)		
Entry	**Cu source**	**83**	**55**	**57**
1	CuBr	51	36	0
2	CuCl	5	43	3
3	CuI	0	84	0
4	$CuSO_4$	0	25	0
5	$CuCl_2$	22	42	2
6	$Cu(CF_3SO_3)_2$	0	0	0
7	$Cu(acac)_2$	0	0	2
8	$Cu(OAc)_2$	0	53	2
9	CuO	0	86	3
10	CuBr.DMSO	7	60	0
11	Cu 2-ethylhexanoate	0	0	0
12	$Cu(ClO_4)_2.6H_2O$	0	0	0

Table 3: Screening Cu sources for the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.1 M. Alcohol not detected.

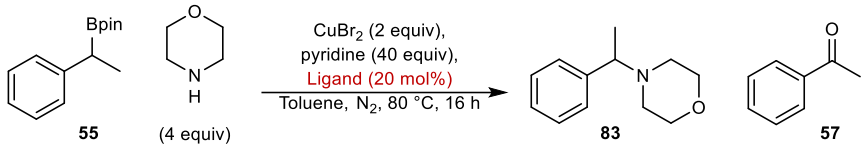
Many Chan-Lam reactions employ organic or inorganic bases fulfilling a dual purpose of ligating copper and neutralisation of acid produced in the reaction.[112] In previous work on the optimisation of the alkylation of anilines with 2° benzylic boronic ester **55**, JDG utilised Cs_2CO_3 to reduce the formation of the oxidation side product ketone **57** and aid amine formation (see Section 2.2.1).[165] Amine bases, including triethylamine, DABCO and DBU produced no coupled product **83**. Inorganic bases were therefore screened to assess if the formation of amine **83** could be increased (Table 4). Both caesium chloride and potassium fluoride halted amine **83** formation (Entry 2 and 4). The use of carbonates (Entry 3, 5 and 7) generally gave the best prospects with comparable yields to the reaction with the absence of base (Table 3, Entry 1). However, the use of base also reduced the amount of unreacted boronic ester, diminishing the potential for increased yields.



Entry	Base	Yield (%)		
		83	**55**	**57**
1	CsF	26	51	0
2	CsCl	0	77	3
3	Cs_2CO_3	29	49	0
4	KF	0	0	13
5	Na_2CO_3	30	32	0
6	$NaHCO_3$	18	64	2
7	K_2CO_3	22	48	0
8	KO^tBu	35	0	0
9	NaOMe	21	64	2

Table 4: Effect of bases on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.1 M. Alcohol not detected.

The use of ligands to aid reactivity in the Chan-Lam reaction has been previously reported.[105,106,110,117,121–128,141–143] However, attempts to use ligands during investigation of our alkyl Chan-Lam coupling with anilines generally shut down the formation of amine **83**. The need for an improved yield and reaction tolerance led to a ligand screening being undertaken (Table 5). If ligands were tolerated in the reaction this could also enable a non-racemic version of the reaction through a chiral ligated Cu species. A range of mono-phosphorus, di-nitrogen and bisphosphorus ligands were tested. A substoichiometric loading of ligand with an excess of $CuBr_2$ was tested as it was hypothesised that the ligand could act as the active catalyst with the remaining $CuBr_2$ acting as an oxidant. All of the ligands trialled in general diminished yields of amine **83** and the quality of starting material remaining was reduced. Bisphosphine ligands largely shut down the reaction and no C-N coupling was observed (Entry 12, 13 and 15).



55 (4 equiv) **83** **57**

Entry	Ligand	Yield (%)		
		83	**55**	**57**
1	1,10 Phen	13	56	0
2	DMPhen	16	46	0
3	2,2'-dipyridyl	20	34	0
4	**128**	9	58	0
5	**129**	13	42	0
6	**130**	0	0	6
7	**131**	18	40	0
8	**132**	35	39	0
9	**133**	17	52	0
10	**134**	16	43	0
11	dppBz	13	56	0
12	dppm	0	0	6
13	dppe	0	0	6
14	BINAP	25	0	0
15	Xantphos	0	0	0
16	DPPF	18	61	0
17	**135**	13	60	0
18	RuPhos	22	0	0

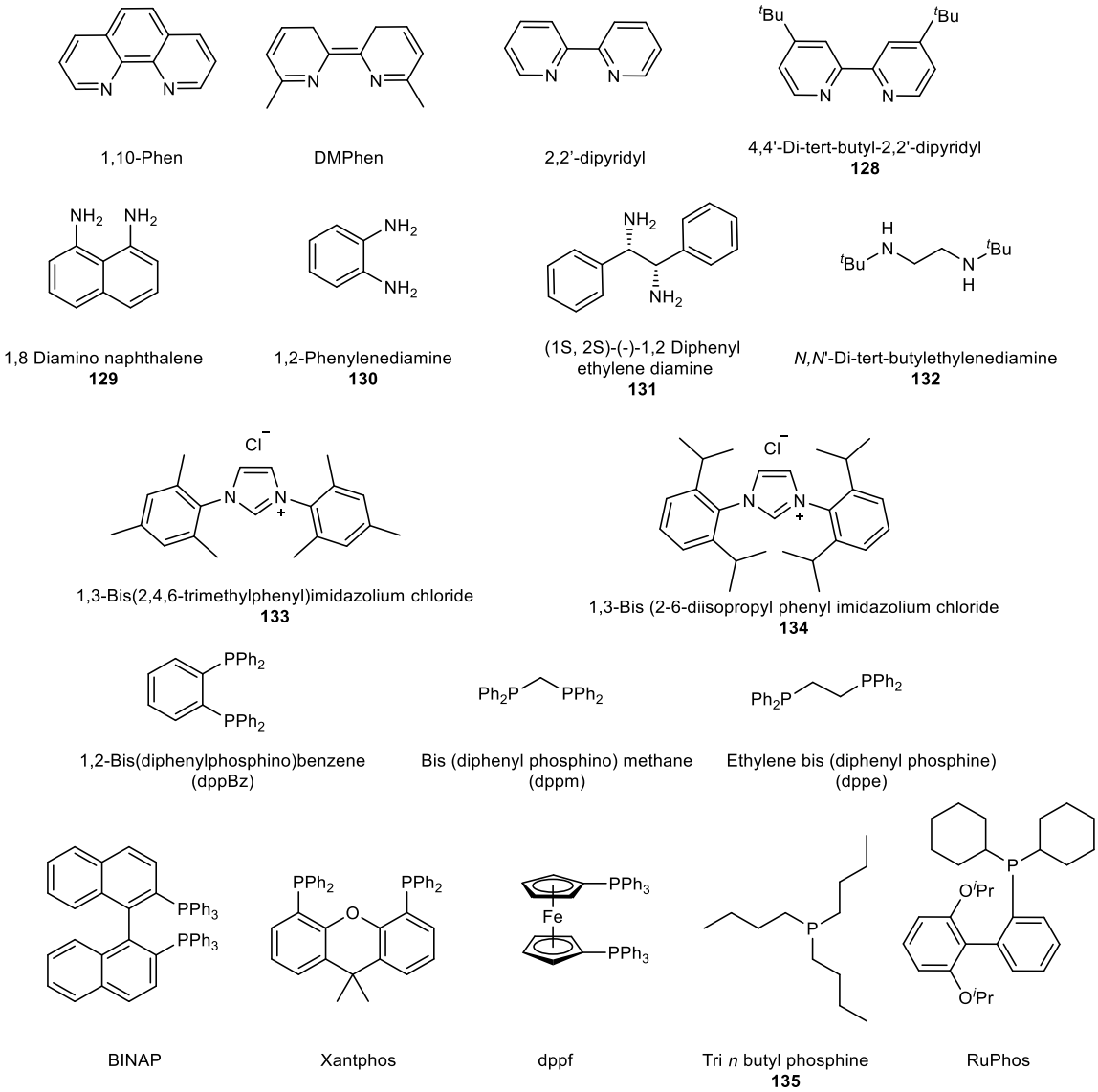
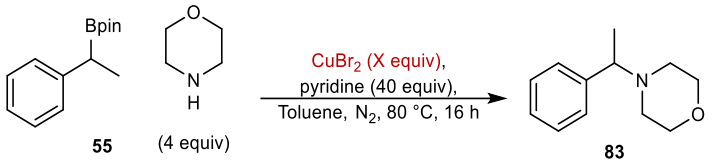


Table 5: Effect of ligands on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.16 M. Alcohol not detected.

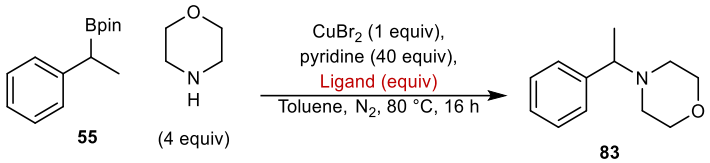
The potential for the reduction of Cu equivalency was then considered (Table 6). Employing only 1 equivalent of Cu produced comparable results to using Cu in superstiochiometric quantities (Table 6, Entry 1). This result also showed the most potential for an increase in product yield due to the large amount of boronic ester **55** remaining. The use of substoichiometric Cu reduced yield of amine **83** alongside a reduction in starting material present (Entry 2 and 3). The formation of amine **83** when using substiochiometric quantities of Cu shows potential for the reaction to be performed catalytically with further optimisation.



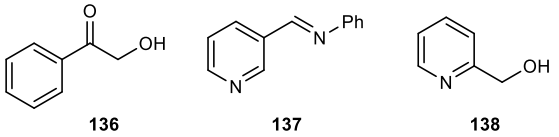
Entry	Cu eq	Morpholine eq	Yield (%)	
			83	55
1[a]	1	4	33	68
2[a]	0.5	4	34	45
3[a]	0.3	4	13	82
4	0.5	2	11	72
5[b]	1	4	53	70

Table 6: Alteration of Cu equivalency for the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55** Reaction concentration of 0.16 M. a) Average of 3 reactions. b) 0.3 M. Alcohol and ketone not detected.

A further screening of ligands was undertaken (Table 7). A number of bidentate ligands and Schiff bases were tested. Di-oxygen ligand **136** and Schiff base **137** formed amine **83** in moderate yield with diminished starting material **55** remaining. Pyridyl ligand **138** reduced coupled product **83** yield. Nac-Nac ligand **139** which had been previously utilised within the group for the oxidation of boronic esters and by Watson for amide Chan-Lam coupling was examined.[159,164] Ligand **139** produced amine **83** in poor yield but did not produce any oxidised product (Table 7, Entry 6).[164] Ligand **140**, dba, produced a moderate yield of product **83** albeit with decreased starting material remaining (Entry 7). Schiff base **141** (Entry 8) gave amine **83** in 49% yield with 52% starting material **55** remaining to further develop the reaction.



Entry	Ligand	Ligand eq	Yield (%)	
			83	**55**
1	**136**	1	33	50
2		0.5	14	85
3	**137**	1	32	65
4		0.5	30	53
5	**138**	1	23	67
6	**139**	1	22	63
7	**140**	0.5	37	52
8	**141**	**0.5**	**49**	**52**



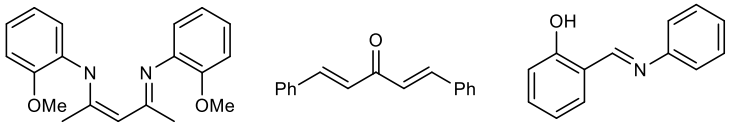
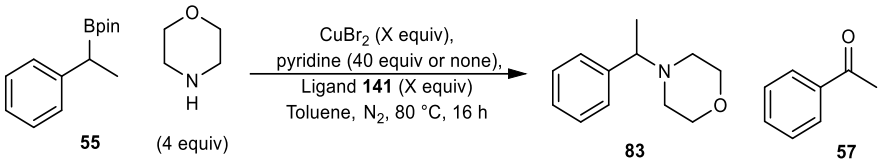


Table 7: Effect of ligands on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.16 M. Alcohol and ketone not detected.

Schiff bases are a class of organic ligands synthesised from condensation reactions of anilines and aldehydes and have been used widely in catalysis.[174] These ligands are able to form stable complexes with metals and a number of Cu complexes have been reported.[174,175] Cu complexes using Schiff base **141** have been reported and used in *N*-arylation reactions.[176] Schiff type *N*- *O*- tetradentate ligands have been previously used in Chan-Lam coupling of arylboronic acids and anilines.[143] Schiff base **141** was subjected to systematic alteration of reaction conditions (Table 8). Using 1 equivalent of Cu with only 0.25 equivalents of ligand **141** produced good yields of amine **83** (Entry 1 and 2). Using pyridine appeared to decrease starting material boronic ester **55** (Entry 1). Increasing the ligand equivalency had a detrimental effect on production of coupled product **83** (Entries 3-8). Decreasing the amount of Cu to match the ligand loading of 25 mol% significantly diminished the yield of amine **83** (Entry 9).



Entry	141 equiv	Cu eq	Pyr eq	Yield (%)		
				83	55	57
1	0.25	1	40	49	30	3
2	0.25	1	-	62	43	6
3	0.5	1	40	30	52	0
4	0.5	1	-	23	91	0
5	1	1	40	21	69	0
6	1	1	-	30	97	0
7	2	1	40	56	54	0
8	2	1	-	18	79	0
9	0.25	0.25	-	7	91	0

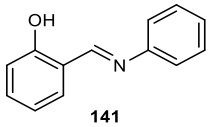
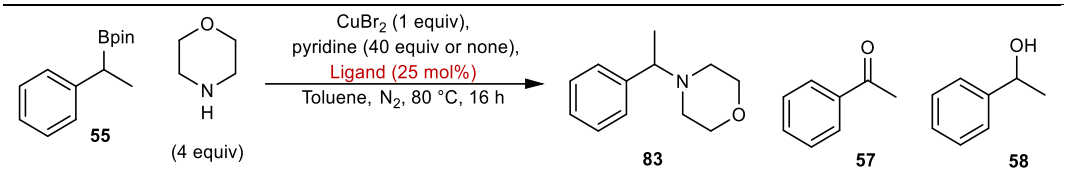


Table 8: Effect of ligand and Cu equivalency on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.16 M. a) Reaction conducted open to air. Alcohol not detected.

A further range of Schiff base ligands were synthesised to test the effect of the electronics and sterics of the imine part of the molecule (Table 9). Ligand **142** with an *o*-OMe substituent produced amine **83** in comparable yields to that of ligand **141** (Table 9, Entry 1 and 2, see Table 8, Entry 2). However, no starting material was detected when using ligand **142** with pyridine, though without pyridine yield of amine **83** was decreased (Entry 1 and 2). Ligands **143** and **144** with *para* substituents formed coupled product **83** in moderate yield (Entry 3-6). With di-substituted ligands **145** and **146** also producing amine **83** in modest yield. Dimethoxy ligand **146** saw an increase in formation of ketone **57**. Repeating the use of ligand **141** without pyridine and increased concentration (Entry 11) gave concordant results to Entry 3 Table 8. The role of the base in this instance could be fulfilled by the ligand or the amine.[112]



Entry	Ligand	Pyr eq	Yield (%)			
			83	55	57	58
1	**142**	40	60	ND	4	0
2		-	47	64	0	0
3	**143**	40	34	50	5	0
4		-	34	69	3	6
5	**144**	40	49	ND	0	0
6		-	20	89	0	0
7	**145**	40	36	37	0	0
8		-	49	34	6	0
9	**146**	40	35	36	12	0
10		-	36	57	15	0
11[a]	**141**	-	61	45	6	0

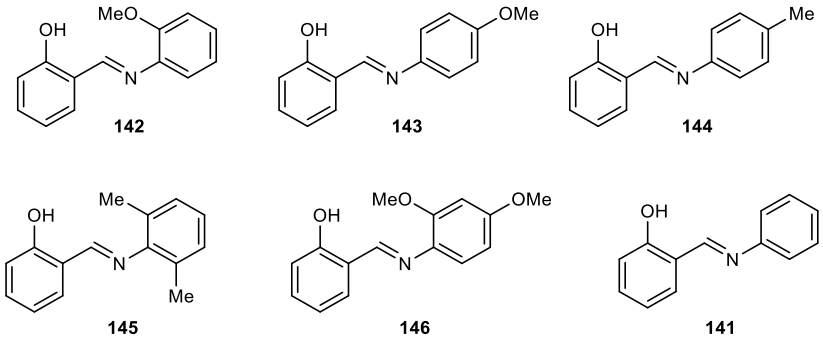
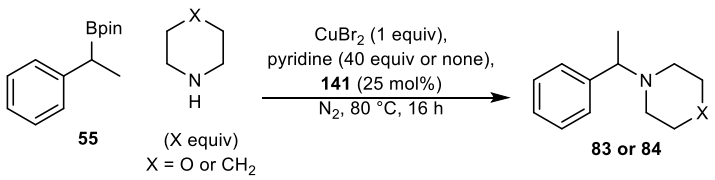


Table 9: Effect of ligands on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.16 M. a) Reaction concentration of 0.3 M.

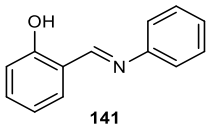
The importance of solubility in the Chan-Lam reaction has been noted, with solubility of Cu salts likely to be crucial.[112] At this point in reaction optimisation it was observed that current reaction conditions were unable to fully solvate $CuBr_2$. As increasing concentration had been seen to be beneficial to reaction yield (see Table 9, Entry 11) it was decided to test running the reaction neat. To this end reactions were conducted with either 40 or 10 equivalents of amine and no solvent (Table 10). Encouragingly full conversion to amine **83** was achieved when running the reaction in 40 equivalents of either morpholine or piperidine (Entry 1 and 2). The solubility of the reactions was visibly increased. When no ligand **141** was employed this resulted in a drop in yield of amine **83** (Entry 3). Lowering the amine equivalency to 10 with no pyridine present produced comparable results to using 40 equivalents of amine (Entry 4). The use of pyridine under these reaction conditions led to a reduction in formation of amine

83, though the boronic ester **55** was also consumed (Entry 5 and 6). Whilst promising results, the viability of using the starting material amine in such excess would not be suitable except for the most inexpensive amines.



55 (X equiv) X = O or CH_2 **83 or 84**

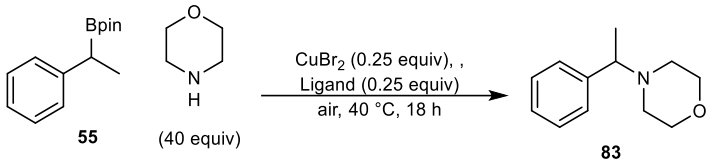
Entry	Amine	Amine eq	Pyr eq	Yield (%)	
				83 or 84	**55**
1[a]	Morpholine	40	-	>95	<5
2[a]	Piperidine	40	-	>95	<5
3[a,b]	Morpholine	40 no ligand	-	69	<5
4[c]	Morpholine	10	-	92	<5
5[c]	Morpholine	10	20	70	<5
6[c]	Piperidine	10	20	53	<5



141

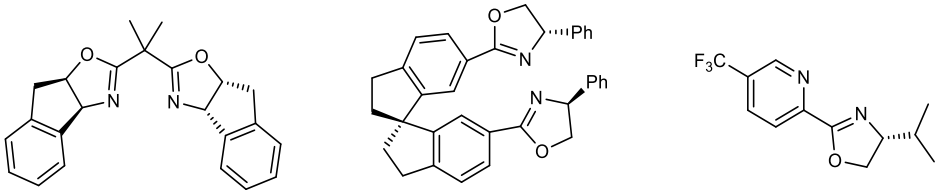
Table 10: Absence of solvent on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. a) Reaction concentration of 0.025 M. b) No ligand. c) Reaction concentration of 0.1 M. Alcohol and ketone not detected.

With a consistent method to produce coupled amine **83**, albeit with large quantities of amine required, efforts were turned to using chiral ligands to try and deliver a non-racemic reaction method (Table 11). Commercially available ligands **147**, **148** and **149** were used in the first instance. Due to lower temperatures often enhancing stereoselectivity, the reaction temperature was also lowered to 40 °C for non-racemic method development. Bis-oxazoline and Phox ligand **155** have been used in various asymmetric Cu-catalysed transformations.[177,178] However, the use of these ligands in the amination reaction gave only racemic amine **83** (Entry 1, 2 and 3).



55 (40 equiv) 83

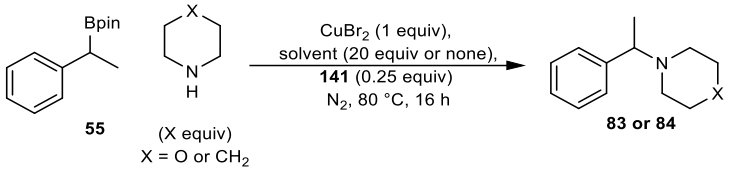
Entry	Ligand	*e.r.*	Yield (%)	
			83	**55**
1	**147**	50:50	95	<5
2	**148**	50:50	84	<5
3	**149**	50:50	67	<5



147 **148** **149**

Table 11: Effect of chiral ligands on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. a) Reaction concentration of 0.025 M. ARA. Alcohol and ketone not detected.

With the aim of increasing the solubility of Cu, the use of amine-based solvents was tested (Table 12). Using either *N*-methylmorpholine or pyridine as a solvent led to reduced yields of coupled product **83** with both morpholine and piperidine substrates (Entry 1-4). Reducing the equivalency of amine when running the reaction neat decreased the yield of coupled product **83** with both amine substrates but more dramatically for morpholine (Entry 5 and 6). Yields of coupled amine **83** could not be translated when performing the current best neat reactions at preparative scale (Entry 8 and 9). Encouragingly, the reaction could be carried out under air when using 10 equivalents of amine to provide amine **83** in excellent yield with no oxidative side-products formed (Entry 10). This could provide an opportunity to perform the reaction catalytically using air as an oxidant.



55 (X equiv) X = O or CH_2 — 83 or 84

Entry	Amine	Amine eq	Solvent	Yield (%)	
				83 or 84	55
1[a]	Morpholine	4	*N*-methyl morpholine	13	116
2[a]	Morpholine	4	pyridine	53	19
3[a]	Piperidine	4	*N*-methyl morpholine	23	104
4[a]	Piperidine	4	pyridine	17	72
5[b]	Morpholine	5	-	20	75
6[b]	Piperidine	5	-	64	0
8[cd]	Morpholine	10	-	27	82
9[cd]	Morpholine	5	-	28	84
10[ce]	**Morpholine**	**10**	**-**	**93**	**0**

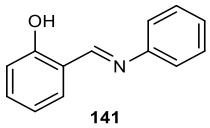


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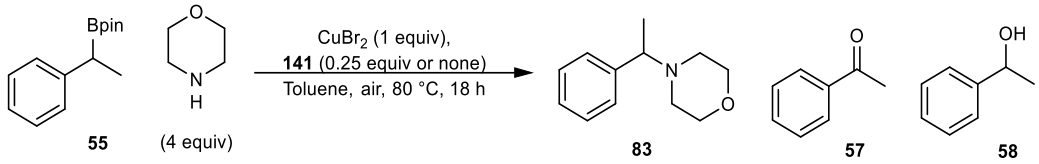
Table 12: Solvent effects on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. A) Reaction concentration of 0.05 M. b) Reaction concentration of 0.2 M. c) Reaction concentration of 0.1 M. d) Reactions conducted on a 0.5 mmol scale of **55**. E) Reaction conducted under air. Alcohol and ketone not detected.

With large excesses of amine starting material producing the best yields but not providing a practical solution an alternative strategy was tested. It was noted when performing tests for the kinetic reactions at ROAR that order of the addition of reagents was linked to coupled product yields (see section 2.3.6). In the coupling of aniline, incubating boronic ester **83** with Cu prior to the addition of amine resulted in good yields. Cruces and co-workers have also highlighted the importance of the order of addition.[154] Modest yields were only achieved when incubation of Cu and aniline was performed in the coupling with alkylboronic esters. Order of addition tests were therefore performed. Previously in method development reagents were all added to the reaction vessel before solvent and then heating in a 'one pot' method. Pre-formation methods, either incubating Cu, ligand and boronic ester **83** for 30 mins or Cu, ligand and amine for 30 mins were tested (Table 13). Incubating boronic ester **55** first generally produced better yields of coupled product **83** than incubating amine first (Entry 3, 6 and 8). Reactions performed without ligand resulted in lower yields of amine **83** (Entry 6 and 7). Opening the reaction to air led to an increase in oxidised products **57** and **58** (Entry 1, 3-7) when compared to Entry 2 which was performed under N_2. When using only 0.25 equivalents of Cu and incubating with boronic ester first gave comparable yields to using 1 equivalent of

Cu (Entry 8 versus 3). Importantly, this reaction demonstrated for the first time that turnover of the Cu-catalyst could be achieved, using air as the oxidant, to give amine **83** as the major product.



Entry	Order of addition	Yield (%)			
		83	**55**	**57**	**58**
1	One Pot	27	47	31	17
2[a]	One Pot	31	>95	1	3
3	Bpin first	47	85	30	8
4	Amine first	53	37	12	0
5[b]	One Pot	0	0	32	13
6[b]	Bpin first	29	18	31	9
7[b]	Amine first	19	45	11	0
8[c]	Bpin first	47	0	16	0

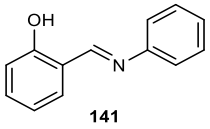
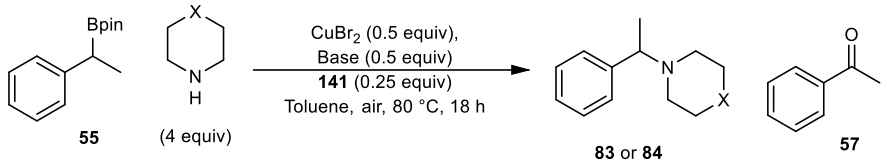


Table 13: Order of addition effects on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.16 M. a) Reaction performed under N_2. b) No ligand. c) 0.25 equivalents of $CuBr_2$ and ligand used.

Addition of a base to the incubation of boronic ester **55** prior to addition of amine was tested to try and decrease the presence of ketone **57** (Table 14). Bases previously investigated and shown to produce amine **83** were investigated again here (see Table 4). Alongside this, boric acid was examined due to its reported use in previous Chan-Lam couplings.[109] Boric acid can form esters with pinacol, effectively diminishing pinacol's inhibitory effects through coordination to Cu.[109,179–181] None of the bases tested reduced the yield of ketone **57** significantly. The use of cesium and sodium carbonate halted production of amine **84** when using piperidine as a substrate (Entry 7 and 8). Conversely, when sodium carbonate was used when coupling morpholine, a moderate yield of amine **83** and a slightly reduced formation of ketone **57** was observed (Entry 2). The use of sodium bicarbonate and sodium methoxide has a beneficial impact on the yield when using piperidine only (Entry 10 and 11). Boric acid appeared to have a positive impact on coupling with piperidine and a non-detrimental influence on the formation of amine **83** when coupling with morpholine (Entry 6 and 12).



Entry	Base	Substrate	Yield (%)		
			83 or 84	55	57
1	Cs_2CO_3	Morpholine	30	<5	34
2	Na_2CO_3	Morpholine	54	<5	13
3	KO*t*Bu	Morpholine	40	<5	11
4	$NaHCO_3$	Morpholine	49	<5	18
5	NaOMe	Morpholine	35	<5	14
6	Boric acid	Morpholine	48	<5	10
7	Cs_2CO_3	Piperidine	0	<5	24
8	Na_2CO_3	Piperidine	0	<5	20
9	KO*t*Bu	Piperidine	70	<5	13
10	$NaHCO_3$	Piperidine	85	<5	11
11	NaOMe	Piperidine	70	<5	16
12	Boric acid	Piperidine	78	<5	12

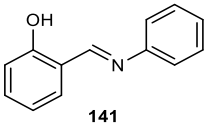


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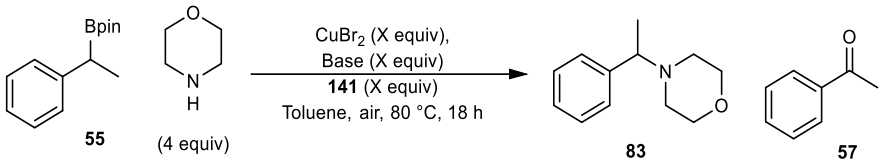
Table 14: Base effects on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.16 M. $CuBr_2$, ligand **141**, base and boronic ester 55 incubated at 80 °C for 30 mins prior to addition of amine. Alcohol not detected.

The best performing bases were next tested with decreasing ratios of Cu:ligand:base (Table 15). The use of sodium carbonate in all instances formed more amine **83** than incorporating boric acid into the reaction conditions (Entries 1, 3, 5, 7, 9). The formation of ketone **57** was only negated when using a 1:1:1 ratio of Cu:ligand:Na_2CO_3 (Entry 1). Decreasing the equivalents of Cu:ligand:base produced a drop off in yield of coupled product **83** (Entry 9 and 10).



Entry	Cu:Ligand:Base eq	Base	Yield (%)		
			83	**55**	**57**
1	1:1:1	Na_2CO_3	83	<5	ND
2	1:1:1	Boric acid	28	<5	40
3	1:0.5:0.5	Na_2CO_3	93	<5	7
4	1:0.5:0.5	Boric acid	66	<5	13
5	0.5:0.5:0.5	Na_2CO_3	57	<5	17
6	0.5:0.5:0.5	Boric acid	43	<5	22
7	0.5:0.25:0.5	Na_2CO_3	56	<5	25
8	0.5:0.25:0.5	Boric acid	51	<5	9
9	0.25:0.25:0.25	Na_2CO_3	30	<5	12
10	0.25:0.25:0.25	Boric acid	45	<5	20

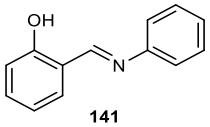
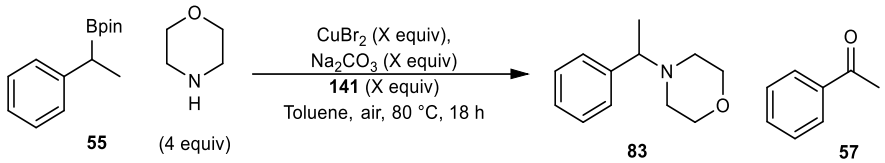


Table 15: Effects of decreasing catalyst and base loading on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.16 M. $CuBr_2$, ligand **141**, boronic ester **55** and base incubated at 80 °C for 30 mins prior to addition of amine. Alcohol not detected.

Increased loadings of Na_2CO_3 and decreased catalyst loading were subsequently tested to assess if this could further decrease ketone **57** formation (Table 16). Increasing the base loading only served to increase ketone **57** formation (Entry 2-5) when compared to Table 15, Entry 5, 7 and 9. The only exception being Entry 1, however, amine **83** formation was reduced compared to the use of greater catalyst loading (see Table 15, Entry 1, 3, 5 and 7). The incubation method and one pot method both appeared to produce comparable results in both the production of coupled product **83** and ketone formation **57** (Entry 3 and 4). Overall, it was determined the addition of Na_2CO_3 as a base was not beneficial to the reaction compared to yields achieved in its absence (see Table 9, Entry 11).



55 (4 equiv) 83 57

Entry	Cu:Ligand:Base eq	Order of addition	Yield (%)		
			83	**55**	**57**
1	0.5:0.5:1	Bpin first	43	<5	16
2	0.25:0.25:1	Bpin first	30	<5	26
3	0.5:0.25:1	Bpin first	56	<5	31
4	0.5:0.25:1	One pot	50	<5	27
5	1:0.5:0.5	One pot	45	<5	24

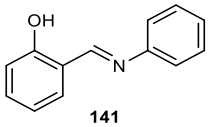


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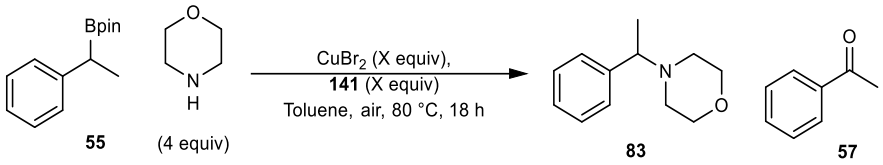
Table 16: Effects of decreasing catalyst and base loading on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.16 M. $CuBr_2$, ligand **141**, boronic ester **55** and base incubated at 80 °C for 30 mins prior to addition of amine. No alcohol detected.

A final test of incubation conditions with and without the addition of ligand was carried out (Table 17). Lowering the Cu loading, even with incubation, decreased the yield of amine **83** (Entry 2 and 3). The addition of ligand **141** did appear to have a beneficial impact on the formation of coupled product **83** (Entry 4). However, yields using preformation did not improve upon using 1 equivalent of Cu alongside 0.25 equivalents of ligand (see Table 9, Entry 11).



Entry	Ligand eq	Cu eq	Order addition	Yield (%)		
				83	55	57
1	-	1	Bpin first	43	0	10
2	-	0.5	Bpin first	45	0	13
3	-	0.25	Bpin first	25	0	9
4	0.25	0.5	Bpin first	52	0	16

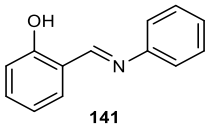
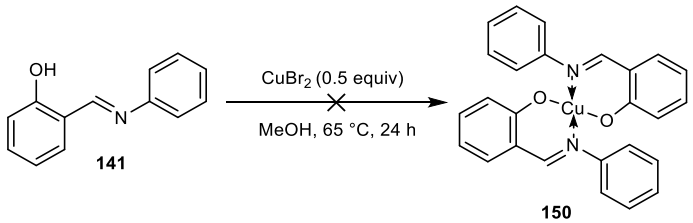
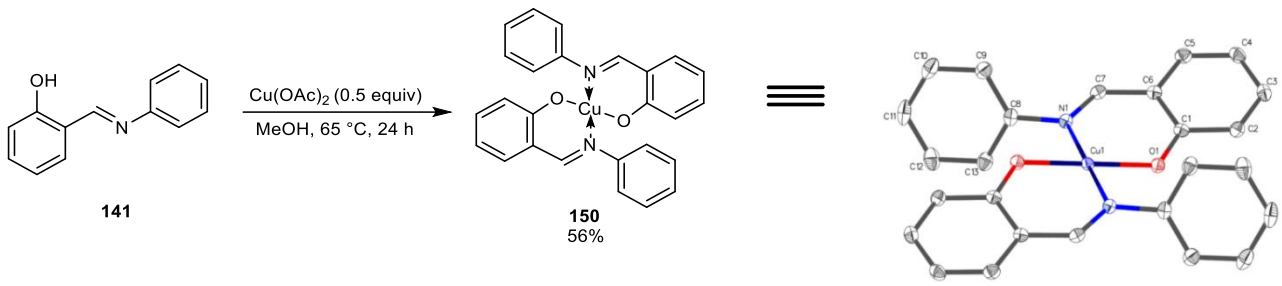


Table 17: Effects of decreasing Cu and ligand loading on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **55**. Reaction concentration of 0.16 M. $CuBr_2$, ligand **142**, boronic ester **55** and base incubated at 80 °C for 30 mins prior to addition of amine. No alcohol detected.

At this stage it was decided to test if preformation of Cu-complex **150** and its addition to the reaction conditions could improve coupling product **83** yield. Cu-complexes have been previously used in Chan-Lam conditions successfully.[105,106,110,117,129] Complex synthesis was initially attempted using a modification of a procedure by Nordlander and co-workers using $CuBr_2$ (Scheme 69).[176,182] Unfortunately all efforts to form the complex via this method were unsuccessful. However, when using $Cu(OAc)_2$, complex **150** was obtained in moderate yield (Scheme 70).[182] The structure of **150** was confirmed by X-ray crystallography.

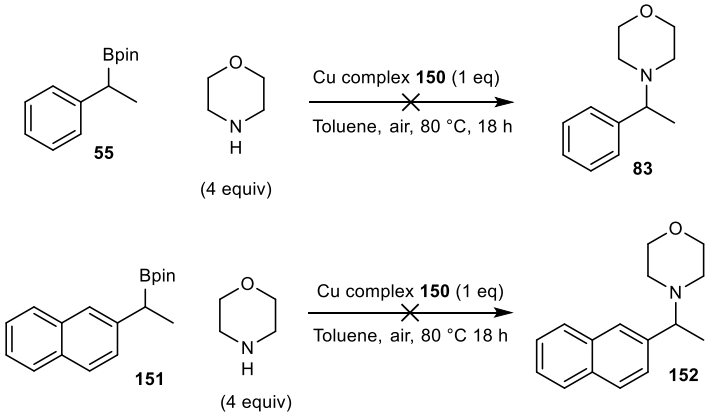


Scheme 69: Attempted synthesis of Cu-complex **150** using $CuBr_2$.



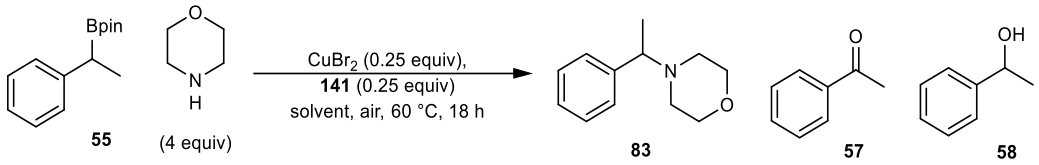
Scheme 70: Synthesis of Cu-complex **150** using $Cu(OAc)_2$. Reaction concentration of 0.33 M.

Cu-complex **150** was then submitted to the current reaction conditions (Scheme 71). Boronic ester **151** was additionally tested due to its easier visualisation of the corresponding product on TLC during purification. However, the reaction of both boronic ester **55** and **151** produced no coupled amine product (**83** and **152**) under these reaction conditions. This suggests that bis-ligation to Cu does not lead to an active catalyst. This is presumably due to Cu being coordinatively saturated, with ligand dissociation sluggish under the reaction conditions.



Scheme 71: Submission of Cu-complex **150** to the amination of boronic ester **55** and **151**. Reactions conducted on a 0.5 mmol scale of **55** and **151**. Reaction concentration of 0.1 M.

Parallel work was undertaken by Antonio Romero-Arenas (ARA) to alter solvent conditions to enable a reduction in catalyst loading (Table 18). Alcoholic media was tested due to its beneficial results, often when using $Cu(OAc)_2$ to promote Cu dissociation.[108,109] However, the use of IPA could also lead to competing etherification.[161] Promisingly, excellent results were achieved with only 25 mol% catalyst loading with both polar protic and non-polar aprotic solvents. Oxidation side-products **57** and **58** are present when using singular solvent systems (Entry 1, 3, and 7). The use of IPA both on its own and in mixtures with dioxane, propylacetate and toluene produced amine **83** in excellent yield with very minimal oxidation side-products observed and no etherification product detected (Entry 2, 4, 5, 6 and 8).



Entry	Solvent	Solvent II	Ratio	Yield (%)			
				83	**55**	**57**	**58**
1	Toluene	-	-	91	<5	10	11
2	IPA	-	-	>95	<5	<5	3
3	Dioxane	-	-	>95	<5	11	2
4	Toluene	IPA	1:1	>95	<5	<5	2
5	Toluene	IPA	3:1	>95	<5	<5	3
6	Dioxane	IPA	1:1	>95	<5	5	1
7	PrOAc	-	-	>95	<5	6	3
8	PrOAc	IPA	1:1	96	<5	<5	2

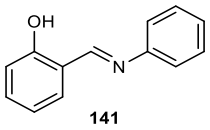
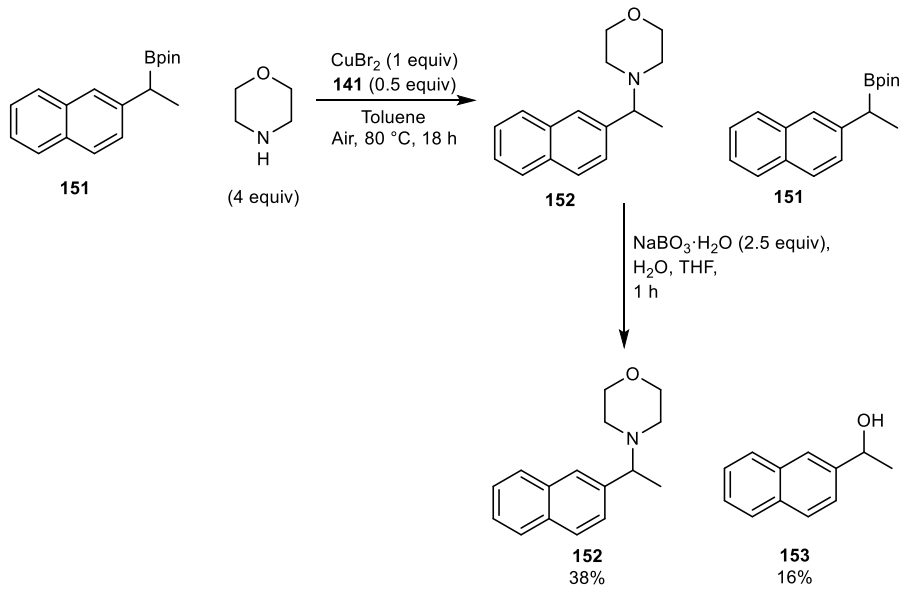


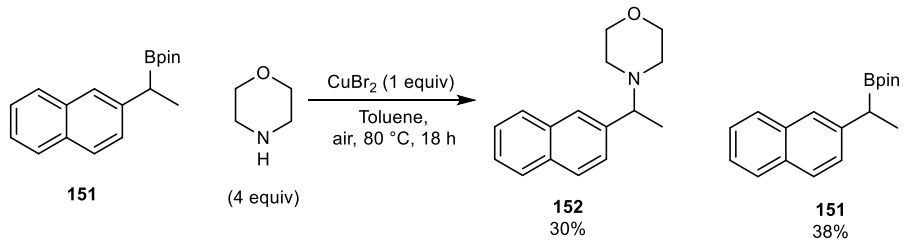
Table 18: Effects of solvent on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.25 mmol scale of **55**. Reaction concentration of 0.3 M. ARA.

At this point in optimisation, it was decided to test viable reaction conditions on preparative scale to assess the effect on the yield of amine **83** upon scale-up. Boronic ester **151** was used throughout the coupling reactions due to ease of visualisation during purification. Use of 1 equivalent of Cu together with 0.5 equivalents of ligand **141** was first examined (Scheme 72). Upon completion of the reaction, it was decided to oxidise boronic ester **151** to allow easier separation during initial purification. Coupled product **152** was isolated in a moderate yield alongside oxidised alcohol product **153**. No alcohol **153** was identified in the crude reaction mixture so it can be assumed the mass of isolated alcohol **153** is derived from boronic ester **151**. The decrease in yield of amine **152** when compared to test scale optimisation reactions could be related to solubility issues or oxidative turnover being decreased due to decreased surface area.



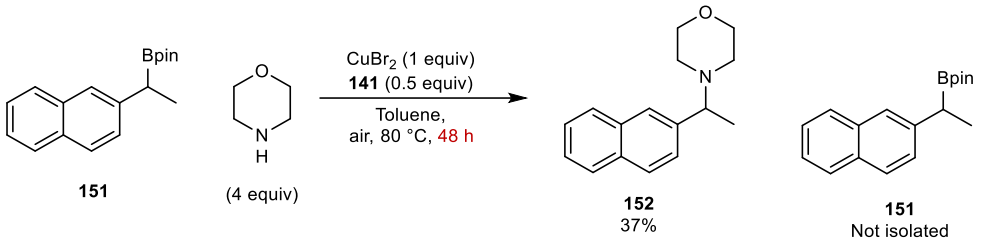
Scheme 72: Preparative scale amination of boronic ester **151** with oxidative work-up. Reaction conducted on a 0.5 mmol scale of **151**. Reaction concentration of 1 M.

The necessity of ligand **141** in the coupling reaction was then investigated (Scheme 73). The formation of amine **152** was reduced when compared to the yield obtained when using ligand **141** (see Scheme 72). No oxidised side-products were isolated, although a return of 38% of starting material boronic ester **151** was obtained.



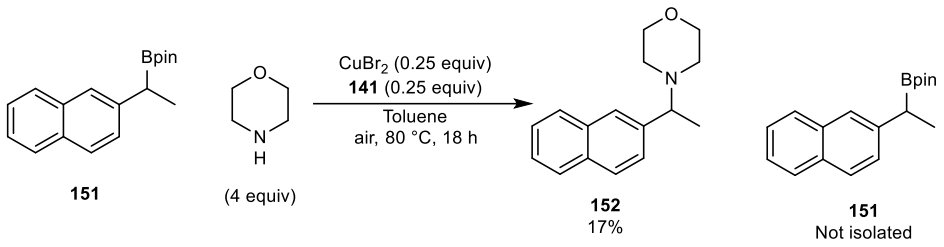
Scheme 73: Preparative scale amination of boronic ester **151**. Reaction conducted on a 0.5 mmol scale of **151**. Reaction concentration of 1 M.

Due to the presence of boronic ester **151** remaining, the potential for an increase in reaction time to promote formation of amine **152** was tested (Scheme 74). Leaving the reaction for 48 h provided no increase in yield of amine **152** when compared to the standard reaction time (see Scheme 72).



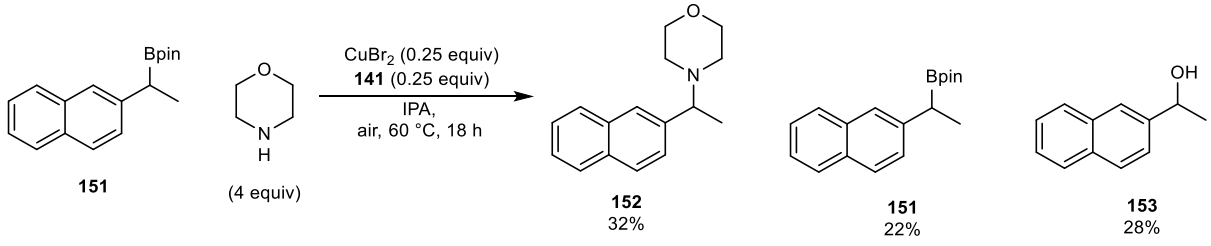
Scheme 74: Preparative scale amination of boronic ester **151**. Reaction conducted on a 0.5 mmol scale of **151**. Reaction concentration of 1 M.

Applying sub-stoichiometric quantities of catalyst to the reaction was subsequently tested (Scheme 75). This approach produced coupled product **152** in a decreased yield compared to using a stoichiometric quantity of Cu (see Scheme 72).



Scheme 75: Preparative scale amination of boronic ester **151**. Reaction conducted on a 0.5 mmol scale of **151**. Reaction concentration of 1.6 M.

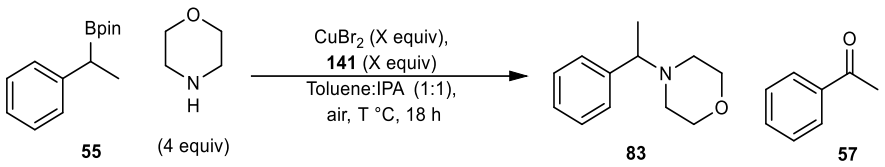
Finally, sub-stoichiometric quantities of catalyst were examined using IPA as an alternative solvent with a lower reaction temperature (Scheme 76). These conditions provided a similar yield of amine **152** to stoichiometric conditions used (see Scheme 72). However, this method also produced a significant amount of alcohol **153**. This could be due to increased water content from using an alcoholic media which has been noted to increase oxidised by-product formation.[104] With unsatisfactory yields of amine **152** obtained using current best conditions, optimisation was continued.



Scheme 76: Preparative scale amination of boronic ester **151**. Reaction conducted on a 0.5 mmol scale of **151**. Reaction concentration of 1.6 M.

A re-examination of a combination of the best reaction conditions thus far was undertaken (Table 19). A solvent mixture of 1:1 toluene to IPA was employed. Using stoichiometric Cu produced amine **83** in moderate yield (Entry 1). Decreasing the Cu and

ligand loading to 25 mol% at 60 °C, Entry 2 provided a similar yield of amine **83** to Entry 1. However, at this temperature and catalyst loading ketone **57** was present in a significant quantity (Entry 2). Fortunately, increasing the temperature to 80 °C, negated the production of ketone **57** and formed amine **83** in excellent yield (Entry 3).



55 (4 equiv) 83 57

Entry	Cu:Ligand eq	Temperature (°C)	Yield (%)		
			83	**55**	**57**
1	1:0.5	80	59	<5	0
2	0.25:0.25	60	57	<5	15
3	0.25:0.25	80	94	<5	0

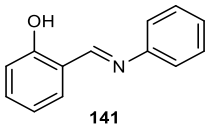


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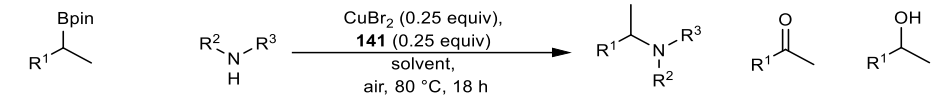
Table 19: Effects of decreasing Cu and ligand loading on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.1 mmol scale of **55**. Reaction concentration of 0.3 M. No alcohol detected.

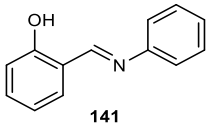
A larger screening of substrates with varying solvents was performed to determine the wider effects of the solvent (Table 20). For the coupling of boronic ester **55** with morpholine both toluene:IPA 3:1 and its inverse provided good yields of amine **83** (Entry 2 and 4). Coupling piperidine performed best when using a 3:1 mix of toluene:IPA (Entry 6). Using tetrahydroisoquinoline as a coupling partner formed the desired coupled product in poor yield independent of solvent used (Entry 7 and 8). Naphthylboronic ester **151** produced amine **152** in improved yield when using a 1:1 mixture of toluene:IPA (Entry 9). Coupling acyclic 2° *N*-methylbenzylamine preferred the opposite solvent system of 3:1 toluene:IPA to afford more coupled product. The *N*-alkylation of *N*-methylbenzylamine was performed on preparative scale with a toluene:IPA 1:1 solvent system (Entry 13). The isolated yield was considerably reduced when compared to NMR yield (Entry 11).



R^1 = Ph (**55**)
= 2-naphthyl (**151**)

(4 equiv)

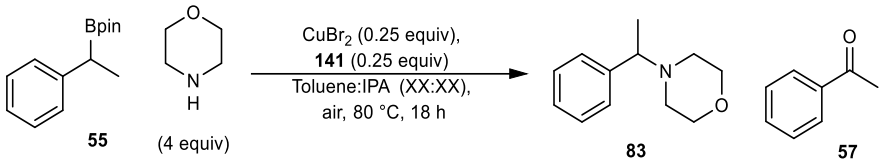
Entry	Bpin	Amine	Solvent	Yield (%)	
				Product	Starting material
1	**55**	Morpholine	Toluene:IPA 1:1	57	28
2	**55**	Morpholine	Toluene:IPA 3:1	77	28
3	**55**	Morpholine	Dioxane:IPA 1:1	62	37
4	**55**	Morpholine	Toluene:IPA 1:3	76	22
5	**55**	Piperidine	Toluene:IPA 1:1	72	<5
6	**55**	Piperidine	Toluene:IPA 3:1	90	<5
7	**55**	Tetrahydroisoquinoline	Toluene:IPA 1:1	25	62
8	**55**	Tetrahydroisoquinoline	Toluene:IPA 3:1	26	59
9	**151**	Morpholine	Toluene:IPA 1:1	76	<5
10	**151**	Morpholine	Toluene:IPA 3:1	49	<5
11	**55**	*N*-Me benzylamine	Toluene:IPA 1:1	54	<5
12	**55**	*N*-Me benzylamine	Toluene:IPA 3:1	62	<5
13[a]	**55**	*N*-Me benzylamine	Toluene:IPA 1:1	31	<5



141

Table 20: Effects of solvent on the amination of **55** and **151**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.25 mmol scale of **55** or **151**. Reaction concentration of 0.3 M. a) Reaction conducted on a 0.5 mmol scale. No alcohol or ketone detected.

To try and improve yield upon scale-up an increase in concentration was tested. Alongside this larger reaction vessels were investigated (Table 21). The aim of using a larger vessel was to enable a greater surface area to come in to contact with air, allowing a faster catalyst turnover. Using standard microwave vials (5 mL), which had been used throughout optimisation, produced good yields of amine **83** alongside significant amounts of ketone **57** in either IPA or a 3:1 toluene:IPA mix (Entry 1 and 2). Performing the reaction in either a large microwave vial (20 mL) or round-bottom flask (10 mL) formed amine **83** in quantitative yield with no side-products detected (Entry 3 and 4). The use of large microwave vials was deemed advantageous due to the ease of use. Therefore, this reaction vessel was used for all future coupling reactions.



Entry	Solvent toluene:IPA	Vessel	Yield (%)	
			83	**55**
1	3:1	Standard microwave vial	67	39
2	IPA	Standard microwave vial	70	35
3	3:1	Large microwave vial	>95	<5
4	3:1	RBF with condenser	>95	<5

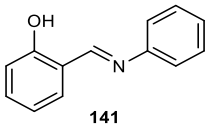
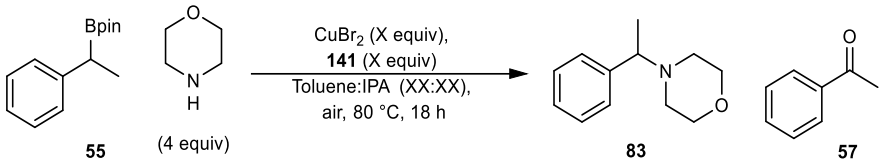


Table 21: Effects of solvent and reaction vessel on the amination of **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.5 mmol scale of **55**. Reaction concentration of 0.6 M. No alcohol or ketone detected.

At this point in the optimisation, due to good conversions to amine **83** it was decided to challenge the reaction conditions by lowering amine and catalyst loadings (Table 22). Generally, decreased catalyst loadings led to decreased amine **83** production. Lowering the amine equivalency to 3 whilst also lowering the catalyst loading to 15 mol% and below led to a drop off in formation of coupled product **83** (Entries 7, 8, 11 and 12). Ketone **57** formation was generally larger with a 3:1 solvent ratio with decreased catalyst loading (Entry 10 and 12). Yields of coupled amine **83** were mostly greater when employing a 1:1 ratio of toluene:IPA solvent mix. Consequently, this solvent mixture was applied to all further coupling reactions.



55 (4 equiv) 83 57

Entry	Cu and Ligand eq	Toluene:IPA	Amine equiv	Yield (%) 83	55	57
1	0.25	1:1	4	87	<5	10
2	0.25	3:1	4	93	<5	3
3	0.25	1:1	3	>95	<5	6
4	0.25	3:1	3	>95	<5	7
5	0.15	1:1	4	>95	<5	3
6	0.15	3:1	4	80	<5	<5
7	0.15	1:1	3	74	<5	9
8	0.15	3:1	3	71	<5	10
9	0.1	1:1	4	>95	<5	3
10	0.1	3:1	4	82	<5	19
11	0.1	1:1	3	79	<5	6
12	0.1	3:1	3	77	<5	15

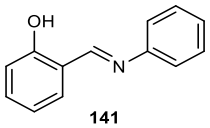


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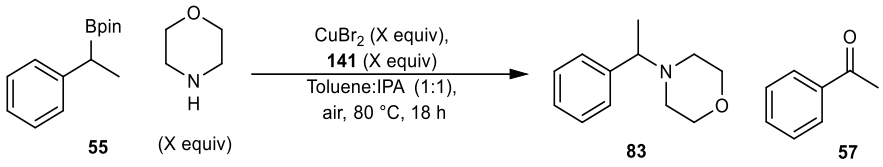
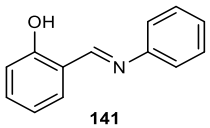
Table 22: Effect of decreasing catalyst and amine equivalency on the amination of boronic ester **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.5 mmol scale of **55**. Reaction concentration of 0.6 M. No alcohol detected.

A range of amine equivalencies were tested with both 15 and 20 mol% of catalyst (Table 23). Using a catalyst loading of 15 mol% and amine equivalencies of either 3.5 or 4 produced good yields of amine **83** and minimal ketone **57** (Entry 3 and 4). Reducing amine equivalency at this catalyst loading to 3 or 2 was deemed unfavourable due to the slightly reduced yield of amine **83** (Entry 1 and 2). Increased catalyst loading of 20 mol% provided no benefit with respect to amine **83** production (Entry 5 and 6). The reduction of amine to 3.5 equivalencies and the use of 15 mol% catalyst loading seemed a viable solution to decreasing both catalyst loading and substrate required (Entry 3).



55 (X equiv) 83 57

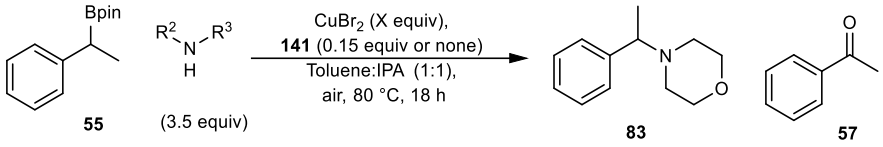
Entry	Cu and Ligand eq	Amine eq	Yield (%)		
			83	**55**	**57**
1	0.15	2	77	<5	7
2	0.15	3	84	<5	9
3	0.15	3.5	89	<5	9
4	0.15	4	90	<5	11
5	0.2	3	85	<5	6
6	0.2	3.5	83	<5	7



141

Table 23: Effect of decreasing catalyst and amine equivalency on the amination of boronic ester **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.5 mmol scale of **55**. Reaction concentration of 0.6 M. Reactions performed in duplicate and are reported as averages. No alcohol detected.

In a final effort to simplify reaction conditions, removal of ligand **141** was tested alongside decreasing Cu loadings (Table 24). If the reaction performed well without the ligand **141** this would make the reaction more accessible, both avoiding the need to synthesise the ligand and also providing a simplification of the reaction procedure. Formation of amine **83** without ligand using only 10 mol% Cu loading produced comparable result to inclusion of ligand **141** (Entry 3 versus 1). Reducing catalyst loading to 5 mol% produced an unacceptable decrease in yield of amine **83** and formation of more ketone **57**. The addition of ligand **141** had a beneficial impact on the yield of amine **83** during early optimisation. The role of ligand **141** is presumably aiding solvation of the Cu salt rather than the formation of an active Cu catalyst.



Entry	Cu and Ligand eq	Substrate	Ligand	Yield (%)		
				83	**55**	**57**
1[a]	0.15	Morpholine	Yes	93	<5	5
2[b]	0.15	Morpholine	-	83	<5	6
3[c]	0.10	Morpholine	-	99	<5	0
4	0.05	Morpholine	-	78	<5	7
5	0.15	*N*-Methyl benzlamine	-	90	<5	15
6	0.15	Piperidine	-	87	<5	3

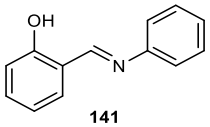


Table 24: Effect of decreasing catalyst equivalency and removal of ligand on the amination of boronic ester **55**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.5 mmol scale of **55**. Reaction concentration of 0.6 M. a) Average of 4 yields. b) Average of 3 yields. c) Average of 2 yields. No alcohol detected.

3.2.2 Control reactions

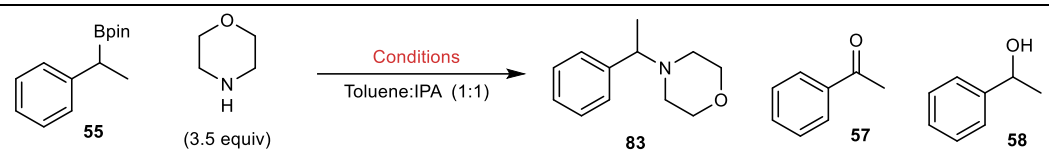
Several control reactions were undertaken deviating from standard reaction conditions (Table 25). Using no $CuBr_2$ in the reaction produced no coupled amine product **83** (Table 25, Entry 1). This suggests that amine formation is a metal-mediated process. In this reaction, formation of alcohol **57** presumably occurs through direct reaction with oxygen from the air.

With the vessel sealed a slight decrease in the formation of amine **83** was observed, presumably as the reaction stalls once all of the O_2 present is consumed (Entry 2). In the absence of air, performing the reaction under an argon atmosphere formation of amine **83** was halted with starting material boronic ester **55** remaining and no oxidative side products detected (Entry 2 and 3). This suggests that O_2 from air is acting as an oxidant to turnover the catalyst.

When the reaction was stopped after 4 h, a 55% yield of amine **83** was produced with no other side products detected and only starting material remaining. This rate of reaction is consistent with *N*-alkylation of aniline with alkylboronic esters in the same timeframe.[163]

Performing the reaction at room temperature produced amine **83** in reduced yield, with larger amounts of ketone **57** and alcohol **58** observed, along with starting material remaining (Entry 5). The formation of relatively large quantities of alcohol **58** could be attributed to

decreased solubility of Cu at lower temperatures allowing oxidation of boronic ester **55** to proliferate. The reduced temperature could also reduce reaction rate allowing the formation of increased oxidation side products. Inverting the stoichiometries of boronic ester and amine resulted in a poor yield of coupled product **83** (Entry 6). Utilising first-generation conditions with inverse stoichiometries and only one equivalent of amine produced moderate yields of coupled product (see Table 1, Entry 10). This is supported by the second-generation conditions dependence on amine concentration for good yields (see Table 10).



Entry	Deviation from standard	Yield (%)			
		83	**55**	**57**	**58**
1	No Cu	<5	<5	4	58
2	No needle (not purged)	>95	<5	5	0
3	Purged Ar	3	93	0	0
4	4 h	55	44	0	0
5	Room temperature	13	52	6	31
6	Inverse equiv of morpholine and Bpin	10	105	ND	0
7	Standard	>95	<5	0	0

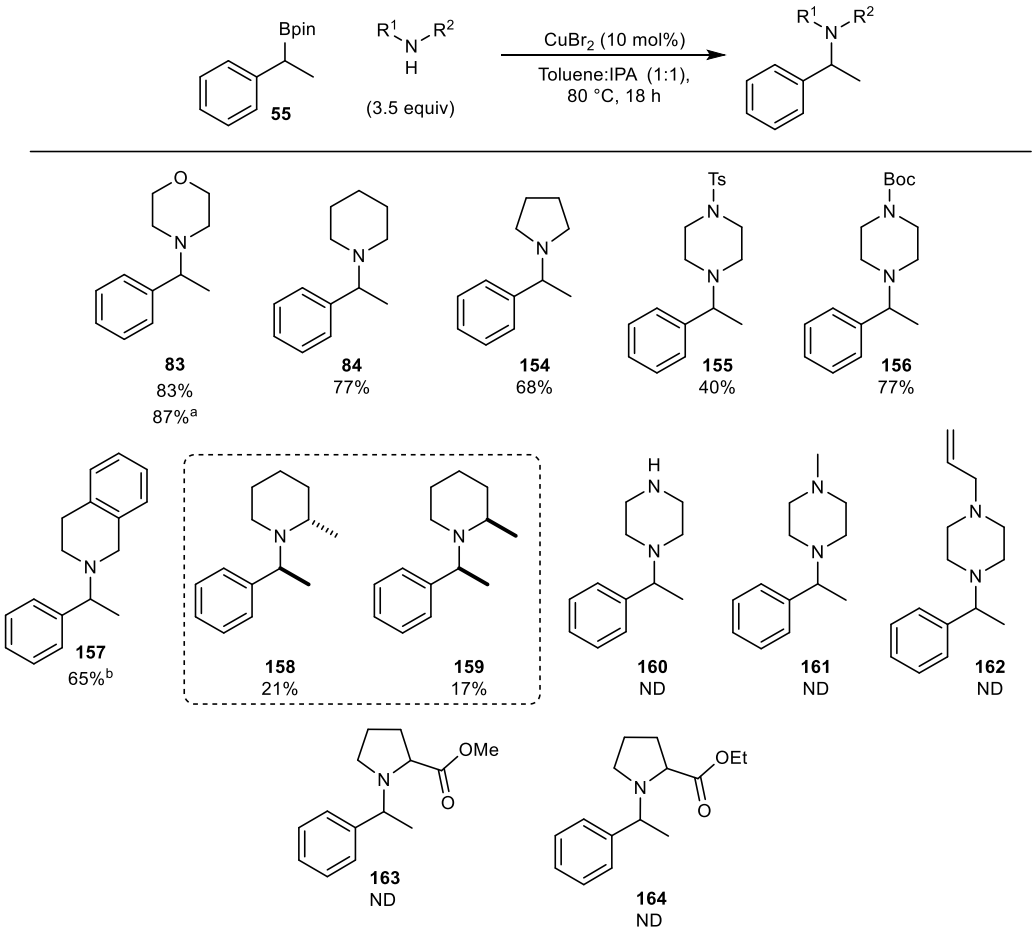
Table 25: Control reactions deviating from standard conditions. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.5 mmol scale of **55**. 18 h reaction time. Reaction concentration of 0.6 M.

3.3 Scope of Reaction for the Alkyl Amination of Alkylboronic Esters

Using the optimised conditions, a selection of 1° and 2° cyclic and acyclic amines were coupled with a range of boronic esters. In a limited number of cases, co-elution of the amine product and ketone side product occurred during chromatographic purification. In these instances, an additional step to reduce the ketone using $NaBH_4$ was carried out to aid purification. No significant loss of amine product was observed when employing this reductive work-up. Work on expanding the scope of the reaction with respect to both coupling partners is on-going within the group.

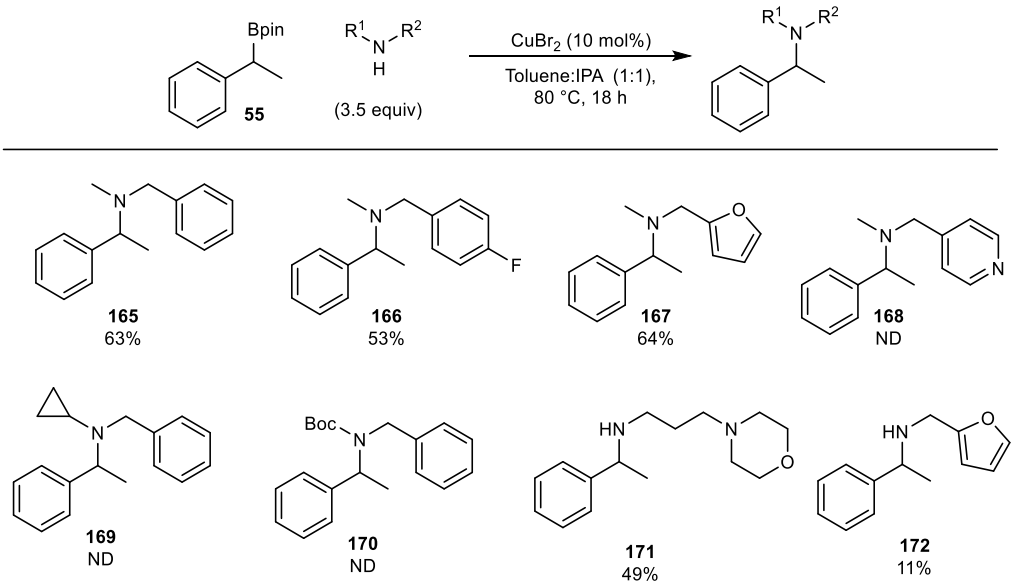
3.3.1 Amine Scope

The scope of the reaction coupling boronic ester **55** with 2° cyclic amines was investigated (Scheme 77). Five and six membered rings, including protected piperazines and tetrahydroisoquinoline were tolerated. Common amine protecting groups were tolerated, with no deprotection observed, when using Tosyl or Boc-piperazine (**155** and **156**). Submitting 2-methylpiperidine to the reaction conditions produced a 1:1.2 d.r. of amines **158** and **159**, suggesting the reaction is not diastereoselective, which is consistent with a radical mechanism. Attempts to use unprotected, *N*-methyl and *N*-allylpiperazine were unsuccessful (**160**, **161** and **162**). Only ketone, alcohol and returned starting material were observed in these cases. This could be due to decreased solubility of simple piperazines or that ligation of the 3° amine to Cu inhibits the catalyst.[183] Proline esters also failed to produce coupled amine product **163** and **164**. This is presumably due to α-aminoesters potential ability to chelate to Cu, or insolubility of the amines under the reaction conditions.[152]



Scheme 77: Scope of 2° cyclic amines coupled with boronic ester **55**. a) Reaction performed on a 1 g scale, b) Reductive work-up.

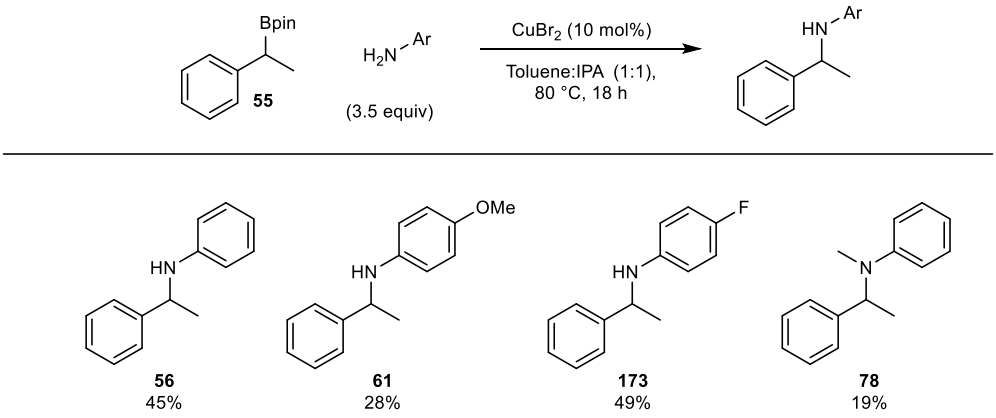
A range of 2° acyclic and 1° aliphatic amines were next explored (Scheme 78). 2° *N*-methylamines were generally coupled in good yield (**165**, **166** and **167**). However, pyridyl containing *N*-methylamine **168** returned starting material and produced ketone and alcohol by-products only. This difficulty when coupling substrates with a chelating nitrogen has been previously noted by Lam and co-workers.[147,167] Issues arose when trying to couple more sterically demanding 2° amines. Replacing methyl with a cyclopropyl group, failed to produce amine **169** and returned starting material **55**, presumably due to increased steric hindrance around nitrogen, which has been noted in other Chan-Lam reactions.[117] The use of Boc-protected amine was unsuccessful **170**, presumably due to deactivation of the amine. Coupling with 1° amines was achieved, albeit with decreased reactivity when compared to 2° non-cyclic amines. Using a morpholine-containing amine provided coupled product **171** in moderate yield. However, only a low yield was obtained when using furfurylamine **172**. Reduced compatibility with 1° amines could be in part due to their decreased nucleophilicity. Benzylic 1° amines have also been reported to undergo aerobic oxidation with Cu(I/II) bromide to the imine.[184,185] An alternative competing pathway of oxidative *N*-dealkylation has also been reported for amines with an α-hydrogen.[186,187] Consistent to findings with the coupling of anilines (see Chapter 2), no dialkylation products were observed.



Scheme 78: Scope of 2° non-cyclic and 1° amines coupling with boronic ester **55**.

Whilst these conditions were optimised for the coupling of alkylamines, attempts were made to explore if anilines were also reactive (Scheme 79). Under forced aniline coupling conditions, morpholine could be used as a substrate to form amine **83** in 31% yield (see Section 2.3.1, Scheme 48). Aniline and electron donating and withdrawing substituents on the arene

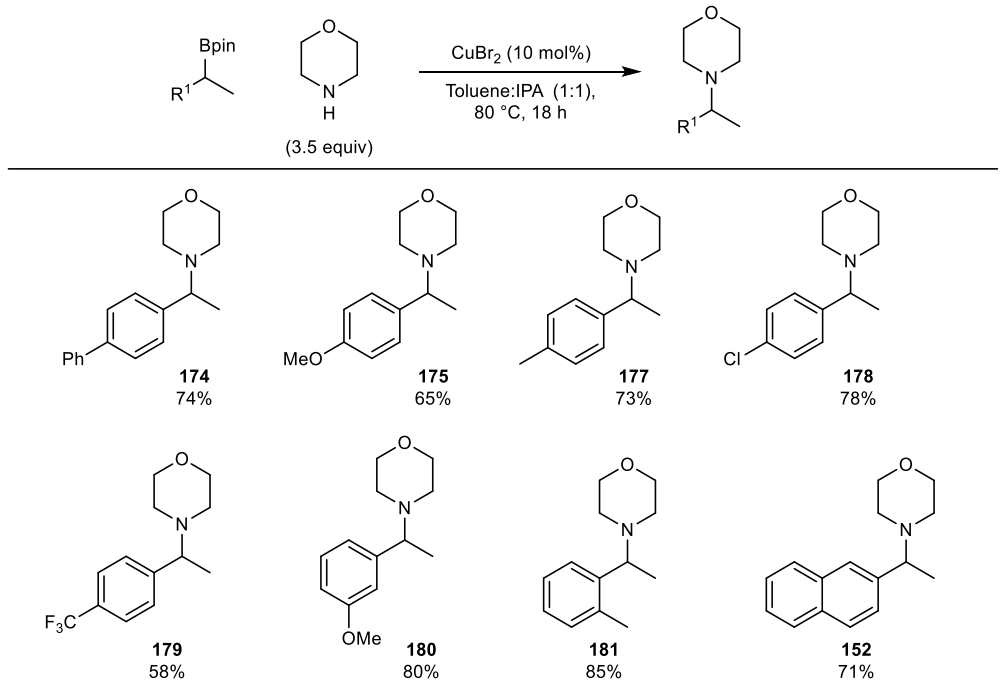
could be coupled under current conditions with no modification, albeit in moderate yield (**56**, **61** and **173**). Under previous aniline coupling conditions electron donating anilines performed best, with electron withdrawing substrates generally coupling in lower yields (see Scheme 46). The opposite trend was observed using alkylamine coupling conditions with *p*-fluoroaniline performing better than *p*-anisidine. Coupling with *N*-methylaniline was poor, consistent with lower yielding results for more sterically demanding alkylamines (**78**) (Scheme 78, **169** and **170**). The boronic ester **55** was fully consumed and alcohol and ketone side-products were present for all reactions with anilines



Scheme 79: Coupling of boronic ester **55** with anilines.

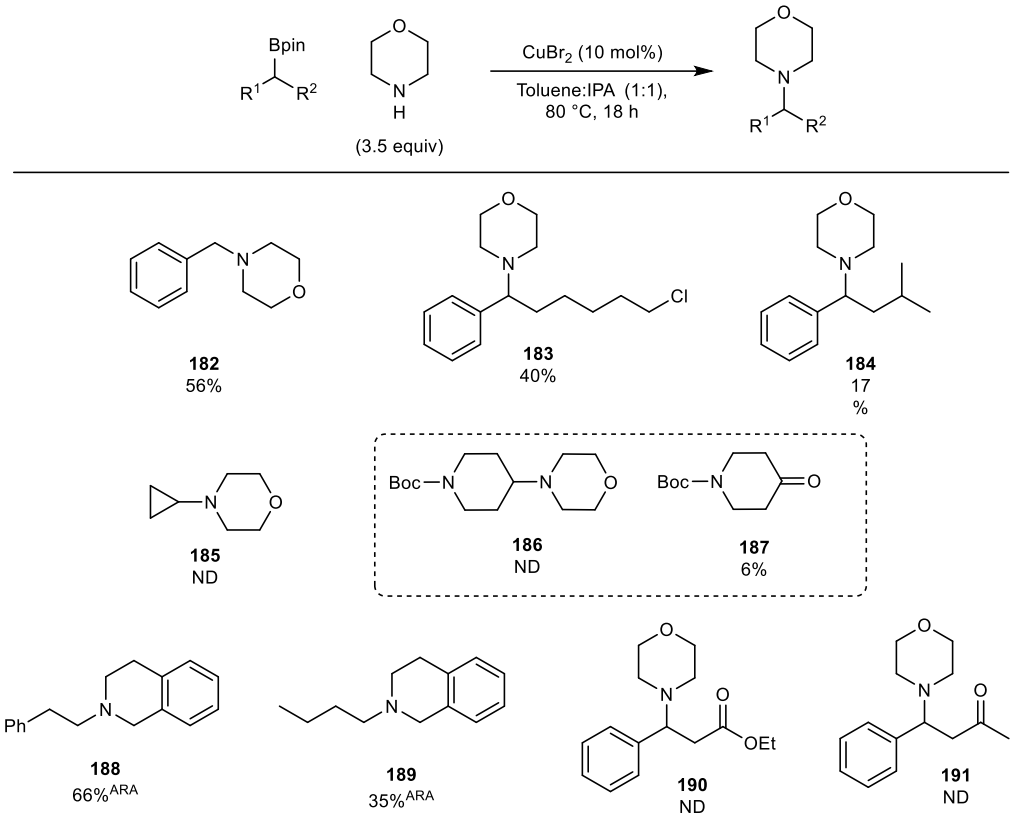
3.3.2 Boronic Ester Scope

The scope with respect to boronic ester was next explored. All boronic esters presented in the scope were prepared using known literature methods. Several 2° benzylic boronic esters with both electron donating and withdrawing groups on the aryl ring are tolerated (Scheme 80). All amines were formed in good yield, with a deactivating trifluoromethyl group still producing 58% yield of amine **179** without the need for an extended reaction time. When aryl halide **178** was subjected to the reaction conditions no Ullman coupling products were observed.



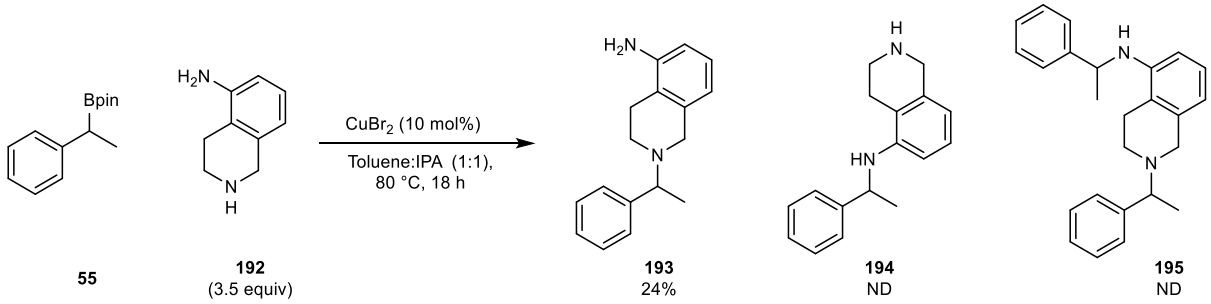
Scheme 80: Scope of the amination of 2° benzylic boronic esters with morpholine.

Additional classes of boronic esters were investigated (Scheme 81). 1° Benzylic boronic ester was coupled in moderate yield (**182**). Increasing the chain length of the benzylic boronic ester was also explored, though a decrease in yield of amine **183** was noted when compared to α-Me boronic esters. Importantly, amination of the boronic ester was selective to give **183**, with nucleophilic substitution of the alkyl chloride not observed. Reaction of isobutyl-substituted boronic ester gave amine **184**, albeit in low yield. Presumably the increased steric hindrance reduces the reaction efficiency. The reactions of 2° non-benzylic boronic esters did not form any coupling product (**185** and **186**). In the case of cyclopropylboronic ester the starting material boronic ester was returned unreacted. Mass spectrometry data suggested amine **186** was present, however ketone **187** was the only isolatable side-product with presumed degradation of boronic ester. Pleasingly 1° non-benzylic boronic esters could be coupled with tetrahydroisoquinoline to form amine **188** and **189**. Tetrahydroisoquinoline was used in place of morpholine for the coupling of these boronic esters to ease visualisation during purification. The unsuccessful attempts to couple 2° non-benzylic boronic esters could be repeated with tetrahydroisoquinoline as a coupling partner. β-ester and β-ketoboronic esters in contrast to first generation conditions did not produce any coupled product (**190** and **191**) (see Section 2.3.2, Scheme 52). The elimination product was identified in the crude reaction mixture. This could be attributed to a retro-Mannich reaction of the coupled product.



Scheme 81: Extended scope of the amination of 1°, 2° and non-benzylic boronic esters with morpholine.

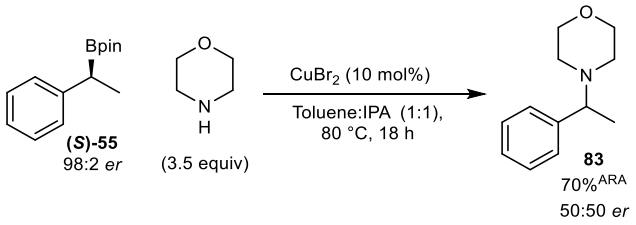
A test of the chemoselectivity of the reaction was undertaken using a competition experiment (Scheme 82). Amine **192** containing both an aniline and 2° amine moiety was submitted to the reaction conditions. Coupling with 2° amine to form **193** was observed in 24% yield. Starting material boronic ester **55**, ketone **57** and alcohol **58** side-products were observed in the crude reaction mixture but were not isolated. No coupling with aniline to form amine **194** or dialkylation coupling product **195** was isolated. Despite the relatively low yield, these results initially suggest the reaction conditions are chemoselective for alkylamines rather than anilines. An intermolecular competition experiment could provide more insight into the chemoselectivity of these reaction conditions.



Scheme 82: Competition experiment with amine **192**.

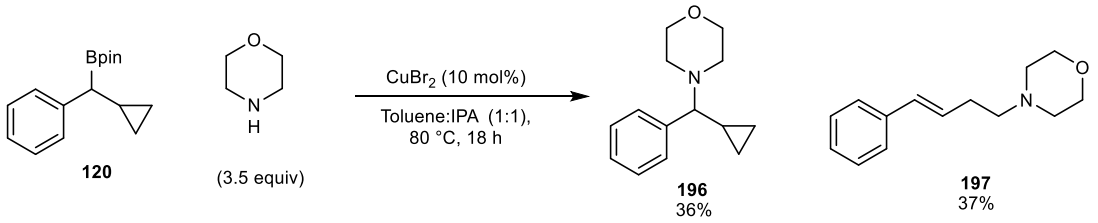
3.3.3 Investigation into the Mechanism of the Reaction

To assess whether the alkyl amination reaction is stereoselective, enantiomerically enriched boronic ester **(*S*)-55** was submitted to the reaction conditions (Scheme 83). As with the amination utilising aniline (see Section 2.3.4) a total loss of stereochemical information was observed. This similarly suggests the potential formation of either a radical intermediate or the configurational instability of an organocuprate intermediate.



Scheme 83: Alkyl amination of boronic ester **(*S*)-55**.

To investigate whether an alkyl radical is formed during the amination reaction a radical clock experiment was performed using cyclopropylboronic ester **120**. If ring opening of the cyclopropyl is observed a radical intermediate could occur. Alternatively, if the cyclopropane ring remains this would suggest that transmetalation occurs through a two-electron process. This experiment had been previously undertaken to assess the outcome with the aniline coupling conditions (see Section 2.3.4, Scheme 56), providing ring opened aminated product **121** only. In contrast, under these amination conditions when coupling morpholine, both ring closed **196** and ring opened products **197** were observed (Scheme 84). The observation of both compounds suggests that a single electron transfer pathway is occurring, but that recombination with Cu occurs on a comparable rate to ring opening of the cyclopropane (Figure 17).



Scheme 84: Amination of cyclopropyl boronic ester **120**.

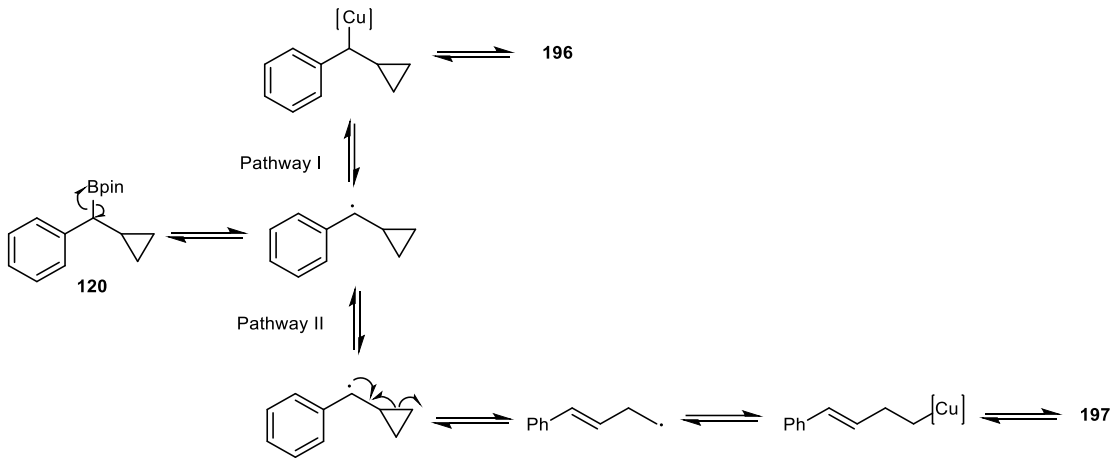
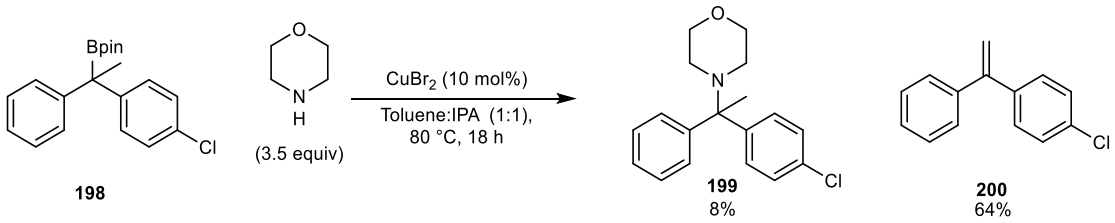


Figure 17: Possible mechanism for the alkyl amination of boronic ester **120**.

3.3.4 Alkyl Amination of 3° Alkylboronic Esters

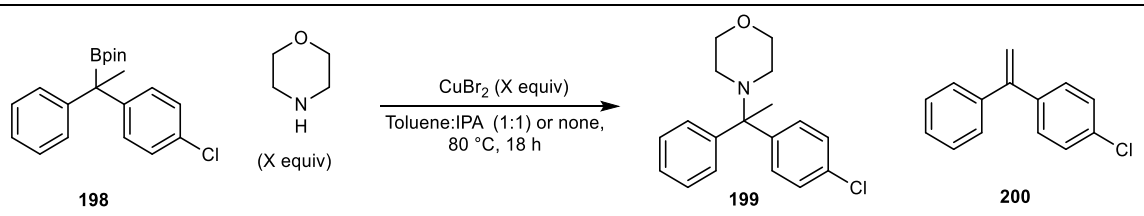
With the previous success of the amination of 3° boronic esters with aniline (see Section 2.3.3), coupling of 3° boronic ester **198** with morpholine was attempted under the standard reaction conditions (Scheme 85). Coupling product **199** was formed, albeit in low yield. However, the major product from the reaction was the elimination product alkene **200**. These alkene side-products have been previously identified to form from dehydration of the corresponding 3° alcohol, which could form from oxidation of the boronic ester.[163] In this case no alcohol product was identified, suggesting this degradation pathway could occur more quickly under these reaction conditions. Alternatively, the boronic ester is more susceptible to this elimination under these conditions or the product **199** is also unstable.



Scheme 85: Reaction of boronic ester **198** with morpholine.

Due to the observation of alkene side product **200** test reactions with various reaction conditions were trialled (Table 26). Completing the reaction under standard alkylamine coupling conditions produced only a very minimal amount of amine **199** alongside an equal amount of starting material **198** and alkene **200** (Entry 1). When the reaction was performed in the absence of Cu, only starting material **198** was returned, though presumably

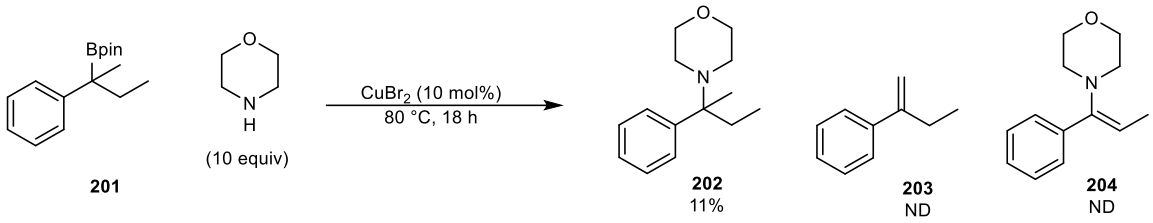
protodeboronation occurred due to the low mass balance (Entry 2). Running the reaction in neat morpholine, which has been seen to improve yields with 2° amines (see Table 10), did not increase amine **199** yield (Entry 3). Under these neat conditions no starting material **198** was returned and only some alkene **200** was formed. Interestingly, when the morpholine coupling partner is omitted, starting material **198** is returned completely (Entry 4). Stoichiometric quantities of Cu were next tested to try and mitigate side-product formation and protodeboronation (Entry 5). Unfortunately, only starting material **198**, a very small amount of alkene **200** and presumably protodeboronation occurred. Lower temperatures were next employed as this had been beneficial in coupling 3° boronic esters and anilines (see Scheme 54). At both 50 °C and room temperature, the main component of the reaction mixture was returned starting material boronic ester **198** (Entry 6 and 7). Lower temperatures appear to decrease protodeboronation and alkene **200** formation when compared to using standard reaction temperature (Entry 1). The exclusion of oxygen under stoichiometric conditions was examined (Entry 8). This provided no improvement in yield of amine **199**, but did improve on the reducing the amount of protodeboronation occurring.



Entry	Cu equiv	T °C	Atmos	Morpholine equiv	Yield (%) 199	198	200
1	0.1	80	Air	3.5	4	27	27
2	-	80	Air	3.5	0	30	0
3[a]	0.1	80	Air	10	5	0	17
4	0.1	80	Air	-	0	100	0
5	1.0	80	Air	3.5	1	65	4
6	0.1	RT	Air	3.5	0	83	0
7	0.1	50	Air	3.5	3	73	11
8	1.0	80	Ar	3.5	2	95	8

Table 26: Systematic variation of conditions on the alkylation of boronic ester **198**. Yields determined using ^{1}H-NMR analysis and 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.25 mmol scale of **198**. Reaction concentration of 0.63 M. a) Reaction run neat.

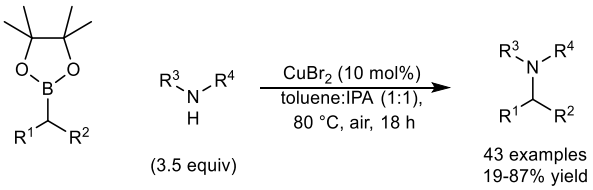
With no clear pathway for improving amination using diaryl 3° boronic ester **198**, attention was turned to reaction of dialkyl 3° boronic ester **201**. Amination of boronic ester **201** was performed under neat conditions and gave amine **202** in low yield (Scheme 86). However, unlike with boronic ester **198**, no side products were observed such as alkenes **203** and **204**. Also, no boronic ester **201** starting material was returned. Unfortunately, no further side products could be identified from the complex crude reaction mixture.



Scheme 86: Amination of 3° boronic ester **201** with morpholine.

3.4 Conclusions and Future Work

This work was directed at the development of a methodology for the amination of alkylboronic esters with alkylamines. Optimisation reactions focused on the use of benzylic boronic ester **55** due to the potential for charge stabilisation of an organocuprate intermediate. Through the systematic alteration of conditions, a practically simple and mild procedure for the coupling of a range of boronic esters and alkylamines has been developed. Catalytic quantities of Cu can be efficiently used with air as an oxidant. Previously reported successful couplings of alkylboronic acids and alkylamines are limited to the cyclopropylation of alkylamines.[152] Coupling with anilines under these second-generation conditions produce reduced yields in comparison to first-generation conditions.



Scheme 87: Overview of alkylboronic ester amination with alkylamines.

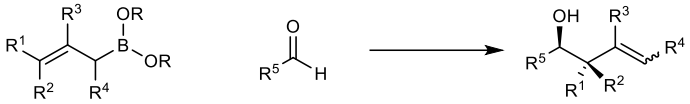
Preliminary mechanistic investigations, indicated by loss of stereochemical information and cyclopropyl ring opening suggests the formation of a radical intermediate.

Future work would look at the expansion of substrate scope to incorporate further ‘un-activated boronic esters’, potentially with the use of more forcing reaction conditions. Investigations to overcome troublesome side products during the alkylation of 3° boronic esters would be undertaken.

4. Development of a Nickel Catalysed Allylboration of Boronic Esters

4.1 Allylboration Reactions

Homoallylic alcohols are common intermediates in pharmaceuticals and natural product synthesis.[188] These products contain an alcohol and alkene moiety, which can both serve as a functional handles for further transformations.[188,189] The use of allylboronates and their addition to aldehydes is a common method to produce homoallylic alcohols (Scheme 88). The construction of homoallylic alcohols is subsequently the most prevalent use of allylboronates in synthesis.[1,190]



Scheme 88: Overview of the addition of allylboronates to aldehydes to produce homoallylic alcohols.[1]

The extended use of allylboronates in this area is down to their increased stability when compared to allylboranes. This is due to the partial donation of the lone pair of electrons on the oxygen atoms into the empty *p*-orbital of boron.[1] Organoboronates also typically exhibit low-toxicity, and are consequently assumed to be environmentally benign substrates.[191,192] Another reason for their popularity is the high degree of diastereoselectivity obtained in allylboration reactions. They can therefore be reliably used when planning a synthesis of a complex molecule.[193] This method has also been extended to allow the production of chiral non-racemic products using either a chiral boron reagent or a chiral catalyst during asymmetric synthesis.[1]

4.1.1 Reaction Selectivity

Allylation reactions generally proceed with predictable outcomes, this was noted by Denmark and Weber who proposed an allylation classification system.[194] This enabled the prediction of allylation products dependent on the metal and starting material used (Figure 18). Allylboration is thought to proceed through a six-membered, chair-like transition state **A**, which is an example of a Type I allylation reaction. The diastereoselectivity of Type I reactions is dependent on the starting allyl geometry (Figure 18).[1,190] Other allylation reagents for example, trialkylsilanes, are categorised as Type II reactions. These reactions often require the addition of a Lewis acid (L.A.). Type II reactions proceed through an alternative open transition

state **B**, mainly forming *syn*-homoallylic alcohols, independent of initial allyl geometry (Figure 18).[1] Type III allylations can also occur via addition of allylic organometallic reagents (Cr, Zn, Ti) generated in situ from the corresponding allylic halides, proceeding through a closed chair-like transition state **C**. Type III reactions predominantly form *anti*-homoallylic alcohols independent of the initial allyl halide geometry, due to the organometallics lack of configurational integrity (Figure 18).[195]

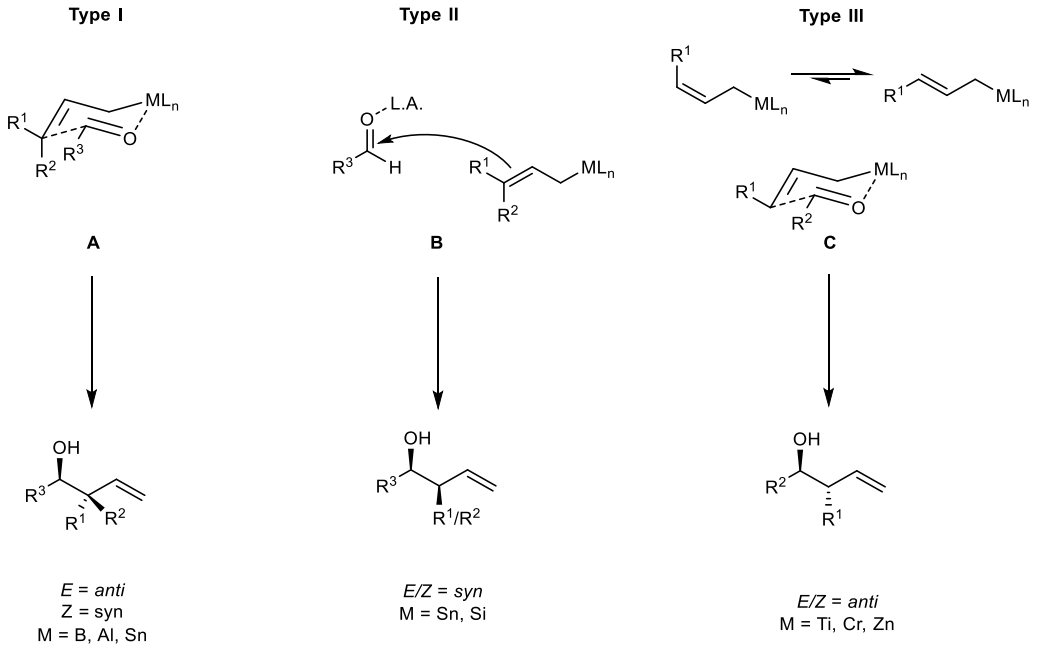
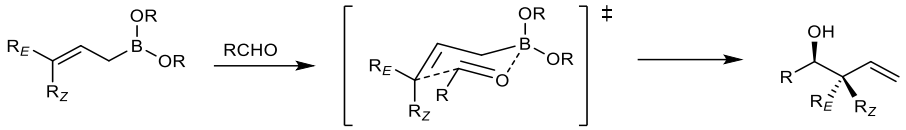


Figure 18: Type I, Type II and Type III allylation reactions and their respective stereochemical outcomes.

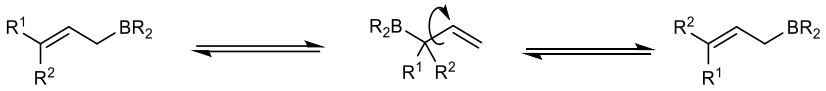
The high stereoselectivity of the allylboration reaction is thought to be due to this cyclic chair-like transition state of Type I, due to its closed nature. The diastereoselectivity achieved is therefore often superior to those of Type II reactivity.[196] This enables the prediction of the stereochemical outcome for the majority of allylborations. The reaction usually proceeds with retention of the allylboronates geometry, with *E*-allylboronates **(R_E)** leading to *anti*-products and *Z*-allylboronates **(R_Z)**, leading to *syn*-products (Scheme 89).[1] In all cases, the aldehyde is oriented so that the R group is in the equatorial position in order to minimise sterics between the aldehyde and the substituents on the allylboron.[193] Density Functional Theory (DFT) calculations have suggested that the six-membered cyclic transition structure is the lowest energy state relative to other possibilities.[197,198] This helps to explain the high stereoselectivity obtained when pure *E*- or *Z*-allylboronates are reacted with aldehydes.[193] The strength of the interaction between the coordination bond of the boron to the carbonyl oxygen of the aldehyde

is the most significant factor in regulating the overall reaction rate of the production of the alcohol.[197]



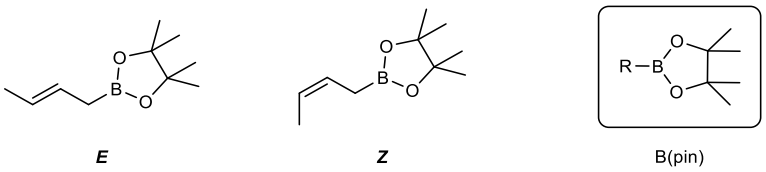
Scheme 89: Initial allylboronate geometry transferred to product diastereoselectivity.

A potential source of difficulty whilst using allylboron compounds is this stereochemical dependence of the starting material. Allylboron reagents, in particular, boranes, are able to undergo reversible borotropic rearrangements, which can result in the scrambling of the *E/Z* geometry (Scheme 90).



Scheme 90: Representation of borotropic rearrangement.[1]

Conversely allyl pinacol boronic esters are configurationally stable, therefore they are much less prone to rearrangement and are generally more widely deployed in this area of chemistry (Figure 19).[1,192, 199]



E ***Z***

Figure 19: *E/Z* isomers of allyl pinacol boronic esters stable enough to prepare independently.

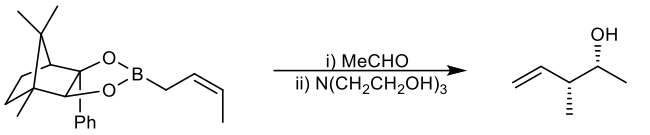
4.1.2 Allylboration

Mikhailov and Bubnoz reported the first acknowledged addition of an allylboron reagent to a carbonyl in 1964.[200] They were able to react triallylborane with various aldehydes. The same group were also accountable for the first evidence of the addition of an allylboronic ester to a carbonyl compound.[201] Allylboronates have become prevalent in stereoselective synthesis due to their predictable diastereoselectivity, this was first documented by Hoffmann and Zeiss in 1979.[202]

4.1.3 Asymmetric Allylboration

There were initially two main strategies for controlling the absolute stereochemistry of allylboration reactions. The first strategy is to use allylboronates with an α-chiral carbon, which are generally hard to prepare. The alternative is to use boronates with a chiral back bone which help to control addition to one face of the aldehyde.[1]

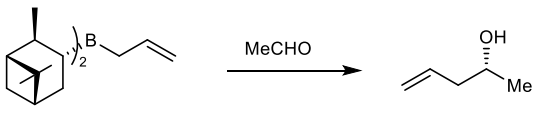
Hoffmann and Herold reported the first asymmetric version of the allylboration reaction (Scheme 91).[203] In this instance they used a modified camphor based scaffold, altering the boron backbone **205**. This helped to control the absolute stereochemistry of the 2° homoallylic alcohol **206**. This initial modest production of asymmetry piqued interest, encouraging further exploration to produce efficient stereoselective allylboration methods.



205 **206**
93%, 60-70% *ee*

Scheme 91: First asymmetric allylboration using a camphor-based scaffold.[203]

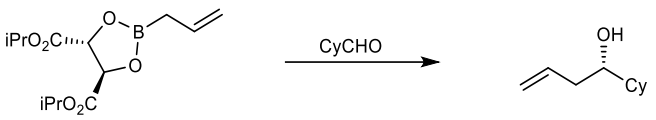
Brown and Jadhav reported the use of a dialkyl allylborane to induce stereoselectivity.[204] Natural α-pinene-derived allyl borane **207** reacted with aldehydes to produce highly enantioselective homoallylic alcohols **208** (Scheme 92).



207 **208**
>99% ee

Scheme 92: α-pinene based allylboration producing high enantioselectivity.[204]

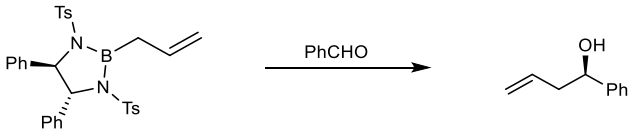
Another attractive development in the production of asymmetric allylations was detailed by Roush and co-workers.[205] They described the use of diisopropyl tartrate (DIPT) as a chiral auxiliary to derivatise allylboronate **209** to produce enantioenriched alcohol **210** (Scheme 93). The group later reported enhanced allylboration stereoselectivity when using tartrate allylboronates.[206]



209 **210**
72%, 87% ee

Scheme 93: Implementing the use of DIPT as a chiral auxiliary in allylborations.[205]

Corey and co-workers documented the use of the readily accessible and recoverable tosyl amide of 1,2-diamino-1,2-diphenylethane as a chiral auxillary **211,** enabling the formation of alcohol **212**.[207] A limited number of homoallylic alcohols are reported albeit in high enantiomeric excess (Scheme 94).



211 **212**
90%, 95% ee

Scheme 94: Production of homoallylic alcohols from tosyl amide boronates.[207]

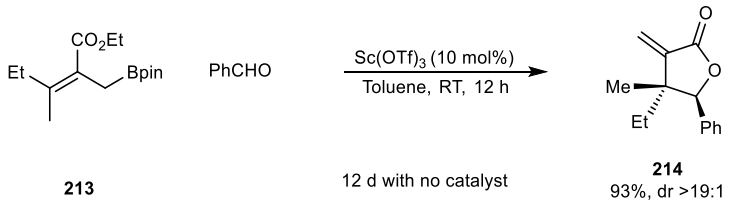
The enantioselective examples above proceed via substrate control, requiring stoichiometric levels of chiral boron compounds. An alternative method is to use catalyst control. This approach uses achiral boron reagents, where enantioselectivity is induced using a chiral catalyst in substiochiometric levels. This potentially leads to increased efficiency and decreased costs. This method has been implemented using Lewis acids (L.A.), Brønsted acids, or metal catalysts which all employ a chiral ligand as well as chiral diols functioning independently. These scenarios will be discussed further in this section.

4.1.4 Lewis Acid Catalysed Allylboration

Generally an aldehyde and allylboron reagent do not require an external additive to react.[1,192] It would therefore appear that the addition of a promoting agent would be of limited benefit. The introduction of an external catalyst (e.g. Lewis acid) could potentially compete with the boron for the aldehyde, feasibly leading to a less selective Type II open-chain mechanism (see Figure 18, Section 4.4.1), resulting in detrimental selectivity.[1] Recently however, reports have shown the addition can be advantageous to the reaction, owing to large rate enhancements.[208]

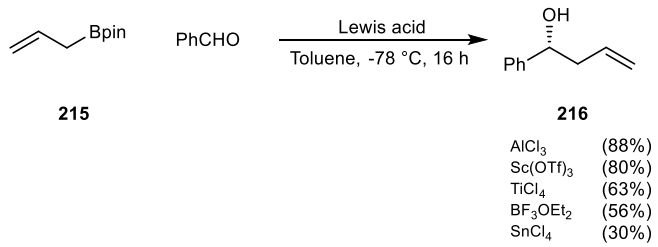
Protection of an allylboron with pinacol increases compound stability, enabling easier handling and purification at room temperature.[190] This improved stability can in turn mitigate reactivity in allyboration reactions.[209,210] The electronic effect of the pinacol renders the empty boron *p*-orbital less accessible.[192] The Lewis acidity of pinacol allylboronates is therefore reduced leading to diminished reactivity with carbonyls.[209] Implementation of an external catalyst could therefore enhance the reactivity of pinacol boronic esters.

Despite concerns of reduced diastereoselectivity Kennedy and Hall initially reported rate enhancements based on the addition of a L.A. catalyst (Scheme 95).[208] The reaction was seen to proceed at 100 °C lower than that of the uncatalysed reaction, whilst retaining the same level of stereoselectivity. This therefore suggested that the reaction was proceeding via the same chair-like transition state. The addition of 2-carboxyester allylboronates **213** to benzaldehyde gave lactone **214**, from the cyclisation of the homoallylic alcohol group with the carboxyester group. Under uncatalysed conditions the reaction took 2 weeks, however with the presence of the L.A. catalyst, $Sc(OTf)_3$, the reaction was complete within 12 h, highlighting the possible rate enhancements achievable when using L.A. catalysts.



Scheme 95: Lewis acid catalysed allylboration.[208]

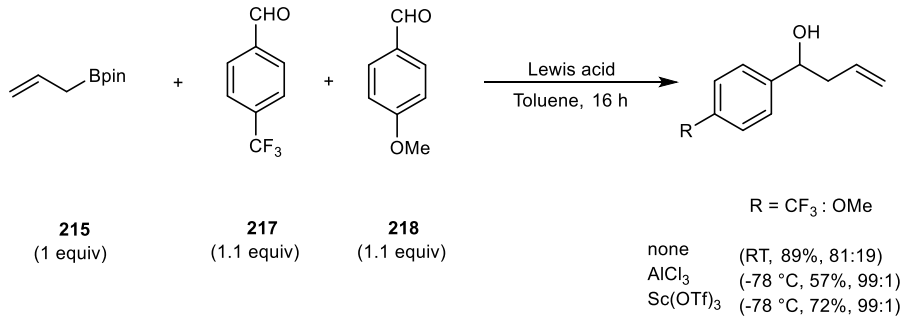
Miyaura and co-workers later screened a variety of L.A. catalysts in the reaction of pinacol allylboronate **215** with benzaldehyde forming alcohol **216** (Scheme 96).[211] The screening showed numerous Lewis acids were able to catalyse the reaction, most notably $AlCl_3$ and $Sc(OTf)_3$. At -78 °C, in the absence of a Lewis acid the reaction did not proceed.



Scheme 96: Screening of Lewis acid catalysts for allylboration.[211]

The same group also investigated competitive allylation of electronically divergent aldehydes. Under L.A. catalysed conditions an electron-poor aldehyde **217** was found to be

allylated preferentially in the presence of a more electron-rich aldehyde **218** (Scheme 97).[211] During uncatalysed reaction conditions at room temperature, only mild selectivity was imparted and a mixture of allylboration products was formed. However, no reaction was carried out at room temperature with a L.A. for comparison. Selectivity is controlled by the relative reactivity of the electrophiles. Addition of a L.A. allows the reaction to occur at a lower temperature, which in turn imparts a larger effect on the different transition state energies.



Scheme 97: Selective allylboration of aldehydes under Lewis acid catalysis conditions.[211]

The control of diastereoselectivity in L.A. catalysed allylboration suggests that the reaction mechanism still occurs through the six-membered chair-like transition state (see Figure 18, Type I, Section 4.4.1). The production of isomerically pure *anti*- and *syn*-homoallylic alcohols from *E*- or *Z*-allylboronic esters respectively suggests a Type II reaction is not induced (see Figure 18, Section 4.1.1).[211]

The enhanced reactivity when using Lewis acids is thought to be due to an increase in electrophilicity of the boron atom following binding of the L.A. to one of the boronate oxygens (T.S. A, Figure 20) as opposed to one of the carbonyl oxygens (T.S. B, Figure 20). Transition state **A** with coordination of the L.A. to the boronate oxygen is thought to disrupt the orbital overlap of the empty *p*-orbital of boron with the oxygen lone pairs, rendering the boron centre more electron-deficient. The boron centre compensates by strengthening the boron-carbonyl interaction, therefore lowering the activation energy of the reaction.[1,208] This theory follows the calculations of Omoto and Fujimoto, who showed the coordination between boron and the aldehyde carbonyl in the allylboration reaction is the turnover-limiting step.[212]

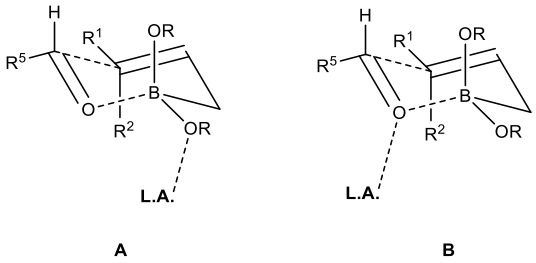
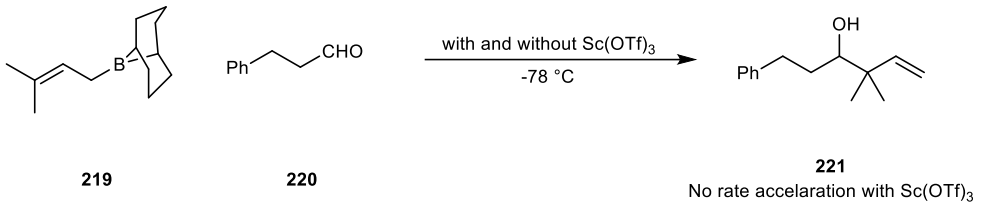


Figure 20: Possible transition states for Lewis acid catalysed allylboration.[1]

Further mechanistic studies have been undertaken to differentiate between the two possible modes of L.A. activation. Prenyl BBN **219** was reacted with aldehyde **220** at - 78 °C with and without $Sc(OTf)_3$ (Scheme 98).[213] No rate enhancement for the formation of alcohol **221** with the LA. present was observed, this therefore suggests that the boronate oxygens are required for the L.A. activation to take place, consistent with T.S. **A** (see Figure 20).



Scheme 98: Mechanistic study into the mode of Lewis acid rate enhancement.[213]

DFT calculations have been used to investigate the coordination of the L.A. to the two possible boronate oxygens.[214] The L.A. could operate through coordination to the accessible pseudoequatorial boronate position T.S. **A** or the basic pseudoaxial oxygen T.S. **B** (Figure 21). Coordination of the L.A. closest to the allyl group, T.S. **B**, is 6.2 kcal/mol higher in energy compared to the L.A. coordination further from the allyl group, T.S. **A**. This energy difference was assigned to the distortion that occurs in the dioxoborolane ring attributed to repulsive forces between the allyl group and the L.A.[214]

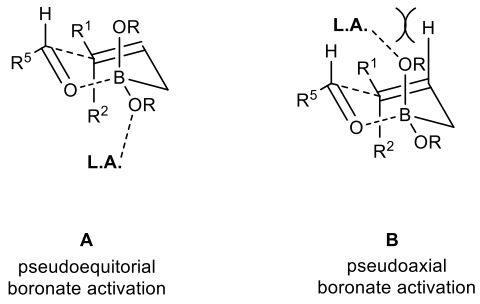
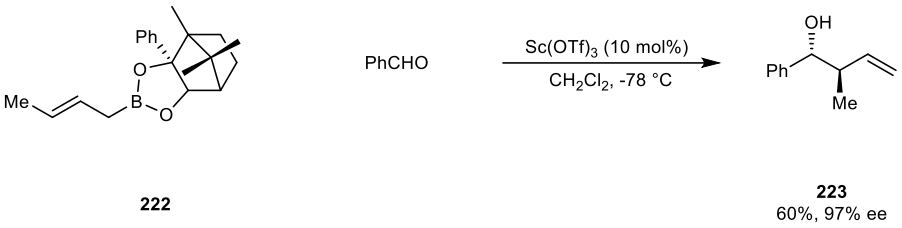


Figure 21: Possible Lewis acid boronate activation sites.[1]

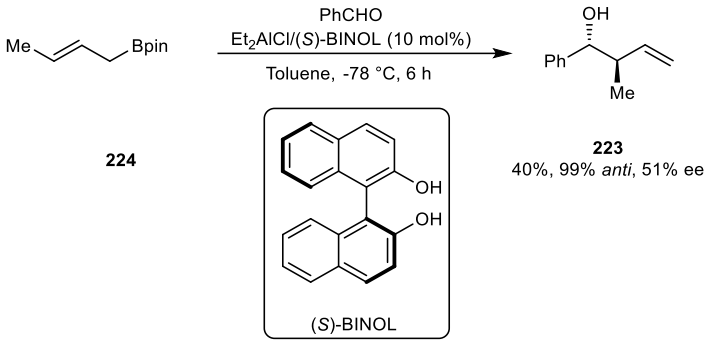
In another study, allylboronates containing chiral diols **222** were subjected to L.A. catalysis and produced enantioenriched products **223** (Scheme 99).[215] This suggests

transmetalation from boron to the L.A. is improbable, otherwise the chiral auxiliary would be lost and a racemic product would be formed.



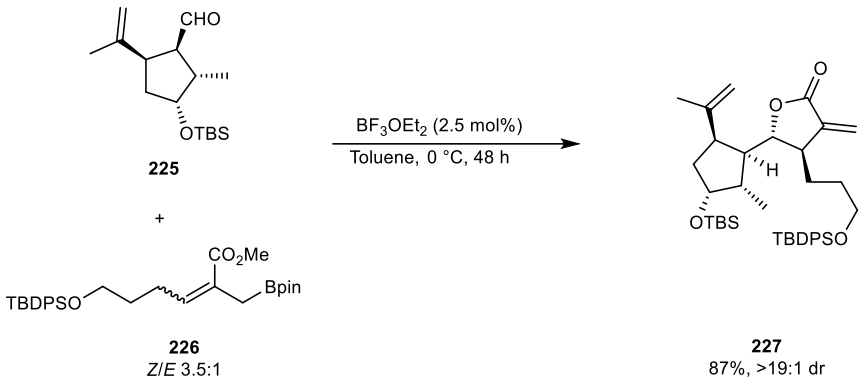
Scheme 99: Enantioenriched product using a Lewis acid catalyst.[215]

Miyaura and co-workers were the first to report a catalytic asymmetric allylation of an allylboronate **224** using substoichiometric amounts of chiral director.[211] They obtained modest chiral induction and excellent diastereoselectivity of alcohol **223** using the L.A. diethylaluminium chloride and (*S*)-BINOL as a ligand (Scheme 100).



Scheme 100: Allylboration using (*S*)-BINOL to induce enantioselectivity.

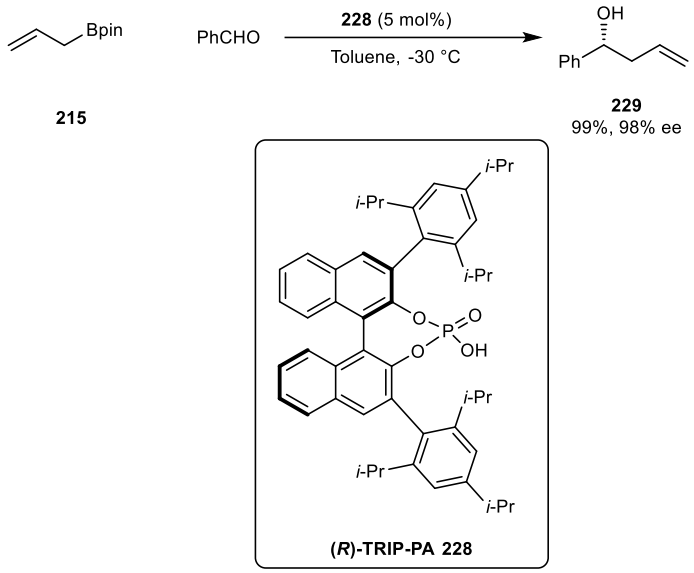
Lewis acid catalysed allylborations have been employed in the production of natural product precursors. Elford and Hall completed the synthesis of a precursor to chinensiolide B, which has been shown to display cytotoxic behaviour against human primary liver cancer (HepG2) (Scheme 101).[216] The L.A. catalysed tandem allylboration/lactonisation of 2-alkoxycarbonyl allylic boronate **225** with a chiral α-substituted aldehyde **226** was a key step in producing an advanced intermediate **227** in the total synthesis of the diterpene. Without the L.A. catalyst present no reaction occurred. The reaction proceeded with *trans*-diastereoselectivity, this is consistent with reaction through a six-membered chair-like transition state, reacting selectively with the *Z*- allylboronate.



Scheme 101: Lewis acid catalysed allylboration/lactonisation forming a diastereoselective product.[216]

4.1.5 Brønsted Acid Catalysed Allylboration

Jain and Antilla and described the first highly stereoselective chiral-Brønsted acid catalysed allylboration of aldehydes in the absence of a L.A.[217] The group employed chiral phosphoric catalyst (*R*)-TRIP-PA **228** in the allylation of benzaldehyde to produce the homoallylic alcohol **229** in excellent yield and stereoselectivity (Scheme 102).



Scheme 102: Brønsted acid catalysed allylboration of aldehydes.[217]

Production of *anti*- and *syn*- diastereomers from the corresponding *E/Z* allylboron starting materials led the group to suggest the reaction was indeed proceeding through a six-membered chair-like transition state of Type I, similar to that of the L.A. promoted reactions.[217] They proposed the reaction was activated via protonation of the boronate oxygen by the chiral phosphoric acid catalyst (Figure 22). Other Brønsted acid catalysed reactions of carbonyl compounds have now been reported.[218]

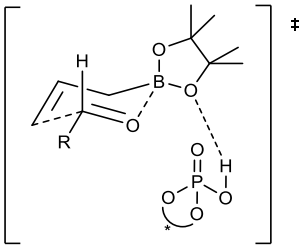


Figure 22: Proposed transition-state for chiral phosphoric acid catalysed allylation of aldehydes.[217]

Goodman and co-workers performed DFT and QM/MM hybrid calculations on the addition of 1° allylboronates to aldehydes.[219] The results suggested, in agreement with Antilla and co-workers, that phosphoric acid-catalysed allylborations involved a six-membered chair-like transition state (Figure 23). Within this transition state there is reported to be a hydrogen-bonding interaction from the catalysts hydroxyl group to the pseudoaxial oxygen of the cyclic boronate. There is also thought to be an additional stabilising interaction from the phosphoryl oxygen of the catalyst to the hydrogen of the aldehyde.

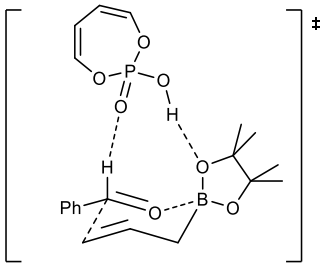


Figure 23: Computational calculations proposing a double coordination mode of phosphoric acid-catalysed allylborations.[219]

Malkov and co-workers also performed DFT calculations to determine the influence of steric bulk of the cyclic boronate moiety on the *E/Z* ratio of the homoallylic alcohol when using a Brønsted acid catalyst.[220] The group also aimed to investigate if the double coordination mode proposed by Goodman and co-workers would extend to 2° allylboronates (see Figure 23).[219] This theory held and the two-point activation mode was favoured for all boronate fragments (Figure 24). The steric size of the boronate fragment appeared to influence *E/Z* preference, with the larger steric boronates (ii (Epin) > i (Bpin) > iii) having the greater preference for the *Z* isomer. This knowledge enabled the group to use Epin to favour the *Z*-selective pathway, highlighting the reaction tunability of allylboration based on substrate and catalyst.

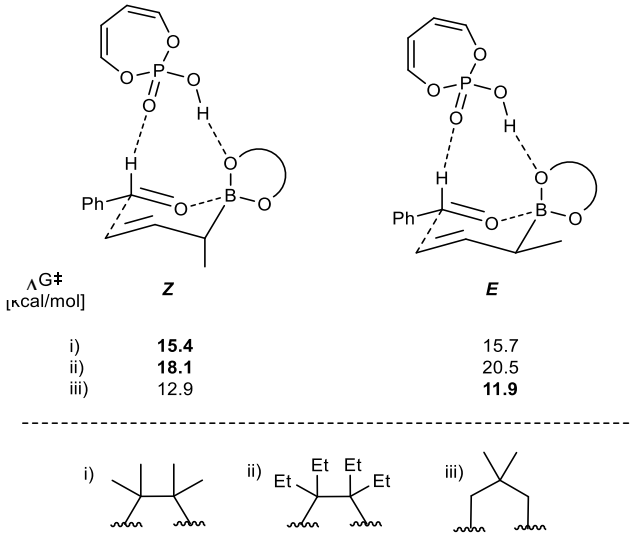
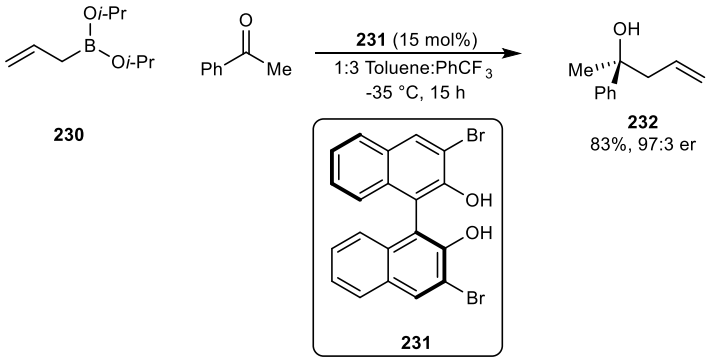


Figure 24: Computational calculations of transition state structures of varying 2° boronate fragments.[220]

4.1.6 Chiral Diol Catalysed Allylboration

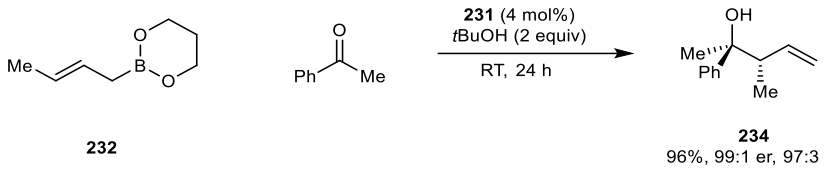
Schaus and co-workers reported the first catalytic asymmetric allylboration employing substoichiometric diols (Scheme 103).[221] They postulated that chiral diols would act as exchangeable ligands with Brønsted acid characteristics to promote the allylboration of ketones. After optimisation, (*S*)-3,3'-Br_2-BINOL **231** catalysed the reaction between allyldiisopropoxyborane **230** and acetophenone producing the 3° homoallylic alcohol **232** in good yield and stereoselectivity. Interestingly, the reaction did not proceed when allylboronic acid pinacol ester is used, this is thought to be due to the stability of the cyclic boronate resulting in diminished reactivity.



Scheme 103: Catalytic chiral diol promoting the allylboration of ketones.[221]

Further optimisation by the same group enabled a reduction in catalyst loading **231** to as little as 2 mol% upon the addition of *t*BuOH (Scheme 104).[222] It was also noted that the reaction proceeded without solvent and at room temperature. The use of cyclic boronate

allyldioxaborinane **233** was also tolerated under these allylboration conditions to produce the 3° homoallylic alcohol **234** in excellent yield and stereoselectivity.

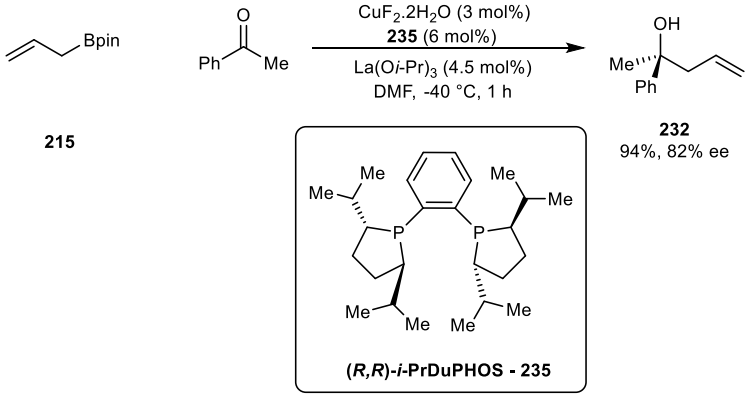


Scheme 104: Improved asymmetric allylboration of ketones using chiral diol catalyst.[222]

4.1.7 Metal-catalysed Allylboration

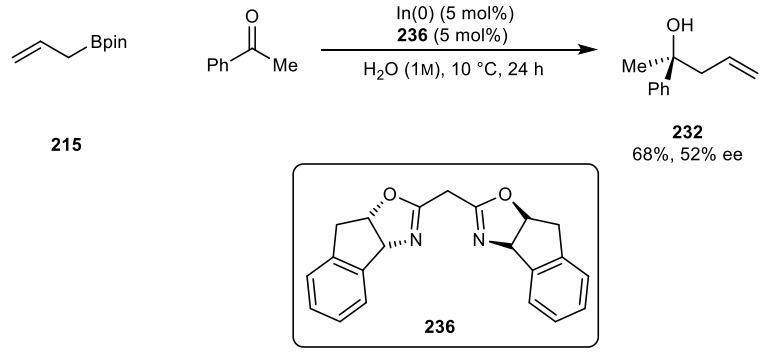
Metal salts and chiral ligands have also been used in stereoselective allylborations. Previous metals reported to catalyse allylboration reactions are extensive and include: Pd,[13, 223–228,229–235] Cu,[236–242] Co,[243,244] In,[245] Ir,[246,247] Zn,[248] and Rh.[249–251] Conversely Ni-catalysed transformations of allylboron reagents are understudied.[252,253]

Shibasaki and co-workers reported the first catalytic stereoselective allylboration of ketones using 3 mol% of $CuF_2.2H_2O$ and 6 mol% of **235** as a chiral catalyst, La(O*i*-Pr)$_3$ was employed as a cocatalyst (Scheme 105).[236,237] Allylboronic ester **215** could be coupled in high yield and stereoselectivity to form 3° alcohol **232**. Under these optimised conditions allylboration of a wide range of ketones proceeded in high yield and good stereoselectivity to produce 3° homoallylic alcohols. ^{11}B NMR experiments suggest the mechanism of allylation proceeds through transmetalation of the boron to an allylcopper species. It is suggested that the addition of La(O*i*-Pr)$_3$ aids transmetalation aiding production of the active allylcopper reagent without interfering with the transition state structure.



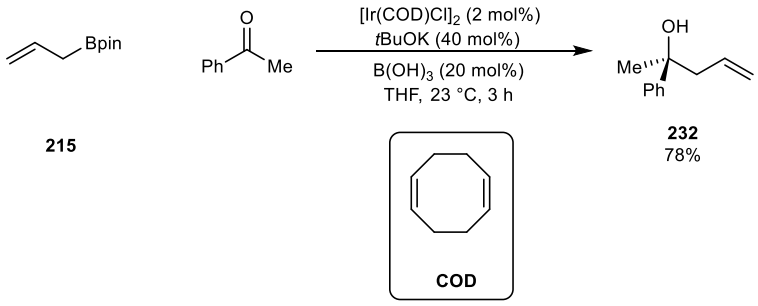
Scheme 105: Copper catalysed enantioselective allylboration of ketones.[236,237]

Kobayashi and co-workers reported an unprecedented example of the catalytic use of In(0) in asymmetric allylboration in water (Scheme 106).[245] The allylation of acetophenone with allylboronic ester **215** using 5 mol% of In(0) combined with chiral bis(oxazoline) ligand **236** gave the homoallylic alcohol **232** in a high yield in water. The reaction is thought to proceed via catalytic transmetalation at the In surface. This is seen as a significant discovery in metal-catalysed allylations; other high yielding reactions previously required strictly anhydrous conditions. The implementation of In(0) is also an important move towards catalysts that are nontoxic, inexpensive and water-compatible.



Scheme 106: In(0) catalysed allylboration of ketones in water.[245]

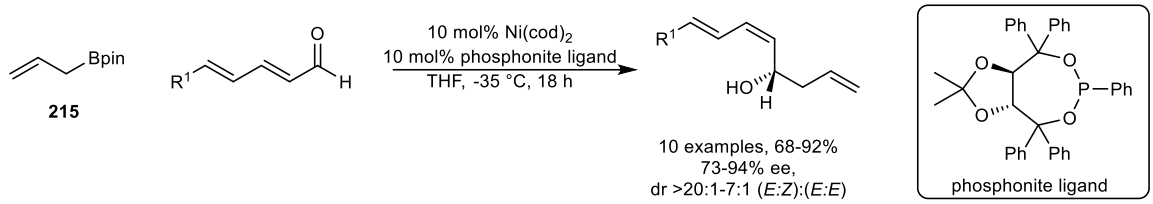
Barker and Jarvo reported the use of iridium to catalyse the allylboration of ketones.[246] They used $[Ir(cod)Cl]_2$ as a catalyst for the production of homoallylic alcohol **232** from boronic ester **215** (Scheme 107). The reaction proceeded at room temperature, employing a diene ligand to afford the 3° homoallylic alcohol **232** in good yield. The group screened chiral ligands with limited success producing both enantiomers in equal quantities, highlighting there is scope for improvement in metal-catalysed enantioselective allylborations.



Scheme 107: Ir catalysed allylboration of ketones.

Zhang and Morken reported the use of nickel to catalyse the 1,2-addition of boronic ester **215** to dienals (Scheme 108).[253] The rate acceleration using nickel was limited to dienals. The catalysed reaction produced an inversion of substrate olefin geometry to provide the major *E:Z*

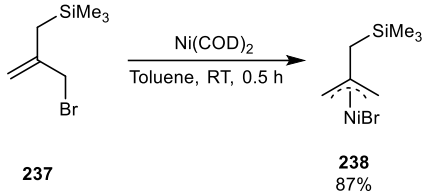
isomer. The enantioselectivity and stereoselectivity of the reaction could be improved by performing the reaction at -35 °C. Scope of the reaction was limited to functionalisation at the δ carbon.



Scheme 108: Nickel catalysed allylation of dienals.

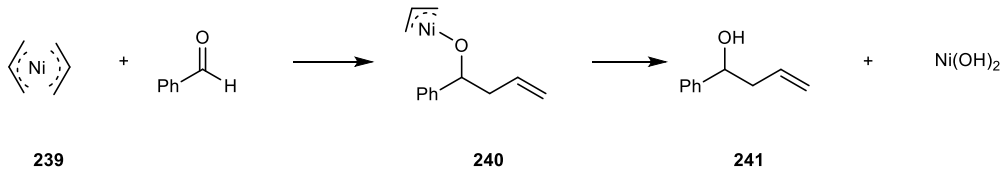
4.1.8 π-Allyl Nickel Species

Molander and co-workers have previously reported the formation of a nickel π-allyl complex.[254] Treatment of **237** with nickel(0) cod after only half an hour led to quantitative conversion to the corresponding trimethylsilyl-substituted π-allyl nickel halide complex **238** (Scheme 109).



Scheme 109: Formation of a π-allyl nickel complex.[254]

In an earlier study Heimbach and co-workers reported a bis-π-allyl nickel species **239** formed **240** when reacted with benzaldehyde which, when hydrolysed, produced homoallylic alcohol **241** (Scheme 110).[255] This shows precedence for the formation of a nickel π-allyl species reacting with a carbonyl, which could be a plausible reaction pathway for nickel-catalysed allylborations.

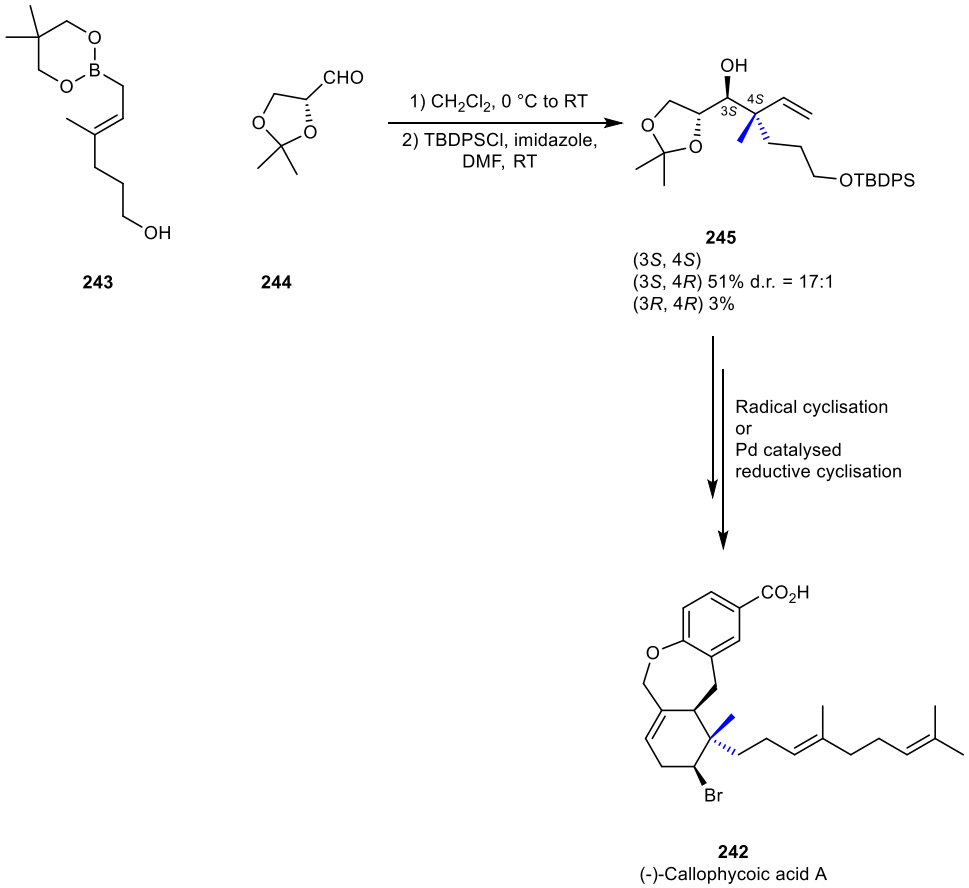


Scheme 110: Reaction of a bis-π-allyl nickel species with an aldehyde to form a homoallylic alcohol.[255]

4.1.9 Applications of Homoallylic Alcohols

The homoallylic alcohol products formed in the allylboration reaction are important starting materials, intermediates or motifs in pharmaceuticals, polyketides, natural products and pesticides.[256–259]

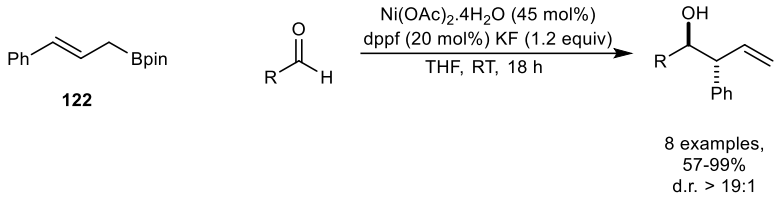
Recently Takao and co-workers[260] performed the first synthetic analysis on (–)-callophycoic acid A **242** (Scheme 111). Compound **242** has been shown to have antimalarial properties and cytotoxicity against human cancer cell lines.[261,262] The synthetic strategy the group utilised to form the all-carbon quaternary stereocentre was allylboration of **243** with aldehyde **244** to form the homoallylic alcohol **245**. Neopentylglycolester **243** was the preferred boronic ester due to increased diastereoselectivity for the desired isomer of **245 (3*S*,4*R*)**. Selective silylation was utilised to aid separation from the starting material **243**. A number of further transformations were performed in order to form the tricyclic core of **242**.



Scheme 111: Quaternary stereocentre formed by allylboration in the total synthesis of (–)-callophycoic acid A.[260]

4.2 Aims

During my Masters' project the reaction conditions for the nickel-catalysed allylboration of aldehydes was optimised and a small test of the reaction scope was undertaken (Scheme 112). The excess nickel to ligand ratio was unintentional, however, inverse ratios were tested and gave comparative yields.



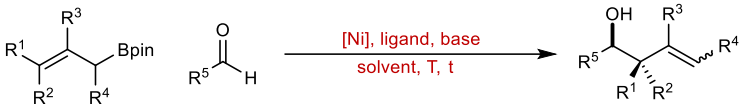
Scheme 112: Previously optimised nickel-catalysed allylboration conditions.

The focus of this project is to further optimise the nickel-catalysed allylboration reaction with an emphasis on decreasing catalyst loading. The scope of the allylboration reaction will then be explored to assess the generality of the reaction conditions. A variety of 1° and 2° allylboronic esters will be synthesised in order to investigate their reactivity and stereochemical outcomes under the nickel-catalysed conditions. Another main objective will be to explore whether the nickel-catalysed reaction proceeds via L.A. activation or *via* transmetalation. Such insight is important to the design of further nickel-catalysed transformations. Producing an asymmetric nickel-catalysed allylboration will also be attempted with the use of chiral ligands.

4.3 Results and Discussion: Nickel-catalysed Allyboration

4.3.1 Previous Optimisation

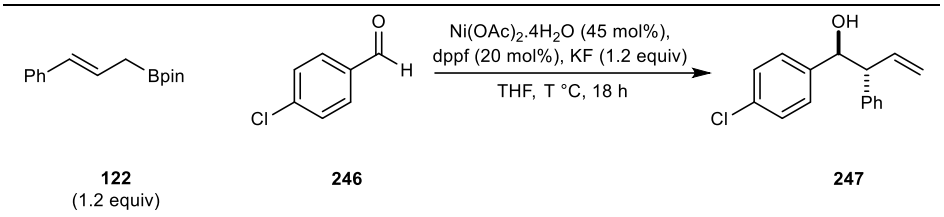
Some initial optimisation of the nickel-catalysed allylboration of aldehydes was undertaken and encompasses my Masters' project within the same research group (see Scheme 112). The optimisation reactions were carried out using phenyl allylboronic ester with substituted benzaldehydes to form homoallylic alcohols. Variables including ligand, temperature, base, solvent, nickel catalyst, catalyst loading, and stoichiometry of starting materials were all investigated in order to improve the yield and diastereoselectivity of the reaction (Scheme 113). This section gives a brief overview of some of the optimisation results obtained in order to give a background to the chosen reaction conditions.



Scheme 113: Optimisation of nickel-catalysed allylboration of aldehydes.

4.3.1.1 Temperature Variation

After an initial ligand screening, the reaction temperature was varied (Table 27). Room temperature led to the highest yield of homoallylic alcohol **247** (Entry 2). Both higher and lower temperatures led to decreased yield of **247**. This is consistent with a report of Brown and co-workers, who observed a similar temperature dependence for allylboration reactions with allylboronates,[210] as well as other groups employing metal catalysts for allylboration.[246,248] At higher temperatures, it is presumed that competitive protodeboronation reduces the efficiency of allylboration.



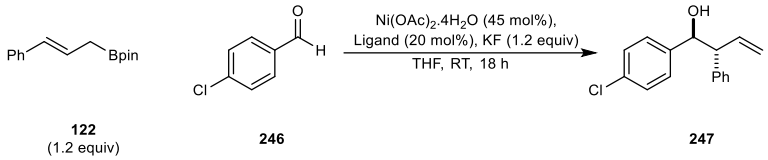
122 (1.2 equiv) **246** **247**

Entry	*T* (°C)	Yield 247 (%)
1	0	39
2	RT	70
2	40	28
3	65	29

Table 27: Effect of temperature variation on the allylboration of **122**. Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **122**. Reaction concentration of 0.11 M.

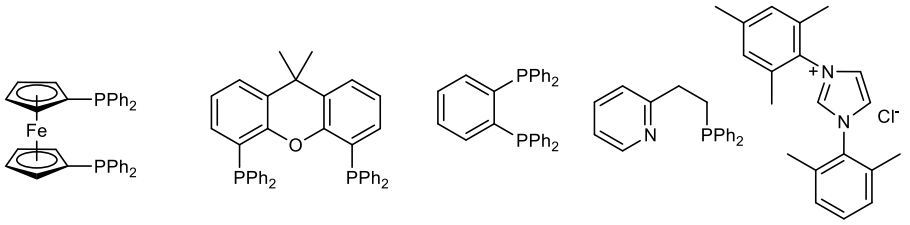
4.3.1.2 Ligand Variation

From an initial ligand screen, the use of dppf gave the highest yield of product **247**. However, this test was carried out while the reaction was still undergoing optimisation. Therefore, a further ligand screen was conducted using improved conditions (Table 28). Bisphosphine ligands (Entries 1, 2 and 3) generally led to the highest yield of **247**, but the use of bidentate nitrogen-based ligands (Entry 6 and 10) also gave a high yield. None of the ligands tested gave an improvement upon the 84% yield obtained when using dppf as a ligand (Entry 1).

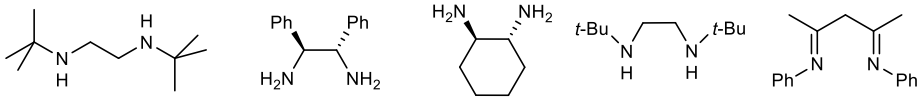


122 (1.2 equiv) **246** **247**

Entry	Ligand	Yield (%)
1	dppf	84
2	Xantphos	78
3	dppbz	82
4	PyPhos	52
5	IMes	42
6	**248**	68
7	**249**	54
8	**250**	20
9	**133**	68
10	**251**	81



dppf **XantPhos** **dppbz** **PyPhos** **IMes**

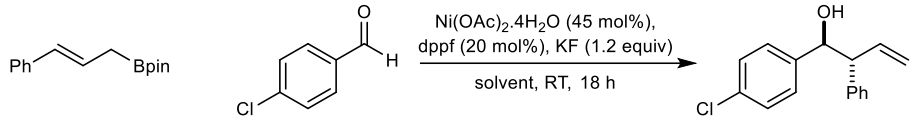


248 **249** **250** **133** **251**

Table 28: Effect of ligands on the allylboration of **122**. Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **122**. Reaction concentration of 0.11 M.

4.3.1.3 Solvent variation

The effect of solvent on the yield of allylboration to form alcohol **247** was investigated (Table 29). Polar and non-polar solvents performed equally. While the use of DCM, EtOAc and petroleum ether all led to acceptable yields of **247**, performing the reaction in THF (Entry 8) gave the highest yield of 84%.



122 (1.2 equiv) **246** **247**

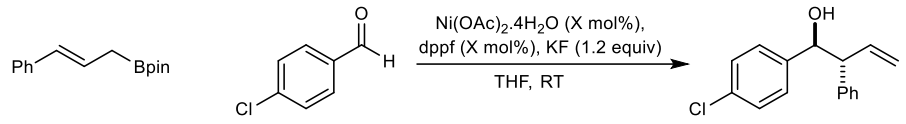
Entry	Solvent	Yield 247 (%)
1	DCM	77
2	Diethyl ether	56
3	Dimethyl carbonate	44
4	DMF	5
5	Ethyl acetate	74
6	Petrol 40/60	72
7	Toluene	50
8	THF	84

Table 29: Effect of solvent on the allylboration of **122**. Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **122**. Reaction concentration of 0.11 M.

4.3.2 New Optimisation Work

4.3.2.1 Decreasing Catalyst Loading

Having established the best ligand, solvent, base and temperature for the nickel-catalysed allylboration reaction, catalyst loading was investigated. A series of reactions with different catalyst loadings were performed, with aliquots taken over the course of the reaction (Table 30). The reaction without catalyst (background reaction) showed a consistent yield of around 30% of **247** between 2 and 24 h (Entries 9-12). The use of 30 mol% $Ni(OAc)_2$ gave 85% yield of **247** after 8 hours (Entry 3), whereas a 12 mol% loading led to a moderate 55% yield of **247** (Entry 8). The aim was to reduce catalyst loading to below 20 mol% and so a further test was conducted.

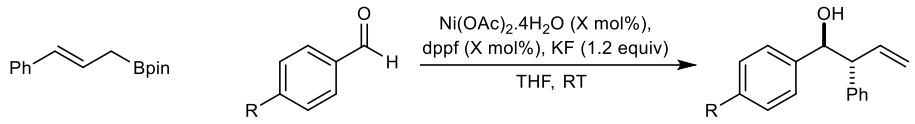


123 (1.2 equiv) **246** **247**

Entry	Loading of [Ni] (X mol%)	Loading of dppf (X mol%)	*T* (h)	247 (%)
1	30	15	2	48
2	30	15	4	75
3	30	15	8	85
4	30	15	24	72
5	12	5.5	2	49
6	12	5.5	4	53
7	12	5.5	8	54
8	12	5.5	24	55
9	0	0	2	33
10	0	0	4	38
11	0	0	8	29
12	0	0	24	34

Table 30: Effect of catalyst loading on the allylboration of **122**. Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **122**. Reaction concentration of 0.11 M.

To confirm whether it was viable to reduce catalyst loading below 20 mol%, four further reactions were carried out to determine yields of isolated product, primarily to reduce any uncertainty associated with NMR yields. The catalyst loading was varied for two different time frames using two different aldehydes (Table 31). Comparable yields of isolated product were achieved for both catalyst loadings over their respective time frames. The allylboration of *p*-chlorobenzaldehyde **246** gave homoallylic alcohol **247** in 76% yield over 4 h using 30 mol% of Ni (Entry 1). However, lowering the catalyst loading to 12 mol% and increasing the reaction time to 18 h gave an equivalent result of 74% yield (Entry 2). Similar results were obtained when using the more electron-poor *p*-cyanobenzaldehyde **252**. A slightly higher yield of **253** was achieved when employing 12 mol% of Ni over 18 h (Entry 4) compared to the reaction over 4 h using 30 mol% Ni (Entry 3). With the two different catalyst loadings mirroring yields over different time frames, a concession of either time or catalyst loading would need to be made. Compromising a shorter reaction time for a lower catalyst loading was seen as the better option, due to reduced cost which could make the reaction more viable on larger scale. Therefore, all further reactions used 12 mol% of $Ni(OAc)_2.4H_2O$ and were conducted over 18 h.



122 (1.2 equiv)

R = Cl **246**
R = CN **252**

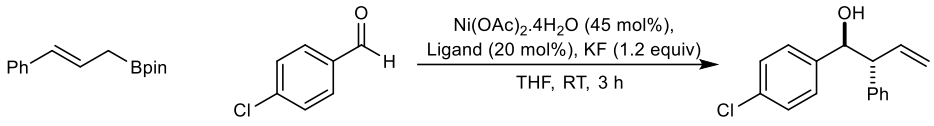
R = Cl **247**
R = CN **253**

Entry	R	Loading of [Ni] (X mol%)	Loading of dppf (X mol%)	*T* (h)	Yield 247 or 253 (%)
1	Cl	30	15	4	76
2	Cl	12	5.5	18	74
3	CN	30	15	4	67
4	CN	12	5.5	18	70

Table 31: Effect of catalyst loading on the allylboration of **122**. Isolated yield. Reactions conducted on a 0.33 mmol scale of **122**. Reaction concentration of 0.11 M.

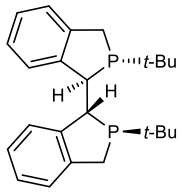
4.3.2.2 Asymmetric Allylboration

Next, the possibility of developing an enantioselective variant of the reaction was explored, by employing a number of chiral ligands in place of dppf (Table 32). The $Ni(OAc)_2.4H_2O$, potassium fluoride and chiral ligand were mixed in THF for 30 min prior to the addition to the aldehyde and allylboronic ester **122** in order to allow ligation of the Ni catalyst. To try and overcome the known racemic background reaction, the catalyst loading was increased for these tests. The yields of **247** varied within the ligand classes. However, generally bidentate nitrogen ligands (Entry 6 and 7) did not work well. Bulkier bisphosphine ligands (Entry 3 and 4) largely outperformed the less bulky ligands (Entry 1 and 5). P,N-ligand **259**, is a class of ligand used in a range of enantioselective intramolecular 1,2- and 1,4-addition reactions, which also led to a high yield of alcohol **247**.[263–265] However, despite trialling a variety of chiral ligands, all reactions returned racemic product. This could be due to inefficient ligation, so that a well-defined catalyst does not form *in situ*. Another possible factor hindering formation of the asymmetric variant could be the catalysts lack of discrimination between the aldehydes Re/Si faces.

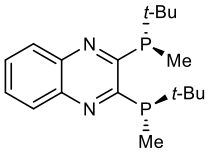


122 (1.2 equiv) **246** **247**

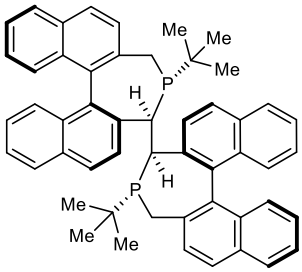
Entry	Ligand	247 (%)	*e.r.*
1	Duanphos	31	50:50
2	Quinox P	67	50:50
3	*S*-Binapine	50	50:50
4	**254**	71	50:50
5	**255**	44	50:50
6	**256**	58	50:50
7	**257**	21	50:50
8	**258**	81	50:50



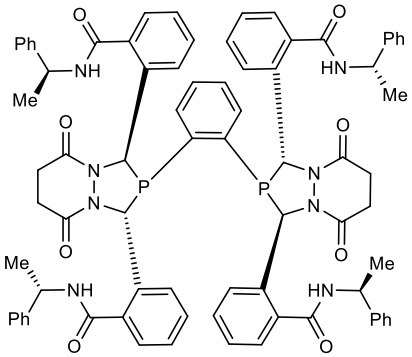
Duanphos



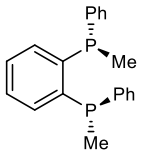
Quinox P



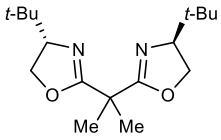
(*S*)-Binapine



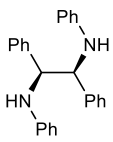
254



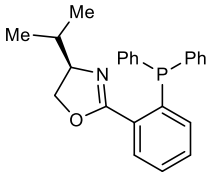
255



256



257

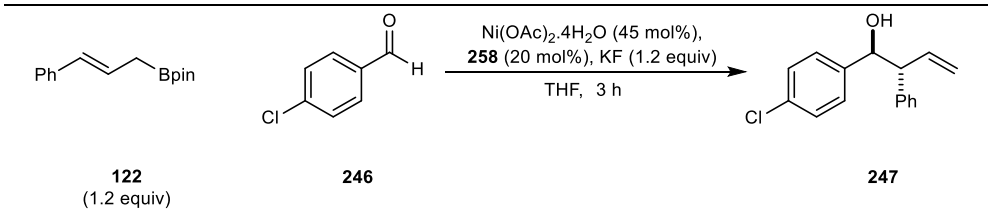


258

Table 32: Use of chiral ligands in the allylboration of **122**. Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **122**. Reaction concentration of 0.11 M.

Previous reports of asymmetric allylboration reactions employing chiral ligands generally used low temperatures ranging from 0 °C to −78 °C.[266] This is presumably due to a decreased relative rate of uncatalysed racemic background reaction in comparison to the

catalysed allylation at lower temperatures. Therefore, as ligand **258** led to the highest yield, comparable with dppf, it was decided to try decreasing the temperature of the reaction to 0 °C (Table 33, Entry 2) and -35 °C (Entry 3) to assess if the catalysed reaction could be promoted. A small amount of homoallylic alcohol **247** was formed at -35 °C, however, no internal standard was added, in order to make purification easier prior to HPLC analysis, and so no NMR yield is available for this entry. It was found that decreasing the temperature led to lower yields of **247** and still no stereoselectivity was induced. At this point, it was decided not to pursue an asymmetric variant further.



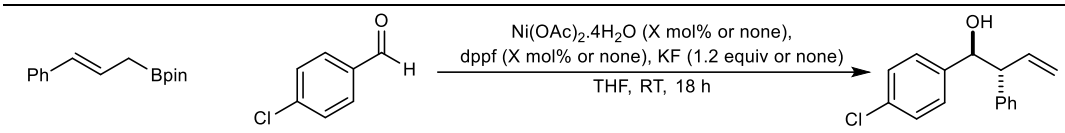
122 (1.2 equiv) **246** **247**

Entry	*T* (°C)	Yield 247 (%)	*er*
1	RT	81	50:50
2	0	38	50:50
3	-35	-	50:50

Table 33: Effect of temperature variation using chiral ligands in the allylboration of **122**. Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **122**. Reaction concentration of 0.11 M.

4.3.2.3 Control Reactions

In order to investigate the roles of each reagent, a number of control reactions were undertaken (Table 34). When the reaction was performed without catalyst the background reaction gave a 41% yield of alcohol **247** (Entry 1). When utilising only potassium fluoride in the allylboration reaction a 34% yield of **247** was achieved (Entry 2). This shows the presence of KF does not increase the yield of background reaction alone, and the d.r. remained unchanged when compared to catalysed reaction conditions. Removing potassium fluoride from the reaction and using a higher loading of $Ni(OAc)_2$ and dppf, gave a decreased yield of 70% for the formation of **247** (Entry 3) when compared to the final optimised conditions (Entry 5). Altering the relative stoichiometry of $Ni(OAc)_2$ and dppf to equal loadings (Entry 4) gave a slight decrease in yield of alcohol **247** when compared to the optimised conditions (Entry 5).



122 (1.2 equiv) **246** **247**

Entry	Nickel (mol%)	dppf (mol%)	KF (equiv)	Yield 247 (%)
1	-	-	-	41
2	-	-	1.2	34
3	45	20	-	70
4	5	5	1.2	79
5	12	5.5	1.2	84

Table 34: Control reactions of the allylboration of **122**. Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. Reactions conducted on a 0.05 mmol scale of **122**. Reaction concentration of 0.11 M.

4.3.3 Scope of the Nickel-catalysed Allylboration Reaction

4.3.3.1 Allylboration of Aldehyde Compounds

With optimised conditions in hand, the scope of the allylboration was tested with a number of different aldehydes using boronic ester **122** (Scheme 114). In all cases the *anti*-diastereoisomer of the corresponding homoallylic alcohol was produced with d.r. > 95:5 in good to excellent yield. The reaction is general and functional group tolerant producing yields of up to 95%. The allylboration proceeds well with substituted benzaldehydes tolerating methoxy, nitro, nitrile, trifluoromethyl and halide groups (**259**, **268**, **253**, **263** and **262**, **267**). Substitution at the hindered ortho-position did not diminish yield (**266**-**268**). A variety of heteroaromatics, pyridyl-, furyl- and thiophenyl-derived aldehydes were also tolerated, albeit reacting in slightly lower yields (**270**-**272**). The process was not limited to benzaldehydes and undergoes reaction with 1° and 2° aliphatic aldehydes in good yield (**273** and **274**). However, the reaction did not proceed with hexanal and isobutyraldehyde showing there are small limitations to the reaction of long chain alkyl groups and sterically hindered aldehydes.

The relative configuration of the homoallylic alcohol **253** was unambiguously assigned by X-ray crystallography (Figure 25). This confirms the relative stereochemistry of the product showing that the *anti*-homoallylic alcohol is formed. The remainder of the products were assigned based on the literature data or by analogy to **253**.

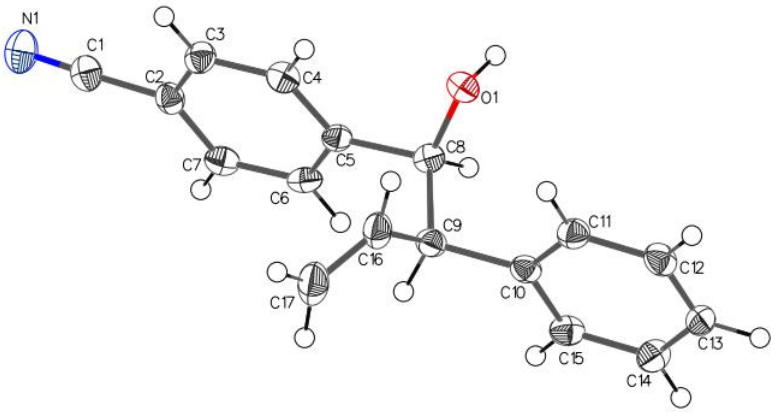
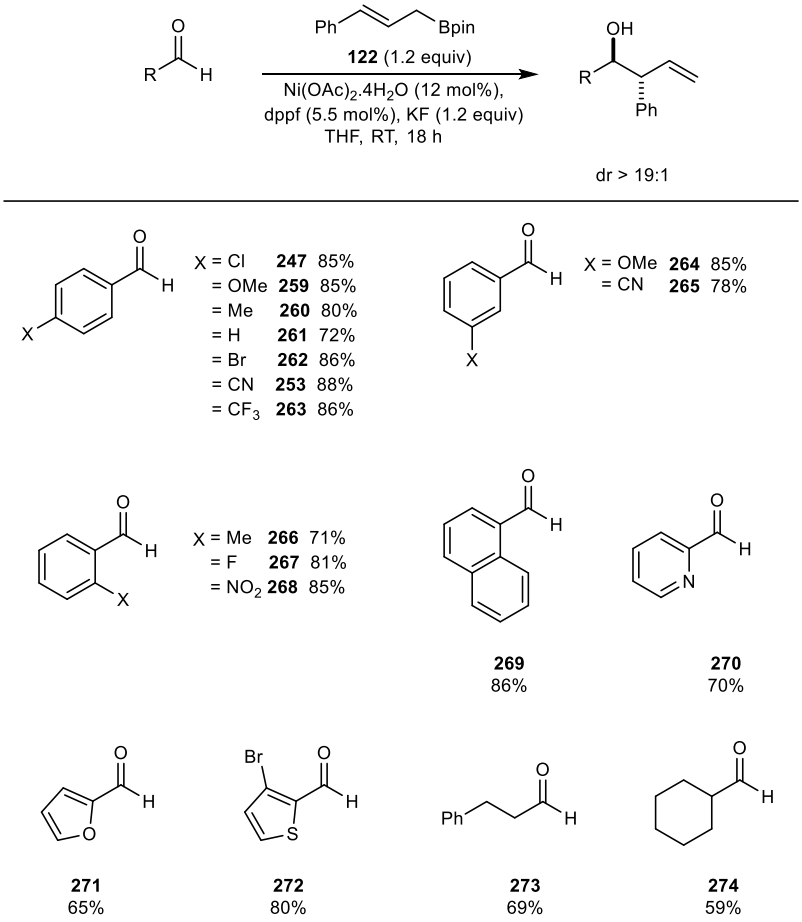
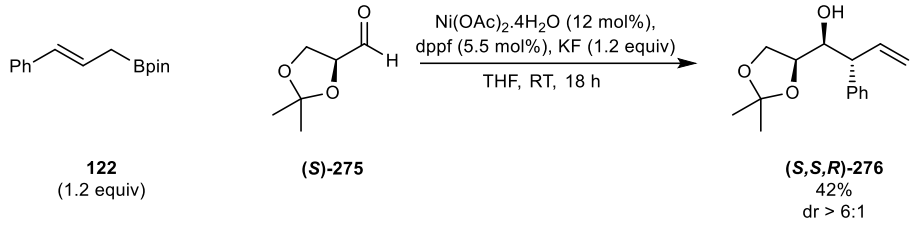


Figure 25: X-ray structure depicting stereochemistry of **253**.



Scheme 114: Scope of the reaction of the allylboration of **122**.

The reaction of **(*S*)-275** provided homoallylic alcohol **(*S*,*S*,*R*)-276**, isolated as the single *syn,anti* diastereomer (Scheme 115). The absolute configuration was confirmed by X-ray crystallography (Figure 26).



122 (1.2 equiv) | **(*S*)-275** | **(*S*,*S*,*R*)-276** 42% dr > 6:1

Scheme 115: Employing a chiral aldehyde under nickel catalysed allylboration reaction conditions.

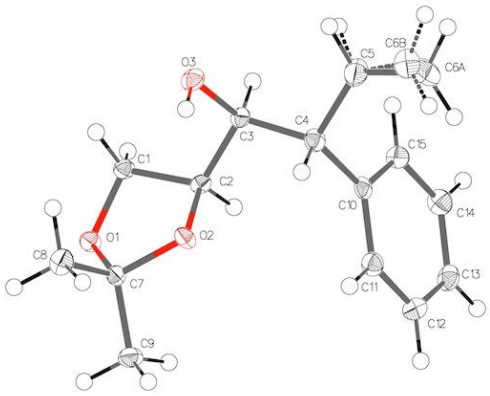


Figure 26: X-ray structure of **(*S*,*S*,*R*)-276**.

The diastereoselectivity (>6:1) is greater than for the corresponding reaction of aldehyde **(*S*)-275** with boronic ester **122** as described by Roush and co-workers, which gave a 1:1 mixture of *syn,anti* and *anti,anti* products.[267] The formation of the major *syn,anti* diastereoisomer is consistent with a chelate controlled anti-Cram addition to aldehyde **(*S*)-275** (Figure 27, Chelation model).[268,269] Presumably, the α-alkoxy aldehyde coordinates to the metal providing an additional 'five-membered ring' stabilisation preventing bond rotation and enhancing the electrophilicity of the carbonyl. The alternate minor *anti*- diastereomer would be formed through the lowest energy Felkin-Anh model, with attack occurring at the least hindered trajectory (Figure 27, Felkin-Anh model).[270,271]

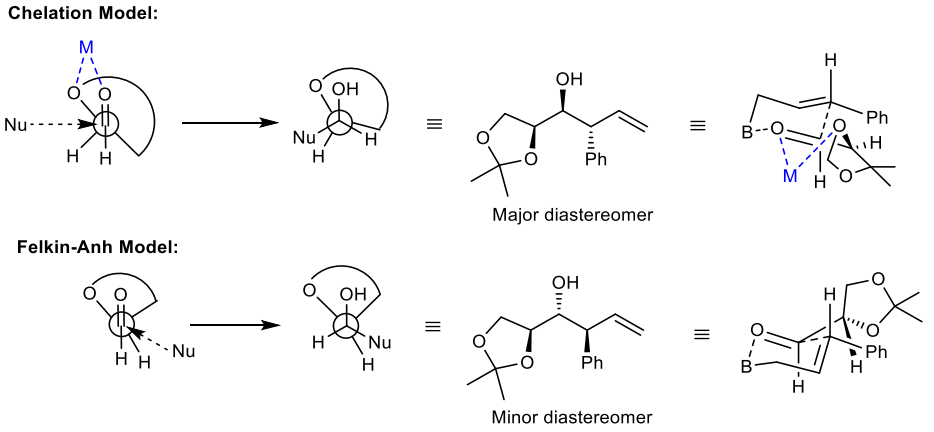
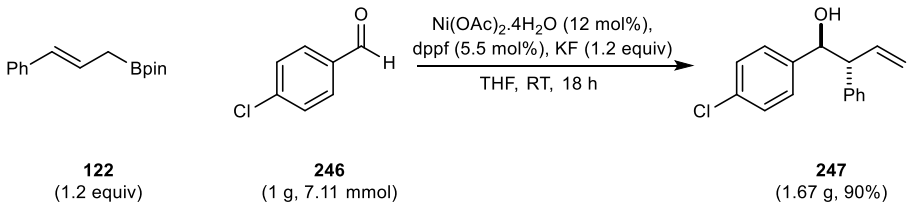


Figure 27: Models to determine diastereoselective outcomes of the reaction of carbonyls.

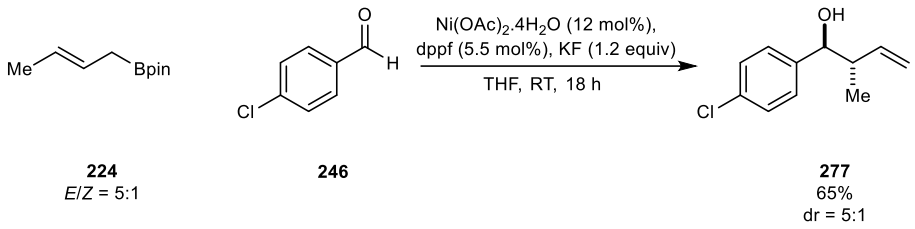
The nickel-catalysed allylboration reaction between aldehyde **246** and an allylboronic ester **122** was scaled up to a gram-scale without loss of efficiency producing the *anti*-homoallylic alcohol **247** in excellent yield (Scheme 116).



Scheme 116: Gram-scale nickel catalysed allylboration reaction.

4.3.3.2 Allylboration of Boronic Ester Compounds

A variety of boronic esters were reacted under standard nickel catalysed allylboration conditions with aldehyde **246**. All boronic esters presented in the scope were prepared using known literature methods. The allylboration of the linear boronic ester **224** gave the branched *anti*-homoallylic alcohol **277** (Scheme 117). The production of **277** in lower diastereomeric ratio is thought to be due to using the starting material **224** as a mix of the *E/Z* isomers, as the same ratio is carried through to the product. This is presumably due to the *E*-isomer producing the *anti*-homoallylic alcohol and the *Z*-isomer forming the *syn*-isomer, with no isomerisation occurring on the allylboration timescale, therefore the ratio does not change.



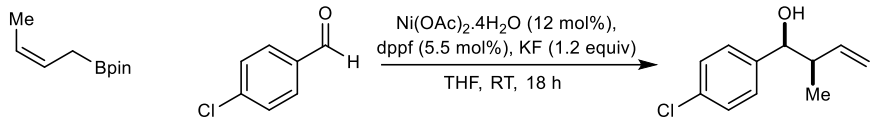
224
E/*Z* = 5:1

246

277
65%
dr = 5:1

Scheme 117: Allylboration using the linear methyl boronic ester.

To test if the diastereoselectivity of the reaction would be altered by changing the stereoisomer of the allylboronic ester, commercially available *Z*-crotylboronic ester **278** was reacted, to give *syn*-homoallylic alcohol **279** in excellent yield (Scheme 118). This is consistent with having used pure *Z*-isomer of boronic ester **278**, as only one diastereomer is obtained. This outcome of the diastereoselective dependency on the starting materials geometry is consistent with reaction occurring through a 6-membered transition state.[1] In addition, isomerisation of the double bond does not occur during the reaction.



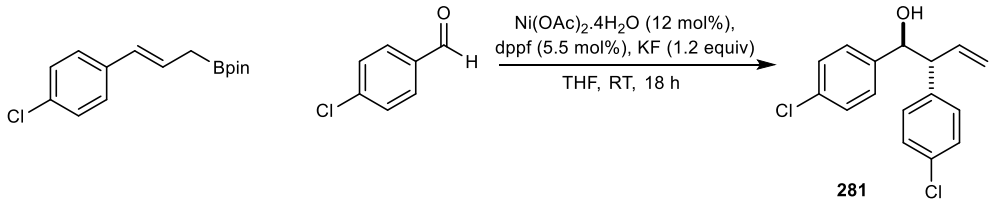
278

246

279
99%

Scheme 118: Allylboration using *Z*-methyl linear boronic ester.

The use of *p*-chlorocinnamylboronic ester **280** in the allylboration would gauge if adding a mildly electron-withdrawing group to the cinnamylboronic ester would impact on reactivity (Scheme 119). Reactivity was not hindered and proceeded well producing the *anti*-homoallylic alcohol **281** in good yield and excellent dr.



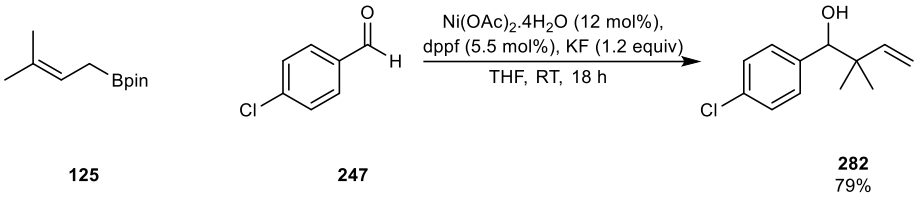
280

246

281
89%
dr > 19:1

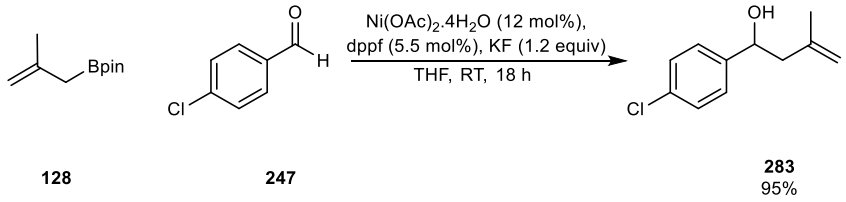
Scheme 119: Allylboration using the *p*-chlorocinnamylboronic ester.

The trisubstituted boronic ester **125** was synthesised to determine if a quaternary centre could be formed. Allylboration proceeded well and homoallylic alcohol **282** was formed in good yield (Scheme 120). This reaction also demonstrates that 1,3-allylic transposition does not occur prior to allylation.[272]



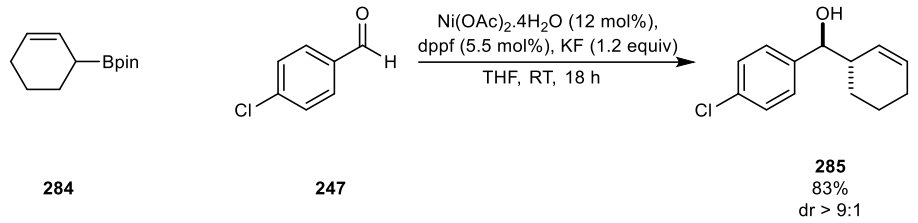
Scheme 120: Allyboration of trisubstituted boronic ester to form a new quaternary centre.

The reaction of the 2-substituted allylboronic ester **128** proceeded in high yield to form the 2-substituted homoallylic alcohol **283** (Scheme 121).



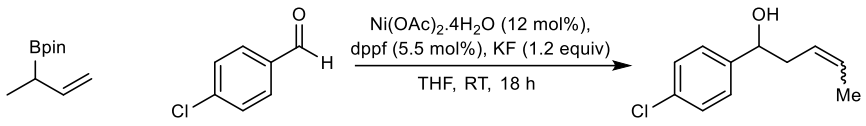
Scheme 121: Allylboration to form a 2-substitued homoallylic alcohol.

Cyclohexylboronic ester **284** was reacted under the standard reaction conditions to give *syn*-homoallylic alcohol **285** (Scheme 122). The *syn*-isomer is formed due to the fixed *Z*-isomer of the boronic ester. This demonstrates that Ni-catalysed allylboration is not limited to 1° allylboron reagents.



Scheme 122: Allylboration using the cyclohexylboronic ester.

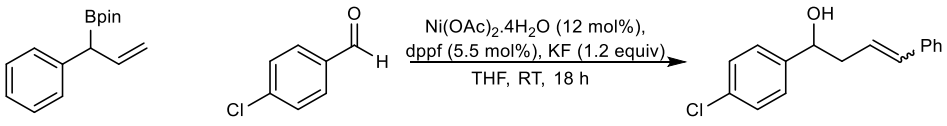
The 2° methylboronic ester **286** was reacted with 4-chlorobenzaldehyde **246** under standard reaction conditions to give *Z*-homoallylic alcohol **287** in modest selectivity in good yield (Scheme 123). The formation of the *Z*-homoallylic alcohol **287** as the major product from the reaction of a 2° boronic ester is consistent with a number of other previous allylborations. Hoffmann and Weidmann used the same 2° allylboronic ester to form the homoallylic alcohol in 77:23 *Z:E* ratio with benzaldehyde.[273] Malkov and co-workers also reported on the same reaction a 67:33 *Z:E* ratio of the homoallylic alcohol product in the presence of (*R*)-TRIP. [220]



286 **246** **287** 75% *E*/*Z* = 1:3

Scheme 123: Allylboration using the 2° methyl boronic ester.

In contrast, 2° phenylboronic ester **288** reacted to give *E*-homoallylic alcohol as the major product **289** (Scheme 124). Usually in order to produce an *E*-selective homoallylic alcohol a sterically unhindered allylboronic ester is required.[274–279] However, it has been previously noted that formation of the *E*-homoallylic alcohol occurs preferentially when using aryl substituted 2° allylboronic ester.[280,281] This switch to *E*-selectivity could be accounted for by Ni acting as L.A. catalyst. This moderate change in selectivity has been previously observed when using a L.A. catalyst.[282–284]



288 **246** **289** 76% *E*/*Z* = 9:1

Scheme 124: Allylboration using the 2° phenyl boronic ester.

The isomeric ratios when reacting 2° allylboronic esters **286** and **288** can be explained using Figure 28.[285] Transition state **A** shows the formation of the *E*-homoallylic alcohol. In T.S. **A**, steric clashes are present between the pinacol backbone and the R group of the 2° boronic ester.[220,273] This interaction, however, is relatively small when R = phenyl, due to the flat nature of the aryl ring. In comparison, T.S. **B** forms the *Z*-homoallyic alcohol, where there is a 1,3-diaxial interaction between the R-group and a pseudo-axial hydrogen. Presumably, when R = phenyl, this 1,3-diaxial interaction is greater than the steric clash present in T.S. **A**, resulting in ***E***-homoallylic alcohol as the major product.[281] Instead, when R = methyl, presumably the steric clash between the methyl group and the boronate in T.S **A** is greater than the 1,3-diaxial interaction in T.S **B**, resulting in ***Z***-homoallylic alcohol as the major stereoisomer.

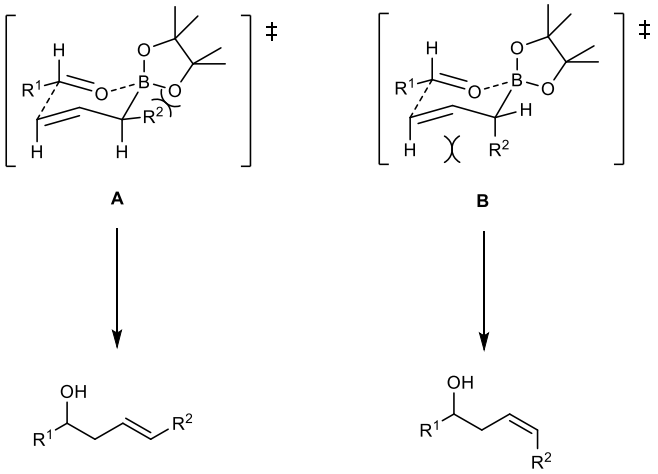


Figure 28: Allylboration transition states of 2° allylboronic esters forming either *E* or *Z* isomers.

The observed diastereoselectivities from the reaction of the boronic esters suggests that the nickel-catalysed allylboration occurs through a well-defined 6-membered cyclic transition state. However, the mode of action of the nickel catalyst could be due to several possibilities, namely by nickel promoting the reaction by acting as a Lewis acid (Figure 29, Pathway 1 and 2) or alternatively by transmetalation from boron-to-nickel to generate a nucleophilic allylnickel species (Figure 29, Pathway 3 and 4). This Lewis acid catalysis could occur through coordination of nickel to an oxygen of either the boronate or the aldehyde. Formation of the *E*-homoallylic alcohol is unfavoured under nickel-catalysed conditions. The Lewis acid activation of the boronate group by Ni is unlikely to reduce the steric environment in T.S. **B**, therefore favouring Pathway 1 and the formation of the *Z*-homoallylic alcohol. This provides tentative evidence that such a Lewis acid mechanism is in operation.

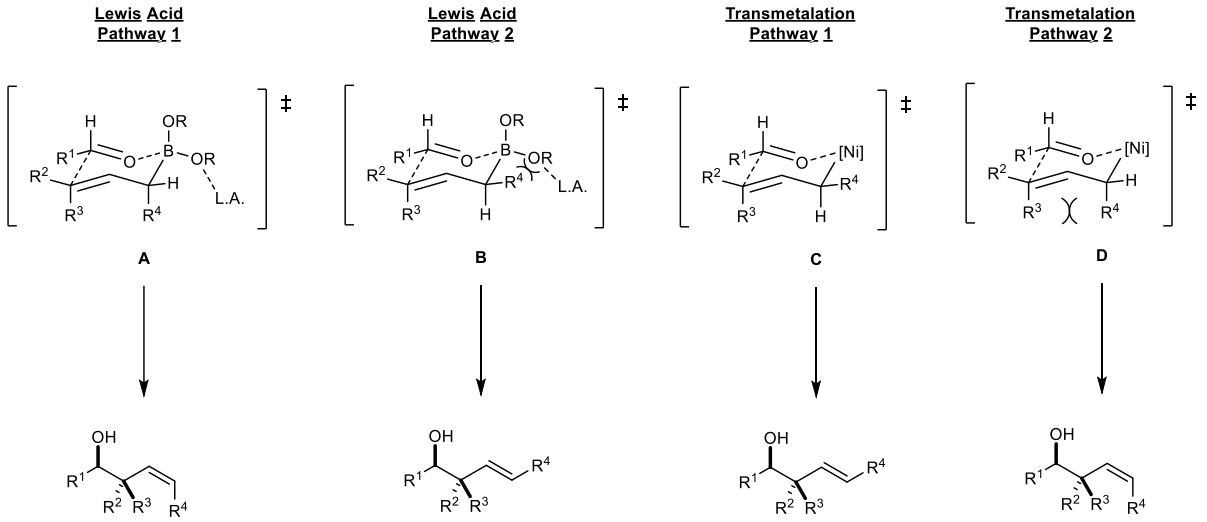


Figure 29: Allylboration transition states under Lewis acid catalysis **A** and **B**, Nickel transmetalation transition states **C** and **D**.

During nickel catalysed allylboration 1° boronic esters form only branched *anti*/*syn* homoallylic alcohols dependent on the starting allylboronic ester geometry, whereas 2° boronic esters react to form solely linear homoallylic alcohols. This suggests allylation occurs prior to allylic isomerisation of the intermediates. This is juxtaposed to reports on Rh catalysed allylborations of trifluoroborates by Lam and co-workers.[250,251] Branched α-methyl substituted trifluoroborates undergo allylic transposition prior to allylation (Figure 30). The new C-C bond forms solely at the most substituted end of the allyl fragment resulting in branched homoallylic alcohols, suggesting the allylation proceeds *via* an allylrhodium species. The ratio of *anti:syn* products is dependent on the *E/Z* ratio of the intermediates formed in the initial transmetalation.

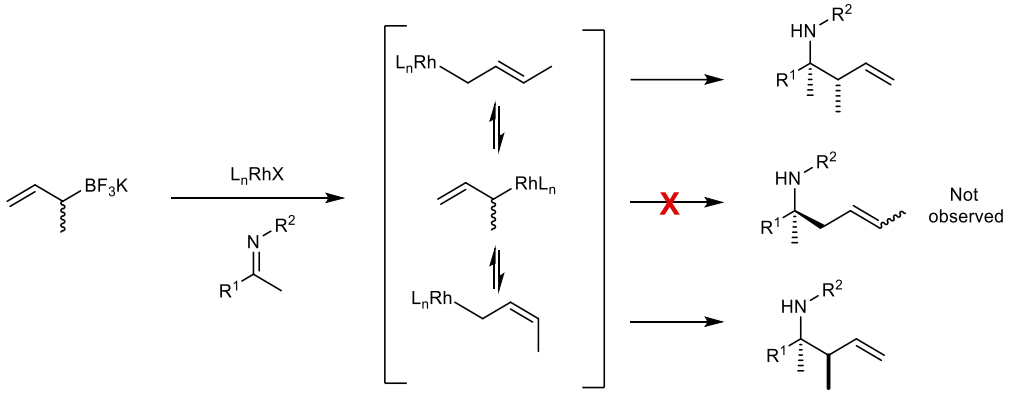


Figure 30: Rhodium catalysed allylboration of imines proceeding via an allylrhodium species.

4.3.3.3 NMR Studies

To give further insight into the role of the Ni catalyst, a series of ^{11}B NMR experiments were undertaken (Figure 31). First a solution containing $Ni(OAc)_2$, dppf, KF and boronic ester **122** in THF was analysed. A characteristic peak for a boronic ester was observed at 33 ppm. This signal remained unchanged over a 3 h period. Subsequently, 1 equivalent of **246** was added to the solution and the mixture was reanalysed. Within 30 minutes, a new peak was observed by ^{11}B NMR at 22 ppm, which is consistent with a borate, presumably structure **290** formed through allylboration. This suggests that the Ni catalyst is unlikely to undergo transmetalation with the boronic ester, as an AcO-Bpin by-product was not observed before addition of the aldehyde. Instead, the data are more consistent with Ni acting as a Lewis acid catalyst.

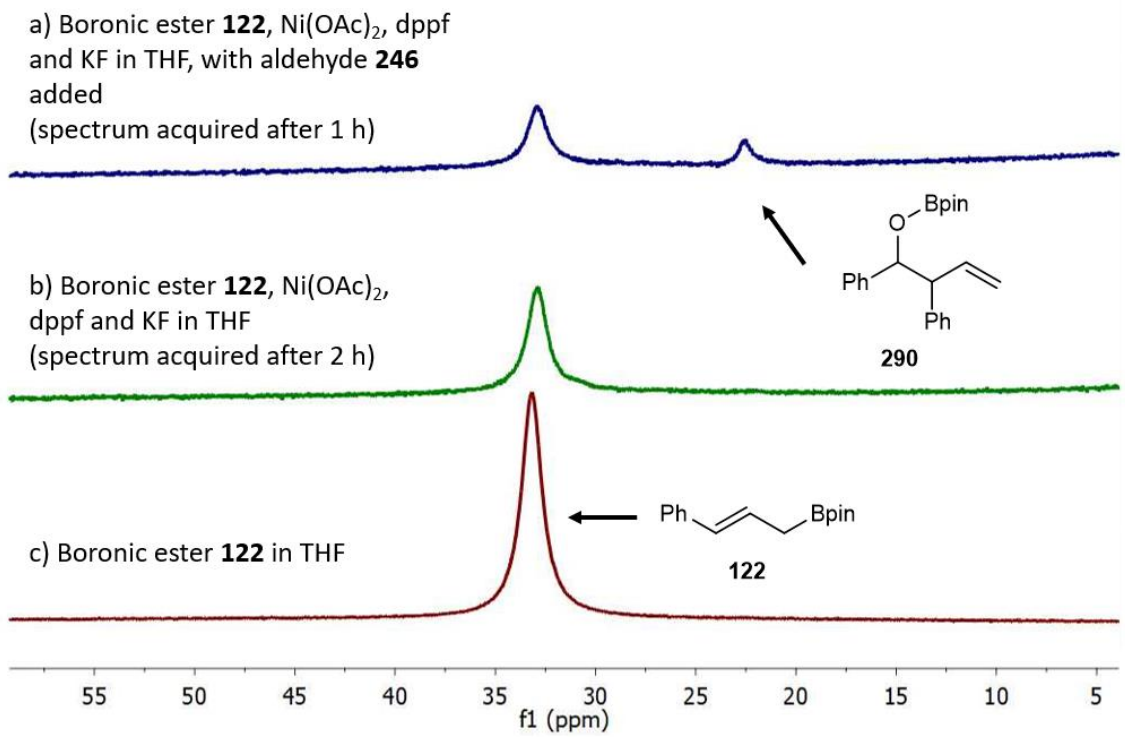
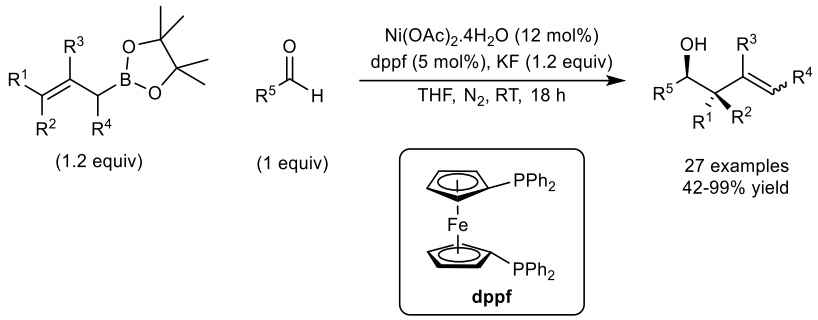


Figure 31: Overlaid ^{11}B NMR spectra for (a) boronic ester **122** in the presence of the Ni catalyst with aldehyde **246** added after 3 hours, b) boronic ester **122** in the presence of the Ni catalyst, c) boronic ester **122**.

4.4 Conclusions and Future Work

A procedure for a nickel-catalysed allylboration of aldehydes has been optimised, providing homoallylic alcohols in good to excellent yields and high diastereoselectivity (Scheme 125). The reaction proceeds well with a broad range of benzaldehydes, with both electron donating and withdrawing substituents, as well as heteroaromatic and aliphatic aldehydes. All *E*-linear boronic esters formed the *anti*-homoallylic alcohols with d.r. > 95:5, whereas a *Z*-linear boronic ester produced the *syn*-homoallylic alcohol exclusively. 2° methyl and phenyl boronic esters produced *Z*- and *E*- homoallylic alcohols respectively as the major diastereoisomer. From the results obtained it is proposed that the reaction proceeds through a six-membered chair-like transition state, of Type I shown in Figure 18 in Section 4.1.1, with Ni acting as a Lewis acid catalyst.[1]



Scheme 125: Nickel-catalysed allylboration conditions.

Further reaction optimisation could increase substrate generality, potentially widening the scope of the reaction to the less reactive ketones and imines, which have been long-standing problems in allylboration. These reactions would allow the production of 3° homoallylic alcohols and homoallylic amines, which are both employed as chemical building blocks.[245,251]

Additional investigation should focus on the feasibility of making the reaction enantioselective with the use of a suitable chiral ligand.[253] This would make this nickel-catalysed process complimentary to existing methods. This would allow the production of chiral 2° and 3° homoallylic alcohols as well as homoallylic amines, which are much sought after substrates.

5. Experimental

5.1 General Experimental

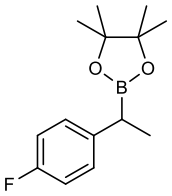
All of the reagents and solvents used were supplied by commercial sources without further purification unless specified. p-Anisidine was purified by recrystallisation from ethanol, filtered and dried in vacuo for 6 h. *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was distilled over NaH and stored under nitrogen prior to use. All air-sensitive reactions were carried out under a nitrogen or argon atmosphere using oven-dried apparatus. Anhydrous CH_2Cl_2, Et_2O, DMF, petrol, THF and toluene were dried and purified by passage through activated alumina columns using a solvent purification system. All petroleum ether used was 40-60 °C petroleum ether. Thin layer chromatography (TLC) was performed on aluminium-backed plates pre-coated with silica. Compounds were visualised by exposure to UV light or by dipping the plates into solutions of vanillin, ninhydrin, $KMnO_4$ or phosphomolybdic acid followed by heating. All flash column chromatography was carried out using silica gel mesh 40-63.

Infra-red spectra were recorded on a Perkin Elmer 100 FT instrument on the neat compound. NMR spectra were recorded on Bruker Advance 400 and 500 instruments at the indicated 101, 128, 126, 377 and 400 MHz as dilute solutions in the indicated deuterated solvent at ambient temperature. All chemical shifts (δ) reported in parts per million (ppm) relative to residual protio solvent peaks, ($CHCl_3$ δH = 7.27 ppm) or the solvent itself (δC = 77.0 ppm). All multiplets are designated by the following abbreviations: s = singlet, br s = broad singlet, d = doublet, dd = doublet doublet, dt = doublet triplet, td = triplet doublet, ddd = doublet doublet doublets, q = quartet, br q = broad quartet, m = multiplet. All coupling constants (*J*) are reported in Hertz (Hz). ^{13}C NMR spectra were acquired as decoupled spectra and assignments determined using CPD experiments. ^{19}F NMR spectra acquired as decoupled spectra. High-resolution mass spectra were recorded using electrospray ionization (ESI) or electron ionisation (EI) or quadrupole time of flight (Q-TOF) at the Department of Chemistry, University of Sheffield. Melting points measured using Linkam HFs91 heating stage, used in conjunction with a TC92 controller and are uncorrected.

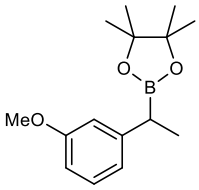
Single crystal intensity data was collected at 100 K on a Bruker D8 Venture diffractometer equipped with a Photon 100 CMOS detector using a CuKα microfocus X-ray source from crystals mounted in fomblin oil on a MiTiGen microloop and cooled in a stream of cold N_2. Data were corrected for absorption using empirical methods (SADABS)[286] based

upon symmetry equivalent reflections combined with measurements at different azimuthal angles.[287] The crystal structures were solved and refined against F^2 values using ShelXT[288] for solution and ShelXL[289] for refinement accessed via the Olex2 program.[290] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions with idealized geometries and then refined by employing a riding model and isotropic displacement parameters.

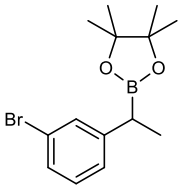
5.2 Compounds Supplied by Members of The Partridge Group



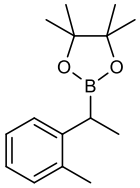
291



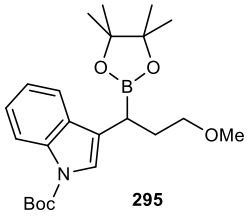
292



293



294

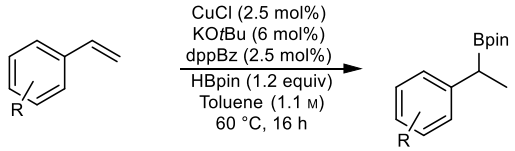


295

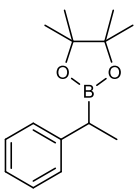
5.3 Preparation of Boronic Esters

5.3.1 Cu-Catalysed Hydroboration of Alkenes

General Procedure 1: Cu-Catalysed Hydroboration of Styrene and Styrene Derivatives



Using a variation of the procedure of Yun and co-workers,[38] an oven-dried flask was charged with CuCl (2.5 mol%), tBuOK (6 mol%) and dppBz (2.5 mol%) and purged with N_2. Anhydrous toluene (1.1 M) was added, and the mixture was stirred at room temperature for 10 min. Pinacolborane (1.2 equiv) was added and the mixture was stirred for 10 min. The corresponding alkene (1 equiv) was added and the mixture heated to 60 °C for 16 h. Upon completion (as determined by TLC) the mixture was cooled to room temperature, passed through a bed of Celite eluting with EtOAc (10 mL), and concentrated *in vacuo*. The crude material was purified by flash chromatography to give the corresponding boronic ester.



55

(±)-4,4,5,5-Tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane (55)

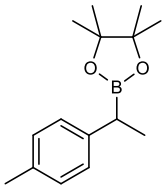
The title compound was prepared according to General Procedure **1** using CuCl (0.356 g, 3.6 mmol), *t*BuOK (0.970 g, 8.6 mmol), dppBz (1.607 g, 3.6 mmol), pinacolborane (25.1 mL, 173 mmol) and styrene (16.5 mL, 144 mmol). Flash

chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **55** (30.7 g, 92%) as a colourless oil. The data were consistent with the literature.[38]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.19 (4H, m, Ar**H**), 7.19-7.08 (1H, m, Ar**H**), 2.45 (1H, q, *J* = 7.5 Hz, C**H**), 1.34 (3H, d, *J* = 7.5 Hz, CHC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 128.3 (2 × CH), 127.8 (2 × CH), 125.1 (CH), 83.3 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 17.0 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.5.



296

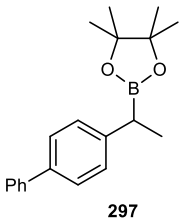
(±)-4,4,5,5-Tetramethyl-2-(1-p-tolylethyl)-1,3,2-dioxaborolane (296)

The title compound was prepared according to General Procedure **1** using CuCl (0.104 g, 1.05 mmol), *t*BuOK (0.285 g, 2.54 mmol), dppBz (0.469 g, 1.05 mmol), pinacolborane (7.36 mL, 50.8 mmol) and 4-methylstyrene (5.57 mL, 42.3 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **296** (5.34 g, 51%) as a colourless oil. The data were consistent with the literature.[38]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.05 (2H, d, *J* = 8.1 Hz, Ar**H**), 2.40 (1H, q, *J* = 7.6 Hz, C**H**), 2.31 (3H, s, ArC**H$_3$**), 1.31 (3H, d, *J* = 7.6 Hz, CHC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (C), 134.4 (C), 129.0 (2 × CH), 127.6 (2 × CH), 83.2 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 21.0 (CH_3), 17.0 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.6.



297

(±)-2-(1-[1,1'-Biphenyl]-4-ylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (297)

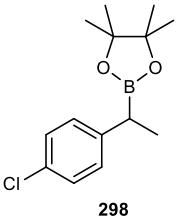
The title compound was prepared according to General Procedure **1** using CuCl (0.004 g, 0.035 mmol), *t*BuOK (0.0077 g, 0.068 mmol), dppBz (0.015 g, 0.035 mmol), pinacolborane (0.25 mL, 1.7 mmol) and 4-vinylbiphenyl (0.025 g, 1.4 mmol). Flash chromatography (4% EtOAc/petroleum ether) of the crude material gave boronic ester **297** (0.206 g, 47%) as a white solid. The data were consistent with the literature.[291]

m.p. 72-73 °C (petroleum ether); literature = 60 °C (not specified).[292]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.55 (2H, m, Ar**H**), 7.54-7.47 (2H, m, Ar**H**), 7.46-7.39 (2H, m, Ar**H**), 7.35-7.27 (3H, m, Ar**H**), 2.49 (1H, q, *J* = 7.5 Hz, C**H**), 1.37 (3H, d, *J* = 7.5 Hz, CHC**H$_3$**), 1.24 (6H, s, 2 × CC**H$_3$**), 1.23 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (C), 141.2 (C), 137.9 (C), 128.6 (2 × CH), 128.1 (2 × CH), 127.0 (2 × CH), 126.9 (2 × CH), 126.8 (CH), 83.3 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 17.1 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.5.



298

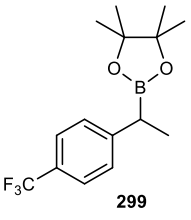
(±)-2-[1-(4-Chlorophenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (298)

The title compound was prepared according to General Procedure **1** using CuCl (0.045 g, 0.45 mmol), *t*BuOK (0.121 g, 1.08 mmol), dppBz (0.200 g, 0.45 mmol), pinacolborane (3.13 mL, 21.6 mmol) and 4-chlorostyrene (2.16 mL, 18 mmol). Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave boronic ester **298** (1.41 g, 81%) as a white solid. The data were consistent with the literature.[38]

^{1}H NMR (400 MHz, $CDCl_3$) 7.25-7.22 (2H, m, Ar**H**), 7.17-7.14 (2H, m, Ar**H**), 2.41 (1H, q, *J* = 7.5 Hz, C**H**), 1.31 (3H, d, *J* = 7.5 Hz, C**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**), 1.20 (6 H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (C), 130.7 (C), 129.1 (2 × CH), 128.3 (2 × CH), 83.4 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 16.9 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.3.



299

(±)-2-[1-(4-Trifluoromethylphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (299)

The title compound was prepared according to General Procedure **1** using CuCl (0.014 g, 0.145 mmol), *t*BuOK (0.038 g, 0.34 mmol), dppBz (0.65 g, 0.014 mmol), pinacolborane (1.0 mL, 7.0 mmol) and 4-(trifluoromethyl)styrene (0.86 mL, 5.8 mmol). Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave boronic ester **299** (1.41 g, 81%) as a white solid. The data were consistent with the literature.[293]

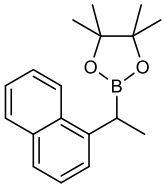
m.p. 53-54 °C (petroleum ether); no literature value available.[293]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.32 (2H, d, *J* = 8.2 Hz, Ar**H**), 2.51 (1H, q, *J* = 7.5 Hz, C**H**), 1.35 (3H, d, *J* = 7.5 Hz, CHC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ149.3 (C), 128.8-127.6 (CCF_3, m), 128.0 (2 × CH), 125.2 (2 x CH, q, $J_{C\text{-}F}$ = 3.6 Hz), 124.5 (C, q, $J_{C\text{-}F}$ = 271.4 Hz), 83.5 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 16.7 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.3.

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.2.



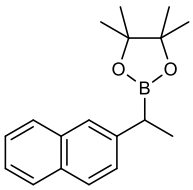
300

(±)-4,4,5,5-Tetramethyl-2-[1-(1-naphthalen-1-yl)ethyl]-1,3,2-dioxaborolane (300)

The title compound was prepared according to General Procedure **1** using CuCl (0.016 g, 0.16 mmol), *t*BuOK (0.44 g, 0.39 mmol), dppBz (0.72 g, 0.16 mmol), pinacolborane (1.1 mL, 7.8 mmol) and 1-vinylnaphthalene (0.96 mL, 6.5 mmol). Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave boronic ester **300** (0.987 g, 54%) as a colourless oil. The data were consistent with the literature.[38]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14-8.09 (1H, m, Ar**H**), 7.87-7.82 (1H, m, Ar**H**), 7.70-7.66 (1H, m, Ar**H**), 7.52-7.38 (4H, m, Ar**H**), 3.13 (1H, q, *J* = 7.5 Hz, C**H**), 1.51 (3H, d, *J* = 7.5 Hz, CHC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4 (C), 133.9 (C), 132.0 (C), 128.7 (CH), 125.8 (2 × CH), 125.3 (CH), 125.2 (CH), 124.2 (CH), 124.1 (CH), 83.4 (2 × C), 24.7 (2 × CH_3), 24.5 (2 × CH_3), 16.4 (CH_3). **^{11}B NMR** (128 MHz, $CDCl_3$) δ 33.4.



151

(±)-4,4,5,5-Tetramethyl-2-[1-(2-naphthalen-1-yl)ethyl]-1,3,2-dioxaborolane (151).

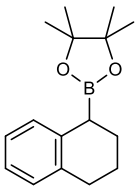
The title compound was prepared according to General Procedure **1** using CuCl (0.64 g, 0.65 mmol), *t*BuOK (0.174 g, 1.55 mmol), dppBz (0.290 g, 0.65 mmol), pinacolborane (4.5 mL, 31.1 mmol) and 2-vinylnaphthalene (4.0 g, 26.0 mmol). Flash chromatography (4% EtOAc/petroleum ether) of the crude material gave boronic ester **151** (6.2 g, 84%) as a white solid. The data were consistent with the literature.[294]

m.p 80-81 °C (EtOAc); literature = 61-63 °C (not specified).[295]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.74 (3H, m, Ar**H**), 7.65 (1H, s, Ar**H**), 7.45-7.37 (3H, m, Ar**H**), 2.62 (1H, q, *J* = 7.5 Hz, C**H**), 1.43 (3H, d, *J* = 7.5 Hz, CHC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6 (C), 133.8 (C), 131.7 (C), 127.6 (CH), 127.5 (CH), 127.5 (CH), 127.2 (CH), 125.6 (CH), 125.2 (CH), 124.7 (CH), 83.4 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 16.8 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 34.0.



301

(±)-4,4,5,5-Tetramethyl-2-(1,2,3,4-tetrahydronaphthalen-1-yl)-1,3,2-dioxaborolane (301).

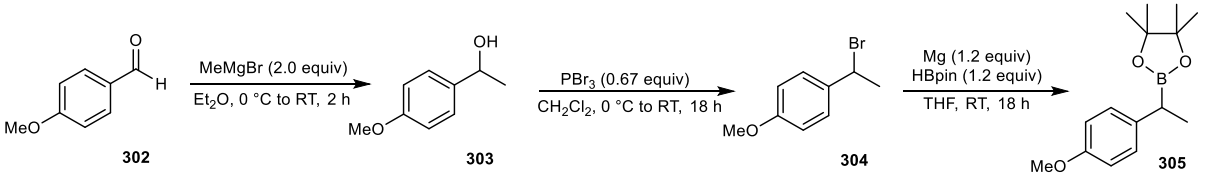
The title compound was prepared according to General Procedure **1** using CuCl (0.019 g, 0.19 mmol), *t*BuOK (0.052 g, 0.46 mmol), dppBz (0.086 g, 0.19 mmol), pinacolborane (1.33 mL, 9.2 mmol) and 1,2-dihydronaphthalene (1.0 mL, 7.68 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **301** (1.14 g, 58%) as a colourless oil. The data were consistent with the literature.[296]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-6.98 (4H, m, Ar**H**), 2.84-2.71 (2H, m, C**H$_2$**), 2.66-2.49 (1H, m, C**H**), 1.97-1.81 (3H, m, C**H$_2$**), 1.80-1.65 (1H, m, C**H$_2$**), 1.25 (6H, s, 2 × CC**H$_3$**), 1.24 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6 (C), 136.6 (C), 129.3 (CH), 129.3 (CH), 125.3 (CH), 124.7 (CH), 83.3 (2 × C), 29.7 (CH_2), 25.1 (CH_2), 24.7 (2 × CH_3), 24.6 (2 × CH_3), 22.7 (CH_2).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.6.

(±)-2-[1-(4-Methoxyphenyl)ethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (305)



302 303 304 305

Using a modification of the procedure of Peters and co-workers,[297] *p*-Anisaldehyde **302** (2.00 g, 14.7 mmol, 1.00 equiv) was dissolved in Et_2O (45 mL), cooled to 0 °C and methylmagnesium bromide (3.0 M in Et_2O, 10 mL, 29.4 mmol, 2.00 equiv) added dropwise. The mixture was stirred at room temperature for 2 h and carefully quenched with saturated aqueous NH_4Cl (25 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL), the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 1-(4-methoxyphenyl)ethanol **303**, which was used without further purification. The residue was dissolved in CH_2Cl_2 (56 mL) and the mixture was cooled to 0 °C. PBr_3 (0.92 mL, 9.83 mmol, 0.67 equiv) was added dropwise, and the mixture was stirred for 18 h at room

temperature. Water (30 mL) was added, and the organic phase was extracted with saturated aqueous $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 1-bromo-4-methoxybenzene **304**, which was used without further purification.

Using a modification of the procedure by Ley and co-workers,[298] an oven dried flask was charged with Mg (0.349 g, 14.4 mmol, 1.2 equiv) purged with argon. Anhydrous THF (30 mL) was added followed by HBpin (2.08 mL, 14.4 mmol, 1.2 equiv). A solution of 1-bromo-4-methoxybenzene **304** (2.6 g, 12.0 mmol, 1.0 equiv) in anhydrous THF (5 mL) was added dropwise over 10 min. After stirring the mixture for 18 h at room temperature it was cooled to 0 °C and acidified with HCl (25 mL, 1 M) (Caution! Hydrogen evolution). The mixture was allowed to warm to room temperature over 1 h. The mixture was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The crude material was purified by flash chromatography (5% EtOAc/hexane) to give boronic ester **305** (1.04 g, 33%) as a colourless oil. The data were consistent with the literature.[295]

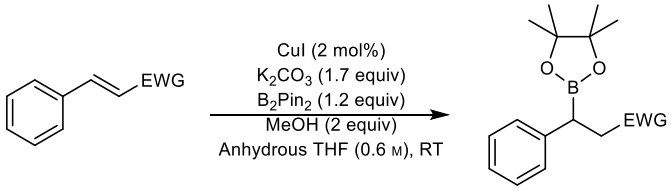
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.83 (2H, d, *J* = 8.7 Hz, Ar**H**), 3.80 (3H, s, OC**H$_3$**), 2.39 (1H, q, *J* = 7.5 Hz, C**H**), 1.31 (3H, d, *J* = 7.5 Hz, CHC**H$_3$**), 1.23 (6H, s, 2 × CC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$)**.

^{13}C NMR(101 MHz, $CDCl_3$) δ 157.2 (C), 137.0 (C), 128.6 (2 × CH), 113.7 (2 × CH), 83.2 (2 × C), 55.2 (CH_3), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 17.4 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 34.0.

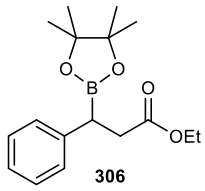
5.3.2 Cu-Catalysed 1-4 Borylation

General Procedure 2: Cu-Catalysed 1,4-Borylation of Michael Acceptors.



Using a modification of the procedure by Zeng and co-workers,[299] an oven dried flask was charged with CuI (2 mol%), K_2CO_3 (1.7 equiv) and purged with N_2. Anhydrous THF (0.6 M in total) was added, and the mixture was stirred at room temperature for 10 min. A solution of bis(pinacolato)diboron (1.2 equiv) in anhydrous THF (0.2 M) was added and the mixture was stirred for 10 min. The alkene (1 equiv) was added followed by methanol (2 equiv), and the mixture stirred at room temperature. Upon completion (as determined by TLC) the mixture

was diluted with EtOAc (40 mL), washed with brine (3 × 20 mL), dried (MgSO4), filtered, and concentrated in vacuo. The crude material was purified by flash chromatography to give the boronic ester.



306

(±)-Ethyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (306)

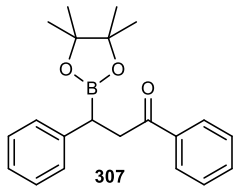
The title compound was prepared according to General Procedure **2** using CuI (0.081 g, 0.43 mmol), K_2CO_3 (5.08 g, 36.8 mmol), bis(pinacolato)diboron (6.59 g, 26.0 mmol), ethyl cinnamate (4.0 mL, 21.6 mmol), THF (35 mL) and methanol (1.38 ml), stirring for 24 h. The crude material was purified by flash chromatography (10% EtOAc/petroleum ether) to give boronic ester **306** (6.18 g, 94%) as a white solid. The data were consistent with the literature.[299]

m.p. 47-49 °C (petroleum ether). No literature value available.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.20 (4H, m, Ar**H**), 7.19-7.13 (1H, m, Ar**H**), 4.17-4.06 (2H, m, CH_3CH_2), 2.89 (1H, dd, *J* = 16.0, 9.9 Hz, CC**H$_A$**H$_B$), 2.74 (1H, dd, *J* = 9.9, 6.0 Hz, C**H**), 2.66 (1H, dd, *J* = 16.0, 6.0 Hz, CCH$_A$**H$_B$**), 1.25-1.21 (9H, m, 2 × CC**H$_3$**, CH_2C**H$_3$**), 1.18 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (C), 141.4 (C), 128.4 (2 x CH), 128.1 (2 × CH), 125.6 (CH), 83.5 (2 × C), 60.3 (CH_2), 37.3 (CH_2), 24.7 (2 × CH_3), 24.7 (2 × CH_3), 14.2 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.9.



307

(±)-1,3-Diphenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-one (307)

The title compound was prepared according to General Procedure **2** using CuI (0.081 g, 0.43 mmol), K_2CO_3 (5.08 g, 36.8 mmol), bis(pinacolato)diboron (6.59 g, 26.0 mmol), chalcone (3.16 g, 21.6 mmol), THF (35 mL) and methanol (1.38 ml), stirring for 24 h. The crude material was purified by flash chromatography (10% EtOAc/petroleum ether) to give boronic ester **307** (4.23 g, 71%) as a white solid. The data were consistent with the literature.[299]

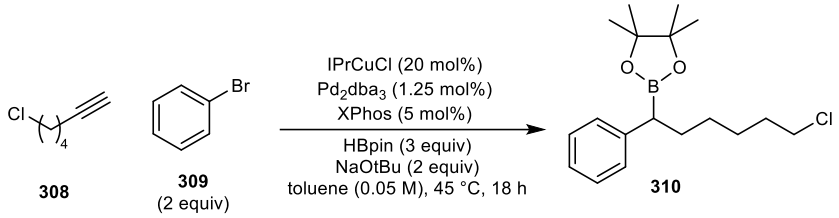
m.p. 79-81 °C (n-pentane); literature: 75-77 °C (not specified).[299]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-7.97 (2H, m, Ar**H**), 7.60-7.52 (1H, m, Ar**H**), 7.51-7.44 (2H, m, Ar**H**), 7.38-7.27 (4H, m, Ar**H**), 7.24-7.17 (1H, m, Ar**H**), 3.60 (1H, dd, *J* = 18.3, 10.9 Hz, CC**H$_A$**H$_B$), 3.46 (1H, dd, *J* = 18.3, 5.0 Hz, CCH$_A$**H$_B$**), 2.85 (1H, dd, *J* = 10.9, 5.0 Hz, C**H**), 1.29 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6 (C), 141.9 (C), 136.7 (C), 132.9 (CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.0 (2 × CH), 125.5 (CH), 83.3 (2 × C), 43.2 (CH_2), 24.5 (2 × CH_3), 24.5 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.9

2-[6-Chloro-1-(phenyl)hexyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (310)



308 **309** (2 equiv) **310**

Using a modification of the procedure by Lalic and Armstrong,[300] a Schlenk flask containing NaO^{t}Bu (0.384 g, 4.00 mmol, 2.0 equiv), IPrCuCl (0.195 g, 0.400 mmol, 0.20 equiv), was backfilled with nitrogen three times. HBpin (0.767 g, 6.00 mmol, 3.0 equiv), anhydrous toluene (40 mL, 0.05 M) and 6-chloro-1-hexyne (0.233 g, 2.00 mmol, 1.0 equiv) were added, and the mixture was stirred at 45 °C until the yellow colour disappeared (~5 mins). Pd_2dba_3 (22.9 mg, 0.025 mmol, 0.0125 equiv), XPhos (47.2 mg, 0.1 mmol, 0.025 equiv) and bromobenzene (0.628 g, 4.00 mmol, 2.0 equiv) were added, and the mixture was vigorously stirred at 45 °C for 18 h. The mixture was cooled to room temperature, diluted with Et_2O (20 mL), and washed with 1 M HCl (20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4), filtered through a pad of silica gel eluting with Et_2O, and concentrated *in vacuo*. Flash chromatography (100% hexane → 100% DCM) of the crude material gave *boronic ester* **310** (0.215 g, 33%) as a colourless oil.

IR 2978, 2932, 1371, 1321, 1142 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.19 (4H, m, Ar**H**), 7.16-7.11 (1H, m, Ar**H**), 3.50 (2H, t, *J* = 6.8 Hz, C**H$_2$**Cl), 2.30 (1H, t, *J* = 7.9 Hz, C**H**), 1.91-1.80 (1H, m, C**H$_A$**H$_B$), 1.79-1.70 (2H, m, C**H$_2$**CH$_2$Cl), 1.69-1.62 (1H, m, CH$_A$**H$_B$**), 1.49-1.39 (2H, m, C**H$_2$**), 1.33-1.28 (2H, m, C**H$_2$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.20 (6H, s, 2 × CC**H$_3$**).

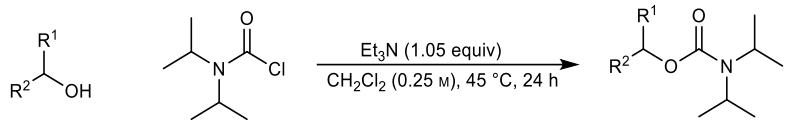
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (C), 128.4 (2 × CH), 128.3 (2 × CH), 125.2 (CH), 83.4 (2 × C), 45.2 (CH_2), 32.5 (CH_2), 32.4 (CH_2), 28.5 (CH_2), 26.9 (CH_2), 24.7 (2 × CH_3), 24.6 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 34.0.

HRMS (QTOF) Exact mass calcd for $C_{18}H_{28}{}^{11}B^{35}ClO_2$ $[M+H]^+$: 323.1994, found: 323.1959.

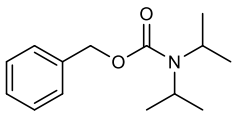
5.3.3 Preparation of Carbamates

General Procedure 3: Carbamate formation from 1° and 2° Alcohols



(1.05 equiv)

N,*N*-Diisopropylcarbamoyl chloride (1.05 equiv) was added to a mixture of corresponding alcohol (1 equiv) and Et_3N (1.05 equiv) in CH_2Cl_2 (0.25 M). The mixture was stirred at 45 °C for 24 h, cooled to room temperature, washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography to give the corresponding carbamate.



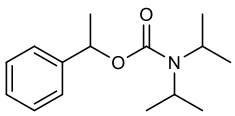
311

(±)-Benzyl *N,N*-diisopropylcarbamate (311)

The title compound was prepared according to General Procedure **3** using *N*,*N*-diisopropylcarbamoyl chloride (12.7 g, 77.7 mmol), benzyl alcohol (8.0 g, 74.0 mmol) and Et_3N (10.8 mL, 77.7 mmol). Flash chromatography (10% EtOAc/petroleum ether) of the crude material gave carbamate **311** (17.4 g, 61%) as a colourless oil. The data were consistent with the literature.[301]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.34 (4H, m, Ar**H**), 7.34-7.29 (1H, m, Ar**H**), 5.15 (2H, s, C**H$_2$**), 4.23-3.71 (2H, m, 2 × NC**H**), 1.23-1.22 (12H, m, 4 × NCHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (C), 137.1 (C), 128.4 (2 × CH), 127.9 (2 × CH), 127.7 (CH), 66.5 (CH_2), 45.8 (br, 2 × CH), 20.7 (4 × CH_3).



312

(±)-1-Phenylethyl *N,N*-diisopropyl carbamate (312)

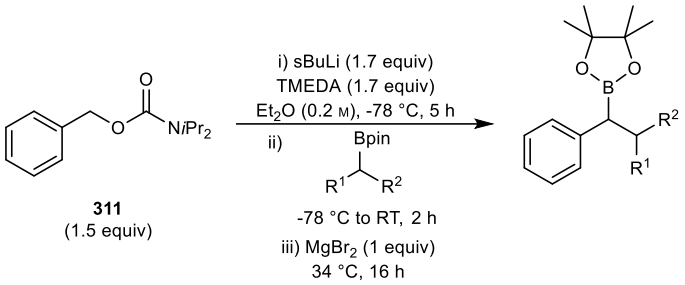
The title compound was prepared according to General Procedure **3** using *N*,*N*-diisopropylcarbamoyl chloride (4.1 g, 25 mmol), (±)-1-phenylethanol (2.9 mL, 24 mmol) and Et_3N (3.5 mL, 25 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave carbamate **312** (4.5 g, 72%) as a colourless oil. The data were consistent with the literature.[302]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.29 (4H, m, Ar**H**), 7.32-7.23 (1H, m, Ar**H**), 5.85 (1H, q, *J* = 6.6 Hz, ArC**H**), 4.26-3.62 (2H, m, 2 × NC**H**), 1.56 (3H, d, *J* = 6.6 Hz, ArCHC**H$_3$**), 1.22-1.20 (12H, m, 4 × NCHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (C), 142.8 (C), 128.4 (2 × CH), 127.4 (CH), 126.0 (2 × CH), 72.7 (CH), 46.3 (br, 2 × CH), 22.9 (CH_3), 21.4 (2 × CH_3), 20.6 (2 × CH_3).

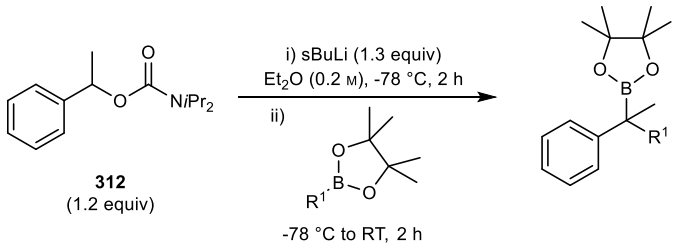
5.3.4 Lithiation Borylation Reactions

General Procedure 4: Lithiation-Borylation of Carbamate 311 with Boronic Esters



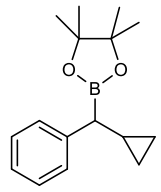
Using a modification of the procedure by Aggarwal, Crudden and co-workers,[13] a Schlenk flask containing carbamate **311** (1.5 equiv) was backfilled with nitrogen three times. TMEDA (1.7 equiv) and anhydrous Et_2O (0.2 M) were added and the mixture was cooled to –78 °C. *s*BuLi (1.7 equiv) was added dropwise and the mixture was stirred at –78 °C for 4 h. The boronic ester (1 equiv) was added dropwise, and the mixture was stirred at –78 °C for 1 h. A solution of $MgBr_2$ in Et_2O[i] (1 equiv) was added dropwise and the mixture was stirred at 34 °C for 16 h. The mixture was cooled to room temperature, and saturated aqueous NH_4Cl (20 mL) and Et_2O (15 mL) were added. The mixture was extracted with Et_2O (3 × 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The mixture was purified by flash chromatography to give the boronic ester.

General Procedure 5: Lithiation-Borylation of Carbamate 312 with Boronic Esters



Using a modification of the procedure by Aggarwal and co-workers,[303] a Schlenk flask containing carbamate **312** (1.2 equiv) was backfilled with nitrogen three times. Anhydrous Et_2O (0.2 M) was added, and the mixture was cooled to –78 °C. *s*BuLi (1.3 equiv) was added dropwise and the mixture was stirred at –78 °C for 1 h. The boronic ester (1 equiv) was added dropwise, and the mixture was stirred at –78 °C for 1 h and then at room temperature for 2 h. H_2O (20 mL) and Et_2O (15 mL) were added, and the mixture extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

i Freshly prepared before use, by the following procedure: A flask was charged with Mg turnings (1.1 equiv) and purged with N_2. Et_2O (3 mL) followed by 1,2-dibromoethane (1 equiv) were added, and the mixture was stirred at room temperature for 2 h.



120

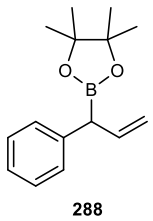
(±)-2-(Cyclopropylphenylmethyl)-4,4,5,5-tetramethyl-1,3,2- dioxaborolane (120)

The title compound was prepared according to General Procedure **4** using carbamate **311** (1.08 g, 4.59 mmol), TMEDA (0.69 mL, 4.6 mmol), *s*BuLi (1.3 M in cyclohexane, 3.6 mL, 4.6 mmol) and cyclopropyl pinacol boronic ester (0.5 mL, 2.7 mmol). Flash chromatography (1% Et_2O/petroleum ether) of the crude material gave boronic ester **120** (0.53 g, 76 %) as a colourless oil. The data were consistent with the literature.[296]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (4H, m, Ar**H**), 7.19-7.11 (1H, m, Ar**H**), 1.77-1.69 (1H, m, C**H**), 1.24 (6H, s, 2 × CC**H$_3$**), 1.23 (6H, s, 2 × CC**H$_3$**), 1.20-1.11 (1H, m, C**H**CH_2), 0.63-0.53 (1H, m, CHC**H$_2$**), 0.53-0.43 (1H, m, CHC**H$_2$**), 0.30-0.21 (1H, m, CHC**H$_2$**), 0.14-0.07 (1H, m, CHC**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (C), 128.2 (2 × CH), 128.2 (2 × CH), 125.2 (CH), 83.3 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 13.1 (CH), 5.0 (CH_2), 4.7 (CH_2).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.4.



288

(±)2-(1-Phenyl-2-propen-1-yl)-4,4,5,5-tetramethyl-1,3,2-Dioxaborolane (288)

The title compound was prepared according to General Procedure **4** using carbamate **311** (1.16 g, 4.97 mmol), TMEDA (0.74 mL, 4.97 mmol), *s*BuLi (1.3 M in cyclohexane, 3.80 mL, 4.67 mmol) and 2-vinyl boronic acid pinacol ester (0.5 mL, 2.9 mmol). Flash chromatography (2% Et_2O/petroleum ether) of the crude material gave boronic ester **288** (451 mg, 64%) as a colourless oil. The data were consistent with the literature.[304]

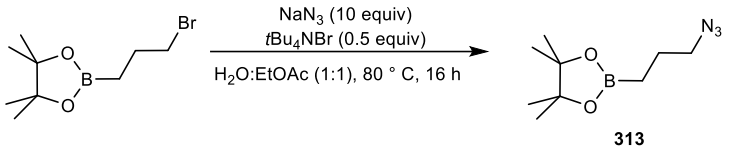
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.11 (5H, m, Ar**H**), 6.10 (1H, ddd, *J* = 17.1, 10.2, 8.2 Hz, CH_2=C**H**), 5.02-5.00 (2H, m, C**H$_2$**), 3.23 (1H, d, *J* = 8.2 Hz, ArC**H**), 1.21 (12H, s, 4 × C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (C), 138.7 (CH), 128.4 (4 × CH), 125.5 (CH), 114.5 (CH_2), 83.6 (2 × C), 24.6 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.2.

HRMS (EI) Exact mass calculated for $C_{15}H_{21}BO_2$ [M+]: 244.1634, found 244.1629.

2-(3-Azidopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (313)



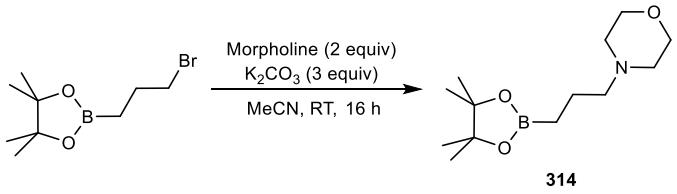
Using a modification of the procedure by Aggarwal and co-workers,[305] 2-(3-bromopropyl)- 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.1 mL, 10 mmol) was added to a mixture of sodium azide (6.5 g, 100 mmol) and tetrabutylammonium bromide (1.6 g, 5.0 mmol) in H_2O (25 mL) and EtOAc (25 mL). The mixture was stirred at 80 °C for 16 h. The mixture was cooled to room temperature, extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (100% Et_2O) to give the boronic ester **313** (2.12 g, 82%) as a colourless oil. The data were consistent with the literature.[305]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (2H, t, *J* = 7.0 Hz, C**H$_2$**N), 1.72 (2H, tt, *J* = 7.0 Hz, 7.7 Hz, C**H$_2$**CH_2N), 1.26 (12H, s, 4 × CC**H$_3$**), 0.85 (2H, t, *J* = 7.7 Hz, BC**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 83.2 (2 × C), 53.4 (CH_2), 24.8 (4 × CH_3), 23.5 (CH_2).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7.

4-[3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)propyl]morpholine (314)

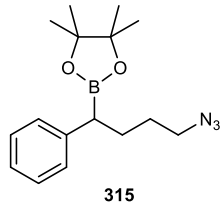


2-(3-Bromopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.84 mL, 4.0 mmol) and morpholine (0.70 mL, 8.0 mmol) was added to a mixture of K_2CO_3 (1.66 g, 12 mmol) in MeCN (10.5 mL). The mixture was stirred at room temperature for 16 h. H_2O (20 mL) was added and the mixture extracted with EtOAc (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by passing through a plug of silica eluting with Et_2O giving the boronic ester **314** (0.967 g, 95%) as a colourless oil. The data were consistent with the literature.[164]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74-3.67 (4H, m, 2 × OC**H$_2$**), 2.48-2.38 (4H, m, 2 × NC**H$_2$**), 2.34- 2.26 (2H, m, NC**H$_2$**), 1.67-1.51 (2H, m, BCH_2C**H$_2$**), 1.24 (12H, s, 4 × CC**H$_3$**), 0.81-0.71 (2H, m, BC**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 83.0 (2 × C), 67.0 (2 × CH_2), 61.4 (CH_2), 53.7 (2 × CH_2), 24.8 (2 × CH_3), 24.8 (2 × CH_3), 20.9 (CH_2).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.9.



315

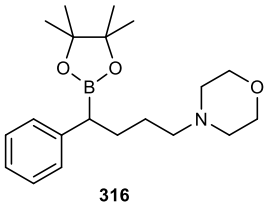
(±)-2-(4-Azido-1-phenylbutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (315)

The title compound was prepared according to General Procedure **4** using carbamate **311** (2.30 g, 9.6 mmol), TMEDA (1.62 mL, 10.85 mmol), *s*BuLi (1.3 M in cyclohexane, 9.0 mL, 10.8 mmol), and boronic ester **313** (1.35 g, 6.38 mmol). Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave boronic ester **315** (0.956 g, 50%) as a colourless oil.[164]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.24 (2H, m, Ar**H**), 7.24-7.12 (3H, m, Ar**H**), 3.27-3.21 (2H, m, C**H**$_2$$N_3$), 2.34-2.27 (1H, m, C**H**CH_2), 1.98-1.86 (1H, m, CHC**H**$_A$$H_B$), 1.78-1.69 (1H, m, $CHCH_A$**H**$_B$), 1.62-1.54 (2H, m, $CHCH_2$C**H**$_2$), 1.22 (6H, s, 2 × CC**H**$_3$), 1.20 (6H, s, 2 × CC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5 (C), 128.4 (2 × CH), 128.3 (2 × CH), 125.4 (CH), 83.4 (2 × C), 51.4 (CH_2), 29.5 (CH_2), 28.3 (CH_2), 24.6 (2 × CH_3), 24.5 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.4.



316

(±)-4-[4-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]morpholine (316)

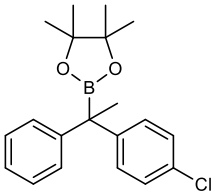
The title compound was prepared according to a modification of General Procedure **4**, using carbamate **311** (0.958 g, 4.10 mmol), TMEDA (0.614 mL, 4.1 mmol), *s*BuLi (1.3 M in cyclohexane, 3.2 mL, 4.1 mmol) and boronic ester **314** (0.800 g, 3.13 mmol). The mixture was worked up using H_2O (20 mL) and Et_2O (15 mL), instead of saturated aqueous NH_4Cl. Flash chromatography (50% EtOAc/petroleum ether) of the crude material gave boronic ester **316 (**0.674 g, 62%) as a white solid.[164]

m.p. 45-47 °C (50% EtOAc/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.22 (2H, m, Ar**H**), 7.22-7.18 (2H, m, Ar**H**), 7.15-7.10 (1H, m, Ar**H**), 3.72-3.65 (4H, m, 2 × OC**H**$_2$), 2.42-2.26 (7H, m, 3 × NC**H**$_2$ and C**H**) 1.90-1.80 (1H, m, CHC**H**$_A$$H_B$), 1.73-1.62 (1H, m, $CHCH_A$**H**$_B$), 1.50-1.41 (2H, m, NCH_2C**H**$_2$), 1.21 (6H, s, 2 × CC**H**$_3$), 1.19 (6H, s, 2 × CC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0 (C), 128.3 (2 × CH), 128.3 (2 × CH), 125.2 (CH), 83.3 (2 × C), 67.0 (2 × CH_2), 59.0 (CH_2), 53.7 (2 × CH2), 30.3 (CH_2), 26.0 (CH_2), 24.6 (2 × CH_3), 24.6 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2.



198

(±)-2-[1-(4-Chlorophenyl)-1-phenylethyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (198)

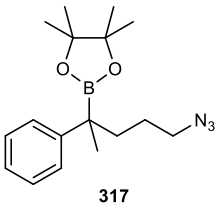
The title compound was prepared according to General Procedure **5** using carbamate **312** (2.43 g, 9.75 mmol), *s*BuLi (1.3 M in cyclohexane, 8.4 mL, 11.0 mmol) and 4-chlorophenylboronic acid pinacol ester (1.94 g, 8.13 mmol) added in Et_2O (4 mL). Flash chromatography (4% EtOAc/petroleum ether) of the crude material gave boronic ester **198** (2.07 g, 74%) as an off white solid. The data were consistent with the literature.[303]

m.p. 74-75 °C (petroleum ether); no literature value available.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (1H, m, Ar**H**), 7.26-7.15 (8H, m, Ar**H**), 1.67 (3H, s, BCC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2 (C), 146.2 (C), 131.1 (C), 129.9 (2 × CH), 128.4 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 125.6 (CH), 83.9 (2 × C), 25.7 (CH_3), 24.5 (2 × CH_3), 24.4 (2 × CH_3).

^{11}B NMR (128 MHz, CDCl3) δ 33.1.



317

(±)-2-(5-Azido-2-phenylpentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (317)

The title compound was prepared according to General Procedure **5** using carbamate **312** (2.27 g, 9.66 mmol), *s*BuLi (1.3 M in cyclohexane, 8.7 mL, 10.5 mmol) and boronic ester **313** (1.70 g, 8.05 mmol). Flash chromatography (1% EtOAc/petroleum ether) of the crude material gave boronic ester **317** (1.64 g, 65%) as a colourless oil.

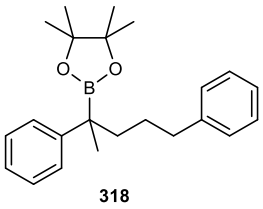
IR 2977, 2932, 2092, 1350, 1312, 1145 cm-^{1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (4H, m, Ar**H**), 7.18-7.12 (1H, m, Ar**H**), 3.25-3.17 (2H, m, C**H$_2$**N), 1.88-1.72 (2H, m, C**H$_2$**CH_2N), 1.55-1.42 (2H, m, CC**H$_2$**), 1.36 (3H, s, BCC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4 (C), 128.2 (2 × CH), 126.8 (2 × CH), 125.3 (CH), 83.5 (2 × C), 52.1 (CH_2), 36.5 (CH_2), 24.9 (CH_2), 24.6 (2 × CH_3), 24.5 (2 × CH_3), 21.3 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7.

HRMS (Q-TOF) Exact mass calcd for $C_{17}H_{26}BN_3O_2$ $[M+Na]^+$: 338.2016, found: 338.2017.



318

(±)-2-(2,5-Diphenylpentan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (318)

The title compound was prepared according to General Procedure **5** using carbamate **312** (1.00 g, 4.25 mmol), *s*BuLi (1.3 M in cyclohexane, 5.2 mL, 6.2 mmol) and 2-(1-methyl-4-phenylbutyl)- 4,4,5,5-tetramethyl-1,3,2-Dioxaborolane (0.900 g, 3.65 mmol) added. Flash chromatography (1% EtOAc/petroleum ether) of the crude material gave boronic ester **318** (0.697 g, 57%) as a colourless oil.

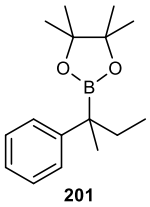
IR 2976, 2933, 2857, 1495, 1311, 1143 cm-^{1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (6H, m, Ar**H**), 7.20-7.13 (4H, m, Ar**H**), 2.68-2.56 (2H, m, ArC**H$_2$**), 1.96-1.86 (1H, m, BCC**H$_A$**H$_B$), 1.82-1.74 (1H, m, BCCH$_A$**H$_B$**), 1.61-1.53 (2H, m, ArCH$_2$C**H$_2$**), 1.36 (3H, s, BCC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2 (C), 142.8 (C), 128.3 (2 × CH), 128.2 (2 × CH), 128.0 (2 × CH), 126.8 (2 × CH), 125.5 (CH), 125.0 (CH), 83.3 (2 × C), 39.2 (CH_2), 36.7 (CH_2), 29.7 (C), 27.5 (CH_2), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 21.6 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.9.

HRMS (Q-TOF) Exact mass calcd for $C_{23}H_{35}BNO_2$ $[M+NH_4]^+$: 368.2761, found: 368.2755.



201

(±)-2-(2-Phenylbut-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (201)

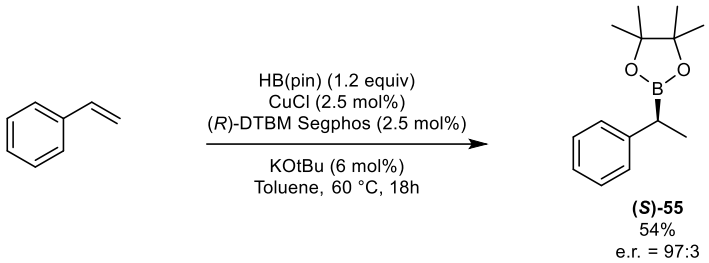
The title compound was prepared according to General Procedure **5** using carbamate **312** (1.81 g, 7.69 mmol), *s*BuLi (1.3 M in cyclohexane, 6.4 mL, 8.3 mmol) and ethylboronic acid pinacol ester (1.00 g, 6.41 mmol). Flash chromatography (4% EtOAc/petroleum ether) of the crude material gave boronic ester **201** (1.08 g, 65%) as a yellow oil. The data were consistent with the literature.[303]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (4H, m, Ar**H**), 7.17-7.11 (1H, m, Ar**H**), 1.89 (1H, dq, *J* = 14.7, 7.4 Hz, CC**H$_A$**H$_B$), 1.72 (1H, dq, *J* = 14.7, 7.4 Hz, CCH$_A$**H$_B$**), 1.34 (3H, s, BCC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 0.84 (3H, t, *J* = 7.4 Hz, CH$_2$C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3 (C), 128.0 (2 × CH), 126.9 (2 × CH), 124.9 (CH), 83.2 (2 × C), 31.9 (CH_2), 24.6 (4 × CH_3), 21.0 (CH_3), 10.0 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.7.

(*S*)-4,4,5,5-Tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane ((*S*)-55)



Following the procedure by Yun and co-workers,[39] a mixture of CuCl (20.8 mg, 0.211 mmol), KOtBu (56.7 mg, 0.506 mmol) and (*R*)-DTBM-Segphos (250.0 mg, 0.211 mmol) in anhydrous toluene (5.0 mL) was stirred for 30 min under an atmosphere of nitrogen. Pinacolborane (10.1 mmol, 1.46 mL) was added to the reaction mixture and stirred for 10 min. Styrene (8.44 mmol, 0.97 mL) was added and the mixture was stirred at 60 °C for 18 h. The reaction mixture was cooled, filtered through a pad of Celite eluting with EtOAc, and concentrated *in vacuo*. The product was purified by column chromatography (5% Et_2O/petroleum ether) to give the boronic ester (***S*)-55** (1.10 g, 54%) as a colourless oil. The data were consistent with the literature.[38]

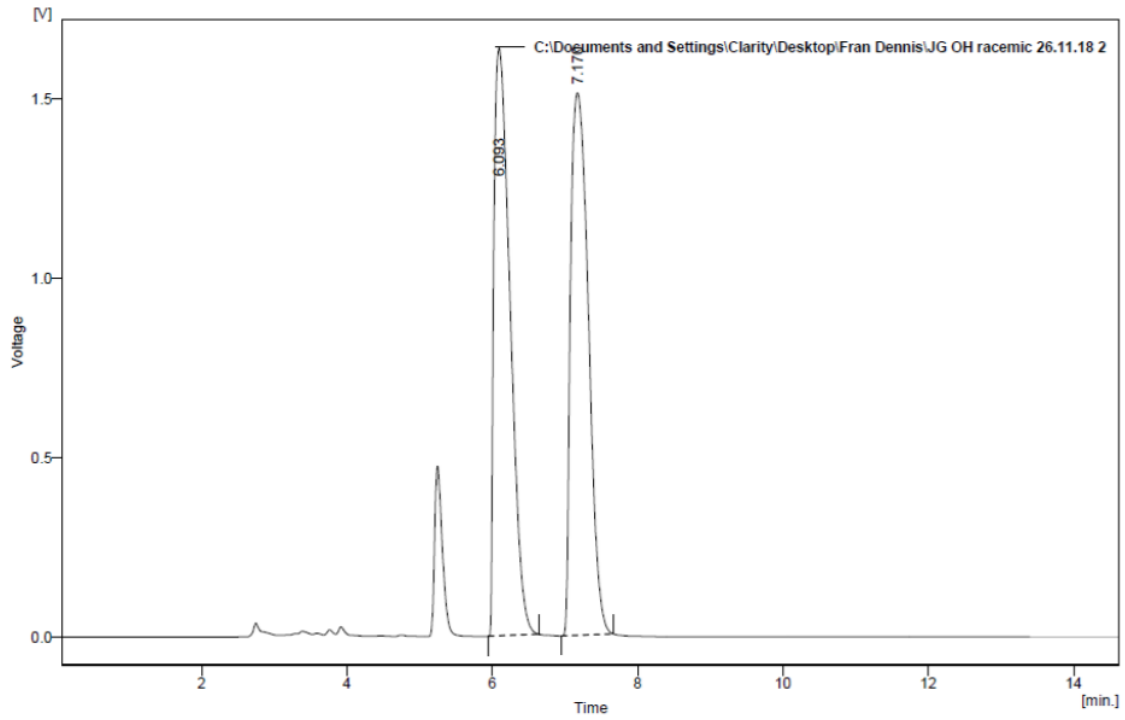
[α]$_D$ ^{21} +12.0 (c 1.00, $CHCl_3$); lit. [α]$_D$ ^{23} +11.9 (c 1.08, $CHCl_3$) 97:3 *e.r.* (*S*).[306]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.19 (4H, m, Ar**H**), 7.19-7.08 (1H, m, Ar**H**), 2.45 (1H, q, *J* = 7.5 Hz, C**H**), 1.34 (3H, d, *J* = 7.5 Hz, CHC**H$_3$**), 1.22 (6H, s, 2 × CC**H$_3$**), 1.21 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (C), 128.3 (2 × CH), 127.8 (2 × CH), 125.1 (CH), 83.3 (2 × C), 24.6 (2 × CH_3), 24.6 (2 × CH_3), 17.0 (CH_3).

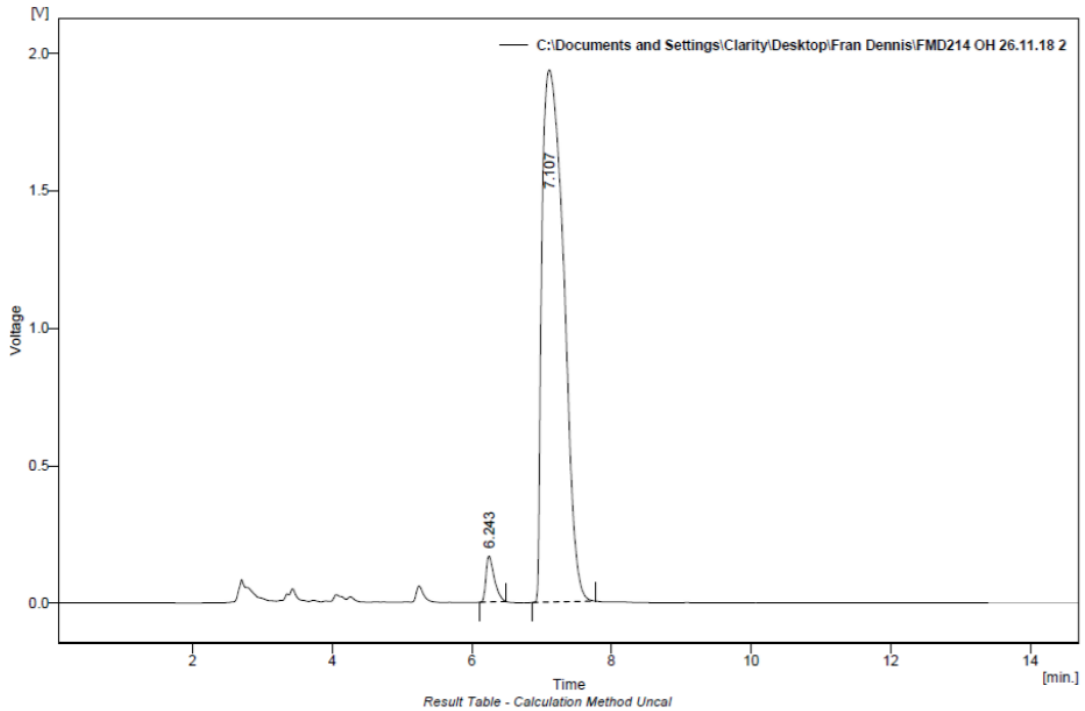
^{11}B NMR (128 MHz, $CDCl_3$) δ 33.5.

e.r. = 97:3, measured through chiral HPLC analysis of the corresponding alcohol obtained after oxidation. Phenomenex Cellulose-1 column (250 × 4.6 mm), IPA:hexane = 10:90, 1.0 mL/min, (*R*)-isomer t_r = 6.2 min and (*S*)-isomer t_r = 7.1 min.



Result Table - Calculation Method Uncal

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	6.1	25426.4	1638.4	49.7	52.0	0.26
2	7.2	25734.5	1512.2	50.3	48.0	0.28
	Total	51160.8	3150.6	100.0	100.0	

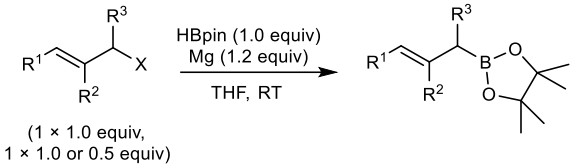


Result Table - Calculation Method Uncal

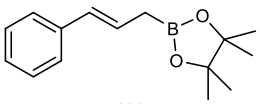
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	6.2	1395.5	167.2	3.2	8.0	0.13
2	7.1	41692.9	1935.9	96.8	92.0	0.37
	Total	43088.5	2103.2	100.0	100.0	

5.3.5 Borylation of 1° and 2° Alkyl Halides

General Procedure 6



Following the procedure by Singaram and co-workers,[22] an oven dried flask was charged with magnesium turnings (1.2 equiv) and purged with nitrogen. Anhydrous THF (0.6 M) was added followed by pinacolborane (1.0 equiv). Allyl halide (1.0 equiv) was added dropwise over 5 min at room temperature. The mixture was stirred for 1 h, and another portion of allyl halide (0.5 or 1.0 equiv) was added. After 5 h of stirring at room temperature the magnesium turnings were fully consumed. The reaction was diluted with hexanes (20 mL) and quenched with aqueous HCl (0.1 M, 60 mL) (Caution! Hydrogen evolution). The mixture was extracted with hexanes (2 × 20 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The crude material was purified by flash column chromatography to give the corresponding boronic ester.



122

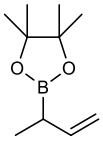
1,3,2-Dioxaborolane,4,4,5,5-tetramethyl-2[(2*E*)-3-phenyl-2-propen-1-yl] (122)

The title compound was prepared according to General Procedure **6** using Mg turnings (0.583 g, 24.0 mmol), pinacolborane (3.0 mL, 20 mmol) and cinnamyl chloride (2.8 mL, 20 mmol and 1.4 mL, 10.0 mmol, 0.5 equiv). Flash chromatography (2% Et_2O/petroleum ether) of the crude material gave boronic ester **122** (1.29 g, 26%) as a colourless oil. The data were consistent with the literature.[307]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.17 (4H, m, Ar**H**), 7.12-7.09 (1H, t, *J* = 7.2 Hz, Ar**H**), 6.30 (1H, d, *J* = 15.8 Hz, PhC**H**=C), 6.20 (1H, dt, *J* = 15.8, 7.2 Hz, PhC=C**H**), 1.86 (2H, d, *J* = 7.2 Hz, C**H$_2$**), 1.24 (12H, s, 4 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (C), 130.2 (CH), 128.4 (2 × CH), 126.5 (CH), 126.3 (CH), 125.8 (2 × CH), 83.4 (2 × C), 24.8 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.9.



288

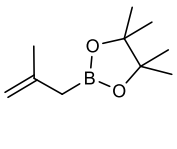
(±)1,3,2-Dioxaborolane,4,4,5,5-tetramethyl-2-(1-methyl-2-propen-1-yl)- (288)

The title compound was prepared according to General Procedure **6** using Mg turnings (0.516 g, 21.2 mmol), pinacolborane (2.5 mL, 17.7 mmol) and crotyl bromide (1.5 mL, 17.7 mmol, 1.0 equiv × 2). Flash chromatography (2% Et_2O/petroleum ether) of the crude material gave boronic ester **288** (1.60 g, 59%) as a colourless oil. The data were consistent with the literature.[24]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (1H, ddd, *J* = 17.3, 10.3, 7.1 Hz, C=C**H**), 4.96 (1H, dt, *J* = 17.3, 1.7 Hz, C=C**H$_A$**H$_B$), 4.91 (1H, dt, *J* = 10.3, 1.7 Hz, C=CH$_A$**H$_B$**), 1.97-1.81 (1H, m, C**H**), 1.23 (12H, s, 4 × CC**H$_3$**), 1.08 (3H, d, *J* = 5.8 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (CH), 111.9 (CH_2), 83.1 (2 × C), 24.6 (4 × CH_3), 14.0 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.2.



128

4,4,5,5-Tetramethyl-2-(2-methallyl)-1,3,2-dioxaborolane (128)

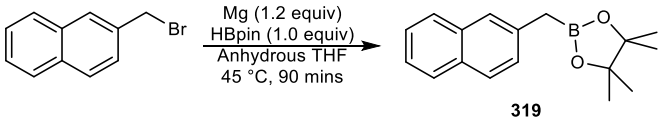
The title compound was prepared according to General Procedure **6** using Mg turnings (0.583 g, 24.0 mmol), pinacolborane (3.0 mL, 20.0 mmol) and 3-Chloro-2-methyl-1-propene (2.0 mL, 20.0 mmol, 1.0 equiv × 2). Flash chromatography (2% Et_2O/petroleum ether) of the crude material gave boronic ester **128** (1.02 g, 27%) as a colourless oil. The data were consistent with the literature.[308]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (2H, d, *J* = 7.2 Hz, C=C**H$_2$**), 1.76 (3H, s, CH_2=CC**H$_3$**), 1.71 (2H, s, BC**H$_2$**), 1.24 (12H, s, 4 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9 (C), 110.2 (CH_2), 83.2 (2 × C), 24.7 (4 × CH_3), 24.5 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.7.

4,4,5,5-Tetramethyl-2-(naphthalen-2-ylmethyl)-1,3,2-dioxaborolane (319)



319

An oven dried two-neck flask fitted with a condenser was charged with magnesium turnings (0.121 g, 4.98 mmol) and purged with argon. Anhydrous THF (15 mL) was added followed by pinacolborane (0.722 ml, 4.2 mmol). 1-Bromo-3-phenylpropane (0.65 ml, 4.52 mmol) was added dropwise over 5 min and the mixture was stirred at 25 °C. After 30 min

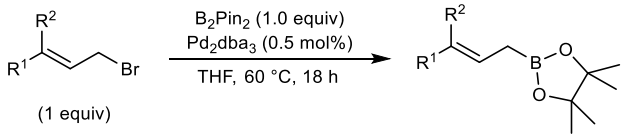
1-bromo-3- phenylpropane (1.0 g, 4.52 mmol) was added and the mixture heated at 45 °C for 90 min. The mixture was cooled to room temperature, diluted with hexane, and quenched with aqueous HCl (0.1 M, 10 mL). The mixture was separated and the organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (10%EtOAc/petroleum ether) to give the boronic ester **319** (1.01 g, 83%) as a colourless oil. The data were consistent with the literature.[309]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (2H, m, Ar**H**), 7.21-7.14 (3H, m, Ar**H**), 2.65-2.58 (2H, m, ArC**H$_2$**), 1.79-1.69 (2H, m, C**H$_2$**), 1.25 (12H, s, 4 x CC**H$_3$**), 0.87-0.81 (2H, m, BC**H$_2$**).

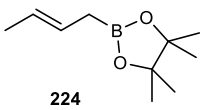
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7 (C), 128.5 (2 × CH), 128.1 (2 × CH), 125.5 (CH), 82.9 (2 × C), 38.6 (CH_2), 26.1 (CH_2), 24.8 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 34.0.

General Procedure 7



Following the procedure by Morken and co-workers,[310] a flask containing $Pd_2(dba)_3$ (5 mol%) and bis(pinacolto)diboron (1.0 equiv) was purged with nitrogen and charged with anhydrous THF (7 mL) followed by the corresponding allyl bromide (1.0 equiv). The mixture was stirred at 60 °C for 18 h, cooled to room temperature, concentrated in *vacuo* and purified by flash column chromatography on silica gel to give the corresponding boronic ester.



224

1,3,2-Dioxaborolane, 2-(2*E*)-2-buten-1-yl-4,4,5,5-tetramethyl- (224)

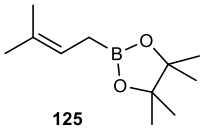
The title compound was prepared according to General Procedure **7** using $Pd_2(dba)_3$ (66.3 mg, 0.075 mmol), bis(pinacolto)diboron (3.80 g, 15.0 mmol) and crotyl bromide (1.50 mL, 15.0 mmol). Flash chromatography (2% Et_2O/petroleum ether) of the crude material gave boronic ester **224** (905 mg, 34%) as a colourless oil. The data were consistent with the literature.[307]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57-5.40 (2H, m, **H**C=C**H**), 1.67-1.65 (3H, m, C**H$_3$**), 1.62-1.60 (2H, m, C**H$_2$**), 1.24 (12, s, 4 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ *E* isomer: 125.9 (CH), 125.3 (CH), 83.1 (2 × C), 24.8 (4 × CH_3), 18.1 (CH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ *Z* isomer: 125.0 (CH), 123.8 (CH), 14.3 (CH_3)

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.7.



125

4,4,5,5-Tetramethyl-2-(3-methyl-2-buten-1-yl)-1,3,2-dioxaborolane (125)

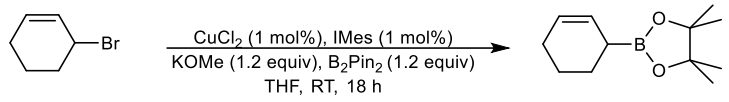
The title compound was prepared according to General Procedure **7** using $Pd_2(dba)_3$ (24.3 mg, 0.027 mmol), bis(pinacolto)diboron (1.34 g, 5.30 mmol) and by 1-bromo-3-methyl-2-butene (0.9 mL, 5.3 mmol). Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave boronic ester **125** (699 mg, 67%) as a colourless oil. The data were consistent with the literature.[311]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (1H, ddd, *J* = 7.6, 4.7, 1.5 Hz, C**H**), 1.70 (3H, s, C**H$_3$**), 1.60 (5H, m, C**H$_3$** and C**H$_2$**), 1.25 (12H, m, 4 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 131.5 (C), 118.5 (CH), 83.1 (2 × C), 25.7 (CH_3), 24.8 (4 × CH_3), 17.6 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.8.

(±)2-(Cyclohex-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-Dioxaborolane (284)



(1 equiv) **284**

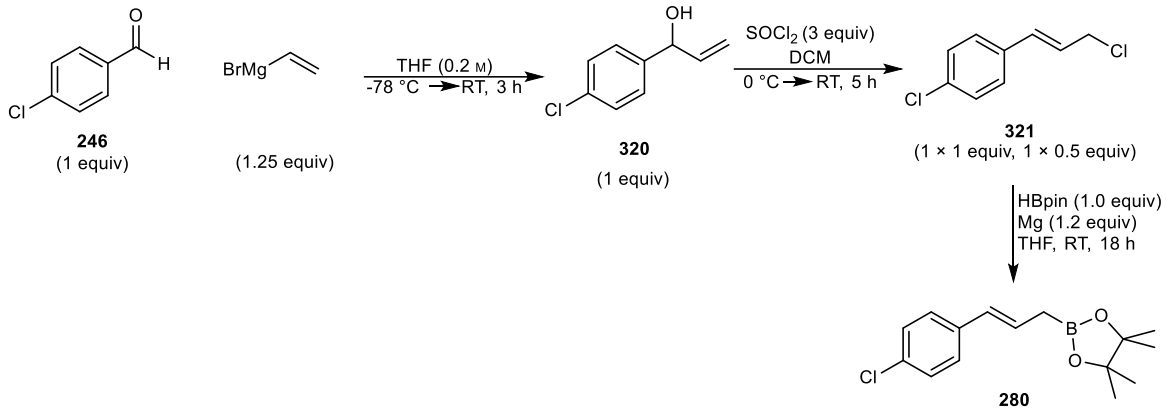
Following the procedure by Marder and co-workers,[312] a flask containing $CuCl_2$ (8.0 mg, 0.06 mmol), IMes (20.0 mg, 0.06 mmol) was purged with nitrogen and anhydrous THF (12 mL) was added and stirred for 10 min. B_2Pin_2 (1.83 g, 7.2 mmol) and KOMe (252 mg, 3.60 mmol) were added and the mixture was stirred for 10 min. 3-Bromocyclohexene (0.69 mL, 6.0 mmol) was added and the mixture was stirred vigorously for 18 h. The mixture was diluted with Et_2O (20 mL) and filtered through a plug of celite eluting with Et_2O and concentrated in *vacuo*. The crude material was purified by flash column chromatography on silica gel (5% Et_2O/petrol), to give boronic ester **284** (844 mg, 68%) as a colourless oil. The data were consistent with the literature.[312]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86-5.56 (2H, m, **H**C=C**H**), 2.11-1.94 (2H, m, C**H$_2$**), 1.87-1.72 (2H, m, C**H$_2$**), 1.71-1.54 (3H, m, C**H$_2$**C**H**), 1.24 (12H, s, 4 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 127.6 (C=CH), 126.1 (C=CH), 83.1 (2 × C), 25.0 (CH_2), 24.8 (2 × CH_3), 24.7 (2 × CH_3), 24.1 (CH_2), 22.5 (CH_2).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.4.

4,4,5,5-Tetramethyl-2-[(2E)-3-(4-chlorophenyl)prop-2-en-1-yl]-1,3,2-Dioxaborolane (280)



Following the procedure by Morken and co-workers,[313] an oven-dried flask containing aldehyde (2.00 g, 14.0 mmol), was purged with nitrogen and anhydrous THF (70 mL) was added and the mixture was cooled to −78 °C. Vinyl magnesium bromide (25 mL, 17.0 mmol) was added and the mixture was warmed to room temperature and stirred for 3 h. Saturated aqueous ammonium chloride (40 mL) was added, and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give alcohol **320** (2.40 g, 100%) as an orange oil. The material was used without further purification.

An oven-dried round bottom flask containing allyl alcohol (1.00 g, 6.00 mmol) was purged with nitrogen and CH_2Cl_2 (10 mL) was added and the mixture was cooled to 0 °C. $SOCl_2$ (1.29 mL, 17.9 mmol) was added and the mixture was stirred at 0 °C for 3 h and then at room temperature for 2 h. The mixture was quenched with ice water (30 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give allyl chloride **321** (1.11 g, 100%) as a brown solid. The material was used without further purification.

Following the procedure by Singaram and co-workers,[22] a round bottom flask containing magnesium turnings (127 mg, 5.29 mmol) was purged with nitrogen. Anhydrous THF (15 mL) was added followed by pinacolborane (0.6 mL, 4.40 mmol). Allyl chloride (0.83 g, 4.4 mmol) was added dropwise over 5 min at room temperature. The mixture was stirred for 1 h and allyl chloride (0.41 g, 2.2 mmol) was added. After stirring at room temperature for 18 h the magnesium turnings were fully consumed. The mixture was diluted with hexanes (10 mL) and quenched with aqueous HCl (0.1 M, 30 mL) (Caution! Hydrogen evolution). The mixture was extracted with hexane (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash column

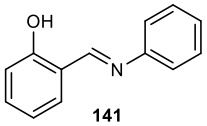
chromatography on silica gel (2% Et_2O/petroleum ether) to give boronic ester **280** (94.4 mg, 5%) as a pale yellow oil. The data were consistent with the literature.[314]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.20 (4H, m, Ar**H**), 6.29-6.26 (2H, m, **H**C=C**H**), 1.86 (2H, d, *J* = 6.5 Hz, C**H$_2$**), 1.23 (12H, s, 4 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6 (C), 132.0 (C), 129.1 (CH), 128.5 (2 × CH), 127.1 (2 × CH), 127.0 (CH), 83.5 (2 × C), 24.8 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 32.7.

5.3.6 Synthesis of Ligands and Miscellaneous Compounds



141

2-[(Phenylimino)methyl]phenol (141)

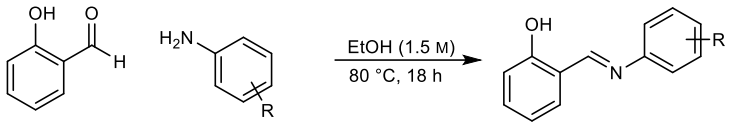
Using a modification of the procedure by Repo and co-workers,[315] 2-hydroxybenzaldehyde (3.2 mL, 30 mmol) and aniline (2.7 mL, 30 mmol) were dissolved in MeOH (15 mL) and stirred at room temperature for 18 h. The mixture was concentrated to half volume *in vacuo*. Petroleum ether (10 mL) was added and a yellow precipitate formed, the solid was filtered, washed with petroleum ether and vacuum dried and gave imine **141** (5.01 g, 85%) as a yellow solid. The data were consistent with the literature.[316]

m.p. 59-60 °C (petroleum ether). Literature 46-48 °C (H_2O).[317]

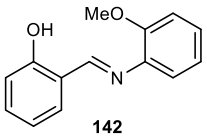
^{1}H NMR (400 MHz, $CDCl_3$) δ 13.26 (1H, s, O**H**), 8.64 (1H, s, C**H**=N), 7.497-7.36 (4H, m, Ar**H**), 7.33-7.27 (3H, m, Ar**H**), 7.06-7.03 (1H, m, Ar**H**), 6.98-6.93 (1H, m, Ar**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7 (CH), 161.1 (C), 148.5 (C), 133.1 (CH), 132.3 (CH), 129.4 (2 × CH), 126.9 (CH), 121.2 (2 × CH), 119.2 (C), 119.0 (CH), 117.3 (CH).

General Procedure 8



Using a modification of the procedure by Biswas and co-workers,[318] 2-hydroxybenzaldehyde (1.0 equiv) and aniline derivative (1.0 equiv) were dissolved in EtOH (1.5 M) and heated to reflux for 18 h. The mixture was cooled to room temperature and concentrated *in vacuo.* The crude material was purified by recyrystallisation.



142

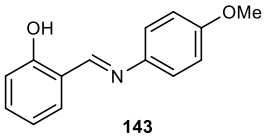
2-[2-Methoxyphenylimino)methyl]phenol (142)

The title compound was prepared according to General Procedure **8** using 2-hydroxybenzaldehyde (0.63 mL, 6.0 mmol) and *o*-anisidine (0.68 mL, 6.0 mmol) heating for 18 h. Recrystallisation of the crude material from EtOH (10 mL) gave imine **142** (0.303 g, 22%) as a yellow solid. The data were consistent with the literature.[319]

m.p. 64-65 °C (EtOH). No literature value available.[319]

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.85 (1H, s, O**H**), 8.72 (1H, s, C**H**=N), 7.42-7.34 (2H, m, Ar**H**), 7.28-7.21 (2H, m, Ar**H**), 7.06-6.98 (3H, m, Ar**H**), 6.96-6.91 (1H, m, Ar**H**), 3.91 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (CH), 161.6 (2 × C), 153.0 (C), 132.9 (CH), 132.0 (CH), 127.9 (CH), 121.0 (CH), 119.7 (CH), 119.5 (C), 118.7 (CH), 117.4 (CH), 111.9 (CH), 55.9 (CH_3).



143

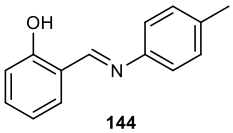
2-[(4-Methoxyphenylimino)methyl]phenol (143)

The title compound was prepared according to General Procedure **8** using 2-hydroxybenzaldehyde (0.63 mL, 6.0 mmol) and *p*-anisidine (0.74 g, 6.0 mmol) heating for 18 h. Recrystallisation of the crude material from EtOH (10 mL) gave imine **143** (0.761 g, 56%) as a pale green solid. The data were consistent with the literature.[320]

m.p. 91-92 °C (EtOH). Literature 76–77 °C (no solvent given).[321]

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.45 (1H, s, O**H**), 8.63 (1H, s, C**H**=N), 7.42-7.34 (2H, m, Ar**H**), 7.32-7.27 (2H, m, Ar**H**), 7.06-7.00 (2H, m, Ar**H**), 6.98-6.92 (2H, m, Ar**H**), 3.86 (3H, s, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9 (C), 160.4 (CH), 158.8 (C), 141.4 (C), 132.7 (CH), 131.9 (CH), 122.3 (2 × CH), 119.4 (C) 119.0 (CH), 117.1 (CH), 114.6 (2 × CH), 55.5 (CH_3).



144

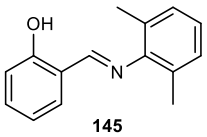
2-[(4-Methylphenylimino)methyl]phenol (144)

The title compound was prepared according to General Procedure **8** using 2-hydroxybenzaldehyde (0.63 mL, 6.0 mmol) and *p*-toluidine (0.64 g, 6.0 mmol) heating for 18 h. Recrystallisation of the crude material from EtOH (10 mL) gave imine **144** (0.561 g, 44%) as a yellow solid. The data were consistent with the literature.[322]

m.p. 100-101 °C (EtOH). Literature 91-93 °C (EtOH).[174]

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.39 (1H, s, O**H**), 8.64 (1H, s, C**H**=N), 7.42-7.36 (2H, m, Ar**H**), 7.26-7.19 (4H, m, Ar**H**), 7.05-7.01 (1H, m, Ar**H**), 6.97-6.92 (1H, m, Ar**H**), 2.40 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7 (CH), 161.1 (C), 145.9 (C), 136.9 (C), 132.9 (CH), 132.1 (CH), 130.0 (2 × CH), 121.0 (2 × CH), 119.3 (C), 119.0 (CH), 117.2 (CH), 21.1 (CH_3).



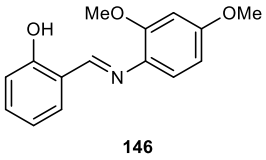
145

2-[(2,6-Dimethylphenylimino)methyl]phenol (145)

The title compound was prepared according to General Procedure **8** using 2-hydroxybenzaldehyde (0.63 mL, 6.0 mmol) and 2,6-Dimethylaniline (0.74 mL, 6.0 mmol) heating for 18 h. Recrystallisation of the crude material from EtOH (10 mL) gave imine **145** (1.31 g, 97%) as a yellow solid. The data were consistent with the literature.[323]

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.09 (1H, s, O**H**), 8.35 (1H, s, C**H**=N), 7.45-7.34 (2H, m, Ar**H**), 7.14-6.94 (5H, m, Ar**H**), 2.22 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (CH), 161.3 (C), 148.2 (C), 134.9 (C), 133.2 (CH), 132.2, 128.3 (3 × CH), 128.3 (C), 124.9 (CH), 118.9 (CH), 118.8 (C), 117.3 (CH), 18.5 (2 × CH_3).



146

2-[(2,4-Dimethoxylphenylimino)methyl]phenol (146)

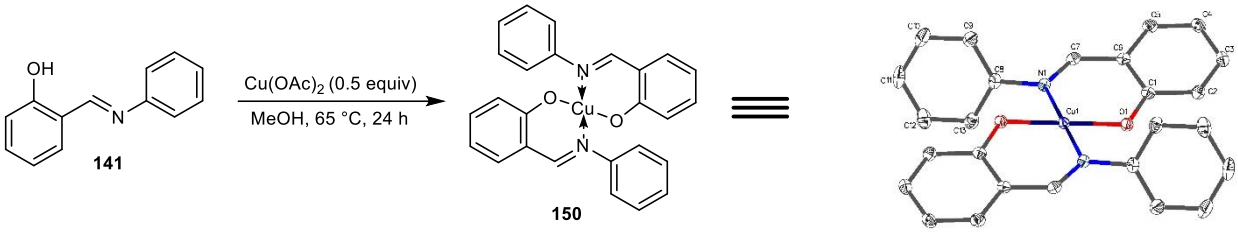
The title compound was prepared according to General Procedure **8** using 2-hydroxybenzaldehyde (0.63 mL, 6.0 mmol) and 2,4-Dimethoxyylaniline (0.85 mL, 6.0 mmol) heating for 18 h. Recrystallisation of the crude material from EtOH (10 mL) gave *imine* **146** (1.53 g, 99%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 14.07 (1H, s, O**H**), 8.72 (1H, s, C**H**=N), 7.38-7.31 (2H, m, Ar**H**), 7.24-7.20 (1H, m, Ar**H**), 7.03-6.99 (1H, m, Ar**H**), 6.94-6.88 (1H, m, Ar**H**), 6.57-6.51 (2H, m, Ar**H**), 3.90 (3H, s, C**H$_3$**), 3.86 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4 (C), 159.9 (C), 159.6 (CH), 153.5 (C), 138.8 (C), 132.4 (CH), 131.6 (CH), 119.8 (CH), 119.6 (C) 118.6 (CH), 117.3 (CH), 104.6 (CH), 99.5 (CH), 55.9 (CH_3), 55.6 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{15}H_{15}NO_3$ $[M+H]^+$: 258.1125, found: 258.1133.

Bis[*N*-(phenyl)-salicyladiminato] copper (II) synthesis (150)



Using a modification of the procedure by Nordlander and co-workers,[182] an oven dried flask was charged with copper acetate (0.596 g, 3.3 mmol, 0.5 equiv) and phenol **141** (1.30 g, 6.60 mmol, 1.0 equiv) and purged with N_2, methanol (20 mL) was added. The resulting mixture was stirred at reflux for 24 h. During this time a solid precipitated from solution. The reaction mixture was cooled to 0 °C for approximately 15 min and the solid isolated by vacuum filtration. Recrystallisation of the crude material by slow diffusion of ethanol into a concentrated dichloromethane solution of the complex at −4 °C gave complex **150** (847 mg, 56%) as a green solid.

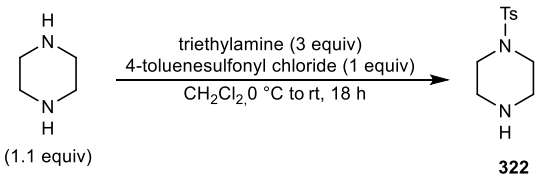
IR 3027, 1606, 1467, 1446, 1328 cm^{-1}.

m.p. 250-251 °C (EtOH). Literature 239-242 °C (EtOH).[317]

HRMS (ES^+) Exact mass calcd for $[C_{26}H_{20}N_2O_2Cu]$ + $[M+Na]^+$: 478.0718, found: 478.0717.

X-ray Crystallography Data for $C_{26}H_{20}CuN_2O_2$ (M =455.98 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 11.7458(5) Å, b = 7.5907(3) Å, c = 12.3991(5) Å, β = 110.910(2)°, V = 1032.68(7) $Å^3$, Z = 2, T = 100.0 K, μ(CuKα) = 1.699 mm^{-1}, *Dcalc* = 1.466 g/cm^3, 14561 reflections measured (8.906° ≤ 2Θ ≤ 133.288°), 1821 unique (R_{int} = 0.0259, R_{sigma} = 0.0141) which were used in all calculations. The final R_1 was 0.0252 (I > 2σ(I)) and wR_2 was 0.0700 (all data).

1-Tosylpiperazine (322)



Using a modification of the procedure by Kamal and co-workers,[324] triethylamine (22.0 mL, 158 mmol, 3 equiv) was added dropwise to a solution of piperazine (5.0 g, 58 mmol, 1.1 equiv) in CH_2Cl_2 (58 mL) at 0 °C. Toluene sulfonyl chloride (10.0 g, 52.8 mmol, 1 equiv)

was added, and the mixture was stirred overnight at room temperature. The mixture was quenched with H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give 1-tosylpiperazine **322** (5.0 g, 40%) as a white solid. The data were consistent with literature.[325]

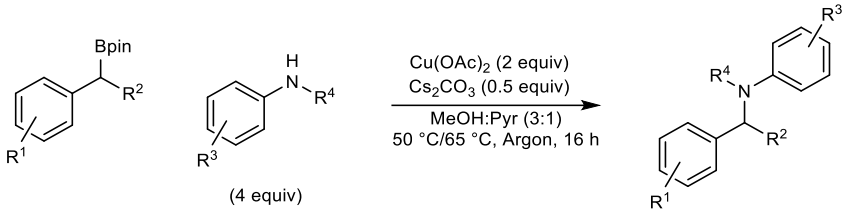
m.p. 101-103 °C (CH_2Cl_2). Literature 96.2-97.1 °C (EtOAc).[325]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.33 (2H, d, *J* = 7.2 Hz, Ar**H**), 3.01-2.91 (8H, m, 4 × C**H$_2$**), 2.47 (3H, s, C**H$_3$**), 1.59 (1H, br s, N**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6 (C), 132.7 (C), 129.6 (2 × CH), 127.8 (2 × CH), 46.8 (2 × CH), 45.3 (2 × CH), 21.5 (CH_3).

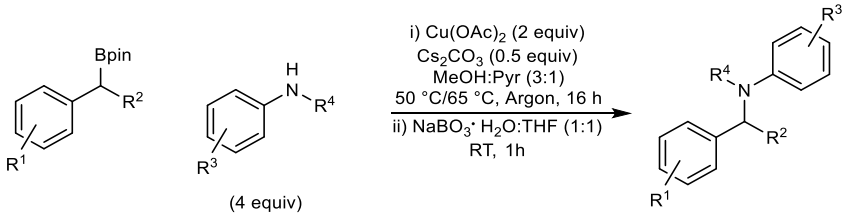
5.4 Cu-mediated C-N Bond Formation with Anilines

General Procedure 9: Cu-Mediated Coupling of N-Nucleophiles and Alkylboronic Acid Pinacol Esters.



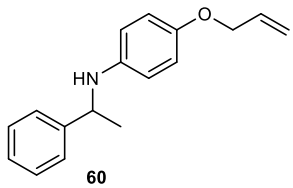
A flask containing the corresponding boronic ester (0.50 mmol, 1 equiv), aniline (2.00 mmol, 4 equiv), $Cu(OAc)_2$ (0.182 g, 1.00 mmol) and Cs_2CO_3 (0.0820 g, 0.252 mmol) was purged with argon. Methanol (1.0 mL) and pyridine (0.33 mL) were added, and the mixture was stirred at 50 °C or 65 °C until the reaction was complete (as determined by TLC). The mixture was cooled to room temperature, NH_4OH (10 % w/v, 10 mL) was added, and the mixture was extracted with Et_2O (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by column chromatography.

General Procedure 10: Cu-Mediated Coupling of N-Nucleophiles and Alkylboronic Acid Pinacol Esters with an Oxidative Workup.



A flask containing the corresponding boronic ester (0.50 mmol, 1 equiv), aniline (2.00 mmol, 4 equiv), $Cu(OAc)_2$ (0.182 g, 1.00 mmol) and Cs_2CO_3 (0.082 g, 0.25 mmol) was purged with argon. Methanol (1.0 mL) and pyridine (0.33 mL) were added, and the mixture was stirred at 50 °C or 65 °C until the reaction was complete (as determined by TLC). The mixture was cooled to room temperature, NH_4OH (10 % w/v, 10 mL) was added, and the mixture was extracted with Et_2O (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. THF (1 mL), H_2O (1 mL) and sodium perborate (0.382 g, 2.50 mmol) were added, and the mixture stirred at room temperature for 1 h. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by column chromatography.

5.4.1 Scope with Respect to Amine for the Amination of Boronic Ester 55



60

(±)-*N*-(1-Phenylethyl)-4-(prop-2-en-1-yloxy)aniline (60)

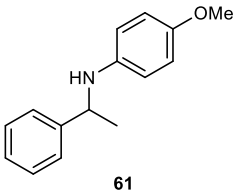
The title compound was prepared according to General Procedure **10** using boronic ester **55** (0.116 g, 0.500 mmol) and 4-amino phenyl allyl ether (0.299 g, 2.00 mmol), heating at 50 ºC for 48 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave *amine* **60** (86 mg, 68%) as a yellow oil.

IR 3404, 3025, 2866, 1508, 1229 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (2H, m, Ar**H**), 7.36-7.30 (2H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 6.72 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.47 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.03 (1H, ddt, *J* = 17.2, 10.6, 5.4 Hz, C**H**=CH_2), 5.37 (1H, dd, *J* = 17.2, 1.5 Hz, CH=C**H$_A$**H$_B$), 5.24 (1H, dd, *J* = 10.6, 1.5 Hz, CH=CH_A**H$_B$**), 4.46-4.39 (3H, m, NC**H**, OC**H$_2$**), 3.80 (1H, s, N**H**), 1.51 (3H, d, *J* = 6.7 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8 (C), 145.4 (C), 141.7 (C), 133.9 (CH), 128.6 (2 × CH), 126.8 (CH), 125.9 (2 × CH), 117.3 (CH_2), 115.8 (2 × CH), 114.4 (2 × CH), 69.6 (CH_2), 54.2 (CH), 25.1 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{17}H_{20}NO$ $[M+H]^+$: 254.1545, found: 254.1539.



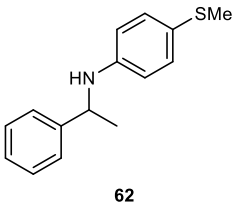
61

(±)-4-Methoxy-*N*-(1-phenylethyl)aniline (61)

The title compound was prepared according to General Procedure **10** using boronic ester **55** (0.116 g, 0.501 mmol) and *p*-anisidine (0.246 g, 2.00 mmol) heating at 50 ºC for 16 h. Flash chromatography (4% EtOAc/petroleum ether) of the crude material gave amine **61** (82 mg, 72%) as a yellow oil. The data were consistent with the literature.[326]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.39 (2H, m, Ar**H**), 7.39-7.33 (2H, m, Ar**H**), 7.39-7.33 (1H, m, Ar**H**), 6.75 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.52 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.46 (1H, q, *J* = 6.7 Hz, C**H**), 3.82 (1H, s, N**H**), 3.74 (3H, s, OC**H$_3$**), 1.54 (3H, d, *J* = 6.7 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8 (C), 145.4 (C), 141.5 (C), 128.5 (2 × CH), 126.8 (CH), 125.8 (2 × CH), 114.7 (2 × CH), 114.5 (2 × CH), 55.7 (CH_3), 54.2 (CH), 25.1 (CH_3).



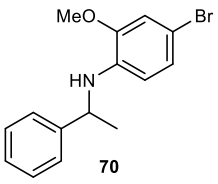
62

(±)-4-(Methylthio)-*N*-(1-phenylethyl)aniline (62)

The title compound was prepared according to General Procedure **9** using boronic ester **55** (0.115 g, 0.495 mmol), 4-(methylthio)aniline (0.25 mL, 2.0 mmol), heating at 50 ºC for 16 h. Flash chromatography (5% EtOAc/petroleum ether) of the crude material gave amine **62** (74 mg, 62%) as a brown oil. The data were consistent with the literature.[327]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.20 (4H, m, Ar**H**), 7.17-7.12 (1H, m, Ar**H**), 7.04 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.37 (2H, d, *J* = 8.7 Hz, Ar**H**), 4.37 (1H, q, *J* = 6.7 Hz, NC**H**), 3.96 (1H, s, N**H**), 2.27 (3H, s, SC**H$_3$**), 1.42 (3H, d, *J* = 6.7 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1 (C), 144.9 (C), 131.3 (2 × CH), 128.7 (2 × CH), 126.9 (CH), 125.8 (2 × CH), 124.0 (C), 113.8 (2 × CH), 53.5 (CH), 25.0 (CH_3), 19.1 (CH_3).



70

(±)-4-Bromo-2-methoxy-*N*-(1-phenylethyl)aniline (70)

The title compound was prepared according to General Procedure **10** using boronic ester **55** (0.119 g, 0.514 mmol) and 4-Bromo-2-methoxyaniline (0.409 g, 2.02 mmol), heating at 50 ºC for 16 h. Flash chromatography (2% EtOAc/petroleum ether) of the crude material gave *amine* **70** (84 mg, 54%) as a light brown solid.

m.p. 95-97°C

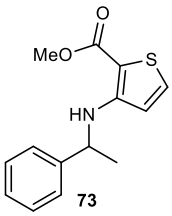
IR 3425, 2963, 2933, 1590, 1506, 1223 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (4H, m, Ar**H**), 7.26-7.20 (1H, m, Ar**H**), 6.85 (1H, d,

J = 2.1 Hz, Ar**H**), 6.79 (1H, dd, *J* = 8.4, 2.1 Hz, Ar**H**), 6.17 (1H, d, *J* = 8.4 Hz, Ar**H**), 4.60 (1H, s, N**H**), 4.49-4.39 (1H, m, C**H**), 3.88 (3H, s, OC**H**$_3$), 1.55 (3H, d, *J* = 6.7 Hz, CHC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1 (C), 144.8 (C), 136.2 (C), 128.6 (2 × CH), 126.9 (CH), 125.7 (2 × CH), 123.6 (CH), 112.6 (CH), 111.8 (CH), 107.7 (C), 55.7 (CH_3), 53.2 (CH), 25.1 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{15}H_{18}{}^{79}BrNO$ $[M+H]^+$: 306.0494, found: 306.0488.



73

(±)-Methyl 3-[(1-phenylethyl)amino]thiophene-2-carboxylate (73)

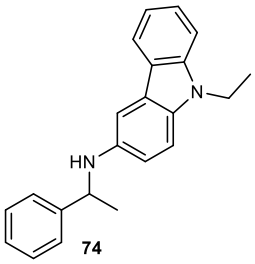
The title compound was prepared according to General Procedure **10** using boronic ester **55** (0.117 g, 0.504 mmol) and methyl 3-amino-2-thiophenecarboxylate (0.316 g, 2.01 mmol), heating at 65 ºC for 48 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave *amine* **73** (60 mg, 45%) as a yellow oil.

IR 3364, 2950, 1663, 1566, 1246 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.32 (4H, m, Ar**H**), 7.25-7.23 (1H, m, Ar**H**), 7.19-7.18 (1H, d, *J* = 5.4 Hz, Ar**H**), 6.36 (1H, d, *J* = 5.4 Hz, Ar**H**), 4.60 (1H, p, *J* = 6.8 Hz, NHC**H**), 3.86 (3H, s, OC**H**$_3$), 1.58 (3H, d, *J* = 6.8 Hz, CHC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5 (C), 155.4 (C), 144.9 (C), 132.0 (CH), 128.7 (2 × CH), 127.1 (CH), 125.7 (2 × CH), 117.2 (CH), 98.9 (C), 54.8 (CH_3), 51.1 (CH), 24.9 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{14}H_{16}NO_2S$ $[M+H]^+$: 262.0857, found: 262.0896.



74

(±)-9-Ethyl-*N*-(1-phenylethyl)-9H-carbazol-3-amine (74)

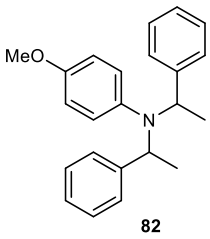
The title compound was prepared according to General Procedure **9** using boronic ester **55** (0.117 g, 0.500 mmol) and 3-amino-9-ethylcarbazole (0.425 g, 2.02 mmol), heating at 65 ºC for 48 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave *amine* **74** (46 mg, 29%) as a red solid.

m.p. 148-150 °C (petroleum ether).

IR 3381, 2975, 2928, 1633, 1471, 1218 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.47 (2H, d, *J* = 7.7 Hz, Ar**H**), 7.39-7.30 (4H, m, Ar**H**), 7.25-7.22 (2H, m, Ar**H**), 7.18 (1H, d, *J* = 8.6 Hz, Ar**H**), 7.11 (1H, t, *J* = 7.4 Hz, Ar**H**), 6.82 (1H, dd, *J* = 8.6, 2.2 Hz, Ar**H**), 4.61 (q, *J* = 6.7 Hz, NHC**H**), 4.27 (2H, q, *J* = 7.2 Hz, C**H**$_2$), 3.96 (1H, s, N**H**), 1.59 (3H, d, *J* = 6.7 Hz, CHC**H**$_3$), 1.37 (3H, t, *J* = 7.2 Hz, CH_2C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7 (C), 140.8 (C), 140.2 (C), 133.8 (C), 128.6 (2 × CH), 126.8 (CH), 126.0 (2 × CH), 125.2 (CH), 123.5 (C), 122.5 (C), 120.3 (CH), 117.7 (CH), 114.5 (CH), 108.9 (CH), 108.2 (CH), 104.2 (CH), 54.7 (CH), 37.4 (CH_2), 25.1 (CH_3), 13.8 (CH_3).



82

(±)-4-Methoxy-*N*,*N*-bis(1-phenylethyl)aniline (82)

The title compound was prepared according to General Procedure **9** using boronic ester **55** (0.0603 g, 0.260 mmol) and (±)-4-Methoxy-N-(1-phenylethyl)aniline (**62**) (0.226 g, 1.00 mmol) heating at 50 ºC for 48 h. Flash chromatography (5% EtOAc/petroleum ether) of the crude material (d.r. 1:1) gave *amine* **82** (0.0016 g, 18%, isolated d.r = 1.8:1 A:B) as a yellow oil, and amine **61** was recovered (183 mg, 80%). Upon further purification, diastereomer B was isolated as a single diastereomer.

IR (ATR) 3028, 2971, 1507, 1243, 1036, 699 cm^{-1}.

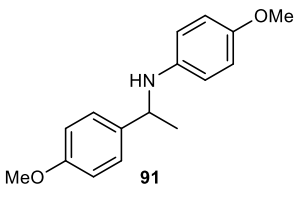
^{1}H NMR (diastereomer A) (400 MHz, $CDCl_3$) 7.33-7.29 (4H, m, Ar**H**), 7.25-7.19 (6H, m, Ar**H**), 6.73-6.71 (4H, m, Ar**H**), 4.26 (2H, q, *J* = 6.8 Hz, 2 × C**H**), 3.80 (3H, s, OC**H$_3$**), 1.18 (6H, d, *J* = 6.8 Hz, 2 × C**H$_3$**).

^{1}H NMR (diastereomer B) (400 MHz, $CDCl_3$) δ 7.30-7.29 (8H, m, Ar**H**), 7.24-7.20 (2H, m, Ar**H**), 6.71 (2H, d, *J* = 9.0 Hz, Ar**H**), 6.65 (2H, d, *J* = 9.0 Hz, Ar**H**), 4.45 (2H, q, *J* = 6.7 Hz, 2 × C**H**), 3.74 (3H, s, C**H$_3$**), 1.27 (6H, d, *J* = 6.7 Hz, 2 × C**H$_3$**).

^{13}C NMR (diastereomer B) (101 MHz, $CDCl_3$) δ 156.4 (C), 145.1 (C), 143.8 (C), 138.0 (C), 130.8 (CH), 128.7 (2 × CH), 127.9 (4 × CH), 127.8 (CH), 126.7 (2 × CH), 112.8 (2 × CH), 112.6 (2 × CH), 58.3 (CH), 57.9 (CH), 55.3 (CH_3), 22.0 (CH_3), 18.2 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{23}H_{25}NO$ $[M+H]^+$: 332.1970, found: 332.2009.

5.4.2 Scope with Respect to Secondary Boronic Esters



91

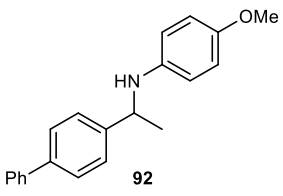
(±)-4-Methoxy-*N*-(1-(4-methoxyphenyl)ethyl)aniline (91)

The title compound was prepared according to General Procedure **9** using boronic ester **55** (0.143 g, 0.507 mmol) and *p*-anisidine (0.249 g, 2.02 mmol), heating at 50 ºC for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **91** (90 mg, 69%) as a yellow oil. The data were consistent with the literature.[326]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.87 (2H, d, *J* = 8.7 Hz, Ar**H**),

6.71 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.49 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.39 (1H, q, *J* = 6.7 Hz, C**H**), 3.80 (3H, s, OC**H**$_3$), 3.71 (3H, s, OC**H**$_3$), 1.48 (3H, d, *J* = 6.7 Hz, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (C), 151.8 (C), 141.6 (C), 137.5 (C), 126.9 (2 × CH), 114.7 (2 × CH), 114.6 (2 × CH), 113.9 (2 × CH), 55.7 (CH_3), 55.2 (CH_3), 53.6 (CH), 25.1 (CH_3).



92

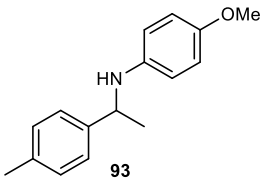
(±)-*N*-(1-(Biphenyl-4-yl)ethyl)-4-methoxyaniline (92)

The title compound was prepared according to General Procedure **9** using boronic ester **55** (0.156 g, 0.507 mmol), *p*-anisidine (0.247 g, 2.01 mmol), heating at 50 ºC for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **92** (98 mg, 63%) as an orange solid. The data were consistent with the literature.[328]

m.p. 85-86 °C (petroleum ether); no literature value available.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.50 (4H, m, Ar**H**), 7.48-7.38 (4H, m, Ar**H**), 7.37-7.31 (1H, m, Ar**H**), 6.72 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.51 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.47 (1H, q, *J* = 6.7 Hz, NC**H**), 3.79 (1H, s, N**H**), 3.71 (3H, s, OC**H**$_3$), 1.55 (3H, d, *J* = 6.7 Hz, CHC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (C), 144.6 (C), 141.6 (C), 141.0 (C), 139.7 (C), 128.7 (2 × CH), 127.4 (2 × CH), 127.1 (CH), 127.0 (2 × CH), 126.3 (2 × CH), 114.8 (2 × CH), 114.6 (2 × CH), 55.7 (CH_3), 54.0 (CH), 25.1 (CH_3).



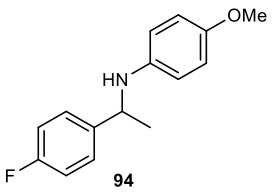
93

(±)-4-Methoxy-*N*-(1-p-tolylethyl)aniline (93)

The title compound was prepared according to General Procedure **9** using boronic ester **55** (0.123 g, 0.500 mmol) and *p*-anisidine (0.246 g, 2.00 mmol), heating at 50 ºC for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **93** (85 mg, 71%) as an orange oil. The data were consistent with the literature.[326]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.14 (2H, d, *J* = 7.9 Hz, Ar**H**), 6.70 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.49 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.40 (1H, q, *J* = 6.7 Hz, NC**H**), 3.75 (1H, br. s, N**H**), 3.71 (3H, s, OC**H**$_3$), 2.33 (3H, s, CC**H**$_3$), 1.49 (3H, d, *J* = 6.7 Hz, CHC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8 (C), 142.4 (C), 141.6 (C), 136.3 (C), 129.3 (2 × CH), 125.8 (2 × CH), 114.7 (2 × CH), 114.5 (2 × CH), 55.7 (CH_3), 53.9 (CH), 25.2 (CH_3), 21.1 (CH_3).



94

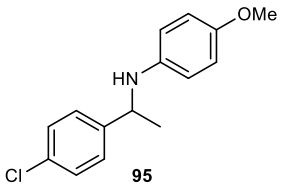
(±)-*N*-(1-(4-Fluorophenyl)ethyl)-4-methoxyaniline (94)

The title compound was prepared according to General Procedure **9** using boronic ester 55 (0.122 g, 0.488 mmol) and *p*-anisidine (0.246 g, 2.00 mmol), heating at 50 ºC for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **94** (84 mg, 70%) as an orange oil. The data were consistent with the literature.[326]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (2H, m, Ar**H**), 7.04-6.97 (2H, m, Ar**H**), 6.70 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.45 (2H, d, *J* = 8.7 Hz, Ar**H**), 4.40 (1H, q, *J* = 6.7 Hz, C**H**), 3.77 (1H, s, N**H**), 3.71 (3H, s, OC**H$_3$**), 1.48 (3H, d, *J* = 6.7 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7 (C, d, J_F = 244.1 Hz), 151.9 (C), 141.1 (C, d, J_F = 3.0 Hz), 127.3 (2 × CH, d, J_F = 8.0 Hz), 115.4 (2 × CH, J_F = 21.3 Hz), 114.7 (2 × CH), 114.5 (2 × CH), 55.7 (CH_3), 53.6 (CH), 25.3 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ -116.3.



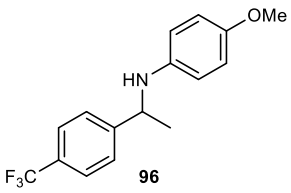
95

(±)-4-Methoxy-*N*-(1-p-chlorophenylethyl)aniline (95)

The title compound was prepared according to General Procedure **9** using boronic ester **55** (0.133 g, 0.499 mmol) and *p*-anisidine (0.246 g, 2.00 mmol) heating at 50 ºC for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **95** (73 mg, 56%) as an orange oil. The data were consistent with the literature.[329]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (4H, m, Ar**H**), 6.70 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.44 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.39 (1H, q, *J* = 6.7 Hz, NC**H**), 3.70 (3H, s, OC**H$_3$**), 1.48 (3H, d, *J* = 6.7 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (C), 144.1 (C), 141.3 (C), 132.4 (C), 128.8 (2 × CH), 127.3 (2 × CH), 114.8 (2 × CH), 114.6 (2 × CH), 55.7 (CH_3), 53.8 (CH), 25.1 (CH_3).



96

(±)-4-Methoxy-*N*-(1-(4-(trifluoromethyl)phenyl)ethyl)aniline (96)

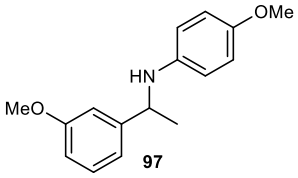
The title compound was prepared according to General Procedure **9** using boronic ester **55** (0.148 g, 0.493 mmol) and *p*-anisidine (0.249 g, 2.02 mmol), heating at 65 ºC for 48 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **96** (61 mg, 42%) as a yellow oil. The data were consistent with the literature.[326]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.49 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.70 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.43 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.46 (1H, q, *J* = 6.8 Hz, C**H**),

3.70 (3H, s, OC**H**$_3$), 1.51 (3H, d, *J* = 6.8 Hz, CHC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2 (C), 149.8 (C), 141.0 (C), 129.1 (C, q, J_F = 32.3 Hz), 126.2 (2 × CH), 125.6 (2 × CH q, J_F = 3.7 Hz), 124.2 (C, q, J_F = 270.4 Hz), 114.8 (2 × CH), 114.5 (2 × CH), 55.7 (CH_3), 54.0 (CH), 25.1 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.4.



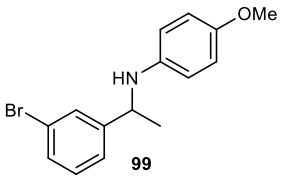
97

(±)-4-Methoxy-*N*-(1-(3-methoxyphenyl)ethyl)aniline (97)

The title compound was prepared according to General Procedure **9** using boronic ester **55** (0.129 g, 0.493 mmol) and *p*-anisidine (0.246 g, 2.03 mmol), heating at 50 ºC for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **97** (100 mg, 79%) as a yellow oil. The data were consistent with the literature.[330]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.22 (1H, m, Ar**H**), 7.00-6.96 (1H, m, Ar**H**), 6.94 (1H, s, Ar**H**), 6.80-6.75 (1H, m, Ar**H**), 6.71 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.49 (2H, d, *J* = 8.8 Hz, Ar**H**), 4.39 (1H, q, *J* = 6.7 Hz, NC**H**), 3.80 (3H, s, CCHCOC**H**$_3$), 3.71 (3H, s, CHCHCOC**H**$_3$), 1.50 (3H, d, *J* = 6.7 Hz, CHC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9 (C), 151.8 (C), 147.4 (C), 141.5 (C), 129.6 (CH), 118.2 (CH), 114.7 (2 × CH), 114.5 (2 × CH), 111.9 (CH), 111.6 (CH), 55.7 (CH_3), 55.1 (CH_3), 54.3 (CH), 25.1 (CH_3)



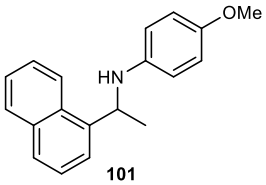
99

(±)-*N*-[1-(3-Bromophenyl)ethyl]-4-methoxyaniline (99)

The title was prepared according to General Procedure **9** using boronic ester **55** (0.153 g, 0.490 mmol) and *p*-anisidine (0.252 g, 2.04 mmol), heating at 50 ºC for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **99** (74 mg, 49%) as a brown oil. The data were consistent with the literature.[331]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, s, Ar**H**), 7.36 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.30 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.19 (1H, t, *J* = 7.7 Hz, Ar**H**), 6.71 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.45 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.37 (1H, q, *J* = 6.7 Hz, C**H**), 3.79 (1H, s, N**H**), 3.71 (3H, s, OC**H**$_3$), 1.49 (3H, d, *J* = 6.7 Hz, CHC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (C), 148.2 (C), 141.1 (C), 130.2 (CH), 130.0 (CH), 129.0 (CH), 124.5 (CH), 122.8 (C), 114.8 (2 × CH), 114.5 (2 × CH), 55.7 (CH_3), 54.0 (CH), 25.2 (CH_3).



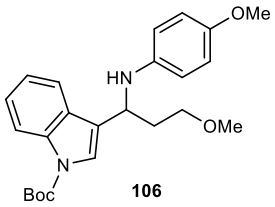
101

(±)-*N*-(4-Methoxyphenyl)-α-methyl-1-naphthalenemethanamine (101)

The title compound was prepared according to General Procedure **9** using boronic ester **55** (0.141 g, 0.499 mmol) and *p*-anisidine (0.249 g, 2.02 mmol), heating at 65 °C for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **101** (62 mg, 45%) as a yellow solid. The data were consistent with the literature.[332]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20− 8.18 (1H, m, Ar**H**), 7.93−7.91 (1H, m, Ar**H**), 7.77−7.75 (1H, m, Ar**H**), 7.68−7.66 (1H, m, Ar**H**), 7.60−7.51 (2H, m, Ar**H**), 7.44−7.41 (1H, m, Ar**H**), 6.67 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.45 (2H, d, *J* = 8.8 Hz Ar**H**), 5.23 (1H, q, *J* = 6.6 Hz, NC**H**), 3.96 (1H, br s, N**H**), 3.69 (3H, s, OC**H$_3$**), 1.66 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8 (C), 141.3 (C), 140.1 (C), 134.1 (C), 130.7 (C), 129.1 (CH), 127.3 (CH), 126.0 (CH), 125.9 (CH), 125.4 (CH), 122.6 (CH), 122.3 (CH), 114.7 (2 × CH), 114.2 (2 × CH), 55.7 (CH_3), 50.1 (CH), 23.8 (CH_3).



106

(±)-tert-Butyl 3-(3-Methoxy-1-[(4-methoxyphenyl)amino]- propyl)-1H-indole-1-carboxylate (106)

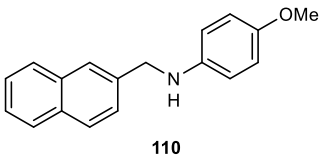
The title compound was prepared according to General Procedure **9** using boronic ester **55** (0.208 g, 0.500 mmol) and *p*-anisidine (0.249 g, 2.02 mmol), heating at 65 °C for 48 h. Flash chromatography (10% EtOAc/petroleum ether) of the crude material gave *amine* **106** (151 mg, 73%) as a dark yellow oil.

IR 2932, 2832, 2248, 1726, 1510, 906 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, s, Ar**H**), 7.65 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.53 (1H, s, Ar**H**), 7.36−7.32 (1H, m, Ar**H**), 7.26−7.24 (1H, m, Ar**H**), 6.73 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.60 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.77 (1H, t, *J* = 6.3 Hz, NC**H**), 3.72 (3H, s, ArOC**H$_3$**), 3.60−3.55 (1H, m, C**H$_A$**H$_B$O), 3.51− 3.46 (1H, m, CH$_A$**H$_B$**O), 3.37 (3H, s, CH$_2$OC**H$_3$**), 2.26−2.18 (2H, m, CHC**H$_2$**), 1.67 (9H, s, 3 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (C), 149.7 (C), 141.7 (C), 135.8 (C), 129.0 (C), 124.4 (2 × CH), 123.0 (CH), 122.4 (2 × CH), 119.3 (CH), 115.4 (CH), 114.7 (2 × CH), 83.6 (C), 70.3 (CH_2), 58.8 (CH_3), 55.7 (CH_3), 50.4 (CH), 36.3 (CH_2), 28.2 (3 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{24}H_{30}N_2O_4$ $[M+Na]^+$: 433.2106, found 433.2098.



110

4-Methoxy-*N*-(naphthalen-2-ylmethyl)aniline (110)

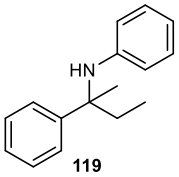
The title compound was prepared according to General Procedure **9** using boronic ester **55** (0.135 g, 0.505 mmol) and *p*-anisidine (0.249 g, 2.02 mmol), heating at 50 °C for 16 h. Flash chromatography (6% EtOAc/ petroleum ether) of the crude material gave amine **110** (83 mg, 62%) as a yellow solid. The data were consistent with the literature.[333]

m.p. 106−108 °C (petroleum ether); no literature value available.

^{1}H NMR (400 MHz, CDCl3) δ 7.88−7.78 (4H, m, Ar**H**), 7.54−7.42 (3H, m, Ar**H**), 6.79 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.66 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.46 (2H, s, C**H$_2$**), 3.75 (3H, s, OC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2 (C), 142.4 (C), 137.2 (C), 133.5 (C), 132.7 (C), 128.3 (CH), 127.7 (CH), 127.7 (CH), 126.1 (CH), 125.9 (CH), 125.8 (CH), 125.7 (CH), 114.9 (2 × CH), 114.2 (2 × CH), 55.8 (CH_3), 49.4 (CH_2).

5.4.3 Scope with Respect to the Amination of 3° Boronic Esters



119

(±)-*N*-(2-Phenylbutan-2-yl)aniline (119)

The title compound was prepared according to General Procedure **9** using boronic ester **201** (0.130 g, 0.500 mmol) and aniline (0.18 mL, 2.0 mmol), heating at 50 °C. Flash chromatography (1% EtOAc/petroleum ether) of the crude material gave amine **119** (47 mg, 41%) as a yellow oil. The data were consistent with the literature.[334]

IR 3359, 2918, 2850, 1600, 1468, 1263 cm^{-1}.

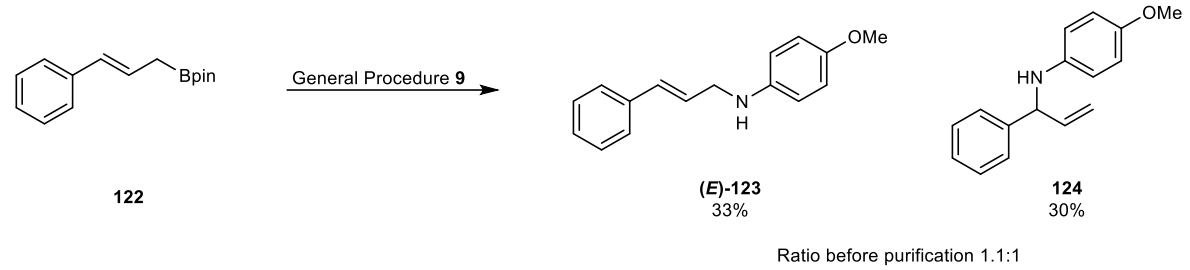
^{1}H NMR (400 MHz, CDCl3) δ 7.52−7.45 (2H, m, Ar**H**), 7.36−7.30 (2H, m, Ar**H**), 7.26−7.21 (1H, m, Ar**H**), 7.04−6.95 (2H, m, Ar**H**), 6.65−6.56 (1H, m, Ar**H**), 6.38−6.30 (2H, m, Ar**H**), 4.01 (1H, s, N**H**), 1.92 (2H, q, *J* = 7.4 Hz, C**H$_2$**), 1.63 (3H, s, CC**H$_3$**), 0.83 (3H, t, *J* = 7.4 Hz, CH_2C**H$_3$**).

^{13}C NMR (400 MHz, $CDCl_3$) δ 146.3 (C), 146.0 (C), 128.7 (2 × CH), 128.3 (2 × CH), 126.2 (3 × CH), 116.9 (CH), 115.1 (2 × CH), 58.4 (C), 36.4 (CH_2), 25.3 (CH_3), 8.2 (CH_3).

HRMS (ESI) Exact mass calcd for $C_{16}H_{19}N$ $[M + H]^+$: 226.1590; found 226.1597.

5.4.4 Scope Using Allylboronic Esters

(*E*)-*N*-Cinnamyl-4- methoxybenzenamine ((*E*)-123) and (±)-*N*-(4-Methoxyphenyl)-1-phenyl-2-propenylamine (124)



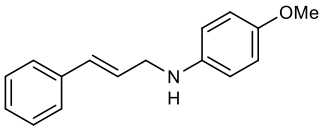
122

(*E*)-123
33%

124
30%

Ratio before purification 1.1:1

The title compounds were prepared according to General Procedure **9** using boronic ester **122** (0.126 g, 0.516 mmol) and *p*-anisidine (0.250 g, 2.03 mmol) heating at 50 ºC for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine (*E*)-**123** (40 mg, 33%) and amine **124** (0.0368 g, 30%) as yellow oils. The data were consistent with the literature.[335]

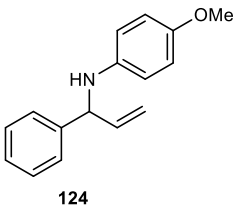


(*E*)-123

(*E*)-*N*-Cinnamyl-4- methoxybenzenamine ((*E*)-123)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (4H, m, Ar**H**), 7.26-7.22 (1H, m, Ar**H**), 6.82-6.80 (2H, m, Ar**H**), 6.70-6.68 (2H, m, Ar**H**), 6.63 (1H, d, *J* = 15.9 Hz, ArC**H**), 6.35 (1H, dt, *J* = 15.9, 5.9 Hz, ArCH=C**H**), 3.91 (2H, d, *J* = 5.9 Hz, C**H$_2$**), 3.76 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7 (C), 141.6 (C), 136.8 (C), 131.8 (CH), 128.6 (2 × CH), 127.5 (2 × CH), 127.0 (CH), 126.3 (CH), 114.9 (2 × CH), 114.9 (2 × CH), 55.8 (CH_3), 47.6 (CH_2).



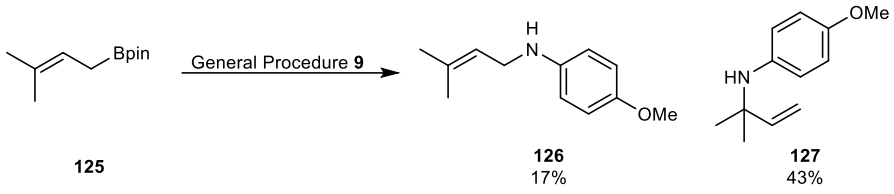
124

(±)-*N*-(4-Methoxyphenyl)-1-phenyl-2-propenylamine (124)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (5H, m, Ar**H**), 6.75-6.73 (2H, m, Ar**H**), 6.59-6.57 (2H, m, Ar**H**), 6.09-6.00 (1H, ddd, *J* = 17.1, 10.2, 6.0 Hz, CH_2=C**H**), 5.28 (1H, d, *J* = 17.1 Hz, CH=C**H$_A$**H$_B$), 5.22 (1H, d, *J* = 10.2 Hz, CH=CH$_A$**H$_B$**), 4.86 (1H, d, *J* = 6.0 Hz, NC**H**), 3.73 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2 (C), 142.1 (C), 141.4 (C), 139.5 (CH), 128.7 (2 × CH), 127.4 (2 × CH), 127.1 (2 × CH), 115.9 (CH), 114.9 (CH_2), 114.7 (2 × CH), 61.8 (CH), 55.7 (CH_3)

(±)-4-Methoxy-*N*-(3-methyl-2-buten-1-yl)benzenamine (126) and (±)-4-Methoxy-*N*-(1,1-Dimethyl-2-propen-1-yl)benzenamine (127)



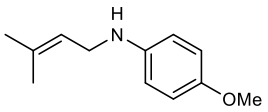
125

126 17%

127 43%

Ratio before purification 1:2.6

The title compounds were prepared according to General Procedure **9** using boronic ester **125** (0.0985 g, 0.502 mmol) and *p*-anisidine (0.247 g, 2.00 mmol), heating at 50 ºC for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **126** (0.0167 g, 17%) and amine **127** (41 mg, 43%) as a pale yellow oils. The data were consistent with the literature.[336,337]

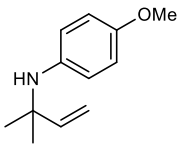


126

(±)-4-Methoxy-*N*-(3-methyl-2-buten-1-yl)benzenamine (126)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83-6.78 (2H, m, Ar**H**), 6.63-6.58 (2H, m, Ar**H**), 5.34 (1H, t, *J* = 6.7 Hz, C**H**), 3.76 (3H, s, OC**H$_3$**), 3.66 (2H, d, *J* = 6.7 Hz, C**H$_2$**), 1.76 (3H, s, CC**H$_3$**), 1.72 (3H, s, CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (C), 142.7 (C), 135.3 (C), 121.9 (CH), 114.9 (2 × CH), 114.2 (2 × CH), 55.8 (CH_3), 43.0 (CH_2), 25.7 (CH_3), 18.0 (CH_3).



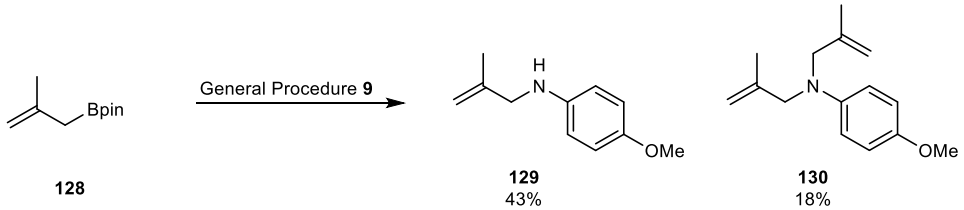
127

(±)-4-Methoxy-*N*-(1,1-Dimethyl-2-propen-1-yl)benzenamine (127)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (4H, s, Ar**H**), 6.02 (1H, dd, *J* = 17.5, 10.7 Hz, C**H**), 5.15 (1H, dd, *J* = 17.5, 1.0 Hz, C**H$_A$**H$_B$), 5.08 (1H, dd, *J* = 10.7, 1.0 Hz, CH$_A$**H$_B$**), 3.75 (3H, s, OC**H$_3$**), 1.34 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9 (C), 146.6 (CH), 140.2 (C), 119.1 (2 × CH), 114.2 (2 × CH), 112.4 (CH_2), 55.6 (CH_3), 55.1 (C), 28.1 (2 × CH_3).

(±)-4-Methoxy-*N*-(2-methyl-2-propen-1-yl)benzenamine (129) and (±)-4-methoxy-N,N-bis(2-methylpropyl)aniline (130)



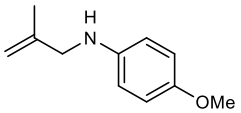
128

129 43%

130 18%

Ratio before purification 3.2:1

The title compounds were prepared according to General Procedure **9** using boronic ester **128** (0.092 g, 0.506 mmol) and *p*-anisidine (0.253 g, 2.05 mmol) heating at 50 ºC for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **129** (0.0384 g, 43%) as a pale yellow oil and *amine* **130** (10 mg, 18%) as a pale yellow oil. The data for **129** were consistent with the literature.[338]

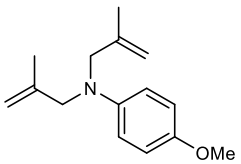


129

(±)-4-Methoxy-*N*-(2-methyl-2-propen-1-yl)benzenamine (129)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80-6.77 (2H, m, Ar**H**), 6.61-6.58 (2H, d, m, Ar**H**), 4.97 (1H, s, C**H$_A$**H$_B$=C), 4.89 (1H, s, CH$_A$**H$_B$**=C), 3.75 (3H, s, OC**H$_3$**), 3.65 (3H, s, C**H$_2$**N and N**H**), 1.79 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (C), 143.1 (C), 142.5 (C), 114.8 (2 × CH), 114.0 (2 × CH), 110.8 (CH_2), 55.8 (CH_3), 50.8 (CH_2), 20.5 (CH_3).



130

(±)-4-Methoxy-*N*,*N*-bis(2-methylpropyl)aniline (130)

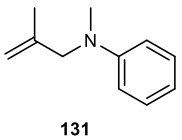
IR 2916, 2849, 1729, 1646, 1512, 1178 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81-6.76 (2H, m, Ar**H**), 6.61-6.57 (2H, m, Ar**H**), 4.85 (2H, s, 2 × C**H$_A$**H$_B$=C), 4.80 (2H, s, 2 × CH$_A$**H$_B$**=C), 3.77 (4H, s, 2 × C**H$_2$**), 3.75 (3H, s, OC**H$_3$**), 1.74 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9 (C), 143.6 (C), 141.2 (2 × C), 114.5 (2 × CH), 113.2 (2 × CH), 110.3 (2 × CH_2), 57.0 (2 × CH_2), 55.7 (CH_3), 20.1 (2 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{15}H_{21}NO$ $[M+H]^+$: 232.1696, found: 232.1692.

(±)-*N*-Methyl-*N*-(3-methylbut-2-en-1-yl)aniline (131)



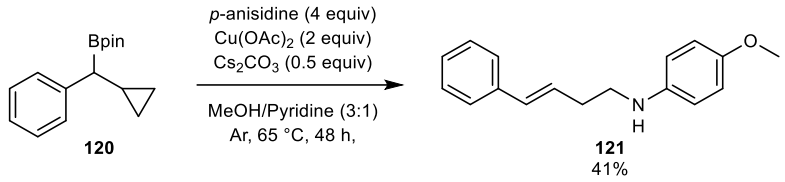
131

The title compound was prepared according to General Procedure **9** using boronic ester **129** (0.093 g, 0.509 mmol) and *N*-methyl aniline (0.216 g, 2.01 mmol), heating at 50 ºC for 16 h. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave amine **132** (46 mg, 57%) as a pale yellow oil. The data were consistent with the literature.[339]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.21 (2H, m, Ar**H**), 6.71-6.68 (3H, m, Ar**H**), 4.86 (1H, s, C=C**H$_A$**H$_B$), 4.81 (1H, s, C=CH$_A$**H$_B$**) 3.81 (2H, s, NC**H$_2$**), 2.97 (3H, s, NC**H$_3$**), 1.74 (3H, s, CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6 (C), 141.5 (C), 129.0 (2 × CH), 116.1 (CH), 111.9 (2 × CH), 110.7 (CH_2), 58.8 (CH_2), 38.2 (CH_3), 20.0 (CH_3).

5.4.5 Reaction of Cyclopropane-containing Boronic Ester (120)



A flask containing boronic ester **120** (0.131 g, 0.507 mmol), *p*-anisidine (0.251 g, 2.04 mmol), $Cu(OAc)_2$ (0.184 g, 1.01 mmol) and Cs_2CO_3 (0.0858 g, 0.263 mmol) was purged with argon. Methanol (1.0 mL) and pyridine (0.33 mL) were added, and the mixture was stirred at 65 °C for 48 h. The mixture was cooled to room temperature, NH_4OH (10 mL) was added, and the mixture was extracted with Et_2O (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash chromatography (6% EtOAc/petroleum ether) of the crude material gave *amine* **121** (50 mg, 39%) as an orange oil.

IR 3390, 2929, 2831, 1510, 1233 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (2H, m, Ar**H**), 7.36-7.29 (2H, m, Ar**H**), 7.27-7.20 (1H, m, Ar**H**), 6.81 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.62 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.51 (1H, dt, *J* = 15.9, 1.1 Hz, PhC**H**), 6.24 (1H, dt, *J* = 15.9 7.1 Hz, PhCH=C**H**), 3.77 (3H, s, OC**H$_3$**), 3.47 (1H, s, N**H**), 3.25 (2H, t, *J* = 6.7 Hz, C**H$_2$**N), 2.55 (2H, dtd, *J* = 7.1, 6.7, 1.1 Hz, C**H$_2$**CH_2N).

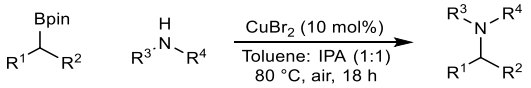
^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2 (C), 142.5 (C), 137.3 (C), 132.2 (CH), 128.5 (2 × CH), 127.5 (CH), 127.2 (CH), 126.1 (2 × CH), 115.0 (2 × CH), 114.3 (2 × CH), 55.8 (CH_3), 44.3 (CH_2), 33.0 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $C_{17}H_{20}NO$ $[M+H]^+$: 254.1545, found: 254.1539.

5.5 Cu-catalysed C-N bond formation with Alkylamines

General Procedure 11

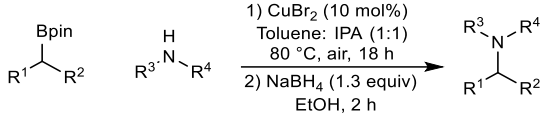
Preparative scale Cu-catalysed amination of alkylboronic esters



Isopropyl alcohol (0.38 mL) and toluene (0.38 mL) were added to a flask containing the corresponding boronic ester (0.50 mmol, 1 equiv.), amine (1.75 mmol, 3.5 equiv.) and $CuBr_2$ (0.05 mmol, 10 mol%), and the mixture was stirred under air at 80 °C until the reaction was complete (as determined by TLC). The mixture was cooled to room temperature, passed through a plug of silica eluting with Et_2O, and concentrated *in vacuo*. The crude material was purified by column chromatography.

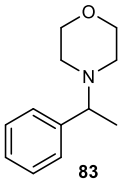
General Procedure 12

Preparative scale Cu-catalysed amination of alkylboronic esters with reductive workup.



Isopropyl alcohol (0.38 mL) and toluene (0.38 mL) were added to a flask containing the corresponding boronic ester (0.50 mmol, 1 equiv), amine (1.75 mmol, 3.5 equiv) and $CuBr_2$ (0.05 mmol, 10 mol%), and the mixture was stirred under air at 80 °C until the reaction was complete (as determined by TLC). The mixture was cooled to room temperature, passed through a plug of silica eluting with Et_2O, and concentrated *in vacuo*. EtOH (1 mL) and $NaBH_4$ (0.025 g, 0.65 mmol) were added, and the mixture stirred at RT for 2 h. The mixture was diluted with EtOAc (10 mL) and H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography.

5.5.1 Scope with Respect to Amine for the Alkyl Amination of Boronic ester 55



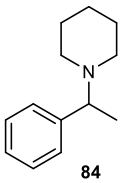
83

(±)-*N*-(1-Phenylethyl)morpholine (83)

Isopropyl alcohol (2.75 mL) and toluene (2.75 mL) were added to a flask containing boronic ester **55** (1.00 g, 4.31 mmol), morpholine (1.31 g, 15.1 mmol) and $CuBr_2$ (96.3 mg, 0.43 mmol), and the mixture was stirred under air at 80 °C for 18 h. The mixture was cooled to room temperature, passed through a plug of silica eluting with Et_2O and EtOAc, and concentrated *in vacuo*. Flash column chromatography (69% hexane/30% EtOAc/1% triethylamine) of the crude material gave amine **83** (72 mg, 87%) as a colourless oil. The data were consistent with literature.[340]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (4 H, m, Ar**H**), 7.22-7.17 (1H, m, Ar**H**), 3.67-3.61 (4H, m, 2 × OC**H₂**), 3.25 (1H, q, *J* = 6.6 Hz, C**H**), 2.51-2.41 (2H, m, NC**H₂**), 2.35-2.29 (2H, m, NC**H₂**), 1.31 (3H, d, *J* = 6.6 Hz, C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 128.3 (2 × CH), 127.6 (2 × CH), 127.0 (CH), 67.2 (2 × CH_2), 65.4 (CH), 51.3 (2 × CH_2), 19.8 (CH_3).



84

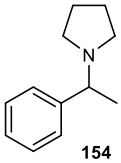
(±)-*N*-(1-Phenylethyl)piperidine (84)

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.117 g, 0.504 mmol) and piperidine (0.150 g, 1.76 mmol), heating for 18 h. Flash column chromatography (69% hexane/30% EtOAc/1% triethylamine)

of the crude material gave amine **84** (74 mg, 77%) as a colourless oil. The data were consistent with literature.[341]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (4H, m, Ar**H**), 7.27-7.18 (1H, m, Ar**H**), 3.38 (1H, q, *J* = 6.7 Hz, C**H**), 2.45-2.37 (4H, m, 2 × NC**H$_2$**), 1.55-1.50 (4H, m, 2 × NCH_2C**H$_2$**), 1.39-1.34 (5H, m, C**H$_3$** and NCH_2CH_2C**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (C), 128.0 (2 × CH), 127.8 (2 × CH), 126.7 (CH), 65.2 (CH), 51.5 (2 × CH_2), 26.2 (2 × CH_2), 24.5 (CH_2), 19.4 (CH_3).



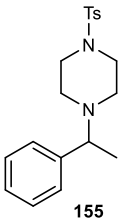
154

(±)-*N*-(1-Phenylethyl)pyrrolidine (154)

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.118 g, 0.508 mmol) and pyrrolidine (124.8 mg, 1.75 mmol), heating for 18 h. Flash column chromatography (99% EtOAc/1% Et_3N) of the crude material gave amine **154** (61 mg, 68%) as a colourless oil. The data were consistent with literature.[342]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (4H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**) 3.20 (1H, q, *J* = 6.5 Hz, C**H**), 2.62-2.53 (2H, m, NC**H$_2$**), 2.43-2.34 (2H, m, NC**H$_2$**), 1.81-1.73 (4H, m, 2 × C**H$_2$**), 1.43 (3H, d, *J* = 6.5 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6 (C), 128.2 (2 × CH), 127.2 (2 × CH), 126.8 (CH), 66.0 (CH), 53.0 (2 × CH_2), 23.4 (2 × CH_2), 23.1 (CH_3).



155

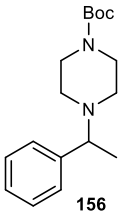
(±)-1-[(4-Methylphenyl)sulfonyl]-4-(1-phenylethyl)piperazine (155)

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.117 g, 0.504 mmol) and *N*-tosylpiperizine (0.422 g, 1.76 mmol), heating for 18 h. Flash column chromatography (59% hexane/40% EtOAc/1% triethylamine) of the crude material gave amine **155** (70 mg, 40%) as a white solid. The data were consistent with literature.[343]

m.p. 148-149 °C (hexane). No literature value available.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.59 (2H, m, Ar**H**), 7.35-7.18 (7H, m, Ar**H**), 3.36 (1H, q, *J* = 6.6 Hz, C**H**), 3.03-2.92 (4H, m, 4 × C**H$_2$**), 2.62-2.52 (2H, m, C**H$_2$**), 2.50-2.40 (5H, m, C**H$_2$** and ArC**H$_3$**), 1.32 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6 (C), 143.3 (C), 132.4 (C), 129.6 (2 × CH), 128.3 (2 × CH), 127.9 (2 × CH), 127.5 (2 × CH), 127.1 (CH), 64.4 (CH), 49.5 (2 × CH_2), 46.3 (2 × CH_2), 21.5 (CH_3), 19.5 (CH_3).



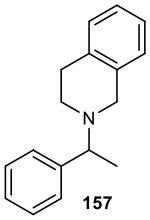
156

(±)-1-Piperazinecarboxylic acid, 4-(1-phenylethyl)-, 1,1-dimethylethyl ester (156)

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.116 g, 0.502 mmol) and *N*-Bocpiperizine (0.326 g, 1.75 mmol), heating for 18 h. Flash column chromatography (69% hexane/30% EtOAc/1% triethylamine) of the crude material gave amine **156** (112 mg, 77%) as a colourless oil. The data were consistent with literature.[340]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (4H, m, Ar**H**), 7.28-7.23 (1H, m, Ar**H**), 3.45-3.35 (5H, m, 2 × C**H$_2$** and C**H**), 2.50-2.40 (2H, m, C**H$_2$**), 2.38-2.30 (2H, m, C**H$_2$**), 1.45 (9H, s, 3 × CC**H$_3$**), 1.38 (3H, d, *J* = 6.7 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7 (C), 143.6 (C), 128.2 (2 × CH), 127.6 (2 × CH), 126.9 (CH), 79.4 (C), 64.7 (CH), 50.2 (4 × CH_2), 28.4 (3 × CH_3), 19.6 (CH_3).



157

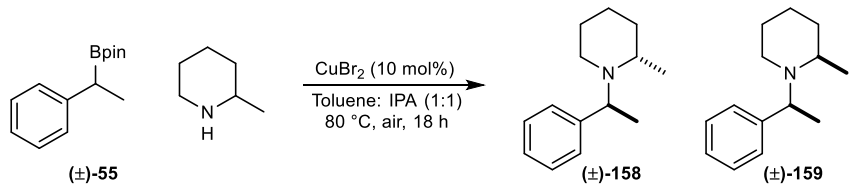
(±)-1,2,3,4-Tetrahydro-2-(1-phenylethyl)isoquinoline (157)

The title compound was prepared according to General Procedure **12** using boronic ester **55** (0.118 g, 0.506 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.238 g, 1.79 mmol), heating for 18 h. Flash column chromatography (79.5% hexane/20% EtOAc/0.5% triethylamine) of the crude material gave amine **157** (78 mg, 65%) as a yellow oil. The data were consistent with literature.[340]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.38 (2H, m, Ar**H**), 7.36-7.32 (2H, m, Ar**H**), 7.29-7.25 (1H, m, Ar**H**), 7.14-7.08 (3H, m, Ar**H**), 7.02-6.99 (1H, m, Ar**H**), 3.83 (1H, d, *J* = 14.8 Hz, ArC**H$_A$**CH$_B$N), 3.62-3.54 (2H, m, C**H** and ArCH$_A$C**H$_B$**N), 2.96-2.77 (3H, m, C**H$_2$** and **N**C**H$_C$**CH$_D$), 2.67-2.60 (1H, m, NCH$_C$C**H$_D$**), 1.49 (3H, d, *J* = 6.7 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (C), 135.2 (C), 134.6 (C), 128.6 (CH), 128.3 (2 × CH), 127.6 (2 × CH), 126.9 (CH), 126.8 (CH), 126.0 (CH), 125.5 (CH), 64.4 (CH), 53.6 (CH_2), 48.0 (CH_2), 29.3 (CH_2), 20.1 (CH_3).

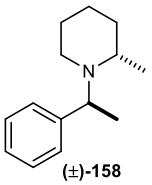
(±)-2-Methyl-1-(1-phenylethyl)piperidine (158 and 159)



(±)-55 (±)-158 (±)-159

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.117 g, 0.504 mmol) and 2-methyl piperidine (0.175 g, 1.76 mmol), heating for 18 h. Flash

column chromatography (69% hexane/30% EtOAc/1% triethylamine) of the crude material gave amine **158** (21 mg, 21%) as a yellow oil and amine **159** (17 mg, 17%) as a yellow oil. The data for **158**[344] (1*S*2*S*) and **159**[345] (1*R*1*S*) were consistent with literature.



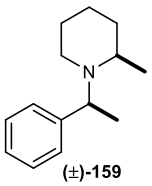
(±)-(*S*,*S*)-2-Methyl-1-(1-phenylethyl)piperidine (158)

IR 2930, 2793, 1447, 1373, 1279, 1066 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.42 (2H, m, Ar**H**), 7.35-7.29 (2H, m, Ar**H**), 7.24-7.20 (1H, m, Ar**H**), 4.07 (1H, q, *J* = 6.7 Hz, ArC**H**), 2.87-2.80 (1H, m, NC**H**CH_2), 2.40-2.33 (1H, m, C**H$_A$**CH_B**)**, 2.20-2.12 (1H, m, CH_AC**H$_B$**), 1.75-1.68 (1H, m, C**H$_C$**CH_D), 1.67-1.59 (1H, m, C**H$_E$**CH_F), 1.47-1.31 (4H, m, C**H$_2$** and CH_CC**H$_D$**, CH_EC**H$_F$**), 1.27 (3H, d, *J* = 6.7 Hz, ArCHC**H$_3$**), 1.14 (3H, d, *J* = 6.3 Hz, CH_2CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8 (C), 127.9 (2 × CH), 127.7 (2 × CH), 126.2 (CH), 56.6 (CH), 52.0 (CH), 44.9 (CH_2), 34.7 (CH_2), 26.4 (CH_2), 23.4 (CH_2), 17.0 (CH_3), 12.5 (CH_3).

HRMS (QTOF) Exact mass calcd for $C_{14}H_{21}N$ $[M+H]^+$: 204.1747, found: 204.1751.



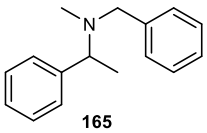
(±)-(*R*,*S*)-2-Methyl-1-(1-phenylethyl)piperidine (159)

IR 2940, 2523, 1455, 1205, 1064 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (5H, m, Ar**H**), 4.10 (1H, q, *J* = 6.9 Hz, ArC**H**), 2.89-2.83 (1H. m, C**H$_A$**CH_B), 2.39-2.32 (1H, m, NC**H**CH_2), 2.18-2.09 (1H, m, CH_AC**H$_B$**), 1.64-1.50 (4H, m, C**H$_2$** and C**H$_C$**CH_D and C**H$_E$**CH_F), 1.42 (3H, d, *J* = 6.9 Hz, ArCHC**H$_3$**), 1.39-1.29 (1H, m, CH_CC**H$_D$**), 1.25-1.17 (1H, m, CH_EC**H$_F$**), 1.14 (3H, d, *J* = 6.2 Hz, CH_2CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8 (C), 128.1 (2 × CH), 127.8 (2 × CH), 126.6 (CH), 57.4 (CH), 52.4 (CH), 44.8 (CH_2), 34.7 (CH_2), 26.5 (CH_2), 22.9 (CH_2), 20.1 (CH_3), 17.3 (CH_3).

HRMS (QTOF) Exact mass calcd for $C_{14}H_{21}N$ $[M+H]^+$: 204.1747, found: 204.1754.

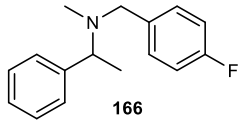


(±)-*N*-α-Dimethyl-*N*-(phenylmethyl)benzenemethanamine (165)

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.116 g, 0.503 mmol) and *N*-methylbenzylamine (0.214 g, 1.77 mmol), heating for 18 h. Flash column chromatography (94% hexane/5% EtOAc/1% triethylamine) of the crude material gave amine **165** (71 mg, 63%) as a colourless oil. The data were consistent with literature.[346]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.41 (2H, m, Ar**H**), 7.37-7.31 (6H, m, Ar**H**), 7.28-7.22 (2H, m, Ar**H**), 3.66 (1H, q, *J* = 6.8 Hz, C**H**), 3.60 (1H, d, *J* = 13.3 Hz, C**H$_A$**H$_B$), 3.32 (1H, d, *J* = 13.3 Hz, CH$_A$**H$_B$**), 2.15 (3H, s, NC**H$_3$**), 1.44 (3H, d, *J* = 6.8 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2 (C), 140.1 (C), 128.7 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.7 (2 × CH), 126.8 (CH), 126.7 (CH), 63.2 (CH), 58.9 (CH_2), 38.3 (CH_3), 18.4 (CH_3).



166

(±)-[(4-Fluorophenyl)methyl](methyl)(1-phenylethyl)amine (166)

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.116 g, 0.503 mmol) and *N*-methyl-4-fluorobenzylamine (0.245 g, 1.76 mmol), heating for 18 h. Flash column chromatography (94% hexane/5% EtOAc/1% triethylamine) of the crude material gave *amine* **166** (64 mg, 53%) as a colourless oil.

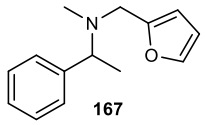
IR 2981, 2790, 1604, 1506, 1453, 1125 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.34 (4H, m, Ar**H**), 7.31-7.24 (3H, m, Ar**H**), 7.04-7.96 (2H, m, Ar**H**), 3.65 (1H, q, *J* = 6.7 Hz, C**H**), 3.55 (1H, d, *J* = 13.3 Hz, C**H$_A$**H$_B$), 3.28 (1H, d, *J* = 13.3 Hz, CH$_A$**H$_B$**), 2.14 (3H, s, NC**H$_3$**), 1.44 (3H, d, *J* = 6.7 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9 (C, d, J_F = 245.5 Hz), 144.1 (C), 135.7 (C), 130.1 (2 × CH, d, J_F = 8.4 Hz), 128.2 (2 × CH), 127.6 (2 × CH), 126.8 (CH), 114.9 (2 × CH, d, J_F = 20.5 Hz), 63.2 (CH), 58.1 (CH_2), 38.2 (CH_3), 18.4 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ -116.5.

HRMS (Q-TOF) Exact mass calcd for $C_{16}H_{18}FN$ $[M+H]^+$: 244.1496, found: 244.1508.



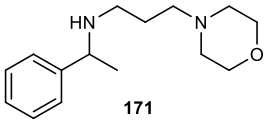
167

(±)-*N*-Methyl-*N*-(furan-2-ylmethyl)-1-phenylethanamine (167)

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.117 g, 0.504 mmol) and *N*-methylfurfurylamine (0.196 g, 1.76 mmol), heating for 18 h. Flash column chromatography (94% hexane/5% EtOAc/1% Et_3N) of the crude material gave amine **167** (70 mg, 64%) as a colourless oil. The data were consistent with literature.[347]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.32 (5H, m, Ar**H**), 7.29-7.24 (1H, m, Ar**H**), 6.33 (1H, dd, *J* = 3.1, 1.9 Hz, Ar**H**), 6.17 (1H, d, *J* = 3.1 Hz, Ar**H**), 3.67 (1H, d, *J* = 14.4 Hz, C**H$_A$**CH$_B$), 3.58 (1H, q, *J* = 6.7 Hz, C**H**), 3.44 (1H, d, *J* = 14.4 Hz, CH$_A$C**H$_B$**), 2.23 (3H, s, NC**H$_3$**), 1.44 (3H, t, *J* = 6.7 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9 (C), 143.8 (C), 141.9 (CH), 128.2 (2 × CH), 127.7 (2 × CH), 126.9 (CH), 109.9 (CH), 108.3 (CH), 62.7 (CH), 51.0 (CH_2), 38.9 (CH_3), 19.6 (CH_3).



171

(±)-[3-(morpholin-4-yl)propyl](1-phenylethyl)amine (171)

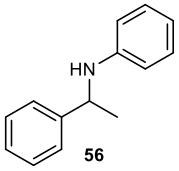
The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.117 g, 0.504 mmol) and 3-morpholinopropylamine (0.253 g, 1.78 mmol), heating for 18 h. Flash column chromatography (97% CH_2Cl_2/2% MeOH/1% Et_3N) of the crude material gave *amine* **171** (62 mg, 49%) as a yellow oil.

IR 2960, 2810, 1675, 1455, 1275, 1118 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (4H, m, Ar**H**), 7.27-7.22 (1H, m, Ar**H**), 3.77 (1H, q, *J* = 6.6 Hz, C**H**), 3.68 (4H, t, *J* = 4.7 Hz, 2 × OC**H$_2$**), 2.65-2.57 (1H, m, CHNC**H$_A$**CH_B), 2.54-2.32 (7H, m, $CHNCH_AC$**H$_B$**, C**H$_2$**$N(CH_2)_2$ and 2 × NC**H$_2$**CH_2O), 1.76-1.63 (2H, m, NCH_2C**H$_2$**CH_2), 1.39 (3H, d, *J* = 6.6 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1 (C), 128.4 (2 × CH), 127.0 (CH), 126.5 (2 × CH), 66.9 (2 × CH_2), 58.4 (CH), 57.5 (CH_2), 53.7 (2 × CH_2), 46.5 (CH_2), 26.3 (CH_2), 24.0 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{15}H_{24}N_2O$ $[M+H]^+$: 249.1961, found: 249.1970



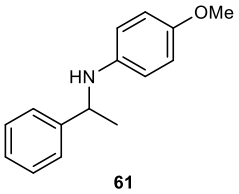
56

(±)-*N*-(1-Phenylethyl)aniline (56)

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.117 g, 0.505 mmol) and aniline (0.163 mg, 1.75 mmol), heating for 18 h. Flash column chromatography (98% hexane/2% EtOAc) of the crude material gave amine **56** (44 mg, 45%) as an orange oil. The data were consistent with literature.[326]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (2H, m, Ar**H**), 7.37-7.32 (2H, m, Ar**H**), 7.27-7.23 (1H, m, Ar**H**), 7.15-7.09 (2H, m, Ar**H**), 6.70-6.65 (1H, m, Ar**H**), 6.56-6.52 (2H, m, Ar**H**), 4.51 (1H, q, *J* = 6.7 Hz, C**H**), 4.16 (1H, br s, N**H**), 1.55 (3H, d, *J* = 6.7 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1 (C), 145.1 (C), 129.1 (2 × CH), 128.6 (2 × CH), 126.9 (CH), 125.8 (2 × CH), 117.3 (CH), 113.4 (2 × CH), 53.5 (CH), 25.0 (CH_3).



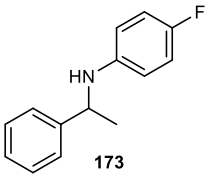
61

(±)-4-Methoxy-*N*-(1-phenylethyl)aniline (61)

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.117 g, 0.505 mmol) and *p*-anisidine (0.217 g, 1.76 mmol), heating for 18 h. Flash column chromatography (96% hexane/4% EtOAc) of the crude material gave amine **61** (32 mg, 28%) as an orange oil. The data were consistent with literature.[326]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.37 (2H, m, Ar**H**), 7.36-7.32 (2H, m, Ar**H**), 7.31-7.21 (1H, m, Ar**H**), 6.75-6.69 (2H, m, Ar**H**), 6.53-6.47 (2H, m, Ar**H**), 4.44 (1H, q, *J* = 6.7 Hz, C**H**), 3.72 (3H, s, OC**H$_3$**), 1.52 (3H, d, *J* = 6.7 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9 (C), 145.4 (C), 141.5 (C), 128.6 (2 × CH), 126.8 (CH), 125.9 (2 × CH), 114.7 (2 × CH), 114.6 (2 × CH), 55.7 (CH_3), 54.3 (CH), 25.1 (CH_3).



173

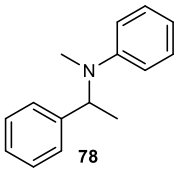
(±)-4-Fluoro-*N*-(1-phenylethyl)aniline (173)

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.116 g, 0.500 mmol) and 4-fluoroaniline (0.196 g, 1.76 mmol), heating for 18 h. Flash column chromatography (98% hexane/2% EtOAc) of the crude material gave amine **173** (53 mg, 49%) as an orange oil. The data were consistent with literature.[348]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.33 (4H, m, Ar**H**), 7.27-7.23 (1H, m, Ar**H**), 6.85-6.78 (2H, m, Ar**H**), 6.48-6.43 (2H, m, Ar**H**), 4.44 (1H, q, *J* = 6.7 Hz, C**H**), 4.04 (1H, br s, N**H**), 1.53 (3H, d, *J* = 6.7 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (C, d, J_F = 234.6 Hz), 144.9 (C), 143.5 (C), 128.7 (2 × CH), 127.0 (CH), 125.8 (2 × CH), 115.5 (2 × CH, d, J_F = 22.3 Hz), 114.1 (2 × CH, d, J_F = 7.1 Hz), 54.1 (CH), 25.0 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ -128.2.



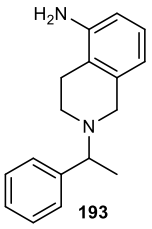
78

(±)-*N*-Methyl-*N*-(1-phenylethyl)aniline (78)

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.117 g, 0.505 mmol) and *N*-methylaniline (0.163 g, 1.52 mmol), heating for 18 h. Flash column chromatography (98% hexane/2% EtOAc) of the crude material gave amine **78** (20 mg, 19%) as an orange oil. The data were consistent with literature.[349]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (4H, m, Ar**H**), 7.29-7.22 (3H, m, Ar**H**), 6.89-6.82 (2H, m, Ar**H**), 6.77-6.71 (1H, m, Ar**H**), 5.15 (1H, q, *J* = 6.8 Hz, C**H**), 2.69 (3H, s, NC**H$_3$**), 1.57 (3H, d, *J* = 6.8 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2 (C), 142.8 (C), 129.2 (2 × CH), 128.4 (2 × CH), 126.9 (2 × CH), 126.8 (CH), 116.6 (CH), 113.0 (2 × CH), 56.5 (CH), 31.8 (CH_3), 16.3 (CH_3).



193

(±)-2-(1-Phenylethyl)-1,2,3,4-tetrahydroisoquinolin-5-amine (193)

The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.117 g, 0.505 mmol) and 5-amino-1,2,3,4-tetrahydroisoquinoline (0.260 mg, 1.75 mmol), heating for 18 h. Flash column chromatography (49% hexane/50% EtOAc/1% triethylamine) of the crude material gave *amine* **193** (31 mg, 24%) as a colourless oil.

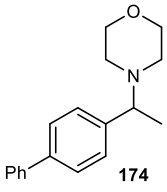
IR 2976, 2796, 1624, 1472, 1292 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.38 (2H, m, Ar**H**), 7.37-7.31 (2H, m, Ar**H**), 7.30-7.24 (1H, m, Ar**H**), 6.96 (1H, t, *J* = 7.7 Hz, Ar**H**), 6.54 (1H, d, *J* = 7.7 Hz, Ar**H**), 6.48 (1H, d, *J* = 7.7 Hz, Ar**H**), 3.79 (1H, d, *J* = 14.8 Hz, ArC**H$_A$**CH$_B$N), 3.58-3.52 (2H, m, C**H** and ArCH$_A$C**H$_B$**N), 2.90-2.83 (1H, m, NC**H$_A$**CH$_B$CH$_2$), 2.73-2.65 (1H, m, NCH$_A$C**H$_B$**CH$_2$), 2.60-2.46 (2H, m, CH$_2$C**H$_2$**Ar), 1.48 (3H, d, *J* = 6.7 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (C), 144.0 (C), 136.1 (C), 128.3 (2 × CH), 127.6 (2 × CH), 126.9 (CH), 126.3 (CH), 119.6 (C), 117.2 (CH), 112.5 (CH), 64.2 (CH), 53.8 (CH_2), 47.9 (CH_2), 24.6 (CH_2), 20.3 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{17}H_{20}N_2$ $[M+H]^+$: 253.1699, found: 253.1706.

5.5.2 Scope with Respect to Boronic Ester for the Alkyl Amination of Boronic Esters



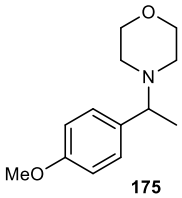
174

(±)-*N*-[(1-([1,1'-Biphenyl]-4-yl)ethyl)morpholine (174)

The title compound was prepared according to General Procedure **11** using boronic ester **297** (0.155 g, 0.503 mmol) and morpholine (0.156 g, 1.79 mmol), heating for 18 h. Flash column chromatography (59% hexane/40% EtOAc/1% triethylamine) of the crude material gave amine **174** (100 mg, 74%) as a colourless oil. The data were consistent with literature.[350]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.55 (4H, m, Ar**H**), 7.49-7.39 (4H, m, Ar**H**), 7.39-7.33 (1H, m, Ar**H**), 3.77-3.70 (4H, m, 2 × OC**H$_2$**), 3.38 (1H, q, *J* = 6.6 Hz, C**H**), 2.61-2.51 (2H, m, 2 × NC**H**), 2.48-2.38 (2H, m, 2 × NC**H**), 1.41 (3H, d, *J* = 6.6 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0 (C), 140.9 (C), 139.9 (C), 128.7 (2 × CH), 128.0 (2 × CH), 127.1 (CH), 127.0 (4 × CH), 67.2 (2 × CH), 65.1 (CH), 51.3 (2 × CH), 19.7 (CH_3).



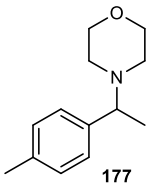
175

(±)-*N*-[1-(4-Methoxylphenyl)ethyl]morpholine (175)

The title compound was prepared according to General Procedure **11** using boronic ester **365** (0.133 g, 0.507 mmol) and morpholine (0.153 g, 1.76 mmol), heating for 18 h. Flash column chromatography (69% hexane/30% EtOAc/1% Et_3N) of the crude material gave amine **175** (73 mg, 65%) as a colourless oil. The data were consistent with literature.[340]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (2H, d, *J* = 8.7 Hz, Ar**H**), 6.86 (2H, d, *J* = 8.7 Hz, Ar**H**), 3.80 (3H, s, OC**H$_3$**), 3.71-3.67 (4H, m, 2 × OC**H$_2$**), 3.27 (1H, q, *J* = 6.7 Hz, C**H**), 2.52-2.43 (2H, m, 2 × NC**H**), 2.40-2.32 (2H, m, 2 × NC**H**), 1.34 (3H, d, *J* = 6.7 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (C), 135.8 (C), 128.6 (2 × CH), 113.6 (2 × CH), 67.2 (2 × CH_2), 64.6 (CH), 55.2 (CH_3), 51.2 (2 × CH_2), 19.7 (CH_3).



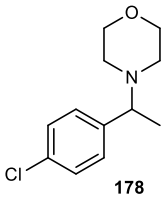
177

(±)-*N*-[1-(4-Methylphenyl)ethyl]morpholine (177)

The title compound was prepared according to General Procedure **11** using boronic ester **296** (0.124 g, 0.504 mmol) and morpholine (0.153 g, 1.76 mmol), heating for 18 h. Flash column chromatography (70% hexane/30% EtOAc) of the crude material gave amine **177** (75 mg, 73%) as a colourless oil. The data were consistent with literature.[350]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.14 (2H, d, *J* = 7.9 Hz, Ar**H**), 3.72-3.68 (4H, m, 2 × OC**H$_2$**), 3.29 (1H, q, *J* = 6.7 Hz, C**H**), 2.49 (2H, br s, 2 × NC**H**), 2.40-2.36 (2H, m, 2 × NC**H**), 2.35 (3H, s, ArC**H$_3$**), 1.35 (3H, d, *J* = 6.7 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7 (C), 136.6 (C), 129.0 (2 × CH), 127.6 (2 × CH), 67.2 (2 × CH_2), 65.1 (CH), 51.3 (2 × CH_2), 21.0 (CH_3), 19.8 (CH_3).



178

(±)-*N*-[1-(4-Chlorophenyl)ethyl]morpholine (178)

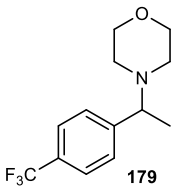
The title compound was prepared according to General Procedure **11** using boronic ester **298** (0.134 g, 0.504 mmol) and morpholine (0.154 g, 1.77 mmol), heating for 19 h. Flash column chromatography (59% hexane/40% EtOAc/1% triethylamine) of the crude material gave *amine* **178** (88 mg, 78%) as a colourless oil.

IR 2960, 2854, 2907, 1490, 1272, 1116 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.24 (4H, m, Ar**H**), 3.71-3.67 (4H, m, 2 × OC**H₂**), 3.29 (1H, q, *J* = 6.7 Hz, C**H**), 2.52-2.44 (2H, m, 2 × NC**H**), 2.38-2.32 (2H, m, 2 × NC**H**), 1.32 (3H, d, *J* = 6.7 Hz, C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7 (C), 132.5 (C), 128.9 (2 × CH), 128.5 (2 × CH), 67.2 (2 × CH_2), 64.7 (CH), 51.2 (2 × CH_2), 19.8 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{12}H_{16}{}^{35}ClNO$ $[M+H]^+$: 226.0993, found: 226.1004.



179

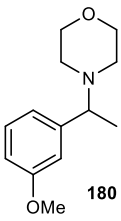
(±)-*N*-[1-[4-(Trifluoromethyl)phenyl]ethyl]morpholine (179)

The title compound was prepared according to General Procedure **11** using boronic ester **229** (0.150 g, 0.501 mmol) and morpholine (154 g, 1.77 mmol), heating for 18 h. Flash column chromatography (69% hexane/30% EtOAc/1% triethylamine) of the crude material gave amine **179** (76 mg, 58%) as a colourless oil. The data were consistent with literature.[340]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.55 (2H, m, Ar**H**), 7.52-7.42 (2H, d, Ar**H**), 3.78-3.65 (4H, m, 2 × OC**H₂**), 3.43-3.31 (1H, m, C**H**), 2.61-2.45 (2H, m, 2 × NC**H**), 2.41-2.28 (2H, m, 2 × NC**H**), 1.35 (3H, d, *J* = 3.9 Hz, C**H₃**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4 (C), 129.3 (C, q, J_{C-F} = 31.7 Hz), 127.9 (2 × CH), 125.3 (2 × CH, q, J_{C-F} = 4.4 Hz), 124.4 (C, q, J_{C-F} = 271.0 Hz), 67.1 (2 × CH_2), 65.1 (CH), 51.2 (2 × CH_2), 19.7 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.4.



180

(±)-*N*-[1-(3-Methoxylphenyl)ethyl]morpholine (180)

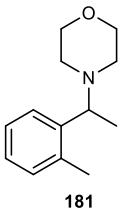
The title compound was prepared according to General Procedure **11** using boronic ester **292** (0.131 g, 0.500 mmol) and morpholine (0.154 g, 1.77 mmol), heating for 18 h. Flash column chromatography (69% hexane/30% EtOAc/1% Et_3N) of the crude material gave *amine* **180** (88 mg, 80%) as a colourless oil.

IR 2958, 2853, 1585, 1264, 1116 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.21 (1H, m, Ar**H**), 6.97-6.88 (2H, m, Ar**H**), 6.82-6.76 (1H, m, Ar**H**), 3.82 (3H, s, OC**H$_3$**), 3.75-3.66 (4H, m, 2 × OC**H$_2$**), 3.32-3.22 (1H, m, C**H**), 2.57-2.45 (2H, m, 2 × NC**H**), 2.44-2.34 (2H, m, 2 × NC**H**), 1.35 (3H, d, *J* = 6.4 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6 (C), 145.8 (C), 129.2 (CH), 120.0 (CH), 113.3 (CH), 112.1 (CH), 67.2 (2 × CH_2) , 65.4 (CH), 55.2 (2 × CH_2), 51.3 (CH_3), 19.9 (CH_3).

HRMS (QTOF) Exact mass calcd for $C_{13}H_{19}NO_2$ $[M]^+$: 221.1410, found: 221.1417.



181

(±)-*N*-[1-(2-Methylphenyl)ethyl]morpholine (181)

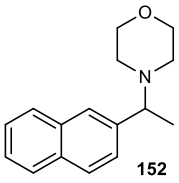
The title compound was prepared according to General Procedure **11** using boronic ester **294** (0.124 g, 0.505 mmol) and morpholine (0.153 g, 1.76 mmol), heating for 19 h. Flash column chromatography (69% hexane/30% EtOAc/1% Et_3N) of the crude material gave *amine* **181** (88 mg, 85%) as a colourless oil.

IR 2958, 2852, 1454, 1261, 1116 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.42 (1H, m, Ar**H**), 7.22-7.15 (1H, m, Ar**H**), 7.15-7.11 (2H, m, Ar**H**), 3.74-3.64 (4H, m, 2 × OC**H$_2$**), 3.54 (1H, q, *J* = 6.6 Hz, C**H**), 2.56-2.48 (2H, m, 2 × NC**H**), 2.42-2.38 (2H, m, 2 × NC**H**), 2.37 (3H, s, ArC**H$_3$**), 1.29 (3H, d, *J* = 6.6 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6 (C), 135.8 (C), 130.4 (CH), 126.8 (CH), 126.4 (CH), 126.0 (CH), 67.3 (2 × CH_2), 60.8 (CH), 51.3 (2 × CH_2), 19.5 (CH_3), 18.6 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{13}H_{19}NO$ $[M+H]^+$: 206.1539, found: 206.1549.



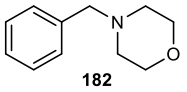
152

(±)-*N*-[1-(2-Naphthalenyl)ethyl]morpholine (152)

The title compound was prepared according to General Procedure **11** using boronic ester **151** (0.142 g, 0.503 mmol) and morpholine (0.155 mg, 1.78 mmol), for 18 h. Flash column chromatography (69% hexane/30% EtOAc/1% Et_3N) of the crude material gave amine **152** (86 mg, 71%) as a colourless oil. The data were consistent with literature.[340]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.80 (3H, m, Ar**H**), 7.74 (1H, s, Ar**H**), 7.58-743 (3H, m, Ar**H**), 3.72 (4H, m, 2 × OC**H$_2$**), 3.51-3.45 (1H, m, C**H**), 2.62-2.51 (2H, m, 2 × NC**H**), 2.45-2.41 (2H, m, 2 × NC**H**), 1.45 (3H, d, *J* = 6.4 Hz, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7 (C), 133.3 (C), 132.8 (C), 128.1 (CH), 127.7 (CH), 127.6 (CH), 126.2 (CH), 126.0 (CH), 125.8 (CH), 125.6 (CH), 67.2 (2 × CH_2), 65.6 (CH), 51.5 (2 × CH_2), 19.8 (CH_3).

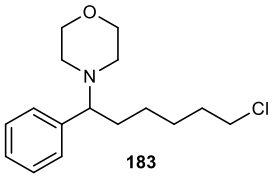


(±)-*N*-benzylmorpholine (182)

The title compound was prepared according to General Procedure **11** using benzyl boronic ester (0.110 g, 0.504 mmol) and morpholine (0.154 mg, 1.78 mmol), for 18 h. Flash column chromatography (69% hexane/30% EtOAc/1% Et_3N) of the crude material gave amine **182** (50 mg, 56%) as a colourless oil. The data were consistent with literature.[351]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.31 (4H, m, Ar**H**), 7.29-7.25 (1H, m, Ar**H**), 3.75-3.70 (4H, m, 2 × OC**H$_2$**), 3.52 (2H, s, ArC**H$_2$**), 2.49-2.43 (4H, m, 2 × NC**H$_2$**CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7 (C), 129.2 (2 × CH), 128.2 (2 × CH), 127.1 (CH), 67.0 (2 × CH_2), 63.4 (CH_2), 53.6 (2 × CH_2).



(±)-*N*-(6-chloro-1-phenylhexyl)morpholine (183)

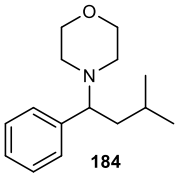
The title compound was prepared according to General Procedure **11** using boronic ester **55** (0.9000 g, 0.28 mmol) and morpholine (87.0 mg, 0.99 mmol), for 18 h. Flash column chromatography (69% hexane/30% EtOAc/1% Et_3N) of the crude material gave *amine* **183** (32 mg, 40%) as a colourless oil.

IR 2935, 2856, 1450, 1683, 1273, 1116.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (2H, m, Ar**H**), 7.28-7.21 (3H, m, Ar**H**), 3.72-3.65 (4H, m, 2 × OC**H$_2$**), 3.46 (2H, t, *J* = 6.7 Hz, C**H$_2$**Cl), 3.24-3.20 (1H, m, C**H**), 2.35-2.32 (4H, m, 2 × NC**H$_2$**), 1.96-1.87 (1H, m, C**H$_A$**CH_B), 1.76-1.64 (3H, m, CH_AC**H$_B$** and C**H$_2$**), 1.44-1.34 (2H, m, C**H$_2$**), 1.20-1.13 (1H, m, C**H$_C$**CH_D), 1.12 -1.02 (1H, m, CH_CC**H$_D$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7 (C), 128.5 (2 × CH), 128.1 (2 × CH), 127.2 (CH), 70.5 (CH), 67.2 (2 × CH_2), 51.1 (2 × CH_2), 45.0 (CH_2), 32.3 (2 × CH_2), 26.9 (CH_2), 25.3 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $C_{16}H_{24}{}^{35}ClNO$ $[M+H]^+$: 282.1619 found: 282.1631.



(±)-4-(2-Phenylbutan-2-yl)morpholine (184)

The title compound was prepared according to General Procedure **11** using 1, 3,2-dioxaborolane,4,4,5,5-tetramethyl-2-(3-methyl-1-phenylbutyl (0.137 g, 0.501 mmol) and morpholine (153 mg, 1.76 mmol), for 18 h. Flash column chromatography (79% hexane/20% EtOAc/1% Et_3N) of the crude material gave *amine* **184** (20 mg, 17%) as a colourless oil.

IR 2955, 2854, 1451, 1270, 1117 cm^{-1}.

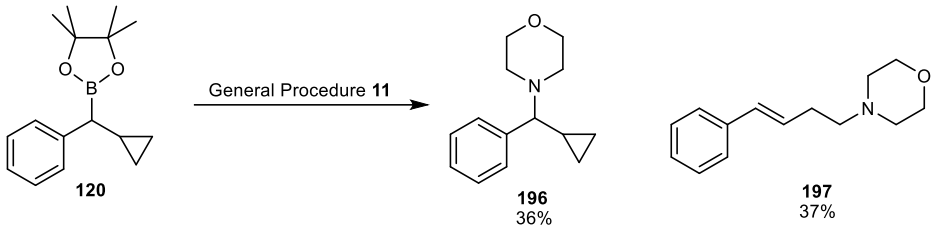
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.30 (2H, m, Ar**H**), 7.29-7.21 (3H, m, Ar**H**), 3.74-3.60 (4H, m, 2 × OC**H$_2$**), 3.34 (1H, dd, *J* = 9.4, 5.6 Hz, ArC**H**), 2.51-2.41 (2H, s, 2 × NC**H**), 2.41-

2.32 (2H, dd, *J* = 10.1, 5.1 Hz, 2 × NC**H**), 1.79-1.63 (2H, m, CHC**H₂**), 1.35-1.26 (1H, m, C**H**CH_3), 0.88 (3H, d, *J* = 6.6 Hz, C**H₃**), 0.84 (3H, d, *J* = 6.6 Hz, C**H₃**).

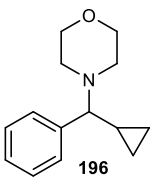
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0 (C), 128.7 (2 × CH), 128.0 (2 × CH), 127.1 (CH), 68.5 (CH), 67.3 (2 × CH_2), 50.9 (2 × CH_2), 41.3 (CH_2), 25.0 (CH_3), 23.7 (CH), 21.9 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{15}H_{23}NO$ $[M+H]^+$: 234.1852 found: 234.1862.

(±)-*N*-[Cyclopropyl(phenyl)methyl]morpholine (196) and (±)-*N*-[(3*E*)-4-Phenylbut-3-en-1-yl]morpholine (197)



The title compounds were prepared according to General Procedure **11** using boronic ester **120** (0.129 g, 0.501 mmol) and morpholine (0.154 mg, 1.78 mmol), for 18 h. Flash column chromatography (69% hexane/30% EtOAc/1% Et_3N) of the crude material gave *amine* **196** (40 mg, 36%) as a colourless oil and *amine* **197** isolated alongside pinacol (40 mg, 37%) as a pale yellow oil.



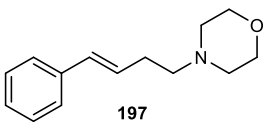
(±)-*N*-[Cyclopropyl(phenyl)methyl]morpholine (196)

IR 2959, 2804, 1451, 1278, 1117 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (4H, m, Ar**H**), 7.28-7.23 (1H, m, Ar**H**), 3.77-3.65 (4H, m, 2 × OC**H₂**), 2.86-2.62 (2H, m, 2 × NC**H**), 2.42-2.32 (2H, m, 2 × NC**H**), 2.24 (1H, d, *J* = 9.2 Hz, NC**H**), 1.10-0.96 (1H, m, cyC**H**), 0.82-0.72 (1H, m, CHC**H$_A$**H$_B$), 0.48-0.40 (1H. m, CHCH$_A$**H$_B$**), 0.40-0.31 (1H, m, CHC**H$_C$**H$_D$), 0.065-0.01 (1H, m, CHCH$_C$**H$_D$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (C), 128.2 (2 × CH), 127.9 (2 × CH), 126.9 (CH), 76.5 (CH), 67.2 (2 × CH_2), 52.4 (2 × CH_2), 15.5 (CH), 8.6 (CH_2), 2.00 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $C_{14}H_{19}NO$ $[M+H]^+$: 218.1539 found: 218.1549.



(±)-*N*-[(3*E*)-4-Phenylbut-3-en-1-yl]morpholine (197)

IR 2956, 2854, 2806, 1698, 1447, 1271, 1116 cm^{-1}.

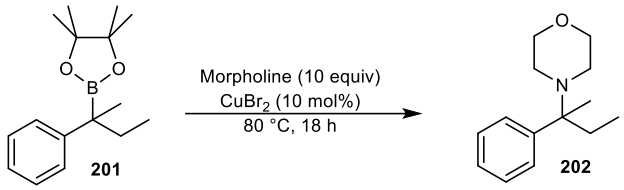
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (4H, m, Ar**H**), 7.24-7.18 (1H, m, Ar**H**), 6.45 (1H, d, *J* = 15.9 Hz, C**H**), 6.22 (1H, dt, *J* = 15.9, 6.1 Hz, C**H**), 3.79-3.71 (4H, m, 2 × OC**H$_2$**), 2.59-2.48 (6H, m, 3 × NC**H$_2$**), 2.47-2.39 (2H, m, C=CC**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5 (C), 131.1 (CH), 128.5 (2 × CH), 128.0 (CH), 127.0 (CH), 126.0 (2 × CH), 66.9 (2 × CH_2), 58.6 (CH_2), 53.6 (2 × CH_2), 30.3 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $C_{14}H_{19}NO$ $[M+H]^+$: 218.1539 found: 218.1541.

5.5.3 Amination of 3° Alkylboronic Esters

(±)-4-(3-Methyl-1-phenylbutyl)morpholine (202)



Morpholine (0.218 g, 2.5 mmol, 10 equiv) was added to a flask containing boronic ester **201** (0.65 g, 0.25 mmol, 1 equiv) and $CuBr_2$ (5.6 mg, 0.025 mmol, 10 mol%), and the mixture was stirred under air at 80 °C for 18 h. The mixture was cooled to room temperature, passed through a plug of silica eluting with Et_2O, and concentrated *in vacuo*. Flash chromatography (89% hexane/10% EtOAc/1% Et_3N) of the crude material gave and *amine* **202** (6 mg, 11%) as a colourless oil.

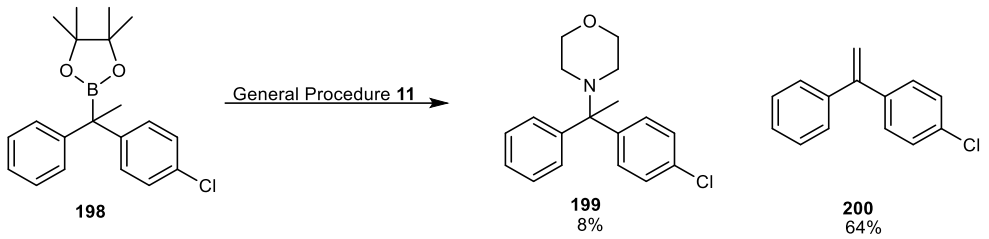
IR 2966, 2851, 1493, 1446, 1273, 1118 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.46 (2H, m, Ar**H**), 7.34-7.28 (2H, m, Ar**H**), 7.23-7.18 (1H, m, Ar**H**), 3.75-3.64 (4H, m, 2 × OC**H$_2$**), 2.60-2.42 (2H, m, 2 × NC**H**), 2.44-2.37 (2H, m, 2 × NC**H**), 1.81-1.71 (1H, m, C**H$_A$**H$_B$CH$_3$), 1.68 – 1.59 (1H, m, CH$_A$**H$_B$**CH$_3$), 1.34 (3H, s, CC**H$_3$**), 0.58 (3H, t, *J* = 7.4 Hz, CH$_2$C**H$_3$**).

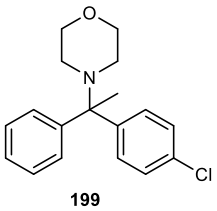
^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8 (C), 127.7 (2 × CH), 127.3 (2 × CH), 126.1 (CH), 67.9 (2 × CH_2), 62.8 (C), 46.8 (2 × CH_2), 33.8 (CH_2), 15.7 (CH_3), 8.7 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{14}H_{21}NO$ $[M+H]^+$: 220.1696 found: 220.1703.

4-[1-(4-Chlorophenyl)-1-phenylethyl]morpholine (199) and 1-(4-Chlorophenyl)-1-phenylethylene (200)



The title compounds were prepared according to General Procedure **11** using boronic ester **198** (0.171 g, 0.502 mmol) and morpholine (0.153 g, 1.76 mmol). Flash chromatography (89% hexane/10% EtOAc/1% Et_3N) of the crude material gave and *amine* **199** (8 mg, 8%) and alkene **200** (69 mg, 64%) as colourless oils.


199

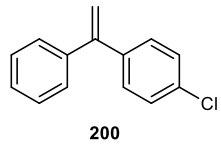
4-[1-(4-Chlorophenyl)-1-phenylethyl]morpholine (199)

IR 2958, 2851, 1488, 1267, 1114 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.43 (4H, m, Ar**H**), 7.32-7.22 (4H, m, Ar**H**), 7.21-7.16 (1H, m, Ar**H**), 3.77-3.72 (4H, m, 2 × OC**H$_2$**), 2.46-2.38 (4H, m, 2 × NC**H$_2$**), 1.77 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (C), 144.2 (C), 132.0 (C), 128.9 (2 × CH), 128.1 (4× CH), 127.4 (2 × CH), 126.5 (CH), 67.7 (2 × CH_2), 66.4 (C), 47.7 (2 × CH_2), 18.9 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $C_{18}H_{20}{}^{35}ClNO$ $[M+]^+$: 301.1228 found: 301.1220.


200

1-(4-Chlorophenyl)-1-phenylethylene (200)

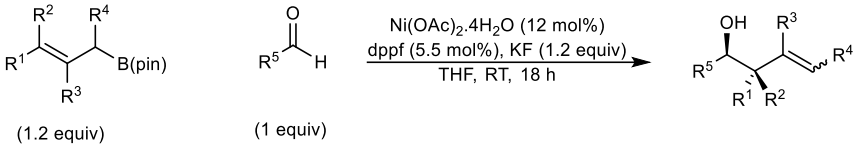
The data were consistent with the literature.[352]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (9H, m, Ar**H**), 5.49 (1H, s, C**H$_2$**), 5.46 (1H, s, C**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0 (C), 141.0 (C), 139.9 (C), 133.6 (C), 129.5 (2 × CH), 128.3 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 114.7 (CH_2).

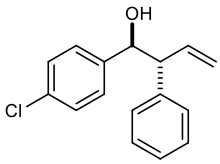
5.6 Nickel Catalysed Allylboration of Aldehydes

General procedure 13



An oven-dried flask was charged with aldehyde (0.330 mmol, 1.0 equiv), $Ni(OAc)_2.4H_2O$ (10.0 mg, 0.040 mmol, 12 mol%), KF (21.0 mg, 0.390 mmol, 1.2 equiv) and dppf (9.5 mg, 0.017 mmol, 5.5 mol%) and purged under nitrogen for 1 h. Boronic ester (0.390 mmol, 1.2 equiv) and THF (3 mL) was added, and the mixture stirred at room temperature for 18 h. Water (10 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography.

5.6.1 Scope of the Reaction with Respect to Aldehyde



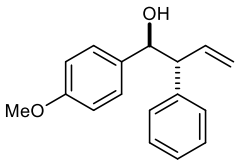
247

(±)-*anti*-1-(4-Chlorophenyl)-2-phenyl-but-3-en-1-ol (247)

The title compound was prepared according to General Procedure **13** from 4-chlorobenzaldehyde (45.3 mg, 0.330 mmol) and boronic ester **122** (99.3 mg, 0.406 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/petroleum ether) to give alcohol **247** (70.4 mg, 84%) as a colourless oil. The data were consistent with the literature.[353]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.15 (5H, m, Ar**H**), 7.07-7.03 (4H, m, Ar**H**), 6.24 (1H, ddd, *J* = 17.1, 10.2, 9.6 Hz, CH_2=C**H**), 5.28 (1H, dd, *J* = 10.2, 1.2 Hz, CH=C$\mathbf{H_A}H_B$), 5.24 (1H, dd, *J* = 17.1, 1.2 Hz, C=$CH_A\mathbf{H_B}$), 4.81 (1H, d, *J* = 7.9 Hz, HOC**H**), 3.48 (1H, dd, *J* = 9.6, 7.9 Hz, C=CC**H**), 2.39 (1H, d, *J* = 2.2 Hz, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3 (C), 140.1 (C), 137.5 (CH), 133.0 (C), 128.4 (2 × CH), 128.2 (2 × CH), 128.0 (4 × CH), 126.7 (CH), 118.7 (CH_2), 76.5 (CH), 59.3 (CH).



259

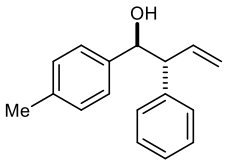
(±)-*anti*-1-(4-Methoxyphenyl)-2-phenyl-but-3-en-1-ol (259)

The title compound was prepared according to General Procedure **13** from *p*-anisaldehyde (45.5 mg, 0.330 mmol) and boronic ester **122** (97.5 mg, 0.399 mmol). The crude material was purified by flash column

chromatography on silica gel (10% Et_2O/petroleum ether) to give alcohol **259** (70.4 mg, 83%) as a colourless oil. The data were consistent with the literature.[354]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.09 (2H, m, Ar**H**), 7.17-7.13 (1H, m, Ar**H**), 7.10-7.05 (4H, m, Ar**H**), 6.77-6.69 (2H, m, Ar**H**), 6.27 (1H, ddd, *J* = 17.0, 10.2, 9.0 Hz, CH_2=C**H**), 5.30-5.23 (2H, m, C=C**H$_2$**), 4.81 (1H, d, *J* = 7.9 Hz, HOC**H**), 3.76 (3H, s, C**H$_3$**), 3.55 (1H, dd, *J* = 9.0, 7.9 Hz, C=CC**H**), 2.32 (1H, s, O**H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8 (C), 140.7 (C), 138.2 (CH), 134.0 (C), 128.3 (4 × CH), 127.8 (2 × CH), 126.5 (CH), 118.2 (CH_2), 113.3 (2 × CH), 76.8 (CH), 59.3 (CH), 55.1 (CH_3).



260

(±)-*anti*-1-(4-Methylphenyl)2-phenyl-but-3-en-1-ol (260)

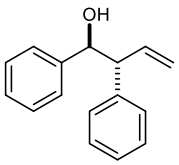
The title compound was prepared according to General Procedure **13** from *p*-tolualdehyde (42.3 mg, 0.330 mmol) and boronic ester **122** (99.7 mg, 0.408 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/petroleum ether) to give *alcohol* **260** (67.4 mg, 80%) as a colourless oil.

IR 3437 (O-H), 3025, 1636, 1492, 1178, 915, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.04 (3H, m, Ar**H**), 7.09-7.01 (6H, m, Ar**H**), 6.26 (1H, ddd, *J* = 17.1, 10.2, 9.1 Hz, C**H**=CH_2), 5.28 (1H, d, *J* = 10.2 Hz, C=C**H$_A$**H$_B$), 5.22 (1H, d, *J* = 17.1 Hz, C=CH$_A$**H$_B$**), 4.84 (1H, d, *J* = 7.8 Hz, HOC**H**), 3.57 (1H, dd, *J* = 9.1, 7.8 Hz, C=CC**H**), 2.29 (3H, s, C**H$_3$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8 (C), 138.8 (C), 138.0 (CH), 137.0 (C), 128.6 (2 × CH), 128.3 (3 × CH), 126.6 (2 × CH), 126.5 (2 × CH), 118.2 (CH_2), 77.0 (CH), 59.1 (CH), 21.1 (CH_3).

HRMS (ESI) Exact mass calculated for $C_{17}H_{18}O$ $[M+Na]^+$: 261.1250, found 261.1246.



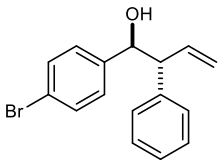
261

(±)-*anti*-1,2-Diphenyl-but-3-en-1-ol (261)

The title compound was prepared according to General Procedure **13** from benzaldehyde (37.0 mg, 0.330 mmol) and boronic ester **122** (100.9 mg, 0.413 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/petroleum ether) to give alcohol **261** (54.4 mg, 72%) as a colourless oil. The data were consistent with the literature.[355]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.14 (8H, m, Ar**H**), 7.08-7.06 (2H, m, Ar**H**), 6.27 (1H, ddd, *J* = 17.2, 10.3, 8.4 Hz, 1H, CH_2=C**H**), 5.30-5.22 (2H, m, C=C**H$_2$**), 4.87 (1H, d, *J* = 7.8 Hz, HOC**H**), 3.57 (1H, dd, *J* = 8.4, 7.8 Hz, C=CC**H**), 2.30 (1H, d, *J* = 2.3 Hz, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8 (C), 140.6 (C), 137.8 (CH), 128.3 (2 × CH), 128.3 (2 × CH), 127.9 (2 × CH), 127.4 (CH), 126.7 (2 × CH), 126.6 (CH), 118.4 (CH_2), 77.2 (CH), 59.2 (CH).



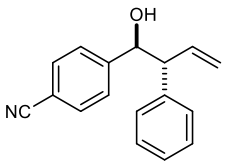
262

(±)-*anti*-1-(4-Bromophenyl)-2-phenylbut-3-en-1-ol (262)

The title compound was prepared according to General Procedure **13** from 4-bromobenzaldehyde (62.9 mg, 0.330 mmol) and boronic ester **122** (99.4 mg, 0.407 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give alcohol **262** (88.3 mg, 85%) as a pale yellow oil. The data were consistent with the literature.[355]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (2H, m, Ar**H**), 7.24-7.16 (3H, m, Ar**H**), 7.05-7.00 (4H, m, Ar**H**), 6.23 (1H, ddd, *J* = 17.0, 10.1, 9.1 Hz, CH_2=C**H**), 5.32-5.24 (2H, m, C=C**H$_2$**), 4.80 (1H, dd, *J* = 8.3, 2.3 Hz, HOC**H**), 3.48 (1H, dd, *J* = 9.1, 8.3 Hz, C=CC**H**), 2.36 (1H, d, *J* = 2.3 Hz, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7 (C), 140.1 (C), 137.5 (CH), 131.0 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 128.2 (2 × CH), 126.8 (CH), 121.2 (C), 118.8 (CH_2), 76.6 (CH), 59.3 (CH).



253

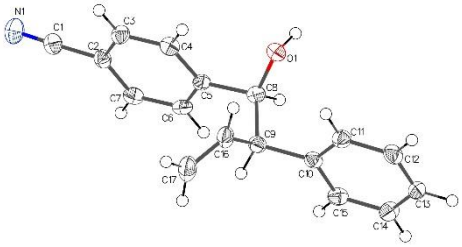
(±)-*anti*-1-(4-Cyanophenyl)-2-phenyl-but-3-en-1-ol (253)

The title compound was prepared according to General Procedure **13** from 4-cyanobenzaldehyde (42.7 mg, 0.330 mmol) and boronic ester **122** (96.1 mg, 0.394 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/petroleum ether) to give alcohol **253** (72 mg, 89%) as a white solid. The data were consistent with the literature.[356]

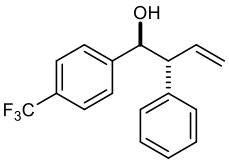
m.p. 98-100 °C (petroleum ether), literature 93-94 °C (Carbon tetrachloride).[357]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (2H, m, Ar**H**) 7.26-7.19 (5H, m, Ar**H**), 7.04-7.02 (2H, m, Ar**H**), 6.23 (1H, dt, *J* = 17.1, 9.7 Hz, CH_2=C**H**), 5.34-5.25 (2H, m, C=C**H$_2$**), 4.87 (1H, d, *J* = 7.9 Hz, HOC**H**), 3.46 (1H, dd, *J* = 9.7, 7.9 Hz, C=CC**H**), 2.48 (1H, s, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1 (C), 139.6 (C), 136.9 (CH), 131.7 (2 × CH), 128.7 (2 × CH), 128.1 (2 × CH), 127.3 (2 × CH), 127.1 (CH), 119.4 (CH_2), 118.8 (C), 111.1 (C), 76.6 (CH), 59.5 (CH).



Crystal Data for $C_{17}H_{15}NO$ (M =249.30 g/mol): monoclinic, space group Pn (no. 7), a = 5.6870(3) Å, b = 7.5687(4) Å, c = 15.6726(8) Å, β = 93.158(2)°, V = 673.57(6) Å^3, Z = 2, T = 99.99 K, μ(CuKα) = 0.598 mm^{-1}, $Dcalc$ = 1.229 g/cm^3, 18609 reflections measured (5.648° ≤ 2Θ ≤ 133.094°), 2317 unique (R_{int} = 0.0648, R_{sigma} = 0.0345) which were used in all calculations. The final R_1 was 0.0327 (I > 2σ(I)) and wR_2 was 0.0875 (all data).



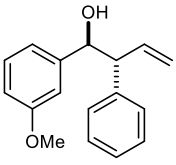
263

(±)-*anti*-1-(4-Trifluoromethyl)-2-phenylbut-3-en-1-ol (263)

The title compound was prepared according to General Procedure **13** from 4-(trifluoromethyl)benzaldehyde (55.2 mg, 0.330 mmol) and boronic ester **122** (104.0 mg, 0.426 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give alcohol **263** (88.3 mg, 95%) as a pale yellow oil. The data were consistent with the literature.[355]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (2H, d, J = 8.1 Hz, Ar**H**), 7.27-7.19 (5H, m, Ar**H**), 7.10-7.05 (2H, m, Ar**H**), 6.25 (1H, ddd, J = 17.1, 10.2, 9.0 Hz, CH_2=C**H**), 5.36-5.21 (2H, m, C=C**H$_2$**), 4.91 (1H, dd, J = 7.7, 2.2 Hz, OHC**H**), 3.52 (1H, dd, J = 9.0, 7.7 Hz, C=CC**H**), 2.40 (1H, d, J = 2.2 Hz, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7 (C), 139.9 (CH), 137.2 (CH), 129.5 (C, q, J_F = 32.3 Hz),128.6 (2 × CH), 128.2 (2 × CH), 127.0 (2 × CH), 124.8 (2 × CH, q, J_F = 3.8 Hz), 123.7 (CF_3, br q, J_F = 272.4 Hz), 119.1 (CH_2), 76.6 (CH), 59.3 (CH).



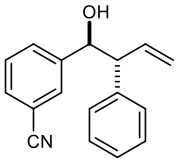
264

(±)-*anti*-1-(3-Methoxyphenyl)-2-phenylbut-3-en-1-ol (264)

The title compound was prepared according to General Procedure **13** from *m*-anisaldehyde (44.7 mg, 0.330 mmol) and boronic ester **122** (101.0 mg, 0.414 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give alcohol **264** (70.5 mg, 84%) as a colourless oil. The data were consistent with the literature.[355]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.16 (2H, m, Ar**H**), 7.12-7.08 (4H, m, Ar**H**), 6.75-6.70 (3H, m, Ar**H**), 6.26 (1H, ddd, J = 17.1, 10.2, 8.9 Hz, CH_2=C**H**), 5.30-5.21 (2H, m, C=C**H$_2$**), 4.84 (1H, d, J = 7.6 Hz, HOC**H**), 3.69 (3H, s, C**H$_3$**), 3.54 (1H, dd, J = 8.9, 7.6 Hz, C=CC**H**), 2.29 (1H, d, J = 2.5 Hz, O**H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2 (C), 143.5 (C), 140.6 (C), 137.8 (CH), 128.9 (CH), 128.3 (4 × CH), 126.6 (CH), 119.0 (CH), 118.4 (CH_2), 113.2 (CH), 111.9 (CH), 77.3 (CH), 59.1 (CH), 55.1 (CH).



265

(±)-*anti*-1-(3-Cyanophenyl)-2-phenyl-but-3-en-1-ol (265)

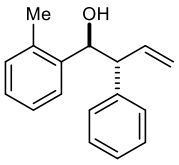
The title compound was prepared according to General Procedure **13** from 3-cyanobenzaldehyde (45.3 mg, 0.330 mmol) and boronic ester **122** (99.3 mg, 0.408 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/petroleum ether) to give *alcohol* **265** (67.3 mg, 78%) as a colourless oil.

IR 3450 (O-H), 2230 (C≡N), 1600, 1493, 920, 799 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.45 (2H, m, Ar**H**), 7.31-7.22 (5H, m, Ar**H**), 7.04-7.02 (2H, m, Ar**H**), 6.23 (1H, dt, *J* = 17.1, 9.7 Hz, CH_2=C**H**), 5.35-5.25 (2H, m, C=C**H$_2$**), 4.86 (1H, d, *J* = 7.9 Hz, HOC**H**), 3.46 (1H, dd, *J* = 9.7, 7.8 Hz, C=CC**H**), 2.46 (1H, s, O**H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2 (C), 139.5 (C), 136.9 (CH), 131.1 (2 × CH), 130.3 (CH), 128.7 (2 × CH), 128.6 (CH), 128.1 (2 × CH), 127.1 (CH), 119.5 (CH_2), 118.8 (C), 111.9 (C), 76.3 (CH), 59.6 (CH).

HRMS (ESI) Exact mass calculated for $C_{17}H_{16}NO$ $[M+H]^+$: 250.1226, found 250.1231.



266

(±)-*anti*-1-(2-Methyl phenyl)-2-phenyl-but-3-en-1-ol (266)

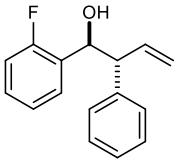
The title compound was prepared according to General Procedure **13** from *o*-tolualdehyde (41.3 mg, 0.330 mmol) and boronic ester **122** (97.8 mg, 0.400 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/petroleum ether) to give *alcohol* **266** (58 mg, 71%) as a colourless oil.

IR 3416 (O-H), 2920, 1600, 1452, 1178, 918, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.23-7.16 (7H, m, Ar**H**), 6.99 (1H, d, *J* = 7.5 Hz, Ar**H**), 6.35 (1H, ddd, *J* = 17.1, 10.2, 8.9 Hz, CH_2=C**H**), 5.30 (1H, dd, *J* = 10.2, 1.2 Hz, C=C**H$_A$**H$_B$), 5.20 (1H, dd, *J* = 17.1, 1.2 Hz, C=CH$_A$**H$_B$**), 5.12 (1H, d, *J* = 7.1 Hz, HOC**H**), 3.62 (1H, dd, *J* = 8.9, 7.1 Hz, C=CC**H**), 2.06 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (C), 140.2 (C), 137.3 (CH), 135.1 (C), 130.0 (CH), 128.3 (4 × CH), 127.2 (CH), 126.6 (CH), 126.5 (CH), 125.8 (CH), 118.6 (CH_2), 73.1 (CH), 57.7 (CH), 19.1 (CH_3).

HRMS (ESI) Exact mass calculated for $C_{17}H_{18}O$ $[M+Na]^+$: 261.1250, found 261.1250.



267

(±)-*anti*-1-(2-Fluorophenyl)-2-phenyl-but-3-en-1-ol (267)

The title compound was prepared according to General Procedure **13** from 2-fluorobenzaldehyde (41.3 mg, 0.330 mmol) and boronic ester **122** (97.2 mg, 0.398 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/petroleum ether) to give *alcohol* **267** (66.4 mg, 82%) as a pale yellow oil.

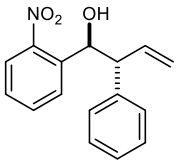
IR 3411 (O-H), 2915, 1489, 1221, 1030, 918, 796 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.39 (1H, m, Ar**H**), 7.24-7.19 (6H, m, Ar**H**), 7.08 (1H, td, *J* = 7.5, 2.5 Hz, Ar**H**), 6.90-6.87 (1H, m, Ar**H**), 6.29-6.23 (1H, m, CH_2=C**H**), 5.26-5.23 (2H, m, C=C**H$_A$**H$_B$ and HOC**H**), 5.16 (1H, dd, *J* = 17.7, 1.7 Hz, C=CH$_A$**H$_B$**), 3.69 (1H, dd, *J* = 8.2, 7.8 Hz, C=CC**H**), 2.25 (1H, br s, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (d, J_F = 245.6 Hz, C), 140.5 (C), 137.2 (C), 129.1 (d, J_F = 12.8 Hz, CH), 128.9 (d, J_F = 8.4 Hz, CH), 128.3 (d, J_F = 21.0 Hz, CH), 128.2 (d, J_F = 4.4 Hz, CH), 126.7 (CH), 123.9 (d, J_F = 3.4 Hz, CH), 118.5 (CH_2), 115.0 (d, J_F = 22.1 Hz, CH), 71.2 (CH), 57.5 (CH).

^{19}F NMR (377 MHz, $CDCl_3$) δ -118.5.

HRMS (EI) Exact mass calculated for $C_{16}H_{15}FO$ [M+]: 242.1101, found 242.1112.



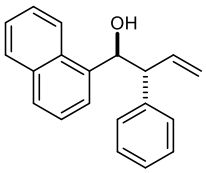
268

(±)-*anti*-1-(2-Nitrophenyl)-2-phenylbut-3-en-1-ol (268)

The title compound was prepared according to General Procedure **13** from 2-nitrobenzaldehyde (50.2 mg, 0.330 mmol) and boronic ester **122** (98.6 mg, 0.404 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give alcohol **268** (70.4 mg, 79%) as a colourless oil. The data were consistent with the literature.[355]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (1H, dd, *J* = 8.2, 1.2 Hz, Ar**H**), 7.76-7.75 (1H, m, Ar**H**), 7.58 (1H, dd, *J* = 11.0, 4.2 Hz, Ar**H**), 7.40-7.34 (1H, m, Ar**H**), 7.31-7.20 (5H, m, Ar**H**), 6.37-6.28 (1H, m, CH=C**H**), 5.64 (1H, d, *J* = 5.3 Hz, 1H, HOC**H**), 5.20 (1H, dd, *J* = 10.2, 1.5 Hz, C=C**H$_A$**H$_B$), 5.03 (1H, dd, *J* = 17.1, 1.0 Hz, C=CH$_A$**H$_B$**), 3.75 (1H, dd, *J* = 9.2, 5.3 Hz, C=CC**H**), 2.38 (1H, s, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0 (C), 140.7 (C), 137.3 (C), 135.7 (CH), 132.8 (CH), 129.4 (CH), 128.7 (2 × CH), 128.1 (3 × CH), 127.0 (CH), 124.3 (CH), 119.1 (CH_2), 72.6 (CH), 56.7 (CH).



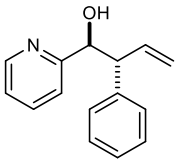
269

(±)-*anti*-1-(1-Naphthyl)-2-phenyl-but-3-en-1-ol (269)

The title compound was prepared according to General Procedure **13** from 1-naphthaldehyde (50.5 mg, 0.330 mmol) and boronic ester **122** (99.0 mg, 0.406 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/petroleum ether) to give alcohol **269** (75.8 mg, 85%) as a pale yellow oil. The data were consistent with the literature.[358]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.87-7.85 (1H, m, Ar**H**), 7.75 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.56-7.40 (4H, m, Ar**H**), 7.27-7.23 (4H, m, Ar**H**), 7.20-7.16 (1H, m, Ar**H**), 6.37-6.28 (1H, m, CH_2=C**H**), 5.73-5.71 (1H, m, HOC**H**), 5.22 (1H, d, *J* = 10.3 Hz, C=C**H$_A$**H$_B$), 5.00 (1H, d, *J* = 17.2 Hz, C=CH$_A$**H$_B$**), 3.94 (1H, dd, *J* = 8.4, 5.5 Hz, C=CC**H**), 2.30 (1H, d, *J* = 3.2 Hz, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6 (C), 137.7 (CH), 136.7 (C), 133.7 (C), 130.5 (C), 128.9 (CH), 128.5 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 126.7 (CH), 125.9 (CH), 125.3 (CH), 125.0 (CH), 124.5 (CH), 123.1 (CH), 118.6 (CH_2), 74.2 (CH), 56.6 (CH).



270

(±)-*anti*-2-Phenyl-1-(pyridine-2-yl) but-3-en-1-ol (270)

The title compound was prepared according to General Procedure **13** from 2-pyridinecarboxaldehyde (35.7 mg, 0.330 mmol) and boronic ester **122** (95.0 mg, 0.389 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/petroleum ether) to give *alcohol* **270** (52 mg, 69%) as a pale yellow oil.

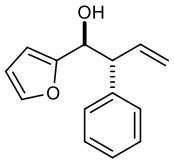
m.p. 75-77 °C (petroleum ether).

IR 3250 (O-H), 3080, 2441, 2159, 1973, 1598, 1433, 1066, 928, 756, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (1H, d, *J* = 4.5 Hz, Ar**H**), 7.60-7.56 (1H, m, Ar**H**), 7.29-7.19 (6H, m, Ar**H**), 6.98 (1H, d, *J* = 7.9 Hz, Ar**H**), 6.24 (1H, ddd, *J* = 17.1, 10.3, 8.3 Hz, CH_2=C**H**), 5.16-5.13 (1H, dd, *J* = 10.7, 1.2 Hz, HOC**H**), 5.07-5.01 (2H, m, C=C**H$_2$**), 4.25 (1H, br s, O**H**), 3.78-3.71 (1H, m, C=CC**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0 (CH), 148.2 (C), 141.2 (C), 137.1 (CH), 136.1 (CH), 128.5 (2 × CH), 128.4 (2 × CH), 126.6 (CH), 122.4 (CH), 121.5 (CH), 117.6 (CH_2), 76.2 (CH), 57.8 (CH).

HRMS (ESI) Exact mass calculated for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1226, found 226.1230.



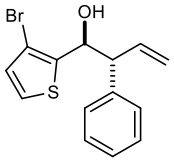
271

(±)-*anti*-1-(Furan-2-yl)-2-phenyl-but-3-en-1-ol (271)

The title compound was prepared according to General Procedure **13** from furaldehyde (35.8 mg, 0.330 mmol) and boronic ester **122** (96.2 mg, 0.394 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/petroleum ether) to give alcohol **271** (49.1 mg, 62%) as a pale yellow oil. The data were consistent with the literature.[358]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.15 (6H, m, Ar**H**), 6.25-6.20 (2H, m, Ar**H**), 6.06 (1H, ddd, *J* = 17.2, 10.2, 8.3 Hz, CH_2=C**H**), 5.31-5.25 (2H, m, CH=C**H$_2$**), 4.90 (1H, d, *J* = 8.3 Hz, HOC**H**), 3.85 (1H, t, *J* = 8.3, Hz, C=CC**H**), 2.27 (1H, s, O**H**).

^{13}C NMR 154.2 (C), 141.8 (CH), 140.4 (C), 137.6 (CH), 128.4 (2 × CH), 128.1 (2 × CH), 126.8 (CH), 118.5 (CH_2), 110.1 (CH), 107.6 (CH), 71.0 (CH), 55.9 (CH).



272

(±)-*anti*-1-(3-Bromothiophen-2-yl)-2-phenylbut-3-en-1-ol (272)

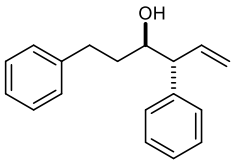
The title compound was prepared according to General Procedure **13** from 3-bromothiophene-2-carboxaldehyde (63.9 mg, 0.330 mmol) and boronic ester **122** (100.6 mg, 0.412 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/pentane) to give *alcohol* **272** (83 mg, 80%) as a colourless oil.

IR 3414 (O-H), 3038, 2904, 2174, 1601, 1494, 920, 870, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.20 (6H, m, Ar**H**), 6.81 (1H, d, *J* = 5.3 Hz, Ar**H**), 6.31 (1H, ddd, *J* = 17.1, 10.2, 8.9 Hz, CH_2=C**H**), 5.30-5.28 (2H, m, C=C**H$_A$**CH_B and HOC**H**), 5.26-5.21 (1H, m, C=CH_A**C**$\mathbf{H_B}$), 3.78-3.70 (1H, m, C=CC**H**), 2.44 (1H, d, *J* = 2.9 Hz O**H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.3 (C), 139.9 (C), 136.8 (CH), 129.5 (CH), 128.5 (2× CH), 128.2 (2 × CH), 126.9 (CH), 125.1 (CH), 119.0 (CH_2), 108.6 (C), 72.4 (CH), 57.9 (CH).

HRMS (ESI) Exact mass calculated for $C_{14}H_{13}{}^{81}BrOS$ $[M+Na]^+$: 332.9742, found: 332.9742.



273

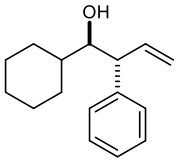
(±)-*anti*-1,4-Diphenylhex-5-en-3-ol (273)

The title compound was prepared according to General Procedure **13** from 3-phenylpropionaldehyde (44.2 mg, 0.330 mmol) and boronic ester **122** (97.3 mg, 0.399 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/petroleum ether) to give alcohol **273** (57.2 mg, 69%) as a colourless oil. The data were consistent with the literature.[359]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, t, *J* = 7.3 Hz, Ar**H**), 7.27-7.22 (3H, m, Ar**H**), 7.18-7.17 (3H, m, Ar**H**), 7.12 (2H, d, *J* = 7.0 Hz, Ar**H**), 6.16-6.07 (1H, m, CH_2=C**H**), 5.25 (1H, dd,

J = 10.2, 1.1 Hz, C=C**H**$_A$H$_B$), 5.22 (1H, d, *J* = 17.4, 1.1 Hz, C=CH$_A$**H$_B$**), 3.83-3.76 (1H, m, HOC**H**), 3.30-3.26 (1H, m, C=CC**H**), 2.88-2.81 (1H, m, PhC**H$_A$**H$_B$), 2.67-2.59 (1H, m, PhCH$_A$**H$_B$**), 1.88-1.86 (1H, m, PhCH$_2$C**H$_A$**H$_B$), 1.70-1.61 (1H, m, PhCH$_2$CH$_A$**H$_B$**), 1.58 (1H, s, O**H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0 (C), 141.4 (C), 138.3 (CH), 128.7 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.0 (2 × CH), 126.7 (CH), 125.7 (CH), 118.0 (CH_2), 73.2 (CH), 57.5 (CH), 36.0 (CH_2), 32.0 (CH_2).



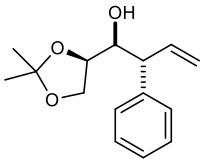
274

(±)-*anti*-1-Cyclohexyl-2-phenylbut-3-en-1-ol (274)

The title compound was prepared according to General Procedure **13** from cyclohexane carboxaldehyde (38.9 mg, 0.347 mmol) and boronic ester **122** (99.6 mg, 0.408 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/petroleum ether) to give alcohol **274** (47.2 mg, 59%) as a colourless oil. The data were consistent with the literature.[360]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.32 (2H, m, Ar**H**), 7.27-7.22 (3H, m, Ar**H**), 6.15 (1H, dd, *J* = 17.0, 9.7, 8.7 Hz, C**H**=CH_2), 5.24-5.18 (2H, m, CH=C**H$_2$**), 3.60-3.58 (1H, m, HOC**H**), 3.47 (1H, dd, *J* = 8.7, 7.8 Hz, C=CC**H**), 1.83-1.82 (1H, m, Cy), 1.73-1.59 (4H, m, Cy), 1.27-1.01 (6H, m, Cy).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1 (C), 138.4 (CH), 128.7 (2 × CH), 127.9 (2 × CH), 126.5 (CH), 117.7 (CH_2), 78.1 (CH), 53.7 (CH), 39.5 (CH), 30.2 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 26.0 (CH_2).



276

(+)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl-2-phenylbut-3-en-1-ol (276)

The title compound was prepared according to General Procedure **13** from 2,3-*O*-isopropylidene-*D*-glyceraldehyde (50% w/w in dichloromethane 175.5 mg, 0.674 mmol) and boronic ester **122** (196.6 mg, 0.805 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give *alcohol* **276** (70.6 mg, 42%) as a pale yellow solid.

$[\alpha]_D^{20}$ +82 (*c* = 0.22, $CHCl_3$)

m.p. 54–56 °C (pentane).

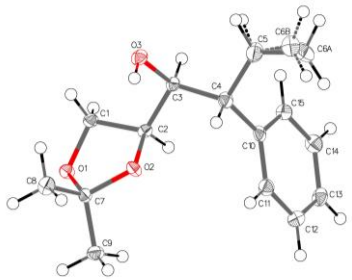
IR 3480 (O-H), 1600, 1454, 1370, 1157, 917, 796 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ Major diastereomer: 7.35-7.32 (2H, m, Ar**H**), 7.26-7.24 (3H, m, Ar**H**), 6.25 (1H, ddd, *J* = 17.2, 10.2, 8.5 Hz, CH_2=C**H**), 5.21 (1H, d, *J* = 10.2 Hz, C=C**H$_A$**H$_B$), 5.15 (1H, d, *J* = 17.2 Hz, C=CH$_A$**H$_B$**) 3.92 (1H, td, *J* = 6.7, 4.8, OC**H**CH_2), 3.77-

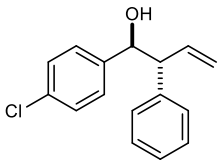
3.70 (2H, m, OC**H**$_c$H$_D$ and C**H**OH), 3.62 (1H, t, *J* = 6.7 Hz, OCH$_c$**H$_D$**), 3.39 (1H, t, *J* = 8.5 Hz, C=CC**H**), 2.31 (1H, s, O**H**), 1.44 (3H, s, C**H$_3$**), 1.31 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ Major diastereomer: 140.8 (C), 138.1 (CH), 128.7 (2 × CH), 128.2 (2 × CH), 126.9 (CH), 117.2 (CH_2), 109.1 (C), 76.5 (CH), 74.3 (CH), 66.1 (CH_2), 54.1 (CH), 26.4 (CH_3), 25.3 (CH_3).

HRMS (Q-TOF): Exact mass calculated for $C_{15}H_{21}O_3$ $[M + H]^+$: 249.1446, found: 249.1485.



Crystal Data for $C_{15}H_{20}O_3$ (*M* =248.31 g/mol): monoclinic, space group $P2_1/n$ (no. 14), *a* = 13.102(3) Å, *b* = 5.5167(13) Å, *c* = 18.442(5) Å, *β* = 91.914(5)°, *V* = 1332.2(6) Å^3, *Z* = 4, *T* = 100 K, μ(MoKα) = 0.085 mm^{-1}, *Dcalc* = 1.238 g/cm^3, 18892 reflections measured (3.754° ≤ 2Θ ≤ 55.276°), 3078 unique (R_{int} = 0.0564, R_{sigma} = 0.0440) which were used in all calculations. The final R_1 was 0.0536 (I > 2σ(I)) and wR_2 was 0.1197 (all data).

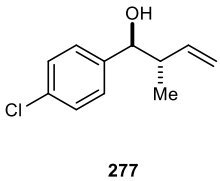


247

(±)-*anti*-1-(4-Chlorophenyl)-2-phenyl-but-3-en-1-ol (247) (Gram Scale)

The title compound was prepared according to General Procedure **13** from 4-chlorobenzaldehyde (1.00 g, 7.11 mmol) and boronic ester **122** (2.09 g, 8.53 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give alcohol **247** (1.67 g, 90%) as a pale yellow oil. The data were consistent with the literature.[353] (See above for NMR data).

5.6.2 Scope of the Reaction with Respect to Boronic Esters



277

(±)-*anti*-1-(4-Chlorophenyl)-3-methyl-but-3-en-1-ol (277)

The title compound was prepared according to General Procedure **13** from 4-chlorobenzaldehyde (48.3 mg, 0.33 mmol) and boronic ester **224** (72.8 g, 0.039 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/pentane) to give alcohol **277** (44.2 mg, 65%) as a pale yellow oil. The data were consistent with the literature.[361]

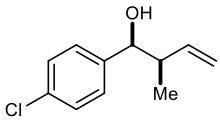
^{1}H NMR (400 MHz, $CDCl_3$) δ *anti* isomer: 7.35-7.23 (4H, m, Ar**H**), 5.82-5.68 (1H, m, C=C**H**), 5.23-5.22 (2H, m, C=C**H$_2$**), 4.36 (1H, d, *J* = 7.8 Hz, HOC**H**), 2.45-2.41 (1H, m, C=CC**H**), 2.16 (1H, s, O**H**), 0.88 (3H, d, *J* = 6.8 Hz, C**H$_3$**).

Characteristic signals from the minor diastereoisomer were:

^{1}H NMR (400 MHz, $CDCl_3$) δ *syn* isomer: 5.11-4.99 (1H, m, C=C**H$_2$**), 4.62 (1H, d, *J* = 5.4 Hz, HOC**H**), 2.59-2.48 (m, 1H, C=CC**H**), 1.93 (s, 1H, O**H**), 1.00 (d, *J* = 6.8 Hz, 1H, C**H$_3$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ *anti* isomer: 140.8 (C), 140.2 (CH), 133.3 (C), 128.4 (2 × CH), 128.2 (2 × CH), 117.3 (CH_2), 76.5 (CH), 46.4 (CH), 16.4 (CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ *syn* isomer: 140.9 (C), 139.8 (CH), 133.0 (C), 127.8 (2 × CH), 116.0 (CH_2), 77.1 (CH), 44.6 (CH), 13.8 (CH_3).



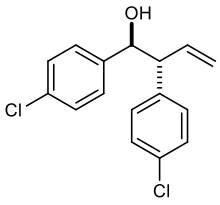
279

(±)-*syn*-1-(4-Chlorophenyl)-3-methylbut-3-en-1-ol (279)

The title compound was prepared according to General Procedure **13** from 4-chlorobenzaldehyde (42.3 mg, 0.330 mmol) and boronic ester **278** (73.6 mg, 0.390 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give alcohol **279** (59.0 mg, 99%) as a colourless oil. The data were consistent with the literature.[361]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (2H, m, Ar**H**), 7.27-7.24 (2H, m, Ar**H**), 5.75 (1H, ddd, *J* =17.3, 10.6, 7.0 Hz, C=C**H**), 5.13-5.02 (2H, m, C=C**H$_2$**), 4.62 (1H, d, *J* =5.4 Hz, HOC**H**), 2.56 (1H, dt, *J* = 6.8, 5.7 Hz, C=CC**H**), 1.92, (1H, s, O**H**), 1.00 (3H, d, *J* = 6.8 Hz, C**H$_3$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.0 (C), 139.9 (CH), 133.0 (C), 128.2 (2 × CH), 127.9 (2 × CH), 116.0 (CH_2), 76.5 (CH), 44.6 (CH), 13.8 (CH_3).



281

(±)-*anti*-1,2-bis(4-chlorophenyl) but-3-en-1-ol (281)

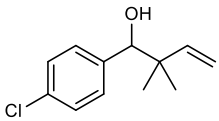
The title compound was prepared according to General Procedure **13** from 4-chlorobenzaldehyde (47.1 mg, 0.330 mmol) and boronic ester **280** (111.1 mg, 0.390 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give *alcohol* **281** (87.4 mg, 89%) as a colourless oil.

IR 3418 (O-H), 2904, 1596, 1490, 1090, 1013, 923, 820 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.16 (4H, m, Ar**H**), 7.06 (2H, dd, *J* = 8.7, 2.1 Hz, Ar**H**), 7.00-6.90 (2H, m, Ar**H**), 6.18 (1H, ddd, *J* = 17.1, 10.1, 8.9 Hz, CH_2C**H**), 5.31 (1H, dd, *J* = 10.1, 0.8 Hz, C=C**H$_A$**CH_B), 5.24 (1H, *J* = 17.1, 0.8 Hz, C=CH_AC**H$_B$**), 4.76 (1H, dd, *J* = 7.9, 2.2 Hz, HOC**H**), 3.48 (1H, dd, *J* = 8.9, 7.9 Hz, C=CC**H**), 2.32 (1H, d, *J* = 2.2 Hz, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0 (C), 138.7 (C), 137.1 (CH), 133.3 (C), 132.6 (C), 129.6 (2 × CH), 128.6 (2 × CH), 128.2 (2 × CH), 128.0 (2 × CH), 119.1 (CH_2), 76.5 (CH), 58.6 (CH).

HRMS (ES+) Exact mass calculated for $C_{16}H_{14}O^{35}Cl_2$ [M+Na^+]: 315.0319, found 315.0322.



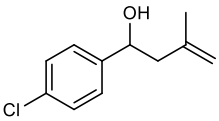
282

1-(4-Chlorophenyl)-2,2-dimethylbut-3-en-1-ol (282)

The title compound was prepared according to General Procedure **13** from 4-chlorobenzaldehyde (47.8 mg, 0.340 mmol) and boronic ester **129** (81.4 mg, 0.415 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give alcohol **282** (56.7 mg, 79%) as a colourless oil. The data were consistent with the literature.[362]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.25 (4H, m, Ar**H**), 5.91 (1H, dd, *J* = 17.5, 10.8 Hz, 1H, C**H**=CH_2), 5.19 (1H, dd, *J* = 10.8, 1.1 Hz, C=C**H$_A$**C**H$_B$**), 5.11 (1H, dd, *J* = 17.5, 1.1 Hz, C=CH_AC**H$_B$**), 4.44 (1H, s, C**H**OH), 2.06 (1H, d, *J* = 2.1 Hz, O**H**), 1.02 (3H, s, C**H$_3$**), 0.97 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (CH), 139.1 (C), 133.1 (C), 129.1 (2 ×CH), 127.6 (2 × CH), 114.4 (CH_2), 79.9 (CH), 42.3 (C), 24.4 (CH_3), 20.7 (CH_3).



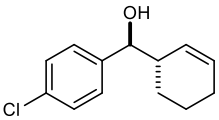
283

(±)-1-(4-Chlorophenyl)-3-methylbut-3-en-1-ol (283)

The title compound was prepared according to General Procedure **13** from 4-chlorobenzaldehyde (46.7 mg, 0.332 mmol) and boronic ester **126** (77.6 mg, 0.426 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give alcohol **283** (61.8 mg, 95%) as a pale yellow oil. The data were consistent with the literature.[353]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (4H, s, Ar**H**), 4.95 (1H, d, *J* = 1.4 Hz, C=C**H$_A$**C**H$_B$**), 4.87 (1H, d, *J* = 1.4 Hz, C=CH_AC**H$_B$**), 4.80 (1H, ddd, *J* = 7.8, 5.6, 2.2 Hz, HOC**H**), 2.48-2.33 (2H, m, CHC**H$_2$**), 2.16 (1H, d, *J* = 2.2 Hz, O**H**), 1.81 (s, 3H, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5 (C), 142.0 (C), 133.1 (C), 128.5 (2 × CH), 127.1 (2 × CH), 114.5 (CH_2), 70.7 (CH), 48.4 (CH_2), 22.3 (CH_3).



285

(±)-*anti*-(4-Chlorophenyl)(cyclohex-2-en-1-yl)methanol (285)

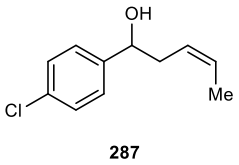
The title compound was prepared according to General Procedure **13** from 4-chlorobenzaldehyde (49.9 mg, 0.330 mmol) and boronic ester **284** (85.3 mg, 0.390 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give *alcohol* **285** (54.9 mg, 70%) as a colourless oil.[356]

IR 3377 (O-H), 2920, 2870, 1597, 1490, 1012, 904, 815 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (4H, m, Ar**H**), 5.83 (1H, ddd, *J* = 10.0, 6.1, 3.5 Hz, CHCH=C**H**), 5.37 (1H, dd, *J* = 10.0, 1.9 Hz, CHC**H**=CH), 4.57 (1H, d, *J* = 6.2 Hz, OHC**H**), 2.54-2.45 (1H, m, CH=CHC**H**), 2.20-1.93 (2H, m, CH=CHC**H_2**), 1.92 (1H, s, O**H**), 1.75 (1H, ddd, *J* = 14.7, 9.2, 4.8 Hz, CHC**H_A**H_B), 1.61 (1H, ddd, *J* = 17.0, 9.4, 5.5 Hz, $CHCH_2C$**H_A**H_B), 1.54-1.45 (2H, m, $CHCH_2CH_A$**H_B** and $CHCH_A$**H_B**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2 (C), 133.0 (C), 130.9 (CH), 128.3 (2 × CH), 127.8 (2 × CH), 127.6 (CH), 76.6 (CH), 43.0 (CH), 25.2 (CH_2), 23.5 (CH_2), 21.0 (CH_2).

HRMS (EI) Exact mass calculated for $C_{13}H_{15}{}^{35}ClO$ [M^+]: 222.0804, found 222.0804.



287

(±)-(*Z*)-1-(4-Chlorophenyl)-pent-3-en-1-ol (287)

The title compound was prepared according to General Procedure **13** from 4-chlorobenzaldehyde (45.2 mg, 0.330 mmol) and boronic ester **286** (72.5 mg, 0.390 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give alcohol **287** (47.3 mg, 75%) as a colourless oil. The data were consistent with the literature.[220]

The literature data for the ***E*-287** and ***Z*-287** isomers has inconsistencies. Based on reference[220] we have assigned the major isomer as ***Z*-287**.

^{1}H NMR (400 MHz, $CDCl_3$) δ *Z* isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (4H, m, Ar**H**), 5.70-5.66 (1H, m, C=C**H**), 5.45-5.38 (1H, m, C=C**H**), 4.74-4.71 (1H, m, HOC**H**), 2.64-2.34 (2H, m, C**H_2**), 1.96 (1H, br s, O**H**), 1.62 (3H, d, *J* = 7.4 Hz, C**H_3**).

Characteristic signals from (*E*)-**287** were observed at:

^{1}H NMR (400 MHz, $CDCl_3$) δ *E* isomer: 4.66-4.59 (1 H, m, HOC**H**), 1.71 (3H, d, *J* = 6.4 Hz, C**H_3**).

^{13}C NMR (101 MHz, $CDCl_3$) *Z* isomer: δ 142.5 (C), 133.1 (C), 128.5 (2 × CH), 128.1 (CH), 127.2 (2 × CH), 125.2 (CH), 73.1 (CH), 37.0 (CH_2), 13.0 (CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) *E* isomer: δ 133.0 (C), 130.0 (C), 127.8 (2 × CH), 127.2 (2 × CH), 126.3 (CH), 72.7 (CH) 42.8 (CH_2) 18.1 (CH_3)

Data from reference 220:

Z-isomer:[220]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.32 (4H, m, Ar**H**), 5.69-5.62 (1H, m, CH=C**H**), 5.36-5.43 (1H, m, CH=C**H**), 4.70 (1H, br t, *J* = 6.4 Hz, ArC**H**), 2.58-2.50 (1H, m, 1H, C**H_A**CH_B CHC**H_A**H_B), 2.47-2.40 (1H, m, $CHCH_A$**H_B**), 2.02 (1H, br s, O**H**), 1.59 (3H, dt, *J* = 6.8, 0.8 Hz, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5 (C), 133.1 (C), 128.4 (CH), 128.1 (CH), 127.2 (CH), 125.1 (CH), 73.1 (CH), 37.0 (CH_2), 13.0 (CH_3).

Data from reference 363:

E-isomer:[363]

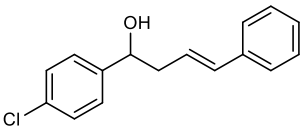
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (4H, m), 5.70-5.56 (1H, m,), 5.43-5.36 (1H, m), 4.72-4.68 (1H, m), 2.58-2.31 (2H, m), 2.05 (1H, s), 1.60 (3H, d, *J* = 6.0 Hz).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.57, 133.11, 128.49, 128.49, 128.05, 127.24, 127.24, 125.21, 73.14, 36.95, 12.96.

Z-isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67–4.64 (1H, m), 2.10 (1H, s), 1.69 (3H, d, *J* = 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.53, 133.02, 129.91, 128.47, 128.47, 127.20, 127.20, 126.31, 72.74, 42.81, 18.02.



289

(±)-(*E*)-1-(4-Chlorophenyl)4-phenylbut-3-en-1-ol (289)

The title compound was prepared according to General Procedure **13** from 4-chlorobenzaldehyde (40.8 mg, 0.280 mmol) and boronic ester **288** (82.9 mg, 0.330 mmol). The crude material was purified by flash column chromatography on silica gel (10% Et_2O/*n*-hexane) to give alcohol **289** (57.2 mg, 76%) as a white solid. The data were consistent with the literature.[364]

m.p. 123-125 °C (Petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$) δ *E* isomer: 7.38-7.21 (9H, m, Ar**H**), 6.51 (1H, d, *J* = 15.9 Hz, C=C**H**Ph), 6.27-6.12 (1H, m, C**H**=CHPh), 4.81 (1H, ddd, *J* = 8.1, 5.2, 3.2 Hz, HOC**H**), 2.73-2.58 (2H, m, C**H$_2$**), 2.08 (1H, d, *J* = 3.2 Hz, O**H**).

^{1}H NMR (400 MHz, $CDCl_3$) δ *Z* isomer: 6.60 (1H, d, *J* = 12.4 Hz C=C**H**Ar), 5.79-5.65 (1H, m C**H**=CHPh), 2.88-2.80 (2H, m, C**H$_2$**), 1.97 (1H, d, *J* = 3.51, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) *E* isomer: δ 142.3 (C), 137.0 (C), 133.9 (CH), 133.2 (C), 128.6 (2 × CH), 128.6 (2 × CH), 127.5 (CH), 127.2 (2 × CH), 126.2 (2 × CH), 125.3 (CH), 73.0 (CH), 43.1 (CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) *Z* isomer: 132.1 (C), 128.7 (2 × CH), 128.2 (2 × CH), 127.3 (2 × CH), 126.9 (CH), 73.5 (CH), 38.2 (CH_2).

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