Synthesis and Suzuki-Miyaura Cross-Coupling of α-Borylated Pyrrolidines

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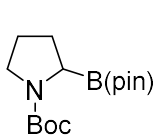
Abstract

This thesis describes the steps taken towards the development of a methodology for the synthesis and Suzuki-Miyaura cross-coupling of *α*-borylated pyrrolidines. Two main methods were explored for the synthesis of *α*-borylated pyrrolidines. A Rh-catalysed approach, reported in Section 2.2, was unsuccessful in our hands. In contrast, the use of lithiation-trapping chemistry described in Section 2.3 delivered gram quantities of 2-B(pin) *N*-Boc pyrrolidine **A** without the need for chromatography. Using this method and subsequent *N*-functionalisation or boronate modification, a range of other *α*-borylated pyrrolidines (**B**-**G**) were prepared for subsequent Suzuki-Miyaura cross-coupling studies. Two sets of conditions, described in Section 3.2, were investigated for the Suzuki-Miyaura cross-coupling to form *α*-arylated pyrrolidines, one focusing on B(pin) functionalised pyrrolidines and the other applied to BF_3K functionalised pyrrolidines, but unfortunately, these reactions were not successful.



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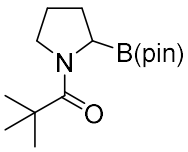

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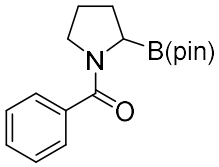

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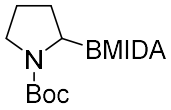

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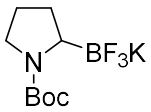

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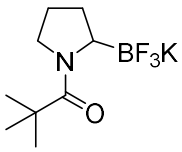

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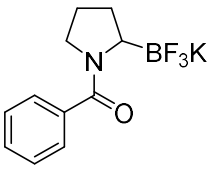

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Author's Declaration

I declare that this thesis is a presentation of original work, and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

Chloe Elizabeth Howman

Abbreviations

°C	Degrees Celsius
Ac	Acetyl
Ad	Adamantyl
Ar	Aryl
ATR	Attenuated total reflectance
BIDA	*N*-2-Benzyloxycyclopentyl-iminodiacetic acid
BINOL	1,1′-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butoxylcarbonyl
Bu	Butyl
cod	1,5-Cyclooctadiene
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
D	Dimensional
dba	Dibenzylideneacetone
de	Diastereomeric excess
dec	Decomposition
DEPT	Distortionless enhancement by polarisation transfer
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
ent	Enantiomer of
eq.	Molar equivalents
er	Enantiomeric ratio
es	Enantiospecificity
ESI	Electrospray ionisation
Et	Ethyl
FDA	US Food and Drug Administration
h	Hours
HMQC	Heteronuclear multiple quantum coherence

HPLC	High-powered liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
i-Pr	*iso*-Propyl
IR	Infrared
L	Ligand
LED	Light-emitting diode
M	Mega
Me	Methyl
MIDA	*N*-Methylimidoacetic acid
min	Minutes
Ms	Mesyl
MTBE	Methyl *tert*-butyl ether
NMR	Nuclear magnetic resonance
Ph	Phenyl
pin	Pinacol, 2,3-dimethylbutane-2,3-diol
ppm	Parts per million
rac	Racemic
rt	Room temperature
S_NAr	Nucleophilic aromatic substitution
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
tol	Tolyl

1. Introduction

1.1 Importance of saturated *N*-heterocycles

In 2014, Njardarson *et al.*[1] published an in-depth analysis on the presence of nitrogen heterocycles in FDA approved drugs. Their investigation focused on small-molecule drugs, discounting other therapeutics such as peptides. Within this database of 1994 pharmaceuticals, 640 (59%) contained nitrogen heterocycles; of those, 367 (18%) were non-aromatic heterocycles. It was found that piperidines were the most common, followed by pyrrolidines. At the time of publication, there were 37 small-molecule drugs contained pyrrolidine, with the most common substitution patterns being *N*- and *α*-substitution. In contrast, 72 small-molecule drugs contained piperidine, with the most common substitution patterns being *N*- and 4-subsitution.[1] Since 2014, an average of 32 therapeutics a year have been approved by the FDA,[2] meaning that increasing numbers of nitrogen heterocycles are entering the pharmaceutical pipeline. A selection of biologically active pharmaceuticals and natural products containing arylated. A selection of biologically active pharmaceuticals and natural products containing arylated pyrrolidines are shown in Figure 1.1.

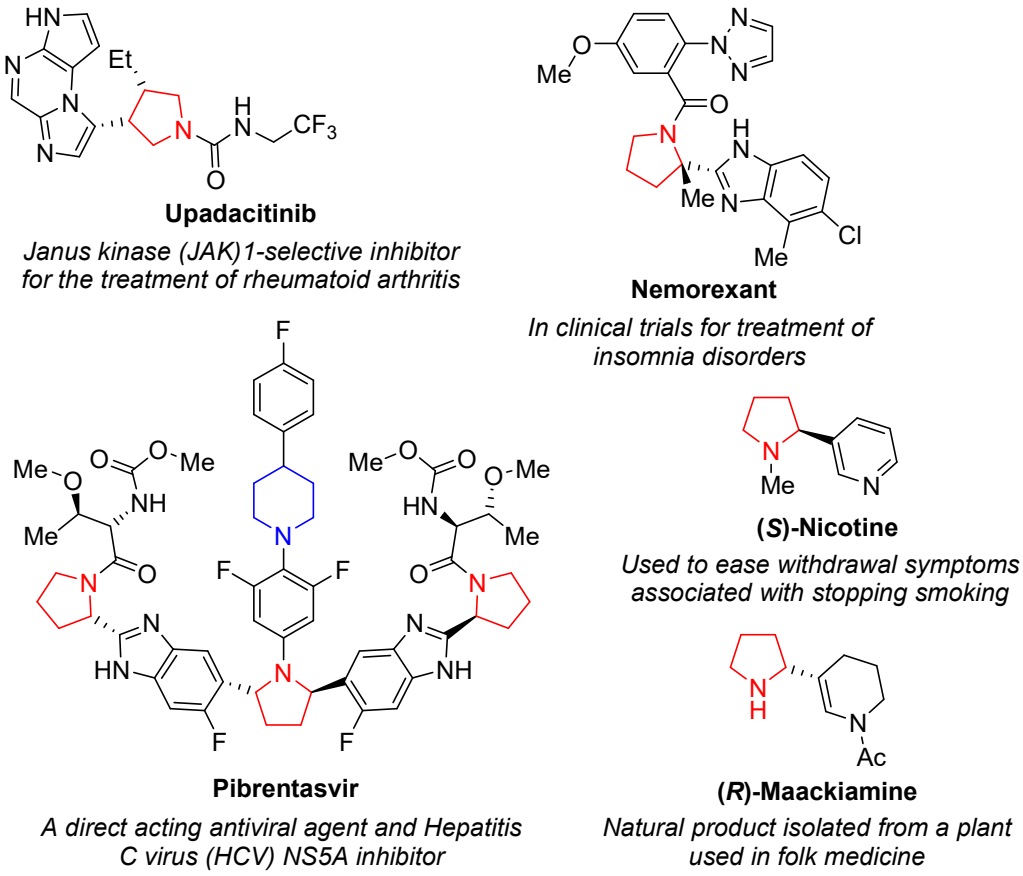


Figure 1.1 Selection of saturated N-heterocycle containing pharmaceuticals and natural products.

1.2 Suzuki-Miyaura cross-coupling and 3-D pharmaceutical space

In 2011, Roughley and Jordan[3] performed an analysis of the reactions used by AstraZeneca, GlaxoSmithKline and Pfizer in their pursuit of small-molecule drug candidates. Examination of the reactions presented in papers published in the three highest impact medicinal chemistry journals by the three pharmaceutical companies allowed a systematic breakdown of the synthetic transformations used. This data found that C-C bond formation reactions accounted for 11.5% of all reactions published by the three pharmaceutical companies. Within these C-C bond forming reactions, Suzuki-Miyaura cross-coupling reactions were the favoured transformation method, representing 40.2% of C-C bond forming reactions.

The popularity of Suzuki-Miyaura cross-coupling reactions in the analysis by Roughley and Jordan[3] is unsurprising. The reagents employed in these cross-couplings, namely boronic esters, boronic acids and organotrifluoroborate salts, are known to be bench-stable, often taking the form of solids which are easily weighable, and can be stored for years without degradation.[4] Further, these reagents are relatively safe to use, making them comparatively easier to handle than those used in other cross-coupling reactions, such as the toxic stannanes used in Stille cross-couplings.

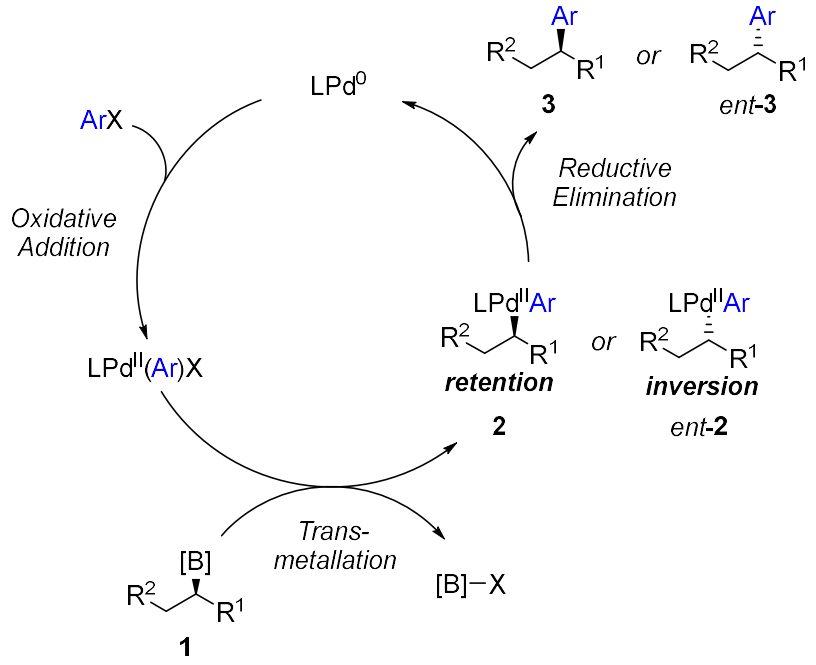
As Brown and Boström[5] demonstrated in their 2016 analysis, there are issues with the widespread use of Suzuki-Miyaura cross-coupling reactions in pharmaceutical discovery. For example, they are often used for $C(sp^2)$-$C(sp^2)$ bond formation reactions, resulting in an over-occupancy of linear- and disc-shaped molecules, and neglecting more 3-D compounds. This results in a lack of shape diversity within potential pharmaceuticals..

In 2009, Lovering, Bikker and Humblet analysed the correlation between increased saturation in small-molecule drug candidates and their in-clinic success.[6] It was hypothesised that the inclusion of more sp^3-hybridised carbons would increase chemical space diversity in an 'out-of-plane' fashion, while requiring only a small increase in molecular weight.[7] Analysis of small molecules throughout the drug discovery pipeline revealed that small-molecules with a greater degree of saturation are more likely to succeed and become approved drugs. This is due to their increased solubilities and lower melting points. This analysis further supports the argument for the development of methodologies beyond $C(sp^2)$-$C(sp^2)$ bond formation reactions.

1.3 Stereospecific C(sp^3)-C(sp^2) Suzuki-Miyaura cross-coupling

The applications of Pd-catalysed Suzuki-Miyaura cross-couplings for the formation of C(sp^2)-C(sp^2) bonds are well known.[8] In contrast, a somewhat less developed area is the application of Suzuki-Miyaura cross-couplings to the more challenging C(sp^3)-C(sp^2) bond forming reactions. In particular, starting with stereodefined alkyl boronates and alkyl boronate derivatives, it has proven relatively challenging, though not impossible, to develop Pd-catalysed stereospecific C(sp^3)-C(sp^2) cross-couplings. This section covers leading research in this area, focusing on the scope and limitations of the aforementioned cross-coupling reactions.

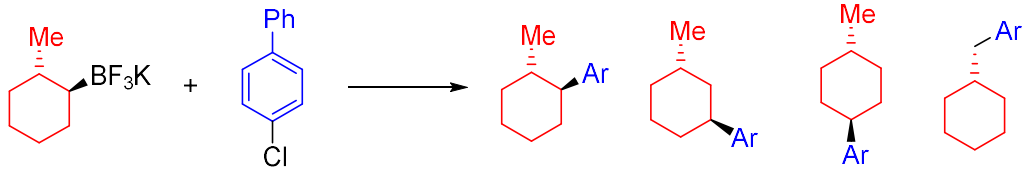
The use of secondary organometallics in cross-coupling reactions can be difficult for two key reasons. Firstly, the transmetallation step becomes much slower with secondary organometallics. Secondly, competing reactions such as *β*-hydride elimination and reductive elimination can give undesired by-products, including the potential for Pd to migrate to different positions.[9] A mechanistic overview for a typical Suzuki-Miyaura cross-coupling reaction of a stereodefined alkyl boronate **1** with an aryl halide (Ar-X) to give the cross-coupled arylated product **3** (stereoretentive) or *ent*-**3** (stereoinvertive) is shown in Scheme 1. It has been shown that the transmetallation step of alkyl boronate **1** to give organopalladium intermediate **2** or *ent*-**2** is the mechanistic step which determines the overall stereochemical outcome of the cross-coupling reaction.[9]



Scheme 1.1[9] Suzuki-Miyaura catalytic cycle when forming C(sp^3)-C(sp^2) bonds, demonstrating that the stereochemical outcome of the reaction is dependent on the transmetallation step.

The stereofidelity of the transmetallation step is dependent on many factors, such as the alkyl boronate substrate, the catalyst/ligand employed, and the reaction conditions (*e.g.* the base used).[9] As such, these factors are explored in this overview, with examples of both stereoretentive and stereoinvertive Suzuki-Miyaura C(sp^3)-C(sp^2) cross-coupling reactions presented.

In 2008, as part of a wider study of cyclic alkyl trifluoroborate cross-couplings, Molander *et al.*[10] investigated the stereospecificity of forming C(sp^3)- C(sp^2) bonds *via* Suzuki-Miyaura cross-couplings. Reaction of potassium trifluoroborate *trans*-**4** with 4-chlorobiphenyl **5** in the presence of $Pd(OAc)_2$ (2 mol%), *n*-Bu_2PAd_2 (3 mol%) and Cs_2CO_3 in toluene-water at 100 °C for 24 h gave an 80% yield of a mixture of four products: *trans*-**6**, *trans*-**7**, *trans*-**8**, and **9** (Table 1, entry 1). However, these conditions had poor selectivity for the direct retentive Suzuki-Miyaura product *trans*-**6**. In contrast, use of $Pd(OAc)_2$ (5 mol%) and *t*-Bu_3P (7.5 mol%) for a prolonged reaction time of 72 h gave a 48% yield of the four products, with a much greater selectivity for the arylated cyclohexane *trans*-**6** (entry 2). In this case, a greater amount of regioisomeric aryl cyclohexane **9** was also observed. Using $Pd(OAc)_2$ (5 mol%) and PhP*t*-Bu_2 (7.5 mol%) as the ligand, with a 72 h reaction time, the overall yield was 72%, with the highest selectivity in favour of the arylated cyclohexane *trans*-**6** (entry 3). Although other regioisomers were generated, the formation of arylated cyclohexane *trans*-**6** was the first example of a stereospecific Suzuki-Miyaura cross-coupling reaction. Of note, the reaction proceeded with retention of configuration.

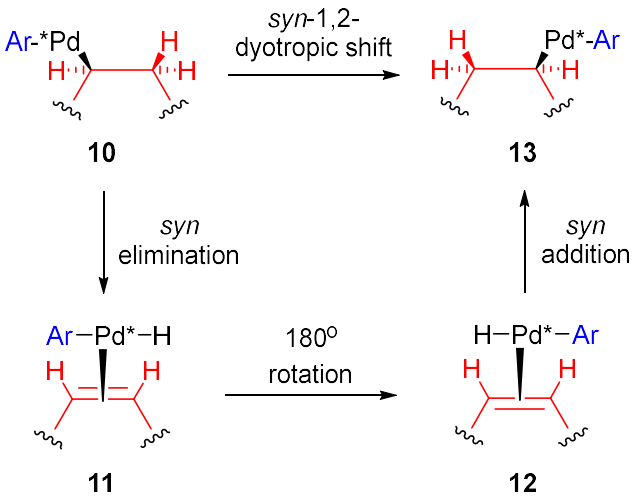


trans-**4** **5** *trans*-**6** *trans*-**7** *trans*-**8** **9**

Entry	Ligand	Conditions	*trans*-6	*trans*-7	*trans*-8	*9*	Yield (%)
1	*n*-BuPAd$_2$	A	4.4	1.0	2.0	1.4	80
2	*t*-Bu$_3$P	B	16.0	1.0	1.0	6.0	48
3	PhP*t*-Bu$_2$	B	27.7	1.6	1.0	8.1	72

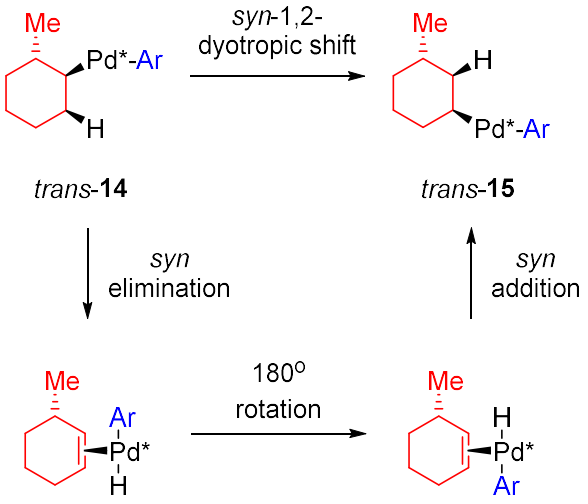
*Table 1.1 Cross-coupling of a non-symmetric secondary alkylboron with an aryl halide, showing the different isomeric outcomes. Conditions: (A) $Pd(OAc)_2$ (2 mol%), ligand (3 mol%), **5** (1.1 eq.), Cs_2CO_3 (3 eq.), and toluene-water (10:1), 100 °C, 24 h. (B) $Pd(OAc)_2$ (5 mol%), ligand (7.5 mol%), **5** (1.3 eq.), Cs_2CO_3 (3 eq.), and toluene-water (10:1), 100 °C, 72 h.*[10]

An explanation for the formation of the three other regioisomeric products, *trans*-**7**, *trans*-**8**, and **9**, is that the Pd migrated to a different position before arylation occurred. Previously, Keay *et al.*[11] had reported that the migration of Pd can occur *via* two key mechanisms: *syn*-1,2,-dyotropic shifts, or *syn*-chain-walking (Scheme 1.2). When a *syn*-1,2-dyotropic shift occurs, the two sigma bonds (C–Pd and C–H) would migrate simultaneously in an intramolecular fashion, i.e. **10** would be converted directly into **13**, with the Pd and hydrogen atoms transposed. Alternatively, a chain-walking mechanism may occur, wherein the Pd would repeatedly undergo *β*-hydride elimination, rotation, and addition, i.e. **10** → **11** → **12** → **13**. The crucial aspect of this Pd migration is that the Pd remains co-ordinated to the same face of the alkene at all times, resulting in a stereospecific *syn* rearrangement.



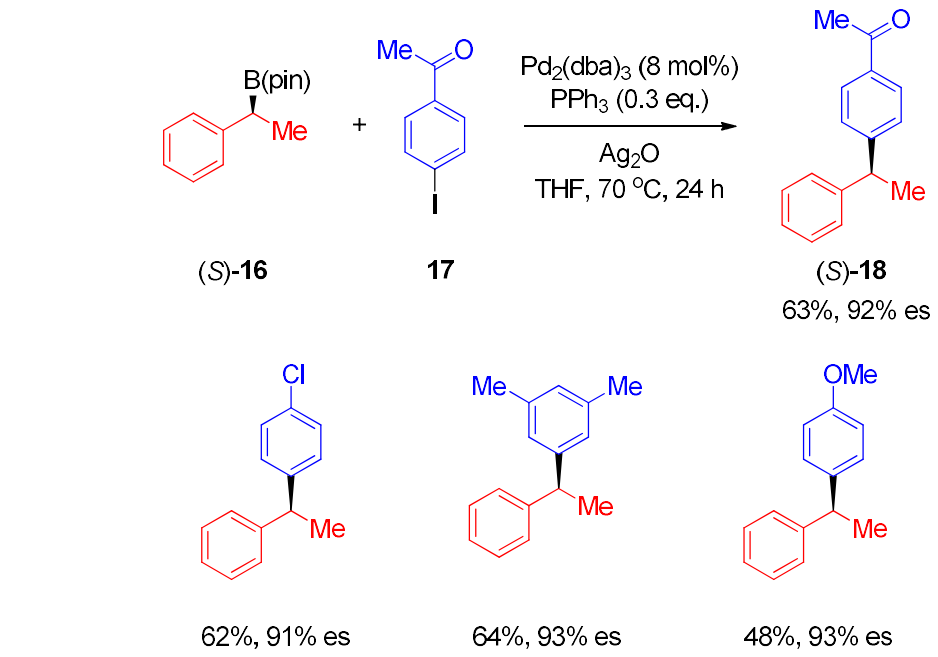
Scheme 1.2 Two possible Pd migration mechanisms: syn-*1,2-dyotropic shift and syn-chain-walking, which results in the formation of regioisomers when non-symmetrical alkyl substrates are used in Suzuki-Miyaura cross-coupling reactions.*

When Keay's mechanistic knowledge is applied to Molander's examples in Table 1.1, it can be seen that such Pd migrations would lead to an overall loss of regiocontrol. To illustrate this, consider Pd species *trans*-**14** which could rearrange to *trans*-**15** from which cross-coupling *via* reductive elimination would generate the observed arylated cyclohexane *trans*-**7** (Scheme 3). Similar mechanisms can also be used to rationalise the formation of regioisomeric arylated cyclohexanes *trans*-**8** and **9**. As shown in Table 1, as the steric bulk of the ligand employed in the reaction increased, a higher selectivity was found in favour of the direct retentive Suzuki-Miyaura product *trans*-**6**. Presumably, based on the mechanistic reasoning above, the sterically hindered ligands make Pd migrations less kinetically favourable.



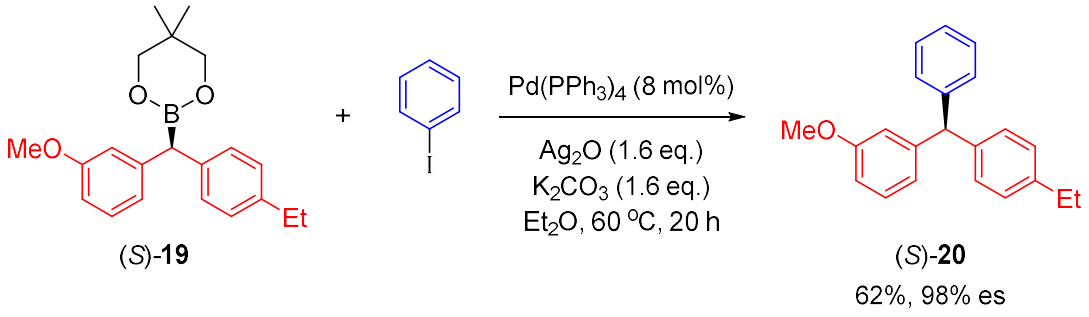
Scheme 1.3 Two possible Pd migration mechanisms applied to the formation of the regioisomer trans-*7 in Molander* et al.*'s work.*[10]

Following on from Molander's initial result, in 2009, Crudden *et al.*[12] undertook an investigation into the enantiospecific coupling of stereochemically defined benzylboron esters with aryl halides in a C(sp^3)-C(sp^2) bond forming Suzuki-Miyaura reaction. For example, benzylboronic ester (*S*)-**16** was reacted with aryl iodide **17** in the presence of $Pd_2(dba)_3$ (8 mol%, 8 equivalents of PPh_3 per Pd) and Ag_2O. This reaction in THF at 70 °C for 24 h gave arylated product (*S*)-**18** in 63% yield with 92% enantiospecificity, with the major pathway proceeding with retention of configuration (Scheme 4). Use of other bases such as K_2PO_4 and Cs_2CO_3, or the use of less equivalents of PPh_3 resulted in far worse yields. Ag_2O was employed as the base in this reaction due to the belief that it would increase the rate of the transmetallation step. Further investigation of scope, as highlighted in Scheme 4, used a range of aryl halides, with each reaction giving moderate yields (38 – 64%) but with excellent enantiospecificities (84 – 94%), and all proceeding with retention of configuration.



Scheme 1.4 Four examples of Crudden et al.*'s use of benzylboronic esters in C(sp^3)-C(sp^2) bond forming Suzuki-Miyaura cross-coupling reactions, all proceeding with retention of configuration and high enantiospecificity.*[12]

Triarylmethanes are interesting structural motifs which have been shown to be biologically active, as well as having useful materials properties. In 2014, Crudden *et al.*[13] investigated the application of enantiospecific Suzuki-Miyaura cross-couplings in the synthesis of enantioenriched triarylmethanes, starting from diarylmethanes. For example, dibenzylicboronic ester (*S*)-**19** was reacted with iodobenzene in the presence of $Pd(PPh_3)_4$ (8 mol%), Ag_2O and K_2CO_3 in Et_2O at 60 °C for 20 h. In this way, triarylmethane (*S*)-**20** was formed in 62% yield with 98% enantiospecificity *via* a retentive cross-coupling reaction.



Scheme 1.5 Example of a stereoretentive Suzuki-Miyaura coupling by Crudden et al.[13] *to form a triarylmethane from a diarylmethane.*

The scope of the reaction was explored and a wide range of yields (46 – 82%) were obtained, albeit with good enantiospecificities (78 -100%), a selection of which are shown in Figure 1.2. It was found that the reaction yield was affected by steric hindrance and heteroaromatic electrophiles, but all reactions showed good enantiospecificities.

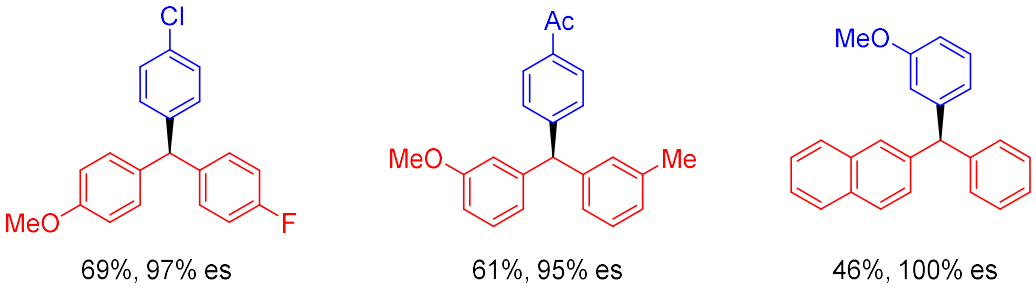
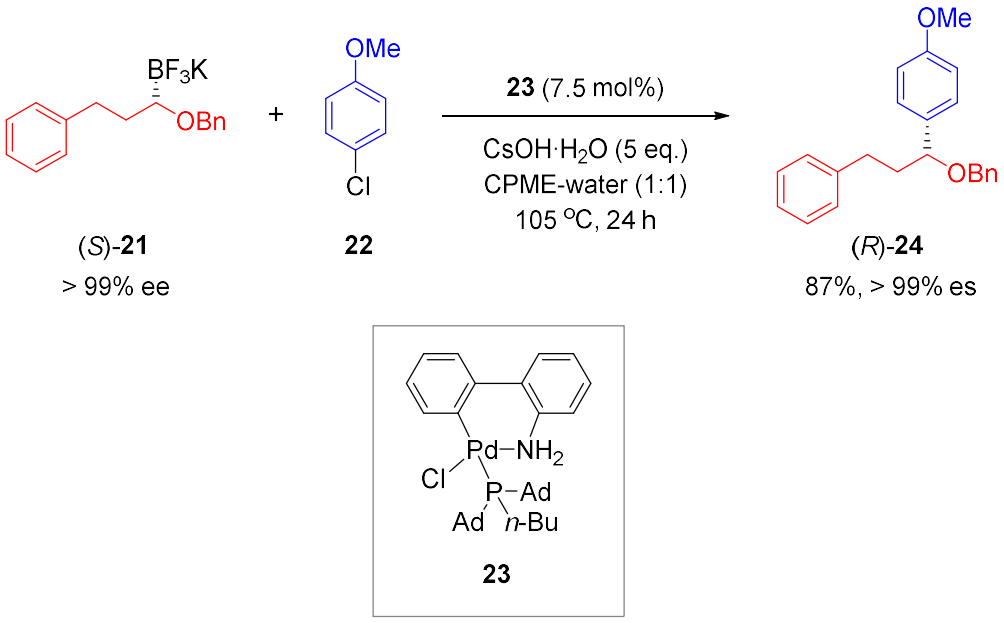


Figure 1.2 Further examples of stereoretentive Suzuki-Miyaura couplings to form a range of triarylmethanes with high enantiospecificity.[13]

Molander and Wisniewski,[14] in 2012, undertook a detailed study into the use of C(sp^3)-C(sp^2) bond forming Suzuki-Miyaura couplings to produce secondary benzylic alcohols. Reaction of trifluoroborate (*S*)-**21** with aryl chloride **22** in the presence of cataCXium ligand-containing second generation Buchwald precatalyst **23**[15] (7.5 mol%) and $CsOH{\cdot}H_2O$ (5 eq.) in a CPME-water solvent mixture at 105 °C for 24 h afforded aryl ether (*R*)-**24**. Using these reaction conditions, (*R*)-**24** was formed in 97% yield and > 99% enantiospecificity, with the reaction proceeding with retention of configuration.



Scheme 1.6 Example of Molander and Wisniewski's work using Suzuki-Miyaura cross-couplings to synthesise secondary benzylic alcohols.[14]

Previous investigations had shown that electron donating groups which can co-ordinate to the diorganopalladium species in these reactions reduce the level of competing β-hydride elimination. Further, the presence of electron-withdrawing groups α to the Pd-coordinated carbon can also reduce the extent of β-hydride elimination by removing electron density from the β-hydrogens which disfavours agostic interaction with the Pd. For these reasons, the study

used a benzyl protected secondary alcohol which can coordinate to the Pd through an η^2 interaction, as well as being inductively electron-withdrawing. The use of water in this reaction was crucial; reducing the water content led to a reduction in yield, consistent with Lloyd-Jones and Lennox[16] who determined that water increases the rate of cross-coupling relative to the rate of proto-deborylation. Additionally, the use of $CsOH{\cdot}H_2O$ was employed following previous findings by Hartwig and Carrow[17] where it was found that a hydroxide base increased the rate of the rate-determining transmetallation step by forming the more active ArPd(OH)L species. Molander postulated that the observed retention of configuration in the formation of arylated (*R*)-**24** is due to the formation of a four-membered metallocycle transition state, in which the hydroxide coordinated to the Pd also donates into the vacant orbital on the boron (Figure 2). In addition, the benzyl group could coordinate to the Pd in an η^2 coordination, which also helps to reduce the amount of *β*-hydride elimination.

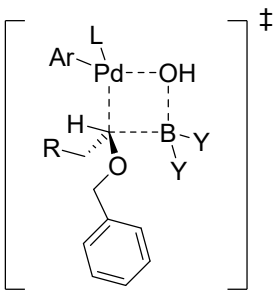
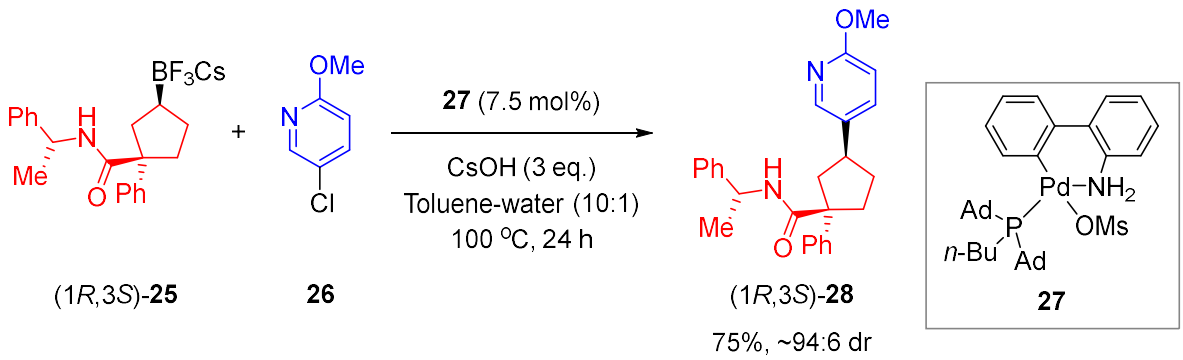


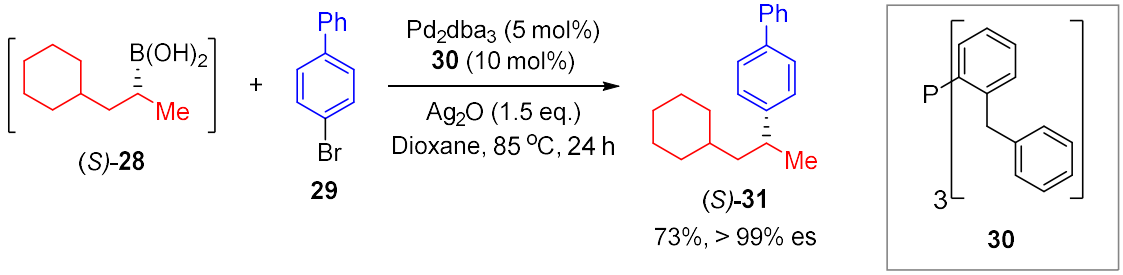
Figure 1.3 Transition state preceding the transmetallation step which results in the formation of a stereoretentive product in this reaction.[14]

In 2015, Takacs *et al.*[18] explored the use of cyclic γ-borylated amides in $C(sp^3)$-$C(sp^2)$ bond forming Suzuki-Miyaura cross-couplings. For example, caesium trifluoroborate (1*R*,3*S*)-**25** was reacted with chloropyridine **26** in the presence of CataCXium ligand-containing Buchwald Pd precatalyst **27**[15] (7.5 mol%) and CsOH in a toluene-water mixture at 100 °C for 24 h. This gave arylated cyclopentane (1*R*,3*S*)-**28** in 75% yield and ~94:6 dr, with the reaction proceeding *via* retention of configuration. Although reactions between a few different cyclic *γ*-borylated amides and aryl halides were described, there is no in-depth study into the enantiospecificity of each reaction and therefore the scope of the reaction in terms of its stereofidelity could not be fully assessed. Of note, however, the other possible regioisomer was not observed, in contrast to Molander *et al.*'s results with potassium trifluoroborate *trans*-**4**[10] (see Table 1.1).



Scheme 1.7 Example of a cyclic alkyl substrate in a C(sp^3)-C(sp^2) bond forming Suzuki-Miyaura cross-coupling, employed by Takacs et al.[18]

More recently, Burke *et al.*[19] investigated ways to promote the stereoretentive pathway over the stereoinversion pathway in C(sp^3)-C(sp^2) bond-forming Suzuki-Miyaura cross-coupling reactions by exploring the spatial effects of the phosphine ligands employed. The group made use of BBIDA complexes, chiral analogues of the more often used BMIDA functionality, as these gave easy access to boronic acids in high enantiomeric ratio by separation of diastereomers by chromatography. As an example, one BBIDA complex was converted *in situ* into boronic acid (*S*)-**28** and reacted with 4-bromobiphenyl **29** in the presence of Pd_2dba_3 (5 mol%) and ligand **30** (10 mol%) with Ag_2O in dioxane at 85 °C for 24 h. The reaction proceeded with retention of configuration, giving arylated product (*S*)-**31** in 73% yield and with > 99% enantiospecificity (Scheme 1.8).



Scheme 1.8 Example of manipulating the transmetallation pathway of a Suzuki-Miyaura cross-coupling reaction using the spatial properties of the phosphine ligand employed.[19]

It is known that the transmetallation pathway determines whether the product of C(sp^3)- C(sp^2) bond-forming Suzuki-Miyaura couplings show stereoretention or stereoinversion. In the case of the retentive pathway, a closed, four-membered transition state of a square planar Pd(II) structure is involved **(**Figure 3). This step is preceded by the complexation of the boronic acid with a Pd(II)-hydroxo species.[20] Conversely, the invertive pathway proceeds *via* a backside electrophilic attack by the Pd(II) species on an anionic trihydroxyborate at the boron-bearing carbon. In this mechanism, the alkyl coupling partner would approach orthogonally to the

square plane of the Pd(II) species. Using X-ray crystallography, Burke *et al.* took advantage of the spatial differences between these two pathways, allowing them to screen ligands which would axially shield the Pd by projecting steric bulk above and below the Pd(II) plane, theoretically blocking the stereoinvertive pathway. Ligand screening resulted in the discovery of tri(2-benzyl-phenyl)phosphine, **30**, which yielded excellent enantiospecificities, as demonstrated with the formation of (*S*)-**31** (Scheme 1.4).

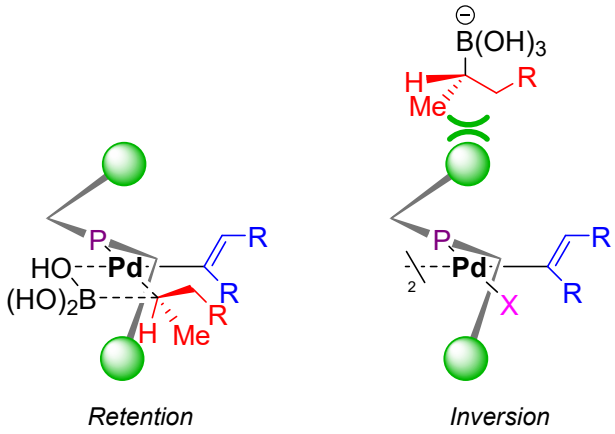
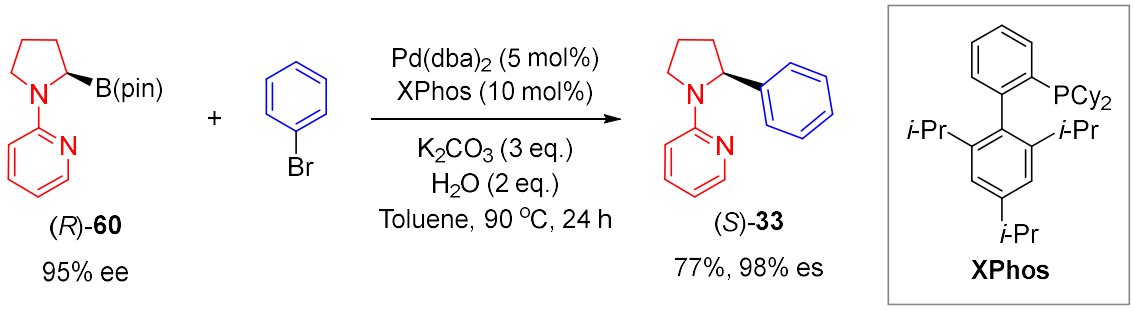


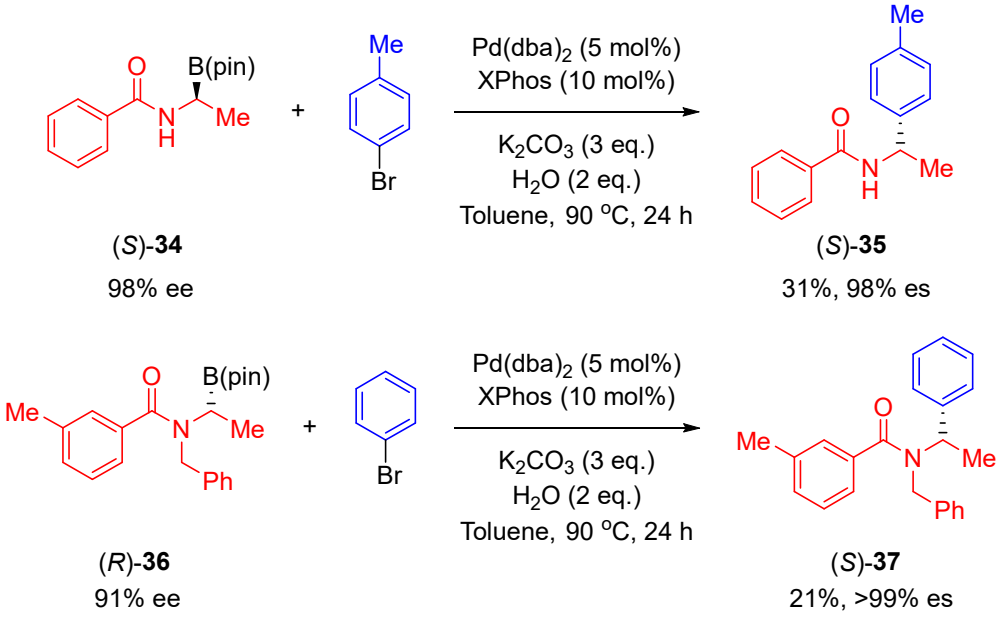
Figure 1.4 A visual representation of how the phosphine ligand employed in this reaction prevents the inversion pathway from occurring.[19]

As part of a wider study on the synthesis and applications of α-aminoboronates, in 2020, Sawamura *et al.*[21] investigated the stereospecificity of C(sp^3)-C(sp^2) bond forming Suzuki-Miyaura cross-couplings involving enantioenriched *N*-pyridyl heterocyclic alkyl boronates. For example, α-pyrrolidinyl boronic ester (*R*)-**32** was reacted with bromobenzene in the presence of $Pd(dba)_2$ (5 mol%), XPhos (10 mol%), K_2CO_3 (3 eq.) and H_2O (2 eq.) in toluene at 90 °C for 24 h. The use of these reaction conditions gave arylated product (*S*)-**33** in 77% yield and 98% enantiospecificity, proceeding with retention of configuration. Of much significance, this is the first example of a Suzuki-Miyaura cross-coupling of a saturated nitrogen heterocycle containing an α-boronate substituent. Furthermore, it proceeded with very high stereofidelity.



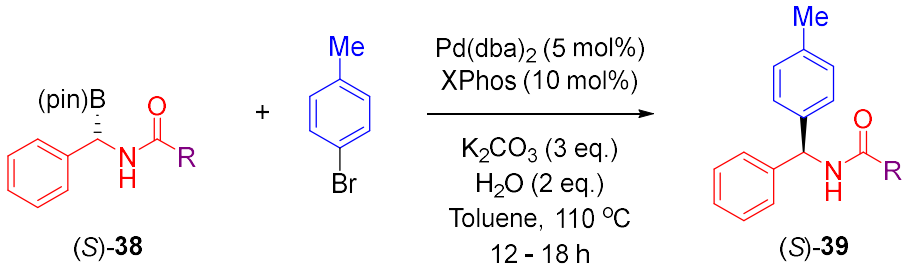
Scheme 1.9 Example of an N*-heterocyclic alkyl substrate in a C(sp^3)-C(sp^2) bond forming Suzuki-Miyaura cross-coupling which proceeds with retention of configuration, as demonstrated by Sawamura et al.*[21]

In order to further investigate the substrate dependence on the configurational outcome of this type of cross-coupling, two different boronates were explored (Scheme 10). A secondary *α*-amidoboronate (*S*)-**34** was reacted with 4-bromotoluene, under the reaction conditions used in Scheme 9, to giver arylated product (*S*)-**35** in 31% yield with 98% enantiospecificity, proceeding with inversion of stereochemistry. In contrast to this, tertiary *α*-amidoboronate (*R*)-**36** was reacted with bromobenzene using the same conditions and arylated product (*S*)-**37** was isolated in 21% yield and > 99% enantiospecificity with retention of configuration. Based on these results, it was concluded that tertiary *α*-aminoboronates proceed with retention of configuration, whereas secondary *α*-aminoboronates proceed with inversion. This is believed to be due to the deprotonation of the secondary nitrogen under the basic conditions used in these reactions, which promotes the inversion pathway.



Scheme 1.10 Reaction of secondary and tertiary α*-amidoboronates, as a comparison to work by Ohmura and Suginome*[22] *which proceeded with either inversion, in agreement with their findings, or retention, demonstrating that it is the substrate which determines the stereochemical outcome of this Suzuki-Miyaura coupling.*[21]

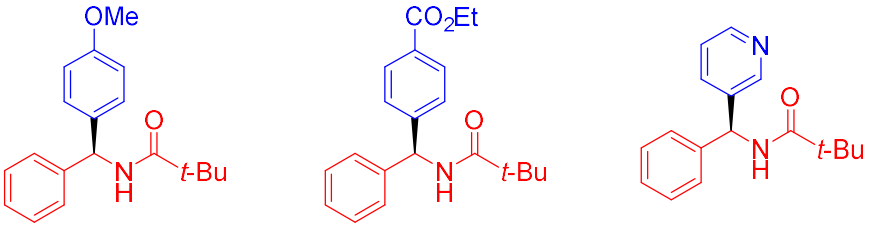
In 2010, Ohmura, Suginome and Awano[22] provided a detailed study of what was at the time the first C(sp^3)-C(sp^2) bond forming Suzuki-Miyaura reaction that proceeded with inversion of configuration. In order to examine the enantiospecificity of this reaction, the effect of the acyl group in benzylic-α-(acylamino)alkylboronates was investigated. Reaction of benzylic-α-(acylamino)alkylboronic ester (*S*)-**38** (R = Me) with 4-bromotoluene in the presence of $Pd(dba)_2$ (5 mol%), XPhos (10 mol%) and K_2CO_3 with water in toluene at 110 °C for 18 h gave (*S*)-**39** in 95% yield, but poor enantiospecificity of 59% (Table 2, entry 1). Use of (*S*)-**38** (R = Et) gave a reduced yield (85%) but increased enantiospecificity (68%) (entry 2). With R = Ph in (*S*)-**39** (entry 3) a lower yield (65%) was obtained, but there was a large increase in enantiospecificity (89%). The use of a *t*-butyl functionality on the acyl group, (*S*)-**38** (R = *t*-Bu), gave an 80% yield and excellent 97% enantiospecificity (entry 4).



Entry	R	Yield (%)	% es
1	Me (87% ee)	95	59
2	Et (95% ee)	85	68
3	Ph (87% ee)	65	89
4	*t*-Bu (96% ee)	80	97

Table 1.2 Coupling of several α-amidoboronates with the acyl group varied from a methyl through to a t-butyl, with the effect on yield and enantiospecificity shown.[22]

Once an acyl group yielding high enantiospecificities was identified, the scope of the reaction was investigated. A study of ten aryl bromides at a lowered reaction temperature of 80 °C gave consistently excellent results of 71 – 89% yield with 92 – 98 % enantiospecificity, a selection of which are shown in Figure 1.5. An aryl chloride study also gave similar results.



76%, 97% es 87%, 97% es 83%, 92% es

Figure 1.5 Examples of the stereoinvertive cross-coupling employed by Ohmura, Suginome and Awano in this investigation.[22]

The inversion of stereochemistry in this reaction was rationalised using the transition state shown in Figure 1.6. Coordination of the carbonyl group to the boron forces an attack on the Pd opposite to the boron-bonded carbon. This differs from the transition state of the retention pathway transition (see Figure 1.4 for an example), as the four-membered transition state is not formed.

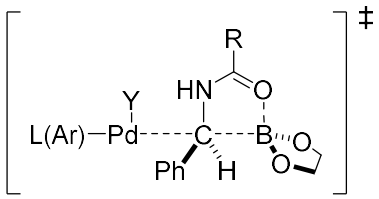
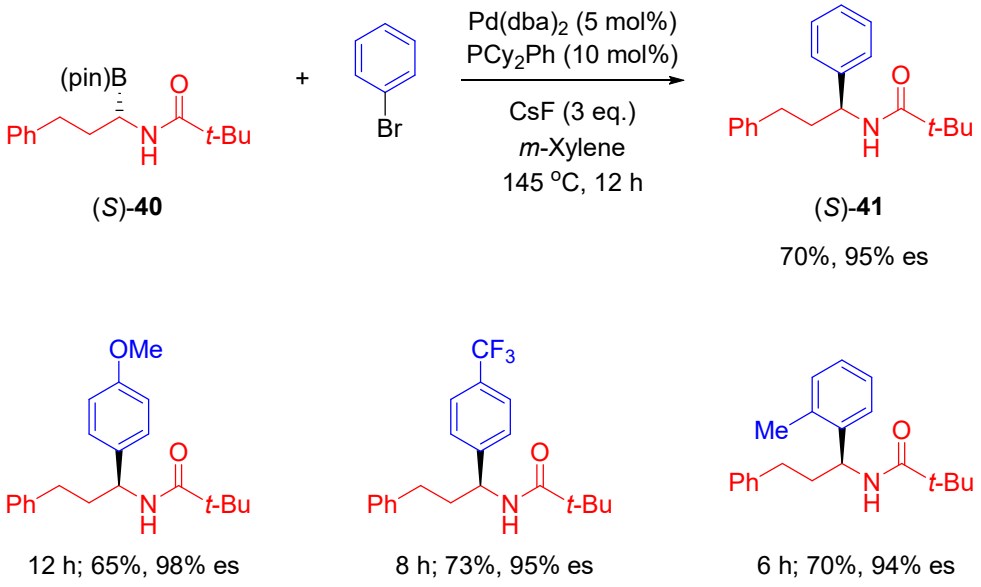


Figure 1.6 Transition state preceding the transmetallation step, demonstrating how an invertive pathway is preferred.[22]

A key issue relating to the use of alkylboron reagents in C(sp^3)-C(sp^2) bond forming Suzuki-Miyaura cross-couplings is that the increased covalency and stability of the carbon-boron bond leads to a reduction in nucleophilicity, which results in slower transmetallation steps and an increase in competing β-hydride elimination. One strategy to reduce these effects utilises an α-heteroatom to increase the speed of the slow transmetallation step,[23] which is an added benefit of using an adjacent amido group in these cross-coupling reactions.

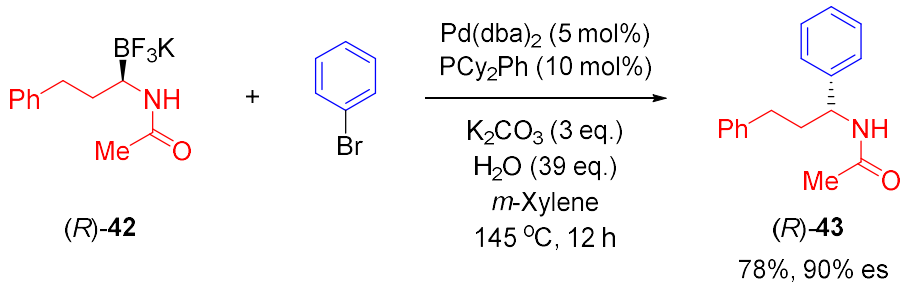
In 2018, Ohmura, Suginome and Awano[24] investigated Suzuki-Miyaura cross-couplings using non-benzylic-α-(acylamino)alkylboron compounds. For example, reaction of α-(acylamino)alkylboronic ester (*S*)-**40** with bromobenzene in the presence of $Pd(dba)_2$ (5 mol%), PCy_2Ph (10 mol%) and CsF in *m*-xylene at 145 °C for 12 h gave arylated product (*S*)-**41** in 70% yield with 95% enantiospecificity (Scheme 11). The reaction proceeded with inversion of stereochemistry. Interestingly, the reaction conditions used with (*S*)-**38** (R = *t*-Bu) ($Pd(dba)_2$ (5 mol%), XPhos (10 mol%) and K_2CO_3) did not give any product with (*S*)-**40**, suggesting that the reaction of non-benzylic derivatives proceeds in a different fashion to their benzylic counterparts. Investigation of the scope of the reaction with (*S*)-**40** implemented the

use of several aryl halides and differing reaction times (6 – 12 h), all giving a wide range of yields (35 – 85%) albeit in good enantiospecificities (73 – 99%).



Scheme 1.11 Further exploration of α-amidoboronates by Ohmura, Suginome and Awano using non-benzylic substrates to give inversion of configuration in a Suzuki-Miyaura cross-coupling.[24]

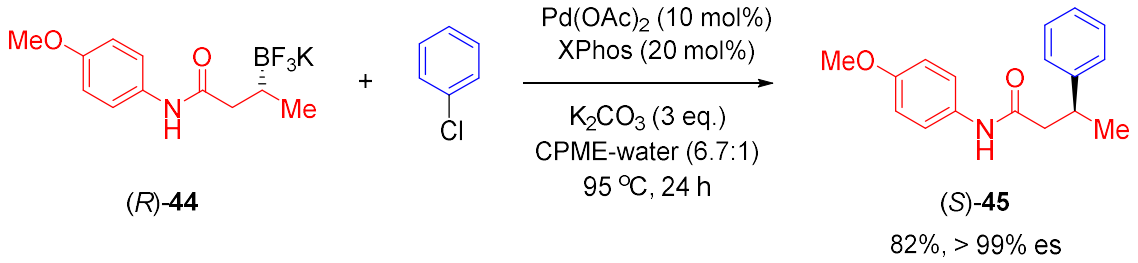
The use of potassium trifluoroborate salts in non-benzylic-*α*-(acylamino)alkylboron compounds was also investigated. For example, potassium *α*-(acylamino)alkyltrifluoroborate (*R*)-**42** was reacted with bromobenzene in the presence of $Pd(dba)_2$ (5 mol%), PCy_2Ph (10 mol%), K_2CO_3 and a water additive in *m*-xylene at 145 °C for 12 h to afford arylated product (*R*)-**43** in 78% yield with 90% enantiospecificity (Scheme 1.12). As expected, this reaction proceeded with inversion of stereochemistry.



Scheme 1.12 Application of the non-benzylic Suzuki-Miyaura cross-couplings to potassium trifluoroborate substrates.[24]

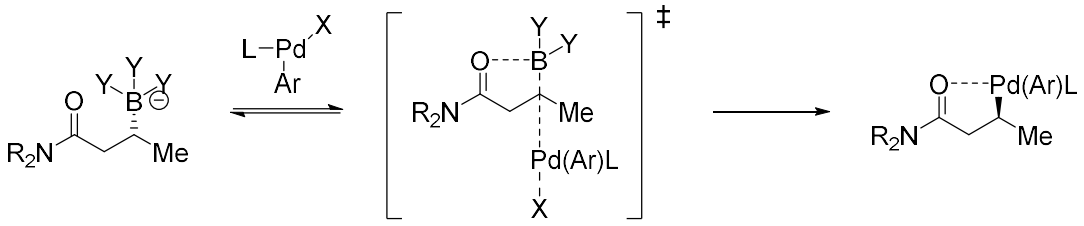
In 2010, Molander *et al.*[25]also reported the use of non-benzylic alkylborons in the formation of $C(sp^3)$-$C(sp^2)$ bonds *via* Suzuki-Miyaura coupling. Enantioenriched potassium trifluoroborate (*R*)-**44** and chlorobenzene were reacted in the presence of $Pd(OAc)_2$ (10 mol%), XPhos (20 mol%) and K_2CO_3 in a CPME-water mixture at 95 °C for 24 h. This gave arylated amide (*S*)-**45** in 82% yield and > 99% enantiospecificity, with inversion of stereochemistry (Scheme

1.13). The reaction yielded less than 2% of β-hydride elimination products, a result which is believed to be due to the presence of the proximal carbonyl group.



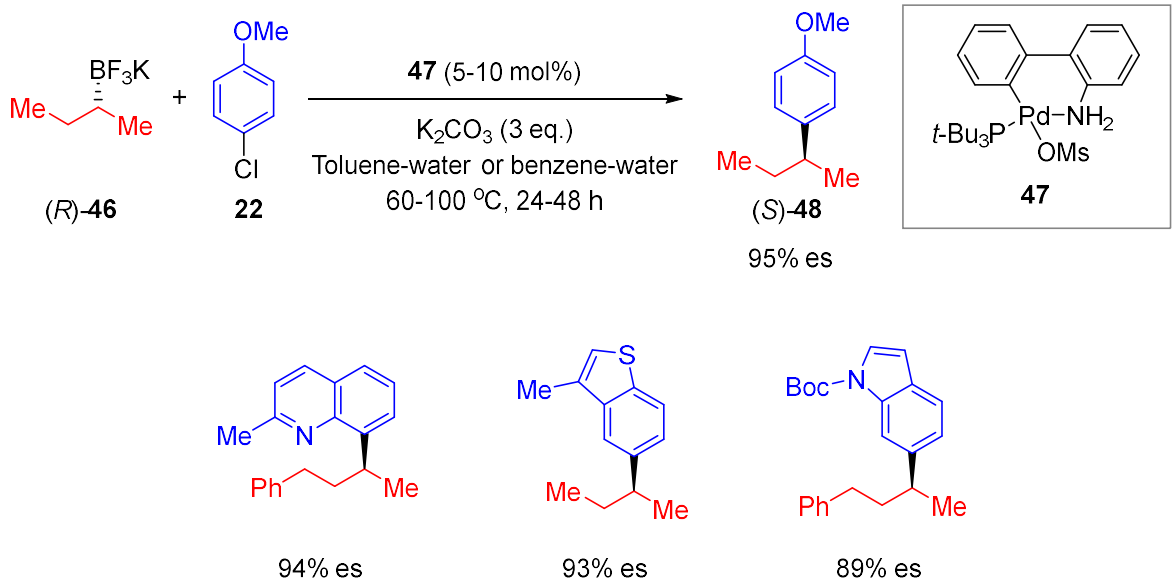
Scheme 1.13 Example by Molander et al. *of intramolecular coordination in Suzuki-Miyaura couplings with a resulting stereoinvertive product.*[25]

The proposed explanation for the inversion of stereochemistry is shown in Scheme 14. Intramolecular coordination of the carbonyl oxygen to the boron causes the boron-bearing carbon to approach the Pd on the opposite side to the boron. This leads to the inversion of stereochemistry observed in this reaction. The coordination to the diorganopalladium species then prevents β-hydride elimination, reducing the formation of undesired by-products.



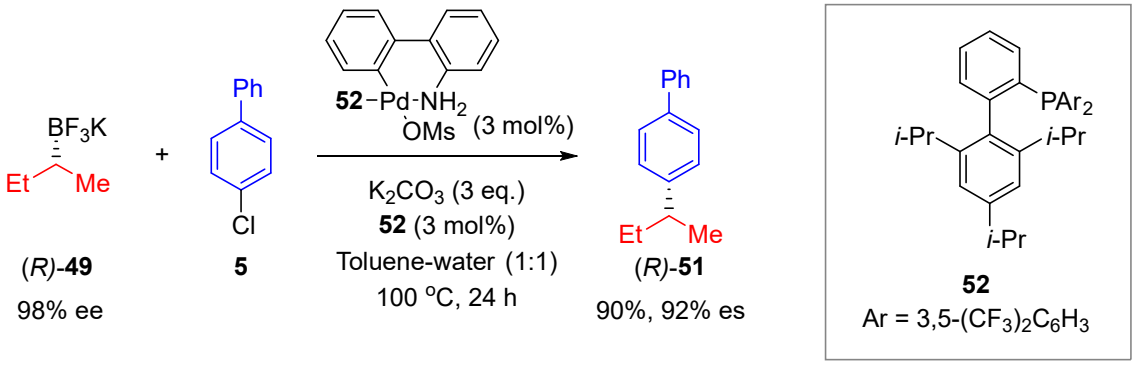
Scheme 1.14 Transition state of the transmetallation step demonstrating how the intramolecular coordination of the carbonyl group aids the invertive pathway of this Suzuki-Miyaura coupling.[25]

In 2014, Biscoe *et al.*[26] examined the stereofidelity of C(sp^3)-C(sp^2) bond forming Suzuki-Miyaura cross-couplings which utilised unactivated secondary alkylboron compounds. The exemplar reaction of enantioenriched potassium alkyltrifluoroborate (*R*)-**46** with aryl chloride **22** in the presence of Pd precatalyst **47** (5 – 10 mol%) with K_2CO_3 in either a toluene-water or benzene-water mixture at 60 °C for 48 h proceeded with inversion of configuration, giving arylated alkane (*S*)-**48** with 95% enantiospecificity (Scheme 15). Of note in this study, the use of heteroaromatic electrophiles led to arylated products with high enantiospecificities.



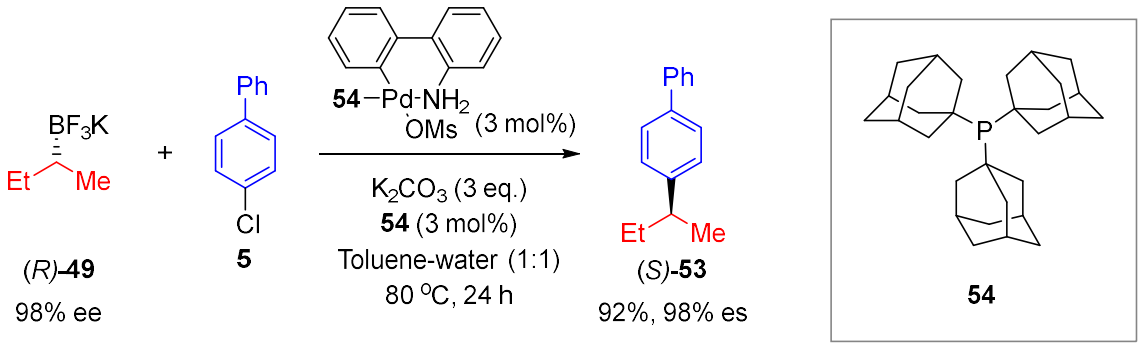
Scheme 1.15 Examples of non-activated alkyl substrates in Suzuki-Miyaura couplings resulting in inversion of configuration with high enantiospecificity.[26]

Subsequently, in 2018, Biscoe and Sigman *et al.*[9] investigated the stereofidelity of forming C(sp^3)-C(sp^2) bonds *via* Suzuki-Miyaura cross-coupling reactions under different reaction conditions. Reaction of potassium *sec*-butyltrifluoroborate (*R*)-**49** with aryl chloride **5** in the presence of a Pd catalyst with ligand **52** (3 mol%) and K_2CO_3 in a toluene-water mixture at 100 °C for 24 h gave arylated alkane (*R*)-**53** in 90% yield with 92% enantiospecificity (Scheme 16). The major pathway for this reaction resulted in retention of configuration.



Scheme 1.16 Use of an aryl phosphine ligand to promote the retentive transmetallation pathway in a Suzuki-Miyaura cross-coupling.[9]

Potassium *sec*-butyltrifluoroborate (*R*)-**49** and aryl halide **5** were also reacted in the presence of a Pd catalyst (3 mol%), and a different ligand **54**, with K_2CO_3 in a toluene-water mixture for 24 h at 80 °C. In this way, arylated alkane (*S*)-**53** was produced in 92% yield with 98% enantiospecificity (Scheme 17). In stark contrast to the reaction shown in Scheme 16, the major pathway proceeded with inversion of configuration.



Scheme 1.17 Use of an alkyl phosphine ligand to promote the invertive transmetallation pathway in a Suzuki-Miyaura cross-coupling.[9]

Predictive statistical modelling was used to investigate the mechanistic reasoning for the opposite stereochemical outcomes of the C(sp^3)- C(sp^2) bond-forming Suzuki-Miyaura cross-couplings shown in Schemes 16 and 17. A ligand parameterisation tool was developed to probe the correlation between the phosphine ligand and the stereofidelity of a range of reactions, analysing both the electronic and steric aspects of the ligands. Overall, it was found that the electronic properties of the phosphine ligands determined the mechanism of the transmetallation step.

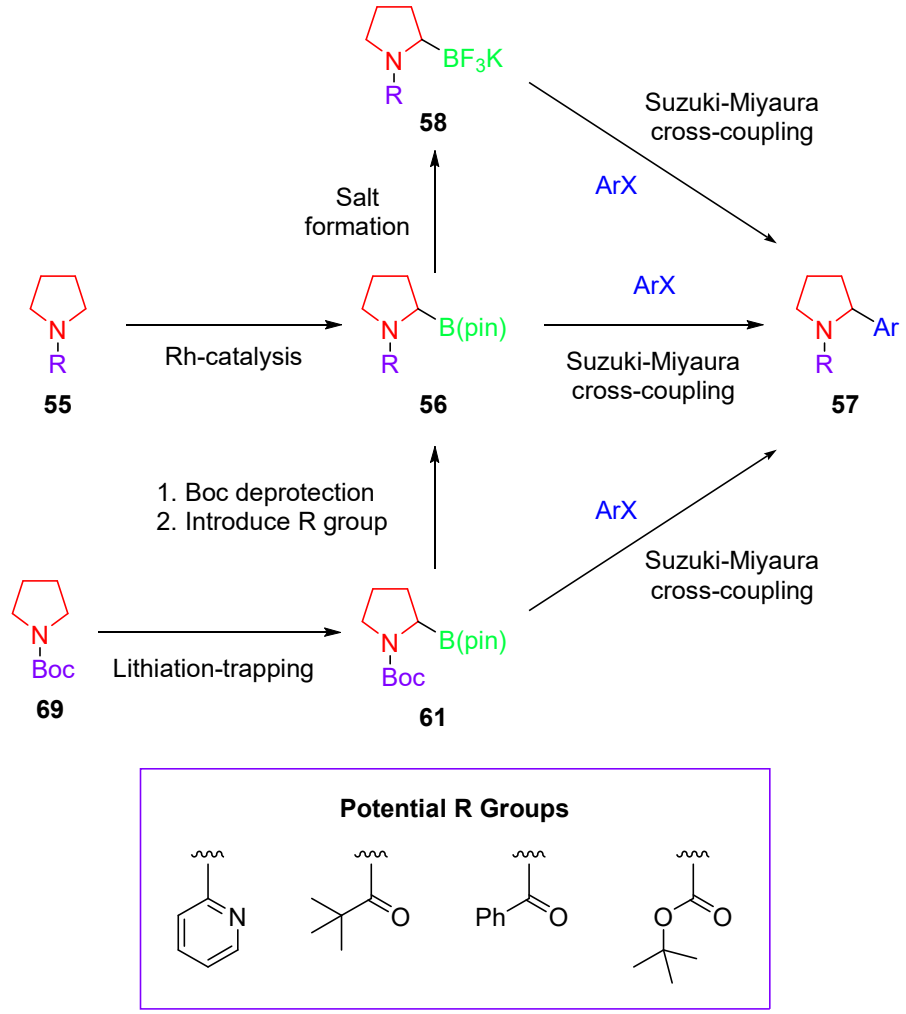
After screening fifteen phosphine ligands, two illustrative ligands were found which promoted stereoretentive and stereoinvertive pathways, generating (*R*)-**51** and (*S*)-**53**, respectively. Further ligand probing using multivariate linear regression analysis found that these pathways could be predicted using two easily obtained terms: the energy of the P-C anti-bonding orbital, which represents the level of π-back bonding, and the energy of the phosphorus lone pair orbital, which can be used to measure the ligand's σ-bonding ability. Overall, the stereoinvertive pathway, (formation of (*S*)-**53**) was promoted using a phosphine ligand with strong σ-donating abilities, such as the adamantyl phosphine **54**, as this is believed to stabilise a two-coordinate Pd complex. Conversely, a stereoretentive pathway, (formation of (*R*)-**51**), can be promoted by using a phosphine ligand which provides a high level of π-back bonding, such as the aryl phosphine **52**. This is believed to be due to the stabilising effect of the co-ordination of a π-donor ligand.

In summary, in the area of C(sp^3)-C(sp^2) bond forming Suzuki-Miyaura cross-couplings of stereodefined boronate derivatives, both stereoretentive and stereoinvertive outcomes are now well documented, with the outcome being promoted by a change in substrate, catalyst, or ligand. Electronics are a key aspect of the cross-coupling reactions. For example, intramolecular coordination within a substrate, or the electronic properties of the phosphine

ligand employed can determine the stereochemical outcome of the cross-coupling. However, as shown in this overview there have been limited examples of cyclic substrates, and, notably, only one example using saturated nitrogen heterocycles, reported in 2020 by Sawamura *et al*.[21]

1.4 Project Outline

As outlined in the previous sections, forming C(sp^3)-C(sp^2) bonds is crucial for the synthesis of more drug-like and pharmaceutically-relevant molecules. The ability to undergo a facile Suzuki-Miyaura cross-coupling with an sp^3 hybridised carbon in a saturated *N*-heterocycle would be a transformative approach for exploring 3-D pharmaceutical space. The overall aim of this project was to try to develop a new methodology for the stereospecific Suzuki-Miyaura cross-coupling of *α*-borylated pyrrolidines as a route to *α*-aryl pyrrolidines. The planned work is summarised in Scheme 1.18.



Scheme 1.18 Outline of the chemistry to be explored within this project.

In order to achieve the overall aim of this project outlined above, two key objectives were identified, namely (i) the development of methodology for the synthesis of *α*-borylated pyrrolidines with a range of different *N*-substituents and boron functionalities (e.g. **61**, **56**, and **58**) and (ii) exploration of the Suzuki-Miyaura cross-coupling of the *α*-borylated pyrrolidines to give *α*-aryl pyrrolidines **57**. The plan was to explore the *N*-substituted B(pin) derivatives of

56 using Rh-catalysis and lithiation-trapping approaches. For the lithiation-trapping approach, Boc removal and *N*-functionalisation would be used. The plan was to investigate a range of boron functionalities, including B(pin), BF_3K and BMIDA. Chapter 2 describes our efforts on the synthesis of a range of racemic α-borylated pyrrolidines containing pyridine, amide and Boc groups on the nitrogen.

Efforts towards the Suzuki-Miyaura cross-couplings of these substrates was then to be explored. Sawamura *et al*.[21] have provided excellent precedent for the stereospecific cross-coupling of α-borylated *N*-heterocycles such as *N*-pyridyl pyrrolidine boronate **60**. In addition, Dombrowski *et al*.[27] at AbbVie had also provided insight into the use of the BF_3K functionality in these Suzuki-Miyaura cross-coupling reactions. As shown in Scheme 1.18, the Suzuki-Miyaura cross-coupling of α-borylated pyrrolidines **61**, **56** and **58** with aryl bromides would be explored. The replication of this work will provide a good foundation for further exploring the stereospecific nature of these substrates in Suzuki-Miyaura cross-couplings. The results of these studies are described in Chapter 3.

2. Synthesis of *α*-Borylated *N*-Heterocycles

In this Chapter, several different routes to *α*-borylated *N*-heterocycles are described. The initial plan was to follow the work of Sawamura *et al.*[21] in synthesising *N*-pyridyl pyrrolidine boronate **60**. However, issues with this synthesis led to the exploration of a more diverse range of *N*-substituents, as well as differentiating the boron functionality of these compounds. A summary of the *α*-borylated compounds synthesised in this Chapter is presented in Figure 2.1.

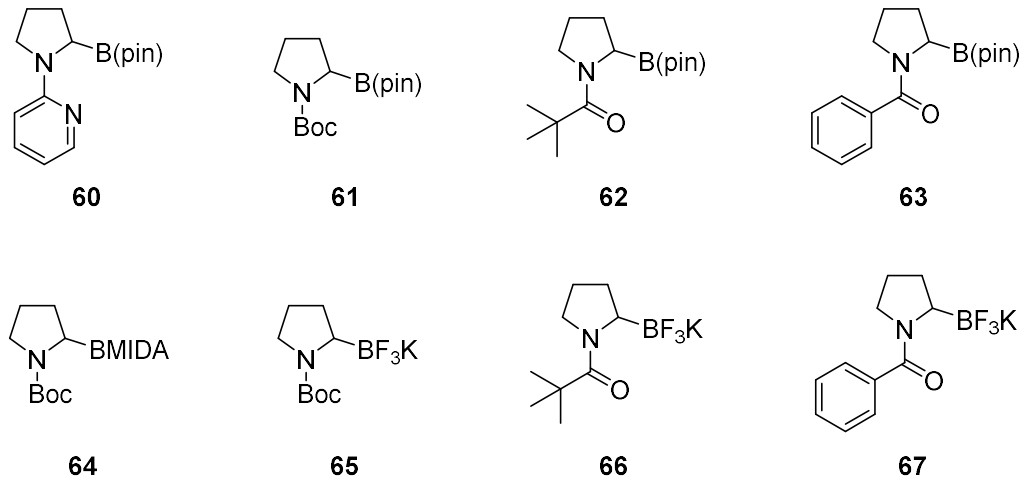
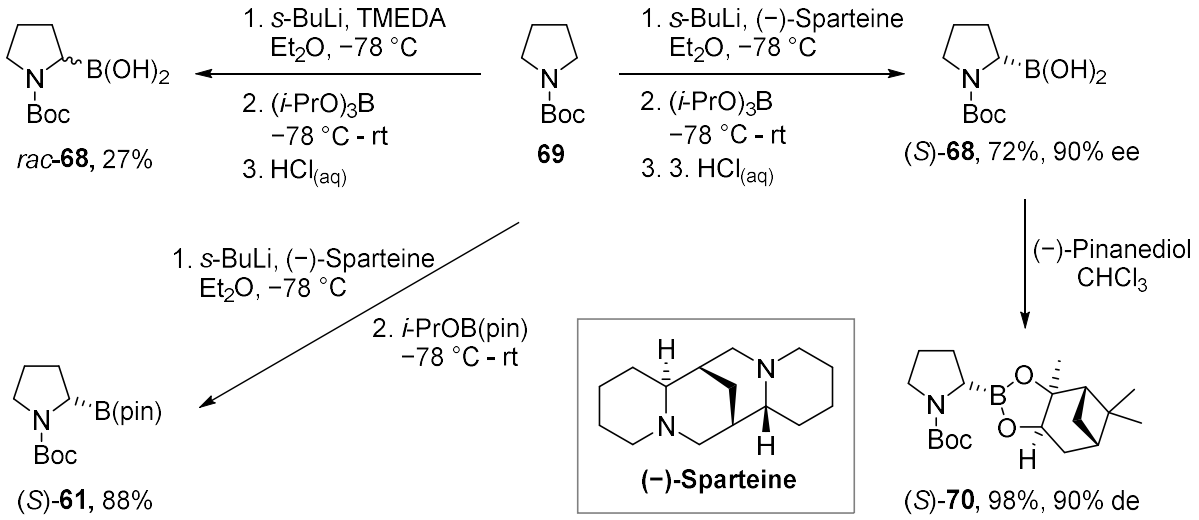


Figure 2.1 The α-borylated N-heterocycles synthesised in this chapter.

The literature presented in Section 2.1 gives the relevant background for this Chapter, outlining previous attempts at synthesising *α*-borylated pyrrolidines and other *N*-heterocycles. Section 2.2 outlines the attempts to carry out the synthesis of *N*-pyridyl pyrrolidine boronate **60**. Section 2.3 summarises our attempts to access a more diverse range of *α*-borylated *N*-heterocycles using Beak *et al.*'s[28] lithiation-trapping methodology. Finally, Section 2.4 provides a look at the attempts to change the boron functionality of these compounds by synthesising their MIDA and BF_3K analogues.

2.1 Overview of synthetic approaches to α-borylated *N*-heterocycles

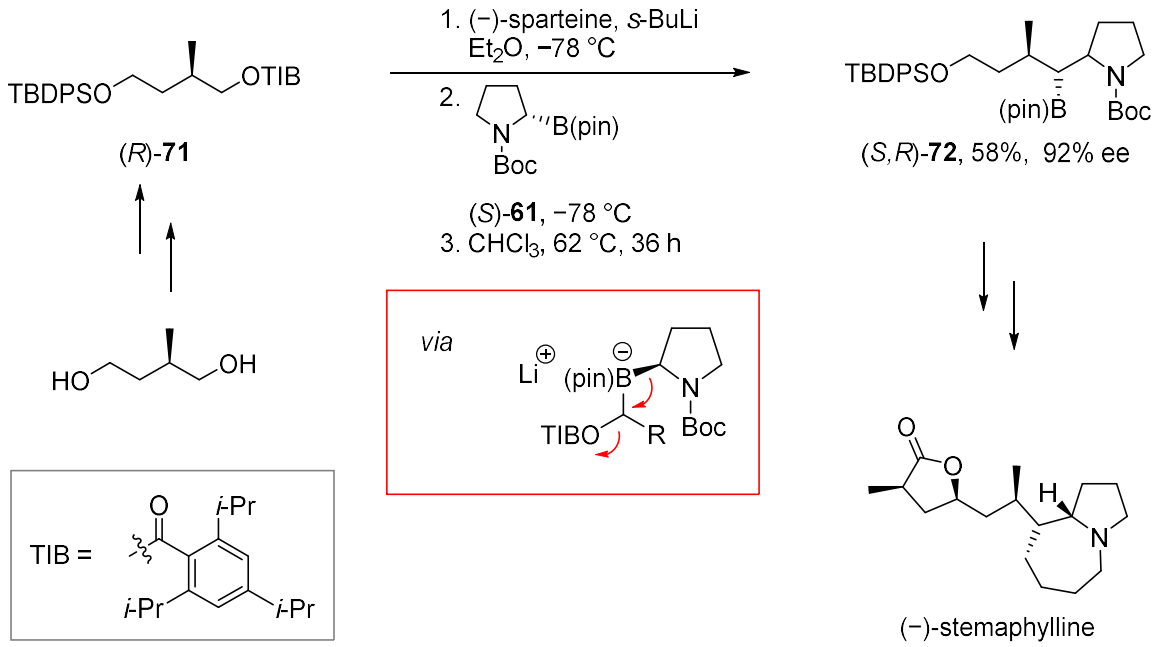
In 2007, Whiting *et al.*[29] outlined the synthesis of Boc-protected α-borylated pyrrolidines. Initially focusing on a racemic approach, *N*-Boc pyrrolidine **69** was reacted with *s*-BuLi and TMEDA in Et_2O at −78 °C to give the lithiated pyrrolidine. Subsequent reaction with triisopropyl borate at −78 °C before warming to room temperature gave α-boronic acid pyrrolidine *rac*-**68** (27% yield) after an aqueous acidic work-up (Scheme 2.1). Further, it was demonstrated that enantioenriched α-borylated pyrrolidine (*S*)-**61** could be synthesised using a similar method with a chiral diamine ligand. Thus, reaction of *N*-Boc pyrrolidine **69** with *s*-BuLi and (−)-sparteine in Et_2O at −78 °C gave the lithiated pyrrolidine and subsequent reaction with triisopropyl borate gave enantioenriched α-borylated pyrrolidine (*S*)-**68** (72% yield, 90% ee) (Scheme 2.1). Pyrrolidine (*S*)-**68** (90% ee) was then reacted with (−)-pinanediol in $CHCl_3$ to give diastereomeric α-borylated pyrrolidines **70** (98% yield, 90% de). It was also shown that a pinacol boronate functionality could be directly accessed using this asymmetric lithiation methodology. Reaction of *N*-Boc pyrrolidine **69** with *s*-BuLi and (−)-sparteine followed by reaction with isopropoxy borolane pinacol ester gave enantioenriched α-borylated pyrrolidine (*S*)-**61** (88% yield) (Scheme 2.1).



Scheme 2.1 A summary of Whiting et al.[29] *'s use of (−)-sparteine for enantioenriched* α*-borylated* N*-heterocycles.*

Whiting's lithiation-borylation method is the seminal work in the lithiation approach to α-borylated *N*-heterocycles. More recently, Aggarwal *et al.*[30] utilised Whiting's method for use in the exploration of enantiospecific couplings to form $C(sp^3)$-$C(sp^2)$ bonds, forming enantioenriched α-borylated pyrrolidine (*S*)-**61** (88% yield, 90% ee). This success led to the use of a similar method in Aggarwal *et al.*'s[31] pursuit of a stereocontrolled total synthesis of (−)-stemaphylline. Protected alcohol (*R*)-**71** was lithiated α to the OTIB functionality using

s-BuLi and (−)-sparteine and then reacted with *α*-borylated pyrrolidine (*S*)-**61**. Heating in $CHCl_3$ at 62 °C for 36 h allowed the stereocontrolled 1,2-metalate rearrangement to take place, giving *α*-substituted pyrrolidine (*S,R*)-**72** (58% yield, 92% ee) (Scheme 2.2).

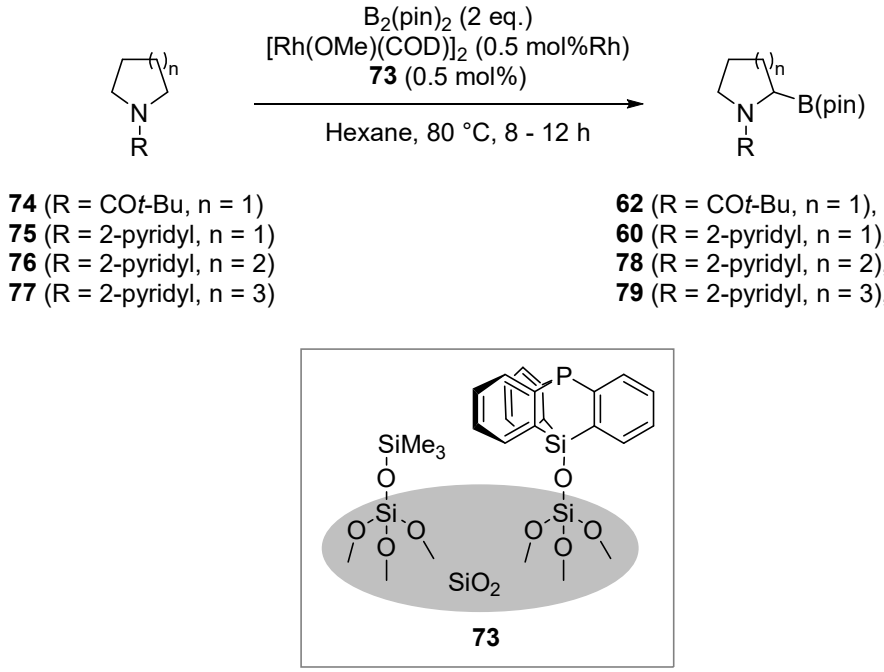


Scheme 2.2 Use of Whiting et al. *'s methodology by Aggarwal* et al.[31] *in the synthesis of (−)-stemaphylline.*

The method pioneered by Whiting *et al*. has been shown to be efficient, high yielding and useful in a range of syntheses. However, the use of organolithiums and very low temperatures mean that it is not the most attractive synthesis.

In 2012, Sawamura *et al.*[32] outlined the Rh-catalysed formation of *α*-borylated *N*-based substrates under relatively mild conditions. A highlight of the work is the use of silica-supported triarylphosphine ligand **73** (Scheme 2.3). Several different ligand systems, including a non-silica-supported version of **73**, and other triaryl- and trialkylphosphines, did not give any hits in terms of reactivity. Sawamura hypothesised that the immobilised catalyst system on the silica is critical for borylation activity. The report explored a range of *N*-based substrates, including amines, ureas and *N*-heterocycles. Reaction of pivaloyl amide **74** with $B_2(pin)_2$ in the presence of $[Rh(OMe)(cod)]_2$ and ligand **73** at 80 °C for 5 h gave *α*-borylated pivaloyl amide **62** (107% yield) (Scheme 2.3). Sawamura *et al*. explain yields in excess of 100% as arising due to the reaction of the starting material with the H-B(pin) byproduct, which itself is less reactive than the $B_2(pin)_2$, which is the limiting reagent in the reaction. The subsequent scope exploration also used the *N*-heterocyclic catalyst-directing group pyridine with a range of *N*-

heterocycles, all giving yields exceeding 100% (**60**, 125%, **78**, 130%, **79**, 101%), therein illustrating the efficacy of Sawamura's method.

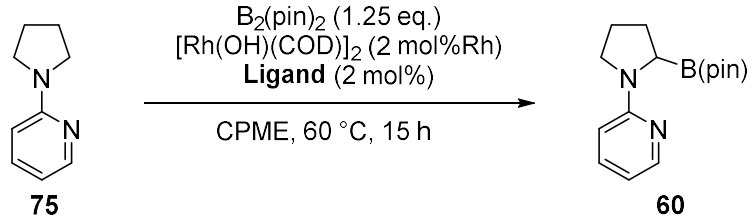


Scheme 2.3 Synthesis of several α-borylated pyrrolidines by Sawamura et al.[32]

Subsequently, in 2017, Sawamura *et al*. further developed this work with a view to an enantioselective Rh-catalysed borylation method.[33] The modification of the previously used[32] silica-supported heterogeneous ligand **73** proved difficult in comparison to the ease of a homogeneous catalytic system. Thus, this work focused on the utilisation of homogeneous catalyst-ligand systems. As an initial exploration, Sawamura *et al.* reacted *N*-pyridyl pyrrolidine **75** with $B_2(pin)_2$ in the presence of $[Rh(OH)(cod)]_2$ and a common monophosphine ligand at 80 °C for 8-12 h. The investigation proved the reactivity of the homogeneous ligands, particularly P(*o*-tol)$_3$ and P(*t*-Bu)$_3$ which gave excellent yields of *α*-borylated pyrrolidine **60** (99% and 98% respectively).

Following the success of the homogeneous catalysts, focus turned to the asymmetric reaction. A ligand screening was undertaken with a series of BINOL-based phosphoramidite ligands (Table 2.1). Reaction of *N*-pyridyl pyrrolidine **75** with $B_2(pin)_2$ in the presence of $[Rh(OH)(cod)]_2$ and a phosphoramidite ligand gave *α*-borylated pyrrolidine **60**. Variation of both the 'BINOL' element of the ligand and the amine functionality resulted in wildly varying yields and enantiomeric excesses of *α*-borylated pyrrolidine **60** (Table 2.1). The most successful ligand in terms of both yield and resulting enantiomeric excess was the

phosphoramidite **81**, which gave α-borylated pyrrolidine **60** in 95% yield with 31% enantiomeric excess.



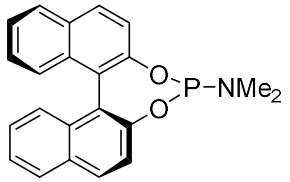
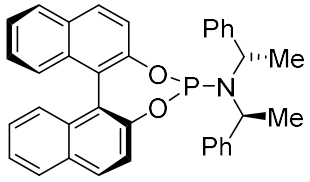
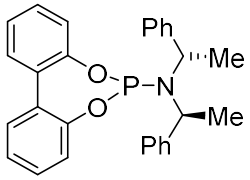
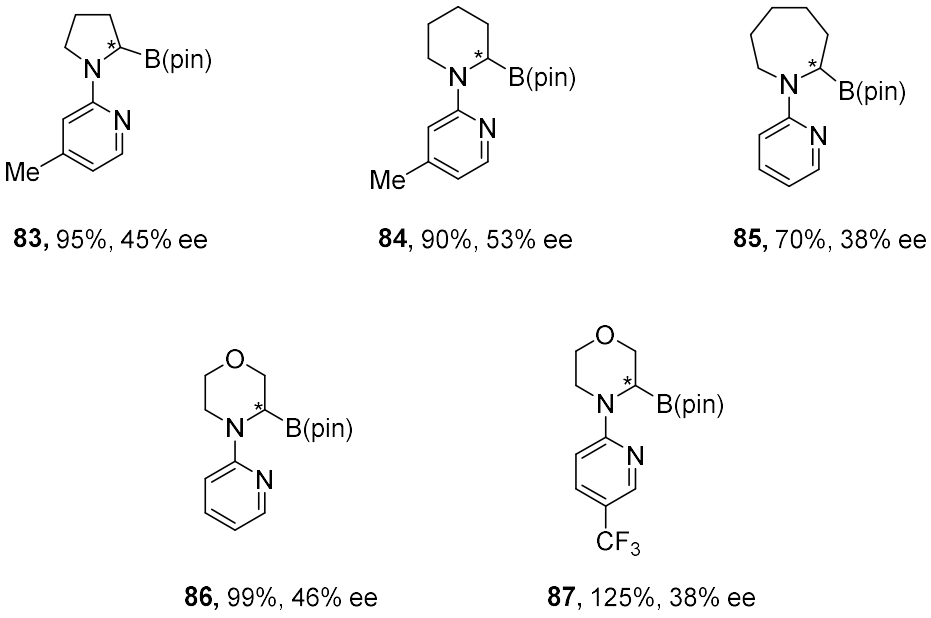
Ligand	Yield of 60/%	ee of 60/%
 **80**	10	3
 **81**	95	31
 **82**	45	7

Table 2.1 Sawamura et al. *'s*[33] *screening of phosphoramidite ligands for use in* α*-borylated* N*-heterocycle formation.*

Following the identification of a successful homogeneous ligand, although it only gave modest enantioselectivity, an investigation into the scope of the method for various *N*-heterocycles was undertaken. Following the procedure outlined in Table 2.1, *N*-pyridyl heterocycles were reacted with $B_2(pin)_2$ in the presence of $[Rh(OH)(cod)]_2$ and phosphoramidite ligand **81** to give α-borylated heterocycles. For the 5-, 6- and 7-membered saturated *N*-heterocycles, this method gave α-borylated heterocycles **83**, **84** and **85** in excellent yields (70 – 95%) and modest enantiomeric excesses (38 – 55% ee) (Figure 2.2). Interestingly, Sawamura *et al*. expanded the scope of the method to morpholines. α-Borylated morpholines **86** and **87** were generated in

yields of 99% and 125%, with respect to the molar ratio of $B_2(pin)_2$ used. Enantiomeric excesses were thus only moderate.



83, 95%, 45% ee

84, 90%, 53% ee

85, 70%, 38% ee

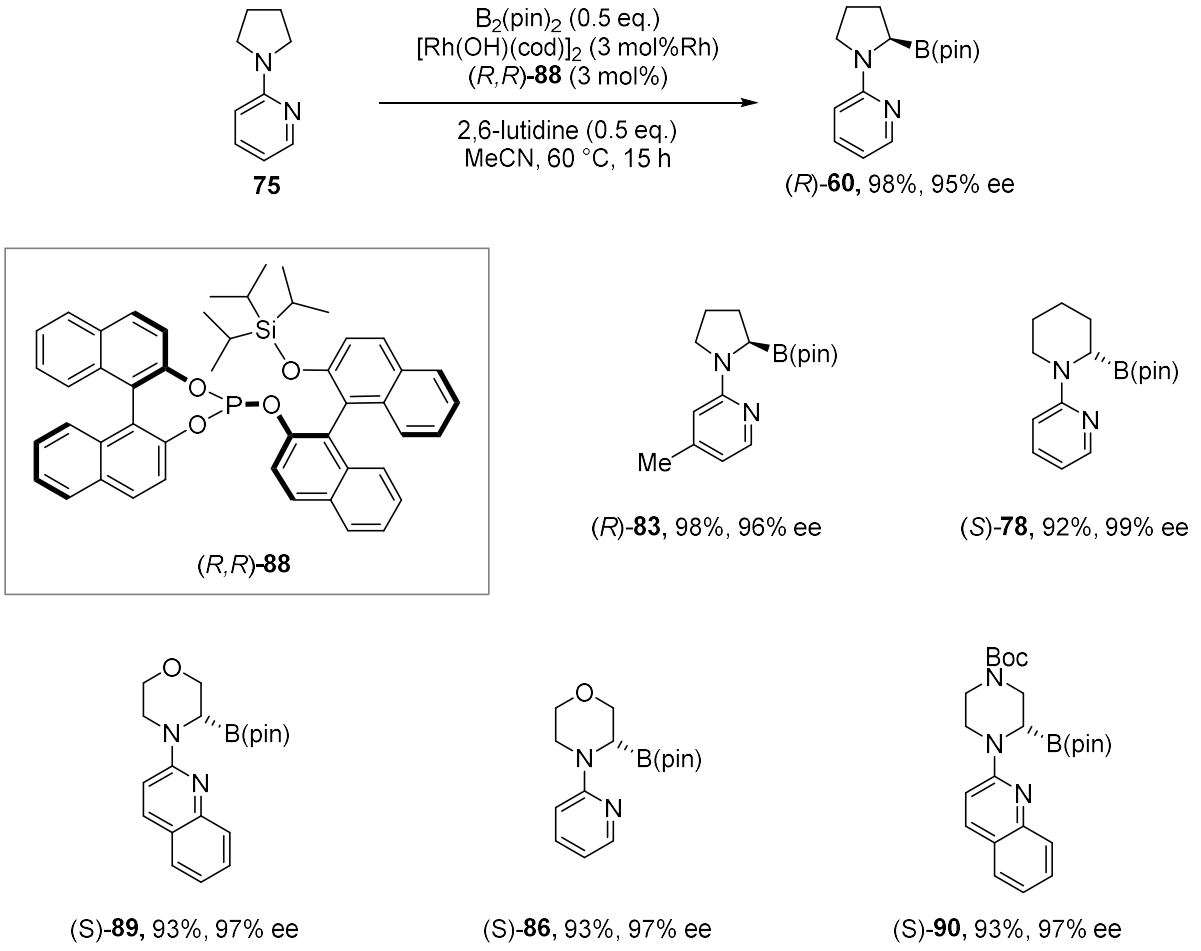
86, 99%, 46% ee

87, 125%, 38% ee

Figure 1.2 α-*Borylated* N-*heterocycles synthesised by Sawamura* et al.[33] *using their phosphoramidite ligand* ***81***.

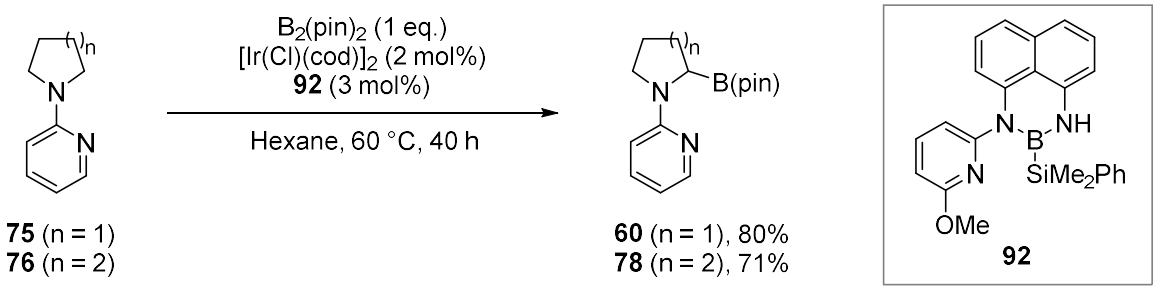
Continuing this work in 2020, Sawamura *et al.*[21] reported the highly enantioselective Rh-catalysed borylation of several *N*-heterocycles. Following screening of reaction conditions, it was found that the reaction of *N*-pyridyl pyrrolidine **75** with $B_2(pin)_2$ in the presence of $[Rh(OH)(cod)]_2$, phosphoramidite (*R*,*R*)-**88** and 2,6-lutidine in MeCN at 60 °C for 15 h gave *α*-borylated *N*-pyridyl pyrrolidine (*R*)-**60** (98% yield, 95% ee) (Scheme 2.4). Through the screening process, it was established that solvent had a sizeable impact on reactivity; ether-based solvents performed well whereas non-polar solvents, such as hexane, gave limited reactivity. A further development from Sawamura *et al.*'s previous work in this area was the inclusion of the additive 2,6-lutidine. It was proposed that the asymmetric borylation takes places in a narrow chiral reaction pocket and the HB(pin) generated as a byproduct in the reaction is small enough to block the catalytic system by forming an undesirable Rh-H complex. The addition of 2,6-lutidine results in a more favourable interaction with the HB(pin) due to the inductive effects of the methyl groups on the aromatic ring. This side-complexation frees up the catalyst for its interactions with the desired reactant, leading to the high yields and enantiomeric excesses observed in Scheme 2.4. The method developed in this work was assessed for scope across a wide range of *N*-heterocycles, including piperidines ((*S*)-**78**, 92% yield, 99% ee), morpholines ((*S*)-**89**, 93% yield, 97% ee and (*S*)-**90**, 93% yield, 97% ee) and a

piperazine((*S*)-**90**, 92% yield, 99% ee) (Scheme 2.4). The (*S*) enantiomers were generated using the enantiomeric phosphoramidite (*S,S*)-**88**.



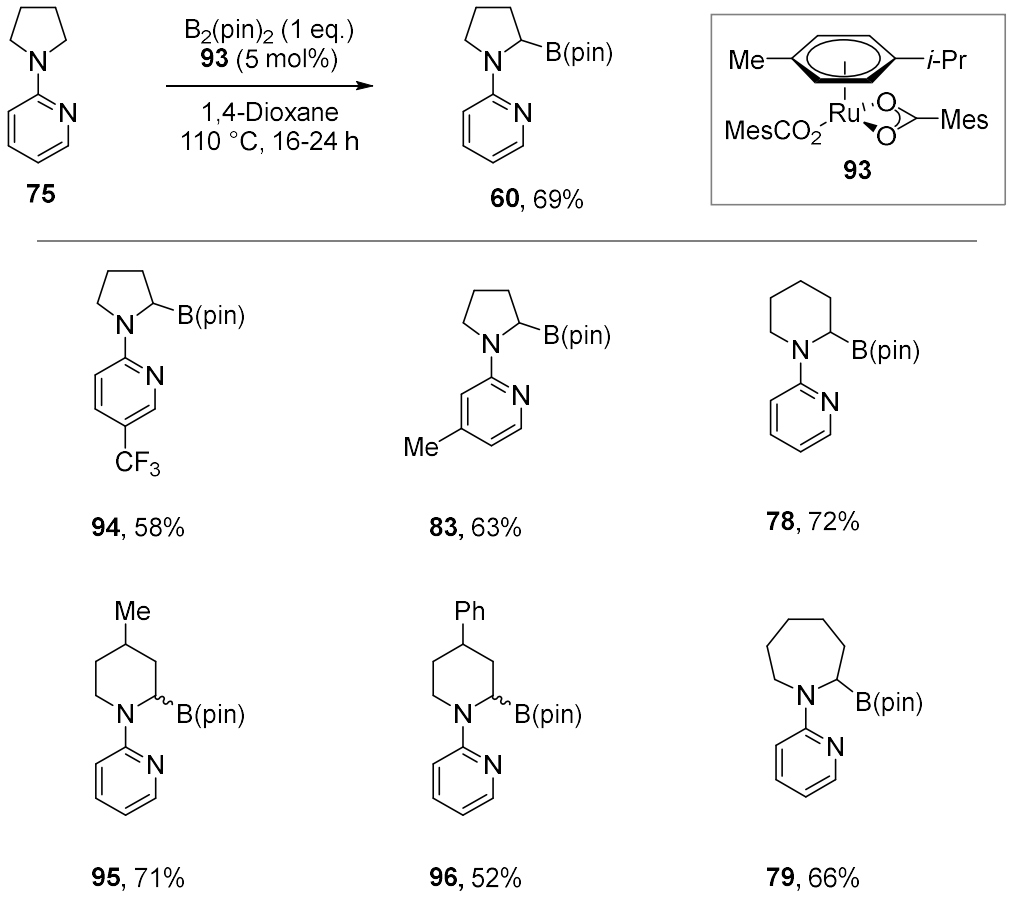
Scheme 2.4 A range of α*-borylated* N*-heterocycles synthesised by Sawamura* et al.[21] *in their 2020 paper.*

Other groups, such as Li *et al.*,[34] have also investigated the use of transition metal-catalysed borylation reactions. In this case, the development of an N-B bidentate ligand in order to form an iridium pre-catalyst system was explored. Following screening of several silylborane ligands and their reactivity towards *ortho*-borylation of methyl benzoate, ligand **92** showed great promise in terms of reactivity and selectivity. As part of the scope exploration, the investigation focused on the borylation of C(sp^3)-H bonds. The reaction of *N*-pyridyl amines **75** and **76** with $B_2(pin)_2$ in the presence of $[Ir(Cl)(cod)]_2$ and silylborane ligand **92** in hexane at 60 °C for 40 h afforded *α*-borylated *N*-pyridyl amines **60** and **78** (80% and 71% yields respectively) (Scheme 2.5).



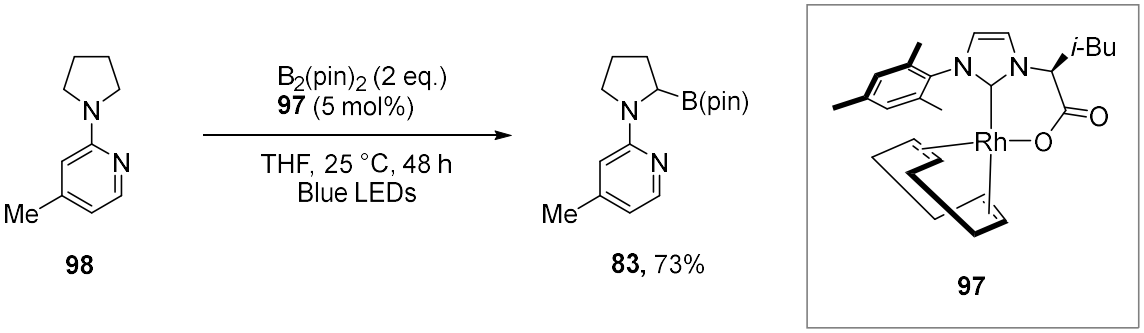
Scheme 2.5 Li et al.*'s*[34] *Ir-catalysed approach to the synthesis of* α*-borylated* N*-heterocycles.*

Ackermann *et al.*[35] outlined a Ru-catalysed method for the borylation of α-C(sp^3)-H bonds in 2017. The optimisation of the ruthenium catalyst gave a bench-stable compound which did not require additional additives to boost reactivity; greatly improving the method's atom efficiency. For example, reaction of *N*-pyridyl pyrrolidine **75** with $B_2(pin)_2$ in the presence of ruthenium catalyst **93** in 1,4-dioxane at 110 °C for 16 h gave α-borylated *N*-pyridyl pyrrolidine **60** (69% yield) (Scheme 2.6). Further scope exploration demonstrated that Ackermann *et al.*'s method tolerated variation of the pyridyl group well (**94** and **83**), as well as being useful for the α-borylation of 1,3-substituted piperidines (**95** and **96**) and even larger ring sizes (**79**).



Scheme 2.6 Ackermann et al.*'s*[35] *Ru-catalysed approach to the synthesis of* α*-borylated* N*-heterocycles.*

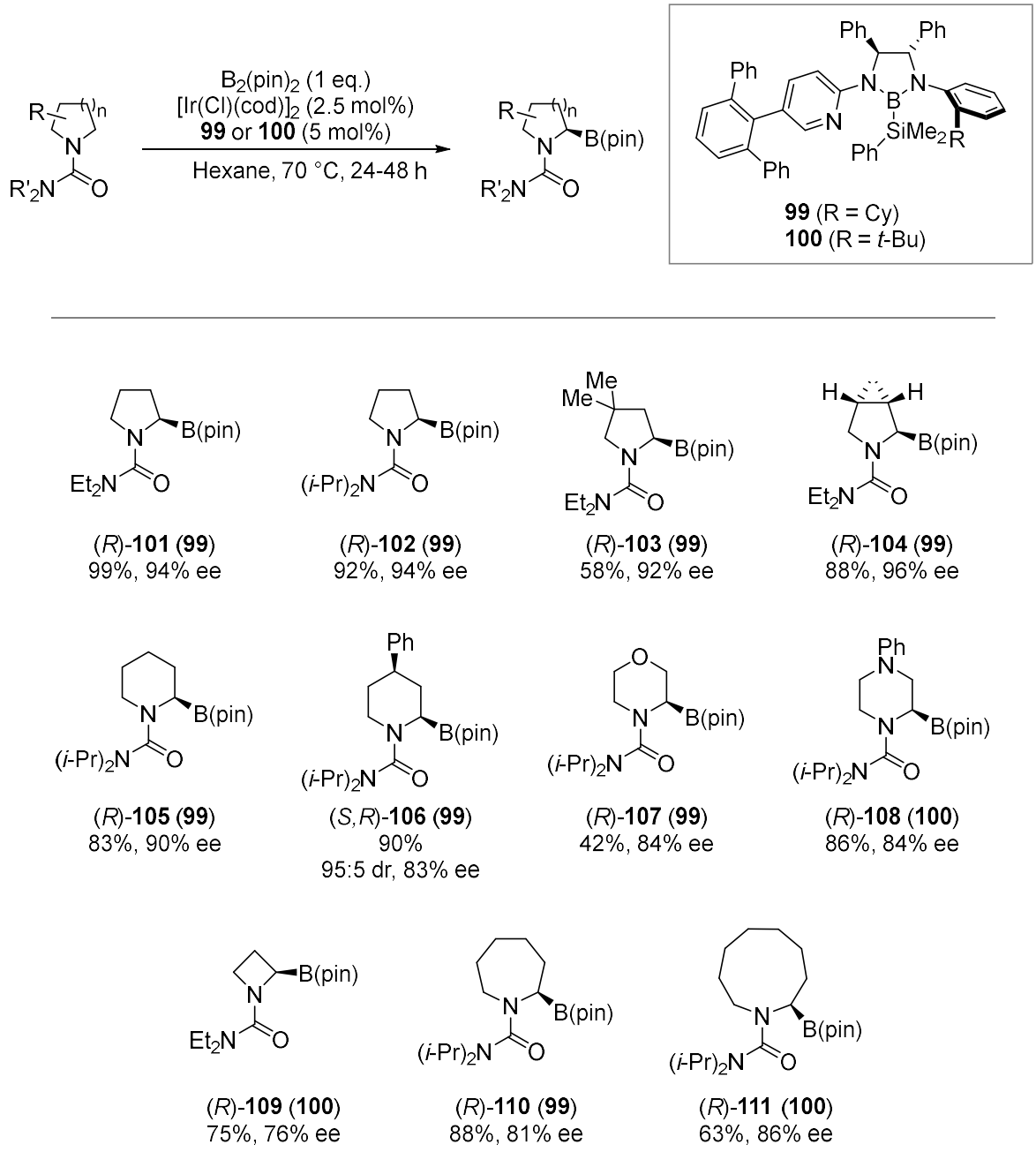
One approach to further improve transition metal-catalysis and the harsh conditions often associated with its use in C(sp^3)-H activation is to incorporate photocatalysis. Baslé *et al*.[36] designed a Rh-based catalyst **97** which was capable of both harvesting visible light and activating the stable C(sp^3)-H bond. The use of the bidentate *N*-heterocyclic carbene ligand with the added benefit of the electron-donating *i*-Bu group, showed excellent photocatalytic activity when applied to the borylation of aromatic C-H bonds. Further investigation into the suitability of Baslé's method for the borylation of C(sp^3)-H bonds involved the reaction of *N*-pyridyl pyrrolidine **98** with $B_2(pin)_2$ in the presence of Rh-based catalyst **97** (5 mol%) in THF at rt for 48 h under blue LEDs (ν_{max} = 460 nm). The reaction gave *α*-borylated pyrrolidine **83** in good yield (73%) (Scheme 2.7).



98 **83**, 73% **97**

Scheme 2.7 The photocatalysis methodology used by Baslé et al.[36] *for the synthesis of* α*-borylated pyrrolidine* ***83****.*

Most recently, Xu *et al*.[37] reported an Ir-catalysed enantioselective method for *α*-borylation of saturated *N*-heterocycles. This work outlines a series of chiral bidentate boryl ligands which can be adapted for optimisation with differing substrates. The scope investigation concerning saturated *N*-heterocycles used the ligands **99** and **100**. The reaction of *N,N*-diethylpyrrolidine-1-carboxamide with $B_2(pin)_2$ in the presence of $[Ir(Cl)(cod)]_2$ and ligand **99** in hexane at 70 °C gave *α*-borylated pyrrolidine (*R*)-**101** in excellent yield (99%) and high enantioselectivity (94% ee) (Scheme 2.8). Xu's method showed excellent tolerance for variation of the *N,N*-substituent ((*R*)-**102**, 92% yield, 94% ee), as well as further substitution of the pyrrolidine ring ((*R*)-**103**, 58% yield, 92% ee and (*R*)-**104**, 88% yield, 96% ee). The method also demonstrated good tolerance of ring size ((*R*)-**105,** (*R*)-**109,** (*R*)-**110,** (*R*)-**111**). Morpholines ((*R*)-**107**, 42% yield, 84% ee) and piperazines ((*R*)-**108**, 86% yield, 84% ee) also exhibited moderate reactivities with consistently good enantioselectivities. The formation of disubstituted piperidine (*S,R*)-**106** also proceeded with good yield and excellent enantioselectivity (90% yield, 83% ee, 95:5 dr) (Scheme 2.8).

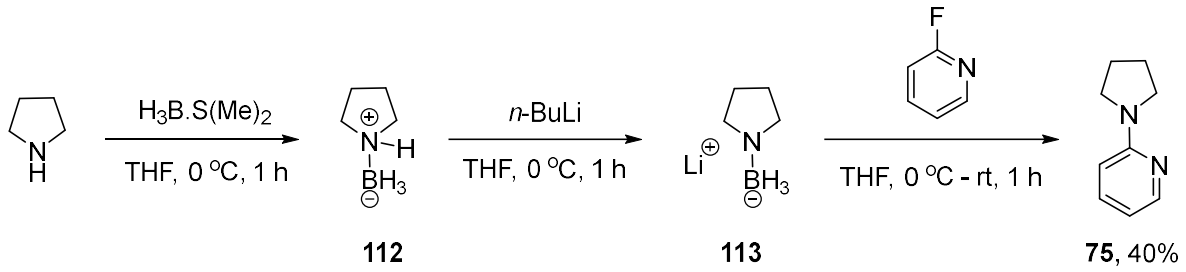


Scheme 2.8 Xu et al.*'s*[37] *Ir-catalysed method for synthesising a broad range of* α*-borylated* N*-heterocycles.*

In summary, there are two main approaches to synthesising *α*-borylated *N*-heterocycles. Whiting *et al.*'s[29] lithiation-trapping approach provided *α*-borylated *N*-heterocycles with good yields and excellent enantioselectivities. There are also several transition metal-catalysed approaches, including Sawamura *et al.*'s[21,32,33] Rh-catalysed formation of *α*-borylated *N*-heterocycles, such as pyrrolidines, morpholines and piperazines in excellent yields and enantioselectivities. Efforts have also been made to reduce the requirements for harsh reaction conditions, such as using the photocatalysis method outlined by Baslé *et al.*[36] which gave good yields, although has not yet been applied to an asymmetric reaction.

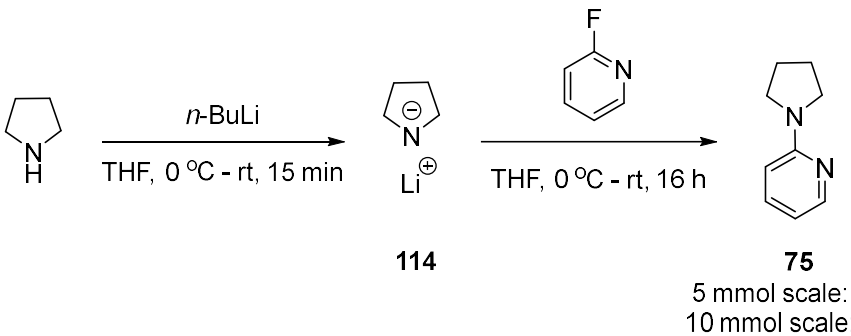
2.2 Rh-catalysed synthesis of α-borylated *N*-pyridyl pyrrolidine

Based on the successful results reported by Sawamura *et al.*,[21] our initial plan was to synthesise enantioenriched α-borylated *N*-pyridyl pyrrolidine (*R*)-**60** using their methodology (see Scheme 2.4). For this, the synthesis of *N*-pyridyl pyrrolidine **75** was required. Following the literature procedure reported by Singaram *et al.*,[38] pyrrolidine was reacted with borane dimethylsulfide in THF at 0 °C to give amine borane complex **112**. Then, in the same flask, *n*-BuLi was added to deprotonate **112** and form **113** which was added slowly to a cooled solution of 2-fluoropyridine before stirring at rt for 1 h. After chromatography, the desired *N*-pyridyl pyrrolidine **75** was obtained in 40% yield. In our hands, *N*-pyridyl pyrrolidine **75** was obtained in significantly lower yield than the 81% reported.[38]



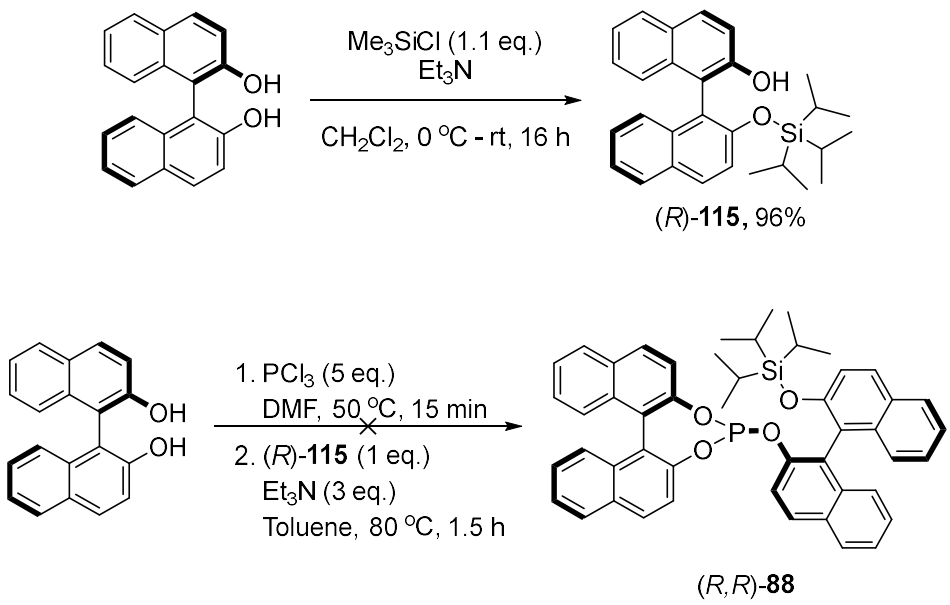
Scheme 2.9 Synthesis of N-*pyridyl pyrrolidine* ***75*** *based on the method by Singaram* et al.[38]

Since the required α-borylated *N*-pyridyl pyrrolidine (*R*)-**60** was an important starting material for the planned Suzuki-Miyaura cross-coupling studies, a higher yield for this first step in the synthesis was desired. Our attention was drawn to a simpler procedure, where the borane dimethylsulfide was not needed, that was also reported by Singaram *et al.*[39] Thus, direct lithiation of pyrrolidine using *n*-BuLi in THF at 0 °C gave lithium amide **114**, which was then reacted with 2-fluoropyridine and stirred at rt for 16 h. This gave *N*-pyridyl pyrrolidine **75** in an improved 72% yield after chromatography (Scheme 2.10). This reaction was then repeated on a larger 10 mmol scale, providing the *N*-pyridyl pyrrolidine **75** in 75% yield. Both of these results were far more in line with the 80% yield reported by Singaram *et al.* [39]



Scheme 2.10 Improved synthesis of N-*pyridyl pyrrolidine* ***75*** *based on the method by Singaram* et al.[39]

A key aspect of Sawamura *et al.*'s methodology was the use of the chiral ligand (*R,R*)-**88** to form the *α*-borylated *N*-pyridyl pyrrolidine (*R*)-**60** in 95% ee. Ligand (*R,R*)-**88** is not commercially available and therefore it was necessary to carry out its synthesis. The route described by Sawamura *et al.* involved synthesis of BINOL-monoTIPS (*R*)-**115** and subsequent reaction with (*R*)-BINOL-phosphorochloridite, generated from (*R*)-BINOL. The first step of the synthesis proceeded uneventfully. Monosilylation of (*R*)-BINOL with triisopropylsilyl chloride in the presence of Et_3N gave BINOL-monoTIPS (*R*)-**115** in 96% yield after chromatography (Scheme 2.11). The second step of this synthesis initially required the formation of (*R*)-BINOL-phosphorochloridite from (*R*)-BINOL and phosphorus trichloride in DMF at 50 °C. Then, reaction with (*R*)-BINOL to give the desired ligand (*R,R*)-**88**. Disappointingly, this method did not work over multiple attempts.

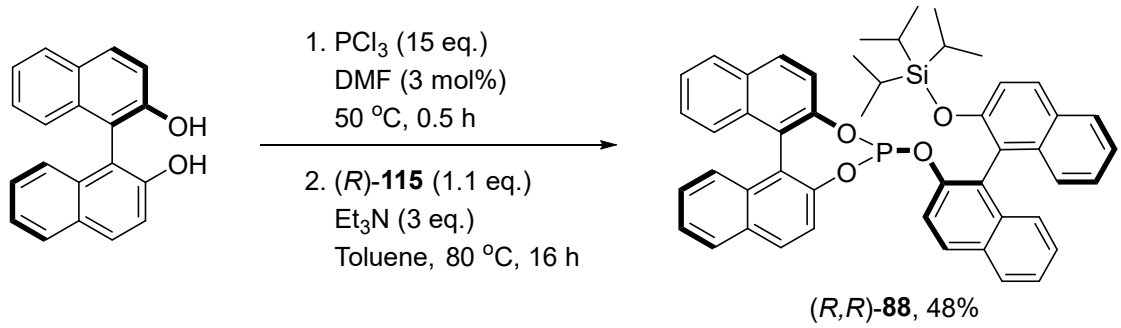


*Scheme 2.11 Synthesis route to phosphoramidite ligand (*R,R*)-**88** based on the method by Sawamura* et al.[21]

The reactivity of the (*R*)-BINOL-phosphorochloridite requires the reaction to be carried out under a rigorously dry Ar atmosphere. When the reaction to form ligand (*R,R*)-**88** was first carried out, removal of the DMF solvent and excess phosphorus trichloride was carried out using a standard rotary evaporator. This exposed the phosphochloridite to air for a short amount of time, and the high boiling point of DMF also meant that rotary evaporation was not satisfactory for its removal. A second attempt was made, this time using a cold finger set-up on the high vacuum. However, it still proved difficult to remove the DMF from the reaction and the phosphorochloridite was exposed to air in the process. A third attempt used a three-

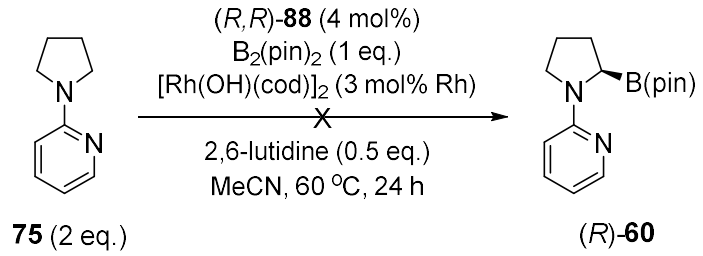
way tap, allowing access to both Ar and high vacuum in the round bottomed flask, which did reduce the risk of exposure to air. However, the volume of the reaction meant that a large round bottomed flask was required, and evaporation of the DMF and excess phosphorus trichloride still proved difficult. As a result, all three attempts did not produce any of ligand (*R,R*)-**88**.

Fortunately, James Rossi-Ashton (Unsworth group) had experience of preparing similar phosphorochloridite ligands, and so their method was attempted next.[40] In this case, (*R*)-BINOL was reacted with an excess of phosphorus trichloride in the presence of catalytic DMF (3 mol%) at 50 °C for 30 min before being cooled to rt. Then, the reaction flask was placed under high vacuum to remove the excess phosphorus trichloride, aided with a toluene azeotrope. The resulting white solid (presumed to be the desired phosphorochloridite) was then dissolved in toluene and reacted with BINOL-monoTIPS (*R*)-**115** at 80 °C for 16 h. Throughout this process there was no exposure to air. Pleasingly, following work-up and purification by chromatography, ligand (*R,R*)-**88** was isolated in 48% yield (Scheme 10). The optical rotation of ligand (*R,R*)-**88** was $[\alpha]_D$ −61.2 (*c* 1.0 in CH_2Cl_2) and it compared well with that reported in the literature ($[\alpha]_D$ −64.4 (*c* 0.3 in MeOH)).[21]



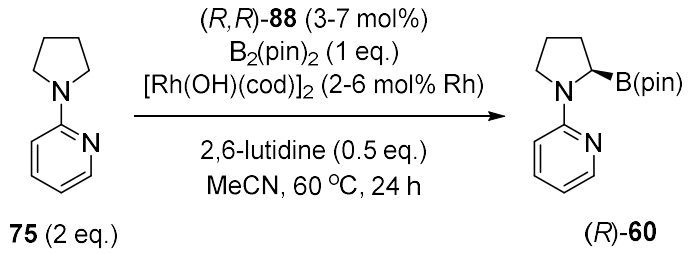
*Scheme 2.12 Successful synthesis of phosphoramidite ligand (*R,R*)-**88**.*

The successful synthesis of *N*-pyridyl pyrrolidine **75** and chiral ligand (*R*,*R*)-**88** meant that the Rh-catalysed enantioselective borylation could now be attempted. Ligand (*R,R*)-**88**, $B_2(pin)_2$ and $[Rh(OH)(cod)]_2$ were placed in a reaction flask which was evacuated and back-filled with Ar three times. Degassed MeCN was then added, and the solution was stirred at rt for 5 min. *N*-Pyridyl pyrrolidine **75** and 2,6-lutidine were then added and the mixture was stirred and heated at 60 °C for 24 h. In our hands, using 3 mol% $[Rh(OH)(cod)]_2$ and 4 mol% ligand (*R,R*)-**88**, none of *α*-borylated *N*-pyridyl pyrrolidine (*R*)-**60** was generated as shown by the ^{1}H NMR spectrum of the crude product (Scheme 2.13). A range of experiments were designed to explore whether we could reproduce the Sawamura reaction. These are summarised in Table 2.2, with the original reaction from Scheme 2.13 included as entry 1.



Scheme 2.13 Attempted synthesis of α*-borylated* N*-pyridyl pyrrolidine (*R*)-**60** based on the method by Sawamura* et al.[21]

As the reaction is air-sensitive, it was repeated but this time with addition of the MeCN and degassing directly in the pressure tube, rather than evacuating and backfilling. However, this still produced no *α*-borylated *N*-pyridyl pyrrolidine (*R*)-**60** (entry 2). A higher ligand:catalyst ratio (4 mol% (*R,R*)-**88**, 2 mol% $[Rh(OH)(cod)]_2$) also gave no *α*-borylated *N*-pyridyl pyrrolidine (*R*)-**60** (entry 3). Increasing both the ligand and catalyst loading gave the first indication of the formation of *α*-borylated *N*-pyridyl pyrrolidine (*R*)-**60** in the crude reaction mixture. Following purification by chromatography, a co-eluted fraction contained a 30:70 mixture of starting pyrrolidinyl pyridine **75** and 2-B(pin) pyrrolidine **60**. For this mixture, a 9% yield of 2-B(pin) pyrrolidine **60** was calculated (entry 4). Attempts to increase the yield by separately degassing a solution of $[Rh(OH)(cod)]_2$ in MeCN before adding to the solution did not work, only resulting in a 98:2 mixture of starting pyrrolidinyl pyridine **75** and 2-B(pin) pyrrolidine **60** in the crude mixture (entry 5). Diluting the solution and using the initial procedure also gave no product (entry 6).



75 (2 eq.) (*R*)-**60**

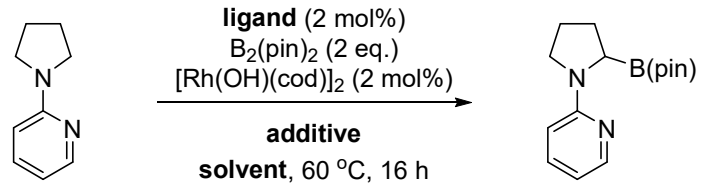
Entry	Eq. 75	mol% (*R,R*)-88	mol% [Rh(OH)(cod)]$_2$	mol $B_2(pin)_2$/ mL MeCN	Procedure	Outcome
1	2.1	4	3	0.650	*a*	No product[d]
2	2.2	4	4	0.430	*b*	No product[d]
3	1.9	4	2	0.714	*a*	No product[d]
4	2.0	5	6	0.699	*a*	9%[e]
5	2.0	7	4	0.154	*c*	4%[f]
6	2.0	3	4	0.351	*a*	No product[d]

Table 2.2 Various attempts at the asymmetric Rh-catalysed borylation of N*-pyridyl pyrrolidine* ***75****. Procedures a, b and c are outlined in detail in the experimental. d – No product observed by* ^{1}*H NMR spectroscopy. e – Determined from the mass of a co-eluted column fraction and the ratios of starting material and product resonances in the* ^{1}*H NMR spectrum. f –98:2 mixture of starting material and product determined from the* ^{1}*H NMR spectrum of the crude product.*

In previous work, Sawamura *et al.*[33] had reported the racemic synthesis of *α*-borylated *N*-pyridyl pyrrolidine **60** using simpler phosphine ligands. Following the lack of success with the asymmetric approach, it was decided to explore the racemic approach as this would allow us to study the subsequent Suzuki-Miyaura cross-coupling reaction. Thus, P(*o*-tol)$_3$ (2.0 mol%), $B_2(pin)_2$ (1.3 eq.) and MeCN (1.0 mL) were placed in a pressure tube. In a separate flask, a solution of [Rh(OH)(cod)]$_2$ in MeCN was degassed and 1.5 mL of the resulting solution (containing 2.0 mol% Rh) was added to the pressure tube. *N*-Pyridyl pyrrolidine **75** (1.0 eq.) was added and the resulting solution was stirred and heated at 60 °C for 16 h. Following work-up, none of the desired borylated pyrrolidine **60** was detected in the ^{1}H NMR spectrum or by mass spectrometry of the crude reaction mixture (Table 2.3, entry 1).

The ligand P(*t*-Bu)$_3$ in CPME solvent was explored next. Thus, P(*t*-Bu)$_3$HBF$_4$ (2.0 mol%), $B_2(pin)_2$ (1.3 eq.) and CPME (1.0 mL) were placed in a pressure tube. In a separate flask, a solution of [Rh(OH)(cod)]$_2$ (2.0 mol% Rh) in CPME (1.5 mL) was degassed and added to the pressure tube. *N*-Pyridyl pyrrolidine **75** (1.0 eq.) was added and the resulting solution was stirred and heated at 60 °C for 16 h. Following work-up, none of the desired borylated pyrrolidine **60** was detected in the ^{1}H NMR spectrum or by mass spectrometry (entry 2).

It was further speculated that the use of 2,6-lutidine, used by Sawamura *et al*.[21] in their 2020 paper to react with the HB(pin) generated in the reaction, may suppress any catalyst deactivation. The procedure in entry 2 was carried out with the addition of 2,6-lutidine (0.65 eq.). However, following work-up, none of the desired borylated pyrrolidine **60** was detected in the ^{1}H NMR spectrum or by mass spectrometry (entry 3).



75 **60**

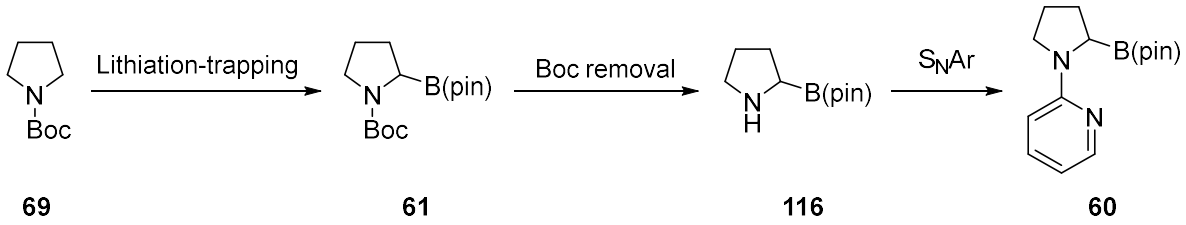
Entry	Ligand	Additive	Solvent	Outcome
1	P(*o*-tol)$_3$	None	MeCN	No product[a]
2	P(*t*-Bu)$_3$HBF$_4$	None	CPME	No product[a]
3	P(*t*-Bu)$_3$HBF$_4$	2,6-lutidine	CPME	No product[a]

Table 1.3 Various attempts at the racemic Rh-catalysed borylation of N*-pyridyl pyrrolidine* ***75****. a - No product observed by* ^{1}*H NMR spectroscopy and mass spectrometry.*

Following this series of unsuccessful syntheses, Sawamura was contacted directly in order to provide further insight into the intricacies of the reaction. Matthew Gill (O'Brien group) also worked through the rigorous protocols provided but we were still unable to carry out the borylation of *N*-pyridyl pyrrolidine **75**. Andres Gomez-Angel (O'Brien group) followed the synthesis protocol outlined by Ackermann *et al*. (see Scheme 2.6),[35] using a Ru-catalysed approach and purifying by chromatography on alumina. In this case, 2-B(pin) pyrrolidine **60** (95% purity) was isolated in 32% yield. Nonetheless, it proved difficult to synthesise and purify 2-B(pin) pyrrolidine **60** even using this method. In our hands, it was not possible to prepare 2-B(pin) pyrrolidine **60** using Sawamura's methods.

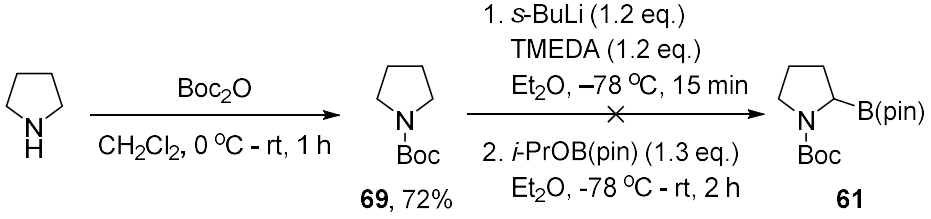
2.3 Synthesis of α-borylated pyrrolidines *via* lithiation-trapping

As outlined in Section 2.1, both Whiting *et al.*[29] and Aggarwal *et al.*[30,31] have synthesised α-borylated pyrrolidines using a lithiation-trapping strategy (see Schemes 2.1 and 2.2). Lithiation-trapping is also a common procedure used for the functionalisation of different *N*-Boc heterocycles in the O'Brien group.[41–45] Therefore, following the lack of success with the Rh-catalysed route outlined in the previous section, the attention of the project was re-directed to developing a lithiation-trapping methodology for the synthesis of the targeted α-borylated pyrrolidines. As outlined in Scheme 2.14, it was hypothesised that lithiation-trapping of *N*-Boc pyrrolidine **69**, followed by Boc removal and a subsequent S_NAr to install the pyridinyl functionality would furnish the desired 2-B(pin) pyridinyl pyrrolidine **60**. Furthermore, we also envisaged that in this approach, by using 2-B(pin) *N*-Boc pyrrolidine **61** as a key intermediate, it should be possible to synthesise a range of B(pin) pyrrolidines with different *N*-substituents.



Scheme 2.14 Proposed route to form α*-borylated* N*-pyridyl pyrrolidine* ***60*** *using a lithiation-trapping methodology.*

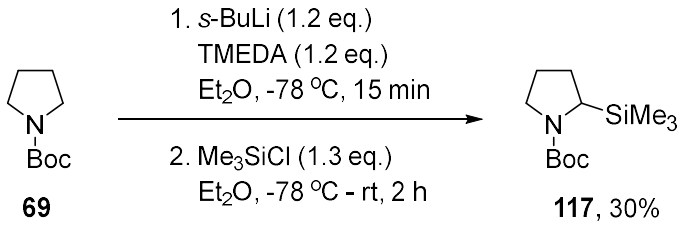
To start, pyrrolidine was reacted with Boc_2O in CH_2Cl_2 at 0 °C for 1 h to give *N*-Boc pyrrolidine **69** in 72% yield after purification *via* chromatography. Moving on to the lithiation-trapping reaction, work in the O'Brien group[46] has shown that complete lithiation of *N*-Boc pyrrolidine **69** in Et_2O at –78 °C can be achieved using *s*-BuLi and TMEDA in <5 min. Therefore, using a procedure based on that published by Aggarwal *et al.*,[31] *N*-Boc pyrrolidine **69** was lithiated using *s*-BuLi and TMEDA in Et_2O at –78 °C for 15 min before trapping with *i*-PrOB(pin) (1 h, –78 °C). Disappointingly, following acidic work-up, the ^{1}H NMR spectrum of the crude product showed no evidence of the desired 2-B(pin) *N*-Boc pyrrolidine **61** (Scheme 2.15).



Scheme 2.15 Attempted synthesis of table N*-Boc pyrrolidine* ***61*** *based on the work by Aggarwal* et al.[31]

To explore the problem with the procedure, several different variables were examined. The initial unsuccessful reaction shown in Scheme 2.15 involved purification of *N*-Boc pyrrolidine **69** *via* Kugelrohr distillation. The ^{1}H NMR spectrum of *N*-Boc pyrrolidine **69** post-purification on the Kugelrohr appeared to indicate the presence of water. Therefore, a silica plug was instead used to purify *N*-Boc pyrrolidine **69**. However, despite this, the ^{1}H NMR spectrum of the crude product still showed no indication that the desired 2-B(pin) *N*-Boc pyrrolidine **61** had formed.

In order to investigate whether the electrophile was affecting the outcome of the reaction, Me_3SiCl was used to trap the lithiated species. Me_3SiCl is a known well-performing electrophile in the O'Brien group.[46] Thus, lithiation of silica plug-purified *N*-Boc pyrrolidine **69** was carried out in the usual way and the lithiated species was reacted with Me_3SiCl. This bestowed *α*-silyl pyrrolidine **117** in 30% yield following purification *via* chromatography (Scheme 2.16). Clearly, this promising result suggested that the *i*-PrOB(pin) electrophile might be the problem.



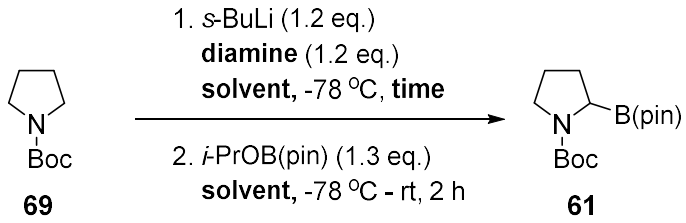
*Scheme 2.16 Synthesis of α-silyl pyrrolidine **117**.*

At this point, we returned to the reactions with *i*-PrOB(pin) and explored further variables (Table 2.4). First, the borylation was attempted with a new bottle of *i*-PrOB(pin). This gave 2-B(pin) *N*-Boc pyrrolidine **61** in 6% yield after chromatography (entry 1).

Previous work in the O'Brien group has investigated diamine-free lithiation-trapping reactions with success,[47] and so this was explored next. Thus, *N*-Boc pyrrolidine **69** was reacted with *s*-BuLi in THF at –78 °C for 1 h before trapping with *i*-PrOB(pin) (1 h, –78 °C). In this case 2-B(pin) *N*-Boc pyrrolidine **61** was isolated *via* chromatography in 32% yield (entry 2). It was hypothesised that a further improvement in reactivity may be seen if *i*-PrOB(pin) was freshly prepared *via* distillation over CaH_2. Pleasingly, this gave a 48% yield of 2-B(pin) *N*-Boc pyrrolidine **61** (entry 3).

It was also noticed that although the ^{1}H NMR spectra of the crude products indicated a significant amount of 2-B(pin) *N*-Boc pyrrolidine **61** was formed, yields after chromatography

were moderate at best (32-48%). It was speculated that lower yields were due to 2-B(pin) *N*-Boc pyrrolidine **61** 'sticking' to the silica. Since the pure 2-B(pin) *N*-Boc pyrrolidine **61** is a crystalline solid, purification by recrystallisation of the crude product was attempted next. After replicating the reaction conditions of entry 3 with distilled *i*-PrOB(pin), the crude product was dissolved in a minimal volume of hot hexane and left to crystallise for 16 h. This gave 2-B(pin) *N*-Boc pyrrolidine **61** in an excellent 81% yield (entry 4). The reaction was carried out on a 5.0 mmol scale and gave 1.2 g of 2-B(pin) *N*-Boc pyrrolidine **61**. When the reaction was scaled up to 20 mmol, a 3.6 g (59%) batch of 2-B(pin) *N*-Boc pyrrolidine **61** was produced. This protocol represents a very efficient way of generating multi-gram quantities of 2-B(pin) *N*-Boc pyrrolidine **61** without the need for chromatography. The ^{1}H and ^{13}C NMR spectroscopic data for 2-B(pin) *N*-Boc pyrrolidine **61** matched those reported in the literature.[29]

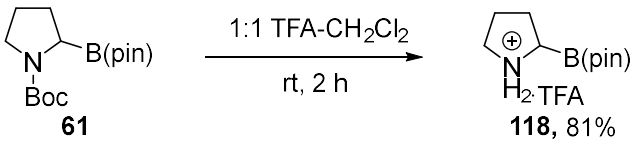


69 **61**

Entry	69 (mmol)	Diamine	Solvent	Lithiation time	Electrophile	Yield (%)[c]
1	2.5	TMEDA	Et_2O	15 min	*i*-PrOB(pin)[a]	6
2	2.5	None	THF	1 h	*i*-PrOB(pin)[a]	32
3	2.5	TMEDA	Et_2O	15 min	*i*-PrOB(pin)[b]	48
4	5.0	TMEDA	Et_2O	15 min	*i*-PrOB(pin)[b]	81

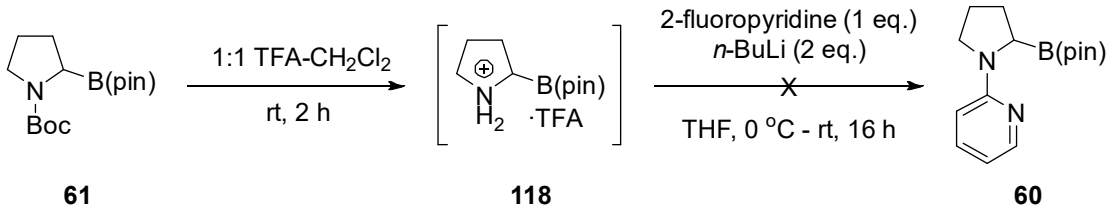
*Table 2.4 Examination of the different variables affecting the yield of the lithiation and subsequent electrophile trapping of N-Boc pyrrolidine **69**.[a] i-PrOB(pin) 100 g bottle, new stock. [b] i-PrOB(pin) 100 g bottle, new stock, distilled over CaH_2 under vacuum at 140 °C. [c] Yield after purification by recrystallisation from hot hexane.*

Once 2-B(pin) *N*-Boc pyrrolidine **61** had been successfully synthesised, it was next necessary to remove the Boc group protecting the amine. Initially, based on a procedure in a patent,[48] 2-B(pin) *N*-Boc pyrrolidine **61** was reacted with 4 M hydrochloric acid in 1,4-dioxane (1.5 eq.). However, surprisingly, there was no evidence of deprotection. This reaction was then repeated with 3.0 and 6.0 equivalents of hydrochloric acid, however, no evidence of deprotection was seen *via* TLC or ^{1}H NMR of the crude solution. Alternatively, 2-B(pin) *N*-Boc pyrrolidine **61** was reacted with a 1:1 mixture of trifluoroacetic acid and CH_2Cl_2.[49] Evaporation of the solvent and trifluoroacetic acid, aided by azeotroping with toluene, followed by high vacuum drying gave TFA salt **118** in 81% yield (Scheme 2.17).



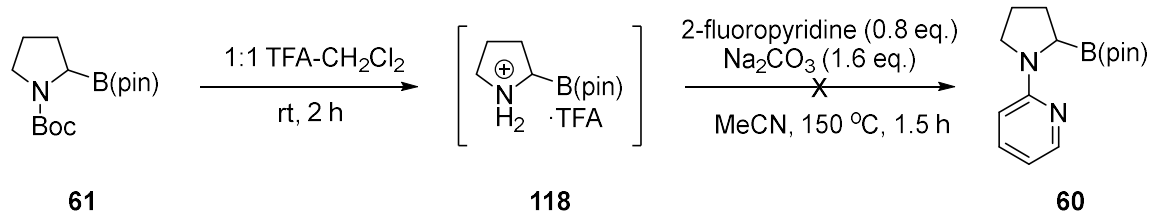
*Scheme 2.17 Boc-removal to form TFA salt **118.***

With a successful method for Boc group removal in place, installation of the *N*-pyridyl group in order to afford the desired *N*-pyridyl pyrrolidine boronate **60** was explored. A methodology was initially investigated based on the work of Singaram *et al.*[39] which we had used to synthesise *N*-pyridyl pyrrolidine **75**. Thus, the TFA salt **118** was generated using trifluoroacetic acid in CH_2Cl_2 and then it was reacted with *n*-BuLi (2 eq.) to form the lithium amine. Subsequent reaction with 2-fluoropyridine in THF for 16 h gave a crude mixture which unfortunately contained none of the desired *N*-pyridyl pyrrolidine boronate **60** (Scheme 2.18). It is likely that the B(pin) group may not be compatible with *n*-BuLi and that this led to an unsuccessful reaction in this case.



*Scheme 2.18 Attempted synthesis of α-borylated N-pyridyl pyrrolidine **60**.*

Thus, more classical S_NAr reaction conditions were then used, based on literature precedent.[50] TFA salt **118**, generated in the usual way, was reacted with 2-fluoropyridine and Na_2CO_3 in MeCN. This reaction was attempted at 150 °C in a sealed pressure tube behind a blast shield. However, after reaction for 1.5, h the crude mixture showed no indication of the desired *N*-pyridyl pyrrolidine boronate **60** (Scheme 2.19), with ^{1}H NMR of the crude mixture showing no discernible contents.

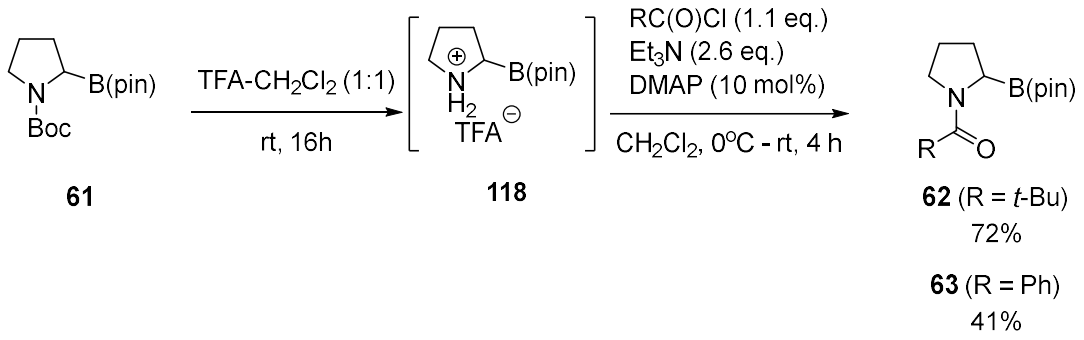


*Scheme 2.19 Attempted synthesis of α-borylated N-pyridyl pyrrolidine **60**.*

As our attempts to access *N*-pyridyl pyrrolidine boronate **60** had so far proved unsuccessful, attention was turned to alternative *N*-substituents. In previous work by Ohmura, Awano and

Suginome,[22] successful Suzuki-Miyaura cross-couplings with tertiary α-borylated amides had been described. Therefore, we decided to explore the synthesis of 2-B(pin) pyrrolidine amides **62** and **63**, with pivalamide and benzamide functionality, respectively. The plan was to start with 2-B(pin) *N*-Boc pyrrolidine **61** and then carry out Boc removal and *N*-acylation under standard amide forming conditions with the corresponding acyl chlorides.

Thus, the Boc group of 2-B(pin) *N*-Boc pyrrolidine **61** was removed using our standard conditions (1:1 trifluoroacetic acid-CH_2Cl_2) to give crude TFA salt **118**. This intermediate was not purified and was instead reacted with an acyl chloride, Et_3N and a catalytic amount of DMAP. Stirring in CH_2Cl_2 at rt for 4 h afforded α-borylated amides **62** and **63** in 72% and 41% yield, respectively (Scheme 2.20). These amides were difficult to purify; once loaded onto the column they were often stuck there and difficult to remove, which accounts for the relatively low overall yield of benzamide **63**.

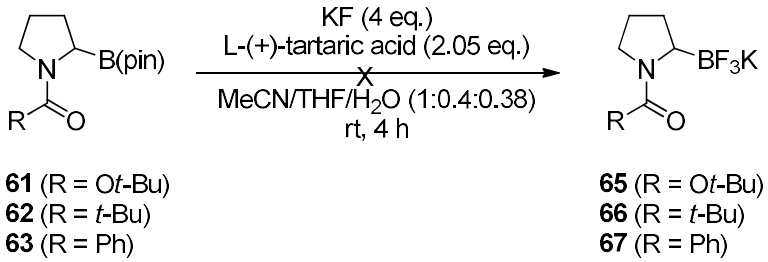


Scheme 2.20 Synthesis of α*-borylated amides* ***62*** *and* ***63.***

2.4 Synthesis of α-borylated pyrrolidines with trifluoroborate and MIDA groups

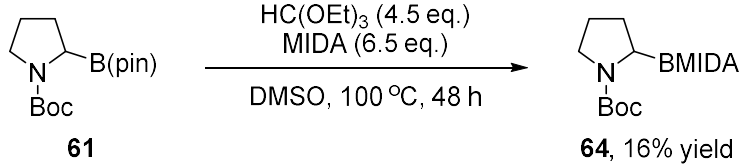
For our planned Suzuki-Miyaura cross-coupling studies, it was also of interest to explore other organoboron functionalities. With this in mind, Molander *et al.*[4] popularised the use of organotrifluoroborates which can sometimes lead to more efficient cross-coupling reactions than boronic acids and other boronates. Organotrifluoroborates are usually crystalline, air- and moisture-stable making them convenient for use in Suzuki-Miyaura cross-couplings.[10]

To start, using a literature procedure,[51] 2-B(pin) *N*-Boc pyrrolidine **61** was reacted with KF and L-(+)-tartaric acid in a MeCN-THF-H_2O mixture at rt for 4 h. Following purification with a cold MeOH wash a white powder was collected, although none of the desired potassium *N*-Boc pyrrolidine trifluoroborate salt **65** appeared in the ^{1}H NMR (Scheme 2.21). This method was also carried out on the analogous pivalamide **62** and benzamide **63** which also failed to give the desired trifluoroborate salt products. All three reactions gave mostly insoluble white powders.



*Scheme 2.21 Synthesis of trifluoroborate salts **65**, **66** and **67**.*

In 2009, Burke *et al.*[52] outlined the use of *N*-methyliminodiacetic acid (MIDA) boronates in cross-coupling reactions. These MIDA boronates were bench-stable and provided excellent ability to slowly release[53] *in situ* boronic acids for Suzuki-Miyaura cross-coupling reactions. For this reason, the synthesis of a MIDA boronate was also explored in this project.



*Scheme 2.22 Synthesis of MIDA boronate **64**.*

According to a procedure by Wang *et al.*,[54] 2-B(pin) *N*-Boc pyrrolidine **61** was reacted with triethyl orthoformate and MIDA in DMSO at 100 °C for 48 h. Following purification by chromatography, the desired MIDA boronate **64** was obtained in 16% yield (Scheme 2.22).

Thus, it was shown that it was possible to synthesise both trifluoroborate salts and one MIDA boronate starting from 2-B(pin) *N*-Boc pyrrolidine **61**.

2.5 Conclusions

In summary, two main methods were explored for the synthesis of α-borylated pyrrolidines. The Rh-catalysed approach reported by Sawamura *et al.*[21] was unsuccessful in our hands. We suspect that highly fine-tuned reaction conditions are required to successfully carry out this procedure. In contrast, we had more success using Whiting *et al.*'s[29] lithiation-trapping approach. This delivered gram quantities of 2-B(pin) *N*-Boc pyrrolidine **61** without the need for chromatography. Using chiral diamine ligands, it would also be possible to generate enantioenriched 2-B(pin) *N*-Boc pyrrolidine **61** as shown by Whiting *et al.*[29] Using this method and subsequent *N*-functionalisation or boronate modification, a range of other pyrrolidines were prepared for subsequent Suzuki-Miyaura cross-coupling studies (Figure 2.3).

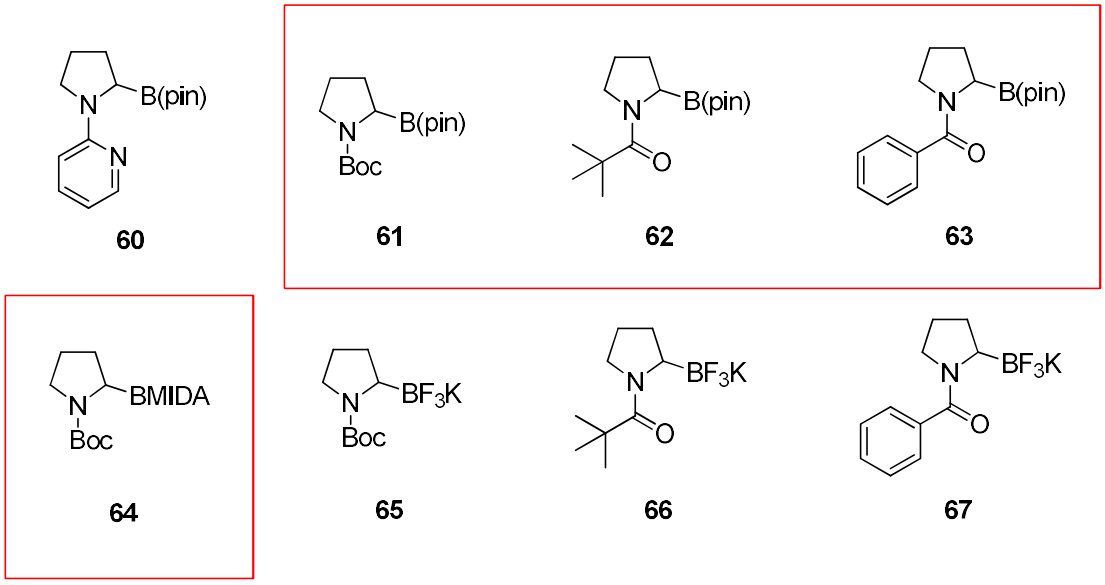
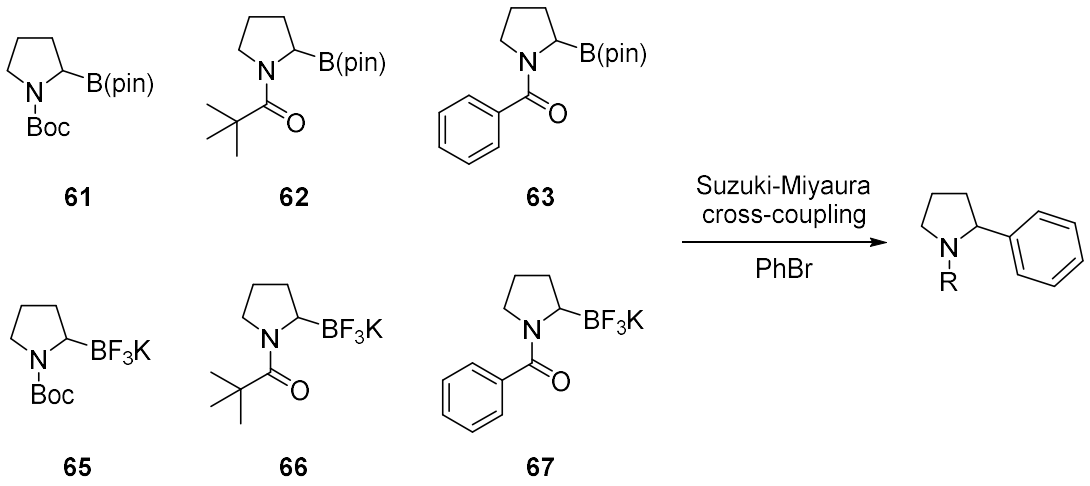


Figure 2.3 Substrates synthesised (in red), or attempted to be synthesised, in Chapter 2.

3. Suzuki-Miyaura Cross-Coupling of *α*-Borylated *N*-Heterocycles

In this Chapter, two key approaches to the Suzuki-Miyaura cross-coupling of the substrates synthesised in Chapter 2 were undertaken. The methodology outlined by Sawamura *et al*.[21] was applied to the Suzuki-Miyaura cross-coupling of B(pin) functionalised pyrrolidine substrates, while the methodology developed by Dombrowski *et al*.[27] at AbbVie could have been applied to the BF_3K functionalised pyrrolidine substrates.



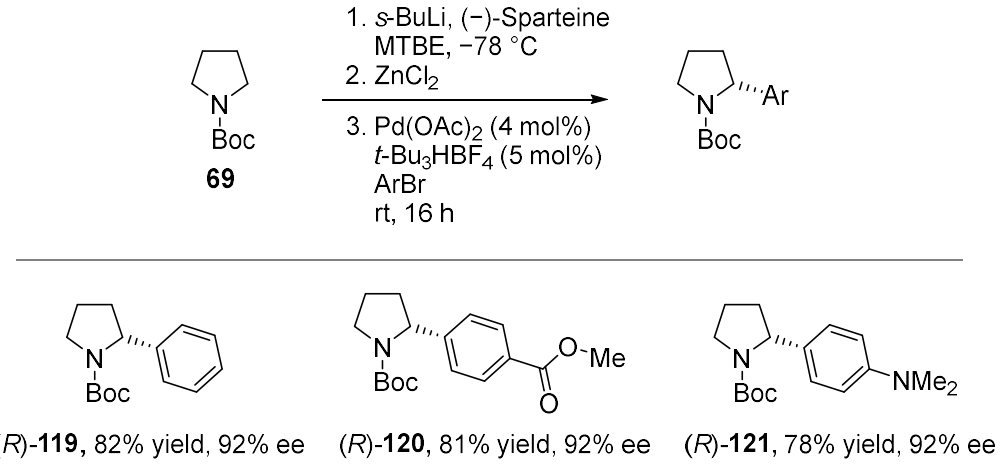
Scheme 3.1 α-Borylated N-pyrrolidines subject to Suzuki-Miyaura cross-coupling reactions in this chapter.

The literature presented in Section 3.1 gives the relevant background for this Chapter, outlining existing Pd-catalysed cross-coupling approaches to the synthesis of *α*-arylated *N*-heterocycles, with a particular focus on pyrrolidines. Section 3.2 outlines the two cross-coupling approaches undertaken in the attempt to synthesise *α*-arylated pyrrolidines from the substrates shown in Scheme 3.1.

3.1 Overview of Pd-catalysed cross-coupling approaches to α-arylated *N*-heterocycles

There are a range of examples of the Pd-catalysed cross-coupling route to α-arylated *N*-heterocycles. These include Negishi, Stille and Suzuki-Miyaura cross-coupling reactions. This section summarises key examples of each class of reaction, focusing in particular on the routes to enantioenriched α-aryl pyrrolidines.

In 2006, Campos *et al.*[55] outlined the first enantioselective Pd-catalysed α-arylation of *N*-Boc pyrrolidine. Their work put forward the use of existing α-lithiation methodology developed by Beak *et al.*,[28,56] and combined it with the subsequent formation of the secondary alkylzinc necessary for Negishi cross-coupling. Following screening of reaction conditions, the reaction of *N*-Boc pyrrolidine **69** with *s*-BuLi and (−)-sparteine in MTBE at −78 °C reliably produced the lithiated species. Subsequent reaction with $ZnCl_2$ resulted in facile formation of the organozinc species. Subsequent reaction with bromobenzene in the presence of $Pd(OAc)_2$ and *t*-$Bu_3P{\cdot}HBF_4$ at rt for 16 h gave enantioenriched α-aryl pyrrolidine (*R*)-**119** (82% yield, 92% ee) (Scheme 3.2). This methodology tolerated a range of functional groups, including both electron-withdrawing and electron-donating groups on the aryl bromide (generating (*R*)-**120** and (*R*)-**121**).

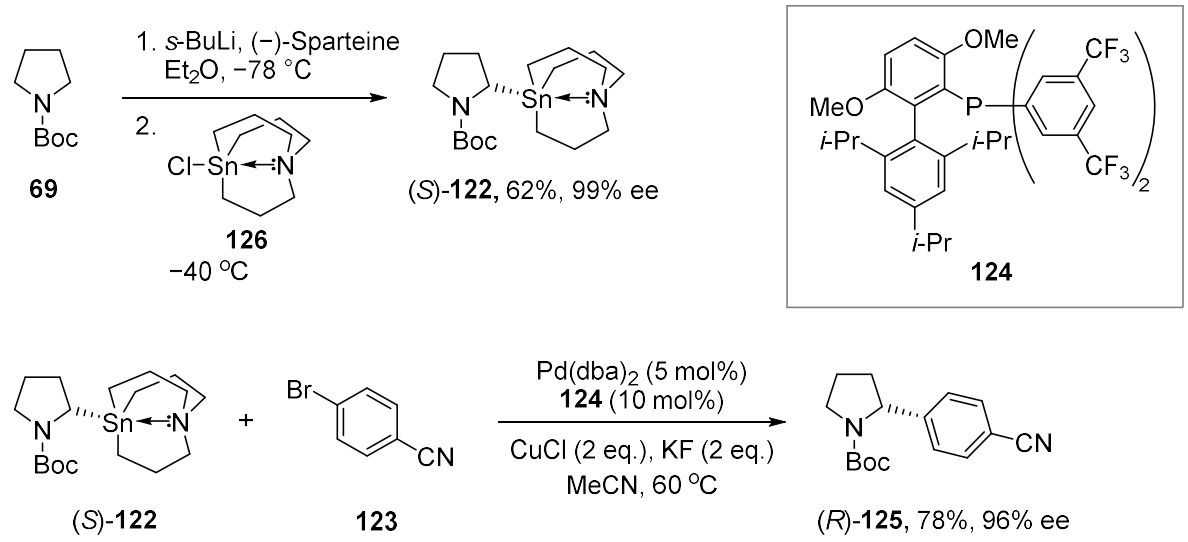


Scheme 3.2 Campos et al.*'s*[55] *lithiation-trapping approach, followed by a Negishi cross-coupling to product* α*-arylated* N*-Boc pyrrolidines.*

In work undertaken by Campos and O'Brien *et al.*,[57] further mechanistic details of the lithiation–transmetalation–α-arylation were uncovered. React IR spectroscopy experimentation revealed that the transmetalation from lithium to zinc took place under −60 °C, which was consistent with the configurational instability of the *N*-Boc pyrrolidine at higher temperatures. Furthermore, monitoring of the Boc $\nu_{C=O}$ showed that lithiation of *N*-Boc

pyrrolidine **69** with *s*-BuLi and (−)-sparteine was complete in 1 h. Monitoring of the $\nu_{C=O}$ in α-aryl pyrrolidine (*R*)-**119** also proved to be a useful tool for monitoring the cross-coupling reaction.

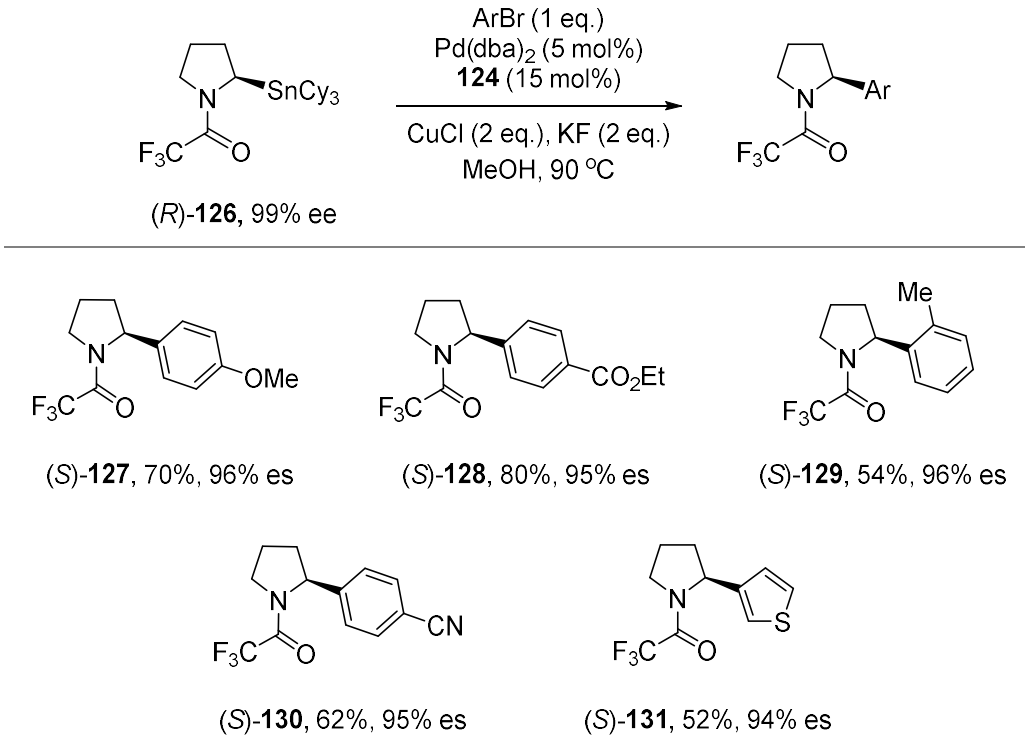
Biscoe *et al*.[58] undertook an investigation into the use of secondary alkyl azastannatranes for enantioselective Stille cross-couplings, reported in 2013. The use of these internally co-ordinated stannanes eliminates the need for wastage of three other, potentially high value, alkyl groups, during transmetallation. Using the enantioselective lithiation method pioneered by Beak,[28,56] *N*-Boc pyrrolidine **69** was lithiated and further reacted with chloroazastannatrane **126** at −40 °C to give the configurationally stable 2-stannylpyrrolidine (*S*)-**122** in 62% yield and 99% ee (after purification with preparatory HPLC). Subsequent Stille cross-coupling of 2-stannylpyrrolidine (*S*)-**122** with 4-bromobenzonitrile **123** was undertaken using $Pd(dba)_2$ (5 mol%) and phosphine ligand **124** (10 mol%) in the presence of CuCl and KF in MeCN at 60 °C. This gave enantiomerically enriched 2-arylpyrrolidine (*R*)-**125** in 78% yield and 96% ee.



Scheme 3.3 Biscoe et al. *'s*[58] *Stille cross-coupling methodology for synthesising enantioenriched* α*-arylated* N*-pyrrolidine.*

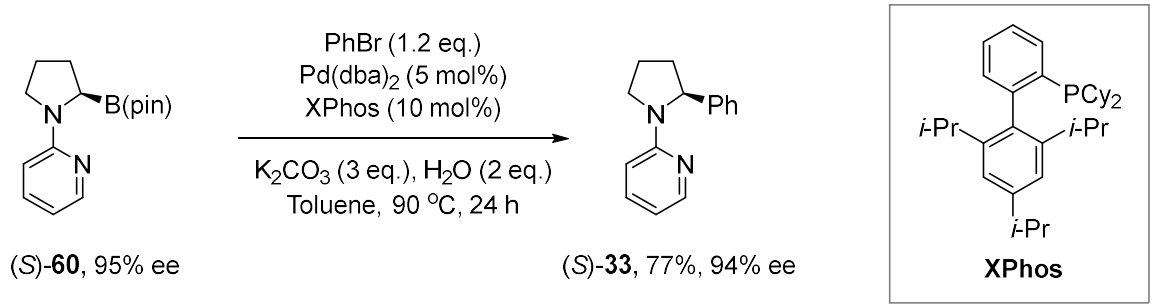
In 2020, Biscoe *et al*.[59] expanded their previous work in order to explore the scope of this reaction more fully. For this study, a simple alkyltin pyrrolidine (*R*)-**126** was employed, rather than the previously used azastannatrane. The use of tricyclohexylstannanes has advantages over the more frequently used tributylstannanes as the tricyclohexylstannanes are highly crystalline compounds that have been shown to exhibit lower toxicity. Reaction of 2-stannylpyrrolidine (*R*)-**126** (of 99% ee) with an arylbromide in the presence of $Pd(dba)_2$ (5 mol%), ligand **124** (15 mol%), CuCl and KF in MeOH at 90 °C resulted in a range of successful

Stille cross-coupling products (*S*)-**127** and (*S*)-**128** with good to high yields and excellent enantiospecificities (94-96% es) (Scheme 3.4). Biscoe's methodology tolerates a range of aryl groups, including both electron-rich and electron-deficient coupling partners (to give (*S*)-**129**) and (*S*)-**130**)), as well as heteroaryl groups (to give (*S*)-**131**)). However, it still requires the use of stannanes which are generally unpopular in the pharmaceutical industry due to their toxicity.



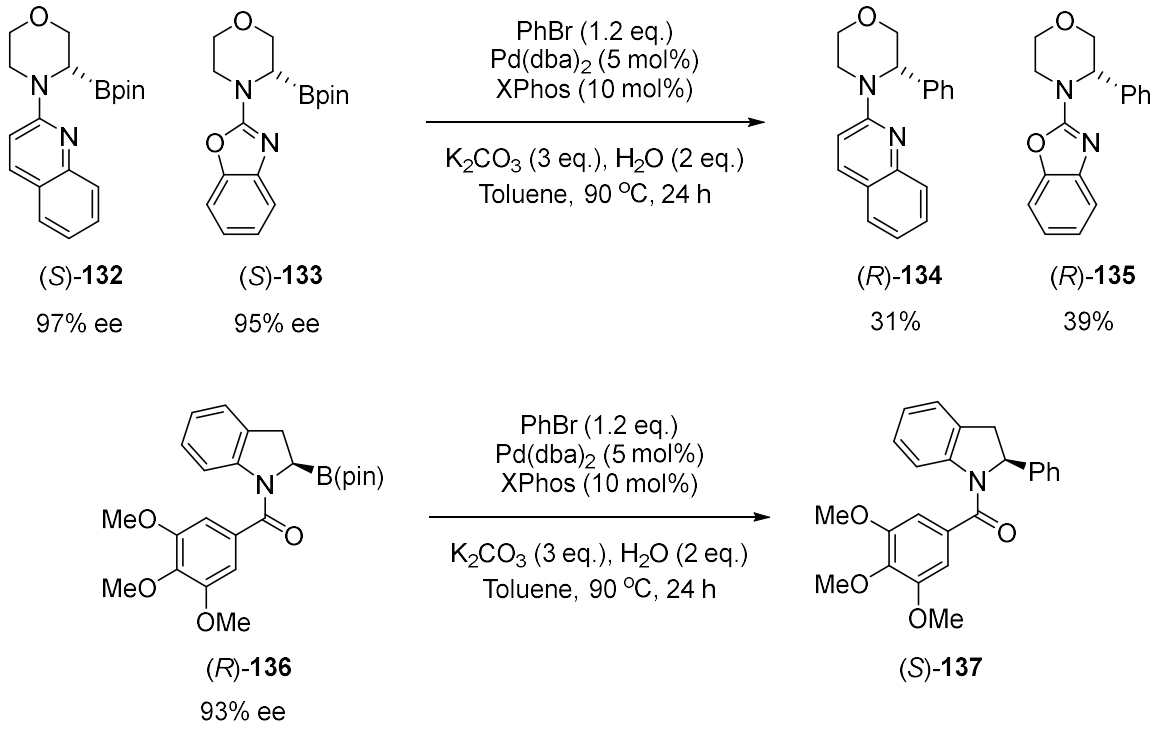
Scheme 3.4 Overview of Biscoe et al. *'s*[59] *2020 Stille cross-coupling methodology giving a range of* α*-arylated* N*-pyrrolidines.*

In 2020, Sawamura *et al*. reported the first example of a stereospecific Suzuki-Miyaura cross-coupling reaction utilising a saturated nitrogen heterocycle substrate. α-Phenyl pyrrolidine (*S*)**-33** was synthesised in 77% yield and 94% ee from a Suzuki-Miyaura cross-coupling of *N*-pyridyl pyrrolidine boronate (*S*)**-60** of 95% ee (synthesised by Rh catalysis, see Scheme 2.4) and bromobenzene. Cross-coupling took place with $Pd(dba)_2$ (5 mol%) and XPhos (10 mol%) in the presence of K_2CO_3 and H_2O in toluene at 90 °C for 24 h (Scheme 3.5).



Scheme 3.5 Sawamura et al.*'s*[21] *Suzuki-Miyaura cross-coupling methodology for the formation of* α*-arylated* N*-pyrrolidine.*

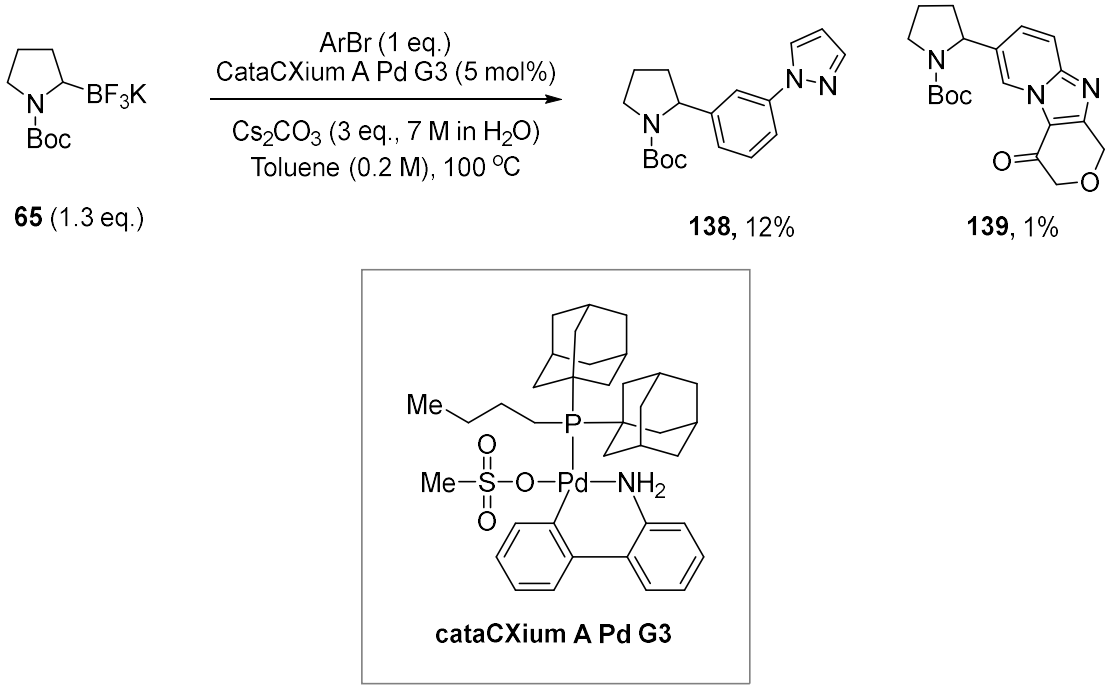
A few further examples were described in the supporting information of Sawamura's paper since the reactions were used to synthesise known *α*-phenyl products for proof of stereochemistry. For example, the cross-coupling of morpholines (*S*)-**132** (97% ee) and (*S*)-**133** (95% ee) with bromobenzene in the presence of $Pd(dba)_2$, XPhos and K_2CO_3 produced α-phenyl morpholines (*R*)-**134** in 31% yield and (*R*)-**135** in 39% yield (Scheme 3.6). However, there was no data given regarding enantiospecificity for these reactions. Similarly, cross-coupling of indolinoamide (*R*)-**137** (93% ee) with bromobenzene was presented but with no yield or data regarding the enantiospecificity of the reaction (Scheme 3.6).



Scheme 3.6 Further scope exploration using Sawamura et al.*'s*[21] *Suzuki-Miyaura cross-coupling methodology.*

In 2020, Dombrowski *et al.*[60] from AbbVie reported an investigation of several different $C(sp^3)$-$C(sp^2)$ cross-coupling methods on a range of substrates. Their investigations included the Suzuki-Miyaura cross-coupling of racemic *N*-Boc pyrrolidine trifluoroborate **65** with two

different aryl bromides in the presence of cataCXium A Pd G3 (5 mol%) and Cs_2CO_3. The reactions gave α-aryl pyrrolidines **138** (12% yield) and **139** (1% yield) (Scheme 3.7). The stereospecificity of these two Suzuki-Miyaura cross-coupling reactions was not explored as the starting material was racemic. However, the successful synthesis of α-arylated pyrrolidines **138** and **139** does further demonstrate that saturated nitrogen heterocycles are able to participate in Suzuki-Miyaura cross-coupling reactions.



Scheme 3.7 Suzuki-Miyaura cross-coupling presented by Dombrowski et al.[60]

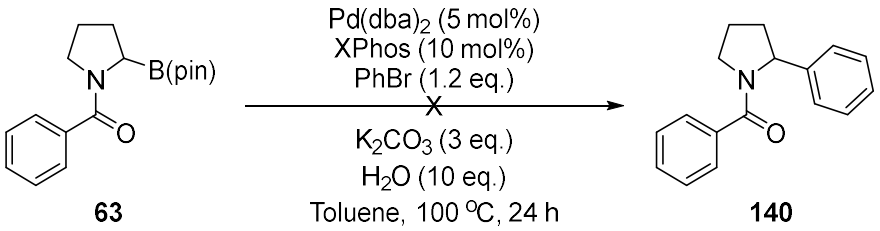
In summary, Campos[55] and Biscoe[58,59] *et al*. have presented methods utilising Negishi and Stille cross-coupling methods respectively to form *α*-aryl pyrrolidines in good to excellent yields and enantiospecificities. These reactions are less attractive due to the air-sensitive preparation of the organozinc intermediates, and the relative toxicity of organostannanes. Conversely, the Suzuki-Miyaura cross-couplings presented by Sawamura[21] and Dombrowski[27] *et al*. show an exciting pathway to forming *α*-aryl pyrrolidines using reaction conditions that could be of wide applicability and generality, for use in the pharmaceutical industry.

3.2 Attempted Suzuki-Miyaura cross-couplings of *α*-borylated *N*-heterocycles

As highlighted in the previous section, there are limited examples of Suzuki-Miyaura cross-coupling reactions with *α*-borylated pyrrolidines. The most successful example was that reported by Sawamura *et al*.[21] using *N*-pyridyl pyrrolidine boronate (*S*)-**60** (see Scheme 3.5) and we speculate that the presence of the pyridine nitrogen coordinating to the boron may lead to more efficient transmetallation. Unfortunately, as we were unable to prepare *N*-pyridyl pyrrolidine boronate (*S*)-**60**, further studies into Sawamura's Suzuki-Miyaura cross-coupling reaction could not be carried out, and so we were unable to explore this idea in more detail. However, during the course of our work in Chapter 2, we had successfully prepared a range of *N*-acyl pyrrolidine boronate derivatives which would allow us to explore the role of (i) the *N*-acyl group and (ii) the organoboron functionality on the Suzuki-Miyaura cross-coupling.

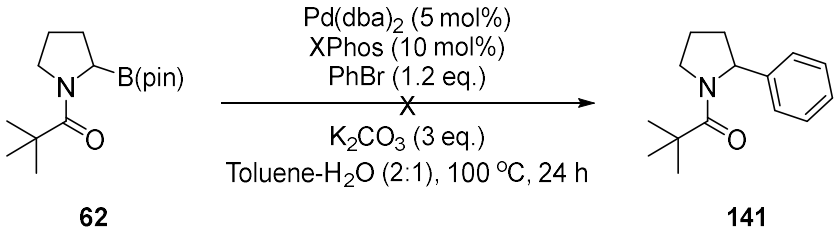
For our studies, we decided to explore two main types of reaction conditions. One set would be based on those used by Sawamura *et al*.[21] (see Scheme 3.5), namely $Pd(dba)_2$ (5 mol%), XPhos (10 mol%), K_2CO_3 (3 eq.) and bromobenzene (1.2 eq.) in toluene with water (10 eq.) and would utilise the B(pin) compounds. The other was based on those developed by Dombrowski *et al*.[27] at AbbVie involving the trifluoroborate salts and reaction using CataCXium A Pd G3 (5 mol%), Cs_2CO_3 (3 eq.) and bromobenzene (1.2 eq.) in toluene-water (2:1).

Initial attempts to apply the Suzuki-Miyaura cross-coupling work of Sawamura *et al*.[21] focused on using the benzamide pyrrolidine boronate **63**. Thus, benzamide pyrrolidine boronate **63** was placed in a pressure tube with $Pd(dba)_2$ (5 mol%), XPhos (10 mol%) and K_2CO_3 (3 eq.) and reacted with bromobenzene (1.2 eq.) in toluene with water (10 eq.). The number of equivalents of water used in this reaction are slightly higher than that reported by Sawamura *et al*., due to solubility issues with the K_2CO_3. The resulting mixture was heated at 100 °C for 24 h. Following work-up, there was none of the desired arylated benzamide **140** detectable *via* ^{1}H NMR spectroscopy or mass spectrometry (Scheme 3.8). The ^{1}H NMR spectrum of the crude mixture also showed evidence of starting benzamide pyrrolidine boronate **63**. This indicated that hydrolysis of the B(pin) functionality to the boronic acid was not taking place, which was ultimately impacting on the transmetallation step of the Suzuki-Miyaura cross-coupling reaction.



*Scheme 3.8 Attempted Suzuki-Miyaura cross-coupling of benzamide **140** with bromobenzene.*

A similar Suzuki-Miyaura cross-coupling reaction was carried out on pivalamide pyrrolidine boronate **62**. In this case, to improve the amount of K_2CO_3 going into solution and to hopefully enable a greater amount of B(pin) hydrolysis, the equivalents of water were increased with a solvent mixture of 2:1 toluene-water mixture was used. Pivalamide pyrrolidine boronate **62** was placed in a pressure tube with $Pd(dba)_2$ (5 mol%), XPhos (10 mol%) and K_2CO_3 (3 eq.) and reacted with bromobenzene (1.2 eq.) in toluene-water (2:1). The resulting mixture was heated at 100 °C for 24 h. Following work-up, there was none of the desired arylated pivalamide **141** detectable using ^{1}H NMR spectroscopy or mass spectrometry.



*Scheme 3.9 Attempted Suzuki-Miyaura cross-coupling of pivalamide **141** with bromobenzene.*

The ^{1}H NMR spectrum of the crude mixture formed in the reaction in Scheme 3.9 showed evidence of starting material, pivalamide pyrrolidine boronate **62**. As shown in Figure 3.1, there was a characteristic doublet doublet peak at 2.90 ppm which was due to the proton α to the boron and nitrogen.

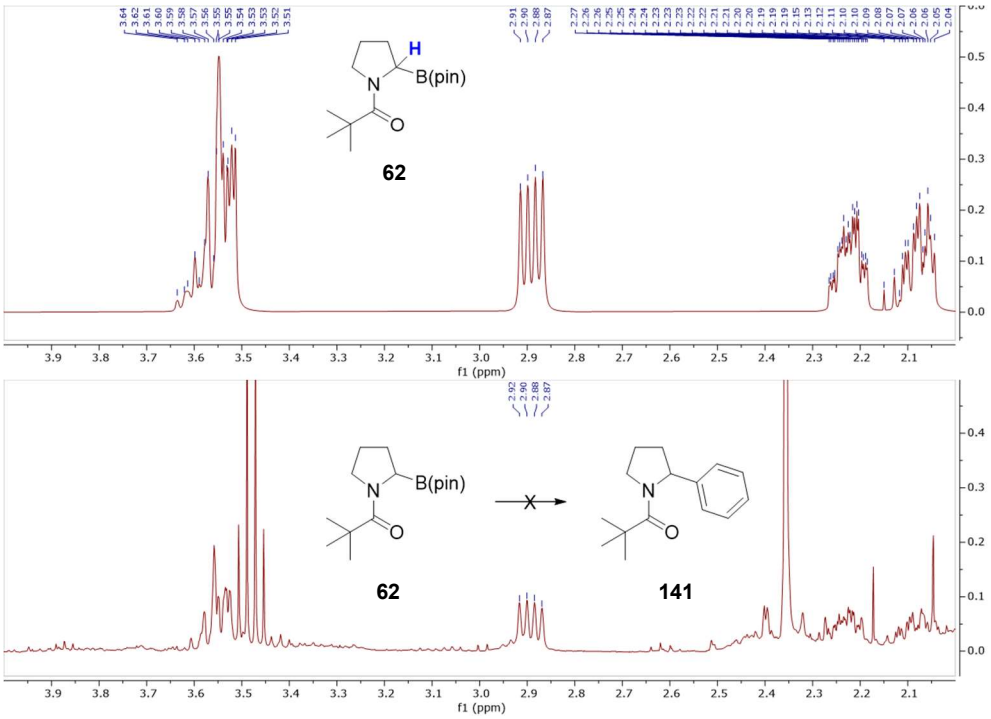
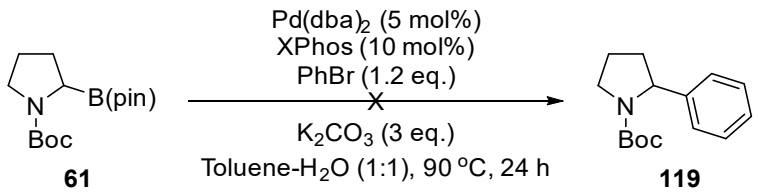


*Figure 3.1 A comparison of the ^{1}H NMR spectra of the substrate **62** and the crude mixture formed in the reaction in Scheme 3.9.*

Next, it was decided to explore the use of *N*-Boc pyrrolidine boronate **61** under Sawamura *et al.*'s conditions. The equivalents of water were increased even further for the Suzuki-Miyaura cross-coupling of *N*-Boc pyrrolidine boronate **61** since related reactions by a fellow group member on similar substrates had shown that protodeborylation *via* hydrolysis was not taking place.[61] Thus, *N*-Boc pyrrolidine boronate **61** was placed in a pressure tube with $Pd(dba)_2$ (5 mol%), XPhos (10 mol%) and K_2CO_3 (3 eq.) and reacted with bromobenzene (1.2 eq.) in toluene-water (1:1). The resulting mixture was heated at 100 °C for 24 h. Following work-up, there was none of the desired arylated *N*-Boc pyrrolidine **119** present by ^{1}H NMR spectroscopy or mass spectrometry (Scheme 3.10). There was, however, some starting material remaining.



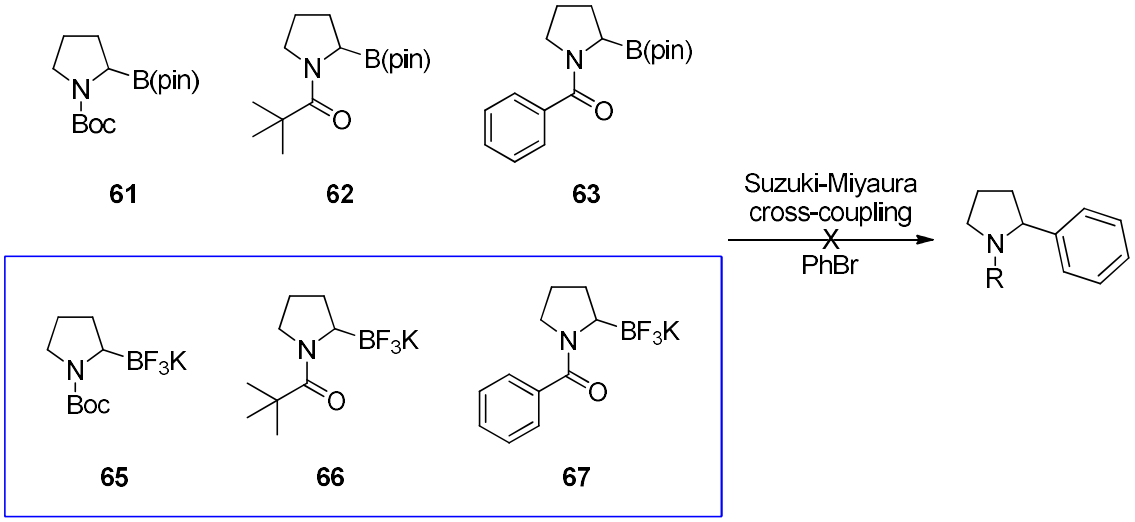
*Scheme 3.10 Attempted Suzuki-Miyaura cross-coupling of N-Boc pyrrolidine boronate **61** with bromobenzene.*

As discussed in Chapter 1 and Section 3.1, organotrifluoroborates are often used for Suzuki-Miyaura cross-coupling reactions involving secondary boron functionalities.[4] Indeed, Dombrowski *et al.*[60] successfully used *N*-Boc pyrrolidine trifluoroborate **65** in the Suzuki-Miyaura cross-coupling to form α-arylated pyrrolidine **138** in a 12% yield (see Scheme 3.7).

Therefore, initially the conditions developed by Dombrowski *et al*. were to be explored with the synthesised potassium trifluoroborate pyrrolidine salts. However, as shown in Scheme 2.21, these compounds were not able to be synthesised, and so could not be further explored.

3.3 Conclusions

In summary, two main methods were explored for the Suzuki-Miyaura cross-coupling to form *α*-arylated pyrrolidines. The methodology presented by Sawamura *et al*.[21] was unsuccessful when applied to B(pin) functionalised pyrrolidines. Similarly, the methodology from Dombrowski *et al*.[27] at AbbVie also yielded no reactivity when applied to BF_3K functionalised pyrrolidines. Clearly, further investigation is required, and a full reaction condition screening will be necessary to unlock their Suzuki-Miyaura cross-coupling potential.



Scheme 3.14 Attempts made towards the Suzuki-Miyaura cross-coupling of α-borylated pyrrolidines in Chapter 3. Compounds in blue were unable to be investigated due to issues with substrate synthesis, discussed in Chapter 2.

4. Conclusions and Future Work

This thesis described the steps taken towards the development of a methodology for the synthesis and Suzuki-Miyaura cross-coupling of *α*-borylated pyrrolidines. Two main methods were explored for the synthesis of *α*-borylated pyrrolidines. A Rh-catalysed approach based on the work of Sawamura *et al.*[21], reported in Section 2.2, was unsuccessful in our hands. It is suspected that highly fine-tuned reaction conditions would be required to successfully carry out this procedure. In contrast, the use of lithiation-trapping chemistry based on the work of Whiting *et al.*,[29] described in Section 2.3, delivered gram quantities of 2-B(pin) *N*-Boc pyrrolidine **61** without the need for chromatography. Using this method and subsequent *N*-functionalisation *via* acylation delivered the amidoboronates **62** and **63** in good yields. Boronate modification furnished *α*-borylated pyrrolidines containing B(pin) and BMIDA functionalities (Figure 4.1). Two methods, described in Chapter 3, were investigated for the Suzuki-Miyaura cross-coupling to form *α*-arylated pyrrolidines, focusing on B(pin) functionalised pyrrolidines. However, the methodology presented by Sawamura *et al.*[21] was unsuccessful when applied to the B(pin) functionalised pyrrolidines. Unfortunately, the methodology from Dombrowski *et al.*[60] at AbbVie was unable to be explored due to issues with the synthesis of the trifluoroborate salt substrates.

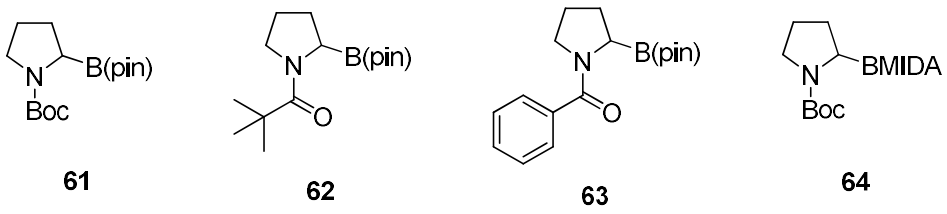
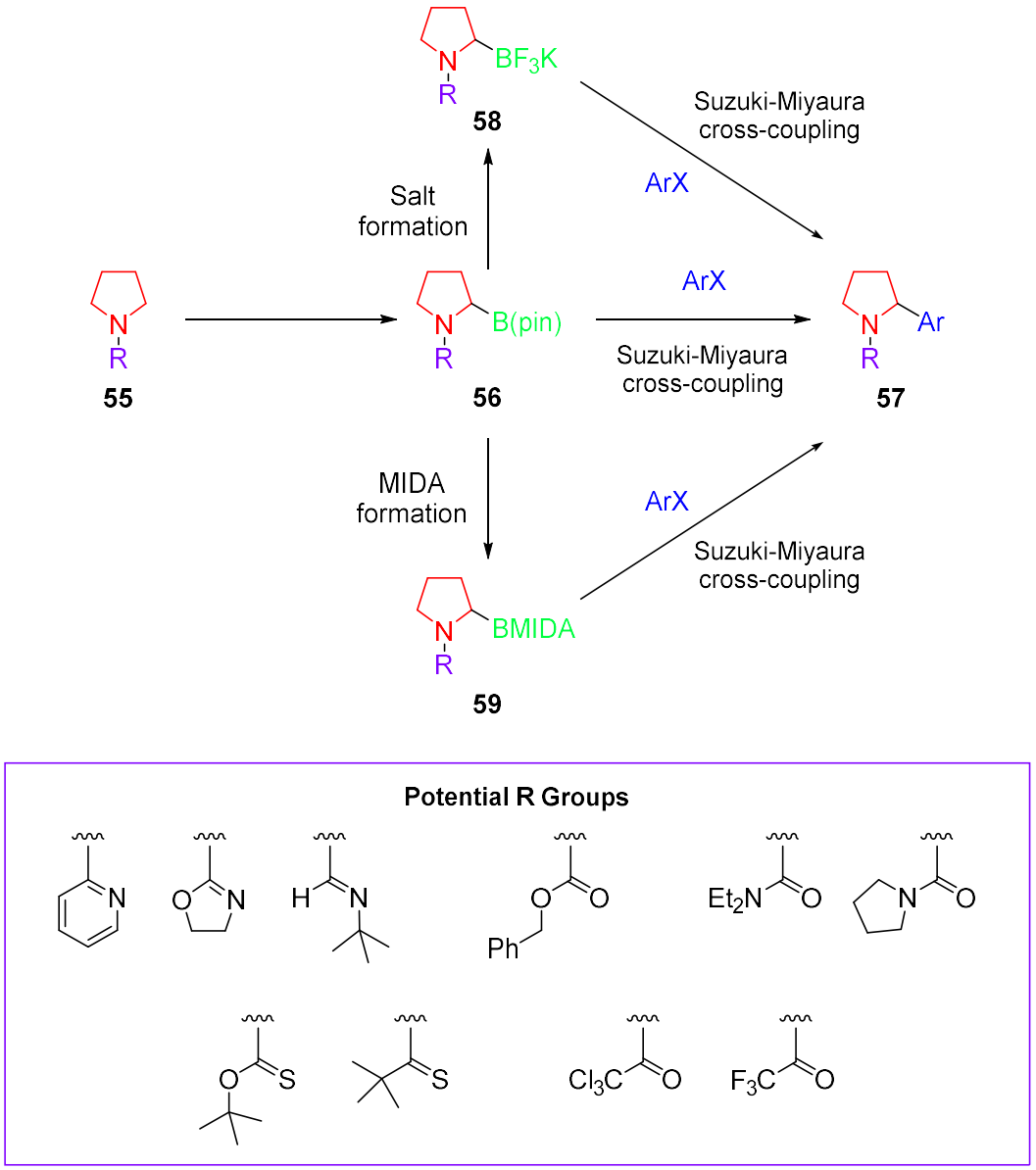


Figure 4.1 Successful syntheses of α-borylated N-functionalised pyrrolidines.

In the future, further work on the synthesis of *α*-borylated *N*-heterocycles may look to reproduce the work of Xu *et al.*[37] using the Ir-catalysed method (see Scheme 2.8), although this would involve the synthesis of the complex ligands **99** and **100**. Alternatively, Baslé *et al.*'s[36] photocatalytic method (see Scheme 2.7), harnessing readily-available carbene chemistry, would provide a more facile route to the much desired *α*-borylated *N*-heterocycles. Furthermore, a more extensive range of *N*-substituents should be explored. This would allow a deeper understanding of the steric and electronic effects these groups have on the Suzuki-Miyaura cross-coupling reaction and a selection of possible groups are shown in Scheme 4.1.



Scheme 4.1 Outline of future avenues which could be explored using the findings in this thesis.

5. Experimental

5.1 General methods

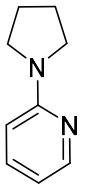
All-non aqueous reactions were carried out under O_2−free Ar using flame-dried glassware. THF was freshly distilled from sodium and benzophenone. Alkyllithiums were titrated against *N*-benzylbenzamide before use.[62] Other reagents from commercial suppliers were used without purification, unless specified. Brine refers to a saturated $NaCl_{(aq)}$ solution. Water is deionised water.

Flash column chromatography was carried out using Fluka Chemie GmbH silica (220-440 mesh). Thin layer chromatography was carried out using commercially available Merck F254 aluminium backed silica plates. Proton (400 MHz), carbon (100.6 MHz), boron (77 MHz), silicon (79.5 MHz) and fluorine (375 MHz) NMR spectra were recorded on a Jeol ECX-400 instrument using an internal deuterium lock. For samples recorded in $CDCl_3$, chemical shifts are quoted in parts per million relative to $CHCl_3$ (δ_H 7.26) and $CDCl_3$ (δ_C 77.0, central line of triplet). For samples recorded in D_2O, chemical shifts are quoted in parts per million relative to H_2O (δ_H 4.79). Carbon NMR spectra were recorded with broad band proton decoupling and assigned using DEPT and 2-D NMR experiments (HMQC and COSY). Coupling constants (*J*) are quoted in Hertz. Melting points were carried out on a Gallenkamp melting point apparatus. Infrared spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Electrospray high and low resonance mass spectra were recorded at room temperature on a Bruker Daltronics microOTOF spectrometer.

In order to further purify TMEDA, distillation under Ar over CaH_2 provided the dry reagent. For isopropoxyboronic acid pinacol ester, distillation under vacuum over CaH_2 provided the dry reagent.

5.2 Experimental procedures and characterisation data

2-Pyrrolidin-1-ylpyridine 75



75

n-BuLi (3.3 mL of a 1.5 M solution in hexane, 5.0 mmol 1.0 eq.) was added dropwise to a stirred solution of pyrrolidine (0.42 mL, 5.0 mmol, 1.0 eq.) in THF (4.0 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 15 min. This solution was then added dropwise to a stirred solution of 2-fluoropyridine (0.47 mL, 5.5 mmol, 1.1 eq.) in THF (3.0 mL) at 0 °C under Ar. Upon addition, the colour of the solution became bright red. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. The solvent was evaporated under pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave pyrrolidinyl pyridine **75** (540 mg, 72%) as a colourless oil, IR (ATR) 2967, 2850, 1595, 1497, 1481, 1442 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 5.0, 2.0 Hz, 1H, Ar), 7.40 (ddd, *J* = 8.5, 7.0, 2.0 Hz, 1H, Ar), 6.49 (dd, *J* = 7.0, 5.0 Hz, 1H, Ar), 6.33 (d, *J* = 8.5 Hz, 1H, Ar), 3.45-3.39 (m, 4H, NCH_2), 2.00-1.93 (m, 4H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.4 (*ipso*-Ar), 148.2 (Ar), 137.0 (Ar), 111.1 (Ar), 106.6 (Ar), 46.7 (NCH_2), 25.6 (CH_2); HRMS (ESI) *m/z* calcd for $C_9H_{12}N_2$ $(M + H)^+$ 149.1075, found 149.1073 (+0.8 ppm error). Spectroscopic data consistent with those reported in the literature.[63]

Lab book reference: **CEH-1-25**

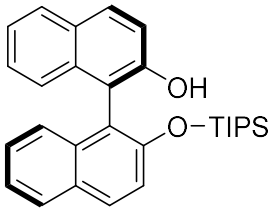
n-BuLi (6.4 mL of a 1.6 M solution in hexane, 10 mmol 1.0 eq.) was added dropwise to a stirred solution of pyrrolidine (0.84 mL, 10 mmol, 1.0 eq.) in THF (8.0 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 15 min. This solution was then added dropwise to a stirred solution of 2-fluoropyridine (0.95 mL, 11 mmol, 1.1 eq.) in THF (6.0 mL) at 0 °C under Ar. Upon addition, the colour of the solution became bright red. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. The solvent was evaporated under pressure to give the crude product. Purification by flash column chromatography on silica using 30:70 acetone-hexane as eluent gave pyrrolidinyl pyridine **75** (1.10 g, 75%) as a colourless oil.

Lab book reference: **CEH-1-79**

Borane dimethylsulfide (7.5 mL of a 2.0 M solution, 15 mmol, 1.0 eq.) was added dropwise to a stirred solution of pyrrolidine (1.3 mL, 15 mmol, 1.0 eq.) in THF (6.5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. *n*-BuLi (6.3 mL of a 2.4 M solution in hexane, 15 mmol, 1.0 eq.) was added dropwise at 0 °C. The resulting solution was stirred at 0 °C for 1 h. The solution was then added dropwise to a solution of 2-fluoropyridine (1.2 mL, 0.9 eq.) at 0 °C under Ar. Upon addition, the colour of the solution became bright red. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, 3.0 M $HCl_{(aq)}$ (20 mL) was added slowly. Upon addition, the colour of the solution became yellow. The THF solvent was evaporated under pressure. The resulting aqueous solution was washed with Et_2O (2 x 20 mL). Then, $NaOH_{(s)}$ was added to the aqueous layer until pH >10 was reached. The aqueous layer was then extracted with 1:1 Et_2O-THF (2 x 20 mL) and the organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 30:70 acetone-hexane (1% $NH_4OH_{(aq)}$) as eluent gave pyrrolidinyl pyridine **75** (800 mg, 40%) as a colourless oil.

Lab book reference: **CEH-1-11**

(*R*)-1-(2-Triisopropylsilyloxy-1-naphthyl)naphthalen-2-ol (*R*)-115



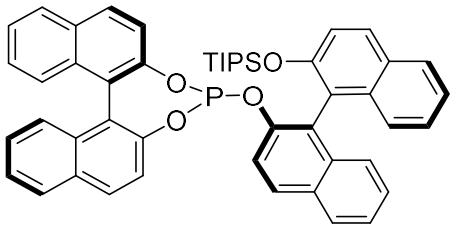
(*R*)-**115**

Et_3N (1.1 mL, 7.7 mmol, 1.1 eq.) and triisopropylsilyl chloride (1.7 mL, 7.7 mmol, 1.1 eq.) were added to a stirred solution of (*R*)-BINOL (2.0 g, 7.0 mmol, 1 eq.) in CH_2Cl_2 (80 mL) at 0 °C under Ar. The resulting solution was stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (5.0 mL) was added. The two layers were separated, and the organic layer was washed with brine (3 x 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 90:10 hexane-EtOAc as eluent gave mono silyl ether (*R*)-**115** (3.0 g, 96%) as a colourless oil, IR (ATR) 3542 (OH), 2944, 2866, 1620, 1592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89-7.78 (m, 4H, Ar), 7.34-7.21 (m, 6H, Ar), 7.19-7.15 (m, 1H, Ar), 7.09-7.07 (m, 1H, Ar), 1.09-0.97 (m, 3H, C*H*Me_2), 0.82 (d, *J* = 7.5 Hz, 9H, CH*Me*), 0.76 (d, *J* = 7.5 Hz, 9H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 152.8 (*ipso*-Ar), 151.4 (*ipso*-Ar), 134.5 (*ipso*-Ar), 133.9 (*ipso*-Ar), 130.7 (Ar), 129.7 (Ar), 129.4

(*ipso*-Ar), 129.3 (*ipso*-Ar), 128.2 (Ar), 128.0 (Ar), 127.2 (Ar), 126.2 (Ar), 125.3 (Ar), 125.2 (Ar), 124.1 (Ar), 123.2 (Ar), 120.6 (Ar), 117.5 (Ar), 117.2 (*ipso*-Ar), 115.8 (*ipso*-Ar), 17.74 (Me), 17.67 (Me), 12.9 (*C*HMe$_2$); ^{29}Si NMR (79.5 MHz, CDCl$_3$) 16.69; HRMS (ESI) *m/z* calcd for $C_{29}H_{34}O_2Si$ $(M + H)^+$ 443.2401, found 443.2402 (+0.3 ppm error).

Lab book reference: **CEH-1-9**

(11b*R*)-4-(((*R*)-2'-((Triisopropylsilyl)oxy)-[1,1'-binaphthalen]-2-yl)oxy)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine (*R,R*)-88



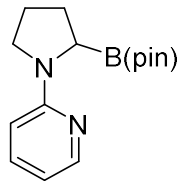
(*R,R*)-**88**

DMF (5.0 µL, 3.0 mol%) was added to a stirred solution of (*R*)-BINOL (810 mg, 2.8 mmol, 1.0 eq.) and phosphorous trichloride (3.3 mL, 38 mmol, 14 eq.) at rt under Ar. The resulting solution was stirred and heated at 50 °C under Ar for 30 min. The solution was allowed to cool to rt and the solvent and excess phosphorous trichloride were evaporated under reduced pressure, assisted by azeotroping with toluene (3 x 1.5 mL). This gave the crude phosphorochloridite as a white solid. Et_3N (1.1 mL, 8.0 mmol, 3.0 eq.) and a solution of mono silyl ether (*R*)-**115** (1.2 g, 2.7 mmol, 1.0 eq.) in toluene (4.0 mL) were added dropwise to a stirred solution of the crude phosphorochloridite in toluene (10 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt. The solution was then stirred and heated at 80 °C for 20 h. After being allowed to cool to rt, the solids were removed by filtration through celite, and the filtrate was evaporated under reduced pressure. CH_2Cl_2 (20 mL) was added, and the organic layer was washed with brine (3 x 20 mL) and saturated $NH_4Cl_{(aq)}$ (3 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 1:5 acetone-hexane as eluent gave phosphephine (*R,R*)-**88** (940 mg, 48%) as a colourless, crystalline solid, IR (ATR) 3055, 2942, 2864, 1687 (Ar), 1620, 1589, 1503, 1213 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.00 (d, J = 9.0 Hz, 1H, Ar), 7.92 (d, J = 9.0 Hz, 2H, Ar), 7.90 (d, J = 9.0 Hz, 2H, Ar), 7.86 (d, J = 9.0 Hz, 1H, Ar), 7.84 (d, J = 9.0 Hz, 1H, Ar), 7.62 (d, J = 9.0 Hz, 1H, Ar), 7.52 (d, J = 9.0 Hz, 1H, Ar), 7.44 – 7.14 (m, 14H, Ar), 6.31 (d, J = 9.0 Hz, 1H, Ar), 0.94 (septet, J = 7.5 Hz, 3H, C*H*Me$_2$), 0.66 (d, J = 7.5, 9H, Me), 0.65 (d, J = 7.5, 9H, Me); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 152.1 (*ipso*-Ar),

147.9(*ipso*-Ar), 147.8 (*ipso*-Ar), 147.7 (*ipso*-Ar), 147.3 (*ipso*-Ar), 134.7 (*ipso*-Ar), 134.4 (*ipso*-Ar), 132.9 (*ipso*-Ar), 132.5 (*ipso*-Ar), 131.6 (*ipso*-Ar), 131.2 (*ipso*-Ar), 131.2 (*ipso*-Ar), 130.2 (*ipso*-Ar), 129.6 (Ar), 129.6 (Ar), 129.4 (Ar), 129.1 (Ar), 128.4 (Ar), 128.3 (Ar), 128.0 (Ar), 127.1 (Ar), 127.0 (Ar), 126.8 (Ar), 126.6 (Ar), 126.5 (Ar), 126.2(Ar), 125.9(Ar), 125.6(Ar), 125.1(Ar), 124.9(Ar), 124.8(Ar), 124.4 (*ipso*-Ar), 123.8 (Ar), 122.6 (*ipso*-Ar), 122.0 (Ar), 121.9 (Ar), 120.9 (Ar), 120.8 (Ar), 120.3 (Ar), 119.8 (*ipso*-Ar), 17.8 (Me), 17.7 (Me), 12.8 (*C*HMe$_2$); HRMS (ESI) *m/z* calcd for $C_{49}H_{45}O_4PSi$ $(M + H)^+$ 757.2897, found 757.2921 (±3.1 ppm error); $[\alpha]_D$ −61.2 (*c* 1.0 in CH_2Cl_2) (lit.[21] $[\alpha]_D$ −64.4 (*c* 0.3 in MeOH)).

Lab book reference: **CEH-1-8**

2-[2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidine-1-yl]pyridine 60



60

Phosphephine (*R,R*)-**88** (14 mg, 1.4 μmol, 4.0 mol%), $B_2(pin)_2$ (89 mg, 0.35 mmol, 1.0 eq.) and $[Rh(OH)(cod)]_2$ (6.2 mg, 2.1 μmol, 6.0 mol% Rh) were placed in a pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, MeCN (0.50 mL) was added, and the resulting solution was stirred at rt for 5 min. Pyrrolidinyl pyridine **75** (100 mg, 0.68 mmol, 2.1 eq.) and 2,6-lutidine (20 μL, 0.17 mmol, 0.50 eq.) were added and the pressure tube was sealed. The resulting solution was stirred and heated at 60 °C for 16 h. After being allowed to cool to rt, Et_2O (1 mL) was added. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 3:7 acetone-hexane (1% $NH_4OH_{(aq)}$) gave a 30:70 mixture of starting pyrrolidinyl pyridine **75** and 2-B(pin) pyrrolidine **60** (13 mg, i.e. 9.6 mg (9%) of 2-B(pin) pyrrolidine **60**). Diagnostic signals for 2-B(pin) pyrrolidine **60**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (d, J = 9.0 Hz, 1H, Ar), 3.11-3.03 (m, 1H, NCH), 2.76 (dd, J = 12.0, 6.0 Hz, 1H, NCHB).

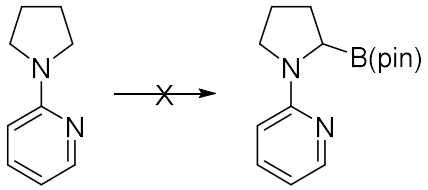
Lab book reference: **CEH-1-17**

Phosphephine (*R,R*)-**88** (16 mg, 2.1 μmol, 7.0 mol%), $B_2(pin)_2$ (78 mg, 0.31 mmol, 1.0 eq.) were placed in a pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, MeCN (1.0 mL) was added. In a separate vial, $[Rh(OH)(cod)]_2$ (4.0 mg, 1.3 μmol, 4.0 mol% Rh) and MeCN (1.0 mL) were degassed and added to the pressure tube. Pyrrolidinyl

pyridine **75** (90 mg, 0.61 mmol, 2.0 eq.) and 2,6-lutidine (18 µL, 0.15 mmol, 0.50 eq.) were added and the pressure tube was sealed. The resulting solution was stirred and heated at 60 °C for 16 h. After being allowed to cool to rt, Et_2O (1 mL) was added. The solvent was evaporated under reduced pressure to give the crude product containing a 98:2 mixture of starting pyrrolidinyl pyridine **75** and 2-B(pin) pyrrolidine **60** (173 mg). Ratio calculated using ^{1}H NMR data.

Lab book reference: **CEH-1-18**

Attempted synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidine-1-yl]pyridine 60



75 **60**

Phosphephine (*R,R*)-**88** (10 mg, 1.4 µmol, 4.0 mol%), $B_2(pin)_2$ (83 mg, 0.33 mmol, 1.0 eq.) and $[Rh(OH)(cod)]_2$ (3.2 mg, 1.1 µmol, 3.0 mol% Rh) were placed in a pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, MeCN (0.50 mL) was added, and the resulting solution was stirred at rt for 5 min. Pyrrolidinyl pyridine **75** (100 mg, 0.68 mmol, 2.1 eq.) and 2,6-lutidine (20 µL, 0.17 mmol, 0.50 eq.) were added and the pressure tube was sealed. The resulting solution was stirred and heated at 60 °C for 16 h. After being allowed to cool to rt, Et_2O (1 mL) was added. The solvent was evaporated under reduced pressure to give the crude product which contained none of the desired borylated pyrrolidine **60** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-10**

Phosphephine (*R,R*)-**88** (22 mg, 2.9 µmol, 4.0 mol%), $B_2(pin)_2$ (164 mg, 0.65 mmol, 1.0 eq.) and $[Rh(OH)(cod)]_2$ (7.4 mg, 2.5 µmol, 4.0 mol% Rh) were placed in a pressure tube. Then, MeCN (1.5 mL) was added, and the resulting solution was degassed by bubbling Ar through for 10 min. Pyrrolidinyl pyridine **75** (200 mg, 1.4 mmol, 2.2 eq.) and 2,6-lutidine (40 µL, 0.34 mmol, 0.50 eq.) were added and the pressure tube was sealed. The resulting solution was stirred and heated at 60 °C for 16 h. After being allowed to cool to rt, Et_2O (1 mL) was added. The

solvent was evaporated under reduced pressure to give the crude product which contained none of the desired borylated pyrrolidine **60** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-13**

Phosphephine (*R,R*)-**88** (11 mg, 1.4 μmol, 4.0 mol%), $B_2(pin)_2$ (91 mg, 0.36 mmol, 1.0 eq.) and $[Rh(OH)(cod)]_2$ (2.4 mg, 1.1 μmol, 2.0 mol% Rh) were placed in a pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, MeCN (0.50 mL) was added, and the resulting solution was stirred at rt for 5 min. Pyrrolidinyl pyridine **75** (100 mg, 0.68 mmol, 1.9 eq.) and 2,6-lutidine (20 μL, 0.17 mmol, 0.50 eq.) were added and the pressure tube was sealed. The resulting solution was stirred and heated at 60 °C for 16 h. After being allowed to cool to rt, Et_2O (1 mL) was added. The solvent was evaporated under reduced pressure to give the crude product which contained none of the desired borylated pyrrolidine **60** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-16**

Phosphephine (*R,R*)-**88** (42 mg, 5.5 μmol, 3.0 mol%), $B_2(pin)_2$ (450 mg, 1.8 mmol, 1.0 eq.) and $[Rh(OH)(cod)]_2$ (21 mg, 7.0 μmol, 4.0 mol% Rh) were placed in a pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, MeCN (5.0 mL) was added, and the resulting solution was stirred at rt for 5 min. Pyrrolidinyl pyridine **75** (530 mg, 3.6 mmol, 2.0 eq.) and 2,6-lutidine (0.1 mL, 0.86 mmol, 0.50 eq.) were added and the pressure tube was sealed. The resulting solution was stirred and heated at 60 °C for 16 h. After being allowed to cool to rt, Et_2O (5 mL) was added. The solvent was evaporated under reduced pressure to give the crude product which contained none of the desired borylated pyrrolidine **60** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-37**

P(*o*-tol)$_3$ (3.0 mg, 10 μmol, 2.0 mol%) and $B_2(pin)_2$ (150 mg, 0.63 mmol, 1.3 eq.) were placed in a pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, MeCN (1.0 mL) was added, and the resulting solution was stirred at rt for 5 min. In a separate flask, a solution of $[Rh(OH)(cod)]_2$ (11 mg) in MeCN (7.5 mL) was degassed by bubbling Ar through the solution and 1.5 mL of the resulting solution (containing 2.2 mg $[Rh(OH)(cod)]_2$, 5 μmol, 2.0 mol% Rh) was added to the pressure tube. Pyrrolidinyl pyridine **75** (74 mg, 0.5 mmol, 1.0 eq.) was added and the pressure tube was sealed. The resulting solution was stirred and heated at 60 °C for 16 h. After being allowed to cool to rt, the mixture was filtered through

cotton wool and the filtrate was evaporated under reduced pressure to give the crude product which contained none of the desired borylated pyrrolidine **60** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-82**

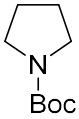
P(*t*-Bu)$_3$HBF$_4$ (3.0 mg, 10 μmol, 2.0 mol%) and $B_2(pin)_2$ (150 mg, 0.63 mmol, 1.3 eq.) were placed in a pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, CPME (1.0 mL) was added, and the resulting solution was stirred at rt for 5 min. In a separate flask, a solution of [Rh(OH)(cod)]$_2$ (2.7 mg, 10 μmol, 2.0 mol% Rh) in CPME (1.5 mL) was degassed by bubbling Ar through the solution and the resulting solution was added to the pressure tube. Pyrrolidinyl pyridine **75** (74 mg, 0.5 mmol, 1.0 eq.) was added and the pressure tube was sealed. The resulting solution was stirred and heated at 60 °C for 16 h. After being allowed to cool to rt, the mixture was filtered through cotton wool and the filtrate was evaporated under reduced pressure to give the crude product which contained none of the desired borylated pyrrolidine **60** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-86**

P(*t*-Bu)$_3$HBF$_4$ (3.0 mg, 10 μmol, 2.0 mol%) and $B_2(pin)_2$ (150 mg, 0.63 mmol, 1.3 eq.) were placed in a pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, CPME (1.0 mL) was added, and the resulting solution was stirred at rt for 5 min. In a separate flask, a solution of [Rh(OH)(cod)]$_2$ (2.7 mg, 10 μmol, 2.0 mol% Rh) in CPME (1.5 mL) was degassed by bubbling Ar through the solution and the resulting solution was added to the pressure tube. Pyrrolidinyl pyridine **75** (74 mg, 0.5 mmol, 1.0 eq.) and 2,6-lutidine (38 μL, 33 μmol, 0.65 eq.) were added and the pressure tube was sealed. The resulting solution was stirred and heated at 60 °C for 16 h. After being allowed to cool to rt, the mixture was filtered through cotton wool and the filtrate was evaporated under reduced pressure to give the crude product which contained none of the desired borylated pyrrolidine **60** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-87**

***tert*-Butyl pyrrolidine-1-carboxylate 69**

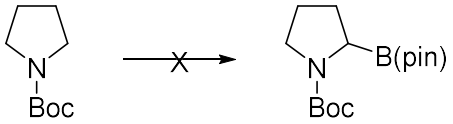


69

Pyrrolidine (2.5 mL, 30 mmol, 1.2 eq.) was added dropwise to a stirred solution of di-*tert*-butyl carbonate (5.5 g, 25 mmol, 1 eq.) in CH_2Cl_2 (80 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 3 h. The solvent was evaporated under pressure to give the crude product. Purification by silica plug chromatography using 15:85 EtOAc-hexane gave *N*-Boc pyrrolidine **69** (3.80 g, 74%) as an orange oil, IR (ATR) 2973, 2874, 1691 (C=O), 1397 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.33-3.20 (m, 4H, NCH_2), 1.84-1.72 (m, 4H, CH_2), 1.45 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.9 (C=O), 79.0 ($OCMe_3$), 45.9 (NCH_2), 28.7 (CMe_3), 25.5 (CH_2). Spectroscopic data consistent with those reported in the literature.[64]

Lab book reference: **CEH-1-36**

Attempted synthesis of *tert*-Butyl 2-(4,4,5,5-tetramethyl-1,3,2,dioxaborolan-2-yl)pyrrolidine-1-carboxylate 61



69 **61**

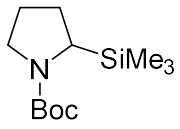
s-BuLi (2.3 mL of a 1.31 M solution in hexane, 3.0 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **69**, purified by Kugelrohr distillation, (0.44 mL, 2.5 mmol, 1.0 eq.) and TMEDA (0.45 mL, 3.0 mmol, 1.2 eq.) in Et_2O (20 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, isopropoxyboronic acid pinacol ester (0.66 mL, 3.3 mmol, 1.3 eq.) was added and the solution was stirred at –78 °C for 1 h. The solution was allowed to warm to rt and 2.0 M $HCl_{(aq)}$ (20 mL) was added. The two layers were separated, and the organic layer was washed with brine (3 x 20 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of the desired borylated pyrrolidine **61** (by ^1H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-20**

s-BuLi (2.3 mL of a 1.31 M solution in hexane, 3.0 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **69**, purified by silica plug chromatography, (0.44 mL, 2.5 mmol, 1.0 eq.) and TMEDA (0.45 mL, 3.0 mmol, 1.2 eq.) in Et_2O (20 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, isopropoxyboronic acid pinacol ester (0.66 mL, 3.3 mmol, 1.3 eq.) was added and the solution was stirred at –78 °C for 1 h. The solution was allowed to warm to rt and 2.0 M $HCl_{(aq)}$ (20 mL) was added. The two layers were separated, and the organic layer was washed with brine (3 x 20 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of the desired borylated pyrrolidine **61** (by ^1H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-24**

***tert*-Butyl 2-trimethylsilylpyrrolidine-1-carboxylate 117**

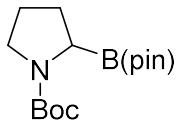


117

s-BuLi (2.3 mL of a 1.31 M solution in hexane, 3.0 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **69**, purified by silica plug chromatography, (0.44 mL, 2.5 mmol, 1.0 eq.) and TMEDA (0.45 mL, 3.0 mmol, 1.2 eq.) in Et_2O (20 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, trimethylsilylchloride (0.41 mL, 3.3 mmol, 1.3 eq.) was added and the solution was stirred at –78 °C for 1 h. The solution was allowed to warm to rt and 2.0 M $HCl_{(aq)}$ (20 mL) was added. The two layers were separated, and the organic layer was washed with brine (3 x 20 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 15:85 EtOAc-hexane as eluent gave silylated pyrrolidine **117** (180 mg, 30%) as a colourless oil, IR (ATR) 2965, 2875, 1689 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.61-3.40 (m, 1H, NCHSi), 3.35-3.08 (m, 2H, NCH), 2.06-1.90 (m, 1H, CH), 1.84-1.70 (m, 3H, CH), 1.45 (s, 9H, CMe_3), 0.03 (s, 9H, $SiMe_3$); HRMS (ESI) *m/z* calcd for $C_{12}H_{25}NO_2Si$ $(M + Na)^+$ 266.1547, found 266.1547 (+0.1 ppm error). Spectroscopic data consistent with those reported in the literature.[47]

Lab book reference: **CEH-1-27**

***tert*-Butyl 2-(4,4,5,5-tetramethyl-1,3,2,dioxaborolan-2-yl)pyrrolidine-1-carboxylate 61**



61

s-BuLi (4.4 mL of a 1.37 M solution in hexane, 6.0 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **69**, purified by silica plug chromatography, (0.88 mL, 5.0 mmol, 1.0 eq.) and TMEDA (0.9 mL, 6.0 mmol, 1.2 eq.) in Et_2O (20 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Freshly distilled isopropoxyboronic acid pinacol ester (1.4 mL, 6.5 mmol, 1.3 eq.) was added and the solution was stirred at –78 °C for 1 h. The solution was allowed to warm to rt and 2.0 M $HCl_{(aq)}$ (20 mL) was added. The two layers were separated, and the organic layer was washed with brine (3 x 20 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by recrystallisation from hot hexane gave pyrrolidine boronate **61** (1.20 g, 81%) as colourless crystals, mp 71-73 °C (lit.[29] 107 °C dec for (*S*)-**61**); IR (ATR) 2970, 2872, 1675 (C=O), 1476, 1449, 1413, 1369, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.31-3.25 (m, 2H, NCH), 3.04 (dd, *J* = 10.0, 6.5 Hz, 1H, NCH), 1.96-1.87 (m, 2H, CH), 1.82-1.73 (m, 2H, CH), 1.40 (s, 9H, CMe_3), 1.21 (s, 12H, CMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.0 (C=O), 83.5 (O*C*Me_2), 79.0 (O*C*Me_3), 46.2 (NCH_2), 28.7 (OC*Me*$_3$), 28.2 (CH_2), 26.7 (CH_2), 25.2 (C*Me*$_2$), 24.6 (C*Me*$_2$), (NCHB resonance not resolved); ^{11}B NMR (77 MHz, $CDCl_3$) δ 32.0; HRMS (ESI) *m/z* calcd for $C_{15}H_{28}BNO_4$ $(M + Na)^+$ 320.2004, found 320.2005 (+0.4 ppm error). Spectroscopic data consistent with those reported in the literature.[29]

Lab book reference: **CEH-1-38**

s-BuLi (17.5 mL of a 1.37 M solution in hexane, 24 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **69**, purified by silica plug chromatography, (3.5 mL, 20 mmol, 1.0 eq.) and TMEDA (3.6 mL, 24 mmol, 1.2 eq.) in Et_2O (100 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Freshly distilled isopropoxyboronic acid pinacol ester (5.3 mL, 26 mmol, 1.3 eq.) was added and the solution was stirred at –78 °C for 16 h. The solution was allowed to warm to rt and 2.0 M $HCl_{(aq)}$ (40 mL) was added. The two layers were separated, and the organic layer was washed with brine (3 x 40 mL). The

aqueous layer was extracted with Et_2O (3 x 40 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by recrystallisation from hot hexane gave pyrrolidine boronate **61** (3.6 g, 59%) as colourless crystals.

Lab book reference: **CEH-1-69**

s-BuLi (2.3 mL of a 1.31 M solution in hexane, 3.0 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **69**, purified by silica plug chromatography, (0.44 mL, 2.5 mmol, 1.0 eq.) and TMEDA (0.45 mL, 3.0 mmol, 1.2 eq.) in Et_2O (20 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, isopropoxyboronic acid pinacol ester from a fresh bottle (0.66 mL, 3.3 mmol, 1.3 eq.) was added and the solution was stirred at –78 °C for 16 h. The solution was allowed to warm to rt and 2.0 M $HCl_{(aq)}$ (40 mL) was added. The two layers were separated, and the organic layer was washed with brine (3 x 40 mL). The aqueous layer was extracted with Et_2O (3 x 40 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by recrystallisation from hot hexane gave pyrrolidine boronate **61** (44 mg, 6.0%) as colourless crystals.

Lab book reference: **CEH-1-29**

s-BuLi (2.3 mL of a 1.31 M solution in hexane, 3.0 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **69**, purified by silica plug chromatography, (0.44 mL, 2.5 mmol, 1.0 eq.) in THF (18 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 15 min. Then, isopropoxyboronic acid pinacol ester from a fresh bottle (0.66 mL, 3.3 mmol, 1.3 eq.) was added and the solution was stirred at –78 °C for 16 h. The solution was allowed to warm to rt and 2.0 M $HCl_{(aq)}$ (40 mL) was added. The two layers were separated, and the organic layer was washed with brine (3 x 40 mL). The aqueous layer was extracted with Et_2O (3 x 40 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by recrystallisation from hot hexane gave pyrrolidine boronate **61** (260 mg, 32%) as colourless crystals.

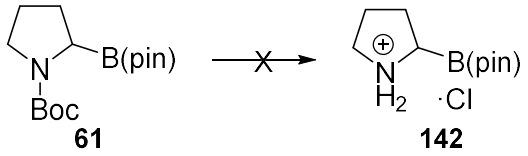
Lab book reference: **CEH-1-31**

s-BuLi (2.3 mL of a 1.31 M solution in hexane, 3.0 mmol, 1.2 eq.) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **69**, purified by silica plug chromatography, (0.44 mL, 2.5 mmol, 1.0 eq.) in THF (18 mL) at –78 °C under Ar. The resulting solution was stirred at

–78 °C for 15 min. Freshly distilled isopropoxyboronic acid pinacol ester from a fresh bottle (0.66 mL, 3.3 mmol, 1.3 eq.) was added and the solution was stirred at –78 °C for 16 h. The solution was allowed to warm to rt and 2.0 M $HCl_{(aq)}$ (40 mL) was added. The two layers were separated, and the organic layer was washed with brine (3 x 40 mL). The aqueous layer was extracted with Et_2O (3 x 40 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by recrystallisation from hot hexane gave pyrrolidine boronate **61** (330 mg, 48%) as colourless crystals.

Lab book reference: **CEH-1-34**

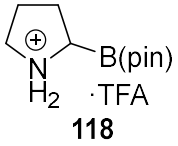
Attempted synthesis of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-ium chloride 142



Hydrochloric acid (0.75 mL of a 4.0 M solution in dioxane, 3.0 mmol, 1.5 eq) was added dropwise to a stirred solution of pyrrolidine boronate **61** (600 mg, 2.0 mmol, 1.0 eq.) in Et_2O (15 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 2 h. The solvent was evaporated under reduced pressure to give the crude product which contained none of the desired borylated pyrrolidine **142** (by ^1H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-40**

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-ium trifluoroacetate salt 118

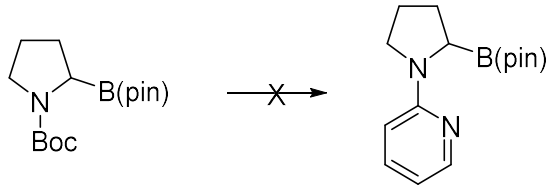


Trifluoroacetic acid (3.0 mL) was added to a stirred solution of pyrrolidine boronate **61** (100 mg, 0.7 mmol, 1.0 eq.) in CH_2Cl_2 (3.0 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h. The solvent was evaporated under reduced pressure. Toluene (3.0 mL) was added to the residue and the solvent was evaporated under reduced pressure. This procedure was repeated two more times to give the crude TFA salt. Drying under high vacuum for 1 h gave the TFA salt **118** (86 mg, 81%) as a white solid, ^1H NMR (400 MHz, $CDCl_3$) δ 9.62 (s,

1H, NH), 9.07 (s, 1H, NH), 3.43-3.29 (m, 2H, NCH), 3.23-3.14 (m, 1H, NCH), 2.27-2.18 (m, 1H, CH), 2.07-1.99 (m, 2H, CH), 1.96-1.86 (m, 1H, CH), 1.26 (s, 12H, CMe_2).

Lab book reference: **CEH-1-76**

Attempted synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidine-1-yl]pyridine 60



61 **60**

Trifluoroacetic acid (1.2 mL, 16 mmol, 50 eq.) was added to a stirred solution of pyrrolidine boronate **61** (100 mg, 0.32 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL) at rt under Ar. The resulting solution was stirred at rt for 3 h. The solvent was evaporated under reduced pressure. Toluene (3.0 mL) was added to the residue and the solvent was evaporated under reduced pressure. This procedure was repeated two more times to give the crude TFA salt **118**. *n*-BuLi (0.4 mL of a 1.6 M solution in hexane, 0.64 mmol, 2.0 eq.) was added dropwise to a stirred solution the crude TFA salt **118** in THF (1.5 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 15 min. This solution was then added dropwise to a stirred solution of 2-fluoropyridine (30 µL, 0.35 mmol, 1.1 eq.) in THF (1.0 mL) at 0 °C under Ar. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. The solvent was evaporated under reduced pressure to give the crude product which contained none of the desired borylated pyrrolidine **60** (by ^{1}H NMR spectroscopy and mass spectrometry).

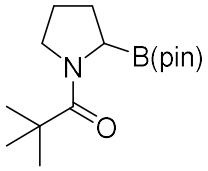
Lab book reference: **CEH-1-77**

Trifluoroacetic acid (1.2 mL, 16 mmol, 50 eq.) was added to a stirred solution of pyrrolidine boronate **61** (100 mg, 0.32 mmol, 1.0 eq.) in CH_2Cl_2 (3 mL) at rt under Ar. The resulting solution was stirred at rt for 3 h. The solvent was evaporated under reduced pressure. Toluene (3.0 mL) was added to the residue and the solvent was evaporated under reduced pressure. This procedure was repeated two more times to give the crude TFA salt **118**. 2-Fluoropyridine (23 µL, 0.27 mmol, 0.8 eq.) was added to a pressure tube containing the crude TFA salt **118**,

Na_2CO_3 (60 mg, 0.5 mmol, 1.6 eq.) and MeCN (1.5 mL). The pressure tube was sealed, and the solution was stirred and heated at 150 °C for 1.5 h. After being allowed to cool to rt, EtOAc (3.0 mL) was added, and the solids were removed by filtration through celite. The filtrate was evaporated under reduced pressure to give the crude product which contained none of the desired borylated pyrrolidine **60** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-78**

2,2-Dimethyl-1-[2-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]propan-1-one 62



62

Trifluoroacetic acid (2.7 mL, 35 mmol, 50 eq.) was added to a stirred solution of pyrrolidine boronate **61** (200 mg, 0.7 mmol, 1.0 eq.) in CH_2Cl_2 (4.0 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h. The solvent was evaporated under reduced pressure. Toluene (3.0 mL) was added to the residue and the solvent was evaporated under reduced pressure. This procedure was repeated two more times to give the crude TFA salt **118**. Then, DMAP (8.3 mg, 0.07 mmol, 0.1 eq.) and trimethylacetyl chloride (94 μL, 0.77 mmol, 1.1 eq.) were added to a solution of the crude TFA salt **118** in CH_2Cl_2 (5.0 mL) at 0 °C under Ar. Et_3N (0.25 mL, 1.8 mmol, 2.5 eq.) was added dropwise and the solution was stirred at 0 °C for 10 min. The resulting solution was allowed to warm to rt and stirred at rt for 3 h. Then, CH_2Cl_2 (5.0 mL) and water (5.0 mL) were added, and the two layers were separated. The organic layer was washed with 2.0 M $HCl_{(aq)}$ (5.0 mL) and sat. $NaHCO_{3(aq)}$ (5.0 mL) and the combined aqueous layers were extracted with EtOAc (5.0 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 1:1 acetone-hexane as eluent gave pivalamide boronate **62** (48 mg, 26%) as an off-white solid, mp 72-74 °C (lit.[32] 114-115 °C); IR (ATR) 2968, 1682 (C=O), 1561, 1493, 1123 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58-3.53 (m, 2H, NCH), 2.90 (dd, *J* = 12.5, 6.5 Hz, 1H, NCH), 2.25-2.22 (m, 1H, CH), 2.10-2.07 (m, 1H, CH), 1.80 (dddd, *J* = 13.0, 7.0, 7.0 6.5 Hz, 1H, CH), 1.64 (dddd, *J* = 13.0, 12.5, 12.5, 7.0 Hz, 1H, CH), 1.27 (s, 9H, CMe_3), 1.19 (s, 6H, CMe), 1.18 (s, 6H, CMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.8 (C=O), 80.3 (O*C*Me$_2$), 46.3 (NCH_2), 36.2 (*C*Me$_3$), 30.1 (CH_2), 27.1 (C*Me*$_3$), 25.1 (C*Me*), 24.92 (C*Me*),

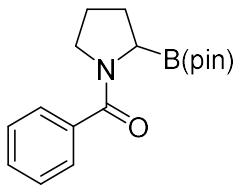
24.85 (CH_2) (NCHB resonance not resolved); ^{11}B NMR (77 MHz, $CDCl_3$) δ 12.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{28}BNO_3$ $(M + Na)^+$ 304.2054, found 304.2055 (+0.8 ppm error). Spectroscopic data consistent with those reported in the literature.[32]

Lab book reference: **CEH-1-70**

Trifluoroacetic acid (3.0 mL, 39 mmol, 115 eq.) was added to a stirred solution of pyrrolidine boronate **61** (100 mg, 0.3 mmol, 1.0 eq.) in CH_2Cl_2 (3.0 mL) at rt under Ar. The resulting solution was stirred for 2 h. The solvent was evaporated under reduced pressure. Toluene (3.0 mL) was added to the residue and the solvent was evaporated under reduced pressure. This procedure was repeated two more times to give the crude TFA salt **118**. Then, DMAP (6.2 mg, 0.05 mmol, 0.15 eq.) and trimethylacetyl chloride (50 µL, 0.4 mmol, 1.3 eq.) were added to a solution of the crude TFA salt **118** in CH_2Cl_2 (1.4 mL) at 0 °C under Ar. Et_3N (0.40 mL, 2.9 mmol, 10 eq.) was added dropwise and the solution was stirred at 0 °C for 10 min. The resulting solution was allowed to warm to rt and stirred at rt for 3 h. Then, CH_2Cl_2 (5.0 mL) and water (5.0 mL) were added, and the two layers were separated. The organic layer was washed with 2.0 M $HCl_{(aq)}$ (5.0 mL) and sat. $NaHCO_{3(aq)}$ (5.0 mL) and the combined aqueous layers were extracted with EtOAc (5.0 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 1:1 acetone-hexane as eluent gave pivalamide boronate **62** (60 mg, 72%) as an off-white solid.

Lab book reference: **CEH-1-73**

Phenyl-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]methanone 63



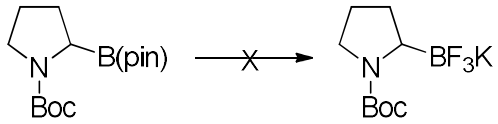
63

Trifluoroacetic acid (3.0 mL, 39 mmol, 110 eq.) was added to a stirred solution of pyrrolidine boronate **61** (100 mg, 0.35 mmol, 1 eq.) in CH_2Cl_2 (3.0 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h. The solvent was evaporated under reduced pressure. Toluene (3.0 mL) was added to the residue and the solvent was evaporated under reduced pressure. This procedure was repeated two more times to give the crude TFA salt **118**. Then, DMAP (6.0 mg, 0.05 mmol, 10 mol%) and benzoyl chloride (48 µL, 0.39 mmol, 1.1 eq.) were added to a

solution of the crude TFA salt **118** in CH_2Cl_2 (3.0 mL) at 0 °C under Ar. Et_3N (0.18 mL, 1.0 mmol, 2.5 eq.) was added dropwise and the resulting solution was stirred at 0 °C for 10 min. The resulting solution was allowed to warm to rt and stirred at rt for 16 h. Then, CH_2Cl_2 (5.0 mL) and water (5.0 mL) were added, and the two layers were separated. The organic layer was washed with 2.0 M $HCl_{(aq)}$ (5.0 mL) and sat. $NaHCO_{3(aq)}$ (5.0 mL) and the combined aqueous layers were extracted with EtOAc (5.0 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 3:7 acetone-hexane as eluent gave amide boronate **63** (46 mg, 41%) as an off-white solid, mp 90-92 °C; IR (ATR) 2968, 1592 (C=O), 1554, 1269, 1121 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72-7.70 (m, 2H, Ph), 7.53-7.49 (m, 1H, Ph), 7.44-7.40 (m, 2H, Ph), 3.69 (ddd, *J* = 11.0, 9.0, 4.0 Hz, 1H, NCH), 3.46 (ddd, *J* = 11.0, 8.0, 4.0 Hz, 1H, NCH), 3.08 (dd, *J* = 11.5, 7.0 Hz, 1H, NCH), 2.16-2.07 (m, 2H, CH), 1.93 (dddd, *J* = 12.5, 7.0, 7.0, 2.5 Hz, 1H, CH), 1.75 (m, 1H, CH), 1.25 (s, 12H, CMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.2 (C=O), 132.5 (Ph), 129.5 (*ipso*-Ph), 129.4 (Ar), 128.5 (Ph), 81.0 (*C*Me_2), 48.3 (NCH_2), 28.9 (CH_2), 25.5 (CH_2), 25.2 (C*Me*$_2$), 25.0 (C*Me*$_2$), (NCHB resonance not resolved); ^{11}B NMR (77 MHz, $CDCl_3$) δ 17.1; HRMS (ESI) *m/z* calcd for $C_{17}H_{24}BNO_3$ $(M + Na)^+$ 324.1741, found 324.1745 (–0.2 ppm error).

Lab book reference: **CEH-1-50**

Potassium (1-*tert*-butoxycarbonylpyrrolidin-2-yl)trifluoroborate 65

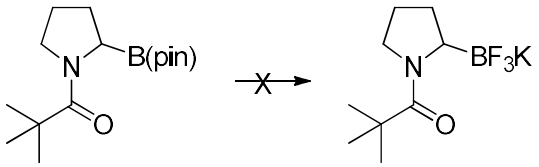


65

A solution of (L)-(+)-tartaric acid (240 mg, 1.6 mmol, 2.1 eq.) in THF (2.2 mL) was added dropwise to a stirred solution of pyrrolidine boronate **61** (230 mg, 0.8 mmol, 1.0 eq.) and KF (180 mg, 3.1 mmol, 4.0 eq.) in MeCN (3.0 mL) and water (1.2 mL). The resulting solution was stirred at rt for 1 h and then the solvent was evaporated under reduced pressure to give the crude product as a white solid. MeOH (3.0 mL) was added and the solid was collected by filtration which contained none of the desired trifluoroborate salt **65** (by ^1H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-57**

Potassium [1-(2,2-dimethylpropanoyl)pyrrolidin-2-yl]trifluoroborate 66

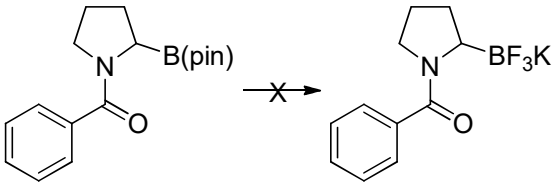


66

A solution of (L)-(+)-tartaric acid (62 mg, 0.4 mmol, 2.1 eq.) in THF (0.6 mL) was added dropwise to a stirred solution of pyrrolidine boronate **62** (60 mg, 0.2 mmol, 1.0 eq.) and KF (46 mg, 0.8 mmol, 4.0 eq.) in MeCN (1.0 mL) and water (0.4 mL). The resulting solution was stirred at rt for 4 h and then the solvent was evaporated under reduced pressure to give the crude product as a white solid. MeOH (3.0 mL) was added and the solid was collected by filtration which contained none of the desired trifluoroborate salt **66** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-63**

Potassium (1-benzoylpyrrolidin-2-yl)trifluoroborate 67

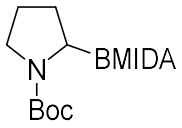


67

A solution of (L)-(+)-tartaric acid (180 mg, 1.2 mmol, 2.1 eq.) in THF (1.7 mL) was added dropwise to a stirred solution of pyrrolidine boronate **63** (170 mg, 0.6 mmol, 1.0 eq.) and KF (130 mg, 2.2 mmol, 4.0 eq.) in MeCN (4.3 mL) and water (1.6 mL). The resulting solution was stirred at rt for 1 h and then the solvent was evaporated under reduced pressure to give the crude product as a white solid. MeOH (3.0 mL) was added and the solid was collected by filtration which contained none of the desired trifluoroborate salt **67** (by ^{1}H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-74**

***tert*-Butyl 2-(5-methyl-3,7-dioxo-2,8-dioxa-5-azanuida-1-boroniabicyclo[3.3.0]octan-1-yl)pyrrolidine-1-carboxylate 64**

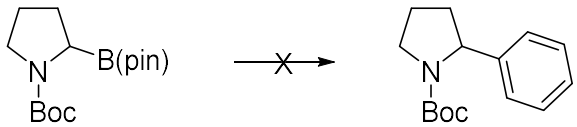


64

Triethyl orthoformate (0.48 mL, 2.9 mmol, 4.5 eq.) and MIDA (620 mg, 4.2 mmol, 6.5 eq) were added to a stirred solution of pyrrolidine boronate **61** (200 mg, 0.64 mmol, 1 eq.) in DMSO (5.0 mL) at rt. The resulting solution was stirred and heated at 100 °C for 48 h. After being allowed to cool to rt, sat. $NH_4Cl_{(aq)}$ (3.0 mL) was added. The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with brine (3 x 10 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica using 10:90 acetone-CH_2Cl_2 as eluent gave pyrrolidine MIDA boronate **64** (33 mg, 16% yield) as a white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (d, *J* = 15.5 Hz, 1H, N*C*HCO), 3.79 (d, *J* = 16.5 Hz, 1H, N*C*HCO), 3.73 (d, *J* = 16.5 Hz, 1H, N*C*HCO), 3.66 (d, *J* = 15.5 Hz, 1H, N*C*HCO), 3.44-3.36 (m, 2H, NCH), 3.32 (s, 3H, NMe), 3.30-3.19 (m, 1H, NCH), 2.13-2.05 (m, 1H, CH), 2.01-1.82 (m, 2H, CH), 1.78-1.70 (m, 1H, CH), 1.40 (s, 9H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.1 (NCH_2*C*=O), 167.3 (NCH_2*C*=O), 155.7 (C=O), 79.3 (O*C*Me_3), 63.9 (N*C*H_2CO), 61.7 (N*C*H_2CO), 47.5 (NCH_2), 45.6 (NMe), 29.1 (CH_2), 28.6 (C*Me*$_3$), 25.3 (CH_2) (NCHB resonance not resolved).

Lab book reference: **CEH-1-83**

Attempted synthesis of *tert*-butyl 2-phenylpyrrolidine-1-carboxylate 119



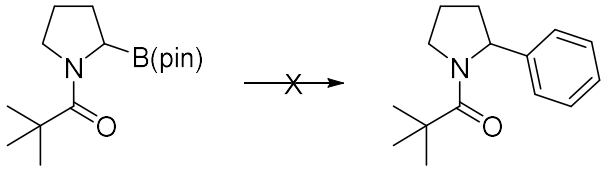
61 **119**

Pyrrolidine boronate **61** (50 mg, 0.17 mmol, 1.0 eq.), $Pd(dba)_2$ (5.2 mg, 9.0 µmol, 5 mol%), XPhos (8.6 mg, 18 µmol, 10 mol%) and K_2CO_3 (71 mg, 0.5 mmol, 3 eq.) were placed in a pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, toluene (1.5 mL) and water (1.5 mL) were added, and the resulting solution was stirred at rt for 5 min. Then, bromobenzene (21 µL, 0.20 mmol, 1.2 eq.) was added. The pressure tube was sealed, and the solution was stirred and heated at 90 °C for 24 h. After being allowed to cool to rt, Et_2O

(5.0 mL) and water (5.0 mL) were added, and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5.0 mL), and the combined organic extracts were washed with brine (3 x 5.0 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of the desired phenyl pyrrolidine **119** (by ^1H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-56**

Attempted synthesis of 2,2-dimethyl-1-(2-phenylpyrrolidine-1-yl)propan-1-one 141

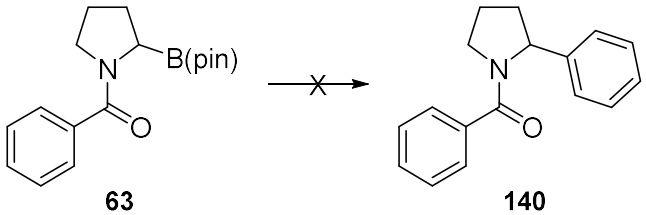


62 **141**

Amide boronate **66** (28 mg, 0.10 mmol, 1.0 eq.), $Pd(dba)_2$ (3.0 mg, 5.0 µmol, 5 mol%), XPhos (4.8 mg, 10 µmol, 10 mol%) and K_2CO_3 (41 mg, 0.3 mmol, 3 eq.) were placed in a pressure tube. The pressure tube was evacuated and refilled with Ar three times. Then, toluene (0.5 mL) and water (0.3 mL) were added, and the resulting solution was stirred at rt for 5 min. Then, bromobenzene (13 µL, 0.12 mmol, 1.2 eq.) was added. The pressure tube was sealed, and the solution was stirred and heated at 100 °C for 24 h. After being allowed to cool to rt, Et_2O (5.0 mL) and water (5.0 mL) were added, and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5.0 mL), and the combined organic extracts were washed with brine (3 x 5.0 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of the desired phenyl pyrrolidine **141** (by ^1H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-85**

Attempted synthesis of phenyl-(2-phenylpyrrolidin-1-yl)methanone 140



63 **140**

Amide boronate **63** (44 mg, 0.17 mmol, 1.0 eq.), $Pd(dba)_2$ (5.2 mg, 9.0 µmol, 5 mol%), XPhos (8.6 mg, 18 µmol, 10 mol%) and K_2CO_3 (71 mg, 0.5 mmol, 3 eq.) were placed in a pressure

tube. The pressure tube was evacuated and refilled with Ar three times. Then, toluene (2.5 mL) and water (31 μL, 1.7 mmol, 10 eq.) were added and the resulting solution was stirred at rt for 5 min. Then, bromobenzene (21 μL, 0.20 mmol, 1.2 eq.) was added. The pressure tube was sealed, and the solution was stirred and heated at 90 °C for 24 h. After being allowed to cool to rt, Et_2O (5.0 mL) and water (5.0 mL) were added, and the two layers were separated. The aqueous layer was extracted with Et_2O (3 x 5.0 mL), and the combined organic extracts were washed with brine (3 x 5.0 mL). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained none of the desired phenyl pyrrolidine **140** (by ^1H NMR spectroscopy and mass spectrometry).

Lab book reference: **CEH-1-55**

6. References

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