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Cyclisation Strategies for the Synthesis of Novel Boron-Containing Heterocyclic Scaffolds

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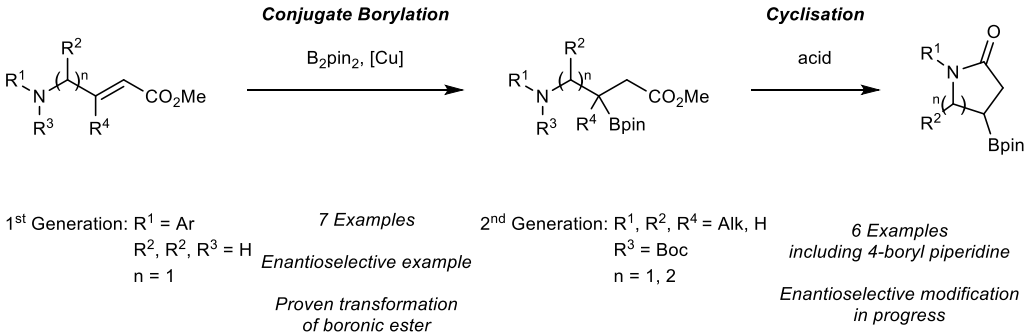
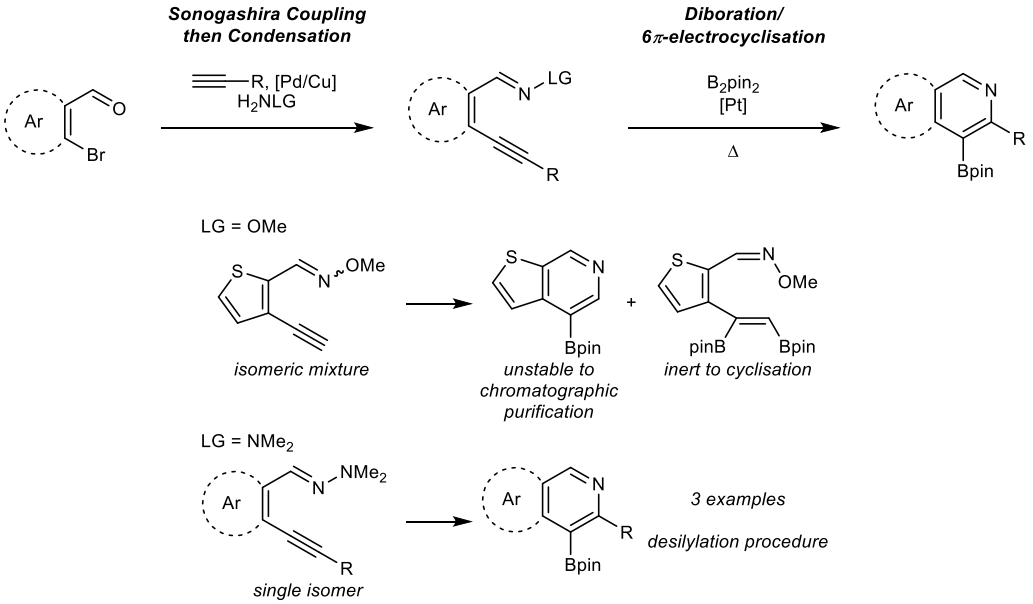
Abstract

Heterocycles are prevalent within biologically active molecules, with >70% of FDA approved drugs featuring at least one nitrogen heterocycle. Analysis of the literature has revealed that over the past 40 years, chemists have shifted from using cyclisation reactions to incorporating cyclic motifs using pre-formed building blocks. Boronic acid derivatives represent a versatile class building blocks due to their routine preparation, scope of transformations, stability, and ease of handling. However, there is a significant disparity in the number of heterocyclic boronates reported in the literature compared with carbocyclic. This discrepancy is further exacerbated by comparisons in the availability of sp^2-rich boronates compared with saturated heterocyclic building blocks.

We have developed two synthetic routes to borylated lactams using a reliable conjugate borylation/cyclisation strategy. Initial investigation of our first methodology revealed *N*-alkyl amino enoates cyclise upon borylation, with the resulting borylated lactams showing an intolerance to chromatographic purification. Reducing the nitrogen nucleophilicity through the preparation of *N*-aryl amino enoates halts the cyclisation during the conjugate borylation reaction, allowing for isolation of the linear boronic ester products. Acid-mediated cyclisation then furnishes the desired lactams without the need for further purification. We have demonstrated that this process can be made enantioselective through using a Cu-catalyst ligated with a chiral phosphine ligand. Furthermore, we have shown that these scaffolds are suitable for a range of transformation including reduction to the corresponding cyclic amine and Suzuki-Miyaura coupling with aryl bromides. Building on this success, we have developed a second methodology utilising *N*-Boc amino enoates that allows for expanded complexity of the scaffolds such as increased ring size, substitution on the ring and alkyl or no substitution on the nitrogen. In addition to this we have optimised an enantioselective conjugate borylation procedure which furnishes boryl amino esters with excellent distereo- and enantioselectivities.



Additionally, pyridines are an important unsaturated motif within biologically active molecules, which can influence the potency and pharmacokinetic properties of the molecule. Borylated pyridines are typically obtained through Miyaura or C-H borylation. There exist relatively few examples of anulative methods to directly prepare borylated pyridines, which is surprising considering the synthetic value of these building blocks. We have expanded on the diboration/6π-electrocyclisation previously reported by Harrity and co-workers to incorporate hydrazones, as a suitable alternative to aldoxime ethers, overcoming issues observed with isomeric mixtures. Using this procedure, we have prepared three examples of the thienopyridine scaffold. We have also shown that a desilylation procedure offers improved combined yield, compared with the previously reported one step procedure, for the preparation of monosubstituted scaffolds.



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I am eternally indebted to my parents for their unwavering support and for helping me to accomplish all that I have.

But most of all I am extremely thankful that Steven Armes has not yet asked me about how the polymer aspect of my project is coming along.

The most exciting phrase to hear in science, the one that heralds new discoveries, is not 'Eureka!' but 'That's funny...'

-Isaac Asimov

2-mphen	2-Methylphenanthroline
4-F-dppbz	1,1′-(1,2-Phenylene)bis[1,1-bis(4-fluorophenyl)phosphine]
acac	Acetylacetone
Alk	Alkyl
Ar	Aryl
B_2cat_2	Bis(catecholato)diboron
B_2pin_2	Bis(pinacolato)diboron
Bdan	Diaminonaphthalene boronic acids
BF_3K	Organotrifluoroborates
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BMIDA	*N*-Methyliminodiacetic acid boronic esters
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Botc	*tert*-Butoxythiocarbonyl
BOX	2,2′-(1-Methylethylidene) bis[3a,8a-dihydro-8H-indeno [1,2-d]oxazole]
Bpin	Pinacolato boronic ester
Bz	Benzoyl
CAAC	Cyclic (alkyl)(amino)carbene
CatacXium A	Di(1-adamantyl)-*N*-butylphosphine
CFL	Compact fluorescent lamp
cod	1,5-Cyclooctadiene
Cp*	Pentamethylcyclopentadienyl
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
CyPr	Cyclopropyl
d.e.	Diastereomeric excess
d.r.	Diastereomeric ratio
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DG	Directing group
DIANANE	*endo*,*endo*-2,5-Diaminonorbornane
Dipp	2,6-Diisopropylphenyl
DME	Dimethyl etheylene glycol
DMF	Dimethylforamide
DMP	Dess-Martin periodinane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino) ferrocene
DTBM-SEGPHOS	5,5'-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole
DTBP	Di-*tert*-butyl peroxide
dtbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl
DuanPhos	Di-*tert*-butyl-2,3,2′,3′-tetrahydro-1H,1′H-(1,1′)biisophosphindolyl
e.e.	Enantiomeric excess
e.s.	Enantiospecifity
FOXAP	1-[-4,5-Dihydro-4-(1-methylethyl)-2-oxazolyl]-2-(diphenylphosphino)ferrocene
HAT	Hydrogen atom transfer
HG-II	2nd Generation Hoveyda–Grubbs catalyst
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
Imes	1,3-Bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene
IPA	Isopropyl alcohol
^{i}Pr-PHOX	2-[2-(Diphenylphosphino)phenyl]-4-isopropyl-4,5-dihydrooxazole
J	Coupling constant
JosiPhos 1	1-[2-(Dicyclohexylphosphino) ferrocenyl]ethyldiphenyl phosphine
JosiPhos 2	1-[2-(Diphenylphosphino) ferrocenyl]ethyldicyclohexyl phosphine
LG	Leaving group
LiTMP	Lithium tetramethylpiperidide

MandyPhos	2,2'-Bis[(N,N-dimethylamino)(phenyl)methyl]-1,1'-bis(diphenylphosphino)ferrocene
MeO-BIPHEP	2,2'-Bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl
MeO-DTBM-BIPHEP	2,2'-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl
mes	1,3,5-trimethylbenzene
MHz	Megahertz
Ms	methanesulfonyl
n.d.	Not determined
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NHC 1	1-(2,4,6-Trimethylphenyl)-3-[(2*S*)-4-methyl-1-pentanol]-imidazol-2-ylidene
NHC 2	1-(2,4,6-Trimethylphenyl)-3-[(1*R*,2*R*,3*R*,5*S*)-(-)-isopinocampheyl]-imidazol-2-ylidene
NHC 3	1,3-Bis(4-methyl[1,1′-biphenyl]-2-yl)-4,5-diphenyl-imidazol-2-ylidene
SEGPHOS	5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
SImes	1,3-Dimesityl-imidazol-4,5-dihydro-2-ylidene
S_NAr	Nucleophilic aromatic substitution
SpiroBOX	7,7-Bis[(4S)-(phenyl)oxazol-2-yl)]-2,2,3,3-tetrahydro-1,1-spirobiindane
^{t}Am	*tert*-Amyl
taniaphos	1-[(Dimethylamino)[2-(diphenyl phosphino)phenyl]methyl]-2-(diphenylphosphino)ferrocene
TBAF	Tetra-*n*-butylammonium fluoride
TBDMSO	*tert*-Butyldimethylsilyl ether
^{t}Bu	*tert*-Butyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Toluenesulfonyl
δ	Chemical shift
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
Ns	Nitrobenzenesulfonyl
o.n.	Over night
***o*-DCB**	1,2-Dichlorobenzene
PE	Petroleum ether 40 - 60°C
PG	Protecting group
phen	Phenanthroline
Piv	Pivalate
PMHS	Polymethylhydrosiloxane
ppy	2-Phenylpyridine
PyBOX	2,6-Bis[4,5-dihydro-4-(1-methylethyl)-2-oxazolyl]pyridine
QuinoxP*	2,3-Bis(tert-butylmethyl phosphino)quinoxaline
r.r.	Regiomeric ratio
r.t.	Room temperature
rac	Racemic
RSM	Returned starting material
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl

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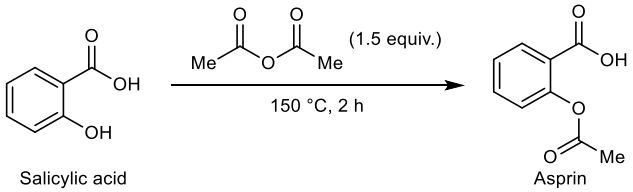
Synthesis of Fused-Ring Boryl Pyridines via a Diboration/6π-Electrocyclisation Strategy

Experimental

1.1 Privileged Scaffolds in Medicinal Chemistry

Over the past century, medicinal chemistry has undergone a rapid and seismic change. At the turn of the 20th century, drug molecules were simple modifications of the active ingredients found in traditional remedies. For example, willow bark has been used for centuries to treat simple aches and pains due to its high concentration of salicylic acid. One common side effect of this drug was stomach pains, which could often be worse than the ailment they would be treating. Conversion of the alcohol functionality to the corresponding acetyl ester alleviated these issues in the form of Aspirin, the world's first blockbuster drug.[1]



Scheme 1: Hoffman's original patented route to Aspirin.[2]

In the late 1980s, Evans coined the term "privileged structures" to describe the relationship between a particular structural motif and the therapeutic use of the molecule in question.[3] As the field of medicinal chemistry has expanded synonyms with slightly different meanings have appeared. Concerning this work, the term "molecular scaffold" describes a building block molecule featuring a desirable motif with potential therapeutic qualities.[4]

Aspirin is not the only drug based on the molecular framework of salicylic acid. Numerous aminosalicylates have anti-inflammatory properties; Mycophenolic acid is an immunosuppressant used to prevent organ rejection in transplant patients; and Repaglinide is an antidiabetic drug and possible alternative to insulin therapy (Figure 1).[5–8] In total, there are 30 approved drugs based on this "privileged structure", showing the specific therapeutic utility of the motif.[9] Very few of these molecules can be prepared directly from salicylic acid, therefore, it is not considered a scaffold by this definition.

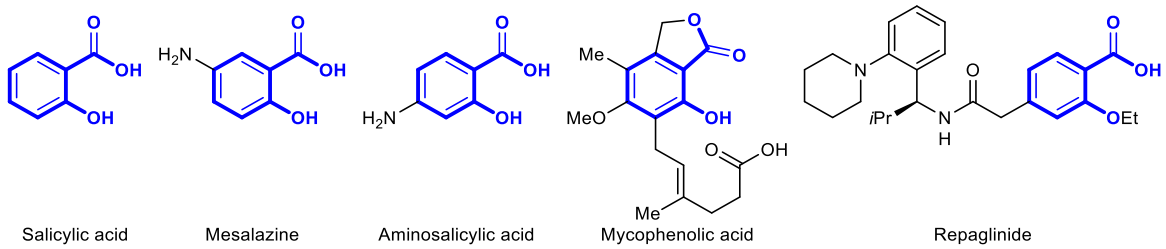


Figure 1: Approved drug molecules based on the molecular framework of Salicylic acid

Over the 20th century, there was a dramatic shift in medicine away from traditional remedies and toward rational drug design. Many natural products, including those found in traditional remedies, have either been used as drug candidates or served as inspiration for their design. However, studying natural products is highly challenging and has led many pharmaceutical companies to try different strategies.[10]

Trends in natural products, bioactive molecules and successful drug candidates have been studied and used as a guideline for rational drug design. Lipinski developed his "Rule of Five", defining molecular properties relevant to a drug's pharmacokinetics.[11] As is the nature of rules, they are often broken, and many new drugs do not obey these rules.[12,13] Analysis shows that 85% of biologically active molecules feature a heterocycle, with piperidines, pyridines, piperazines and pyrrolidines being among the most common motif found in FDA approved drugs.[14,15] This observed preference for saturation was also noted by Lovering *et al.*, who found that an increased number of sp^3 carbons correlated to the increased complexity of molecules and translated to increased success during clinical studies.[16]

Over the last 50 years, medicinal chemists have developed a robust toolbox of reactions that consistently give economic yields.[17–21] At the same time, new parallel methodologies such as High-Throughput and DNA Encoded Library Screening have made the development of large libraries featuring hundreds of thousands of screening molecules advantageous and desirable for the successful development of new pharmaceutical entities.[22–25] By virtue of this, there is a preference to use building block molecules with a plethora of orthogonally reactive functional handles that can be quickly diversified in a divergent bottom-up fashion. In turn, this has driven the demand by the pharmaceutical industry for increasingly novel building blocks in the pursuit of differentiating their libraries from the competition.[26,27]

Analysis of literature relevant to the development of pharmaceutical drugs shows that roughly half of all transformations undertaken by medicinal chemists are carbon-heteroatom formations, which can be further divided in half to represent acylation and alkyl-/arylations, whilst carbon-carbon bond formations account for only a tenth of the reactions.[20,21] This suggests that medicinal chemists rely heavily on inefficient protection/deprotection strategies of preformed building blocks, despite advances in modern carbon-carbon bond forming methodologies. The single most employed carbon-carbon bond-forming strategy is Suzuki-Miyaura coupling, which couples aryl halides with boronic acid derivatives. Due to its robust reliability and regioselectivity, it is typically only when this reaction fails that other carbon-carbon bond-forming reactions are employed.[20] This indicates the types of functional handle of most interest to medicinal chemists are: heteroatom-hydrogen (amines, alcohols, thiols, amides, etc.), protected heteroatoms, carbonyls (carboxylic acids, aldehydes, acyl halides, ketone, etc.), alkyl-/aryl-(pseudo)halides and boronic acid derivatives.[27]

Given the prevalence of heterocycles within drug molecules, roughly only 8% of reactions lead to the formation of heterocyclic rings.[20] Analysis of the *Journal of Medicinal Chemistry* highlighted that heterocycle synthesis has diminished from 1984 to 2014. In 1984 this was the most common reaction class reported in the journal, whereas in 2014, it had dropped to seventh.[21] Despite this, analysis of patent literature by Schneider *et al.* indicated that occurrence of heterocycle formation had remained constant for the past 50 years.[18]

Journal data primarily represents the research and development aspects of drug design, whilst patent data depicts the industrial processes used in large scale production. The combination of these two data sets implies that modern medicinal chemists depend on preformed building blocks to introduce heterocyclic motifs during the drug design process. Given the utility of Suzuki-Miyaura coupling, amongst other transformations, heterocyclic boronates represent a very desirable class of building blocks.

1.2 Synthesis of Saturated Heterocyclic Boronate Scaffolds

Boronic acid derivatives have become ubiquitous in modern synthetic chemistry due to their stability and vast array of possible transformations. The Lewis acidity, and fundamental reactivity of boron originates from its vacant p-orbital; the result of its three valence electrons forming three sp^2 hybridised orbitals in a trigonal planar fashion. When the p-orbital is attacked by a nucleophile it forms a tetrahedral boronate anion, activating the weakest bond (typically carbon-boron) to become nucleophilic itself.

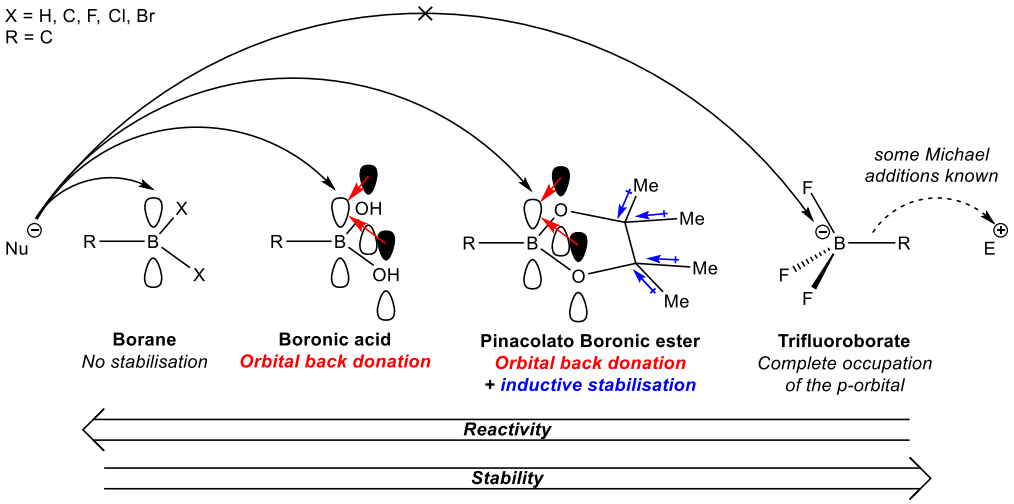
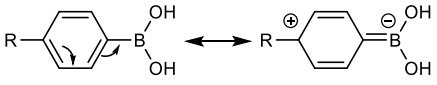


Figure 2: Reactivity and stability of boronic acid derivatives

Boranes feature boron atoms bonded to a combination of three carbon, hydrogen, or halogen atoms, which offer minimal stabilisation to the vacant p-orbital (Figure 2). Typically, these organoboron compounds are the most electrophilic. They are highly susceptible to attack by a nucleophile and consequently the least stable. On the other hand, boronic acids are more stable; featuring two hydroxyl groups on the boron which donate electron density from the oxygen lone pairs to the vacant p-orbital, stabilising it and reducing electrophilicity (Figure 2).

The hybridisation of the adjacent carbons can also play an important role in the stability of boronic acid derivatives. The C-B bonds of aryl and alkenyl boronic acids are stronger than their alkyl counterparts because of a small π-bonding effect. This is the result of the mesomeric capability of the α and β sp^2 carbons being able to resonance stabilise the vacant p-orbital (Scheme 2). This translates to their high stability with regards to aerobic oxidation and protodeboronation under neutral conditions.[28] On the other hand, alkylboronic acids are relatively stable to protodeboronation but are liable to sluggish atmospheric and basic oxidation.



Scheme 2: Mesomeric stabilisation aryl boronic acids

Replacing the hydroxyl groups with alkoxy groups give the structure of boronic esters which offer increased stability, a result of the inductive effect of the alkyl groups (Figure 2). The most common boronic esters featured in the literature are pinacolato boronic esters (Bpin) since they offer the best trade-off between stability and reactivity. Another factor in their prevalence is the ease of handling of bis(pinacolato)diboron (B_2pin_2) and pinacolborane (HBpin), common reagents in borylation reactions.

The stability can be increased further by using B-protected boronic acids.[29] The three most common are *N*-methyliminodiacetic acid boronic esters (BMIDA), boronamide diaminonaphthalene boronic acids (Bdan) and organotrifluoroborates (BF_3K) (Figure 3). These operate by increasing the electron density of the p-orbital, reducing their reactivity and synthetic utility. In the case of BF_3K, the p-orbital is completely occupied, and requires *in situ* transformation to the boronic acid through hydrolysis or the borane by fluorine abstraction to participate in certain reactions, although the C-BF_3 bond is nucleophilic enough to participate in some Michael additions (Figure 2).[30–32]

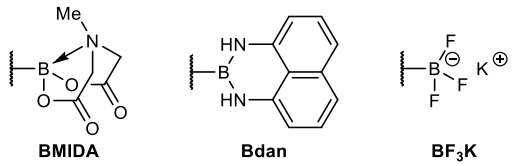
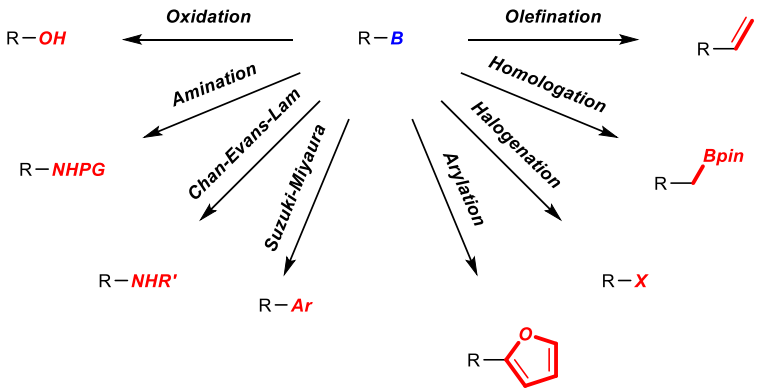


Figure 3: Structure of B-protected boronic acids

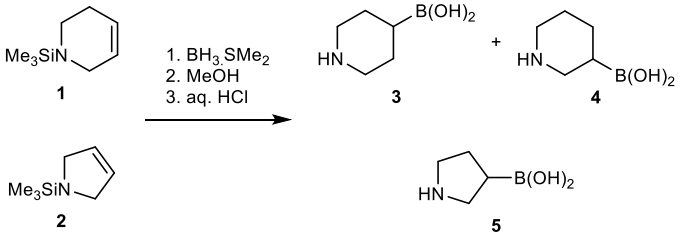
Given the wide range of methods available to form boronic acid derivatives, the focus of this section will be to specifically examine methodologies that have been used to prepare saturated borylated heterocycles. Although this section does not go into detail regarding the transformation of boronic acid derivatives, the majority of these reports feature study of the onward reactivity of their scaffolds, especially the more recent publications. Typically, they demonstrated the oxidation of the boronic acid derivative, although more interesting derivatisations have been performed such as aminations (including Chan-Evans-Lam), arylation (including Suzuki-Miyaura), halogenation, homologations and olefinations (Scheme 3).



Scheme 3: Possible transformation of borylated scaffolds describe in **Section 1.2**

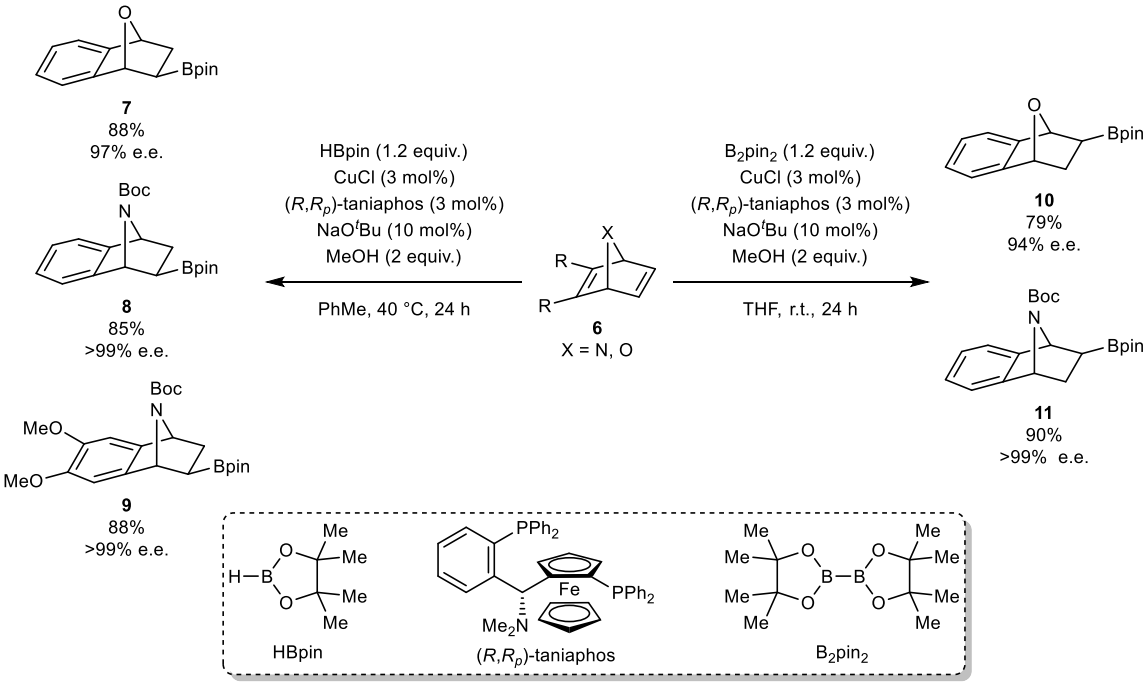
1.2.1 Hydroboration

The first example of the preparation of saturated boryl heterocycle was achieved by the hydroboration of silyl protected allylic amines. Baboulene and co-workers showed that after treatment with borane the resultant amino boranes could be deprotected by stirring in protic solvents, oxidised to the aminoboronic acid by refluxing in dilute aqueous HCl (Scheme 4).[33] Hydroboration of terminal alkenes using boranes typically gives *anti*-Markovnikov products, although regioselectivity in reactions of internal alkenes is less well defined and a limitation of this methodology. Aminoboronic acids **3** and **4** were found to be inseparable and although the ratio of products was determined by GC the ratio and yields were not reported.[34,35]



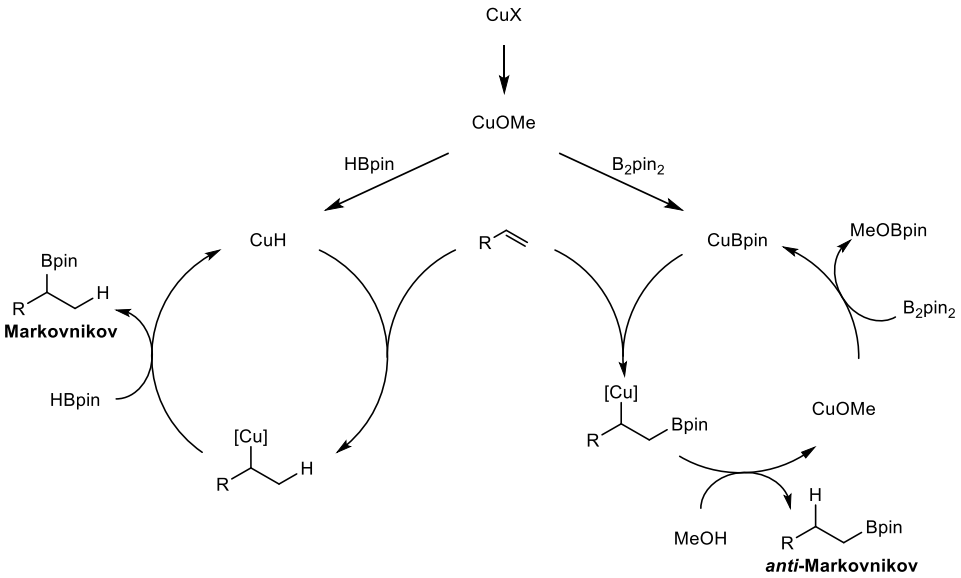
Scheme 4: Preparation of aminoboronic acids via hydroboration

Hydroboration with less reactive boron reagents, HBpin and B_2pin_2, requires the use of an activated alkenes, catalysis, or a combination of the two. These reagents also typically give much better regioselectivity and the ability to control the stereochemical outcome with chiral ligands. The choice of boron reagent can also influence regioselectivity. Reagent-mediated regioselectivity was exploited by Yun and co-workers in a divergent strategy for the borylation of hetero-norbornadienes (**6**) using a Cu catalyst ligated with bisphosphine (R,R_p)-taniaphos (Scheme 5).[36]



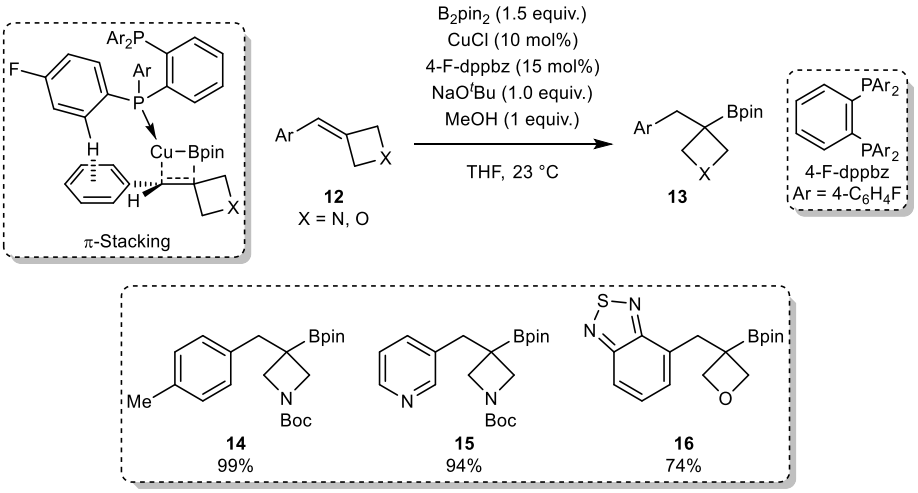
Scheme 5: Boron reagent controlled regio-divergent hydroboration

The origin of the observed regioselectivity originates with the initial formation of active catalyst. HBpin will react with the alkoxy cuprates to form a nucleophilic metal hydride, addition to an alkene followed by transmetalation with another molecule of HBpin ultimately gives the Markovnikov borylated product. Conversely using B_2pin_2 generates a nucleophilic boryl-cuprate which undergoes the same addition to the alkene, instead depositing the boron functionality instead of the hydride, ultimately giving the *anti*-Markovnikov product (Scheme 6).



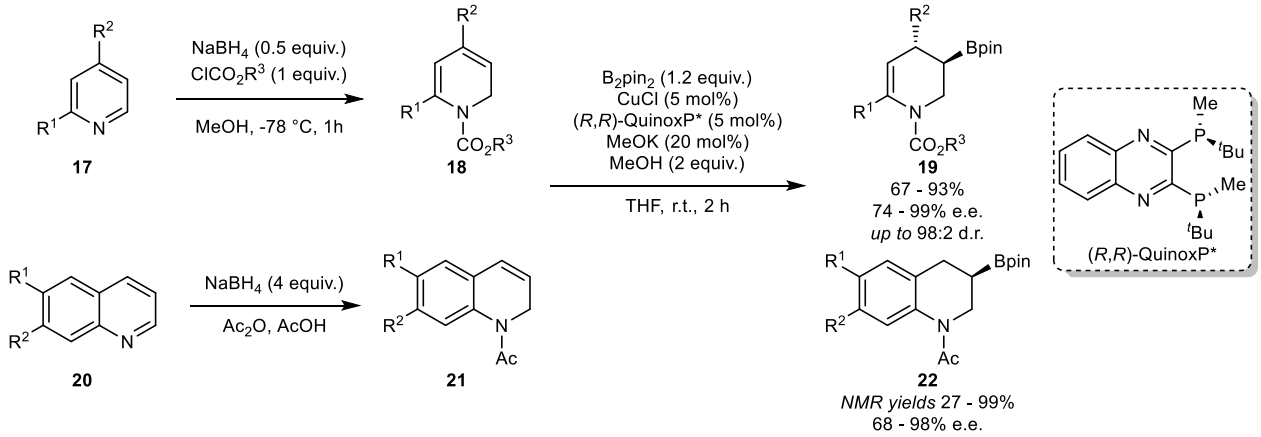
Scheme 6: Mechanistic explanation of the boron reagent controlled regio-divergent hydroboration

The most straightforward method for controlling regioselectivity is by the incorporation of a ligand. Engle and co-workers used a bisphosphine ligated Cu catalyst to perform a hydroboration on benzylidene-azetidines and -oxetanes **12** to give the *anti*-Markovnikov borylated products **13** (Scheme 7).[37] In this example, it is believed that π-stacking interactions between the ligand and substrate aid the regioselectivity of this reaction.



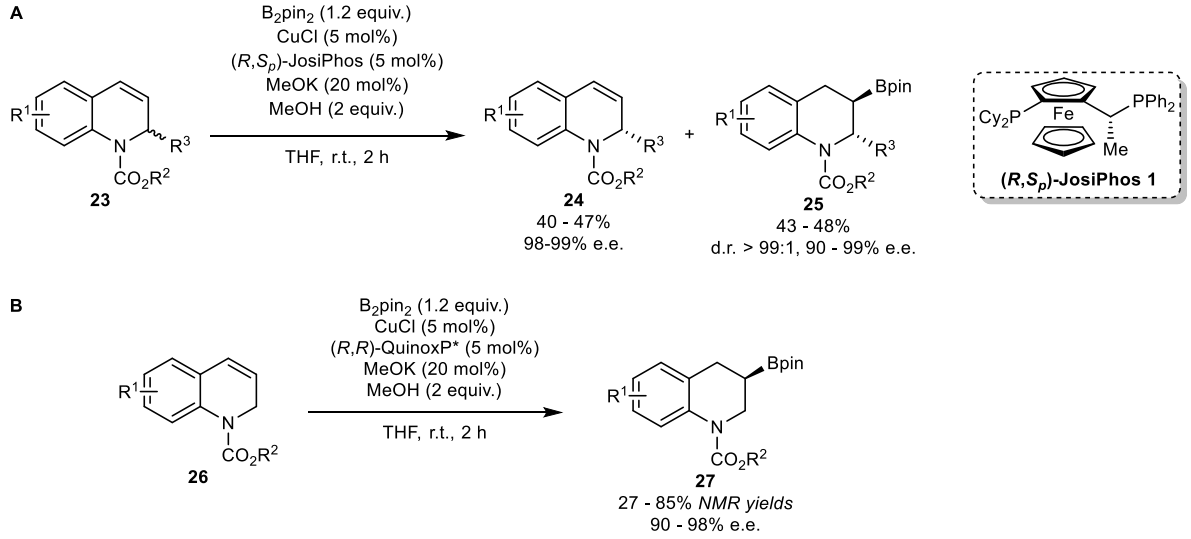
Scheme 7: Hydroboration of benzylidene-azetidines and -oxetanes

Ito and co-workers developed a dearomatisation/borylation strategy to prepare borylated 1,2,3,4-tetrahydro-pyridines and -quinolines; a common motif in optically active biologically relevant molecules.[38,39] Hydride reduction of the heterocycle leads to the activated diene **18** or styrene **21** functionalities suitable for metal hydroboration, with the addition of (*R*,*R*)-QuinoxP* as a ligand resulting in excellent enantioselectivity (Scheme 8).



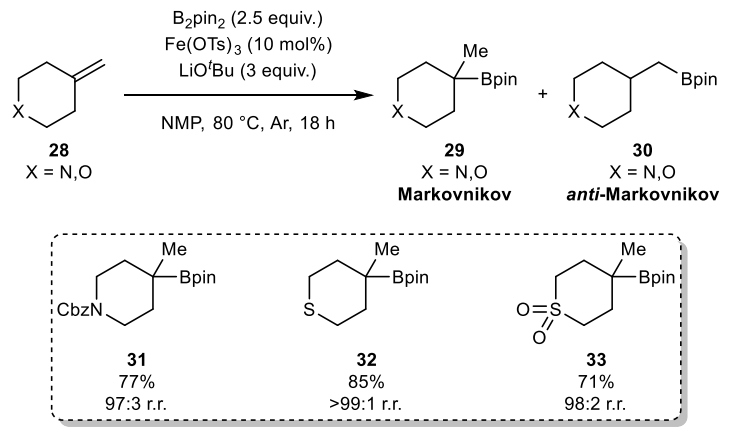
Scheme 8: Dearomatisation/borylation strategy for borylated 1,2 dihydropyridines and 1,2,3,4-tetrahydroquinolines

Hou and co-workers also investigated Cu-catalysed hydroboration of 1,2-dihydroquinolines (Scheme 9).[40,41] In this work they found that the an efficient kinetic resolution could be performed using substrates substituted at the 2-position. Borylation only occurred to give the *syn*-product **25** whilst **24** was returned unreacted in high e.e. (Scheme 9A).[40] When d^4-MeOH was used in the reaction, deuterium incorporation was only observed in the borylated product, showing that the *S*-dihydroquinoline is unable to coordinate to the ligated Cu species and undergo borylation. This selectivity is not observed without substitution at the 2-position (Scheme 9B).[41]



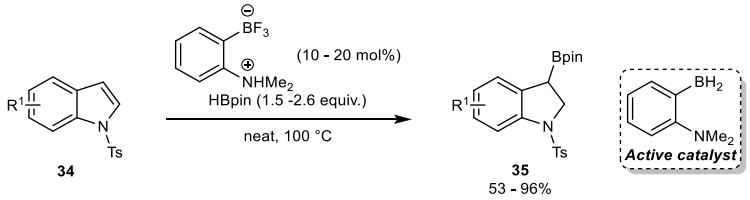
Scheme 9: Cu-catalysed hydroboration of 1,2-dihydroquinoline

Solvents can also influence the regioselectivity of a reaction; Liu and co-workers found that when *N*-methylpyrrolidone (NMP) was used as a solvent the Markovnikov product (**29**) was observed using B_2pin_2.[42] Deuterium labelling experiments showed that this was the result of hydrogen atom transfer (HAT), due to the active catalyst's ability to abstract a proton from the amide solvent, forming a metal hydride that behaves in the same way as previously mentioned (Scheme 6). Although this reaction is catalysed by iron, the proposed Fe^{II} cycle for solvents incapable of HAT is the same as the cycle previously described for Cu^{I}. Using this method, they were able to prepare 3° borylated piperidines, a thiane and a thiane-1,1-dione using an iron-based catalyst (Scheme 10).



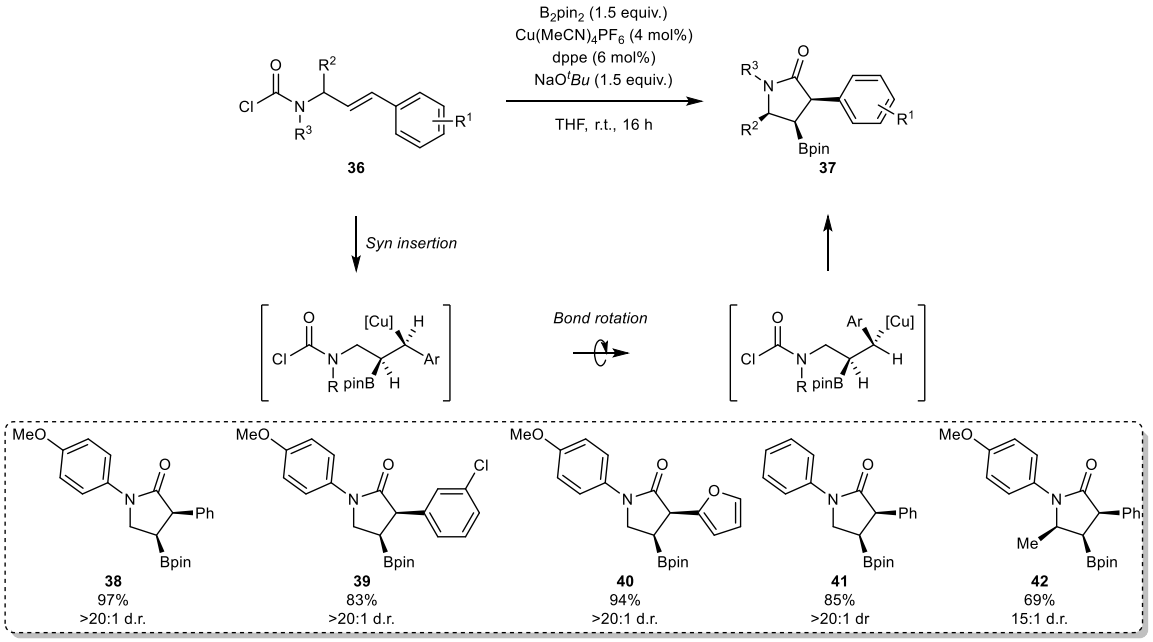
Scheme 10: Ligand-free iron catalysed regioselective hydroboration of terminal alkenes

Hydroboration has also been achieved using a boron-based catalyst. Fontaine and co-workers found that aminoboranes undergo hydroboration with indoles **34**, followed by σ-bond metathesis with HBpin to give the 1,2-dihydroindoles **35** with Markovnikov regioselectivity and regeneration of the catalyst (Scheme 11).[43] Further study showed that borane was a more efficient catalyst and allowed for easier purification of the borylated products, due to quantitative conversion.



Scheme 11: Borane-catalysed dearomative hydroboration of indoles

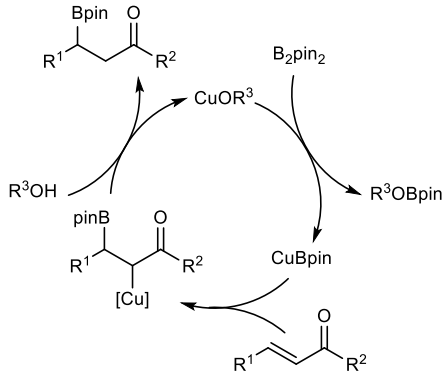
Lautens and co-workers have also applied hydroboration to the direct synthesis of borylated lactams using a carbamoyl chloride to intercept the alkyl cuprate, leading to lactam formation (Scheme 12).[44] The >20:1 *cis*-diastereoselectivity they observed is rationalised by the bond rotation to the thermodynamically favourable transition state after *syn*-insertion across the double bond. In the case of lactam **42** only two diastereoisomers were observed by ^{1}H NMR analysis, with the completely *syn* product being identified as major by NOSEY experiments, with no reference to other diastereoisomers formed.



Scheme 12: Intramolecular cyclisation triggered by hydroboration

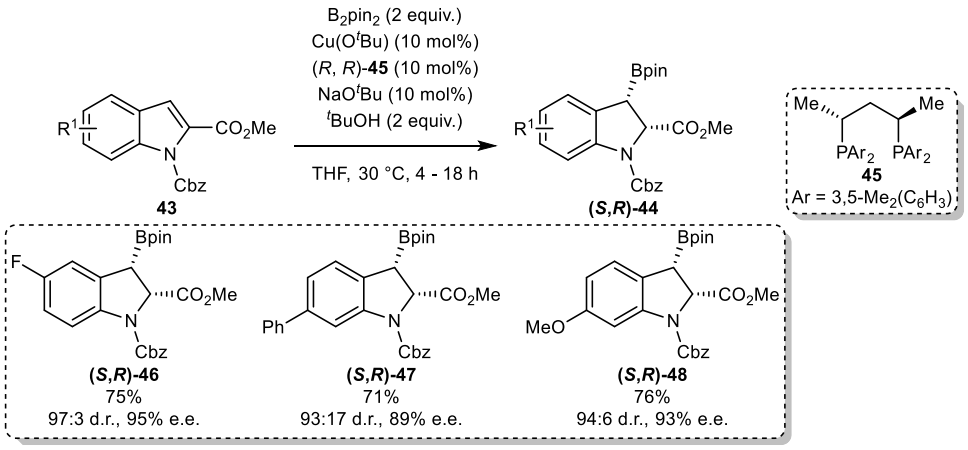
1.2.2 Conjugate Borylation

Conjugate borylation, similar to some hydroboration methods, uses metal catalysis to generate a weak boron nucleophile. Due to its weakly nucleophilic nature it is able to partake in Michael additions with electron deficient acceptors at the β position.[45] A proposed catalytic cycle is outlined in Scheme 13 with formation of the key boryl cuprate thought to occur through σ-bond metathesis between the alkoxy cuprate and diboron reagent. Ligation of the Cu to the alkene triggers the 1,4-addition to generate the β-borylalkyl cuprate which will react with an alcohol additive to yield the product and the regenerate the alkoxy cuprate.



Scheme 13: Conjugate borylation catalytic cycle

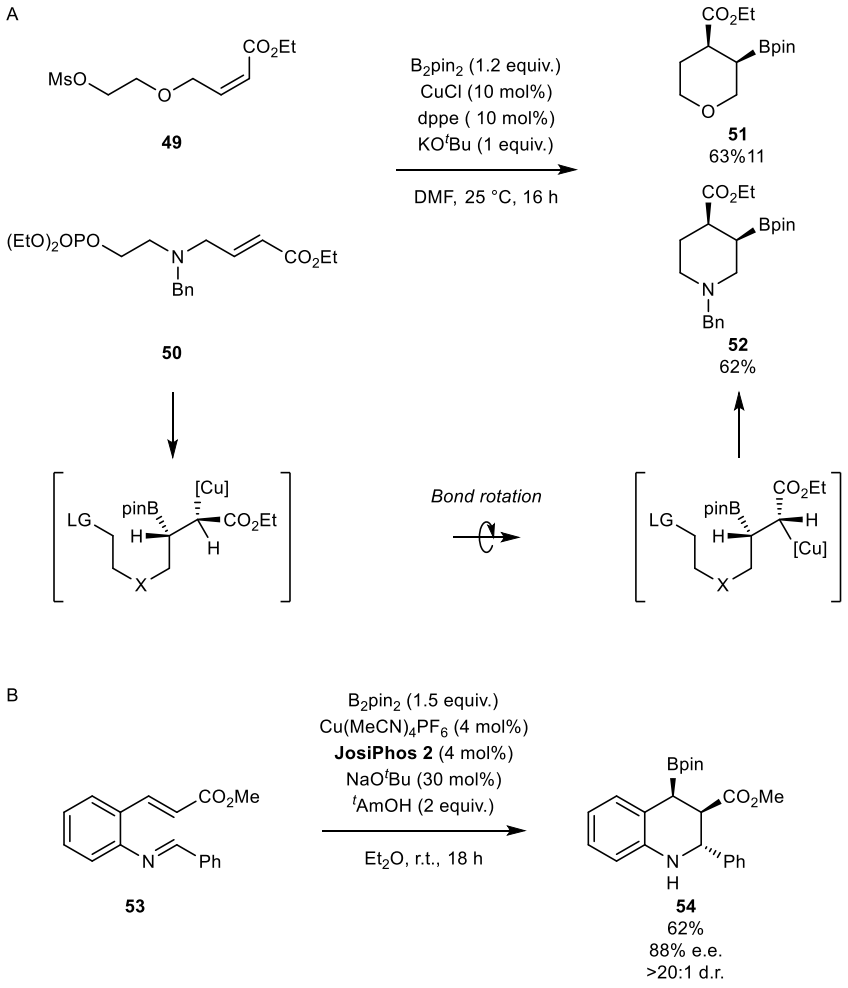
Ito and co-workers initially applied this reaction to the synthesis of *cis*-borylated dihydroindoles (**44**), imparting enantioselectivity with chiral bisphosphine ligand **45** (Scheme 14).[46] This study showed that the methodology was general in providing excellent enantio- and diastereoselectivity, although *N*-methylated and Fmoc protected indoles failed to participate in the reaction. Similar work was reported by Xu and co-workers showing that ketone and nitrile functionalities could be used as the electron withdrawing functionalities.[47]



Scheme 14: Enantioselective conjugate borylation of indoles

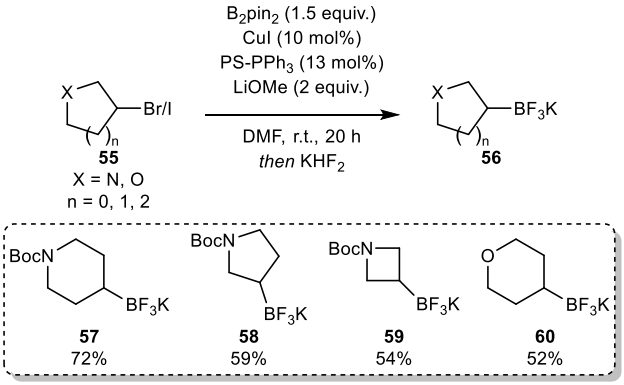
Alcoholysis is not the only route in which the alkoxy cuprate can be regenerated to continue the catalytic cycle. Pendent mesylates or phosphonates feature an electrophilic α carbon which can be used to turn over the catalyst. Zhong and co-workers were able to force an intramolecular cyclisation of enoates (**49** and **50**) to give *cis*-borylated heterocycles (**51** and **52**) using these internal electrophiles (Scheme 15A).[48] Mechanistic investigation suggest that the turnover limiting step of the reaction is addition of the boryl cuprate, and the diastereoselectivity of ring closure is controlled through the coordination of the enolate oxygen to the boron atom.

Lautens and co-workers have also reported an intramolecular cyclisation that is triggered via conjugate borylation. They were able to prepare tetrahydroquinolines (**54**) through a Mannich cyclisation with the alkyl cuprate formed from borylation (Scheme 15B).[49] Again coordination between the carbonyl and boron is thought to help explain the observed completely *syn*-relationship between the boronic and methyl esters. This helps control the conformation of the alkyl cuprate, which undergoes Mannich cyclisation, presumably through a half-chair transition state, to give the major product where there is a *trans* relationship between the ester and phenyl groups. No reference to other diastereoisomers was given by the authors.



Scheme 15: Intramolecular cyclisation of enoates via conjugate borylation

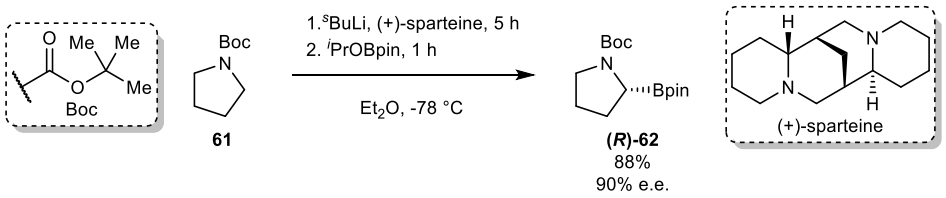
The previously mentioned weak boryl nucleophile generated through Cu catalysis has also been shown to take part in substitution reactions.[50,51] Molander and co-workers used this methodology to prepare borylated piperidines, pyrroles, azetidines, tetrahydropyrans, and oxetanes from the corresponding alkyl bromide or iodide (**55**) moderate yields (Scheme 16).[52] Although not a conjugate borylation, the reactivity profile of this transformation is comparable.



Scheme 16: Synthesis of borylated heterocycles by nucleophilic substitution.

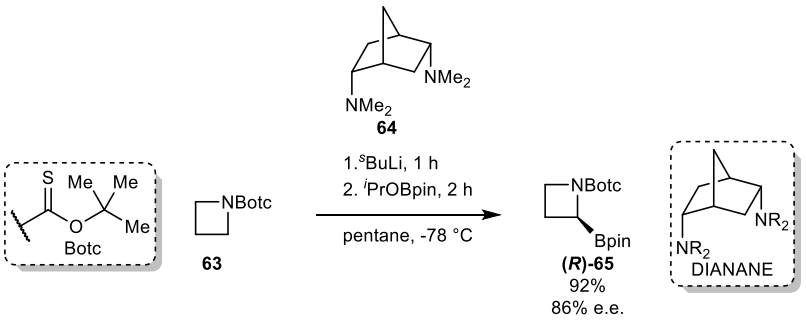
1.2.3 Lithiation-Borylation and Homologation

Using lithium bases to generate nucleophiles for addition to boron has also been proven to be a useful technique to prepare borylated heterocycles. When treated with *sec*-butyl lithium, *N*-Boc pyrrolidine **61** is deprotonated α to the nitrogen, and the subsequent organolithium can undergo addition to the borate reagent. Including a chiral diamine ligand such as sparteine enables the deprotonation step to occur enantioselectively. The final boronic ester (**62**) is generated through hydrolysis of the boronate anion (Scheme 17).[53,54]



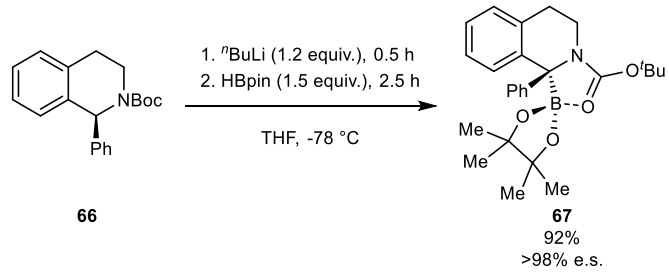
Scheme 17: Enantioselective borylation of pyrrolidine

Due to the high cost and fluctuation in the availability of sparteine, researchers have tested a number of diamine ligands for asymmetric lithiation reactions, notably DIANANE ligands.[55] Hodgson and co-workers used DIANANE **64** to borylate *tert*-butoxythiocarbonyl (Botc) protected azetidine yielding the enantioenriched building block **65** (Scheme 18).[56] It is notable that the Botc protecting group is used due to its superior directing effects, compared with other carbamates, leading to greater enantioselectivity for azetidines.[57]



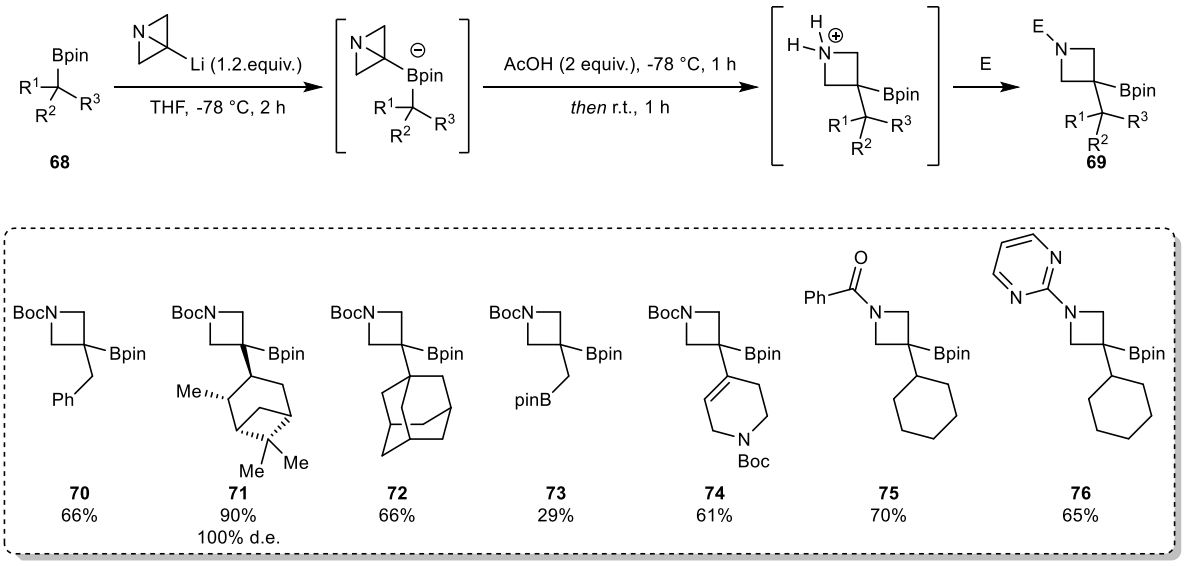
Scheme 18: Preparation of enantioenriched boryl azetidine

However, the *tert*-butoxycarbonyl (Boc) group is still a useful directing group for the α-deprotonation of azacycles due to the configurational stability of the organolithium intermediates; as well as extending stabilisation to the boronate. Enantioenriched Boc protected tetrahydroisoquinoline **66** has been borylated using this methodology (Scheme 19).[58]



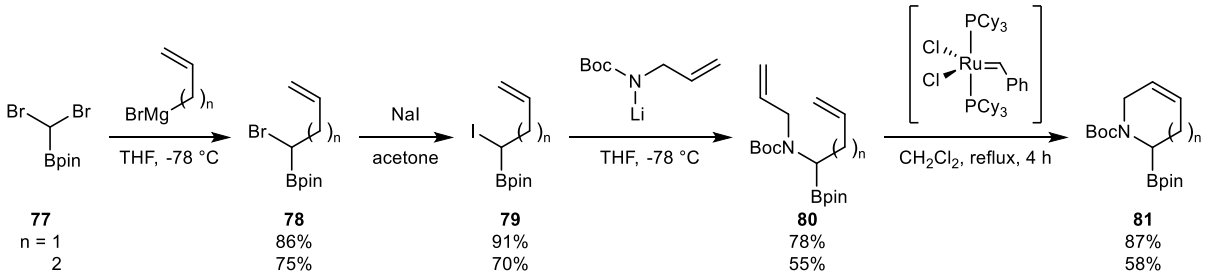
Scheme 19: Enantiospecific borylation of Boc protected tetrahydroisoquinoline

Alkyl lithiums will also attack the boron centre of boronic esters forming a borate anion. If there is a sufficient leaving group α to the newly formed C-B bond, this addition triggers a 1,2-migration. This sequence is called homologation and was exploited in the synthesis of a range of 3° azetidine boronic esters by Aggarwal and co-workers.[59] Although the nitrogen atom of the azabicyclo[1.1.0]butane is not a formal leaving group, it will undergo 1,2-migration upon protonation through a strain release driven process (Scheme 20). It was also shown that other electrophilic functionalisation of the nitrogen, beyond Boc protection, could be used; notably S_NAr reactions (**76**).



Scheme 20: Strain release driven borylation of azabicyclo[1.1.0]butane

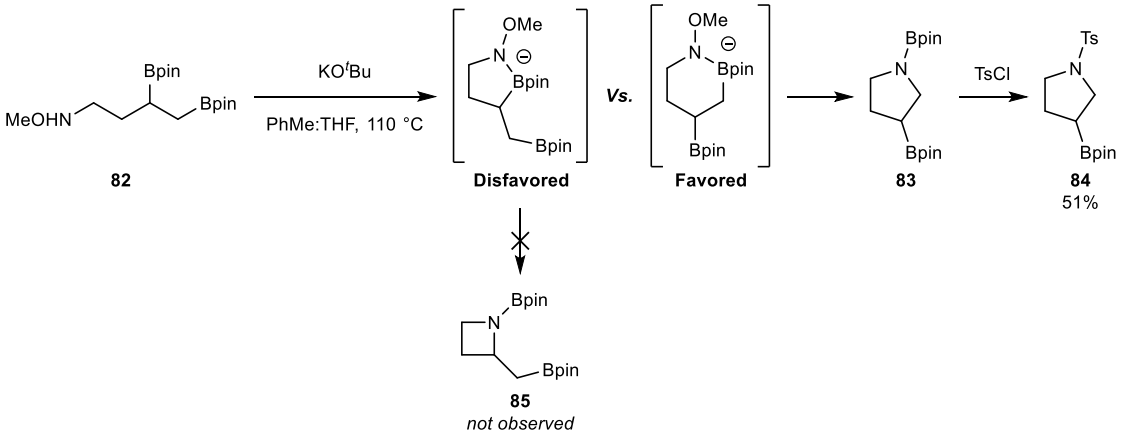
Homologations have also been useful in the preparation of substrates that can be transformed into borylated heterocycles. Carboni and co-workers used Matteson homologation to synthesise α-halo boronic esters, which upon treatment with a lithium amide gave the corresponding α-aminoboronates featuring pendent alkenes (**80**) (Scheme 21). Using ring closing metathesis they were able to prepare a range of borylated cyclic allylic amines **81**.[60]



77 n = 1, 2 | **78** 86%, 75% | **79** 91%, 70% | **80** 78%, 55% | **81** 87%, 58%

Scheme 21: Matteson homologation/ring closing metathesis route to borylated cyclic allylic amines

Homologations do not always require strong alkyl lithium bases if the proton being removed has a low enough pKa. Continuing from their studies of the amination of boronic esters using electrophilic amines under basic conditions, Morken and co-workers turned their attention to intramolecular cyclisations.[53-55] Whilst studying the regioselectivity of the reaction, they showed that the 6-membered ring intermediate, formed upon treatment of amine **82** with potassium *tert*-butoxide, furnished borylated pyrrolidine **84**, not azetidine **85** (Scheme 22).

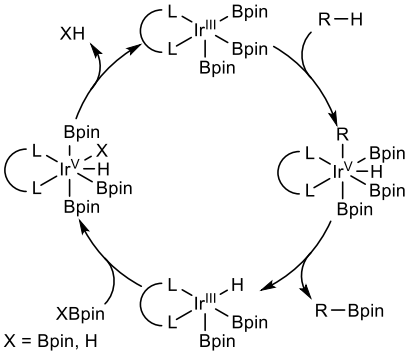


82 | **Disfavored** | **Favored** | **83** | **84** 51% | **85** *not observed*

Scheme 22: Regioselectivity in nitrogen centred homologations

1.2.4 C-H Borylation

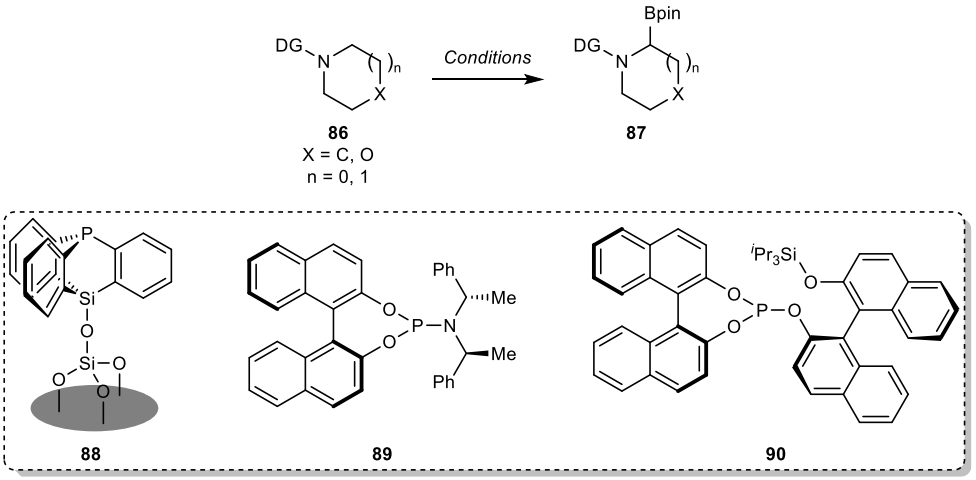
C-H activation is an appealing methodology for borylation as the substrates typically require no pre-functionalisation, and so potentially can be applied to late-stage modification of complex molecules. Given the possible onward reactivity of boronic acid derivatives, C-H borylation has been used in multiple studies to prepare borylated heterocycles. The catalysts used in these reactions are usually electron-rich late transition metals such as the Pt group of metals (Ir, Os, Pd, Pt, Rh and Ru) and the catalytic cycle typically follows a M^n/M^{n+2} pathway where polyboryl M^n is the active catalyst. The proposed catalytic cycle of Ir-catalysed C-H borylation is shown below (Scheme 23).[64] The active catalyst, generated by the addition of B_2pin_2 to the pre-catalyst, undergoes oxidative addition with the C-H, followed by reductive elimination of product. Regeneration of the active catalyst is achieved by oxidative addition of B_2pin_2 (or the HBpin by-product) followed by reductive elimination of HBpin (or H_2 if oxidative addition with the by-product occurred).



Scheme 23: Ir catalysed C-H borylation

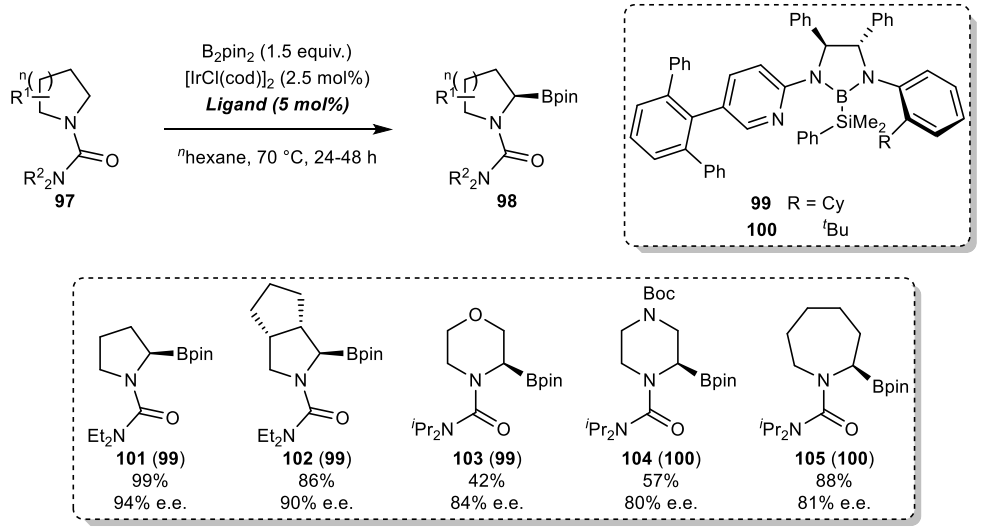
The regioselectivity of C-H borylation can be dependent on multiple factors including sterics, electronics and C-H bond strengths. One of the most effective methods for controlling the regioselectivity is by way of a directing group. Amides, hydrosilanes, pyridines and ureas have all been shown to be efficient directing group for the C-H borylation of azacycles.

Sawamura and co-workers achieved *N*-adjacent borylation of cyclic amides and amines using Rh catalysis ligated with silica-supported triaryl phosphine **88** (Scheme 24A).[65] Due to the formation of HBpin as a by-product in the reaction and its suitability as a coupling partner, they found that using B_2pin_2 in sub-stoichiometric amounts yields above 100% where observed (relative to the diboron reagent). Following on from this work they were able to impart moderate enantioselectivity using phosphoramidite ligand **89** and expanded the scope to the synthesis of a borylated morpholine **(+)-95** (Scheme 24B).[66] Significant improvement of the enantioselectivity was achieved using monophosphite ligand **90** (Scheme 24C).[67] Similar pyridine directed borylations have been reported by Ackermann and co-workers using Ru catalysis.[68]



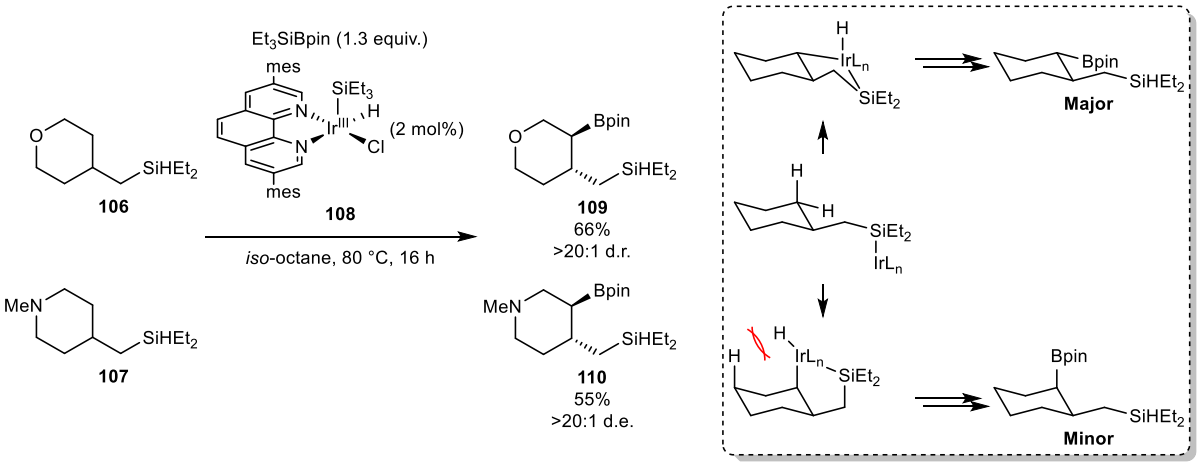
Scheme 24: C-H borylation of azacycles using amide and pyridine directing groups

Xu and co-workers developed their own novel chiral bidentate boryl ligands (**99** and **100**) for enantioselective Ir-catalysed sp^3 C-H borylation.[69] Although the yields and stereoselectivity of this work are comparable to the methods described by Sawamura, the number of sp^3-rich boryl-azacycles that they were able to prepare is significant (Scheme 25).



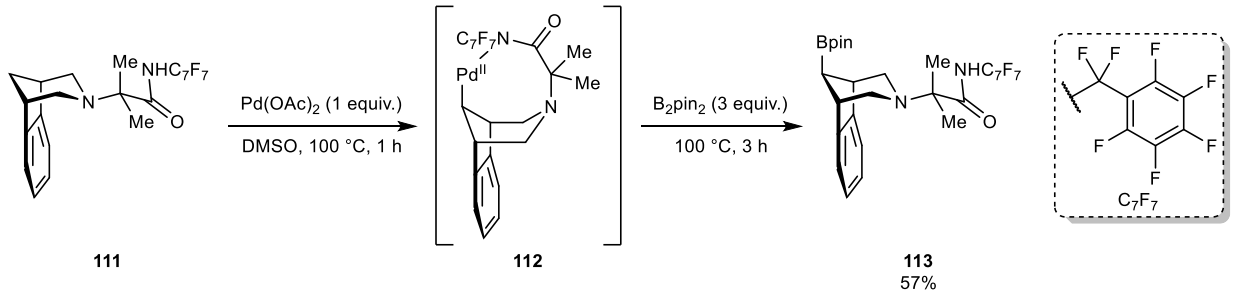
Scheme 25: Diverse enantioselective C-H borylation of saturated azacycles

Hartwig and co-workers showed that hydrosilyl groups could be used for γ-directed C-H activation using an Ir catalyst.[70] When using borylsilane, $Et_3SiBpin$, as the boron reagent superior yields were obtained due to efficient generation of the active catalyst when compared to B_2pin_2. Boryl-piperidines and oxanes where only isolated in modest yields due to bis-borylation occurring (Scheme 26). The excellent diastereoselectivity of this reaction is attributed to the metal's preference to sit in a pseudo equatorial position in the transition state leading to *anti*-selectivity.



Scheme 26: C-H borylation of heterocycles using a hydrosilyl directing group

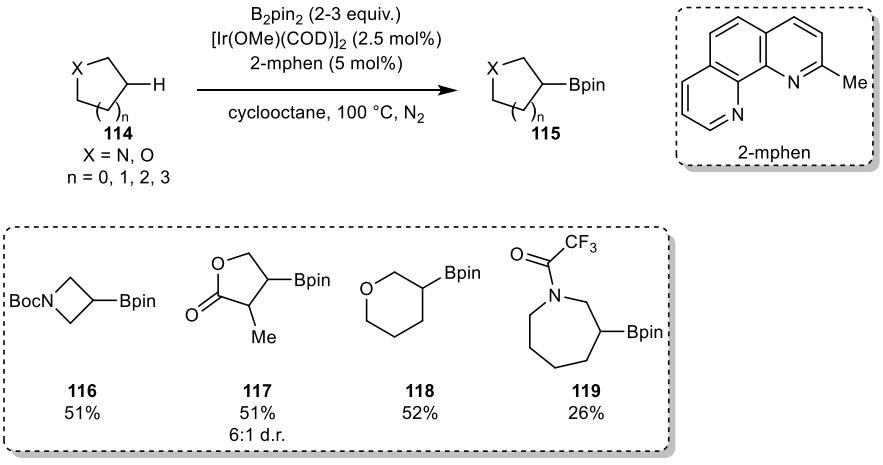
When a directing group is bound to a nitrogen, activation typically occurs on the adjacent α-CH, which led Aguilera and Sanford to develop a γ-directed methodology using Pd (Scheme 27).[71] Previous methods to achieve this goal involve either sterically blocking the αC-H or deactivating via protonation of the amine. However, they were able to use a pendent fluorinated amide as the directing group to initiate Cγ-H activation, proposed to occur through the formation of boat-like transition state **112**. After preformation of this intermediate, it was found to be reactive with a range of electrophiles, including B_2pin_2.



111 **112** **113** 57%

Scheme 27: γ-Directed C-H borylation

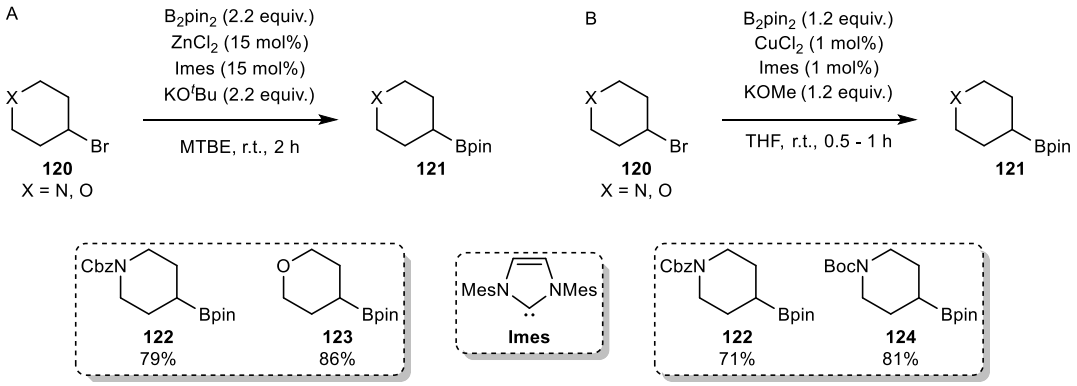
C-H activation of heterocycles typically favours C-H bonds α to heteroatom due to the weaker bond strength. Using a phenanthroline-ligated Ir catalyst, Hartwig and co-workers reported the remarkable undirected borylation of saturated heterocycles which occurred at the β and γ positions (Scheme 28).[72] Although diastereoselectivity for the borylation of substituted heterocycles is poor, improved *syn*-selectivity of the more conformationally rigid tetrahydropyran **117** suggests the catalyst preferentially reacts at an equatorial C-H bond. The true origin of this reaction selectivity is not fully understood. Computational studies of similar reactions suggest the C-H activation at the α-position is reversible but that the energy barrier for borylation at this position is too high, instead promoting borylation at the β-position.[73]



Scheme 28: Undirected Cβ/γ-H borylation of saturated heterocycles

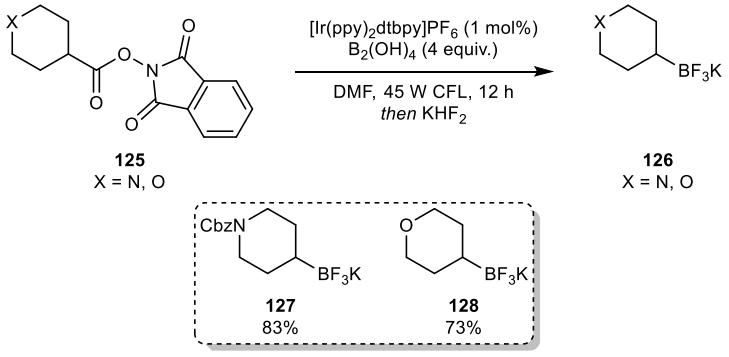
1.2.5 Radical Borylation

Generation of radical species for the formation of carbon-boron bonds is another powerful strategy for the formation of borylated heterocycles, with the major advantage being the high functional group tolerance. The use of catalytic Zn^{II} by Marder and co-workers provided the first example of this and although not conclusive, the demonstration of a radical clock experiment strongly suggests the reaction involves the formation of a radical (Scheme 29A).[74] A similar catalytic pathway was also shown to be achievable using a Cu^{II} catalyst (Scheme 29B).[75] With both reactions it is not clear whether homolytic cleavage of the C-X bond initiates the reaction, or the generation of an unobserved radical boryl species.



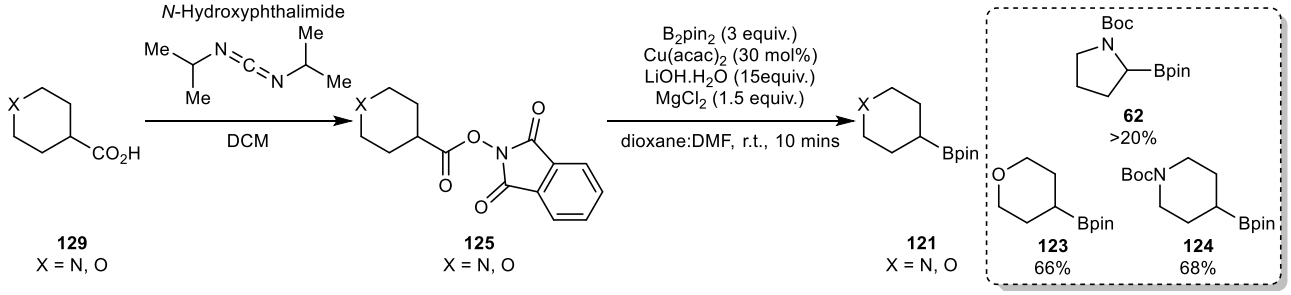
Scheme 29: Radical borylation methods reported by Marder and co-workers

The mechanism for the addition of alkyl radical species to boron reagents has been more thoroughly documented within the literature. The most prominent methodologies employ photocatalysed decarboxylation to generate an alkyl radical, typically this is done through the activation of a carboxylic acid redox active esters such as *N*-acyloxyphthalimides (Scheme 30).[76,77]



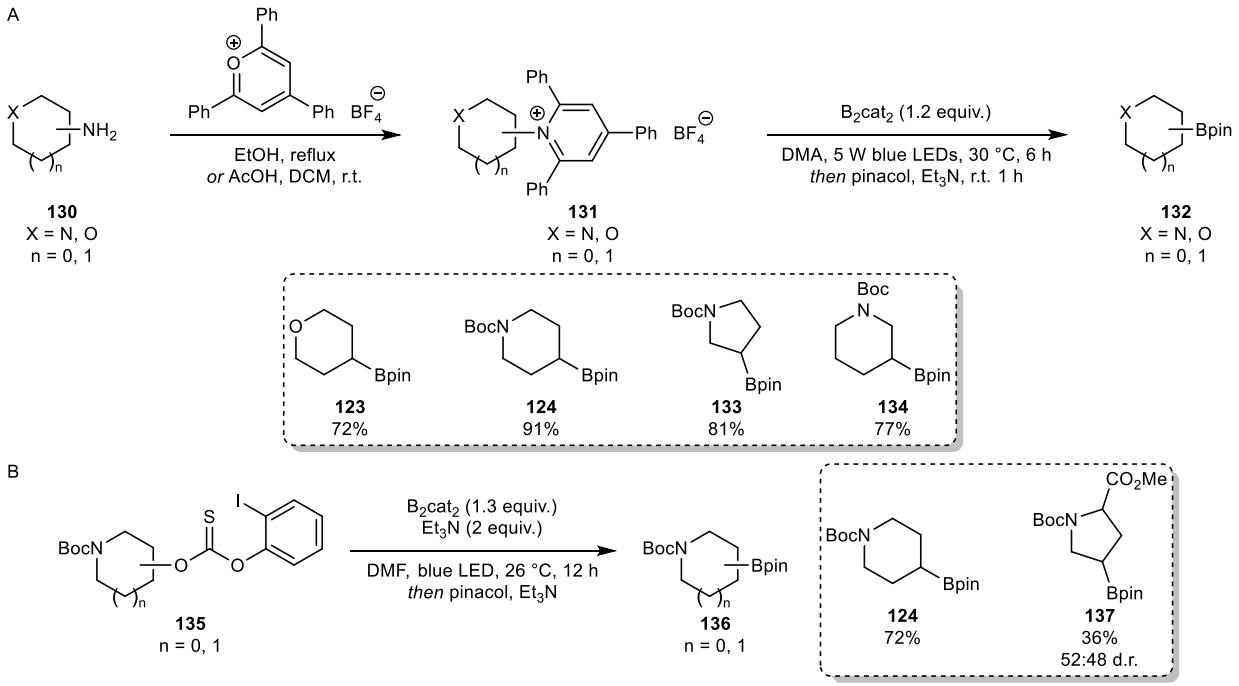
Scheme 30: Ir catalysed radical borylation of *N*-acyloxyphthalimides

Baran and co-workers found that the same precursors could generate alkyl radicals, which could be borylated using a Cu^{II} catalyst under basic conditions without promotion by light (Scheme 31).[78] The mechanism of this transformation is believed to occur by formation of a Cu^{I} boryl species that promotes a SET with the phthalimide substrate. This generates both a Cu^{II} boryl species and an alkyl radical, with the former being able to borylate the radical and regenerate the Cu^{I} catalyst. The report by Baran and co-workers suggests that radical α-borylation of heterocycles is less efficient than CH-activation and lithiation strategies.



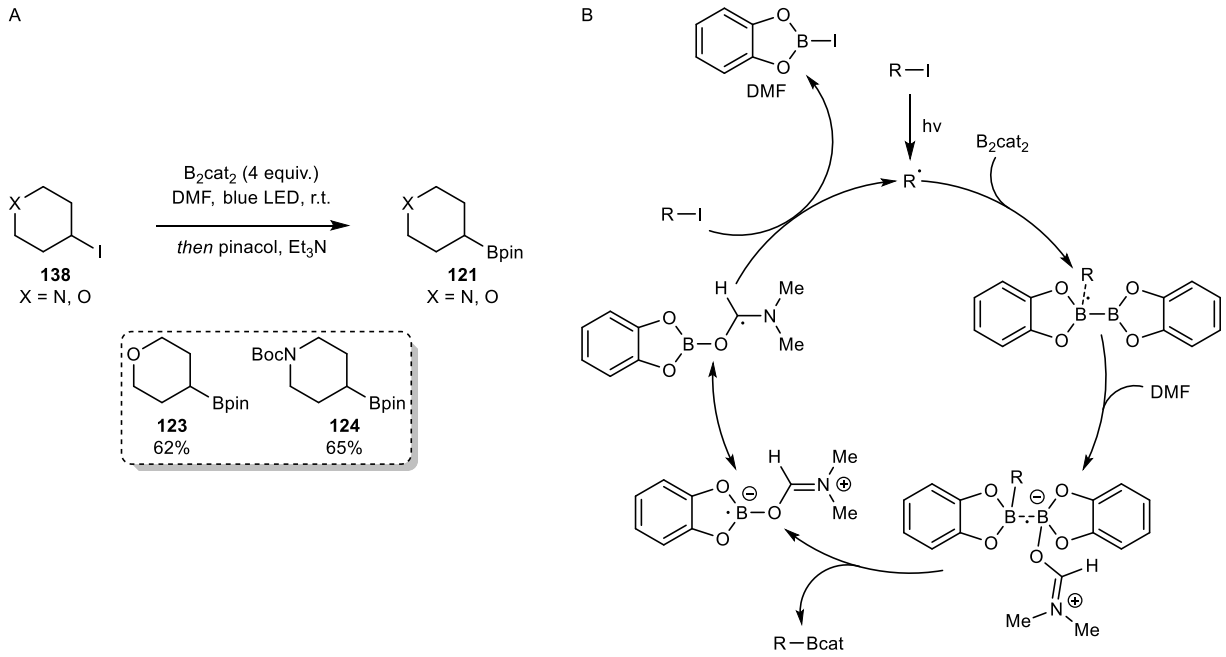
Scheme 31: Cu-catalysed radical borylation of *N*-acyloxyphthalimides

Other functional groups can be activated in order to undergo light-mediated radical borylation; amines can be converted to Katritzky salts through the reaction with pyrylium salts (Scheme 32A)[79,80]: in addition, alcohols can be converted to the photo-active xanthate functionality (Scheme 32B).[81,82] In both of these methods bis(catechol)diboron (B_2cat_2) is required as the boron reagent and then converted to the pinacol ester through transesterification. This is due to the increased ability of catecholboranes to stabilise the radical through delocalisation over π-orbitals.[83]



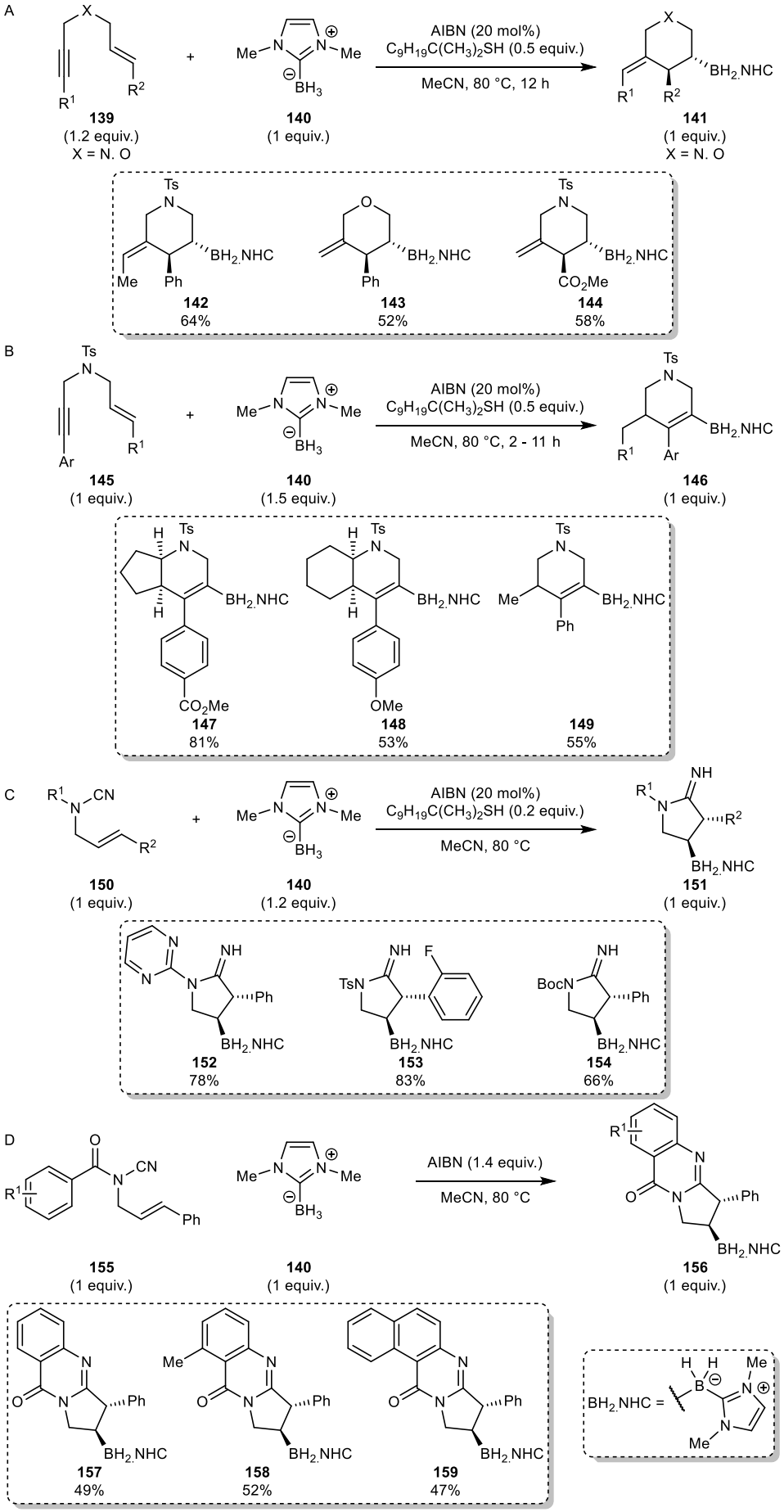
Scheme 32: Radical borylation of alkyl Katritzky salts and xanthates

It is also possible to perform transition metal free radical borylations without "pre-functionalisation" of the substrate. Struder and co-workers were able to homolytically cleave carbon-iodine bonds to generate alkyl radical for borylation using just visible light in DMF (Scheme 33A).[84] After addition of the radical to B_2cat_2, DMF traps out the boryl radical promoting carbon-boron bond formation and breaking of the one electron σ-bond (Scheme 33B).



Scheme 33: Radical borylation of alkyl iodides

Boron-centred radicals can also be utilised in the synthesis of heterocycles. Wang and co-workers used a nucleophilic NHC-stabilised boryl radical, generated from borane complex **140** with a radical initiator, for the cascade cyclisation of enynes. The electronic properties of the unsaturated carbon bonds dictate the regioselectivity within the reaction, with the boryl addition occurring at the most electron deficient position. Addition to enoates and styrenes **139** formed completely saturated heterocycles **141** (Scheme 34A), whereas addition to phenyl acetylenes **145** gave borylated alkenyl heterocycles **146** (Scheme 34B).[85] As a continuation to this work they also disclosed that *N*-allylcyanamides **150** and **155** could be used to form cyclic amidines **151** and quinazolinones **156** respectively (Scheme 34C, D).[86] All 3 reports showed that the products could be converted into the more synthetically useful pinacol ester.

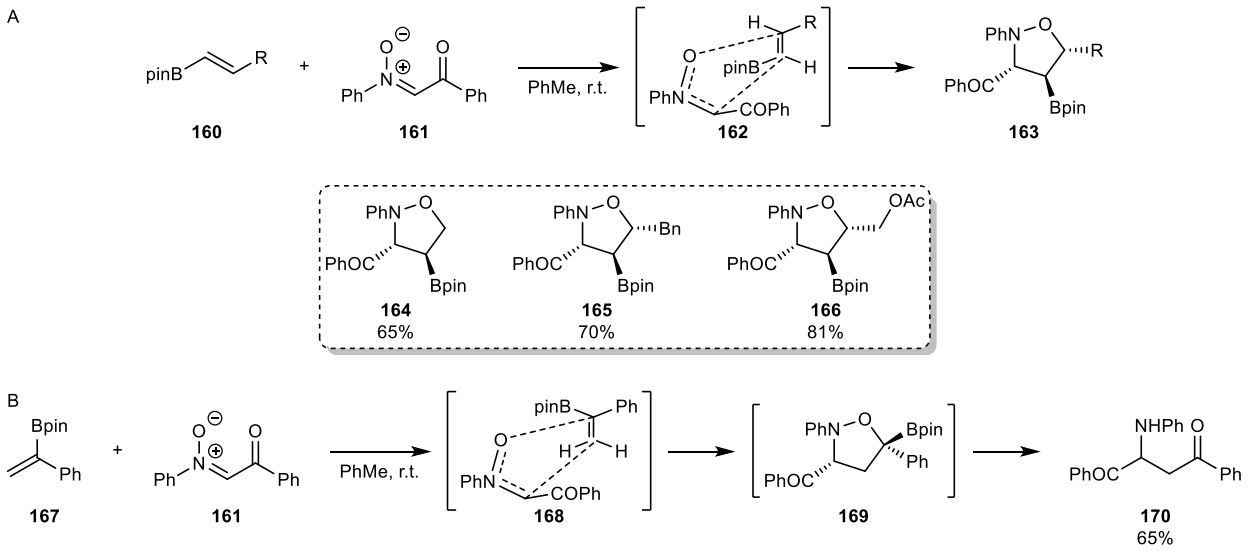


Scheme 34: Sythesis of heterocycles using boryl centred radicals

1.2.6 Cycloadditions

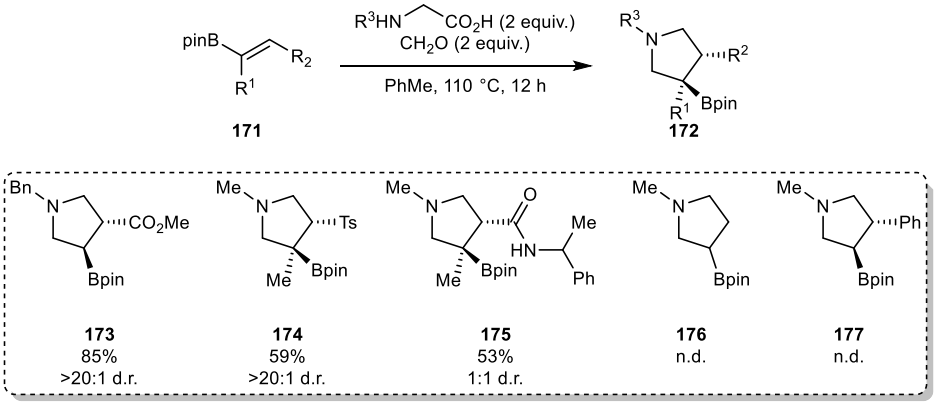
Alkenes have a similar reactivity profile to aromatics, and methods like Miyaura type borylation are applicable to the synthesis of vinyl boronates.[87] These vinyl substrates can also be prepared through hydroboration of alkynes using various catalytic systems.[88] Multiple 1,3-dipolar-cycloaddition protocols have been developed for the coupling of alkenes with ylides to form new heterocycles.[89] Given the plethora of vinyl boronates available as building blocks, cycloadditions have also been explored as a route to novel sp^3-rich borylated heterocycles.

An early study by Carboni and co-workers found that the regioselectivity of cycloaddition for vinyl boronates **160** with nitrone **161** was crucial. For the majority of substrates a dominant transition state is preferred leading to complete regio- and stereo-selectivity (Scheme 35A).[90] However, when a 1,1-substituted vinyl boronate **167** was used instead, the regioselectivity was flipped giving rise to 5-boryl-1,2-oxazolidine **169**. Due to the boron being α to oxygen, this compound was prone to aerobic oxidation and subsequent ring opening (Scheme 35B).



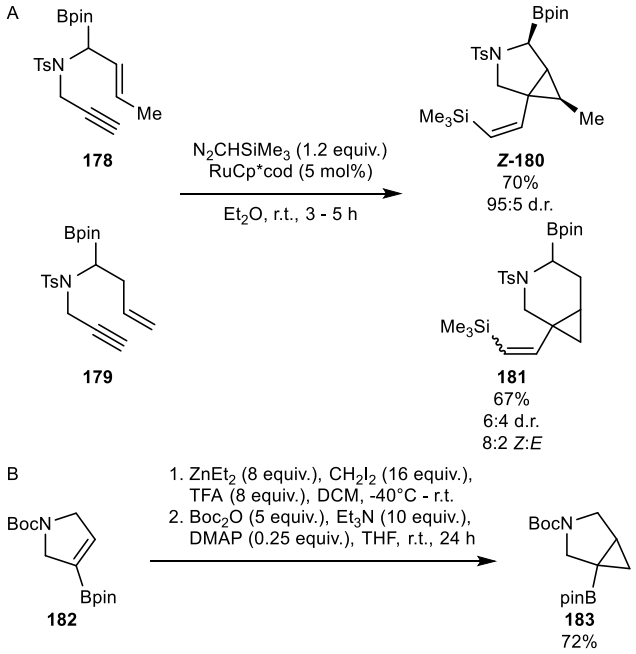
Scheme 35: Cycloaddition of vinyl boronates with isoazolidines

Less exotic boryl pyrrolidines can be formed using azomethine ylides generated from the decarboxylation of amino acids with formaldehyde. As shown by Carboni and co-workers, this cycloaddition could only take place if the vinyl boronate **171** features an electron withdrawing group (ester, sulfone or amide) to activate the alkene. When tested monosubstituted vinyl boronate and styrylboronate failed to yield the desired cycloadduct (Scheme 36).[91] In the case pyrrolidine **175** the lack of diastereoselectivity suggests the cycloaddition does not occur through a concerted mechanism.



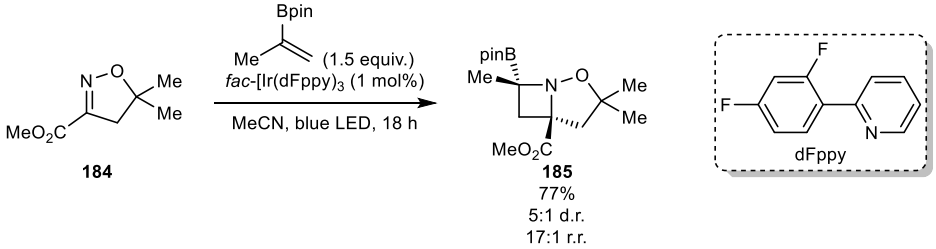
Scheme 36: Cycloaddition of vinyl boronates with azomethine

Cycloadditions are not limited to 1,3-dipoles, Dérien and co-workers used a Rh-catalysed carbene insertion on amino enynes (**178** and **179**) to generate borylated azabicycloheptane scaffolds (**180** and **181**) (Scheme 37A), whilst Harris and co-workers performed Simmons-Smith reactions on cyclic allylic amine **182** in order to obtain similar bicyclic scaffolds **183** (Scheme 37B).[92,93] These are both formally 1,1-dipolar-cycloadditions that occur through the generation of either a carbene or a methylene radical, respectively.



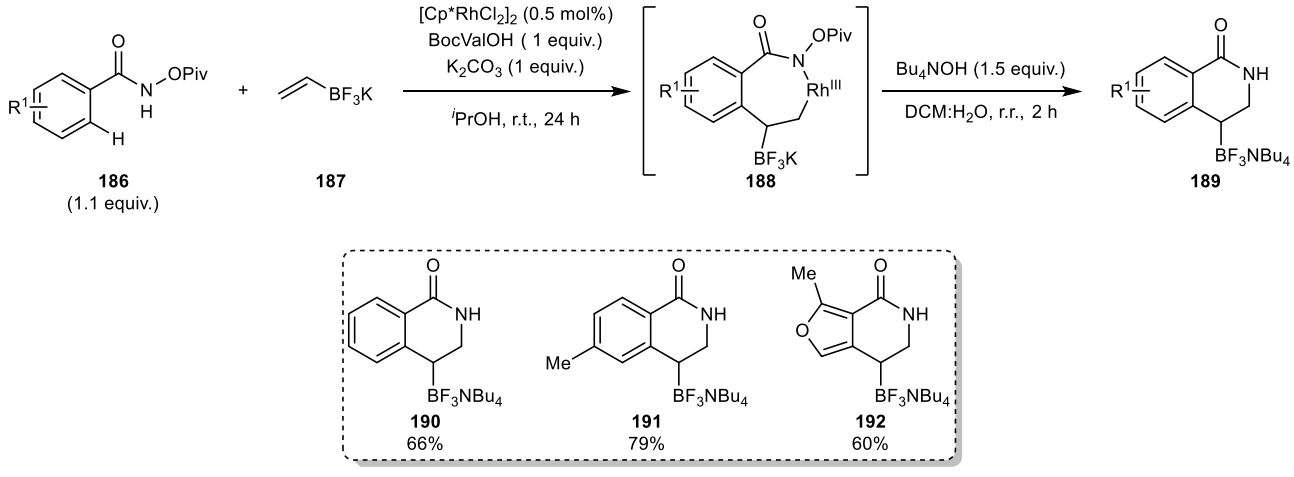
Scheme 37: Synthesis of borylated azabicycloheptane scaffolds

As with other thermally disallowed cycloaddition it is possible to promote cyclisation using a photocatalyst and light irradiation. Schindler and co-workers used an Ir photocatalyst to excite cyclic oximes **184** to the triplet state so that they can take part in a [2+2] cycloaddition with unactivated alkenes (Scheme 38). However, in this work they were able to prepare only a single example of the unusual borylated 2-oxa-1-azabicyclo[3.2.0]heptane scaffold **185**.[94] Again, due to the nature of these reactions, stereoselectivity is at the discretion of the substrate.



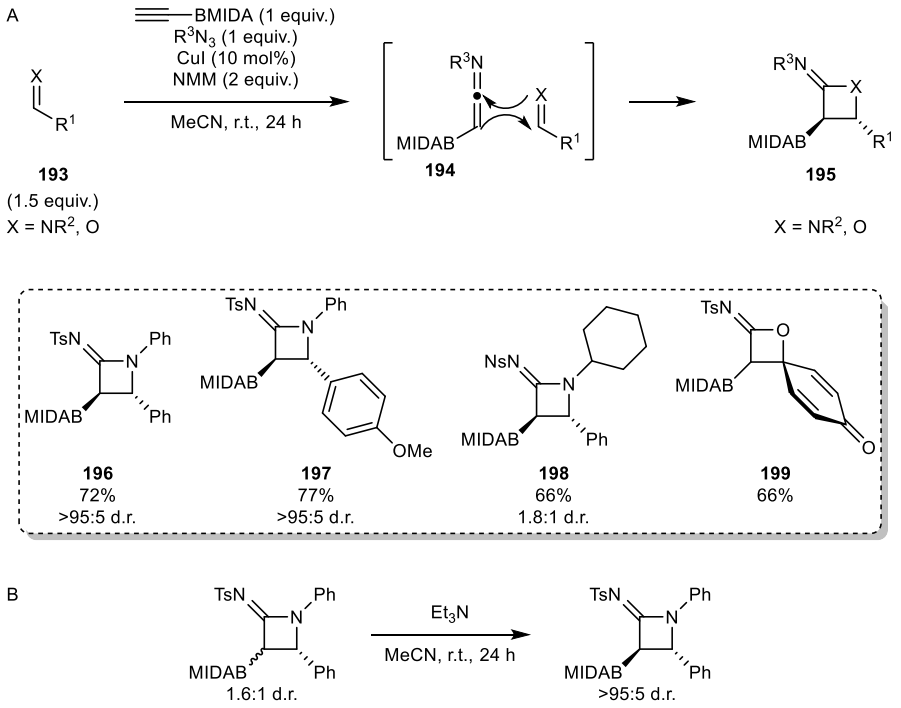
Scheme 38: Photochemical [2+2] cycloaddition for the synthesis of borylated heterocycles

Molander and co-workers used a Rh-catalysed C-H functionalisation to perform a formal [4+2] cycloaddition, or alkene insertion, to prepare boryl tetrahydroisoquinoline **189**.[95] Ligation of Rh to the amido pivalate functionality directed C-H activation to the *ortho* aromatic C-H bond, which can insert into the alkene **187**. The Rh-alkyl intermediate **188** could then undergo C-N reductive elimination and subsequent reoxidation of the Rh through reaction with the weak N-O bond (Scheme 39). The regioselectivity of this reaction is isomeric compared with other alkenes, which is believed to be an electronic effect unique to the reaction. It is also beneficial as it blocks β-hydride elimination, further promoting reoxidation of the catalyst.[96]



Scheme 39: C-H activation of sp^2-H for alkene cycloaddition

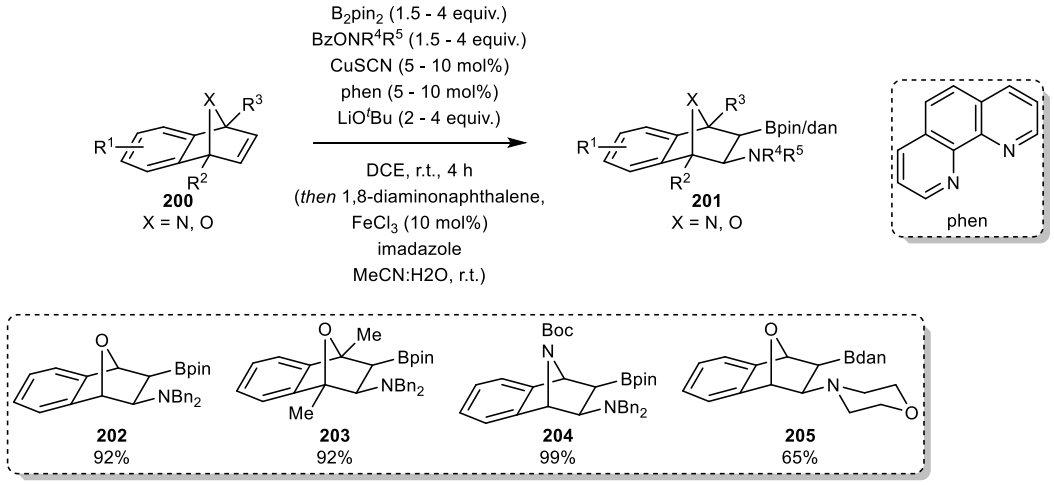
As an extension to the use of vinyl boronates, Yudin and co-workers have developed a route to BMIDA-substituted azetidimines from alkenyl boronates. This relies on formation of a MIDA-borylketenimine intermediate **194** as a linchpin in the Cu-catalysed cycloaddition with imines and ketones to give the boryl-azetidimines and an -oxetanimine **195** (Scheme 40A).[97] The products were obtained in good diastereoselectivity for reaction of *N*,*C*-diaryl substituted imines, conversely *N*-alkyl imines gave poor selectivities. Diastereomeric mixtures can be epimerised using triethylamine to give the thermodynamically favoured product (Scheme 40B).



Scheme 40: Use of Borylketenimine to synthesise boryl-azetidimines and -oxetanimines

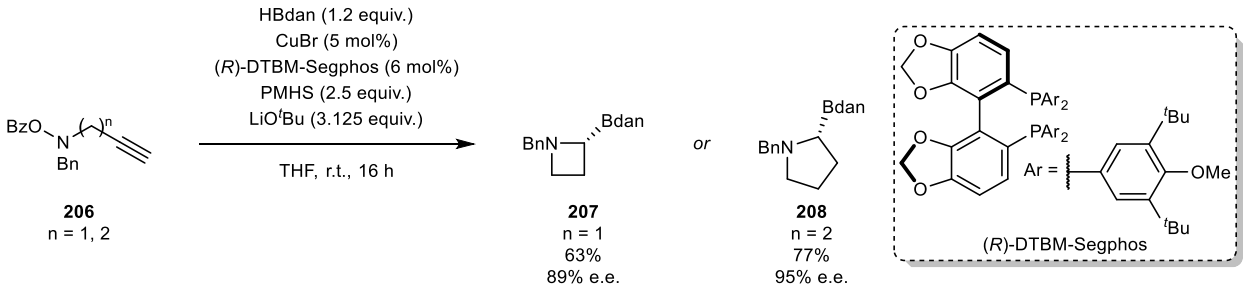
1.2.7 Difunctional Borylations

In the previously mentioned Cu-catalysed borylation reaction elimination of the product and regeneration of the catalyst is usually triggered by the introduction of an electrophile. So far this has been limited to HBpin, B_2pin_2, an alcohol or an internal electrophile. In the pursuit of increasing molecular complexity multiple studies have shown that many electrophiles can take part in such reactions. Miura and co-workers were able to incorporate both the boryl and amino functionalities across hetero-norbornadienes **200** by using electrophilic amine coupling partners (Scheme 43).[98]



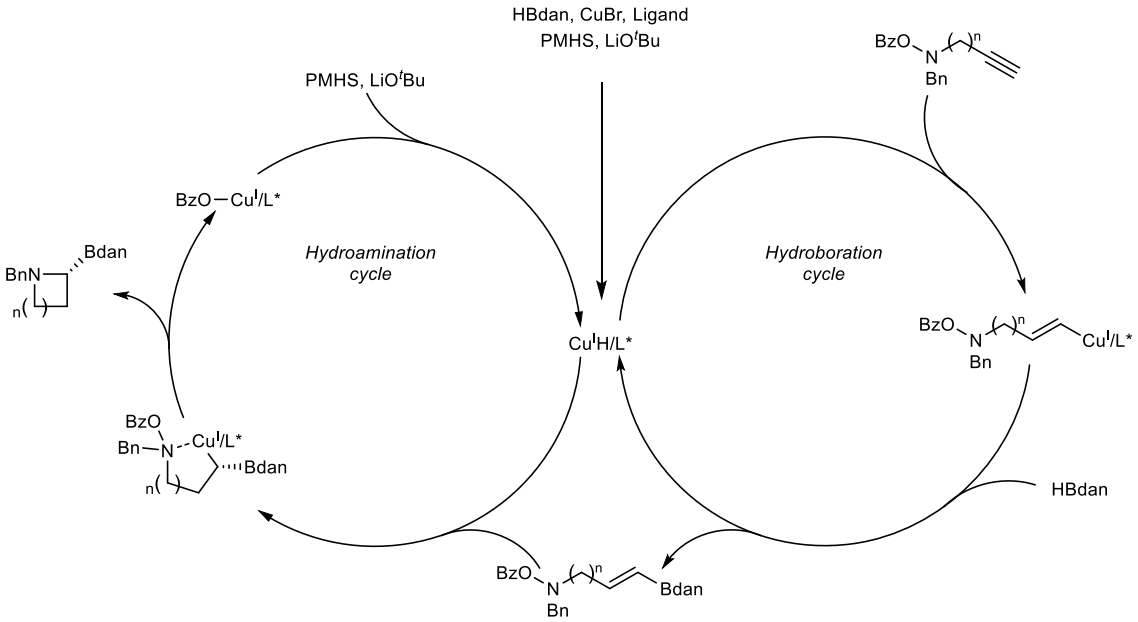
Scheme 41: 1,2-Aminoboration of hetero-norbornadienes

Aminoboration reactions are not limited to 1,2-additions; Engle and co-workers showed that 1,1-difuntionalisation was possible using a sterically encumbered ligand to control the hydroamination.[99] Using an alkyne tethered to an electrophilic amine **206** they were able to form a borylated azetidine **207** and pyrrolidine **208** (Scheme 43).



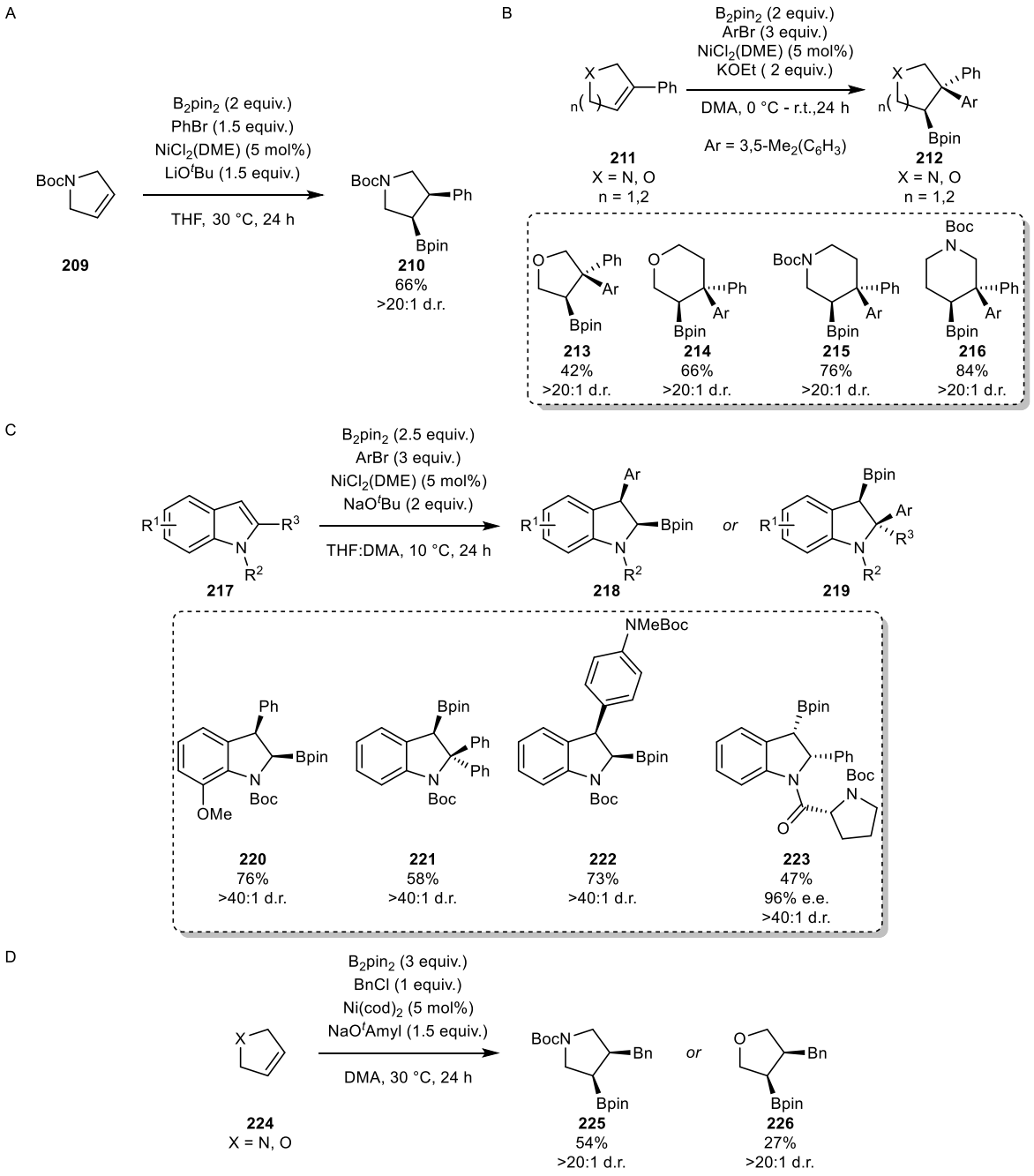
Scheme 42: 1,1-Aminoboration of alkynes featuring penden electrophilic amines

Using HBdan as the boron reagent with a Cu^I catalyst generates a metal hydride that hydroborates an alkyne, the vinyl boronate product can then be subjected to a hydroamination reaction with the same active catalyst (Scheme 43). Regeneration of the catalyst in the hydroamination cycle is achieved through the addition of poly(methylhydrosiloxane) (PMHS).



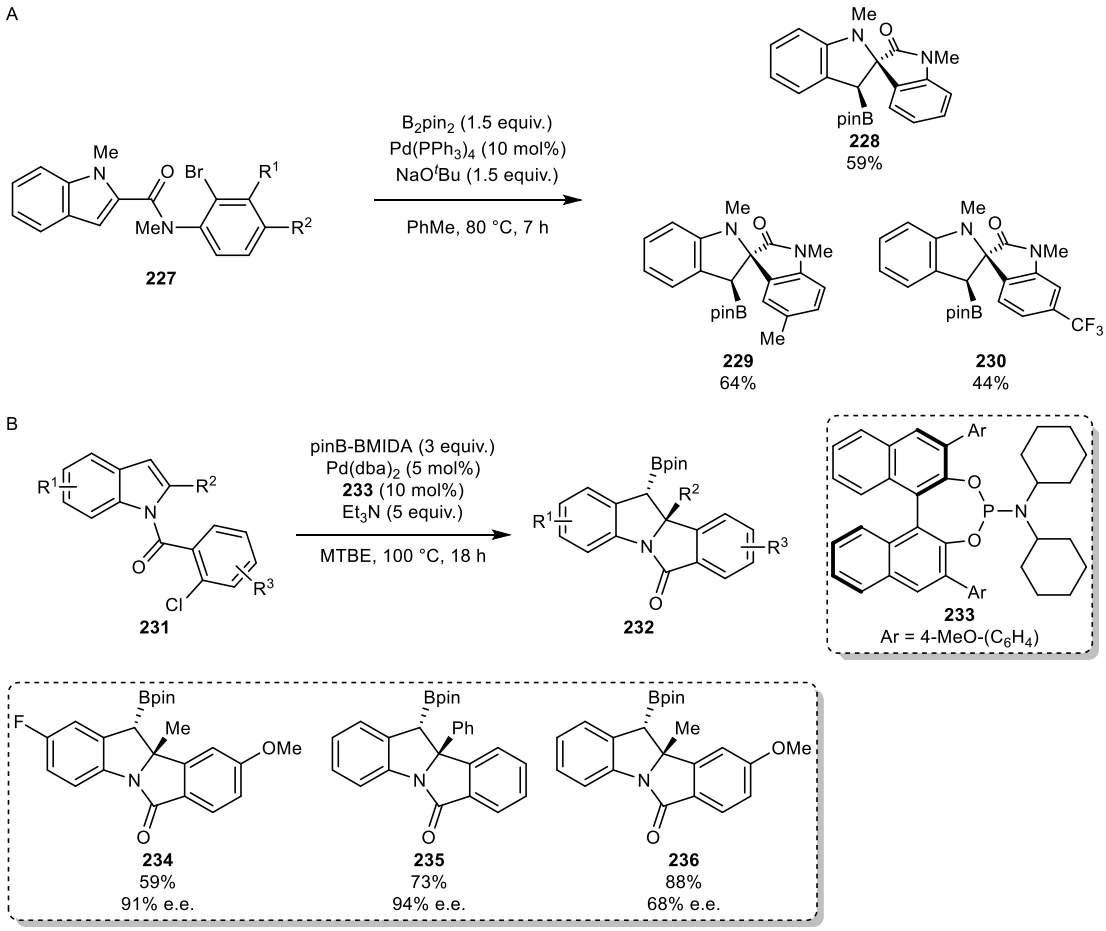
Scheme 43: Combined hydroboration/hydroamination cycle for 1,1-Aminoboration of alkynes

Arylborations are another reaction of interest for the preparation of borylated heterocycles, although due to the large oxidation potential associated with the Cu^I/Cu^{III} cycle, Cu will not undergo oxidative addition aryl halides electrophiles without the use of electron rich ligands.[100] Ni on the other hand has been shown to be a much better catalyst for such reactions. Ni-catalysed arylborations have been shown to work for unactivated cyclic allylic amines **209**, heterocyclic styrenes **211** and indoles **217** (Scheme 44A, B, C).[101–103] In the latter example regioselectivity can be controlled by substituting the indole at the 2 position (**221**) or alternating the position of the protecting group (**223**). The chirality of the substrates not featuring the protecting group on the indole were found to impart enantioselectivity on the reaction (**223**). The low oxidation potential of Ni^I/Ni^{III} has even been shown to be suitable for the oxidative addition of benzyl chloride (Scheme 44D).[104] All examples gave the *syn*-diastereoisomer due to the *syn*-migratory insertion of the boryl Ni catalyst into the alkene.



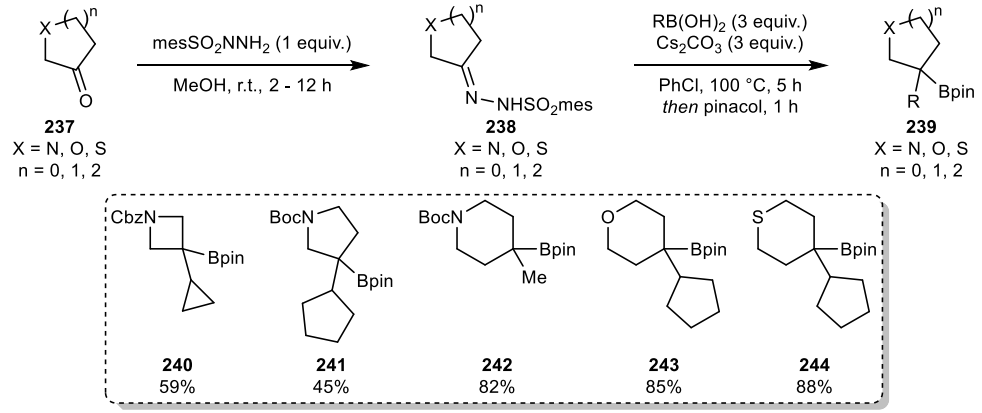
Scheme 44: Ni-catalysed carboborations of alkenes

The groups of Xu and Lautens have both used Pd-catalysed borylation to synthesis scaffolds based on indole. Xu and co-workers showed that in the σ-Pd intermediate of a intra molecular Heck reaction will react with B_2pin_2 to form spirocyclic boronates (Scheme 45A).[105] Lautens and co-workers also employed a Heck reaction to perform arylboration on indole substrates, through the use of a chiral phosphoramidite ligand and diboron reagent they were able to impart enantioselectivity on to the reaction. (Scheme 45B).[106]



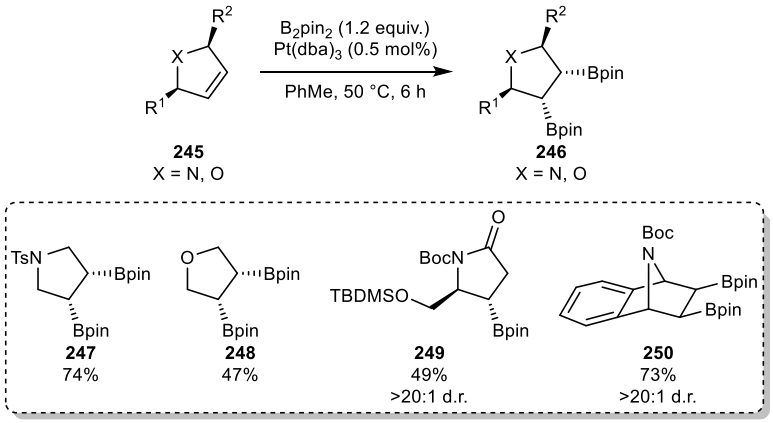
Scheme 45: Pd-catalysed carboborations of alkenes

1,1-Carboboration has also been exploited for the synthesis of heterocyclic boronic esters. Base-promoted decomposition of sulfonylhydrazones **238** leads to the generation of carbene intermediates, which in the presence of a boronic acid, insert into the C-B bond. This cross coupling strategy was utilised by Qin and co-workers in order to form novel 3° heterocyclic boronates **239** (Scheme 46).[107]



Scheme 46: Carbene insertion of heterocycles into boronic acids

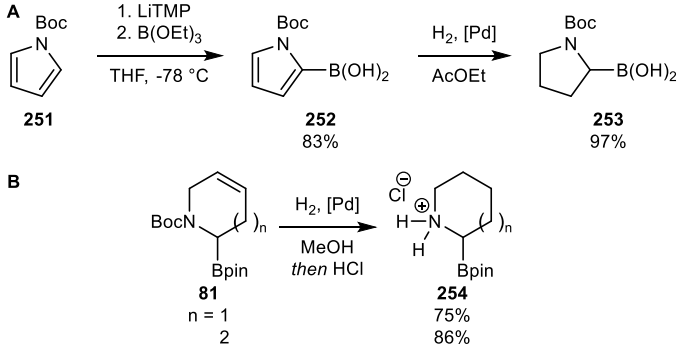
The insertion of two boron functionalities across an unactivated alkene bond has also been reported by Morken and co-worker through a Pt catalysed diborylation (Scheme 47).[108] The origin of the diastereoselectivity of this reaction is believed to be due to the *syn*-addition of the bis-boryl Pt catalyst. It has previously be observed that generation of the active bis-boryl Pt(0) complex from $Pt(PPh_3)_4$ is too slow for insertion in to alkene bond to generate a catalytic cycle, whereas $Pt_2(dba)_3$ serves as a much more efficient pre-catalyst for this transformaton.[109]



Scheme 47: Diborylation of unactivated alkenes

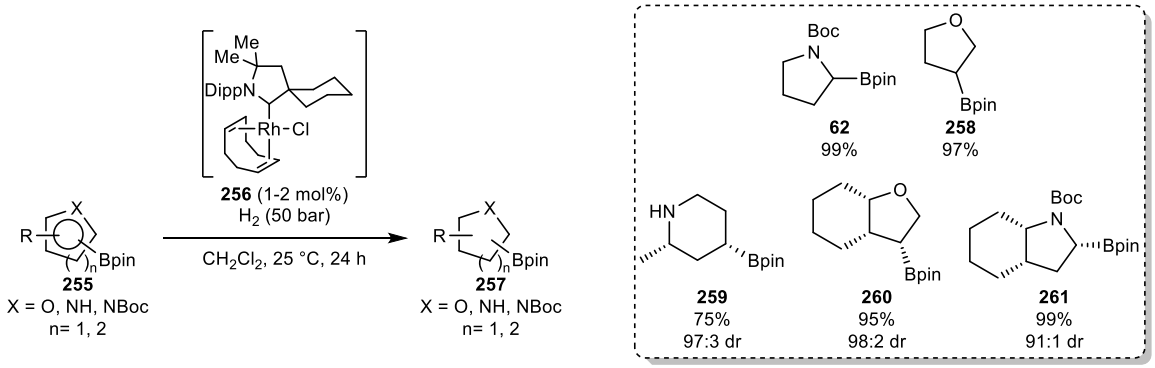
1.2.8 Reduction of sp^2-Rich Heterocycles

Direct reduction of sp^2-rich heterocycles is also an efficient strategy for the synthesis of borylated saturated heterocycles. Given their richness within the literature (Table 1), such methods could be expedient for transforming the wide range of commercially available boronates into sp^3-rich building blocks. One of the earliest reports for the synthesis of a borylated heterocycle was achieved in this manner. Kelly and co-workers employed a lithiation-borylation strategy to prepare *N*-Boc-pyrrole-2-boronic acid (**252**) and reduced it through a Pd-catalysed hydrogenation (Scheme 48A).[110] Similarly, Carboni and co-workers also accomplished hydrogenation of their partially saturated heterocycles (**81**) formed through the cycloaddition reaction discussed earlier (Scheme 48B).[60]



Scheme 48: A. Lithiation-borylation/hydrogenation of pyrrole, B. Hydrogenation of borylated cyclic allylic amine

The most significant work in this area has been undertaken by Glorius and co-workers, who were able to prepare a range of pyrrolidine, piperidines, octahydroindoles and octahydrobenzofurans through Rh-catalysed hydrogenation (Scheme 49).[111,112] They found that the use of a cyclic (alkyl)(amino)carbene (CAAC) ligated Rh catalyst **256** was crucial in this both step-economical and diastereoselective reaction.



Scheme 49: Rh-catalysed reduction of borylated heterocycles

1.3 Conclusions

More than 85% of the of protocols reported previously for the synthesis of saturated borylated heterocycles have been disclosed in the last 10 years, suggesting that the new synthetic methods to prepare this class of building block are of considerable interest to current synthetic chemists. Furthermore, a significant number of the more recent reports also feature concentrated study of the synthetic value of the boronate building blocks, through their elaboration. This indicates that the development of novel borylated scaffolds represents a current interest of synthetic chemists aiming to expand the possibilities of building block design.

Our analysis of boronate building blocks is summarised in Table 1, focusing mainly on mono-nitrogen heterocycles, with borylated benzenes and cyclohexanes for comparison. Initial observations show a wealth of heteroaryl boronates in the literature, with more than >10,000 building blocks being commercially available. Boronic acid, pinacol esters and trifluoroborates appear to be the most common boron functional handles. Given this lack of sp^3-rich boronate building blocks, we noticed a sufficient gap in the literature (and market) that merits investigation. The development of novel functionality-rich boronic acid scaffolds could benefit medicinal chemistry by enabling rapid access to new areas of underexplored chemical space.

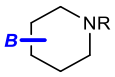
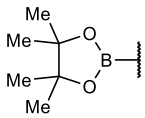
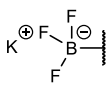
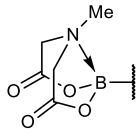
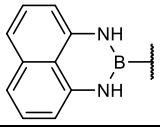
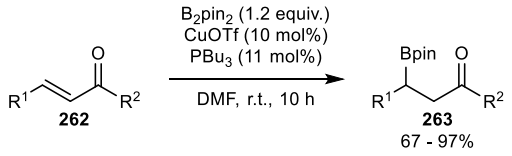
		 Benzene	 Pyridine	 Pyrrole	 Cyclohexane	 Piperidine	 Pyrrolidine
Boronic acid		>59,000	>6,000	744	156	78	>1,000
		>19,000	>3,000	341	38	7	226
Bpin		>83,000	>13,000	>1,000	886	281	392
		>19,000	>8,000	539	90	38	19
BF_3K		>3,000	362	89	130	72	12
		466	74	20	13	8	1
BMIDA		883	125	81	17	1	5
		111	34	6	1	0	0
BDan		617	11	16	33	0	19
		48	0	0	1	0	0

Table 1: Analysis of 5- and 6-membered *N*-heterocyclic boronates **known in the literature** and **commercially available**[113]

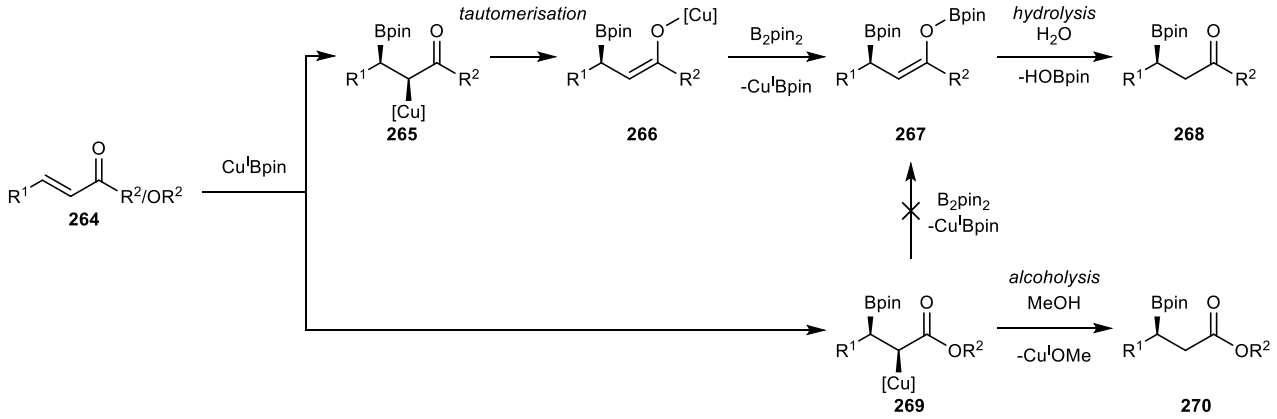
2.1 Cu-Catalysed Conjugate Borylation

Cu-catalysed conjugate borylation was first reported by Ito and co-workers at the turn of the millennium.[114] In this seminal work they found that the use of a phosphine ligated Cu^{I} catalyst could suitably activate diboron reagents for 1,4-addition (Scheme 50). They noted the requirement of alkyl phosphine ligand, as less electron rich ligands gave only moderate yields, and polar solvents are preferred. NMR experiments confirmed that the dominant role of the phosphine was coordination to the Cu and considered this to be an important factor in diboron activation. It is worth noting that no electrophilic proton source is added to this reaction unlike other conjugate borylations.[45]



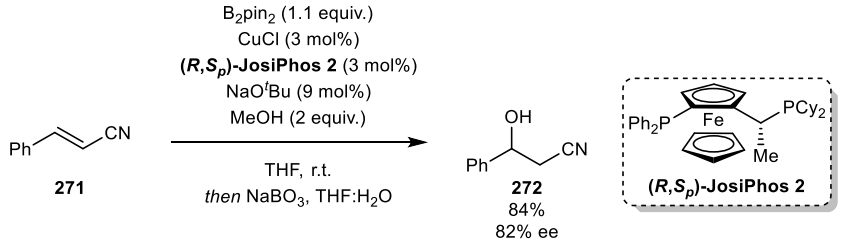
Scheme 50: First reported Cu-catalysed conjugate borylation

The catalytic cycle of this reaction, briefly discussed in Section 1.2.2 (Scheme 13), has been examined *in silico* by Marder and co-workers to investigate the specifics of the mechanism (Scheme 51).[115] These studies were able to explain why Ito and co-workers did not require a proton source in their reaction. Nucleophilic addition of the boryl ligand to the 4-position of a carbonyl enoate **264** generates alkyl Cu enolate **265** which cannot undergo σ-bond metathesis with an additional molecule of the diboron reagent. Instead, the Cu migrates to the oxygen of the enolate through a tautomerisation, which is suitable for σ-bond metathesis with B_2pin_2 without the need for an electrophilic proton source. When the carbonyl enoate is replaced with a carboxyl enoate, tautomerisation of cuprate **269** does not occur due to the lower reactivity of the ester functionality. To promote the reaction introduction of electrophilic proton source is required for alcoholysis/hydrolysis of the alkyl cuprate. Addition of an alcohol to reactions such as Ito's will not increase the rate as the energy barrier for addition across the alkene is rate determining.



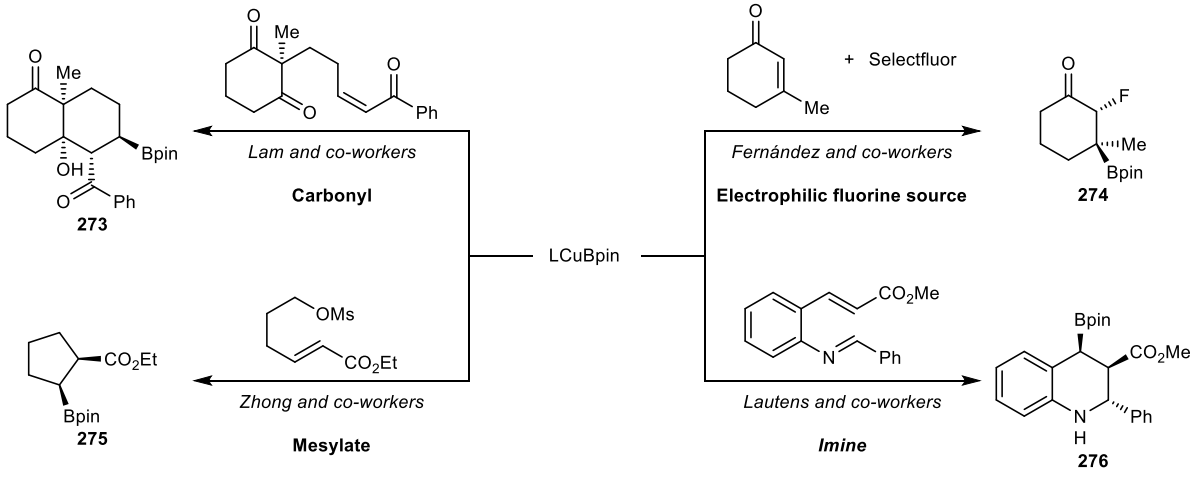
Scheme 51: Substrate control of conjugate borylation mechanism

Yun and co-workers were the first to achieve an enantioselective variant by using chiral JosiPhos as a ligand (Scheme 52).[116] Since this many chiral phosphine ligands have been employed in the reaction as well as some chiral NHC ligands, which can promote the borylation of challenging sterically encumbered enoates.[117–123]



Scheme 52: Enantioselective conjugate borylation

Protic solvents are not the only electrophiles suitable for reaction with the alkyl cuprate. Several studies have shown specifically that aldehydes, ketones, Selectfluor, sulfonate esters and imines can be used as electrophiles in Cu-catalysed conjugate borylations/electrophile addition tandem reactions (Scheme 53).[48,49,124–128]



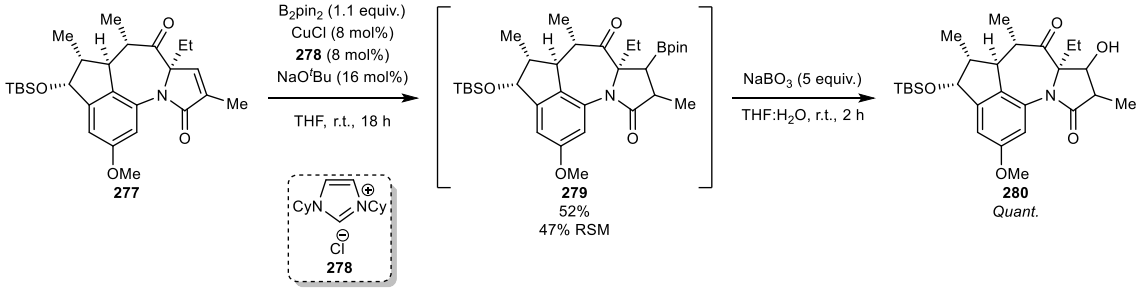
Scheme 53: Alternative electrophiles for Cu catalysed conjugate borylation

As previously mentioned in Section 1.2.2, conjugate borylation has been employed in three studies to prepare borylated heterocycles. However, the scope is somewhat limited. Ito's and Lautenss methods produce heterocycles in which the fused-ring is only partially saturated, whereas Zhong and co-workers generated completely saturated borylated rings, but only two six-membered heterocyles.[46,48,49] What is notable in all of these studies is that the reaction design enabled high distereo- and enantioselectivity to be achieved through the addition of a chiral ligand. Additionally, the methodologies described by Zhong and Lautens use the alkyl cuprate formed in the catalysis to trigger a cyclisation via reaction with an intramolecular electrophile.

These initial investigations give the proof that conjugate borylation can be utilised for the synthesis of heterocyclic building blocks. Given the relatively underdeveloped scope of heterocycles that have so far been prepared, utilisation of this strategy could be advantageous in preparing more biologically relevant structures; such as piperidines and pyrrolidines.[15]

Conjugate borylation has been demonstrated to be suitable for the borylation α,β-unsaturated amides.[119] Additionally lactams can be reduced to the corresponding cyclic amines.[129] By analogy it should be possible to prepare borylated lactams, from the corresponding α,β-unsaturated carbonyl, which could serve as suitable precursors for the synthesis of novel piperidine and pyrrolidine building blocks.

Given the above it is surprising there exists only a single example of the direct borylation of an α,β-unsaturated lactam in the literature. In their derivatisations of tetrapetalone **277**, Marcus and Sarpong found conjugate borylation on such a substrate to be sluggish; 52% yield and 47% returned starting material (Scheme 54).[130] Furthermore in this report they did not isolate the borylated intermediate **279**, instead oxidising to give alcohol **280**.



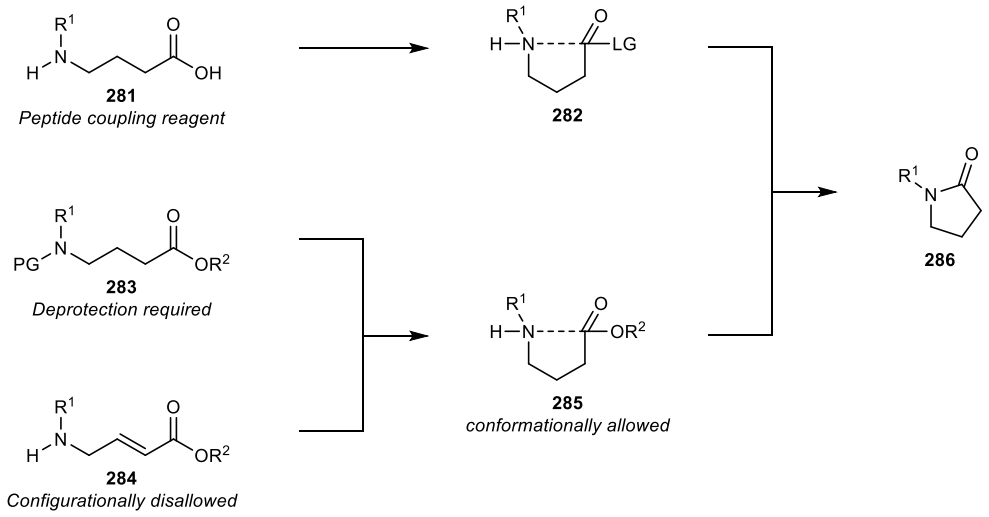
Scheme 54: Conjugate Borylation of an α,β-unsaturated lactam

2.2 Aims

α,β-Unsaturated lactams are most commonly prepared from ring closing metathesis of dieneyl amides using a Ru Grubbs-type catalysts.[131,132] Currents trends in transition metal catalysis focus on the shift away from scarce and depletable 2nd and 3rd row transitions metals to more earth abundant first row elements.[133] Cu is an earth abundant transition metal with a strong precedent for catalytic borylation methodologies available, so we chose this to be the focus of our studies.[134]

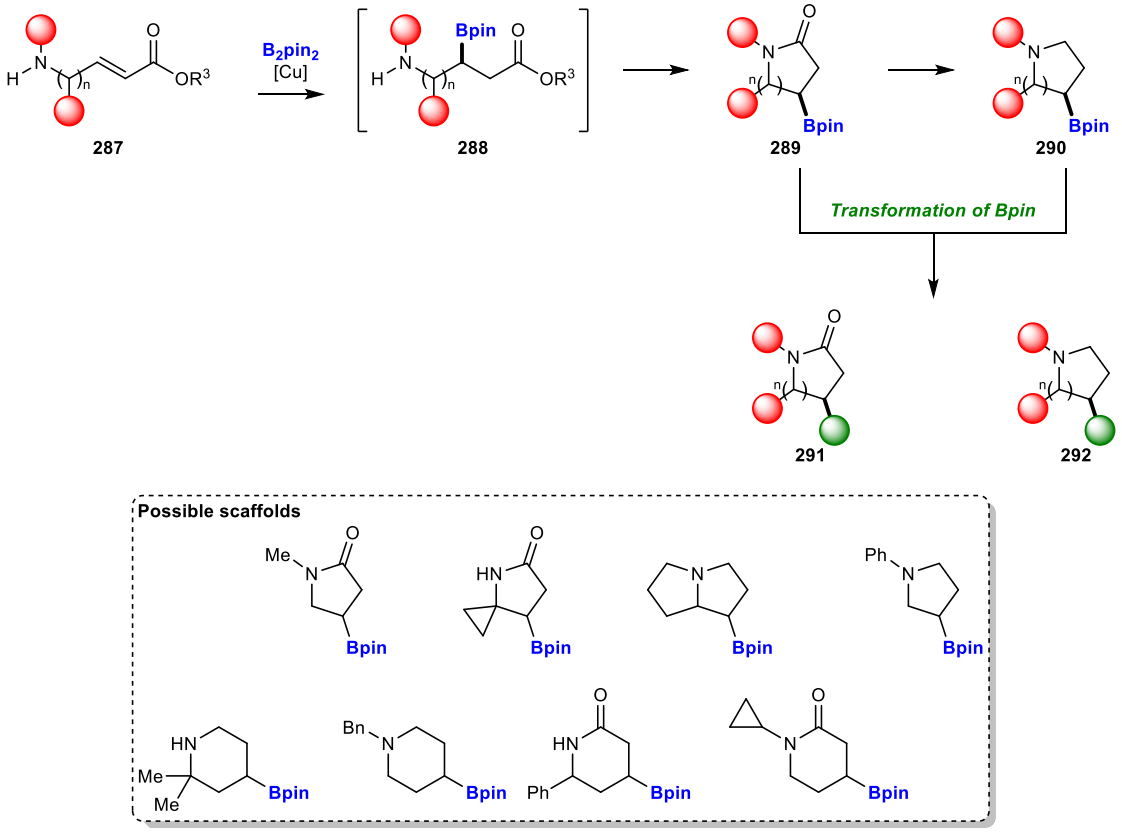
Furthermore, transformation of α,β-unsaturated lactams would require their preformation, which is an additional synthetic step. Given that several tandem borylation/cyclisations have been reported (Section 1.2), we envisioned tandem conjugate borylation/lactamisation could be a more step-economic methodology for the synthesis of borylated lactam building blocks. In turn, the reduction of the lactams could yield elusive and desirable boryl pyrrolidines and piperidines. If successful, the development of an enantioselective procedure should be relatively straightforward through the addition of a chiral ligand.

Another common method for the synthesis of lactams is the intramolecular cyclisation of amino esters (**283**) and is preferable to use of amino acids (**281**) which require activation with a peptide coupling reagent.[135–137] It is such a powerful strategy that unprotected 1° and 2° amino esters (**285**) will readily cyclise to the corresponding lactam if configurationally allowed.[138–140] Removal of this barrier, through the reduction of an enoate (**283**) will allow carbon-carbon bond rotation to a conformation suitable (**285**) for the cyclisations of 1° and 2° amino esters.[141–143]



Scheme 55: Synthesis of lactams from amino acid derivatives

E-Amino enoate esters **287** are one such example in which cyclisation is configurationally disfavoured. To the best of our knowledge, these substrates have not yet been investigated in the conjugate borylation reaction. Therefore, our aims are to produce a range of amino enoates and develop a protocol for their transformations into borylated lactams and determine if they can be reduced to boryl cyclic amines. Lastly, we will test the onwards reactivity of the of the products, confirming their application as heterocyclic scaffolds (Scheme 56).



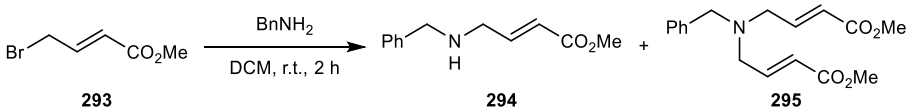
Scheme 56: Proposed synthetic route to borylated lactams and cyclic amines

2.3 Results and Discussion

2.3.1 Initial Investigation of the Conjugate Borylation of *N*-Alkyl Amino Enoates

In order to initiate our studies, we had to select a model substrate for the conjugate borylation procedure. Baldwin's rules outline the feasibility of ring closures based on the angle of attack of an nucleophile and intramolecular electrophile; in addition the 5-*exo*-*trig* cyclisation is significantly faster then 6-*exo*-*trig* due to better alignment of orbitals.[144–146] With this in mind we decided that a model substrate for the initial investigation of conjugate borylation would be a (2*E*)-4-aminobutenoate type structure (**287**, n = 1).

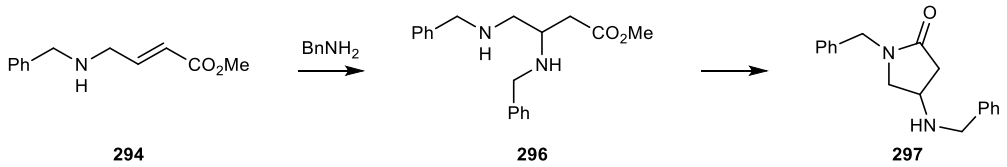
The two most common methods for the synthesis of amines are alkylation and reductive amination. Given the multiple electrophilic sites in the enoate structure, we decided that reductive amination would be unsuitable. We instead decided to alkylate an amine with methyl 4-bromocrotonate **293**. Alkylation of 1° amines is notoriously difficult due to the increased nucleophilicity of the product leading to over alkylation. The main way to control this is through the adjusting the stoichiometry of amine and alkyl halide so that one reagent is in excess. In order to improve the yield of the desired product (**294**) we first screened the stoichiometry of the alkylation benzylamine (Table 2). As expected, a 1:1 stoichiometry leads to a significant amount of dialkylation, and in order to promote monoalkylation an excess of the amine is required. However, when 4 or 5 equivalents of the amine are used the crude NMR showed a complex mixture. The most likely explanation for this is that the additional benzyl amine undergoes a Michael addition with **294** to generate amino ester **296**, which could cyclise to give lactam **297** (Scheme 57).



293 **294** **295**

Entry	$BnNH_2$ (equiv.)	294	295
1	1	0%	31%
2	2	63%	8%
3	3	72%	6%
4	4	*complex mixture*	
5	5	*complex mixture*	

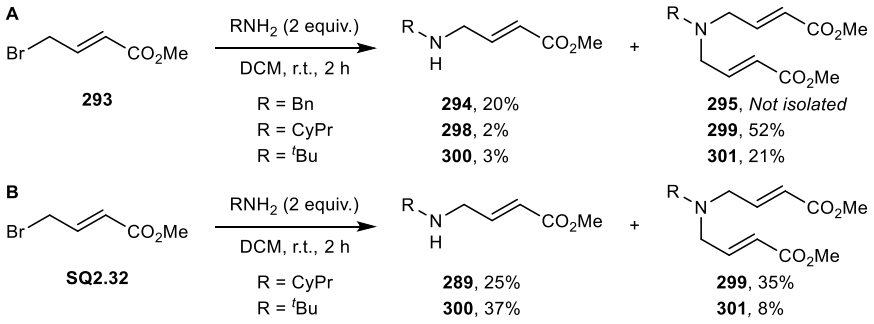
Table 2: Stoichiometry screen for the alkylation of benzylamine (NMR yields calculated using 1,3,5-trimethoxybenzene as an internal standard)



294 296 297

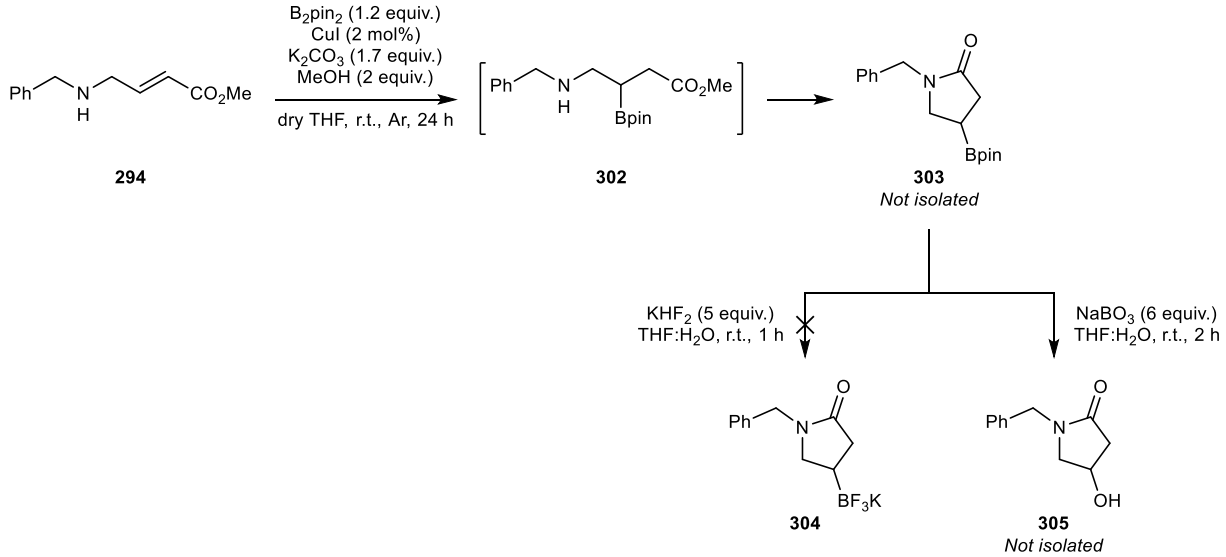
Scheme 57: Possible side reaction in the alkylation reaction of benzylamine with **293**

When the reaction was run using 3 equivalents of benzylamine the crude NMR showed mostly formation of **294**, as consistent with the screening experiment, although after purification, instead of the desired product, impure fractions of lactam **297** where obtained. Silica gel used in chromatography is slightly acidic, which may have promoted the unwanted Michael addition with the excess amine on the column. The reaction was rerun using only 2 equivalents of benzylamine, which furnished amino enoate **294** in poor yield of 20% (Scheme 58A). This poor isolated yield of the product is likely caused by the side reaction on the column. The reaction was repeated using cyclopropyl amine and *tert*-butyl amine, however in these reactions the dialkylated product was isolated as the major product with the monoalkylated product only being isolated in trace amounts (Scheme 58A). These two reactions were repeated using 2.5 equivalents of the amine, which although yielding a modest amount of the desired product also gave significant amounts of the dialkylated product (Scheme 58B).



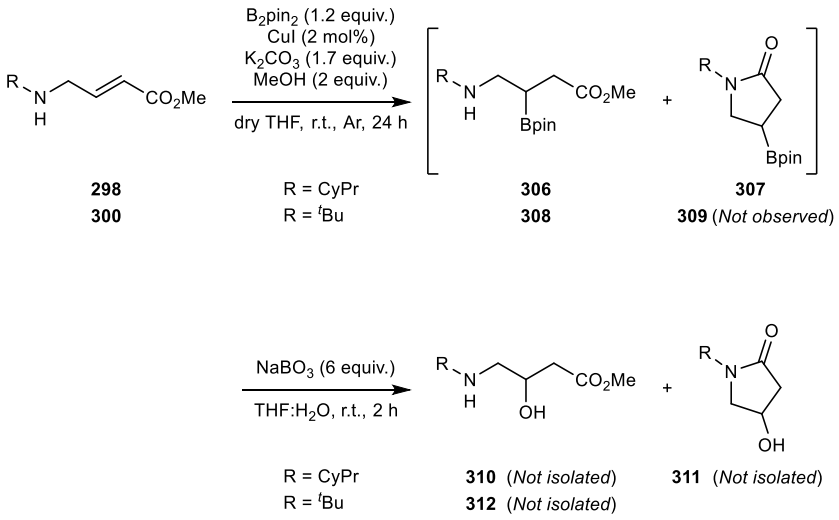
Scheme 58: Synthesis of *N*-Alkyl amino enoates

With the *N*-alkyl amino enoates in hand we turned our attention to the conjugate borylation reaction. Using the procedure described by Zeng and co-workers, we submitted enoate **294** to the reaction conditions under an inert atmosphere (Scheme 59).[147] To our initial delight, the crude NMR showed not only that the borylation had occurred, but also that borylated amino ester **301** had also cyclised under the reaction conditions to lactam **303**. However, isolation of the product through either column chromatography or distillation failed to yield the product. From our analysis of the residue returned after attempted purification it was not entirely clear why this compound degraded, we assume this is due to either protodeboronation or oxidation of the boronic ester. Attempts were made to transform the boronate into the more stable trifluoroborate salt and alcohol. After treatment with KHF_2 the expected product trifluoroborate **303** was not observed. Oxidation using H_2O_2/NaOH was attempted but no alcohol was observed, likely due to a degradation pathway resulting from the strong interaction between hydroxide and the boron atom. When oxidation using the less nucleophilic $NaBO_3$ was carried out, crude NMR showed oxidation had occurred but the alcohol **305** was not isolated.



Scheme 59: Conjugate borylation and attempted derivatisation of **294**

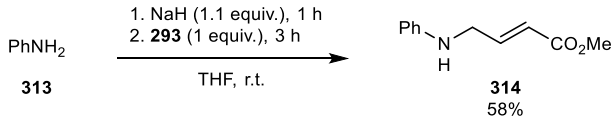
Given the oxyphilic nature of boron and the ability of neighbouring carbonyl oxygens to stabilise boronic esters through donation into the vacant p-orbital, we wondered if sterically restricting cyclisation would allow for isolation of the borylated amino enoates.[58] The amine functionality of both **298** and **300** features adjacent carbons with increasing substitution, 3° and 4° respectively, which could possibly hinder cyclisation. Conjugate borylation of **298** gave a mixture of both the uncyclised **306** and cyclised **307** products, whereas **300** gave only the uncyclised product **308** (Scheme 60). Attempts to isolate these compounds were unsuccessful, we believe instability of these compounds is similar to lactam **303**. Submission of the crude mixtures of the boronic esters to the oxidation procedure was successful but isolation of the alcohols **310**, **311** and **312** was not possible.



Scheme 60: Conjugate borylation and attempted oxidation of **298** and **300**

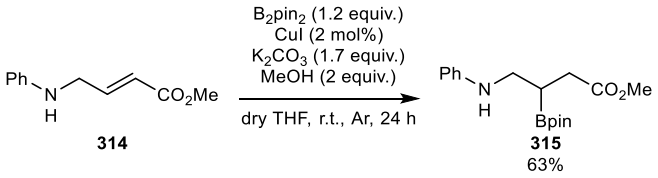
2.3.2 Initial Investigation and Development of a Conjugate Borylation/Cyclisation Procedure for *N*-Aryl Amino Enoates

Given the attempt to sterically hinder the cyclisation had not allowed for the successful isolation of either the borylated amino ester or lactam, we instead attempted to reduce the nucleophilicity of the nitrogen atom. Aromatic amines are known to be less nucleophilic than their aliphatic counterparts due to delocalisation of electron density into the aromatic system. We decided that *N*-aryl amino enoate **314** would serve as a better model substrate. To prepare this amino enoate, aniline was treated with NaH to generate an amide, which underwent nucleophilic substitution with methyl 4-bromocrotonate (Scheme 61). This alkylation methodology is significantly more efficient than the previously described method, giving a 58% of the desired product.



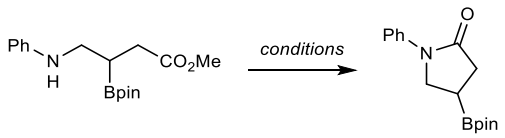
Scheme 61: Initial synthesis of *N*-aryl amino enoate **314**

As expected, when submitted to the conjugate borylation conditions only the borylated amino enoate was observed in the crude NMR. More importantly, this compound was found to be stable to chromatography on silica which allowed our first isolation of a borylated product, **315** (Scheme 62). This result suggests the amino esters **306** and **308** should have been stable to silica and isolable. It is possible that they in fact cyclise on the column generating the unstable *N*-lactams **307** and **309**.



Scheme 62: Conjugate borylation of **314**

We could now turn our attention to the cyclisation of the amino enoate **315**. Given the difficulties observed with the purification of the *N*-alkyl boryl lactams, we would have to develop a procedure with two main features: 1) the reaction must give 100% conversion of the amino ester into lactam; and 2) any additives used must be easily removed such that the lactam is isolated clean from the work up. The most obvious method of cyclisation would be to stir the amino enoate at elevated temperatures, although this gave only 21% yield of the product (entry 1, Table 3). With this sample we also noted degradation of the boronic ester (33.1 ppm) due to the appearance of a borate (22.5 ppm) in ^{11}B NMR analysis of the crude material. Next, we decided to examine possible additives. Bases were found to be ineffective in the promotion of cyclisation (entries 2-4, Table 3), and a small amount of degradation of the boryl amino ester were also noticed when pyridine was used. Acids were significantly more effective; whilst the use of aqueous HCl gave a 71% yield it also led to degradation of the boronic ester (entry 5, Table 3), whereas the use of AcOH, with THF as a co-solvent, gave a quantitative yield of the product without any degradation of the boronic ester (entry 6, Table 3).



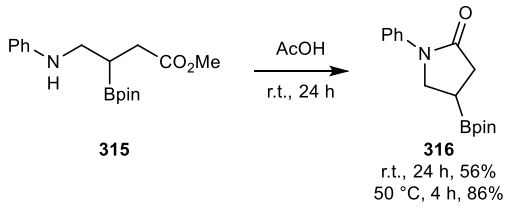
315 **316**

Entry	Conditions	Yield	Observation
1	THF, 70 °C, 40 h	21%	Partial degradation of boronate
2	NaH (1.2 equiv.), anhydrousTHF, 0 °C, 4 h	0%	No degradation of boronate
3	THF:Et_3N, r.t., 40 h	0%	No degradation of boronate
4	THF:pyridine, r.t., 40 h	0%	Some degradation of boronate
5	THF:1 M aq. HCl, r.t., 40 h	71%	Partial degradation of boronate
6	THF:AcOH, r.t., 40 h	>99%	No degradation of boronate

Table 3: Screen of cyclisation condition for **315**, NMR yields calculated using 1,3,5-trimethoxybenzene as an internal standard

With this positive development, we decided to explore room temperature acetic acid promoted cyclisation further. Using acetic acid as the solvent 78% conversion was measured after 18 h without any degradation of the boronic ester. Extending the reaction time to 24 h only increased the conversion to 100%, with boryl lactam **316** being isolated in a moderate yield of 56% (Scheme 63). This low yield is thought to be due to aqueous solubility of the product leading to loss in the work-up. Although this significant loss of mass is undesirable, we chose to explore further these initial cyclisation conditions.

We next wanted to reduce the reaction time for this reaction, which should be possible through the increasing the reaction temperature. Monitoring of the reaction at 50 °C revealed that complete cyclisation occurs after 4 hours. Combined with using the minimum amount of sat. Na_2CO_3 to remove the AcOH during the work-up, we were able to isolate the product in 86% yield (Scheme 63).

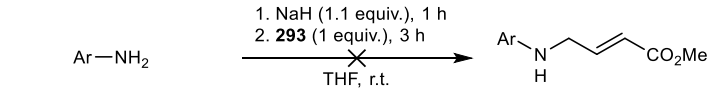


315 **316**
r.t., 24 h, 56%
50 °C, 4 h, 86%

Scheme 63: Synthesis of boryl lactam **316**

2.3.3 Synthesis of *N*-Aryl Amino Enoates

With the cyclisation now optimised for *N*-aryl amino enoates, we embarked on the task of synthesising a range of enoates. The previously described method using NaH for the alkylation of aniline unfortunately proved to less general than we were hoping. When using toluidine, 3-bromoaniline and 2,5-xylidine only the starting aniline were returned from the reaction mixture (Scheme 64).

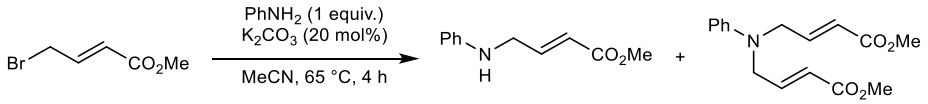


317, Ar = 4-Me(C_6H_4)
318, Ar = 3-Br(C_6H_4)
319, Ar = 2,5-Me_2(C_6H_4)

320, Ar = 4-Me(C_6H_4)
321, Ar = 3-Br(C_6H_4)
322, Ar = 2,5-Me_2(C_6H_4)

Scheme 64: Unsuccessful *N*-alkylation of anilines **317**, **318** and **319**

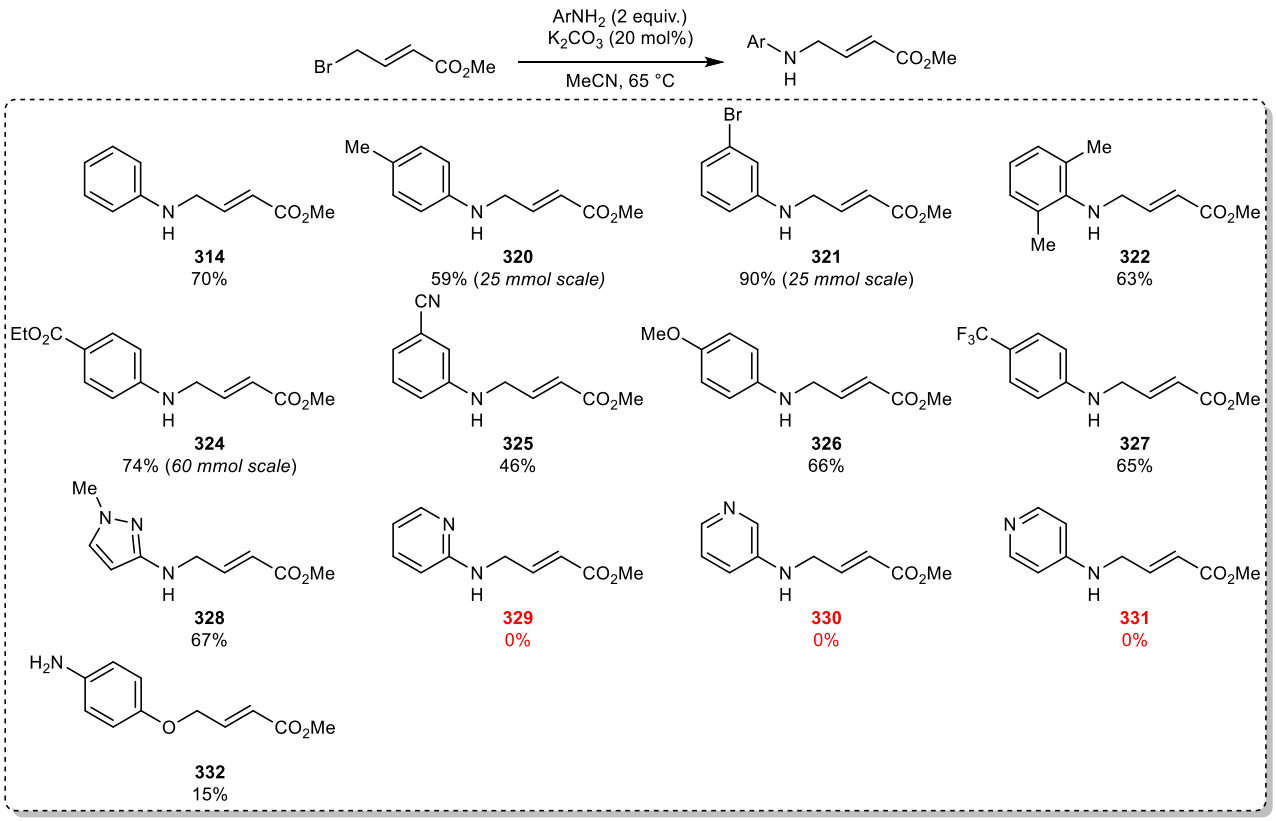
Instead of using a stoichiometric base we found that using 20 mol% of K_2CO_3 in MeCN to be suitable for the alkylation of aniline. However, when using the same stoichiometry of aniline as alkylating agent over alkylation of the aniline was observed (Scheme 65).



293 **314** 14% **323** 33%

Scheme 65: K_2CO_3 promoted alkylation of aniline in MeCN

So instead, using 2 equivalents of the aniline we were able to promote monoalkylation to prepare *N*-aryl amino enoates. These reactions typically took 4 hours, although all reaction were monitored by TLC and run to completion (Scheme 66). The reaction proceeded smoothly for the majority of aniline substrates tested and was able to furnish enoates with alkyl (**320, 322**), ester (**324**), halide (**321**), nitrile (**325**), methoxy (**326**) and trifluoromethyl (**327**) functionalities on the aromatic ring, with **320**, **321** and **324** all being prepared on multigram scales. Although one heteroaryl example was achieved using an amino pyrazole substrate, the reaction of every isomer of aminopyridine failed to yield any reaction, which could be a result of the increase nucleophilicity of the pyridine nitrogen over the amino (**329 - 331**).[148] In addition we found phenol to be an unsuitable functional group, presumably due to the in situ formation of phenoxide, which has increased nucleophilicity of the oxygen atom compared with the aniline, leading to *O*-alkylation (**332**).

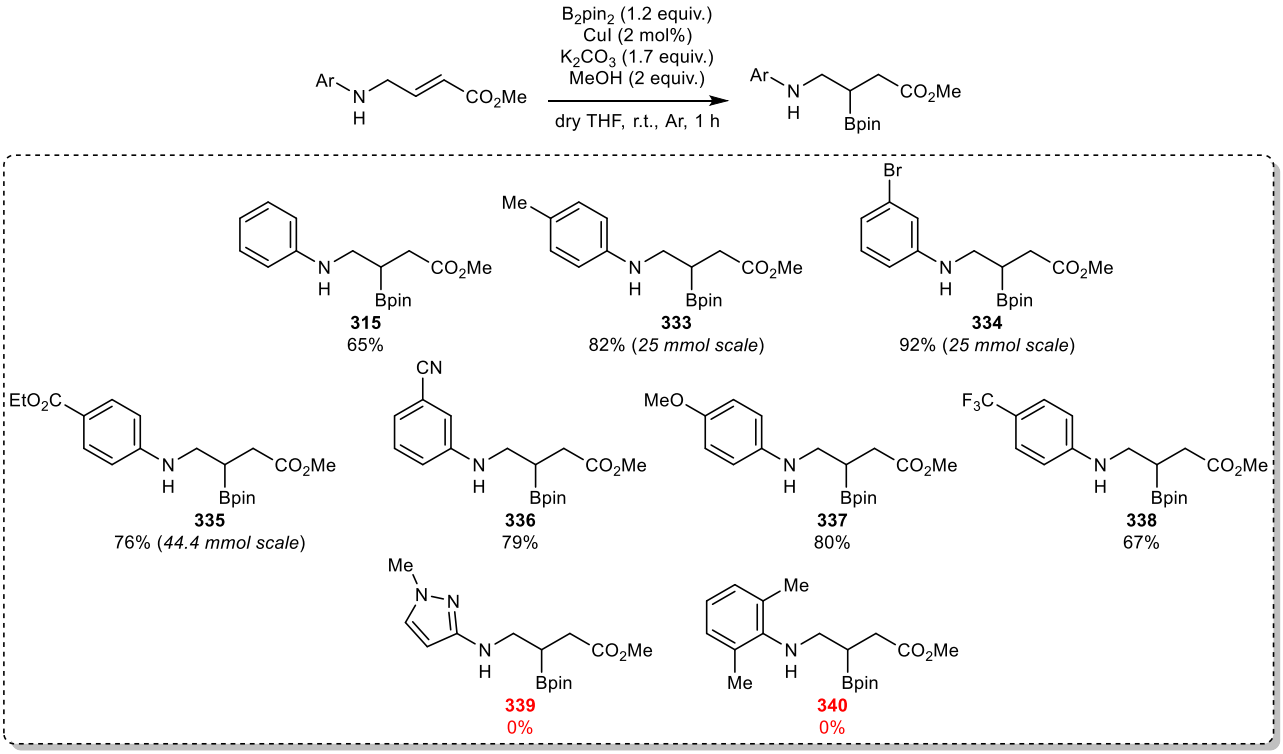


Scheme 66: Scope of *N*-aryl amino enoate synthesis (5 mmol scale)

In the case of amino esters **333**, **334**, **336** and **338** a second upfield signal was observed by ^{11}B NMR at roughly 20 ppm. Initially we believed this was the MeOBpin by-product of the conjugate borylation, however, this was not observed by ^{1}H NMR analysis. We believe that the extra signal in the ^{11}B NMR spectra is due to the formation of a Lewis adduct with the boron atom. It is not known whether this is an intra- or intermolecular adduct.

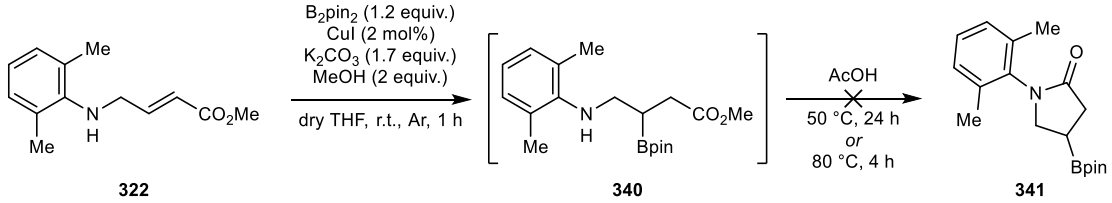
2.3.4 Conjugate Borylation/Cyclisation of *N*-Aryl Amino Enoates

Gratifyingly all the *N*-aryl amino enoates prepared underwent successful conjugate borylation, and most were successfully isolated (Scheme 67). Monitoring of these reaction by ^{1}H NMR analysis revealed that borylation occurred in under 1 h, significantly shorter than the 30 h reported by Zeng and co-workers.[147] Unfortunately, boryl amino esters **339** and **340** could not be isolated from the mixture due to their instability to chromatography; despite crude NMR confirming complete conversion.



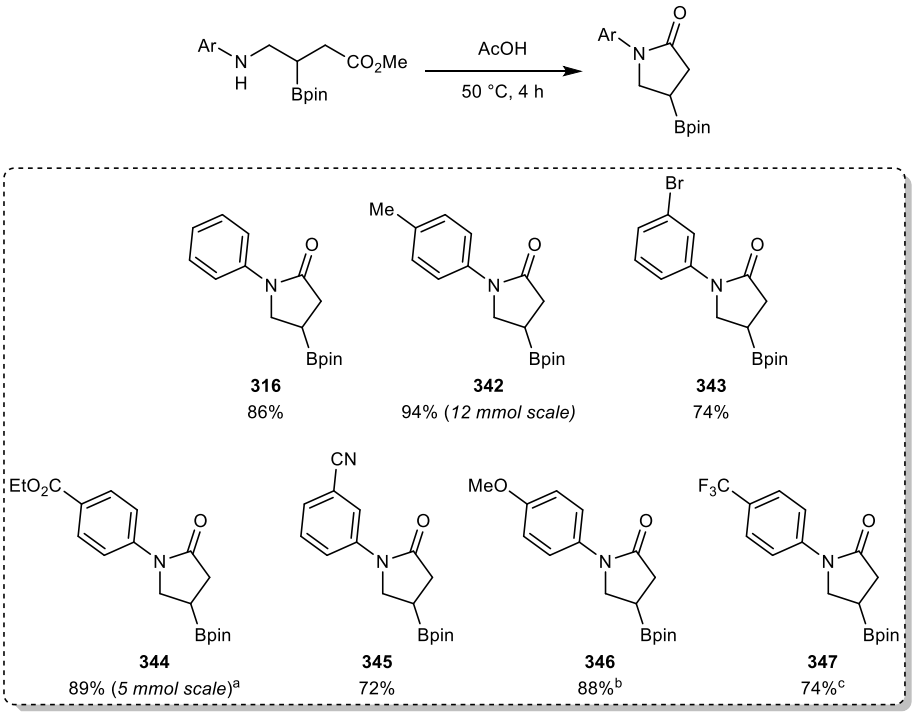
Scheme 67: Scope of boryl *N*-aryl amino ester synthesis (1 mmol scale)

Although this instability would most likely be mirrored in the boryl lactam, we decide to attempt to cyclise the amino ester **340** and isolate it as the oxidised product (Scheme 68). Alas this was not possible as the substrate did not cyclise with extended reaction times or elevated temperature and so we deemed that this substrate would not be suitable for the methodology we had developed.



Scheme 68: Incomplete synthesis of boryl lactam **341**

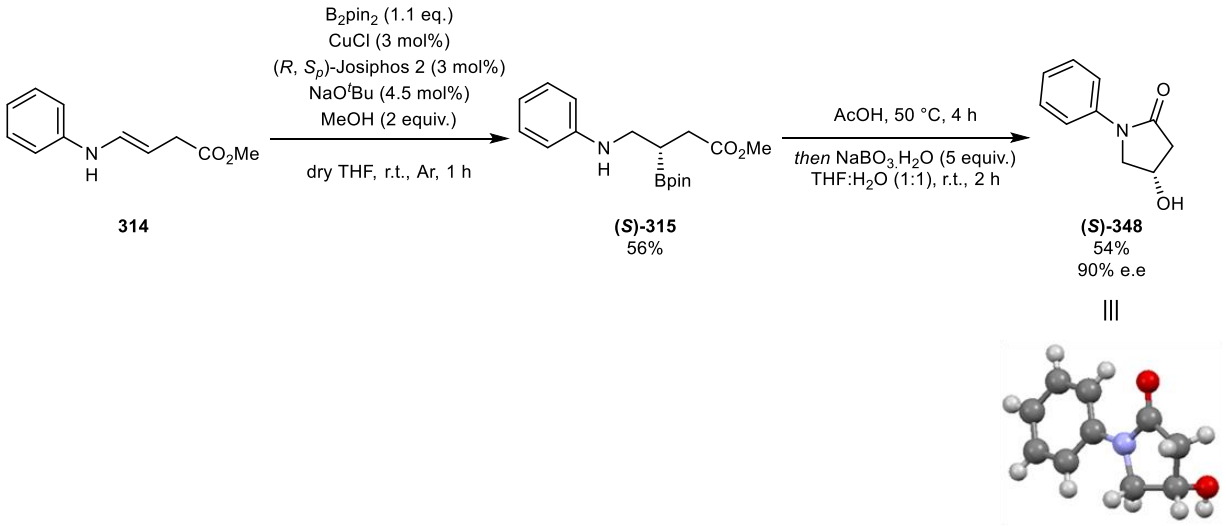
The cyclisation of the other amino enoates was relatively straight forward, all those isolated were converted to the corresponding lactams using our reaction conditions (Scheme 69). Monitoring of the reaction by ^{1}H NMR analysis revealed that electron withdrawing substituents on the aromatic ring reduced nucleophilicity of the nitrogen, such that complete cyclisation required extended reaction times.



Scheme 69: Scope of boryl *N*-aryl lactams (0.5 mmol scale), [a] reaction extended to 24 h, [b] reaction extended to 5 h, [c] reaction extended to 9 h

The most similar procedure reported in the literature for the preparation of borylated lactams is the procedure described by Lautens and co-workers (Scheme 12). A limitation of their procedure was that the hydroboration required a styrene type substrate, which would impart an aryl ring α to the carbonyl. This position features relatively acidic protons, which can be deprotonated to form reactive enolates for further functionalisation. Our procedure furnishes lactams with no substitution α to the carbonyl. This in turn leaves this position free for the user of the scaffold to further functionalise the lactam at the α-position with substituents beyond aryl units.

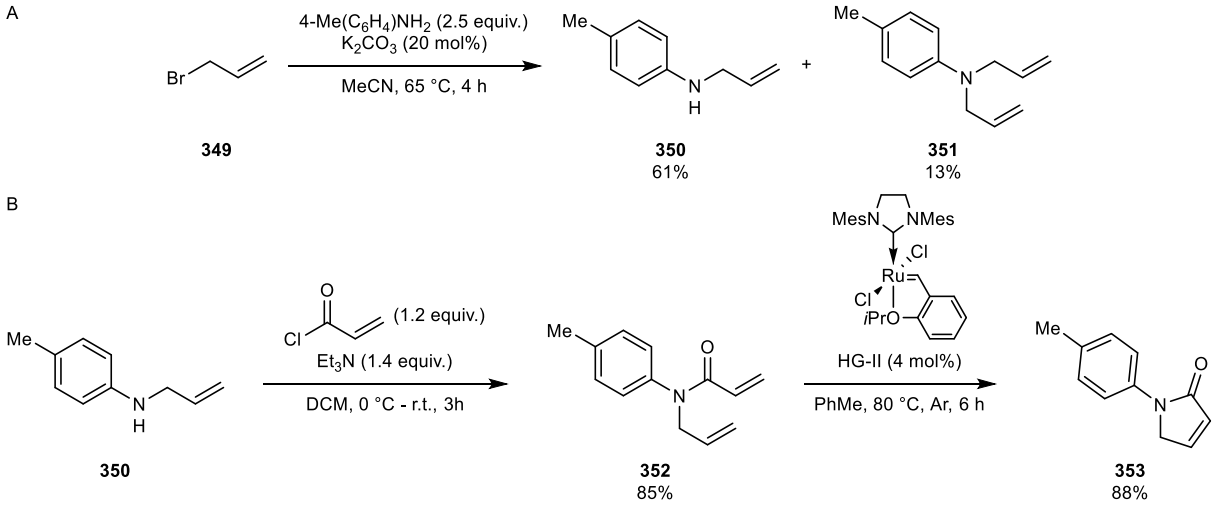
Given the success of our racemic procedure we decided to try using an asymmetric variant. Based on the asymmetric conjugate borylation procedure reported by Lee and Yun, we choose to use a JosiPhos type ligand to impart stereoselectivity in our borylation reaction.[117] Upon successful isolation of the borylated amino ester, we submitted it to the cyclisation conditions followed by boronic ester oxidation (Scheme 70). The 1,2 metallate rearrangement involved in the oxidation of boronic acid derivatives is stereospecific, occurring without loss of stereochemical integrity. HPLC analysis and X-ray crystallography of the resultant alcohol **(*S*)-348** was used to determine that this specific ligand favoured formation of the *S*-enantiomer in 90% enantiomeric excess.



Scheme 70: Asymmetric borylation and cyclisation of **314**

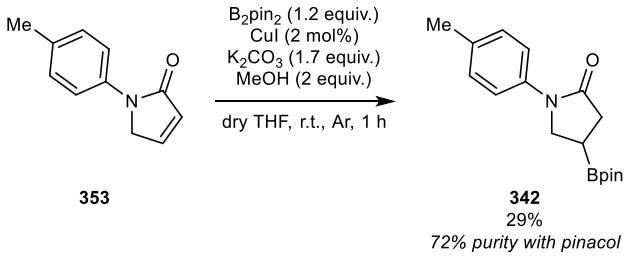
2.3.5 Comparison with the Conjugate Borylation of α,β-Unsaturated Lactams

As stated in the aims of this project, the most obvious way to prepare borylated lactams is through the conjugate borylation of an α,β-unsaturated lactams. So, we decided that we should prepare **342** in this manner for comparison to our methodology. To prepare the α,β-unsaturated lactam we first alkylated toluidine with allyl bromide **349**, which yielded both the mono- and di-alkyl products (Scheme 71A). The mono-alkyl amine **350** was then acylated with acryloyl chloride, followed by ring closing metathesis with Hoveyda-Grubbs G2 catalyst to yield lactam **353** (Scheme 71B).



Scheme 71: Synthesis of α,β-unsaturated lactam **353**

Unlike the conjugate borylation reported by Marcus and Sarpong, our rection gave full conversion to the boronic ester; most likely due to the less sterically encumbered nature of our substrate.[130] Like our previous attempts to isolate the borylated lactam directly from the conjugate borylation reaction mixture, **342** was unstable to column chromatography (Scheme 72). Furthermore, when recrystallisation was attempted, the product was inseparable from a pinacol impurity giving the lactam **342** in 29% yield with a purity of 72%.



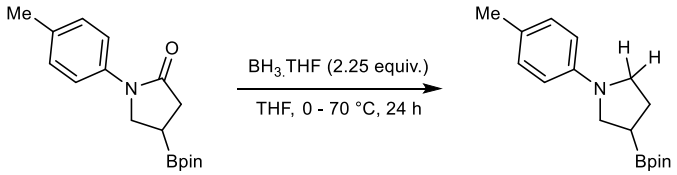
Scheme 72: Conjugate borylation of lactam **353**

This result demonstrates that our methodology is superior to the conjugate borylation of α,β-unsaturated lactams as isolation of pure product was not achieved. Moreover, our method is more step economical, requiring only three steps and two purifications to the desired lactam compared to the extra step and purification required via this route.

2.3.6 Transformation of *N*-Aryl Borylated Lactams

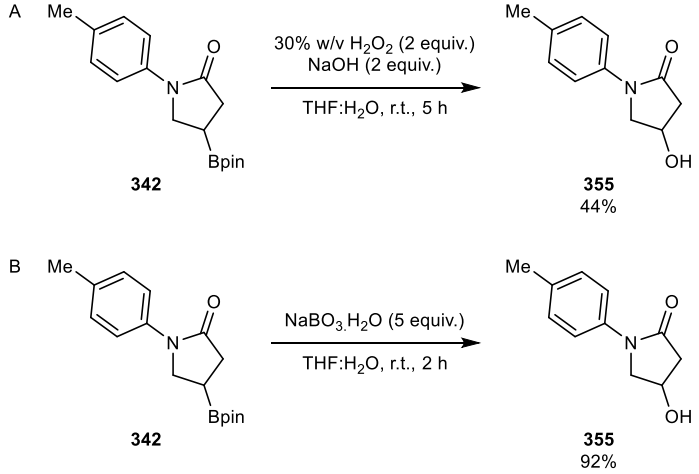
For these borylated lactams to be considered scaffolds we next needed prove their onward reactivity. Given that there may be difficulties understanding any issues encountered in these reactions, ^{1}H NMR analysis of reaction mixtures may be useful. Due to the simplified aromatic region and the easily identifiable methyl signal, we choose to use lactam **342** as a model substrate for these transformations.

Given that one of the aims of this project was to use the conjugate borylation/cyclisation strategy to prepare boryl cyclic amines, reduction of the lactams would be an important reaction to achieve. An initial attempt at the reduction of lactam **342** with two equivalents of borane in refluxing THF for 3 h yielded no reaction. It was found that increasing the equivalency of borane and reaction time was required to in order to promote the reduction to boryl lactam **342** (Scheme 73). Interestingly this compound was stable to chromatography, suggesting that some function of the carbonyl group is involved in the observed degradation of the lactam boronic esters.



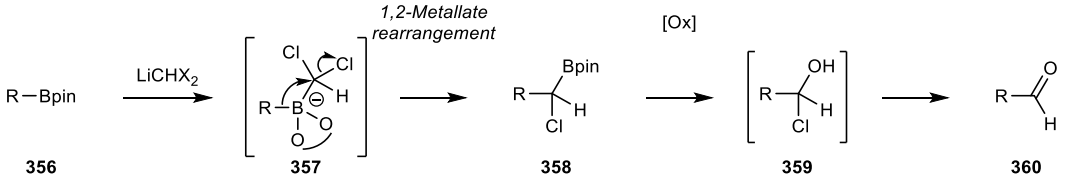
Scheme 73: Reduction of lactam **342**

We chose to begin our boronate diversification studies with oxidation, as this is the most common transformation of boronic acid derivatives.[149] We had previously had issues using H_2O_2/NaOH for the oxidation of boryl lactams from crude mixtures (Scheme 59, **305**). Using this oxidation methodology, the alcohol was only isolated in poor yield (Scheme 74A). Gratifyingly using $NaBO_3$ as the oxidant instead we were able to isolate alcohol **355** directly from work-up in excellent yield (Scheme 74B).



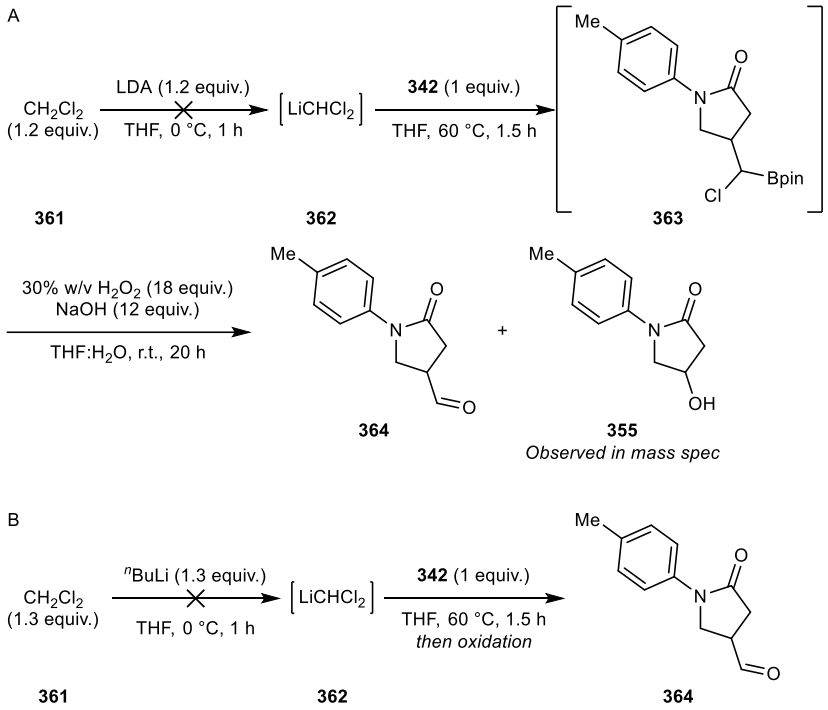
Scheme 74: Oxidation of lactam **342**

Aldehydes are a more reactive functional handle then alcohols due to their electrophilic nature and so their synthesis with regards to building blocks is of interest. They can be formed from boronic acid derivatives **356** through sequential Matteson homologation and oxidation of the resultant α-halo boronate **358** (Scheme 75).



Scheme 75: Mechanism for formylation of boronic acid derivatives

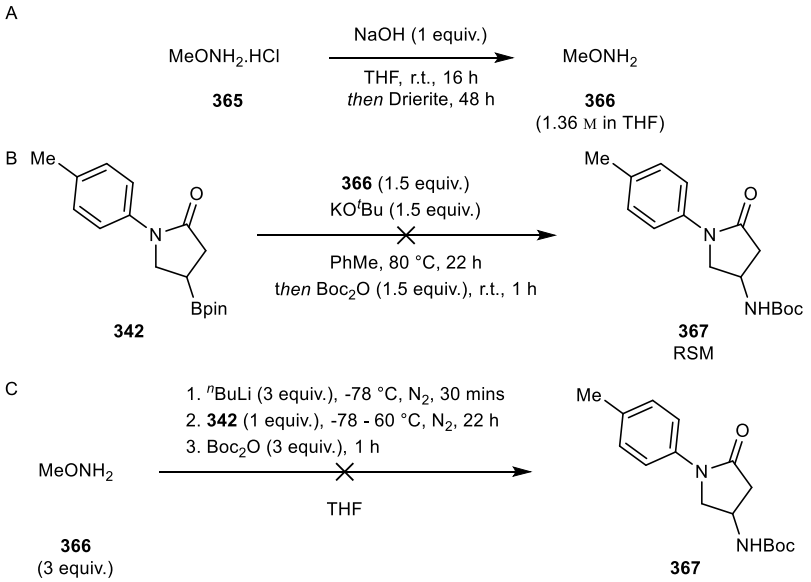
Boronic ester **342** was subjected to this Matteson homologation procedure. Mass spectrometry analysis of the crude material from our first attempt at the formylation of **342** identified alcohol **355** (*m/z* 192.1 Da) as the only identifiable product (Scheme 76A). This result suggests that the initial homologation of the boronic ester with alkyl lithium **362** does not occur, suggesting the alkyl lithium had not been formed or did not undergo homologation with our substrate. Variations on the conditions used to generate the alkyl lithium also failed to give the desired product **364** (Scheme 76B). It was decided at this point not to pursue alternative conditions for this transformation.



Scheme 76: Attempted formylation of lactam **342**

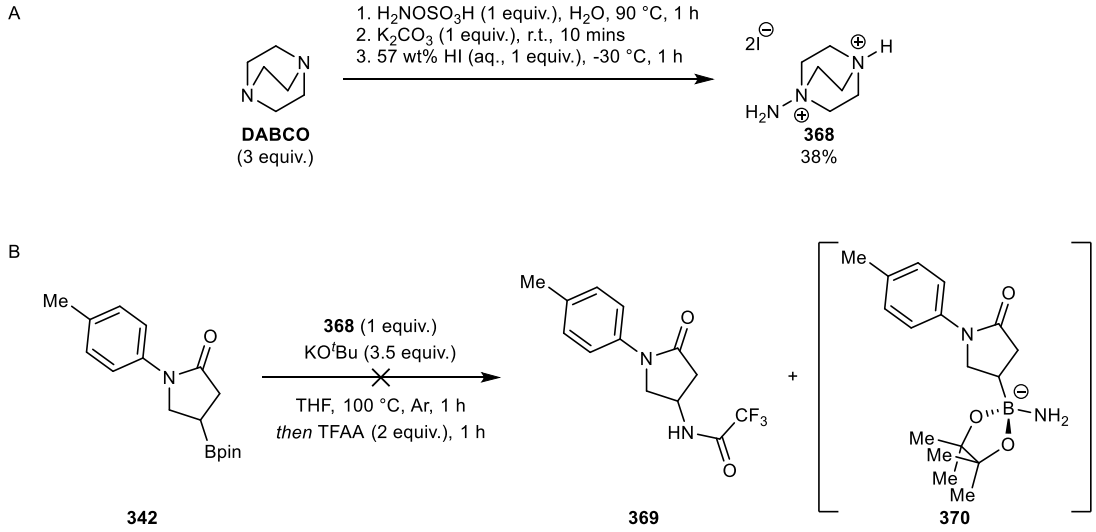
Amines are also of synthetic value and can be prepared from boronic esters. A common method to do this is through Chan-Lam-Evans cross coupling with amines. However, the application of this reaction to alkyl boronic esters is significantly underdeveloped and challenging, so we decided not to investigate this.[150] Instead there exist methods more similar mechanistically to oxidation that utilise an electrophilic nitrogen with a sufficient leaving group. The conditions for these reactions are considerably harsher than those required in the H_2O_2/NaOH oxidation. Although this may hinder the transformation, we believed that the value of the product merited investigation.

Both procedures reported by Morken and co-workers require the use of anhydrous NH_2OMe, which due to its hydroscopic nature must be prepared beforehand by stirring with NaOH and a desiccant.[61,62] Using this method we prepared a 1.36 M solution of NH_2OMe in THF, the concentration was calculated using 1,3,5-trimethoxybenzene as an internal standard and ^1H NMR analysis confirmed the solution was anhydrous (Scheme 77A). The exact yield of this reaction could not be calculated as the volume of solution was not determined. The second reported method developed by Morken and co-workers uses a weaker base and capable of aminating sterically hindered 3° boronic esters, so we began our investigation with this method. Unfortunately, after stirring at 80 °C for 22 h no conversion was observed, and the reaction returned boronic ester **342** unchanged from the reaction (Scheme 77B). So, we then attempted their first procedure using ^{n}BuLi as a base. This gave a complex mixture from which we were unable to isolate any products (Scheme 77C), although it was clear that the boronic ester had either been consumed in this reaction. This suggested that both this aminating reagent and ^{n}BuLi were unsuitable reagents for the amination of the substrate.



Scheme 77: Attempted amination of **342** using methods developed by Morken and co-workers

Liu and co-workers have developed another electrophilic amination reagent **368** that is based on a DABCO salt that is reported to be bench-stable (Scheme 78A).[151] When submitted to the reaction conditions the ^{1}H NMR analysis of the crude product revealed a complex mixture (Scheme 78B). Whereas the simpler ^{11}B NMR analysis showed the expected boronic ester signal (33.7 ppm) alongside a new upfield signal (7.5 ppm) (Figure 4). The origin of this signal is most likely from the formation of an amidoborate, such as **370**. This implies that although amination of the boronate occurs, the reaction conditions are not forcing enough to promote the 1,2-metallate rearrangement. Given the difficulties so far experienced with amination of **342** we decided to focus our efforts exploring other literature reactions.



Scheme 78: Attempted amination of **342** using methods developed by Liu and co-workers

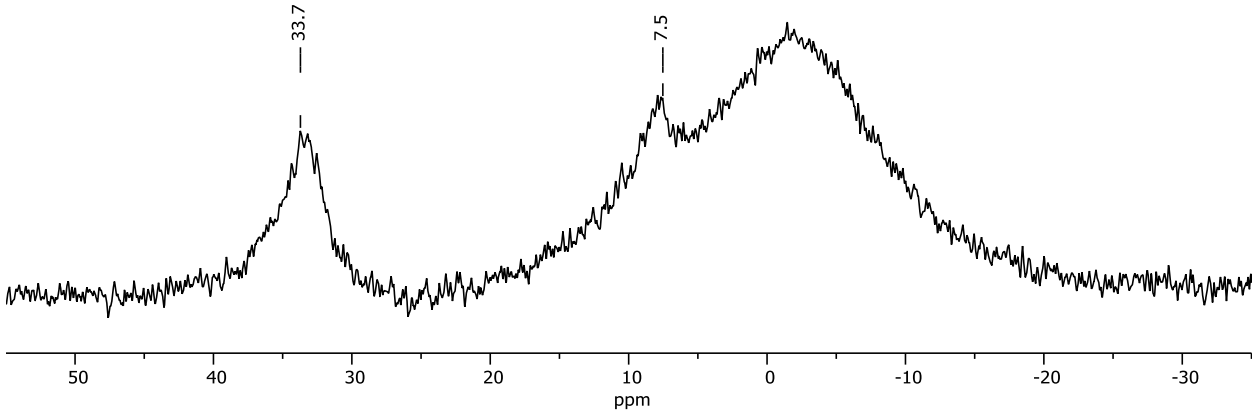
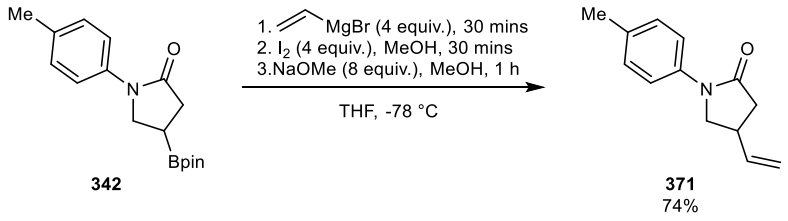


Figure 4: ^{11}B NMR of crude reaction mixture from Scheme 78B

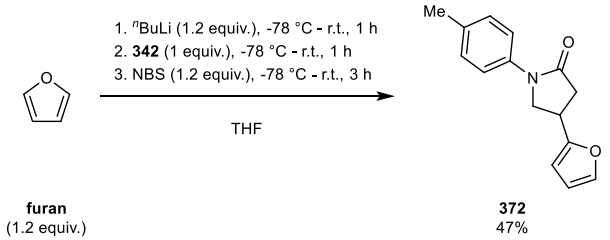
We decided to turn our attention to carbon-carbon bond-forming reactions. Given that alkyl/amide lithium reagents are highly nucleophilic, we believed that reactions employing Grignard reagents may be more successful. The reduced nucleophilicity of these reagents is the result of the metal's electronegativity, leading to reduced ionic character and thus a strong carbon-metal bond.[152] Gratifyingly our first attempt at Zweifel olefination of **342** furnished the desired product **371** in good yield without the need for optimisation (Scheme 79).[153]



Scheme 79: Zweifel olefination of **342**

This result led us to ponder whether our previously unsuccessful attempts to using alkyl/amide lithium was not due just to the strength of the nucleophile, but due to the lack of stabilisation of boronate. Although the Zweifel olefination reaction is facilitated by the large excess of Grignard forming a tetracoordinate borate, any trigonal borane intermediates could be stabilised by the C-sp^2-hybridised substituents.

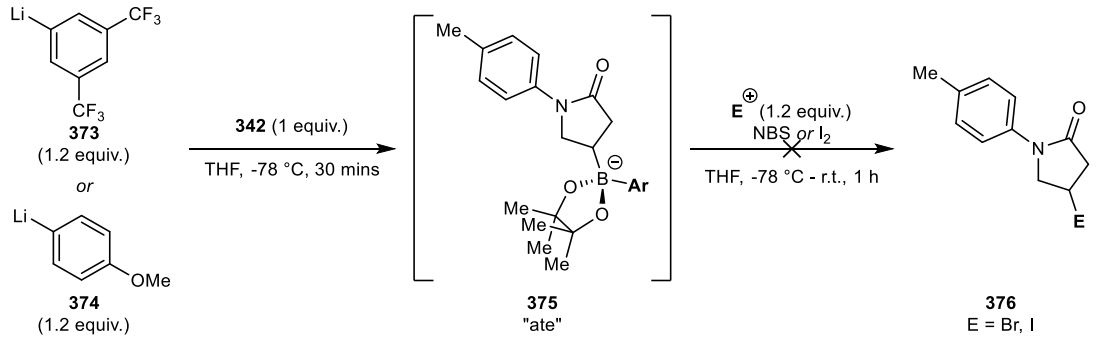
We began to investigate methodologies that are facilitated by the addition of a sp^2-hybridised organolithium to trigger the nucleophilicity of the carbon-boron bond, as these may better stabilise the tetrahedral boron intermediate. To test this hypothesis, we attempted the arylation procedure described by Aggarwal and co-workers using furan as our coupling partner (Scheme 80).[154] As we anticipated this reaction gave the desired coupled product **372** in moderate yield. Along with the postulated stabilisation imparted from sp^2-organometallics, both this reaction and the olefination are facilitated through a 1,2-metallate rearrangement.



Scheme 80: Organolithium-mediated arylation of **342**

Under similar conditions, a halogenation reaction has also been reported by Aggarwal and co-workers.[155] In this reaction the boronate is activated through the formation of an "ate" complex with an electron deficient aryl lithium to facilitate an S_N2 reaction. Unfortunately, when the reported conditions were applied to **342** no discernible product was observed by NMR analysis or mass spectrometry (Scheme 81). Alternating the electronics of the aryl lithium and electrophilic coupling partner, either *N*-bromosuccinimide (NBS) or iodine, did not lead to successful halogenation.

To better understand this reaction, we took an aliquot of the reaction between **342** and **373** and analysed the mixture using ^{11}B NMR spectroscopy. Due to the sensitive nature of the intermediate, the aliquot was dissolved in chloroform-d without removal of the reaction solvent and immediately analysed. Although the spectrum was weak, the absence of a peak around 30 ppm indicates that the reaction consumed the starting boronic ester. Furthermore, the only observable peak is at 5.7 ppm signifies that "ate" complex **375** was formed with no degradation of the boronic ester. This suggests that although **375** was formed, the S_N2 reaction is not possible with our substrate under these conditions, presumably due to the steric congestion from using a cyclic (rather than acyclic) boronic ester.



Scheme 81: Generation of "ate" complexes of **342** with aryl lithiums and attempted S_N2 halogenation

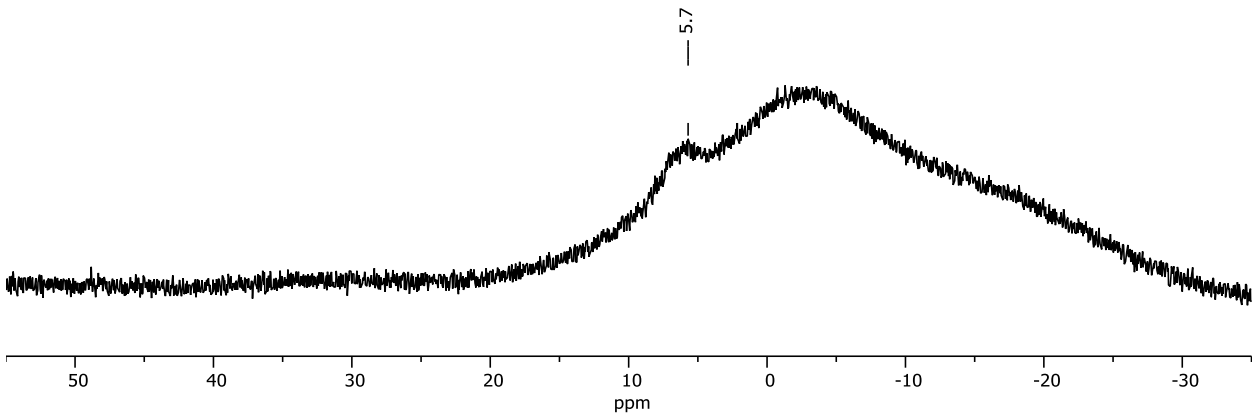


Figure 5: ^{11}B NMR analysis of "ate" complex formed under by reaction between **342** with aryl lithium **373**

In combination, these results indicate that the nucleophile's strength does not wholly dictate the favourability of the transformation. Instead, the way the nucleophilic carbon-boron bond transitions is key for successful reaction. Oxidation, olefination and arylation reactions shown previously all feature the intramolecular 1,2-metallate rearrangement as a key step in their respective mechanisms (Figure 6A), whereas the unsuccessful halogenation reaction operates through an intermolecular transition of the carbon-boron bond (Figure 6B). It is also worth noting that stoichiometry may play a significant role in these transformations. Both the formylation and amination reactions would also function through a 1,2-metallate rearrangement but were not successful (Scheme 76-Scheme 78). The olefination reaction utilised a large excess of reagents compared with the previous reactions (Scheme 79). Using a large excess of the arylating (**362**) or aminating (**366** or **368**) reagents could lead to the generation of boronates similar to those observed as intermediates in reactions of borane-derived 'ate'-complexes (Figure 6C).[156] Given that there is a precedent for these reactions to operate intermolecularly, this stoichiometry change may promote successful transformations of our boronic ester. Due to time constraints this premise was not examined, and we continued to investigate other transformations.

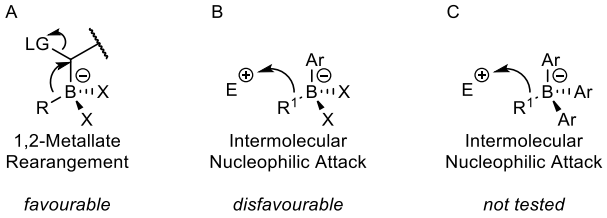
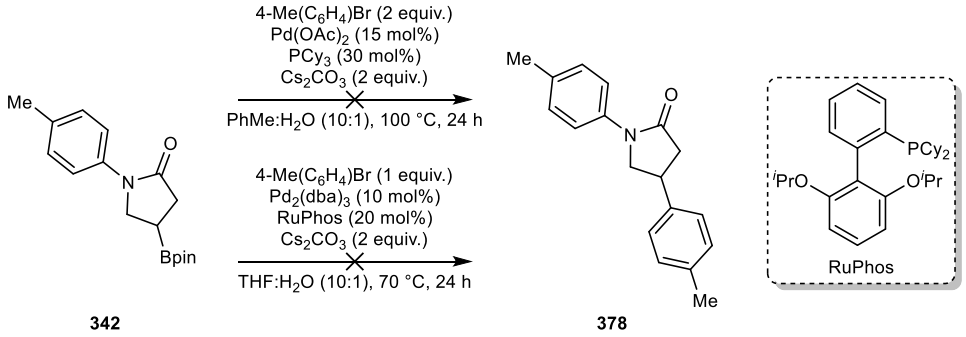


Figure 6: Possible transition pathways of nucleophilic carbon-boron bonds

To halogenate boryl lactam **342** we had to use transition metal catalysis. Li and co-workers have reported a Ag-catalysed fluorination procedure for alkyl boronates.[157] When applied to **342**, we were able to isolate fluorolactam **377** in moderate yield (Scheme 82). It is noteworthy that unlike the other procedures listed so far, this reaction proceeds through a radical mechanism, which presumably would lead to racemic products from chiral non-racemic boronates. However, this was not a concern for our study as **342** was used as a racemate.

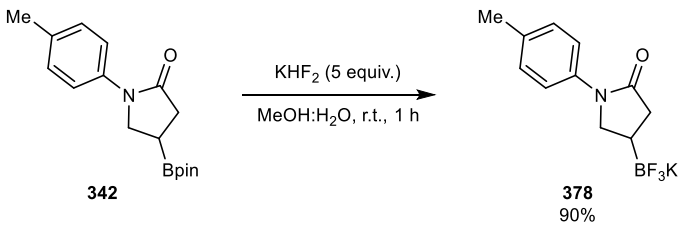
Scheme 82: Ag-catalysed fluorination of **342**

With the knowledge that transition metal catalysed reactions were suitable for our chosen substrate, we returned our focus to carbon-carbon bond-forming reactions. In recent years there have been numerous advances in Suzuki-Miyaura coupling that have allowed for the use of alkyl boronic acid derivatives as suitable nucleophilic coupling partners.[158–162] These methods typically employ electron rich phosphine ligands to overcome issues with the difficult transmetallation step of the reaction. Choosing 4-bromotoluene as a the model electrophile coupling partner we initiated our studies of this transformation by trialling two reported cross-coupling procedures (Scheme 83).[163,164] Unfortunately after 24 h neither of the reaction mixtures showed any conversion from ^{1}H NMR analysis.



Scheme 83: Attempted Suzuki-Miyaura coupling of **342**

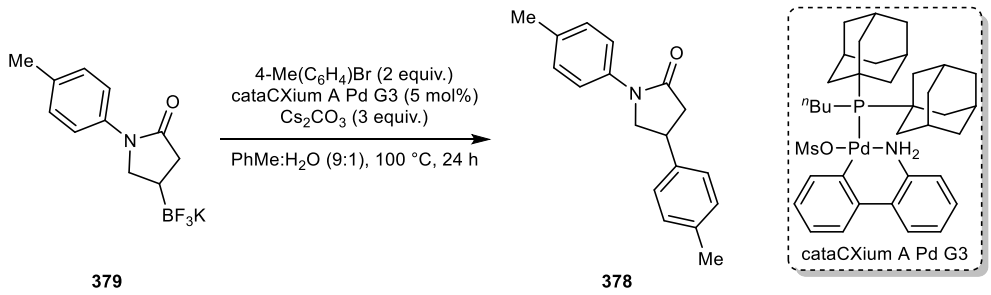
The lack of reactivity in these reactions is believed to be a result of the boronic ester's low Lewis acidity, hindering transmetallation. Trifluoroborate salts have been reported to be suitable coupling partners for Suzuki-Miyaura reactions. Lloyd-Jones and co-workers have studied such reactions and found that the borate is hydrolysed to the corresponding boronic acid under the reaction conditions.[31] This process is slow and avoids accumulation of the more reactive boronic acid, which in turn also reduce any possible degradative side reactions. To test the suitability of trifluoroborates for Suzuki-Miyaura coupling with aryl halides, boronate **379** was prepared according to a literature procedure (Scheme 84).[165]



Scheme 84: Preparation of trifluoroborate salt **378**

Londregan and co-workers have reported a coupling procedure optimised for boryl pyrrolidines using a third generation Buchwald precatalyst (cataCXium A Pd G3).[92] Pleasingly when **342** was submitted to these reaction conditions, coupled product **378** was observed but only isolated in poor yield (Table 4, Entry 1).

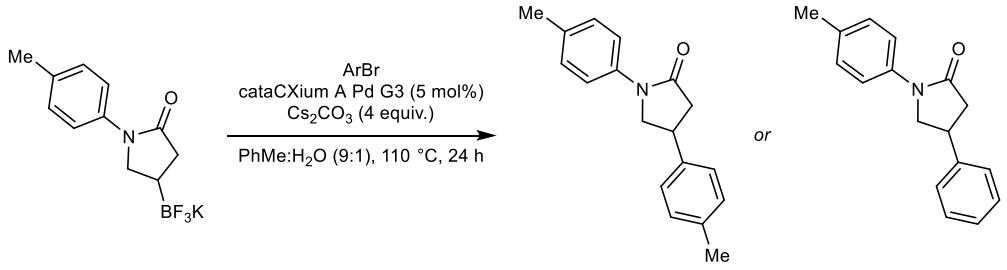
With this promising result in hand, we turned our attention to improving the reaction conditions, detailed in Table 4. Increasing the temperature to 110 °C had a positive effect on yield (Entry 2), but further increase in temperature only hindered the reaction (Entry 3). This could be due to an increase in the rate of hydrolysis being greater than the increase in the rate of transmetallation, leading to an increase in degradative side reactions. Alternating the base had little effect on the yield (Entry 4), whilst increasing the equivalency led to a significant increase in yield (Entry 5). The addition of Cu_2O gave a slight improvement in yield at 100 °C (Entry 6), presumably due to its ability to aid in transmetallation as a cocatalyst.[166] Combinations of the most promising results revealed that the best yield was achieved running the reaction at 110 °C with 4 equivalents of Cs_2CO_3 (Entry 7). All combinations featuring the addition of Cu_2O showed a reduction of yield compared to the results where the additive was omitted (Entries 8 - 10).



Entry	Devation from standard conditions	Yield
1	None	23% (9%)
2	110 °C	34%
3	120 °C	26%
4	K_3PO_4 instead of Cs_2CO_3	22%
5	4 equiv. Of Cs_2CO_3	45%
6	Addition of 1 equiv. Of Cu_2O	30%
7	110 °C, 4 equiv. Of Cs_2CO_3	54%
8	110 °C, Addition of 1 equiv. Of Cu_2O	20%
9	4 equiv. Of Cs_2CO_3, Addition of 1 equiv. Of Cu_2O	35%
10	110 °C, 4 equiv. Of Cs_2CO_3, Addition of 1 equiv. Of Cu_2O	41%

Table 4: Initial optimisation of Suzuki-Miyaura coupling, NMR yields calculated using 1,3,5-trimethoxybenzene as an internal standard, isolated yields given in parentheses

We then looked to further optimise these new conditions by alternating the stoichiometry of the reactants and solvent composition (Table 5). Increasing the concentration of water in the reaction led to significant reduction in the yield (Entries 2 and 3). Reducing the stoichiometry of the boronate gave the best yield observed yet, whereas making the aryl bromide the limiting reagent led to a reduction in yield (Entries 4 and 5). We tested conditions reported by Biscoe and co-workers (Entry 6), however found our conditions to be superior for reaction of **379**.[160] Finally we tested whether our conditions would work for boronic ester **342**, but unfortunately the coupled product **378** was only detected in poor yield (Entry 7). Disappointingly, when the reaction was performed on larger scale using phenyl bromide, we were only able to isolate the product in a yield of 30% (Entry 8).

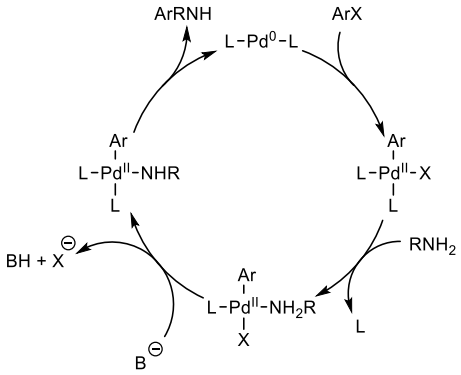


379 **378** **380**

Entry	RBF_3K	4-Me(C_6H_4)Br	PhMe:H_2O	Devation from standard conditions	Yield
1	1 equiv.	2 equiv.	9:1	-	54%
2	1 equiv.	2 equiv.	2:1	-	6%
3	1 equiv.	2 equiv.	1:1	-	2%
4	1 equiv.	1 equiv.	9:1	-	66%
5	1.5 equiv.	1 equiv.	9:1	-	30%
6	1.5 equiv.	1 equiv.	2:1	K_2CO_3 (3 equiv.)	6%
7	-	1 equiv.	9:1	RBpin (1 equiv.)	5%
8	1 equiv.	-	9:1	PhBr (1 equiv.)	(30%)

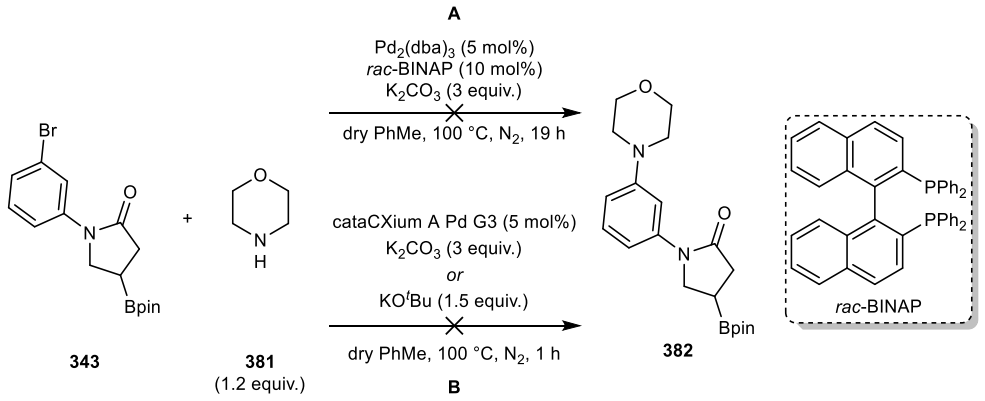
Table 5: Further optimisation of Suzuki-Miyaura coupling, NMR yields calculated using 1,3,5-trimethoxybenzene as an internal standard, isolated yields given in parentheses

Throughout our investigations of the Suzuki-Miyaura coupling of **342**, NMR and mass spectrometry analysis showed that the boronic ester did not take part in the reaction and was returned with minimal degradation. This led us to consider whether the boron moiety could be orthogonal to other Pd-mediated transformations. Whilst exploring the scope of the reaction we were able to prepare a boryl lactam featuring the aryl bromide functionality **343**. Due to the large prevalence of nitrogen containing bioactive molecules, Buchwald-Hartwig coupling has quickly become the third most used method for carbon-nitrogen bond formation in medicinal chemistry.[20] The mechanism of coupling is similar to that of Suzuki-Miyaura coupling. The major differences are that the nucleophilic coupling partner coordinates directly to the metal, with a stronger sterically hindered base being required to promote the reductive elimination (Scheme 85).[167] Due to this the reaction can, and often is, carried out under dry conditions. Under these conditions, the lactam boronic ester should be stable to degradation. There is no water to promote hydrolysis and the weakly nucleophilic nature of the base shouldn't promote other degradative pathways for the boronic esters.



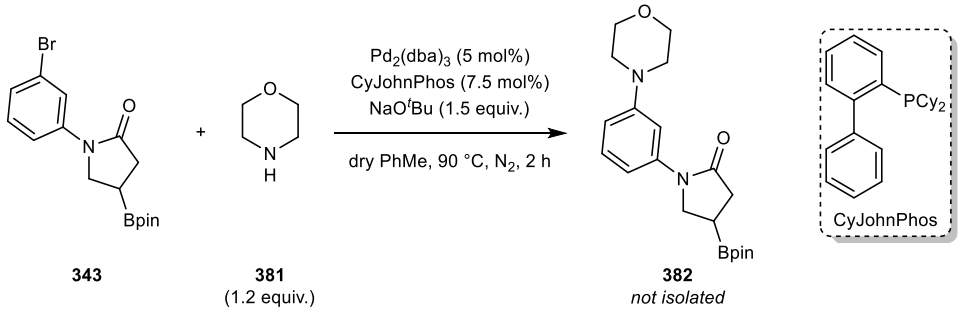
Scheme 85: Mechanism of Buchwald-Hartwig coupling

The first attempt at this coupling using a literature procedure with morpholine, $Pd_2(dba)_3$ and *rac*-BINAP failed to give any of the desired product **382** (Scheme 86A).[168] We next attempted to use these conditions again, instead switching the Pd ligand combination for the precatalyst (cataCXium A Pd G3). This again failed to yield morpholine **382**, which we assumed was a result of the weak base, however, use of a stronger base was also unsuccessful (Scheme 86B).



Scheme 86: Initial attempts at Buchwald-Hartwig coupling of **343** with morpholine.

Instead, we found that CyJohnPhos was crucial in order to promote the coupling. Using a literature procedure, we were able to synthesis morpholine **382** but disappointingly we were not able to purify the crude material (Scheme 87).[169] The issues with isolation were attributed to the low stability of the boryl lactam on silica. This result is similar to those observed with the isolation of **342** from the conjugate borylation of α,β-unsaturated lactam **353**. This indicates that although our lactam scaffold can feature orthogonal functionalities, priority should be given to the transformation of the boronic ester in a reaction sequence for successful derivatisation of our scaffolds.



Scheme 87: Buchwald-Hartwig coupling of **343** and morpholine

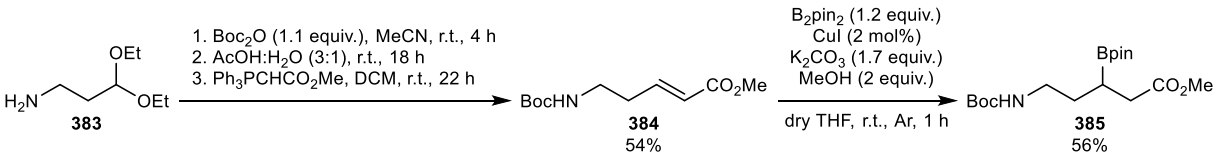
2.3.7 Initial Investigation of the Conjugate Borylation/Cyclisation of *N*-Boc Amino Enoates

The overriding objective of this study is to prepare sp^3-rich borylated heterocycles. However the lactams that we have so prepared are completely saturated in the heterocyclic ring, they also feature an aryl substituent on the nitrogen atom. Although this has allowed us to hinder cyclisation in borylation stage of our procedure to better understand the cyclisation, it is somewhat counterintuitive to our aims. To prepare scaffolds that have increased functionality and are sp^3-rich we decided to study a new model substrate.

The most obvious way to add an extra reactive handle would be to remove the nitrogen substituent completely. For the cyclisation to be possible and the scaffold to retain a NH functional handle, the model substrate would require a primary amine. To the best of our knowledge the conjugate borylation of a substrate featuring a 1° alkyl amine as a non-participating functional group has yet to be reported in the literature. This lack of data could be a result of the functionality not being tolerated by the reaction conditions. We observed no issues borylating 2° alkyl amines (**294**, **298** and **300**); except for the problematic purification of the lactam boronic esters.

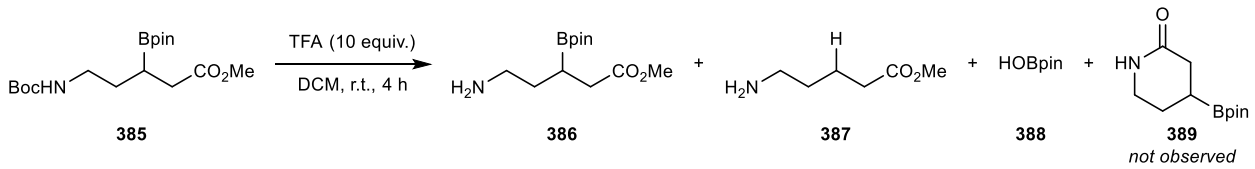
To avoid complicating our studies further we decided to design a new substrate with a Boc protecting group on the nitrogen. This would deactivate the amine functionality, hopefully both making it compatible with the Cu-catalysed borylation and shutting down reactivity with regards to cyclisation. Also, as previously stated, the 5-*exo*-*trig* transition is preferential to 6-*exo*-*trig*, thus increasing the carbon chain length by one should further hinder cyclisation. Furthermore, Boc protected amines have been shown to be suitable for a range of 5-*exo*-*trig* cyclisations but not 6-*exo*-*trig*.[170–172]

By combining these requirements, we choose **384** as our model substrate. This was prepared through the sequential Boc protection of amine **383**, hydrolysis of the acetal and a Wittig reaction of the aldehyde with methyl (triphenylphosphoranylidene)acetate (Scheme 88). This sequence is straight forward, no purification is required between each step and gives enoate **384** in moderate yield. ^{1}H NMR analysis of the crude material showed the Wittig reaction to be completely *E*-selective, evidenced by the coupling constant of the alkenyl protons (J = 15.8 Hz). As designed, when **384** was submitted to the borylation conditions only the boryl amino ester **385** was observed and isolated from the reaction mixture.



Scheme 88: Synthesis of boryl amino ester **385**

Removal of the Boc protecting group is typically achieved through the addition of an acid. These acidic conditions could also be suitable to promote the cyclisation of the boryl amino ester. Deprotection is typically achieved through the addition of trifluoroacetic acid (TFA) which generates isobutylene and CO_2 as the by-products. Both TFA and isobutylene are volatile and easily removed through evaporation which should simplify the isolation of the desired boryl lactam **389**. Analysis of the crude material by ^{1}H and ^{11}B NMR showed that cyclisation had not occurred (Scheme 89). Instead, the amine had been deprotected and a signal at 22.8 ppm in ^{11}B spectrum indicated the boronic ester had been partially hydrolysed liberating hydroxy borate **388** (Figure 7, Lit. 22.4 ppm).[173]



Scheme 89: Deprotection of **385** using TFA

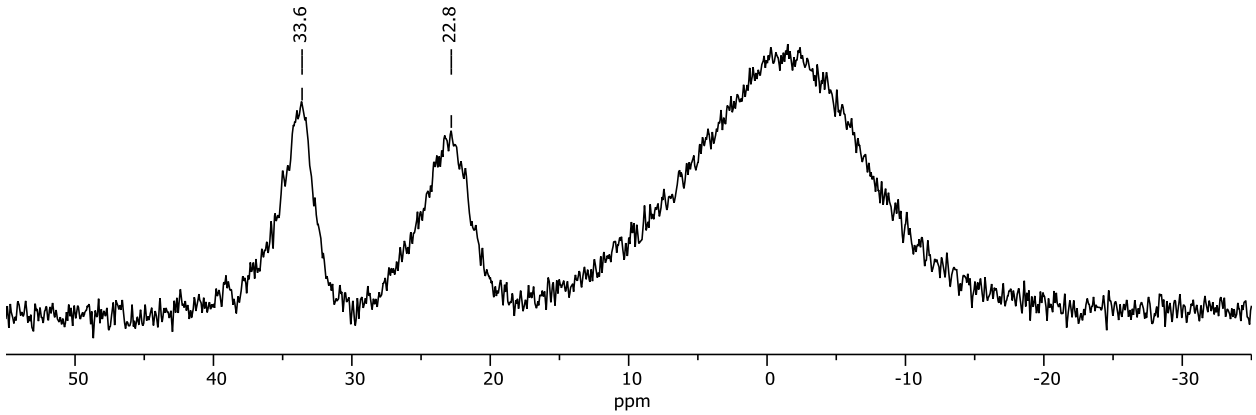
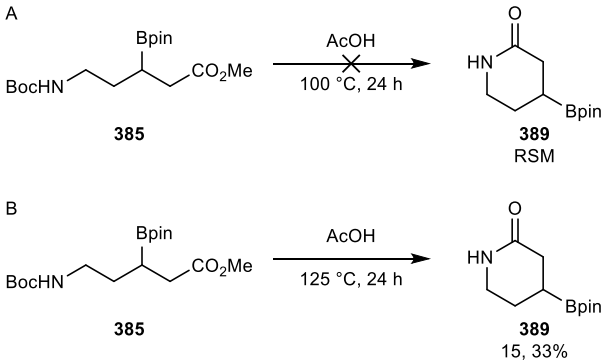


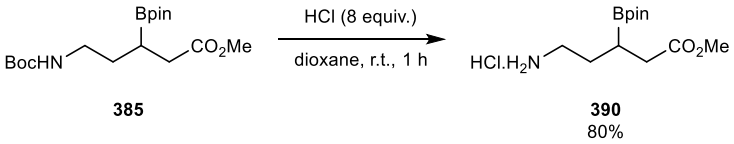
Figure 7: ^{11}B NMR spectrum of the crude reaction mixture for the TFA mediated deprotection of **385**

TFA is a stronger acid than acetic acid, but we were surprised to observe the apparent hydrolysis given that the *N*-aryl amino esters had all been stable to the previously described acidic conditions. Predicting **385** would not undergo deprotection or cyclisation in acetic acid at 50 °C, we tried stirring at 100 °C. This too was unsuccessful, returning only the starting material unchanged. However, increasing the temperature to 125 °C gave the desired lactam **389**, but with significant mass loss (15% yield of **389**). The reaction was repeated, although the yield had improved (33%) there was no immediate explanation for the mass loss, as lactam **389** was obtained clean from the work-up. Reaction monitoring experiments revealed that complete conversion of amino ester **385** to lactam **389** occurred within 1 h, with no observed degradation of the boron functionality. The intermediate deprotected amine **386** was not observed in these experiments suggesting that at this temperature the amino ester immediately cyclises.



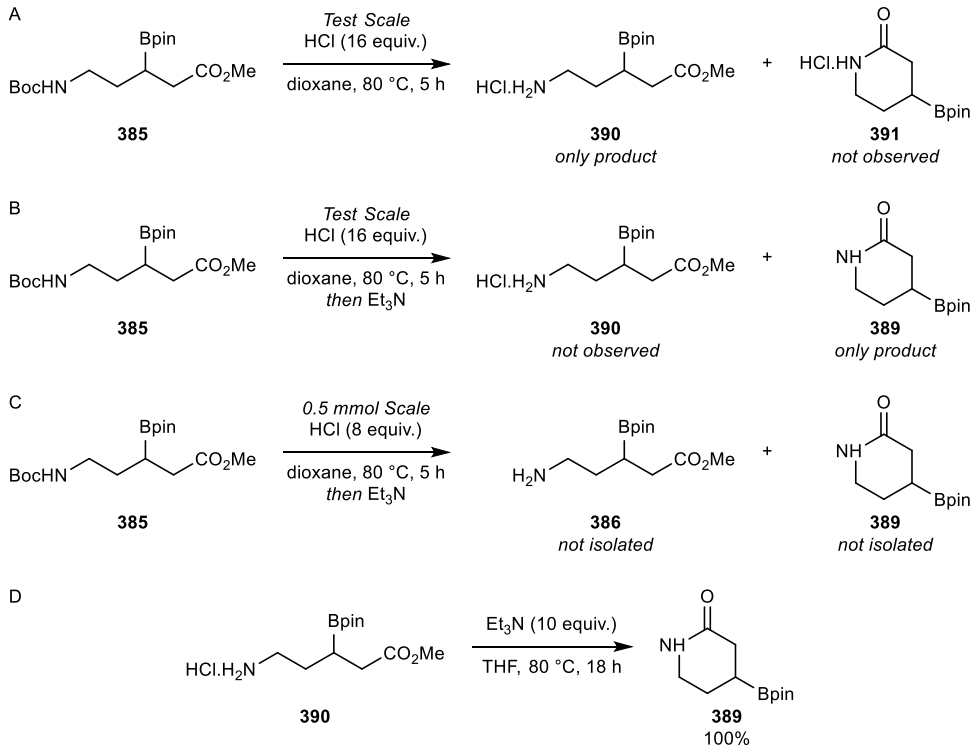
Scheme 90: Acetic acid deprotection/cyclisation of **385**

Given the lack of decomposition products observed and the significant mass loss, it was concluded that this was a result of the aqueous solubility of the lactam **389**. To improve the yield of this reaction we decided to try to optimise a procedure in which the lactam does not encounter water at any stage. HCl dissolved in organic solvents is another common reagent for removal of Boc groups, which is usually removed by evaporation to give the hydrochloride amine salt. As expected, when amino ester **385** was stirred at room temperature only hydrochloride amine salt **390** was isolated (Scheme 91).



Scheme 91: Synthesis of hydrochloride amino salt **390**

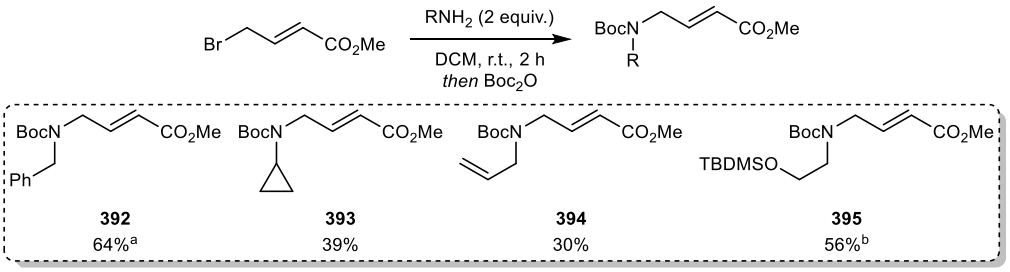
We next decided to investigate whether increasing the reaction temperature could trigger the cyclisation, giving the hydrochloride salt of the lactam **391**. A test scale reaction revealed that running the reaction at 80 °C still only gave only the hydrochloride amine salt **390** (Scheme 92A). In this reaction, double the volume of HCl in dioxane was used to ensure stirring of the reaction mixture, given the small reaction volume on this reduced scale. When the reaction was quenched with Et_3N and diluted with Et_2O, so that Et_3N.HCl could be removed by filtration, only desired lactam **389** was observed (Scheme 92B). Unfortunately, when repeated on a large scale for isolation, the reaction produced a mixture of the free amino ester **386** and lactam **389**; making the small-scale reaction somewhat anomalous (Scheme 92C). This is likely due to the cyclisation of the amino ester requiring elevated temperatures to cyclise, which are not provided from the large-scale reaction. Presumably the reason we observed only the lactam in the small-scale experiment is due to the heat transfer from the vial being sufficient for the transformation. When hydrochloride amine salt **390** was treated with Et_3N at 80 °C in THF the lactam **389** was isolated in quantitative yield (Scheme 92D). The reaction was repeated, and the result replicated confirming the reproducibility of our new procedure (Scheme 92D).



Scheme 92: Optimisation of the synthesis of **389**

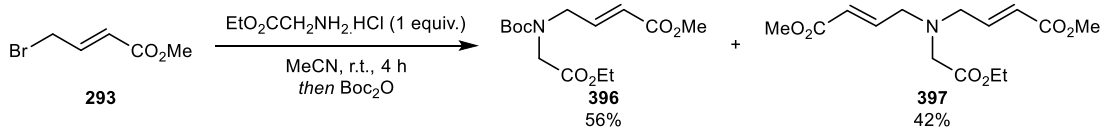
2.3.8 Synthesis of *N*-Boc Amino Enoates

With the knowledge that our deprotection/cyclisation strategy was possible, we desired to isolate the *N*-alkyl borylated lactams, which had previously not been possible. In order to do this, we decided to modify our synthetic procedure for *N*-alkyl amino enoates to prepare the required substrates. Addition of di-*tert*-butyl dicarbonate to the crude mixture along with further stirring gave the desired *N*-Boc amino enoates (Scheme 93), featuring alkene (**394**) and silyl ether (**395**) functional handles.



Scheme 93: Synthesis of *N*-Boc amino enoates from free amine ([a]$BnNH_2$ (2.5 equiv.), [b]$TBDMSO(CH_2)_2NH_2$ (2.2 equiv.))

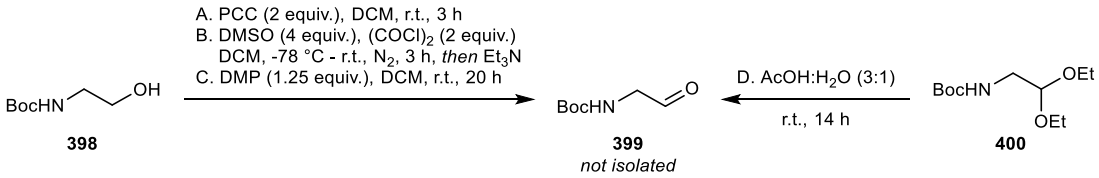
Amino acids, and their derivatives, are a valuable feedstock in chemical synthesis due to their relatively simple biosynthesis from sugars with modified bacteria.[174] Using a literature procedure for the alkylation of alkyl bromides with hydrochloride amine salts, we prepared **396** with a pendent ester group from glycine methyl ester hydrochloride (Scheme 94).[175] Dialkylated amine **397** was isolated as the minor product.



Scheme 94: Synthesis of enoate **396**

As a continuation to the previous section, we wished to prepare the boryl γ-lactam with no substitution on the nitrogen. This could possibly be done using the same synthetic procedure as we had used for enoate **384** using an acetal protected amino acetaldehyde. However amino alcohols are a more common chemical feedstock, readily prepared from the reduction of amino acids. We believed that the development of a synthetic procedure for the conversion of amino alcohols into the corresponding amino enoates could be advantageous. Given the vast numbers of commercially available amino alcohols this should allow us to readily prepare substrates that could have increased complexity on the heterocyclic ring system.

Unfortunately, we were unable to prepare aldehyde **399** using several standard oxidation procedures (Scheme 95A, B or C). Typically, in the reactions using chromium reagents or Swern conditions very little product was observed by ^{1}H NMR analysis of the crude material. Dess-Martin periodinane (DMP) gave complete conversion of the alcohol to aldehyde. Furthermore, the ^{1}H NMR analysis of this crude reaction mixture showed that **399** was the major component (Figure 8). However, the product that was detected in the crude material could not be isolated upon purification from any of the oxidation methods. To check this result, we attempted the hydrolysis of acetal **400**, but the same issues with isolation were also observed (Scheme 95D).



Scheme 95: Attempted preparation of aldehyde **399**

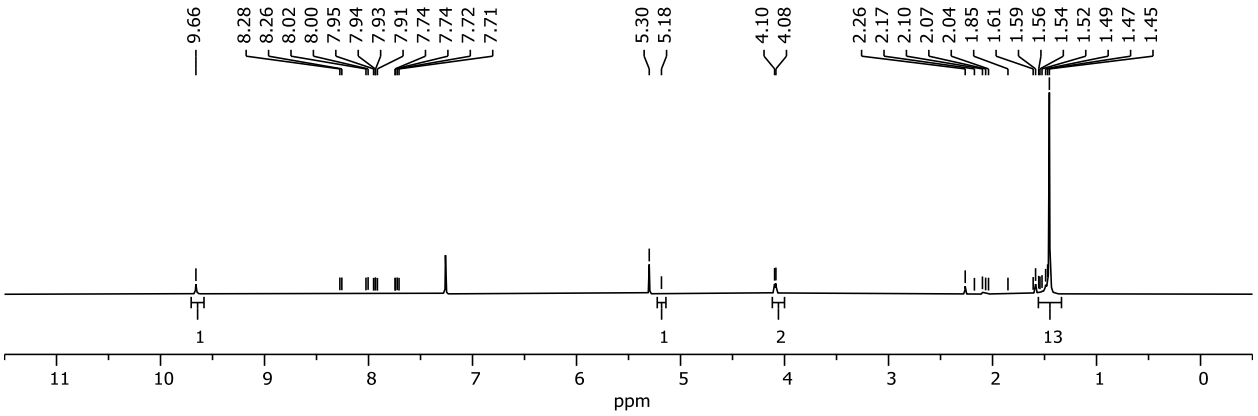
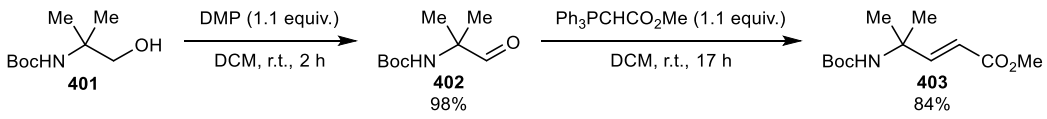


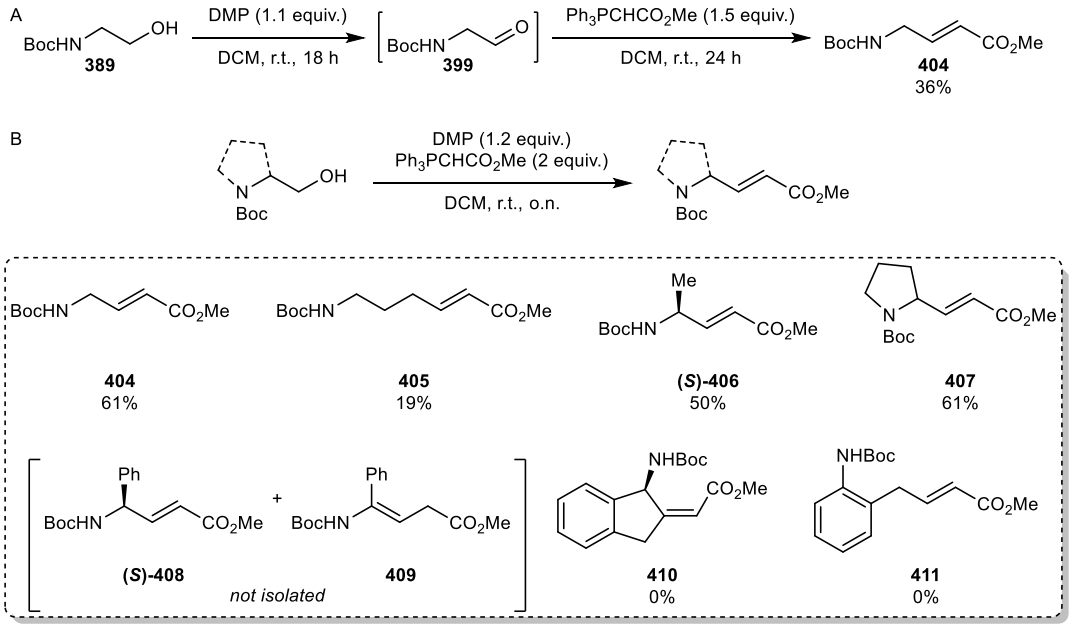
Figure 8: Crude ^{1}H NMR analysis of oxidation of **398** using DMP

We believed that the instability of aldehyde **399** could be result of its mildly acidic protons α to the nitrogen atom. Their enolisable nature could lead to unwanted aldol-type side reactions. We tested this theory by oxidising alcohol **401**, which feature *gem*-dimethyl substitution α to the nitrogen eliminating self-condensation of the product. Treatment of the alcohol with DMP gave the desired aldehyde **402** in quantitative yield clean from work-up (Scheme 96). Olefination of the aldehyde using a Wittig procedure occurred without issue producing enoate **403** as a single stereoisomer, assigned *E* by ^{1}H NMR analysis of the alkenyl protons (J = 15.9 Hz)



Scheme 96: Synthesis of enoate **403**

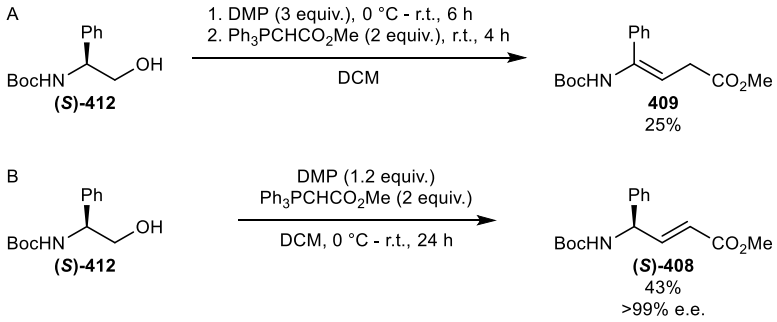
In order to overcome the instability of **399** we submitted the crude oxidation product of **398** to the Wittig olefination conditions. The yield of this reaction was poor even if it did allow for the isolation of enoate **404** (Scheme 97A). Marsden and co-workers have reported the synthesis of the ethyl ester of **404** using a one-pot oxidation/Wittig procedure.[176] This should reduce any possible aldol-type side reaction as they would now be in competition with the olefination. Using an adaption of this procedure we were able prepare **404** alongside three other *N*-Boc amino enoate, which could be used to prepare borylated lactams with different ring sizes and substitution patterns on the ring (Scheme 97B). All enoates were formed as single stereoisomers. Unfortunately, this procedure was not suitable for all of the alcohols that we used. Alkene **408** could not be easily separated from alkene migration product **409**. Additionally, the attempted syntheses of **410** and **411** were not successful.



Scheme 97: One-pot Oxidation/Wittig synthesis of *N*-Boc amino enoates

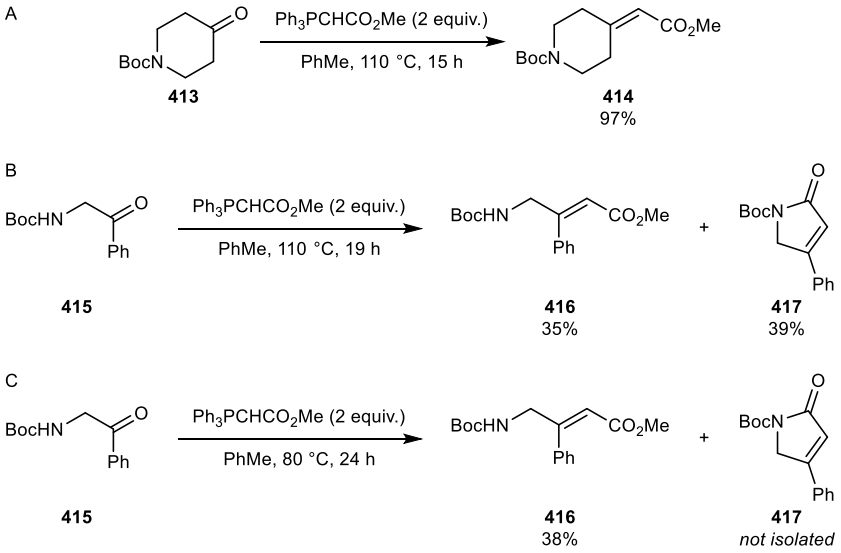
The limitations of this procedure would appear to be the use of 2-phenylethanol derivatives, as we were also unable to prepare **410** or **411**. This is most likely due to labile benzylic proton causing an unwanted side reaction. Enoate **410** was not observed by ^{1}H NMR analysis, which is not surprising given the low reactivity of the ketone intermediate (Scheme 98A). In the case of **411**, mass spectrometry analysis of the crude material showed a small peak that could possibly correspond to the Na adduct of **411** (*m/z* 314.1 Da), although it could also be the alkene migration product similar to **409**.

Attempts to increase the yield of **408** by separating the oxidation and olefination reactions failed to give the desired product. Instead, only enamine **409** was isolated in poor yield (Scheme 98A). We found the best way to increase the yield of this product was to initiate the reaction at 0 °C before warming to room temperature, this still gave a modest yield of 43% (Scheme 98B). HPLC analysis of enoate **408** showed that the starting material was enantiopure and no erosion of the stereocentre had occurred in the reaction.



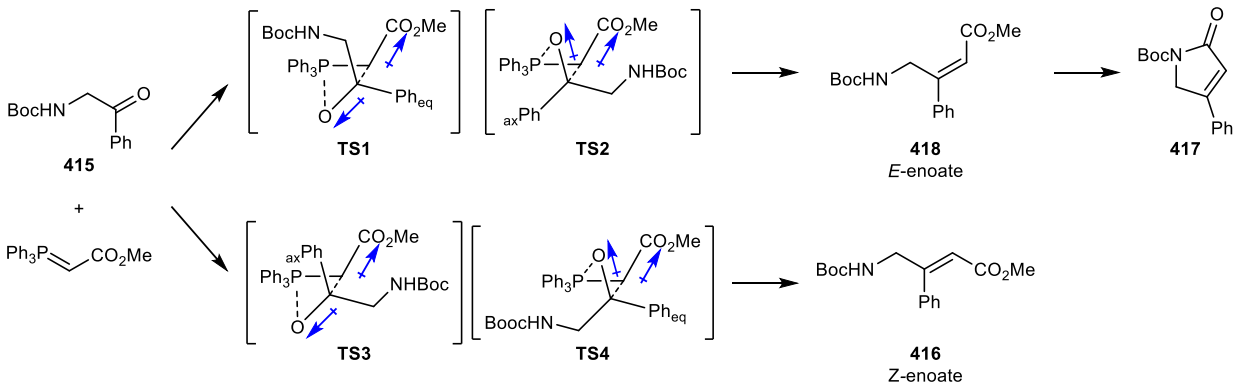
Scheme 98: Improvements to the synthesis of enoate **408**

The synthesis of enoate **414** was considerably simpler. Refluxing ketone **413** with ylide gave the desired product in quantitative yield without need for further purification (Scheme 99A). This successful reaction prompted us to test unsymmetrical ketone **415**. Using the same conditions we observed roughly equal formation of enoate **416** and α,β-unsaturated lactam **417** (Scheme 99B). The lactam most likely originates from the cyclisation of *E*-enoate **418** at elevated temperatures, given that enoate **416** has not cyclised under these conditions it is assumed that this is the *Z*-enoate. Attempts to lower the reaction temperature had no effect on the stereoselectivity of the reaction (Scheme 99C). Analysis of the crude materials by ^{1}H NMR spectroscopy showed both products were formed but only the *Z*-enoate was isolated.



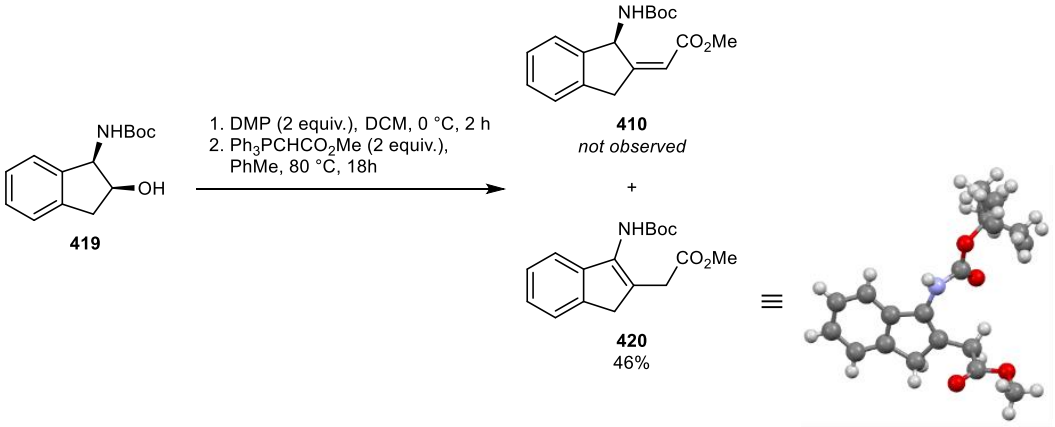
Scheme 99: Wittig reactions of ketones **413** and **415**

Independent of ylide stabilisation effects, with a few exceptions, Wittig reactions are thought to be under kinetic control, irreversibly forming an oxaphosphetane intermediate through a cycloaddition.[177] The stereochemical outcome of the reaction is determined at this point by steric and electrostatic interactions in the transition state (Scheme 100). It has been proposed that the factors influencing transition states are dominated by minimisation of the dipole-dipole interactions; which for stabilised ylide, such as the one used, is large.[178] The next determinant factor is the sterics of the ketone substituents. From this perspective, formation of *E*-enoate **418** should be favoured due to the larger A-value of the phenyl substituent, preferring the pseudo-equatorial position (TS1) Prediction of the dominant transition state is complicated by the additional electrostatic interactions of the pendent amine. Unfortunately, our reactions on ketone **415** did not result in an excess of one *E*/*Z* isomer. Instead, it is assumed under our reaction conditions the corresponding transitions states for formation of the *E* and *Z* isomers are of similar energy, resulting in both stereoisomers being formed.



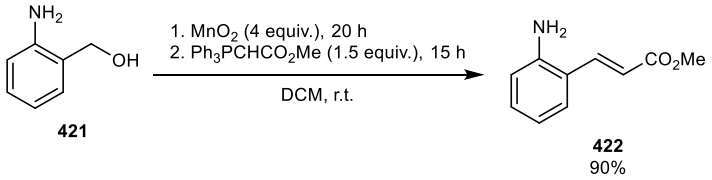
Scheme 100: Possible transition states in the Wittig reaction of enoate **415**

We returned to the transformation of alcohol **419** in order to prepare **410** using elevated temperature to promote reaction with ylide. However, the desired product was not observed in the ^{1}H NMR analysis of the crude mixture. Initially unsure of what had been isolated from this reaction, we analysed the product by single crystal X-ray diffraction. This revealed that alkene bond migration had occurred for this substrate giving enamine **420** as the only product (Scheme 101). **410** was not observed in the by ^{1}H NMR analysis of the crude material and so we decided not to investigate the compound any further.



Scheme 101: Synthesis of enamine **420**

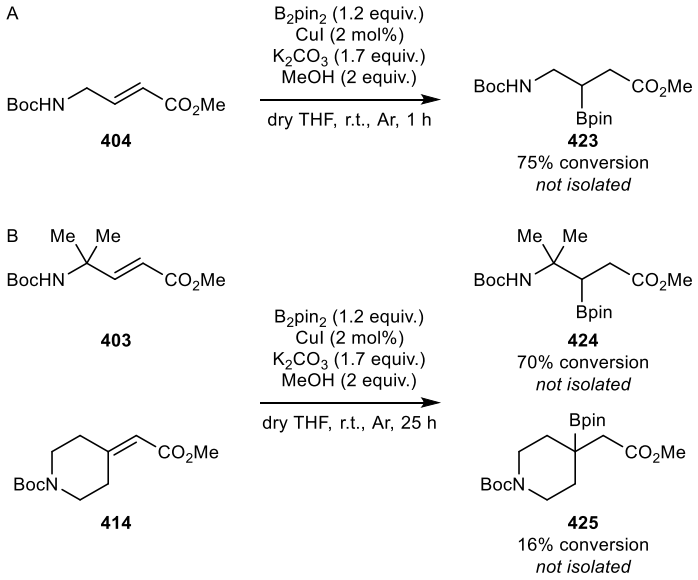
Given that the synthesis of enoates **410** and **411** had been unsuccessful, we still wished to prepare a substrate that could be used to prepare a partially saturated polycyclic scaffold. Given the issues that we had so far observed in the synthesis of enoates we decided to be selective about what substrate we should use. We need to select an alcohol which upon oxidation would feature no benzylic or enolisable protons. The simplest alcohol fitting this description is 2-aminobenzylalcohol **421**. Oxidation using MnO_2 followed by olefination via a Wittig reaction furnished desired enoate **422** in excellent yield (Scheme 102). ^{1}H NMR analysis of the alkenyl protons indicate this also was the *E*-enoate (J = 15.8 Hz). Although this enoate does not feature a Boc protecting group to hinder cyclisation, we believed that the weak nucleophilic of the aniline should be sufficient.



Scheme 102: Synthesis of enoate **422**

2.3.9 Development of a Conjugate Borylation/Cyclisation Procedure for *N*-Boc Amino Enoates

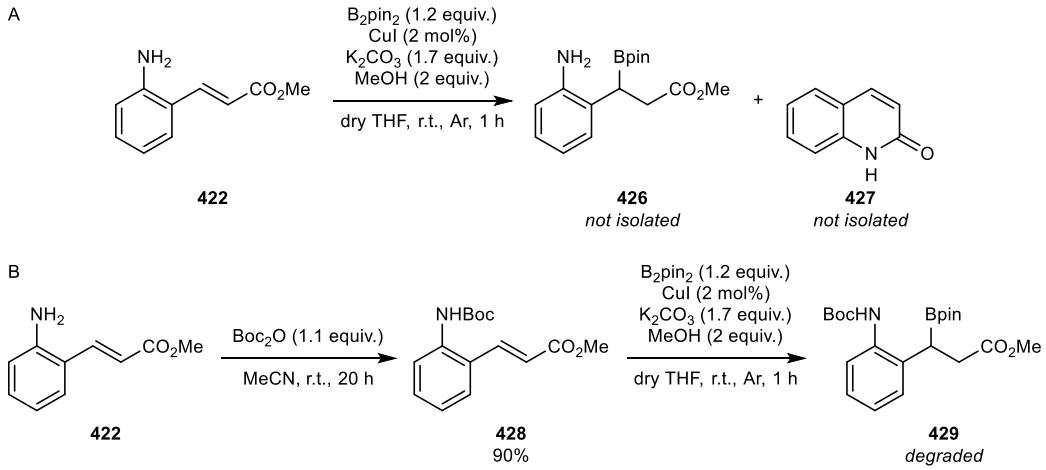
Some of the enoates we had prepared in the previous section are significantly more complex than those that have so far been tested. We began our development by running test reactions on some of the enoates using the previous borylation conditions. When enoate **404** was submitted to the reaction we only observed 75% conversion to amino ester **423** after 1 h (Scheme 103A). Attempts to separate the product from the starting materials by chromatography were unsuccessful due to the extremely similar polarities of the two species. Likewise, when enoates **403** and **414** were submitted to the reaction conditions, incomplete conversions were observed (Scheme 103B). These results showed that this borylation method would not be suitable for the *N*-Boc amino enoates.



Scheme 103: Test conjugate borylation of enoates **403**, **404** and **415**

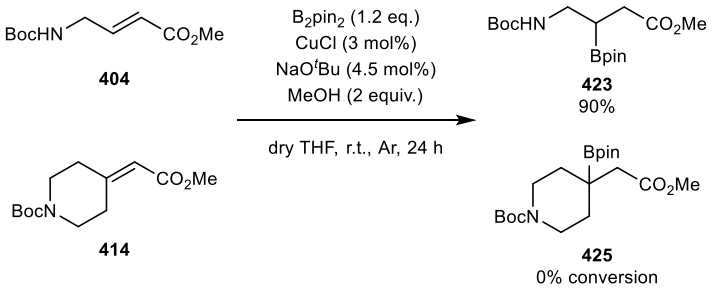
Before testing other borylation procedures we also investigated the borylation of **422** using the previous conditions (Scheme 104A). Interestingly ^{1}H NMR analysis of the crude material from this reaction revealed that the amino ester had cyclised, but it was unclear which compounds were in the residue. Mass spectrometry revealed that amino ester **426** was predominantly cyclised and oxidised to 2-hydroxyquinoline **427** (*m/z* 146.1 Da). The cyclisation of amino ester **426** was somewhat surprising due to the amine functionality being an aniline. In our previous studies we had specifically used aniline to stop cyclisation in order in isolate a more stable intermediate. Furthermore, this is a 6-*exo*-*trig* cyclisation, which should be less favourable than the previous 5-*exo*-*trig* cyclisation, which required promotion using an acid solvent. We deduced that the cyclisation of this substrate must be a result of the rigid nature of the fused aromatic ring, similar to the cyclisation that resulted in the formation of lactam **417**. Additionally, the generation of aromaticity through oxidation likely also promotes this reaction.

To stop the cyclisation, we decided to protect the amine functionality of **422** using a Boc group (Scheme 104B). When submitted to the borylation condition we found that this was sufficient to stop cyclisation, furnishing amino ester **429**. Unfortunately, whilst developing column conditions we noticed a significant difference in the TLC plates obtained immediately after work-up and the ones that were currently being prepared. Re-analysis of the crude material by ^{1}H NMR revealed that the compound had degraded significantly. Due to time constraints, this reaction was not investigated further.



Scheme 104: Attempts to borylate enoate **422**

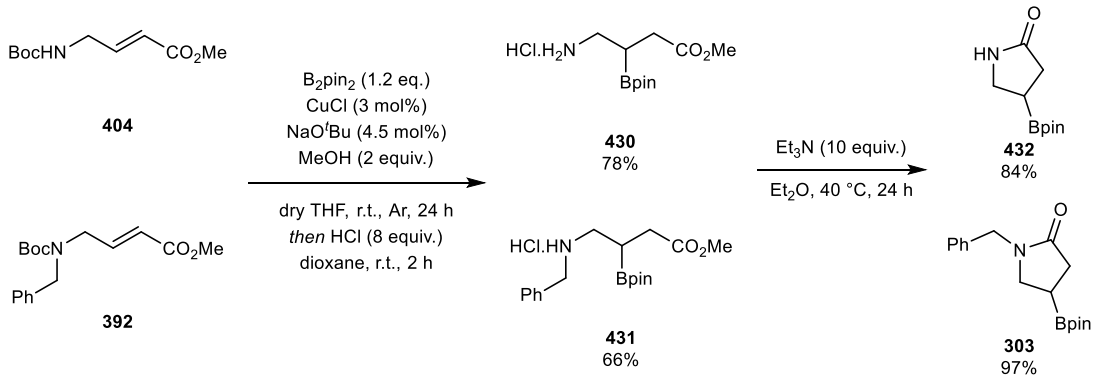
Continuing our examination of borylation procedure, we began to adapt the procedure reported by Lee and Yun, starting with reactions without an ancillary ligand. Under these conditions, the boryl amino ester **423** was isolated in excellent yield (Scheme 105). However, under the same conditions enoate **414** failed to react.



Scheme 105: Conjugate borylation of enoates **404** and **414**

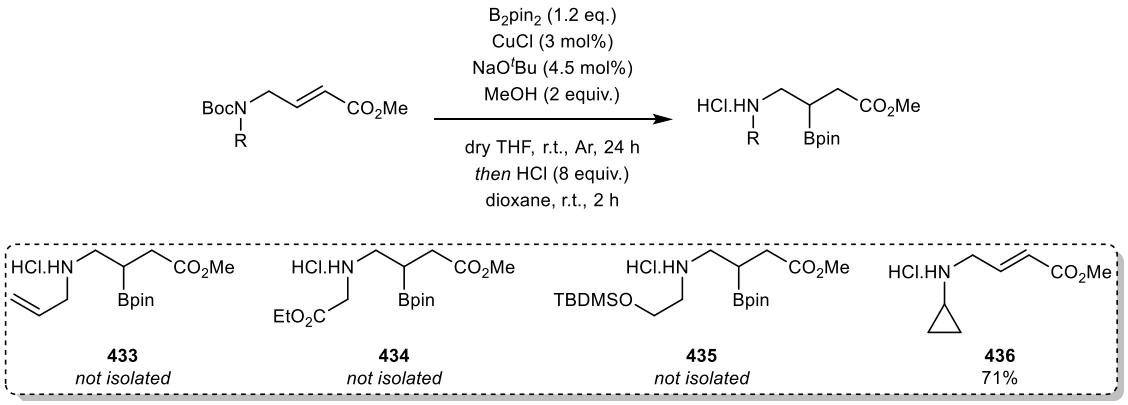
This result led us to question if it would be possible to simplify our methodology by telescoping the reaction sequence from the *N*-Boc amino enoates to the boryl lactams without chromatographic purification. Our initial investigations for the borylation/cyclisation revealed that the deprotection of *N*-Boc amino esters generates hydrochloride amine salts (section 2.3.7). If crashed out with a suitable solvent (Et_2O) these salts are easily isolated from crude mixture through filtration. Borylation of the enoates typically gave complete conversion to the boryl amino ester, with the Cu and base being removed by filtration through a plug of celite. ^{1}H and ^{11}B NMR analysis of the crude material showed the presence of only the product, remaining B_2pin_2 and the borate by-product MeOBpin. The diboron and borate should be unchanged by the acidic deprotection and are soluble in Et_2O. If the hydrochloride amino salt can successfully be precipitated from the crude mixture, the impurities should be easily removed from the reaction mixture by further filtration. This strategy would allow for conversion of the enoates into the boryl lactams without the need for column purification, which had previously caused considerable issues.

Although this methodology might not be suitable for some of the enoates we had so far prepared, we believed the potential simplification it could offer merited investigation. Using the previously described borylation procedure followed by removal of the insoluble components of the reaction gave the crude boronic ester intermediate, as observed by NMR analysis. After borylation of enoate **404** and treatment with HCl, we were able to isolate amine salt **430** by removal of the reaction solvent, trituration with Et_2O followed by filtration. It was possible to cyclise the amino ester to the desired lactam with Et_3N refluxing in Et_2O. Finally, filtration and concentration of the reaction mixture gave boryl lactam **432** in very good yield. Enoate **392** also underwent efficient conversion to boryl lactam **303** using this procedure. The only alteration we made to the procedure was not concentrating the mixture before trituration with Et_2O. We believe that the moderate yield of amine salt **431** is a result of the compound partial solubility in dioxane. This is a significant result as our previous methodology had been unsuitable for the preparation borylated *N*-alkyl lactams, particularly **303**.



Scheme 106: Synthesis of boryl lactams **303** and **342**

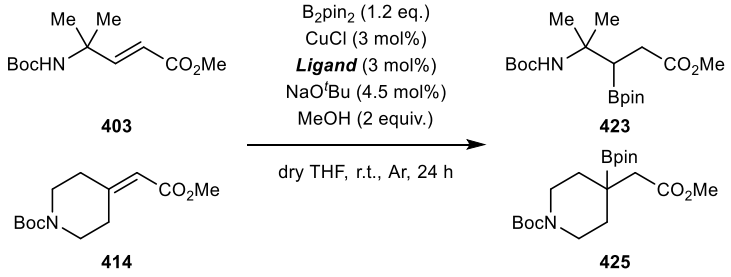
Unfortunately, significant issues were found when we began to examine some of the other enoates. The isolation of amino salts **433 - 435** by precipitation was found not to be possible. In addition to this, the mass returned from the reaction was considerably lower than expected. The most extreme intolerance to the procedure was enoate **393**, which failed to undergo borylation under the reaction conditions; instead yielding amino salt **436**. We presume this is due to the steric hindrance of the 2° amine substituent preventing borylation. This unfortunately meant that our simplified general procedure was not sufficiently general, and so we would need to isolate the borylated *N*-Boc amino esters instead.



Scheme 107: Attempted borylation/deprotection of enoates **393 - 396**

Given that it was clear that a ligand would be required in order to develop a general conjugate borylation procedure, we focused our attention on the optimisation of this reaction. Both enoates **403** and **414** represent two of the most challenging substrates to borylate; **403** features a quaternary carbon substituted alkene, whereas **414** contains a trisubstituted alkene. We used both substrates in ligand screening experiments to identify a suitable ligand for these reactions. We based our screening experiments on the procedure from Lee and Yun, as this was proven to be suitable for phosphine ligands.[117] We explored the use of a range of ancillary ligands, including phosphines and a *N*-heterocyclic carbene, the results of which are summarised in Table 6. All reactions in the screen were prepared using a stock solution of all the reagents except the ligands and additional base required for the tetrafluoroborate salts.

These results show that SImes is the best general catalyst for the borylation of our substrates (Entry 7), though use of bisphosphine dppBz gave only slightly lower yield (entry 3). Interestingly, whilst PCy_3 proved to be an excellent catalyst for the borylation of enoate **403**, the same was not true for the reaction of **414** (Entry 6). Both PCy_3 and CyJohnPhos performed poorly in the borylation reaction with **414** (Entries 1, 6 and 7). Given the success of the electron rich NHC ligand, the poor yield with PCy_3 and CyJohnPhos could be explained by the bulky phosphine substituents forming a Cu-catalyst that is too large to react with the sterically encumbered trisubstituted enoate.



Entry	Ligand	423	425
1	No ligand	23%	3%
2	PPh_3	94%	52%
3	dppBz	>99%	87%
4	*rac*-BINAP	80%	55%
5	CyJohnPhos	54%	9%
6[a]	PCy_3-HBF_4	>99%	1%
7[a]	SImes-HBF_4	>99%	91%

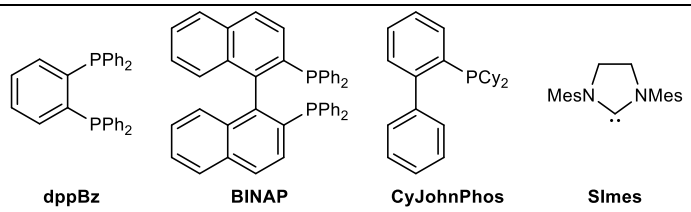
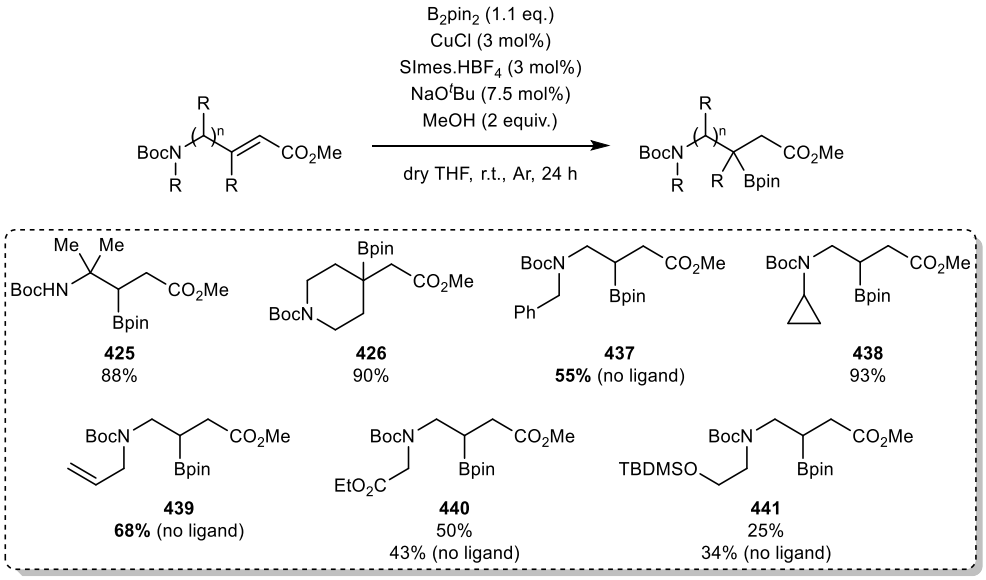


Table 6: Ligand screen for borylation of enoates **403** and **414**, NMR yields calculated using 1,3,5-trimethoxybenzene as an internal standard, [a]7.5 mol% of NaO^{t}Bu used

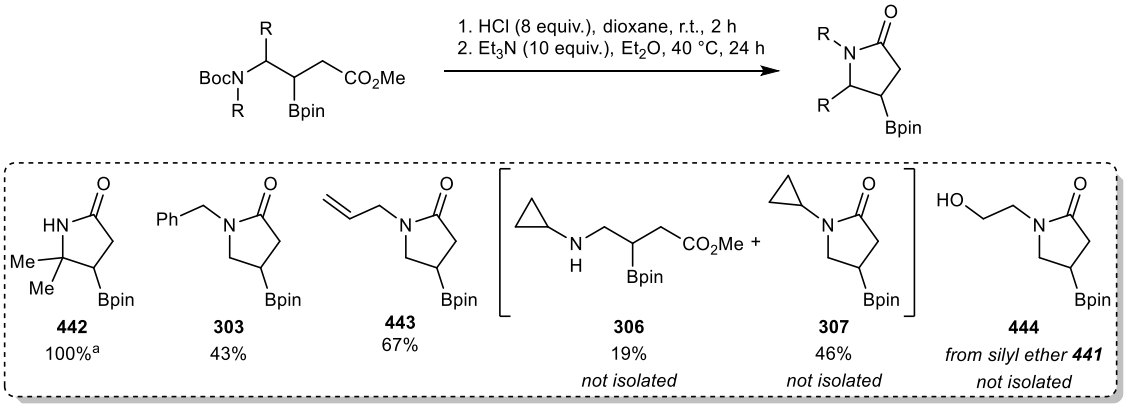
Using SImes as a ligand, the borylation procedure was applied to a range of the enoates, with the only modification to the procedure being a reduction in the stoichiometry of B_2pin_2 used. Using this method, we were able to borylate a range of enoates (Scheme 108). From our previous studies, we know that complete borylation occurs without the need for a ligand. Some of these substrates were rerun using SImes.HBF_4. The higher yields observed in these reactions are not thought to be due to an improvement in the reaction but instead improvement in the purification of some of the less stable boronic esters.



Scheme 108: Synthesis of borylated *N*-Boc amino esters, the reaction run without a ligand used 4.5 mol% of NaO^{t}Bu

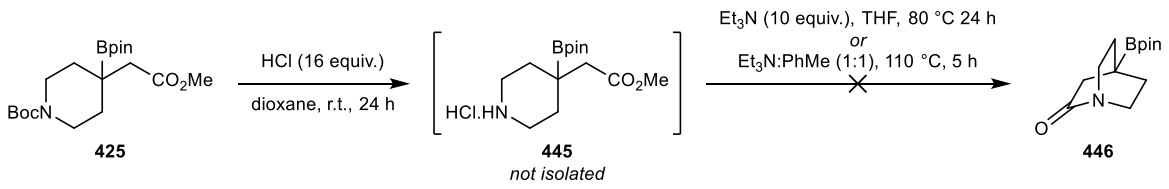
We then explored deprotection of the Boc group and cyclisation, without isolating the intermediate amine salt. Concentration of the reaction mixture within the reaction vessel, followed by addition of the Et_3N and Et_2O would minimise any possible loss of mass associated with transfer of materials, which can be particularly problematic on small scale. For reaction of amino ester **424**, we used twice the amount of HCl and extended the reaction time to 24 h, due to degradation of the 4 M HCl in dioxane by the time this substrate was tested (Scheme 109). We do not believe the quantitative yield observed with this substrate is a result of these modifications. If the cyclisation conditions had not been sufficient, we would have expected to observe the linear deprotected amine alongside the lactam. This was the case for lactam **307**, which was isolated from the reaction mixture alongside amine **306**. We believe that the low yield for lactams **303** and **443** is believed to the result of mass loss through our extraction procedure, although, this was not an issue for **442**.

Finally, we found that amino ester **441** featuring a silyl protected alcohol underwent deprotection upon treatment with HCl, resulting in lactam **444** featuring a pendent alcohol instead of the silyl ether. Unfortunately, the material was recovered contaminated with the silyl residue after our attempted extraction. Given that we want to avoid any purification of the final product due to the instability of the boronic esters to silica chromatography, this substrate would require isolation after Boc deprotection to remove the silyl byproduct. We do not consider it to be a major issue that the silyl groups had been removed from lactam **444**, as the silyl group only served as a protecting group for the alcohol functionality.



Scheme 109: Cyclisation of *N*-Boc amino enoates, [a]16 equiv. of HCl used and reaction time extended to 24 h

Given that the deprotection/cyclisation of amino ester **425** would require the require the formation of a nitrogen bridge head, we anticipated that more forcing conditions would be required. We again decided isolation of the amino salt intermediate would not be require using our extraction process. Both refluxing in THF and use of Et_3N as a co-solvent refluxing with toluene failed to yield the borylated quinuclidinone **446** (Scheme 110). The crude material isolated from multiple attempts at these reactions often showed mixtures of the amine salt (**445**) and free amine occasionally with degradation of the boronic ester. Although our efforts with this substrate have been unsuccessful, it is worth noting that **425** is itself a borylated heterocyclic scaffold. Alongside the boronic ester functionality it features both a protected amine and carboxylate functionality. These functional handles are amongst the most commonly used by synthetic medicinal chemists.[20]



Scheme 110: Attempts to prepare quinuclidinone **446**

2.3.10 Development of an Asymmetric Conjugate Borylation Procedure

The conjugate borylation procedure we had so far developed is not enantioselective. Enoates **406** and **408** both feature stereogenic centres α to the nitrogen. If we used our symmetric borylation procedure for these substrates we would generate diastereomers, the selectivity of which we would aim to control through catalyst- rather than substrate-control.

We began this study by screening potential ligands (Figure 9: Ligands used in screening experiments) in the borylation reaction of **(*S*)-408**. Yields and d.r. of the borylated products were calculated by ^{1}H NMR analysis with the use of an internal standard (Table 7). For HPLC analysis of the product, boronic ester **447** was oxidised to the corresponding alcohol with $NaBO_3$ (the yields for these reactions were not determined). Chiral HPLC analysis was used to determine the e.e. through comparison to a racemic sample containing both diastereomers, prepared from the ligand free borylation of enoate **(±)-408**.

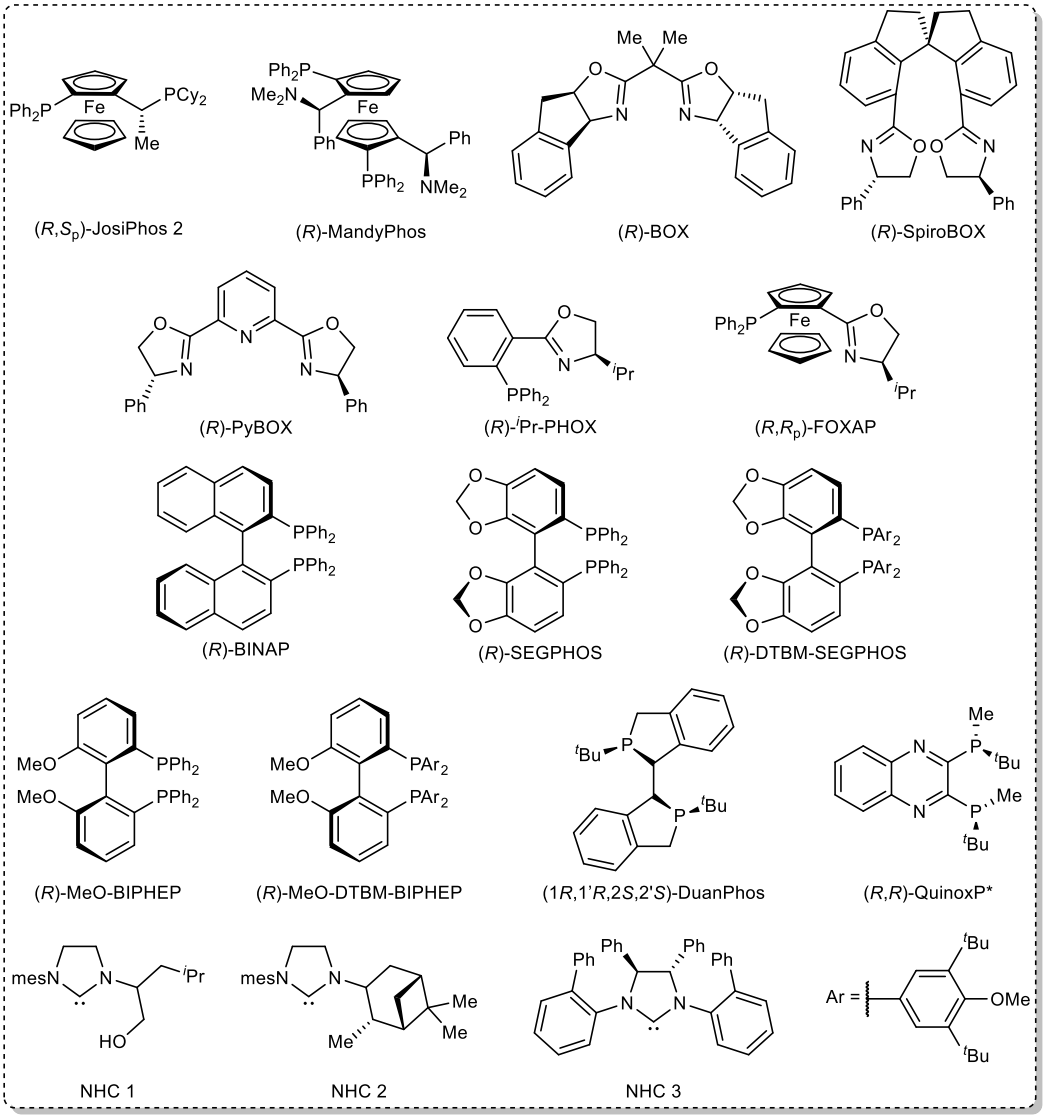
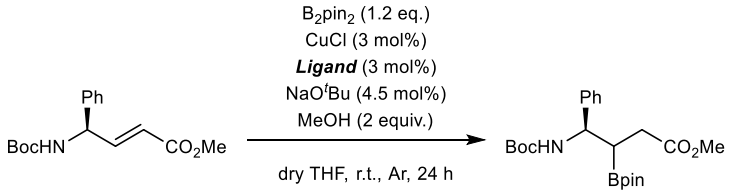


Figure 9: Ligands used in screening experiments



(*S*)-408
>99% e.e.

447

Entry	Ligand	yield	d.r.	e.e. of Diastereoisomer	
				A	**B**
1	No ligand	>99%	1.3:1	>99%	>99%
2	(*R*)-MandyPhos	99%	4:1	>99%	>99%
3	(R,S_p)-JosiPhos 2	>99%	1.2:1	>99%	>99%
4	(*R*)-BOX	46%	1:1	>99%	>99%
5	(*R*)-SpiroBOX	>99%	1.2:1	>99%	>99%
6	(*R*)-PyBOX	69%	1.1:1	>99%	>99%
7	(*R*)-^{i}Pr-PHOX	>99%	1:1	>99%	>99%
8	(R,R_p)-FOXAP	98%	<1:20	n.d.	>99%
9	(*R*)-BINAP	>99%	5.0:1	>99%	89%
10	(*R*)-SEGPHOS	97%	3.2:1	>99%	>99%
11	(*R*)-DTBM-SEGPHOS	14%	n.d.	>99%	>99%
12	(*R*)-MeO-BIPHEP	>99%	>20:1	>99%	>99%
13	(*R*)-DTBM-BIPHEP	0%	n.d.	n.d.	n.d.
14	(1*R*,1'*R*,2*S*,2*S*')-DuanPhos	97%	3.6:1	>99%	>99%
15	(*R*,*R*)-QuinoxP*	>99%	2.3:1	>99%	>99%
16[a]	NHC 1 (HBF_4 precatalyst)	>99%	3:1	>99%	>99%
17[a]	NHC 2 (HBF_4 precatalyst)	99%	2:1	>99%	>99%
18[a]	NHC 3 (HBF_4 precatalyst)	91%	>20:1	>99%	>99%

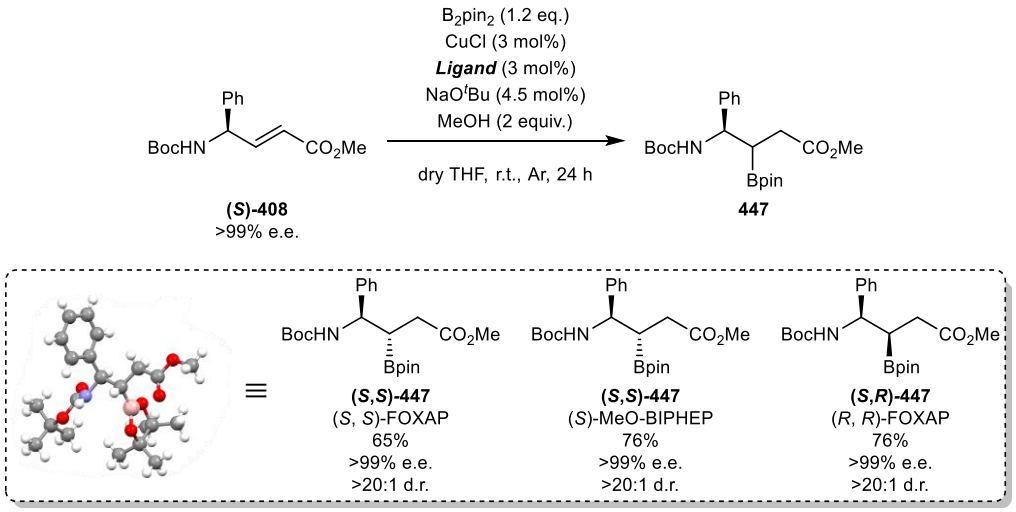
Table 7: Ligand screen for the asymmetric borylation of enoate **(*S*)-408**, NMR yields calculated using 1,3,5-trimethoxybenzene as an internal standard, HPLC analysis using a Daicel Chiralpak amylose-ID S-5 µm column with IPA:hexane (25:85, 1.1 mL/min, 22°C) as the eluent (λ = 204 nm), [a]7.5 mol% of NaO^{t}Bu used

The reaction without a ligand gave **447** in a quantitative yield, albeit in low d.r. (Entry 1). Importantly, the reaction occurred without epimerisation of the existing stereogenic centre. HPLC analysis of enoate **(*S*)-408** showed that the compound we had prepared was enantiopure. Alkene bond migration to **409** was found to be an issue in the synthesis and purification of this compound. Styrenes similar to **409** are known to undergo hydroboration under similar condition as ours.[36–41] Migration followed by hydroboration could provide a route to epimerisation. However, during the ligand screen experiments no epimerisation was observed. This evidence suggests that under the reaction conditions alkene bond migration does not occur, leading to the high enantiopurity of the each diastereoisomer. We do not have any evidence that enoate **409** would not undergo hydroboration under these conditions as this was not tested.

The reactions using (*R*)-BOX, (*R*)-PyBOX, (*R*)-DTBM-SEGPHOS and (*R*)-DTBM-BIPHEP showed significant reduction in yield, compared to the reaction without a ligand, suggesting these ligands generate a less active catalysts (Entries 4, 6, 11 and 13).

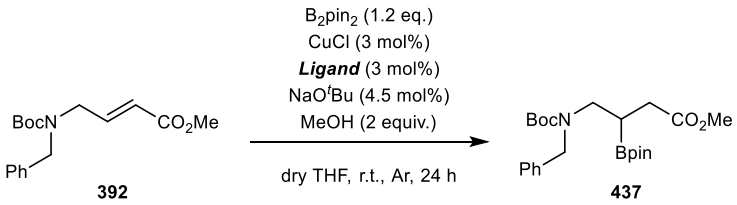
Across all ligand classes tested, the diastereoselectivity of the reactions were generally modest. However, ^{1}H NMR analysis of the crude mixture using (*R*,*R*)-FOXAP only showed a single diastereomer (Entry 8). This was also true for (*R*)-MeO-BIPHEP and NHC 3 but the opposite diastereomer was observed (Entries 12 and 18). Given the slightly lower yield observed with NHC 3, we selected (*R*,*R*)-FOXAP and (*R*)-MeO-BIPHEP as our best ligands for further study. The reactions of both of these ligands gave the product in high excellent diastereo- and enantioselectivity, and quantitative yield on test scale.

We decided to scale up these reactions to determine if these results could be replicated and the products isolated. Along with (*R*,*R*)-FOXAP and (*R*)-MeO-BIPHEP, we tested (*S*,*S*)-FOXAP to determine if the opposite enantiomer of ligand would give the other diastereomer. When submitted to the reaction conditions all three ligands gave the corresponding boronic esters without enantioerosion and high diastereoselectivity. Furthermore, (*S*,*S*)-FOXAP gave the opposite diastereomer as expected and the product of this reaction was analysed by single crystal X-ray diffraction. This showed that both (*S*,*S*)-FOXAP and (*R*)-BIPHEP gave the *anti*-diastereomer and by analogy (*R*,*R*)-FOXAP must give the *syn*-product.



Scheme 111: Asymmetric conjugate borylation of enoate **(*S*)-408**

Finally, we also wanted to perform a ligand screen for the reaction of achiral enoates. Using enoate **392** as our model substrate, we investigate a smaller range of the more successful ligands previously tested, using the same analytical procedures as before. From our previous studies we were aware that this reaction did not require a ligand, which gave access to racemic product (Entry 1). We also included (*R*)-DTBM-BIPHEP, the worst ligand tested above, to confirm its poor compatibility with our reaction. This ligand again performed poorly, giving the product **437** in poor yield and low enantioselectivity (Entry 8). All other reactions gave **437** in quantitative yield. The reactions using most of ligands occurred in modest enantioselectivity with the exception of two. (*R*,S_p)-JosiPhos 2 gave the product in a promising 80% e.e. (Entry 2). However, the best selectivity was again observed when using (*R*,*R*)-FOXAP (Entry 4). Both (*R*)-^{i}Pr-PHOX and (*R*,*R*)-FOXAP gave the opposite enantiomer to the rest of the ligand screen (Entries 3 and 4).



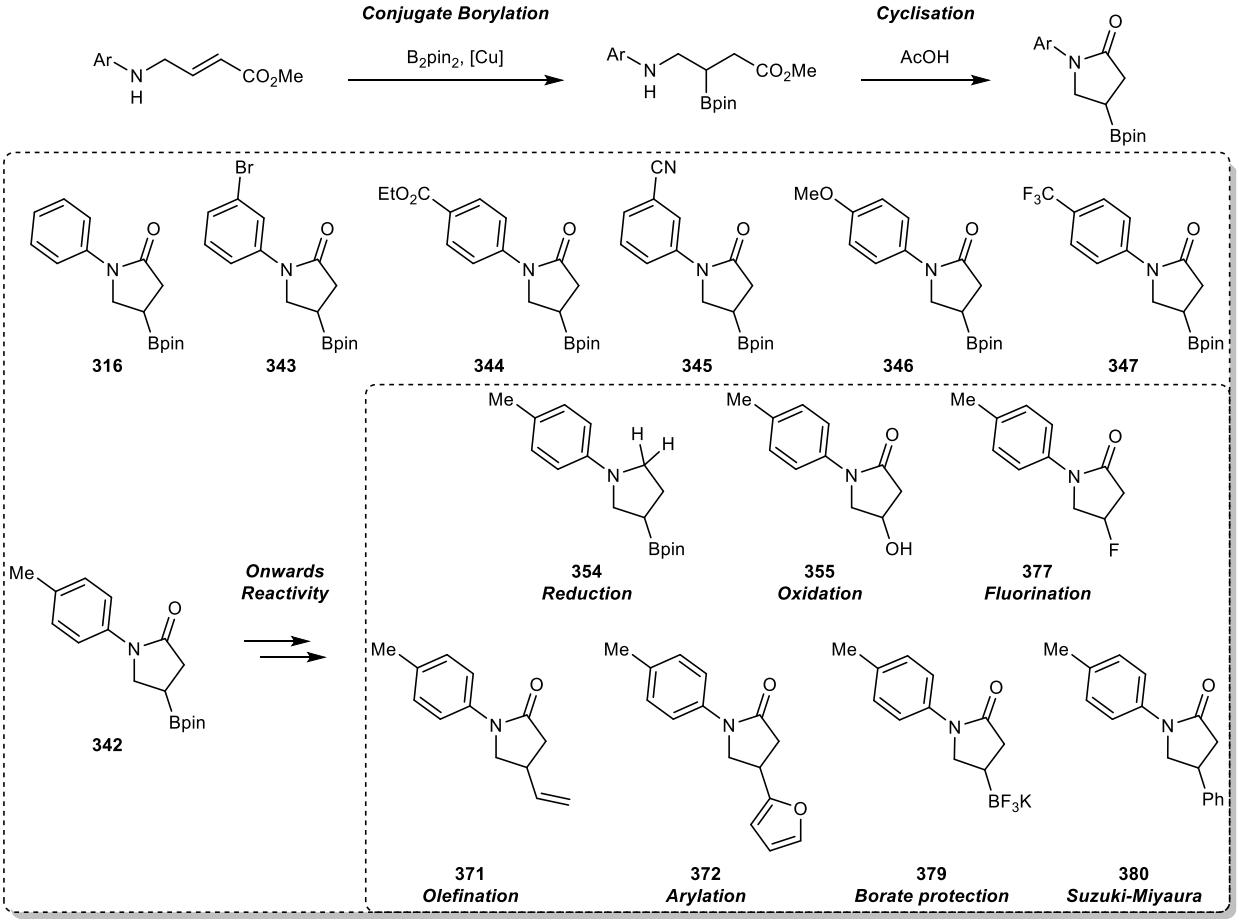
Entry	Ligand	yield	e.e.
1	No ligand	>99%	0%
2	(*R*,S_p)-JosiPhos 2	99%	80%
3	(*R*)-^{i}Pr-PHOX	99%	-45%
4	(*R*,R_p)-FOXAP	98%	-94%
5	(*R*)-BINAP	>99%	72%
6	(*R*)-SEGPHOS	>99%	55%
7	(*R*)-MeO-BIPHEP	>99%	57%
8	(*R*)-DTBM-BIPHEP	33%	21%
9[a]	NHC 2 (HBF_4 precatalyst)	>99%	35%
10[a]	NHC 3 (HBF_4 precatalyst)	>99%	-4%

Table 8: Ligand screen for the asymmetric borylation of enoate **392**, NMR yields calculated using 1,3,5-trimethoxybenzene as an internal standard, HPLC analysis using a YMC Chiral Art amylose-SA S-5 μm column with IPA:hexane (5:95, 1.0 mL/min, 22°C) as the eluent (λ = 210 nm), negative e.e. indicates the alternative enantiomer is the major product, [a]7.5 mol% of NaO^{t}Bu used

We have not yet isolated the enantioenriched product of these reaction and so the absolute configuration of the product has not been confirmed. Due to time constraints none of the enantioenriched borylated *N*-Boc amino esters have been converted to the corresponding lactams.

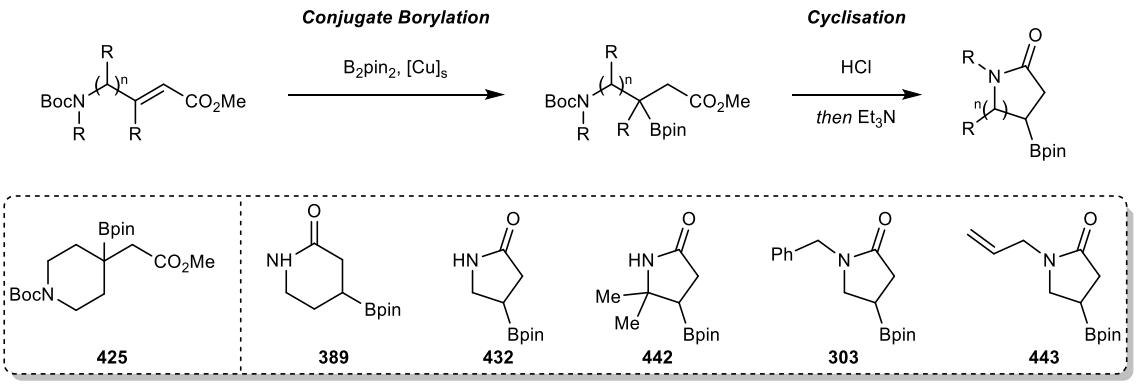
2.4 Conclusions and Future Work

Our initial investigations of the conjugate borylation reaction revealed that the *N*-alkyl lactams and their amino ester precursors were unstable to silica chromatography. Our first procedure took advantage of the reduced nucleophilicity of anilines to stop cyclisation before purification of the borylated amino esters (Scheme 112). These could be conveniently converted to the lactam through heating in AcOH. This method gave us our first 7 borylated lactams and could be performed enantioselectively using a catalyst generated from CuCl and a JosiPhos ligand. There were some significant limitations; 1) all examples featured an aryl substituent on the nitrogen atom of the lactam; 2) heteroaryl amines we tested were not tolerated; 3) 2,6-disubstitution on the aromatic ring prevented cyclisation; and 4) we had so far only prepared γ-lactams. In order to prove the suitability of our borylated lactams as possible scaffolds we successfully performed a range of transformations including a Suzuki-Miyaura cross coupling (Scheme 112). Although transformation of orthogonal functional handle is possible, isolation of the products is difficult due to the stability of the boronic ester. We imagine the obvious work around to this would be to design a reaction sequence for the scaffolds in which the boron functionality is modified first.



Scheme 112: Synthesis of borylated *N*-aryl lactams via our first procedure and their transformations

To overcome some of the deficiencies of our initial method, we investigated the use of *N*-Boc amino enoates that would be incapable of cyclisation upon borylation. Using this method so far, we have generated 5 more borylated lactams. We discovered that the resultant lactams are considerably water soluble, and so required an aqueous free reaction and work up procedure. This was achieved by using HCl in dioxane to deprotect the borylated amino ester and Et_3N to cyclise the hydrochloride amino salt intermediate. This expanded our scope to scaffolds with alkyl substituents and no substituent on the nitrogen of the lactam. In addition, we were also able to increase the ring size and include substitution on the ring itself. We have developed a highly stereoselective borylation procedure through the incorporation of a FOXAP type ligand but have not yet used to the procedure to prepare an enantioenriched lactam. Although we have so far been unable to cyclise **426**, this is a further borylated heterocycle that could be of significant interest amongst our other heterocycles. The aims for this project were not solely to prepare borylated lactams but also cyclic amines. This was achieved through reduction of the lactam to produce a further scaffold.

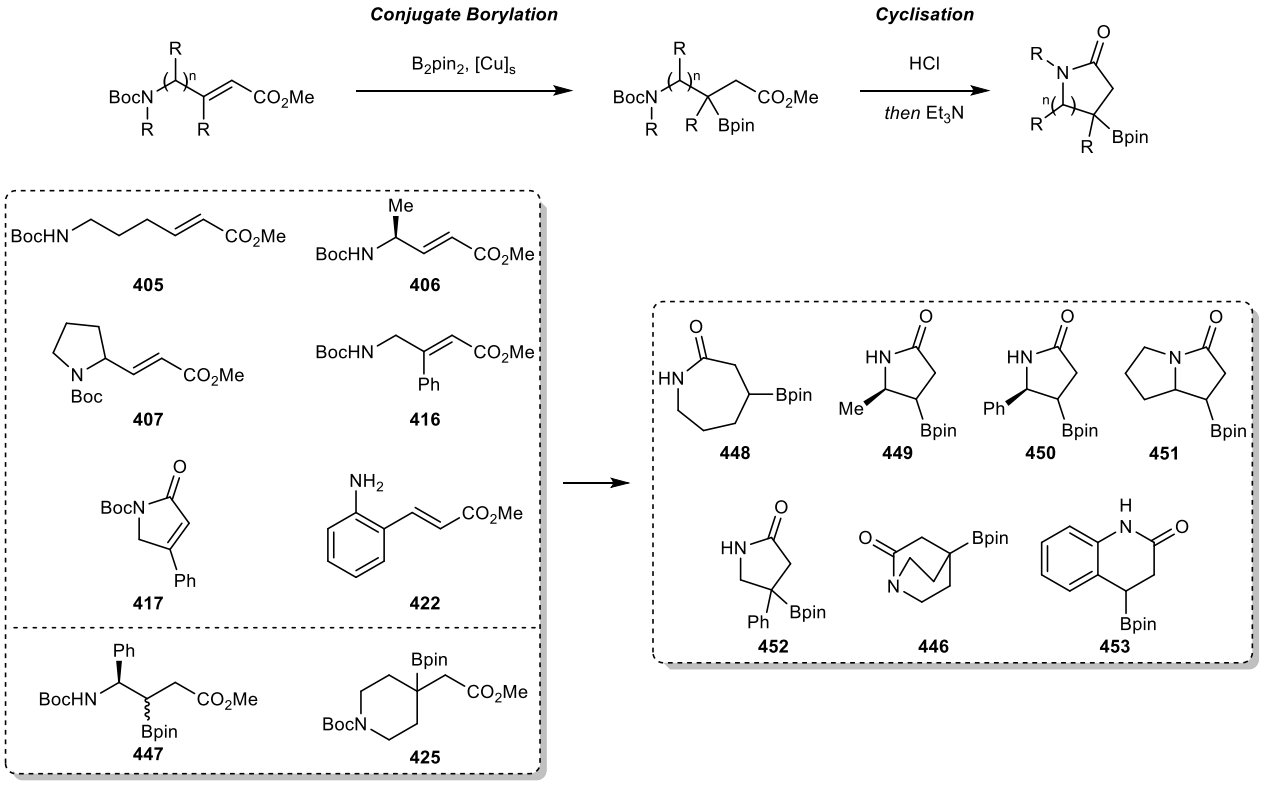


Scheme 113 Synthesis of borylated heterocycles via our second procedure

In conclusion, we have developed two methodologies for the preparation of borylated lactams based on a conjugate borylation/cyclisation strategy, preparing a total of 14 novel boron-containing heterocycles. We believe that these scaffolds could be of great benefit to synthetic chemist, wishing to prepare new biologically active C-sp^3 rich molecule through diversification of building block structures.

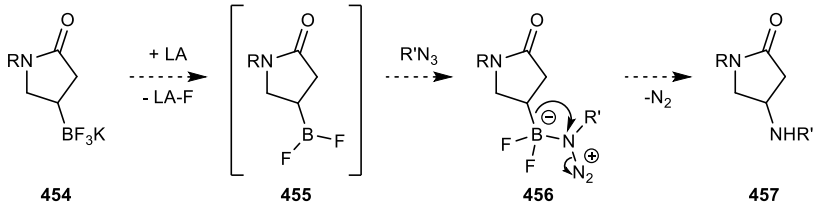
2.4.1 Future Work

We are still in the development stages for the transformation of *N*-Boc amino enoates into lactams. Having only just begun to explore the scope of this methodology, an immediate continuation would be to convert all the borylated *N*-Boc amino esters and *N*-Boc amino enoates into the corresponding lactams (Scheme 114). Moreover, given that we have optimised a stereoselective procedure, it would be desirable to apply these conditions to prepare enantioenriched lactams from all of *N*-Boc amino enoates we have prepared.



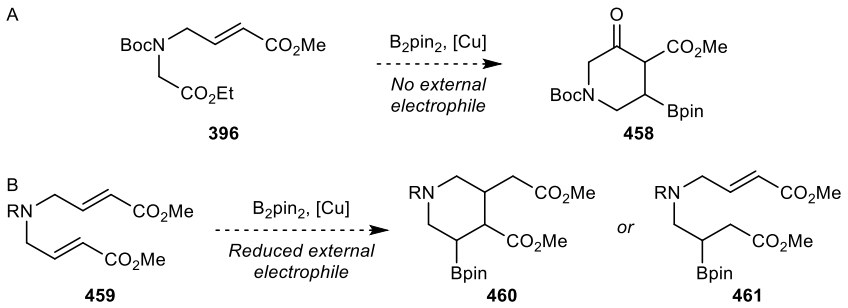
Scheme 114: Continued exploration of the scope of our second procedure

We have shown that our scaffolds can undergo a range of useful transformations. However, we were unsuccessful with homologation, amination and borate mediated halogenation. These would all be attractive transformations to help bolster the potential of our scaffolds and should be investigated further. For example, we appear to have exhausted amination procedure which used electrophilic nitrogen sources. Recent reports appear to show the amination of trifluoroborates through the addition of a Lewis acid and organoazides is a more convenient strategy than procedure that we have so far attempted (Scheme 115).[49,85]



Scheme 115: Amination of trifluoroborates with azides via Lewis acid activation

There are possibly more interesting structures that we can prepare from some of the materials prepared in these studies. With methanol serving as a proton source in the reaction we were able to prepare amino ester **440** featuring a pendent electrophile. Similar to the studies of Lautens and co-workers, we envisage that with the removal of the proton source we should be able to trigger a Dieckmann-type cyclisation, from the intermediate enolate, to give borylated 3-piperidinones. If successful, this could also be applied to the undesired dialkylated side products to prepare increasingly novel borylated heterocycles.



Scheme 116: Hypothetical heterocycles formed through conjugate borylation of some of the amino enoates prepared in our studies.

3.1 Introduction

3.1.1 Pyridine Scaffolds

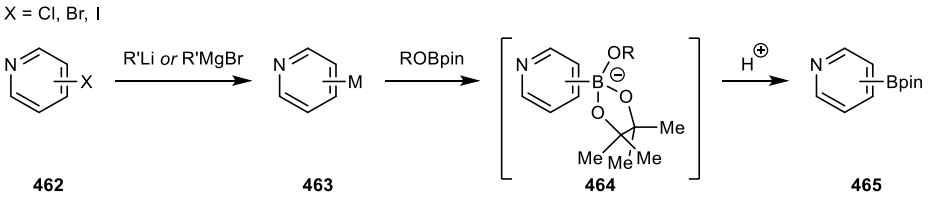
So far, we have only considered the synthesis of completely saturated *N*-heterocycles due to their prevalence in biologically active molecules and relative lack of sp^3-rich borylated heterocycles in the literature. However, pyridines are the second most common *N*-heterocycle found in drug molecules.[15] Their prevalence is a result of their substantial ability to improve metabolic stability and increase potency.[179] The replacement of phenyl rings with pyridines has been shown in certain studies to increase the potency of drug molecules by >150-fold.[180,181]

Given this apparent enhancement that incorporation of pyridines offer; the fact that synthetic medicinal chemists prefer to add preformed cyclic motifs over forming them; and the utility of Suzuki-Miyaura coupling for the formation of carbon-carbon bonds, it is somewhat surprising the disparity in the availability of pyridine boronates compared with their phenyl counterparts (Table 1). Typically these are prepared by Miyaura borylation from the corresponding aryl halide, for which synthesis has its own challenges. Furthermore, these building blocks are often monocyclic, featuring halogens as secondary functional handles, making them less attractive as Suzuki-Miyaura coupling partners.

3.1.2 Borylation of Pyridines

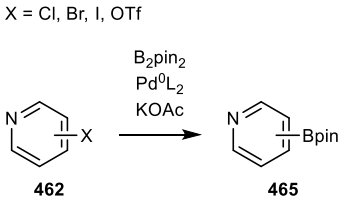
There are three major methods for the borylation of pyridines; 1) borylation of organometallics with borates; 2) Miyaura borylation of halo-pyridines via a Pd catalyst; and 3) C-H borylations of pyridine via Ir and Ru catalysts. Methods utilising pre-functionalised halo pyridines present their own issues. Halogenations of arenes is typically achieved through electrophilic aromatic substitutions and radical methods, which lead to mixture of regioisomers, which is a significant issue with radical borylations.[182]

In the first method a halo-pyridine **462** is treated with either an alkyl lithium or Grignard to generate an organometallic **463** (Scheme 117).[183] Addition with the borate leads to boronate **464** which is hydrolysed to the boronic ester **465**. Cyclic borate such as MeOBpin and ^{i}PrOBpin are commonly used, although pinacol boronic esters can be formed by reaction of acyclic borates followed by transesterification with pinacol.



Scheme 117: Borylation of halo-pyridines through metalation/exchange reactions

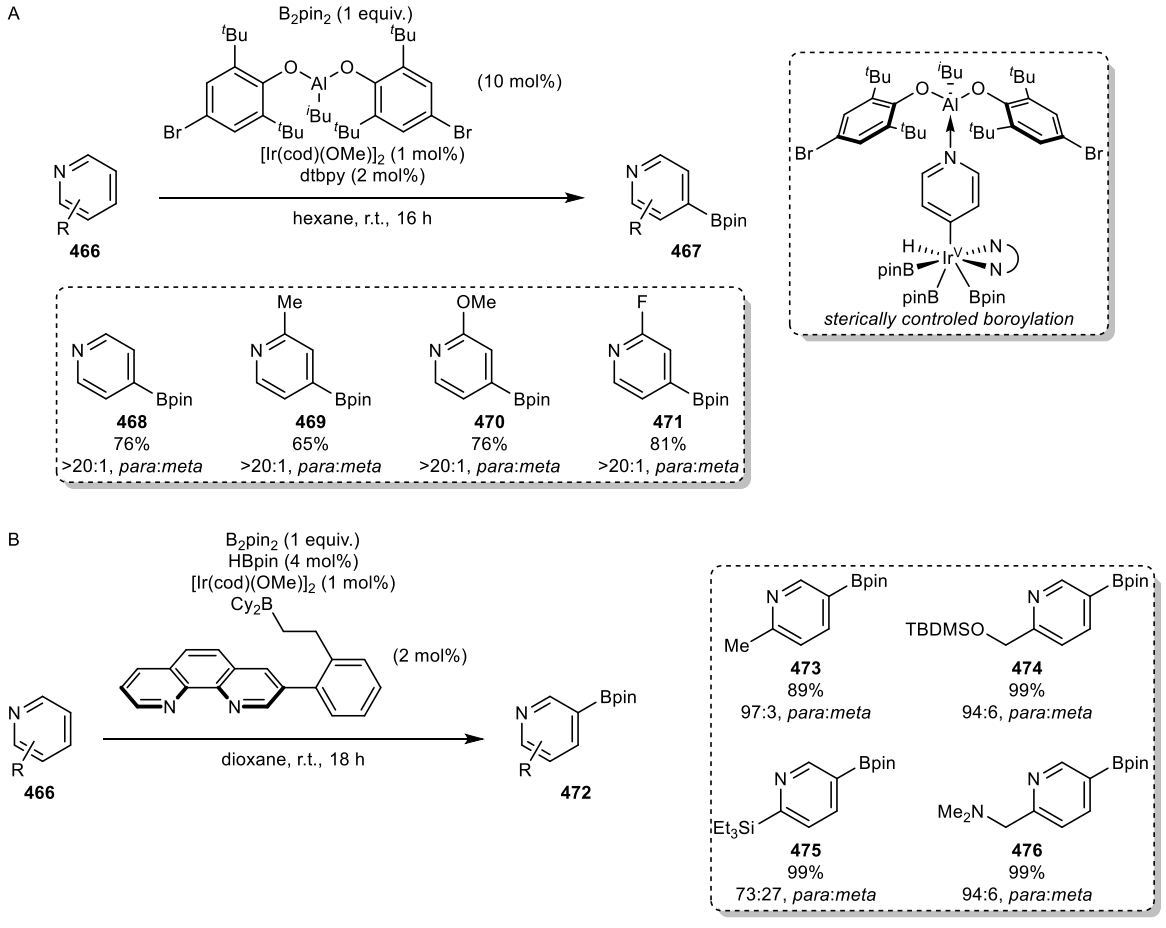
The second methodology is an adaption of the Suzuki-Miyaura cross-coupling in which the organoboronate nucleophilic coupling partner is replaced with a diboron reagent (Scheme 118).[184] This method combines excellent functional group tolerance with procedural simplicity, which has led to its wide spread use. One subtle difference between this method and the Suzuki-Miyaura reaction, is the requirement of a weak base (KOAc); use of stronger base promotes the formal homocoupling between the product and halo-pyridine.



Scheme 118: Miyaura borylation of (pseudo)halo-pyridines

C-H borylation of pyridines represents the most attractive method for the borylation of pyridines as the precursors require no pre-functionalisation and the reaction offers excellent atom economy.[185] Using Ir-catalysed conditions from Hartwig, Ishiyama and Miyaura, borylation does not occur *ortho* to the nitrogen of pyridine, typically giving borylation at the least sterically hindered site.[186] However, early examples had required elevated temperatures (compared with other heteroarenes) whilst furnishing statistical mixtures of regioisomers, unless suitable blocking groups are employed. Incorporation of boron on pyridines at the *ortho*-position is possible through other methods, although the reduced stability of products makes these compounds less attractive.[187,188]

There are two reports in the literature that stand out, offering excellent regioselectivities through catalytic control. Nakao and co-workers achieved *para*-selective borylation of pyridines through the combination of an Ir catalyst and a bulky aluminium based Lewis acid (Scheme 119A).[189] ^{1}H NMR analysis revealed that the pyridine and Lewis acid forms an adduct, which the authors suggest blocks the *ortho*- and *meta*-position promoting borylation at the *para*-position. As a continuation of this procedure, Nakao and co-workers went on to develop a bipyridine ligand featuring a tethered Lewis acid which selectively activates the *meta*-position (Scheme 119B).[190]

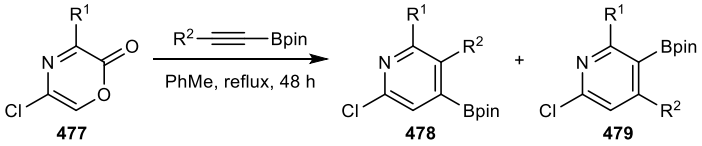


Scheme 119: Catalyst-controlled regioselective C-H borylation of pyridines

3.1.3 Synthesis of Borylated Pyridines through Anulative Strategies

The previously mentioned methods all require preformed pyridine substrates. There are a plethora of condensation and cycloaddition strategies for the synthesis of pyridines, but there are very few which have been shown to be capable of furnishing borylated pyridines.

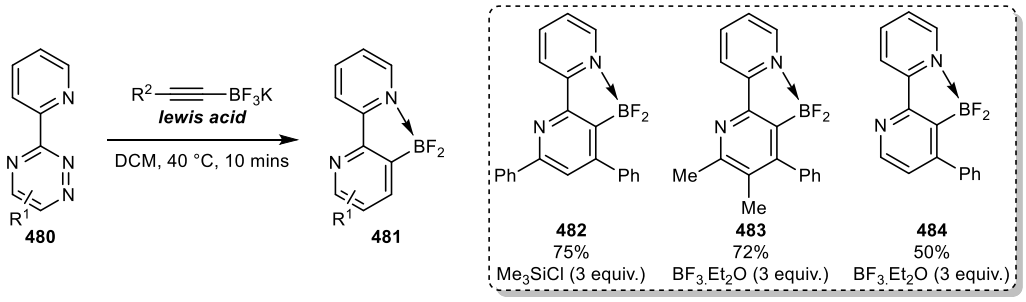
Harrity and co-workers showed that alkynylboronates can be used in the [4+2] cycloaddition of 1,4-oxazin-2-one **477** as a direct route to boryl piperidines (Table 9).[191] This reaction struggles with regioselectivity, although increasing sterics of both the alkyne and oxazine can promote formation of the *para*-boryl pyridine **478**.



Entry	R^1	R^2	Yield	478:479
1	H	Ph	72%	5:1
2[a]	Cl	Ph	78%	5:1
3	Br	Ph	74%	20:1
4	H	^{n}Bu	67%	2:1
5[a]	Cl	^{n}Bu	82%	9:1
6	Br	^{n}Bu	82%	10:1
7	H	H	88%	1:2
8[a]	Cl	H	84%	1:1
9	Br	H	83%	3:2

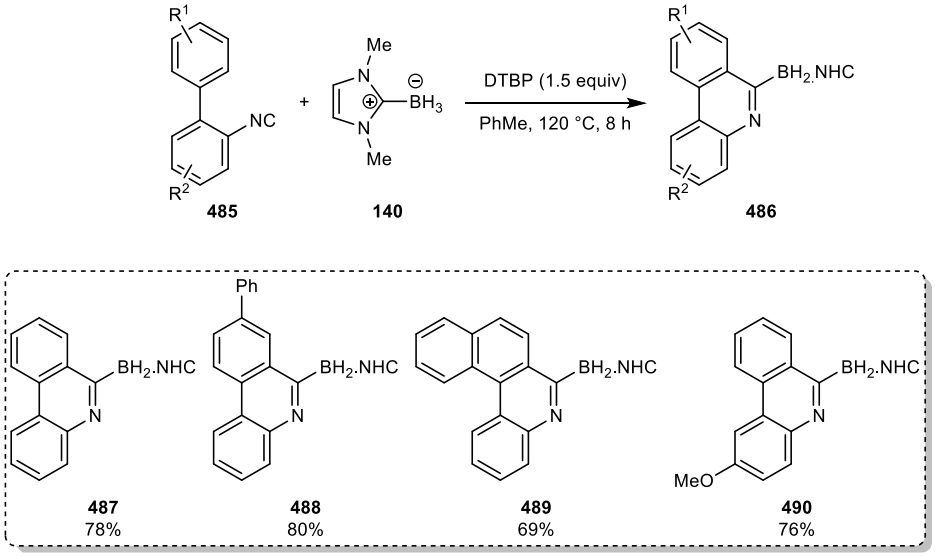
Table 9: [4+2] cycloaddition route to borylated pyridines, [a]*o*-DCB at 190 °C for 4 h

As a continuation to this procedure they found that a pendent pyridine could be used to increase the regioselectivity in the cycloaddition of alkynylboronates with 1,2,4-triazine **480** (Scheme 120).[192] In this procedure, boronic esters were found to show poor reactivity. Generation of difluoroboranes from alkynyltrifluoroborates by treatment with a Lewis acid was found to be superior, giving complete conversion within 10 mins to furnish the *para*-difluoroborylpyridine **481**.



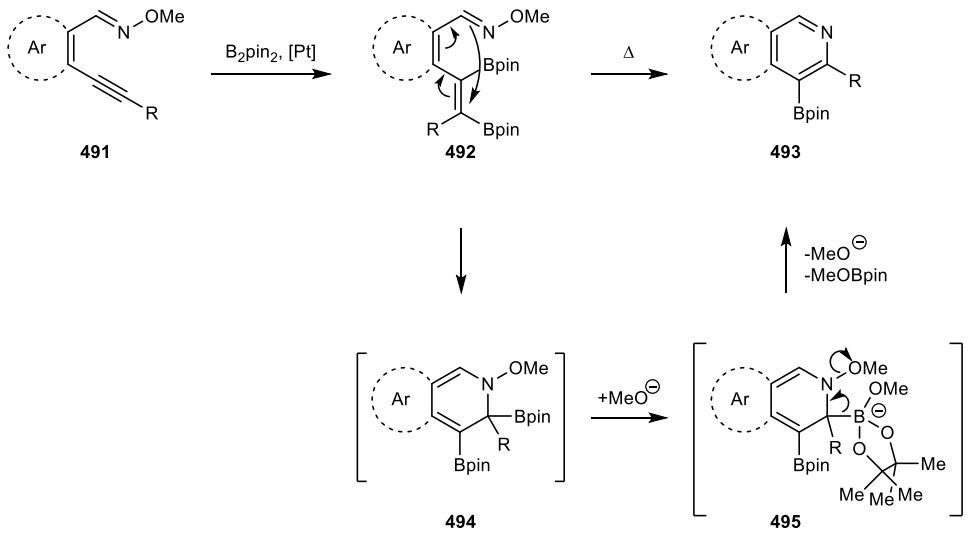
Scheme 120: Synthesis of borylated pyridines through a pyridine directed [4+2] cycloaddition

Wang and co-workers have developed a radical borylation procedure which yields phenanthridines **486** borylated at the *ortho*-position (Scheme 121).[193] Radical initiation of NHC-borane complex **140** generates boryl centred radicals through a hydrogen abstraction process. The boryl radical adds to the isocyanide forming a carbon centred radical which undergoes an intramolecular cyclisation followed by oxidation to yield the borylated product **486**. Although *ortho*-boryl pyridines are notoriously unstable, the use of the NHC complex stabilises the final product. Furthermore, conversion of the boron moiety to the difluoroborane allowed for Suzuki-Miyaura coupling of the final products.



Scheme 121:Synthesis of borylated phenanthridines via a radical borylation/cyclisation

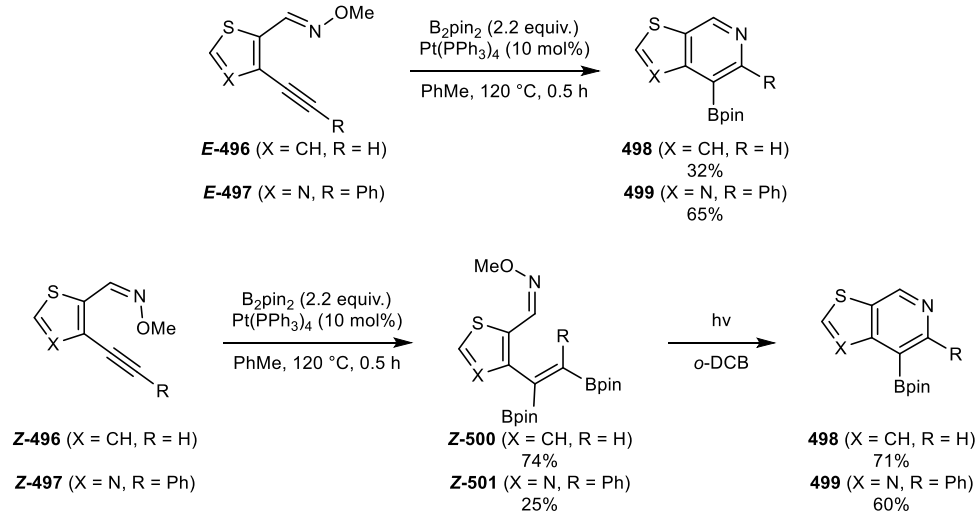
Recently Harrity and co-workers have disclosed successive reports outlining their diboration/6π-electrocyclisation strategy for the synthesis of borylated fused-ring pyridines.[194–197] Their first methodology employs the Pt-catalysed diboration of the alkyne functionality of 1-azadieneynes **491** generating diboryl 1-azatrienes **492** (Scheme 122). Upon heating these undergo a 6π-electrocyclisation to form a 1,2-dihydro pyridine **494**. Elimination of MeOBpin and methoxide is driven by the reformation of aromaticity. The methoxide generated from this elimination can coordinate to the boron α to the nitrogen, activating the carbon-boron bond towards elimination. In turn, this promotes further elimination of the methoxide, giving the borylated pyridine **493**.



Scheme 122: Diboration/6π-electrocyclisation route to fused-ring pyridines

In this work the central "ene" motif is typically part of an aromatic ring. The majority of products described in the initial studies by Mora-Radó *et al*. feature benzene as the fused ring counterpart to yield borylated isoquinolines. However, the use of indoles, furans, pyrazoles, thiazoles and thiophenes have also been shown to be tolerated giving the fused heterocycle-pyridine boronic esters. These combinations of heterocycles are of particular interest due to the prevalence in biologically active molecules.[198,199]

In this study there was one result that was particularly puzzling. The condensation reaction used to produce the aldoxime ethers **491** typically gave *E*-isomer. However, in the case of thiazole and thiophene substrates the condensation yielded a mixture of isomers with the *Z*-isomer being the major component (Scheme 123). Diborylation of these reactions gave a mixture both the formed pyridine and the diboryl 1-azatriene featuring the *Z*-aldoxime ether. Separation of the isomers of the azatrienes and resubmission to the borylation conditions revealed that whilst *E*-aldoxime ethers could undergo the cyclisation, *Z*-aldoxime ether were thermally inert to this transformation. Furthermore, the thiophene example represents the single lowest yield of a borylated pyridine reported in their studies.



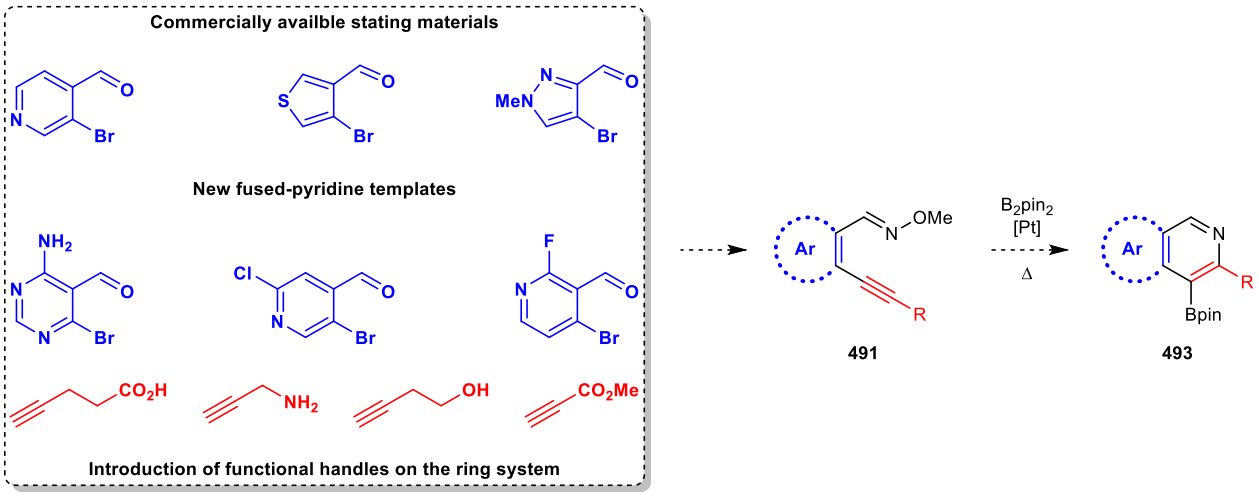
Scheme 123: Synthetic investigation of the synthesis of borylated thienopyridine **498** and thiazolopyridine **499**

3.2 Aims

Our studies are a continuation of the work done by Mora-Radó during their PhD, using their thesis and the first publication as a reference to initiate our studies.[194,195] The work reported here runs in parallel with the second and third publications from Harrity and co-workers.[196,197]

The diboration/6π-electrocyclisation strategy has so far been used to prepare a range of borylated fused-ring pyridines, including fused-heterocyclic compounds. In this work the synthesis of thienopyridine represents an outlier to the rest of the substrates that have so far been prepared. This molecule represents the lowest yielding thermal cyclisation that was reported. We will initiate our study by preparing thienopyridine **498**, hopefully gaining better understanding of the reaction such that we can optimise its synthesis (Scheme 123).

Another feature of the original study is the lack of functional diversity. Although the structures all feature the synthetically versatile boronic ester moiety, substituents in the ring system were carbon-rich and lacked further handles for functionalisation. Desirable building block molecules typically feature multiple reaction vectors allowing for divergent elaboration of the structure. The procedure used for the preparation of the azadieneynes involved the coupling of 1,2-bromo carbaldehyde heteroaromatics with terminal alkynes. Examples of alkynes featuring functional groups such as alcohols, amines and esters are readily available. In addition, polyfunctional heteroaromatics are highly sought after by synthetic chemists, and as a result they are also plentiful in their availability. We envisaged this would be an advantageous step to add extra synthetic utility to our scaffolds, whilst also modifying fused heterocyclic motif to prepare some more exotic fused heterocyclic motif to prepare some more exotic fused-ring systems (Scheme 124).

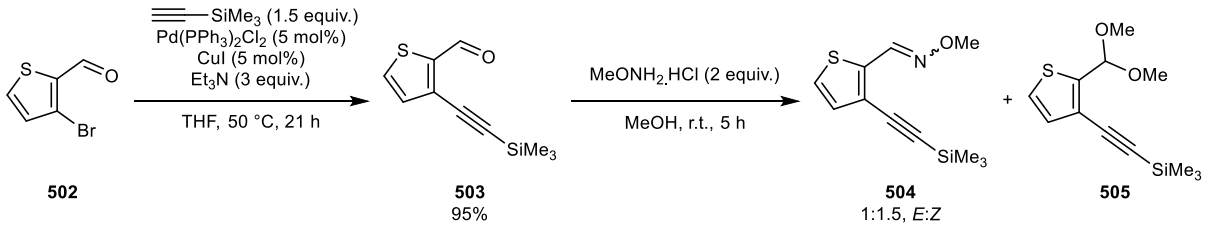


Scheme 124: Increasing the complexity of fused-ring pyridines obtained from the diboration/6π-electrocyclisation strategy

3.3 Results and Discussion

3.3.1 Investigation of Aldoxime Ethers for Diboration/6π-Electrocyclisation

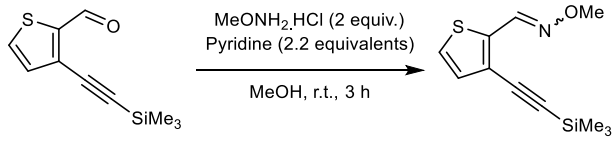
Evidently the failure of the thermal cyclisation of azatriene **496** appeared to be due to the formation of the *Z*-aldoxime ether as the major product in the condensation reaction. We decided to initiate our studies by trying to optimise this reaction. Aldehyde **503** was prepared via Sonogashira coupling of heteroaryl bromide **502** with trimethylsilylacetylene in quantitative yield. Previously this was desilylated at this point, however we choose to omit this step to observe whether the silyl group influenced the E/Z ratio of the oxime. The previously reported condensation procedure also used pyridine to promote the reaction. Condensation reactions are known to be both base and acid promoted. Given that the hydroxylamine source we were using was the hydrochloride salt we decided to remove the base from the reaction. It was our theory that the pyridine base could be generating an unknown intermediate in the reaction that preferentially gave rise to the *Z*-aldoxime ether **504** (Scheme 125). ^{1}H NMR analysis of the crude mixture revealed that although this had slightly reduced the formation of ***Z*-504**, the aldehyde had also been converted to the dimethyl acetal under these conditions. Isolation was not attempted due to the poor performance of the reaction.



Scheme 125: Synthesis of aldehyde **503** and initial attempts to influence the stereoselectivity of the aldoxime condensation reaction

This result indicates the requirement for a base to promote the reaction and minimise the formation of other side products. We next decided to investigate how solvent affects the reaction (Table 10). Unfortunately, these experiments provided no positive improvement, the previously used solvent MeOH shown to be best.

Disregarding the anomalous result with EtOH the reaction appears to favour polar protic solvents, additionally these also gave the best ratios *E*:*Z* of the aldoxime geometry (Entries 1-4). MeCN and $CHCl_3$ gave good yields for the reaction but undesirable ratios of the products (Entries 4 and 9). All other solvents gave poor yields for the reaction, which is believed to be due their inability to solubilise the amine salt. Using MeOH with pyridine we were able to isolate aldoxime ether **504** with a marginally lower *E*:*Z* ratio than previously reported but we were unable to separate the mixture of isomers (Entry 1).



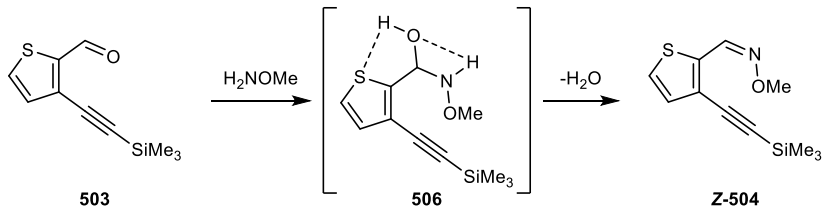
503 **504**

Entry	Solvent	*E*:*Z*	Yield
1[a]	MeOH	1:1.8	(86%)
2	EtOH	1:1.9	45%
3	IPA	1:2.7	76%
4	MeCN	1:3.2	82%
5	THF	1:4.6	41%
6	AcOEt	1:7.0	24%
7	Et_2O	1:7.6	12%
8	DCM	1:6.0	37%
9	$CHCl_3$	1:6.3	77%
10	PhMe	1:7.4	36%

Table 10: Solvent screen for the aldoxime condensation reaction, NMR yields calculated using 1,3,5-trimethoxybenzene as an internal standard, isolated yields given in parentheses, [a]Reaction complete by TLC after 5 h

Waldo and Larock have previously investigated similar condensation reactions for the synthesis of aldoxime ethers.[200] Their studies suggest that steric factors dominate the stereochemical outcome of such condensation reactions. However, this contradicts the observation we have made here, as the *E*-aldoxime should be less sterically congested. They also observed a single substrate which also gave a mixture of isomers whilst using pyridine as co-solvent. Given the apparent lack of influence that increasing the stoichiometry of base has the reaction, we decide that screening bases would not be a valuable experiment.

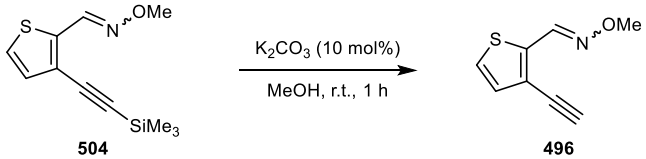
From these results, we believe that the preference for the *Z*-aldoxime is an impassable feature of having a sulfur atom at this specific position in the aromatic ring. A possible explanation is that there is a hydrogen bonding effect between the sulfur atom and the hydroxyl in intermediate **506** (Scheme 126). This would promote the elimination to occur from the conformation which would result in the Z-oximine product. Due to the increased size of the outer shell of sulfur, its lone pairs are considerably more diffuse than those of nitrogen and oxygen. In the case of furans and pyrazoles, which gave the *E*-aldoxime, presumably the corresponding hydrogen bonding conformation formed would be more strained, making this less favourable. This could explain why polar protic solvents give lower E/Z ratios in the product compared with aprotic solvents, as the protic solvent could disrupt these hydrogen bonding interactions.



503 **506** ***Z*-504**

Scheme 126: Possible mechanism for the preferential synthesis of aldoxime ether ***Z*-504**

We continued to the desilylation step to see if *E*/*Z* isomers of this product would be separable by chromatography, this gave the terminal alkyne **496** in moderate yield (Scheme 127). However, again we were unable to separate the two isomers, though we were able to remove some of the excess *Z*-isomer during in the purification.

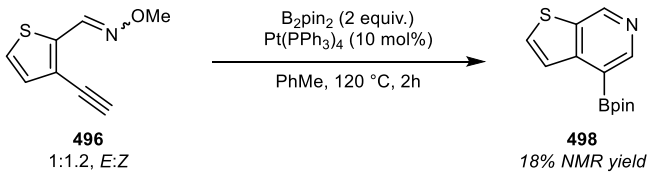


504
1:1.8, *E*:*Z*

496
47%
1:1.2, *E*:*Z*

Scheme 127: Desilylation of aldoxime ether **504**

We submitted our mixture of azadienyne stereoisomers **496** to the previously reported reaction (Scheme 128). Multiple attempts to isolate the product through chromatography were unsuccessful. The yield of the reaction was measured to 18% by NMR using 1,3,5-trimethoxybenzene as an internal standard. This result is comparable to the previously reported yield for thienopyridine **498** (29-32%).[195,197]

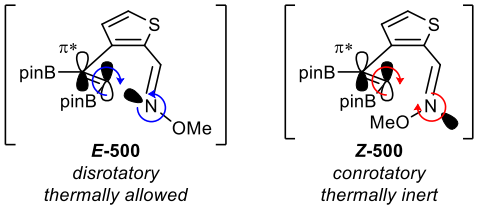


496
1:1.2, *E*:*Z*

498
18% NMR yield

Scheme 128: Diboration/6π-electrocyclisation of aldoxime ether **496**

Harrity and co-workers have studied this reaction *in silico* to try to understand why *Z*-aldoxime ethers are inert to cyclisation.[196] They calculated that the activation energy for *Z*-aldoximes are roughly between 20-30 kcal mol^{-1} higher than that of the *E*-isomer; which they determined would be inaccessible even if running the reaction in excess of 200 °C. Modelling of the transition state revealed that the iminic lone pair points to towards the diborylated alkene in the lower energy transition states. This modelling suggests that the initiation of the 6π-electrocyclisation is a result of the iminic lone pair donating electron density into the antibonding π* orbital (Figure 10). This gives give rise to a disrotatory cyclisation which is thermally allowed, ***Z*-500** would require a conrotatory cyclisation which is thermally disallowed.



***E*-500**
disrotatory
thermally allowed

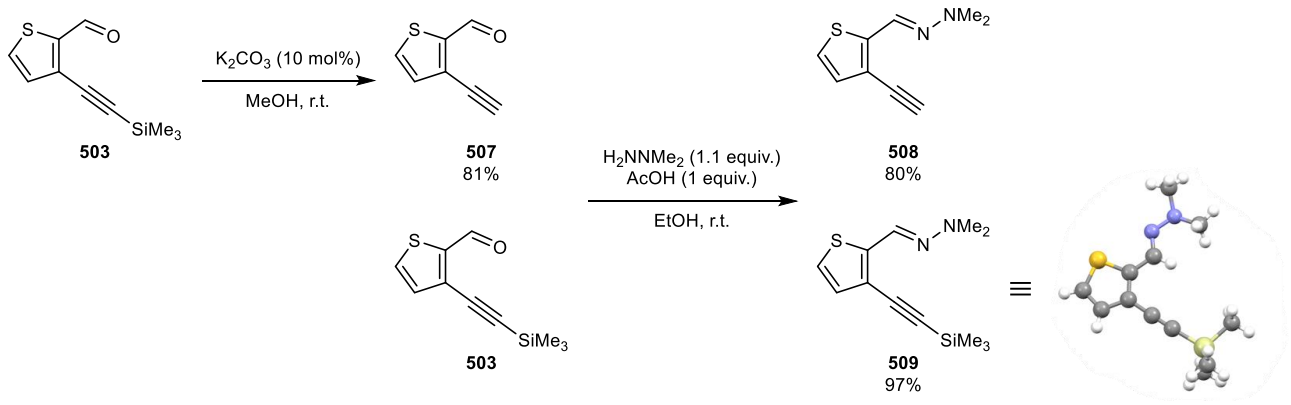
***Z*-500**
conrotatory
thermally inert

Figure 10: Relative conformations of azatriene intermediates (**500**) formed in the diboration reaction

3.3.2 Investigation of Hydrazones for Diboration/6π-Electrocyclisation

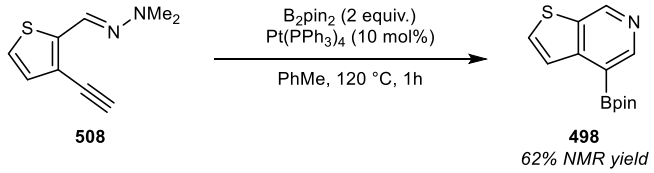
Given that we have been unable to optimise the synthesis of *E*-aldoxime ether **496,** or separate the isomers, and that we have not been able to isolate pyridine **497**, we decided to look for an alternative azatriene precursor. *N*,*N*-dimethylhydrazones are easily prepared through condensation of a carbonyl with the corresponding hydrazine. It was our belief that the increased steric bulk of the dimethyl amine, compared with the methoxy of the aldoxime ethers, should favour the formation of the *E*-hydrazone despite any unprecedented electronic effects. In addition, hydrazones are known to undergo thermal isomerisation in conjugated systems at temperature lower than those used in our borylation procedure.[201,202] This should allow the procedure to tolerate isomeric mixture hydrazone functionalised azatrienes. Furthermore they have already been exploited previously in similar electrocyclisation reactions.[203]

To qualitatively test this against both the previously reported procedure and our aldoxime synthesis, we desilylated aldehyde **503** to give an anologous starting material. Both aldehydes **503** and **507** where then submitted to the condensation reaction (Scheme 129). ^{1}H NMR analysis of both the crude mixtures revealed only a single isomer hydrazone had been formed in each reaction. The iminic proton signals of **504** and **496** revealed that *Z*-iminic protons are more downfield, presumably a result of their less shielded nature. Initial comparison of the iminic proton signal led us to believe that **509** was the *Z*-hydrazone, due to their similar chemical shifts. However, X-ray crystallography of **509** revealed that we had in fact prepared the desired *E*-hydrazone **509**, by analogy we assigned **508** to have same stereochemistry.



Scheme 129: Synthesis of hydrazones **508** and **509**

With the synthesis of these hydrazones complete, we turned our attention to the diboration/6π-electrocyclisation. Hydrazone **508** was submitted to the same diborylation conditions we had previously used (Scheme 130). Gratifyingly ^{1}H NMR analysis of the crude mixture showed complete consumption of the hydrazone to the thienopyridine and an NMR yield of 62% was determined. The significantly higher yield of this reaction confirmed that hydrazones could serves as superior azatriene precursors in these reactions. Unfortunately, exhaustive attempts to isolate this compound failed.



508 **498**

62% NMR yield

Scheme 130: Diboration/6π-electrocyclisation of hydrazone **508**

^{11}B NMR analysis of the crude mixture showed that along with boronic ester **509** we were observing large amounts of what we believe is the Me_2NBpin by-product (Figure 11). We believed that the similar polarity of this side product coupled with the low stability of the product on both silica and Florisil were the main factor in our difficulties with purification.

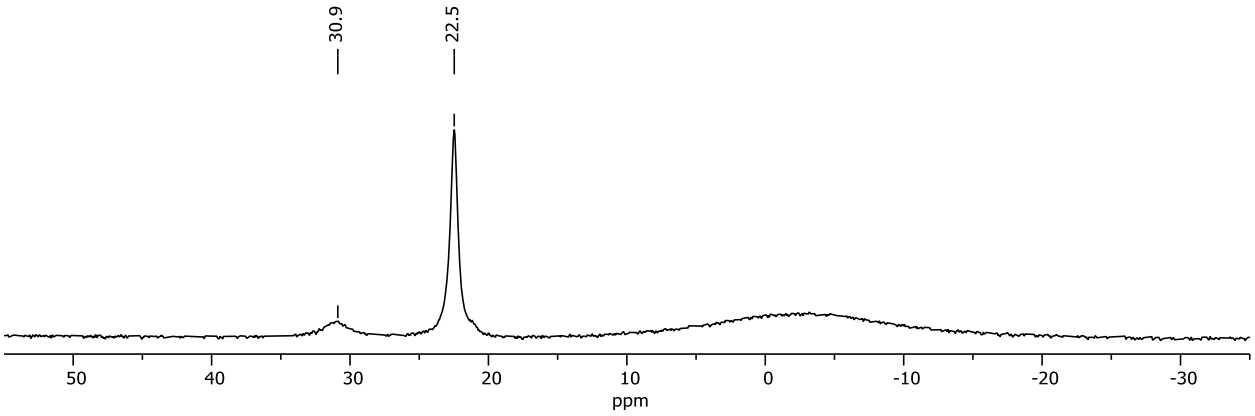
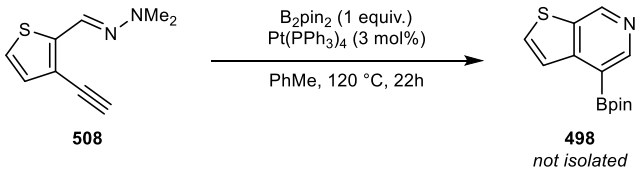


Figure 11: ^{11}B NMR analysis of the crude mixture obtained from the diboration/6π-electrocyclisation of hydrazone **508**

In order to minimise any possible boron side products, we decide to lower the equivalencies of the diboron reagent. Given that we had proven the reaction worked we decide that this would be the optimal time to begin reducing the loading of the precious Pt catalyst. To mitigate the slower reaction caused by the reduction in reagents and catalyst the reaction time was extended to 22 h (Scheme 131). Again, NMR analysis of the crude mixture showed that complete consumption had occurred, but the product was still inseparable from the reaction mixture.

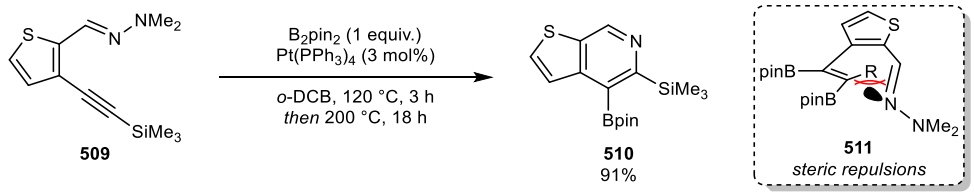


508 **498** *not isolated*

Scheme 131: Alternative diboration/6π-electrocyclisation procedure for hydrazone **508**

Due the large number of substrates that have previously been shown to be suitable in this methodology, we presume that the issues with purification are a singular feature of this thienopyridine.[194,195] We did not believe this was an issue with the thiophene moiety of the fused-ring, as thiazolopyrinde **499** was isolated from the reaction without any reported issues. The major difference between thienopyridine **498** and all other fused ring pyridine is that this is this is the only example which does not feature substitution at the 5-position of the fused ring. It is likely that the fused ring and the ring of the boronic ester will lie perpendicular to each other, without a substituent in the 5-position this would leave the vacant boron orbital open to attack. In addition, the introduction of highly lipophilic substituents should lower the polarity, aiding with separation from the by-products of the reaction.

To test our hypothesis, we submitted hydrazone **509** to the reaction conditions. After 22 h, ^{1}H NMR analysis showed that only trace amounts of the thienopyridine **510** were present. This is similar to many of the other previously reported substrates, which required elevated temperature for the cyclisation; due to steric repulsions in intermediate **511**. Replacing toluene with a higher *o*-dichlorobenzene (*o*-DCB) allowed us to run the reaction at 200 °C to overcome the barrier to cyclisation. Although not stable to silica chromatography, thienopyridine **510** could be isolated through chromatography using Florisil, to give the product in good yield (Scheme 132).

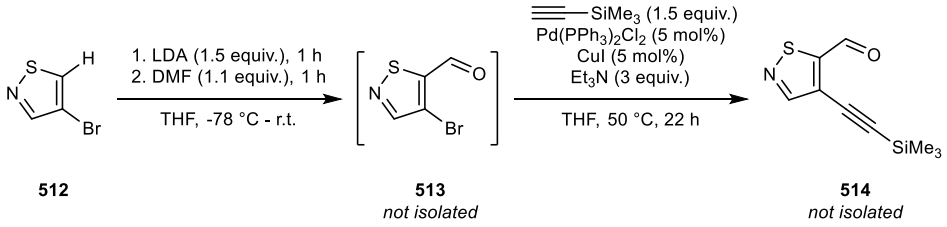


509 **510** 91% **511** *steric repulsions*

Scheme 132: Synthesis of thienopyridine **510**

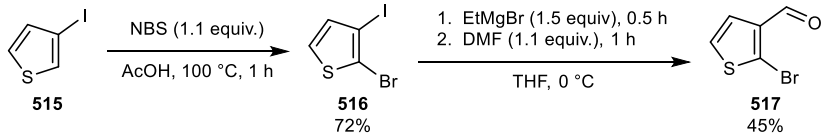
3.3.3 Synthesis of Hydrazones and Conversion into Borylated Fused-Ring Pyridines

With the constraints of the fused-ring pyridine synthesis now clearly understood we decided to elaborate on the scope of the transformation. Isothiazoles have yet to be incorporated into this methodology to give borylated isothiazolopyridine. Compounds featuring isothiazoles have been shown to have increased potency when compared to their analogues and their incorporation would highly advantageous.[204] Although we were able to formylate isothiazole **512**, we were unable to isolate the product from the crude reaction mixture. ^{1}H NMR analysis of the material obtained after purification showed a complex mixture in the upfield region of the spectrum. Isothiazoles featuring suitable leaving group such as **512** are known to degrade under basic conditions.[205] Although we do not know what the complex mixture in the NMR spectrum is, it is possible that a similar degradation pathway has occurred with our compound. Attempts to carry crude formylisothiazole **513** forward in the reaction sequence were unsuccessful. Alkyne coupling was observed by ^{1}H NMR analysis but isothiazole **514** was inseparable from the reaction mixture.



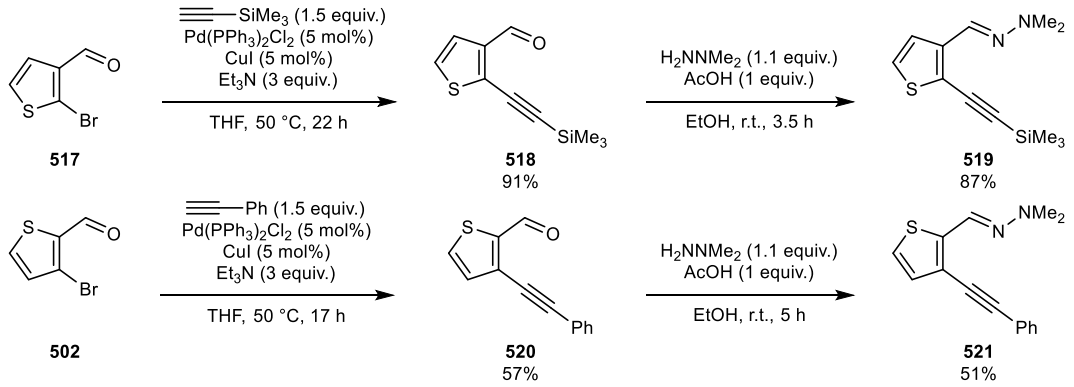
Scheme 133: Attempted synthesis of isothiazole azadienyne **514**

Wanting to prepare a new fused-ring system we sought to prepare the [3,2-c] regioisomer of thienopyridine **510**, as thiophenes have proven to be tolerant in this procedure. In order to do this, we need to alternate the substitution pattern of thiophene **509**. This was achieved through the successive bromination and formylation of 3-iodothiophene **515** (Scheme 134). The low yield in the formylation step is attributed to the poor regioselectivity of this reaction.



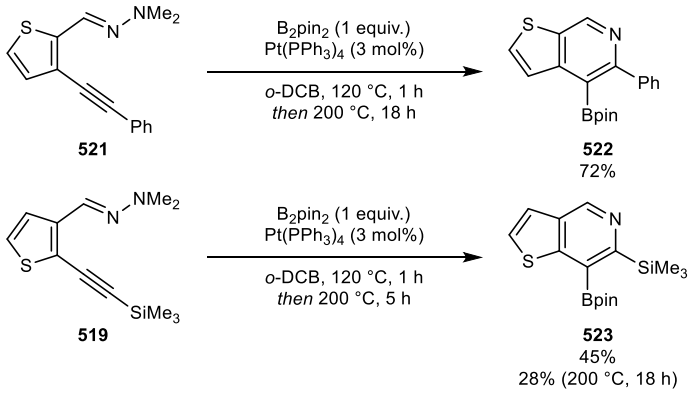
Scheme 134: Synthesis of thiophene **517**

Alongside the Sonogashira coupling of thiophene **517**, we also coupled phenylacetylene with the original starting thiophene **502** (Scheme 135). The resulting aldehydes were the converted to the corresponding hydrazone. Again ^{1}H NMR analysis of the crude mixture revealed only a single isomer of each hydrazone had been formed, which was also assigned as having the *E*-configuration by analogy to our previous results.



Scheme 135: Synthesis of hydrazones **519** and **521**

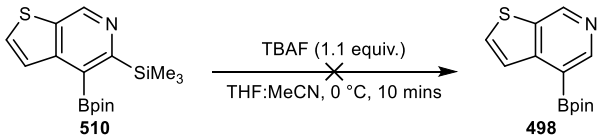
When hydrazones **519** and **521** were submitted to the diboration conditions, monitoring of the rection revealed complete consumption of the starting material after 1 h; no cyclisation was observed, which we assume to be again caused by the sterically crowded azatriene intermediate **511** (Scheme 136). Increasing the temperature of the reaction to 200 °C gave the desired fused-ring pyridine scaffolds. Again, reaction monitoring via TLC was used to confirm the end of the reaction. For hydrazone **521** the reaction was stopped after 22 h and [2,3-c] thienopyridine **522** was isolated in good yield. In the case of hydrazone **519**, reaction monitoring prompted us to stop the cyclisation after only 5 h, however, [3,2-c] thienopyridine was only isolated in 45% yield. Believing that our reaction monitoring had not accurately shown completion we extend the cyclisation time to 18 h. However, this led to a lower yield which suggests the [3,2-c] thienopyridines are less stable than their isomeric counterparts and has either degraded in the reaction or during purification. We are unsure of the reason for this observed instability.



Scheme 136: Synthesis of thienopyridines **522** and **523**

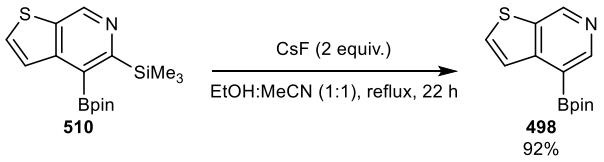
3.3.4 Transformation of Borylated Fused-Ring Pyridines

We still wished to obtain borylated thienopyridine **598** and considered desilylation of thienopyridine **510** as a possible strategy. Although we have shown that this reaction can be done under weakly basic conditions, it is more commonly achieved through the addition of a fluoride source such as tetrabutylammonium fluoride (TBAF). We believe that a fluoride-based reagent would be more suitable for our substrate, as a basic alcohol solution may promote hydrolysis of boronic ester. When we attempted this, we observed complete degradation of the boron moiety by ^{1}H NMR analysis within 10 mins (Scheme 137). This could be due to fluoride reacting at boron, as B-F and Si-F bonds have comparable bond strengths.[206]



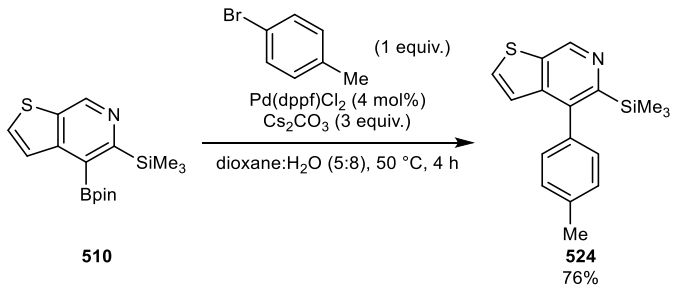
Scheme 137: Attemted TBAF desilylation of **510**

CsF has previously been shown to be a sufficient desilylation reagent that is also tolerant of boronic esters.[207] Using a modified procedure we were able to selectively remove the silyl group, giving thienopyridine **498** in excellent yield after recrystallisation of the crude reaction mixture (Scheme 138).



Scheme 138: Optimised synthesis of thienopyridine **498**

Finally, given the previously mentioned importance of Suzuki-Miyaura, we decide to perform a cross coupling reaction using **510**. Using an adaption of a literature procedure,[208] biaryl **524** was isolated in good yield (Scheme 139).

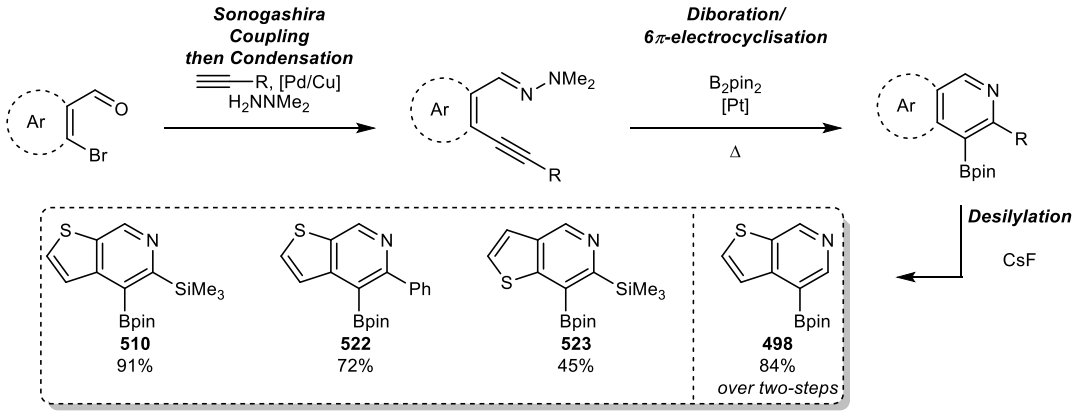


Scheme 139: Suzuki-Miyaura coupling of **510** with bromotoluene

3.4 Conclusions and Future Work

Our initial attempts to replicate the results reported by Mora-Radó failed. We were unable to optimise the synthesis of azadienyne **496** to give only the *E*-isomer and were unable to separate the isomeric mixture. The major *Z*-component of this mixture was inert to cyclisation and attempts to isolate thiophene **498** were unsuccessful. Translation of the aldoxime ether functionality to hydrazones alleviated issues relating the formation of *Z*-azadienyne. These hydrazones were found to smoothly undergo borylation under the previously reported conditions and required additional heating for cyclisation to furnish the thienopyridines **510**, **522** and **523** (Scheme 140).

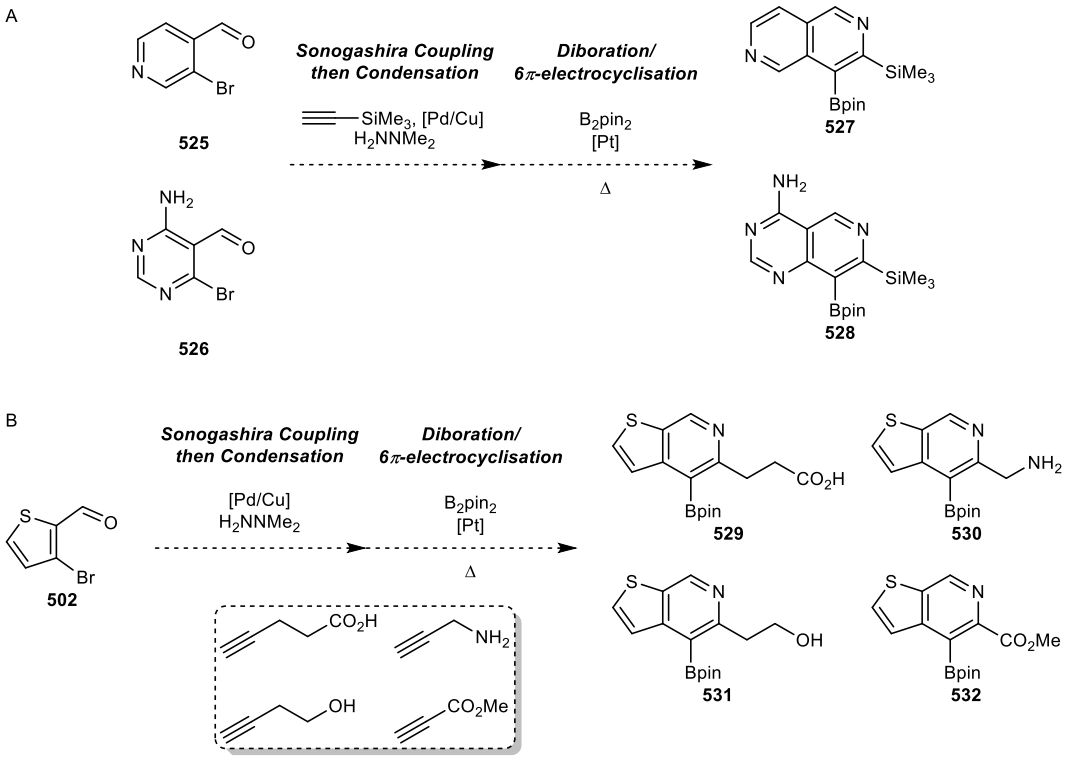
Even with this adaption we were unable to isolate monosubstituted thienopyridine **498** directly from the diboration/6π-electrocyclisation reaction due to its poor stability to standard purification methods. However we found thienopyridine **510** could be desilylated to give **498** in a combined yield of 84%; greater than the previously reported one step procedures (Scheme 140).[196,197] In summary, we have prepared 4 borylated fused-ring pyridines using the diboration/ 6π-electrocyclisation methodology, in the process extending the scope of the transformation to include the [3,2-c] thienopyridine template.



Scheme 140: Scope of thienopyridines synthesised

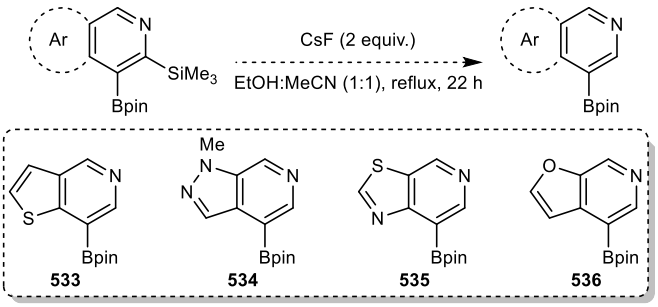
3.4.1 Future Work

Our major aim for this project was to expand upon the scope of the diboration/6π-electrocyclisation previously developed by Harrity and co-workers.[194–197] We were unable to incorporate a new heterocyclic moiety into the procedure. In addition to this we were not able to incorporate any new alkyne coupling partners to add new functional handles. An immediate continuation would be to start exploring with heterocyclic starting materials, choosing ones that are commercially available so we can be confident that their synthesis can be achieved (Scheme 141A). We could also begin to use thiophene **502** to evaluate which functionalised alkynes can be used to incorporate additional functional handles (Scheme 141B).



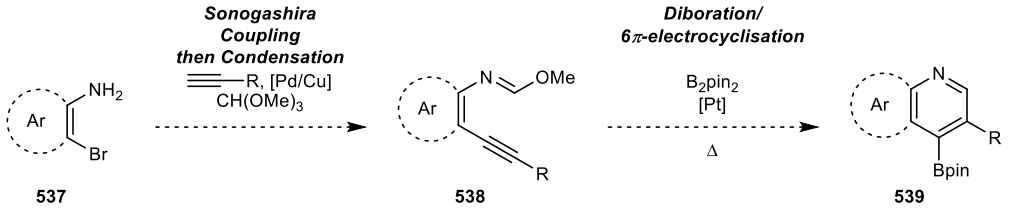
Scheme 141: Routes to expanding the scope of the diboration/6π-electrocyclisation strategy

Thienopyridine **498** represents the only monosubstituted fused-ring pyridine that has been prepared using the diboration/6π-electrocyclisation strategy. We envisage that this two-step procedure could be used with some of the other fused-ring systems that have already been prepared (Scheme 142). The benefit of this would be the reduced molecular weight of the scaffold could make them more attractive building blocks. Very often medicinal chemists set upper limits for the weight of building blocks so that final products conform to pre-set guidelines for drug design. It is also possible to perform *ortho* C-H functionalisation of pyridine without the need for substrate direction; meaning this site could feature as a functional handle for further transformation.[209]



Scheme 142: Proposed desilylation of *N*-α silyl borylated fused-ring pyridines

Electrocyclisations of azatrienes are not limited to substrates in which the nitrogen functionality is in the 1-position.[210] Incorporation of dienynes similar to **538** would yield fused ring pyridines in which the boron moiety is *para* to the nitrogen, effectively giving access to a new subset of scaffold (Scheme 143).



Scheme 143: Proposed utilisation of 2-azatrienes diboration/6π-electrocyclisation

4.1 General Information

All reagents and solvents used were supplied by commercial sources without further purification. All air-sensitive reactions were carried out under either a N_2 or Ar atmosphere using oven-dried apparatus. H_2O used for reactions and work-ups was deionised. Anhydrous THF was dried and purified by passage through activated alumina columns using a solvent purification system. Anhydrous MeOH and *o*-DCB were dried over $MgSO_4$, stored over molecular sieves under a nitrogen atmosphere and used immediately. All petroleum ether used was 40-60 °C boiling fraction.

Thin layer chromatography (TLC) was performed on aluminium-backed plates pre-coated with silica. Compounds were visualised by exposure to UV light or by dipping the plates into solutions of vanillin, ninhydrin, phosphomolybdic acid or potassium permanganate followed by heating. All flash chromatography was carried out using silica gel mesh 40-63 unless otherwise stated.

Infra-red spectra were recorded on a Perkin Elmer 100 FT instrument on the neat compound. NMR spectra were recorded on Bruker Advance 400 and 500 instruments at the indicated 101, 128, 126, 377 and 400 MHz as dilute solutions in the indicated deuterated solvent at ambient temperature. All chemical shifts (δ) reported in parts per million (ppm) relative to residual protio solvent (δH: $CHCl_3$ = 7.26 ppm, d_6-DMSO = 2.50 ppm) or the solvent itself (δC: $CDCl_3$ = 77.0 ppm, d_6-DMSO = 39.52 ppm). All multiplets are designated by the following abbreviations: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublets of doublets, ddt = doublet of doublets of triplets, dddd = doublet of doublets of doublets of doublets, ddddd = doublet of doublets of doublets of doublets of doublets, t = triplet, tdd = triplet of doublets of doublets, q = quartet, m = multiplet. All coupling constants (*J*) are reported in Hertz (Hz). ^{13}C NMR spectra were acquired as DEPT-Q experiments as standard; regular ^{13}C NMR experiments were acquired when quaternary carbons were hard to distinguish by DEPT-Q. Some quaternary centres were not observed due to quadrupolar relaxation. Compounds which are rotameric and have more signals than expected are labelled "rotamers" after the list of signals. ^{19}F NMR spectra were acquired as proton decoupled spectra. High-resolution mass spectra were recorded using either electrospray ionization (ESI) or electron ionisation (EI) by the Mass Spectrometry Service at the Department of Chemistry, University of Sheffield. The m/z values of major peaks are reported in Daltons, Da. Melting points were measured using Linkam HFs91 heating stage, used in conjunction with a TC92 controller and are uncorrected. HPLC analysis was performed using an Agilent 1260 Infinity II LC

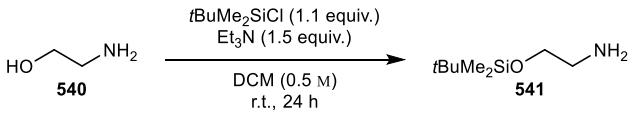
system. Boronic esters were oxidised to the corresponding alcohol for HPLC analysis using $NaBO_3.H_2O$ at r.t. in a THF:H_2O mixture.

Single crystal X-ray intensity data was collected at 100 K on a Bruker D8 Venture diffractometer equipped with a Photon 100 CMOS detector using a CuKα microfocus X-ray source from crystals mounted in fomblin oil on a MiTiGen microloop and cooled in a stream of cold N_2. Data were corrected for absorption using empirical methods (SADABS)[211] based upon symmetry equivalent reflections combined with measurements at different azimuthal angles.[212] The crystal structures were solved and refined against F^2 values using ShelXT[213] for solution and ShelXL[214] for refinement accessed via the Olex2 program.[215] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions with idealized geometries and then refined by employing a riding model and isotropic displacement parameters.

4.2 Synthesis and Transformations of Boryl Lactams

4.2.1 Preparation of Miscellaneous Compounds

(2-Aminoethoxy)(*tert*-butyl)dimethylsilane (541)

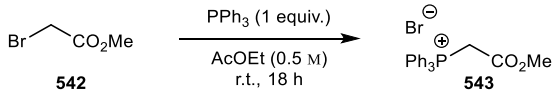


Based on the procedure by Middleton[216], triethylamine (10.45 ml, 75.0 mmol) was added dropwise to a stirring solution of ethanolamine (3.02 ml, 50.0 mmol) and *tert*-butyldimethylsilyl chloride (8.29 g, 55.0 mmol) in CH_2Cl_2 (100 ml) and stirred at r.t. for 24 h. Upon completion the mixture was washed with H_2O (3 × 100 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by distillation under reduce pressure to give silyl ether **541** (7.93 g, 90%) as a colourless oil. The data were consistent with the literature.[217]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (2H, t, *J* = 5.2 Hz, OC**H**$_2$), 2.78 (2H, t, *J* = 5.2 Hz, NC**H**$_2$), 1.73 (2H, br s, N**H**$_2$), 0.90 (9H, s, 3 × C**H**$_3$), 0.06 (6H, s, 2 × C**H**$_3$).

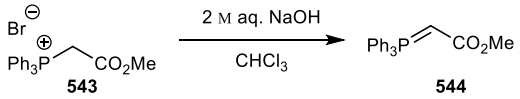
^{13}C NMR (101 MHz, $CDCl_3$) δ 65.3 (CH_2), 44.3 (CH_2), 25.8 (3 × CH_3), 18.2 (C), -5.4 (2 × CH_3).

(2-Methoxy-2-oxoethyl)triphenylphosphanium bromide (543)



Based on the procedure by Kumar and Chein[218], methyl bromoacetate (25.0 ml, 264 mmol) was added to a stirring solution of triphenylphosphine (69.2 g, 264 mmol) in AcOEt (500 ml) and stirred at r.t. for 18 h. The precipitate was filtered, washed with AcOEt (2 × 250 ml), and dried *in vacuo* to give phosphonium salt **543** (108 g, 99%) as a white solid that was used without further purification.

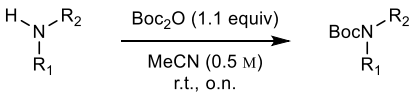
(Carbomethoxymethylene)triphenylphosphorane (544)



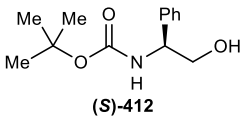
Based on the procedure by Kumar and Chein,[218] phosphonium salt **543** (15.0 g, 36.1 mmol) was dissolved in $CHCl_3$ (200 ml) and shaken vigorously in a separating funnel with 2M NaOH aq. (200 ml). The organics were dried over Na_2SO_4 and concentrated *in vacuo* to give ylide **544** (12.1 g, 100%) as a white solid that was used without further purification.

4.2.2 Boc Protection of Amines

General Procedure 1: Boc protection of amines



Di-*tert*-butyl dicarbonate (1.1 equiv.) was added to a stirring solution of amine (1 equiv.) in MeCN (0.5M) and stirred at r.t. overnight. The mixture was concentrated *in vacuo* and purified by chromatography, precipitation or recrystallisation as required.



(*S*)-*tert*-Butyl *N*-[(*S*)-1-hydroxy-2-methylpropan-2-yl]carbamate ((*S*)-412)

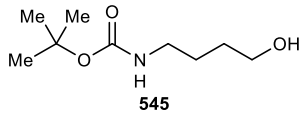
The title compound was prepared according to **General Procedure 1** using (2*S*)-2-phenyl-2-aminoethanol (3.43 g, 25.0 mmol), di-*tert*-butyl dicarbonate (6.00 g, 27.5 mmol) and MeCN (50 ml). The crude residue was recrystalised from hot AcOEt to give amine **(*S*)-412** (5.90 g, 99%) as an off-white solid. The data were consistent with the literature.[219]

$[\alpha]_D^{21}$ +36.0 (c 1, $CHCl_3$), Lit. $[\alpha]_D^{27}$ +38.7 (c 1, $CHCl_3$).[219]

m.p. = 149 - 141 °C (MeCN), Lit. 136-137 °C (no solvent reported).[219]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.32 (2H, m, Ar**H**), 7.33 - 7.27 (3H, m, Ar**H**), 5.24 (1H, s, 1H, NC**H**), 4.78 (1H, br s, N**H**), 3.86 - 3.83 (2H, m, C$\mathbf{H}_2$), 2.34 (1H, br s, O**H**), 1.43 (9H, s, 3 × C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C), 139.4 (C), 128.8 (2 × CH), 127.8 (CH), 126.6 (2 × CH), 80.0 (C), 67.0 (CH_2), 56.9 (CH), 28.3 (3 × CH_3).



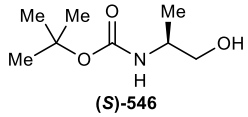
545

***tert*-Butyl *N*-(4-hydroxybutyl)carbamate (545)**

The title compound was prepared according to **General Procedure 1** using 4-amino-1-butanol (3.69 ml, 40.0 mmol), di-*tert*-butyl dicarbonate (9.60 g, 44.0 mmol) and MeCN (80 ml). The crude residue was purified by column chromatography (hexane:AcOEt 1:1→0:1) to give amine **545** (7.32 g, 97%) as a colourless oil. The data were consistent with the literature.[220]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (1H, br s, N**H**), 3.65 (2H, br s, OC**H**$_2$), 3.26 - 3.03 (2H, m, NC**H**$_2$), 2.07 (1H, br s, O**H**), 1.68 - 1.52 (4H, m, C**H**$_2$C**H**$_2$CH_2O), 1.42 (9H, s, 3 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1 (C), 79.1 (C), 62.2 (CH_2), 40.3 (CH_2), 29.7 (3 × CH_3), 28.4 (CH_2), 26.5 (CH_2).



(*S*)-546

***tert*-Butyl *N*-[(2*S*)-1-hydroxypropan-2-yl]carbamate ((*S*)-546)**

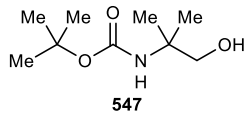
The title compound was prepared according to **General Procedure 1** using L-alaninol (3.76 g, 50.0 mmol), di-*tert*-butyl dicarbonate (12.0 g, 55.0 mmol) and MeCN (100 ml). The reaction gave amine **(*S*)-546** (8.75 g, 100%) as a white solid. The data were consistent with the literature.[221]

$[\alpha]_D^{21}$ -9.0 (c 1, $CHCl_3$), Lit. $[\alpha]_D^{20}$ -9.1 (c 1, $CHCl_3$).[221]

m.p. = 57 - 60 °C (MeCN), Lit. 59-61 °C (no solvent reported).[221]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 - 4.71 (1H, m, C**H**), 3.75 (1H, br s, N**H**), 3.68 - 3.54 (1H, m, C**H**$_A$H$_B$), 3.54 - 3.41 (1H, m, CH$_A$**H**$_B$), 2.88 (1H, br s, O**H**), 1.43 (9H, s, 3 × C**H**$_3$), 1.13 (3H, d, *J* = 6.8 Hz, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4 (C), 79.7 (C), 67.3 (CH_2), 48.5 (CH), 28.3 (3 × CH_3), 17.3 (CH_3).



547

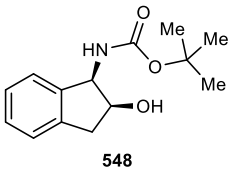
***tert*-Butyl *N*-(1-hydroxy-2-methylpropan-2-yl)carbamate (547)**

The title compound was prepared according to **General Procedure 1** using 2-amino-2-methyl-1-propanol (9.54 ml, 100 mmol), di-*tert*-butyl dicarbonate (24.0 g, 110 mmol) and MeCN (200 ml). The reaction gave amine **547** (18.9 g, 100%) as a white solid. The data were consistent with the literature.[222]

m.p. = 55 - 57 °C (MeCN), Lit. 59.5 - 70.5 °C (no solvent reported).[223]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (1H, br s, N**H**), 4.10 (1H, br s, O**H**), 3.58 (2H, d, *J* = 6.2 Hz, C**H**$_2$), 1.42 (9H, s, 3 × C**H**$_3$), 1.24 (6H, s, 2 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2 (C), 79.8 (C), 70.9 (CH_2), 54.3 (C), 28.3 (3 × CH_3), 24.7 (2 × CH_3).



548

tert-Butyl *N*-[(1*R*,2*S*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamate (548)

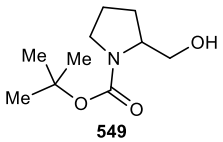
The title compound was prepared according to **General Procedure 1** using (1*R*,2*S*)-1-Amino-2-indanol (3.73 g, 25.0 mmol), di-*tert*-butyl dicarbonate (6.00 g, 27.5 mmol) and MeCN (50 ml). The crude residue dissolved in the minimum amount of hot CH_2Cl_2 and precipitated in hexane to give amine **548** (5.90 g, 94%) as an off-white solid. The data were consistent with the literature.[224]

$[\alpha]_D^{21}$ -7.0 (c 1, $CHCl_3$), Lit. $[\alpha]_D^{27}$ -13.6 (c 3, $CHCl_3$).[224]

m.p. = 71 -72 °C (MeCN), Lit. 76-77 °C (no solvent reported).[224]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.20 (4H, m, Ar**H**), 5.26 - 4.97 (2H, m, N**H** + NC**H**), 4.61 (1H, br s, OC**H**), 3.14 (1H, dd, *J* = 16.5, 5.2 Hz, C$\mathbf{H_A}H_B$), 2.93 (1H, dd, *J* = 16.5, 1.8 Hz, $CH_A\mathbf{H_B}$), 2.05 (1H, s, O**H**), 1.51 (9H, s, 3 × C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3 (C), 140.8 (CH), 139.8 (C), 128.2 (CH), 127.1 (CH), 125.3 (CH), 124.5 (C), 79.89 (C), 73.7 (CH), 58.9 (CH), 39.4 (CH_2), 28.4 (3 × CH_3).



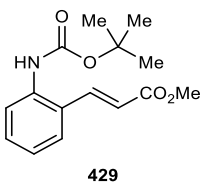
549

(±)-*tert*-Butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (549)

The title compound was prepared according to **General Procedure 1** using pyrrolidin-2-yl methanol (1.01 g, 10.0 mmol), di-*tert*-butyl dicarbonate (2.40 g, 11.0 mmol) and MeCN (20 ml). The reaction gave amine **549** (1.79 g, 89%) as a pale-yellow oil. The data were consistent with the literature.[225]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (1H, br s, O**H**), 4.07 - 3.84 (1H, m, NC**H**), 3.71 - 3.52 (2H, m, OC$\mathbf{H}_2$), 3.49 - 3.37 (1H, m, NC$\mathbf{H_A}H_B$), 3.35 - 3.21 (1H, m, $NCH_A\mathbf{H_B}$), 2.07 - 1.67 (4H, m, $NCH_2C\mathbf{H}_2C\mathbf{H}_2$), 1.45 (9H, s, 3 × C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2 (C), 80.2 (C), 67.7 (CH_2), 60.2 (CH), 47.5 (CH_2), 28.7 (CH_2), 28.4 (3 × CH_3), 24.0 (CH_2).



429

Methyl (2*E*)-3-(2-{[(tert-butoxy)carbonyl]amino}phenyl)prop-2-enoate (429)

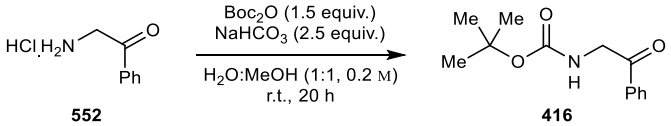
The title compound was prepared according to **General Procedure 1** using amine **423** (0.886 g, 5.00 mmol), di-*tert*-butyl dicarbonate (1.20 g, 5.50 mmol) and MeCN (10 ml). The crude residue was purified by column chromatography (hexane:AcOEt 9:1) to give amine **429** (4.25 g, 90%) as a pale-yellow solid. The data were consistent with the literature.[226]

m.p. = 114 - 117 °C (MeCN), Lit. 83-85 °C (no solvent reported).[226]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, d, *J* = 15.8 Hz, ArC**H**=CH), 7.78 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.51 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.37 (1H, dd, *J* = 8.2, 7.3 Hz, Ar**H**), 7.12 (1H, dd, *J* = 7.7, 7.3 Hz, Ar**H**), 6.47 (1H, br s, N**H**), 6.39 (1H, d, *J* = 15.8 Hz, C**H**CO), 3.82 (3H, s, OC**H**$_3$), 1.53 (9H, s, 3 × CC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (C), 153.3 (C), 152.9 (C), 139.6 (CH), 136.6 (C), 130.9 (CH), 127.1 (CH), 124.4 (CH), 122.9 (CH), 120.1 (CH), 81.2 (C), 51.8 (CH_3), 28.3 (3 × CH_3).

tert-Butyl *N*-(2-oxo-2-phenylethyl)carbamate (416)



552 416

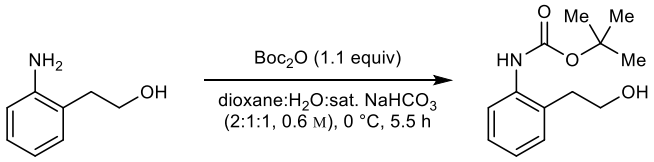
Based on the procedure by Barrios-Rivera *et al.*[227], a solution of di-*tert*-butyl dicarbonate (6.46 g, 30.0 mmol) in MeOH (50 ml) was added to a solution of 2-aminoacetophenone hydrochloride (3.42 g, 20.0 mmol) and $NaHCO_3$ (4.20 g, 50.0 mmol) in H_2O (50 ml) and stirred at r.t. for 20 h. The mixture was then poured over ice cold water (500 ml), the precipitate was filtered and dried *in vacuo* to give amine **416** (2.30 g, 49%) as a white solid. The data were consistent with the literature.[228]

m.p. = 59 - 62 °C (CH_2Cl_2), Lit. 63-65 °C (no solvent reported).[228]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, *J* = 7.4 Hz, Ar**H**), 7.61 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.49 (t, *J* = 7.4 Hz, Ar**H**), 5.55 (1H, br s, N**H**), 4.66 (2H, d, *J* = 4.1 Hz, C**H$_2$**), 1.48 (9H, s, 3 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.4 (C), 155.8 (C), 134.5 (C), 133.9 (CH), 128.9 (2 × CH), 127.8 (2 × CH), 79.8 (C), 47.5 (CH_2), 28.3 (3 × CH_3).

tert-Butyl *N*-[2-(2-hydroxyethyl)phenyl]carbamate (551)



550 551

Based on the procedure by Crich and Hao[229], di-*tert*-butyl dicarbonate (8.75 g, 40.1 mmol) was added dropwise to a stirring solution of 2-(2aminophenyl)ethanol (5.00 g, 36.4 mmol) in dioxane (30 ml), H_2O (15 ml) and sat. $NaHCO_3$ (aq., 15 ml) at 0 °C and stirred for 5.5 h. Upon completion the solution was diluted with H_2O (50 ml) and aqueous phase extracted with AcOEt (3 × 50 ml). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The mixture was recrystallised from AcOEt to give amine **551** (7.19 g, 83%) as a pale pink solid. The data were consistent with the literature.[229]

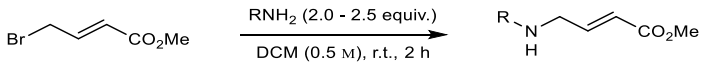
m.p. = 133 - 135 °C (AcOEt), Lit. 128-129 °C (no solvent reported).[229]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (1H, d, *J* = 7.2 Hz, Ar**H**), 7.60 (1H, br s, N**H**), 7.23 (1H, t, *J* = 7.5, 7.7 Hz, Ar**H**), 7.14 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.05 (1H, dd, *J* = 7.2, 7.7 Hz, Ar**H**), 3.95 - 3.87 (2H, m, CH_2), 2.87 - 2.78 (2H, m, CH_2), 1.51 (9H, s, 3 × C**H**$_3$).

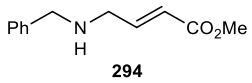
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7 (C), 137.1 (C), 130.7 (C), 130.2 (CH), 127.3 (CH), 124.2 (CH), 122.9 (CH), 80.1 (C), 64.3 (CH_2), 34.6 (CH_2), 28.4 (3 × CH_3).

4.2.3 Preparation of Amino Enoates

General Procedure 2: Preparation of alkyl amino enoates



Methyl 4-bromocrotonate (1.18 ml, 10.0 mmol) and amine (20.0 - 25.0 mmol) were dissolved in CH_2Cl_2 (10 mL), and the mixture was stirred at r.t. for 2 h. Saturated aqueous Na_2CO_3 (50 ml) was added, and the mixture was extracted with AcOEt (3 × 50 ml). The combined organic phases were washed with brine (50 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by chromatography.



294

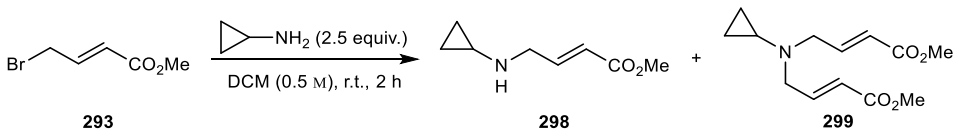
Methyl (2*E*)-4-(benzylamino)but-2-enoate (294)

The title compound was prepared according to **General Procedure 2** using methyl 4-bromocrotonate (1.18 ml, 10.0 mmol) and benzylamine (2.18 ml g, 20.0 mmol). The crude residue was purified by column chromatography (hexane:Et_2O 1:0→3:2) to give amine **294** (409 mg, 20%) as an amber oil. The data were consistent with the literature.[230]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.15 (5H, m, Ar**H**), 6.96 (1H, dt, *J* = 15.8, 5.4 Hz, NCH_2C**H**CH), 5.98 (1H, dt, *J* = 15.8, 1.9 Hz, NCH_2CHC**H**), 3.74 (2H, s, ArC**H**$_2$), 3.68 (3H, s, C**H**$_3$), 3.36 (2H, dd, *J* = 5.4, 1.9 Hz, N**H**$_2$CHCH).

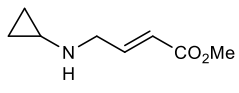
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (C), 146.9 (CH), 139.7 (C), 128.3 (2 × CH), 128.0 (2 × CH), 127.0 (CH), 121.0 (CH), 53.1 (CH_2), 51.4 (CH_3), 49.4 (CH_2).

Methyl (2*E*)-4-(cyclopropylamino)but-2-enoate (298), Methyl (2*E*)-4-{cyclopropyl[(2*E*)-4-methoxy-4-oxobut-2-en-1-yl]amino}but-2-enoate (299)



293 **298** **299**

The title compounds were prepared according to **General Procedure 2** using methyl 4-bromocrotonate (1.18 ml, 10.0 mmol) and cyclopropylamine (1.73 ml g, 25.0 mmol). The crude residue was purified by column chromatography (hexane:Et_2O, 1:0→1:1) to give amine **298** (393 mg, 25%) as a pale-yellow oil and amine **299** (446 mg, 35%) as a pale yellow oil.



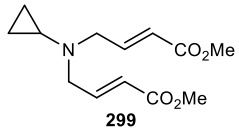
298

IR 3088 (NH), 2945 (CH), 1723 (C=O), 1164, 1019, 832 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (1H, dt, *J* = 15.7, 5.7 Hz, $NCH_2C\mathbf{H}CH$), 5.95 (1H, dt, *J* = 15.7, 1.8 Hz, $NCH_2CHC\mathbf{H}$), 3.72 (3H, s, CH_3), 3.46 (2H, dd, *J* = 5.7, 1.8 Hz, $NC\mathbf{H_2}$), 2.28 - 2.12 (1H, m, $NC\mathbf{H}CH_2$), 0.50 - 0.30 (4H, m, 2 × $NCHC\mathbf{H_2}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (C), 147.2 (CH), 121.0 (CH), 51.5 (CH_3), 50.1 (CH_2), 30.0 (CH), 6.5 (2 × CH_2).

HRMS (Q-TOF) Exact mass calcd for $[C_8H_{14}NO_2]^+$ $[MH]^+$ calcd. 156.1019, found 156.1026.



299

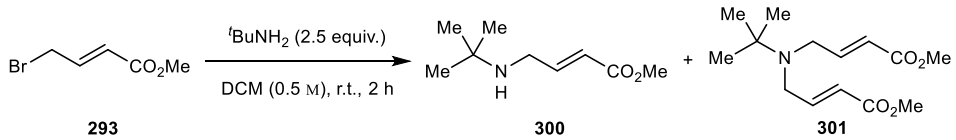
IR 2951 (CH), 1721 (C=O), 1269, 1162, 1017, 828 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$δ 6.93 (2H, dt, *J* = 15.1, 6.4 Hz, 2 × $NCH_2C\mathbf{H}CH$), 5.90 (2H, dt, *J* = 15.1, 1.5 Hz, 2 × $NCH_2CHC\mathbf{H}$), 3.70 (6H, s, 2 × NCH_3), 3.33 (4H, dd, *J* = 6.4, 1.5 Hz, 2 × $NC\mathbf{H_2}$), 1.95 - 1.71 (1H, m, $NC\mathbf{H}CH_2$), 0.89 - 0.28 (4H, m, 2 × $NCHC\mathbf{H_2}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (2 × C), 145.5 (2 × CH), 122.6 (2 × CH), 55.5 (2 × CH_2), 51.4 (2 × CH_3), 36.3 (CH), 7.3 (2 × CH_2).

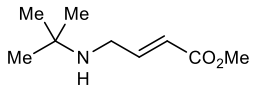
HRMS (Q-TOF) Exact mass calcd for $[C_{13}H_{20}NO_4]^+$ $[MH]^+$ calcd. 254.1387, found 254.1390.

Methyl (2*E*)-4-(tert-butylamino)but-2-enoate (300), Methyl (2*E*)-4-{tert-butyl[(2*E*)-4-methoxy-4-oxobut-2-en-1-yl]amino}but-2-enoate (301)



293 300 301

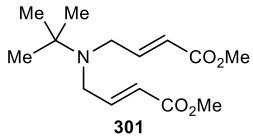
The title compounds were prepared according to **General Procedure 2** using methyl 4-bromocrotonate (1.18 ml, 10.0 mmol) and *tert*-butylamine (2.63 ml g, 25.0 mmol). The crude residue was purified by column chromatography (hexane:Et_2O 1:0→1:1) to give amine **300** (630 mg, 37%) as a brown oil and amine **301** (110 mg, 8%) as a white solid. The data were consistent with the literature.[230,231]



300

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (1H, dt, *J* = 15.7, 5.4 Hz, $NCH_2CHC\mathbf{H}$), 5.98 (1H, dt, *J* = 15.7, 1.1 Hz, $NCH_2C\mathbf{H}CH$), 3.70 (3H, s, $C\mathbf{H_3}$), 3.35 (2H, dd, *J* = 5.4, 1.1 Hz, $C\mathbf{H_2}$), 1.09 (9H, s, 3 × $C\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (C), 148.2 (CH), 120.5 (CH), 51.4 (CH_3), 50.5 (C), 43.7 (CH_2), 29.0 (3 × CH_3).



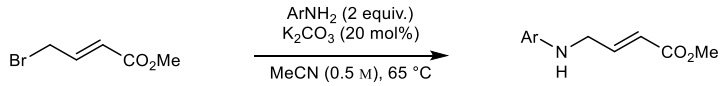
301

m.p. = 48 -50 °C (CH_2Cl_2), no literature value reported.

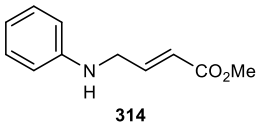
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (2H, dt, *J* = 15.6, 5.7 Hz, 2 × $NCH_2C\mathbf{H}CH$), 5.97 (2H, dt, *J* = 15.6, 1.6 Hz, 2 × $NCH_2CHC\mathbf{H}$), 3.72 (6H, s, 2 × $C\mathbf{H_3}$), 3.31 (4H, dd, *J* = 5.7, 1.6 Hz, 2 × $C\mathbf{H_2}$), 1.08 (9H, s, 3 × $C\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (2 × C), 149.0 (2 × CH), 121.2 (2 × CH), 55.1 (C), 51.5 (2 × CH_3), 50.5 (2 × CH_2), 27.5 (3 × CH_3).

General Procedure 3: Preparation of aryl amino enoates



Methyl 4-bromocrotonate (0.59 ml, 5.00 mmol), aniline (10.0 mmol) and K_2CO_3 (138 mg, 1.00 mmol) were dissolved in MeCN (10 mL), and the mixture was stirred at 65 °C. Upon completion of the reaction (as determined by TLC), the mixture was cooled to RT. Saturated aqueous Na_2CO_3 (50 mL) was added, and the mixture was extracted with AcOEt (3 × 50 ml). The combined organic phases were washed with brine (50 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by either chromatography or recrystallisation.



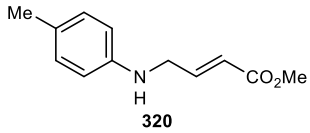
314

Methyl (2*E*)-4-(phenylamino)but-2-enoate (314)

The title compound was prepared according to **General Procedure 3** using methyl 4-bromocrotonate (0.59 ml, 5.00 mmol) and aniline (931 mg, 10.0 mmol). The crude residue was purified by column chromatography (CH_2Cl_2:petroleum ether 1:1→1:0) to give amine **314** (672 mg, 70%) as a brown oil. The data were consistent with the literature.[232]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (2H, dd, *J* = 7.8 Hz, Ar**H**), 7.04 (1H, dt, *J* = 15.7, 4.6 Hz, CH_2C**H**=CH), 6.74 (1H, t, *J* = 7.8 Hz, Ar**H**), 6.60 (2H, d, *J* = 7.8 Hz, Ar**H**), 6.06 (1H, dt, *J* = 15.7, 2.0 Hz, CH_2CH=C**H**), 3.96 (2H, dd, *J* = 4.6, 2.0 Hz, C**H$_2$**), 3.73 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (C), 147.2 (C), 145.8 (CH), 129.3 (2 × CH), 121.4 (CH), 118.0 (CH), 112.9 (2 × CH), 51.5 (CH_3), 44.8 (CH_2).



320

Methyl (2*E*)-4-[(4-methylphenyl)amino]but-2-enoate (320)

The title compound was prepared according to **General Procedure 3** using methyl 4-bromocrotonate (4.47 g, 25.0 mmol), p-toluidine (5.36 g, 50.0 mmol), K_2CO_3 (691 mg, 5.00 mmol) in MeCN (50 ml). The crude residue was purified by column chromatography (petroleum ether:AcOEt 9:1) to give *amine* **320** (3.04 g, 59%) as an amber solid.

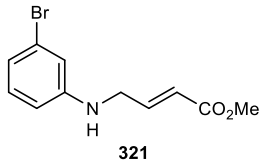
m.p. = 51-53 °C (CH_2Cl_2).

IR 3389 (NH), 2948, 1703 (C=O), 1520, 1284, 808 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (1H, dt, *J* = 15.7, 4.6 Hz, CH_2C**H**=CH), 7.00 (2H, d, *J* = 8.3 Hz, Ar**H**), 6.53 (2H, d, *J* = 8.3 Hz, Ar**H**), 6.05 (1H, dt, *J* = 15.7, 1.9, CH_2CH=C**H**), 3.93 (2H, dd, *J* = 4.6, 1.9 Hz, C**H$_2$**CH=CH), 3.73 (3H, s, OC**H$_3$**), 2.25 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (C), 146.0 (CH), 144.8 (C), 129.8 (2 × CH), 127.3 (C), 121.3 (CH), 113.1 (2 × CH), 51.5 (CH_3), 45.2 (CH_2), 20.3 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{12}H_{16}NO_2]$+ [MH]+ calcd. 206.1176, found 206.1178.



321

Methyl (2*E*)-4-[(3-bromophenyl)amino]but-2-enoate (321)

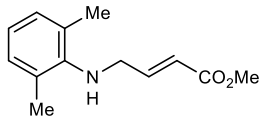
The title compound was prepared according to **General Procedure 3** using methyl 4-bromocrotonate (4.47 g, 25.0 mmol), 3-bromoaniline (5.44 ml, 50.0 mmol), K_2CO_3 (691 mg, 5.00 mmol) and MeCN (50 ml). The crude residue was purified by column chromatography (petroleum ether:AcOEt 9:1→3:2) to give *amine* **321** (6.04 g, 90%) as a brown oil.

IR 3390 (NH), 2950, 1709 (C=O), 1594, 1276, 1169, 985, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.01 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.99 (1H, dt, *J* = 15.6, 4.6 Hz, CH_2C**H**=CH), 6.84 (1H, ddd, *J* = 8.0, 2.0, 0.8 Hz, Ar**H**), 6.71 (1H, t, *J* = 2.0 Hz, Ar**H**), 6.49 (1H, ddd, *J* = 8.0, 2.0, 0.8 Hz, Ar**H**), 6.02 (1H, dt, *J* = 15.6, 2.0 Hz, CH_2CH=C**H**), 3.93 (2H, dd, *J* = 4.6, 2.0 Hz, C**H$_2$**), 3.73 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C), 148.5 (C), 145.0 (CH), 130.6 (CH), 123.3 (C), 121.6 (CH), 120.8 (CH), 115.5 (CH), 111.6 (CH), 51.6 (CH_3), 44.5 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $[C_{11}H_{13}{}^{79}BrNO_2]^+$ [MH]$^+$ calcd. 270.0124, found 270.0130.



325

Methyl (2*E*)-4-[(2,6-dimethylphenyl)amino]but-2-enoate (322)

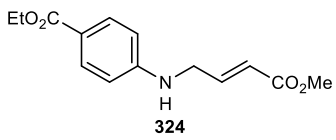
The title compound was prepared according to **General Procedure 3** using methyl 4-bromocrotonate (0.59 ml, 5.00 mmol) and 2,6-dimethylaniline (1.21 g, 10.0 mmol). The crude residue was purified by column chromatography ($CHCl_3$:AcOEt 1:0→19:1) to give amine **322** (692 mg, 63%) as an amber oil.

IR 3375 (NH), 2950, 1717 (C=O), 1268, 1168, 765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (1H, dt, *J* = 15.6, 5.1 Hz, CH_2C**H**=CH), 7.01 (2H, d, *J* = 7.5 Hz, Ar**H**), 6.86 (1H, t, *J* = 7.5, Ar**H**), 6.14 (1H, dt, *J* = 15.6, 2.1 Hz, CH_2CH=C**H**), 3.76 (3H, s, OC**H$_3$**), 3.75 (2H, dd, *J* = 5.1, 2.1 Hz, C**H$_2$**), 2.28 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (C), 146.5 (CH), 145.1 (C), 129.8 (C), 128.9 (2 × CH), 122.5 (CH), 121.1 (CH), 51.6 (CH_3), 49.1 (CH_2), 18.3 (2 × CH_3)

HRMS (Q-TOF) Exact mass calcd for $[C_{13}H_{18}NO_2]^+$ [MH]$^+$ calcd. 220.1332, found 220.1341.



324

Ethyl 4-{[(2*E*)-4-methoxy-4-oxobut-2-en-1-yl]amino}benzoate (324)

The title compound was prepared according to **General Procedure 3** using methyl 4-bromocrotonate (10.7 g, 60.0 mmol), ethyl 4-aminobenzoate (19.8 g, 120 mmol), K_2CO_3 (1.66 g, 12.6 mmol) and MeCN (120 ml). The crude residue was purified by column chromatography (petroleum ether:AcOEt, 1:1) to give *amine* **324** (11.7 g, 74%) as an off-white solid.

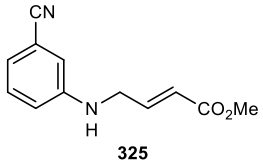
m.p. = 62-65 °C (EtOH).

IR 3354 (NH), 2987, 1718 (C=O), 1679, 1343, 1272, 1169, 840, 767 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, *J* = 8.8 Hz, Ar**H**), 7.00 (1H, dt, *J* = 15.7, 4.6 Hz, CH_2C**H**=CH), 6.55 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.01 (1H, dt, *J* = 15.7, 2.0 Hz, CH_2CH=C**H**), 4.39 (1H, t, *J* = 6.0 Hz, N**H**), 4.31 (2H, q, *J* = 7.1 Hz, OC**H$_2$**CH_3), 4.02 (2H, ddd, *J* = 6.0, 4.6, 2.0 Hz, C**H$_2$**CH=CH), 3.73 (3H, s, OC**H$_3$**), 1.36 (3H, t, *J* = 7.1 Hz, OCH_2C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (C), 166.5 (C), 150.9 (C), 144.5 (CH), 131.5 (2 × CH), 121.8 (CH), 119.6 (C), 111.7 (2 × CH), 60.3 (CH_2), 51.7 (CH_3), 44.2 (CH_2), 14.4 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{14}H_{18}NO_4]^+$ $[MH]^+$ calcd. 264.1230, found 264.1237.



325

Methyl (2*E*)-4-[(4-cyanophenyl)amino]but-2-enoate (325)

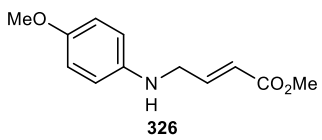
The title compound was prepared according to **General Procedure 3** using methyl 4-bromocrotonate (0.59 ml, 5.00 mmol) and 3-aminobenzonitrile (1.18 g, 9.99 mmol). The crude residue was purified by column chromatography (CH_2Cl_2:petroleum ether 3:1→1:0) to give *amine* **325** (492 mg, 46%) as a pale-yellow oil.

IR 3390 (NH), 2951, 2227, (C≡N), 1709 (C=O), 1602, 1273, 1168, 780 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.19 (1H, m, Ar**H**), 7.03-6.94 (2H, m, Ar**H** and CH_2C**H**=CH), 6.83-6.75 (2H, m, Ar**H**), 6.01 (1H, dt, *J* = 15.7, 2.0, CH_2CH=C**H**), 3.96 (2H, dd, *J* = 4.5, 2.0 Hz, C**H$_2$**), 3.73 (3H, s, OC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C), 147.4 (C), 144.3 (CH), 130.0 (CH), 121.8 (CH), 121.4 (CH), 119.2 (C), 117.3 (CH), 115.1 (CH), 113.0 (C), 51.6 (CH_3), 44.3 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $[C_{12}H_{13}N_2O_2]^+$ $[MH]^+$ calcd. 217.0972, found 217.0980.



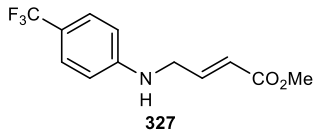
326

Methyl (2*E*)-4-[(4-methoxyphenyl)amino]but-2-enoate (326)

The title compound was prepared according to **General Procedure 3** using methyl 4-bromocrotonate (0.59 ml, 5.00 mmol) and *p*-anisidine (1.23 g, 9.99 mmol). The crude residue was purified by column chromatography (petroleum ether:AcOEt 1:0→7:3) to give amine **326** (735 mg, 66%) as an amber oil. The data were consistent with the literature.[232]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (1H, dt, *J* = 15.7, 4.7 Hz, CH_2C**H**=CH), 6.78 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.58 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.05 (1H, dt, *J* = 15.7, 1.9 Hz, CH_2CH=C**H**), 3.92 (2H, dd, *J* = 4.7, 1.9 Hz, C**H$_2$**), 3.75 (3H, s, ArOC**H$_3$**), 3.73 (3H, s, CO_2C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (C), 152.7 (C), 145.9 (CH), 141.1 (C), 121.5 (CH), 115.0 (2 × CH), 114.5 (2 × CH), 55.8 (CH_3), 51.6 (CH_3), 45.8 (CH_2).



327

Methyl (2*E*)-4-{[4-(trifluoromethyl)phenyl]amino}but-2-enoate (327)

The title compound was prepared according to **General Procedure 3** using methyl 4-bromocrotonate (0.59 ml, 5.00 mmol) and 4-(trifluoromethyl)aniline (1.64 g, 10.2 mmol). The crude residue was purified by column chromatography (CH_2Cl_2:petroleum ether 1:1→1:0) to give *amine* **327** (843 mg, 65%) as pale-yellow solid.

m.p. = 79-81 °C (CH_2Cl_2).

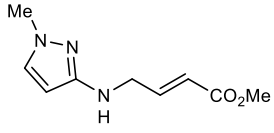
IR 3368 (NH), 2957, 1716 (C=O), 1614, 1315, 1104, 822 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.01 (1H, dt, *J* = 15.7, 4.4 Hz, CH_2C**H**=CH), 6.59 (2H, d, *J* = 8.6 Hz, Ar**H**), 6.02 (1H, dt, *J* = 15.7, 2.0 Hz, CH_2CH=C**H**), 4.29 (1H, s, N**H**), 4.00 (2H, dd, *J* = 4.4, 2.0 Hz, C**H$_2$**), 3.73 (3H, s, OC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C), 149.7 (C), 144.6 (CH), 126.7 (2 × CH, q, *J* = 3.8 Hz), 124.8 (C, q, *J* = 270.4 Hz), 121.8 (CH), 119.6 (C, q, *J* = 32.8 Hz), 112.0 (2 × CH), 51.7 (CH_3), 44.3 (CH_2).

^{19}F NMR (377 MHz, $CDCl_3$) δ −61.2 (s).

HRMS (Q-TOF) Exact mass calcd for $[C_{12}H_{13}F_3NO_3]^+$ $[MH]^+$ calcd. 260.0893, found 260.0904.



328

Methyl (2*E*)-4-[(1-methyl-4,5-dihydro-1H-pyrazol-3-yl)amino]but-2-enoate (328)

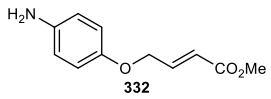
The title compound was prepared according to **General Procedure 3** using methyl 4-bromocrotonate (0.59 ml, 5.00 mmol) and 1-Methyl-1H-pyrazol-3-amine (971 mg, 10.0 mmol). The crude residue was purified by column chromatography (Et_2O) to give amine **328** (654 mg, 67%) as an amber oil.

IR 3359 (NH), 2950 (CH), 1716 (C=O), 1552, 1275, 1170, 736 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, s, Ar**H**), 7.04 (1H, dt, *J* = 15.8, 5.0 Hz, CH_2C**H**=CH), 6.03 (1H, dt, *J* = 15.8, 1.7 Hz, CH_2CH=C**H**), 5.49 (1H, s, Ar**H**), 3.94 (2H, dd, *J* = 5.0, 1.7 Hz, C**H$_2$**), 3.71 (3H, s, NC**H$_3$**), 3.70 (3H, s, OC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (C), 156.3 (C), 146.4 (CH), 131.2 (CH), 120.9 (CH), 90.9 (CH), 51.5 (CH_3), 45.9 (CH_3), 38.5 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $[C_9H_{13}N_3O_2]^+$ $[MH]^+$ calcd. 196.1081, found 196.1088.



332

Methyl (2*E*)-4-(4-aminophenoxy)but-2-enoate (332)

The title compound was prepared according to **General Procedure 3** using methyl 4-bromocrotonate (0.59 ml, 5.00 mmol) and 4-amnophenol (1.09 g, 10.0 mmol). The crude residue was purified by column chromatography (petroleum ether:AcOEt 19:1→4:1) followed by recrystallisation from petroleum ether to give *aniline* **332** (154 mg, 15%) as a yellow oil.

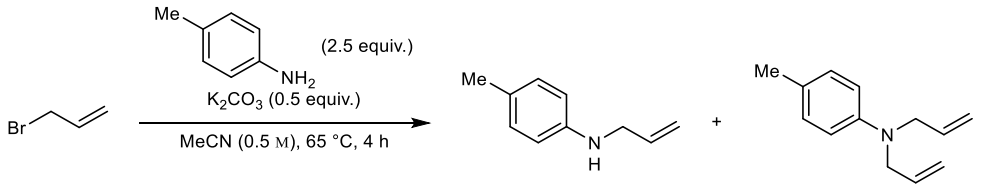
IR 3391 (NH), 2951 (CH), 1699 (C=O), 1514, 1215 (CN), 1020 (CO) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (1H, dt, *J* = 15.7, 4.7 Hz, $CH_2C\mathbf{H}$=CH), 6.70 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.50 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.04 (1H, dt, *J* = 15.7, 1.9 Hz, CH_2CH=C**H**), 3.89 (2H , dd, *J* = 4.7, 1.9 Hz, C**H$_2$**), 3.73 (3H, s, C**H$_3$**), 3.49 (2H, s, N**H$_2$**)

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (C), 148.3 (C), 146.3 (CH), 141.3 (C), 121.3 (CH), 116.3 (2 × CH), 114.5 (2 × CH), 51.6 (CH_3), 45.8 (CH_2).

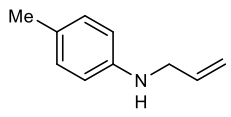
HRMS (Q-TOF) Exact mass calcd for $[C_{11}H_{14}NO_3]^+$ $[M+H]^+$ calcd. 208.0968, found 208.0965.

4-Methyl-*N*-(prop-2-en-1-yl)aniline (350), 4-Methyl-*N*,*N*-bis(prop-2-en-1-yl)aniline (351)



349 **350** **351**

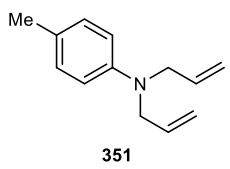
Based on **General Procedure 3**, a solution of allyl bromide (0.86 ml, 10.0 mmol), p-toluidine (2.69 g, 25.0 mmol) and K_2CO_3 (276 mg, 2.0 mmol) in MeCN (20 ml) was stirred at 80 °C for 4 h. The mixture was diluted with sat. Na_2CO_3 (aq., 50 ml) and the aqueous phase extracted with AcOEt (3 × 50 ml). The combined organic phases were washed with brine (100 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:AcOEt 9:1) to give mono-alkyl aniline **350** (901 mg, 61%) and di-alkyl aniline **351** (313 mg, 13%) as red oils. The data were consistent with the literature.[233]



350

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (2H, d, *J* = 8.3 Hz, Ar**H**), 6.58 (2H, d, *J* = 8.3 Hz, Ar**H**), 5.98 (1H, ddt, *J* = 17.2, 10.4, 5.4 Hz, C**H**=CH_2), 5.30 (1H, dd, *J* = 17.2, 1.3 Hz, CH=C**H$_A$**H$_B$), 5.18 (1H, dd, *J* = 10.4, 1.3 Hz, CH=CH$_A$**H$_B$**), 3.78 (2H, d, *J* = 5.4 Hz, NC**H$_2$**), 3.66 (1H, br s, N**H**), 2.27 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ145.8 (C), 135.7 (CH), 129.7 (2 × CH), 126.7 (C), 116.0 (CH_2), 113.1 (2 × CH), 46.9 (CH_2), 20.3 (CH_3).

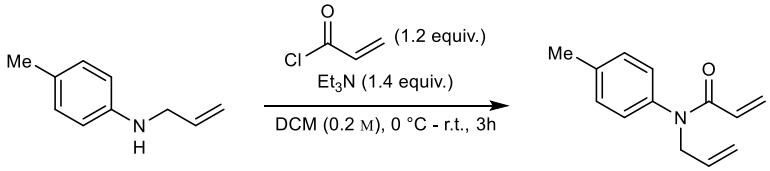


351

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.71 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.02 - 5.80 (2H, m, 2 × C**H**=CH_2), 5.26 (2H, d, *J* = 16.5 Hz, 2 × CH=**CH$_A$**H$_B$), 5.22 (2H, d, *J* = 10.2 Hz, 2 × CH=CH$_A$**H$_B$**), 4.03 - 3.93 (4H, m, 2 × NC**H$_2$**), 2.32 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6 (C), 134.3 (2 × CH), 129.5 (2 × CH), 125.4 (C), 115.9 (2 × CH_2), 112.6 (2 × CH), 52.9 (CH_2), 20.2 (CH_3).

N-(4-Methylphenyl)-N-(prop-2-en-1-yl)prop-2-enamide (352)



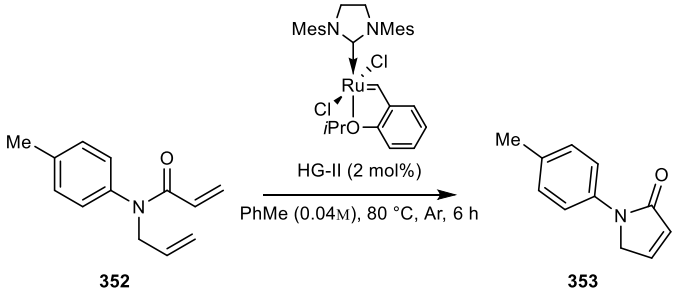
350 352

Based on the procedure by Benedetti *et al.*[131], acryloyl chloride (0.48 ml, 6.00 mmol) was added dropwise to a stirring solution of aniline **350** (736 mg, 5.00 mmol) and Et_3N (0.97 ml, 7.00 mmol) in CH_2Cl_2 (25 ml) at 0 °C. The mixture was then warmed to r.t. and stirred for 3 h. Upon completion the mixture was diluted with H_2O (25 ml) and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 ml). The combined organic were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:Et_2O 7:3) to give amide **352** (855 mg, 85%) as a pale-yellow oil. The data were consistent with the literature.[234]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (2H, d, *J* = 7.4 Hz, Ar**H**), 7.01 (2H, d, *J* = 7.4 Hz, Ar**H**), 6.34 (1H, d, *J* = 16.7 Hz, COCH=C**H$_A$**H$_B$), 6.02 (1H, dd, *J* = 16.7, 10.4 Hz, COC**H**=CH_2), 5.90 (1H, ddt, *J* = 17.7, 9.5, 6.2 Hz, CH_2C**H**=CH_2), 5.47 (1H, d, *J* = 10.4 Hz, COCH=CH$_A$**H$_B$**), 5.09 (1H, d, *J* = 9.5 Hz, CH_2CH=C**H$_A$**H$_B$), 5.08 (1H, d, *J* = 17.7 Hz, CH_2CH=CH$_A$**H$_B$**), 4.34 (2H, d, *J* = 6.2 Hz, NC**H$_2$**), 2.35 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2 (C), 139.2 (C), 137.6 (C), 132.9 (CH), 130.0 (2 × CH), 128.6 (CH), 127.9 (2 × CH), 127.3 (CH_2), 117.7 (CH_2), 52.3 (CH_2), 21.0 (CH_3).

1-(4-Methylphenyl)-2,5-dihydro-1H-pyrrol-2-one (353)



352 353

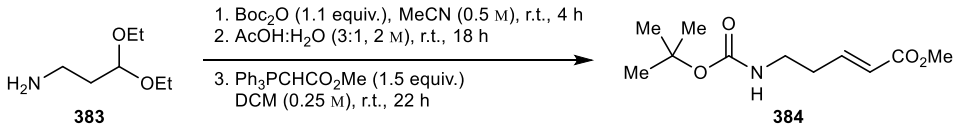
Based on the procedure by Wang *et al*.[234], a flask was charged with amide **352** (503 mg, 2.50 mmol) and Hoveyda-Grubbs catalyst G2 (32.0 mg, 51.1 μmol) and back filled 3 times with argon. The mixture was dissolved in anhydrous PhMe (60 ml) and stirred at 80 °C for 6 h. The mixture was then cooled to room temperature and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:Et_2O 3:2) to give lactam **353** (383 mg, 88%) as an off-white solid. The data were consistent with the literature.[234]

m.p. = 101 - 102 °C (CH_2Cl_2), Lit. 96-97 °C (no solvent reported).[234]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.17 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.14 (1H, dt, *J* = 5.2, 1.7 Hz, COC**H**=CH), 6.25 (1H, dt, *J* = 5.2, 1.7 Hz, COCH=C**H**), 4.40 (2H, dd, *J* = 1.7 Hz, C**H$_2$**), 2.32 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (C), 142.0 (CH), 136.5 (C), 133.8 (C), 129.5 (2 × CH), 129.2 (CH), 119.0 (2 × CH), 53.3 (CH_2), 20.7 (CH_3).

Methyl (2*E*)-5-{[(*tert*-butoxy)carbonyl]amino}pent-2-enoate (384)



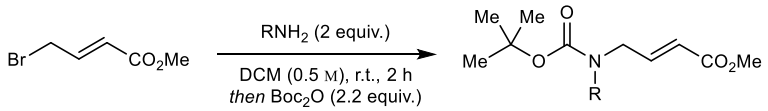
383 384

Based on the procedure by Kyung *et al*.,[235] 1-Amino-3,3-diethoxypropane (8.09 ml, 50.0 mmol) and *tert*-butyl dicarbonate (12.0 g, 55.0 mmol) were dissolved in MeCN (100 ml) and stirred at r.t. for 4 h. The mixture was concentrated *in vacuo*, dissolved in AcOH:H_2O (3:1, 25 ml) and stirred at r.t. for 18 h. Upon completion the mixture was quenched with solid Na_2CO_3, diluted with H_2O (50 ml) and extracted with AcOEt (3 × 50 ml). The combined organic were washed with brine (100 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (200 ml) and Ph_3PCHCO_2Me (25.1 g, 75.0 mmol) and stirred at r.t. for 22 h. The mixture was then concentrated *in vacuo*, dissolved in Et_2O (100 ml), filtered, washed with brine and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:Et2O, 4:1→7:3) to give alkene **384** (6.23 g, 54%) as a colourless oil. The data were consistent with the literature.[236]

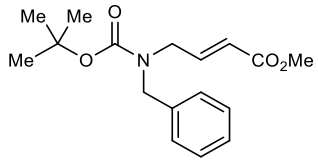
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (1H, dt, *J* = 15.8, 7.1 Hz, CH_2CH=CH), 5.88 (1H, dt, *J* = 15.8, 1.6 Hz, CH_2CH=C**H**), 4.57 (1H, br s, N**H**), 3.73 (3H, s, OC**H$_3$**), 3.29 - 3.24 (2H, m, NC**H$_2$**), 2.45 - 2.36 (2H, m, C**H$_2$**CH=CH), 1.44 (9H, s, 3 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (C), 155.7 (C), 145.7 (CH), 122.8 (CH), 79.3 (C), 51.4 (CH_3), 38.9 (CH_2), 32.7 (CH_2), 28.2 (3 × CH_3).

General Procedure 4: Preparation of *N*-Boc amino enoates using methyl 4-bromocrotonate



Methyl 4-bromocrotonate (1.18 ml, 10.0 mmol), was added to a stirring solution of amine (2 equiv.) in DCM (20 ml) at r.t. and stirred for 2 h after which di-*tert*-butyl dicarbonate (4.37 g, 20.0 mmol) was added and the mixture allowed to stir overnight. The reaction mixture was diluted with AcOEt (100 ml) and washed with sat. Na_2CO_3 (100 ml), brine (100 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography.



392

Methyl (2*E*)-4-{benzyl[(*tert*-butoxy)carbonyl]amino}but-2-enoate (392)

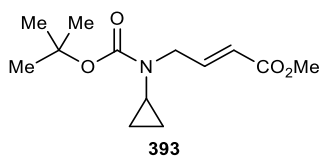
The title compound was prepared according to **General Procedure 4** using methyl 4-bromocrotonate (1.18 ml, 10.0 mmol) and benzyl amine (2.73 ml, 25.0 mmol) and di-*tert*-butyl dicarbonate (5.46 g, 25.0 mmol). The crude residue was purified by column chromatography (hexane:AcOEt 4:1) to give *amine* **392** (1.95 g, 64%) as a colourless oil.

IR 2977 (CH), 1723 (C=O), 1693 (C=O), 1366, 1242, 1159 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.12 (5H, m, Ar**H**), 6.82 (1H, s, CH_2C**H**=CH), 5.84 (1H, m, CH_2CH=C**H**), 4.41 (2H, m, NC**H$_2$**), 3.96 (1H, s, ArC**H$_A$**H$_B$), 3.85 (1H, s, ArCH$_A$**H$_B$**), 3.72 (3H, s, C**H$_3$**), 1.46 (9H, s, 3 × C**H$_3$**). (Rotameric)

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C), 155.3 (C), 143.8 (CH), 137.5 (C), 128.5 (2 × CH), 127.8 (CH), 127.3 (2 × CH), 127.2 (2 × CH), 121.7 (CH), 121.4 (CH), 80.3 (C), 51.5 (CH_3), 50.1 (CH_2), 49.6 (CH_2), 46.9 (CH_2), 46.7 (CH_2), 28.2 (3 × CH_3). (Rotameric)

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{23}NO_4Na]^+$ $[MNa]^+$ calcd. 328.1519, found 328.1521.



393

Methyl (2*E*)-4-{[(*tert*-butoxy)carbonyl](cyclopropyl)amino}but-2-enoate (393)

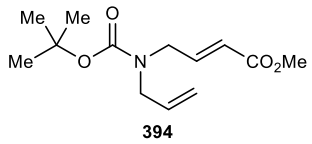
The title compound was prepared according to **General Procedure 4** using methyl 4-bromocrotonate (1.18 ml, 10.0 mmol) and cyclopropyl amine (1.39 ml, 20.0 mmol) and di-*tert*-butyl dicarbonate (4.80 g, 22.0 mmol). The crude residue was purified by column chromatography (hexane:AcOEt 4:1) to give *amine* **393** (1.01 g, 39%) as a colourless oil.

IR 2977 (CH), 1724 (C=O), 1694 (C=O), 1366, 1274, 1141 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (1H, dt, *J* = 15.7, 5.1 Hz, $NCH_2CH{=}CH$), 5.83 (1H, dt, *J* = 15.7, 1.6 Hz, $NCH_2CH{=}C\mathbf{H}$)), 3.96 (2H, dd, *J* = 5.1, 1.6 Hz, $NC\mathbf{H_2}$), 3.73 (3H, s, OCH_3), 2.63 - 2.46 (1H, m, N**C**H), 1.44 (9H, s, 3 × $CC\mathbf{H_3}$), 0.79 - 0.67 (2H, m, $NCHC\mathbf{H_A}H_BC\mathbf{H_C}H_D$), 0.67 - 0.51 (2H, m, $NCHCH_A\mathbf{H_B}CH_C\mathbf{H_D}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (C), 156.3 (C), 145.0 (CH), 121.0 (CH), 80.1 (C), 51.6 (CH_3), 49.1 (CH_2), 29.6 (CH), 28.3 (3 × CH_3), 8.0 (2 × CH_2).

HRMS (Q-TOF) Exact mass calcd for $[C_{13}H_{21}NO_4Na]^+$ $[MNa]^+$ calcd. 278.1363, found 278.1367.



394

Methyl (2*E*)-4-{[(*tert*-butoxy)carbonyl](prop-2-en-1-yl)amino}but-2-enoate (394)

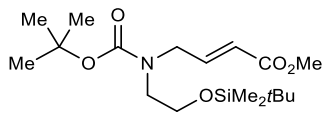
The title compound was prepared according to **General Procedure 4** using methyl 4-bromocrotonate (1.18 ml, 10.0 mmol) and allyl amine (1.49 ml, 20.0 mmol) and di-*tert*-butyl dicarbonate (4.80 g, 22.0 mmol). The crude residue was purified by column chromatography (hexane:Et_2O 7:3) to give *amine* **394** (760 mg, 30%) as a colourless oil.

IR 2977 (CH), 1725 (C=O), 1693 (C=O), 1403, 1246, 1163 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (1H, dt, *J* = 15.5, 4.5 Hz, C**H**=CHCO), 5.82 (1H, d, *J* = 15.5 Hz, CH=C**H**CO), 5.78 - 5.63 (1H, m, C**H**=CH_AH_B), 5.10 (1H, d, *J* = 9.7 Hz, CH=C$\mathbf{H_A}H_B$), 5.07 (1H, d, *J* = 15.5 Hz, $CH{=}CH_A\mathbf{H_B}$), 3.94 (1H, br s, $NC\mathbf{H_A}H_BCH{=}CH$), 3.88 (1H, br s, $NCH_A\mathbf{H_B}CH{=}CH$), 3.81 (1H, br s, $NC\mathbf{H_A}H_BCH{=}CH_2$), 3.74 (1H, br s, $NCH_A\mathbf{H_B}CH{=}CH_2$), 3.70 (3H, s, $OC\mathbf{H_3}$), 1.41 (9H, s, 3 × $CC\mathbf{H_3}$). (Rotameric)

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (C), 155.0 (C), 144.2 (CH), 133.4 (CH), 121.4 (CH), 121.3 (CH), 117.2 (CH2), 116.6 (CH2), 80.1 (C), 51.5 (CH3), 49.5 (CH2), 49.1 (CH2), 46.9 (CH2), 46.8 (CH2), 28.2 (3 × CH3). (Rotameric)

HRMS (Q-TOF) Exact mass calcd for $[C_{13}H_{21}NO_4Na]$+ [MNa]+ calcd. 278.1363, found 278.1370.



395

Methyl (2*E*)-4-{[(*tert*-butoxy)carbonyl][2-(tert-butyldimethylsilyl)ethyl]amino}but-2-enoate (395)

The title compound was prepared according to **General Procedure 4** using methyl 4-bromocrotonate (1.18 ml, 10.0 mmol) and 3-[(1,1-dimethylethyl)dimethylsilyl]-1-propanamine **395** (3.85 ml, 22.0 mmol) and di-*tert*-butyl dicarbonate (4.80 g, 22.0 mmol). The crude residue was purified by column chromatography (hexane:Et_2O 9:1) to give *amine* **395** (2.08 g, 56%) as a colourless oil.

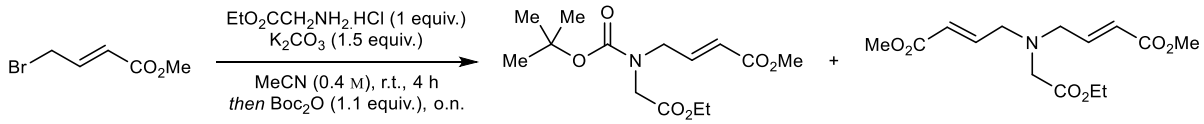
IR 2931 (CH), 1721 (C=O), 1688 (C=O), 1462, 1249, 1168, 826 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (dt, *J* = 15.7, 4.1 Hz, $NCH_2C\mathbf{H}$=CH), 5.83 (1H, d, *J* = 15.7 Hz, NCH_2CH=C**H**), 4.08 (1H, d, *J* = 4.1 Hz, $NC\mathbf{H_A}H_BCH$=CH), 4.04 (1H, d, *J* = 4.1 Hz, $NCH_A\mathbf{H_B}CH$=CH), 3.77 - 3.62 (5H, m, C**H$_3$**, N**C$\mathbf{H_2}$**CH_2), 3.34 - 3.19 (2H, m, C**H$_2$**O), 1.43 (9H, m, 3 × OCC**H$_3$**), 0.87 (9H, s, 3 × SiCC**H$_3$**), 0.03 (6H, s, 2 × SiC**H$_3$**). (Rotameric)

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (C), 166.5 (C), 155.2 (C), 155.1 (C), 144.9 (CH), 144.6 (CH), 121.2 (CH), 120.9 (CH), 80.0 (C), 62.0 (CH_2), 61.8 (CH_2), 51.5 (CH_3), 49.9 (CH_2), 49.6 (CH_2), 49.6 (CH_2), 49.0 (CH_2), 28.4 (3 × CH_3), 28.3 (3 × CH_3), 25.8 (3 × CH_3), -5.5 (CH_3). (Rotameric)

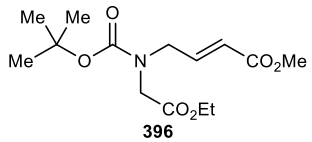
HRMS (Q-TOF) Exact mass calcd for $[C_{18}H_{35}NO_5SiNa]^+$ $[MNa]^+$ calcd. 396.2177, found 396.2178.

Methyl (2*E*)-4-{[(*tert*-butoxy)carbonyl](2-ethoxy-2-oxoethyl)amino}but-2-enoate (396), Methyl (2*E*)-4-[(2-ethoxy-2-oxoethyl)[(2*E*)-4-methoxy-4-oxobut-2-en-1-yl]amino]but-2-enoate (397)



293 396 397

Based on the procedure by Yan *et al*.,[175] methyl 4-bromocrotonate (1.18ml, 10.0 mmol), was added to a stirring solution of hydrochloride salt glycine ethyl ester hydrochloride (1.40 g, 10.0 mmol) and K_2CO_3 (2.07 g, 15.0 mmol) in MeCN (25 ml) at r.t. and stirred for 4h, after which di-*tert*-butyl dicarbonate (2.40 g, 11.0 mmol) was added and the mixture allowed to stir overnight. The reaction mixture was diluted with AcOEt (50 ml) and washed with H_2O (50 ml), brine (50 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:Et_2O 7:3) to give *amine* **396** (1.69 g, 56%) as a colourless oil and *amine* **397** (621 mg, 42%) as a colourless oil.



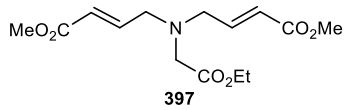
396

IR 2980 (CH), 1750 (C=O), 1724 (C=O), 1699 (C=O), 1367, 1247, 1160, 1028 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 - 6.84 (1H, m, $NCH_2CH=C\mathbf{H}$), 5.95 - 5.88 (1H, m, $NCH_2CH=CH$), 4.22 - 4.16 (2H, m, $OC\mathbf{H_2}$), 4.10 (1H, d, *J* = 4.6 Hz, $NC\mathbf{H_A}H_BCH=CH$), 4.04 (1H, d, *J* = 4.4 Hz, $NCH_A\mathbf{H_B}CH=CH$), 3.94 (1H, s, $C\mathbf{H_2}CO$), 3.83 (1H, s, $C\mathbf{H_2}CO$), 3.75 - 3.73 (3H, m, $OC\mathbf{H_3}$), 1.45 - 1.44 (9H, m, 3 × $C\mathbf{H_3}$), 1.26 (3H, m, $CH_2C\mathbf{H_3}$). (Rotameric)

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (C), 166.5 (C), 166.4 (C), 155.2 (C), 155.0 (C), 143.8 (CH), 122.1 (CH), 121.6 (CH), 81.0 (C), 80.9 (C), 61.2 (CH_2), 51.7 (CH_3), 51.6 (CH_2), 49.2 (CH_2), 48.9 (CH_2), 48.7 (CH_2), 48.4 (CH_2), 28.2 (3 × CH_3), 28.2 (3 × CH_3), 14.2 (CH_3), 14.1 (CH_3). (Rotameric)

HRMS (Q-TOF) Exact mass calcd for $[C_{14}H_{23}NO_6Na]^+$ $[MNa]^+$ calcd. 324.1418, found 324.1431.



397

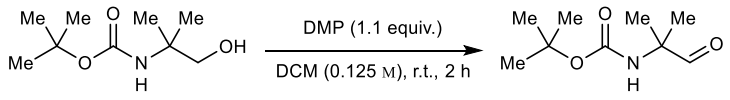
IR 2952 (CH), 1720 (C=O), 1659 (C=O), 1436, 1269, 1169, 1031 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (2H, dt, *J* = 15.7, 5.7 Hz, 2 × $CH_2C\mathbf{H}$=CH), 5.99 (2H, d, *J* = 15.7 Hz, 2 × $CH_2CHC=\mathbf{H}$), 4.12 (2H, q, *J* = 7.1 Hz, $OC\mathbf{H_2}$), 3.70 (6H, s, 2 × $OC\mathbf{H_3}$), 3.41 (4H, d, *J* = 5.7 Hz, 2 × $NC\mathbf{H_2}CH=CH$), 3.32 (2H, s, $C\mathbf{H_2}CO$), 1.23 (3H, t, *J* = 7.1 Hz, $CH_2C\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6 (C), 166.5 (2 × C), 145.2 (2 × CH), 122.9 (2 × CH), 60.5 (CH_2), 54.6 (2 × CH_2), 54.1 (CH_2), 51.5 (2 × CH_3), 14.1 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{14}H_{22}NO_6]^+$ $[MH]^+$ calcd. 300.1442, found 300.1447.

tert-Butyl *N*-(2-methyl-1-oxopropan-2-yl)carbamate (402)



401 **402**

Dess-Martin periodinane (2.33 g, 5.50 mmol) was added to a stirring solution of alcohol **401** (0.946 g, 5.00 mmol) in CH_2Cl_2 (40 ml) and stirred at r.t. for 2 h. The mixture was diluted with AcOEt (50 ml), filtered through celite, washed with a mixture of sat. $NaHCO_3$ (50 ml) and sat. $Na_2S_2O_3$ (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give aldehyde **402** (922 mg, 98 %) as a white solid.

m.p. = 87 - 89 °C (CH_2Cl_2).

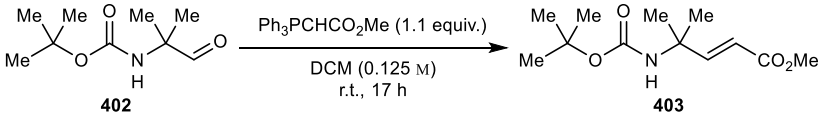
IR 3265 (NH), 2976 (CH), 1697 (C=O), 1365, 1158, 1071, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (1H, s, $C\mathbf{H}O$), 4.98 (1H, br **s**, $N\mathbf{H}$), 1.43 (9H, s, 3 × $OCC\mathbf{H_3}$), 1.32 (6H, s, 2 × $NCC\mathbf{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.8 (CH), 154.7 (C), 80.2 (C), 59.1 (C), 28.2 (3 × CH_3), 21.8 (2 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_9H_{17}NO_3Na]^+$ $[MNa]^+$ calcd. 210.1101, found 210.1105.

Methyl (2*E*)-4-{[(*tert*-butoxy)carbonyl]amino}-4-methylpent-2-enoate (403)



402 403

Ph_3PCHCO_2Me (1.84 g, 5.50 mmol) was added to a stirring solution of aldehyde **402** (936 mg, 5.00 mmol) in CH_2Cl_2 (40 ml) and stirred at r.t. for 17 h. The mixture was concentrate *in vacuo* dissolved in Et_2O (50 ml), the mixture filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:AcOEt, 19:1) to give *alkene* **403** (1.02 g, 84%) as a white solid.

m.p. = 60 - 62 °C (CH_2Cl_2).

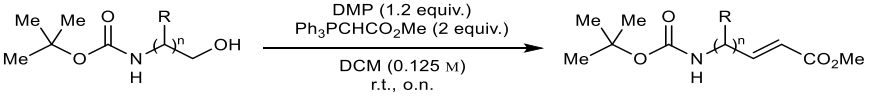
IR 3347 (NH), 2976 (CH), 1705 (C=O), 1651 (C=O), 1525, 1249, 1159, 1075, 976 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, d, *J* = 15.9 Hz, NCC**H**=CH), 5.82 (1H, d, *J* = 15.9 Hz, NCCH=C**H**), 4.66 (1H, br s, N**H**), 3.71 (3H, s, OC**H$_3$**), 1.40 (9H, s, 3 × OCC**H$_3$**), 1.38 (6H, s, 2 × NCC**H$_3$**).

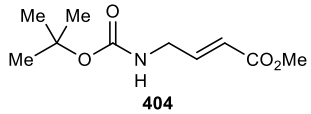
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3 (C), 154.3 (C), 154.0 (CH), 118.2 (CH), 79.6 (C), 53.0 (C), 51.7 (CH_3), 28.5 (3 × CH_3), 27.5 (2 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{12}H_{21}NO_4Na]^+$ $[MNa]^+$ calcd. 266.1363, found 266.1374.

General Procedure 5: Preparation of Amino Enoates via oxidation/Wittig



Dess-Martin periodinane (5.09 g, 12.0 mmol) and Ph_3PCHCO_2Me (6.73 g, 20.0 mmol) was added sequentially to a stirring solution of alcohol (1 equiv.) in CH_2Cl_2 (80 ml) and stirred overnight. Upon completion the mixture was then diluted with AcOEt (100 ml) and washed with sat. $NaHCO_3$ (100 ml), sat. $Na_2S_2O_3$ (100 ml) and concentrated *in vacuo*. The residue was then dissolved in Et_2O (50 ml), the mixture filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography.



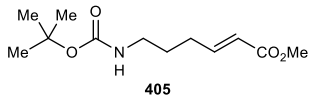
404

Methyl (2*E*)-4-{[(tert-butoxy)carbonyl]amino}but-2-enoate (404)

The title compound was prepared according to **General Procedure 5** using alcohol **398** (1.61 g, 10.0 mmol). The crude residue was purified by column chromatography (hexane:AcOEt, 4:1) to give alkene **404** (1.30 g, 61%) as a colourless oil. The data were consistent with the literature.[236]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (1H, dt, *J* = 15.7, 4.8 Hz, CH_2C**H**=CH), 5.93 (1H, dt, *J* = 15.7, 1.6 Hz, CH_2CH=C**H**), 4.75 (1H, br s, N**H**), 3.90 (2H, br s, C**H$_2$**), 3.72 (3H, s, OC**H$_3$**), 1.44 (9H, s, 3 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5 (C), 155.5 (C), 145.1 (CH), 120.9 (CH), 79.9 (C), 51.6 (CH_3), 41.3 (CH_2), 28.3 (3 × CH_3).



405

Methyl (2*E*)-6-{[(tert-butoxy)carbonyl]amino}hex-2-enoate (405)

The title compound was prepared according to **General Procedure 5** using alcohol **545** (1.89 g, 10.0 mmol). The crude residue was purified by column chromatography (hexane:Et_2O, 3:2) to give *alkene* **405** (456 mg, 19%) as a white solid.

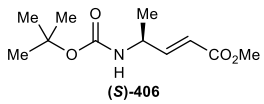
m.p. = 35 - 38 °C (CH_2Cl_2).

IR 3340 (NH), 2949 (CH), 1714 (C=O), 1681 (C=O), 1533, 1365, 1252, 1163, 1009, 879 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (1H, dt, *J* = 15.6, 6.9 Hz, CH_2C**H**=CH), 5.83 (1H, dt, *J* = 15.6, 1.6 Hz, CH_2CH=C**H**), 4.56 (1H, br s, N**H**), 3.71 (3H, s, OC**H$_3$**), 3.18 - 3.07 (2H, m, NC**H$_2$**), 2.28 - 2.17 (2H, m,C**H$_2$**CH=CH), 1.68 - 1.59 (2H, m, NCH_2C**H$_2$**), 1.43 (9H, s, 3 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (C), 155.9 (C), 148.3 (CH), 121.4 (CH), 79.3 (C), 51.4 (CH_3), 40.0 (CH_2), 29.4 (CH_2), 28.5 (CH_2), 28.4 (3 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{12}H_{21}NO_4Na]^+$ $[MNa]^+$ calcd. 266.1363, found 266.1367.



(*S*)-406

Methyl (2*E*, 4*S*)-4-{[(*tert*-butoxy)carbonyl]amino}pent-2-enoate ((*S*)-406)

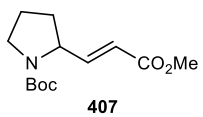
The title compound was prepared according to **General Procedure 5** using alcohol **(*S*)-546** (4.28 g, 25.0 mmol), Dess-Martin periodinane (11.7 g, 27.5 mmol), Ph_3PCHCO_2Me (16.7 g, 50.0 mmol) and CH_2Cl_2 (200 ml). The crude residue was purified by column chromatography (hexane:Et_2O, 3:2) to give *alkene* **(*S*)-406** (2.87 g, 50%) as a white solid. The data were consistent with the literature.[237]

$[\alpha]_D^{19}$ -23.0 (c 1, $CHCl_3$), Lit. $[\alpha]_D^{24}$ -18.5 (CH_2Cl_2).[237]

m.p. = 37 - 39 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (1H, dd, *J* = 15.7, 4.9 Hz, NCHC**H**=CH), 5.90 (1H, dd, *J* = 15.7, 0.8 Hz, NCHCH=C**H**), 4.54 (1H, br s, N**H**), 4.39 (1H, br s, NC**H**CH=CH), 3.73 (3H, s, OC**H$_3$**), 1.43 (9H, s, 3 × OCC**H$_3$**), 1.26 (3H, d, *J* = 7.0 Hz, CHC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (C), 154.9 (C), 149.7 (CH), 119.7 (CH), 79.8 (C), 51.6 (CH_3), 47.0 (CH), 28.3 (3 × CH_3), 20.3 (CH_3).



407

(±)-*tert*-Butyl 2-[(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]pyrrolidine-1-carboxylate (**407**)

The title compound was prepared according to **General Procedure 5** using alcohol **549** (1.01 g, 5.00 mmol), Dess-Martin periodinane (2.55 g, 6.00 mmol), Ph_3PCHCO_2Me (3.36 g, 10.00 mmol) and CH_2Cl_2 (40 ml). The crude residue was purified by column chromatography (hexane:Et_2O:Et_3N, 139:60:1) to give *alkene* **407** (763 mg, 61%) as a pale-yellow oil.

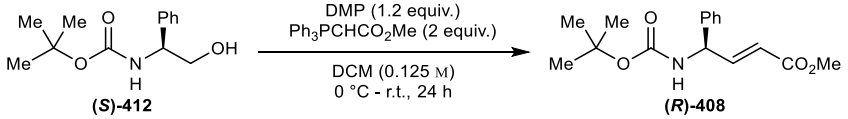
IR 2975 (CH), 1692 (C=O), 1388, 1158, 979 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 - 6.69 (1H, m, CHC**H**=CH), 5.81 (1H, d, *J* = 15.2 Hz, CHCH=C**H**), 4.58 - 4.22 (1H, m, NC**H**), 3.71 (3H, s, OC**H$_3$**), 3.41 (2H, br s, NC**H$_2$**CH_2), 2.05 (1H, br s, $NCH_2C\mathbf{H_A}H_B$), 1.89 - 1.78 (2H, m, $NCH_2C\mathbf{H_2}$), 1.78 - 1.66 (1H, m, $NCH_2CH_A\mathbf{H_B}$), 1.51 - 1.29 (9H, m, 3 × CC**H$_3$**). (Rotameric)

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (C), 154.3 (C), 148.9 (CH), 148.6 (CH), 120.0 (CH), 79.6 (C), 57.8 (CH), 57.5 (CH), 51.5 (CH_3), 46.5 (CH_2), 46.2 (CH_2), 31.7 (CH_2), 30.8 (CH_2), 28.4 (3 × CH_3), 23.5 (CH_2), 22.9 (CH_2). (Rotameric)

HRMS (Q-TOF) Exact mass calcd for $[C_{13}H_{21}NO_4Na]^+$ $[MNa]^+$ calcd. 278.1363, found 278.1379.

Methyl (2*E*, 4*R*)-4-{[(*tert*-butoxy)carbonyl]amino}-4-phenylbut-2-enoate ((*R*)-408)



Dess-Martin periodinane (2.55 g, 6.00 mmol) was added to a stirring solution of alcohol **(*S*)-412** (1.37 g, 5.00 mmol) and Ph_3PCHCO_2Me (3.34 g, 10.0 mmol) in anhydrous CH_2Cl_2 (40 ml) at 0 °C for 2.5 h, after which time the mixture was warmed to r.t. and stirred for a further 21.5 h. The mixture was diluted and AcOEt (100 ml) and washed with sat. $NaHCO_3$ (100 ml), sat. $Na_2S_2O_3$ (100 ml) and concentrated *in vacuo*. The residue was then dissolved in Et_2O (50 ml), the mixture filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:AcOEt, 9:1) to give *alkene* **(*R*)-408** (626 mg, 43%) as a white solid.

$[\alpha]_D^{21}$ +48.0 (c 1, $CHCl_3$).

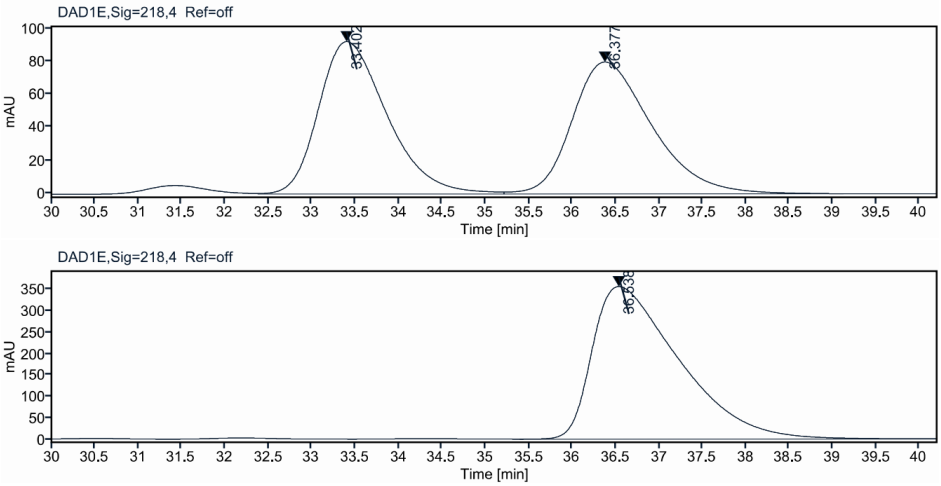
m.p. = 119 - 121 °C (CH_2Cl_2).

IR 3383 (NH), 2979 (CH), 1718 (C=O), 1682 (C=O), 1513, 1289, 1165, 1004, 862 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.23 (5H, m, Ar**H**), 7.07 (1H, dd, *J* = 15.6, 5.2 Hz, CHC**H**=CH), 6.00 (1H, dd, *J* = 15.6, 1.7 Hz, CHCH=C**H**), 5.44 (1H, br s, NC**H**), 4.90 (1H, br s, N**H**), 3.74 (3H, s, OC**H$_3$**), 1.44 (9H, s, 3 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (C), 154.8 (C), 147.4 (CH), 139.2 (C), 129.0 (2 × CH), 128.2 (CH), 127.2 (2 × CH), 121.1 (CH), 80.2 (C), 55.5 (CH), 51.7 (CH_3), 28.3 (3 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{16}H_{21}NO_4Na]^+$ $[MNa]^+$ calcd. 314.1363, found 314.1367. *e.e.* = >99%, measured through chiral HPLC analysis. YMC Chiral Art amylose-SA S-5 μm, IPA:hexane = 1:99, 1.0 mL/min, 22°C, λ = 218 nm, (*R*)-isomer t_r = 33.4 min and (*S*)-isomer t_r = 36.4 min.



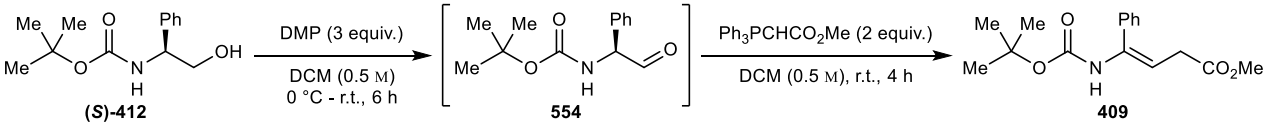
Signal: DAD1E,Sig=218,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
36.538	BB	5.2467	24645.4479	355.9136	100.0000	
		Sum	24645.4479			

Signal: DAD1E,Sig=218,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
33.402	VV	2.8333	5088.3255	92.9458	49.7793	
36.377	VB	3.9100	5133.4539	80.4196	50.2207	
		Sum	10221.7794			

Methyl (3*E*)-4-{[(tert-butoxy)carbonyl]amino}-4-phenylbut-3-enoate (**409**)



(*S*)-412 554 409

Dess-Martin periodinane (8.48 g, 20.0 mmol) was added to a stirring solution of *tert*-butyl *N*-(1-hydroxy-2-methylpropan-2-yl)carbamate **(*S*)-412** (2.37 g, 10.0 mmol) in CH_2Cl_2 (20 ml) at 0 °C and stirred for 2 h. A further portion of Dess-Martin periodinane (4.24 g, 10.0 mmol) and mixture was warmed to r.t. and stirred for 4 h. The mixture was diluted with AcOEt (50 ml), passed through a plug of celite and concentrated *in vacuo*. The residue was dissolved in (20 ml) and Ph_3PCHCO_2Me (6.69 g, 20.0 mmol) was added, and the mixture was stirred at r.t. for 4 h. Upon completion the mixture was concentrated *in vacuo*, dissolved in Et_2O (50 ml), the mixture filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:Et_2O, 4:1) to give *alkene* **409** (730 mg, 25%) as a yellow oil.

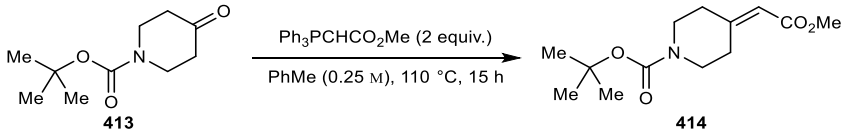
IR 3333 (NH), 2978 (CH), 1696 (C=O), 1156, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 - 7.39 (2H, m, Ar**H**), 7.36 - 7.28 (3H, m, Ar**H**), 6.37 (1H, br s, C=C**H**), 5.71 (1H, br s, N**H**), 3.72 (3H, s, OC**H$_3$**), 3.27 (2H, d, *J* = 7.3 Hz, C**H$_2$**), 1.70 - 1.11 (9H, m, 3 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (C), 153.3 (C), 138.1 (C), 128.8 (C), 128.5 (C), 128.3 (2 × CH), 128.2 (CH), 126.0 (2 × CH), 113.4 (CH), 80.4 (C), 52.0 (CH_3), 33.4 (CH_2), 28.1 (3 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{16}H_{21}NO_4Na]^+$ $[MNa]^+$ calcd. 314.1363, found 314.1372.

***tert*-Butyl 4-(2-methoxy-2-oxoethylidene)piperidine-1-carboxylate (414)**



413 414

Based on the procedure by Smith *et al.*,[238] Ph_3PCHCO_2Me (6.69 g, 20.0 mmol) was added to a solution of 1-Boc-4-piperidone **413** (1.99 g, 10.0 mmol) in PhMe (40 ml) and the mixture stirred at reflux for 15 h. Upon completion the mixture was filtered through a plug of silica followed by hexane:AcOEt (4:1, 100 ml) and concentrated *in vacuo* to give alkene **414** (2.48 g, 97%) as a white solid.

m.p. = 63-64 °C (CH_2Cl_2).

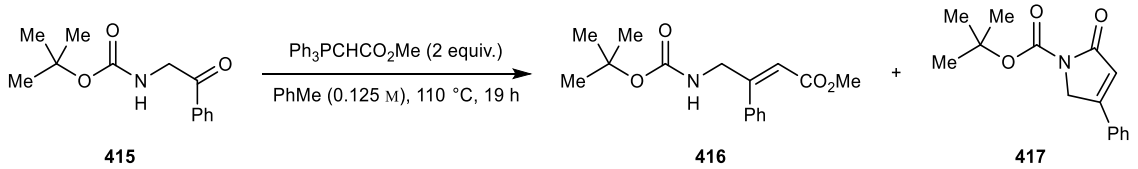
IR 2968 (H), 1680 (C=O), 1424, 1161, 864 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (1H, s, C**H**), 3.69 (3H, s, OC**H$_3$**), 3.57 - 3.35 (4H, m, 2 × NC**H$_2$**), 2.93 (2H, t, *J* = 5.7 Hz, 2 × $NCH_2C\mathbf{H_A}H_B$), 2.27 (2H, t, *J* = 5.7 Hz, 2 × $NCH_2CH_A\mathbf{H_B}$), 1.46 (9H, s, 3 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (C), 158.2 (C), 154.6 (C), 114.8 (CH), 79.8 (C), 51.0 (CH_3), 44.5 (2 × CH_2), 36.4 (CH_2), 29.5 (2 × CH_2), 28.4 (3 × CH_3).

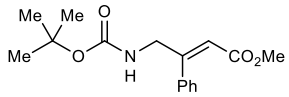
HRMS (Q-TOF) Exact mass calcd for $[C_{13}H_{21}NO_4Na]^+$ $[MNa]^+$ calcd. 278.1363, found 278.1363.

Methyl (2*E*)-4-{[(tert-butoxy)carbonyl]amino}-3-phenylbut-2-enoate (416), *tert*-Butyl 2-oxo-4-phenyl-2,5-dihydro-1H-pyrrole-1-carboxylate (417)



415 416 417

Based on the procedure by Smith *et al.*,[238] Ph_3PCHCO_2Me (3.34 g, 10.0 mmol) was added to a solution of ketone **415** (1.18 g, 5.02 mmol) in PhMe (40 ml) and the mixture stirred at reflux for 19 h. The mixture was concentrate *in vacuo* dissolved in Et_2O (100 ml), the mixture filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:AcOEt, 17:13) to give *alkene* **416** (505 mg, 35%) as a colourless oil and lactam **417** (506 mg, 39%) as an off-white wax. The data were consistent with the literature for lactam **417**.[239]



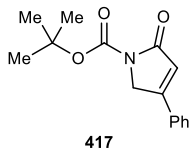
416

IR 3359 (NH), 2978 (CH), 1695 (C=O), 1161, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.31 (3H, m, Ar**H**), 7.23 - 7.15 (2H, m, Ar**H**), 5.99 (1H, s, C**H**), 4.83 (1H, br s, N**H**), 4.04 - 4.02 (2H, m, C**H**$_2$), 3.55 (3H, s, C**H**$_3$), 1.44 (9H, s, 3 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (C), 156.0 (C), 155.5 (C), 137.5 (C), 128.1 (CH), 128.0 (2 × CH), 127.3 (2 × CH), 115.9 (CH), 79.9 (C), 51.1 (CH_3), 47.4 (CH_2), 28.3 (3 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{16}H_{21}NO_4Na]^+$ $[MNa]^+$ calcd. 314.1363, found 314.1366.

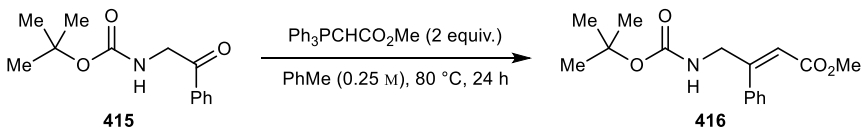


417

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.60 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.48 (2H, dd, *J* = 7.9, 7.4 Hz, Ar**H**), 5.57 (1H, s, C**H**), 4.67 (1H, s, C**H**$_A$H$_B$), 4.65 (1H, s, CH$_A$**H**$_B$), 1.47 (9H, s, 3 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (C), 155.8 (C), 134.5 (C), 133.9 (CH), 130.1 (CH), 128.9 (2 × CH), 128.4 (C), 127.8 (2 × CH), 79.9 (C), 47.5 (CH_2), 28.3 (3 × CH_3).

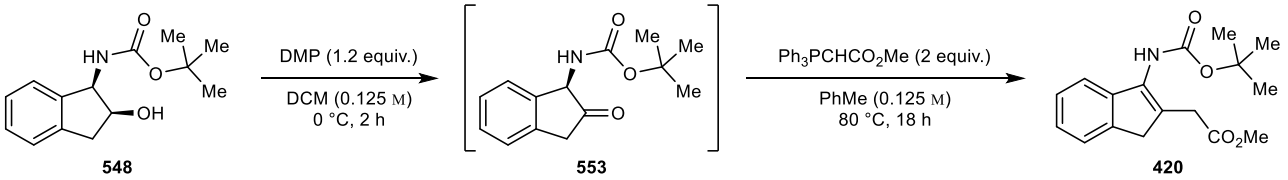
Methyl (2*E*)-4-{[(tert-butoxy)carbonyl]amino}-3-phenylbut-2-enoate (416)



415 416

Based on the procedure by Smith *et al.*,[238] Ph_3PCHCO_2Me (4.68 g, 14.0 mmol) was added to a solution of ketone **415** (1.65 g, 7.01 mmol) in PhMe (40 ml) and the mixture stirred at 80 ° for 24 h. The mixture was concentrate *in vacuo* dissolved in Et_2O (100 ml), the mixture filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:Et_2O 1:0→4:1) to give *alkene* **416** (781 mg, 38%) as a colourless oil. The data matched that of *alkene* **416** above.

Methyl 2-(3-{[(*tert*-butoxy)carbonyl]amino}-1H-inden-2-yl)acetate (420)



Dess-Martin periodinane (2.55 g, 6.00 mmol) was added to a stirring solution of butyl *N*-[(1*R*, 2*S*)-alcohol **548** (1.25 g, 5.00 mmol) in CH_2Cl_2 (80 ml) at 0 °C and stirred for 2 h. The mixture was diluted with AcOEt (100 ml) and washed with sat. $NaHCO_3$ (100 ml), sat. $Na_2S_2O_3$ (100 ml) and concentrated *in vacuo*. The residue was dissolved in PhMe (80 ml) and Ph_3PCHCO_2Me (3.36 g, 10.0 mmol) was added, and the mixture was stirred at 80 °C for 18 h. Upon completion the mixture was concentrated *in vacuo*, dissolved in Et_2O (50 ml), the mixture filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:Et_2O, 7:3) to give *alkene* **420** (700 mg, 46%) as an off-white solid.

m.p. = 132 - 133 °C (CH_2Cl_2).

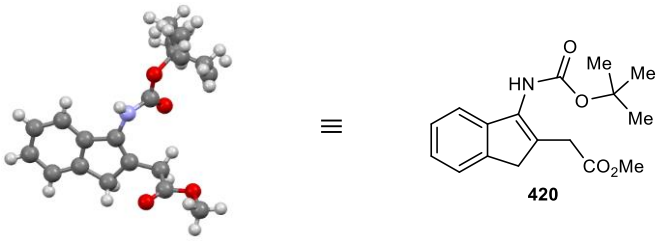
IR 3318 (NH), 2952 (CH), 1732 (C=O), 1693 (C=O), 1517, 1253, 1163, 768 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.35 (1H, m, Ar**H**), 7.33 - 7.27 (2H, m, Ar**H**), 7.22 - 7.16 (1H, m, Ar**H**), 6.39 (1H, br s, N**H**), 3.71 (3H, s, OC**H$_3$**), 3.53 (2H, s, ArC**H$_2$**), 3.45 (2H, s, C**H$_2$**CO), 1.51 (9H, s, 3 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (C), 153.4 (C), 141.7 (C), 141.3 (C), 134.6 (C), 128.1 (C), 126.2 (CH), 125.1 (CH), 123.6 (CH), 118.9 (CH), 80.6 (C), 52.1 (CH_3), 39.3 (CH_2), 34.0 (CH_2), 28.2 (3 × CH_3).

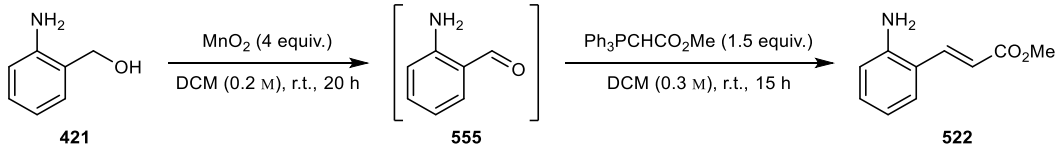
HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{21}NO_4Na]^+$ $[MNa]^+$ calcd. 326.1363, found 326.1373.

Crystals suitable for X-ray diffraction were obtained directly from chromatography fractions.



Crystal Data for $C_{17}H_{21}NO_4$ (M =303.35 g/mol): orthorhombic, space group Fdd2 (no. 43), a = 21.1142(6) Å, b = 59.4260(18) Å, c = 5.00310(10) Å, V = 6277.6(3) Å3, Z = 16, T = 100.01 K, μ(CuKα) = 0.747 mm-1, Dcalc = 1.284 g/cm3, 18708 reflections measured (5.948° ≤ 2Θ ≤ 133.546°), 2606 unique (Rint = 0.0563, Rsigma = 0.0346) which were used in all calculations. The final R1 was 0.0365 (I > 2σ(I)) and wR2 was 0.0849 (all data).

Methyl (2*E*)-3-(2-{[(*tert*-butoxy)carbonyl]amino}phenyl)prop-2-enoate (422)



421 555 522

Based on the procedure by Glinka *et al*.[240], MnO_2 (8.96 g, 100 mmol) was added to a stirring solution of alcohol **421** (3.08 g, 25.0 mmol) in CH_2Cl_2 (125 ml) and stirred at r.t. for 20 h. The mixture was filter through celite and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (80 ml) and Ph_3PCHCO_2Me (12.5 g, 37.5 mmol) added, and the mixture stirred at r.t. for 15 h. The mixture was concentrate *in vacuo* dissolved in Et_2O (100 ml), the mixture filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:AcOEt, 4:1) to give alkene **422** (4.01 g, 90%) as a pale-yellow solid. The data were consistent with the literature.[241]

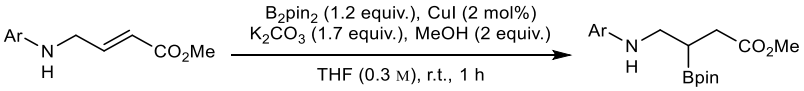
m.p. = 67 - 69 °C (CH_2Cl_2), Lit. 55-57 °C (no solvent reported).[241]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (1H, d, *J* = 15.8 Hz, ArC**H**=CH), 7.38 (1H, dd, *J* = 7.7, 1.5 Hz, Ar**H**), 7.18 (1H, td, *J* = 8.2, 1.5 Hz, Ar**H**), 6.77 (1H, td, J = 7.7, 0.7 Hz, Ar**H**), 6.70 (1H, dd, *J* = 8.2, 0.7 Hz, Ar**H**), 6.36 (1H, d, *J* = 15.8 Hz, ArCH=C**H**), 3.92 (2H, br s, N**H$_2$**), 3.80 (3H, s, C**H$_3$**).

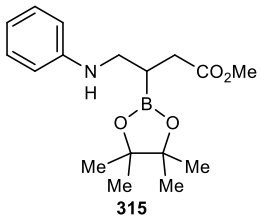
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7 (C), 145.5 (C), 140.3 (CH), 131.3 (CH), 128.1 (CH), 119.8 (C), 119.0 (CH), 117.7 (CH), 116.7 (CH), 51.6 (CH_3).

4.2.4 Conjugate Borylation

General Procedure 6: Conjugate borylation of aryl amino enoates



Based on the procedure by Wang *et al*.,[147] an oven dried Schlenk flask was charged with B_2pin_2 (305 mg, 1.20 mmol), CuI (4.0 mg, 21 μmol), K_2CO_3 (235 mg, 1.70 mmol) and backfilled with Ar. Anhydrous THF (2.00 mL) was added, and the mixture was stirred for 10 mins. A solution of the enoate (1 equiv.) in anhydrous THF (1.30 ml) and MeOH (0.08 ml, 2.00 mmol) was added, and the mixture stirred for 1 h. The mixture was passed through a plug of celite, and the solution was concentrated *in vacuo*. The crude residue was purified by either chromatography or recrystallisation.



315

(±)-Methyl 4-(phenylamino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (315)

The title compound was prepared according to **General Procedure 6** using enoate **314** (191 mg, 1.00 mmol). The crude residue was purified by column chromatography (petroleum ether:AcOEt 9:1) to give *amine* **315** (206 mg, 65%) as an off-white solid.

m.p. = 85-87 °C (CH_2Cl_2).

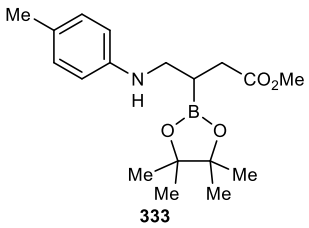
IR 3347, 1732 (C=O), 1603, 1329, 1137, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (2H, dd, *J* = 7.8, 7.3 Hz, Ar**H**), 6.73 (1H, t, *J* = 7.3 Hz, Ar**H**), 6.67 (2H, d, *J* = 7.8 Hz, Ar**H**), 3.66 (3H, s, OC**H$_3$**), 3.27 (1H, dd, *J* = 12.0, 7.3 Hz, NC**H$_A$**H$_B$), 3.20 (1H, dd, *J* = 12.0, 7.3 Hz, NCH$_A$**H$_B$**), 2.59 (1H, dd, *J* = 16.6, 7.1 Hz, C**H$_A$**CH$_B$CO), 2.54 (1H, dd, *J* = 16.6, 6.4 Hz, CH$_A$**CH$_B$**CO), 1.73 (1H, tdd, *J* = 7.3, 7.1, 6.4 Hz, C**H**), 1.25 (12H, s, 4 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2 (C), 148.4 (C), 129.2 (2 × CH), 117.1 (CH), 112.8 (2 × CH), 83.6 (2 × C), 51.6 (CH_3), 44.6 (CH_2), 33.5 (CH_2), 24.7 (2 × CH_3), 24.7 (2 × CH_3).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{27}{}^{11}BNO_4]^+$ [MH]$^+$ calcd. 320.2028, found 320.2028.



333

(±)-Methyl 4-[(3-methylphenyl)amino]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (333)

The title compound was prepared according to a modification of **General Procedure 6** using enoate **320** (5.13 g, 25.0 mmol), B_2Pin_2 (7.62 g, 30.0 mmol), CuI (95.2 mg, 0.500 mmol), K_2CO_3 (5.87 g, 42.5 mmol), MeOH (2.00 ml, 49.4 mmol). The crude residue was purified by recrystallisation from *n*-hexane to give *amine* **333** (6.79 g, 82%) as an off-white solid.

m.p. = 99-102 °C (CH_2Cl_2).

IR 3341 (NH), 2974, 1728 (C=O), 1521, 1325, 1140, 810 cm^{-1}.

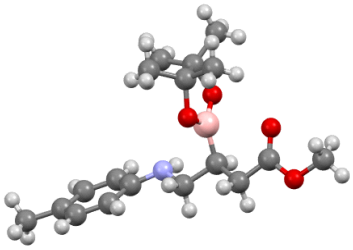
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (2H, d, *J* = 8.3 Hz, Ar**H**), 6.53 (2H, d, *J* = 8.3 Hz, Ar**H**), 3.80 (1H, br s, N**H**), 3.66 (3H, s, OC**H$_3$**), 3.22 (1H, dd, *J* = 12.0, 7.3 Hz, NC**H$_A$**H$_B$), 3.15 (1H, dd, *J* = 12.0, 7.2 Hz, NCH$_A$**H$_B$**), 2.57 (1H, dd, *J* = 16.7, 7.4 Hz, C**H$_A$**H$_B$CO), 2.51 (1H, dd, *J* = 16.7, 6.4 Hz, CH$_A$**H$_B$**CO), 2.22 (1H, s, C**H$_3$**), 1.69 (1H, dddd, *J* = 7.4, 7.3, 7.2, 6.4 Hz, C**H**), 1.24 (12H, s, 4 × C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2 (C), 146.1 (C), 129.6 (2 × CH), 126.3 (C), 113.1 (2 × CH), 83.5 (2 × C), 51.6 (CH_3), 45.0 (CH_2), 33.5 (CH_2), 30.9 (CH), 24.7 (2 × CH_3), 24.7 (2 × CH_3), 20.4 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.3 (br s, boronic ester), 22.5 (br s, adduct).

HRMS (Q-TOF) Exact mass calcd for $[C_{18}H_{29}{}^{11}BNO_4]$+ [MH]+ calcd. 334.2184, found 334.2193.

Crystals suitable for X-ray diffraction were obtained through recrystallisation of **333** in *n*-hexane.



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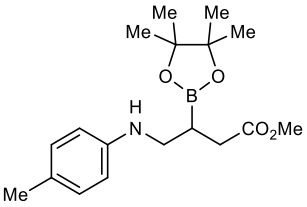
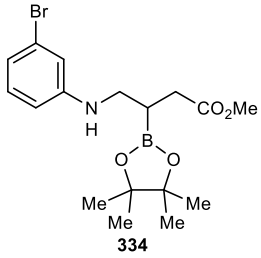


333

Crystal Data for $C_{18}H_{28}BNO_4$ (M =333.22 g/mol): triclinic, space group P-1 (no. 2), a = 8.5685(6) Å, b = 8.8726(5) Å, c = 12.5070(9) Å, α = 100.756(4)°, β = 96.048(4)°, γ = 96.194(4)°, V = 920.98(11) Å3, Z = 2, T = 99.99 K, μ(CuKα) = 0.666 mm-1, Dcalc = 1.202 g/cm3, 28210 reflections measured (7.254° ≤ 2Θ ≤ 144.824°), 3589 unique (Rint = 0.0700, Rsigma = 0.0351) which were used in all calculations. The final R1 was 0.0468 (I > 2σ(I)) and wR2 was 0.1197 (all data).



334

(±)-Methyl 4-[(3-bromophenyl)amino]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (334)

The title compound was prepared according to a modification of **General Procedure 6** using enoate **321** (6.04 g, 22.4 mmol), B_2Pin_2 (6.83 g, 26.9 mmol), CuI (76.0 mg, 0.399 mmol), K_2CO_3 (5.27 g, 38.1 mmol), MeOH (1.81 ml, 44.7 mmol). The crude residue was purified by dissolution in MeCN, filtration of the precipitate followed by concentration *in vacuo* to give *amine* **334** (8.16 g, 92%) as a pale-yellow solid.

m.p. = 81-83 °C (petroleum ether:AcOEt).

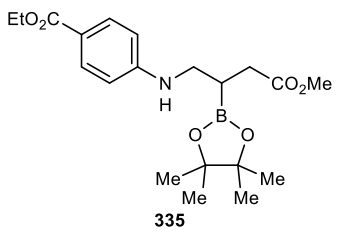
IR 3392 (NH), 2992, 1724 (C=O), 1593, 1381, 1138, 1027, 844 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.77 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.72 (1H, t, *J* = 1.8 Hz, Ar**H**), 6.49 (1H, dd, *J* = 8.0, 1.8 Hz, Ar**H**), 4.08 (1H, s, N**H**), 3.67 (3H, s, OC**H$_3$**), 3.21 (1H, dd, *J* = 12.0, 7.1 Hz, NC**H$_A$**H$_B$), 3.14 (1H, dd, *J* = 12.0, 5.8 Hz, NCH$_A$**H$_B$**), 2.56 (1H, dd, *J* = 17.0, 6.9 Hz, C**H$_A$**CH$_B$CO), 2.51 (1H, dd, *J* = 17.0, 6.5 Hz, CH$_A$**CH$_B$**CO), 1.68 (1H, dddd, *J* = 7.1, 6.9, 6.5, 5.8 Hz, C**H**), 1.25 (12H, s, 4 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 149.7 (C), 130.4 (CH), 123.2 (C), 119.8 (CH), 115.2 (CH), 111.6 (CH), 83.7 (2 × C), 51.7 (CH_3), 44.5 (CH_2), 33.4 (CH_2), 24.7 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.6 (br s, boronic ester), 22.6 (br s, adduct).

HRMS (Q-TOF) Exact mass calcd for [$C_{17}H_{26}NO_4{}^{11}B^{79}Br$]+ [MH]+ calcd. 398.1133, found 398.1129.



335

(±)-Ethyl 4-{[4-methoxy-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]amino}benzoate (335)

The title compound was prepared according to **General Procedure 6** using enoate **324** (11.7 g, 44.4 mmol), B_2pin_2 (13.6 g, 53.5 mmol), CuI (170 mg, 0.893 mmol), K_2CO_3 (10.5 g, 76.0 mmol), MeOH (3.60 ml, 89.0 mmol) and anhydrous THF (150 ml). The crude residue was purified by dissolution in the minimum amount hot diethyl ether and precipitation with petroleum ether to give *amine* **335** (13.3g, 76%) as a white solid.

m.p. = 120-121 °C (CH_2Cl_2).

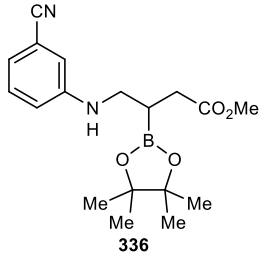
IR 3344 (NH), 2977, 1725 (C=O), 1703 (C=O), 1606, 1320, 1172, 860, 772 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.54 (2H, d, *J* = 8.8 Hz, Ar**H**), 4.49 (1H, br s, N**H**), 4.30 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 3.66 (3H, s, OC**H$_3$**), 3.30 (1H, dd, *J* = 13.0, 7.7 Hz, NC**H$_A$**H$_B$), 3.24 (1H, dd, *J* = 13.0, 6.6 Hz, NCH$_A$**H$_B$**), 2.57 (1H, dd, *J* = 17.2, 7.1 Hz, C**H$_A$**H$_B$CO), 2.51 (1H, dd, *J* = 17.2, 6.9 Hz, CH$_A$**H$_B$**CO), 1.70 (1H, dddd, *J* = 7.7, 7.1, 6.9, 6.6 Hz, C**H**), 1.35 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H$_3$**), 1.25 (12H, s, 4 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 166.9 (C), 152.0 (C), 131.4 (2 × CH), 118.4 (C), 111.4 (2 × CH), 83.7 (2 × C), 60.1 (CH_2), 51.7 (CH_3), 44.1 (CH_2), 33.4 (CH_2), 24.7 (4 × CH_3), 14.5 (CH_3).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{20}H_{31}{}^{11}BNO_6]^+$ $[MH]^+$ calcd. 392.2239, found 392.2256.



336

(±)-Methyl 4-[(3-cyanophenyl)amino]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (336)

The title compound was prepared according to **General Procedure 6** using enoate **325** (216 mg, 1.00 mmol). The crude residue was purified by column chromatography (petroleum ether:AcOEt 9:1→4:1) to give *amine* **336** (271 mg, 79%) as an off-white solid.

m.p. = 89-91 °C (CH_2Cl_2).

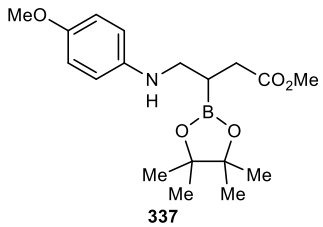
IR 3342 (NH), 2980, 2230 (C≡N), 1727 (C=O), 1327, 1137, 860, 781 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.90 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.77 (1H, s, Ar**H**), 6.76 (1H, d, *J* = 8.0 Hz, Ar**H**), 4.31 (1H, br s, N**H**), 3.65 (3H, s, OC**H**$_3$), 3.22 (1H, dd, *J* = 12.2, 7.3 Hz, NC**H$_A$**H$_B$), 3.17 (1H, dd, *J* = 12.2, 7.3 Hz, NCH$_A$**H$_B$**), 2.56 (1H, dd, *J* = 17.0, 6.7 Hz, C**H$_A$**H$_B$CO), 2.50 (1H, dd, *J* = 17.0, 6.7 Hz, CH$_A$**H$_B$**CO), 1.67 (1H, tt, *J* = 7.3, 6.7 Hz, C**H**), 1.24 (12H, s, 4 × C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 148.5 (C), 129.8 (CH), 120.4 (CH), 119.5 (C), 117.2 (CH), 114.9 (CH), 112.8 (C), 83.7 (2 × C), 51.7 (CH_2), 44.3 (CH_3), 33.3 (CH_2), 24.7 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.3 (br s, boronic ester), 22.4 (br s, adduct).

HRMS (Q-TOF) Exact mass calcd for $[C_{18}H_{26}{}^{11}BN_2O_4]^+$ $[MH]^+$ calcd. 345.1980, found 345.1983.



337

(±)-Methyl 4-[(4-methoxyphenyl)amino]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (337)

The title compound was prepared according to **General Procedure 6** using enoate **326** (221 mg, 1.00 mmol). The crude residue was purified by recrystallisation from *n*-hexane to give *amine* **337** (280 mg, 80%) as a pale brown solid.

m.p. = 84-85 °C (*n*-hexane).

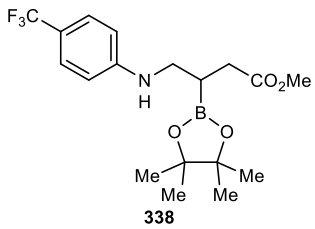
IR 3350 (NH), 2979, 1724 (C=O), 1513, 1141, 826 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (1H, d, *J* = 8.9 Hz, Ar**H**), 6.60 (2H, d, *J* = 8.9 Hz, Ar**H**), 3.74 (3H, s, ArOC**H$_3$**), 3.66 (3H, s, C(O)OC**H$_3$**), 3.21 (1H, dd, *J* = 11.9, 7.4 Hz, NC**H$_A$**H$_B$), 3.14 (1H, dd, *J* = 11.9, 7.2 Hz, NCH$_A$**H$_B$**), 2.57 (1H, dd, *J* = 16.8, 7.3 Hz, **CH$_A$**H$_B$CO), 2.52 (dd, *J* = 16.8, 6.5 Hz, CH$_A$**H$_B$**CO), 1.69 (dddd, *J* = 7.4, 7.3, 7.2, 6.5 Hz, C**H**), 1.25 (12H, s, 4 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2 (C), 152.2 (C), 142.3 (C), 114.9 (2 × CH), 114.5 (2 × CH), 83.6 (2 × C), 55.8 (CH_3), 51.6 (CH_3), 46.0 (CH_2), 33.5 (CH_2), 24.8 (2 × CH_3), 24.7 (2 × CH_3).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{18}H_{29}{}^{11}BNO_5]^+$ $[MH]^+$ calcd. 350.2133, found 350.2141.



338

(±)-Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-{[4-(trifluoromethyl)phenyl]amino}butanoate (338)

The title compound was prepared according to **General Procedure 6** using enoate **327** (259 mg, 1.00 mmol). The crude residue was purified by recrystallisation from *n*-hexane to give *amine* **338** (260 mg, 67%) as an off-white solid.

m.p. = 129-131 °C (*n*-hexane).

IR 3349 (NH), 2982, 1727 (C=O), 1616, 1381, 1317, 1105, 838 cm^{-1}.

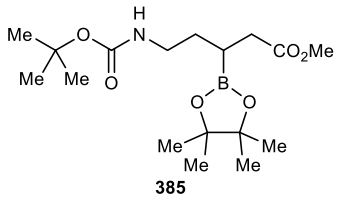
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, d, *J* = 8.6 Hz, Ar**H**), 6.59 (2H, d, *J* = 8.6 Hz, Ar**H**), 4.40 (1H, br s, N**H**), 3.66 (3H, s, OC**H$_3$**), 3.27 (1H, dd, *J* = 12.3, 7.3 Hz, NC**H$_A$**H$_B$), 3.22 (1H, dd, *J* = 12.3, 7.3 Hz, NCH$_A$**H$_B$**), 2.57 (1H, dd, *J* = 17.4, 7.0, C**H$_A$**H$_B$CO), 2.51 (1H, dd, *J* = 17.4, 6.8 Hz, CH$_A$**H$_B$**CO), 1.70 (1H, tdd, *J* = 7.3, 7.0, 6.8, C**H**), 1.25 (12H, s, 4 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 150.8 (C), 126.5 (q, *J* = 3.8 Hz, 2 × CH), 125.0 (q, *J* = 270.2 Hz, CF_3), 118.4 (q, *J* = 32.6 Hz, C), 111.8 (2 × CH), 83.7 (2 × C), 51.7 (CH_3), 44.2 (CH_2), 33.4 (CH_2), 24.7 (4 × CH_3), 20.0 (CH).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.4 (br s), 22.5 (br s).

^{19}F NMR (377 MHz, $CDCl_3$) δ −60.9 (s).

HRMS (Q-TOF) Exact mass calcd for $[C_{18}H_{26}{}^{11}BF_3NO_4]^+$ $[MH]^+$ calcd. 388.1901, found 388.1886.



385

(±)-Methyl 5-{[(*tert*-butoxy)carbonyl]amino}-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate (385)

The title compound was prepared according to a modification of **General Procedure 6** using enoate **384** (6.88 g, 30.0 mmol), B_2Pin_2 (9.14 g, 36.0 mmol), CuI (114 mg, 0.600 mmol), K_2CO_3 (7.05 g, 38.1 mmol), MeOH (2.42 ml, 60.0 mmol). The crude residue was purified by column chromatography (hexane:AcOEt 9:1→4:1) followed by recrystallisation from hexane to give *amine* **385** (6.03 g, 56%) as a white solid.

m.p. = 81 - 82 °C (CH_2Cl_2).

IR 3375 (NH), 2978 (CH), 1735 (C=O), 1714 (C=O), 1519, 1366, 1143 cm^{-1}.

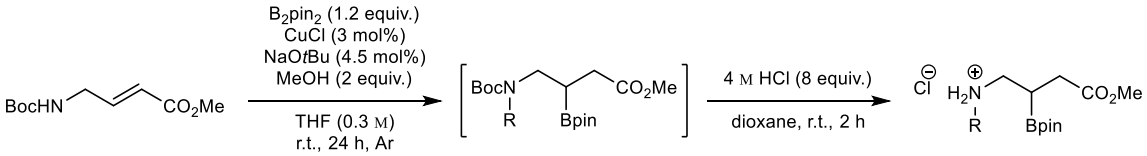
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (1H, br s, N**H**), 3.64 (3H, s, OC**H$_3$**), 3.14 (2H, br s, NC**H$_2$**), 2.47 (1H, dd, *J* = 16.6, 7.9 Hz, C**H$_A$**H$_B$CO), 2.42 (1H, dd, *J* = 16.6, 6.5 Hz, CH$_A$**H$_B$**CO), 1.68 - 1.58 (1H, m, NCH$_2$C**H$_A$**H$_B$), 1.58 - 1.49 (1H, m, NCH$_2$CH$_A$**H$_B$**), 1.42 (9H, s, 3 × COCC**H$_3$**), 1.34 (1H, dddd, *J* = 7.9, 7.0, 6.6, 6.5 Hz, C**H**), 1.24 (6H, s, 2 × BOCC**H$_3$**) , 1.24 (6H, s, 2 × BOCC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 155.8 (C), 83.4 (2 × C), 78.9 (C), 51.4 (CH_3), 39.8 (CH_2), 35.3 (CH_2), 30.6 (CH_2), 28.4 (3 × CH_3), 24.7 (2 × CH_3), 24.7 (2 × CH_3), 17.3 (CH).

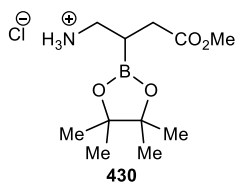
^{11}B NMR (128 MHz, $CDCl_3$) δ 33.9 (br s).

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{32}{}^{11}BNO_6Na]^+$ $[MNa]^+$ calcd. 380.2215, found 380.2230.

General Procedure 7: Conjugate borylation and deprotection to give ammonium hydrochloride boronic esters



An oven dried Schlenk flask was charged with B_2pin_2 (152 mg, 0.600 mmol), CuCl (1.5 mg, 15 μmol), NaO^{t}Bu (2.2 mg, 23 μmol) and backfilled with Ar. Anhydrous THF (1.00 mL) was added, and the mixture was stirred for 10 mins. A solution of the enoate (1 equiv.) in anhydrous THF (0.60 ml) and MeOH (0.04 ml, 1.00 mmol) was added, and the mixture stirred for 24 h. The mixture was passed through a plug of celite, and the solution was concentrated *in vacuo*. The residue was dissolved in 4 M HCl (8 equiv., dioxane) and stirred at r.t. for 2 h. The mixture was diluted with Et_2O (5 ml) and the product isolated by filtration under vacuum.



430

(±)-4-Methoxy-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxazolidin-2-yl)butan-1-aminium chloride (430)

The title compound was prepared according to **General Procedure 7** using enoate **404** (215 mg, 1.00 mmol), B_2pin_2 (305 mg, 1.20 mmol), CuCl (3.0 mg, 30 μmol), NaO^{t}Bu (4.0 mg, 42 μmol), anhydrous THF (3.30 mL), MeOH (0.08 ml, 2.00 mmol), 4M HCl (dioxane, 2 ml) and Et_2O (10 ml). The reaction gave *ammonium hydrochloride salt* **430** (217 mg, 78%) as a white solid.

m.p. = 187 - 189 °C (CH_2Cl_2).

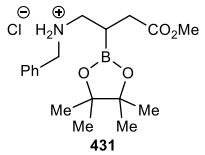
IR 2974 (CH), 2824 (NH), 1726 (C=O), 1314, 1149, 965, 856, 590 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (3H, s, N**H$_3$**), 3.68 (3H, s, OC**H$_3$**), 3.24 (1H, br s, NC**H$_A$**H$_B$), 3.12 (1H, br s, NCH$_A$**H$_B$**), 2.78 (1H, d, *J* = 17.1 Hz, C**H$_A$**H$_B$CO), 2.56 (1H, d, *J* = 17.1 Hz, CH$_A$**H$_B$**CO), 1.76 (1H, br s, C**H**), 1.26 (6H, s, 2 × CC**H$_3$**), 1.24 (6H, s, 2 × CC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 (C), 84.6 (2 × C), 52.1 (CH_3), 41.3 (CH_2), 33.1 (CH_2), 24.8 (2 × CH_3), 24.8 (2 × CH_3).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{11}H_{23}{}^{11}BNO_4]^+$ $[M]^+$ calcd. 244.1715, found 24.1711.



431

(±)-Benzyl[4-methoxy-4-oxo-2-(4,4,5,5-tetramethyl-1,3,2-dioxazolidin-2-yl)butyl]azanium chloride (431)

The title compound was prepared according to **General Procedure 7** using enoate **392** (611 mg, 2.00 mmol), B_2pin_2 (609 mg, 2.40 mmol), CuCl (5.9 mg, 60 μmol), NaO^{t}Bu (8.6 mg, 90 μmol), anhydrous THF (6.60 mL), MeOH (0.16 ml, 4.00 mmol), 4 M HCl (dioxane, 4 ml) and Et_2O (10 ml). The reaction gave *ammonium hydrochloride salt* **431** (505 mg, 68%) as a white solid.

m.p. = 163 - 165 °C (CH_2Cl_2).

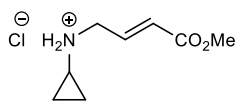
IR 2983 (CH)2781 (NH), 1739 (C=O), 1333, 1146, 696, 482 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (1H, br s, N**H$_A$**H$_B$), 8.83 (1H, br s, NH$_A$**H$_B$**), 7.65 - 7.51 (2H, m, Ar**H**), 7.46 - 7.37 (3H, m, Ar**H**), 4.24 - 4.14 (1H, m, ArC**H$_A$**H$_B$), 4.12 - 3.99 (1H, m, ArCH$_A$**H$_B$**), 3.63 (3H, s, C**H$_3$**), 3.26 - 3.13 (1H, m, NC**H$_A$**H$_B$), 3.09 - 2.93 (1H, m, NCH$_A$**H$_B$**), 2.77 (1H, dd, *J* = 18.2, 5.4 Hz, C**H$_A$**H$_B$CO), 2.69 (1H, dd, *J* = 18.2, 3.9 Hz, CH$_A$**H$_B$**CO), 1.95 - 1.86 (1H, m, C**H**), 1.21 (6H, s, 2 × C**H$_3$**), 1.19 (6H, s, 2 × C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (C), 130.6 (C), 130.0 (2 × CH), 129.5 (CH), 129.2 (2 × CH), 84.5 (2 × C), 52.0 (CH_3), 51.4 (CH_2), 47.8 (CH_2), 32.7 (CH_2), 24.7 (2 × CH_3), 24.7 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 34.5 (br s).

HRMS (Q-TOF) Exact mass calcd for $[C_{18}H_{29}{}^{11}BNO_4]^+$ $[M]^+$ calcd. 334.2184, found 334.2184.



436

***N*-[(2*E*)-4-Methoxy-4-oxobut-2-en-1-yl]cyclopropanaminium chloride (436)**

The title compound was prepared according to **General Procedure 7** using enoate **393** (128 mg, 0.501 mmol). The reaction gave *ammonium hydrochloride salt* **436** (68.1 mg, 71%) as a white solid.

m.p. = 147-149 °C (CH_2Cl_2).

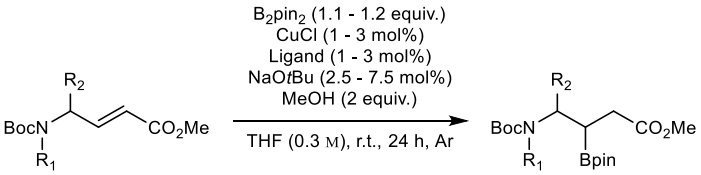
IR 3397 (NH), 2953 (CH), 2728 (CH), 1724 (C=O), 1205, 982, 701, 470 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (2H, br s, N**H$_2$**), 7.08 (1H, dt, *J* = 15.8, 6.9 Hz, CH_2=C**H**CH), 6.25 (1H, d, *J* = 15.8 Hz, CH_2=CHC**H**), 3.82 (2H, d, *J* = 6.9 Hz, NC**H$_2$**), 3.75 (3H, s, C**H$_3$**), 2.60 - 2.49 (1H, m, NC**H**), 1.30 - 1.20 (2H, m, 2 × NCHC**H$_2$**), 0.93 - 0.80 (2H, m, 2 × NCHC**H$_2$**).

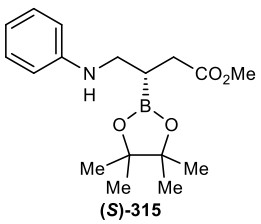
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2 (C), 135.8 (CH), 128.1 (CH), 52.0 (CH_3), 48.4 (CH_2), 29.8 (CH), 3.9 (2 × CH_2).

HRMS (Q-TOF) Exact mass calcd for $[C_8H_{14}NO_2]^+$ $[M]^+$ calcd. 156.1019, found 156.1026.

General Procedure 8: Conjugate borylation of Boc-protected amino enoates and aniline 314



Based on the procedure of Lee and Yun,[117] an oven dried Schlenk flask was charged with B_2pin_2 (305 g, 1.20 mmol), CuCl (1.0 - 3.0 mg, 10 - 30 μmol), ligand (if required, 10 - 30 μmol), NaO^{t}Bu (25 - 75 μmol) and backfilled with Ar. Anhydrous THF (2.00 mL) was added, and the mixture was stirred for 10 mins. A solution of the enoate (1 equiv.) in anhydrous THF (1.50 ml) and MeOH (0.08 ml, 2.00 mmol) was added, and the mixture stirred for 24 h. The mixture was passed through a plug of celite, and the solution was concentrated *in vacuo*. The crude material was purified by either chromatography or recrystallisation.

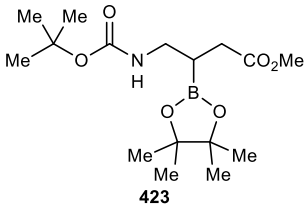


(*S*)-315

(*S*)-Methyl 4-(phenylamino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate ((*S*)-315)

The title compound was prepared according to **General Procedure 8** using enoate **314** (96.0 mg, 0.502 mmol), B_2pin_2 (140 mg, 0.551 mmol), CuCl (1.5 mg, 15 μmol), (*R*, *S*)-Josiphos 2 (9.6 mg, 15 μmol), NaO^{t}Bu (2.1 mg, 22 μmol), MeOH (0.04 ml, 0.99 mmol) and THF (1.5 ml). The crude residue was purified by column chromatography (petroleum ether:AcOEt 9:1) to give *amine* **(*S*)-315** (89.5 mg, 56%) as a pale-yellow oil. The data matched that of racemic **315** above. No HPLC data was collected for this compound, enantiomer was confirmed by analogy to lactam **(*S*)-348.**

$[\alpha]_D^{23}$ +2.2 (c 0.90, $CHCl_3$)



423

(±)-Methyl 4-(tert-butoxycarbonylamino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (423)

The title compound was prepared according to **General Procedure 8** using enoate **404** (215 mg, 0.999 mmol), CuCl (3.0 mg, 30 μmol) and NaO^{t}Bu (3.0 mg, 31μmol). The crude residue was purified by column chromatography (hexane:AcOEt 4:1) to give *amine* **423** (309 mg, 90%) as a colourless oil.

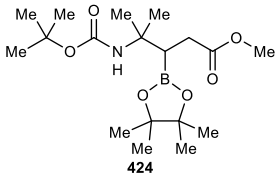
IR 3397 (NH), 2979 (CH), 1697 (C=O), 1366, 1142 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (1H, br s, N**H**), 3.66 (3H, s, OC**H$_3$**), 3.27 – 3.18 (2H, m, NC**H$_2$**), 2.49 (1H, s, C**H$_A$**H$_B$CO), 2.47 (1H, s, CH$_A$**H$_B$**CO), 1.55 – 1.49 (1H, m, C**H**), 1.43 (9H, s, 3 × COCC**H$_3$**), 1.24 (12H, s, 4 × BOCC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 155.9 (C), 83.6 (2 × C), 78.9 (C), 51.6 (CH_3), 41.2 (CH_2), 33.2 (CH_2), 28.4 (3 × CH_3), 24.7 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.8 (br s).

HRMS (Q-TOF) Exact mass calcd for $[C_{16}H_{30}{}^{11}BNO_6Na]^+$ $[MNa]^+$ calcd. 366.2058, found 366.2075.



424

(±)-Methyl 4-{[(tert-butoxy)carbonyl]amino}-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate (424)

The title compound was prepared according to **General Procedure 8** using enoate **403** (243 mg, 0.999 mmol), SIMes.HBF_4 (3.9 mg, 10 μmol) and NaO^{t}Bu (2.4 mg, 25 μmol). The crude residue was purified by column chromatography (hexane:Et_2O 1:0→0:1) to give *amine* **424** (328 mg, 88%) as a colourless oil.

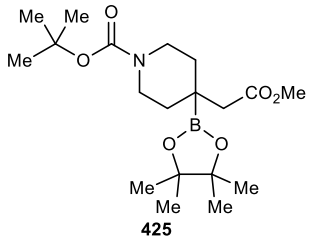
IR 3389 (NH), 2977 (CH), 1720 (C=O), 1366, 1142, 861 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (1H, s, N**H**), 3.62 (3H, s, OC**H$_3$**), 2.63 - 2.33 (2H, m, CH_2), 1.94 - 1.70 (1H, m, C**H**), 1.39 (9H, s, 3 × COCC**H$_3$**), 1.34 (3H, s, NCC**H$_3$**), 1.29 (3H, s, NCC**H$_3$**), 1.23 (6H, s, 2 × BOCC**H$_3$**), 1.21 (6H, s, 2 × BOCC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5 (C), 154.5 (C), 83.4 (2 × C), 78.4 (C), 53.4 (C), 51.5 (CH_3), 31.7 (CH_2), 28.4 (3 × CH_3), 26.4 (2 × CH_3), 25.0 (CH), 24.8 (2 × CH_3), 24.6 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.1 (br s).

HRMS (Q-TOF) Exact mass calcd for $[C_{18}H_{34}{}^{11}BNO_6Na]^+$ $[MNa]^+$ calcd. 394.2371, found 394.2372.



425

***tert*-Butyl 4-(2-methoxy-2-oxoethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)piperidine-1-carboxylate (425)**

The title compound was prepared according to **General Procedure 8** using enoate **414** (255 mg, 0.999 mmol), SIMes.HBF_4 (3.9 mg, 10 μmol) and NaO^{t}Bu (2.4 mg, 25 μmol). The crude residue was purified by column chromatography (hexane:Et_2O 1:0→0:1) to give *amine* **425** (344 mg, 90%) as a white solid.

m.p. = 71 - 73 °C (CH_2Cl_2).

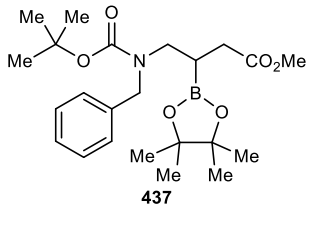
IR 2976 (CH), 1680 (C=O), 1425, 1308, 1141, 851 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 - 3.71 (1H, br s, 2 × NC**H$_A$**H$_B$), 3.58 (3H, s, OCH_3), 2.96 (2H, m, 2 × NCH$_A$**H$_B$**), 2.29 (2H, s, CC**H$_2$**), 1.79 (2H, d, *J* = 13.0 Hz, 2 × NCH_2C**H$_A$**H$_B$), 1.39 (9H, s, 3 × COCC**H$_3$**), 1.20 (12H, s, 4 × BOCC**H$_3$**), 1.12 (2H, td, *J* = 13.0, 4.0 Hz, 2 × NCH_2CH_A**H$_B$**).

^{13}C NMR (101 MHz, $CDCl_3$) 172.8 (C), 154.8 (C), 83.3 (2 × C), 79.0 (C), 51.2 (CH_3), 44.1 (2 × CH_2), 41.5 (C), 33.5 (2 × CH_2), 28.3 (3 × CH_3), 24.8 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 34.2 (br s).

HRMS (Q-TOF) Exact mass calcd for $[C_{19}H_{34}{}^{11}BNO_6Na]^+$ $[MNa]^+$ calcd. 406.2371, found 406.2370.



437

(±)-Methyl 4-{benzyl[(tert-butoxy)carbonyl]amino}-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (437)

The title compound was prepared according to **General Procedure 8** using enoate **392** (305 mg, 0.999 mmol) and NaO^{t}Bu (4.3 mg, 45 μmol). The crude residue was purified by column chromatography (hexane:AcOEt 9:1) to give *amine* **437** (236 mg, 55%) as a colourless oil.

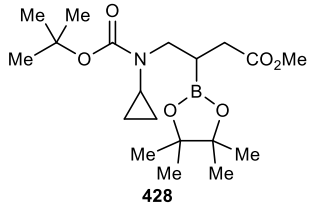
IR 2977 (CH), 1690 (C=O), 1365, 1141, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.10 (5H, m, Ar**H**), 4.63 - 4.29 (2H, m, ArC**H$_2$**), 3.64 (3H, s, OC**H$_3$**), 3.46 - 3.21 (2H, m, NC**H$_2$**CH), 2.52 - 2.41 (2H, m, C**H$_2$**CO), 1.58 - 1.33 (1H, m, C**H**), 1.47 - 1.40 (9H, m, 3 × COCC**H$_3$**), 1.21 (12H, s, 4 × BOCC**H$_3$**). (Rotameric)

^{13}C NMR (101 MHz, CDCl3) δ 174.1 (C), 156.2 (C), 156.0 (C), 138.6 (C), 138.4 (C), 128.4 (2 × CH), 127.5 (CH), 126.9 (2 × CH), 83.4 (2 × C), 79.6 (C), 51.5 (CH_3), 50.2 (CH_2), 49.6 (CH_2), 46.6 (CH_2), 32.7 (CH_2), 28.4 (3 × CH_3), 24.7 (4 × CH_3). (Rotameric)

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

HRMS (Q-TOF) Exact mass calcd for $[C_{23}H_{36}{}^{11}BNO_6Na]^+$ [MNa]$^+$ calcd. 456.2528, found 456.2557.



428

(±)-Methyl 4-{[(tert-butoxy)carbonyl](cyclopropyl)amino}-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (428)

The title compound was prepared according to **General Procedure 8** using enoate **393** (255 mg, 0.999 mmol), SIMes.HBF_4 (11.8 mg, 30.0 μmol) and NaO^{t}Bu (7.2 mg, 75 μmol). The crude residue was purified by column chromatography (hexane:AcOEt 4:1) to give *amine* **428** (357 mg, 93%) as a colourless oil.

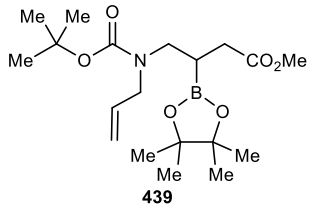
IR 2978 (CH), 1695 (C=O), 1365, 1140, 857 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (1H, m, OC**H$_3$**), 3.44 - 3.37 (1H, m, NC**H$_A$**H$_B$), 3.29 - 3.24 (1H, m, NCH$_A$**H$_B$**), 2.48 - 2.44 (3H, m, C**H$_2$**CO, NC**H**), 1.75 (1H, br s, BC**H**), 1.43 (9H, m, 3 × COCC**H$_3$**), 1.22 (12H, s, 4 × BOCC**H$_3$**), 0.77 - 0.65 (2H, m, 2 × NCHC**H$_A$**H$_B$), 0.64 - 0.50 (2H, m, 2 × NCHCH$_A$**H$_B$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (C), 156.8 (C), 83.3 (2 × C), 79.3 (C), 51.5 (CH_3), 47.0 (CH_2), 32.7 (CH_2), 28.4 (3 × CH_3), 28.4 (CH), 24.7 (4 × CH_3), 8.5 (2 × CH_2), 7.7 (2 × CH_2).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{19}H_{34}{}^{11}BNO_6Na]^+$ [MNa]$^+$ calcd. 406.2371, found 406.2382.



439

(±)-Methyl 4-{[(tert-butoxy)carbonyl](prop-2-en-1-yl)amino}-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (439)

The title compound was prepared according to **General Procedure 8** using enoate **394** (255 mg, 1.00 mmol) and NaO^{t}Bu (4.3 mg, 45 μmol). The crude residue was purified by column chromatography (hexane:AcOEt 9:1) to give *amine* **439** (261 mg, 68%) as a colourless oil.

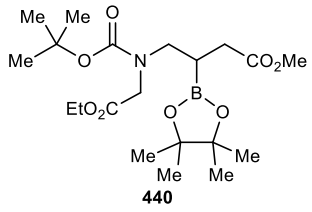
IR 2978 (CH), 1692 (C=O), 1365, 1161, 858 cm^{-1}.

^{1}H NMR δ 5.75 (1H. br s, C**H**C=H$_2$), 5.11 (1H, br s, CH=C**H$_A$**H$_B$), 5.07 (1H, br s, CH=CH$_A$**H$_B$**), 3.96 - 3.67 (2H, m, NC**H$_2$**CH=CH$_2$), 3.65 (3H, s, C**H$_3$**), 3.43 (1H, dd, *J* = 14.4, 10.3 Hz, NC**H$_A$**H$_B$CHB), 3.23 (1H, br d, *J* = 14.4 Hz, NCH$_A$**H$_B$CHB**), 2.47 - 2.45 (2H, m, C**H$_2$**CO), 1.66 (1H, br s, BC**H**), 1.43 (9H, m, 3 × COCC**H$_3$**), 1.23 (12H, s, 4 × BOCC**H$_3$**). (Rotameric)

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 155.7 (CH_2), 134.0 (CH), 116.2 (C), 115.9 (C), 83.4 (2 × C), 79.6 (C), 79.4 (C), 51.5 (CH_3), 49.5 (CH_2), 49.0 (CH_2), 46.6 (CH_2), 32.6 (CH_2), 28.4 (3 × CH_3), 24.7 (4 × CH_3), 19.5 (CH). (Rotameric)

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

HRMS (Q-TOF) Exact mass calcd for $[C_{19}H_{34}{}^{11}BNO_6Na]^+$ [MNa]$^+$ calcd. 406.2371, found 406.2385.



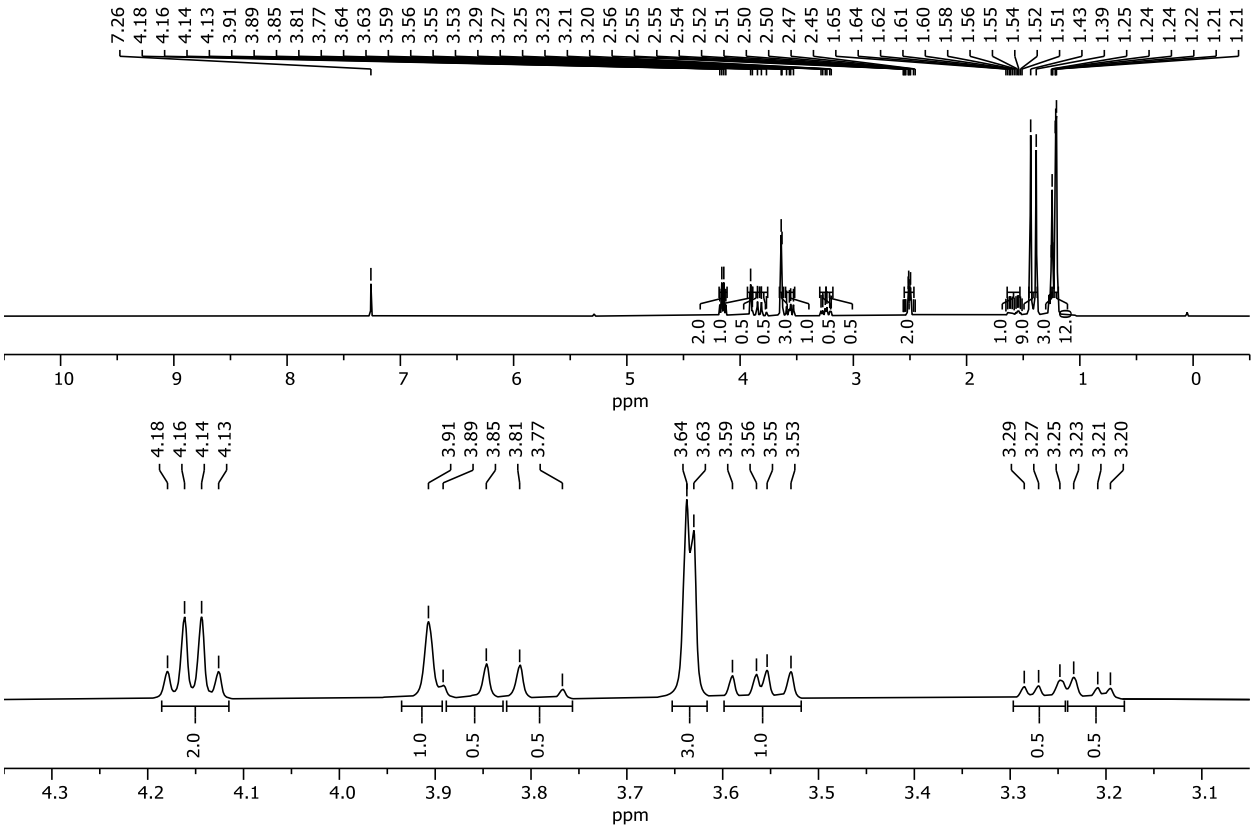
440

(±)-Methyl 4-{[(tert-butoxy)carbonyl](2-ethoxy-2-oxoethyl)amino}-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (440)

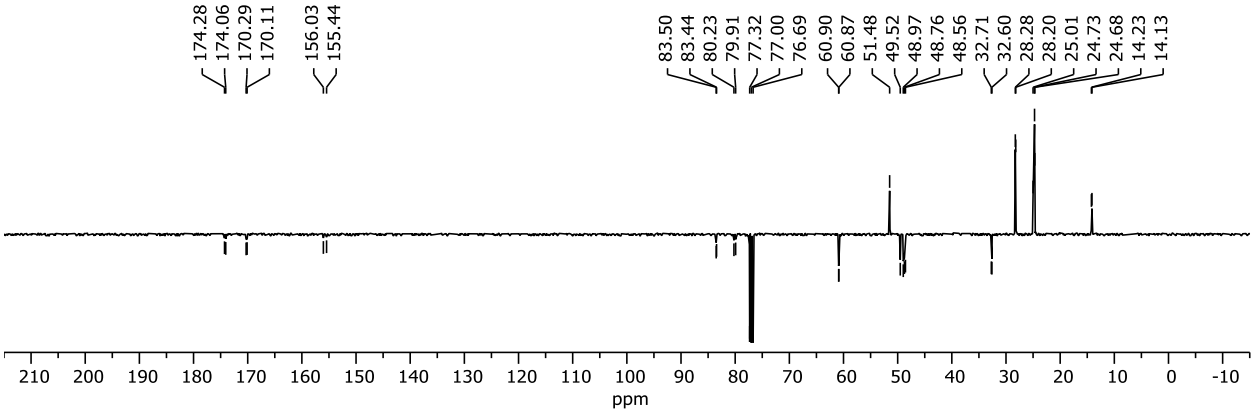
The title compound was prepared according to **General Procedure 8** using enoate **396** (305 mg, 1.01 mmol), SIMes.HBF_4 (11.8 mg, 30.0 μmol) and NaO^{t}Bu (7.2 mg, 75 μmol). The crude residue was purified by column chromatography (hexane:AcOEt 9:1→4:1) to give *amine* **440** (213 mg, 50%) as a colourless oil.

IR 2978 (CH), 1698 (C=O), 1366, 1141, 858 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (2H, q, *J* = 7.1 Hz, OC**H$_2$**), 3.91 (1H, s, OCC**H$_A$H$_B$**N, rotamer 1), 3.87 (0.5 H, d, *J* = 17.9 Hz, CC**H$_A$**H$_B$N), 3.79 (0.5 H, d, *J* = 17.9 Hz, OCCH$_A$**H$_B$**N, rotamer 2), 3.71 - 3.61 (3H, m, OCH_3), 3.56 (1H, dd, *J* = 14.9, 10.0 Hz, NC**H$_A$H$_B$**CH, rotamer 1), 3.26 (0.5H, dd, *J* = 15.2, 5.9 Hz, NC**H$_A$**H$_B$CH, rotamer 2), 3.22 (0.5H, dd, *J* = 15.2, 5.5 Hz, NCH$_A$**H$_B$**CH, rotamer 2), 2.57 - 2.44 (2H, m, CHC**H$_2$**CO), 1.67 - 1.50 (1H, m, C**H**), 1.46 - 1.35 (9H, m, 3 × COCC**H$_3$**), 1.30 - 1.23 (3H, m, OCH_2C**H$_3$**), 1.23 - 1.18 (12H, m, 4 × BOCC**H$_3$**). (Rotameric)

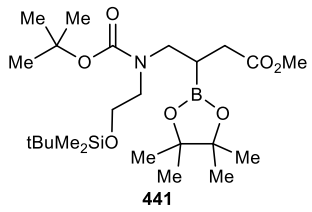


^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3 (C), 174.1 (C), 170.3 (C), 170.1 (C), 156.1 (C), 155.5 (C), 83.5 (2 × C), 83.5 (2 × C), 80.3 (C), 79.9 (C), 60.9 (CH_2), 60.9 (CH_2), 51.5 (CH_3), 49.5 (CH_2), 49.0 (CH_2), 48.8(CH_2), 48.6 (CH_2), 32.7 (CH_2), 32.62 (CH_2), 28.30 (3 × CH_3), 28.2 (3 × CH_3), 25.0 (CH), 24.8 (4 × CH_3), 24.7 (4 × CH_3), 14.3 (CH_3), 14.2 (CH_3). (Rotameric)



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

HRMS (Q-TOF) Exact mass calcd for $[C_{20}H_{36}{}^{11}BNO_8Na]^+$ $[MNa]^+$ calcd. 452.2426, found 452.2455.



441

(±)-Methyl 4-(2,2,3,3,10,10-hexamethyl-8-oxo-4,9-dioxa-7-aza-3-silaundecan-7-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (441)

The title compound was prepared according to **General Procedure 8** using enoate **395** (374 mg, 1.00 mmol) and NaO^{t}Bu (4.3 mg, 45 μmol). The crude residue was purified by column chromatography (hexane:AcOEt 19:1) to give *amine* **441** (126 mg, 25%) as a colourless oil.

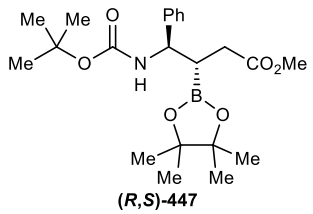
IR 2930 (CH), 1695, (C=O), 1365, 1142, 835 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 - 3.66 (2H, m, NC**H$_2$**CH), 3.64 (3H, s, OC**H$_3$**), 3.55 - 3.45 (1H, m, $NCH_AH_BCH_2$), 3.37 - 3.15 (3H, m, NCH_A**H$_B$**C**H$_2$**), 2.46 - 2.37 (2H, m, C**H$_2$**CO), 1.80 - 1.61 (1H, m, C**H**), 1.42 (9H, s, 3 × COCC**H$_3$**), 1.21 (12H, s, 4 × BOCC**H$_3$**), 0.87 (9H, s, 3 × SiCC**H$_3$**), 0.03 (6H, s, 2 × SiC**H$_3$**). (Rotameric)

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 174.1 (C), 155.7 (C), 155.7 (C), 83.3 (2 × C), 79.3 (C), 79.2 (C), 61.4 (CH_2), 51.4 (CH_3), 49.1 (CH_2), 48.6 (CH_2), 48.1 (CH_2), 32.7 (CH_2), 32.5 (CH_2), 28.4 (3 × CH_3), 25.9 (CH_2), 24.8 (2 × CH_3), 24.7 (2 × CH_3), 18.2 (3 × CH_3), -5.4 (2 × CH_3). (Rotameric)

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

HRMS (Q-TOF) Exact mass calcd for $[C_{24}H_{48}{}^{11}BNO_7SiNa]^+$ $[MNa]^+$ calcd. 524.3185, found 524.3226.



(*R*,*S*)-447

(+)-Methyl (3*S*,4*R*)-4-{[(tert-butoxy)carbonyl]amino}-4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate ((*S*,*R*)-447)

The title compound was prepared according to **General Procedure 8** using enoate **(*R*)-408** (146 mg, 0.501 mmol), B_2pin_2 (152 mg, 0.600 mmol), CuCl (1.5 mg, 15 μmol), (*R*)-MeO-BIPHEP (8.7 mg, 15 μmol), NaO^{t}Bu (2.2 mg, 23 μmol), MeOH (0.04 ml, 1.00 mmol) and anhydrous THF (1.60 ml). The crude residue was purified by column chromatography (hexane:AcOEt 4:1) to give *amine* **(*R*,*S*)-447** (160 mg, 76%, >20:1 d.r.) as an off-white solid.

$[\alpha]_D^{23}$ +9.0 (c 1.0, $CHCl_3$)

m.p. = 83 - 86 °C (CH_2Cl_2).

IR 3384 (NH), 2976 (CH), 1712 (C=O), 1167, 700 cm^{-1}.

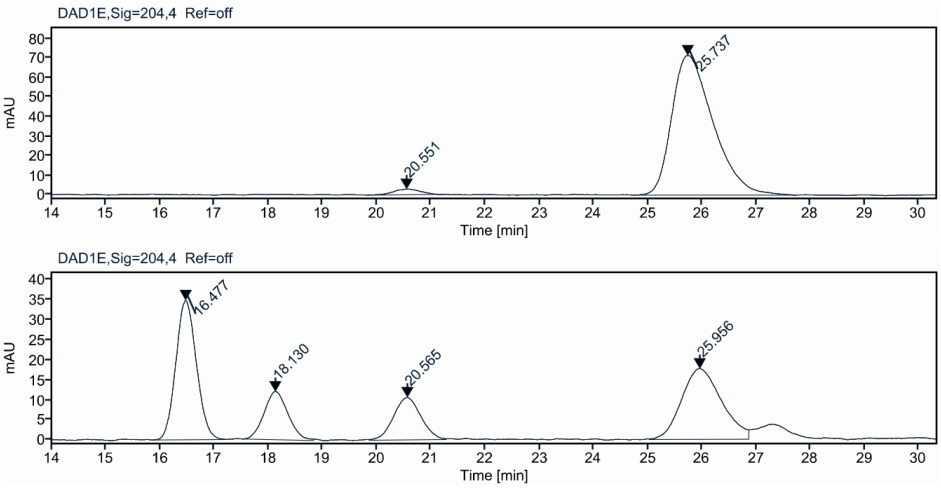
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.11 (5H, m, Ar**H**), 5.47 (1H, br s, N**H**), 4.68 (1H, br s, NC**H**), 3.62 (3H, s, OC**H$_3$**), 2.48 (1H, dd, *J* = 16.6, 10.0 Hz, C**H$_A$**H$_B$), 2.30 (1H, dd, *J* = 16.6, 5.7 Hz, CH$_A$**H$_B$**), 1.89 - 1.83 (1H, m , BC**H**), 1.40 (9H, s, 3 × COCC**H$_3$**), 1.20 (6H, s, 2 × BOCC**H$_3$**), 1.17 (6H, s, 2 × BOCC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 (C), 155.1 (C), 142.7 (C), 128.3 (2 × CH), 127.0 (CH), 126.3 (2 × CH), 83.7 (2 × C), 79.1 (C), 55.6 (CH), 51.6 (CH_3), 33.9 (CH_2), 28.4 (3 × CH_3), 24.6 (4 × CH_3).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{22}H_{34}{}^{11}BNO_6Na]^+$ $[MNa]^+$ calcd. 442.2371, found 442.2397.

e.e. = >99%, measured through chiral HPLC analysis. Daicel Chiralpak amylose-ID S-5 μm, IPA:hexane = 25:85, 1.1 mL/min, 22°C, λ = 204 nm, (*S*, *R*)-isomer t_r = 16.5 min, *syn*-diastereoisomer A *t* = 18.1 min, *syn*-diastereoisomer B t_r = 20.6 min, and (*R*,*S*)-isomer t_r = 26.0 min.



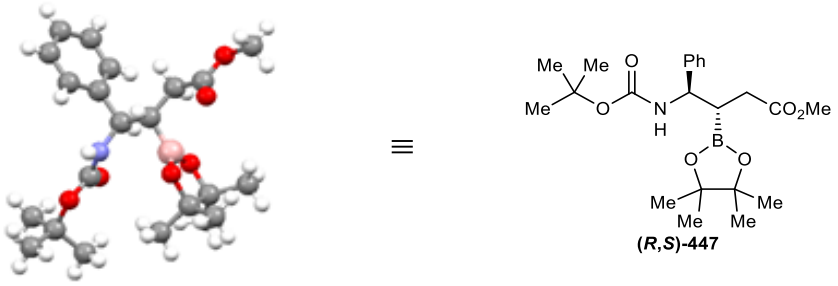
Signal: DAD1E,Sig=204,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
20.551	BB	1.3917	100.3402	2.9067	2.5919	
25.737	BB	2.9852	3770.9637	71.2759	97.4081	
		Sum	3871.3039			

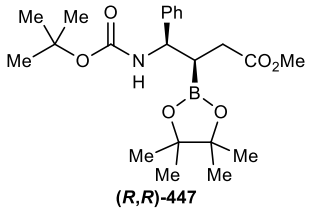
Signal: DAD1E,Sig=204,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
16.477	BB	1.3733	918.6939	34.8234	35.7796	
18.130	BV	1.3173	368.9957	12.0320	14.3710	
20.565	VV	1.4239	370.4347	10.6132	14.4270	
25.956	VM m	0.6129	909.5240	17.7176	35.4225	
		Sum	2567.6484			

Crystals suitable for X-ray diffraction were obtained through recrystallisation of **(*S*,*R*)-447** from *n*-hexane.



Crystal Data for $C_{22}H_{34}BNO_6$ (M =419.31 g/mol): orthorhombic, space group P212121 (no. 19), a = 9.9381(4) Å, b = 11.6297(4) Å, c = 20.5575(7) Å, V = 2375.98(15) Å3, Z = 4, T = 100.01 K, μ(CuKα) = 0.680 mm-1, Dcalc = 1.172 g/cm3, 18814 reflections measured ($8.602° \leq 2\Theta \leq 133.314°$), 4154 unique (Rint = 0.0401, Rsigma = 0.0327) which were used in all calculations. The final R1 was 0.0311 ($I > 2\sigma(I)$) and wR2 was 0.0818 (all data).



(*R*,*R*)-447

(+)-Methyl (3*R*,4*R*)-4-{[(tert-butoxy)carbonyl]amino}-4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate ((*R*,*R*)-447)

The title compound was prepared according to **General Procedure 8** using enoate **(*R*)-408** (146 mg, 0.501 mmol), B_2pin_2 (152 mg, 0.600 mmol), CuCl (1.5 mg, 15 μmol), (*R*, *R*)-FOXAP (7.2 mg, 15 μmol), NaO^{t}Bu (2.2 mg, 23 μmol), MeOH (0.04 ml, 1.00 mmol) and anhydrous THF (1.60 ml). The crude residue was purified by column chromatography (hexane:AcOEt 4:1) to give *amine* **(*R*,*R*)-447** (160 mg, 76%, >20:1 d.r.) as a colourless oil.

$[\alpha]_D^{23}$ +26.0 (c 1.0, $CHCl_3$)

IR 3383 (NH), 2978 (CH), 1712 (C=O), 1141, 700 cm^{-1}.

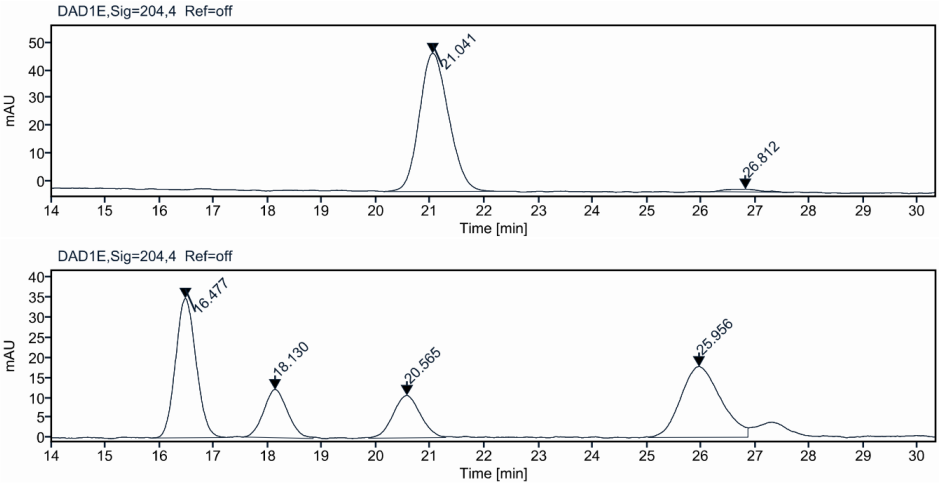
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.16 (5H, m, Ar**H**), 5.25 (1H, d, *J* = 8.4 Hz, N**H**), 4.79 (1H, dd, *J* = 8.4, 7.8 Hz, NC**H**), 3.63 (3H, s, OC**H$_3$**), 2.59 - 2.30 (2H, m, C**H$_2$**), 1.96 - 1.90 (1H, m, BC**H**), 1.49 - 1.24 (9H, m, 3 × COCC**H$_3$**), 1.11 (6H, s, 2 × BOCC**H$_3$**), 1.05 (6H, s, 2 × BOCC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 155.1 (C), 142.2 (C), 128.3 (2 × CH), 127.2 (CH), 126.9 (2 × CH), 83.6 (2 × C), 79.2 (C), 55.5 (CH), 51.6 (CH_3), 32.8 (CH_2), 28.4 (3 × CH_3), 24.7 (2 × CH_3), 24.5 (2 × CH_3).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{22}H_{34}{}^{11}BNO_6Na]^+$ $[MNa]^+$ calcd. 442.2371, found 442.2390.

e.e. = >99%, measured through chiral HPLC analysis. Daicel Chiralpak amylose-ID S-5 μm, IPA:hexane = 25:85, 1.1 mL/min, 22°C, λ = 204 nm, (*S*, *R*)-isomer t_r = 16.5 min, *syn*-diastereoisomer A *t* = 18.1 min, *syn*-diastereoisomer B t_r = 20.6 min, and (*R*,*S*)-isomer t_r = 26.0 min.



Signal: DAD1E,Sig=204,4 Ref=off

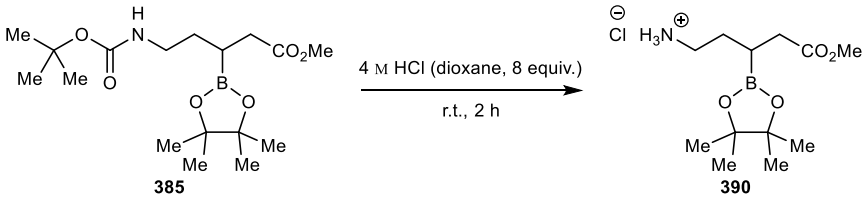
RT [min]	Type	Width [min]	Area	Height	Area%	Name
21.041	BB	2.0597	1866.0971	49.7025	97.6295	
26.812	MM m	0.5357	45.3101	1.0056	2.3705	
		Sum	1911.4072			

Signal: DAD1E,Sig=204,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
16.477	BB	1.3733	918.6939	34.8234	35.7796	
18.130	BV	1.3173	368.9957	12.0320	14.3710	
20.565	VV	1.4239	370.4347	10.6132	14.4270	
25.956	VM m	0.6129	909.5240	17.7176	35.4225	
		Sum	2567.6484			

4.2.5 Deprotection of Boc Protected Amino Esters

(±)-Methyl 5-amino-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate chloride (390)



Amine **385** (357 mg, 1.00 mmol) was dissolved in 4M HCl (dioxane, 2.00 ml, 8.00 mmol) and stirred at r.t. for 1 h. The mixture was concentrated *in vacuo* to give *ammonium hydrochloride salt* **390** (294 mg, 80%) as a white solid.

m.p. = 113-114 °C (CH_2Cl_2).

IR 3385 (NH), 2975 (CH), 1729 (C=O), 1141, 861 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (3H, br s, N**H$_3$**), 3.66 (3H, s, OC**H$_3$**), 3.09 (2H, br s, NC**H$_2$**), 2.51 (1H, dd, *J* = 16.9, 6.3 Hz, $NCH_2C\mathbf{H_A}H_B$), 2.45 (1H, dd, *J* = 16.9, 6.6 Hz, $NCH_2CH_A\mathbf{H_B}$), 2.05 - 1.71 (2H, m, C**H$_2$**CO), 1.51 - 1.32 (1H, m, C**H**), 1.23 (12H, s, 4 × CC**H$_3$**).

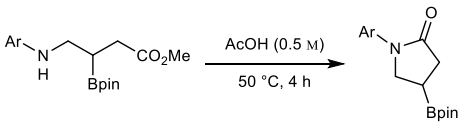
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (C), 84.0 (2 × C), 51.9 (CH_3), 39.5 (CH_2), 35.5 (CH_2), 28.6 (CH_2), 24.9 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 34.2 (br s).

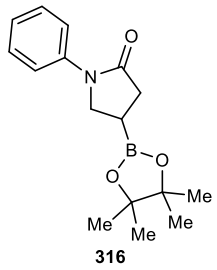
HRMS (Q-TOF) Exact mass calcd for $[C_{12}H_{25}{}^{11}BNO_4]^+$ $[M]^+$ calcd. 258.871, found 258.1873.

4.2.6 Cyclisation of Amino Esters

General Procedure 9: Cyclisation of aryl amino enoates



The corresponding amino ester (0.500 mmol) was stirred in AcOH (1 ml) at 50 °C for 4 h. The mixture was cooled to room temperature, quenched with saturated aqueous Na_2CO_3 (10 ml), and extracted with CH_2Cl_2 (3 × 15 ml). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the lactam. No further purification was carried out unless specified.



316

(±)-1-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-2-one (316)

The title compound was prepared according to **General Procedure 9** using boronic ester **315** (160 mg, 0.501 mmol). The reaction gave *lactam* **316** (124 mg, 86%) as an off-white solid.

m.p. = 88-93 °C (CH_2Cl_2).

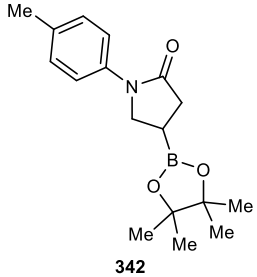
IR 3356, 1678 (C=O), 1385, 1293, 1141, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 7.7 Hz, Ar**H**), 7.36 (2H, t, *J* = 7.7 Hz, Ar**H**), 7.13 (1H, t, *J* = 7.7 Hz, Ar**H**), 3.91 (1H, dd, *J* = 10.3, 8.7 Hz, NC$\mathbf{H_A}H_B$), 3.89 (1H, dd, *J* = 10.3, 8.7 Hz, NC$H_A\mathbf{H_B}$), 2.69 (1H, dd, *J* = 17.1, 10.0 Hz, C$\mathbf{H_A}H_B$CO), 2.60 (1H, dd, *J* = 17.1, 10.8 Hz, C$H_A\mathbf{H_B}$CO), 1.92 (1H, ddt, *J* = 10.8, 10.0, 8.7 Hz, C**H**), 1.28 (12H, s, 4 × C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4 (C), 139.5 (C), 128.8 (2 × CH), 124.4 (CH), 119.9 (2 × CH), 84.0 (2 × C), 50.6 (CH_2), 34.9 (CH_2), 24.8 (CH_3).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{16}H_{23}{}^{11}BNO_3]$+ [MH]+ calcd. 288.1771, found 288.1764.



342

(±)-1-(4-Methylphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-2-one (342)

The title compound was prepared according to **General Procedure 9** using boronic ester **320** (3.95 g, 11.9 mmol) and AcOH (25 ml). The reaction gave *lactam* **342** (3.37 g, 94%) as an off-white solid.

m.p. = 120-121 °C (CH_2Cl_2).

IR 2977, 1690 (C=O), 1514, 1389, 1143, 812 cm^{-1}.

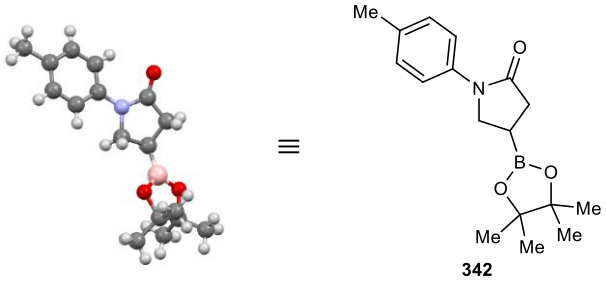
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, d, *J* = 8.4 Hz, Ar**H**), 7.16 (1H, d, *J* = 8.4 Hz, Ar**H**), 3.89 (1H, dd, *J* = 10.5, 8.3 Hz, NC**H**$_A$H$_B$), 3.86 (1H, dd, *J* = 10.5, 8.3 Hz, NCH$_A$**H**$_B$), 2.68 (1H, dd, *J* = 17.0, 10.0 Hz, C**H**$_A$H$_B$CO), 2.59 (1H, dd, *J* = 17.0, 10.7 Hz, CH$_A$**H**$_B$CO), 2.32 (3H, s, ArC**H$_3$**), 1.94 (1H, ddt, *J* = 10.7, 10.0, 8.3 Hz, C**H**), 1.28 (12H, s, 4 × BOCC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2 (C), 137.0 (C), 134.0 (C), 129.3 (2 × CH), 120.0 (2 × CH), 84.0 (2 × C), 50.7 (CH_2), 34.8 (CH_2), 24.8 (4 × CH_3), 20.8 (CH_3).

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

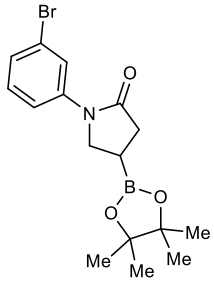
HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{25}{}^{11}BNO_3]^+$ [MH]$^+$ calcd. 302.1922, found 302.1925.

Crystals suitable for X-ray diffraction were obtained through recrystallisation of **342** in *n*-hexane.



342

Crystal Data for $C_{17}H_{24}BNO_3$ (M =301.18 g/mol): monoclinic, space group P21/c (no. 14), a = 11.5464(8) Å, b = 19.6806(13) Å, c = 14.7923(11) Å, β = 94.261(4)°, V = 3352.1(4) Å3, Z = 8, T = 100.0 K, μ(CuKα) = 0.637 mm-1, Dcalc = 1.194 g/cm3, 5846 reflections measured (7.49° ≤ 2Θ ≤ 134.156°), 5846 unique (Rint = ?, Rsigma = 0.1048) which were used in all calculations. The final R1 was 0.2013 (I > 2σ(I)) and wR2 was 0.4099 (all data).



343

(±)-1-(3-Bromophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-2-one (343)

The title compound was prepared according to **General Procedure 9** using boronic ester **321** (199 mg, 0.500 mmol). The reaction gave *lactam* **343** (136 mg, 74%) as an off-white solid.

m.p. = 95-97 °C (CH_2Cl_2).

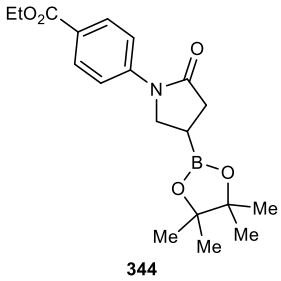
IR 2980, 1692 (C=O), 1327, 1140, 771 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.76 (1H, m, Ar**H**), 7.67-7.62 (1H, m, Ar**H**), 7.25-7.18 (2H, m, Ar**H**), 3.87 (2H, d, *J* = 9.3, NC**H$_2$**), 2.69 (1H, dd, *J* = 17.2, 10.9 Hz, C**H**$_A$H$_B$CO), 2.59 (1H, dd, *J* = 17.2, 9.9 Hz, CH$_A$**H**$_B$CO), 1.95 (1H, ddt, *J* = 10.9, 9.9, 9.3 Hz, C**H**), 1.28 (12H, s, 4 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5 (C), 140.8 (C), 130.0 (CH), 127.2 (CH), 122.5 (C), 122.4 (CH), 118.2 (CH), 84.1 (2 × C), 50.4 (CH_2), 34.8 (CH_2), 24.8 (2 × CH_3), 24.7 (2 × CH_3).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{16}H_{22}{}^{11}BNO_3{}^{79}Br]^+$ $[MH]^+$ calcd. 366.0871, found 366.0874.



344

(±)-Ethyl 4-[2-oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]benzoate (344)

The title compound was prepared according to **General Procedure 9** using **324** (1.96 g, 5.01 mmol) and AcOH (10 ml), the reaction time was extended to 24 h for this substrate. The reaction gave *lactam* **344** (1.61 g, 89%) as an off-white solid.

m.p. = 128-133 °C (CH_2Cl_2).

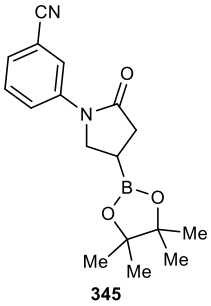
IR 1979, 1708 (C=O), 1691 (C=O), 1267, 1095, 773 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.73 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.36 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 3.94 (1H, dd, *J* = 10.3, 8.8 Hz, NC**H**$_A$H$_B$), 3.91 (1H, dd, *J* = 10.3, 8.8 Hz, NCH$_A$**H**$_B$), 2.72 (1H, dd, *J* = 17.3, 11.0 Hz, C**H**$_A$H$_B$CO), 2.62 (1H, dd, *J* = 17.3, 9.9 Hz, CH$_A$**H**$_B$CO), 1.97 (1H, ddt, *J* = 11.0, 9.9, 8.8 Hz, C**H**), 1.39 (2H, t, *J* = 7.1 Hz, OCH$_2$C**H$_3$**), 1.28 (12H, s, 4 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (C), 166.2 (C), 143.4 (C), 130.4 (2 × CH), 125.8 (C), 118.6 (2 × CH), 84.1 (2 × C), 60.8 (CH_2), 50.3 (CH_2), 35.0 (CH_2), 24.8 (2 × CH_3), 24.8 (2 × CH_3), 14.3 (CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.1 (br s).

HRMS (Q-TOF) Exact mass calcd for $[C_{19}H_{27}{}^{11}BNO_5]^+$ $[MH]^+$ calcd. 360.1982, found 360.1966.



345

(±)-3-[2-Oxo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-1-yl]benzonitrile (345)

The title compound was prepared according to **General Procedure 9** using boronic ester **325** (172 mg, 0.499 mmol), the reaction time was extended to 5 h for this substrate. The reaction gave *lactam* **345** (112 mg, 72%) as an off-white solid.

m.p. = 137-143 °C (CH_2Cl_2).

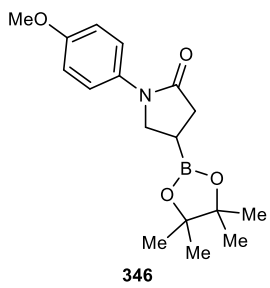
IR 1980, 2230, (C≡N), 1692 (C=O), 1391, 1332, 1140, 790 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.76 (1H, m, Ar**H**), 7.67-7.62 (1H, m, Ar**H**), 7.25-7.18 (2H, m, Ar**H**), 3.87 (2H, d, *J* = 9.3, NC**H$_2$**), 2.69 (1H, dd, *J* = 17.2, 10.9 Hz, C**H**$_A$H$_B$CO), 2.59 (1H, dd, *J* = 17.2, 9.9 Hz, CH$_A$**H**$_B$CO), 1.95 (1H, ddt, *J* = 10.9, 9.9, 9.3 Hz, C**H**), 1.28 (12H, s, 4 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (C), 140.2 (C), 129.6 (CH), 127.4 (CH), 123.5 (CH), 122.4 (CH), 118.6 (C), 112.8 (C), 84.2 (2 × C), 50.1 (CH_2), 34.7 (CH_2), 24.8 (2 × CH_3), 24.7 (2 × CH_3).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{22}{}^{11}BN_2NaO_3]$+ [MNa]+ calcd. 335.1543, found 335.1526.



346

(±)-1-(4-Methoxyphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-2-one (346)

The title compound was prepared according to **General Procedure 9** using boronic ester **326** (50.0 mg, 0.143 mmol) and AcOH (0.3 ml). The reaction gave *lactam* **346** (40.0 mg, 88%) as a dark red oil.

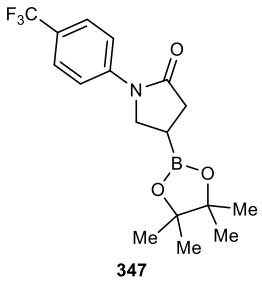
IR 2977, 1689 (C=O), 1511, 1245, 1126, 828 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 9.1 Hz, Ar**H**), 6.88 (2H, d, *J* = 9.1 Hz, Ar**H**), 3.87 (1H, dd, *J* = 11.0, 7.7 Hz, NC**H**$_A$H$_B$), 3.84 (1H, dd, *J* = 11.0, 7.7 Hz, NCH$_A$**H**$_B$), 3.79 (3H, s, OC**H**$_3$), 2.67 (1H, dd, *J* = 17.0, 10.0 Hz, C**H**$_A$H$_B$CO), 2.57 (1 H, dd, *J* = 17.0, 10.6 Hz, CH$_A$**H**$_B$CO), 1.94 (1H, ddt, *J* = 10.6, 10.0, 7.7 Hz, C**H**), 1.27 (12H, s, 4 × BOCC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (C), 156.5 (C), 132.7 (C), 121.8 (2 × CH), 114.0 (2 × CH), 83.9 (2 × C), 55.4 (CH_3), 50.9 (CH_2), 34.6 (CH_2), 24.7 (4 × CH_3).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{25}{}^{11}BNO_4]^+$ [MH]$^+$ calcd. 318.1871, found 318.1966.



347

(±)-4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-one (347)

The title compound was prepared according to **General Procedure 9** using boronic ester **327** (194 mg, 0.501 mmol), the reaction time was extended to 9 h for this substrate. The reaction gave *lactam* **347** (130 mg, 74%) as an off-white solid.

m.p. = 108-112 °C (CH_2Cl_2).

IR 2983, 1689 (C=O), 1324, 1293, 1112, 884 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (1H, d, *J* = 8.7 Hz, Ar**H**), 7.60 (1H, d, *J* = 8.7 Hz, Ar**H**), 3.92 (2H, d, *J* = 9.3 Hz, NC**H**$_2$), 2.72 (1H, dd, *J* = 17.3, 9.9 Hz, C**H**$_A$H$_B$CO), 2.62 (1H, dd, *J* = 17.3, 10.9 Hz, CH$_A$**H**$_B$CO), 1.97 (1H, ddt, *J* = 10.9, 9.9, 9.3 Hz, C**H**), 1.28 (12H, s, 4 × C**H**$_3$).

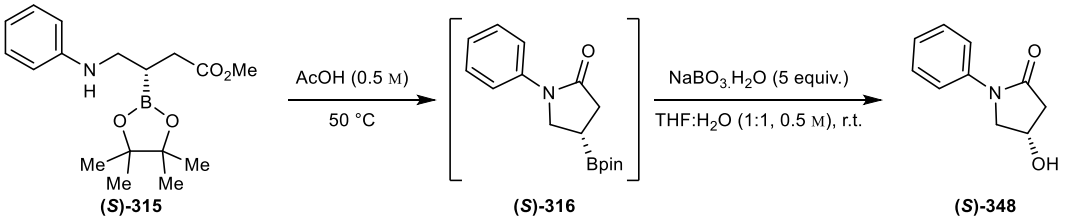
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (C), 142.4 (C), 125.9 (q, *J* = 3.7 Hz, 2 × CH), 125.8 (q, *J* = 32.6 Hz, C), 124.1 (q, *J* = 271.3 Hz, C), 119.1 (2 × CH), 84.1 (2 × C), 50.3 (CH_2), 34.9 (CH_2), 24.8 (2 × CH_3), 24.8 (2 × CH_3).

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

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.1 (s).

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{22}{}^{11}BF_3NO_3]^+$ [MH]$^+$ calcd. 356.1639, found 356.1657.

(*S*)-4-Hydroxy-1-phenylpyrrolidin-2-one ((*S*)-348)



(*S*)-315 (*S*)-316 (*S*)-348

Using a modification of **General Procedure 9**, boronic ester (***S*)-315** (60.0 mg, 0.188 mmol) was stirred in AcOH (0.50 ml) at 50 °C for 4 h. The mixture was cooled to RT, quenched with saturated aqueous Na_2CO_3 (5 ml), and extracted with CH_2Cl_2 (3 × 5 ml). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in THF (0.90 ml) and a solution of $NaBO_3.H_2O$ (90.0 mg, 0.902 mmol) in H_2O (0.9 ml) added, and the mixture was stirred for 1.5 h. The mixture was quenched with saturated aqueous NH_4Cl (10 ml) and extracted with AcOEt (3 × 10 ml). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether:AcOEt 7:3→0:1) to give *alcohol* (***S*)-348** (18.1 mg, 54%) as a pale brown solid.

$[\alpha]_D^{23}$ +153.2 (c 0.11, $CHCl_3$)

m.p. = 104-109 °C ($CHCl_3$).

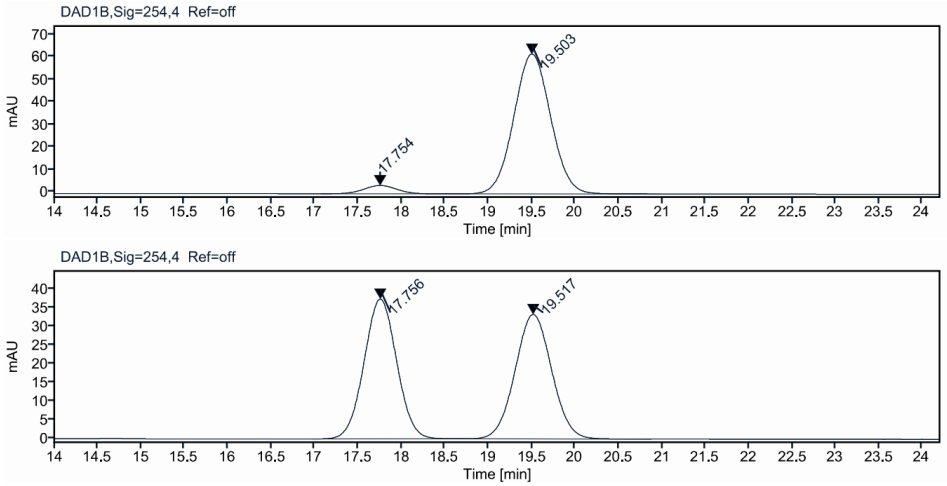
IR 3354 (OH), 2921, 1669 (C=O), 1394, 1221, 758, 655 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 7.7 Hz, Ar**H**), 7.36 (2H, dd, *J* = 7.7 Hz, Ar**H**), 7.15 (1H, t, *J* = 7.7 Hz, Ar**H**), 4.60 (1H, dddd, *J* = 6.5, 5.5, 2.5, 1.9 Hz, C**H**OH), 4.08 (1H, dd, *J* = 10.7, 5.5 Hz, NC**H$_A$**H$_B$), 3.77 (1 H, dd, *J* = 10.7, 1.9 Hz, NCH$_A$**H$_B$**), 2.90 (1H, dd, *J* = 17.5, 6.5 Hz, **H$_A$**H$_B$CO), 2.60 (1H, dd, *J* = 17.5, 2.5 Hz, H$_A$**H$_B$**CO), 2.45 (1H, br s, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0 (C), 138.8 (C), 128.9 (2 × CH), 124.9 (CH), 120.2 (2 × CH), 64.0 (CH), 57.5 (CH_2), 42.6 (CH_2).

HRMS (Q-TOF) Exact mass calcd for $[C_{10}H_{12}NO_2]^+$ $[MH]^+$ calcd. 178.0863, found 178.0869.

e.e. = 90%, measured through chiral HPLC analysis. YMC Chiral Art cellulose-SC S-5 μm, IPA:hexane = 20:80, 1.0 mL/min, 22°C, λ = 254 nm, (*R*)-isomer t_r = 17.8 min and (*S*)-isomer t_r = 19.5 min.



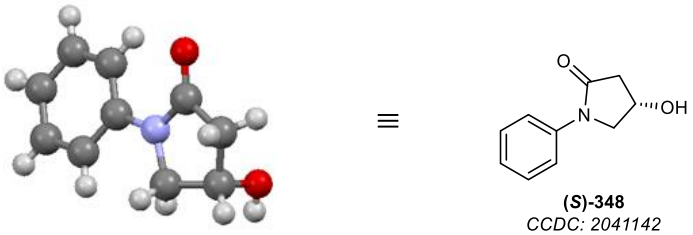
Signal: DAD1B,Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
17.754	BM m	0.3996	95.7583	3.6560	4.9804	
19.503	MM m	0.4583	1826.9517	61.9141	95.0196	
		Sum	1922.7101			

Signal: DAD1B,Sig=254,4 Ref=off

RT [min]	Type	Width [min]	Area	Height	Area%	Name
17.756	BM m	0.4074	986.3136	37.6726	50.0220	
19.517	MB m	0.4548	985.4443	33.5361	49.9780	
		Sum	1971.7580			

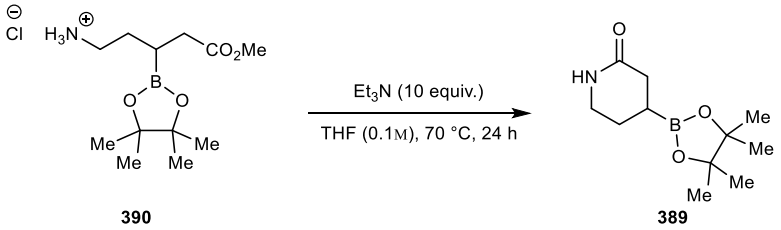
Crystals suitable for X-ray diffraction were obtained through recrystallisation of (***S***)-**348** in *n*-hexane.



(*S*)-348
CCDC: 2041142

Crystal Data for $C_{10}H_{11}NO_2$ (*M* =177.20 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), *a* = 6.1843(2) Å, *b* = 7.6836(3) Å, *c* = 18.4085(7) Å, *V* = 874.73(6) Å^3, *Z* = 4, *T* = 99.96 K, μ(CuKα) = 0.772 mm^{-1}, *Dcalc* = 1.346 g/cm^3, 28908 reflections measured (9.608° ≤ 2Θ ≤ 133.05°), 1537 unique (R_{int} = 0.0380, R_{sigma} = 0.0119) which were used in all calculations. The final R_1 was 0.0272 (I > 2σ(I)) and wR_2 was 0.0687 (all data).

(±)-4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)piperidin-2-one (389)



390 389

Ammonium hydrochloride salt **390** (73.0 mg, 0.249 mmol) and Et_3N (0.35 ml, 2.50 mmol) was dissolved in THF (2.5 ml) and stirred at 70 °C for 24 h. The mixture was concentrated *in vacuo*, triturated with Et_2O (5 ml), filtered and concentrated *in vacuo* to give *lactam* **389** (55.9 mg, 100%) as a white solid.

m.p. = 127 -129 °C (*n*-hexane).

IR 3221 (NH), 2978 (CH), 1662 (C=O), 1324, 1144, 819 cm^{-1}.

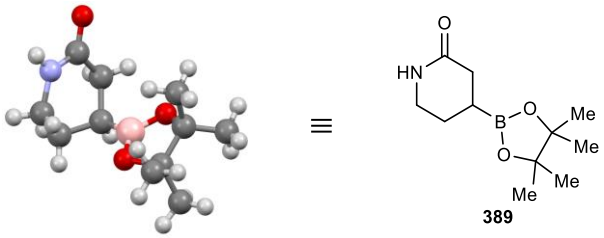
^{1}H NMR (400 MHz, $CDCl_3$) 6.10 (1H, br s, N**H**), 3.42 - 3.23 (2H, m, NC**H_2**), 2.44 (1H, dd, *J* = 18.0, 6.0 Hz, C**H_A**H_BCO), 2.34 (1H, dd, *J* = 18.0, 10.2 Hz, CH_A**H_B**CO), 1.95 - 1.84 (1H, m, NCH_2C**H_A**H_B), 1.77 - 1.62 (1H, m, NCH_2CH_A**H_B**), 1.49 - 1.38 (1H, m, C**H**), 1.24 (12H, s, 4 × C**H_3**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (C), 83.5 (2 × C), 42.8 (CH_2), 32.5 (CH_2), 24.7 (4 × CH_3), 23.7 (CH_2), 16.6 (CH).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.1 (br s).

HRMS (Q-TOF) Exact mass calcd for $[C_{11}H_{21}{}^{11}BNO_3]^+$ $[MH]^+$ calcd. 226.1609, found 226.1619.

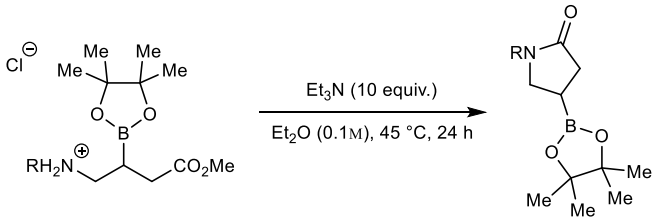
Crystals suitable for X-ray diffraction were obtained through recrystallisation of **389** in *n*-hexane.



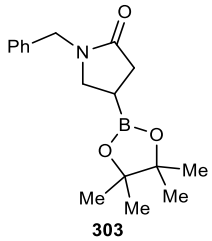
389

Crystal Data for $C_{11}H_{20}BNO_3$ (M =225.09 g/mol): monoclinic, space group C2/c (no. 15), a = 26.1851(11) Å, b = 6.4495(3) Å, c = 17.8522(7) Å, β = 125.813(2)°, V = 2444.87(19) Å3, Z = 8, T = 99.99 K, μ(CuKα) = 0.696 mm-1, Dcalc = 1.223 g/cm3, 15189 reflections measured (8.328° ≤ 2Θ ≤ 133.53°), 2155 unique (Rint = 0.0684, Rsigma = 0.0415) which were used in all calculations. The final R1 was 0.0471 (I > 2σ(I)) and wR2 was 0.1251 (all data).

General Procedure 10: Cyclisation of ammonium hydrochloride enoates



The corresponding ammonium hydrochloride salt (1 equiv.) and Et_3N (10 equiv.) were dissolved in Et_2O (0.1M) and stirred at 45 °C for 24 h. The mixture was concentrated *in vacuo*, triturated with Et_2O, filtered, and concentrated *in vacuo* to give the corresponding lactam.


303

(±)-1-Benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-2-one (303)

The title compound was prepared according to **General Procedure 10** using ammonium hydrochloride salt **431** (96.0 mg, 0.259 mmol), Et_3N (0.35 ml, 2.50 mmol) and Et_2O (2.5 ml). The reaction gave *lactam* **303** (75.3 mg, 97%) as a colourless oil.

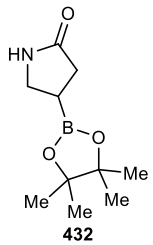
IR 2984 (CH), 1678 (C=O), 1142, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.20 (5H, m, Ar**H**), 4.52 (1H, d, *J* = 14.7 Hz, ArC$\mathbf{H_A}H_B$), 4.35 (1H, d, *J* = 14.7 Hz, ArC$H_A\mathbf{H_B}$), 3.33 (1H, dd, *J* = 9.5, 9.4 Hz, NC$\mathbf{H_A}H_B$CH), 3.27 (1H, dd, *J* = 9.4, 9.1 Hz, NC$H_A\mathbf{H_B}$CH), 2.55 (1H, dd, *J* = 16.9, 9.9 Hz, C$\mathbf{H_A}H_B$CO), 2.44 (1H, dd, *J* = 16.9, 9.7 Hz, C$H_A\mathbf{H_B}$CO), 1.77 (1H, dddd, *J* = 9.9, 9.7, 9.5, 9.1 Hz, C**H**), 1.21 (12H, s, 4 × C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1 (C), 136.6 (C), 128.6 (2 × CH), 128.1 (2 × CH), 127.4 (CH), 83.8 (2 × C), 48.4 (CH_2), 46.7 (CH_2), 33.1 (CH_2), 24.7 (4 × CH_3).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{24}{}^{11}BNO_3Na]^+$ [MNa]$^+$ calcd. 324.1741, found 324.1742.


432

(±)-4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-2-one (432)

The title compound was prepared according to **General Procedure 10** using ammonium hydrochloride salt **430** (140 mg, 0.499 mmol), Et_3N (0.70 ml, 5.00 mmol) and Et_2O (5 ml). The reaction gave *lactam* **432** (88.9 mg, 84%) as a colourless oil.

IR 3246 (NH), 2976 (CH), 1682 (C=O), 1373, 11441, 856, 731 cm^{-1}.

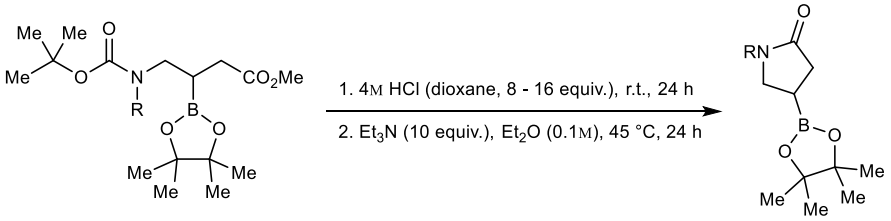
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (1H, br s, N**H**), 3.47 (1H, dd, *J* = 9.4, 9.2 Hz, NC$\mathbf{H_A}H_B$), 3.40 (1H, t, *J* = 9.2 Hz, NC$H_A\mathbf{H_B}$), 2.39 (1H, dd, *J* = 17.0, 9.9 Hz, C$\mathbf{H_A}H_B$CO), 2.31 (1H, dd, *J* = 17.0, 9.9 Hz, C$H_A\mathbf{H_B}$CO), 1.98 (1H, tdd, *J* = 9.9, 9.4, 9.2 Hz, C**H**), 1.26 (12H, s, 4 × C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.1 (C), 83.8 (2 × C), 43.8 (CH_2), 31.9 (CH_2), 24.7 (4 × CH_3).

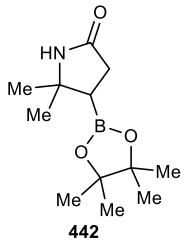
^{11}B NMR (128 MHz, $CDCl_3$) δ 33.8 (br s).

HRMS (Q-TOF) Exact mass calcd for $[C_{10}H_{19}{}^{11}BNO_3]^+$ $[MH]^+$ calcd. 212.1453, found 212.1447.

General Procedure 11: Cyclisation of *N*-Boc amino enoates



The corresponding amino enoate was dissolved in 4 M HCl (dioxane, 8 - 16 equiv.) and stirred at r.t. for 24 h and then concentrated *in vacuo*. The crude residue and Et_3N (10 equiv.) were dissolved in Et_2O (0.1 M) and stirred at 45 °C for 24 h. The mixture was concentrated *in vacuo*, triturated with Et_2O, filtered and concentrated *in vacuo* to give the corresponding lactam.


442

(±)-5,5-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-2-one (442)

The title compound was prepared according to **General Procedure 11** using *N*-Boc amino enoates **424** (100 mg, 0.269 mmol), 4 M HCl (dioxane, 1.08 ml), Et_3N (0.38 ml, 2.70 mmol) and Et_2O (2.7 ml). The reaction gave *lactam* **442** (64.6 mg, 100%) as a white solid.

m.p. = 157 - 160 °C (CH_2Cl_2).

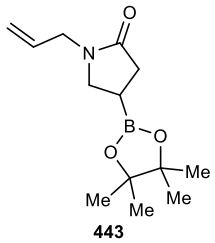
IR 3279 (NH), 2977 (CH), 1659 (C=O), 1317, 1138, 849, 751 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (1H, s, N**H**), 2.55 (1H, dd, *J* = 17.2, 12.1 Hz, C**H**$_A$H$_B$), 2.34 (1H, dd, *J* = 17.2, 9.1 Hz, CH$_A$**H$_B$**), 1.71 (1H, dd, *J* = 12.1, 9.1 Hz, C**H**), 1.37 (3H, s, NCC**H$_3$**), 1.32 - 1.25 (12H, m, 4 × OCC**H**$_3$), 1.22 (3H, s, NCC**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6 (C), 83.7 (2 × C), 58.3 (C), 32.8 (CH_2), 29.9 (CH_3), 26.6 (CH_3), 25.0 (2 × CH_3), 24.8 (2 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 33.0 (b s).

HRMS (Q-TOF) Exact mass calcd for $[C_{12}H_{23}{}^{11}BNO_3]^+$ $[MH]^+$ calcd. 240.1766, found 240.1765.


443

(±)-1-(Prop-2-en-1-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidin-2-one (443)

The title compound was prepared according to **General Procedure 11** using *N*-Boc amino enoates **439** (100 mg, 0.260 mmol), 4 M HCl (dioxane, 0.5 ml), Et_3N (0.36 ml, 2.60 mmol) and Et_2O (2.6 ml). The reaction gave *lactam* **443** (44.0 mg, 67%) as a colourless oil.

IR 2878 (CH), 1669 (C=O), 1381, 1141, 860 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (1H, dddd, *J* = 16.4, 10.2, 6.1, 5.9 Hz, $NCH_AH_BC\mathbf{H}=CH_2$), 5.20 - 5.14 (1H, m, $CH=C\mathbf{H_A}H_B$), 5.13 - 5.11 (1H, m, $CH=CH_A\mathbf{H_B}$), 3.89 (1H, dd, *J* = 15.2, 5.9 Hz, $NC\mathbf{H_A}H_BCH$), 3.77 (1H, dd, *J* = 15.2, 6.1 Hz, $NCH_A\mathbf{H_B}CH_2$), 3.39 (1H, dd, *J* = 9.6, 9.4 Hz, $NC\mathbf{H_A}H_BCHB$), 3.30 (1H, dd, *J* = 9.5, 9.4 Hz, $NCH_A\mathbf{H_B}CHB$), 2.47 (1H, dd, *J* = 16.9, 10.0 Hz, $COC\mathbf{H_A}H_B$), 2.36 (1H, dd, *J* = 16.9, 9.9 Hz, $COCH_A\mathbf{H_B}$), 1.77 (1H, dddd, *J* = 10.0, 9.9, 9.6, 9.5 Hz, BC**H**), 1.21 (12H, s, 4 × C$\mathbf{H}_3$).

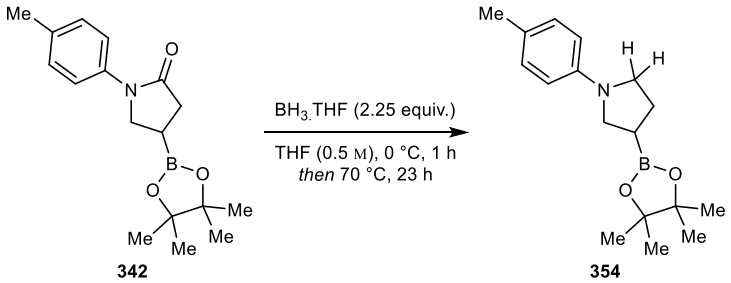
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (C), 132.4 (CH), 117.6 (CH_2), 83.8 (2 × C), 48.5 (CH_2), 45.2 (CH_2), 33.1 (CH_2), 24.6 (4 × CH_3), 14.0 (CH).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{13}H_{22}{}^{11}BNO_3Na]^+$ $[MNa]^+$ calcd. 274.1585, found 274.1575.

4.2.7 Transformations of Boronic Esters

(±)-1-(4-Methylphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrrolidine (354)



Based on the procedure by Buchwald and co-workers,[242] 1M BH_3.THF (2.25 ml, 2.25 mmol) was added dropwise to a solution of boronic ester **342** (301 mg, 0.999 mmol) in THF (2 ml) and stirred at 0 °C for 1 h after which the mixture was heated to 70 °C and stirred for 23 h. The mixture was diluted with H_2O (10 ml) and extracted with AcOEt (3 × 10 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane:AcOEt 19:1) to give *lactam* **354** (233 mg, 81%) as an off-white solid.

m.p. = 50 - 51 °C (CH_2Cl_2).

IR 2830 (CH), 1522, 1364, 1140, 800, 510 cm^{-1}.

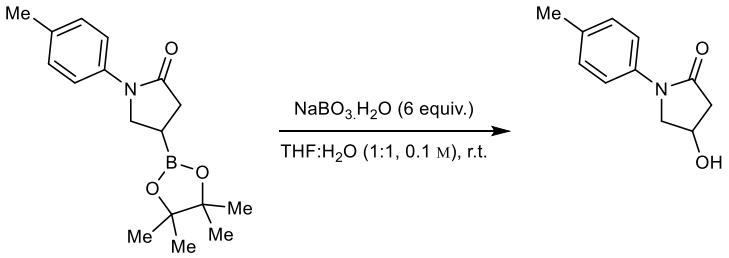
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.52 (2H, d, *J* = 8.5 Hz, Ar**H**), 3.43 (1H, dd, *J* = 8.8, 8.8 Hz, $NC\mathbf{H_A}H_BCH$), 3.35 - 3.19 (3H, m, $NCH_A\mathbf{H_B}CH$, $NC\mathbf{H_2}CH_2$), 2.24 (3H, s, $ArC\mathbf{H_3}$), 2.21 - 2.09 (1H, m, $NCH_2C\mathbf{H_A}H_B$), 2.02 - 1.87 (1H, m, $NCH_2CH_A\mathbf{H_B}$), 1.82 - 1.68 (1H, m, C**H**), 1.26 (12H, s, 4 × C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 129.6 (2 × CH), 120.7 (C), 111.8 (2 × CH), 110.0 (C), 83.4 (2 × C), 49.9 (CH_2), 48.6 (CH_2), 27.8 (CH_2), 24.8 (2 × CH_3), 24.74 (2 × CH_3), 24.56 (CH), 20.30 (CH_3).

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

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{27}{}^{11}BNO_2]^+$ [MH]$^+$ calcd. 288.2129, found 288.2132.

(±)-4-Hydroxy-1-(4-methylphenyl)pyrrolidin-2-one (355)



342 355

Based on a procedure by Marcus and Sarpong,[130] boronic ester **342** (301 mg, 0.999 mmol) was dissolved in THF (5.00 ml), and a solution of $NaBO_3.H_2O$ (599 mg, 6.00 mmol) in H_2O (5.0 ml) added. The mixture was stirred for 2 h, saturated aqueous NH_4Cl (30 ml) was added, and the mixture was extracted with AcOEt (3 × 30 ml). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give *alcohol* **355** (176 mg, 92%) as a white solid.

m.p. = 141-142 °C ($CHCl_3$).

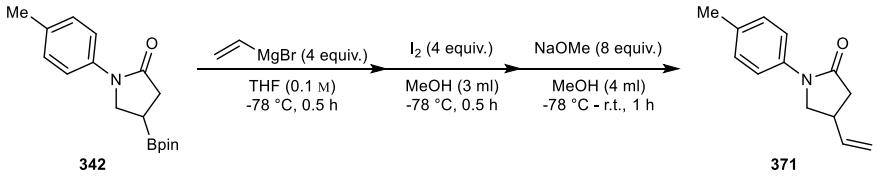
IR 3299 (OH), 2968, 1658 (C=O), 1397, 1298, 821, 510 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.17 (2H, d, *J* = 8.4 Hz, Ar**H**), 4.61 (1H, dddd, *J* = 6.5, 5.5, 2.4, 1.8 Hz, C**H**OH), 4.07 (1H, dd, *J* = 10.7, 5.5 Hz, NC**H$_A$**H$_B$), 3.75 (1H, dd, *J* = 10.7, 1.8 Hz, NCH$_A$**H$_B$**), 2.90 (1H, dd, *J* = 17.5, 6.5 Hz, **H$_A$**H$_B$CO), 2.59 (1H, dd, *J* = 17.5, 2.4 Hz, H$_A$**H$_B$**CO), 2.33 (3H, s, C**H$_3$**), 2.12 (1H, br s, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (C), 136.4 (C), 134.6 (C), 129.4 (2 × CH), 120.3 (2 × CH), 64.2 (CH), 57.6 (CH_2), 42.6 (CH_2), 20.9 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{11}H_{14}NO_2]$+ [MH]+ calcd. 192.1019, found 192.1020.

(±)-4-Ethenyl-1-(4-methylphenyl)pyrrolidin-2-one (371)



Based on the procedure by Aggarwal and co-workers,[153] a Schlenk flask was charged with lactam **342** (75.0 mg, 0.249 mmol), backfilled with argon, dissolved in anhydrous THF (2.5 ml) and cooled to -78 °C. Vinyl magnesium bromide (0.7 M, 1.43 ml, 1.00 mmol) was added dropwise, and the mixture was stirred for 0.5 h. A solution of iodine (254 mg, 1.00 mmol) in anhydrous MeOH (3 ml) was added dropwise, and the mixture was stirred for 0.5 h. A solution of NaOMe (108 mg, 2.00 mmol) in anhydrous MeOH (4 ml) was added dropwise, and the mixture was stirred for 1 h. The mixture was warmed to RT, quenched with saturated aqueous $Na_2S_2O_3$ (15 ml), and extracted with AcOEt (3 × 20 ml). The combined organic phases were washed with brine (60 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether:AcOEt 7:3) to give the *lactam* **371** (37.0 mg, 74%) as an off-white solid.

m.p. = 71 - 81 °C (CH_2Cl_2).

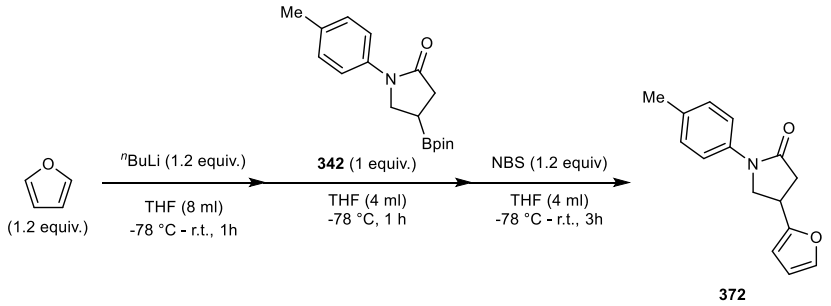
IR 2921, 1687 (C=O), 1332, 816, 506 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.17 (1H, d, *J* = 8.5 Hz, Ar**H**), 5.89 (ddd, *J* = 17.3, 10.2, 7.5 Hz, C**H**=CH_2), 5.19 (1H, d, *J* = 17.3 Hz, CH=C**H$_A$**H$_B$), 5.14 (1H, d, *J* = 10.2 Hz, CH=CH$_A$**H$_B$**), 3.93 (1H, dd, *J* = 9.6, 8.0 Hz, NC**H$_A$**H$_B$), 3.63 (1H, dd, *J* = 9.6, 7.4 Hz, NCH$_A$**H$_B$**), 3.13 (1H, ddddd, *J* = 8.6, 8.5, 8.0, 7.5, 7.4, C**H**), 2.76 (1H, dd, *J* = 16.9, 8.5 Hz, C**H$_A$**H$_B$CO), 2.49 (1h, dd, *J* = 16.9, 8.6 Hz, CH$_A$**H$_B$**CO), 2.33 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9 (C), 138.1 (CH), 136.6 (C), 134.3 (C), 129.4 (2 × CH), 120.0 (2 × CH), 116.2 (CH), 53.8 (CH_2), 38.7 (CH_2), 35.9 (CH), 20.9 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{13}H_{16}NO]^+$ $[M+H]^+$ calcd. 202.1226, found 202.1232.

(±)-4-(Furan-2-yl)-1-(4-methylphenyl)pyrrolidin-2-one (372)



Based on the procedure by Aggarwal and co-workers,[154] a Schlenk flask was charged with furan (0.09 ml, 1.20 mmol), backfilled with argon, and anhydrous THF (8 ml) was added. The mixture was stirred at -78 °C, and ^{n}BuLi (2.5 M, 0.48 ml, 1.20 mmol) was added dropwise. The reaction was warmed to r.t. over 1 h. The mixture was cooled to -78 °C, a solution of lactam **342** (301 mg, 0.999 mmol) in anhydrous THF (4 ml) was added dropwise, and the mixture was stirred for 1 h. A solution of NBS (214 mg, 1.20 mmol) in anhydrous THF (4 ml) was added dropwise, and the mixture stirred for 3 h. The mixture allowed to warm to room temperature, quenched with saturated aqueous. $Na_2S_2O_3$ (30 ml) and extracted with AcOEt (3 × 30 ml). The combined organic phases were washed with brine (100 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether:AcOEt 9:1) to give the *lactam* **372** (114 mg, 47%) as a pale brown solid.

m.p. = 59-62 °C ($CHCl_3$).

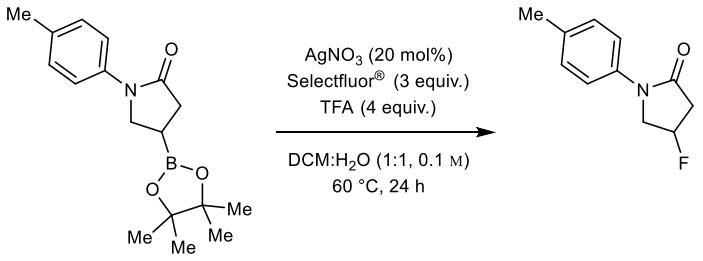
IR 2921, 1691 (C=O), 1351, 814, 738 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.37 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.17 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.33 (1H, dd, *J* = 3.2, 1.5 Hz, Ar**H**), 6.17 (1H, d, *J* = 3.2 Hz, Ar**H**), 4.10 (1H, dd, *J* = 9.5, 8.1 Hz, NC**H$_A$**CH$_B$), 3.95 (1H, dd, *J* = 9.5, 7.0 Hz, NCH$_A$C**H$_B$**), 3.76 (1H, dddd, *J* = 8.8, 8.1, 8.4, 7.0 Hz, C**H**), 2.94 (1H, dd, *J* = 16.9, 8.8 Hz, C**H$_A$**H$_B$CO), 2.84 (1H, dd, *J* = 16.9, 8.4 Hz, CH$_A$**H$_B$**CO).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (C), 154.3 (C), 142.0 (CH), 136.5 (C), 134.5 (C), 129.4 (2 × CH), 120.2 (2 × CH), 110.3 (CH), 105.5 (CH), 53.2 (CH_2), 37.7 (CH_2), 31.0 (CH), 20.9 (CH_3).

HRMS (Q-TOF) Exact mass calcd for [$C_{15}H_{16}NO_2$] [M+H]+ calcd. 242.1176, found 242.1183.

(±)-4-Fluoro-1-(4-methylphenyl)pyrrolidin-2-one (377)



342 **377**

Based on the procedure by Li and co-workers,[157] a Schlenk flask with a screw top lid was charged with lactam **342** (151 mg, 0.501 mmol), $AgNO_3$ (17.0 mg, 100 μmol) and Selectfluor® (518 mg, 1.46 mmol) and backfilled with N_2. CH_2Cl_2 (2.5 ml), H_2O (2.5 ml) and TFA (0.15 ml, 2.00 mmol) were added to the mixture sequentially, and the flask was sealed. The mixture was stirred at 60 °C for 24 h. The mixture was cooled to RT, diluted with H_2O (5 ml), and extracted with CH_2Cl_2 (3 × 30 ml). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by recrystallisation from *n*-hexane to give the *lactam* **337** (51.0 mg, 53%) as a white solid.

m.p. = 91-94 °C ($CHCl_3$).

IR 1927, 1705 (C=O), 1513, 1394, 820, 504 cm^{-1}.

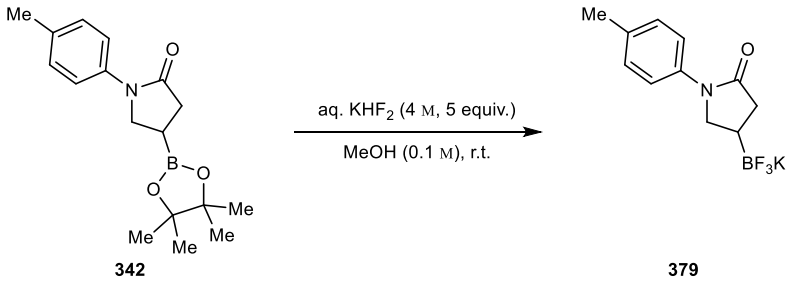
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.19 (2H, d, *J* = 8.5 Hz, Ar**H**), 5.35 (1H, ddd, *J* = 53.3, 5.5, 4.7 Hz, C**H**F), 4.14 (1H, ddd, *J* = 32.2, 12.1, 4.7 Hz, NC**H$_A$**H$_B$), 4.01 (1H, dd, *J* = 25.3, 12.1 Hz, NCH$_A$**H$_B$**), 2.93 (1H, ddd, *J* = 34.6, 18.3, 5.5 Hz, C**H$_A$**H$_B$CO), 2.85 (1H, dd, *J* = 26.4, 18.3 Hz, CH$_A$**H$_B$**CO), 2.33 (3H, s, C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (C), 136.0 (C), 134.9 (C), 129.5 (2 × CH), 120.2 (2 × CH), 85.4 (d, *J* = 178.7 Hz, CH), 55.6 (d, *J* = 25.4 Hz, CH_2), 40.1 (d, *J* = 23.8 Hz, CH_2), 20.9 (CH_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ −173.4 (s).

HRMS (Q-TOF) Exact mass calcd for $[C_{11}H_{13}FNO]^+$ $[M+H]^+$ calcd. 194.0976, found 194.0980.

(±)-Potassium trifluorido[1-(4-methylphenyl)-5-oxopyrrolidin-3-yl]borate (379)



342 **379**

Based on the procedure by Aggarwal and co-workers,[165] boronic ester **342** (1.51 g, 5.01 mmol) was dissolved in MeOH (50 ml), and solution of KHF_2 (1.96 g, 25.1 mmol) in H_2O (4 M, 6.25 ml) was added dropwise. The mixture stirred for 1 h, concentrated to dryness *in vacuo*, and re-dissolved in H_2O:MeOH (1:1, 10 ml). The mixture was concentrated dryness again, and this dissolution-evaporation cycle was repeated 5 times. The crude residue was triturated with hot acetone, and the combined organic phases concentrated *in vacuo* to give the *trifluoroborate salt* **379** (1.27 g, 90%) as a white solid.

m.p. = 141-143 °C (acetone).

IR 2948, 1642 (C=O), 1270, 1090, 951, 619 cm^{-1}.

^{1}H NMR (400 MHz, d_6-DMSO) δ 7.52 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.12 (2H, d, *J* = 8.5 Hz, Ar**H**), 3.56 (1H, dd, *J* = 18.5, 9.3 Hz, NC**H$_A$**H$_B$), 3.54 (1H, dd, *J* = 18.5, 9.3 Hz, NCH$_A$**H$_B$**), 2.25 (3H, s, C**H$_3$**), 2.19 (2H, d, *J* = 10.1 Hz, C**H$_2$**CO), 1.12-1.06 (1H, m, C**H**).

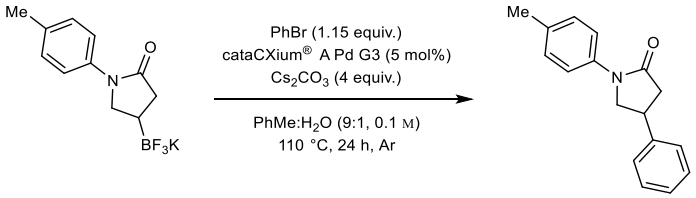
^{13}C NMR (101 MHz, d_6-DMSO) δ 176.4 (C), 138.1 (C), 131.9 (C), 128.9 (2 × CH), 118.8 (2 × CH), 52.2 (CH_2), 36.4 (CH_2), 20.4 (CH_3).

^{11}B NMR (128 MHz, d_6-DMSO) δ 4.2 (br s).

^{19}F NMR (377 MHz, d_6-DMSO) δ −144.3 (s).

HRMS (Q-TOF) Exact mass calcd for $[C_{11}H_{12}{}^{11}BF_3NO]^-$ $[M]^-$ calcd. 242.0970, found 242.0973.

(±)-1-(4-Methylphenyl)-4-phenylpyrrolidin-2-one (380)



379 380

Using an adaptation of the procedure by Harris *et al*,[92] a microwave vial was charged with lactam **379** (281 mg, 1.00 mmol), phenyl bromide (0.12 ml, 1.15 mmol), cataCXium® A Pd G3 (36.0 mg, 49.4 μmol), Cs_2CO_3 (1.30 g, 3.99 mmol) and sealed. Toluene (9 ml) and H_2O (1 ml) were added, and argon was bubbled through the mixture for 15 mins. The mixture was stirred at 110 °C for 24 h. After cooling to RT, the mixture was diluted with saturated aqueous NH_4Cl (10 ml) and extracted with AcOEt (3 × 20 ml). The combined organic phases were washed with brine (100 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography (petroleum ether:AcOEt 9:1) to give the *lactam* **380** (76.0 mg, 30%) as a white solid.

m.p. = 95-87 °C (CH_2Cl_2).

IR 2920 (CH), 1686 (C=O), 1354 (CN), 816, 697, 510 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.41-7.34 (2H, m, Ar**H**), 7.33-7.25 (3H, m, Ar**H**), 7.18 (2H, d, *J* = 8.4 Hz, Ar**H**), 4.18 (1H, dd, *J* = 9.4, 8.4 Hz, NC**H$_A$**H$_B$), 3.88 (1H, dd, *J* = 9.4, 7.5 Hz, NCH$_A$**H$_B$**), 3.70 (1H, dddd, *J* = 8.8, 8.7, 8.4, 7.5 Hz, C**H**), 3.02 (1H, dd, *J* = 16.9, 8.8 Hz, C**H$_A$**H$_B$CO), 2.79 (1H, dd, *J* = 16.9, 8.7 Hz, CH$_A$**H$_B$**CO), 2.34 (3H, s, C**H$_3$**).

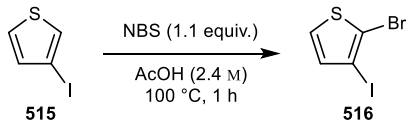
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C), 141.8 (C), 136.7 (C), 134.4 (C), 129.4 (2 × CH), 129.0 (2 × CH), 127.3 (CH), 126.8 (2 × CH), 120.1 (2 × CH), 55.8 (CH_2), 40.3 (CH_2), 37.2 (CH), 20.8 (CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{18}NO]^+$ $[M+H]^+$ calcd. 252.1383, found 252.1393.

4.3 Synthesis and Transformation of Borylated Fused-Ring Pyridines

4.3.1 Preparation of Bromoheteroaryl Aldehydes

2-Bromo-3-iodothiophene (516)

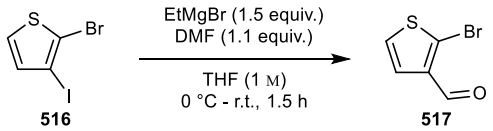


Based on the procedure by Nitti *et al.*,[243] 3-iodothiophene (1.00 g, 4.76 mmol) and NBS (932 mg, 5.23 mmol) were dissolved in acetic acid (2 ml) and the mixture stirred at 100 °C for 1 h. The mixture was then allowed to cool to room temperature and diluted with sat. aqueous $NaHCO_3$ (20 ml), and the aqueous layer extracted with AcOEt (3 × 20 ml). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (*n*-hexane) to give thiophene **516** (1.03 g, 75%) as a pink oil. The data were consistent with the literature.[243]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (1H, d, *J* = 5.7 Hz, Ar**H**), 6.95 (1H, d, *J* = 5.7 Hz, Ar**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2 (CH), 128.7 (CH), 116.7 (C), 85.8 (C).

2-Bromothiophene-3-carbaldehyde (517)



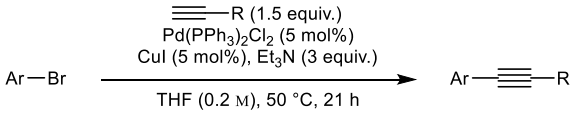
Based on the procedure by Christophersen *et al.*,[244] thiophene **516** (1.38 g, 4.77 mmol) was measure into a Schleck flask equipped with a stirrer bar, flushed with nitrogen, dissolved in anhydrous THF (4.8 ml), and cooled to 0 °C. EtMgBr (2.7 M, 2.65 ml, 7.16 mmol) was then added to the mixture and stirred for 30 mins. Anhydrous DMF (0.40 ml, 5.25 mmol) was added to the mixture and stirred for 1 h. The mixture was allowed to warm to room temperature, quenched with sat. NH_4Cl (aq., 10 ml), and the aqueous layer extracted with Et_2O (3 × 10 ml). The combined organic phases were washed with brine (10 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt) (99:1) to give aldehyde **517** (386 mg, 42%) as a pale brown oil. The data were consistent with the literature.[244]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (1H, s, C**H**O), 7.35 (1H, d, *J* = 5.7 Hz, Ar**H**), 7.28 (1H, d, *J* = 5.7 Hz, Ar**H**).

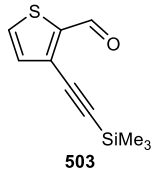
^{13}C NMR (101 MHz, $CDCl_3$) δ 184.6 (CH), 138.4 (C), 126.9 (CH), 126.2 (CH), 125.3 (C).

4.3.2 Sonogashira Coupling Bromothiophenes and Alkynes

General Procedure 12: Sonogashira coupling



Based on the procedure by Mora-Radó *et al.*[196], terminal alkyne (1.5 equiv.) and Et_3N (3 equiv.) were added to a solution of aryl bromide (1 equiv.), $Pd(PPh3)_2Cl_2$ (5 mol%) and CuI (5 mol%) in dry THF and stirred overnight at 50 °C. The mixture was cooled to room temperature, diluted with sat. NH_4Cl (aq., 50 ml) and the aqueous layer extracted with AcOEt. The combined organic phases were washed with 1 M HCl (aq.) and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel



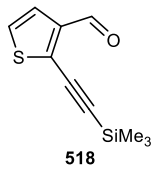
503

3-[2-(Trimethylsilyl)ethynyl]thiophene-2-carbaldehyde (503)

The title compound was prepared according to **General Procedure 12** using 3-bromothiophene-2-carboxaldehyde (1.50 g, 7.5 mmol), trimethylsilylacetylene (1.60 ml, 11.3 mmol), $Pd(PPh3)_2Cl_2$ (263 mg, 0.375 mmol), CuI (75.0 mg, 0.315 mmol), Et_3N (3.15 ml, 22.5 mmol) in anhydrous THF (37.5 ml) and stirred at 50 °C for 21 h. The crude residue was purified by flash column chromatography on silica gel (petroleum ether:AcOEt, 39:1) to give alkyne **503** (1.55 g, 99%) as pale brown oil. The data were consistent with the literature.[196]

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (1H, d, *J* = 1.2 Hz, C**H**O), 7.64 (1H, dd, *J* = 5.2, 1.2 Hz, Ar**H**), 7.17 (1H, d, *J* = 5.2 Hz, Ar**H**), 0.27 (9H, s, 3 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 183.1 (CH), 144.5 (C), 133.7 (CH), 131.7 (CH), 130.9 (C), 102.5 (C), 96.4 (C), -0.3 (3 × CH_3).



518

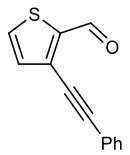
2-[2-(Trimethylsilyl)ethynyl]thiophene-3-carbaldehyde (518)

The title compound was prepared according to **General Procedure 12** using aryl bromide **517** (200 mg, 1.05 mmol), trimethylsilylacetylene (0.21 ml, 1.50 mmol), $Pd(PPh3)_2Cl_2$ (35.0 mg, 49.9 µmol), CuI (10.0 mg, 52.5 µmol), Et_3N (0.42 ml, 3.00 mmol) in anhydrous THF (5 ml) and stirred at 50 °C for 22 h. The crude residue was purified by flash column chromatography on silica gel (petroleum ether:AcOEt, 39:1) to give alkyne **518** (199 mg, 91%) as pale brown oil. The data were consistent with the literature.[245]

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (1H, s, C**H**O), 7.39 (1H, d, *J* = 5.3 Hz, Ar**H**), 7.21 (1H, d, *J* = 5.3 Hz, Ar**H**), 0.28 (9H, s, 3 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 184.8 (CH), 143.6 (C), 134.4 (CH), 127.0 (CH), 124.8 (C), 107.4 (C), 93.7 (C), 0.4 (3 × CH_3).

3-(2-Phenylethynyl)thiophene-2-carbaldehyde (520)



520

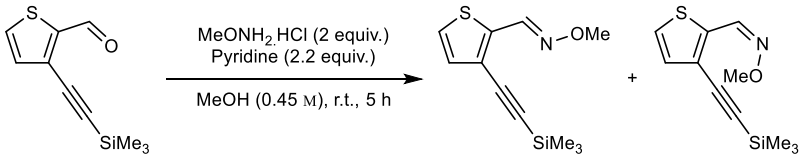
The title compound was prepared according to **General Procedure 12** using 3-bromothiophene-2-carboxaldehyde (1.00 g, 5.23 mmol), phenylacetylene (0.87 ml, 7.98 mmol), $Pd(PPh3)_2Cl_2$ (187 mg, 0.27 mmol), CuI (51 mg, 0.27 mmol), Et_3N (2.56 ml, 16.0 mmol) in anhydrous THF (25 ml) and stirred at 50 °C for 17 h. The crude residue was purified by flash column chromatography on silica gel (petroleum ether:AcOEt, 39:1) to give alkyne **520** (636 mg, 57%) as pale brown oil. The data were consistent with the literature.[197]

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (1H, d, *J* = 0.9 Hz, C**H**O), 7.70 (1H, dd, *J* = 5.0, 0.9 Hz, Ar**H**), 7.60-7.52 (2H, m, Ar**H**), 7.43-7.35 (3H, m, Ar**H**), 7.25 (1H, d, *J* = 5.0 Hz, Ar**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 183.0 (CH), 143.5 (C), 133.9 (CH), 131.8 (2 × CH), 131.6 (CH), 130.9 (CH), 129.3 (C), 128.6 (2 × CH), 122.0 (C), 96.1 (C), 81.5 (C).

4.3.3 Synthesis of Aldoxime Ethers

Methoxy({3-[2-(trimethylsilyl)ethynyl]thiophen-2-yl}methylidene)amine (504)



503 ***E*-504** ***Z*-504**

Based on the procedure by Mora-Radó *et al.*,[196] $MeONH_2$.HCl (159 mg, 1.92 mmol) was added to a stirring solution of aldehyde **503** (200 mg, 0.960 mmol) and pyridine (0.17 ml, 2.10 mmol) in MeOH (2 ml), and the mixture was stirred at room temperature for 5. The mixture was diluted with H_2O (5 ml), and the aqueous phase extracted with AcOEt (3 × 5 ml). The combined organic phases were washed with brine (5 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica (*n*-hexane:AcOEt, 39:1) to give a 1:1.8 E/Z mixture of the *oxime ether* **504** (195 mg, 86 %) as a pale-yellow oil.

E/Z-504 IR 2960, 2151 (C≡C), 1598 (C=N), 1052 cm^{-1}.

***E*-504 ^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (1H, d, *J* = 0.6 Hz, N=C**H**), 7.19 (1H, dd, *J* = 5.2, 0.6 Hz, Ar**H**), 7.02 (1H, d, *J* = 5.2 Hz, Ar**H**), 3.97 (3H, s, OC**H**$_3$), 0.25 (9H, s, 3 × SiC**H**$_3$).

***Z*-504 ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (1H, d, *J* = 0.8 Hz, N=C**H**), 7.40 (1H, dd, *J* = 5.2, 0.8 Hz, Ar**H**), 7.09 (1H, d, *J* = 5.2 Hz, Ar**H**), 4.09 (3H, s, OC**H**$_3$), 0.26 (9H, s, 3 × SiC**H**$_3$).

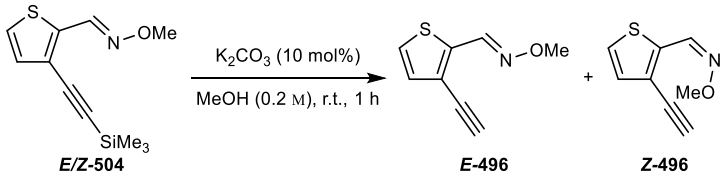
***E*-504 ^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.9 (CH), 138.4 (C), 130.1 (CH), 126.2 (CH), 123.9 (C), 99.9 (C), 97.6 (C), 62.3 (CH_3), -0.1 (3 × CH_3).

***Z*-504 ^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.2 (CH), 133.1 (C), 129.7 (C), 129.0 (CH), 125.2 (CH), 100.2 (C), 98.2 (C), 62.5 (C), -0.1 (3 × CH_3).

E/Z-504 HRMS (Q-TOF) Exact mass calcd. for $[C_{11}H_{16}NOSSi]+$ [MH]+ calcd. 238.0720, found 238.0716.

4.3.4 Desilylation of Trimethylsilyl Alkynes

[(3-Ethynylthiophen-2-yl)methylidene](methoxy)amine (496)



Based on the procedure by Mora-Radó *et al.*,[196] alkyne **504** (100 mg, 0.421 mmol) and K_2CO_3 (6.0 mg, 40 μmol) were dissolved in MeOH (2 ml) and the mixture was stirred at RT for 1 h. The mixture was diluted with H_2O (5 ml), and the aqueous phase extracted with AcOEt (3 × 5 ml). The combined organic phases were washed with brine (5 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel (*n*-hexane) to give a 1:1.2 E/Z mixture of the terminal alkyne **496** (33.0 mg, 47%) as a pale-yellow oil. The data were consistent with the literature.[196]

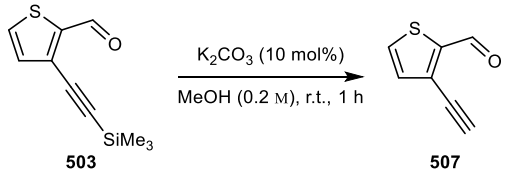
***E*-496 ^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (1H, s, N=C**H**), 7.21 (1H, d, *J* = 5.2 Hz, Ar**H**), 7.05 (1H, d, *J* = 5.2 Hz, Ar**H**), 3.96 (3H, s, C**H**$_3$), 3.32 (1H, s C≡C**H**).

***Z*-496 ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (1H, s, N=C**H**), 7.42 (1H, d, *J* = 5.2 Hz, Ar**H**), 7.13 (1H, d, *J* = 5.2 Hz, Ar**H**), 4.10 (3H, s, C**H**$_3$), 3.38 (1H, s, C≡C**H**).

***E*-496 ^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.7 (CH), 139.1 (C), 130.1 (CH), 126.4 (CH), 122.6 (C), 82.3 (C), 77.32 (CH), 62.3 (CH_3).

***Z*-496 ^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.8 (CH), 133.6 (C), 129.9 (CH), 129.3 (CH), 123.8 (C), 82.4 (C), 76.8 (CH), 62.5 (CH_3).

3-Ethynylthiophene-2-carbaldehyde (507)



Based on the procedure by Mora-Radó *et al.*,[196] alkyne **503** (1.56 g, 7.49 mmol) and K_2CO_3 (103 mg, 0.745 mmol) were dissolved in MeOH (40 ml) and the mixture was stirred at RT for 1 h. The mixture was diluted with H_2O (40 ml), and the aqueous phase extracted with AcOEt (3 × 40 ml). The combined organic phases were washed with brine (40 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by recrystallisation from petroleum ether to give the alkyne **507** (828 mg, 81%) as a dark red solid. The data were consistent with the literature.[196]

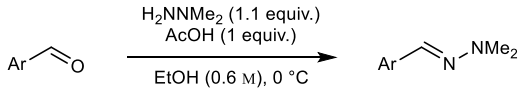
m.p. = 32 - 33 °C (petroleum ether), no literature value reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 (1H, d, *J* = 1.3 Hz, C**H**O), 7.67 (1H, dd, *J* = 5.0, 1.3 Hz, Ar**H**), 7.22 (1H, d, *J* = 5.0 Hz, Ar**H**), 3.46 (1H, s, C≡C**H**).

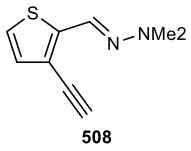
^{13}C NMR (101 MHz, $CDCl_3$) δ 182.7 (CH), 145.2 (C), 133.8 (CH), 131.9 (CH), 129.4 (C), 84.0 (C), 75.8 (CH).

4.3.5 Synthesis of Hydrazones

General Procedure 13: Hydrazone condensation



Based on the procedure by Ball-Jones *et al.*[197], H_2NNMe_2 (1.1 equiv.) was added to a stirring solution of aldehyde (1 equiv.) and AcOH (1 equiv.) in EtOH and the mixture stirred at 0 °C. The mixture was diluted with H_2O (50 ml), and the aqueous layer extracted with AcOEt (3 × 50 ml). The organic phases were washed with brine (100 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography if required.



508

(3-Ethynylthiophen-2-yl)methylidene(prop-1-en-2-yl)amine (508)

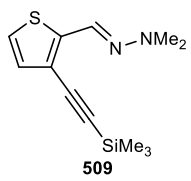
The title compound was prepared according to **General Procedure 13** using aldehyde **507** (828 mg, 6.08 mmol), H_2NNMe_2 (0.50 ml, 6.57 mmol), AcOH (0.35 ml, 6.11 mmol) in EtOH (10 ml) and the mixture stirred at 0 °C for 2 h. The crude residue was purified by flash column chromatography (petroleum ether:AcOEt, 39:1) to give *hydrazone* **508** (870 mg, 81%) as a yellow oil.

IR 3282 (C≡CH), 2853, 2100 (C≡C), 1555 (C=N), 1050 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, s, N=C**H**), 7.00 (1H, d, *J* = 5.2 Hz, Ar**H**), 6.97 (1H, d, *J* = 5.2 Hz, Ar**H**), 3.28 (1H, s, C≡C**H**) 3.00 (6H, s, 2 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9 (CH), 129.9 (C), 125.6 (CH), 122.8 (CH), 116.8 (C), 80.8 (C), 78.3 (CH), 42.7 (2 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_9H_{11}N_2S]+$ [MH]+ calcd. 179.0637, found 179.0633.



509

1,1-Dimethyl-2-({3-[2-(trimethylsilyl)ethynyl]thiophen-2-yl}methylidene)-hydrazine (509)

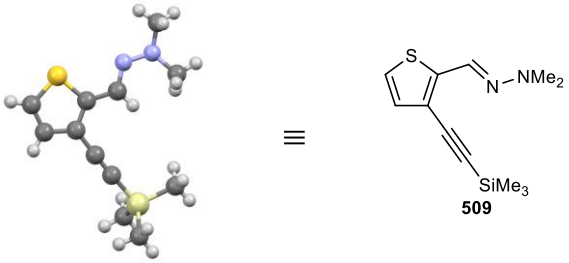
The title compound was prepared according to **General Procedure 13** using aldehyde **503** (2.11 g, 10.1 mmol), H_2NNMe_2 (0.85 ml, 11.2 mmol), AcOH (0.60 ml, 10.5 mmol) in EtOH (17 ml) and the mixture stirred at 0 °C for 2 h. The crude residue was purified by flash column chromatography (petroleum ether:AcOEt, 195:5) to give hydrazone **509** (2.46 g, 97%) as a yellow solid. The data were consistent with the literature.[197]

m.p. = 55 - 56 °C (petroleum ether), no literature value reported.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, s, N=C**H**), 6.98 (1H, d, *J* = 5.2 Hz, Ar**H**), 6.94 (1H, d, *J* = 5.2 Hz, Ar**H**), 2.99 (6H, s, 2 × NC**H**$_3$), 0.25 (s, 9H, 3 × SiC**H**$_3$).

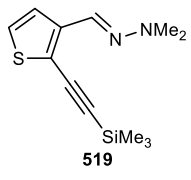
^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4 (CH), 129.5 (C), 126.4 (CH), 122.8 (CH), 118.4 (C), 99.4 (C), 98.3 (C), 42.6 (2 × CH3), 0.1 (3 × CH_3).

Crystals suitable for X-ray diffraction were obtained through recrystallisation of **509** from petroleum ether.



509

Crystal Data for $C_{12}H_{18}N_2SSi$ (M =250.43 g/mol): monoclinic, space group P21/c (no. 14), a = 14.7712(10) Å, b = 8.4445(6) Å, c = 11.7692(8) Å, β = 95.698(3)°, V = 1460.78(17) Å3, Z = 4, T = 100.01 K, μ(CuKα) = 2.568 mm-1, Dcalc = 1.139 g/cm3, 12263 reflections measured (6.012° ≤ 2Θ ≤ 133.464°), 2580 unique (Rint = 0.0548, Rsigma = 0.0356) which were used in all calculations. The final R1 was 0.0372 (I > 2σ(I)) and wR2 was 0.0964 (all data).



519

1,1-Dimethyl-2-({2-[2-(trimethylsilyl)ethynyl]thiophen-3-yl}methylidene)-hydrazine (519)

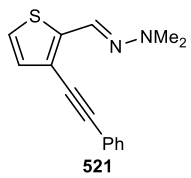
The title compound was prepared according to **General Procedure 13** using aldehyde **518** (105 mg, 0.720 mmol), H_2NNMe_2 (0.06 ml, 0.740 mmol), AcOH (0.04 ml, 0.700 mmol) in EtOH (1 ml) and the mixture stirred at 0 °C for 3.5 h. The crude residue was purified by flash column chromatography (petroleum ether:AcOEt, 99:1) to give *hydrazone* **519** (156 mg, 87%) as a yellow oil.

IR 2961, 2140 (C≡C), 1570 (C=N) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, s, N=C**H**), 7.34 (1H, d, *J* = 5.3 Hz, Ar**H**), 7.11 (1H, d, *J* = 5.3 Hz, Ar**H**), 2.97 (6H, s, 2 × NC**H**$_3$), 0.26 (9H, s, 3 × SiC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (C), 127.5 (CH), 126.4 (CH), 124.1 (C), 117.9 (CH), 102.8 (C), 96.9 (C), 42.6 (2 × CH_3), 0.0 (3 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{12}H_{19}N_2SSi]+$ [MH]+ calcd. 251.1033, found 251.1032.



521

1,1-Dimethyl-2-{[3-(2-phenylethynyl)thiophen-2-yl]methylidene}hydrazine (521)

The title compound was prepared according to **General Procedure 13** using aldehyde **520** (610 mg, 2.87 mmol), H_2NNMe_2 (0.25 ml, 3.29 mmol), AcOH (0.16 ml, 2.97 mmol) in EtOH (5 ml) and the mixture stirred at 0 °C for 5 h. The crude residue was purified by flash column chromatography on silica gel (petroleum ether:AcOEt, 99:1) to give hydrazone **521** (374 mg, 51%) as a yellow solid. The data were consistent with the literature.[197]

m.p. = 71 - 73 °C (CH_2Cl_2), no literature value reported.

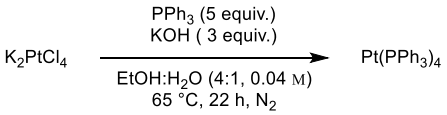
IR 2855, 2208 (C≡C), 1667 (C=N), 1055 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, s, N=C**H**), 7.54 - 7.49 (2H, m, Ar**H**), 7.38 - 7.31 (3H, m, Ar**H**), 7.05 (1H, d, *J* = 5.2 Hz, Ar**H**), 7.03 (1H, d, *J* = 5.2 Hz, Ar**H**), 3.02 (6H, s, 2 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3 (C), 131.4 (2 × CH), 129.7 (CH), 128.4 (2 × CH), 128.2 (CH), 126.2 (CH), 123.4 (CH), 123.0 (C), 93.0 (C), 83.9 (C), 42.7 (2 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{15}H_{15}N_2S]+$ [MH]+ calcd. 255.0950, found 255.0955.

4.3.6 Tetrakis(triphenylphosphine)Pt(0)



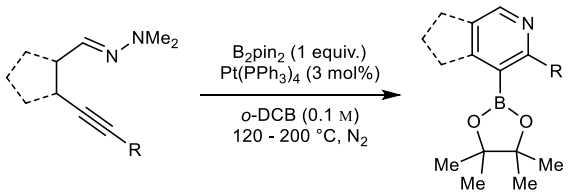
Based on the procedure by Stang and Datta[246], PPh_3 (1.57 g, 6.00 mmol) was added to a Schleck flask equipped with a stirrer bar, and the flask flushed with N_2. Degassed EtOH (20 ml) was added and the mixture was stirred at 65 °C. When the mixture had homogenised, a solution of KOH (202 mg, 3.60 mmol) dissolved in degassed EtOH/ H_2O (4:1, 5 ml) was added followed by a solution K_2PtCl_4 (467 mg, 1.13 mmol) in H_2O (5 ml) which immediately gave a yellow precipitate. The mixture was stirred at 65 °C for 22 h, after which time it was allowed to cool to r.t. and the solvent removed by cannula filtration. The precipitate was washed sequentially with warm EtOH (20 ml), H_2O (5 ml) and cold EtOH (5 ml) under nitrogen. The precipitate was dried in vacuo to give the Pt complex (1.19 g, 85%) as an amorphous yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 - 7.42 (15 H, m, Ar**H**), 7.22 - 6.96 (45H, m, Ar**H**).

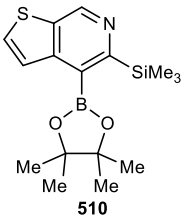
^{31}P NMR (162 MHz, $CDCl_3$) δ 29.10.

4.3.7 Diboration/6π-Electrocyclisation

General Procedure 14: Diboration/6π-Electrocyclisation



Hydrazone (1 equiv.), B_2pin_2 (1 equiv.) and $Pt(PPh_3)_4$ (3 mol%) were added to a Schlenk flask fitted with a screw top, and the flask back filled with N_2 three times. Anhydrous o-DCB (0.1 M) was added under a positive pressure of N_2. The flask was sealed, and the mixture was stirred at 120 °C, followed by stirring at 200 °C. The crude mixture was cooled to room temperature and purified by flash column chromatography.



4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trimethylsilyl)thieno[2,3-c]-pyridine (510)

The title compound was prepared according to **General Procedure 14** using alkyne **509** (500 mg, 2.00 mmol), B_2pin_2 (508 mg, 2.00 mmol) and $Pt(PPh_3)_4$ (74.0 mg, 60.0 μmol) in anhydrous-DCB (20 ml) and stirred at 120 °C for 3 h followed by stirring at 200 °C for 18 h. The crude residue was purified by column chromatography on Florisil® (petroleum ether:AcOEt, 19:1) to give pyridine **510** (605 mg, 91%) as an off-white solid. The data were consistent with the literature.[197]

m.p. = 94 - 95 °C (CH_2Cl_2).

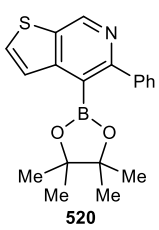
IR 2973, 1388, 1240, 1137 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (1H, d, *J* = 0.8 Hz, Ar**H**), 7.92 (1H, dd, *J* = 5.4, 0.8 Hz, Ar**H**), 7.65 (1H, d, *J* = 5.4 Hz, Ar**H**), 1.43 (12H, s, 4 × CC**H**$_3$), 0.43 (9H s, 3 × SiC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2 (C), 148.1 (CH), 145.1 (C), 135.1 (CH), 130.6 (C), 125.4 (CH), 84.3 (2 × C), 25.3 (4 × CH_3), 0.5 (3 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 31.6.

HRMS (Q-TOF) Exact mass calcd for $[C_{16}H_{25}BNO_2SSi]^+$ $[MH]^+$ calcd. 334.1463, found 334.1469.



520

5-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thieno[2,3-c]-pyridine (522)

The title compound was prepared according to **General Procedure 14** using alkyne **521** (200 mg, 0.786 mmol), B_2pin_2 (200 mg, 0.97 mmol) and $Pt(PPh_3)_4$ (29.0 mg, 20.0 μmol) in anhydrous-DCB (8 ml) and stirred at 120 °C for 1 h followed by stirring at 200 °C for 5 h. The crude residue was purified by column chromatography on Florisil® (petroleum ether:AcOEt 19:1) to give pyridine **522** (190 mg, 71%) as a pale-yellow solid. The data were consistent with the literature.[197]

m.p. = 125 - 126 °C (CH_2Cl_2).

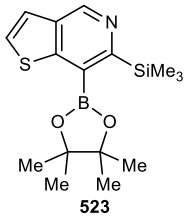
IR 2973, 1536, 1406, 1139 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (1H, d, *J* = 0.7 Hz, Ar**H**), 7.75 (1H, d, *J* = 5.4 Hz, Ar**H**), 7.69 (1H, dd, *J* = 5.4, 0.7 Hz, Ar**H**), 7.70 - 7.66 (2H, m, Ar**H**), 7.46 - 7.37 (3H, m, Ar**H**), 1.30 (12H, s, 4 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 (C), 149.6 (CH), 144.8 (C), 142.4 (C), 134.0 (CH), 132.3 (CH), 129.4 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 124.4 (C), 84.3 (2 × C), 24.8 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 31.7 (br s).

HRMS (Q-TOF) Exact mass calcd for $[C_{19}H_{21}{}^{11}BNO_2S]^+$ $[MH]^+$ calcd. 338.1381, found 338.1387.



523

7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trimethylsilyl)thieno[3,2-c]-pyridine (523)

The title compound was prepared according to **General Procedure 14** using alkyne **519** (100 mg, 3.99 mmol), B_2pin_2 (101 mg, 3.98 mmol) and $Pt(PPh_3)_4$ (12.0 mg, 10.0 μmol) in anhydrous-DCB (4 ml) and stirred at 120 °C for 1 h followed by stirring at 200 °C for 18 h. The crude residue was purified by column chromatography on Florisil® (petroleum ether:AcOEt 19:1) to give *pyridine* **523** (60.0 mg, 45%) as a pale-yellow oil.

IR 2978, 1478, 1373, 1261, 1140 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (1H, s, Ar**H**), 7.49 (1H, d, *J* = 5.6 Hz, Ar**H**), 7.39 (1H, d, *J* = 5.6 Hz, Ar**H**), 1.44 (12H, s, 4 × CC**H**$_3$), 0.43 (9H, s, 3 × SiC**H**$_3$)

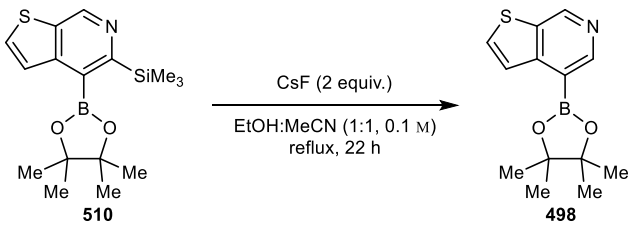
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2 (C), 153.1 (CH), 146.1 (C), 134.1 (CH), 128.6 (CH), 122.0 (C), 84.7 (2 × C), 25.2 (4 × CH_3), 0.4 (3 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 31.4 (br s).

HRMS (Q-TOF) Exact mass calcd for $[C_{16}H_{25}{}^{11}BNO_2SSi]^+$ $[MH]^+$ calcd. 334.1463, found 334.1470.

4.3.8 Transformation of Borylated Pyridines

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)thieno[2,3-c]pyridine (498)



Pyridine **510** (500 mg, 1.50 mmol) and CsF (457 mg, 3.01 mmol) were dissolved in a mixture of EtOH:MeCN (1:1, 15 ml) and stirred at reflux for 22 h. The mixture was cooled to RT, diluted with H_2O (20 ml), and the aqueous layer extracted with AcOEt (3 × 20 ml). The combined organic were washed with brine (20 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Recrystallisation from acetone gave pyridine **498** (361 mg, 92%) as an off-white solid. The data were consistent with the literature.[196]

m.p. = 163 - 164 °C (CH_2Cl_2).

IR 3071, 2972, 1595, 1401, 1154 cm^{-1}.

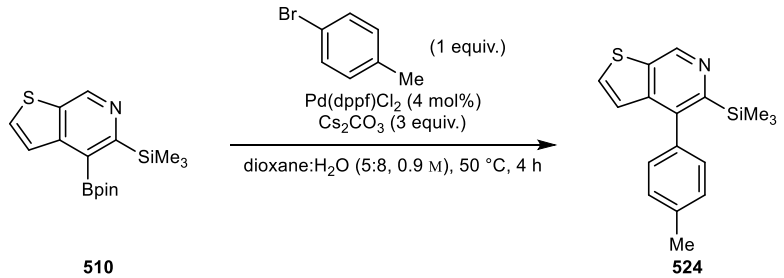
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (1H, s, Ar**H**), 8.88 (1H, s, Ar**H**), 7.96 (1H, d, *J* = 5.4 Hz, Ar**H**), 7.75 (1H, d, *J* = 5.4 Hz, Ar**H**), 1.40 (12H, s, 4 × C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9 (CH), 149.2 (C), 146.8 (CH), 136.0 (CH), 132.2 (CH), 125.2 (C), 84.1 (2 × C), 24.9 (4 × CH_3).

^{11}B NMR (128 MHz, $CDCl_3$) δ 30.9 (br s).

HRMS (Q-TOF) Exact mass calcd for $[C_{13}H_{17}{}^{11}BNO_2S]^+$ $[MH]^+$ calcd. 262.1073, found 262.1067.

4-(4-Methylphenyl)-5-(trimethylsilyl)thieno[2,3-c]pyridine (524)



Based on the procedure by Wilson *et al.*,[208] boronic ester **510** (83.3 mg, 0.250 mmol), 4-bromotoluene (42.8 mg, 0.250 mmol), Pd(dppf)Cl_2 (8.1 mg, 10 μmol) and Cs_2CO_3 (244 mg, 0.750 mmol) were dissolved in dioxane:H_2O (1:1.9 ml) and stirred at 50 °C for 4 h. Upon completion the mixture was diluted water (10 ml), extracted with AcOEt (3 × 10 ml). The combined organic phases were washed with brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by chromatography to give *pyridine* **524** (56.5 mg, 76%) as a pale-yellow solid.

m.p. = 77 - 80 °C (CH_2Cl_2).

IR 2951 (CH), 1242, 836 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 - 9.29 (1H, m, ArH), 7.54 (1H, dt, *J* = 5.4, 1.6 Hz, Ar**H**), 7.28 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.23 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.99 (1H, d, *J* = 5.4 Hz, Ar**H**), 2.46 (3H, s, C**H$_3$**), 0.06 (9H, s, 3 × C**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6 (C), 143.8 (C), 143.4 (CH), 139.4 (C), 137.6 (C), 136.3 (C), 135.3 (C), 130.1 (CH), 129.9 (2 × CH), 128.8 (2 × CH), 123.1 (CH), 21.3 (CH_3), 0.1 (3 × CH_3).

HRMS (Q-TOF) Exact mass calcd for $[C_{17}H_{20}NSSi]^+$ $[MH]^+$ calcd. 298.1080, found 298.1091.

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