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Boronic ester functionalisations for the automated synthesis of natural products

Boronic Ester Functionalisations for the Automated Synthesis of Natural Products

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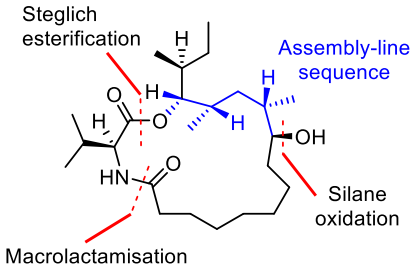
Finally, I would like to thank Mum, Dad and James, and also Sharna, who has supported me throughout, even during the tough times.

Abstract

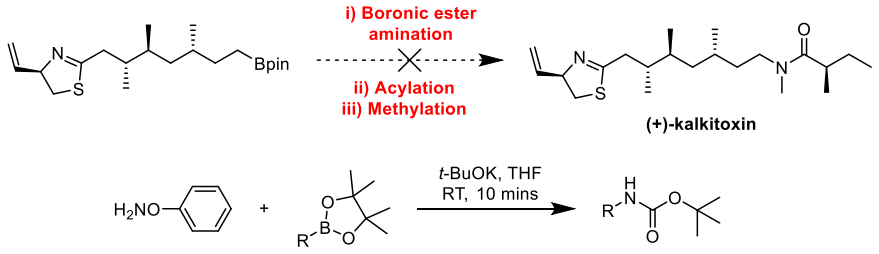
Lipopeptide natural products have garnered significant attention from the synthetic chemist due their potent biological activity against a range of targets. Aggarwal has developed a suite of synthetic methods leveraging boronic-ester homologation chemistry to construct these molecules efficiently.

The macrolipopeptide dysoxylactam A, isolated and characterised in 2019 by Yue and co-workers, was synthesised in 11 steps. Key features of the synthesis are the utilisation of iterative lithiation-borylation reactions (assembly-line synthesis) for the construction of the stereochemically dense lipophilic portion of the molecule, the use of a single protecting group and a total of 5 chromatographic purifications. Other steps include a Steglich esterification, macrolactamisation and Fleming oxidation.



Dysoxylactam A

The automated synthesis of (+)-kalkitoxin required starting with a thiazoline containing boronic ester, performing six automated iterative lithiation-borylation reactions, and then boronic ester amination, acylation and amide methylation. The boronic ester amination proved to be exceptionally challenging due to undesired isomerisation of the thiazoline ring. After extensive investigations into this transformation, a new boronic ester amination procedure was discovered, in which the reaction proceeds rapidly at room temperature. Although this method was unsuitable for the thiazoline containing boronic ester, it represents the mildest and simplest direct conversion of a boronic ester to an amine.



Author's Declaration

I declare that the work in this dissertation was carried out in accordance with the requirements of the University's *Regulations and Code of Practice for Research Degree Programmes* and that it has not been submitted for any other academic award. Except where indicated by specific reference within the text, the work is the candidates own work. Work done in collaboration with, or with the assistance of, others, is indicated as such. Any views expressed in the dissertation are those of the author.

SIGNED:…….. JACK ROGERS…… DATE:…….16/12/2022……

Contents

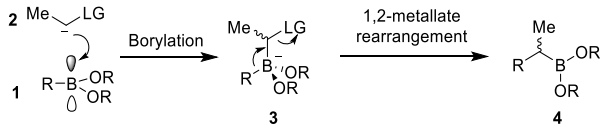
Abbreviations and Acronyms

Å	Angstrom
Ac	acetyl
Ar	aryl
BAIB	bis(acetoxy)iodobenzene
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bop	bis(2-oxo-3-oxazolidinyl)phosphinyl
Bu/*n*-Bu	butyl
Bz	benzoyl
brsm	based on recovered starting material
cat	catechol
cat.	catalytic
Cb	diisopropylcarbamate
Cbz	benzyloxycarbonyl
CDI	carbonlydiimidizole
Cy	cyclohexyl
d	days
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCL	dichloroacetic acid
DG	directing group
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMT	dimethoxytrityl
DNA	deoxyribonucleic acid
dppf	1,1'-*bis*(dipheylphosphino)ferrocene
d.r.	diastereomeric ratio
DTBP	di-*tert*-butylperoxide
E^+	electrophile
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.e.	enantiomeric excess
ent	enantiomer
ESI	Electrospray Ionisation
Fmoc	fluorenylmethoxycarbonyl
h	hours
HATU	(1-[*bis*(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
HMDS	hexamethyldisilazyl
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
i-Bu	isobutyl
Ipc	isopinocamphenyl
i-Pr	isopropyl
IR	infra-red
LED	Light-Emitting Diode
lev	levolinyl

M	Molar ($moldm^{-3}$)
m-CPBA	*meta*-chloroperbenzoic acid
Ms	methanesulfonyl
MS	Mass Spetrometry *or* molecular sieves
MW	Microwave Irradiation
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
PG	protecting group
piv	pivolyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
py	pyridyl
quant.	quantitative
R	alkyl
RT	room temperature
s-Bu	*sec*-butyl
sp	sparteine
sps	sparteine surrogate
t-Bu	*tert*-butyl
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBME	*tert*-butylmethyl ether
TBS	*tert*-butyldimethylsilyl
TBTU	2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
TCCA	trichloroisocyanuric acid
TCBC	trichlorobenzoyl chloride
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilyl
Tf	trifluromethylsulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	1,1,1-trifluoroethanol
THF	tetrahydrofuran
TIB	triisopropylbenzoyl
TLC	Thin Layer Chromatography
TMAF	tetramethylammonium fluoride
TMB	trimethoxybenzene
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Trt	trityl
Ts	toluenesulfonyl
W	Watt
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

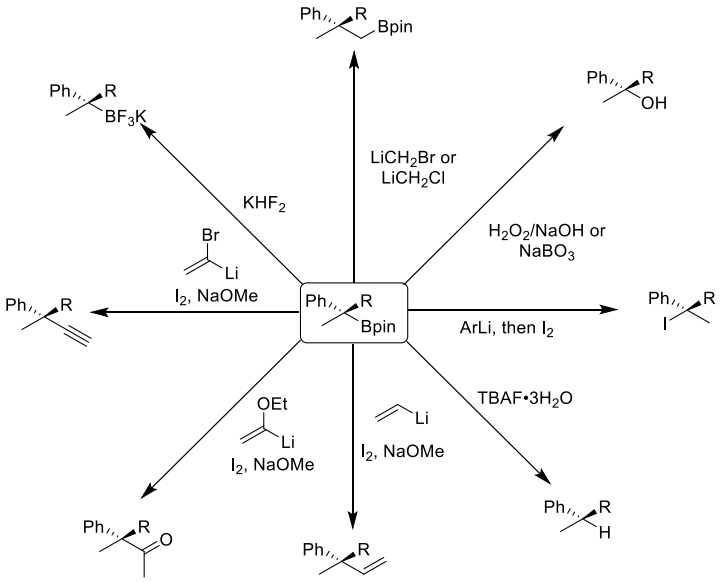
1. The Total Synthesis of Dysoxylactam A

Organoboron compounds are valuable and highly versatile intermediates in organic synthesis. Whilst the initial breakthrough from Herbert C. Brown on the hydroboration of alkenes[1] prompted significant further work on the functionalisation of boranes, these species found their use constrained somewhat by their air and moisture sensitivity. Boronic esters (**1**), in contrast, have significantly improved air and moisture stability since the empty p-orbital on the boron atom receives electron donation from the oxygen atoms of the two alkoxy substituents. The reactivity of boronic esters proceeds through the interaction of the empty p-orbital with a nucleophilic species (such as **2**) to form an anionic 'ate' complex (**3**). If there is enough electron deficiency or a leaving group α to boron, a 1,2-metallate rearrangement can occur in which one group from the anionic boron centre will shift to this area of electron deficiency or to expel the leaving group. Stereochemical requirements of the 1,2-metallate rearrangement dictate that the migrating group and the leaving group be antiperiplanar to allow, in a concerted process, movement of the electron density of the boron-migrating group bond into the σ* orbital of the carbon-leaving group bond to break the latter σ bond, expelling the leaving group (**Scheme 1**).



Scheme 1: Typical reactivity of a nucleophile and boronic ester, followed by a 1,2-metallate rearrangement.

The immense synthetic utility of boronic esters stems from two facts; boronic esters can be efficiently prepared with very high enantioselectivity using catalytic methods such as hydroboration[2] and diboration[3], and stoichiometric methods such as lithiation–borylation[4]; and such boronic esters can be stereospecifically transformed into a plethora of other functional groups (**Scheme 2**).[5]



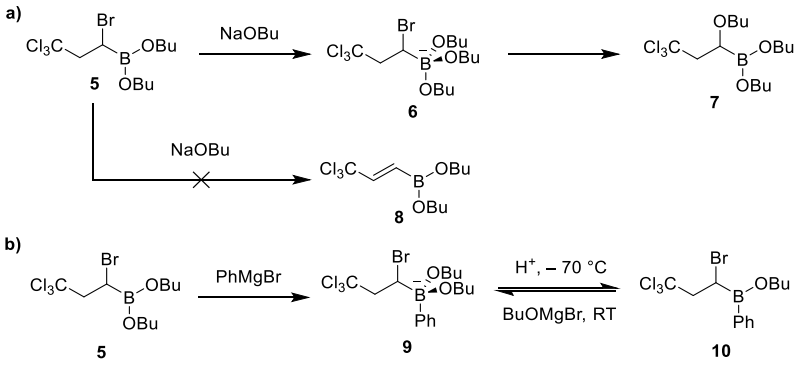
Scheme 2: Selected transformations of boronic esters

1.1. Homologation of Boronic Esters

The nucleophilic and electrophilic properties of metal carbenoids make them ideal reagents for the homologation of boronic esters.[6] In this process, a carbenoid undergoes nucleophilic attack on boron to generate a boronate complex, which is followed by a 1,2-metallate rearrangement of a substituent on the boron atom to expel the leaving group of the carbenoid. To allow the homlogations to be carried out in an enantioselective manner two general methods have emerged: substrate control and reagent control.

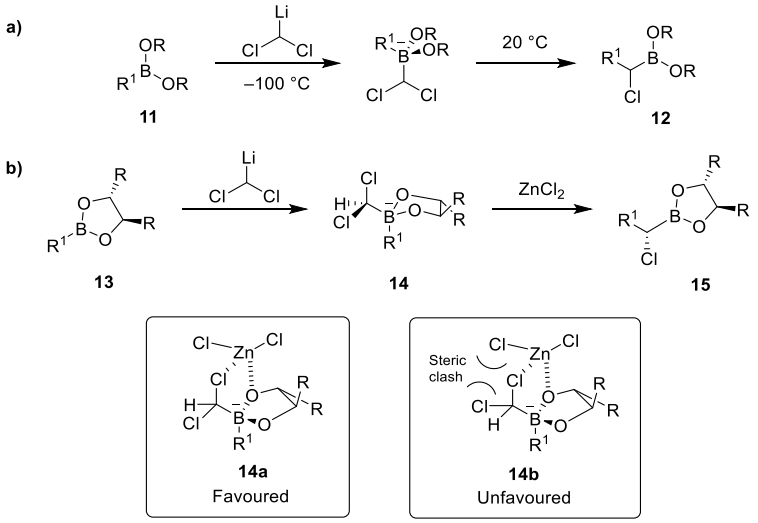
1.1.1. Substrate-Controlled Homologation of Boronic Esters

The seminal work on the homologation of boronic esters was performed by Matteson in 1963. Whilst working on the dehydrobromination of α-bromoboronic esters, Matteson noticed that, upon treatment of α-bromoboronic ester **5** with an alkoxide base NaOBu, adduct **7** was observed instead of the expected dehydrobrominated product **8.** (**Scheme 3a**).[7] Matteson suggested the formation of boronate complex **6** *via* coordination of base to the boronic ester and subsequent 1,2-metallate rearrangement provided the α-alkoxyboronic ester (**7**). The presence of the boronate complex was confirmed by Matteson in a later work (**Scheme 3b**).[8] If instead boronic ester **5** was reacted with a Grignard reagent, boronate complex **9** was formed. Following acidification, this species was hydrolysed to yield borinic ester **10** which was stable at low temperature. Upon warming, the boronate complex reformed and the expected 1,2-metallate rearrangement occurred to give the alkylation product **7**.



Scheme 3: Matteson's early work on showing the existence of boronate complexes.

The value of this observation was not realised until 1980, 17 years after Matteson's initial discovery, with the synthesis of α-chloroboronic esters from the corresponding boronic ester using (dichloromethyl)lithium (**Scheme 4a**).[9] The lithiated species can be prepared using *n*-BuLi to deprotonate dichloromethane, a reaction which is carried out at –100 °C to prevent decomposition of the lithiated species into the carbene. Addition of this species to a boronic ester (**11**) leads a boronate complex, which upon heating above 20 °C, will undergo the 1,2-metallate rearrangement to form the α-chloroboronic ester **12**. This can then be reacted with various nucleophiles to give a diverse range of products, or the reaction could be repeated on the product boronic ester. However, with no form of chiral induction, multiple homologations would soon give numerous diastereoisomers. Matteson overcame this issue with the use of a chiral diol ligand on boron (**Scheme 4b**). The enantiopure boronic ester **13** is reacted with (dichloromethyl)lithium to form the corresponding boronate complex **14**, which, after the addition of zinc chloride will form the α-chloroboronic ester **15** with high diastereoselectivity and in a good yield. It has been proposed that zinc chloride binds to the less hindered oxygen atom of the diol ligand and one of the chlorine groups, whilst avoid a destabilising steric clash, to favour one transition state (**14a**) over the other (**14b**).



Scheme 4: a) The Matteson homologation, b) Substrate-controlled enantioselective homologation.

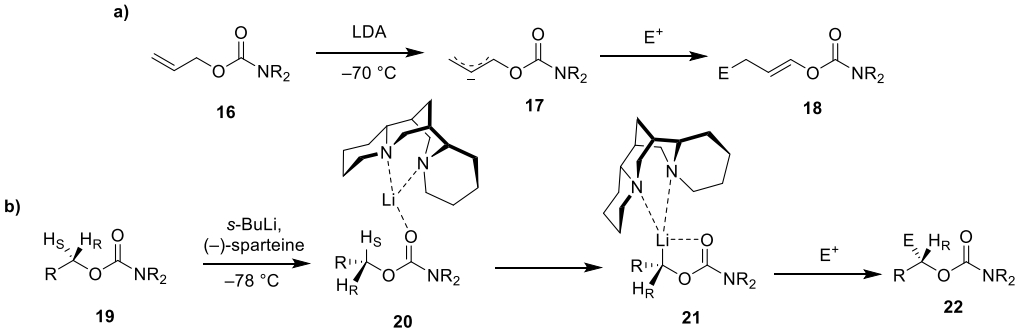
This method has been demonstrated in multiple total syntheses.[10–12] However, its applications are limited, as in order to alternate the diastereoselectivity of each iterative step in the assembly line, the ligand on boron would need to be changed to its enantiomer before each homologation, which is a lengthy three step sequence.

1.1.2. Hoppe's Diisopropylcarbamates.

The laborious transesterification steps required in Matteson's protocol greatly limits its use in an assembly line type synthesis. Clearly a reagent-controlled approach to enantioselective boronic ester homologations was required to make an extensive assembly line type synthesis feasible.

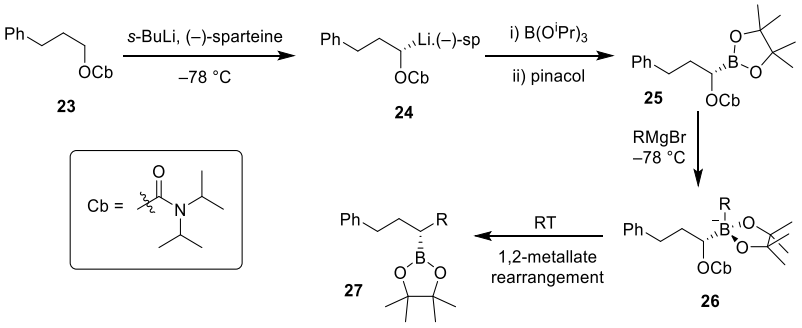
In 1980, Hoppe described the deprotonation of allyl *N*,*N*-dialkylcarbamates (**16**) using lithium diisopropylamide to form dipole and resonance-stabilised carbanion **17** (**Scheme 5a**),[13] which could be trapped with several electrophiles to give products **18**. It was shown that deprotonation proceeded *via* an initial pre-lithiation complex and occurred with retention of configuration. The generated anion was configurationally stable below −40 °C.[14,15] Hoppe demonstrated enantioselective deprotonation of the alkyl carbamate (**19**) with the use of chiral diamine ligand (–)-sparteine at low temperature.[16] This anion was more stable than Matteson's lithiated chlorides due to co-ordination between lithium and the carbonyl of the carbamate (**Scheme 5b**).[17] Subsequent trapping with an electrophile at low temperature gave a variety of α-substituted products (**22**). It should be noted that the sparteine diamine ligand was required not only for enantioselectivity, but also to break up *s*-BuLi aggregates to generate a sufficiently basic species (TMEDA can

be used if no enantiocontrol is required, and that the use of bulky alkyl groups on the carbamate is to prevent direct nucleophilic attack of *s*-BuLi at the carbonyl.



Scheme 5: a) First use of a carbamate directing group in a lithiation. b) Use of the chiral (–)-sparteine to make chiral products from achiral starting materials.

Hoppe then showed that these chiral lithiated carbamates could be trapped with a borate, which, after transesterification to the boronic acid pinacol ester (**25**), could be isolated in good yield and with no erosion of e.e. relative to the lithiated species (**Scheme 6**). These α-carbamoylboronic esters were subsequently trapped with a Grignard reagent to form the boronate complex (**26**) at –78 °C, which underwent a 1,2-metallate rearrangement with inversion of stereochemistry upon warming to room temperature expelling the carbamate group to give the homologated product **27**.[18]

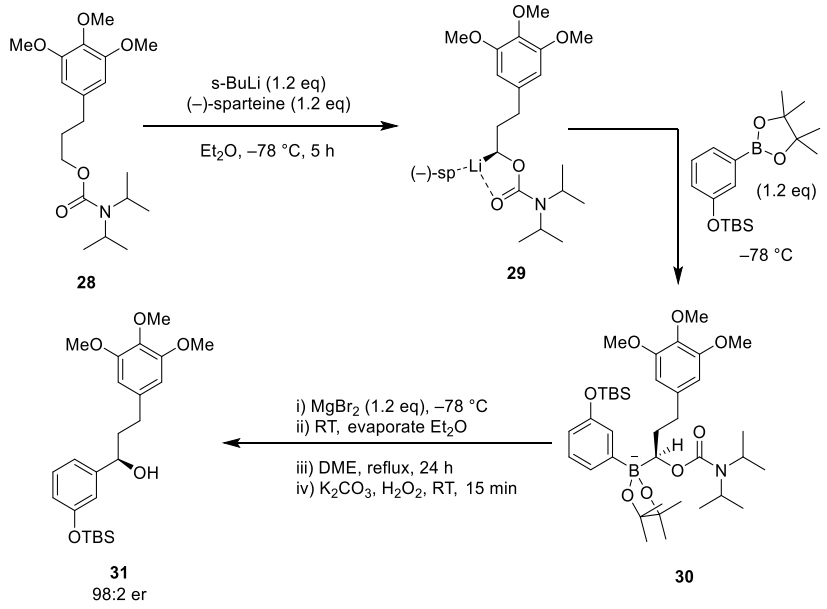


Scheme 6: Quenching the lithiated carbamate with a borate, followed by the formation of a boronate complex with a Grignard reagent and subsequent 1,2-metallate rearrangement

1.1.3. Kocienski's Lithiation–Borylation Methodology

The drawback of Hoppe's boronic ester homologation is that the intermediate pinacol boronic ester must be isolated before treatment with the desired Grignard reagent. In 2006, Kocienski published his synthesis of (*S*)-(–)-*N*-acetylcolchinol, which included as a key step the one-pot lithiation–borylation of a Hoppe carbamate (**Scheme 7**).[19] The formation of the boronate complex **30** was facile, demonstrating that the boronic ester

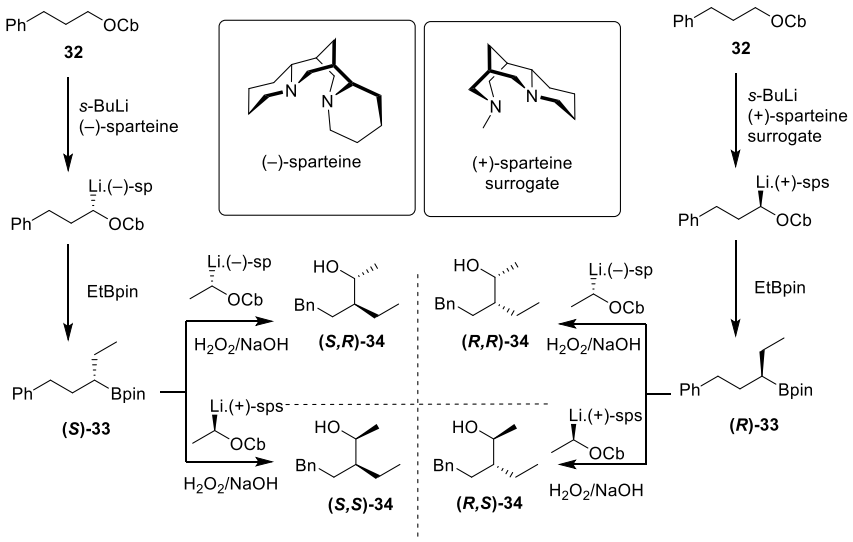
was a suitably electrophilic species for trapping by the lithiated species, but the 1,2-metallate rearrangement proved to be more challenging, and would not initiate upon warming to room temperature. The addition of $MgBr_2$ to bind to the carbamate and increase its leaving group ability was still insufficient. Only after solvent swap to a high boiling solvent, DME, and heating to 85 °C, did the 1,2-metallate rearrangement occur to form the product (**31**) with excellent enantioselectivity.



Scheme 7: Kocienski's one-pot lithiation–borylation-oxidation sequence.

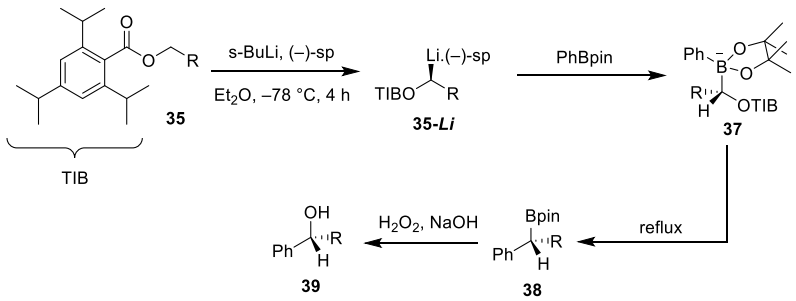
1.1.4. Aggarwal's Lithiation–Borylation Methodology

Aggarwal has since thoroughly explored the scope of this lithiation–boryation methodology.[4] In 2007, using the Hoppe carbamate, Aggarwal synthesised all four stereoisomers of alcohol **34** using two iterative lithiation–borylations on the same achiral starting material (**32**) in excellent enantio- and diastereoselectivity, using (–)-sparteine and a (+)-sparteine surrogate[20] (an alternative to (+)-sparteine which was used due to the commercial unavailability of (+)-sparteine at the time of publication) (**Scheme 8**).[21]



Scheme 8: Aggarwal's iterative homologation of boronic esters to produce four stereoisomers from achiral starting materials.

Particular migrating groups on boron such as phenyl and methyl were troublesome in the 1,2-metallate rearrangement without the addition of $MgBr_2$.[22] However, using the triisopropylbenzoate group (TIB, **35**), originally developed by Beak,[23] in place of the carbamate group allowed these 1,2-metallate rearrangements to occur efficiently simply by refluxing the reaction in its ethereal solvent for two hours. This enhanced aptitude for the 1,2-rearrangement was owed to the increased leaving group ability of the TIB ester (**Scheme 9**).[24]



Scheme 9: Use of a TIB ester in lithiation–borylation.

This methodology has since been applied to the total synthesis of numerous natural products, including (–)-decarestrictine D,[25] solandelactone E[26] and its epimer F,[27] and the Californian Red Scale Beetle Pheromone (**Figure 1**).[28]

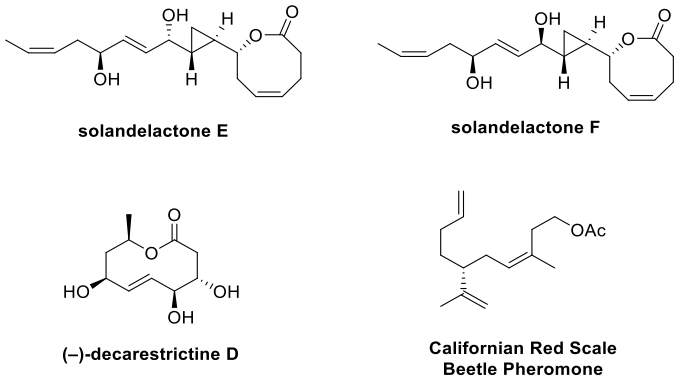
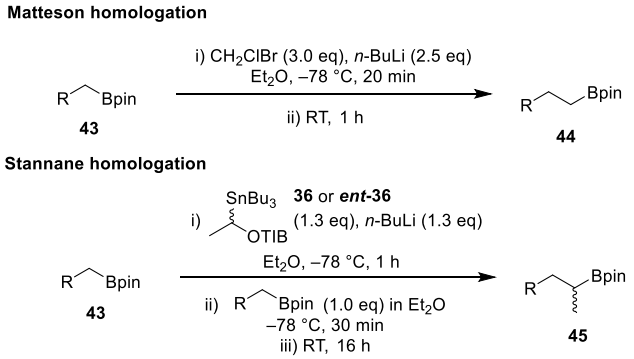


Figure 1: Natural products synthesised using lithiation–borylation methodology by Aggarwal.

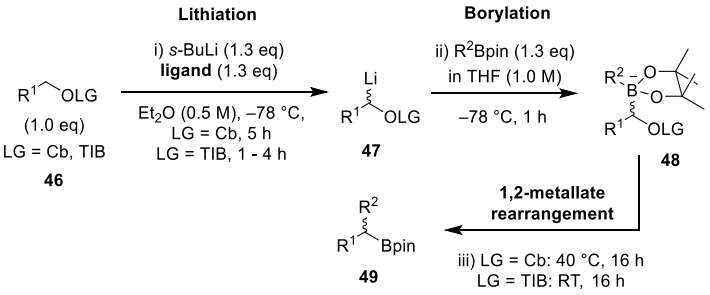
1.1.5. General Lithiation–Borylation Procedures

In the following text, certain lithiation–borylation steps in syntheses are often referred to simply as a 'Matteson homologation' or a 'stannane homologation'. In all cases, unless stated otherwise, these two reactions use the literature conditions shown in **Scheme 10**.[29]



Scheme 10: General conditions for the Matteson and stannane homologations.

Multiple lithiation–borylation reactions are discussed throughout the text. Below is a reference lithiation–borylation for the purposes of comparison from the literature (**Scheme 11**).[24] Small changes to these conditions are common as all stages of a lithiation–borylation reaction can be highly substrate dependant. These may include using different equivalences of boronic ester, changing the reaction concentration and adjusting lithiation, borylation and 1,2-metallate rearrangement times. The choice of diamine ligand dictates the stereoselectivity of the lithiation. Challenging substrates often require more drastic modifications to these conditions, which may include solvent exchanges, modification of the leaving group and the addition of $MgBr_2$ in Et_2O or MeOH.

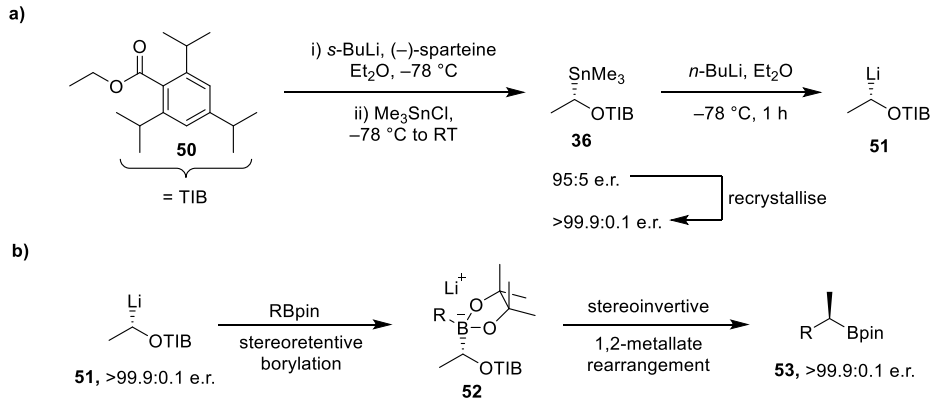


Scheme 11: General conditions for the lithiation–borylation of diisopropyl carbamates and TIB esters.

1.2. Assembly-line methodology in total synthesis

1.2.1. Assembly-line synthesis

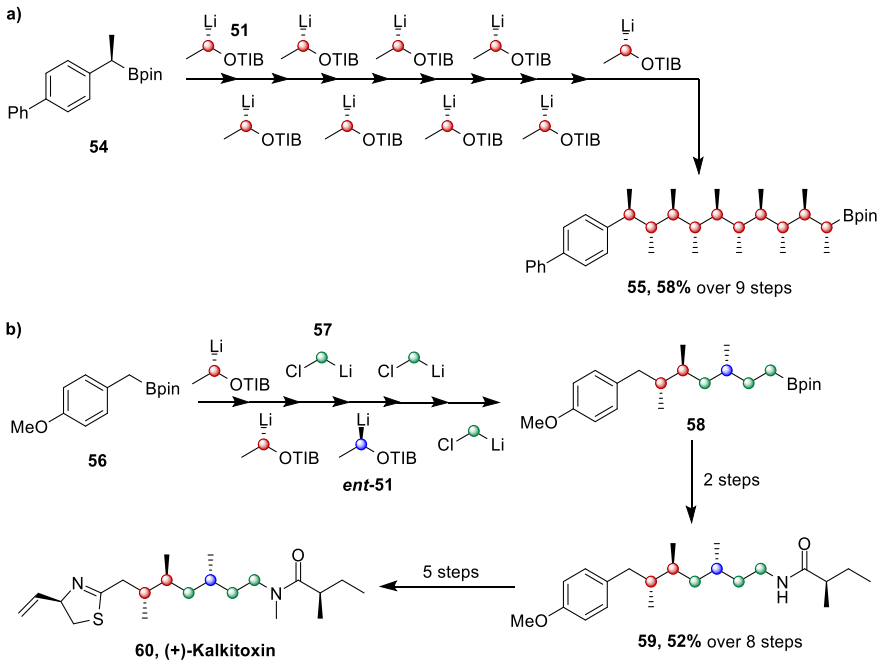
As discussed above, the versatility and applicability of lithiation–borylation has been demonstrated in the synthesis of many natural products – the ability to both maintain a versatile boronic ester functionality whilst also performing a carbon-carbon bond formation is a valuable transformation to the synthetic chemist. Aggarwal demonstrated perhaps the most impressive utilisation of lithiation–borylation chemistry with his 'assembly-line' synthesis, in which a carbon chain was constructed in an iterative manner with complete stereocontrol.[30] The installation of a methylene moiety can be carried out using the homologation chemistry developed by Matteson.[31] The use of α-lithioethyl tri-isopropylbenzoate (**51**), derived from the corresponding stannane (**36**) via tin-lithium exchange, allowed the installation of a methyl group with exceptional stereocontrol. The key to this transformation is that **36**, which is formed with a 95:5 e.r. from a sparteine-mediated lithiation followed by trapping with Me_3SnCl, is a crystalline white solid. This can then be recrystallised to afford **36** in enantiopurities exceeding 99.9% e.e (Scheme **12a**). The stereospecificity of borylation (stereoretentive) and the 1,2-metallate rearrangement (stereoinvertive) ensures that this exceptional enantiopurity is transferred to the product boronic ester (Scheme **12b**).



Scheme 12: a) Generation of enantiopure α-lithioethyl triisopropylbenzoate. b) Stereospecificity of borylation and 1,2-metallate rearrangement.

The ability of the stannane homologation (as well as the Matteson homologation) to be used in an iterative fashion is due to the complete consumption of boronic ester to form a stoichiometric amount of the boronate complex. The excess α-lithioethyl triisopropylbenzoate (**51**) is destroyed at a lower temperature than that required to initiate the 1,2-metallate rearrangement, thus preventing over-homologation. The work up procedure is also operationally simple; the reaction mixture is simply taken up in diethyl

ether and filtered through a pad of silica. This removes any insoluble salts generated in the homologation (LiCl or LiOTIB). The filtrate is then concentrated to give the crude boronic ester which can be immediately used in the next homologation. This process can be repeated multiple times, as was performed by Aggarwal in 2014,[30] to generate multiple contiguous stereocentres with complete stereocontrol, giving the corresponding product (**55**) with excellent diastereoselectivity and quite literally as a single enantiomer (Scheme **13a**). An aqueous work-up was performed every third homologation, and column chromatography carried out only after the ninth homologation (Scheme **7**). Another example of the assembly-line methodology was demonstrated in 2016 by Aggarwal and co-workers, in which the central core of (+)-Kalkitoxin (**60**) was synthesised in a six iterative steps using **51**, ***ent*-51** and **57**, with a simple filtration between each step (**Scheme 13b**).[32]



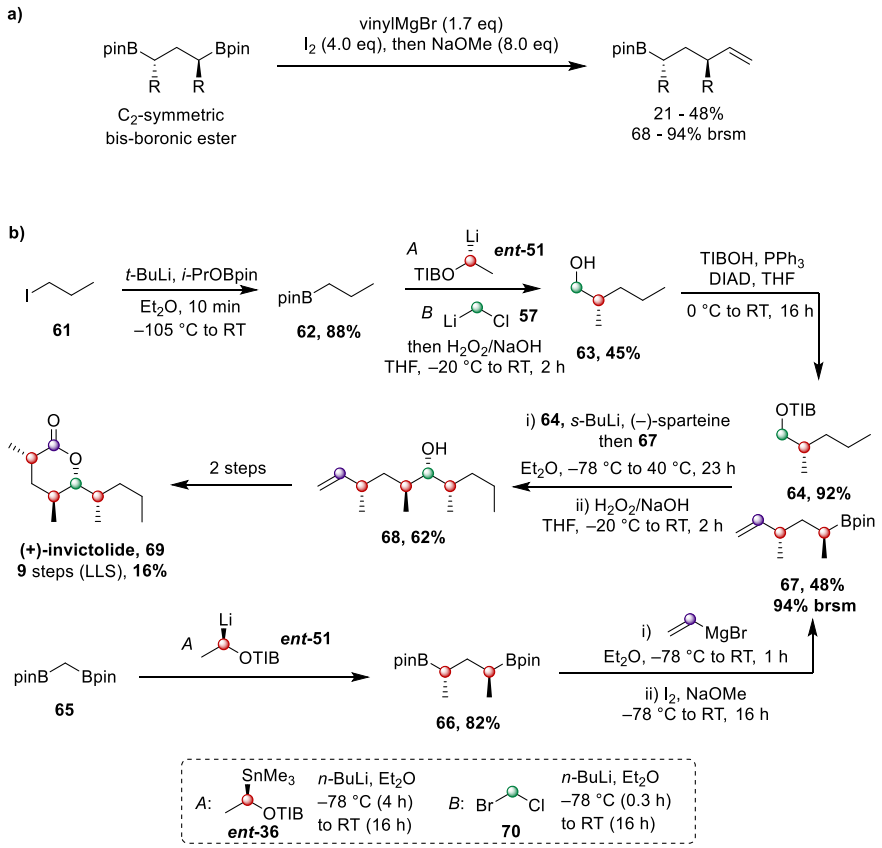
Scheme 13: a) Use of nine iterative lithiation–borylation reactions to synthesise a complex molecule with complete stereocontrol, b) Synthesis of (+)-kalkitoxin using assembly line methodology.

1.2.2. (+)-Invictolide

In 2020, Kalesse published syntheses of the natural products (+)-invictolide and the related natural product serricornin. The synthesis highlighted the applicability of his mono-Zweifel olefination methodology in the desymmetrisation of symmetric bis-boronic esters (Scheme **14a**).[33]

The synthesis of (+)-invictolide utilised lithiation–borylation in the key fragment coupling of **64** and **67** in a lithiation–borylation reaction to give alcohol **68** after oxidation.

Fragment **64** was synthesised from propyl iodide (**61**), which underwent iodide-lithium exchange to give the corresponding pinacol boronic ester **62**. A short assembly-line sequence consisting of a stannane homologation using ***ent*-36**, followed by a Matteson homologation and oxidation gave alcohol **63** in a 45% yield over three steps, which was then esterified using Mitsunobu chemistry to give the TIB ester **64**. The synthesis of fragment **67** started from the geminal bis-boronic ester **65,** which was subjected to a bis-stannane homologation to give the C_2-symmetric boronic ester **66**. Kalesse employed his desymmetrising Zweifel olefination methodology to generate the desired boronic ester **67** in a 48% yield. A sparteine-mediated diastereoselective lithiation of **65**, followed by borylation with boronic ester **67** and then oxidation, afforded alcohol **68**. Two further steps, namely ozonolysis and then oxidation of the resultant lactol to the lactone, afforded (+)-invictolide (**69**) in a 16% overall yield (Scheme **14b**).



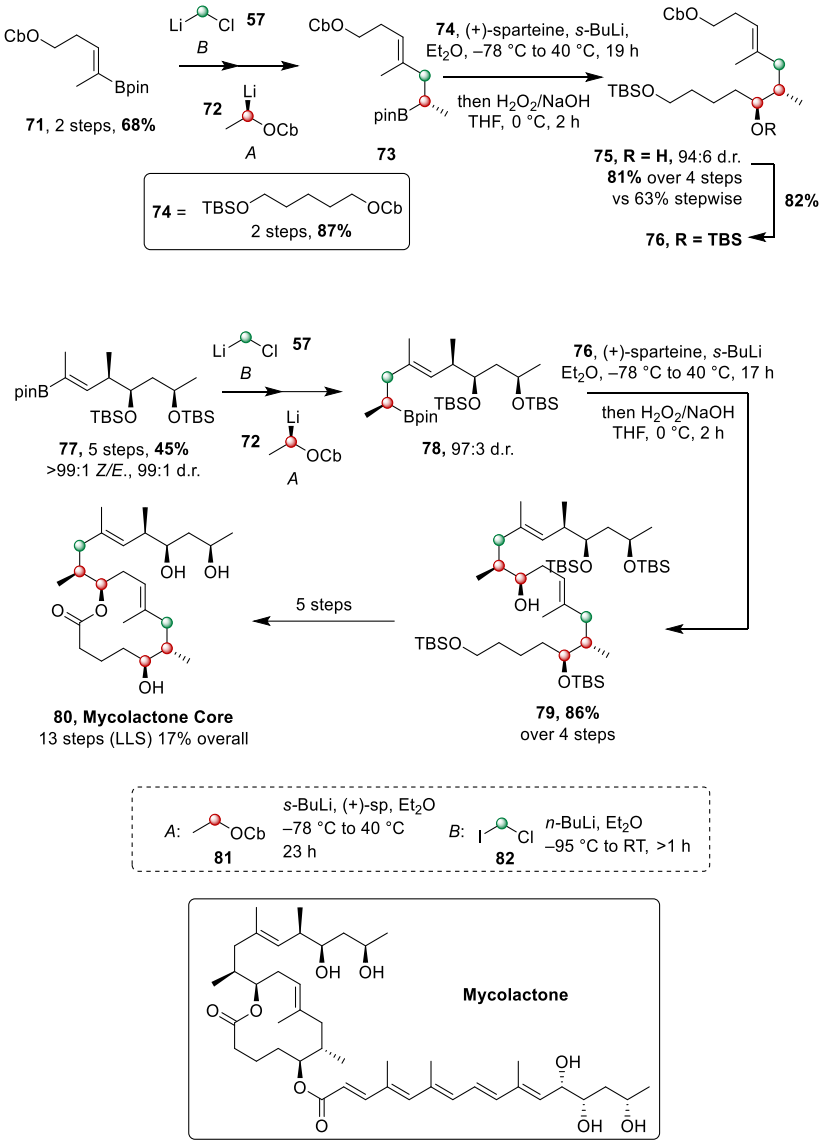
Scheme 14: a) Kalesse's bis-boronic ester desymmetrisation. b) Kalesse's synthesis of (+)-invictolide.

1.2.3. Mycolactone Core

The Aggarwal group demonstrated the value of the assembly-line methodology in their synthesis of the Mycolactone core (**80**) with a longest linear sequence of 13 steps, a total of 17 steps, and an overall yield of 17%.[34] The previously reported synthesis from Kishi

and co-workers had a longest linear sequence of 14 steps, with a total of 28 steps, and an overall yield of 19%.[35] The former synthesis features two four-step assembly line sequences to rapidly construct the lipophilic parts of the molecule with both high yields and excellent stereocontrol.

Commencing from carbamate **71**, which is synthesised in two steps from commercially available starting materials, a four-step assembly-line synthesis was performed, consisting of a Matteson homologation, lithiation–borylation with ethyl carbamate **81**, and then a (+)-sparteine mediated lithiation–borylation with the carbamate **74** to give, after oxidation of the boronic ester, alcohol **75** in an 81% yield over 4 steps. This value is compared to the yield of 63% if each reaction is performed in a stepwise manner (with purification after each reaction). A final protection of the alcohol as the TBS silyl enol ether gave **76**, a carbamate to be used in a late-stage fragment coupling. The synthesis of the second fragment began from complex intermediate **77**, which was synthesised in five steps. Another four-step assembly-line was then performed, consisting of a Matteson homologation and a lithiation–borylation with the carbamate **81**, followed by a final (+)-sparteine mediated lithiation–borylation with boronic ester **78** and **76** to give, after oxidation, the advanced intermediate **79**. Five further steps were then required to complete the synthesis of the mycolactone core **80** (Scheme **15**).



Scheme 15: Synthesis of the mycolactone core by Aggarwal and co-workers.

1.3. Dysoxylactam A

1.3.1. Isolation and Biological Testing

In 2019, a 17-membered macrocyclic lipopeptide, dysoxylactam A (**83**) (**Figure 2**), was isolated by Yue from the bark of the plant *Dysoxylum hongkongense*, which was mainly found to grow in southern parts of China.[36] It contains an L-valine moiety as well as unprecedented branched C19 fatty acid residue.

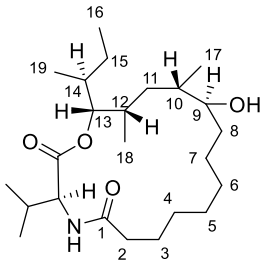


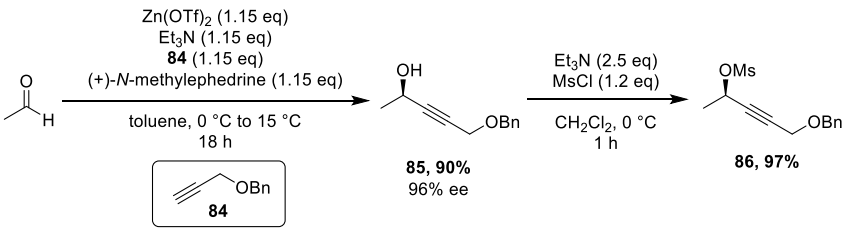
Figure 2: The structure of dysoxylactam A.

Broader studies on cyclolipopeptides have shown that they have a wide spectrum of biological activities which has made them attractive targets for both organic total synthesis[37,38] and biosynthesis,[39] so it would follow that dysoxylactam A may exhibit some biological activity. Indeed, Yue found that at non-cytotoxic levels, dysoxylactam A dramatically reversed multidrug resistance in cancer cells, with fold-reversals as high as 1000-fold.[36] Yue also found that the mode of action of dysoxylactam A was inhibition of the function of P-glycoprotein, a key mediator in drug resistance.

1.3.2. Raghavan's Synthesis of Dysoxylactam A

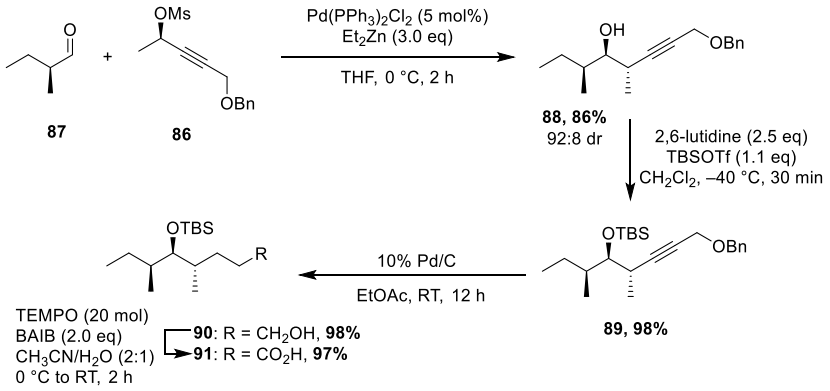
In 2020, Raghavan reported the first total synthesis of dysoxylactam A.[40] The route comprised of 16 steps and was completed with an impressive 22.2% overall yield.

The synthesis starts with subjecting acetaldehyde to the Merck-Carreira propargylation protocol[41] with benzyl-protected propargyl alcohol **84** to give alcohol **85** which was subsequently protected to give mesylate **86** (**Scheme 16**).



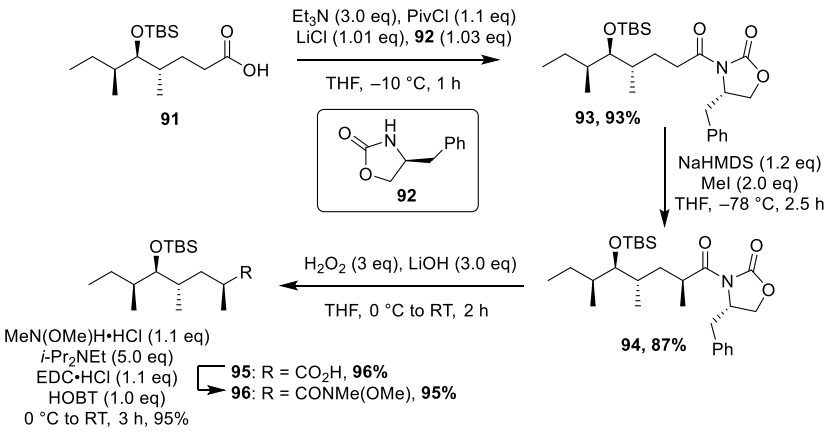
Scheme 16: Merck-Carreira propargylation followed by subsequent mesylation.

Mesylate **86** was then subjected to Marshall's propargylation conditions[42] with aldehyde **87** to give the homopropargylic species **88** with two adjacent stereocentres, which was protected as the TBS ether to give **89**. Concomitant hydrogenation of the alkyne and hydrogenolysis of the benzyl protected alcohol gave **90**, which was subjected to a TEMPO-mediated oxidation with a hypervalent iodine reagent to give the corresponding carboxylic acid **91** (**Scheme 17**).



Scheme 17: Marshall propargylation and subsequent steps.

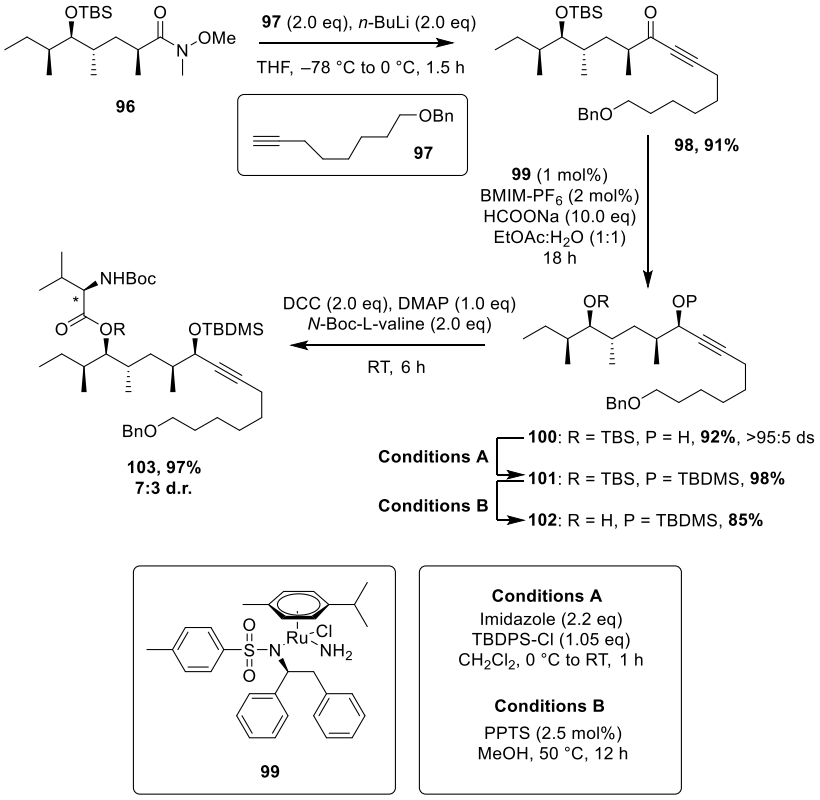
The next stereocentre was installed using Evans alkylation chemistry by initially installing the Evans auxiliary to give imide **93**, which was followed by methylation using MeI and NaHMDS to diastereoselectively furnish compound **94**. Subsequent hydrolysis of the auxiliary gave the free carboxylic acid **95**, which was converted to the corresponding Weinreb amide **96** (**Scheme 18**).



Scheme 18: Evans alkylation and Weinreb amide formation.

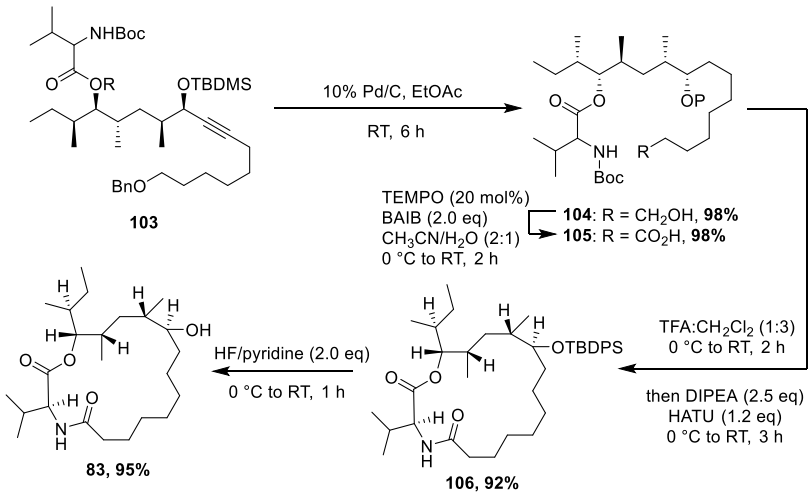
Weinreb amide **96** was then reacted with the lithiated acetamide derived from **97** to give the propargylic ketone, which was then subjected to an enantioselective transfer hydrogenation using the Noyori catalyst (**99**)[43] and ligand BMIM–PF_6 to install the final stereogenic centre, giving alcohol **100**, followed by formation of the TBDPS silyl ether

(**101**). Selective removal of the TBS protecting group gave compound **102** which was ready for coupling with *N*-Boc-L-valine. Raghavan found that this esterification reaction was non-trivial, with no product obtained using many traditional coupling reagents. The reaction proceeded with DCC in the presence of one equivalent of DMAP, albeit producing an inseparable mixture of diastereoisomers of compound **103** (**Scheme 19**).



Scheme 19: Transfer hydrogenation and a challenging esterification.

The epimeric mixture of compound **103** was then subject to hydrogenation conditions to reduce the alkyne and hydrogenolyse the benzyl protected alcohol, giving compound **104** which was, as before, oxidised to the carboxylic acid. Hydrolysis of the carbamate followed by macrolactamisation using DIPEA and HATU gave a separable mixture of diastereoisomers in a 7:3 ratio, with the desired diastereoisomer being the major product (**106**). Simple cleavage of the TBDPS silyl ether using HF/pyridine gave dysoxylactam A (**83**) (**Scheme 20**).

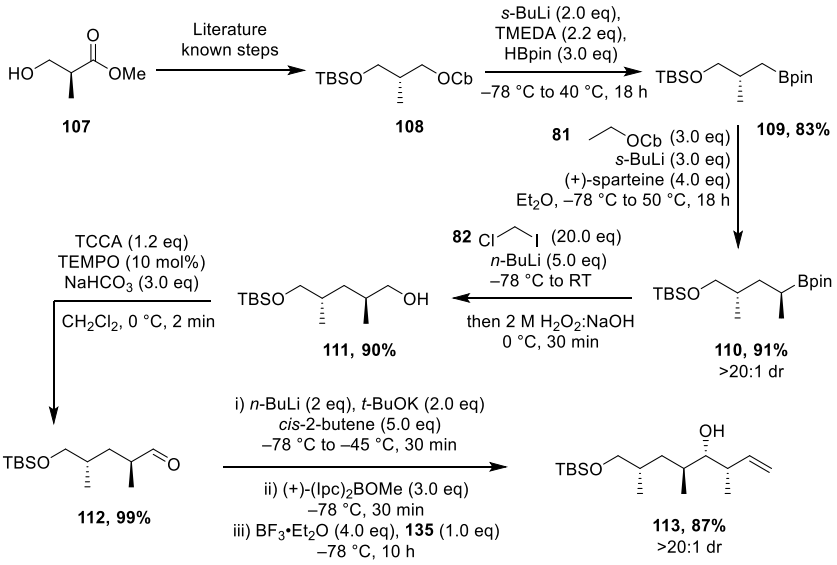


Scheme 20: Endgame steps including macrolactamisation.

1.3.3. Ye's Synthesis of Dysoxylactam A

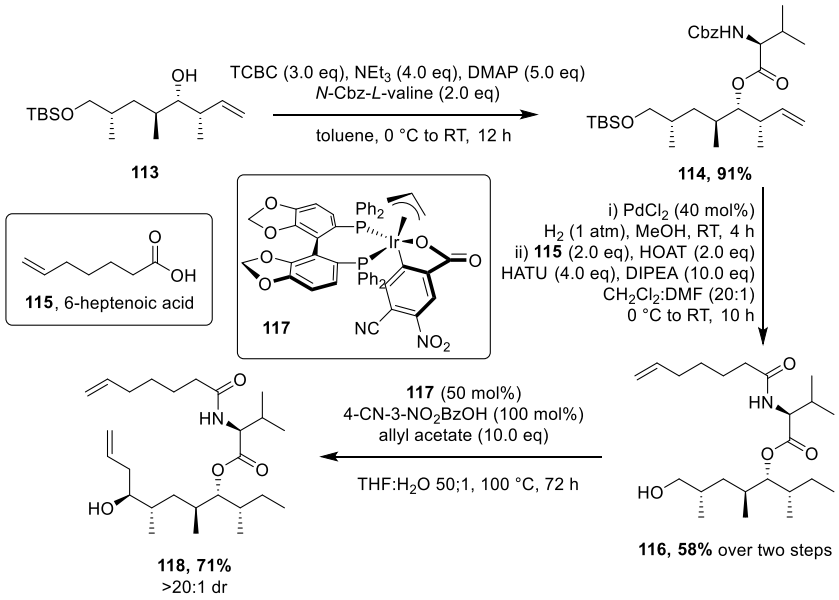
One month after Raghavan's synthesis was published, Ye published his synthesis using different methodology, primarily using iterative techniques including Aggarwal and Matteson homologation, Brown crotylation and Krische allylation.[44] The synthesis was completed in 15 longest linear steps and with an overall yield of 8.8%.

The synthesis started with the commercially available chiral alcohol **107** ((*R*)-Roche ester), which as subjected to known literature conditions to afford the carbamate **108** *via* TBS protection of the alcohol, reduction of the methyl ester to the alcohol and then carbamoylation.[45–47] Lithiation–borylation using pinacol boronic ester afforded the boronic ester **109**, which was followed by a second (+)-sparteine-mediated stannane homologation using ethyl carbamate **81** to afford compound **110** in a high dr. Subsequent Matteson homologation, basic peroxide oxidation of boronic ester and then oxidation of the alcohol (**111**) to the aldehyde afforded compound **112**. It is worth noting the enormous excesses of reagent used in the three lithiation–borylation steps. It is almost certain that these reactions would have worked with a similar yield using significantly lower equivalents based on lithiation studies[48] and previous literature precedence.[24,29] The homoallylic alcohol **113** was then formed *via* a Brown crotylation, giving essentially one diastereoisomer (Scheme **21**).



Scheme 21: Ye's iterative lithiation–borylation approach to install the stereogenic centres of dysoxylactam A.

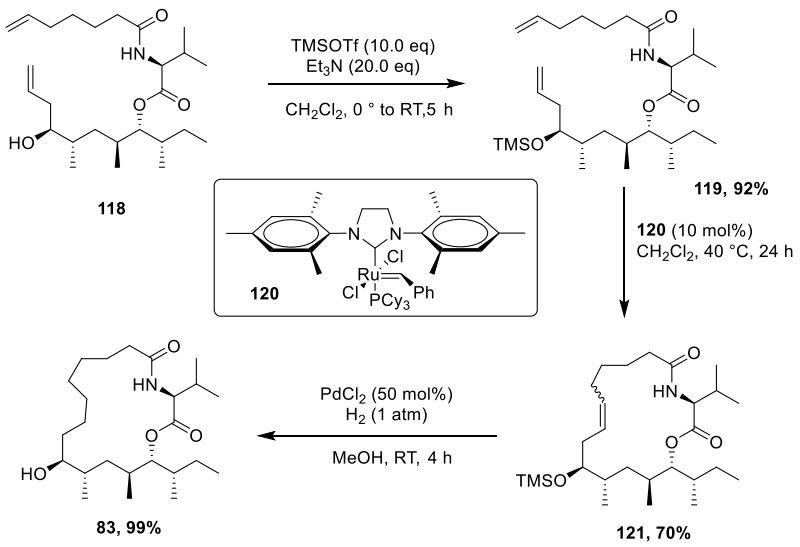
The next steps were an esterification using trichlorobenzoyl chloride and DMAP to couple **113** with *N*-Cbz-L-Valine, followed by concomitant hydrogenation of the alkene, Cbz and TBS removal with $PdCl_2$. This was then followed by a HATU-mediated peptide coupling with **115** to give compound **116**. Invoking the Krische allylation protocol using an iridium catalyst (**117**) gave diene **118** with excellent diastereoselectivity (**Scheme 22**).



Scheme 22: Esterification, reduction, peptide coupling and Krische allylation to install the final stereocentre.

The stage was then set for the alkene metathesis (**Scheme 23**). It was found that the reaction proceeded poorly in the presence of the free alcohol due to sequestration of the ruthenium carbenoid species, so to remedy this, an initial TMS re-protection of the alcohol preceded the successful ring closing metathesis to give **121**. A second alkene

hydrogenation with concomitant hydrogenolysis of the silyl ether afforded dysoxylactam A (**83**).

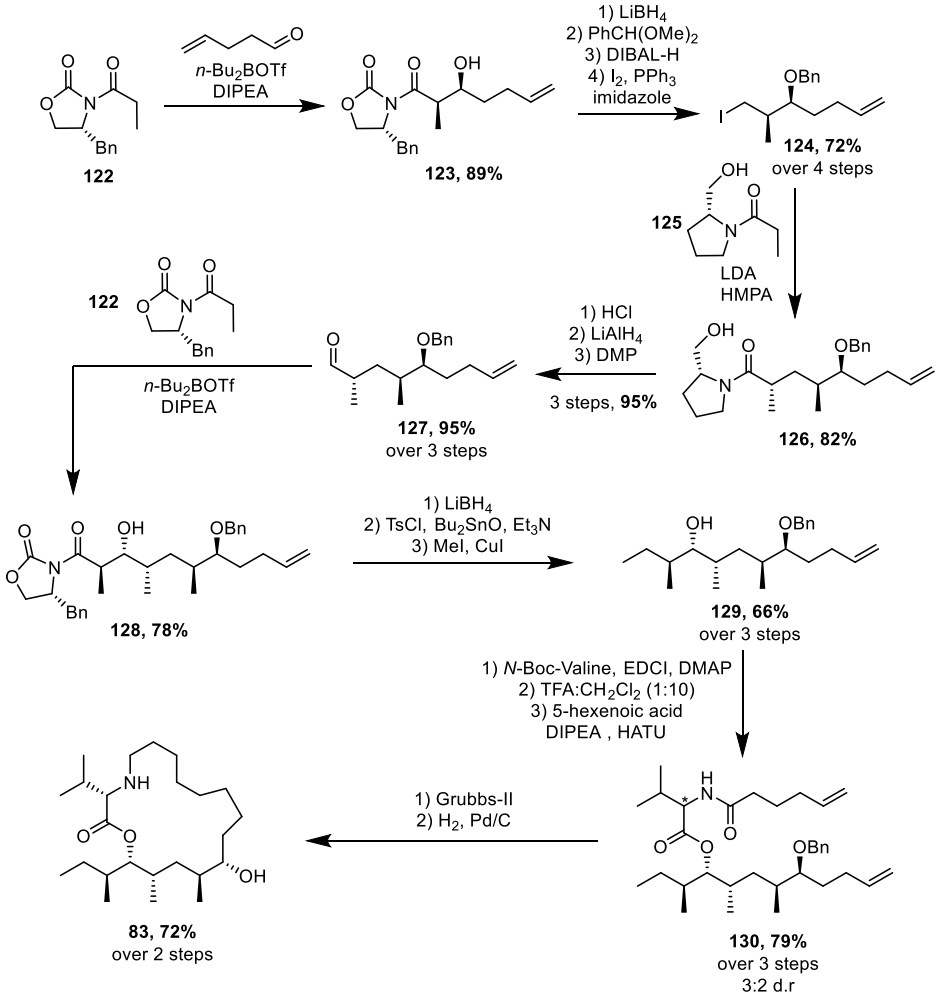


Scheme 23: Endgame steps for the synthesis of dysoxylactam A, including the Grubbs ring-closing metathesis.

1.3.4. Yu's Synthesis of Dysoxylactam A

In 2020, Yu and co-workers published the third total synthesis of dysoxylactam A (Scheme **24**).[49] The route starts from the chiral auxiliary **122**, which was subjected to Evans' aldol chemistry to give **123**. Following this were four functional group interconversions, namely reduction of the chiral auxiliary with $LiBH_4$, acetal formation with $PhCH(OMe)_2$, reduction of this acetal with DIBAL-H to give the mono-benzylated diol, which was then converted to the corresponding alkyl iodide (**124**) using Appel chemistry. This alkyl iodide was reacted with chiral auxiliary **125** in a diastereoselective alkylation reaction to give **126**, which after three more functional group interconversions - acid hydrolysis, $LiAlH_4$ reduction of the carboxylic acid, and then reoxidation of the alcohol - gave the aldehyde **127**. Reacting this aldehyde in a similar diastereoselective aldol with the chiral auxiliary **122** gave **128**, which after three further transformations; $LiBH_4$ reduction of the chiral auxiliary, tosylation of the resultant alcohol, and then methyl cuprate substitution of the tosylate, gave the desired alcohol **129** in 13 steps. Esterification of this alcohol with *N*-Boc-L-valine, subsequent Boc removal, and then amidation of the amine with 5-hexenoic acid gave the advanced intermediate in a 3:2 d.r, due to racemisation of the amino acid stereocentre during the initial esterification of the hindered alcohol. Ring closing metathesis of the diene **130**, followed by concomitant hydrogenation of the resultant alkene and hydrogenolysis of the benzyl protected alcohol

gave dysoxylactam A (**83**) in an overall yield of 9.5%, with a longest linear sequence of 17 steps.



Scheme 24: Yu's synthetic route to dysoxylactam A.

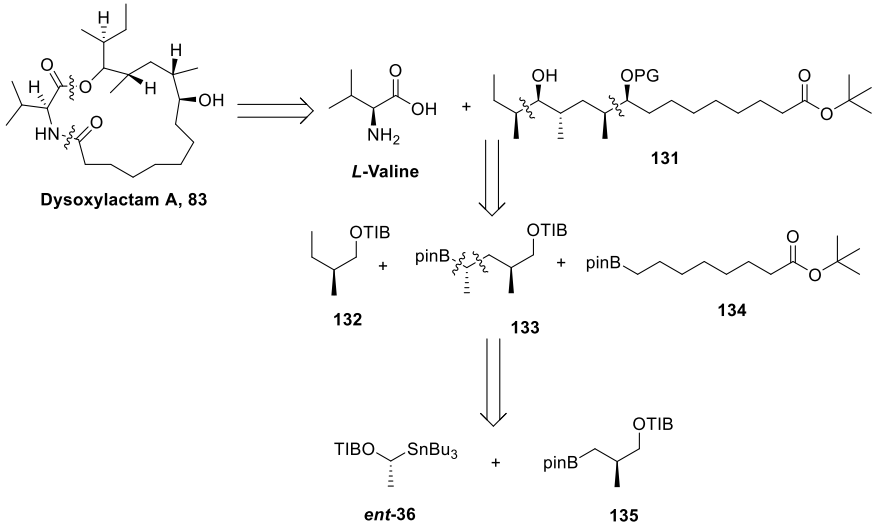
2. Results and Discussion

2.1. First Route for the Total Synthesis of Dysoxylactam A

After Yu's initial isolation of dysoxylactam A and the subsequent biological screening showing that it reversed multidrug resistance in cancer cells, it became a valuable synthetic target, with the potential for the synthesis and discovery of even more potent analogues.

2.1.1. Retrosynthesis

Dysoxylactam A can be disconnected first by an esterification and amide coupling to give L-valine and fragment **131**, with the alcohol and carboxylic acid suitably protected to allow the esterification. These alcohols can be made *via* two lithiation–borylation-oxidation sequences, starting from the three fragments **132**, **133** and **134**. Fragment **133** can be further disconnected into the stannane (***ent*-36**) and compound **135**. These four starting compounds can be easily synthesised from commercially available materials, two of which are from the chiral pool (**Scheme 25**).

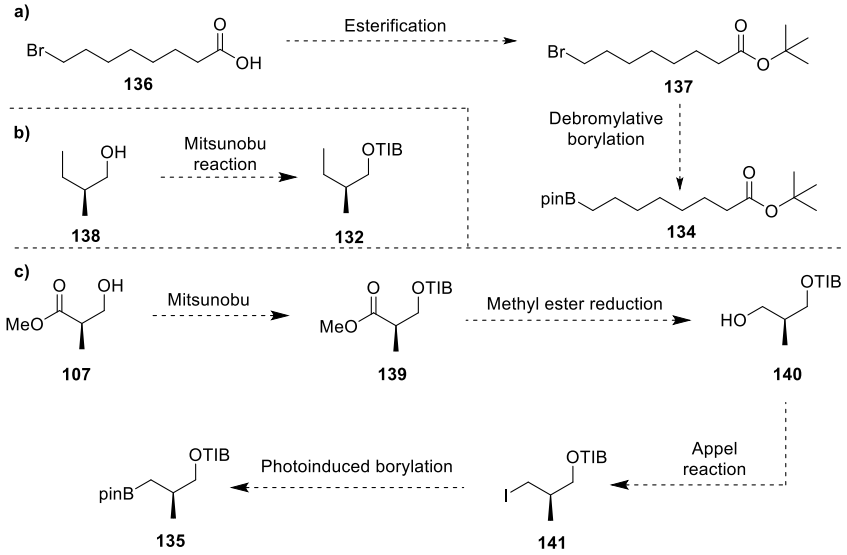


Scheme 25: Retrosynthetic analysis of dysoxylactam A.

2.1.2. Forward Synthesis

Starting fragment **134** couild be synthesised in two steps starting from **136** *via* an esterification with *t*-BuOH, followed by borylation of the alkyl bromide (**Scheme 26a**).[50] Compound **132** could be synthesised simply from the commercially available chiral alcohol **138** *via* a Mitsunobu reaction (**Scheme 26b**). Compound ***ent*-36**, the stannane reagent developed by the Aggarwal group, is synthesised as described above (**Scheme 12a**). The synthesis of **135** is a four step sequence starting from the commercially

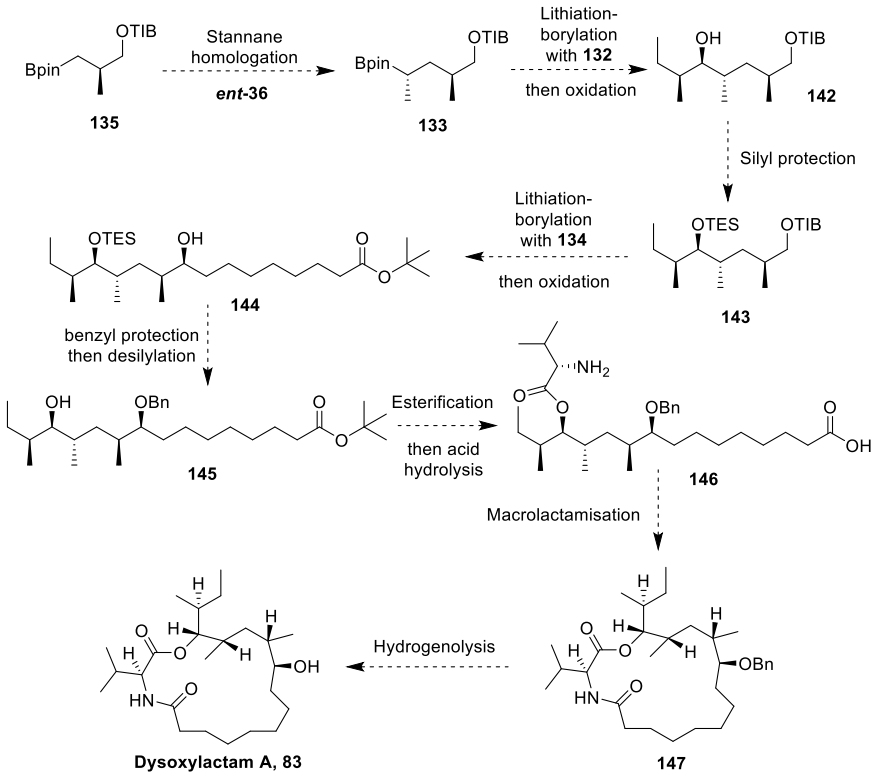
available (*R*)-Roche ester (**107**). A Mitsunobu reaction using TIBOH would give the diester (**139**), followed by selective reduction of the less hindered methyl ester to the alcohol (**140**), an Appel reaction to form the alkyl iodide (**141**), and then photochemical cleavage of the carbon-iodine bond followed by borylation[51] would afford building block **135** (**Scheme 26c**).



Scheme 26: Proposed forward syntheses of the starting blocks.

With the building blocks in hand, the linear sequence (**Scheme 27**) would commence with a stannane homologation using **135** and stannane ***ent*-36** to give **133**. This compound would then be subjected to lithiation–borylation conditions with chiral ester **132** to give the boronic ester, which would be oxidised *in-situ* to give alcohol **142**. Formation of the triethylsilyl ether would protect the alcohol in preparation for the following lithiation–borylation-oxidation sequence to couple together **143** and the final building block, **134**, to give alcohol **144** after peroxide oxidation. Benzyl protection of the free alcohol and removal of the TES group would give alcohol **145** which would undergo an esterification. Originally, the proposal was to perform a peptide coupling with the terminal carboxylic acid (here protected as the *tert*-butyl ester), followed by a macrolactonisation, however Raghavan's synthesis had optimised conditions for what transpired to be a very challenging esterification and macrolactamisation.[40] One could speculate that if the esterification was challenging due to the sterically demanding nature of the substrate, performing a macrolactonisation to form the same ester bond may have been even more so. It was therefore proposed to perform the esterification first followed by macrolactamisation later in the synthesis. With the esterified product in hand, acid

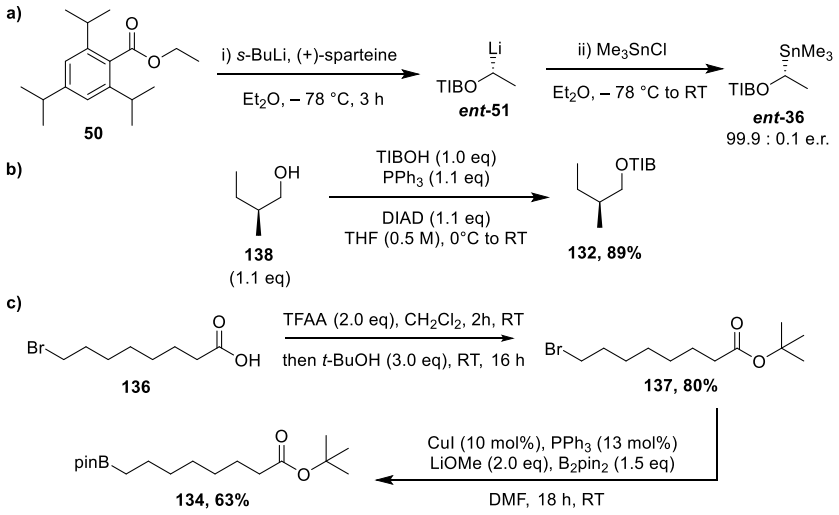
hydrolysis could be used to concomitantly hydrolyse the *tert*-butyl ester and the carbamate to give **146**. From here, the remaining steps are macrolactamisation to give **147**, followed by hydrogenolysis of the benzyl group to give dysoxylactam A (**83**).



Scheme 27: Proposed forward synthesis of Dysoxylactam A.

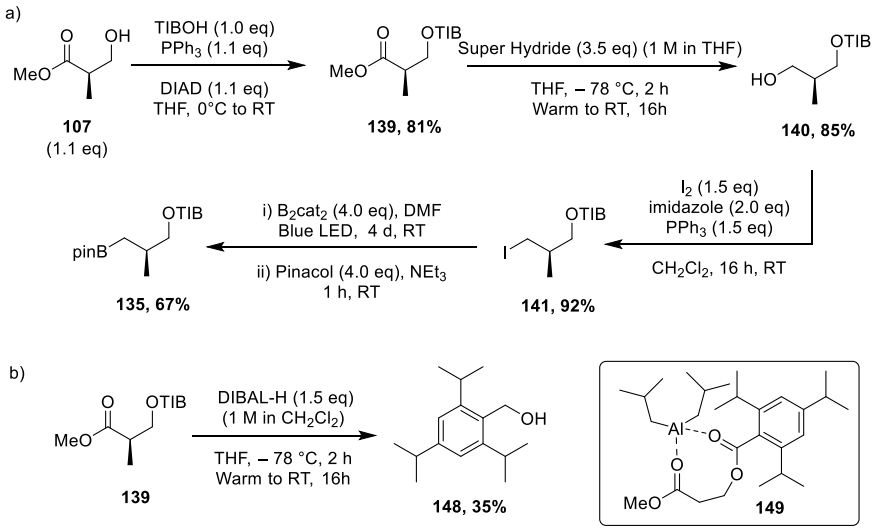
2.1.3. Synthesis of the Starting Blocks

The synthesis of the four building blocks began with synthesis of ***ent*-36**, which is literature known (Scheme **12a**)[30] and ester **132**, prepared *via* a high yielding Mitsunobu reaction.[48] The boronic ester **134** was prepared in two steps from the commercially available compound **136**. Esterification of **136** with TFAA and *t*-BuOH afforded the *tert*-butyl ester **137**, followed by a copper catalysed borylation of the alkyl bromide[52] to give **134** in 63% yield (Scheme **28**).



Scheme 28: a) Synthesis of the stannane ***ent*-36**, b) Synthesis of TIB ester **132**, c) Synthesis of boronic ester **134**.

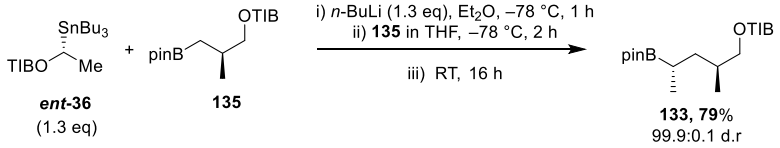
Four steps were required to synthesise boronic ester **135** (**Scheme 29a**), the first of which was subjecting the commercially available (*R*)-Roche ester to Mitsunobu conditions to give the diester **139** in 81%. The methyl ester was then to be reduced in the presence of the TIB ester. Chemoselectivity was not expected to be an issue here, as the carbonyl group of the TIB ester is significantly more hindered than for the methyl ester. As such DIBAL-H was tested as a reductant but proved unsuitable due to competing reduction of the TIB ester, even at molar equivalencies lower than 2, giving 35% yield of compound **148**. It was speculated that the aluminium species could co-ordinate to both carbonyl groups simultaneously (**149**), activating both esters to reduction (**Scheme 29b**). Therefore, we anticipated the use of a similarly hindered but non-coordinating reducing agent would allow regioselective reduction of the methyl ester. This hypothesis was confirmed using Super-Hydride® (lithium triethylborohydride), which delivered the desired alcohol (**140**) in 85% yield. A small amount of the over-reduction product **148** (5% yield) was still formed. This alcohol was subsequently converted to the corresponding alkyl iodide **141** using an Appel reaction in a 92% yield. The final step to obtain **135** was using methodology developed by Studer for the radical borylation of alkyl iodides.[51] There was an initial hesitation to use this method due to the amount of solvent required on a large scale potentially leading to poor light-penetration. On a small scale (1.4 mmol), the reaction proceeded to completion in 24 hours, giving the product in 70% yield. Pleasingly, on a 25 mmol scale (77 mL of solvent), the reaction was completed in 4 days using a 1 L round bottom flask with two 40 W blue LED Kessel lamps, giving a comparable yield of 67% of **135**.



Scheme 29: a) Synthetic route to boronic ester 148. b) Initial attempt at selective reduction of the methyl ester with DIBAL-H.

2.1.4. The Main Sequence

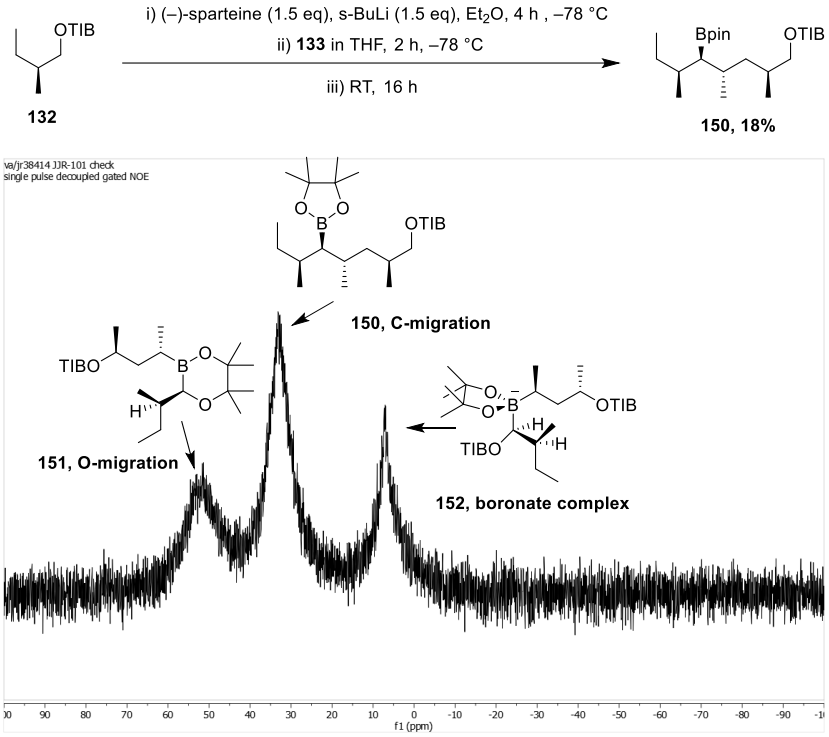
The main sequence started with the homologation of boronic ester **135** with stannane ***ent*-36**, which installed the second stereocentre (**Scheme 30**). This reaction proceeded cleanly, giving the product in 79% isolated yield. This homologation product was often not isolated but used as a crude after a silica plug filtration to remove any insoluble lithium salts.



Scheme 30: The stannane homologation of boronic ester **135**.

The subsequent lithiation–borylation using TIB ester **132** and the product of the above homologation (**133**) proved non-trivial, due to the steric hinderance of both the lithiated TIB ester, and the secondary boronic ester. The reaction was performed using the TIB ester in excess (1.5 eq) as the boronic ester was the valuable substrate (**Scheme 31**). The first step was the stereoselective lithiation of **132** using (–)-sparteine and *s*-BuLi to form a lithiated species which was configurationally stable at –78 °C. This then reacted with the boronic ester **133** added at –78 °C as a solution in THF to form the boronate complex **152**. Warming the reaction permitted the 1,2-metallate rearrangement to commence and the progress of this step of the reaction was monitored by ^{11}B NMR. Under these reaction conditions, the ^{11}B NMR spectrum showed three peaks: 1) the central peak at $\delta \approx 35$ ppm was the desired boronic ester product **150,** which was as a result of C-migration; 2) the

left-hand peak at $\delta \approx 55$ ppm corresponded to unwanted O-migration of one of the pinacol ligand O atoms to displace the leaving group, forming the borinic ester **151**; and 3) the right hand peak at $\delta \approx 5$ ppm corresponded to boronate complex (**152**) which had yet to migrate. Clearly there were two issues to be solved: that of incomplete 1,2-metallate rearrangement, and that of the undesirable occurrence of O-migration.

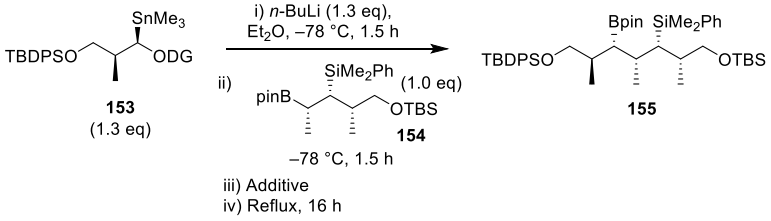


Scheme 31: Lithiation–borylation using substrates **132** and **133** without any additives or heating, and below, the ^{11}B NMR taken after leaving the reaction at room temperature for 16 h.

The Aggarwal group have shown that adding $MgBr_2$ in a solvent to a boronate complex can help encourage a 1,2-metallate rearrangement.[19] Repeating the above reaction but adding $MgBr_2$ in Et_2O at –78 °C before warming resulted in complete 1,2-metallate rearrangement of the boronate complex, but left the ratio of C- and O-migration unaffected at approximately 2:1.

There are very few examples of unwanted O-migration involving boronate complexes in the literature, however work from Aggarwal from 2018 provided an extensive screening of conditions for a similarly hindered lithiation–borylation system (**Scheme 32, Table 1**).[53] Under the typical 1,2-metallate rearrangement conditions, the product (**155**) was obtained in a 36% yield with a 1:1 ratio of C:O migration. Solvent exchange to chloroform and heating to 60 °C lowered the yield, potentially due to decomposition of the product at higher temperatures. Using the diisopropyl carbamate directing group provided the

solution to unwanted O-migration in this instance (Entry 3), and adding $MgBr_2$ in Et_2O further increased the yield (Entry 4). The use of $MgBr_2$ in MeOH allowed the reaction to proceed to completion, delivering an isolated yield of 79% (Entry 5).



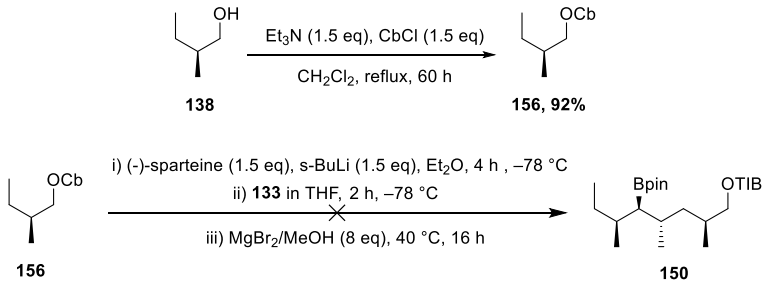
Scheme 32: Literature known lithiation–borylation using very sterically hindered substrates.

Entry	DG	Additive	Yield 155 (%)	Comment
1	TIB	None	36	1:1 C:O migration
2	TIB	Solvent swap to $CHCl_3$, 60 °C	16	1:1 C:O migration
3	Cb	None	40	No O migration, 46% **154** recoverd
4	Cb	$MgBr_2$•Et_2O (8 eq)	51	No O migration, 40% **154** recovered
5	Cb	$MgBr_2$/MeOH (8 eq)	79	No O migration, complete conversion

Table 1: Conditions screened for the above literature described lithiation–borylation.

The stannane (**153**) was pre-formed in the above literature example rather than using sparteine, meaning that the lithiated species was less hindered (no co-ordinating diamine was present) and would more readily form the boronate complex. As the issue with our lithiation–borylation reaction was not associated with boronate complex formation, but with the 1,2-metallate rearrangement, this difference was not concerning.

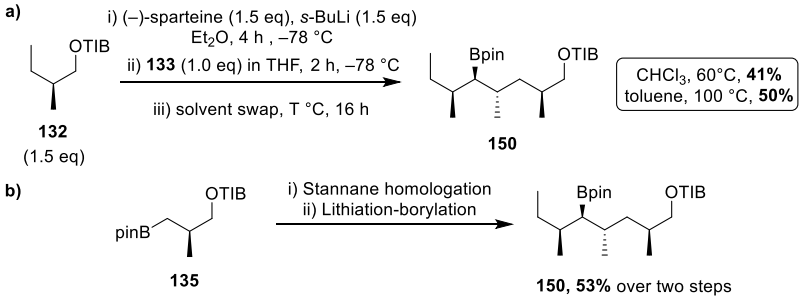
Acknowledging the result in Entry 5 from Table 1, carbamate **156**, an analogue to TIB ester **132**, was prepared and the lithiation–borylation was carried out, with the addition of 8 equivalents of $MgBr_2$/MeOH to initiate the 1,2-metallate rearrangement (**Scheme 33**).



Scheme 33: Use of the carbamate in place of the TIB ester.

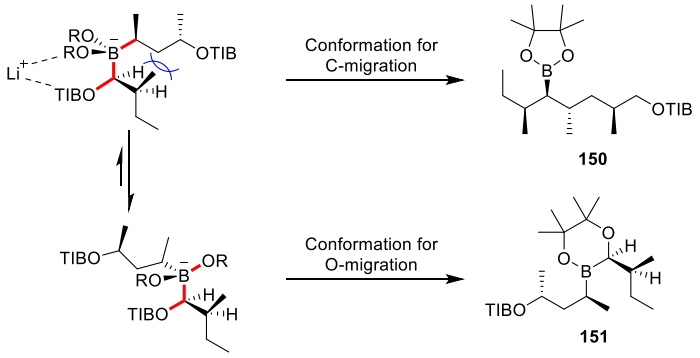
Surprisingly, the ^{11}B NMR showed exclusively O-migration, with no formation of **150**. Unlike Aggarwal's example,[53] the smaller carbamate leaving group favoured the conformation required for O-migration. Clearly the steric and electronic forces at play when predicting C vs O migration were more nebulous than initially thought. Having a boronate complex with two sterically demanding yet conformationally flexible alkyl groups, a large leaving group (TIB or Cb) and a large pinacol ligand on boron makes prediction of the lowest energy conformation of said boronate complex non-trivial.

Next, a solvent exchange to chloroform was attempted, with the possibility of a less polar solvent favouring the conformation required for C-migration over that for O-migration (**Scheme 34a**). Pleasingly, a solvent exchange to chloroform and heating to 60 °C afforded almost exclusive C-migration and no residual boronate-complex remaining. Toluene was also used in an analogous solvent switch, heating in this instance to 100 °C, and the yield of product further increased, with no detectable borinic ester O-migration product. This afforded a two-step procedure consisting of the stannane-homologation and lithiation–borylation: performed on a large scale, this sequence gave a 53% yield over two steps (**Scheme 34b**).



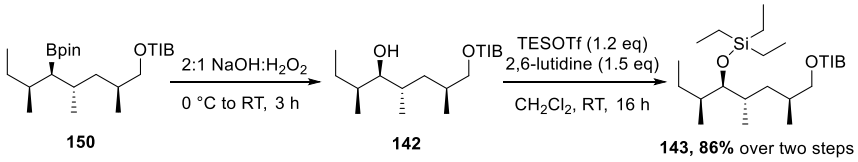
Scheme 34: a) Lithiation–borylation with solvent exchange, b) Two-step homologation lithiation–borylation sequence.

It was believed that the origin of the contra-thermodynamic O-migration was due to the unfavourable steric interaction between the two large groups of the boronic ester and the TIB ester in the conformation required for C-migration. To relieve this steric strain, a rotation about the C-B bond occurs, providing the correct conformation for O-migration. Performing a solvent swap to a less polar (and hence less coordinating) solvent, such as $CHCl_3$ or toluene, allowed a stronger co-ordination of the Li counterion to both the TIB ester and the O atoms of the boronic ester, holding the boronate in the correct conformation for C-migration (**Scheme 35**).



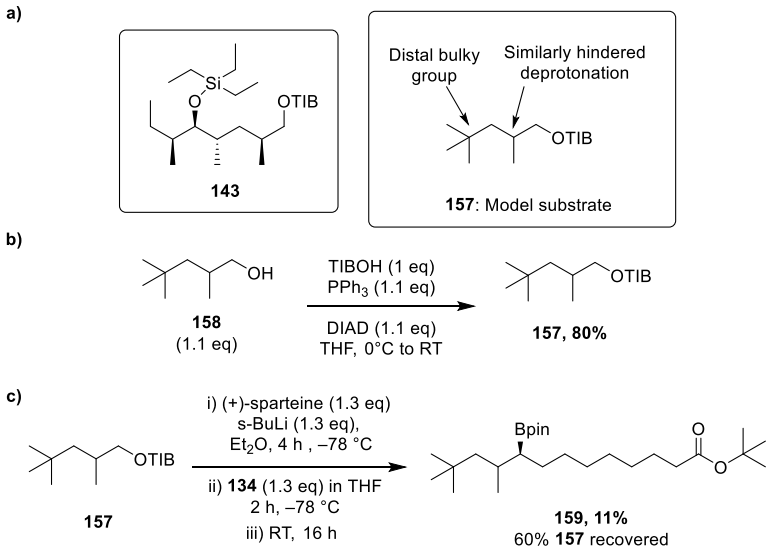
Scheme 35: Conformations required for C and O-migration

The oxidation of the boronic ester and the subsequent TES protection of the alcohol **142** to give **143** proceeded without any issues, giving 86% yield over two steps, with just an aqueous work up between the transformations (**Scheme 36**).



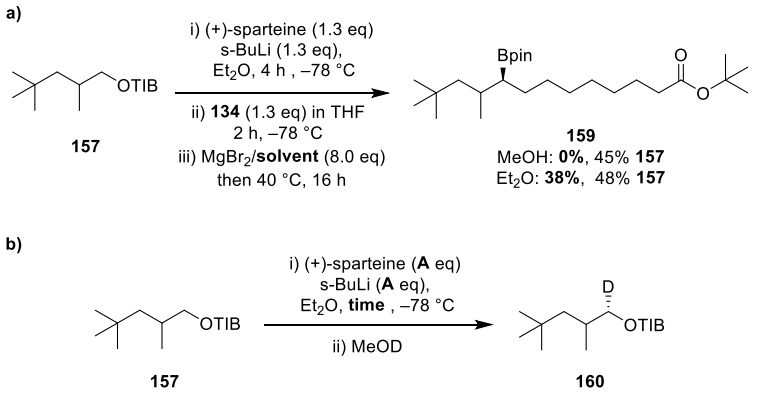
Scheme 36: Oxidation and TES protection.

The next step was the second lithiation–borylation reaction, and it was hoped that given the low steric hinderance of the primary boronic ester, there would be fewer issues with the 1,2-mettalate rearrangement as encountered before. As the TIB ester **143** was valuable, a model substrate **157** was synthesised to test the lithiation–borylation conditions (**Scheme 37a,b)** Using standard lithiation–borylation conditions, the corresponding product (**159**) was obtained in 11% yield, with a significant amount of starting material remaining (**Scheme 37c**).



Scheme 37: a) The model substrate, b) Synthesis of the model substrate, c) Subjecting the model substrate to lithiation–borylation conditions.

Our previous prediction regarding the feasibility of the 1,2-metallate rearrangement had been correct, in this instance the issue was with either the lithiation or borylation. If the boronate complex formation is reversible, then the addition of $MgBr_2$ may help the boronate complex undergo 1,2-metallate rearrangement before dissociating back into the lithiated species and the boronate complex. $MgBr_2$ in both Et_2O and MeOH were used (**Scheme 38a**). No product was observed using MeOH; this is perhaps unsurprising, the lithiated species and boronic ester may exist predominantly as separate species rather than as a boronate complex and the use of a protic solvent will immediately quench the lithiated species. The addition of $MgBr_2$ in Et_2O produced a considerable increase in yield, however there was still a significant amount of starting material remaining. Probing the lithiation of the substrate *via* deuterium trapping and subsequent NMR analysis showed that incomplete lithiation was also an issue with 1.3 equivalents of *s*-BuLi, the limit of lithiation appeared to be around 82%. Raising the equivalents of s-BuLi to 1.5 permitted 97% lithiation of the substrate after 6 hours (**Scheme 38b, Table 2**).

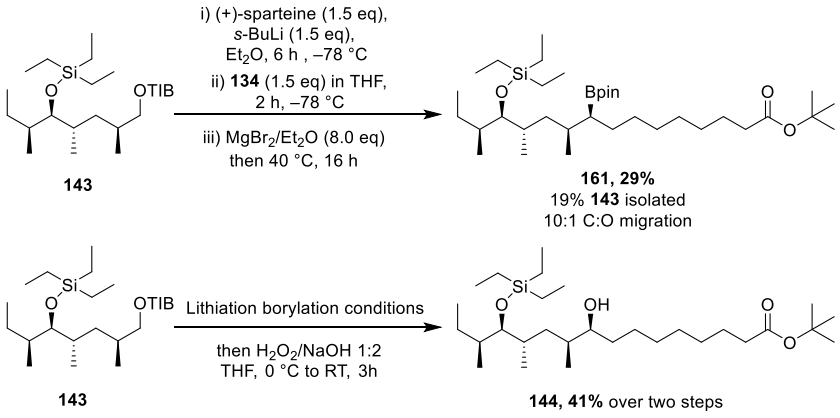


Scheme 38: a) Use of $MgBr_2$ to encourage 1,2-metallate rearrangement, b) Lithiation-deuteration experiments.

A, equivalents of *s*-BuLi/sparteine	**Time**, h	D incorporation, %
1.3	4	68
1.3	6	81
1.3	9	82
1.5	6	97

Table 2: Conditions for the lithiation-deuteration experiments.

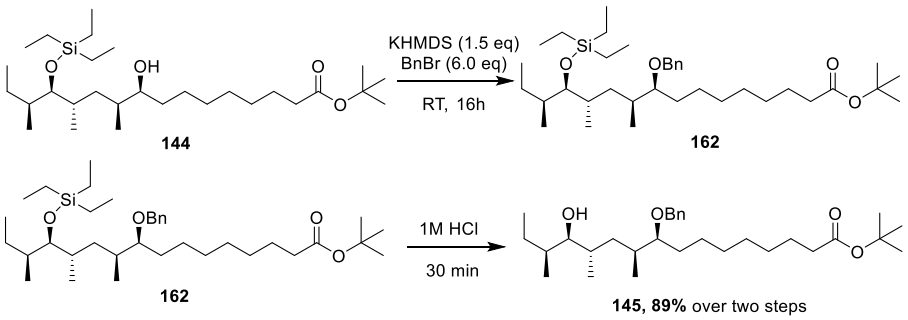
With these results in mind, the actual substrate **143** was subjected to the optimised conditions (**Scheme 39**), giving 29% of product **161** with 19% starting material (**143**) isolated. ^{11}B NMR also showed that there is a roughly 10:1 ratio of C- to O-migration. As the isolated yield of **161** did not match with its NMR yield of 58%, whereas there was a good match between isolated and NMR yield of starting material, it was suspected that the product may be unstable to silica. This was shown to be the case, as immediate oxidation of the crude mixture to the alcohol **144** afforded the product in 41%, a value closer to that of the NMR yield. Only one diastereoisomer was observed by NMR.



Scheme 39: Lithiation–borylation with and without subsequent oxidation.

The following two steps were benzyl protection using benzyl bromide, and concomitant deprotection of the silyl ether and the hydrolysis of the ester to the free acid (**Scheme 40**).

Under these conditions however, the *tert*-butyl ester remained intact, giving compound **145** in 89% yield with no free acid present.



Scheme 40: Benzyl protection and attempted concomitant deprotections.

It was at this point that Ye's synthesis of dysoxylactam A was published. Raghavan's synthesis was very different in terms of methodology utilised, so it was worthwhile continuing with our route, however Ye's synthesis utilised both lithiation–borylation as well as an overall linear approach to generating the required stereocentres. Attention was therefore turned towards the route designed to be more amenable to automation.

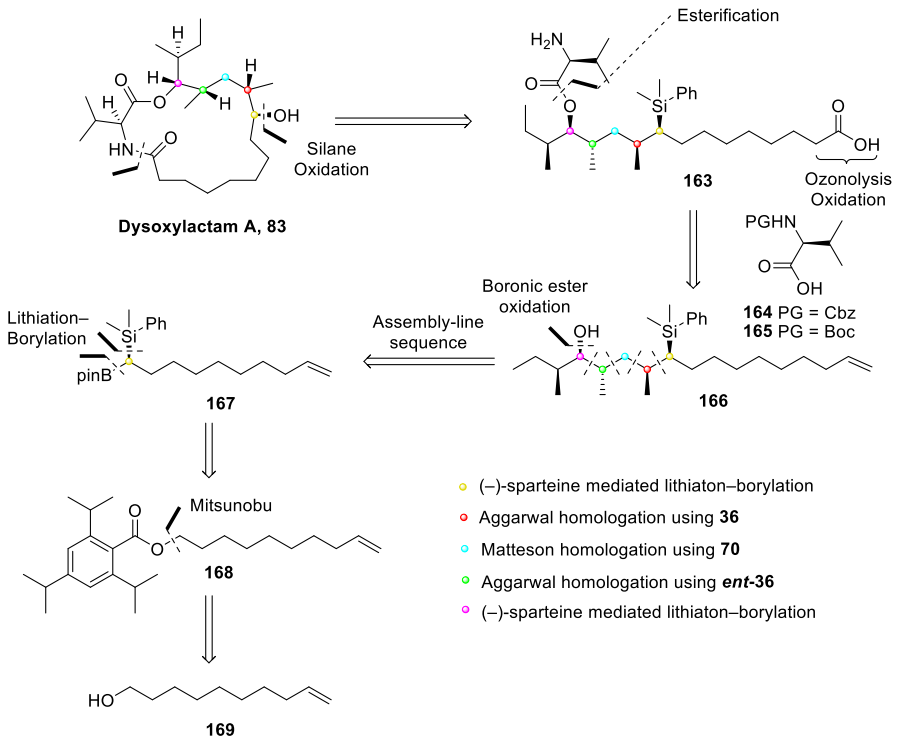
2.2. Automation Amenable Synthesis of Dysoxylactam A

2.2.1. Pre-requisites for Automation

With the aim of using the Chemspeed Automation Platform to assist in the synthesis of dysoxylactam A and analogues thereof, there were criteria to be met by the proposed synthesis to allow the technology to be utilised effectively. The main method of derivatisation of dysoxylactam A was to generate analogues by varying the stereochemistry of the lipophilic backbone; it was therefore necessary to use chemistry amenable to automation to generate this part of the analogues. Once the automated sequence was completed, and multiple analogues had been generated, the aim was to minimise any further synthetic steps to get to the desired dysoxylactam analogue, as performing many transformations outside of an automated setting on multiple analogues would be a laborious affair.

2.2.2. Retrosynthetic Analysis

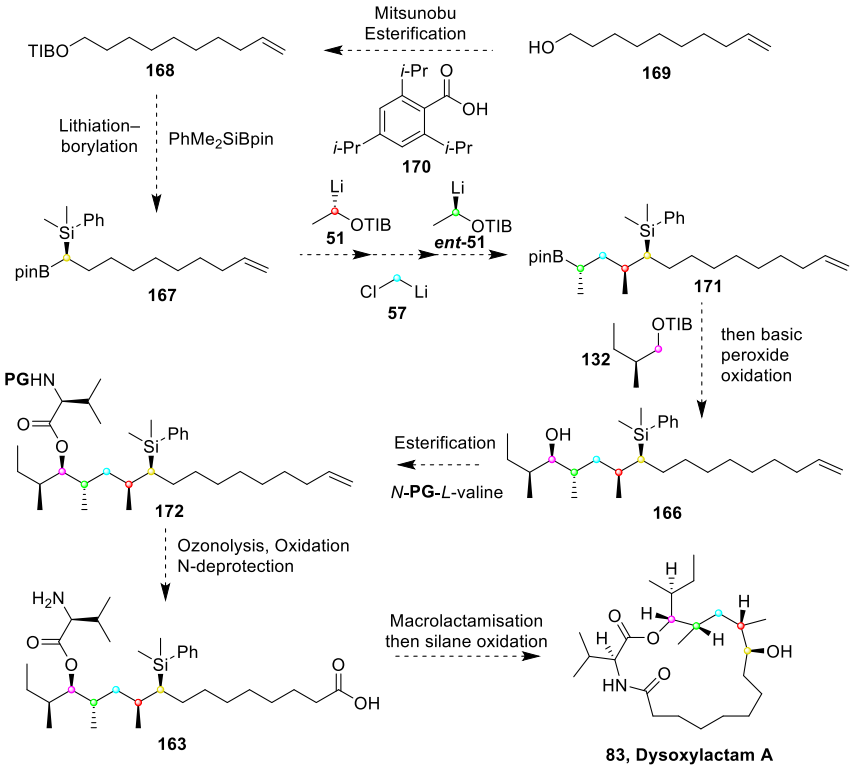
Our retrosynthetic analysis of dysoxylactam A (**83**) had the alcohol present in the natural product being masked as a silane, and the 17-membered macrocycle being formed by macrolactonisation of amino acid **163**. The carboxylic acid was to be masked as an alkene, with the ester bond being formed by esterification of the alcohol **166** with the N-protected amino acid **164** or **165**. The alcohol could be accessed rapidly using a four-step assembly-line synthesis from the chiral α-silylboronic ester **167**. This would be formed via silylboration of the TIB ester **168**, which could be synthesised from the corresponding commercially available alcohol **169** (Scheme **41**).



Scheme 41: Retrosynthetic analysis for dysoxylactam A.

2.2.3. Forward Synthesis

Our planned forward synthesis (Scheme **42**) commences from the commercially available alcohol **169**, which could be transformed into the corresponding TIB **168** ester using Mitsunobu esterification conditions, where the required carboxylic acid is 2,4,6-triisopropylbenzoic acid. Silyl-boration of this species using the Suginome reagent ($PhMe_2SiBpin$) would then give the α-silylboronic ester **167**. It is from this species that the four-step assembly-line synthesis would begin, to provide after four homologations and oxidative work-up, the alcohol **166**, with a single chromatographic purification at the end of the sequence. This alcohol could then be coupled with the desired *N*-protected-L-Valine fragment to give ester **172**. The carboxylic acid, which has been masked as the alkene up to this point in the synthesis, may be revealed by ozonolysis to the aldehyde, followed by oxidation. Deprotection of the protected amine would give the amino acid **163**, which could then be subjected to macrolactamisation conditions to give the macrocyclic silane. A final silane oxidation could then afford dysoxylactam A (**83**).

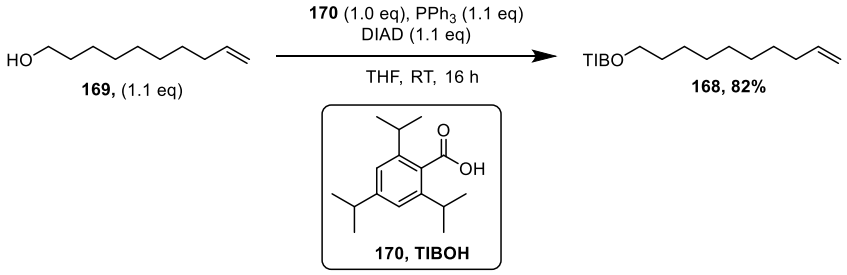


Scheme 42: Proposed forward synthesis of dysoxylactam A.

The criteria regarding the amenability of this synthesis towards automation have been met with this route: the synthesis of the stereochemically dense lipophilic part of the molecule, the main area of derivatisation for the synthesis of analogues, must be performed using chemistry amenable to automation, and the number of post assembly-line steps must be minimised. The homologation chemistry required for the assembly line can be automated reliably and in yield comparable to that obtained in the lab[54] - the fourth boronic ester homologation is expected to perform similarly well using (−)-sparteine (as opposed to using the enantioenriched stannane), and oxidation of the resultant boronic ester would be trivial. Once the assembly-line synthesis has been completed, the following steps, excluding the esterification of the hindered alcohol, are relatively straightforward, established transformations, with steps such as the ozonolysis and oxidation of the resultant aldehyde requiring minimal purification.

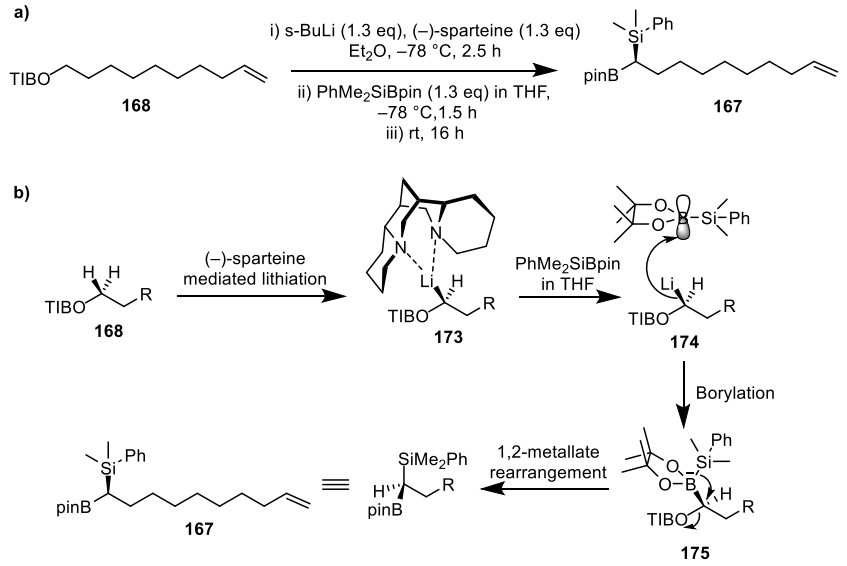
2.2.4. Synthesis of the α-silylboronic ester 167

The α-silylboronic ester **167** was synthesised conveniently in two steps from the commercially available alcohol **169**. A Mitsunobu esterification provided the TIB ester **168** in a high yield (Scheme **43**).



Scheme 43: Mitsunobu esterification of alcohol **169**.

The subsequent silylboration (Scheme **44a**) of this TIB ester often proceeded with a good to excellent yield, however, minor amounts of starting material **168** remained, which were inseparable from the product. The first step of the silylboration was the (−)-sparteine-mediated enantioselective deprotonation of the TIB ester **168** to give the lithiated species **174**, which at −78 °C was configurationally stable. Addition of the boronic ester in THF formed the boronate complex (**175**). This species upon warming to room temperature underwent the stereospecific 1,2-metallate rearrangement, in which the silane migrates from boron to carbon, extruding the TIB carboxylate leaving group and giving the desired product **167** (Scheme **44b**).



Scheme 44: a) Conditions for the silylboration of **168**. b) Mechanism for the silylboration reaction.

Entry	Scale (mmol)	Base/Ligand/Bpin (eq)	Yield of 167	168 remaining
1	2.0	1.3	63%	20%
2	3.0	1.3	73%	18%
3	4.5	1.3	83%	9%

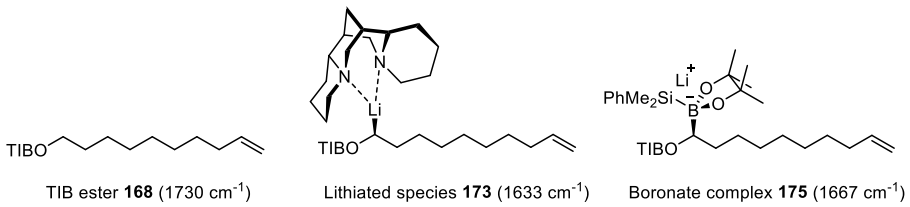
Table 3: Optimisation of scale and stoichiometry of the silylboration reaction.

Performing this reaction using standard lithiation–borylation procedure as shown in Scheme **44a** returned 20% of the starting material whilst also delivering a reasonable

yield of 63% (Table **3**, Entry 1). The scale of the reaction was increased, keeping all other reaction parameters constant; this provided a better conversion of the starting material as well as an increased yield of the product (Entries 2 - 3). Attempts to further improve the reaction yield via increasing the amount of *s*-BuLi also proved to be ineffective.

This unreacted starting material, although inconvenient due to its inseparability from the product, does not present any significant complications in the following assembly-line sequence: the TIB ester **168** can simply be carried through the assembly line sequence as a non-reactive species which can be easily separated from the alcohol **166** at the end. Investigations into this reaction would have stopped at this point, however the need to synthesise more of the α-silylboronic ester (**167**) for the purposes of bringing through material provided further opportunities for investigation. This reaction was in the next instance monitored by in-situ infra-red spectroscopy[48] (React IR) on a 2.0 mmol scale, directly comparable with Entry 1 in Table **3**.

React IR measures the IR spectrum of a mixture at set time intervals (every 30 seconds) by means of a probe that is inserted directly into the reaction mixture. This technique is particularly useful for lithiation–borylation since the TIB ester, the lithiated TIB ester and the boronate complex have different and distinct carbonyl stretching frequencies (1730 cm^{-1}, 1633 cm^{-1} and 1667 cm^{-1} respectively). The intensities of these peaks can be monitored and plotted against time (Figure **3**).



TIB ester **168** (1730 cm^{-1}) Lithiated species **173** (1633 cm^{-1}) Boronate complex **175** (1667 cm^{-1})

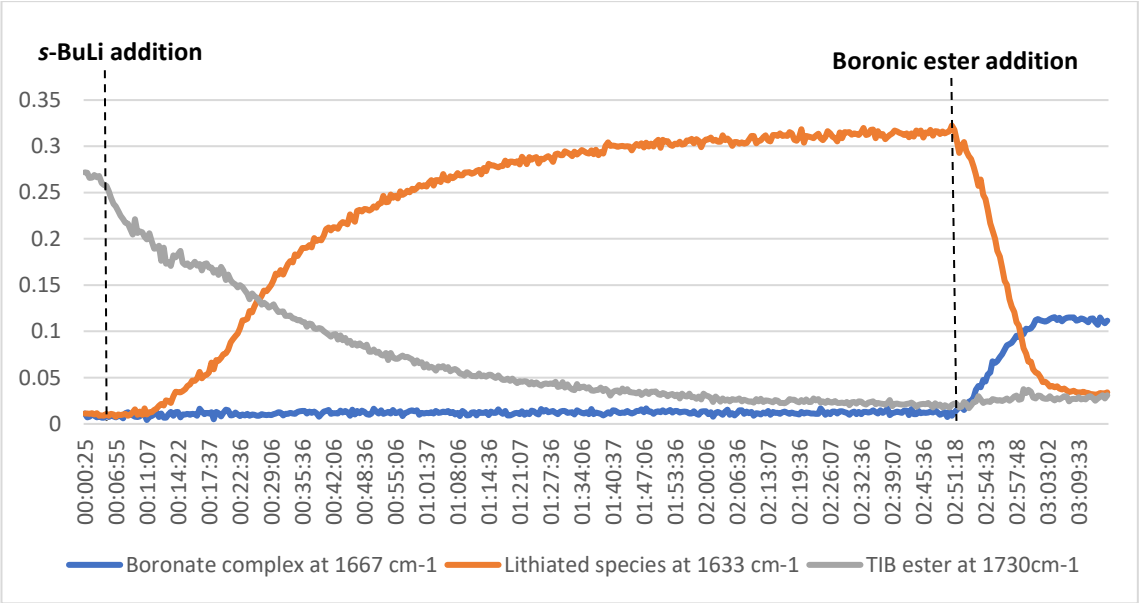
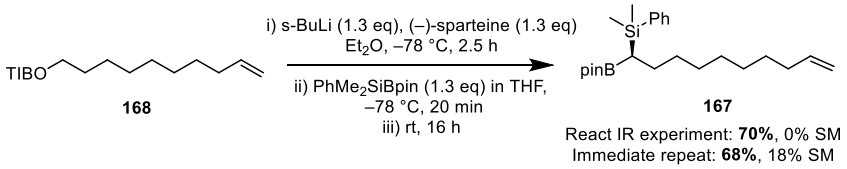


Figure 3: In-situ IR trace of the silylboration of TIB ester **168**.

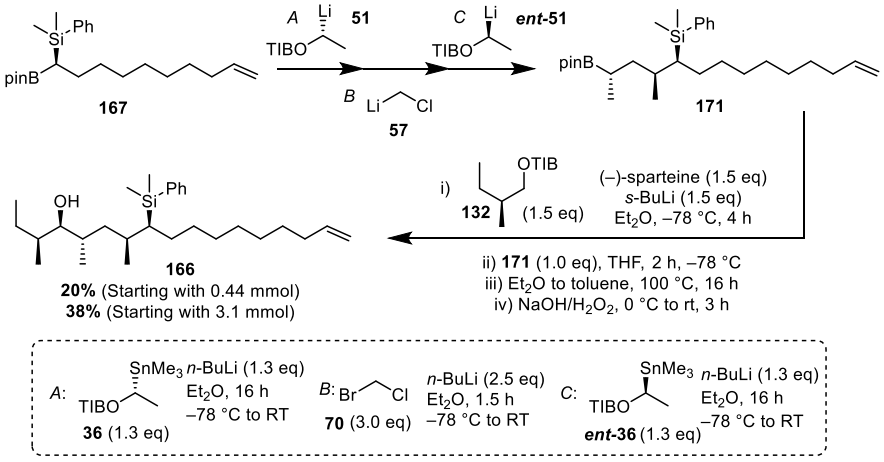
At the beginning of the experiment (t = 0) the only peak present is the peak corresponding to that of the starting material. Upon the addition of *s*-BuLi, at approximately t = 5 min, the intensity of the peak corresponding to the TIB ester decreases and the intensity of the peak corresponding to the lithiated species increases. This continues until the trace for the lithiated species plateaus, at around t = 120 min, indicating complete lithiation (or as much lithiation as will occur under these conditions). At t = 170 min, the boronic ester is added: the peak corresponding to the lithiated species drops rapidly in intensity, accompanied by a new peak corresponding to the boronate complex increasing in intensity, until a plateau is achieved 10 minutes later. These results show that the lithiation takes around 2 h, and that the borylation is in this case quick, taking 10 minutes. In contrast to previous results, the product from this reaction was isolated in 70% yield, with no starting material recovered. An immediate repeat using the exact same reagents and conditions, on a 2 mmol scale, excluding the IR probe, gave a result of 68% yield of the product with 18% starting material remaining (Scheme **45**), which is in line with previous results (Table **3,** Entry 1). It is not clear why the reaction monitored using React IR proceeded to completion, unlike previous silylboration reactions. The problem was not looked at any further.



Scheme 45: Silylboration results using React IR and immediately afterwards.

2.2.5. The Assembly Line Synthesis of 85

A key feature of this synthesis compared to the previous synthetic route towards dysoxylactam A was the utilisation of the assembly-line methodology to construct the lipophilic portion of the molecule with excellent stereocontrol and with only a single chromatographic purification at the end. The assembly-line sequence consisted of a stannane homologation with **36**, derived from (−)-sparteine; a Matteson homologation; a second stannane homologation with ***ent*-36**, derived from (+)-sparteine; and then a final lithiation–borylation with TIB ester **132**, (−)-sparteine, and the boronic ester **171** to give, after oxidative work-up of the boronic ester, the alcohol **166** (Scheme **46**).



Scheme 46: The assembly-line sequence of boronic ester **167** to form alcohol **166**.

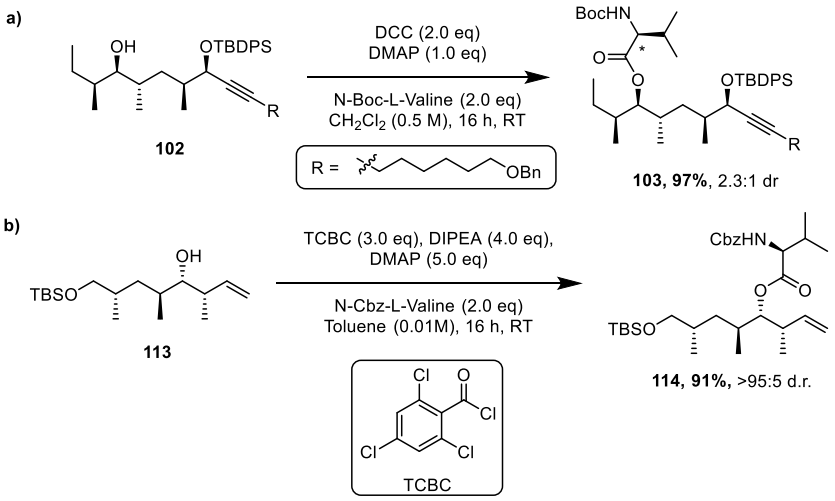
On a small scale the alcohol could be isolated in 20% yield. Performing the assembly-line synthesis on a larger scale gave a better isolated yield of 38% over four steps, perhaps due to the practical advantages of working on a larger scale. Various side products formed throughout the assembly-line synthesis which proved to be difficult to separate from the desired alcohol product. However, using Normal phase Preparatory HPLC (using multiple runs on a large scale) allowed isolation of the desired alcohol.

The conditions typically used in the 1,2-metallate rearrangement of boronate complexes, in which the leaving group is the TIB carboxylate, are to let the reaction mixture stir at ambient temperature overnight. The conditions used for the 1,2-metallate rearrangement

of the final lithiation–borylation with boronic ester **171** were to perform a solvent swap to toluene and then heat to reflux; these conditions were taken from a previously optimised lithiation–borylation in the first proposed synthetic route to dysoxylactam A (Chapter 2.1.4, Scheme **34**). Due to the similarity of the boronic ester **133** to the actual boronic ester substrate **171**, these conditions were used in the assembly-line sequence without any further optimisation.

2.2.6. Cbz as a Protecting Group on N

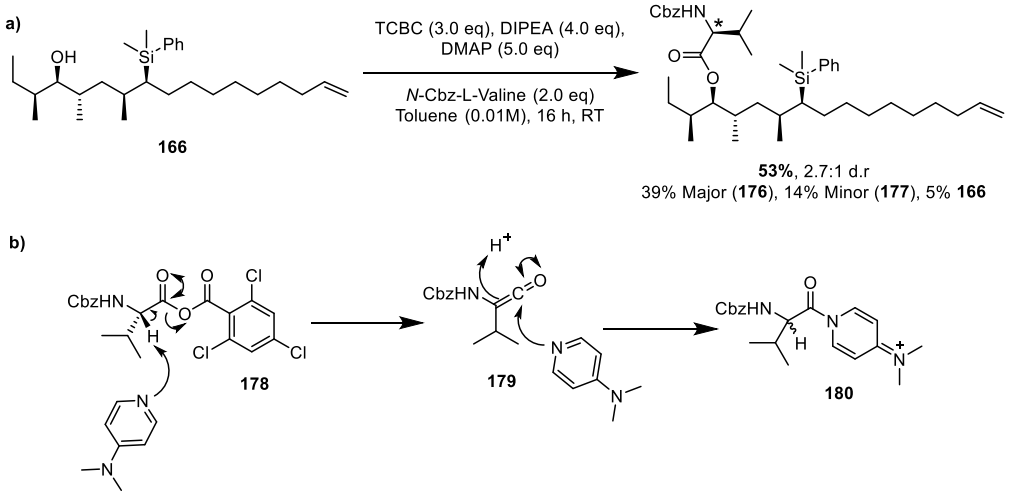
With the assembly-line product **166** in hand, the next step was the esterification of the alcohol with *N*-Cbz-L-valine. Such esterifications are often notoriously difficult, both Raghavan and Ye reported their analogous esterifications to be non-trivial.[40,44] Raghavan had shown that typical conditions such as HOBt/EDCI, HOBt/HATU, DIPEA/BOP-Cl, DIPEA/cyanuric chloride and DCC/DMAP (0.2 eq.) provided no product at all, with only recovery of the starting material. Successful esterification was achieved using DCC with an equivalent of DMAP, providing the product in a 97% yield, with significant epimerisation of the amino acid stereocentre (Scheme **47a**).[40] This epimerisation could be avoided using Yamaguchi esterification conditions,[55] as reported by Ye and co-workers (Scheme **47b**).[44]



Scheme 47: a) Raghavan's Steglich esterification conditions. b) Ye's Yamaguchi esterification conditions.

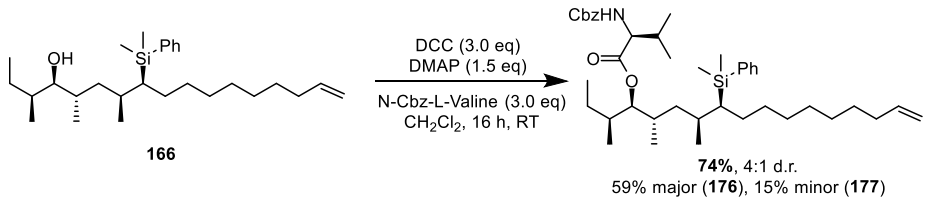
Opting first for Ye's conditions, due to the method reportedly causing no observable epimerisation, a 53% yield was obtained using our substrate, with a small amount of starting material remaining. As was reported by Ye, epimerisation of the amino acid stereocentre was not detected by NMR, however after purification of the reaction mixture using normal-phase preparatory HPLC it was clear by TLC that epimerisation had

occurred, giving a ratio of 2.7:1 of the major epimer to the minor epimer, which corresponded to a 39% yield of the desired diastereoisomer of the product (Scheme **48a**). It is likely that epimerisation of this amino acid stereocentre occurs due to deprotonation by DMAP or DIPEA once the carboxylic acid has been activated by TCBC to form the ketene, which can then be attacked by a nucleophile and re-protonated without stereocontrol (Scheme **48b**).[56]



Scheme 48: a) Ye's esterification conditions applied to **166**. b) A possible mechanism for the epimerisation of the amino acid stereocentre.

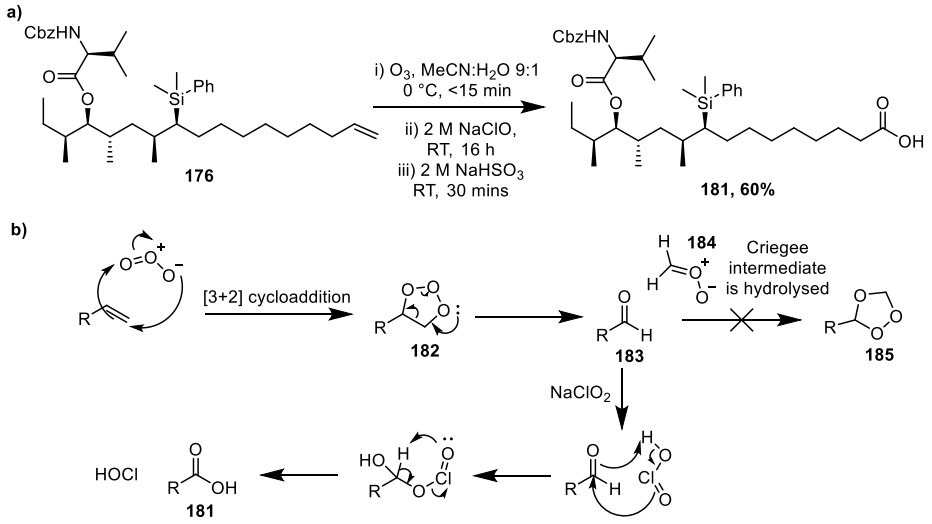
Having obtained a poor yield of the desired diastereoisomer using Yamaguchi esterification conditions, and with the knowledge that the diastereomers resulting from the unwanted epimerisation can in our case be separated, our alcohol was subjected to the Steglich esterification conditions reported by Raghavan. A poor d.r. was once again observed, however the yield was higher, providing the esterified product in a 74% yield and a 4:1 d.r (Scheme **49**). For full consumption of our alcohol, an extra 50% of all reagents was required compared to the reported conditions.



Scheme 49: Steglich esterification conditions on the alcohol **166**.

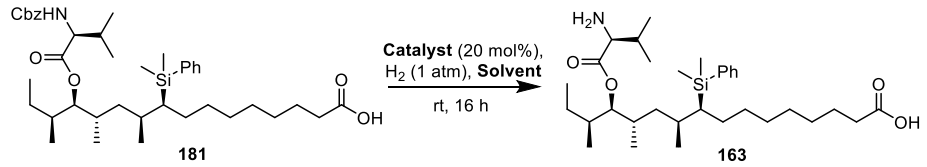
The next step was the one-pot ozonolysis-oxidation described by Cochran,[57] which delivered the desired carboxylic acid in a 60% yield (Scheme **50a**). First, the ozonolysis is performed in a MeCN/H_2O solvent mixture at 0 °C. After fragmentation of the primary

ozonolide **182**, the Criegee intermediate (**184**) is immediately hydrolysed, preventing the formation of the secondary ozonolide (**185**) which would typically require an extraneous oxidant to afford the desired aldehyde. The addition of $NaClO_2$ as a 2 M aqueous solution oxidises the aldehyde to the carboxylic acid (**181**). Typically, the Pinnick reaction would require a hypochlorite scavenger, however the stoichiometric amount of peroxide present in the solution (from hydrolysis of the Criegee intermediate) acts as the scavenger in this case (Scheme **50b**).[58]



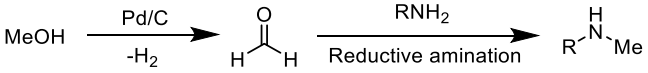
Scheme 50: a) Ozonolysis and oxidation of the alkene **176**. b) The mechanism of the one-pot ozonolysis-oxidation.

The next step in the reaction sequence was the hydrogenolysis of the Cbz group, which would reveal the free amine, ready for the macrolactamisation. Typical conditions for the hydrogenolysis of Cbz groups employ Pd/C (or the in situ generation of Pd(0)) in MeOH.[59–61] However, in our case, poor solubility of the starting material prevented the hydrogenolysis from proceeding to completion. Furthermore, the isolated product was identified to be the N-methylated amino acid. Presumably, dehydrogenation of the solvent by the palladium catalyst formed formaldehyde which condensed with the free amine, and after delivery of hydride by the palladium catalyst formed the irreversibly methylated product, observable using TLC-MS (Scheme **51**). Swapping the solvent from MeOH to EtOAc remedied the latter issue, however the conversion to the product was still very slow. Using $PdCl_2$ with both MeOH and EtOAc produced many undesired side products, observable by TLC (Table **4**).



Entry	Catalyst	Solvent	Comments
1	Pd/C	MeOH	Incomplete conversion, amine methylated
2	Pd/C	EtOAc	Poor conversion
3	$PdCl_2$	MeOH	Complete consumption of **181**, unclean reaction
4	$PdCl_2$	EtOAc	Complete consumption of **181**, unclean reaction

Table 4: Hydrogenolysis conditions used to remove Cbz



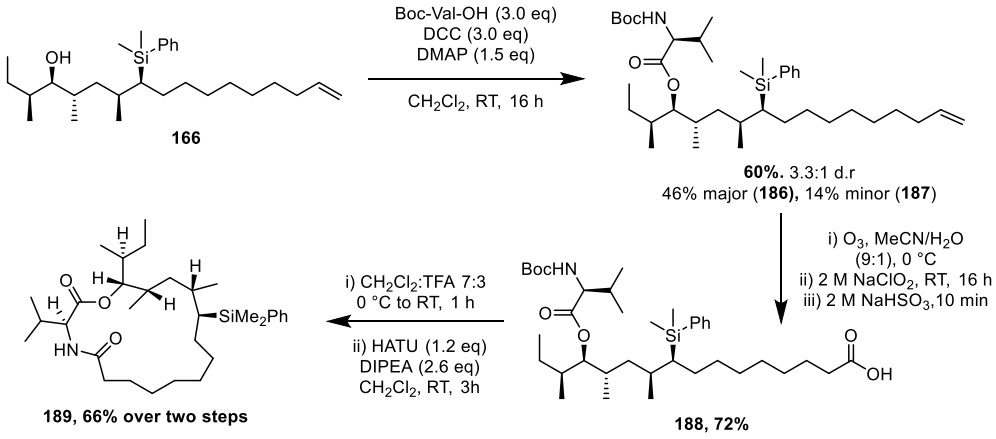
Scheme 51: Amine methylation pathway.[62]

Due to the unexpected issues that arose in the hydrogenolysis of the Cbz group to reveal the free amine, this avenue of investigation was ended.

2.2.7. Boc as a Protecting Group on N

After the issues that arose in the hydrogenolysis of the Cbz group, it was decided to change the *N*-protecting group to Boc. The Boc group would then be removed using TFA to give the amino acid.[40]

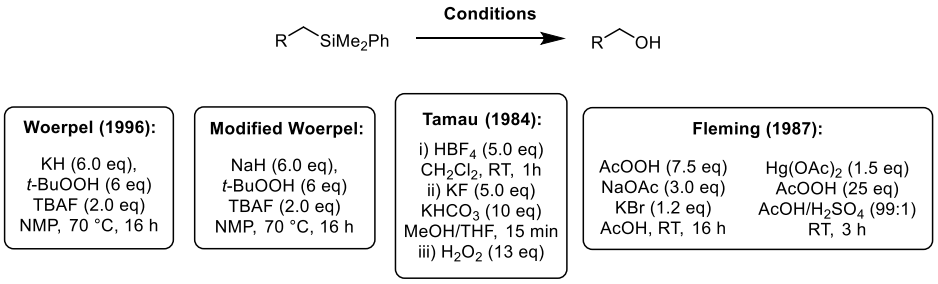
Esterification of the alcohol **166** under identical conditions to before (Scheme **52**) would give the product as a 3.3:1 ratio of epimers, with the major epimer (**186**) formed in a 46% yield, once again separable from the minor epimer using preparatory HPLC. Subjecting this material to the one-pot ozonolysis-oxidation procedure delivered the carboxylic acid (**188**) in 72% yield. This material could be used without purification in a sequence of *N*-deprotection followed by macrolactamisation to give the macrocyclic silane **189** in a 66% yield over two steps, the conditions for which were described by Raghavan (Scheme **52**).[40]



Scheme 52: Synthesis of the macrocyclic silane **189**.

2.2.8. Silane Oxidation

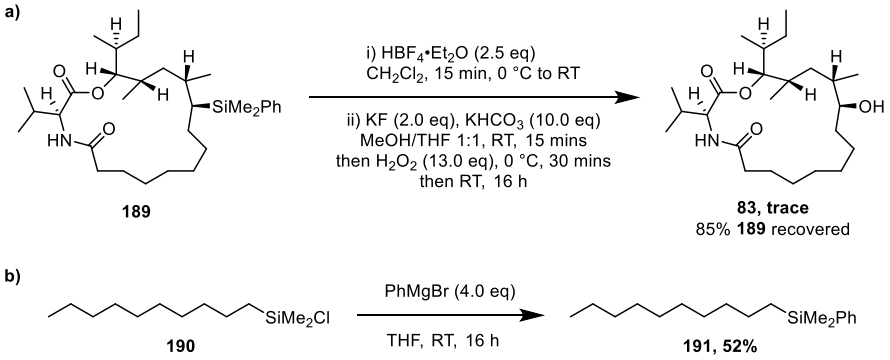
The final step in the synthesis was oxidation of the macrocyclic silane, installed in the second step of the synthesis to act as a masking group for the alcohol. There were different avenues that could be taken for the silane oxidation (Scheme **53**) – Woerpels silane oxidation conditions,[63] with some practical modifications, have previously been used by the Aggarwal group for the oxidation of sterically hindered silanes.[64] Another method developed by Tamao used HBF_4 to generate a reactive fluorosilane, which was then oxidised to the alcohol with peroxide under neutral, acidic, or basic conditions.[65]Alternatively, Fleming developed two sets of conditions for the more convenient one-step silane oxidation, utilising the electrophilicity of Br^+ or Hg^{2+} to activate the phenyl group of the silane.[66,67]



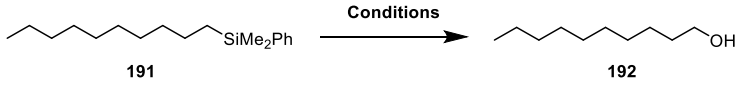
Scheme 53: Silane oxidation conditions.

An initial attempt was made on the macrocyclic silane using Tamao's conditions, described by Ito.[68] These conditions provided a small amount of the desired natural product (enough for HR-MS confirmation), however the conversion was poor and 85% of the silane starting material was reisolated. This material was then subjected to the modified Woerpel conditions described by Aggarwal, which returned only starting material. It was suspected that the issue with Tamao's conditions was the inherent

reactivity of the substrate under the reaction conditions, however the observation that Woerpels conditions gave no conversion at all was more indicative of a reagent being of poor quality (Scheme **54a**). Due to the value of the macrocyclic silane, a model substrate (**191**) was synthesised to test the various silane oxidation conditions (Scheme **54b**, Table **5**).[63]



Scheme 54: a) Tamao's conditions applied to **189**. b) Synthesis of the model substrate.



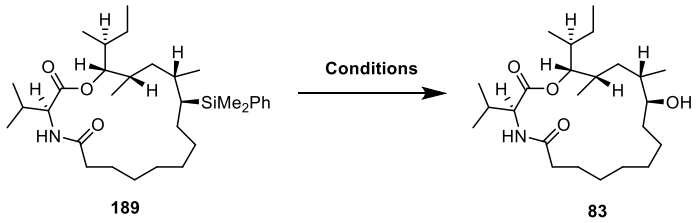
Entry	Conditions	NMR yield
1	Woerpel	86%
2	Modified Woerpel	83%
3	Fleming (KBr)	60%
4	Fleming ($Hg(OAc)_2$)	91%

Table 5: Screening of silane oxidation conditons using the model silane **191**.

The Woerpel (Table **5**, Entry 1) and modified Woerpel (Entry 2) silane oxidation conditions provided very similar yields, indicating that the substitution of KH for the more easily handled NaH did not seem to affect the reaction in this case. Fleming's one-pot oxidation using KBr as a source of Br^+ (generated by the reaction of AcOOH with KBr to give AcOBr as the Br^+ source) provided the product in a 60% NMR yield (Entry 3), whereas using $Hg(OAc)_2$ yielded the product in a 91% NMR yield (Entry 4).

The first conditions attempted on the macrocyclic silane **189** were the modified Woerpel conditions, unfortunately none of the desired natural product was formed, despite the starting material being completely consumed. TLC-MS analysis confirmed the presence of the ($M+H_2O+H^+$) ion of **189** as the major product, indicating that hydrolysis had taken place under the basic Woerpel oxidation conditions, presumably of the more reactive ester bond. Fleming's one-pot silane oxidation conditions using KBr were tried next. Again, the starting material was consumed, and a small amount of product was formed, however

the dominant species were the ketone **194**, representing over-oxidation, and some unidentifiable reaction intermediate containing a dimethylsilyl moiety (**193**). It was then found after the fact that the oxidation of an aliphatic secondary alcohol to the corresponding ketone is known under these conditions.[69] Finally, Fleming's $Hg(OAc)_2$ conditions were tried, and pleasingly the reaction proceeded smoothly, consuming the starting material in three hours and cleanly providing dysoxylactam A (**83**) in a 67% yield).



Entry	Conditions	Result
1	Tamao	<10% **83**, 85% **189** recovered
2	Modified Woerpel	Hydrolysis of **83**
3	Fleming (KBr)	30% **194**, ≈20% **193**, <5% **83**
4	Fleming ($Hg(OAc)_2$)	67% **83**

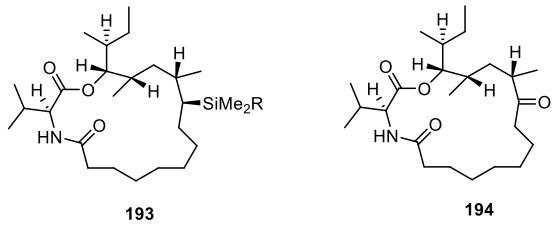


Table 6: Summary of silane oxidation conditions applied to **189**.

With this, the total synthesis of dysoxylactam A was completed. This route featured an assembly line synthesis which rapidly constructed the stereochemically dense lipophilic portion of the molecule in four steps and needed only a single chromatographic purification. The complete sequence only required five chromatographic purifications and the use of a single protecting group, making it the ideal route for the rapid and efficient synthesis of analogues. The obtained experimental data (NMR, mass spectrometry, IR and optical rotation) was consistent with that in the literature.

2.3. Future work

With the total synthesis of dysoxylactam A completed, it would be of interest to look at the synthesis of analogues for biological testing. Our synthesis, utilising assembly-line methodology and minimising chromatographic purifications is ideally suited to this purpose.

Work within the group has demonstrated the ability of the Chemspeed Automation Platform to perform up to six iterative lithiation–borylation reactions in a fully automated setting with only a single purification required at the end.[54] This automated approach could be used to synthesise analogues of the alcohol **166** rapidly (Figure **4**).

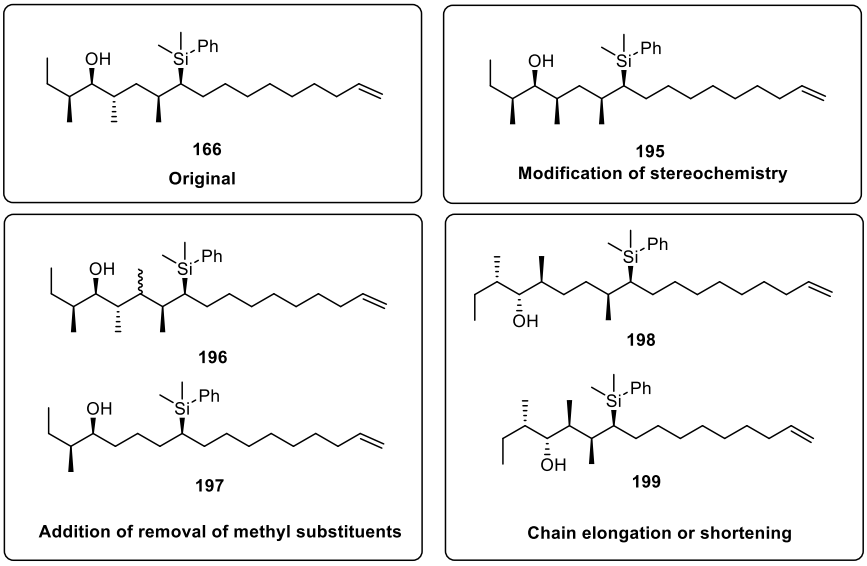


Figure 4: Modification of the alcohol **85** to synthesis analogues of dysoxylactam A.

Modification of the stereochemistry could be simply done by using the opposite enantiomer of the stannane **36**/***ent*-36** for one of the homologations in the assembly line. Addition (**196**) or removal (**197**) of the methyl substituents, which would affect both the lipophilicity and conformational rigidity of the final natural product, could be performed by simply replacing a Matteson homologation for a stannane homologation, or *vice* versa. Finally, adding or removing a homologation would allow for chain elongation (**198**) or shortening (**199**), which would result in a differently sized macrocycle in the final product. There are further options for diversification, however these suggestions present a good starting point utilising chemistry that has been previously optimised for automation.

3. Towards the Automated Total Synthesis of Kalkitoxin

3.1. Automation in Organic Synthesis

In 1984, Robert Bruce Merrifield was awarded the Nobel Prize in Chemistry 'for his development of methodology for chemical synthesis on a solid matrix'. It was in 1963 that Merrifield published his seminal work on the solid phase synthesis of a tetrapeptide which won him this prize.[70] Only two years later, in 1965, Merrifield described the synthesis of a nonapeptide using the aforementioned method on an automated platform[71] – the first automated platform in organic chemistry. This work remains one of the most remarkable achievements in the discipline. In the 57 years that have since passed, there have been fields within organic chemistry that have been discovered, established, and reached maturity, however automation is still very much in its infancy. The challenges that face those in the field are not only chemical in nature, but also technological and mechanical, and this technology is only just catching up to the ambitions and ideas of the chemists. The simple aspects of practical chemistry that can be effortlessly performed by a chemist require a significant amount of ingenuity and resources to be translated to an automated setting. It is for this reason that the scope of chemistry that can be automated has for a long time been limited to the robust and operationally simple C-N (peptide) and P-O (oligonucleotide) bond forming reactions in which the purification is a sequence of washes to remove excess reagents and impurities from the oligomer, which is retained on a solid matrix. In the last decade, there have been significant advances towards the 'universal synthesiser', one which can perform any chemistry, which will be discussed in this chapter.

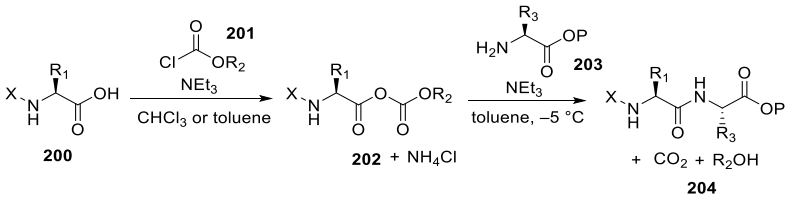
3.1.1. Historical examples

Most examples of automated synthesisers pre-2010 adhere to similar principle: performing two to three robust, high yielding chemical reactions iteratively to build up an oligomer, which is adhered to a solid support, and is purified by multiple solvent washes.

3.1.1.1. Peptide Synthesis

Before Merrifield developed the precursor to the Solid Phase Peptide Synthesiser (SPPS), the synthesis of peptides was a laborious affair. One such example of an early method to synthesis peptides was published by Vaughan in 1952,[72] in which the C-N bond was formed via attack of the free amine of one amino acid (**203**) onto the mixed anhydride

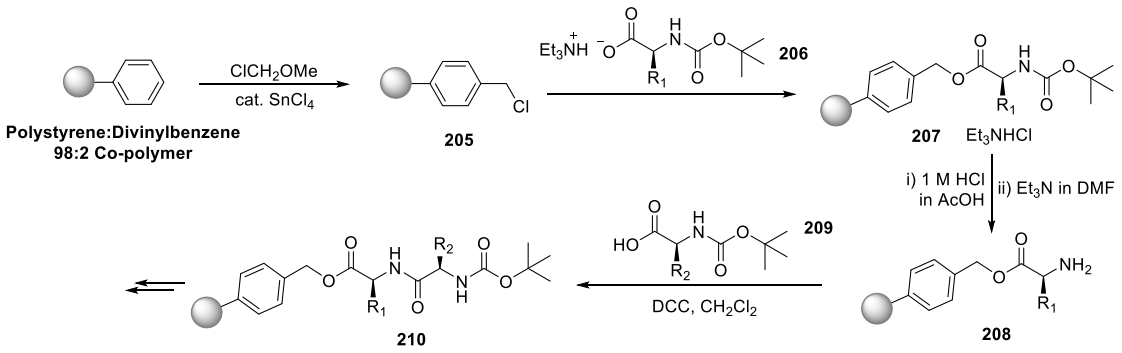
generated from the reaction of the carboxylic acid of another amino acid (**200**) (Scheme 55).



Scheme 55: The mixed-anhydride approach to the synthesis of peptide (C-N) bonds.

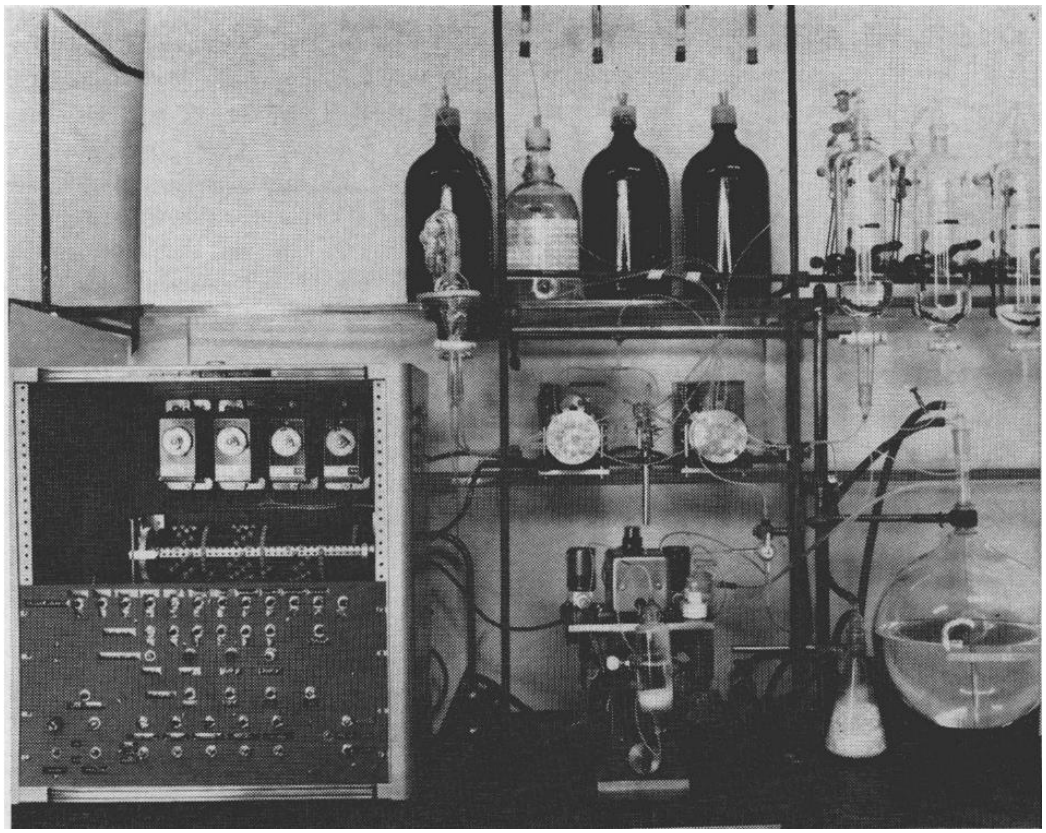
To allow translation of this methodology to an automated platform, there are several difficulties that needed to be considered, and limitations to be overcome. The first, and perhaps the most pertinent challenge is one of purification – the product peptide and its intermediate species were purified by either recrystallisation or column chromatography – both of these methods were clearly not amenable to automation. Another challenge was that each reaction had to be extremely high yielding if a good overall yield of the desired peptide was to be achieved after multiple iterations. To illustrate this point, consider a reaction that delivers the product in an 80% yield, a good yield by most standards. After 20 iterations of this reaction, the yield of the product is only 1.2%. If the yield is 97%, 20 iterations of this reaction gives the product in a 54% yield. These problems are very general and apply to any iterative process, however there are also specific challenges regarding the automation of peptide synthesis; any non-participating functional group in an amino acid must be blocked, and activation of the carboxylic acid could lead to epimerisation of the α-stereocentre via ketene formation.

Merrifield's automated SPPS[71] addressed these issues, the main breakthrough being the use of a solid support, which was a co-polymer of polystyrene and divinylbenzene in a 98:2 ratio. This specific polymer had excellent physical stability, was completely insoluble, and displayed a high degree of swelling in the non-polar reaction solvents, allowing a good level of matrix penetration by the substrate. This matrix could be chloromethylated using chloromethoxymethane and catalytic tin (IV) chloride (Scheme **56**), and then reacted with the triethylammonium salt of a Boc-protected amino acid (**206**). This attached the amino acid to the resin, ready for the iterative construction of the peptide. The key benefit of this approach is that the intermediates do not require extensive purification, the resin is simply washed with solvents and reagents to perform the chemistry and to remove impurities or excess reagents, leaving behind the attached peptide chain.



Scheme 56: Merrifield's Automated SPPS

Once the first amino acid was attached, the resin was washed with 1 M HCl in AcOH to remove the Boc protecting group, followed by washing with Et_3N in DMF to reveal the free amine (**208**). The next Boc-protected amino acid was then added as a mixture with DCC, which formed the activated species which was able to be attacked by the resin-bound free amine to form the C-N bond (**210**). Each reaction of this sequence occurred rapidly and generated the products in essentially quantitative yield. Merrifield used this methodology to synthesise bradykinin (**211**), a nonapeptide, on the automated SPPS. The procedure, from start to finish, took 32 hours, and gave bradykinin in a 68% yield – an immense achievement given the technology available at the time (Figure **5**).



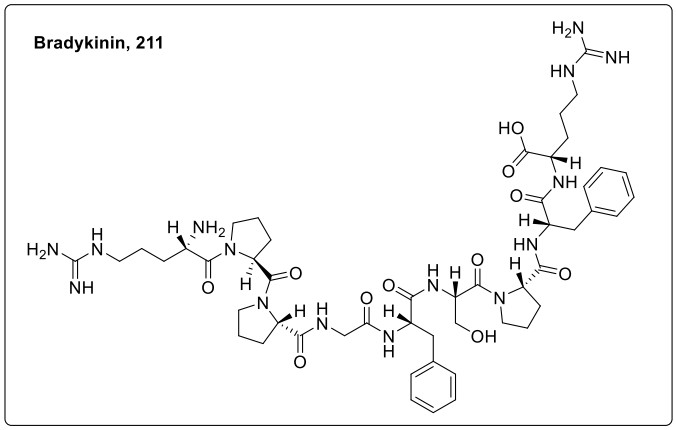
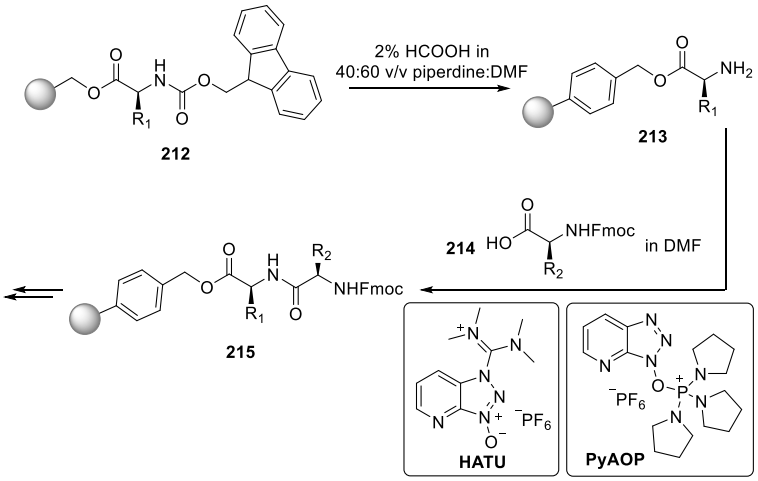


Figure 5: Top: Merrifield's automated SPPS.[76] Bottom: Bradykinin, a nonapeptide.

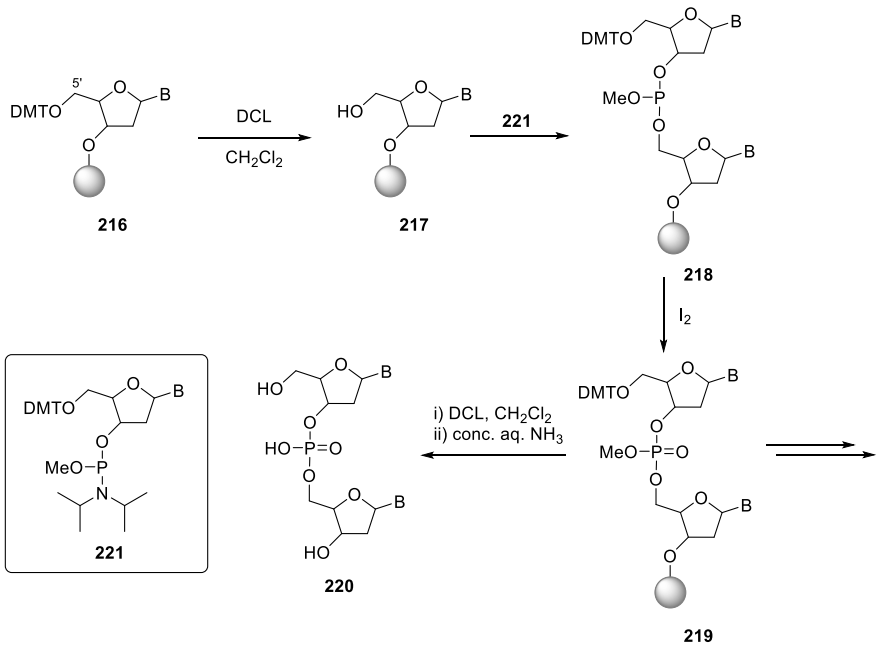
Since Merrifield's original automated SPPS, the field has advanced significantly. In 2020, Pentelute reported the synthesis of Sortase A, a protein comprised of 164 amino acids, using an automated flow peptide synthesiser.[73] The peptides were bound to a solid matrix via the C terminus, with the N terminus being Fmoc protected - this Fmoc group was removed by washing with a 2% HCOOH solution in 40:60 v/v piperdine:DMF. The next Fmoc protected amino acid (**214)** was added, alongside either HATU or PyAOP (depending on the amino acid) to form the C-N bond (Scheme **57**) with no observable epimerisation (**215**). The protein was isolated in a 1% yield over 327 individual chemical reactions, corresponding to around 98.5-99% yield per step, and taking a total of 6.5 hours.



Scheme 57: Automated flow peptide synthesis.

3.1.1.2. Oligonucleotide Synthesis

The automated synthesis of oligonucleotides follows a similar regime to that of automated peptide synthesis, however the sequence is slightly more complicated. Ogilvie, in 1981, was the first to publish an automated synthesis of such gene fragments, in which a tetradecamer (14) was constructed in 6.5 hours.[74] The first nucleotide was attached to the silica solid support (**216**), which was found to be insoluble and able to expand in the reaction solvent. The alcohol of the nucleotide at the 5' position was protected as the DMT ether; deprotection of this alcohol was performed by treating the ether with dichloroacetic acid in CH_2Cl_2. Once the free alcohol (**217**) had been revealed, it could be used to displace a diisopropylamino group from a phosphoramidite present on the next nucleotide (**221**) desired in the oligonucleotide synthesis. This forms the key P-O linkage required for the oligonucleotide backbone. This step was then followed by treatment with iodine to oxidise the phosphite to the corresponding phosphate (**219**). At this point, the construction of the DNA fragment could be continued in a similar manner, or the present fragment could be cleaved from the silica solid matrix, by first revealing the 5' alcohol with DCL, and then treating the compound with concentrated aqueous ammonia to both demethylate the phosphate and release the fragment.



Scheme 58: Ogilvie's automated oligonucleotide synthesiser.

Modern oligonucleotide synthesisers are capable of synthesising DNA fragments up to 200 monomers long using this approach; however the accumulation of errors and presence of side reactions limits the synthesis of longer fragments.[75]

3.1.1.3. Oligosaccharide Synthesis

Whilst the challenges of developing functional automated peptide and oligonucleotide synthesisers had been mostly overcome within the twentieth century, the synthesis of oligosaccharides presented extra challenges; a monosaccharide has five alcohol groups which require a judicious protection/deprotection strategy to permit an iterative, automated process; and the stereochemistry at the anomeric centre of each monosaccharide needed to be controlled. The substitution at the 1 position of a monosaccharide proceeds via a cyclic oxocarbenium ion which can be attacked from the bottom face to form the α-anomer, or from the top face to form the β-anomer (Figure **6**).

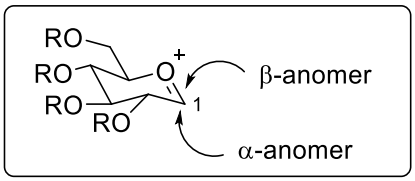
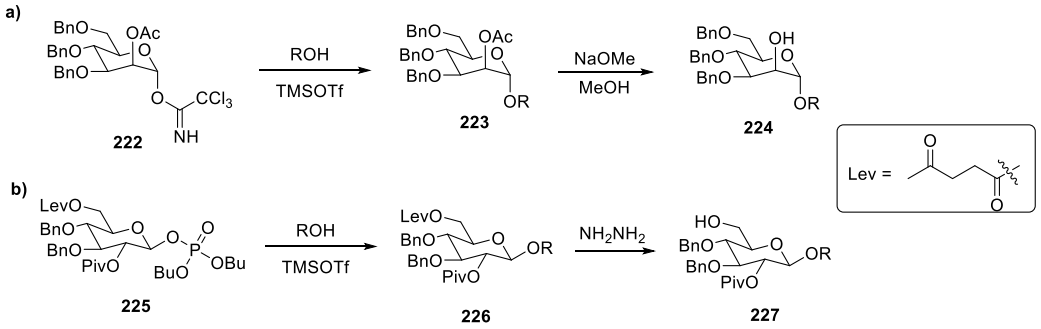


Figure 6: The intermediate oxocarbenium ion generated during substitution at the 1 position of a monosaccharide.

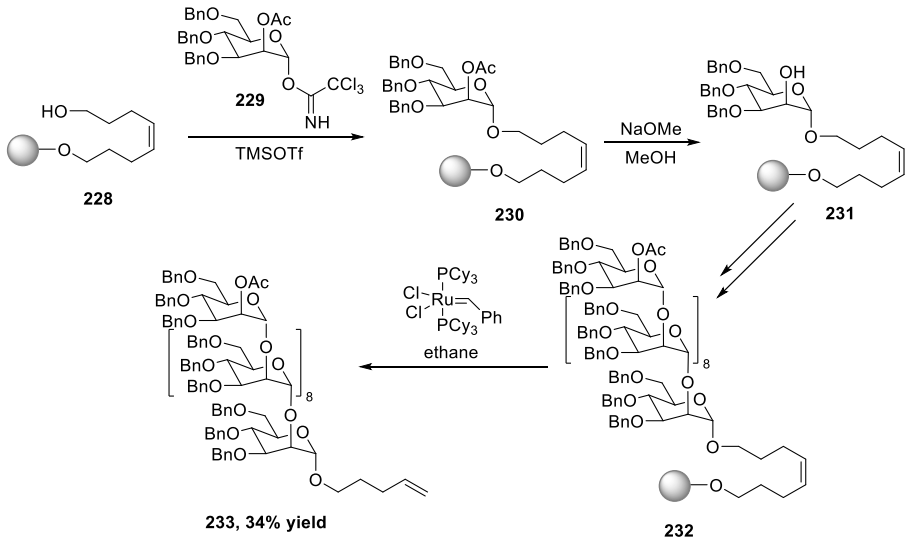
The first automated oligosaccharide synthesiser was developed at the turn of the millennium by Seeberger, who was able to demonstrate the synthesis of a linear

decasaccharide (10) in 34% yield.[76] This process again bore similarity to those mentioned previously for the synthesis of peptides and oligonucleotides; the first monosaccharide was adsorbed onto a octenediol functionalised resin, and each iteration was performed and purified by successive reagent and solvent washes. The α-anomer could be synthesised by leveraging an acetyl protected alcohol at the 2-position (**222**), which would form a cyclic intermediate on the top face of the oxocarbenium ion, permitting the nucleophile to attack only from the bottom face (**223**). This acetyl group could be removed using NaOMe to give the free alcohol (**224**, Scheme **59a**). The β-anomer could be synthesised analogously, using a pivolyl group as the blocking group (Scheme **59b**). In this case, the oligosaccharide was constructed from the alcohol in the 6-position, which was protected as a levolinyl group (**225**). This group was cleaved using hydrazine (**227**).



Scheme 59: a) Synthesis of an α-anomeric bond, b) Synthesis of an β-anomeric bond.

Utilising this chemistry, Seeberger synthesised a linear decasaccharide in 34% yield over 21 individual transformations. As all the anomeric stereocentres were of the α-stereochemistry, the same procedure using building block **229** could be iterated 10 times. Once the oligosaccharide (**223**) has been completed, it was cleaved from the resin using an alkene cross-metathesis (Scheme **60**).



Scheme 60: Seeberger's automated synthesis of a decasaccharide.

3.1.2. Challenges Associated with Automated Synthesis

There are some key similarities between the automated synthesis of peptides (C-N bonds), oligonucleotides (P-O) and oligosaccharides (C-O); all these processes involve simple, robust, high yield chemistry; all use simple solvent washes as a means of purification; and all use a solid support to facilitate this simple method of purification. Each of these automated synthesisers is limited in the sense that it can only perform a well-defined set of chemical manipulations.

To realise a universal automated chemical synthesiser, this machine would have to be able to perform all types of chemistry and be able to do a variety of other manipulations which are commonplace in chemical procedures. One key challenge, especially in the generation of simple organic molecules, is the automation of C-C bond forming reactions.

Another challenge is that of reaction manipulations and chemical processes – the vast majority of organic chemistry is not able to be adhered to a solid matrix to allow facile purification – so this hypothetical universal synthesiser has to be able to perform chemical processes to mimic those performed by a chemist in the lab. Even the automation of simple processes such as stirring of reagents, heating/cooling, reaction quenching, biphasic extractions, evaporation, and purification, present enormous engineering challenges. It is no surprise that up until 45 years after Merrifield's original peptide synthesiser was built, all examples of automated synthesis followed a similar paradigm. The technology to be able to emulate these simple manually executed chemical processes effectively has simply not been available to the organic chemist until much more recently,

and even then, the barrier to entry to automated organic synthesis is high, both financially and academically.

Those that have exploited automation in organic synthesis have used automated platforms that broadly fell into two categories: commercially available automation platforms, such as those developed by Chemspeed, and 'home-made' automation platforms – these are custom built systems that use a mixture of simple hardware components alongside laboratory equipment. Both approaches have found success, and examples of both will be discussed.

3.1.3. Automated Synthesis of Compound Libraries

One of the benefits of the automation of organic chemical processes is that it can increase the volume of work output whilst maintaining unparalleled reproducibility – a robot does not need to stop work to rest and can perform simple manual tasks in an identical manner several times.[77] Freeing the synthetic chemist from performing these laborious tasks allows more time for productive thinking, which may lead to an increase in reaction discovery - for this reason automation becomes an attractive prospect. Institutions around the world are starting to embrace automation in the synthesis of compound libraries using commercially available platforms. Chemspeed automation platforms have been used for copper-catalysed click reactions (2010),[78] enzymatic synthesis of oligosaccharides (2019),[79] and even used in the discovery of a new reaction by a 'strategy of accelerated serendipity' (2011).[80]

In 2016, AbbVie use a customised Chemspeed automation platform (Figure **7**) to synthesise three separate compound libraries.[81]

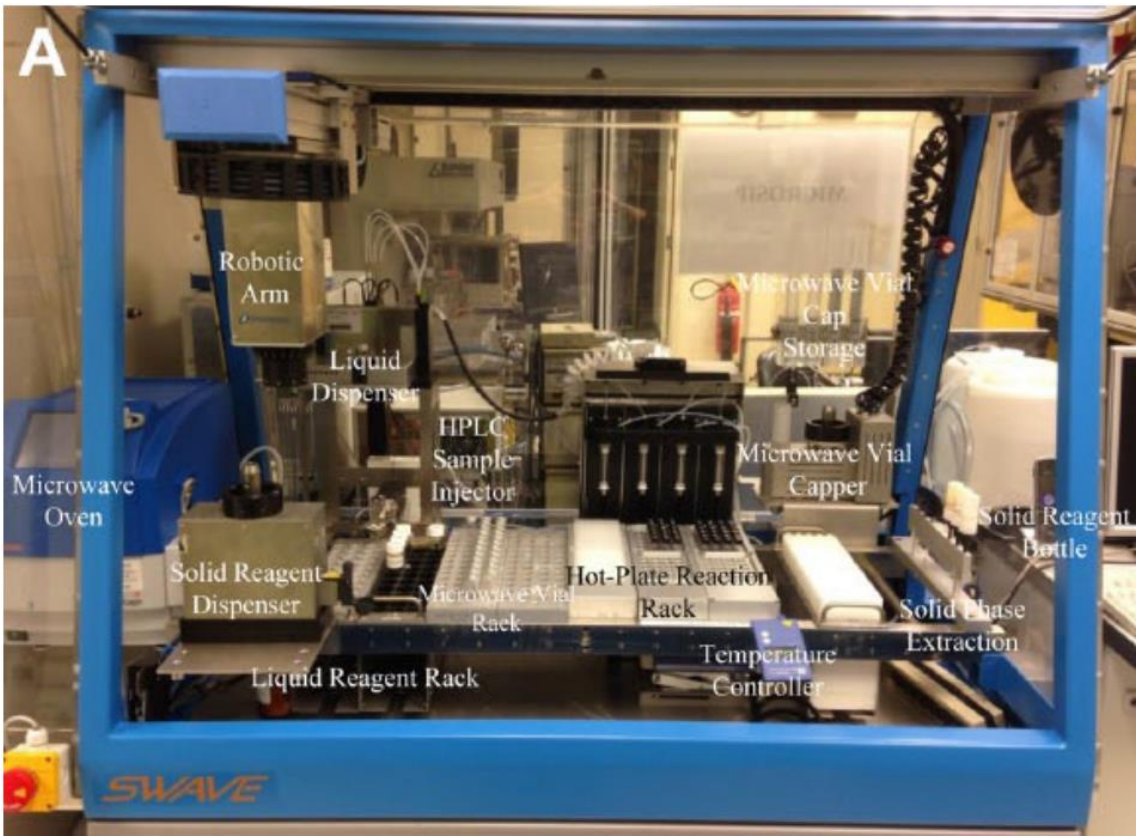
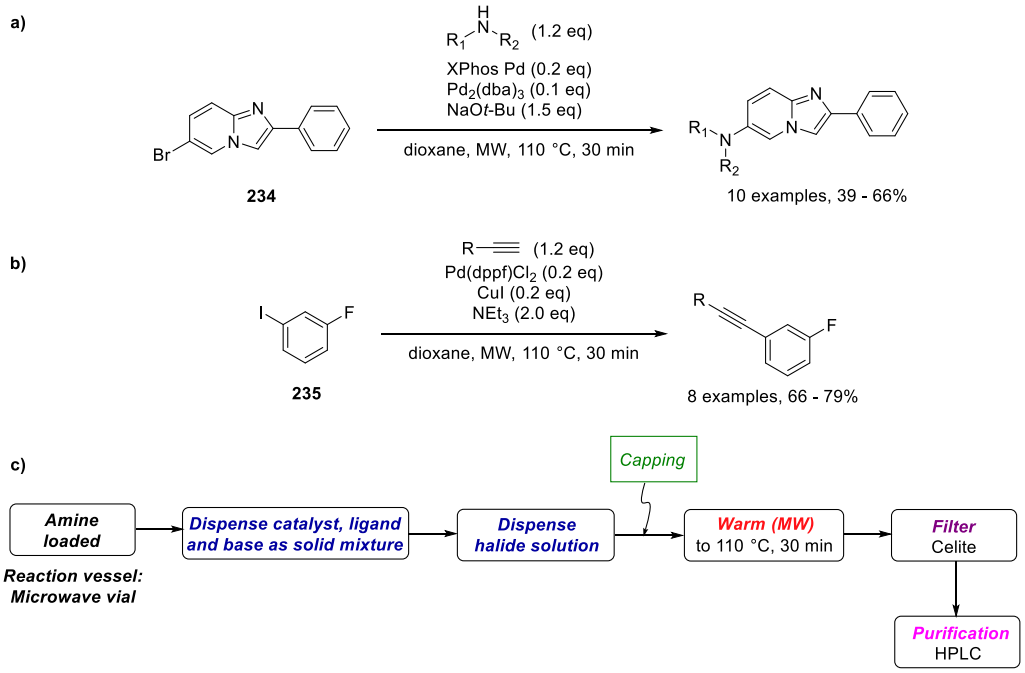


Figure 7: AbbVie's Chemspeed automation platform.

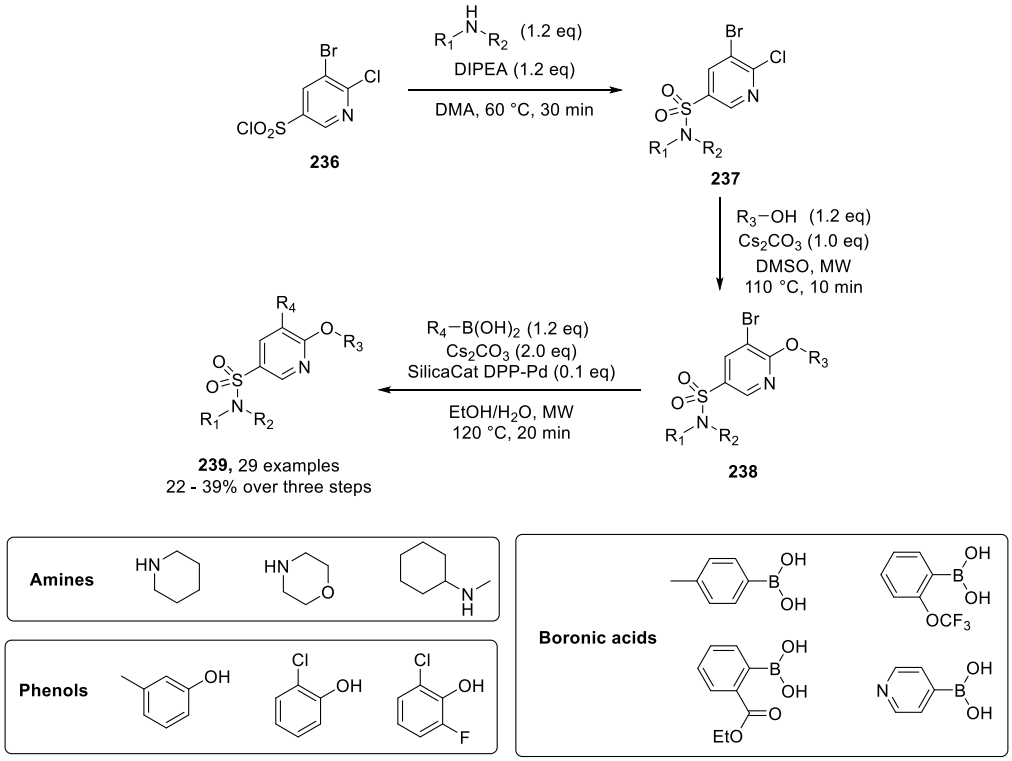
The first library was a library of 8 alkynes generated in yields of 66 – 79% using a Sonogashira coupling between **234** and 8 different terminal alkynes, and the second library was one of 10 compounds generated in yields of 39 – 66% using imidazopyridine (**235**) with 10 different secondary amines in a Buchwald-Hartwig coupling (Scheme **61**).



Scheme 61: a) Sonogashira coupling to generate 8 compounds. b) Buckwald-Hartwig coupling to generate 10 compounds. c) A flowchart to represent the workflow of both reactions.

These two procedures, whilst operationally simple, demonstrate how the Chemspeed automation platform can handle both solid and liquid reagents, perform filtrations, cap, and insert microwave vials into the microwave reactor, and uncap the vials afterwards. The air-sensitive nature of these two transformations was also accounted for as the entire Chemspeed platform could be purged with N_2. The purification of these reactions was carried out by automated online preparatory HPLC purification. Scheme **61c** shows a simplified workflow for both procedures.

The third compound library was generated by performing three sequential chemical transformations on a pre-functionalised core **236** (Scheme **62**). The first reaction was a sulfonamide formation by combination of a sulfonyl chloride and amine, the second was a nucleophilic aromatic substitution at the 2-position of the pyridine, and the third was a Suzuki coupling between the aromatic bromide and the boronic ester. Three amines, three phenols and four boronic esters were used to generate a total of 36 potential different analogues (**239**), of which 29 were synthesised with yields of 22 – 39% over the three telescoped steps.



Scheme 62: A three-step compound library synthesis of 36 compounds.

3.1.4. Automated Multi-Step Synthesis of Complex Molecules

The Chemspeed Automation Platform is designed to be used as a platform for the high throughput screening of reaction conditions, or for the synthesis of analogues using relatively straightforward chemical transformations – it is perhaps less suited to the multistep synthesis of complex molecules. Aggarwal, however, has used the Chemspeed platform to perform a nine-step synthesis of a complex organic molecule.[54] There are also examples of the synthesis of complex natural products using non-commercial synthesisers, such as those built by Burke[82,83] or by Cronin.[84] All three of these examples will be discussed now in detail.

3.1.4.1. Burke's Automated Platform: Catch and Release

In 2015, Burke reported a custom-built automated platform that could synthesise complex natural products using metal cross-coupling reactions from a variety of building blocks.[82] As has been discussed in Chapter 3.1.2, purification remains a principal challenge in extended automated syntheses, a challenge which Burke has addressed using a catch-and-release system. It was the MIDA boronate that was the key functional group or protecting group in this process, this ligand on boron possessed an usual binary affinity for silica which was independent of the rest of the molecule; specifically, the MIDA boronates showed minimal mobility on silica when eluted with Et_2O:MeOH mixture, but eluted

rapidly when the mobile phase is THF. This allowed elution of all side products to waste using the polar MeOH solvent mixture, and subsequent elution of only the product with THF (Figure **8**).

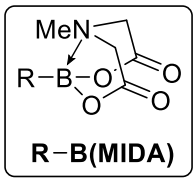


Figure 8: The MIDA boronate.

Burke's automation protocol consisted of three steps; deprotection, coupling and purification; each step occurred within a distinct module that used a series of cartridges. The modules were connected by tubing, with pumps that were controlled by a computer using custom software to operate syringes. These were attached to 8-way valves to allow the aspiration and dispensing of solutions from one module to the next (Figure **9**).

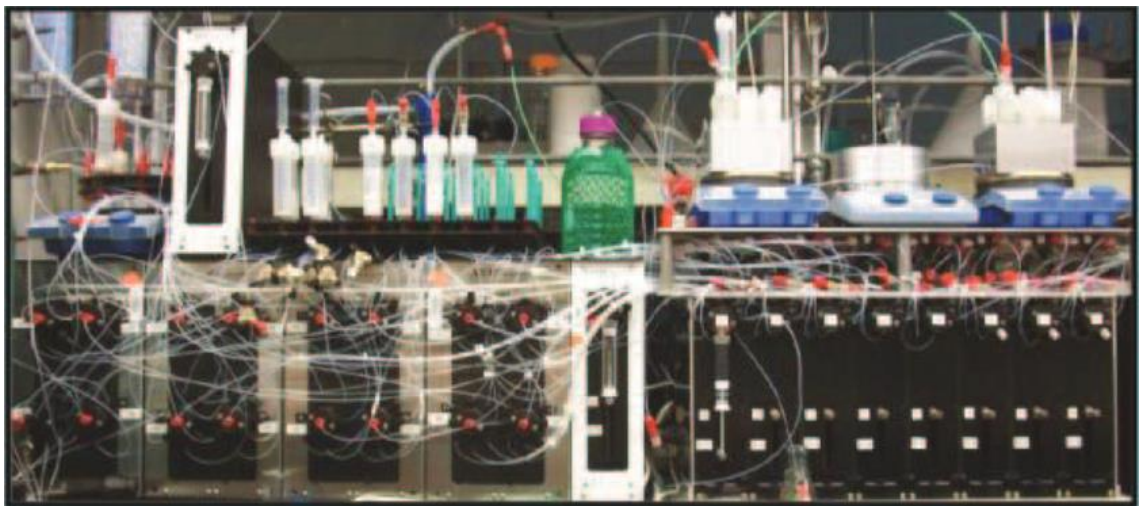


Figure 9: Burke's automation platform.

The first step was the deprotection step, which was the treatment of a MIDA boronate, either as a starting material for a synthesis, or from a previous iteration, with NaOH in a THF:H_2O mixture to give the corresponding boronic acid. This was purified by aqueous work up, in which the aqueous layer was sent to the waste, and the organic layer filtered through a plug of $MgSO_4$ for drying. The resultant solution was then sparged with N_2 gas to deoxygenate. This was then transferred to the second module for the coupling, in which the boronic acid solution was added to a premixed solution of $Pd(OAc)_2$, base and ligand in THF. Once the reaction was complete, the reaction mixture was transferred to the purification module. Hexane was added to precipitate some of the most polar reaction

impurities and the solution was transferred to a silica filter. It was at this point in the protocol that the catch-and-release purification was performed: the filter was first eluted with Et_2O:MeOH mixture to remove all species except the desired MIDA boronate, followed by elution with THF to remove the MIDA boronate cleanly. This solution of MIDA boronate in THF was then transferred to the deprotection module for up to two further iterations (Figure **10**).

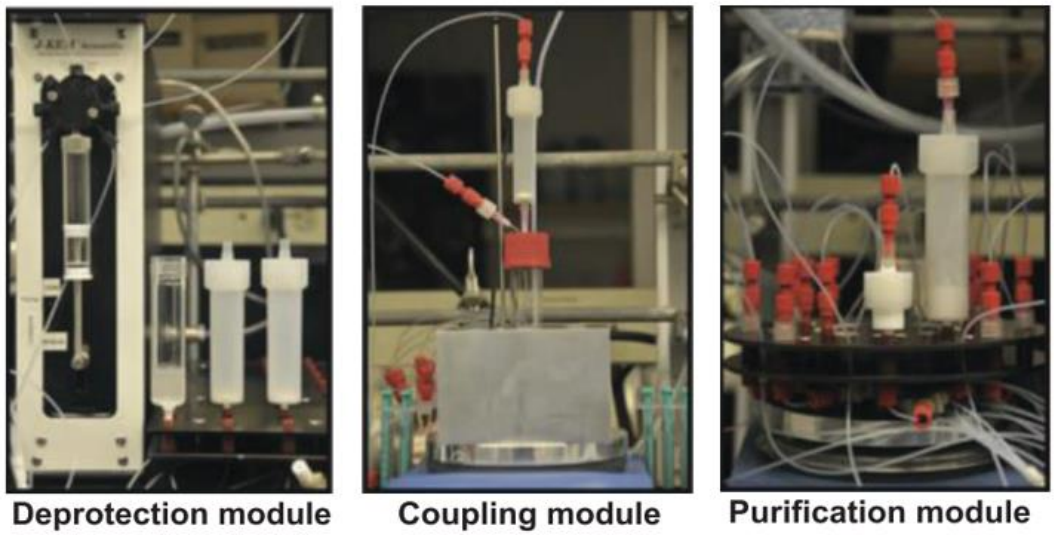
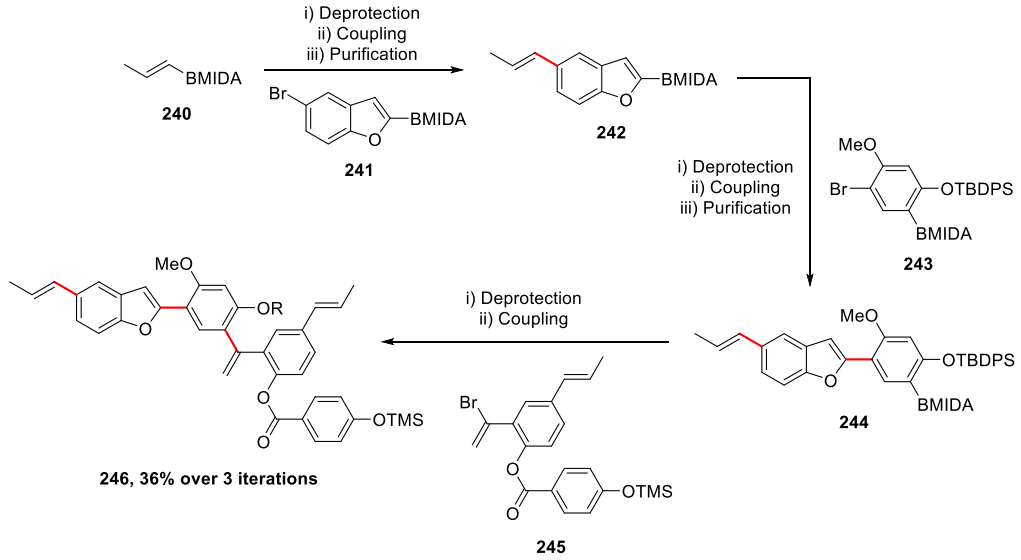


Figure 10: Top: The deprotection, coupling and purification modules. Middle: processes occurring within these modules. Bottom: workflow for Burke's iterative C-C bond forming procedure.

A representative example is shown in Scheme **63**, where this deprotection, coupling, purification protocol was repeated three times to give the product **246** in 36% yield.



Scheme 63: Synthesis of a complex molecule over three iterations of Burke's automated C-C bond forming procedure

In 2022, Burke published a second paper detailing an automated sp^3-sp^3 C-C coupling procedure, using boronic ester homologation chemistry for the key C-C bond forming steps.[83] The principle is similar to the sp^2-sp^2 and sp^2-sp^3 couplings discussed above, however a more stable ligand on boron was required as MIDA boronates were found to be unstable to the strongly nucleophilic organolithium/magnesium bases used in the boronic ester homologation chemistry. Substitution of the backbone of MIDA was found to increase the stability of the boronate to both basic aqueous hydrolysis (due to reduction in the frustrated Lewis acid-base pair behaviour of the B-N bond, the mechanism in which activation of a water molecule leads to hydrolysis), and to nucleophilic attack of the carbonyl (due to sterics). The extent of this stability was found to depend on the extent of substitution. Two geminal di-methyl groups provided total stability towards both alkali and nucleophiles (Figure **11**).

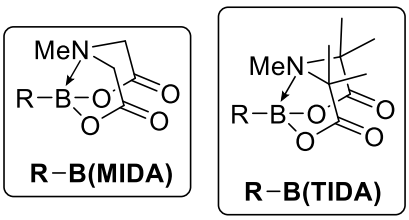
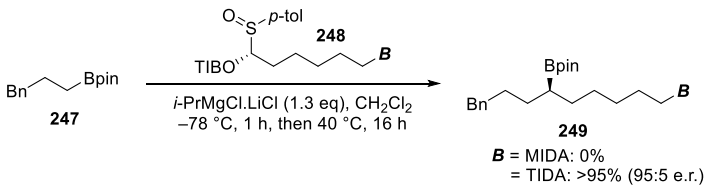


Figure 11: BMIDA and its more stable analogue, BTIDA.

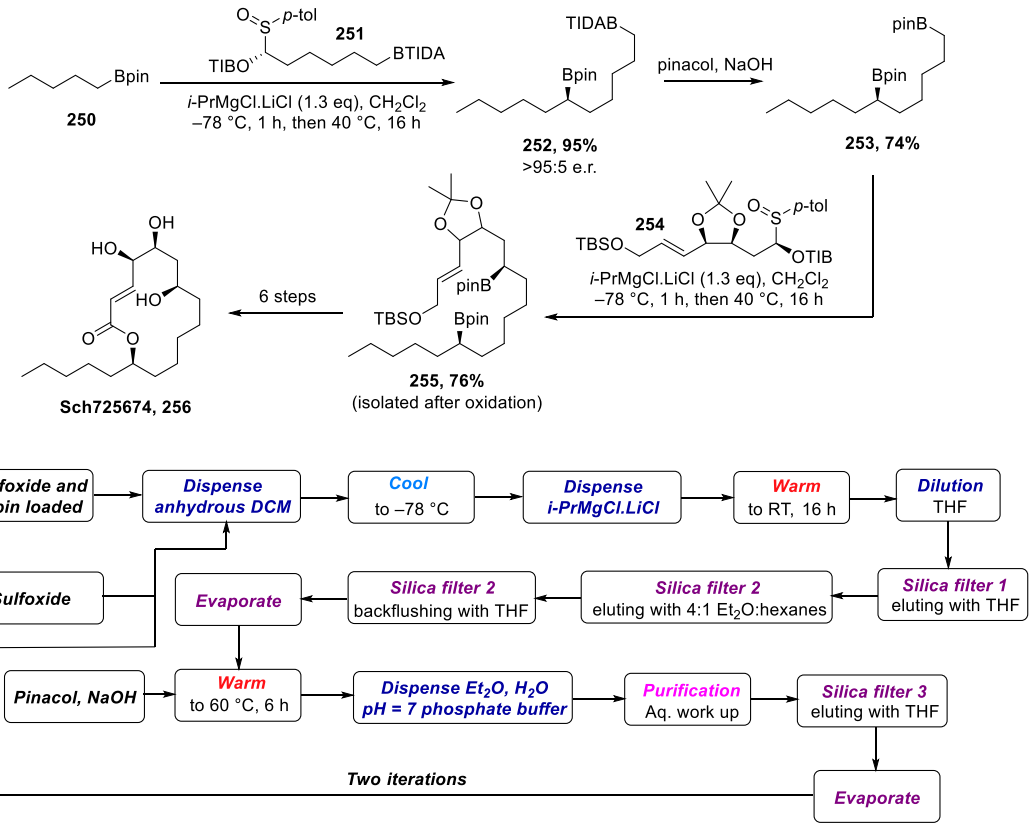
Leveraging this 'hyperstability', Burke was able to demonstrate the homologation of a boronic ester **247** to give **249**. The reaction proceeded via the addition of *i*-PrMgCl·LiCl to a solution of boronic ester **247** and sulfoxide **248** to perform magnesium–sulfoxide exchange followed by formation of the boronate complex. Heating to 40 °C facilitated

the 1,2-metallate rearrangement to deliver the homologated boronic ester **249** in excellent yield and enantiomeric ratio (Scheme **64**).



Scheme 64: Boronic ester homologations could be performed in the presence of BTIDA with no decomposition.

BTIDA possessed a similar binary affinity for silica as BMIDA, allowing its use in a catch-and-release system and therefore in an automated sp^3-sp^3 C-C coupling procedure, comprised of three stages: coupling, purification, and transesterification. These procedures were used to complete a partially automated synthesis of the natural product Sch725674 (**256**) (3 steps out of 9 were automated) – the automated portion of the synthesis included two iterations of the boronic ester homologation with one intermediate automated transesterification. Once the bis-boronic ester **255** has been obtained, it was removed from the platform to be brought through to the natural product manually, taking a total of 6 further steps (Scheme **65**).

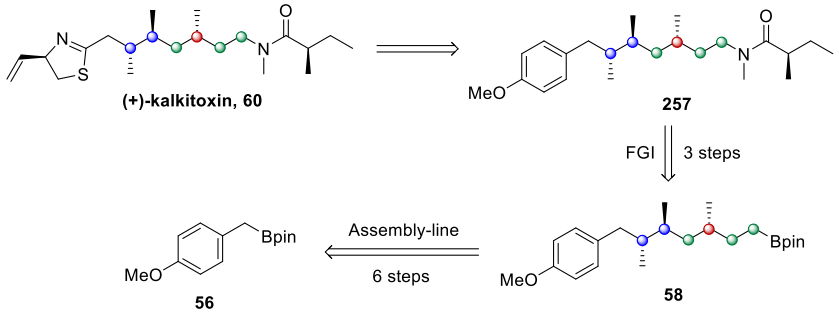


Scheme 65: Top: Burke's partially automated synthesis of the natural product Sch725674 (**256**). Bottom: Automated boronic ester homologation workflow.

The coupling module was cooled down to −78 °C, the required temperature for the boronic ester homologation, using a dry ice bath taped to the side of the cartridge. After reaction completion, the crude reaction mixture was filtered through a plug of silica eluting with THF to remove the insoluble salts (TIDA boronates are very mobile on silica when eluted with THF), and then filtered through a second plug of silica eluting with 4:1 Et_2O:hexanes – this mobile phase eluted all species in the crude except for the TIDA boronate, which remained stationary. After this, the same silica filter was backflushed with THF, which pushed the TIDA boronate off the top and into the transesterification module, where it could be converted to the pinacol boronic ester. This process was then repeated once.

3.1.4.2. Aggarwal's Automated Iterative Boronic Ester Homologations

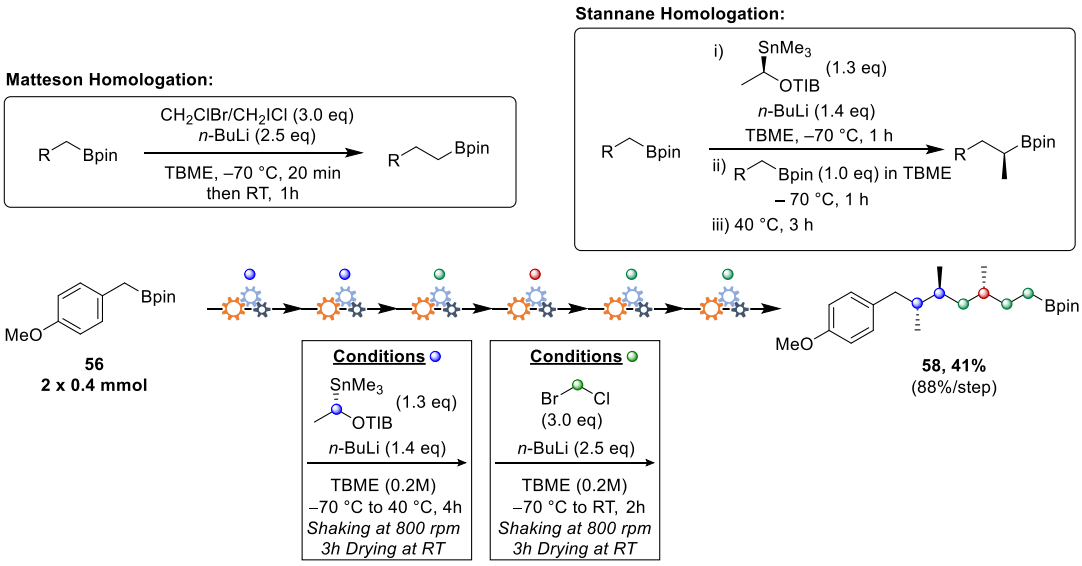
In 2022, Aggarwal also reported the automated synthesis of a complex organic molecule using boronic ester homologations on a Chemspeed automation platform (the practical aspects of this platform are discussed in detail in Chapter 3.2). The synthesis of **257**, a late-stage intermediate in a previous synthesis of (+)-kalkitoxin,[32] was broken into two stages: the 'assembly-line' stage which consisted of six sequential boronic ester homologations, and the 'FGI' stage (functional group interconversion), which was a further three chemical transformations (Scheme **66**).



Scheme 66: Retrosynthetic analysis for the total synthesis of (+)-kalkitoxin.

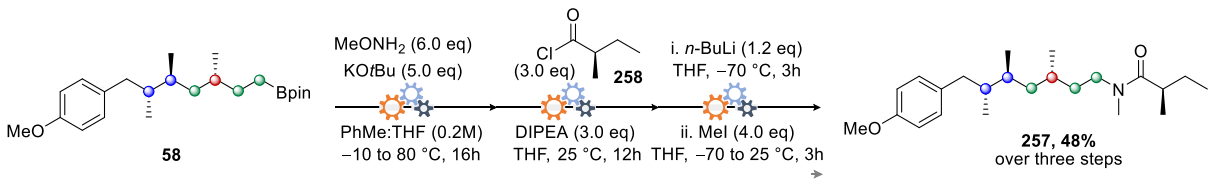
The assembly-line portion of the synthesis was comprised of two key reactions: the Matteson homologation,[31] (Chapter 1.1.5) and the 'stannane homologation'(Chapter 1.1.5) chemistry developed by Aggarwal, which was the installation of a $CHCH_3$ unit into the C-B bond of a boronic ester with complete stereocontrol (Scheme **10**).[30] Both of these chemical reactions were found to be particularly amenable to automation due to the simple method for the work up/filtration of the crude material. Once the reaction had been completed, the crude was simply taken up in Et_2O, filtered through a pad of silica, and

concentrated to give the crude homologated boronic ester at a sufficient purity to be used in the next homologation. Some modifications to the standard conditions for these two reactions had to be made to ensure the chemistry worked well in an automated setting – these will be discussed in detail in Chapter 3.4.1. Ultimately, six homologations were performed without any intermediate aqueous work-up or column chromatography to provide the boronic ester **58** in 41% isolated yield as a single stereoisomer, corresponding to 88% yield per homologation after manual purification.



Scheme 67: Top left: Matteson homologation. Top right: Stannane homologation. Bottom: The assembly-line portion of the automated synthesis of **257**.

The isolated boronic ester **58** could be loaded back onto the automated platform for the final functional group interconversion. The boronic ester was converted directly to the amine using Morken's 2nd generation amination conditions,[85] and then acylated in-situ to generate the secondary amine. This species was *N*-methylated using *n*-BuLi and MeI to give the complex intermediate **257** in a 48% isolated yield over 3 steps.



Scheme 68: Conversion of the boronic ester **58** to the tertiary amide **257**.

The entire nine step sequence was completed in 8 days on the automated platform with only a single intermediate purification to give **257** in a 20% yield over nine steps.

3.1.4.3. Cronin's 'Chemputer'

In 2019, Cronin published research which described the synthesis of three drug molecules using a custom-built automated platform.[84] This platform, along with the software, also custom and open source, was given the name 'Chemputer'.

Despite most chemical procedures being a combination of unit operations, such as reagent mixing, heating, liquid-liquid extractions and so on, the realisation of a general language to describe any synthesis presents significant challenges. Procedures to perform a chemical reaction are written in prose, and often omit details pertaining to the exact protocol to carry out a given procedure; both factors lead to ambiguity, and although an experienced chemist is often able to 'fill in the gaps' in a procedure, an automated program cannot do so. Cronin has developed software which can break down a written procedure into unit operations, such as those mentioned above, which can then be converted into machine operations.

Physically, the automation platform looked familiar to an organic chemist due to the use of common laboratory glassware and apparatus (Figure **12**). The platform was comprised of four modules which used a series of pumps connected to six-way valves assembled on the 'backbone' to control the movement of solvents between modules. The four modules described are as follows: a reaction module which consisted of a two necked round-bottomed flask sitting on a heating block, a filtration module, a liquid-liquid extraction module which leveraged the use of a sensor to detect the phase boundary, and finally an evaporation module which was essentially a rotary evaporator connected to a diaphragm pump. These descriptions are gross oversimplifications and do not emphasise enough the unique challenges that had to be overcome to allow these modules to function effectively.

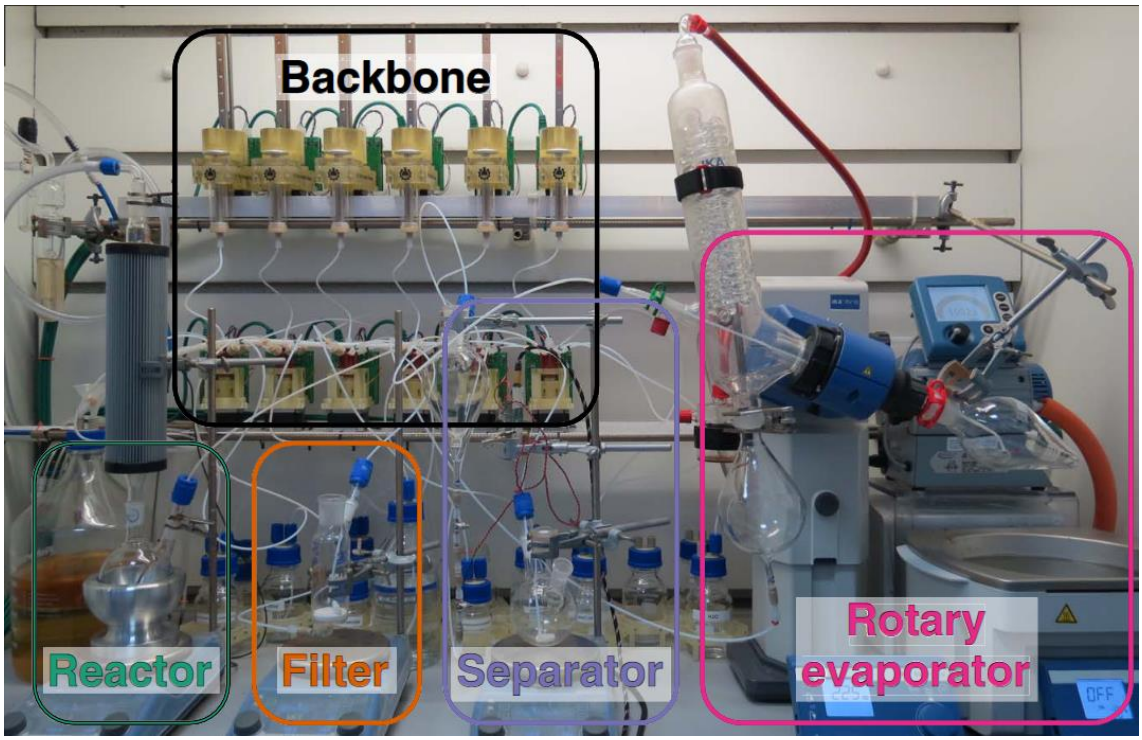
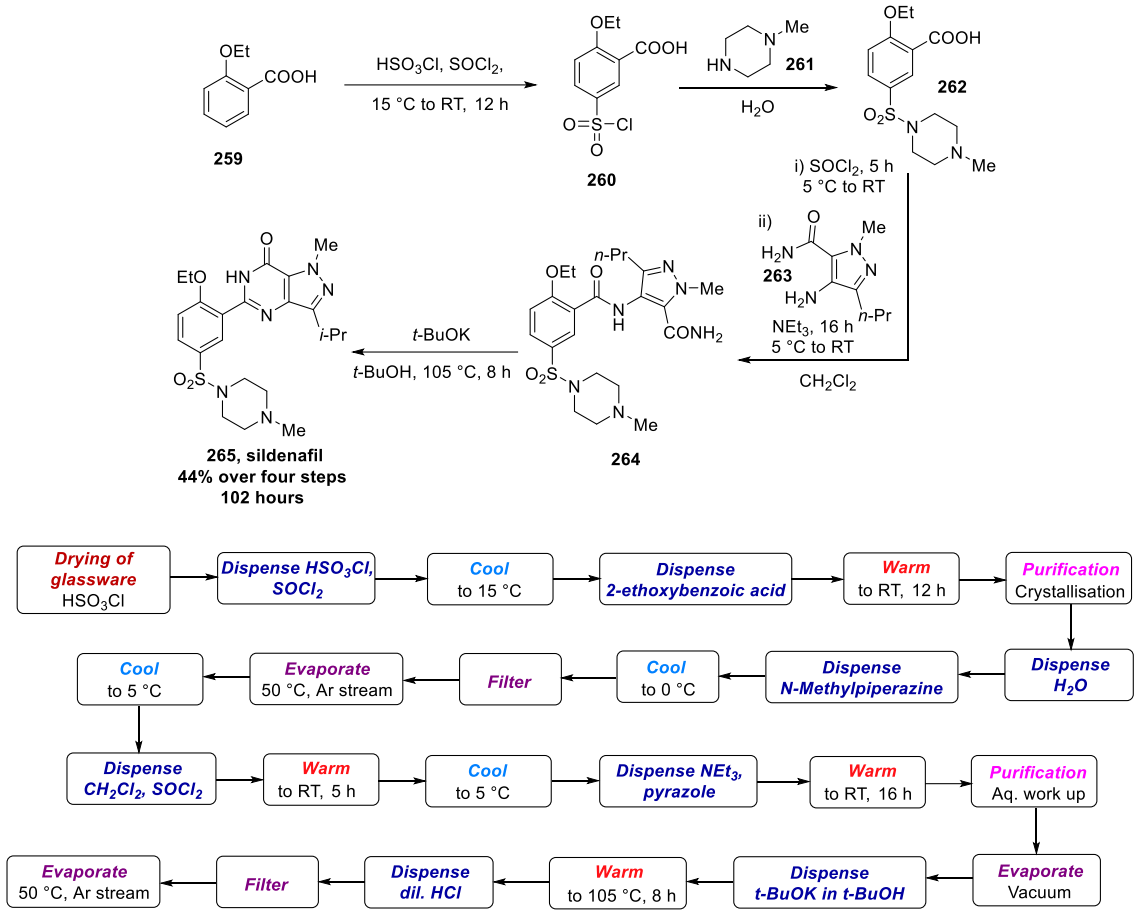


Figure 12: Cronin's automation platform.

Cronin used this automation platform to synthesise three drug compounds without any human intervention; diphenhydramine hydrochloride, rufinamide, and sildenafil, which will be discussed in detail (Scheme **69**). The synthesis of sildenafil started from 2-ethoxybenzoic acid (**259**), which could be chlorosulfonylated using chlorosulfuric acid in thionyl chloride to give **260**. *N*-Methylpiperazine (**261**) was then added, substituting at sulphur to form the sulfonamide **262**. Conversion of the carboxylic acid to the acyl chloride, followed by addition of pyrazole **263** gave the complex intermediate **264**. Upon heating and treatment with *t*-BuOK, the pendant primary amide and the secondary amide condensed to form the pyrimidone ring, completing the synthesis of sildenafil (**265**) in 102 hours and with a yield of 44%.



Scheme 69: Top: Synthetic route to sildenafil. Bottom: Workflow for the automated synthesis of sildenafil.

It is impressive how well this platform has been able to replicate chemistry that would be performed in the lab; the yield per step for the synthesis of diphenhydramine hydrochloride was 87% for the automated synthesis compared to 91% for the manual synthesis. Whilst the chemistry demonstrated by Cronin's automation platform may not be particularly challenging to an experienced organic chemist, it is the possibility of a non-chemist being able to construct a relatively cheap automation platform (compared to an expensive commercially available platform) and use the open-source 'Chempiler' software to synthesise a plethora of organic molecules. The modular design of this automation platform would make modifications to perform a wider range of organic chemistry relatively simple to implement. It is worth mentioning that this automated platform is best suited to the linear, multi-step synthesis of organic molecules, as opposed to the generation of a large compound library as the backbone must be cleaned with solvent between each reaction.

In 2022, Cronin further expanded his idea of a universal chemical synthesis language.[86] As before, software has been used to convert literature procedures into executable code

to be run on a number of custom-built automation platforms, however it is the scale on which this has been applied to enable automated synthesis that made this work so impressive. A reaction database of over 100 commonly performed chemical reactions was generated which represented areas of chemistry including cross-coupling reactions, functional group interconversions, heterocycle forming reactions and three-component reactions. New data from each run of the automated platform (collected by a series of sensors measuring physical variables such as pressure, temperature, and flow rate) was added to the database – this can be data-mined to glean information to assist with further optimisation of reactions. Of these reactions in the database, 53 were performed on the automated platform, obtaining yields which were in many cases comparable to that of an experienced chemist. Moisture sensitive reagents such as BF_3 and KHMDS could be used, as could air sensitive reagents such as the palladium catalysts required for the cross-coupling chemistry. A small library of four compounds were easily synthesised using a three component Ugi reaction on the same reactor using the same stock solutions; the reactions weren't performed simultaneously but could be performed in a multithreaded way – for example, purification of the first substrate in the library could be ongoing as the second substrate was being formed in the reaction vessel. Several multistep syntheses were also performed on the platform. A new addition to Cronin's automated synthesiser was the automated chromatography module – the compound was automatically loaded onto a pre-selected column and the software controlled both the eluent composition and which portion should be collected by continuous monitoring of the UV trace. The entire sequence, from literature procedure, to purified product in hand, is completely automated, including reagent addition, separation of organic and aqueous phases, evaporation of solvent and all aspects of column chromatography. As with Burke's automated platform, this platform was custom-built, however the inclusion of dedicated computational infrastructure brings this work far ahead of other examples of automated organic synthesis in the literature.

3.2. The University of Bristol Chemspeed Automation Platform

The School of Chemistry at the University of Bristol acquired a Chemspeed Automation Platform in 2018 to allow the automation of a broad range of chemistry (Figure **13**). The platform is the approximately glovebox sized and can be closed and purged of air via a simultaneous influx of nitrogen from the bottom of the platform and outflow via a ventilation duct at the top of the platform to allow the handling of air and moisture sensitive reagents. The Chemspeed is controlled by the console to the left using a software package based around a GUI, which can allow easier adoption and set-up than more traditional coding-based software. To the right sits the Huber cryostat which can pump coolant oil around the platform and achieve temperatures ranging from −70 °C to 120 °C. Higher temperatures can be obtained using a different oil. The platform itself is comprised of off-the-shelf components supplied by Chemspeed, which will be discussed in detail (Figure **14**). Note that Chemspeed supply other components that are not present on this configuration and will therefore not be discussed.

Figure 13: The University of Bristol Chemspeed Automation Platform, including Huber cryostat on the right.

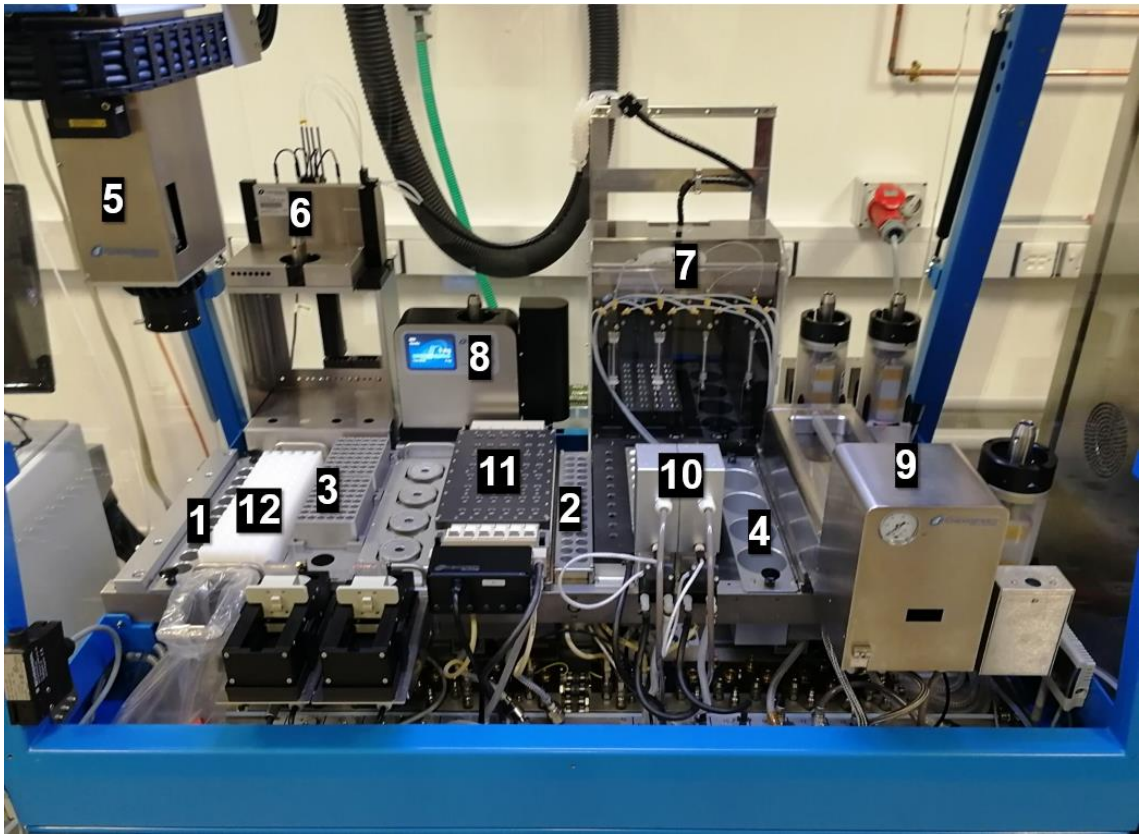


Figure 14: Close up view of the platform.

3.2.1. Reagent racks

The platform is equipped with a 60 mL vial rack (1), an 8 mL vial rack (2), two GC-MS vial blocks (microtitre plates) (3) and a rack for 250 mL Schott bottles (4).

3.2.2. Tools

All material transfers on the platform are performed by the robotic arm (5) which can pick up a selection of tools on the platform. The 4-needle head (6) is used in the aspiration of liquids; each needle is connected via plastic tubing to a six-way valve joined to a 10 mL syringe (7). This six-way valve enables aspiration directly from solvent bottles stored behind the platform. A gravimetric balance (8) is used to dispense solid reagents – this particular model plastic cartridges filled with the solid reagent which is best suited to dispensing amounts between 5 and 100 mg. The solid-phase extraction (SPE) rack (12) allows the filtration of a reaction mixture through a disposable cartridge filled with a solid such as Celite® or silica. The SPE rack has three positions: collect, direct and waste. The collect position is for the collection of the filtrate into a vial, the direct position allows the needle to bypass the filter and enter directly into the collection vial, and the waste position

sits the filter directly over a waste reservoir – this has been used for the wetting of dry silica in a cartridge with solvent in preparation for the filtration of a sample.

3.2.3. Reaction Vessels

There are three reactors on the platform. Perhaps the most general reactor is the ISYNTH (11), which consists of an array of 48 glass vials slotted into a mantle that can be heated up to 200 °C or as low as −20 °C. Each vial is sat on a spring which allows the needles to push into the bottom of the vial to extract as much liquid as possible without damaging the motors that drive the vertical movement of the needles. The vials are sealed by small rubber seals embedded into the lid of the ISYNTH. Each row of vials in the ISYNTH can be independently subjected to vacuum or placed under a N_2 atmosphere, and the entire reactor can be shaken up to 600 rpm.

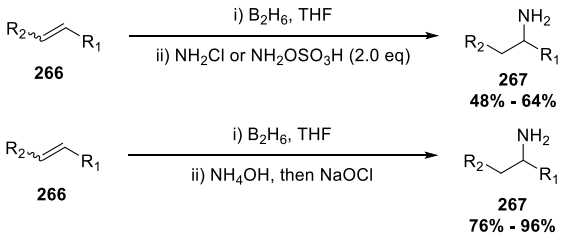
The glass array (10) is two arrays of sixteen jacketed glass reaction vessels sat on top of a vortex (shaking) plate. The jackets are filled with oil from the cryostat which can be cooled down to a temperature of −70 °C and up to 120 °C, making them suitable for low temperature chemistry. Each of the two arrays can be independently placed under vacuum or under inert gas.

The final reaction vessel is the microtitre plate (MTP) block, which can hold one of the two microtitre plates. This reactor can be heated, cooled and stirred in a similar capacity to the iSYNTH, but can also be placed safely under high pressure (5-80 bar). A rupture valve is included as a matter of safety in the event of overpressure, and the platform is fitted with hydrogen and carbon monoxide sensors.

3.3. The Direct Amination of Pinacol Boronic Esters

3.3.1. Amination of Organoboron Compounds

Organoboron compounds are prominent in organic synthesis as the boron functionality is easy to install, usually with high ee values, and once installed, the boron atom can be converted into a plethora of other functional groups. The first direct conversion of a C-B bond to a C-N bond was reported by Brown in 1964: this methodology transformed the borane formed from the hydroboration of an alkene (**266**) to the corresponding amine (**267**) in moderate yield using either chloramine or NH_2OSO_3H.[87] Kabalka later improved on this methodology by using a combination of NH_4OH and NaOCl to generate the amine in high yields.[88]



Scheme 70: Top: Brown's amination. Bottom: Kabalka's amination.

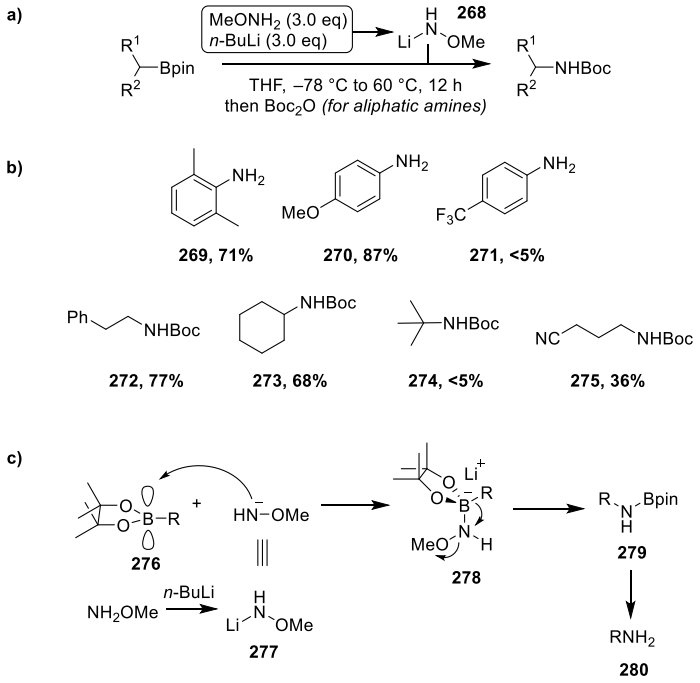
The direct amination of aromatic boronic acids was reported by Chan and Lam in 1998, using stoichiometric copper and NEt_3. These mild conditions were found to be very well tolerated by a plethora of functional groups and became a widely used set of conditions. The use of a stronger oxidant such as di-*tert*-butylperoxide also enabled the use of aliphatic boronic acids [89] A similar transformation could be performed without a metal catalyst using an azide as the N source, which could be subsequently transformed into the amine.[90] The conversion of aliphatic boronic esters to the corresponding amine was a more challenging endeavour as the boron atom was less electrophilic due to donation from the oxygen atoms of the coordinated diol. Brown[91] and Aggarwal[92] both developed multistep procedures to perform this transformation – however it was Morken who reported the first direct, one-pot protocol in 2012.[93]

3.3.2. Morken's 1st Generation Amination Conditions

In 2012, Morken reported the first direct conversion of pinacol boronic esters to the corresponding amines using MeONHLi (**268**), derived from $MeONH_2$ and *n*-BuLi, as the aminating reagent (Scheme **71a**).[93] Unfortunately, the scope of the transformation was relatively limited as the reactive aminating reagent was generated in a large excess and was generally incompatible with other functional groups. Aryl boronic esters generally

worked well, however electron poor aromatic boronic esters such as (4-CF_3)C_6H_4Bpin would only provide trace amounts of product (**271**), presumably as electron poor R-groups are poor migrating groups. Primary and secondary aliphatic boronic esters also delivered the product in good yields, however the more sterically challenging tertiary boronic esters provided little to no product (**274**). The only sensitive functionality present in the scope was example **275**, containing a nitrile, which delivered the product in a moderate 36% yield (Scheme **71b**).

The reaction proceeded via the attack of the boronic ester (**276**) by LiNHOMe (**277**), generated via deprotonation of $MeONH_2$ by *n*-BuLi at −78 °C, to form the boronate complex (**278**). This mixture was then heated to 60 °C to allow the R-group on B to migrate to N, with extrusion of the methoxide leaving group, to form species **279**, which hydrolysed upon work up to give the amine **280** (Scheme **71c**). The excess MeONHLi would decompose at this temperature. For aromatic substrates, this aniline was isolated directly; for aliphatic substrates, Boc_2O was added, and the carbamate was isolated.



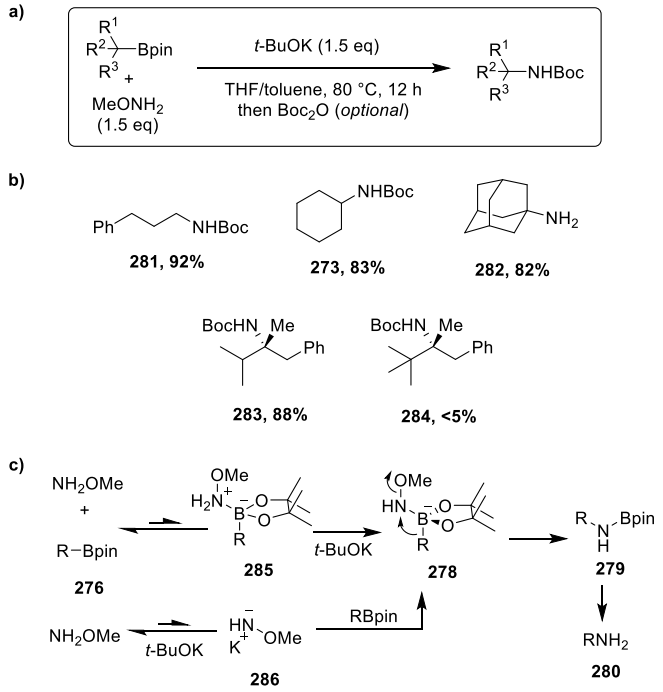
Scheme 71: Morken's 1st generation amination reaction: a) General conditions. b) Selected scope examples. c) Proposed mechanism.

3.3.3. Morken's 2nd Generation Amination Conditions

Morken addressed some of the issues with his seminal amination methodology upon the publication of his 2nd generation boronic ester amination conditions in 2018. Again, the scope of this transformation was somewhat limited to simple hydrocarbon based boronic

esters, however this time with the inclusion of hindered tertiary boronic esters (Scheme **72**). If the boronic esters are made to be extremely hindered, the reaction once again did not proceed (**284**).

This reaction proceeded via a different mechanistic pathway to that of the 1st generation amination: the aminating reagent, $MeONH_2$, and the boronic ester started in the same vessel in a mixture of THF and toluene. *t*-BuOK is then added directly, and the mixture heated to 80 °C. The boronate complex **278** was generated under these conditions in one of two ways: $MeONH_2$ and the boronic ester were in equilibrium with the boronate complex **285**, where the equilibrium lay heavily towards the separate species. This boronate complex was irreversibly deprotonated to form boronate complex **278** which underwent the 1,2-migration to give the product. The same boronate complex was also generated by the attack of a small amount of KNHOMe (**286**), formed via the direct deprotonation of $MeONH_2$ by *t*-BuOK.

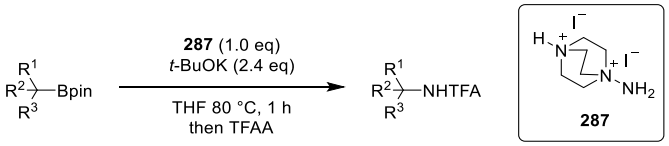


Scheme 72: Morken's 2nd generation amination reaction: a) General conditions. b) Selected scope examples. c) Proposed mechanism.

Although *t*-BuOK was a milder base than *n*-BuLi, the base in this protocol was in direct contact with the boronic ester. This, coupled with the high temperatures to achieve the 1,2-migration, rendered the methodology unsuitable for more sensitive boronic esters.

In 2020, Jin and Liu described the use of a DABCO aminoazanium salt (**287**) to perform the direct amination of aryl and alkyl boronic esters.[94] The reaction was operationally

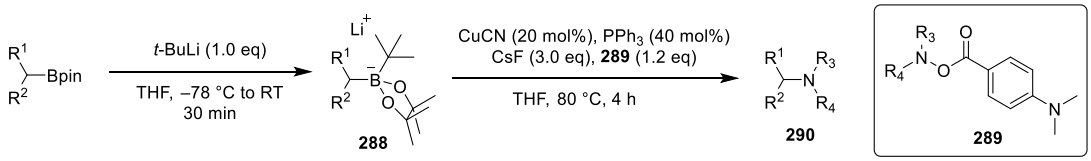
similar to Morken's 2nd generation amination, however **287** is an easily handled bench stable white solid (unlike $MeONH_2$, a volatile and hygroscopic liquid). The reaction still required the use of a strong base and elevated temperatures, so once again displayed poor functional group compatibility (Scheme **73**).



Scheme 73: Direct amination of pinacol boronic esters using DABCO aminoazanium salt.

3.3.4. Morken's Copper Catalysed Amination of Boronic Esters.

In 2022, Morken once again made a contribution to boronic ester amination chemistry by publishing a one-pot copper-catalysed boronic ester amination as part of a larger paper on the stereospecific transformations of boronic esters using copper catalysis.[95] The amination proceeded via the boronate complex **288** formed between the boronic ester and *t*-BuLi, which was coupled to the hydroxylamine derivative **289** using catalytic CuCN. The authors found that the addition of CsF improved the efficiency of the reaction due to the formation of a more reactive boronate complex via caesium-lithium exchange. Hydroxylamine esters are relatively reactive oxidants, able to oxidise Cu(I) to Cu(II), so PPh_3 is added as a sacrificial reductant (Scheme **74**).



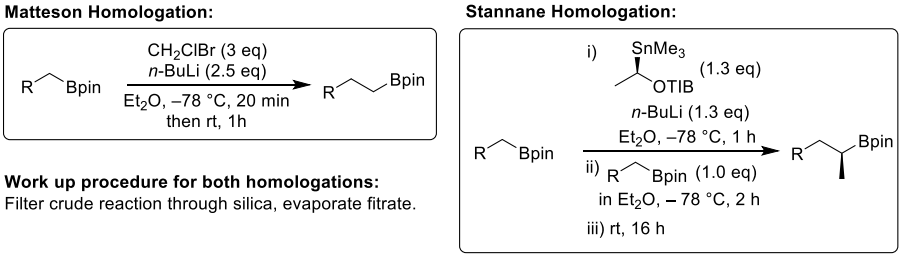
Scheme 74: Morken's copper-catalysed amination of pinacol boronic esters.

3.4. Previous work

Due to both the collaborative nature and the length of this project, several researchers have made contributions to the project – Dr Rory Mykura, Dr Valerio Fasano and Dr James Fordham. All the work described in this chapter has been performed exclusively by these three people and not by the author. The author's contributions to the project will be discussed in Chapter 4.

3.4.1. Towards the Automated Synthesis of 257 and Analogues

The first reactions that were optimised for use on the Chemspeed were the Matteson homologation and the stannane homologation. The typical conditions for the manual execution of these reactions are shown in Scheme **75**. For the Matteson homologation, to a prepared solution of the boronic ester and bromochloromethane in Et_2O at −78 °C was added *n*-BuLi at 0.03 $mLmin^{-1}$ (maintenance of the temperature of the reaction is crucial to prevent over-homologation). After stirring at −78 °C for 20 mins, the reaction was warmed to room temperature for one hour, then filtered through a silica plug and evaporated to leave the product boronic ester. The procedure for the stannane homologation is slightly more complex: to perform tin–lithium exchange, *n*-BuLi was added to a solution of the stannane in Et_2O at −78 °C and stirred for one hour. The boronic ester was then added as a solution in Et_2O dropwise at −78 °C, stirred for two hours at that temperature and then warmed to room temperature for 16 hours. The reaction was then passed through a silica plug and evaporated.

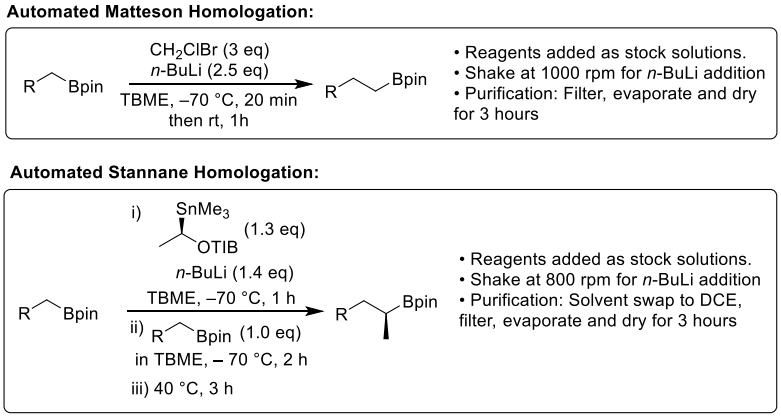


Scheme 75: Typical conditions for the Matteson and Stannane homologations.

To transfer this chemistry to the automated platform, a few changes were made. The solvent was changed from Et_2O to TBME as Et_2O was found to be too volatile to be handled by the platform – there are two reasons for this; the platform will reach an operating temperature of 30 – 35 °C, close to the boiling point of Et_2O, and Et_2O will readily from gas bubbles in the tubing connecting the 4-needle head to the syringes, lowering the accuracy of the liquid transfers. The temperature for lithiation and borylation

was slightly higher; −70 °C is the lowest temperature that the Huber cryostat can reliably cool the platform down to. For the Matteson homologation, it was found that shaking at maximum speed (1000 rpm) during the *n*-BuLi addition allowed the best dissipation of heat during the addition (to prevent over-homologation) and subsequently provided the best results.

The stannane homologation required multiple modifications: The equivalents of *n*-BuLi on the platform was increased slightly to 1.4 eq after a small amount of stannane was remaining in the crude of the reaction; presumably a small amount of the organolithium was being quenched before being added to the stannane. The 1,2-migration conditions were changed from room temperature for 16 hours to 40 °C for 3 h, a decision made to save time. Finally, after the 1,2-migration was completed, a solvent swap from Et_2O to DCE was performed before the transfer to the filter. The LiOTIB by-product formed a gel like consistency in TBME which prevented efficient aspiration of the crude, leaving product in the reaction vessel. It was found that redissolving the crude mixture in DCE would disperse this gel and allow all the crude product to be transferred to the filter, leaving behind the majority of the LiOTIB. The use of THF, for example, dissolved most of the LiOTIB, which would subsequently precipitate on the top of the silica filter, blocking them and causing the filters to burst from over-pressure (Scheme **76**).



Scheme 76: Procedures for the automated Matteson and Stannane homologation.

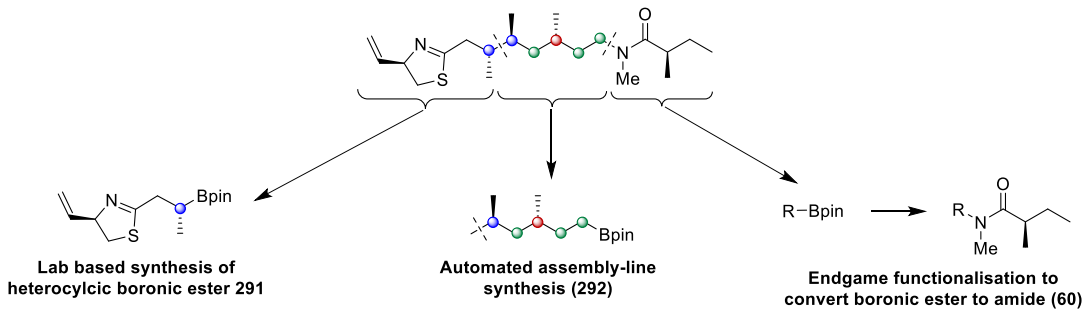
Morken's 2nd generation amination,[85] amine acylation and amide methylation reactions were also optimised for use on the platform, the details of which will not be discussed here. The results of this work culminated in the synthesis of **257** over 9 steps as described in Chapter 3.1.4.2. The next step was to take advantage of the automated platform to perform the synthesis of four analogues of **257** in parallel. This will be discussed in results Chapter 4.1.

3.4.2. Towards the Automated Synthesis of Kalkitoxin

Complex molecule **257** was an intermediate in Aggarwal's synthesis of kalkitoxin (Scheme 12).[29] The original aim of this project was to synthesise kalkitoxin and analogues thereof, however the publication strategy was changed due to the difficulties associated with the functionalisation of the thiazoline containing boronic ester.

3.4.2.1. Proposed Automated Synthesis of Kalkitoxin

A plan for the synthesis of kalkitoxin on the automated platform is shown in Scheme **77**. Two disconnections of kalkitoxin break down the synthesis into three distinct phases: The lab-based synthesis of the heterocyclic boronic ester **291**, the automated five-step assembly-line sequence using **291**, and the final functional group interconversion of the assembly-line boronic ester (**292**) to the desired *N*-methylated tertiary amide. Each of these aspects will be discussed in turn.

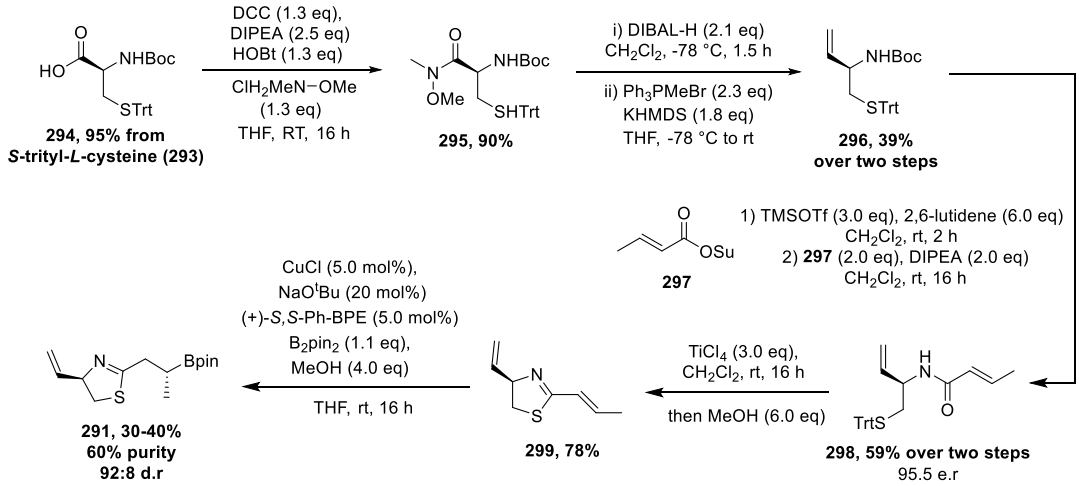


Scheme 77: Plan for the automated synthesis of kalkitoxin.

3.4.2.2. Synthesis of the Heterocyclic Boronic Ester (291)

The 8-step synthesis shown below was developed by Dr Rory Mykura. Minor changes were made by the author, these will be discussed in Chapter 4.2.

The synthesis commenced from *S*-trityl-*L*-cysteine (**293**), which was Boc-protected to give **294** in high yield. The corresponding Weinreb amide (**295**), generated by an amide coupling of $MeONMeH_2Cl$ and **294** using DCC, DIPEA and HOBt, was subjected to a DIBAL-H reduction to the aldehyde, which was used as a crude in the subsequent Wittig reaction to generate the alkene **296**. The N-atom was deprotected and then coupled with the appropriate succinimide ester **297** to give amide **298**. The thiazoline ring was generated via a $TiCl_4$ mediated trityl removal and cyclisation (**299**), followed by a copper-catalysed conjugate borylation to give the heterocyclic boronic ester **291** with high d.r.

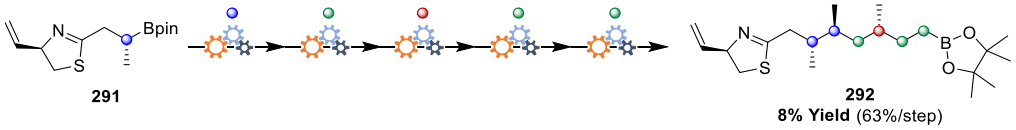


Scheme 78: Synthesis of **291** developed by Dr Rory Mykura.

3.4.2.3. Assembly-line Synthesis on the Boronic Ester 291

The following work was performed by Dr Valerio Fasano and Boris Banecki.

Whilst the automated assembly line synthesis of **58** could be performed in a 41% yield over six steps, the analogous procedure on heterocyclic boronic ester **291**, consisting of five homologations to make **292**, could only be performed in an 8% isolated yield. Lab based results have shown that even a single homologation on **291** would perform to a lower yield than expected (typically 70%, as opposed to 90%) – the thiazoline is only moderately compatible with the assembly-line methodology (Scheme **79**).



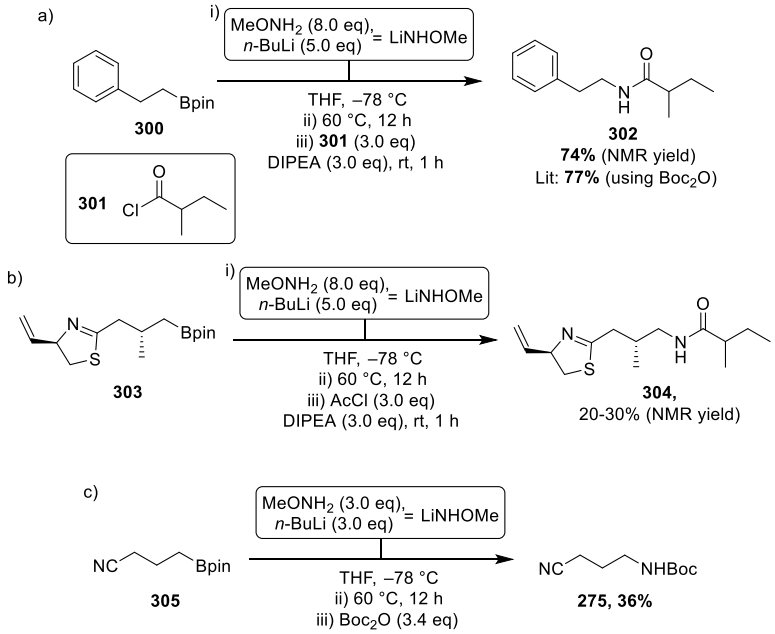
Scheme 79: Automated assembly-line synthesis using **291**.

3.4.2.4. Amination of the heterocyclic boronic ester.

The following work was performed by Dr Valerio Fasano and Dr Rory Mykura.

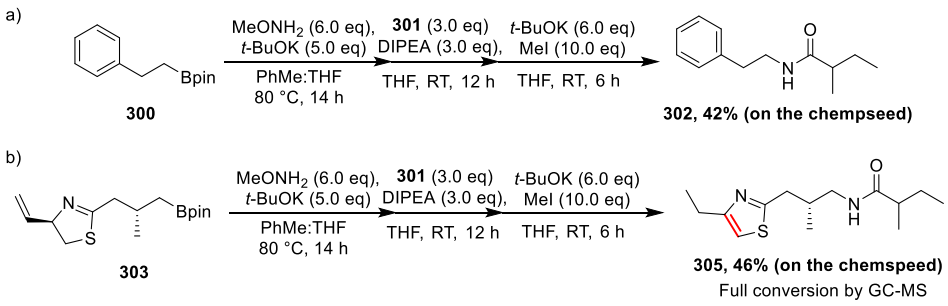
The thiazoline ring of the heterocyclic boronic ester was shown to be only moderately compatible with the conditions required for the assembly-line synthesis. This sensitivity extended also to the conditions for boronic ester amination that were in the literature at that time: Morken's 1st and 2nd generation amination conditions. It was shown that although Morken's 1st generation amination conditions (which had been altered slightly for use on the Chemspeed) worked well on a simple model substrate **300** (Scheme **80a**), they did not work well on a thiazoline containing model substrate **303** (Scheme **80b**), giving only poor yields (by NMR) and correspondingly poor mass balances. It was

suspected that the C-N double bond in the thiazoline ring was electrophilic enough to react with the active aminating reagent – this hypothesis was based on a result from Morken's publication,[93] in which a nitrile containing boronic ester (**305**) performed similarly poorly in the amination – perhaps due to the moderately electrophilic nature of the nitrile group (Scheme **80c**).



Scheme 80: Morken's 1st generation amination conditions: a) on a simple model substrate (**300**). b) on a thiazoline containing model substrate (**303**). c) from Morken's publication, containing a nitrile group.

Morken's 2nd generation amination conditions were tried next – again, the conditions, which had been adapted slightly for use on the Chemspeed, seemed to perform well on **300** (Scheme **81a**). Subjecting the thiazoline containing boronic ester **303** to these same conditions gave the corresponding thiazole **305** in a 46% yield (Scheme **81b**). The formation of the aromatic thiazole is due to the thermodynamically-driven base mediated isomerisation of the alkene in the amination.

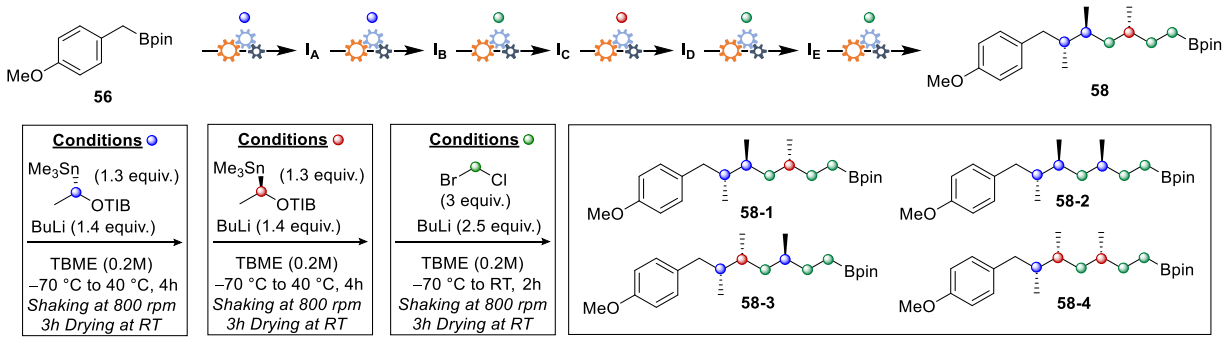


Scheme 81: Morken's 2nd generation amination, acylation and amide methylation performed on the Chemspeed: a) on a simple model substrate. b): on a thiazoline containing model substrate.

4. Results and Discussion

4.1. Automated Synthesis of Four Analogues of 58 in Parallel

As described in Chapter 3.1.4.2, the Aggarwal group have demonstrated the automated synthesis of complex molecule **257** on a Chemspeed Automation Platform in a two-phase procedure – the six-step assembly line synthesis and the three-step functional group interconversion of the boronic ester to the tertiary amide (Schemes **67** and **68**). The value of this protocol is in the ability to perform four reactions in parallel utilising the four-needle head the Chemspeed is equipped with to generate four analogues in the time that a person working in a conventional synthetic laboratory could generate one analogue. To realise this, some simple changes needed to be made to the workflow to allow the addition of the two enantiomers of the stannane to separate reactions to generate these diastereomeric analogues. When performing the second homologation, the (−)-stannane (**36**) would be added to reactions 1 and 2, and the (+)-stannane (***ent*-36**) to reactions 3 and 4, and when performing the fourth homologation, the (−)-stannane would be added to reactions 2 and 3, and the (+)-stannane to reactions 1 and 4.



Scheme 82: Planned synthesis of four analogues in parallel.

4.1.1. Preparation of 56 for the Automated Synthesis of Analogues of 58

A large quantity of **56** was required to perform this experiment, and the synthesis of this material proved to be more difficult than anticipated for two reasons: first, this compound is relatively unstable as the benzylic boronic ester is prone to protodeboronation in the presence of moisture, and secondly since the compound was required in exceptionally high purity by GC-MS analysis (>99.5%). The progress of the automated assembly-line synthesis was monitored by GC-MS (checking for conversion) as shown in Figure **15** – any impurities, even those not visible by NMR, would show up very clearly.

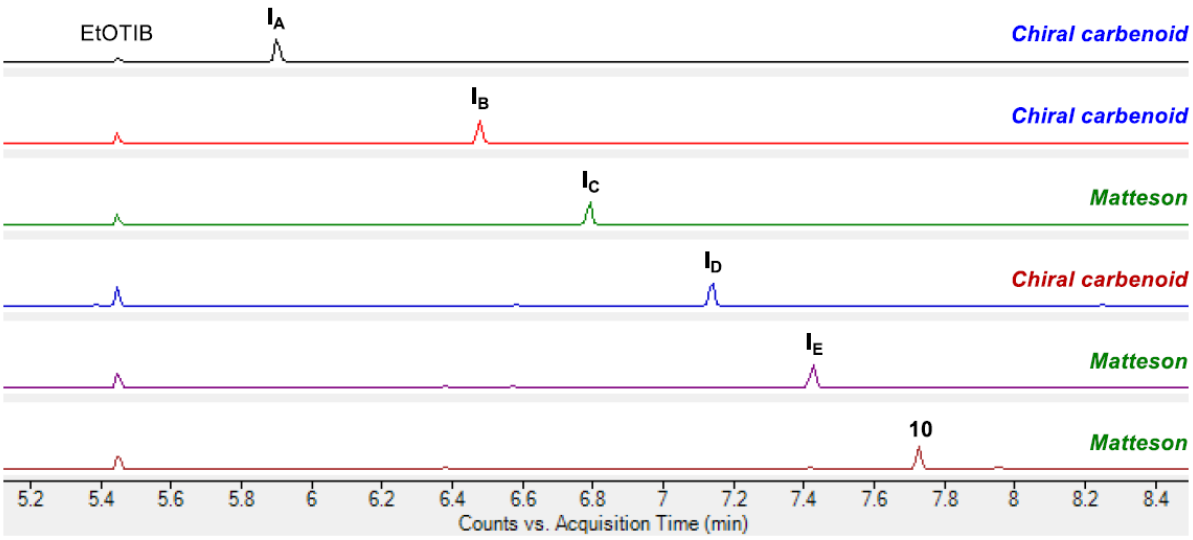
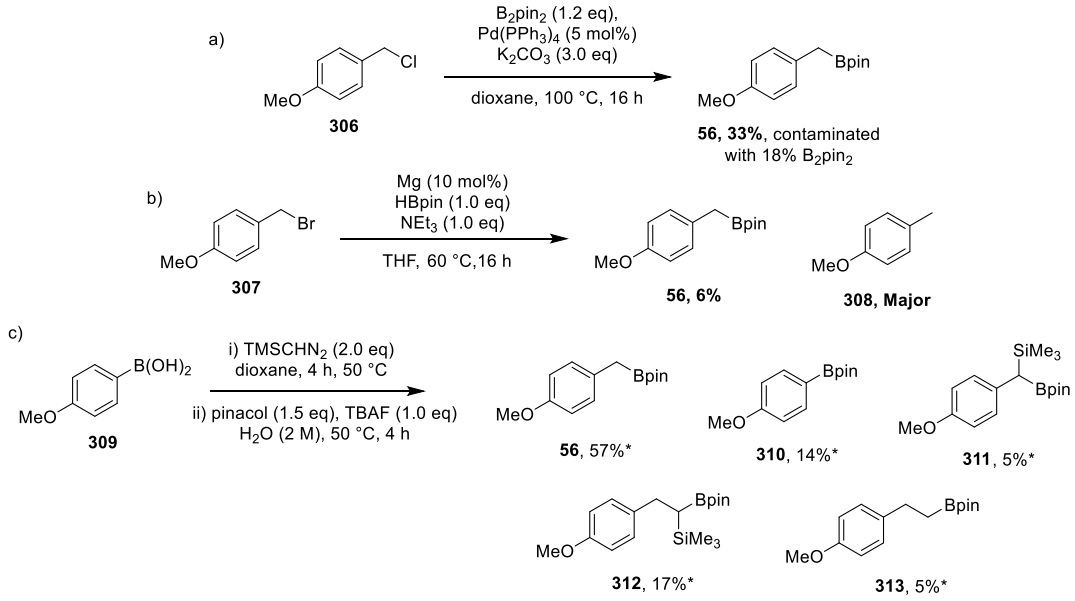


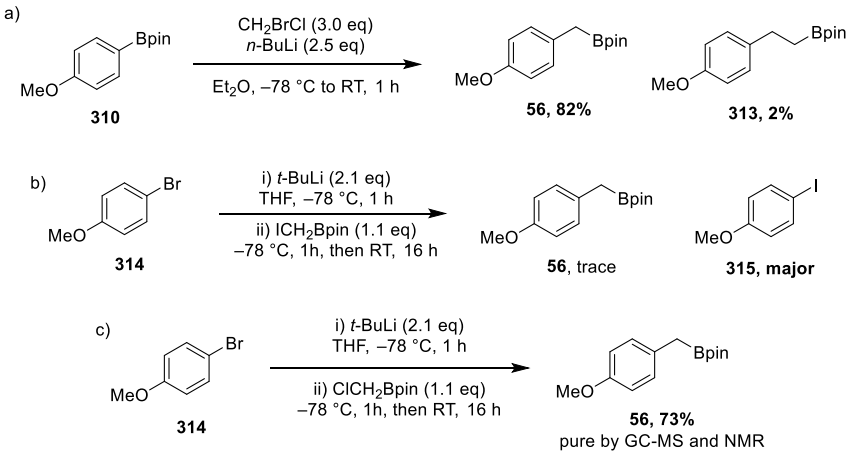
Figure 15: Use of GC-MS to monitor the progress of the automated assembly-line synthesis. Ix refer to the intermediate assembly-line species as shown in Scheme **82**,

The first synthetic procedure investigated was the palladium catalysed cross-coupling of benzylic halides with B_2pin_2.[96] The product was formed in a poor yield, however it was the separation of excess B_2pin_2 that was problematic (Scheme **83a**). Also tested was the magnesium catalysed Grignard-type reaction of benzylic bromides with HBpin, in which HBpin acts both as the electrophile and the reductant to regenerate an organomagnesium species *in situ*.[97] This reaction proceeded very poorly, yielding only a very small amount of **56**, the major product being the protodeboronation product (**308**) (Scheme **83b**). The next procedure attempted was a boronic acid homologation facilitated by $TMSCHN_2$, followed by both protodesilylation and esterification of the boronic acid. This reaction gave a complex mixture of products comprising the product (**56**), unreacted starting material that had been esterified (**310**), homologated silylated product (**311**), the over-homologated product (**313**) and the over-homologated silylated product (**312**) (Scheme **83c**).



Scheme 83: a) Palladium catalysed cross coupling. b) Magnesium catalysed Grignard-type reaction. c) One carbon homologation of a boronic acid using $TMSCHN_2$. *GC-MS ratios.

Subjecting the aromatic boronic ester **310** to a Matteson homologation gave a high yield of product with a small amount of the over-homologated product. In the Matteson homologation, over-homologation is caused by the boronate complex undergoing the 1,2-metallate rearrangement during the *n*-BuLi addition at −78 °C and then reacting with a further equivalent of $LiCH_2Cl$. Most boronate complexes will not undergo the 1,2-metallate rearrangement at −78 °C, however if the addition of the room temperature *n*-BuLi solution to the reaction is too fast, this creates localised hotspots which can allow this rearrangement to occur. In this specific case, even with an extremely slow rate of *n*-BuLi addition (0.01 $mLmin^{-1}$), 2% of the over-homologation product **313** was observed. Clearly this particular boronate complex is liable to undergo the rearrangement initiated by the addition of a single drop of room temperature solution (Scheme **84a**). The same boronate complex could be formed by the addition of the lithiated aromatic compound to a compound of the general formula XCH_2Bpin, in which X^- is a leaving group. When X^- was iodide, the reaction gave only trace of the desired product, with most of the starting material undergoing lithium-iodine exchange with ICH_2Bpin to form **315** (Scheme **84b**). Using $ClCH_2Bpin$ inhibited this undesired pathway completely and provided **56** cleanly in a 73% yield, and more importantly, pure by GC-MS analysis (Scheme **84c**).



Scheme 84: a) Matteson homologation. b) Lithiation-borylation with ICH_2Bpin. c) Lithiation-borylation with $ClCH_2Bpin$.

The benzylic boronic ester **56** showed signs of decomposition by TLC analysis after being stored for two weeks at –20 °C so it must be synthesised and used immediately.

4.1.2. Mechanical Issues with the Chemspeed Automation Platform

With the starting material (**56**) in hand and with all the necessary workflows constructed on the Chemspeed software, the stage was set to perform the assembly-line synthesis and generate four analogues in parallel. Unfortunately, months of mechanical issues with the platform hampered all attempts to do this. Some of these issues are described in this chapter.

Here follows a brief explanation for the terminology used in this section: A 'run' of reactions consists of four reactions performed in parallel. The reactions took place in the glass array (low-temperature reactors), were transferred to the SPE (Solid-Phase Extraction) rack to be filtered, and then transferred back to the glass array to be concentrated ready for the next homologation. These reactions were labelled from 1 – 4, with reaction 1 taking place in glass array 1. Needle 1 performed all aspirating and dispensing for reaction 1, and reaction 1 was filtered through filter 1 (the same principle applies for the other needles). All needles aspirated from a single stock solution for each reagent which were prepared manually and stored on the platform.

The mechanical problems were addressed by both the author and the University of Bristol Chemspeed technician, Rebecca Schultz-Graham.

Solution remaining in glass array 4.

After a completed run of boronic ester homologations, it was noticed that glass array 4 had approximately 5 mL of solution left (this should have been transferred to the filter

after reaction completion). It was not clear where such a quantity of liquid could come from as the amounts of the stock solutions being dispensed for the reaction were much less than 5 mL. NMR analysis revealed that the liquid was ethanol, which was used in the reflux attachment on top of the glass array and had leaked into the reaction vessel due to a crack in the glass connection. The glass array could not be used without the reflux attachment in place due its design. Fortunately, this essential piece of equipment could be fixed by the School of Chemistry glassblower. The glass array could not be sent to be fixed by Chemspeed as they have since discontinued the part.

Reaction 4 consistently performed worse than the other reactions.

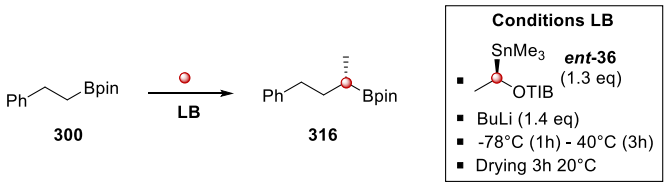
This problem had been documented for about a year and previously did not cause enough of a difference to be thoroughly investigated, however the discrepancy was getting larger and therefore needed to be addressed. The discrepancies were generally issues such as a small amount of starting material remaining or a slightly lower yield for reaction 4 in a run. In our case, this discrepancy would manifest itself as incomplete consumption of the stannane in the stannane homologation (determined by GC-MS analysis), and the fact that the problem was mostly isolated to reaction 4 indicated that the quality of the reagents, used in all 4 reactions during a run, was good. The troublesome step was likely to be the *n*-BuLi addition to perform tin-lithium exchange; if less *n*-BuLi was being added than intended, this would leave behind some stannane. It was initially suspected that the stock solution of *n*-BuLi was slowly evaporating during the time between being loaded onto the platform and being used. This would result in a more concentrated solution; needles 1,2 and 3 would aspirate a set volume, now containing more *n*-BuLi than intended, which would consume all the stannane for reactions 1,2 and 3. This would leave a small amount of *n*-BuLi solution remaining in the stock vial which needle 4 could not aspirate completely, resulting in less *n*-BuLi being added to reaction 4. It should be noted that the 8 mL vial containing the *n*-BuLi stock solution was flat based, therefore a 1 mL excess of stock solution was required to allow the tapered end of a needle to reliably aspirate the correct amount without colliding with the bottom of the vial. To prevent this evaporation, the vials were loaded onto the platform and then immediately covered with a layer of parafilm, which the needles could effortlessly pierce through to aspirate the solution. Unfortunately, the problem persisted after this measure was taken.

When performing an aspiration, the needle will first aspirate a 0.1 mL air gap; this separates the system solvent (which fills all the solvent lines connecting the syringes to

the 4-needle head) from the aspirated reagent stock solution. Then the needle will aspirate 0.1 mL of extra volume of the stock solution, followed by the programmed amount of stock solution. When performing the subsequent dispension, the stock solution is dispensed to the reaction vessel, the extra volume is returned to the stock solution vial (for *n*-BuLi, the extra volume is dispensed to a dedicated *n*-BuLi waste), and the air gap is pushed into the waste. During an aspiration, it was observed that needle 4 was not aspirating the 0.1 mL air gap accurately, occasionally omitting the air gap completely. Without an air gap, the aspirated stock solution was diluted by being able to mix with the system solvent, and in the example of a tin-lithium exchange, an insufficient amount of *n*-BuLi was being added to consume the stannane completely. The solution was not a direct fix, but a software-based workaround; needle 4 was instructed to aspirate an 0.2 mL air gap (instead of 0.1 mL) to artificially force a suitably sized air gap during the aspiration. This seemed to solve the issue, however the cause of needle 4 continually being unable to aspirate an air gap accurately is still unknown.

Inaccurate and irreproducible dispensions.

Even after having solved the issue with the air gap in needle 4, the yields and consumption of the stannane varied significantly not only between runs, but between the reactions within a run. Table **7** shows the yields and remaining stannane for three separate runs of four parallel reactions. The yields were considerably lower than that which had typically been observed for the automated stannane homologation, around 90%, and the amount of stannane **(*ent*-36**) remaining also varied greatly between reactions.



	Run A		**Run B**		**Run C**	
	Yield	***ent*-36** remaining	Yield	***ent*-36** remaining	Yield	***ent*-36** remaining
Reaction 1	67%	30%	75%	11%	64%	0%
Reaction 2	65%	32%	63%	20%	79%	0%
Reaction 3	77%	0%	76%	0%	81%	0%
Reaction 4	67%	4%	63%	0%	68%	0%

Table 7: Three runs of four parallel stannane homologations. NMR yields of **316** and ***ent*-36** are shown, determined using CH_2Br_2 internal standard in $CDCl_3$.

If there was stannane remaining, then an insufficient amount of *n*-BuLi was being added for tin-lithium exchange. A simple dispension test was performed as follows. A stock solution of known concentration containing an internal standard in $CDCl_3$ was dispensed from one position of the platform to another position. A second internal standard was added after the dispension and the mixture was analysed by NMR. If the dispension is perfectly accurate, then there should be an equimolar amount of the two internal standards – too little of the first internal standard present indicates that the amount of stock solution dispensed was too low, and vice versa. Table **8** shows the results of two such dispension tests, performed with the four needles in parallel. A value of 94% indicates that the Chemspeed dispensed 0.94 mL when it was instructed to dispense 1.00 mL. The results were concerning – needles 1 and 2 were not dispensing accurately at all, with needle 2 being 13% percent out in one case.

Needle	Run 1 (NMR yield)	Run 2 (NMR yield)
1	94%	96%
2	87%	90%
3	99%	99%
4	99%	98%

Table 8: Results from two dispension tests. NMR yields determined using CH_2Br_2 internal standard in $CDCl_3$.

What followed was an extensive set of dispension tests, comprising over 100 individual data points, which accounted for factors such as source location, destination location, shaking speed of the destination vial, the rate of aspiration and dispension, and even the orientation of the needle head during the dispension. No clear trends were observed even after subjecting the data to basic statistical analysis. Once again, the root of the problem was not found – in fact, over the months of dispension tests, the results seemed to improve gradually for reasons still unknown. A small manual workaround was also implemented – the volumes of the syringes on the platform that connect to the needle head are 10 mL, this volume was changed on the Chemspeed software to be approximately 9.5 mL, this value being chosen by trial and error. After this, the dispension tests were giving results that were within a reasonable level of accuracy.

Miscellaneous errors:

- During one of the filtrations, the needle didn't enter the top of the filter as intended but hit the side of the lid of the filter. The crude mixture was then dispensed over the top of the filter and was unrecoverable. The cause of this error was due to needle 4 being slightly off centre. After replicating the error, it was found that the

needle would catch on the reflux component on the glass array when dispensing into the glass array, causing the needle to bend slightly and cause its trajectory to be off centre. The solution here was to 'offset' the glass array by 2 mm, meaning that the Chemspeed 'thought' the glass array was 2 mm further to the back of the platform than it actually is.

- One of the needles errored during the filtration whilst inside the filter dispensing the crude mixture onto the silica. The cause of this error is unknown and was not reproducible.
- After a completed workflow, the platform, which is under an inert atmosphere, is opened to air for manual analysis of the reactions. On one occasion, upon opening the platform, a small fire started around the *n*-BuLi solution and lasted for approximately 5 seconds before burning out. The reason for this is due to an erroneous aspiration of the *n*-BuLi – once aspirated, the *n*-BuLi was dripping out of the end of the needle on its way to the destination reaction vessel. These drops of *n*-BuLi in hexanes would sit on the platform under an inert atmosphere and the hexane would evaporate, leaving solid *n*-BuLi that would only be quenched upon exposure to moisture in the air. The exact cause of the error in this case was also unknown and not reproducible.

Outlook

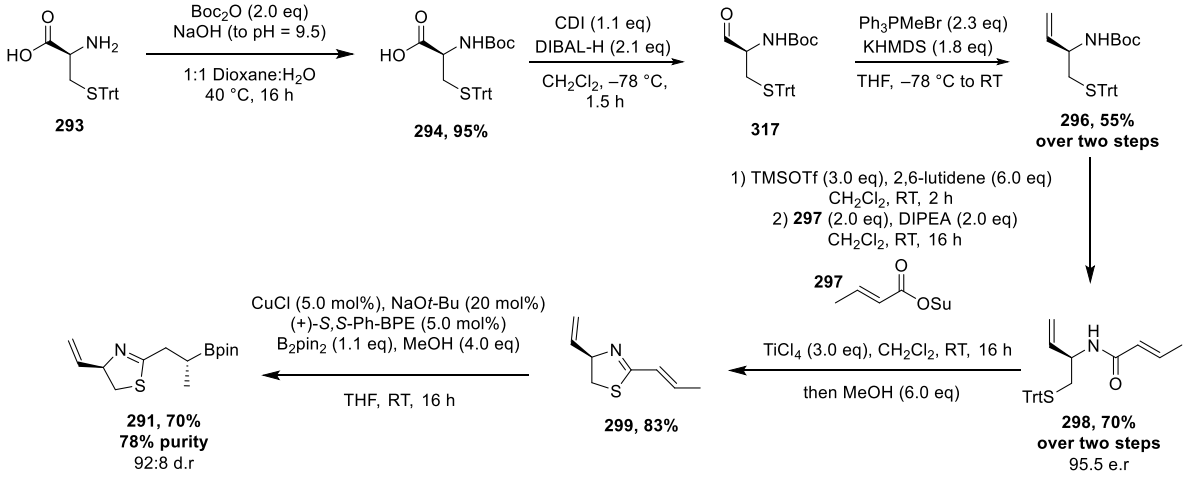
The errors described in this chapter are representative of the enormous practical challenge of running a complex automation platform. Not even a single boronic ester homologation could be performed to the yield that had been attained previously in six months of trying. At this point in time, the platform cannot be trusted to perform the complex workflows required for the boronic ester homologation chemistry without encountering an error which spells the disastrous end of an assembly-line run.

4.2. Heterocycle Synthesis

The route for the synthesis of heterocyclic boronic ester **291** was designed predominantly by Dr Rory Mykura, as outlined in chapter 3.4.2.2. Detailed in this chapter are the contributions made by the author.

4.2.1. General Modifications

For the most part, modifications to the original route were more operational in nature, and these changes resulted in slightly higher yields for most of the steps in the sequence. The first of two major changes to the synthetic route was the direct, one-pot conversion of carboxylic acid **294** to aldehyde **317**. In the first route (Scheme **78**) **294** was converted to the Weinreb amide (**295**), isolated, and then reduced to give **296**, whereas in this route, **294** was activated using CDI, which was reduced in the same pot upon addition of DIBAL-H. This was then added to a solution of the phosphonium ylid as before and delivered alkene **296** in a 55% yield over two steps from **294**, compared to a 35% yield over three steps.



Scheme 85: Updated route for the synthesis of heterocyclic boronic ester **291**.

4.2.2. An Improved Procedure for the Purification of 291

Thiazoline-containing boronic ester **291**, the product of the copper-catalysed conjugate borylation of alkene **299**, could not be separated completely from presumed by-products that were difficult to characterise by ^{1}H NMR analysis. Take for example the spectrum shown in Figure **16**, which appeared to be relatively pure aside from a few minor impurities (3.9, 3.7 ppm) - yet addition of an internal standard revealed that the purity of the material was only 60%. When the region between 1.4 and 1.3 ppm was expanded multiple singlets corresponding to more than one pinacol-containing species were visible.

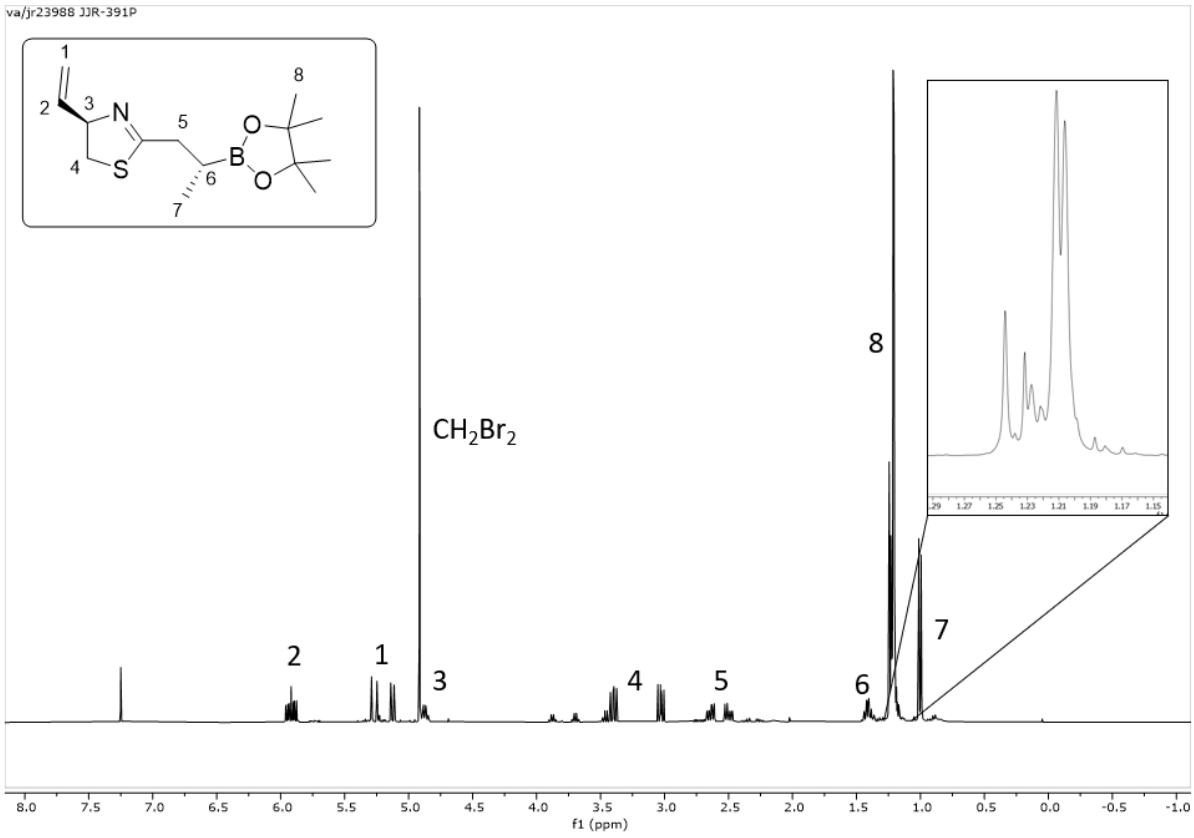


Figure 16: ^{1}H NMR of **291** at 60% purity

The nature of these impurities was revealed upon acquiring a ^{11}B NMR spectrum of the same material (Figure **17**) – these impurities were derived from the pinacol boronic ester. The peak at δ = 32 ppm corresponds to a boronic ester species, such as the product, however it could not be ruled out that there were further boronic ester impurities. The two peaks at δ = 22 and 19 ppm correspond to two separate borate species, and although the identity of these impurities could not be ascertained using NMR analysis alone, GC-MS analysis indicated that these impurities were HOBPin (**318**) and $(Bpin)_2O$ (**319**). Finally, the small peak at δ = 8 ppm corresponds to a boronate complex, which could not be identified, but was likely an adduct of one of the other boronic ester or borate species in the mixture with an adventitious nucleophile.

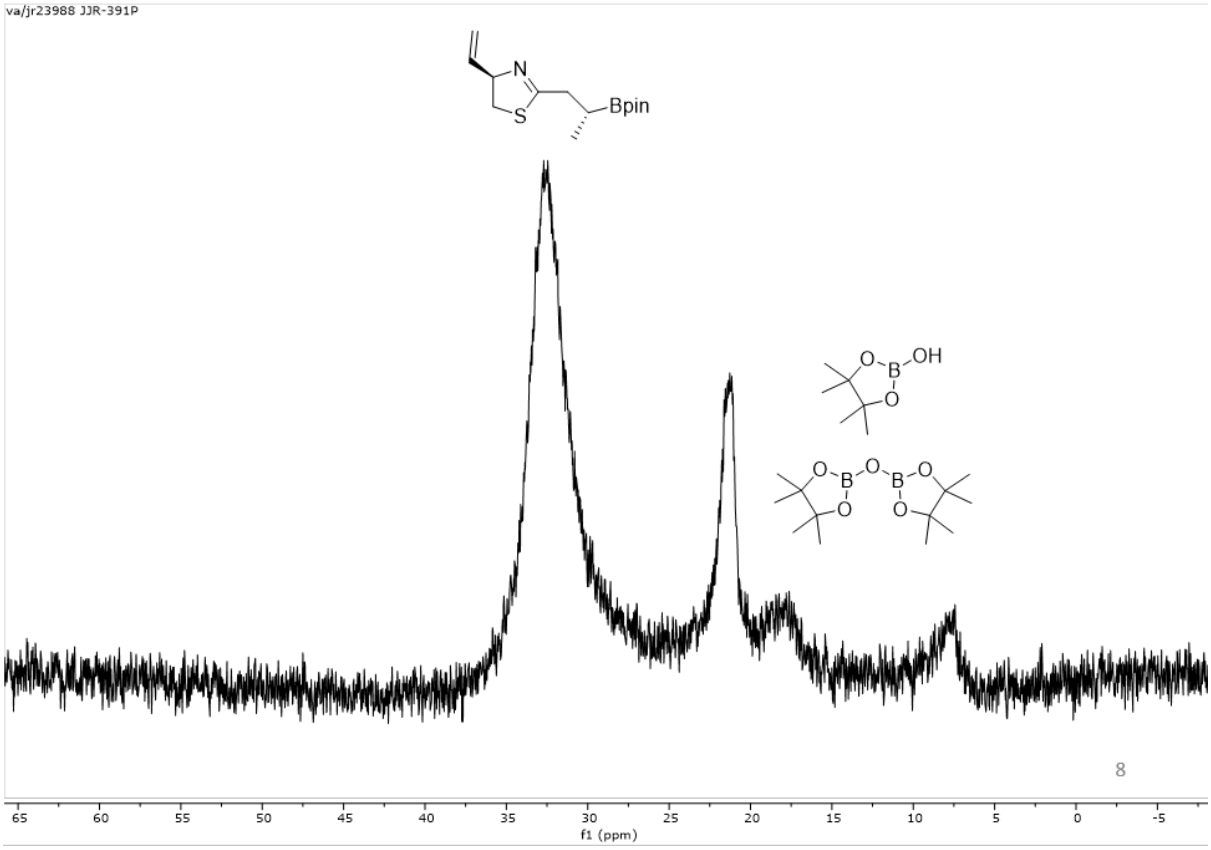
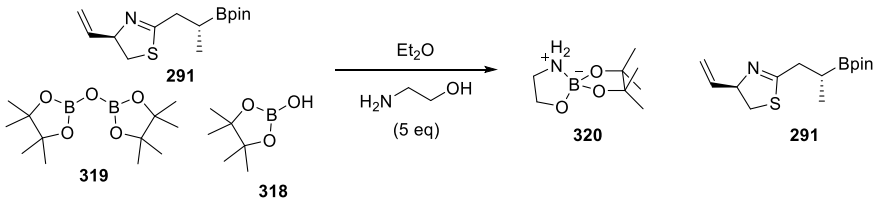


Figure 17: ^{11}B NMR of **291** at 60% purity

Removal of these boron containing impurities proved to be exceptionally challenging for two reasons; firstly, these boron containing impurities streaked through silica and co-distilled with the product during a distillation; and secondly, and perhaps more unfortunately, the thiazoline containing boronic ester was, in our experience, inherently unstable to acidic, basic and neutral aqueous media, and silica gel. This made traditional methods for the purification of difficult to separate mixtures, such as preparative High Performance Liquid Chromatography (HPLC), unsuitable – the aforementioned silica column chromatography had to be performed rapidly at the expense of a good separation to ensure a decent return of product mass. One approach was to use boric acid impregnated silica gel – this was reported to be an effective method for the purification of boron containing compounds bearing the nuisance vacant orbital via capping of the nucleophilic sites of silica gel.[98] It was supposed that this method may partially inhibit the decomposition of the boronic ester on silica, and indeed this was the case as the recovery of the product after chromatography with this impregnated silica was near quantitative, however the ability of the silica to separate compounds is reduced with the addition of boric acid, and the product boronic ester was still impure.

The method that ultimately improved the purity of the product was a chemical one: the result of treating a solution of the boronic ester and impurities in Et_2O with ethanolamine was that the borates (**318**, **319**) reacted to form a boronate complex irreversibly (**320**). The boronate complex formed between ethanolamine and the boronic ester was reversible. This mode of reactivity is made possible by the fact that the OH/OBpin groups on the borates can act as leaving groups, allowing bis-coordination of the ethanolamine to the boron centre. This zwitterionic boronate complex was poorly soluble in Et_2O so could be easily filtered out of the reaction mixture.



Scheme 86: Reaction of the borates with ethanolamine.

^{11}B NMR analysis reflected the effectiveness of this method for the removal of borate impurities from boronic esters (Figure **18**). There was a small amount of borate visible at 22 ppm, but most of this purified mixture was boronic ester. This ^{11}B NMR spectrum looked to be very promising, however NMR analysis of this material revealed the purity was still 78%. The other impurity, presumably a boronic ester, has not been identified.

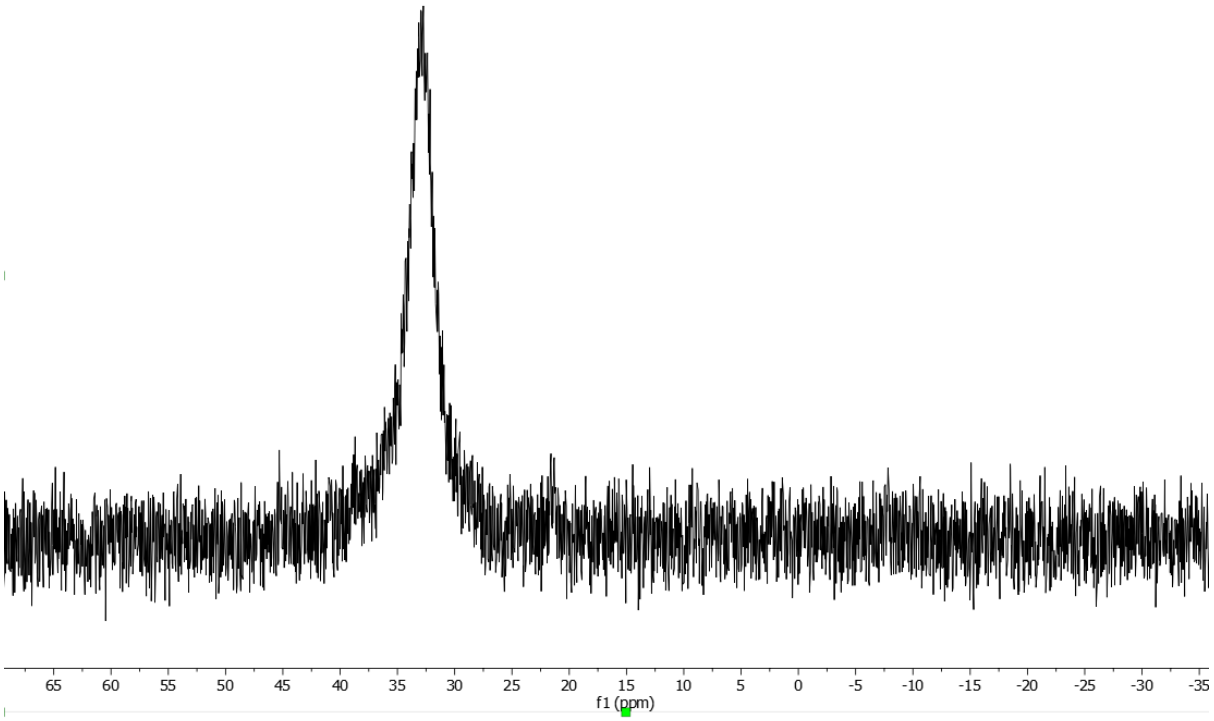
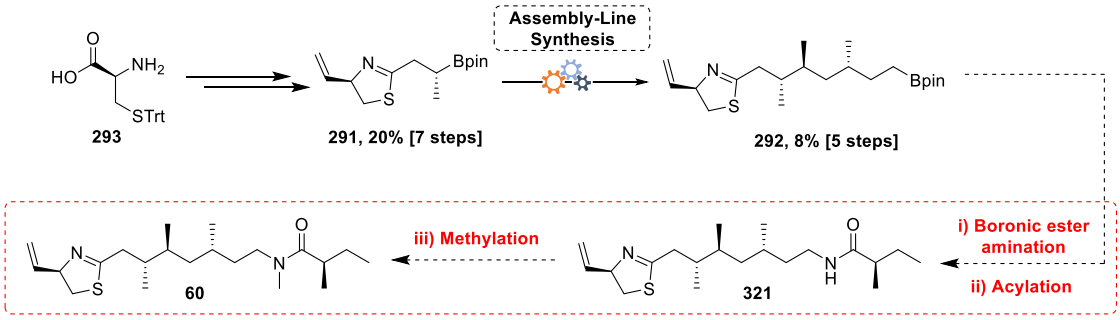


Figure 18: ^{11}B NMR of the impure boronic ester **291** after treatment with ethanolamine

4.3. Conversion of Boronic Ester 292 to Tertiary Amide 60

The proposed forward synthetic route for the partially automated synthesis of kalkitoxin (**60**) is divided into three phases: the manual synthesis of **291**, which has been achieved in a 20% yield over 7 steps, the five-step automated assembly-line synthesis to generate **292** in an 8% yield over five steps, and finally the automated transformation of boronic ester **292** to the tertiary amide present in kalkitoxin (Scheme **87**).

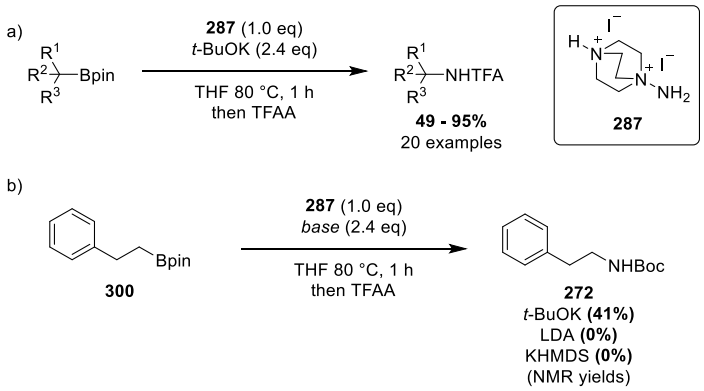


Scheme 87: Forward synthesis of **292** and the proposed conversion of **292** to kalkitoxin (**60**).

Previous work on this final phase of the synthesis had shown that the main methods of the direct conversion of boronic esters to amines in the literature, that is Morken's 1st and 2nd generation amination conditions, were incompatible with the thiazoline moiety (Chapter 3.4.2.4). Described in this chapter are the further attempts at performing this functional group interconversion.

4.3.1. Jin and Liu: Aminoazanium of DABCO

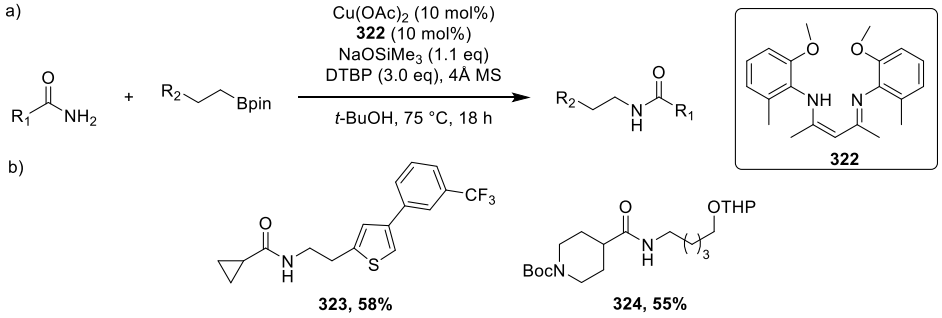
In 2020, Jin and Liu reported a procedure that is mechanistically similar to Morken's 2nd generation amination conditions using a novel amination reagent – the aminoazanium ion of DABCO.[94] The main feature of this method was the ease of handling of this new reagent, it was a bench stable, crystalline solid that could be easily prepared (albeit in a low yield) on a large scale. This contrasts with $MeONH_2$, a volatile liquid that is relatively inconvenient to prepare and use. The procedure described by Jin and Liu using *t*-BuOK as the base and heating at 80 °C afforded a modest 41% yield of protected amine **272** (Scheme **88**). Heterocyclic boronic ester **292** is purported to be incompatible with these conditions (elevated temperatures and strong bases), and so it was proposed that using a different base may result in higher yields of product **321**. However, no product formation was observed with either of the more hindered bases LDA or KHMDS and so further optimisation of this amination reaction was not pursued.



Scheme 88: Amination using the aminoazanium of DABCO: a) Standard conditions. b) Using different bases on a model substrate.

4.3.2. Watson's Cu-catalysed Direct Amidation of Pinacol Boronic Esters

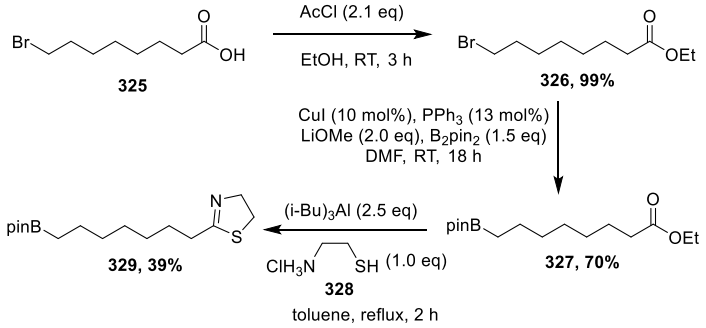
After having exhausted the literature methods for the direct amination of pinacol boronic esters, including both of Morken's amination methods, attention was turned towards other methods. One such method comes from Watson,[99] in which alkyl boronic esters could be reacted with primary amides in the presence of $Cu(OAc)_2$, a 'NacNac' ligand (**322**), $NaOSiMe_3$ and DTBP to give the corresponding secondary amides (Scheme **89a**). The scope with respect to the alkyl boronic ester was broad and tolerated a wide range of functional groups but the amide scope was mostly limited to aromatic primary amides, with only three examples of aliphatic primary amides, two of which were secondary alkyl amides with moderate yields (Scheme **89b**).



Scheme 89: a) Copper-catalysed amidation of pinacol boronic esters. b) Selected substrates formed from aliphatic amides.

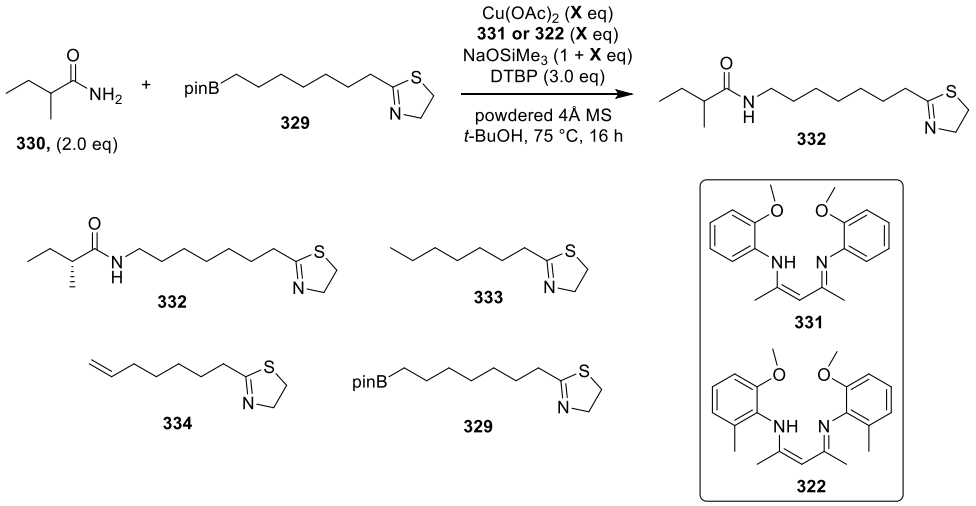
Even though these alkyl amide substrates gave only moderate yields, it was still worthwhile to investigate whether this method would be suitable for the synthesis of kalkitoxin. A suitable model substrate was needed, and this was made in three simple steps from **325**, a commercially available carboxylic acid. Esterification using acetyl chloride in EtOH gave the ethyl ester **326** in quantitative yield. This could then be converted from the alkyl bromide to the alkyl boronic ester (**327**) using Marder's copper

catalysed borylation chemistry.[100] The final transformation to the thiazoline (**329**) was performed using triisobutylaluminium and cysteamine hydrochloride (**328**).[101]



Scheme 90: Synthesis of model thiazoline containing boronic ester **329**.

With the model substrate in hand, as well as two of the 'NacNac' ligands (**331** and **322**) that were found by Marder to be the best performing in the reaction, a number of screening reactions were performed (Table **9**). In general, the reaction was not clean, with the crude mixture often containing amide product **332**, boronic ester starting material **329**, alkane **333**, corresponding to protodeboronation of the starting material, and alkene **334**, corresponding to elimination of the starting material.

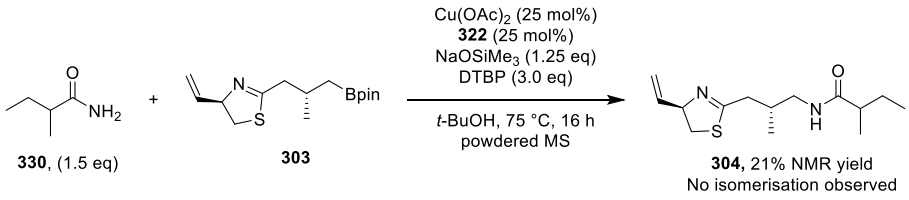


Scheme 91: General conditions for the amidation screening, the ligands used and the various species present in the crude reaction mixture.

Entry	Ligand	X (eq)	Result
1	**331**	0.10	**21%** 'thiazolines', **9% 329** (by NMR)
2	**331**	0.25	**31%** 'thiazolines', **9% 329** (by NMR)
3	**331**	1.0	**0%** 'thiazolines', **329** SM
4	**322**	0.10	**21% 332**, **5% 329** (56% 'thiazolines')
5	**322**	0.25	**27% 332, 7% 329** (45% 'thiazolines')

Table 9: Conditions screened for the amidation of **329**. NMR yields determined using CH_2Br_2 internal standard in $CDCl_3$.

Entries 1 – 3 were performed with ligand **331**, varying the equivalents of the catalyst, ligand and $NaOSiMe_3$. The best yield of 'thiazolines' (the total of **332**, **333** and **334**) was obtained with X = 0.25 (Entry 2), Using stoichiometric ligand and catalyst (Entry 3) resulting in no product or starting material being detected in the crude mixture after 16 hours heating, and no identifiable thiazoline peaks. Entry 4 employed the conditions most often used in the scope of the paper by Watson, in which a more hindered NacNac ligand is used (**322**). This provided a better recovery of 'thiazolines', however upon purification, the yield of the product was determined to be 21%, with 5% of **329** remaining. This yield was improved upon only slightly by increasing the amount of catalyst and ligand (Entry 5). The reaction was then performed on a closer model substrate **303**, with the expectation of a similar result, and this was indeed the outcome of the reaction, delivering the desired product in a 21% NMR yield (Scheme **92**), with no observable isomerisation of the thiazoline. This avenue of investigation was then abandoned.

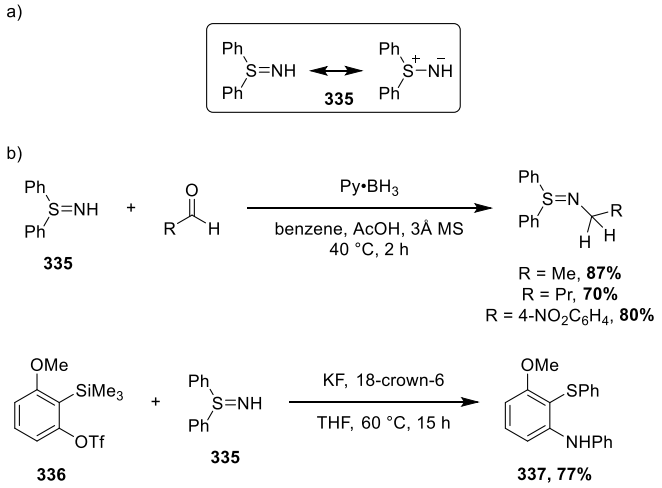


Scheme 92: Copper catalysed amidation of **303**.

4.3.3. Sulfilimines

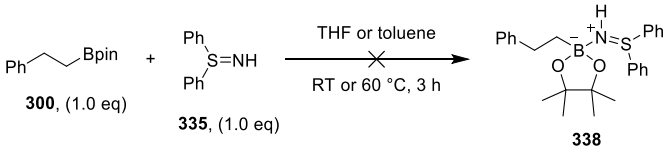
As well as applying methodology reported in the literature, the development of a novel method for the amination of boronic esters was considered, perhaps employing a novel aminating reagent, such as a sulfilimine (**335**). This species contains a sulphur to nitrogen double bond, which is likely to have a significant amount of ylid character, whereby the nitrogen atom will be more electron rich and the sulphur atom electron poor (Scheme

93a). This nitrogen atom has been known to act a nucleophile to aldehydes[102] and benzynes,[103] so it could be reasonably assumed that it may act as a nucleophile towards a boronic ester. Once the nitrogen atom has coordinated to the boronic ester, the diphenylsulfide group on the nitrogen may act as a leaving group to facilitate the migration of an R group from boron to nitrogen.



Scheme 93: a) The ylid-like nature of the sulfilimine. b) Examples of sulfilimines acting as nucleophiles.

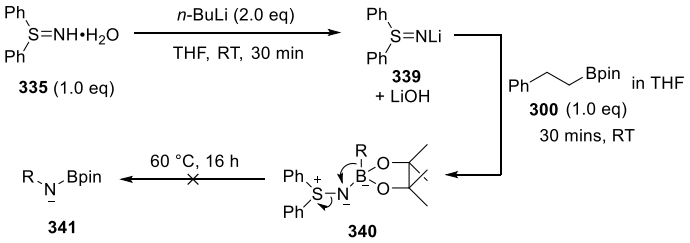
Simply mixing a boronic ester (**300**) with sulfilimine **335** did not result in any reaction; both starting materials could be recovered quantitatively and no boronate complex was formed in either THF or toluene (determined by ^{11}B NMR analysis). Heating the mixture made no difference (Scheme **94**).



Scheme 94: Sulfilimines showed no reactivity towards boronic esters.

The sulfilimine itself did not appear to be nucleophilic enough to attack a boronic ester, however if the nitrogen atom could be deprotonated this would drastically increase the nucleophilicity. The deprotonation of sulfilimines for the generation of *N*-aryl-*S*,*S*-diphenylsulfilimines is known in the literature[104] – the deprotonation is simple to perform on diphenylsulfilimine monohydrate (the commercially available form of the chemical) with two equivalents of *n*-BuLi at room temperature. The solution of the lithiated species is a characteristic deep yellow colour.

A solution of the lithiated sulfilimine was generated in this way using sulfilimine monohydrate **335**. Full formation of the boronate complex **340** between this lithiated species **339** and the boronic ester was confirmed by ^{11}B NMR analysis. Unfortunately, this boronate complex did not undergo the 1,2-metallate rearrangement at room temperature, and upon heating, fell apart to give the boronic ester and the lithiated sulfilimine, the latter of which likely decomposed at these elevated temperatures (Scheme **95**).

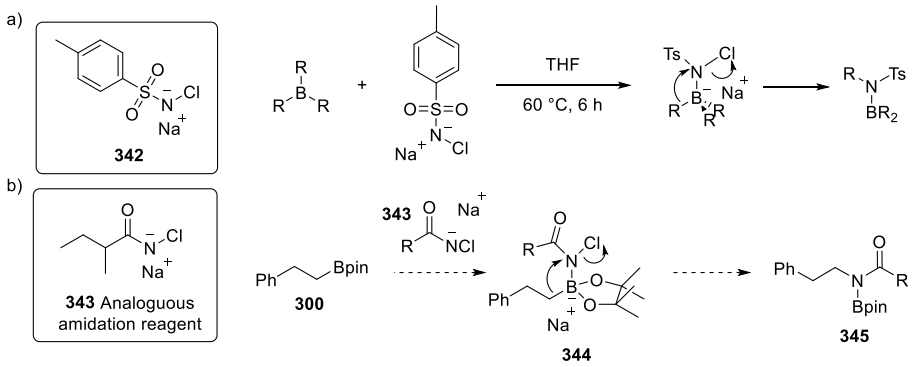


Scheme 95: Attempted amination using lithiated sulfilimines

The sulfilimine was also dried under reduced pressure at 50 °C prior to the lithiation to remove the single molecule of water of crystallisation, however this made no difference to the outcome of the reaction – formation of a persistent boronate complex was observed by ^{11}B NMR analysis.

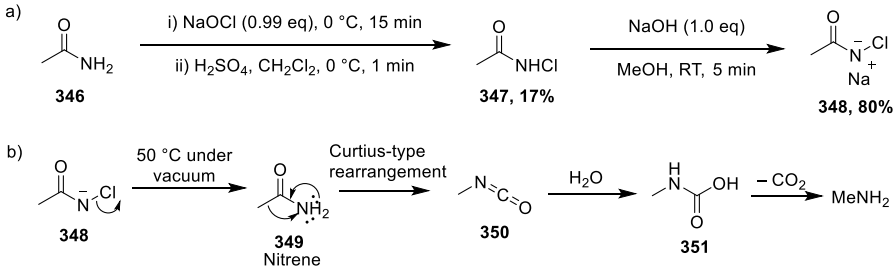
4.3.4. Acylchloroamides

The next novel reagent considered was the acylchloroamide anion. Chloramine T (**342**), a nitrogen centred anion, has been shown to co-ordinate to boranes before the 1,2-migration of an R group of the borane from boron to nitrogen (Scheme **96a**).[105] It was postulated that an analogous amidation reagent such as an acylchloroamide anion (**343**) might behave in a similar way, perhaps even being nucleophilic enough to attack a boronic ester, a species which is less electrophilic than a borane (Scheme **96b**).



Scheme 96: a) Chloramine T can react with boranes to form tosylated amines. b) Ideal reactivity of an analogous acylchloroamide reagent.

To test this proposal, a simple acylchloroamide anion (**348**) was synthesised using a two-step procedure: the first step was mono-chlorination of acetamide **346** using NaOCl, and the second step was deprotonation of chloroacetamide **347** with NaOH (Scheme **97a**) Caution should be taken handling these types of compounds as drying approximately 100 mg of this salt under vacuum at 50 °C to remove water caused the compound to decompose very violently. This was likely via the formation of a nitrene (**349**), which underwent a Curtius-type rearrangement to form an isocyanate (**350**), which was then hydrolysed (**351**) and decarboxylated to form two equivalents of gas, CO_2 and $MeNH_2$ (Scheme **97b**).

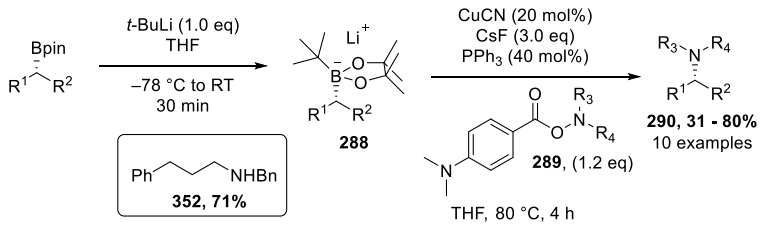


Scheme 97: a) Synthesis of **348**. b) Proposed route for the decomposition of **348**.

When added to a boronic ester in THF, the acylchloroamide did not form a boronate complex. Solubility appeared to be an issue as some of the acylchloroamide salt could be observed suspended in solution, however using DMF as the solvent once again resulted no detectable boronate complex. This poor solubility affecting reactivity along with the likely energetic nature of this class of compounds led to the decision to halt further investigations into the use of acylchloroamides such as **348**.

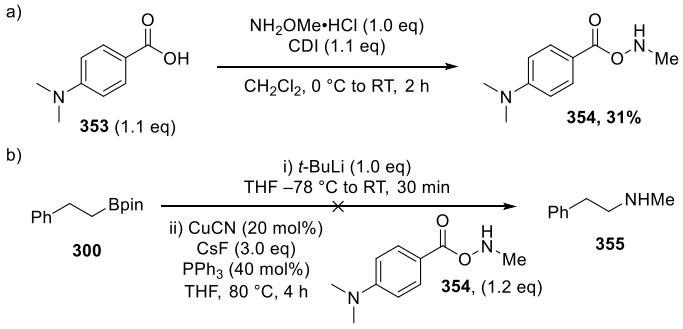
4.3.5. Morken's Benzylamination of Boronic Esters.

In 2022, Morken described the benzylamination of pinacol boronic esters as part of a larger study on the stereospecific transformations of boronic esters using copper catalysis (Chapter 3.3.4).[95]



Scheme 98: Morken's benzylamination of boronic esters.

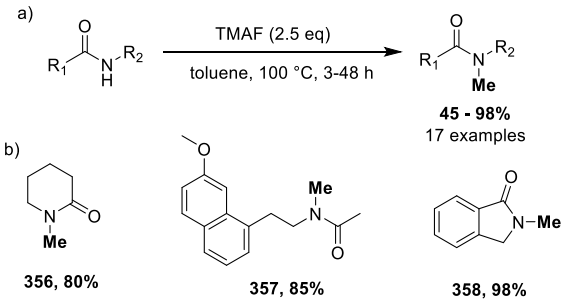
To synthesise kalkitoxin and derivatives thereof, a boronic ester must be converted into a *N*-methylated tertiary amide; if an analogous aminating reagent to **289** could be used to perform a direct methylamination of the heterocyclic boronic ester **292**, this could then be acylated to give the desired amide (**60**). To this effect, the *N*-methylated analogue (**354**) of **289** was synthesised (Scheme **99a**) and subjected to the amination reaction conditions reported by Morken.[95] No product was detected and the starting material remained – analysis of the crude mixture by ^{31}P NMR confirmed that none of the PPh_3 remained, it had been converted completely into PPh_3O – this pointed to **354** being too effective an oxidant (more so than **289**), likely rapidly oxidising the phosphine and the Cu(I) catalyst rather than proceeding down the desired reaction pathway (Scheme **99b**).



Scheme 99: a) Synthesis of **354**. b) Unsuccessful attempt at performing the methylamination reaction.

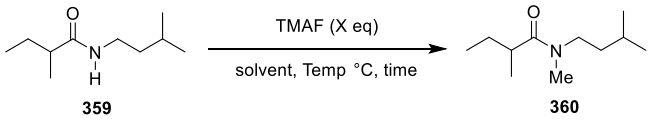
4.3.6. Schoenebeck's Base-free Methylation

Thus far most of the methods discussed for the amination of the heterocyclic boronic ester would provide a secondary amide product (after acylation) which would need to be methylated to give the desired tertiary amide present in kalkitoxin. It has already been established that the heterocyclic boronic ester **292** is sensitive to strong bases, especially at elevated temperatures, therefore it was desirable to look to a method for this final amide methylation which did not require the use of a strong base. In 2020, Schoenebeck described the base free methylation of amides (amongst other nucleophilic functionalities) using tetramethylammonium fluoride at high temperatures (Scheme **100a**).[106] Computational calculations suggested that the reaction proceeded through deprotonation of the imidic acid (tautomeric form of the amide) by a fluoride ion at high temperatures, followed by nucleophilic attack of this anion towards the tetramethylammonium cation. The scope of the reaction with respect to amides was primarily limited to benzylamide derived substrates, with only two examples of aliphatic amides (**356** and **357**) (Scheme **100b**).



Scheme 100: a) Schoenebeck's base-free amide methylation. b) Selected scope examples.

A simple model substrate, **359**, was used to test the viability of this methodology for the synthesis of kalkitoxin (**60**) via the corresponding secondary amide (**321**). Using the exact conditions reported by Schoenebeck resulted in a poor conversion (Table **10**, Entry 1). Increasing the amount of TMAF to 10 equivalents resulted in higher conversion after 4 days, however the yield was still relatively low (Entry 2). Swapping to MeCN as the solvent did not permit the reaction to proceed at all (Entry 3). Swapping to xylene and heating to 130 °C for 3 days consumed almost all the starting material, however the mass return was quite poor with an isolated yield was only 51% (Entry 4). Swapping to the even higher boiling solvent DCE and heating to 150 °C consumed all the starting material, however the yield of the product was only 37% (Entry 5).

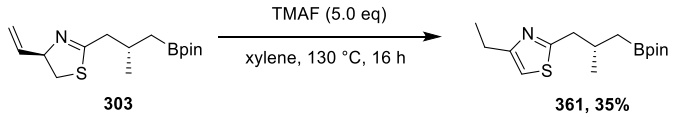


Entry	Solvent	X eq	Temp (°C)	Time	Yield (NMR)
1	PhMe	2.5	100	2 d	N.D
2	PhMe	10.0	100	4 d	47% **360**, 23% **359**
3	MeCN	2.5	80	1 d	0% **360**, 100% **359**
4	Xylene	5.0	130	3 d	51% **360**, 6% **359**
5	DCE	5.0	150	16 h	37% **360**, 0% **359**

Table 10: Conditions screened for the base-free methylation. NMR yields determined using CH_2Br_2 internal standard in $CDCl_3$. N.D. = Not Determined

These results did not look promising – before any further work was performed on this methodology, a compatibility experiment was performed to determine whether the thiazoline was compatible with the conditions described in Table 2, Entry 4. The

thiazoline containing boronic ester **303** was subjected to these conditions, with the ideal outcome being the full recovery of the thiazoline. Unfortunately, none of **303** was recovered, and only 35% yield of thiazole **361** was isolated – clearly the thiazoline is susceptible to both isomerisation and decomposition under these harsh conditions (Scheme **101**).

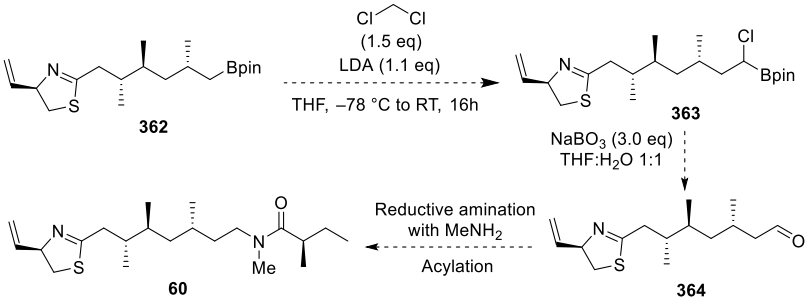


Scheme 101: The thiazoline is incompatible with the bass-free methylation conditions.

4.3.7. Reductive Amination

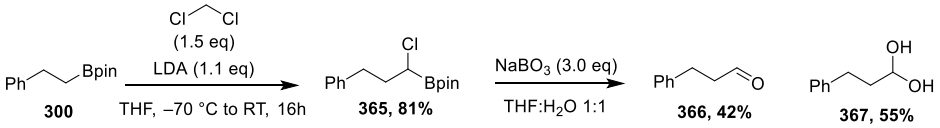
It had been established at this point that both the direct conversion of a pinacol boronic ester to the amine, and the direct methylation of the intermediate secondary amide to the tertiary amide were challenging transformations due to the base/temperature sensitive nature of the thiazoline ring, therefore an alternative approach was considered.

When performing the full six step assembly-line sequence from boronic ester **291**, the final step is a Matteson homologation on boronic ester **362** to give **292.** If instead a similar Matteson homologation reaction is performed with dichloromethane and LDA, the α-chloroboronic ester **363** can be generated. This species could then be oxidised to the aldehyde (**364**) using $NaBO_3$ (the heterocycle is unstable to the more commonly employed basic peroxide conditions), and then used in a reductive amination with $MeNH_2$, followed by acylation with the required acyl chloride to give the tertiary amide (**60**) (Scheme **102**). This route does not require the use of strong base at elevated temperatures and allows the installation of the methyl group on nitrogen first, rendering the direct methylation of **321** with strong base unnecessary.



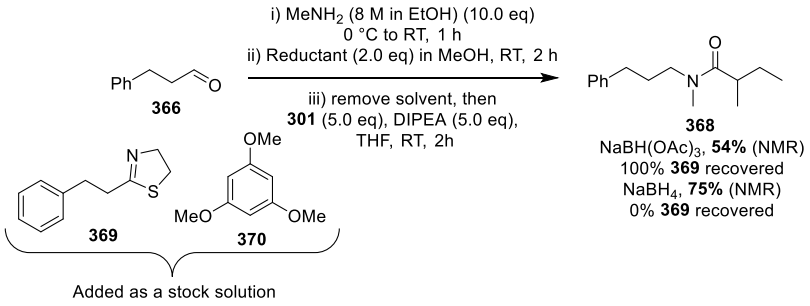
Scheme 102: An alternative route to the tertiary amide via the α-chloroboronic ester **363**.

Using **300** as a model substrate, the homologation to install the α-chloroboronic ester proceeded smoothly, as did the subsequent oxidation, which afforded the product as an inconsequential mixture of aldehyde **366** and its hydrate **367** in a roughly 3:4 ratio by ^{1}H NMR analysis (Scheme **103**).



Scheme 103: Model studies to generate the desired aldehyde.

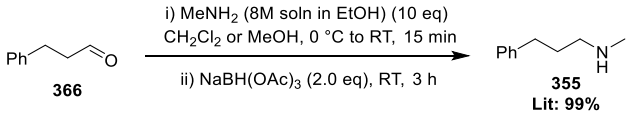
All that was required was to find the correct conditions for the reductive amination, paying particular attention to the reductant, as the thiazoline is likely to be labile to reduction. Three common reductants used in the reductive amination of aldehydes with simple primary amines are $NaBH_4$, $NaBH(OAc)_3$ and $NaBH_3CN$, however the latter of these has been shown to reduce thiazolines to the corresponding tetrahydrothiazole.[107] Therefore $NaBH_4$ and the weaker reductant $NaBH(OAc)_3$ were both tested for suitability for use on a thiazoline containing boronic ester in a compatibility experiment (Scheme **104**). The reductive amination was performed following a procedure from Marsden,[108] with the inclusion of model thiazoline **369** and the inert internal standard trimethoxybenzene (**370**) which were added together as a stock solution at the beginning of the reaction. The amount of thiazoline could then be compared to the amount of inert internal standard in the reaction crude to determine the recovery of thiazoline. The NMR yield of the reaction was determined by the addition of a second internal standard (CH_2Br_2) to the crude mixture. This experiment revealed $NaBH_4$ is completely incompatible with the thiazoline, whereas $NaBH(OAc)_3$ is completely compatible, with 100% recovery of the model thiazoline. The yield of the reaction with $NaBH_4$ was higher, however.



Scheme 104: Reductant compatibility experiment.

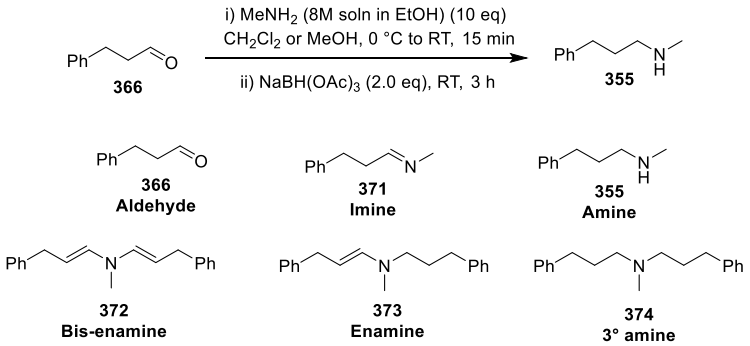
Marsden reported a 99% yield of the secondary amine, for the identical reaction with $NaBH(OAc)_3$, compared to the result of 54% obtained in the above compatibility

experiment (Scheme **104**). Marsden's procedure will now be described here in detail, as what followed was an extensive investigation into this reductive amination reaction (Scheme **105**). Neat methylamine is a gas, and therefore is commercially available as a solution in EtOH. To hydrocinnamaldehyde (**366**) in either CH_2Cl_2 or MeOH was added ten equivalents of this ethanolic solution of $MeNH_2$ at 0 °C. This was left for 15 mins at room temperature to allow quantitative formation of the imine. The reductant, $NaBH(OAc)_3$ was then added as a solid in one portion at 0 °C and the reaction was stirred at room temperature for two hours. At this point, the reaction was then worked up and purified using column chromatography to give the product (**355**) in a reported 99% yield by Marsden and co-workers.



Scheme 105: Marsden's reductive amination.

Upon repeating this procedure, it was clear that some of the aldehyde was being consumed in a deleterious side-reaction; monitoring the imine formation step by GC-MS analysis revealed clearly what the problem was: the imine (**371**), being formed from the aldehyde (**366**) and methylamine, tautomerised to the enamine, which could react further with another molecule of either the aldehyde or the imine to form the undesired bis-enamine (**372**). This reaction would proceed in a similar manner both in CH_2Cl_2 and MeOH. The imine formation is likely to be very fast - during the first few seconds of addition of methylamine to the solution of the aldehyde, the aldehyde is essentially in excess which allowed the formation of the bis-enamine (Table **11**).



GC-MS (%)	Aldehyde	Imine	Bis-enamine
After **i)** (CH_2Cl_2)	6	58	36
After **i)** (MeOH)	0	62	38

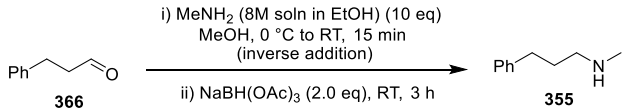
Table 11: GC-MS ratios of the species present during the imine formation.

The above reactions in both CH_2Cl_2 and MeOH were then subjected to the reduction conditions using $NaBH(OAc)_3$, added as a solid (Table **12**). The results showed that the reduction in CH_2Cl_2 was not complete after two hours indicated by the presence of the imine, bis-enamine and the enamine (**373**) by GC-MS analysis – all under-reduced species. The reaction in MeOH proceeded much more rapidly, all imine and bis-enamine species were completely reduced to the corresponding amine (**355**) and 3° amine (**374**) species. This discrepancy in the rate of reduction is likely due to the solubility of the reducing agent – $NaBH(OAc)_3$ is only poorly soluble in CH_2Cl_2, but is completely soluble in MeOH (or reacts to form $NaBH(OMe)_3$ via ligand exchange, which may be the true reductive species).

GC-MS (%)	Aldehyde	Imine	Amine	Bis-enamine	Enamine	3° amine
After **ii)** (CH_2Cl_2)	0	3	47	35	14	0
After **ii)** (MeOH)	0	0	40	0	0	60

Table 12: GC-MS ratios of species present during the reduction.

Two key pieces of information can be garnered from this experiment: the reduction is more efficient in MeOH than it is in CH_2Cl_2, presumably due to the improved solubility of the reductant; and adding $MeNH_2$ to the aldehyde to form the imine favours the undesired formation of the bis-enamine. All further reactions were performed in MeOH, and it was decided that the aldehyde should be added to a solution of the imine, so that $MeNH_2$ would always be in a large excess. The reductant was then added to this solution as before (Table **13**). This change did not completely stop the formation of the bis-enamine but decreased it significantly. After the reductant had been added, there was more enamine and 3° amine than could be expected from the ratio of imine to bis-enamine in the imine forming step – perhaps the amine reacted with the imine to form the enamine at a rate comparable to the direct reduction of the imine to the amine, this enamine would then be slowly reduced to give the 3° amine.

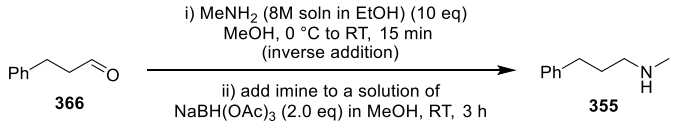


366 355

GC-MS (X)	Aldehyde	Imine	Amine	Bis-enamine	Enamine	3° amine
After **i)**	0	85	N/A	14	N/A	N/A
After **ii)**	0	0	64	0	26	10

Table 13: Addition of the aldehyde to $MeNH_2$, followed by the addition of the reductant.

The imine was clearly reacting with the amine product during the reduction, but perhaps a slow addition of the preformed imine solution to a solution of the reductant would prevent the local concentration of the imine in the solution from being too high at any point and therefore prevent the formation of the bis-enamine. This did improve the ratio of the amine to any over-alkylated products, however the presence of these alkylated products implied either that the imine can react with itself to form the bis enamine (before being added to the reductant solution), or as before that the reduction was slow enough that the condensation of the imine with the amine could proceed instead (Table **14**).



GC-MS	Aldehyde	Imine	Amine	Bis-enamine	Enamine	3° amine
After **i)**	1	88	N/A	11	N/A	N/A
After **ii)**	0	0	83	0	7	10

Table 14: Addition of the aldehyde to $MeNH_2$, followed by the addition of the imine to a solution of the reductant.

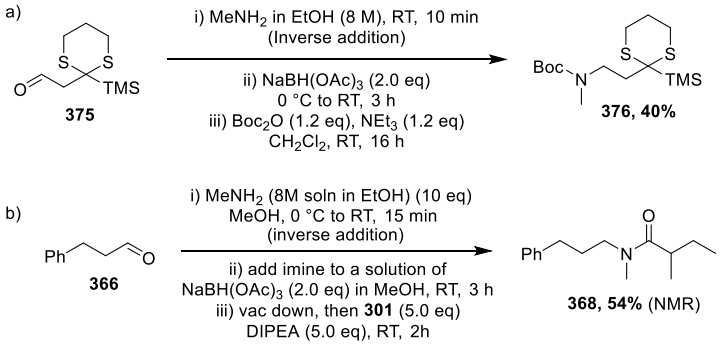
The final modification considered was to add the aldehyde slowly to a solution of both $MeNH_2$ and the reductant – this would ensure that the imine would be reduced as soon as it was formed to prevent it from reacting further with the aldehyde, with a second equivalent of the imine or with the amine product. Unfortunately, this approach gave significantly more of the bis-alkylated products compared to the imine/amine, likely due to the amine product (secondary amine) being significantly more nucleophilic than $MeNH_2$ (primary amine) and reacting with the aldehyde preferentially as soon as it is added to the reaction. The reduction also appeared to be slower under this regime, with enamine remaining in the reaction mixture even after one day (Table **15**).

GC-MS	Aldehyde	Imine	Amine	Bis-enamine	Enamine	3° amine
After **ii)** (2 mins)	0	39	0	60	9	0
After **ii)** (1 h)	0	14	34	7	45	0
After **ii)** (1 d)	0	2	48	0	29	21

Table 15: Addition of the aldehyde to a solution of both $MeNH_2$ and the reductant.

At this point it was clear that this reductive amination was more challenging than expected, and certainly could not be performed in a near quantitative yield. It appears that this problem was not a unique one – Glorius and co-workers also attempted to follow Marsden's reductive amination regime on **375**, having made a similar modification by adding the aldehyde to $MeNH_2$ (inverse to Marsden's procedure), which only provided

the amine product **376** (after Boc protection) in a 40% yield (Scheme **106a**),[109] comparable to the best yield in this work of 54% after acylation (Scheme **106b**).



Scheme 106: a) Reductive amination performed by Glorius. b) Best conditions for the reductive amination acylation reaction.

This approach was also not suitable for the amination in an automated setting due to the tendency to form bis-alkylated side products.

5. A Mild, Rapid Amination of Boronic Esters

As discussed above, it had been established that the heterocyclic boronic ester was unstable to the limited literature methods for the direct amination of boronic esters. Using Morken's 1st generation amination,[110] the heterocycle reacts as an electrophile, and using any conditions with strong base at elevated temperatures,[85,94] the thiazoline, with its pendent alkene, isomerises to the more thermodynamically stable thiazole. It would be beneficial to find a milder method for the amination of boronic esters, ideally at room temperature, to allow the amination of a wider range of more sensitive boronic esters. To realise this goal, changing the leaving group on the nitrogen atom of the aminating reagent was envisaged – Morken used $MeONH_2$, Jin and Liu used a DABCO based reagent (**287**) – our investigation started rather broadly, synthesising a variety of hydroxylamine derivatives (Figure **19**).

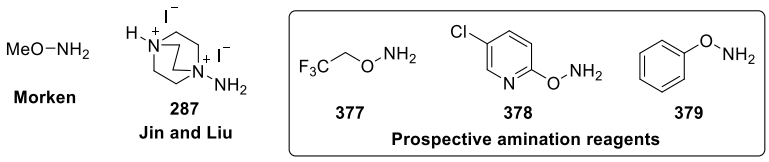


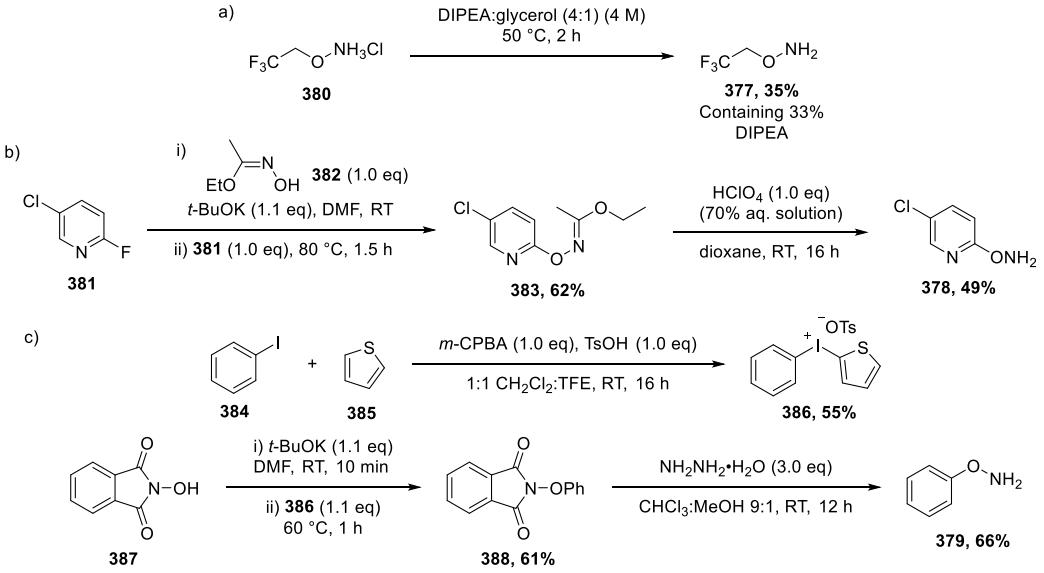
Figure 19: Current and prospective amination reagents.

5.1. Initial Results

The experimental work in Chapter 5.1 was performed by Mr Tom O'Brien, a Masters student under the direct supervision of the author.

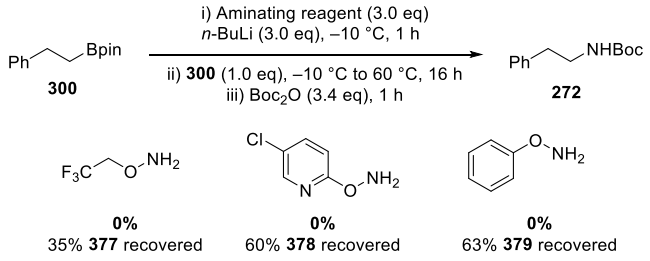
The first aminating reagent to be synthesised was **377**, the hydrochloride salt of which was commercially available - this could be deprotonated in a concentrated mixture of glycerol and DIPEA, and then the free amine removed from the mixture via Kugelrohr distillation. Unfortunately, a significant amount of DIPEA co-distilled with **377**, likely forming an azeotrope; the amination reagent was still able to be subjected to an amination reaction as DIPEA was a non-reactive species. The pyridyl derived hydroxylamine **378** was generated next in two simple steps, the first of which was a nucleophilic aromatic substitution of **381** with **382**, and the second of which was hydrolysis of the acetimidate **383** using aqueous $HClO_4$.[111] Finally, phenoxyamine (**379**) was synthesised in three straightforward steps.[112] The iodonium **386** was synthesised in good yield and was added to a solution of *N*-hydroxyphthalimide (**387**) and *t*-BuOK to give **388**. A simple hydrazine mediated cleavage of the imide gave the free phenoxyamine, which was in this instance

purified by Kugelrohr distillation. A modification to this procedure allowing the synthesis of multi-gram amounts of $PhONH_2$ is described in Chapter 5.2.



Scheme 107: Top: Synthesis of **377**. Middle: Two step synthesis of **378**. Bottom: Three step synthesis of **379**.

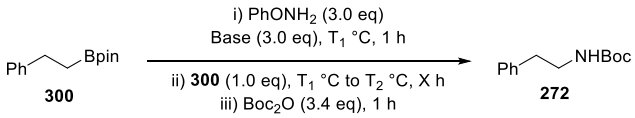
With the three amination reagents in hand, they were each engaged in Morken's 1st generation amination conditions on the model boronic ester **300**, in place of $MeONH_2$, performing the deprotonation step at −10 °C instead of −78 °C. The reported literature yield for this reaction using $MeONH_2$ is 77%. All amination reagents provided no product and returned varying amounts of starting material (Scheme **108**).



Scheme 108: Using the amination reagents in Morken's 1st generation protocol.

This system was clearly not appropriate for the use of these potential amination reagents, so different bases were next investigated. $PhONH_2$ became the aminating reagent of choice due to the availability of the precursor reagents and the relative ease with which large quantities could be synthesised. A selection of bases was then screened (Table **16**). *n*-BuLi, LiHMDS and LDA each provided no product and around 60% of the starting material was recovered (Entries 1 – 3). The use of *t*-BuOK at room temperature for the deprotonation and then raising the reaction temperature to 60 °C to promote the 1,2-

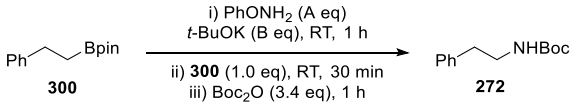
metallate rearrangement consumed the starting material and gave the product **272** in a 50% yield (Entry 4). It was then found that the 1,2-metallate rearrangement was complete after only 30 minutes at room temperature due to the enhanced leaving group ability of phenoxide (compared to methoxide) – the ability to perform the amination at ambient temperature provides a substantial advantage over the current, more forcing conditions described in the literature (Entry 5).[85,94,95,110]



Entry	Base	T_1 °C	T_2 °C	X (h)	272 (%)	300 (%)
1	*n*-BuLi	−10 °C	60	15	0	63
2	LiHMDS	−10 °C	60	15	0	60
3	LDA	0 °C	60	15	0	63
4	*t*-BuOK	RT	60	15	50	0
5	*t*-BuOK	RT	RT	0.5	57*	0

Table 16: Intitial screening of bases in the amination. NMR yields determined using TMB internal standard in $CDCl_3$. *Isolated yield.

A brief investigation into the optimal stoichiometry of the base and the aminating reagent was performed (Table **17**). Entry 1 is the result from Table **16**, Entry 5. Lowering the equivalents of both $PhONH_2$ and *t*-BuOK to 1.3 eq significantly lowered the conversion of the reaction (Entry 2). Lowering the equivalents from 3.0 to 2.0 eq consumed more of the starting material and gave more of the product, as was expected, however the conversion was still incomplete (Entry 3). Keeping the equivalents of $PhONH_2$ at 3.0 but lowering the equivalents of *t*-BuOK to 1.0 (Entry 4) or 2.0 (Entry 5) provided similar results to before, in that in both cases there was starting material remaining. These results show that the actual required amount of $PhONH_2$ and *t*-BuOK was somewhere between 2.0 and 3.0, and that the reactions may in these cases proceed to completion had they been left for longer, however this wasn't investigated further at this stage, and the conditions taken forward were those described in Table **17**, Entry 1.



Entry	A (eq.)	B (eq.)	272 (%)	300 (%)
1	3.0	3.0	57	0
2	1.3	1.3	12	36
3	2.0	2.0	44	6
4	3.0	1.0	35	33
5	3.0	2.0	52	18

Table 17: Investigating the stoichiometry of the reagents. NMR yields determined using TMB internal standard in $CDCl_3$.

An outstanding issue with these results was that the mass balance after the reaction was poor, with the best reaction conditions returning only 57% of product derived species. This was somewhat puzzling as the reaction was very clean, only PhOBoc, Boc_2O and the product were observed by NMR and GC-MS. Perhaps the boronic ester was reacting in some other way to produce a volatile compound which was subsequently removed during drying of the crude under reduced pressure. To test this, the reaction was performed using d^8-THF as the solvent to allow the reaction to be monitored by NMR. Figure **20** shows the spectrum recorded 30 minutes after the addition of the boronic ester. Aside from solvent peaks and various *t*-butyl derived species, the reaction contains only the product amine (or its adduct with Bpin), potassium phenoxide, and the excess aminating reagent. There were no traces of any other starting material derived species.

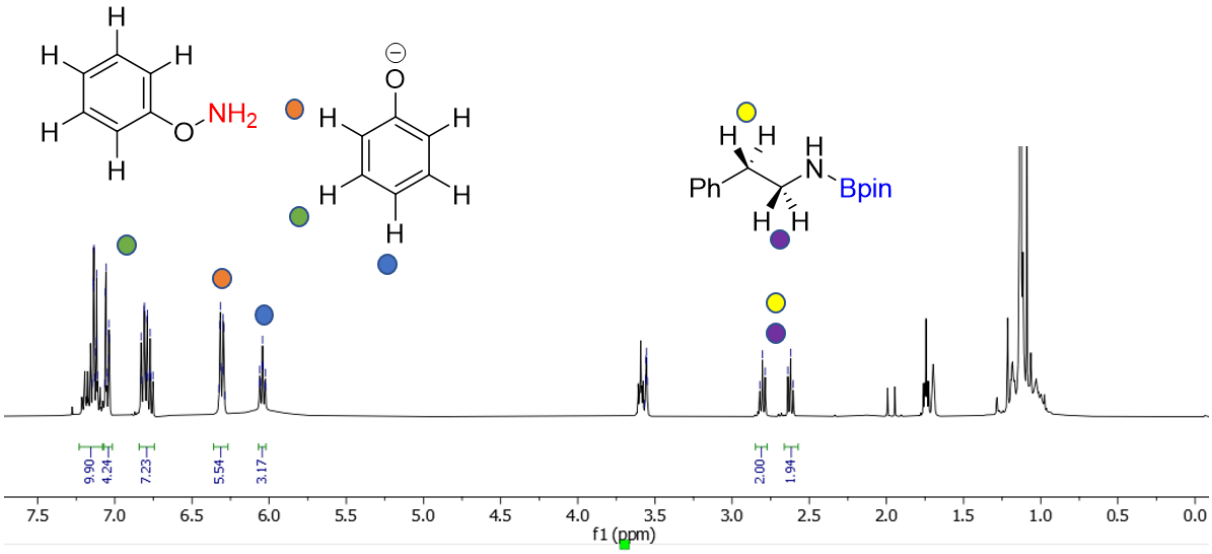
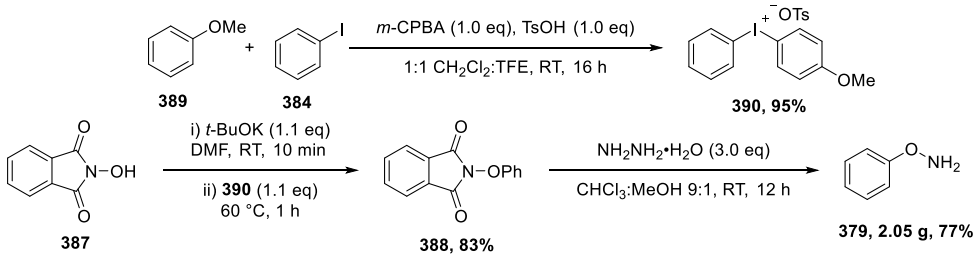


Figure 20: NMR of the reaction 30 min after the addition of the boronic ester.

5.2. Multi-gram Synthesis of $PhONH_2$

The iodonium salt **390** was synthesised instead of **386** as the former was simpler to purify and higher yielding. $PhONH_2$ was previously isolated via distillation from the reaction crude, however, it was found that the compound could be easily purified via column chromatography (although it is unstable to silica). $PhONH_2$ is surprising apolar and was eluted rapidly with a 10% EtOAc in hexane mobile phase. Up to two grams of phenoxyamine were synthesised using this route.



Scheme 109: Multi-gram scale synthesis of $PhONH_2$.

5.3. Optimisation of the Reaction

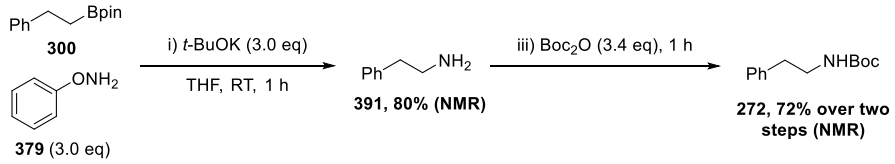
After the initial optimisation, our main concern was that the recovery of mass from the reaction was poor, giving only 57% yield under our optimised conditions. To address this issue, there were some outstanding questions:

- How fast is the reaction? Does the 1,2-migration require 30 minutes?
- Should the boronic ester and the amination reagent be pre-mixed before the addition of the base, as is the case with Morken's 2nd generation amination?[85]
- What is the nature of the product after the amination is complete? Is it the free amine or is the B–N bond still intact? Perhaps if it is the latter species, is this interfering with the subsequent Boc protection to give a poor yield of product?
- Is the Boc protection step high yielding?

Our best reaction conditions so far, based on Morken's 1st generation amination, required the pre-mixing of $PhONH_2$ and *t*-BuOK, followed by the addition of the boronic ester to this solution. It was worth considering how PhONHK was being generated in the pre-mixing step; high levels of direct deprotonation of $PhONH_2$ were not expected since *t*-BuOK is not basic enough. A white precipitate was observed during this pre-mixing, which was postulated to be PhONHK precipitating out of solution and so driving the deprotonation equilibrium. Alternatively, if the precipitate was something else entirely, and so the pre-mixing step was not generating any reactive species, the reaction would

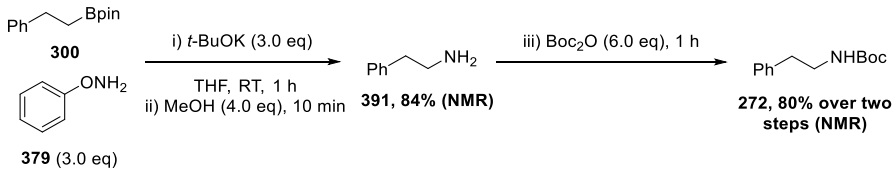
only proceed after the boronic ester is added via a pathway analogous Morken's 2nd generation amination conditions.

With the hypothesis that the pre-mixing of the amination reagent and the base was either not productive, or unnecessary, the procedure was modified to resemble that of Morken's 2nd generation amination, in which that base was added to a mixture of both the amination reagent and the boronic ester (Scheme **72**). This procedure was performed in d_8-THF with the inclusion of an inert internal standard, TMB. Ten minutes after the addition of *t*-BuOK, the starting material was fully consumed, and the amine (**391**) was obtained in an 80% NMR yield. After the addition of Boc_2O and the subsequent filtration through silica, the product was obtained in a 72% NMR yield, corresponding to a 90% yield for the Boc protection (Scheme **110**) showing that this step was not problematic.



Scheme 110: Improved yields due to premixing **300** and $PhONH_2$ (**379**).

The nature of the amine product was still unclear, did this species exist as the free amine or as an amine-boronic ester adduct? The addition of methanol after the 1,2-migration was complete would react with any adduct to reveal the free amine, accompanied by a corresponding change in the chemical shift of the protons adjacent to N in the product, easily observed by NMR analysis (Scheme **111**).

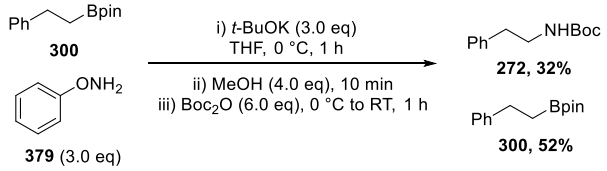


Scheme 111: Addition of MeOH after the amination.

No such change was observed in the shifts of the peaks of the product after the addition of the MeOH to the reaction, implying that the free amine is the species present after the amination. One observable effect of the addition of MeOH was that the precipitate that formed during the amination disappeared. It was suspected that the precipitate that formed was PhONHK for two reasons: the precipitate was only visible once the reaction has proceeded to completion (PhONHK formed before this point would react with the boronic ester starting material), and the addition of MeOH resolubilised the precipitate,

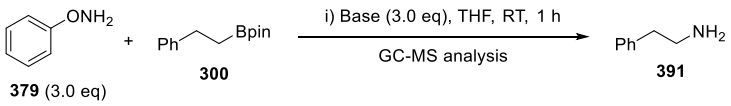
presumably via the protonation of an anionic species more basic than methoxide, this line of reasoning excluded phenoxide anions as the precipitate. Under these conditions, the Boc-protection provided the product in a 95% yield, higher than the 90% previously obtained for this step. The amount of Boc_2O was increased to 6.0 equivalents to account for reaction with the added methanol.

To check if the amination is compatible with lower temperatures, the reaction was also performed at 0 °C, warming to room temperature for the Boc-protection (Scheme **112**). Leaving the amination for 30 minutes at this temperature provided 32% of the product **272**, with 52% of the boronic ester starting material remaining – predictably, the reaction was slower.



Scheme 112: Amination at 0 °C.

Finally, the use of different bases was investigated, and the reaction mixtures were analysed using GC-MS and NMR (Table **18**). When using *t*-BuOK, an 80% yield was obtained as described previously (Entry 1). Full consumption of starting material was observed using NaHMDS and KHMDS, however the NMR yields were lower, 41% and 63% respectively (Entries 2 and 3). NaH also provided the product in a moderate yield of 58%, however these reaction conditions did not fully consume the starting material with three equivalents of base. The weaker bases MeOK, Cs_2CO_3 and DBU did not affect any reactivity, returning only the starting material quantitatively (Entries 5 – 7).



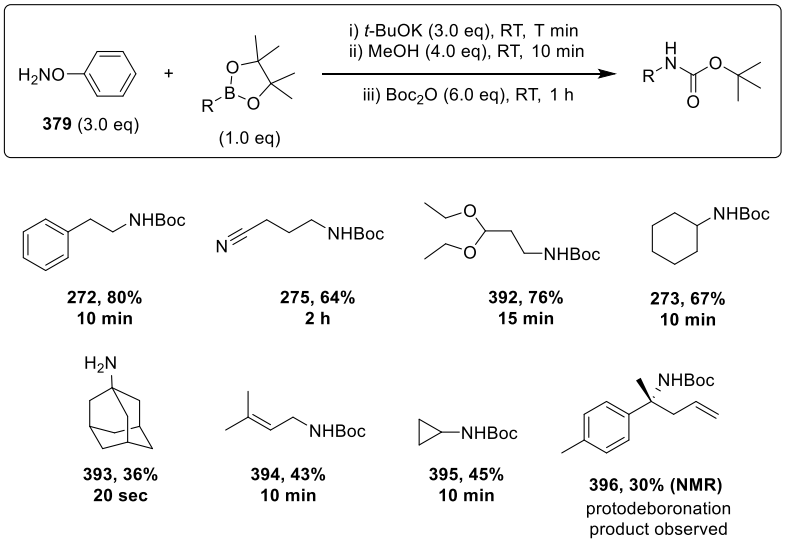
Entry	Base	300 remaining	391 (%)
1	*t*-BuOK	0%	80%*
2	NaHMDS	0%	41%
3	KHMDS	0%	63%
4	NaH	28%	58%
5	MeOK	100%	0%
6	Cs_2CO_3	100%	0%
7	DBU	100%	0%

Table 18: Base screening. NMR yields determined using TMB internal standard in $CDCl_3$. *Isolated yield.

5.4. Boronic Ester Amination Scope

Having settled on *t*-BuOK as the most effective base for the amination, the scope of the reaction was investigated. One major limitation of the current amination methods in the literature is that the scope is mostly limited to simple aliphatic or aromatic compounds, with very few examples of substrates containing any heteroatom functionality. Using $PhONH_2$ as the amination reagent permits the 1,2-migration to proceed under significantly less forcing conditions and may therefore allow the use of more sensitive substrates, such as the thiazoline containing boronic ester **292**.

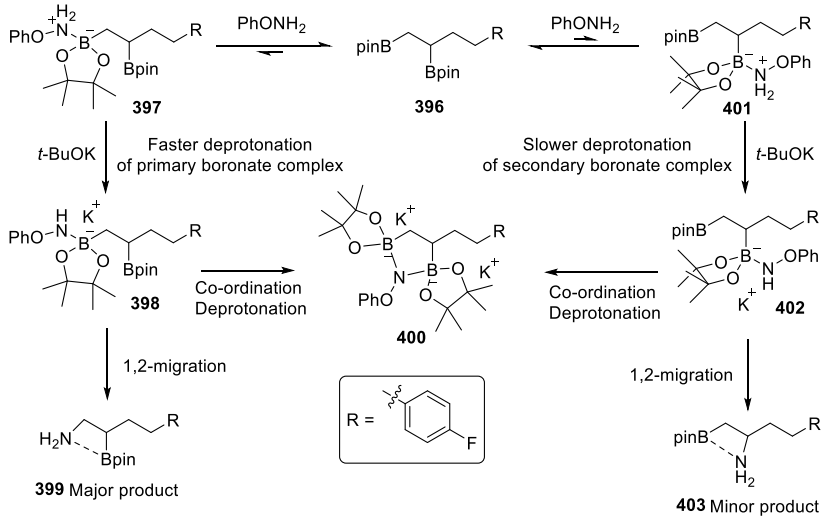
The current substrate scope for the amination is shown below (Scheme **113**), along with the corresponding approximate reaction times (monitored by GC-MS after the observation of the PhONHK precipitate in the reaction). Simple hydrocarbon substrates (**272**, **273**) performed well in the reaction, and functional groups such as nitriles (**275**) and acetals (**392**) were also well tolerated (this is also true for the existing amination methodology in the literature).[85,94,110] The adamantyl substrate **393** appeared to proceed to completion from GC-MS data, however the isolated yield is low due to difficulties with the purification of this substrate. More sensitive boronic esters such as prenyl and cyclopropyl boronic esters gave moderate yields under these conditions (**394**, **395**). A significant amount of protodeboronation was observed when using a tertiary benzylic substrate (**396**) – this is in line with an observation made by Morken with respect to his 2nd generation amination in which benzylic boronic esters were reported to predominantly undergo non-stereospecific protodeboronation.[85]



Scheme 113: Scope of the boronic ester amination

1,2-bis boronic esters such as **396** were also investigated in the amination, since we were interested to see whether there would be any selectivity in this reaction for a particular boronic ester, due to differences in their electronic or steric environment. For example, Morken demonstrated when using NMO in *n*-BuOH that the secondary boronic ester of a 1,2-bis(boronic ester) could be oxidised selectively over the primary boronic ester.[113] This was due to the 1,2-migration being the rate limiting step in the reaction, and coordination of the oxidant to boron being fast and reversible – this resulted in preferential migration of the more substituted electron rich carbon.

The amination requires an irreversible deprotonation of the boronate complex formed between the boronic ester and the amination reagent (Scheme **114**). Formation of the initial boronate complex (**397** or **401**) is assumed to be fast and reversible, so it is likely to be this deprotonation that determines the selectivity – with *t*-BuOK being a hindered base, there may be some bias towards the reactivity of the less hindered primary boronic ester to give **399**. If one boronic ester reacts, the amine would likely coordinate to the other boronic ester, forming a four membered intramolecular adduct **399**, preventing formation of the bis-amine via a second amination. Another potential pathway is that once the boronate has been deprotonated by *t*-BuOK, this immediately coordinates to the second boronic ester to form a bis-boronate **400**, a species which is unable to undergo a 1,2-migration due to the necessity for a ring contraction from a five-membered ring to a four-membered ring.



Scheme 114: Predicting the selectivity of the amination of 1,2-bis boronic esters.

The amination reaction was performed on boronic ester **396** using the optimised amination conditions and monitored by ^{11}B NMR. After two hours at room temperature,

the ^{11}B NMR spectrum showed the presence of two boronate complex peaks at 5.6 ppm and 4.6 ppm. The absence of a boronic ester (30-35 ppm) or a boronate complex in which one of the coordinating atoms is *N* (8-10 ppm) indicated that no desired reactivity had occured. The reaction was then heated to 60 °C for 16 h. The ^{11}B NMR spectrum at this time had three peaks at 7.4, 3.6 and 1.1 ppm, but still no boronic ester (Figure **21**). It was not clear what species had formed in this reaction to correspond to these peaks, however it was assumed from ^{11}B NMR data that the five membered bis-boronate complex **400** had been formed but subsequent 1,2-migration did not take place even at 60 °C as this would require an unfavourable ring contraction from a five to a four-membered ring.

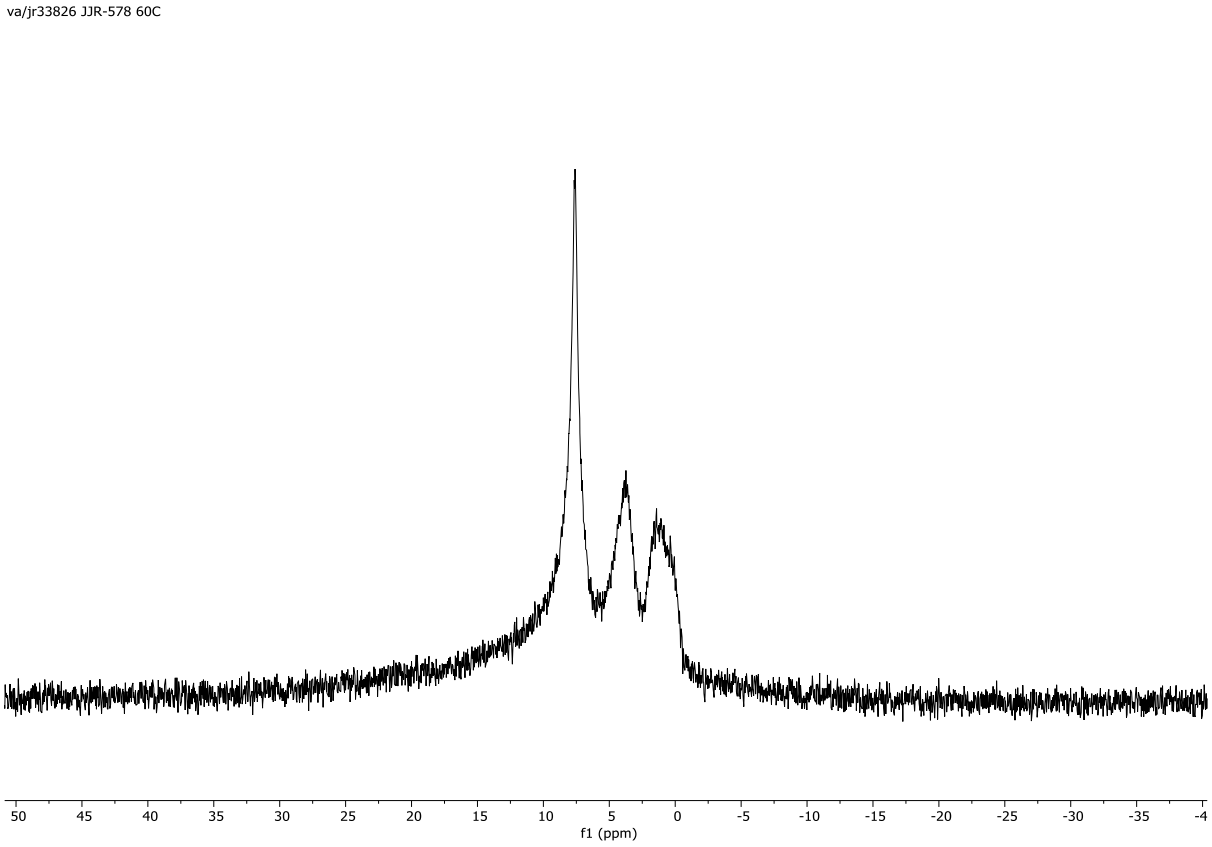


Figure 21: ^{11}B NMR after 16 h at 60 °C.

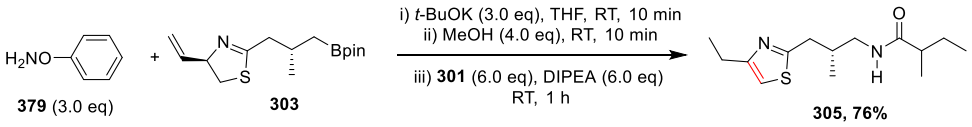
This reaction was repeated as before (conditions in Scheme **113**), however after heating at 60 °C, H_2O_2/NaOH was added to oxidise any boron species to the corresponding alcohols to assist in analysis and purification (persistent boronate complexes are often difficult to handle and characterise. No starting material derived species (such as the 1,2-diol or 1,2-aminoalcohol) could be identified in the crude reaction mixture by NMR or GC-MS, or in the aqueous layer of the reaction mixture by LC-MS. Further investigations

into the reactivity of 1,2-bis boronic esters are required, and perhaps 1,3-bis boronic esters may be more suitable as the analogous bis-boronate would be a six membered ring, more liable to migrate to form a five membered ring.

5.5. Application to the Amination of 292

The investigation into a new boronic ester amination reaction spawned from the difficulties encountered in the amination of the heterocyclic boronic ester **292** (Chapter 4.3). Morken's 2nd generation amination conditions cleanly converted the boronic ester into the corresponding amine (or amide after acylation), however the pendant alkene isomerised into the thiazoline ring to generate the aromatic thiazole (Scheme **81**).

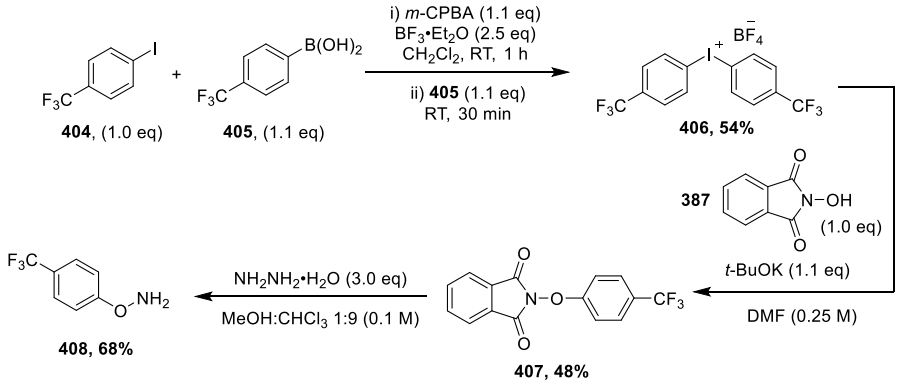
Subjecting the boronic ester **303** to the milder amination conditions using $PhONH_2$ again cleanly converted starting material to a single heterocyclic product (observed by GC-MS), however the alkene had again isomerised to form the thiazole (Scheme **115**).



Scheme 115: Amination of **303** using $PhONH_2$.

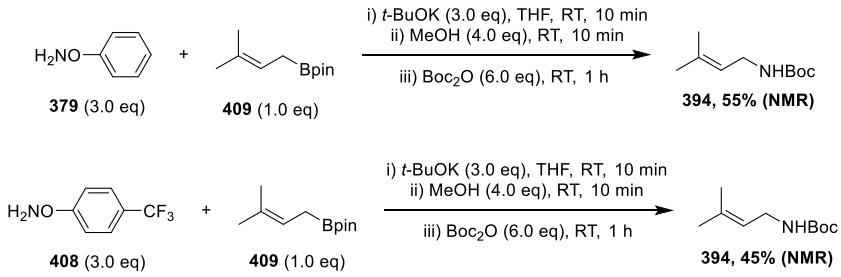
To try and prevent this isomerisation, other weaker bases were first investigated – the results of this are summarised in Table **18**, Chapter 5.3. All bases weaker than *t*-BuOK were non-reactive. NaH, an irreversible base, worked moderately well on the model substrate, and even though isomerisation of the alkene would not be possible using NaH, the position next to the alkene would likely still be deprotonated and racemised upon non-stereoselective reprotonation.

Further increasing the reactivity of the amination reagent by installing a better leaving group on nitrogen, and then lowering the temperature of the amination might both ensure an efficient amination at low temperature and prevent the unwanted isomerisation. To test this hypothesis, **408**, the *p*-CF_3 analogue of $PhONH_2$ was synthesised in three steps (Scheme **116**), the latter two steps being essentially identical to those used in the synthesis of $PhONH_2$.



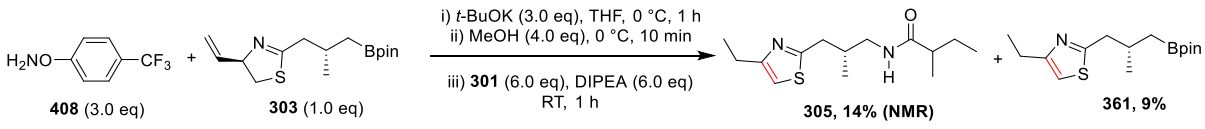
Scheme 116: Synthesis of amination reagent **408**.

This new amination reagent was first tested on boronic ester **409**, a substrate which only provided a moderate isolated yield of 43% using $PhONH_2$ (Scheme **113**). The yield using **408** was slightly lower than that obtained for $PhONH_2$ (**379**), and both reactions were complete within 10 minutes at room temperature (by TLC).



Scheme 117: Direct comparison of amination reagents.

This result did not bode well for the compatibility of **408** with **292**. Nonetheless, the amination was performed with **408** at 0 °C and left for 1 h (Scheme **118**). The speed at which the alkene isomerised was surprising; after 10 minutes at 0 °C, the alkene had completely isomerised (observed by both TLC and GC-MS) – all while the amination reaction was still ongoing. NMR analysis of the crude reaction mixture revealed the isomerised product had been formed in a poor 14% yield, with 9% isomerised starting material remaining. The remaining mass balance could not be accounted for.



Scheme 118: Amination of **303** using aminating reagent **408** at 0 °C.

Even if the yield had been higher and the starting material fully consumed, the alkene isomerisation is so rapid that it would be extremely difficult to prevent in the presence of a base strong enough to perform the amination chemistry.

5.6. Outlook

This boronic ester amination project was conceived to address a specific issue with a sensitive boronic ester. Although the novel amination reagent has not solved this problem, it does represent the mildest boronic ester amination in the literature, proceeding to completion rapidly at room temperature - other procedures in the literature require very low[110] and/or elevated temperatures.[85,94,95,110] To fully realise the potential of this methodology, the substrate scope will be expanded to include more sensitive functionalities. Indeed, certain functional groups are already moderately tolerated, such as the more sensitive prenyl boronic ester (**409**).

The conversion of thiazoline containing boronic ester **292** to the tertiary amide still proves to be exceedingly challenging. Bases strong enough to perform the amination are also strong enough to isomerise the alkene to form the thiazole, and it is the latter process that is faster, even at 0 °C, and even with the use of the more reactive amination reagent **408**.

Closing Thoughts

The Chemspeed is best suited to the screening of conditions for reaction optimisation. That is, a single reaction for which the useful data can be acquired without extensive purification – this has been perfectly demonstrated by the successful optimisation of a Chan-Lam coupling using Design of Experiments (DoE) (unpublished work). It is not well suited to lengthy synthetic sequences. The platform has no method of purification other than simple solid-phase extraction, which limits greatly the number of steps that can be performed without human intervention, and the types of chemistry that are amenable to automation. The Matteson and Stannane homologations are uncommon examples of reactions that can be iterated multiple times with silica-filtration being sufficient purification.

When this automation project was conceived, perhaps earlier than 2016, the field of automated chemical synthesis was one that was underexplored – the best example at the time was Burke's automated synthesiser.[82] The half-decade since has seen a steady improvement in the quality of automated synthesisers, and hence the range of chemistry that can be reliably reproduced and automated has increased considerably. More importantly, the software, prior relegated to the periphery of the work, has seen a dramatic improvement. Complex algorithms have been utilised to create tangible, usable data from automated synthesisers, which has been compiled into a readable database.[86] Machine Learning models can then learn from this database, make the necessary changes and improve future workflows. There is no such infrastructure in place for the collection of data from the Chemspeed – this data is embedded inside 'log-files', user unfriendly blocks of code that describe each individual operation performed. Could these files be mined for data? Perhaps, but doing this is beyond the scope of the synthetic organic chemist.

One goal of automated synthesis is ultimately to remove the chemist from the tedium (and often the danger) of everyday lab-work and make a suite of synthetic organic chemical techniques available to non-chemists. This goal finds an analogy to the current ubiquity of peptide/oligonucleotide synthesisers in modern biology laboratories – these machines are routinely operated by non-chemists to generate complex oligomers. Whist these types of 'universal automated synthesisers' have not yet been realised as fully functional, commercially viable platforms, the rapid advances of the last five years may serve as an indication that we are indeed very close.

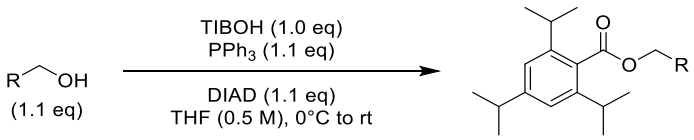
6. Supporting Information

6.1. General Information

Anhydrous solvents were either dried using an Anhydrous Engineering alumina column drying system (THF, Et_2O, toluene, CH_2Cl_2) or obtained as Acroseal bottles and used directly. All other employed solvents were reagent grade solvents and were used directly. Reactions requiring anhydrous conditions (where specified) were conducted under a N_2 atmosphere using standard Schlenk techniques unless otherwise stated. All reagents were purchased from commercial sources and used as received, unless otherwise stated. Flash column chromatography was carried out using Aldrich silica gel (40-63 μm). Reactions were monitored by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F254 fluorescent treated silica which was visualized under UV light (254 nm) or by staining with an aqueous phosphomolybdic acid solution. ^{1}H NMR spectra were recorded using either Jeol ECS/ECZ 400 MHz or Bruker Cryo 500 MHz spectrometers. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). ^{13}C NMR spectra were recorded using either Jeol ECS/ECZ 101 MHz or Bruker Cryo 126 MHz spectrometers. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics Apex IV typically by Electrospray Ionisation (ESI) or the method stated. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR as a thin film. Only selected absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Melting points were recorded in degrees Celsius (°C) using a Stuart SMP30 melting point apparatus. Optical rotations ($[\alpha]_D^T$) were measured on a Bellingham & Stanley Ltd. ADP 220 polarimeter and is quoted in (° ml)(g dm)$^{-1}$. Chiral HPLC was performed on a HP Agilent 1100 with the isocratic gradient specified and the column specified, monitoring by DAD (Diode Array Detector), usually at 210 nm unless otherwise specified. Normal phase analytical and preparatory High Performance Liquid Chromatography were performed on an ACCQPrep HP125 system. Analytical column: Kromasil 60-5SIL 250 mm x 4.6 mm. Preparatory Column: Kromasil 60-5SIL 250 mm x 21.2 mm.

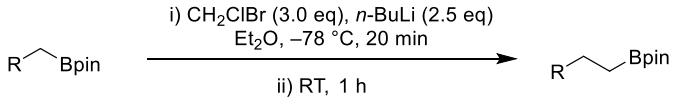
6.2. General Procedures

General Procedure 1: Synthesis of TIB esters.



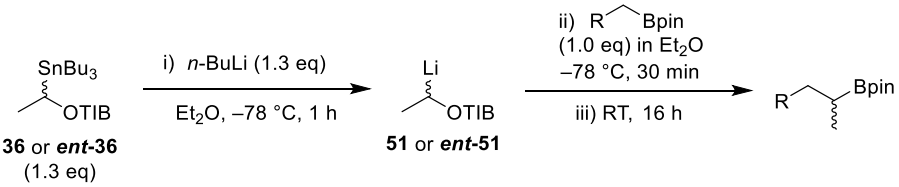
PPh_3 (1.1 eq) and 2,4,6-triisopropylbenzoic acid (TIBOH) (1.0 eq) were combined in a suitable vessel which had been evacuated and refilled with N_2 three times. The alcohol (1.1 eq) and THF (0.5 M) were then added. The vessel was cooled to 0 °C and Diisopropyl azodicarboxylate (DIAD) (1.1 eq) was added dropwise. The solution was warmed to room temperature and stirred for 16 h. The solvent was then removed under reduced pressure to leave an oil which was then triturated with pentane. The resulting precipitate was then filtered off and the collected liquid fraction concentrated under reduced pressure. The crude product was purified using flash column chromatography (Silica gel, EtOAc in pentane).

General Procedure 2: Matteson Homologation



To a solution of the boronic ester (1.0 eq) and chlorobromomethane (3.0 eq) in anhydrous Et_2O (0.2 M) at −78 °C, under N_2 *n*-BuLi (2.5 eq, 1.6 M in hexanes) was added dropwise (syringe pump, 0.05 $mLmin^{-1}$). The reaction was stirred at –78 °C for 20 min, warmed to room temperature and stirred for a further 1 h. The reaction mixture was then filtered through a frit with a 20 mm pad of silica and then concentrated under reduced pressure to give the crude boronic ester that was used directly in the next homologation.

General Procedure 3: Lithiation-Borylation with stannane 36 or *ent*-36



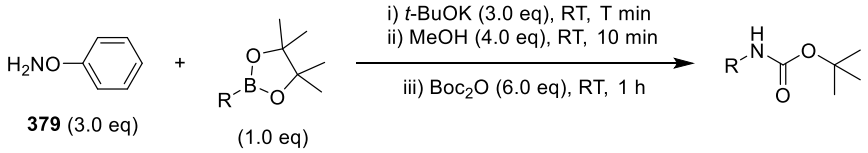
To a solution of (*R*)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (**ent-36**) (1.3 eq) or (*S*)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (**36**) (1.3 eq) in anhydrous Et_2O (0.2 M) at −78 °C, under N_2, *n*-BuLi (1.3 eq, 1.6 M in hexanes) was added dropwise (0.2 $mLmin^{-1}$). The mixture was stirred for 1 h after which the boronic ester (1.0 eq) in

Et_2O (0.5 M) was added dropwise (0.4 $mLmin^{-1}$). The mixture was then stirred for 30 minutes at –78 °C before being warmed to room temperature and stirred for a further 16 h. The reaction mixture was then filtered through a frit with a 20 mm pad of silica and then concentrated under reduced pressure to give the crude boronic ester that was used directly in the next homologation.

Sparteine recovery procedure

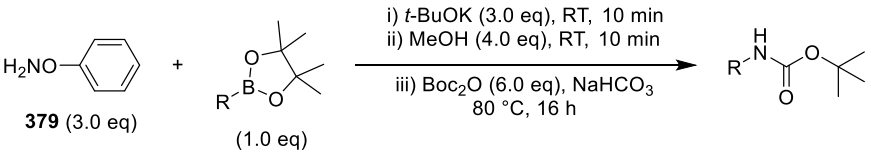
The sparteine was recovered from crude reaction mixtures by extracting the reaction with 2 M HCl or sat. aq. NH_4Cl. The combined acidic aqueous layers were made basic (> pH = 11) with NaOH. The aqueous phase was extracted with Et_2O (5 × 100mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude sparteine, which was then purified via distillation over CaH_2.

General Procedure 4: Boronic Ester Amination using $PhONH_2$ (primary, secondary)



To a flame dried 7 mL vial equipped with a magnetic stirrer was added the boronic ester (1.0 eq), $PhONH_2$ (**379**) (3.0 eq) and THF (0.33 M). *t*-BuOK (3 equiv, 1.0 M in THF) was added to this solution and the reaction was stirred at room temperature for the stated amount of time. MeOH (4.0 eq) was added, and the reaction was stirred for 10 min. Boc_2O (6.0 eq) was added neat and the reaction was stirred for a further 1 h. The reaction was then filtered through a pad of silica, and the solvent evaporated under reduced pressure to give the crude product which was purified using flash column chromatography (Silica gel, EtOAc in pentane).

General Procedure 5: Boronic Ester Amination using $PhONH_2$ (tertiary)

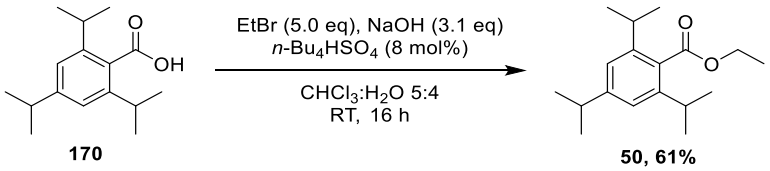


To a flame dried 7 mL vial equipped with a magnetic stirrer was added the boronic ester (1.0 eq), $PhONH_2$ (3.0 eq) and THF (0.33 M). *t*-BuOK (3 equiv, 1.0 M in THF) was added to this solution and the reaction was stirred at room temperature for 10 min. MeOH (4.0

eq) was added, and the reaction was stirred for 10 min. Sat. aq. $NaHCO_3$ was added, followed by the addition of Boc_2O (6.0 eq) neat. The reaction was heated to 80 °C and stirred for 16 h. The reaction was then cooled to room temperature, filtered through a pad of silica, and the solvent evaporated under reduced pressure to give the crude product which was purified using flash column chromatography (Silica gel, EtOAc in pentane).

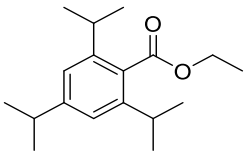
6.3. Experimental Details

Ethyl 2,4,6-triisopropylbenzoate (50)



170 **50, 61%**

A biphasic mixture of 2,4,6-triisopropylbenzoic acid (**170**) (20.2 g, 81.3 mmol, 1.0 eq), $NBu_4(HSO_4)$ (2.21 g, 6.50 mmol, 0.08 eq), NaOH (10.1 g, 252 mmol, 3.1 eq) and bromoethane (30.4 mL, 407 mmol, 5.0 eq) in $CHCl_3$ (400 mL) and H_2O (320 mL) were stirred vigorously overnight at room temperature. The phases were then separated, and the aqueous phase extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were washed with brine (300 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved in pentane (60 mL) and the insoluble salts filtered off. The solvent was removed from the filtrate under reduced pressure to give the title compound (**50**) as a colourless oil (13.6 g, 61% yield).

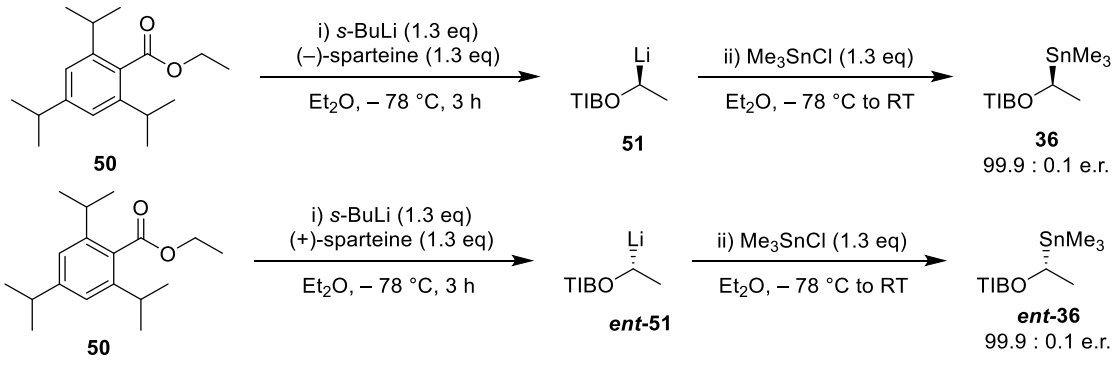


^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.00 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.87 (hept, J = 6.9 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.25 (dd, J = 6.9, 2.7 Hz, 18H).

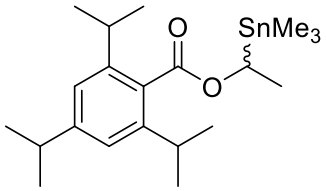
^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.0, 150.2, 144.9, 130.8, 121.0, 60.9, 34.6, 31.6, 24.3, 24.1, 14.4.

The experimental data match that published in the literature.[114]

(*R*)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (*ent*-36) and (*S*)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (36)



To a flame dried flask under N_2 was added ethyl 2,4,6-triisopropylbenzoate **50** (10.0 g, 36.2 mmol, 1.0 eq), (+)-sparteine (11.0 g, 47.1 mmol, 1.3 eq) to synthesise the (*R*)-stannane (***ent*-36**) or (−)-sparteine (11.0 g, 47.1 mmol, 1.3 eq) to synthesise the (*S*)-stannane (**36**), and anhydrous Et_2O (175 mL). The flask was cooled to −78 °C before the dropwise addition of *s*-BuLi (36.2 mL, 47.1 mmol, 1.3 eq, 1.3 M in hexanes,). After stirring at this temperature for 3 h, Me_3SnCl (47.1 mL, 47.1 mmol, 1.3 eq, 1.0 M in hexanes) was added dropwise at –78 °C. The reaction was stirred at this temperature for 20 min before being warmed up to room temperature and stirred for 1 h. The mixture was then diluted with 2 M HCl (100 mL) and stirred for a further 20 min. The layers were separated, and the organic layer washed with 2 M HCl (3 × 100 mL). The combined aqueous layers were extracted with Et_2O (3 × 100 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude stannane. MeOH was then added to the crude stannane (2.0 mLg^{-1}), the round bottomed flask fitted with a condenser, and the solution heated until no solid remained. The mixture was then allowed to cool to room temperature. Crystals of pure stannane appeared after 10 min to 5 h after cooling, which were then filtered and dried under vacuum to give 6.6 g of the title compound, with any uncrystallised product stored in the freezer for later use. The (+)-sparteine or (−)-sparteine was recovered from the aqueous layer as described in the sparteine recovery procedure.

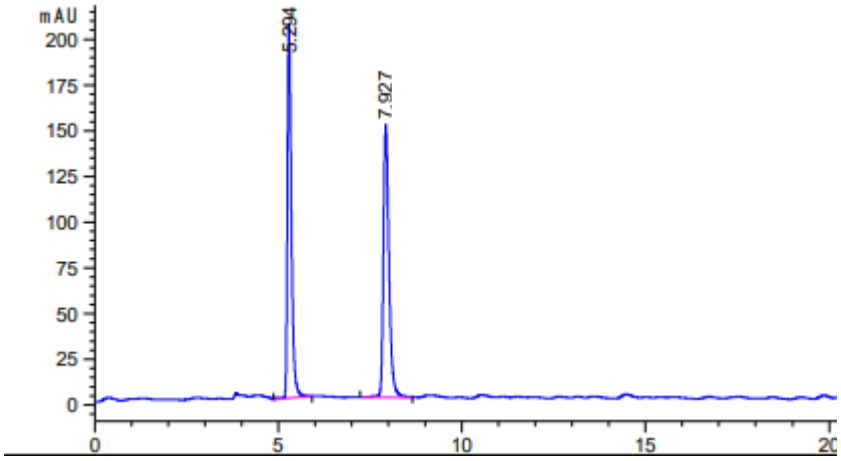


^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.99 (s, 2H), 5.04 (q, *J* = 7.5 Hz, 1H), 2.86 (h, *J* = 6.9 Hz, 1H), 2.85 (h, *J* = 6.9 Hz, 2H), 1.63 – 1.55 (d, *J* = 7.5 Hz 3H), 1.24 (d, *J* = 6.9 Hz, 18H), 0.18 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.4, 150.0, 144.9, 130.9, 120.9, 67.2, 34.5, 31.5, 24.5, 24.2, 24.1, 19.4, -9.8.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ ($CHCl_3$, c = 1) -31 for (*R*)-1-(Trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate, $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ ($CHCl_3$, c = 1) 31 for (*S*)-1-(Trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate

Chiral HPLC (Daicel Chiralpak-IB coumn (25 cm) with guard, hexane, 0.9 ml/min, room temperature, 210.8 nm).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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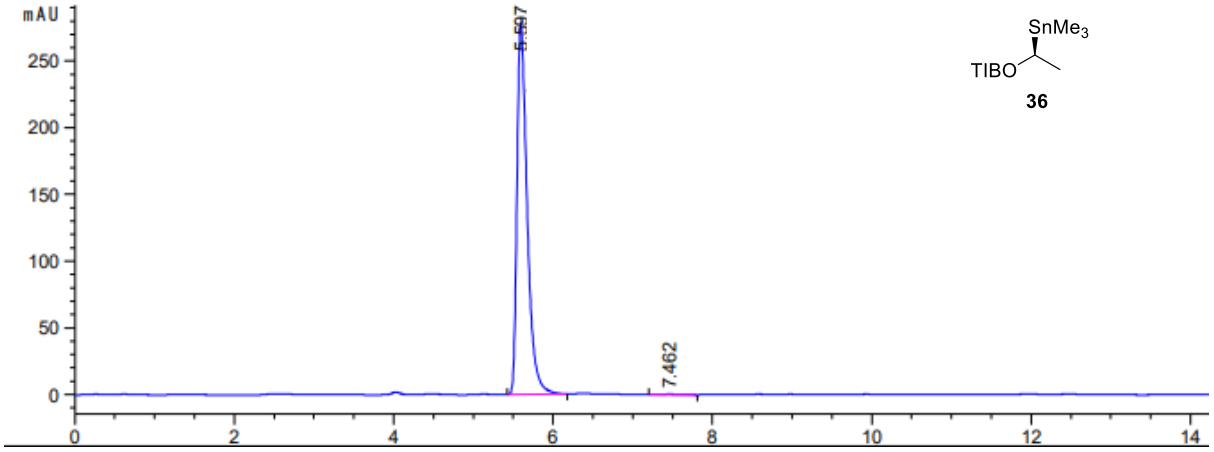
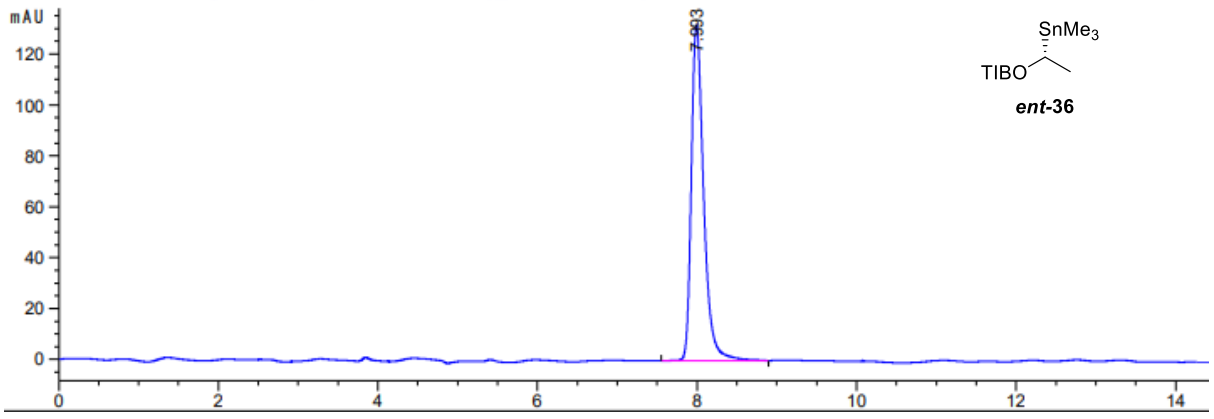
2	7.927	MF	0.1768	1582.95850	149.25142	50.4108



36

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.597	MM	0.1479	2469.44678	278.34476	99.6721
2	7.462	BB	0.2958	8.12377	4.48439e-1	0.3279

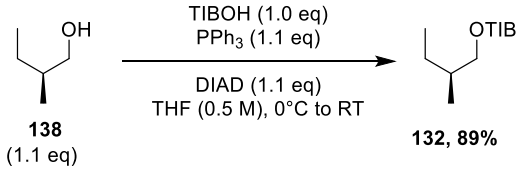


***ent*-36**

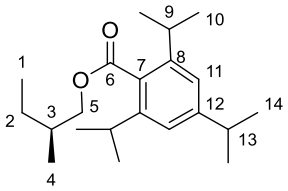
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.993	BB	0.1638	1423.94165	131.85609	100.0000

The experimental data matches that published in the literature.[30]

(*S*)-2-Methylbutyl 2,4,6-triisopropylbenzoate (132)



132 was synthesised according to general procedure 1 using PPh_3 (8.87 g, 33.8 mmol, 1.1 eq), TIBOH (7.65 g, 30.76 mmol, 1.0 eq), (S)-2-methylbutan-1-ol (**138**) (3.64 mL, 33.84 mmol, 1.1 eq) and DIAD (6.64 mL, 33.84 mmol, 1.1 eq). The crude mixture was purified using flash column chromatography (Et_2O in pentane, 1% to 10%) to afford the title compound as a pale-yellow oil (9.05 g, 92% yield).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.03 (s, 2H, C11-H), 4.20 (dd, *J* = 10.9, 5.9 Hz, 1H, C5-H), 4.13 (dd, *J* = 10.9, 6.5 Hz, 1H, C5-H), 2.91 (h, *J* = 6.9 Hz, 1H, C13-H), 2.88 (h, *J* = 6.9 Hz, 2H, C9-H), 1.82 (m, 1H, C3-H), 1.53 (m, 1H, C2-H), 1.27 (m, 1H, C2-H), 1.27 (d, *J* = 6.9 Hz, 12H, C10-H), 1.27 (d, *J* = 6.9 Hz, 6H, C14-H) 1.00 (d, *J* = 6.7 Hz, 3H, C4-H)), 0.95 (t, *J* = 7.5 Hz, 3H, C1-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.4 (C6), 150.1 (C12), 144.8 (C8), 131.0 (C7), 121.0 (C11), 69.8 (C5), 34.5 (C9), 34.2 (C3), 31.7 (C13), 26.2 (C2), 24.3 (C10), 24.1 (C14), 16.7 (C4), 11.3 (C1).

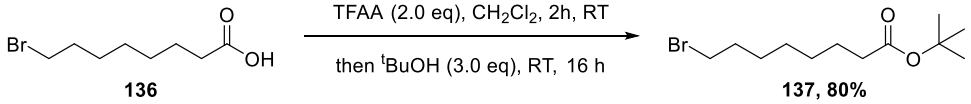
IR νmax/cm^{-1} 2960, 1724 (C=O), 1250, 1073.

HRMS (ESI+) calcd. 319.2632 for [$C_{21}H_{34}O_2$+H], found 319.2630.

R_f = 0.5 in 2% Et_2O in pentane.

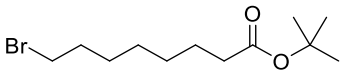
$[\alpha]_D^{24}$ ($CHCl_3$, c = 1) +14.

***Tert*-butyl 8-bromooctanoate (137)**



136 137, 80%

To a round bottomed flask was added 8-bromooctanoic acid (**136**) (4.00 g, 17.9 mmol, 1.0 eq). The flask was evacuated and refilled with N_2 three times. CH_2Cl_2 (55 mL, 0.33 M) was then added to the flask before cooling down to 0 °C. Trifluoroacetic anhydride (4.98 mL, 35.8 mmol, 2.0 eq) was then added slowly. After which the reaction was stirred at 0 °C for 2.5 h. After this, *tert*-butanol (5.10 mL, 53.7 mmol, 3.0 eq) was added, and the reaction was stirred at 0 °C for 1 h, followed by stirring at room temperature for 12 h. The reaction was quenched with sat. aq. $NaHCO_3$, and the aqueous layer extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resultant crude oil was purified using flash column chromatography (10% Et_2O in pentane) to yield the title compound **137** as a yellow oil (4.05 g, 80% yield).

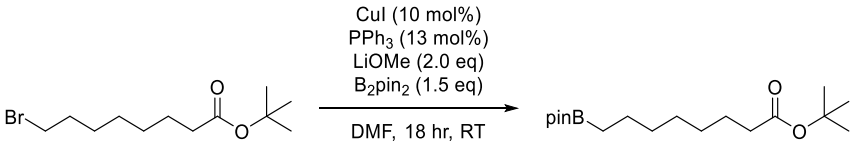


^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.40 – 3.34 (t, *J* = 6.8, 2H,), 2.21 – 2.14 (t, *J* = 7.2, 2H,), 1.87 – 1.78 (tt, *J* = 7.3, 7.2, 2H), 1.61 – 1.51 (m, 2H), 1.45 – 1.37 (m, 11H), 1.30 (m, 4H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.3, 80.1, 35.6, 34.0, 32.8, 29.0, 28.6, 28.2, 28.1, 25.1.

The experimental data match that published in the literature.[115]

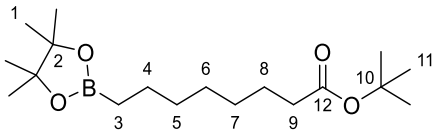
***Tert*-butyl 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octanoate (134)**



137 134, 63%

CuI (205 mg, 1.07 mmol, 0.1 eq), PPh_3 (367 mg, 1.40 mmol, 0.13 eq), LiOMe (816 mg, 21.48 mmol, 2.0 eq) and bis(pinacolato)diboron (4.09 g, 16.11 mmol, 1.5 eq) were added to a Schlenk flask. The vessel was evacuated and refilled with N_2 three times. DMF (21.5

mL, 0.5 M) and *tert*-butyl 8-bromooctanoate (**137**) (3.00 g, 10.74 mmol, 1.0 eq) were the added. The reaction was stirred at room temperature for 16 h. The mixture was then diluted with EtOAc (30 mL), filtered through a pad of silica gel with copious washings and concentrated to leave a crude which was then purified by flash column chromatography (Et_2O in pentane, 3% to 8%) to give the title compound **134** as a yellow oil (2.21 g, 63% yield).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.18 (t, *J* = 7.7 Hz, 2H, C9-H), 1.60 – 1.51 (m, 2H, C8-H), 1.43 (s, 9H, C11-H), 1.41 – 1.34 (m, 2H, C4-H), 1.31 – 1.25 (m, 6H, C5-H, C6-H, C7-H), 1.23 (s, 12H, C1-H), 0.75 (t, *J* = 7.7 Hz, 2H, C3-H).

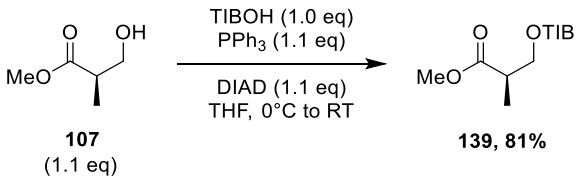
^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.5 (C12), 83.0 (C2), 80.0 (C10), 35.8 (C9), 32.4 (C7), 29.2 (C6), 29.1 (C5), 28.3 (C11), 25.2 (C8), 24.9 (C1), 24.0 (C4). C3 not observed due to quadrupolar relaxation.

IR νmax/cm^{-1} 2928, 1730 (C=O), 1367, 1144.

HRMS (ESI+) calcd. 327.2701 for [$C_{18}H_{35}BO_4$+H], found 327.2710.

R_f = 0.17 in 3% Et_2O in pentane.

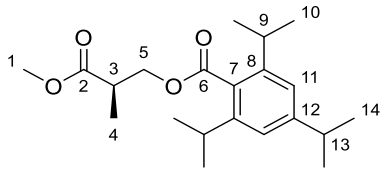
(*R*)-3-Methoxy-2-methyl-3-oxopropyl 2,4,6-triisopropylbenzoate (139)



107
(1.1 eq)

139, 81%

139 was synthesised according to the general procedure 1 using PPh_3 (8.87 g, 33.8 mmol, 1.1 eq), TIBOH (7.65 g, 30.76 mmol, 1.0 eq), methyl (R)-3-hydroxy-2-methylpropanoate (**107**) (3.74 mL, 33.84 mmol, 1.1 eq) and DIAD (6.64 mL, 33.84 mmol, 1.1 eq). The crude mixture was purified using flash column chromatography (Et_2O in pentane, 2% to 20%) to afford the title compound **139** as a colourless oil which crystallised upon standing. (8.61 g, 81% yield). An interesting property of diester **139** is that it often breaks the vial or flask that it crystallises in.



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.00 (s, 2H, C11-H), 4.49 (dd, *J* = 10.5, 7.4 Hz, 1H, C5-H), 4.38 (dd, *J* = 10.5, 5.3 Hz, 1H, C5-H), 3.69 (s, 3H, C1-H), 2.90 (m, 1H, C3-H), 2.88 (hept, *J* = 6.9 Hz, 1H, C13-H), 2.82 (hept, *J* = 6.9 Hz, 2H, C9-H), 1.27 (d, *J* = 7.4 Hz, 3H, C4-H), 1.24 (d, *J* = 6.9 Hz, 6H, C14-H), 1.23 (d, *J* = 6.9 Hz, 12H, C10-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 174.2 (C6), 170.8 (C2), 150.3 (C12), 144.9 (C8), 130.2 (C7), 120.9 (C11), 66.3 (C5), 52.0 (C1), 39.1 (C13), 34.5 (C9), 31.6 (C3), 24.2 (C14), 24.0 (C10), 14.2 (C4).

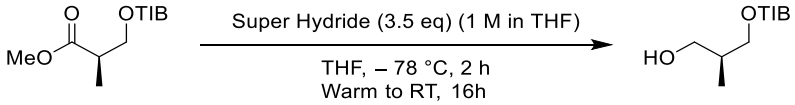
IR νmax/cm^{-1} 2960, 1728 (C=O), 1248, 1067.

HRMS (ESI+) calcd. 371.2193 for [$C_{21}H_{32}O_4$+Na], found 371.2181.

R_f = 0.35 in 5% Et_2O in pentane.

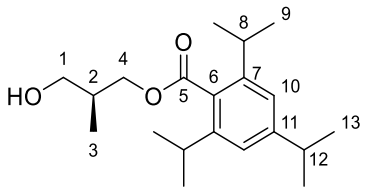
$[\alpha]_D^{24}$ ($CHCl_3$, c = 1) -8

(*S*)-3-Hydroxy-2-methylpropyl 2,4,6-triisopropylbenzoate (**140**)



139 **140, 74%**

To a flame dried flask under nitrogen was added (*R*)-3-methoxy-2-methyl-3-oxopropyl 2,4,6-triisopropylbenzoate (**139**) (12.0 g, 34.4 mmol, 1.0 eq) and THF (170 mL, 0.2 M). The flask was cooled to -78 °C and a 1 M solution of Super Hydride® (lithium triethylborohydride) (120.5 mL, 120.5 mmol, 3.5 eq) in THF was added dropwise. The mixture was stirred at -78 °C for 1 h, then at room temperature for 16 h. Upon reaction completion, Et_2O (100 mL) was added, followed by dropwise addition of water (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resultant crude was purified using flash column chromatography (Et_2O in pentane, 10% to 40%) to give the title compound **140** as a colourless oil (9.33g, 85% yield).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.01 (s, 2H, C10-H), 4.34 (dd, *J* = 11.0, 5.5 Hz, 1H, C5-H), 4.28 (dd, *J* = 11.0, 6.1 Hz, 1H, C5-H), 3.63 (dd, *J* = 10.2, 4.8 Hz, 1H, C1-H), 3.59 (dd, *J* = 10.2, 5.7 Hz, 1H, C1-H), 2.89 (hept, *J* = 7.2 Hz, 1H, C12-H), 2.84 (hept, *J* = 7.2 Hz, 2H, C8-H), 2.15 – 2.05 (m, 1H, C2-H), 1.25 (d, *J* = 7.2 Hz, 18H, C9-H, C13-H), 1.02 (d, *J* = 6.9 Hz, 3H, C3-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.5 (C5), 150.4 (C11), 144.9 (C7), 130.5 (C6), 121.0 (C10), 67.1 (C4), 64.9 (C1), 35.6 (C2), 34.6 (C12), 31.7 (C8), 24.3 (C9), 24.1 (C13), 13.9 (C3).

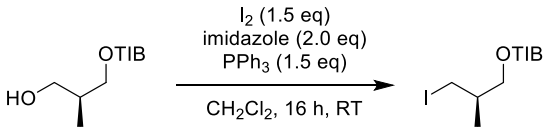
IR νmax/cm^{-1} 3442 (broad, O-H), 2961, 1715 (C=O), 1250, 908.

HRMS (ESI+) calcd. 343.2242 for [$C_{20}H_{32}O_3$+Na], found 343.2244.

R_f = 0.22 in 20% Et_2O in pentane.

$[\alpha]_D^{24}$ ($CHCl_3$, c = 1) -1

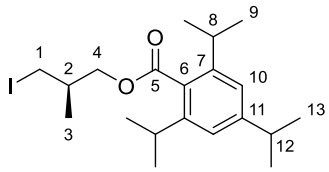
(*R*)-3-Iodo-2-methylpropyl 2,4,6-triisopropylbenzoate (141)



140 **141, 86%**

To a round bottomed flask containing (*S*)-3-hydroxy-2-methylpropyl 2,4,6-triisopropylbenzoate (**140**) (9.00 g, 28.08 mmol, 1.0 eq) was added triphenylphosphine (11.05 g, 42.1 mmol, 1.5 eq) and imidazole (3.82 g, 56.2 mmol, 2.0 eq).The flask was then evacuated and refilled with N_2 three times. CH_2Cl_2 (125 mL, 0.22 M) was then added and all reagents were dissolved before adding iodine portion-wise (10.69 g, 42.1 mmol, 1.5 eq). The reaction was stirred at room temperature for 4 h, saturated aqueous solution of $Na_2S_2O_3$ (100 mL) was then added portion-wise. The layers were separated, and the aqueous phases were extracted with CH_2Cl_2 (3 x 80 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude which was triturated with pentane to remove the triphenylphosphine oxide by-

product. The solid was removed *via* vacuum filtration, and the resultant filtrate was concentrated under reduced pressure to afford the title compound **141** as a colourless oil (11.09 g, 92% yield).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.01 (s, 2H, C10-H), 4.28 (dd, *J* = 11.1, 5.1 Hz, 1H, C4-H), 4.14 (dd, *J* = 11.1, 7.1 Hz, 1H, C4-H), 3.28 (dd, *J* = 9.9, 5.2 Hz, 1H, C1-H), 3.26 (dd, *J* = 9.9, 5.4 Hz, 1H, C1-H), 2.89 (hept, *J* = 6.9 Hz, 1H, C12-H), 2.84 (hept, *J* = 6.9 Hz, 2H, C8-H), 1.92 (m, 1H, C2-H), 1.25 (d, *J* = 6.9 Hz, 6H, C13-H), 1.25 (d, *J* = 6.9 Hz, 12H, C9-H), 1.09 (d, *J* = 6.7 Hz, 3H, C3-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.9 (C5), 150.3 (C11), 144.9 (C7), 130.3 (C6), 121.0 (C10), 68.6 (C4), 34.5 (C12), 34.2 (C2), 31.7 (C8), 24.3 (C9), 24.0 (C13), 17.6 (C3), 12.0 (C1).

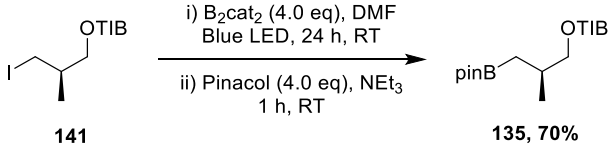
IR νmax/cm^{-1} 2960, 1725 (C=O), 1248, 1072, 755.

HRMS (ESI+) calcd. 431.1441 for [$C_{20}H_{31}IO_2$+Na], found 431.1438.

R_f = 0.65 in 2% Et_2O in pentane.

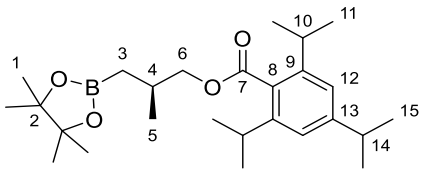
$[\alpha]_D^{24}$ ($CHCl_3$, c = 1) -12

(*S*)-2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl 2,4,6-triisopropylbenzoate (135)



A suitable vessel containing (R)-3-iodo-2-methylpropyl 2,4,6-triisopropylbenzoate (**141**) (11.0 g, 25.6 mmol, 1.0 eq) and bis(catecholato)diboron (24.3 g, 102 mmol, 4.0 eq) was evacuated and refilled with N_2 three times. DMF (77 mL, 0.33 M) was then added and the mixture was stirred under blue LED irradiation for 4 d. Upon reaction completion, a solution of pinacol (12.1 g, 102 mmol, 4.0 eq) in NEt_3 (89.7 mL, 1.14 M) was added and the mixture was stirred for 1h, after which H_2O (100 mL) was added. The layers were

separated, and the organic layer extracted with H_2O (5 x 150 mL) to remove DMF. The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified using flash column chromatography (Et_2O in pentane, 2% to 5%) to afford the title compound **135** as a pale-yellow oil (7.39 g, 67% yield).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.99 (s, 2H, C12-H), 4.12 (dd, *J* = 10.8, 6.3 Hz, 1H, C6-H), 4.10 (dd, *J* = 10.8, 6.5 Hz, 1H, C6-H), 2.86 (hept, *J* = 6.7 Hz, 1H, C14-H), 2.85 (hept, *J* = 6.7 Hz, 2H, C10-H), 2.14 (m, 1H, C4-H), 1.33 – 1.13 (m, 30H, C1-H, C11-H, C15-H), 1.01 (d, *J* = 6.7 Hz, 3H, C5-H), 0.98 – 0.92 (dd, *J* = 15.7, 5.4 Hz 1H, C3-H) 0.72 (dd, *J* = 15.7, 8.7 Hz, 1H, C3-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.3 (C7), 150.0 (C13), 144.8 (C9), 131.0 (C8), 120.9 (C12), 83.2 (C2), 71.7 (C6), 34.5 (C10), 31.6 (C14), 29.2 (C4), 25.0 (C1), 25.0 (C1), 24.3 (C11), 24.1 (C15), 19.4 (C5). C3 not observed due to quadrupolar relaxation.

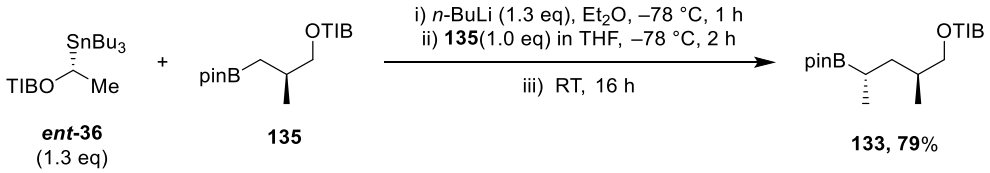
IR νmax/cm^{-1} 2961, 1723 (C=O), 1249, 1136.

HRMS (ESI+) calcd. 431.3327 for [$C_{26}H_{43}BO_4$+H], found 431.3327.

R_f = 0.42 in 5% Et_2O in pentane.

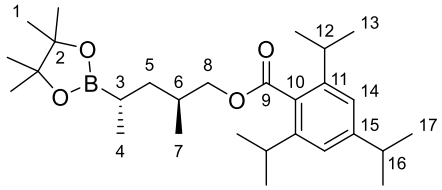
$[\alpha]_D^{24}$ ($CHCl_3$, c = 1) -1.

(2*S*,4*S*)-2-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl 2,4,6-triisopropylbenzoate (146)



To an oven-dried flask charged with (*R*)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (***ent*-36**) (931 mg, 2.12 mmol, 1.3 eq) which had been evacuated and refilled with N_2 three times was added anhydrous Et_2O (10.6 mL). The solution was cooled down to -78 °C before the dropwise addition of *n*-BuLi (1.6 M in hexanes) (1.33 mL, 2.12 mmol, 1.3 eq). The mixture was stirred at -78 °C for 1 h, after which (S)-2-

methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl 2,4,6-triisopropylbenzoate (**135**) (700 mg, 1.63 mmol, 1.0 eq) was added dropwise as a solution in Et_2O (8 mL). The solution was then warmed to room temperature and stirred for 16 h. The reaction was monitored by ^{11}B NMR, and upon completion of the reaction (no boronate complex observed), the mixture was filtered through a pad of silica to remove any insoluble salts. The silica was further washed with Et_2O and the solvent was evaporated under reduced pressure to give a crude mixture which was either used without further purification in the next step, or purified by flash column chromatography (3% Et_2O in pentane) to give the title compound **133** as a colourless oil (79% yield, 0.46 mmol scale).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.00 (s, 2H, C14-H), 4.17 (dd, *J* = 10.7, 5.6 Hz, 1H, C8-H), 4.11 (dd, *J* = 10.7, 6.5 Hz, 1H, C8-H), 2.88 (hept, *J* = 6.9 Hz, 1H, C16-H), 2.85 (hept, *J* = 6.9 Hz, 2H, C12-H), 1.97 (m, 1H, C6-H), 1.44 – 1.33 (m, 2H, C5-H), 1.25 (d, *J* = 6.9 Hz, 6H, C17-H), 1.24 (d, *J* = 6.9 Hz, 12H, C13-H), 1.22 (s, 12H, C1-H) 1.14 – 1.07 (m, 1H, C3-H), 0.95 (d, *J* = 6.7 Hz, 3H, C7-H), 0.94 (d, *J* = 7.4 Hz, 3H, C4-H).

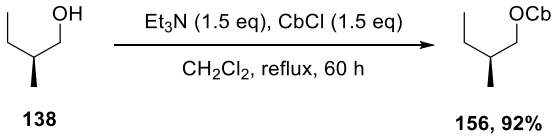
^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.3 (C9), 150.0 (C15), 144.8 (C11), 131.0 (C10), 120.9 (C14), 83.1 (C2), 70.4 (C8), 36.5 (C5), 34.5 (C16), 31.6 (C12), 31.2 (C6), 24.9 (C1), 24.9 (C1), 24.3 (C13), 24.1 (C17), 16.9 (C7), 15.3 (C4). C3 not observed due to quadrupolar relaxation.

IR νmax/cm^{-1} 2961, 1725 (C=O), 1250, 1143.

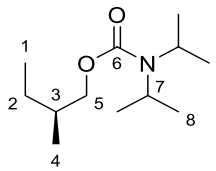
HRMS (ESI+) calcd. 481.3460 for [$C_{28}H_{47}BO_4$+Na], found 481.3474.

R_f = 0.48 in 5% Et_2O in pentane. $[\alpha]_D^{24}$ ($CHCl_3$, c = 1) -7.

(*S*)-2-Methylbutyl diisopropylcarbamate (156)



To a suitable flame dried vessel containing (S)-2-methylbutan-1-ol (**138**) (4.88 mL, 45.4 mmol, 1.0 eq) and Et_3N (9.50 mL, 68.1 mmol, 1.5 eq) in CH_2Cl_2 (76 mL, 0.6 M) was added diisopropylcarbamic chloride (11.1 g, 68.1 mmol, 1.5 eq) portion-wise. The mixture was the refluxed for 60 h. The reaction was then quenched with H_2O and the aqueous layer extracted with CH_2Cl_2 three times (3 x 50 mL). The combined organic layers were dried over$MgSO_4$, filtered and concentrated under reduced pressure to give a crude oil which was purified using flash column chromatography (5% to 10% diethyl ether in pentane) to give the title compound **156** as a yellow oil (8.94 g, 92%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.97 (dd, *J* = 10.6, 5.8 Hz, 1H, C5-H), 3.86 (dd, *J* = 10.6, 6.7 Hz, 1H, C5-H), 1.77 – 1.67 (m, 1H, C3-H), 1.44 (ddd, *J* = 13.3, 7.6, 5.8 Hz, 1H, C2-H), 1.19 (d, *J* = 6.9 Hz, 12H, C2-H, C8-H), 0.93 (d, *J* = 6.6 Hz, 3H, C4-H), 0.90 (t, *J* = 7.6 Hz, 3H, C1-H). (C7-H protons observed as very broad peak at 4.25 – 3.55).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.2 (C6), 69.6 (C5), 45.4 (C7), 34.6 (C3), 26.4 (C2), 21.1 (C8), 16.8 (C1), 11.4 (C4).

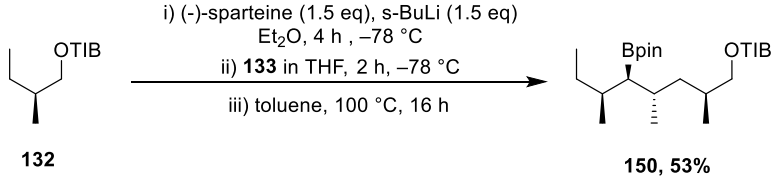
IR νmax/cm^{-1} 2964, 1688 (C=O), 1286, 1057.

HRMS (ESI+) calcd. 216.1958 for [$C_{12}H_{26}NO_2$+H], found 216.1962.

R_f = 0.23 in 5% Et_2O in pentane.

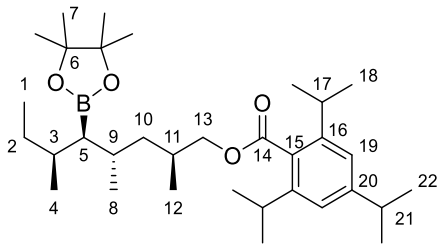
$[\alpha]_D^{24}$ ($CHCl_3$, c = +5) .

(2*S*,4*S*,5*R*,6*S*)-2,4,6-Trimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octyl-2,4,6-triisopropylbenzoate (**150**)



To a suitably size flame dried vessel was added (*S*)-2-methylbutyl 2,4,6-triisopropylbenzoate (**132**) (780 mg, 2.45 mmol, 1.5 eq), (–)-sparteine (0.56 mL, 2.45

mmol, 1.5 eq) and dry Et_2O (7.35 mL). The solution was cooled down to –78 °C before the dropwise addition of *s*-BuLi (1.3 M in hexanes) (1.88 mL, 2.45 mmol, 1.5 eq). The reaction was stirred at –78 °C for 4 h, after which (2*S*,4*S*)-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl 2,4,6-triisopropylbenzoate (**133**) (crude mixture from previous experiment, assumed 1.0 eq) was added as a solution in THF (3.26 mL). After stirring at –78 °C for 2 h, the cooling bath was removed, and the solvent immediately evaporated under reduced pressure on a rotary evaporator. Toluene (10.6 mL) was then added, and the mixture was heated to 100 °C for 16 h. 2 M HCl (20 mL) was then added and the layers were separated. The aqueous layer was extracted three times with Et_2O (3 x 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (Et_2O in pentane, 2%) to give the title compound **150** as a colourless oil (460 mg, 53% yield over two steps).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.98 (s, 2H, C19-H), 4.10 (dd, *J* = 10.7, 5.9 Hz, 1H, C13-H), 4.04 (dd, *J* = 10.7, 6.9 Hz, 1H, C13-H), 2.87 (hept, *J* = 6.9 Hz, 1H, C21-H), 2.84 (hept, *J* = 6.9 Hz, 2H, C17-H), 1.95 (m, 1H, C11-H), 1.77 (m, 1H, C9-H), 1.60 (m, 1H, C3-H), 1.34 (m, 1H, C2-H), 1.23 (d, *J* = 6.9 Hz, 18H, C18-H, C22-H), 1.19 (s, 6H, C7-H), 1.16 (s, 6H, C7-H), 1.16 – 1.05 (m, 3H, C2-H, C10-H), 0.95 (d, *J* = 6.6 Hz, 3H, C12-H), 0.89 – 0.78 (m, 10H, C1-H, C4-H, C5-H, C8-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.3 (C14), 150.0 (C20), 144.8 (C16), 130.9 (C15), 120.9 (C19), 82.8 (C6), 71.3 (C13), 40.4 (C10), 34.5 (C21), 33.3 (C3), 31.6 (C17), 30.4 (C11), 29.6 (C2), 28.7 (C9), 25.2 (C7), 25.0 (C7), 24.3 (C22), 24.1 (C18), 18.4 (C8), 17.3 (C4), 16.3 (C12), 11.8 (C1). C5 not observed due to quadrupolar relaxation.

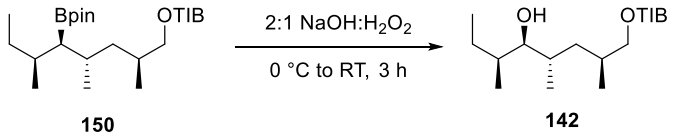
IR νmax/cm^{-1} 2961, 1727 (C=O), 1251, 1142.

HRMS (ESI+) calcd. 551.4248 for [$C_{33}H_{57}BO_4$+Na], found 551.4247.

R_f = 0.60 in 5% Et_2O in pentane.

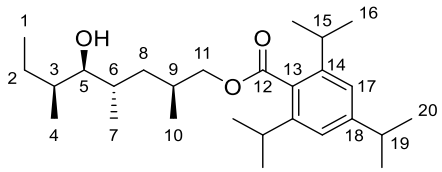
$[\alpha]_D^{24}$ ($CHCl_3$, c = -7) .

(2*S*,4*S*,5*R*,6*S*)-5-Hydroxy-2,4,6-trimethyloctyl 2,4,6-triisopropylbenzoate (142)



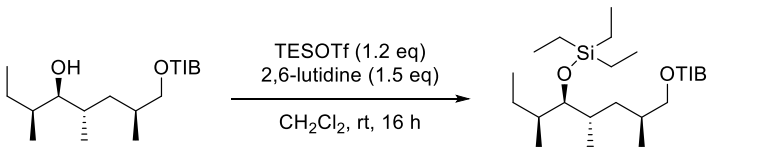
150 **142**

To a suitably sized flamed-dried vessel containing (2*S*,4*S*,5*R*,6*S*)-2,4,6-trimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octyl-2,4,6-triisopropylbenzoate (**150**) (420 mg, 0.80 mmol, 1.0 eq) in THF (8 mL) was added a mixture in a 2:1 ratio of aqueous 2 M NaOH and >30% w/v aqueous H_2O_2 (3 mL) dropwise at 0 °C. The reaction was warmed to room temperature and stirred for 3 h, after which the mixture was diluted with CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product **142** which used without further purification in the next step.



HRMS (ESI+) calcd. 441.3339 for [$C_{27}H_{46}O_3$+Na], found 441.3336.

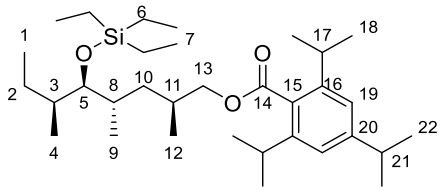
(2*S*,4*S*,5*R*,6*S*)-2,4,6-Trimethyl-5-((triethylsilyl)oxy)octyl 2,4,6-triisopropylbenzoate (143)



142 **143, 86%** over two steps from **150**

To a suitable flame dried vessel containing (2*S*,4*S*,5*R*,6*S*)-5-hydroxy-2,4,6-trimethyloctyl 2,4,6-triisopropylbenzoate (**142**) (crude mixture from previous experiment, assumed 1.0 eq) in CH_2Cl_2 (7.9 mL) was added 2,6-lutidine (0.14 mL, 1.19 mmol, 1.5 eq) and then trimethylsilyl trifluoromethanesulfonate (0.22 mL, 0.95 mmol, 1.2 eq) dropwise at 0 °C. The reaction was then allowed to warm at room temperature and was stirred for 16 h.

H_2O (20 mL) was then added, followed by CH_2Cl_2 (10 mL), the aqueous layer was separated and subsequently extracted with CH_2Cl_2 (3 x 10 mL) three times. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product which was purified using flash column chromatography (Et_2O in pentane, 1.5%) to give the title compound **143** as a colourless oil (316 mg, 86% over two steps).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.01 (s, 2H, C19-H), 4.15 (dd, *J* = 10.7, 6.0 Hz, 1H, C13-H), 4.09 (dd, *J* = 10.7, 6.7 Hz, 1H, C13-H), 3.30 (dd, *J* = 5.9, 3.4 Hz, 1H, C5-H), 2.87 (hept, *J* = 6.8 Hz, 1H, C21-H), 2.84 (hept, *J* = 6.8 Hz, 2H, C17-H), 1.93 (m, 1H, C11-H), 1.68 (m, 1H, C8-H), 1.47 (m, 1H, C3-H), 1.42 – 1.30 (m, 2H, C2-H, C10-H), 1.25 (d, *J* = 6.9 Hz, 18H, C18-H, C22-H), 1.22 – 1.07 (m, 2H, C2-H, C10-H), 0.94 (d, *J* = 6.6 Hz, 3H, C12-H), 0.94 (t, *J* = 8.1 Hz, 9H, C7-H), 0.87 (t, *J* = 7.4 Hz, 3H, C1-H), 0.83 (d, *J* = 6.8, 3H, C4-H), 0.83 (d, *J* = 6.8, 3H, C9-H), 0.59 (q, *J* = 8.1 Hz, 6H, C6-H).

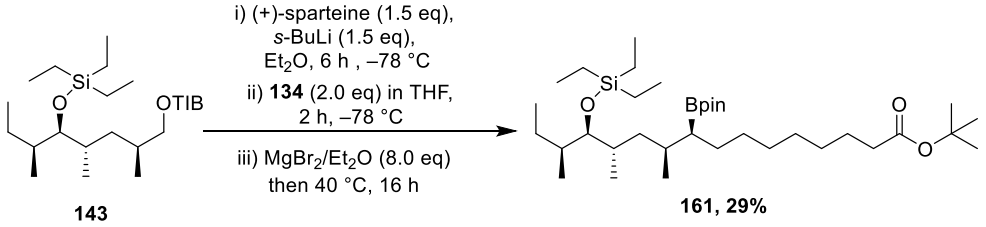
^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.4 (C14), 150.1 (C20), 144.9 (C16), 130.9 (C15), 121.0 (C19), 80.7 (C5), 71.4 (C13), 37.8 (C3), 36.5 (C10), 34.6 (C17), 34.5 (C8), 31.7 (C21), 30.3 (C11), 27.7 (C2), 24.3 (C18), 24.1 (C22), 16.3 (C4), 16.3 (C12), 14.0 (C9), 12.3 (C1), 7.3 (C6), 5.8 (C7).

IR νmax/cm^{-1} 2959, 1727 (C=O), 1250, 1067.

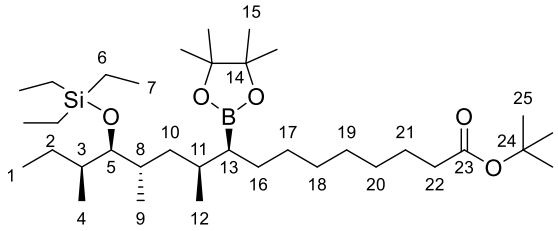
HRMS (ESI+) calcd. 555.4204 for [$C_{33}H_{60}SiO_3$+Na], found 555.4215.

R_f = 0.32 in 2% Et_2O in pentane. $[\alpha]_D^{24}$ ($CHCl_3$, c = -26) .

***Tert*-butyl (9*S*,10*S*,12*S*,13*R*,14*S*)-10,12,14-trimethyl-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-13-((triethylsilyl)oxy)hexadecanoate (161)**



To a suitably size flame dried vessel was added (2*S*,4*S*,5*R*,6*S*)-2,4,6-trimethyl-5-((triethylsilyl)oxy)octyl 2,4,6-triisopropylbenzoate (**143**) (20 mg, 0.038 mmol, 1.0 eq), (+)-sparteine (0.013 mL, 0.056 mmol, 1.5 eq) and dry Et_2O (0.13 mL). The solution was cooled down before the dropwise addition of *s*-BuLi (1.3 M in hexanes) (0.043 mL, 0.056 mmol, 1.5 eq). The reaction was stirred at –78 °C for 6 h, after which *tert*-butyl 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octanoate (**134**) (24.5 mg, 0.075 mmol, 2.0 eq) was added as a solution in THF (0.075 mL). After stirring at –78 °C for 2 h, $MgBr_2$•Et_2O (77.6 mg, 0.3 mmol, 8.0 eq) in Et_2O (0.3 mL) was added and the reaction allowed to warm to room temperature. The mixture was stirred at room temperature for 16 h. 2 M HCl (4 mL) was then added and the layers were separated. The aqueous layer was extracted three times with Et_2O (3 x 4 mL), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product which was used without purification in the next step, or purified using flash column chromatography (Et_2O in pentane, 1% to 4%) to give the title compound **161** as a colourless oil (6.6 mg, 29% yield). (**NOTE:** It is suspected that boronic ester **161** is unstable towards silica, NMR yields and isolated yield exhibited a poor match).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.27 (dd, *J* = 5.5, 3.7 Hz, 1H, C5-H), 2.18 (t, *J* = 7.5 Hz, 2H, C22-H), 1.63 – 1.52 (m, 6H, C2-H, C3-H, C8-H, C10-H), 1.44 (s, 9H, C25-H), 1.36 (m, 1H, C11-H), 1.31 – 1.25 (m, 10H, C17-H, C18-H, C19-H, C20-H, C21-H), 1.24 (s, 12H, C15-H), 0.95 (t, *J* = 7.9 Hz, 9H, C7-H), 0.89 – 0.78 (m, 15H, C1-H, C4-H,

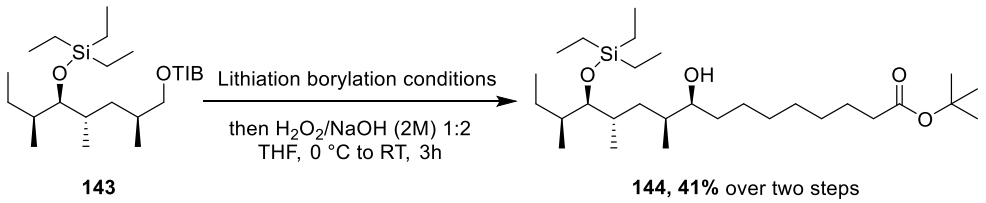
C9-H, C12-H, C13-H, C16-H), 0.60 (q, *J* = 7.9 Hz, 6H, C6-H). **R_f =** 0.5 in 2% Et_2O in pentane.

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.5 (C23), 82.9 (C14), 81.1 (C5), 80.0 (C24), 39.2 ($CHCH_3$), 37.8 ($CHCH_3$), 35.8 (C22), 35.1 ($CHCH_3$), 31.8 ($CHCH_3$), 30.0 (CH_2), 29.8 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 28.7 (CH_2), 28.2 (C25), 27.6 (CH_2), 25.2 (C2), 25.13 (C15), 25.0 (C15), 18.4 (CH_3), 16.2 (CH_3), 14.2 (CH_3), 12.2 (CH_3), 7.3 (C7), 5.7 (C6). C13 not observed due to quadrupolar relaxation.

HRMS (ESI+) calcd. 633.5063 for [$C_{35}H_{71}SiBO_5$+Na], found 633.5071.

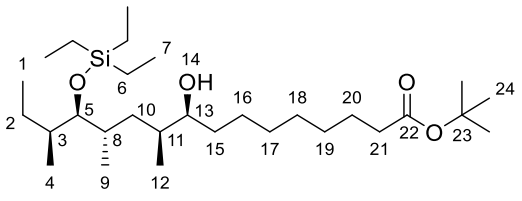
Note: Some experimental data for **161** is missing due to the shutdown of the lab during the pandemic. The synthetic route was changed during this period of inactivity, and as a result these compounds were not remade for the purposes of full characterisation.

***Tert*-butyl (9*S*,10*S*,12*S*,13*R*,14*S*)-9-hydroxy-10,12,14-trimethyl-13-((triethylsilyl)oxy)hexadecanoate (144)**



143 **144, 41%** over two steps

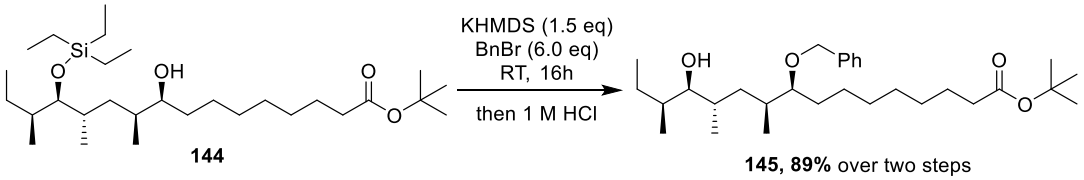
To a suitably sized vessel containing tert-butyl (9*S*,10*S*,12*S*,13*R*,14*S*)-10,12,14-trimethyl-9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-13-((triethylsilyl)oxy)hexadecanoate (**161**) (crude mixture from previous experiment, assumed 1.0 eq) in THF (0.4 mL) a mixture in a 2:1 ratio of aqueous 2 M NaOH and >30% w/v aqueous H_2O_2 (3 mL) was added dropwise at 0 °C. The reaction was warmed to room temperature and stirred for 3 h, after which the mixture was diluted with H_2O (2 mL) and CH_2Cl_2 (2 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL) three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude which was purified using flash column chromatography (Et_2O in pentane, 10% to 25%) to give the title compound **144** as a colourless oil (10.9 mg, 41% over two steps).



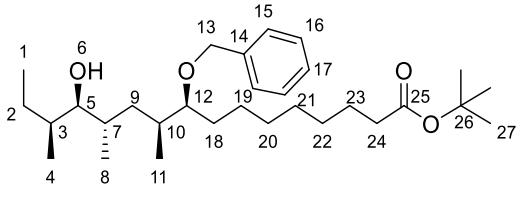
^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.41 (m, 1H, C13-H), 3.30 (m, 1H, C5-H), 2.20 (t, *J* = 7.5 Hz, 2H, C21-H), 1.44 (s, 9H, C24-H), 1.29 (m, 12H), 0.96 (t, *J* = 8.0 Hz, 9H, C7-H), 0.91 – 0.79 (m, 19H), 0.60 (q, *J* = 8.0 Hz, 6H, C6-H).

Note: Some experimental data for **144** is missing due to the shutdown of the lab during the pandemic. The synthetic route was changed during this period of inactivity, and as a result these compounds were not remade for the purposes of full characterisation.

***Tert*-butyl (9*S*,10*S*,12*S*,13*R*,14*S*)-9-(benzyloxy)-13-hydroxy-10,12,14-trimethylhexadecanoate (145)**



To a suitable flame-dried vessel under nitrogen was added tert-butyl (9*S*,10*S*,12*S*,13*R*,14*S*)-9-hydroxy-10,12,14-trimethyl-13-((triethylsilyl)oxy)hexadecanoate **144** (13.9 mg, 0.028 mmol, 1.0 eq), BnBr (0.020 mL, 0.167 mmol, 6.0 eq) and dry THF (0.12 mL). The mixture was cooled to 0°C before the dropwise addition of KHMDS (1 M in THF) (0.042 ml, 0.042 mmol, 1.5 eq). The mixture was warmed to room temperature and stirred for 1 h. H_2O (2 mL) and Et_2O were then added and the phases were separated. The aqueous phase was washed three times with Et_2O (3 x 2 mL), the organic layers combined, dried with $MgSO_4$, filtered and concentrated under reduced pressure to give a crude. This was then dissolved in a 5:1 mixture of THF:H_2O, and 1 M HCl was added. The mixture was stirred for 30 min at room temperature before being diluted with H_2O (2 mL) and Et_2O (2 mL). The layers were separated, the aqueous layer extracted three times with Et_2O (3 x 2 mL), and the organic layers combined, dried with $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product. The crude was purified using flash column chromatography (Et_2O in pentane, 20%) to give the title compound **145** as a colourless oil (11.9 mg, 89% yield over two steps).

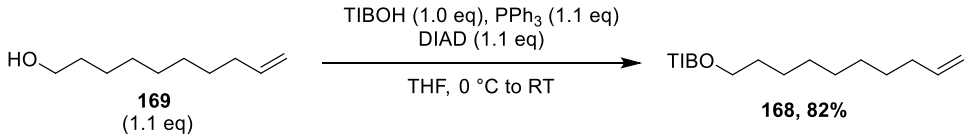


^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.30 (m, 2H, Ar-H), 7.21 – 7.15 (m, 2H, Ar-H), 7.19 – 7.14 (m, 1H, Ar-H), 4.51 (q, *J* = 11.6 Hz, 2H, C13-H), 3.16 (m, 2H, C5-H, C12-H), 2.86 (dd, *J* = 13.7, 9.0 Hz, 1H), 2.70 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.53 (ddd, *J* = 15.0, 9.0, 5.5 Hz, 1H), 1.87 (s, 1H), 1.67 – 1.52 (m, 6H), 1.43 (s, 8H), 1.33 (s, 9H, C27-H), 1.26 (d, *J* = 5.9 Hz, 14H), 0.95 – 0.82 (m, 12H, C1-H, C4-H, C8-H, C11-H).

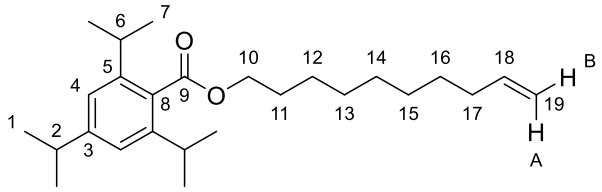
HRMS (ESI+) calcd. 499.3763 for [$C_{30}H_{52}O_4$+Na], found 499.3774.

Note: Some experimental data for **145** is missing due to the shutdown of the lab during the pandemic. The synthetic route was changed during this period of inactivity, and as a result these compounds were not remade for the purposes of characterisation.

Dec-9-en-1-yl 2,4,6-triisopropylbenzoate (168)



168 was synthesised according to General Procedure 1 using PPh_3 (8.18 g, 31.2 mmol, 1.1 eq), 2,4,6-triisopropylbenzoic acid (TIBOH) (7.04 g, 28.4 mmol, 1.0 eq), dec-9-en-1-ol (**169**) (5.57 mL, 31.2 mmol, 1.1 eq) and diisopropyl azadicarboxylate (DIAD) (6.13 mL, 31.2 mmol, 1.1 eq). The crude mixture was purified using flash column chromatography (1% to 5% Et_2O in pentane) to afford the title compound **168** as a colourless oil (8.96 g, 82% yield).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.01 (s, 2H, C4-H), 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, C18-H), 5.00 (ddt, *J* = 16.9, 3.4, 1.5 Hz, 1H, C19-H_A), 4.93 (ddt, *J* = 10.2, 2.1, 1.5 Hz, 1H, C19-H_B), 4.30 (t, *J* = 6.6 Hz, 2H, C10-H), 2.89 (hept, *J* = 6.8 Hz, 1H, C2-H), 2.86 (hept, *J* = 6.8 Hz, 2H, C6-H), 2.05 (tdt, *J* = 8.2, 6.7, 1.5 Hz, 2H, C17-H), 1.73 (tt, apparent quintet, *J* = 6.6, 6.4 Hz, 2H, C11-H), 1.47 – 1.28 (m, 10H, C12-H, C13-H, C14-H, C15-H, C16-H), 1.25 (d, *J* = 6.8 Hz, 12H, C7-H), 1.25 (d, *J* = 6.8 Hz, 6H, C1-H).

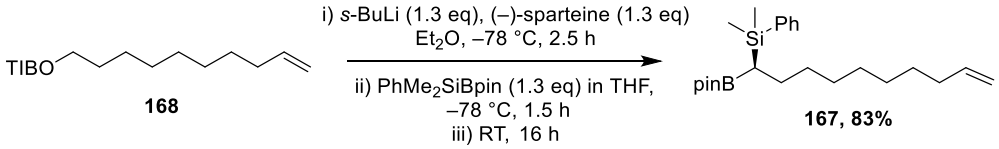
^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.2 (C9), 150.2 (C3), 144.8 (C5), 139.3 (C18), 130.9 (C8), 121.0 (C4), 114.3 (C19), 65.2 (C10), 34.6 (C2), 33.9 (C17), 31.6 (C6), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.8 (C11), 26.2 (CH_2), 24.3 (C7), 24.1 (C1).

IR ν_{max}/cm^{-1} (neat) 2960, 1724 (C=O), 1250, 1075

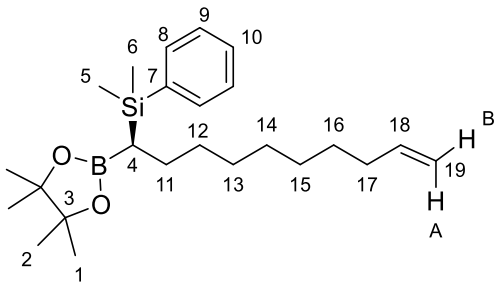
HRMS (ESI+) calcd. 409.3077 for [$C_{26}H_{42}O_2$+Na], found 409.3082.

R_f = 0.35 in 1% Et_2O in pentane

(*R*)-Dimethyl(phenyl)(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-9-en-1-yl)silane (167)



To a flame-dried Schlenk tube containing a solution of dec-9-en-1-yl-2,4,6-triisopropylbenzoate (**168**) (1.74 g, 4.50 mmol, 1.0 eq), (−)-sparteine (1.37 mL, 5.85 mmol, 1.3 eq) and dry Et_2O (18.0 mL, 0.25 M) at −78 °C, under N_2, was added *s*-BuLi (4.50 mL, 5.85 mmol, 1.3 eq, 1.3 M in hexanes) dropwise. The mixture was stirred at this temperature for 2 h before the dropwise addition of $PhMe_2SiBpin$ (1.59 mL, 5.85 mmol, 1.3 eq) in THF (5.85 mL, 1.0 M). The reaction was then stirred at –78 °C for 1.5 h, then warmed to room temperature and stirred for 16 h. Et_2O (20 mL) and 2 M HCl (40 mL) were added, and the phases were separated. The aqueous layer was washed three times with Et_2O (3 x 20 mL). The organic layers were combined and washed three times with 2 M HCl (3 x 20 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product that was filtered through a pad of silica to give a mixture which could be used in the following step. (The acidified aqueous layer can then be processed as outlined in the sparteine recovery procedure to recover the (−)-sparteine.) Alternatively, the crude could be purified using flash silica column chromatography (1% - 5% Et_2O in pentane) to give 1.63 g of an inseparable mixture of the product and starting material, which would correspond to 1.50 g of product **167** in an 83% yield (95:5 e.r) with 9% starting material (**168**) recovered.



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.48 (m, 2H, C9-H), 7.38 – 7.30 (m, 3H, C8-H, C10-H), 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, C18-H), 4.98 (ddt, *J* = 16.9, 3.4, 1.5 Hz, 1H, C19-H_A), 4.92 (ddt, *J* = 10.2, 2.1, 1.5 Hz, 1H, C19-H_B), 2.01 (tdt, *J* = 8.2, 6.7, 1.5 Hz, 2H, C17-H), 1.35 – 1.25 (m, 12H, C11-H, C12-H, C13-H, C14-H, C15-H, C16-H), 1.20 (s, 6H, C1-H), 1.16 (s, 6H, C2-H), 0.63 (dd, *J* = 11.8, 2.5 Hz, 1H, C4-H), 0.31 (s, 3H, C5-H), 0.31 (s, 3H, C6-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 139.4 (C18), 139.3 (C7), 134.0 (C9), 128.9 (C8), 127.7 (C10), 114.2 (C19), 82.8 (C3), 34.0 (C17), 31.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 25.9 (CH_2), 25.2 (C1), 24.8 (C2), 14.3 (C4), -2.2 (C5), -3.2 (C6).

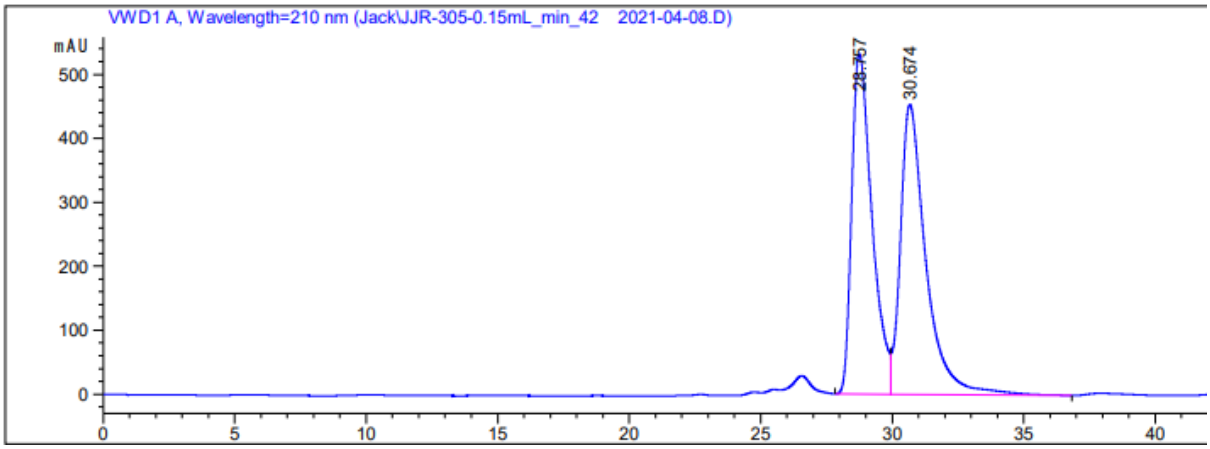
IR ν_{max}/cm^{-1} (neat) 1378, 1143

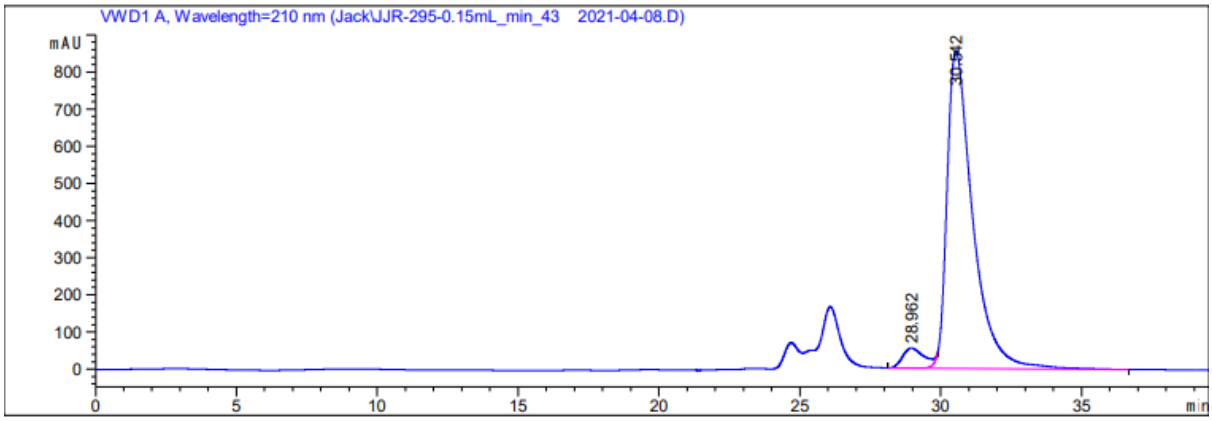
HRMS (ESI+) calcd. 423.2866 for [$C_{26}H_{42}O_2BSi$+Na], found 423.2881.

R_f = 0.35 in 1% Et_2O in pentane

$[\alpha]_D^{24}$ ($CHCl_3$, c = 1) +16.

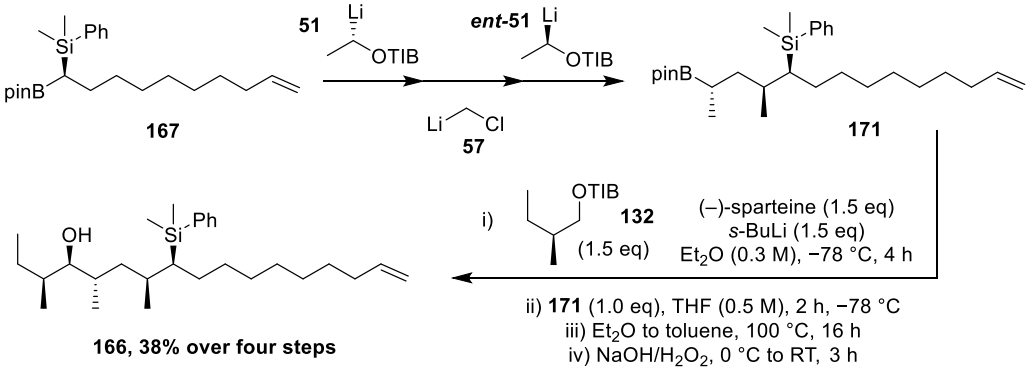
Chiral HPLC (Daicel Chiralpak-IA column (25 cm) with guard, hexane, 0.15 ml/min, room temperature, 210.8 nm). t_R: (*S*) = 28.8 min, (*R*) = 30.7 min.





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.962	BV E	0.8027	2876.61987	53.94535	5.0198
2	30.542	VB R	0.9694	5.44293e4	855.50305	94.9802

(3*S*,4*R*,5*S*,7*S*,8*S*)-8-(Dimethyl(phenyl)silyl)-3,5,7-trimethylheptadec-16-en-4-ol (166)



Compound **171** was synthesised from **167** following the general Matteson and stannane homologation procedures:

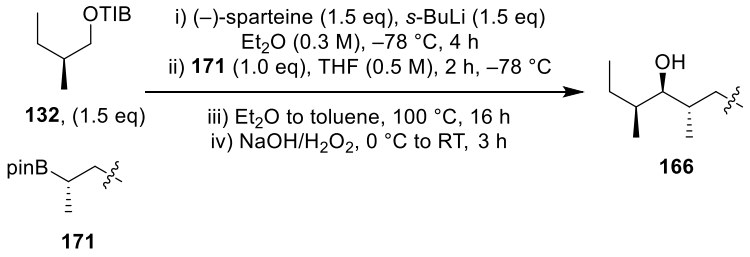
Homologation 1: General Procedure 3 was followed using (*S*)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (**36**) (1.78 g, 4.05 mmol, 1.3 eq), Et_2O (20.3 mL), *n*-BuLi (2.67 mL, 4.05 mmol, 1.3 eq, 1.6 M in hexanes) and (*R*)-dimethyl(phenyl)(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)dec-9-en-1-yl)silane (**167**) (1.25 g, 3.12 mmol, 1.0 eq) dissolved in Et_2O (15.6 mL).

Homologation 2: the General Procedure 2 was followed using the crude boronic ester from the first homologation, chlorobromomethane (**70**) (0.63 mL, 9.36 mmol, 3.0 eq), Et_2O (15.6 mL) and *n*-BuLi (5.13 mL, 7.80 mmol, 2.5 eq, 1.6 M in hexanes).

Homologation 3: General Procedure 3 was followed using (*R*)-1-(trimethylstannyl)ethyl 2,4,6-triisopropylbenzoate (***ent*-36**) (1.78 g, 4.05 mmol, 1.3 eq), Et_2O (20.3 mL), *n*-BuLi

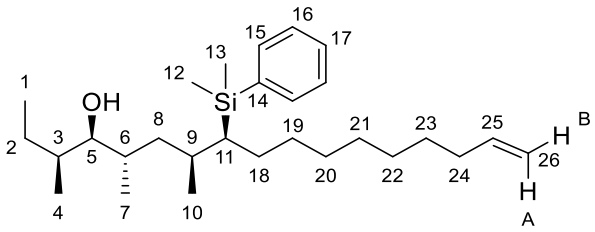
(2.67 mL, 4.05 mmol, 1.3 eq, 1.6 M in hexanes) and the crude boronic ester from the second homologation dissolved in Et_2O (15.6 mL).

Lithiaton-Borylation-Oxidation:



To a solution of (*S*)-2-methylbutyl 2,4,6-triisopropylbenzoate (**132**) (1.49 g, 4.68 mmol, 1.5 eq) and (−)-sparteine (1.08 mL, 4.68 mmol, 1.5 eq) in anhydrous Et_2O (14 mL) at −78 °C, under N_2 was added *s*-BuLi (3.60 mL, 4.68 mmol, 1.5 eq, 1.3 M in hexanes) dropwise. The mixture was stirred at −78 °C for 4 h before the crude boronic ester from the third homologation (**171**) in THF (6.2 mL) was added dropwise at −78 °C. The mixture was then stirred at −78 °C for 2 h. The cooling bath was removed, and the solvent was removed under reduced pressure (N.B. For large scale reactions, this can be done on a rotary evaporator as the boronate complex is air and moisture stable for a short time). Once all the solvent had been removed, toluene (20.2 mL) was added, and the reaction was stirred at 100 °C for 16 h or until the 1,2-metallate rearrangement of the boronate complex was completed (the conversion was monitored by ^{11}B NMR). Sat. aq. NH_4Cl (40 mL) was added to the reaction mixture and the layers were separated. The (−)-sparteine containing aqueous layer was then extracted with Et_2O three times (3 × 20 mL). The combined organic layers were extracted three times with 2 M HCl (3 × 20 mL), dried over anhydrous $MgSO_4$, filtered and the concentrated under reduced pressure to give the crude boronic ester. The acidified aqueous layer can then be processed as outlined in the sparteine recovery procedure to recover the (−)-sparteine. The crude boronic ester was then dissolved in THF (20 mL) and cooled down to 0 °C. A 2:1 mixture of 2 M NaOH: H_2O_2 (9.0 mL) was then added dropwise, and the mixture was stirred at room temperature for 3 h. Once the boronic ester had been consumed (monitored by TLC), the mixture was diluted with water and the layers were separated. The aqueous layer was extracted three times with Et_2O (3 × 15 mL), the organic layers combined, dried with $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product. This was first purified using flash column chromatography (Silica gel, 2% to 4% Et_2O in pentane) to obtain an

impure product, which was then further purified using preparatory HPLC (0 – 4% EtOAc in hexane over 65 min, t_R = 41.0 min, 21.2 mL min^{-1}) to give the title compound **166** as a colourless oil (511 mg, 38% over four steps).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.47 (m, 2H, C16-H), 7.37 – 7.30 (m, 3H, C15-H), 5.81 (ddt, *J* = 16.9, 10.0, 6.7 Hz, 1H, C25-H), 4.99 (ddt, *J* = 16.9, 3.4, 1.5 Hz, 1H, C26-H_A), 4.93 (ddt, *J* = 10.0, 2.2, 1.5 Hz, 1H, C26-H_B), 3.05 (dd, appears as an apparent triplet, *J* = 5.4, 5.3 Hz, 1H, C5-H), 2.02 (tdt, *J* = 8.1, 6.7, 1.5 Hz, 2H, C24-H), 1.88 – 1.76 (m, 1H, C9-H), 1.69 – 0.97 (m, 15H, C2-H (diastereotopic H), C8-H, C18-H, C19-H, C20-H, C21-H, C22-H, C23-H), 0.92 – 0.80 (m, 13H, C1-H, C2-H (diastereotopic H), C3-H, C6-H, C7-H, C10-H, C11-H), 0.72 (d, *J* = 6.7 Hz, 3H, C4-H), 0.32 (s, 3H, C12-H), 0.31 (s, 3H, C13-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 140.7 (C14), 139.4 (C25), 134.1 (16), 128.7 (C17), 127.7 (C15), 114.2 (C26), 79.6 (C5), 38.0 (C2), 36.7 (C6), 34.0 (C23), 33.8 (C11), 30.9 (C9), 30.4 (C3), 29.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 27.4 (CH_2), 26.8 (CH_2), 18.9 (CH_3), 15.9 (C4), 13.0 (CH_3), 11.7 (CH_3), -1.7 (C12), -2.0 (C13).

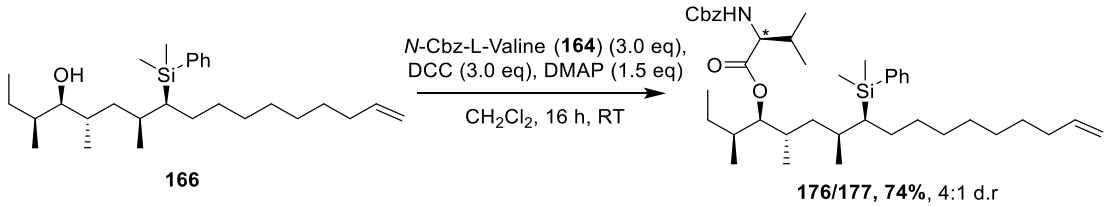
IR ν_{max}/cm^{-1} (neat) 3487 (very broad) (O-H), 2925, 700

HRMS (ESI+) calcd. 453.3523 for [$C_{28}H_{50}OSi$+Na], found 453.3516.

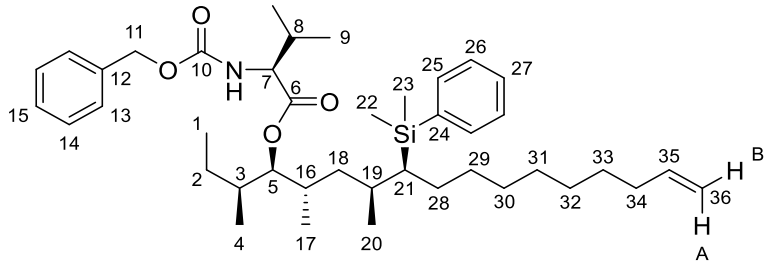
R_f = 0.17 in 2% Et_2O in pentane

$[\alpha]_D^{24}$ ($CHCl_3$, c = 1) −12.

(3*S*,4*R*,5*S*,7*S*,8*S*)-8-(dimethyl(phenyl)silyl)-3,5,7-trimethylheptadec-16-en-4-yl ((benzyloxy)carbonyl)-L-valinate (176)



To a solution of (3*S*,4*R*,5*S*,7*S*,8*S*)-8-(dimethyl(phenyl)silyl)-3,5,7-trimethylheptadec-16-en-4-ol (**166**) (100 mg, 0.23 mmol, 1.0 eq) and ((benzyloxy)carbonyl)-L-valine (**164**) (175 mg, 0.69 mmol, 3.0 eq) in CH_2Cl_2 (0.7 mL, 0.33 M) at 0 °C, under N_2, was added *N*,*N*-dimethylpyridin-4-amine (42.5 mg, 0.35 mmol, 1.5 eq) and *N*,*N*′-dicyclohexylcarbodiimide (144 mg, 0.69 mmol, 3.0 eq). The reaction was stirred at room temperature for 16 h. CH_2Cl_2 (5 mL) and H_2O (15 mL) were added, the layers separated and the aqueous layer extracted three times with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (10 mL), H_2O (10 mL) and then brine (10 mL), dried over $MgSO_4$, fiiltered and concentrated under reduced pressure to give the crude product. This was first purified using flash silica column chromatography to give the product as a mixture of epimers (6% EtOAc in pentane), which were then separated by preporatory HPLC (2 – 6% EtOAc in hexane over 60 min, t_R(major) = 36.5 min, t_R(minor) = 37.8 min, 21.2 mLmin^{-1}) to give the title compound as a colourless oil, as a 4:1 ratio of epimers (Major epimer (**176**): 91.5 mg, 59% yield, and minor epimer (**177**): 23.5 mg, 15% yield).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 – 7.44 (m, 2H, C26-H), 7.39 – 7.29 (m, 8H, C13-H, C14-H, C15-H, C25-H, C27-H), 5.80 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H, C35-H), 5.26 (d, *J* = 9.3 Hz, 1H, N-H), 5.13 (d, *J* = 12.1 Hz, 1H, C11-H (diastereotopic H)), 5.08 (d, *J* = 12.1 Hz, 1H, (diastereotopic H)), 4.99 (ddt, *J* = 16.9, 2.3, 1.6 Hz, 1H, C36-H_A), 4.93 (ddt, *J* = 10.1, 2.3, 1.3 Hz, 1H, C36-H_B), 4.71 (dd, *J* = 6.6, 4.9 Hz, 1H, C5-H), 4.35 (dd, *J* = 9.3, 3.9 Hz, 1H, C7-H), 2.29 – 2.16 (m, 1H, C8-H), 2.06 – 1.97 (m, 2H, C34-H),

1.82 – 1.52 (m, 3H, C3-H, C16-H, C19-H), 1.40 – 1.11 (m, 15H, C2-H (diastereotopic H), C18-H, C28-H, C29-H, C30-H, C31-H, C32-H, C33-H), 1.03 (d, *J* = 6.8 Hz, 3H, C9-H (diastereotopic methyl group)), 0.99 – 0.91 (m, 1H, C2-H (diastereotopic H)), 0.92 – 0.79 (m, 13H, C1-H, C9-H (diastereotopic methyl group), C17-H, C20-H, C21-H), 0.71 (d, *J* = 6.7 Hz, 3H, C4-H), 0.28 (s, 3H, C22-H), 0.28 (s, 3H, C23-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.1 (C6), 156.3 (C10), 140.5 (C27), 139.4 (C35), 136.5 (C15), 134.0 (C26), 134.0 (C14), 128.7 (C24), 128.3 (C12), 128.3 (C13), 127.7 (C25), 114.2 (C36), 82.7 (C5), 67.1 (C11), 59.4 (C7), 37.8 (C2), 35.7 (CH), 33.94 (C34), 33.7 (CH), 32.5 (CH), 31.3 (C8), 30.9 (CH), 30.4 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 27.3 (CH_2), 26.6 (CH_2), 19.7 (C9), 18.5 (CH_3), 17.2 (CH_3), 15.9 (C4), 14.0 (CH_3), 11.6 (CH_3), -1.7 (C22), -2.0 (C23).

IR ν_{max}/cm^{-1} ($CHCl_3$) 2923, 1731 (C=O), 1490, 1161, 988

HRMS (ESI+) calcd. 686.4575 for [$C_{41}H_{65}NO_4Si$+Na], found 686.4578.

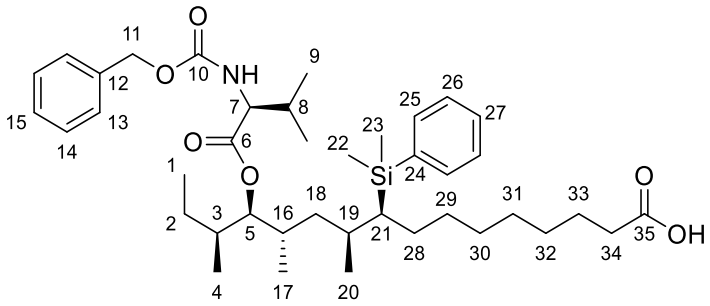
R_f = 0.3 in 6% Et_2O in pentane

$[\alpha]_D^{24}$ ($CHCl_3$, c = 1) +6.

(9*S*,10*S*,12*S*,13*R*,14*S*)-13-((((benzyloxy)carbonyl)-L-valyl)oxy)-9-(dimethyl(phenyl)silyl)-10,12,14-trimethylhexadecanoic acid (181)

(3*S*,4*R*,5*S*,7*S*,8*S*)-8-(dimethyl(phenyl)silyl)-3,5,7-trimethylheptadec-16-en-4-yl ((benzyloxy)carbonyl)-L-valinate (**176**) (20 mg, 0.03 mmol, 1.0 eq) was dissolved in a 9:1 mixture of MeCN (0.45 mL) and H_2O (0.045 mL) (0.1 M total), and then cooled to 0 °C. Sudan Red III was then added as indicator which turned the solution a pale red colour. Ozone was then bubbled gently through the solution with stirring until the red colour disappeared, indicating that the alkene starting material has been consumed. A 2 M aq. solution of $NaClO_2$ (0.06 mL, 4.0 eq) was added and the reaction was stirred at room temperature for 16 h. A 2 M aq. solution of $NaHSO_3$ (0.06 mL, 4.0 eq) was then added slowly and the reaction was stirred for a further 10 min. EtOAc (5 mL) was added,

and the layers were separated. The aqueous layer was then extracted with EtOAc three times (3 × 5 mL), the combined organic layers were then dried over $MgSO_4$, filtered and then concentrated under reduced pressure to give the crude carboxylic acid. This could then be used without further purification in the following steps. Alternatively, the crude could be purified using flash column chromatography (Silica gel, 10% to 30% EtOAc in pentane,) to give the title compound **181** as a clear oil (12.0 mg, 60% yield).



^{1}H NMR (400 MHz, Chloroform-*d*) (Major epimer) δ 7.53 – 7.44 (m, 2H, C26-H), 7.40 – 7.28 (m, 8H, C13-H, C14-H, C15-H, C25-H, C27-H), 5.33 (d, *J* = 9.3 Hz, 1H, N-H), 5.13 (d, *J* = 12.2 Hz, 1H, C11-H (diastereotopic H)), 5.08 (d, *J* = 12.2 Hz, 1H, C11-H (diastereotopic H)), 4.72 (dd, *J* = 6.5, 5.0 Hz, 1H, C5-H), 4.35 (dd, *J* = 9.3, 4.0 Hz, 1H, C7-H), 2.31 (t, *J* = 7.5 Hz, 2H, C34-H), 2.27 – 2.18 (m, 1H, C8-H), 1.82 – 1.66 (m, 2H, C3-H, C16-H), 1.63 – 1.51 (m, 3H, C18-H, C19-H), 1.39 – 1.13 (m, 13H, C2-H (diastereotopic H), C28-H, C29-H, C30-H, C31-H, C32-H, C33-H), 1.03 (d, *J* = 6.8 Hz, 3H, C9-H (diastereotopic methyl group)), 0.95 – 0.80 (m, 14H, C1-H, C2-H (diastereotopic H), C9-H (diastereotopic methyl group), C17-H, C20-H, C21-H), 0.72 (d, *J* = 6.7 Hz, 3H, C4-H), 0.28 (s, 3H, C22-H), 0.27 (s, 3H, C23-H).

^{13}C NMR (101 MHz, Chloroform-*d*) (Major epimer) δ 179.3 (C35), 172.2 (C6), 156.4 (C10), 140.4 (C24), 136.4 (C12), 134.0 (C26), 128.6 (C24, C27), 128.3 (C13), 128.2 (C15), 127.7 (C25), 82.7 (C5), 67.1 (C11), 59.3 (C7), 37.8 (C2), 35.6 (CH), 34.0 (C34), 33.5 (C21), 32.4 (CH), 31.2 (C8), 30.8 (CH), 30.1 (CH_2), 29.8 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 27.2 (CH_2), 26.6 (CH_2), 24.7 (CH_2), 19.6 (C9), 18.4 (CH_3), 17.1 (CH_3), 15.9 (C4), 14.0 (CH_3), 11.6 (CH_3), -1.7 (C22), -2.1 (C23).

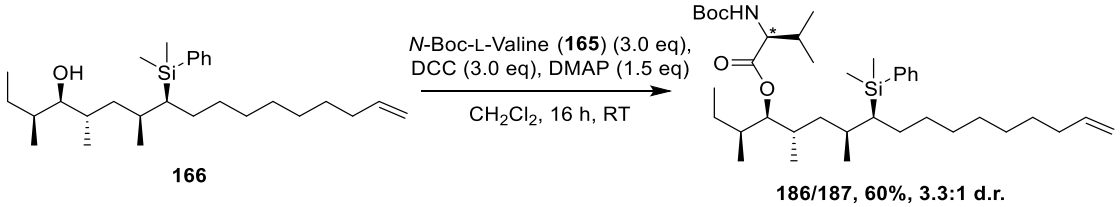
R_f = 0.6 in 30% EtOAc in pentane

IR ν_{max}/cm^{-1} ($CHCl_3$) 3133 (O-H, very broad), 2929, 1713 (C=O), carboxylic acid and ester peaks overlap), 1248, 1161

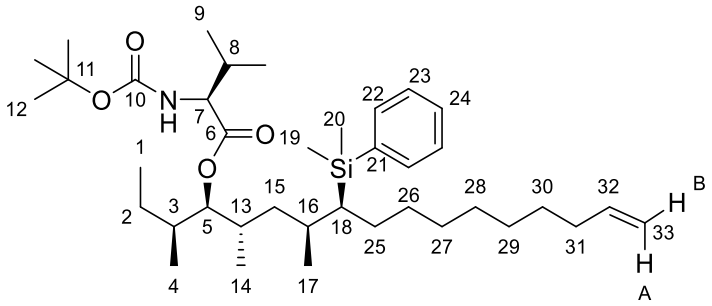
HRMS (EI−) calcd. 680.4346 for [$C_{40}H_{62}NO_6Si$−H], found 680.4366.

$[\alpha]_D^{24}$(Major epimer) ($CHCl_3$, c = 1) +4

(3*S*,4*R*,5*S*,7*S*,8*S*)-8-(Dimethyl(phenyl)silyl)-3,5,7-trimethylheptadec-16-en-4-yl (tert-butoxycarbonyl)-L-valinate (186)



To a solution of (3*S*,4*R*,5*S*,7*S*,8*S*)-8-(dimethyl(phenyl)silyl)-3,5,7-trimethylheptadec-16-en-4-ol (**166**) (85.0 mg, 0.20 mmol, 1.0 eq) and (*tert*-butoxycarbonyl)-L-valine (**165**) (128 mg, 0.59 mmol, 3.0 eq) in CH_2Cl_2 (0.59 mL, 0.33 M) at 0 °C, under N_2, was added *N*,*N*-dimethylpyridin-4-amine (36.1 mg, 0.30 mmol, 1.5 eq) and *N*,*N*′-dicyclohexylcarbodiimide (122 mg, 0.59 mmol, 3.0 eq). The reaction was stirred at room temperature for 16 h. CH_2Cl_2 (5 mL) and H_2O (15 mL) were added, the layers separated and the aqueous layer extracted three times with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (10 mL), H_2O (10 mL) and then brine (10 mL), dried over $MgSO_4$, fiiltered and concentrated under reduced pressure to give the crude product. This was first purified using flash column chromatography to give the product as a mixture of epimers (Silica gel, 5% EtOAc in pentane), which were then separated by preporatory HPLC (0 – 4% EtOAc in hexane over 50 min, t_R(major) = 32.0 min, t_R(minor) = 34.0 min, 21.2 mLmin^{-1}) to give the title compound as a colourless oil, as a 3.3:1 ratio of epimers (Major epimer (**186**): 57.6 mg, 46% yield, and minor epimer (**187**): 17.2 mg, 14% yield).



^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.54 – 7.46 (m, 2H, C23-H), 7.37 – 7.29 (m, 3H, C22-H, C24-H), 5.80 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, C32-H), 4.99 (br s, 1H, N-H), 4.98 (ddt, *J* = 16.9, 3.4, 1.5 Hz, 1H, C33-H_A), 4.92 (ddt, *J* = 10.2, 2.4, 1.5 Hz, 1H, C33-H_B),

4.70 (dd, *J* = 6.6, 4.8 Hz, 1H, C5-H), 4.26 (dd, *J* = 9.3, 4.1 Hz, 1H, C7-H), 2.25 – 2.11 (m, 1H, C8-H), 2.07 – 1.95 (m, 2H, C31-H), 1.81 – 1.52 (m, 3H, C3-H, C13-H, C16-H), 1.44 (s, 9H, C12-H), 1.39 – 1.04 (m, 15H, C2-H (diastereotopic H), C15-H, C25-H, C26-H, C27-H, C28-H, C29-H, C30-H), 1.01 (d, *J* = 6.8 Hz, 3H, C9-H (diastereotopic methyl group)), 0.98 – 0.93 (m, 1H, C2-H (diastereotopic H)), 0.94 – 0.80 (m, 13H, C1-H, C9-H (diastereotopic methyl group), C14-H, C17-H. C18-H), 0.71 (d, *J* = 6.7 Hz, 3H, C4-H), 0.29 (s, 3H, C19-H), 0.29 (s, 3H, C20-H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.4 (C6), 155.7 (C10), 140.5 (C24), 139.4 (C32), 134.0 (C23), 128.6 (C21), 127.7 (C22), 114.2 (C33), 82.4 (C5), 79.6 (C11), 58.9 (C7), 37.9 (C2), 35.8 (CH), 34.0 (C31), 33.7 (CH), 32.5 (CH), 31.3 (C8), 31.0 (CH), 30.4 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 28.5 (C12), 27.30 (CH_2), 26.7 (CH_2), 19.7 (C9), 18.6 (CH_3), 17.3 (CH_3), 15.9 (C4), 14.0 (CH_3), 11.6 (CH_3), -1.6 (C19), -2.0 (C20).

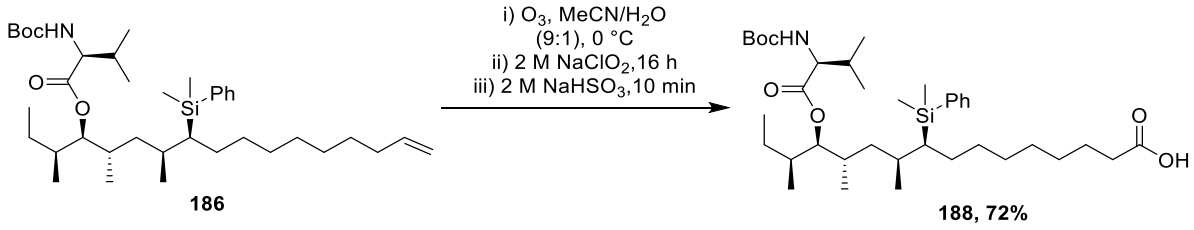
IR ν_{max}/cm^{-1} ($CHCl_3$) 2927, 1722 (C=O), 1496, 1160

HRMS (ESI+) calcd. 652.4732 for [$C_{36}H_{67}NO_4Si$+Na], found 652.4718.

R_f = 0.5 in 7% EtOAc in pentane

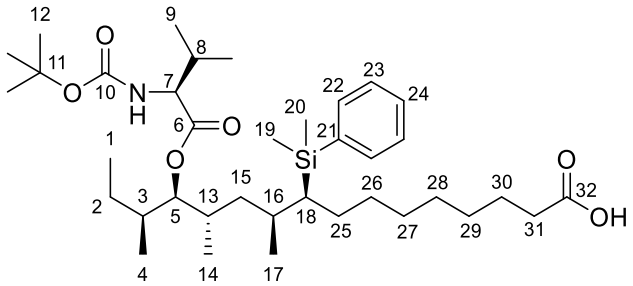
$[\alpha]_D^{24}$ ($CHCl_3$, c = 1) +4.

(9*S*,10*S*,12*S*,13*R*,14*S*)-13-(((T*ert*-butoxycarbonyl)-L-valyl)oxy)-9-(dimethyl(phenyl)silyl)-10,12,14-trimethylhexadecanoic acid (188)



(3*S*,4*R*,5*S*,7*S*,8*S*)-8-(dimethyl(phenyl)silyl)-3,5,7-trimethylheptadec-16-en-4-yl (*tert*-butoxycarbonyl)-L-valinate (**186**) (30 mg, 0.048 mmol, 1.0 eq) was dissolved in a 9:1 mixture of MeCN (0.45 mL) and H_2O (0.045 mL) (0.1 M total), and then cooled to 0 °C. Sudan Red III was then added as indicatore which turned the solution a pale red colour. Ozone was then bubbled gently through the solution with stirring until the red colour disappeared, indicating that the alkene starting material has been consumed. .A 2 M aq.

solution of $NaClO_2$ (0.10 mL, 4.0 eq) was added, the reaction was stirred at room temperature for 16 h. A 2 M aq. solution of $NaHSO_3$ (0.10 mL, 4.0 eq) was then added slowly and the reaction was stirred for a further 10 min. EtOAc (5 mL) was added, and the layers were separated. The aqueous layer was then extracted with EtOAc three times (3 × 5 mL), the combined organic layers were then dried over $MgSO_4$, filtered and the concentrated under reduced pressure to give the crude carboxylic acid. This could then be used without further purification in the following step. Alternatively, the crude could be purified using flash silica column chromatography (5% to 20% EtOAc in pentane,) to give the title compound **188** as a clear oil (22.4 mg, 72% yield).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 – 7.46 (m, 2H, C23-H), 7.35 – 7.29 (m, 3H, C22-H, C24-H), 5.06 (d, *J* = 9.4 Hz, 1H, N-H), 4.70 (dd, *J* = 6.6, 4.9 Hz, 1H, C5-H), 4.26 (dd, *J* = 9.4, 4.0 Hz, 1H, C7-H), 2.31 (t, *J* = 7.5 Hz, 2H, C31-H), 2.23 – 2.14 (m, 1H, C8-H), 1.80 – 1.51 (m, 3H, C3-H, C13-H, C16-H), 1.44 (s, 9H, C12-H), 1.39 – 1.04 (m, 15H, C2-H (diastereotopic H), C15-H, C25-H, C26-H, C27-H, C28-H, C29-H, C30-H), 1.01 (d, *J* = 6.8 Hz, 3H, C9-H (diastereotopic methyl group)), 0.98 – 0.79 (m, 14H, C1-H, C2-H (diastereopic H), C9-H (diastereotopic methyl group), C14-H, C17-H, C18-H), 0.71 (d, *J* = 6.7 Hz, 3H, C4-H), 0.29 (s, 3H, C19-H), 0.29 (s, 3H, C20-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 179.5 (C32), 172.5 (C6), 155.8 (C10), 140.5 (C21), 134.0 (C23), 128.6 (C24), 127.7 (C22), 82.4 (C5), 79.7 (C11), 58.8 (C7), 37.8 (C2), 35.7 (CH), 34.1 (C31), 33.5 (C18), 32.4 (CH), 31.2 (C8), 30.9 (CH), 30.1 (CH_2), 29.6 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 28.5 (C12), 27.2 (CH_2), 26.6 (CH_2), 24.8 (CH_2), 19.7 (C9), 18.5 (CH_3), 17.3 (CH_3), 15.9 (C4), 14.0 (CH_3), 11.6 (CH_3), -1.6 (C19), -2.1 (C20).

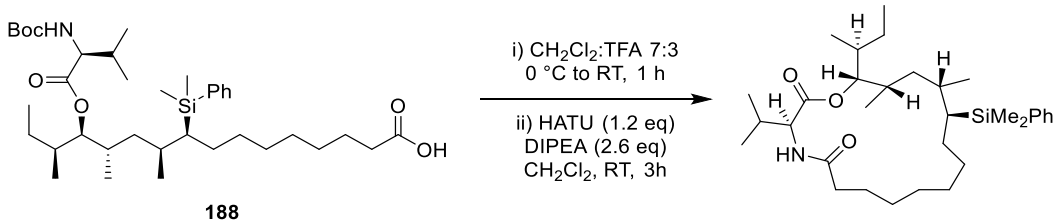
IR ν_{max}/cm^{-1} ($CHCl_3$) 3135 (O-H, very broad), 2929, 1713 (C=O), carboxylic acid and ester peaks overlap), 1248, 1161

HRMS (EI−) calcd. 646.4503 for [$C_{37}H_{64}NO_6Si$−H], found 646.4500.

R_f = 0.6 in 30% EtOAc in pentane

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{24}}$($CHCl_3$, c = 1) +4

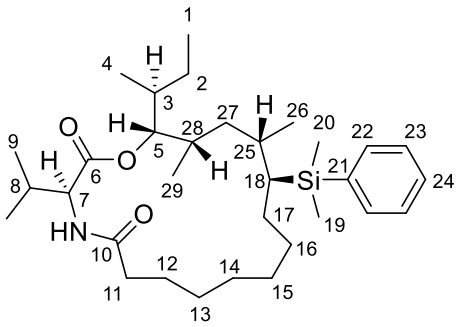
(3*S*,13*S*,14*S*,16*S*,17*R*)-17-((*S*)-*Sec*-butyl)-13-(dimethyl(phenyl)silyl)-3-isopropyl-14,16-dimethyl-1-oxa-4-azacycloheptadecane-2,5-dione (189)



To a solution of (9*S*,10*S*,12*S*,13*R*,14*S*)-13-(((*tert*-butoxycarbonyl)-L-valyl)oxy)-9-(dimethyl(phenyl)silyl)-10,12,14-trimethylhexadecanoic acid (**188**) (60 mg, 0.092 mmol, 1 eq) in CH_2Cl_2 (0.64 mL) at 0 °C was added trifluoroacetic acid (0.28 mL) (0.1 M total) . The reaction was warmed to room temperature and stirred for 1 h. Once completed (monitored by TLC), the reaction was quenched via dropwise addition of sat. aq. $NaHCO_3$ (2 mL) at 0 °C. CH_2Cl_2 (5 mL) was added, and the layers were separated. The aqueous layer was washed with CH_2Cl_2 three times (3 × 5 mL), the organic layers combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude amino acid (**163**) which was used without further purification in the next step.

HRMS (ESI+) calcd. 548.4135 for [$C_{32}H_{57}NO_4Si$+H], found 548.4161.

To a stirred solution of the amino acid **163** from the previous step in CH_2Cl_2 (1.8 mL, 0.05 M) at 0 °C was added *N*,*N*-diisopropylethylamine (DIPEA) (42 µL, 0.24 mmol, 2.6 eq) and 1-bis(dimethylamino)methylene-1*H*-1,2,3-triazolo-4,5-bipyridinium 3-oxid hexafluorophosphate (42.2 mg, 0.11 mmol, 1.2 eq) . The reaction was warmed to room temperature and stirred for 3 h. CH_2Cl_2 (5 mL) and H_2O (5 mL) were added, and the layers separated. The aqueous layer was extracted with CH_2Cl_2 three times (3 × 5 mL), the organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude which was purified by flash silica column chromatography (5% to 8% EtOAc in pentane) to give the title compound **189** as a clear oil (32.0 mg, 66% yield).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 – 7.44 (m, 2H, C23-H), 7.36 – 7.30 (m, 3H, C22-H, C24-H), 6.09 (d, *J* = 8.5 Hz, 1H, N-H), 4.74 (dd, *J* = 9.2, 2.3 Hz, 1H, C5-H), 4.66 (dd, *J* = 8.5, 3.5 Hz, 1H, C7-H), 2.38 (ddd, *J* = 14.4, 7.0, 3.5 Hz, 1H, C11-H (diastereotopic H)), 2.26 – 2.16 (m, 1H, C8-H), 2.12 (ddd, *J* = 14.4, 10.4, 3.5 Hz, 1H, C11-H (diastereotopic H)), 1.93 – 1.80 (m, 1H, C27-H (diastereotopic H)), 1.78 – 1.55 (m, 3H, C3-H, C25-H, C28-H), 1.53 – 1.42 (m, 1H, C27-H (diastereotopic H)), 1.40 – 1.06 (m, 12H, C12-H, C13-H, C14-H, C15-H, C16-H, C17-H), 1.00 – 0.94 (m, 5H, C2-H, C9-H (diastereotopic methyl group)), 0.93 – 0.84 (m, 12H, C1-H, C9-H (diastereotopic methyl group), C26-H, C29-H), 0.80 – 0.75 (m, 1H, C18-H), 0.69 (d, *J* = 6.9 Hz, 3H, C4-H), 0.29 (s, 3H, C19-H), 0.26 (s, 3H, C20-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.1 (C7), 172.9 (C6), 139.9 (C21), 134.0 (C23), 128.7 (C24), 127.8 (127.75), 81.9 (C5), 56.9 (C7), 37.6 (C2), 36.4 (C11), 35.8 (CH), 33.5 (CH), 33.5 (C18), 31.9 (C8), 30.9 (CH_2), 30.5 (CH), 29.3 (CH_2), 28.2 (CH_2), 27.4 (CH_2), 27.3 (CH_2), 25.7 (CH_2), 24.7 (CH_2), 21.6 (CH_3), 19.6 (C9), 17.1 (C9), 15.9 (CH_3), 12.9 (CH_3), 12.1 (CH_3), -2.3 (C19), -2.7 (C20).

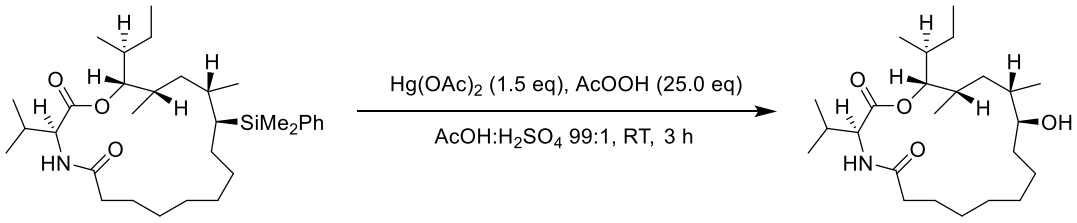
IR ν_{max}/cm^{-1} ($CHCl_3$) 2926, 1734 (C=O), 1654 (C=O), 1462, 1201

HRMS (ESI+) calcd. 552.3843 for [$C_{32}H_{55}NO_3Si$+Na], found 552.3845.

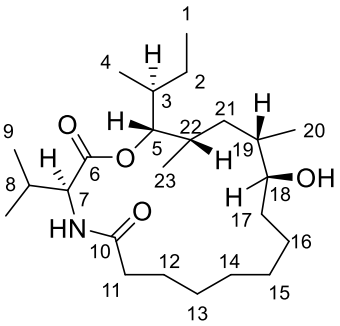
R_f = 0.35 in 8% EtOAc in pentane

$[\alpha]_D^{24}$ ($CHCl_3$, c = 1) +4.

(3*S*,13*S*,14*S*,16*S*,17*R*)-17-((*S*)-*Sec*-butyl)-13-hydroxy-3-isopropyl-14,16-dimethyl-1-oxa-4-azacycloheptadecane-2,5-dione (83)



To a solution of (3*S*,13*S*,14*S*,16*S*,17*R*)-17-((*S*)-sec-butyl)-13-(dimethyl(phenyl)silyl)-3-isopropyl-14,16-dimethyl-1-oxa-4-azacycloheptadecane-2,5-dione (**189**) (3.50 mg, 0.0065 mmol, 1.0 eq) in AcOOH (35% by weight in dilute AcOH) (36.7 µL, 0.169 mmol, 25.0 eq), AcOH (35.2 µL) and H_2SO_4 (0.35 µL/trace amount) was added $Hg(OAc)_2$ (3.10 mg, 0.0098 mmol, 1.5 eq). The reaction was stirred at room temperature for 3 h or until complete consumption of the starting material (monitored by TLC). Et_2O (4 mL) was then added, followed by sat. aq. $Na_2S_2O_3$ (6 mL). The layers were separated, and the aqueous layer extracted with Et_2O three times (3 × 4 mL). The combined organic layers were then washed with water (6 mL), sat. aq. $NaHCO_3$ (6 mL) and then brine (6 mL), dried over $MgSO_4$, filtered and concentrated to give the crude alcohol. This was purified using flash column chromatography (Silica gel, 25% Et_2O in pentane) to give the title compound **83** as a white solid (1.78 mg, 67% yield).



^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.04 (d, *J* = 8.8 Hz, 1H, N-H), 4.81 (dd, *J* = 9.4, 2.4 Hz, 1H, C5-H), 4.66 (dd, *J* = 8.8, 3.6 Hz, 1H, C7-H), 3.26 (ddd, *J* = 8.2, 5.7, 2.1 Hz, 1H, C18-H), 2.36 (ddd, *J* = 14.4, 7.8, 3.5 Hz, 1H, C11-H (diastereotopic H)), 2.23 – 2.14 (m, 2H, C8-H, C11-H (diastereotopic H)), 1.94 – 1.83 (m, 1H, C21-H (diastereotopic H)), 1.83 – 1.75 (m, 1H, C3-H), 1.74 – 1.67 (m, 1H, C22-H), 1.64 – 1.52 (m, 1H, C19-H), 1.53 – 1.43 (m, 2H, C17-H (diastereotopic H), C21-H (diastereotopic H)), 1.37 – 1.06 (m, 12H, C2-H (diastereotopic H), C12-H, C13-H, C14-H, C15-H, C16-H, C17-H

(diastereotopic H)), 0.98 (d, *J* = 6.8 Hz, 3H, C9-H (diastereotopic methyl group), 0.94 – 0.82 (m, 16H, C1-H, C2-H (diastereotopic H), C4-H, C9-H (diastereotopic methyl group), C20-H, C23-H).

^{1}H NMR (500 MHz, Pyridine-*d*$_5$) δ 8.73 (d, *J* = 9.4 Hz, 1H), 5.19 (dd, *J* = 9.4, 4.8 Hz, 1H), 5.09 (dd, *J* = 8.6, 3.0 Hz, 1H), 3.70 (ddd, *J* = 8.1, 5.7, 2.5 Hz, 1H), 2.61 – 2.44 (m, 2H), 2.40 – 2.31 (m, 1H), 2.13 – 2.04 (m, 1H), 2.03 – 1.90 (m, 2H), 1.89 – 1.78 (m, 2H), 1.77 – 1.50 (m, 4H), 1.51 – 1.19 (m, 10H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.99 (d, J = 3.7 Hz, 3H), 0.93 (dt, *J* = 7.5, 4.1 Hz)

^{13}C NMR (126 MHz, Chloroform-*d*) δ 173.1 (C10), 173.0 (C6), 81.9 (C5), 77.3 (C18), 56.9 (C7), 36.7 (C19), 36.3 (C11), 35.9 (C22), 34.1 (CH_2), 32.2 (C3), 31.9 (CH_2), 31.7 (C8), 29.9 (CH_2), 28.1 (CH_2), 27.8 (CH_2), 27.4 (CH_2), 27.3 (CH_2), 25.1 (C21), 25.0 (CH_2), 19.6 (C9), 17.2 (C9), 15.9 (CH_3), 15.4 (CH_3), 13.2 (CH_3), 12.1 (CH_3).

^{13}C NMR (126 MHz, Pyridine-*d*$_5$) δ 173.7, 173.7, 81.6, 76.5, 57.9, 37.8, 36.4, 36.0, 35.1, 33.2, 33.0, 31.8, 30.4, 28.7, 28.2, 28.1, 27.8, 25.9, 25.3, 20.2, 18.1, 16.9, 16.3, 13.9, 12.3.

IR ν_{max}/cm^{-1} ($CHCl_3$) 3377 (very broad, O-H), 2926, 1731 (C=O), 1650 (C=O), 1381, 1202

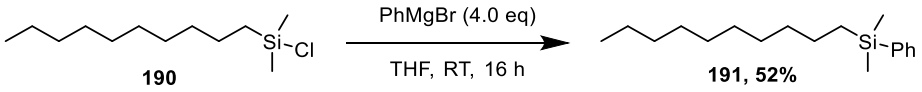
HRMS (ESI+) calcd. 412.3421 for [$C_{24}H_{46}NO_4$+H], found 412.3402.

R_f = 0.25 in 25% EtOAc in pentane

$[\alpha]_D^{24}$ ($CHCl_3$, c = 1) −8.

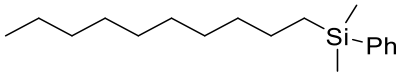
Experimental data matches that from the literature.[36]

Decyldimethyl(phenyl)silane (191)



To a solution of chloro(decyl)dimethylsilane (**190**) (2.70 mL, 10.0 mmol, 1.0 eq) in THF (10 mL, 1.0 M) at 0°C, under N_2, was added PhMgBr (37.7 mL, 40 mmol, 4.0 eq, 1.06 M solution in THF) dropwise. The mixture was warmed to room temperature and stirred for 16 h. A sat. aq. solution NH_4Cl (15 mL) was added and the reaction mixture was concentrated under reduced pressure. The slurry was then extracted with Et_2O (4 × 20 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude silane was purified using flash column

chromatography (Silica gel, hexane) to give the title compound **191** as a colourless oil (1.44 g, 52% yield).



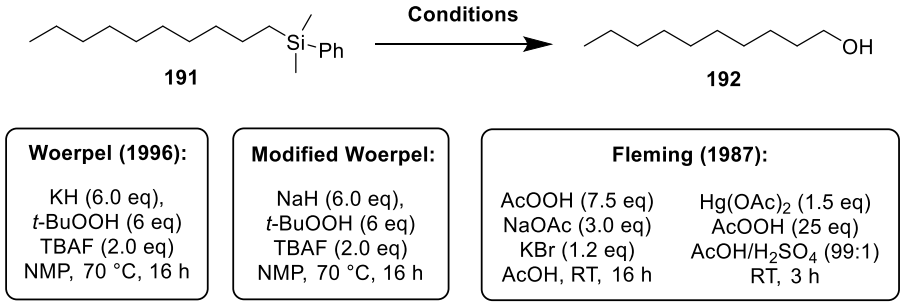
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.40 (m, 2H), 7.34 (m, 3H), 1.29 – 1.22 (m, 16H), 0.87 (t, *J* = 6.9 Hz, 3H), 0.78 – 0.68 (m, 2H), 0.24 (s, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 139.9, 133.7, 128.8, 33.7, 32.0, 29.8, 29.7, 29.5, 29.4, 24.0, 22.8, 15.8, 14.2, -2.9.

LR-MS: Expected mass: 276.2. Mass found 276.2.

The data matches that published in the literature.[63]

Decan-1-ol (192)



Entry	Conditions	NMR yield
1	Woerpel	86%
2	Modified Woerpel	83%
3	Fleming (KBr)	60%
4	Fleming ($Hg(OAc)_2$)	91%

Woerpel's conditions:[63] To a flame dried Schlenk tube under N_2 was added KH (80.9 mg, 2.02 mmol, 6.0 eq, 30% suspension in mineral oil, washed three times with hexane. Anhydrous NMP (1.03 mL, 1.95 M) was added, and the suspension cooled to 0 °C. *t*-BuOOH (0.40 mL, 2.02 mmol, 6.0 eq, 5.0 M solution in decane) was added dropwise, and the solution warmed to room temperature. Decyldimethyl(phenyl)silane (**191**) (92.9 mg, 0.34 mmol, 1.0 eq) in anhydrous NMP (2.1 mL, 0.16 M) was added and the reaction was stirred at room temperature for 10 min. TBAF (0.67 mL, 0.67 mmol, 2.0 eq, 1 M solution in THF) was added, and the reaction was stirred at 70 °C for 16 h. The reaction was then quenched with sat. aq. $Na_2S_2O_3$ (10 mL) at 0 °C and diluted with EtOAc (10 mL). The

aqueous layer was extracted four times with EtOAc (4 x 10 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product. The yield was measured by 1H-NMR using $CHCl_3$ as internal standard (86%).

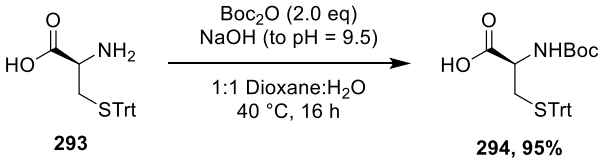
Modified Woerpel's conditions:[53] To a flame dried Schlenk tube under N_2 was added NaH (3.2 mg, 0.079 mmol, 6.0 eq, 60% suspension in mineral oil, washed three times with hexane) followed by anhydrous NMP (40 µL, 1.95 M). The suspension was cooled to 0 °C, *t*-BuOOH (26.4 µL, 2.02 mmol, 6.0 eq, 5.0 M solution in decane) was added dropwise, and the solution warmed to room temperature. Decyldimethyl(phenyl)silane (**191**) (3.6 mg, 0.013 mmol, 1.0 eq) in anhydrous NMP (80 µL, 0.16 M) was added and the reaction was stirred at room temperature for 10 min. TBAF (26.4 µL, 0.026 mmol, 2.0 eq, 1 M solution in THF) was added, and the reaction was stirred at 70 °C for 16 h. The reaction was then quenched with sat. aq. $Na_2S_2O_3$ (1 mL) at 0 °C and diluted with EtOAc (1 mL). The aqueous layer was extracted four times with EtOAc (4 x 1 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product. The yield was measured by 1H-NMR using $CHCl_3$ as internal standard (83%).

Fleming (KBr):[66] To a stirred solution of decyldimethyl(phenyl)silane (**191**) (3.6 mg, 0.013 mmol, 1.0 eq), KBr (1.9 mg, 0.016 mmol, 1.2 eq) and NaOAc (3.2 mg, 0.040 mmol, 3.0 eq) in AcOH (66 µL, 0.2 M) at 0 °C was added AcOOH (20.8 µL, 0.099 mmol, 7.5 eq, 35% by weight in dilute AcOH). The reaction was stirred at room temperature for 16 h. Then, Et_2O (2 mL) was added, followed by the careful addition of sat. aq. $NaHCO_3$ (1 mL). The layers were separated, and the aqueous layer extracted with Et_2O three times (3 × 2 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give the crude product. The yield was measured by 1H-NMR using $CHCl_3$ as internal standard (60%).

Fleming ($Hg(OAc)_2$):[66] To a solution of decyldimethyl(phenyl)silane (**191**) (1.8 mg, 0.0065 mmol, 1.0 eq) in AcOOH (36.7 µL, 0.169 mmol, 25.0 eq, 35% by weight in dilute AcOH), AcOH (35.2 µL) and H_2SO_4 (0.35 µL/trace amount) was added $Hg(OAc)_2$ (3.10 mg, 0.0098 mmol, 1.5 eq). The reaction was stirred at room temperature for 3 h or until complete consumption of the starting material (monitored by TLC). Et_2O (4 mL) was then added, followed by sat. aq. $Na_2S_2O_3$ (6 mL). The layers were separated, and the aqueous

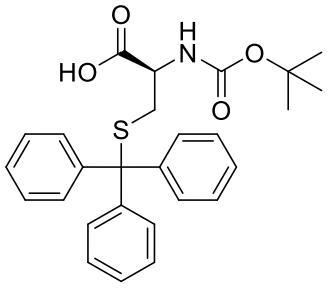
layer extracted with Et_2O three times (3 × 4 mL). The combined organic layers were then washed with water (6 mL), sat. aq. $NaHCO_3$ (6 mL) and then brine (6 mL), dried over $MgSO_4$, filtered and concentrated to give the crude product. The yield was measured by 1H-NMR using $CHCl_3$ as internal standard (91%).

_N_-(_Tert_-butoxycarbonyl)-_S_-trityl-L-cysteine (294)



293 **294, 95%**

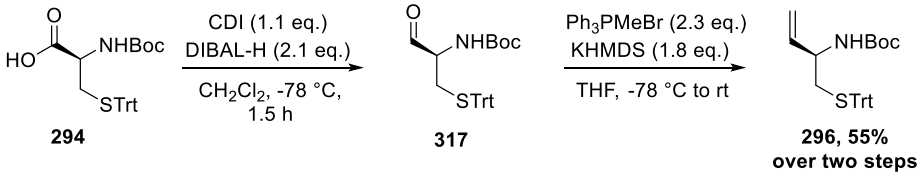
To a solution of *S*-trityl-L-cysteine (**293**) (12.7 g, 35 mmol, 1.0 eq) in dioxane (35 mL) and water (73 mL) was added di-tert-butyl dicarbonate (15.3 g, 70 mmol, 2.0 eq) NaOH was added as a 2 M solution until the reaction reached pH 9.0 (approx. 3.7 g of NaOH in 23 mL H_2O). The reaction was stirred at 40 °C for 16 h, then the solvent was removed and the resultant residue redissolved in H_2O (200 mL) and EtOAc (200 mL). The mixture was cooled down to 0 °C and 2 M HCl was added until the solution reached approximately pH 2.0. The layers were then separated and the aqueous layer extracted three times with EtOAc (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was then redissolved in a minimal amount of Et_2O before hexane was added to precipitate the product. The suspension was cooled to 0 °C then filtered, washed with cold hexane. The solid was then dried to give the title compound (**294**) as a white amorphous solid (15.4 g, 95%)



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.39 (m, 6H), 7.32 – 7.26 (m, 6H), 7.25 – 7.19 (m, 3H), 4.90 (d, *J* = 7.4 Hz, 1H), 4.15 – 4.06 (m, 1H), 2.68 (d, *J* = 5.7 Hz, 2H), 1.45 (d, *J* = 8.4 Hz, 9H).

The data matches that reported in the literature.[116]

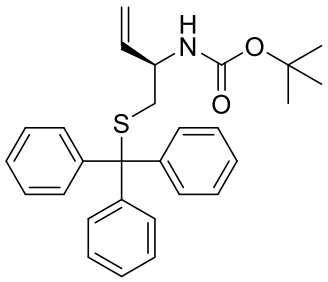
***Tert*-butyl (*R*)-(1-(tritylthio)but-3-en-2-yl)carbamate (296)**



To a solution of *N*-(tert-butoxycarbonyl)-*S*-trityl-L-cysteine (**294**) (7.00 g, 15 mmol, 1.0 eq) in CH_2Cl_2 (98 mL) at 0 °C was added aa solution of 1,1'-carbonyldiimidazole (2.7 g, 16.5 mmol, 1.1 eq) in anhydrous CH_2Cl_2 (15 mL). The mixture was stirred at 0 °C for 1 h, then cooled to −78 °C. Diisobutylaluminium hydride (1 M in CH_2Cl_2) (31.5 mL, 31.5 mmol, 2.1 eq) was then added dropwise (0.3 $mLmin^{-1}$) and the reaction stirred at this temperature for 30 min. EtOAc (30 mL) was added (initially dropwise), the −78 °C cooling bath was removed and a solution of tartaric acid (25 g) in H_2O (75 mL) was added immediately afterwards. The reaction was allowed to warm to room temperature and stirred for a further 1 h. After this time the layers were separated, and the aqueous layer was extracted three times with EtOAc (3 x 100 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to give the crude aldehyde (**317**).

During the DIBAL-H reduction, the ylid was prepared. To a solution of PPh_3MeBr (12.3 g, 34.5 mmol, 2.3 eq) in anhydrous THF (115 mL) at −78 °C KHMDS (1 M in THF) (27 mL, 27 mmol, 1.8 eq) was added dropwise (1.0 $mLmin^{-1}$). The reaction was warmed to room temperature and stirred for 1 h.

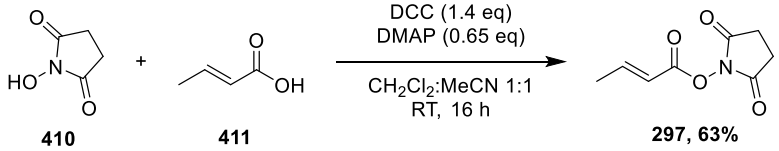
The mixture was cooled to −78 °C and the crude aldehyde (**317**) was added dropwise (0.7 $mLmin^{-1}$). as a solution in anhydrous THF (15 mL). The solution was then warmed to room temperature and stirred for 1 h, after which it was cooled to 0 °C and isopropanol (15 mL) was added (initially dropwise). The mixture was then filtered through silica, washing with Et_2O, and the filtrate concentrated under reduced pressure to give the crude product which was purified using flash column chromatography (3 – 10% EtOAc in pentane) to give the title compound **296** as a viscous yellow oil (2.86 g, 53%).



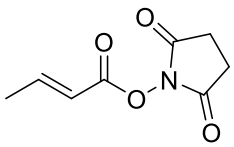
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.29 (m, 6H), 7.25 – 7.19 (m, 6H), 7.17 – 7.12 (m, 3H), 5.57 (ddd, *J* = 17.1, 10.3, 5.2 Hz, 1H), 5.02 (dt, *J* = 17.1, 1.2 Hz, 1H), 4.99 (dt, *J* = 10.3, 1.2 Hz, 1H), 4.50 (s, 1H), 4.09 (s, 1H), 2.39 – 2.21 (m, 1H), 1.36 (s, 9H).

The data matches that reported in the literature.[117]

2,5-Dioxopyrrolidin-1-yl (*E*)-but-2-enoate (297)



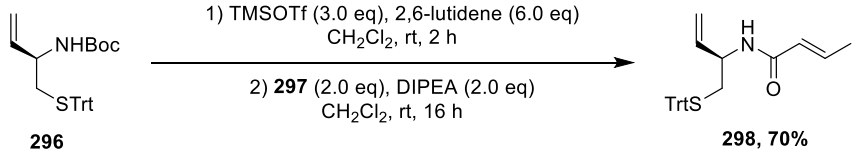
To a solution of (*E*)-but-2-enoic acid (**411**) (8.61 g, 100 mmol, 1.0 eq), *N*-hydroxysuccinamide (**410**) (11.5 g, 100 mmol, 1.0 eq) and *N*,*N*-dimethylpyridin-4-amine (7.99 g, 65 mmol, 0.65 eq) in CH_2Cl_2 (25 mL) and MeCN (25 mL) was added a solution *N*,*N'*-dicyclohexylcarbodiimide (28.9 g, 140 mmol, 1.4 eq) in CH_2Cl_2 (10 mL) and stirred at room temperature for 16 h. The mixture was filtered through a frit, washed with CH_2Cl_2, and the filtrate washed with H_2O (100 mL), dil. HCl (100 mL), H_2O (100 mL) again, sat. aq. $NaHCO_3$ (100 mL) and then H_2O a further three times (3 x 100 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product which was purified using flash column chromatography (20% EtOAc in pentane) to give the title compound **297** as a white solid (11.58 g, 63%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (dq, *J* = 15.6, 6.9 Hz, 1H), 6.04 (dq, *J* = 15.6, 1.7 Hz, 1H), 2.84 (s, 4H), 1.99 (dd, *J* = 6.9, 1.7 Hz, 3H).

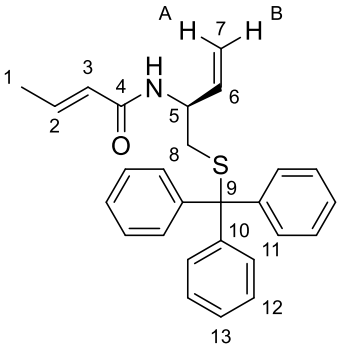
The data matches that reported in the literature.[118]

(*S,E*)-*N*-(1-(Tritylthio)but-3-en-2-yl)but-2-enamide (298)



To a solution of *tert*-butyl (*R*)-(1-(tritylthio)but-3-en-2-yl)carbamate (**296**) (3.83 g, 8.6 mmol, 1.0 eq) and 2,6-lutidene (6.01 mL, 51.6 mmol, 6.0 eq) in anhydrous CH_2Cl_2 (41 mL) at 0 °C was added TMSOTf (4.67 mL, 25.8 mmol, 3.0 eq) dropwise (0.5 $mLmin^{-1}$). The reaction was warmed to room temperature and stirred for 2 h, cooled back down to 0 °C, and MeOH (1 mL) was added dropwise, followed by the addition of H_2O (35mL, initially dropwise). The aqueous layer was extracted with CH_2Cl_2 twice (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude amine.

To a solution of 2,5-dioxopyrrolidin-1-yl (E)-but-2-enoate (**297**) (3.15 g, 17.2 mmol, 2.0 eq) and diisopropylethylamine (2.99 mL, 17.2 mmol, 2.0 eq) in anhydrous CH_2Cl_2 (17 mL) was added the crude amine as a solution in anhydrous CH_2Cl_2 (33 mL). The reaction was stirred at room temperature for 16 h. The solvent was removed, and the reaction was redissolved in MeOH (50 mL). Et_3N (0.8 mL) was added, and the reaction was stirred for 2 h at room temperature. The solvent was again removed and EtOAc (250 mL) was added. This organic phase was washed with 1 M HCl (100 mL) and then with sat. aq. K_2CO_3 five times (5 x 50 mL). The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product which was purified using flash column chromatography (10 – 40% EtOAc in pentane) to give the title compound **298** as a very viscous oil (2.46 g, 70%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.38 (m, 6H, C12-H), 7.34 – 7.27 (m, 6H, C11-H), 7.26 – 7.20 (m, 3H, C13-H), 6.84 (dq, *J* = 15.2, 6.9 Hz, 1H, C2-H), 5.76 (dt, *J* = 15.2, 1.8 Hz, 1H, C3-H), 5.70 (ddd, *J* = 17.0, 10.4, 5.1 Hz, 1H, C6-H), 5.50 (d, *J* = 8.4

Hz, 1H, N-H), 5.14 – 5.11 (m, 1H, C7-A), 5.10 (m, 1H, C7-B), 4.65 (dt, *J* = 11.0, 3.5 Hz, 1H, C5-H), 2.57 (dd, *J* = 12.2, 5.9 Hz, 1H, C8-H), 2.44 (dd, *J* = 12.2, 5.1 Hz, 1H, C8-H), 1.88 (dd, *J* = 6.9, 1.8 Hz, 3H, C1-H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 165.1 (C4), 144.7 (C10), 140.3 (C2), 136.7 (C3), 129.7 (C12), 128.1 (C11), 126.9 (C13), 125.1 (C6), 115.9 (C7), 66.9 (C9), 50.0 (C5), 36.7 (C8), 17.9 (C1).

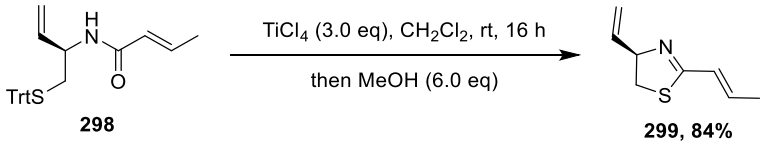
IR ν_{max}/cm^{-1} (neat) 3280, 1675, 1628, 1443

HRMS (ESI+) calcd. 436.1706 for [$C_{27}H_{47}ONS$+Na], found 436.1697.

R_f = 0.29 in 10% EtOAc in pentane

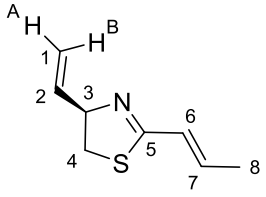
$[\alpha]_D^{24}$ ($CHCl_3$, c = 1) +20. (e.r = 97:3)

(*R*,*E*)-2-(Prop-1-en-1-yl)-4-vinyl-4,5-dihydrothiazole (299)



298 **299, 84%**

To a solution of (*S*,*E*)-*N*-(1-(tritylthio)but-3-en-2-yl)but-2-enamide (**298**) (2.47 g, 5.95 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (60 mL) at 0 °C was added $TiCl_4$ (1.96 mL, 17.9 mmol, 3.0 eq) dropwise (0.1 mLmin^{-1}). The reaction was warmed to room temperature and stirred for 16 h, then cooled back down to 0 °C before MeOH (1.45 mL, 35.8 mmol, 6.0 eq) was added dropwise. Sat. aq. Na_2CO_3 (14 mL) was added, followed by a 10% w/w aq. solution of Rochelle's salt (14 mL), and the solution was stirred at room temperature for a further 1 h. The layers were separated, and the aqueous layer was extracted three times with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and carefully concentrated under reduced pressure (the product is volatile), which gave the crude product that was purified using flash column chromatography (5 – 20% Et_2O in pentane) to give the title compound 299 as a colourless oil (767 mg, 84%).



^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.43 – 6.34 (m, 2H, C6-H, C7-H), 5.96 (ddd, *J* = 17.1, 10.3, 6.8 Hz, 1H, C2-H), 5.30 (dd, *J* = 17.2, 1.3 Hz, 1H, C1-HB), 5.18 (dd, *J* = 10.3, 1.2 Hz, 1H, C1-HA), 5.02 – 4.91 (m, 1H, C3-H), 3.41 (dd, *J* = 10.9, 8.3 Hz, 1H, C4-H), 3.04 (dd, *J* = 10.9, 8.2 Hz, 1H, C4-H), 1.90 (dd, *J* = 4.9, 0.8 Hz, 3H, C8-H).

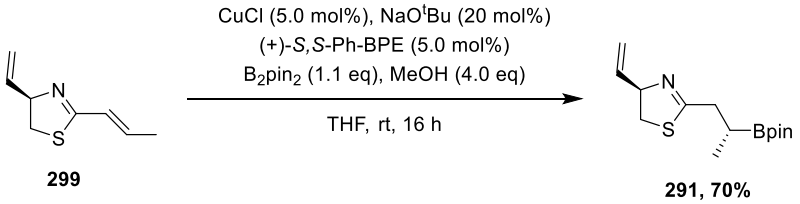
^{13}C NMR (126 MHz, Chloroform-*d*) δ 167.5 (C5), 140.6 (C7), 137.2 (C2), 126.7 (C6), 116.4 (C1), 78.6 (C3), 37.7 (C7), 18.6 (C8).

IR ν_{max}/cm^{-1} (neat) 2972, 2930, 2220, 1582, 910

HRMS (ESI+) calcd. 152.0528 for [$C_8H_{11}NS$+H], found 152.0533.

R_f = 0.19 in 30% EtOAc in pentane

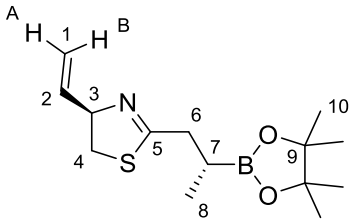
(*R*)-2-((*R*)-2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-4-vinyl-4,5-dihydrothiazole (291)



299 **291, 70%**

To a solution of CuCl (26.6 mg, 0.268 mmol, 0.10 eq) and (+)-1,2-Bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane ((+)-*S*,*S*-Ph-BPE) (136 mg, 0.268, 0.10 eq) in anhydrous THF (8.4 mL) was added *t*-BuONa (0.27 mL, 0.536 mmol, 0.2 eq) dropwise. The reaction was stirred for 1 h, over the course of which the mixture turned brown. B_2pin_2 (750 mg, 2.95 mmol, 1.1 eq) was then added as a solution in anhydrous THF (2.2 mL) (the solution instantly turns black) and the reaction was stirred for a further 10 min, then cooled to 0 °C before the addition of (*R*,*E*)-2-(prop-1-en-1-yl)-4-vinyl-4,5-dihydrothiazole (**299**) (410 mg, 2.68 mmol, 1.0 eq) as a neat oil, followed immediately by the addition of anhydrous MeOH (0.43 mL, 10.7 mmol, 4.0 eq). The reaction was allowed to come to room temperature and stirred for 16 h. The reaction was filtered through boric acid treated silica, the solvent removed under reduced pressure, and the resultant crude residue redissolved in Et_2O (10 mL). Ethanolamine (0.94 mL, 15.5 mmol, 5.0 eq) was then added and the reaction was stirred at room temperature for 30 min before being cooled to 0 °C and filtered through a pad of boric acid treated silica. The solvent was removed under reduced pressure to give the title compound as a pale yellow oil (615 mg, 70%). This sample was

determined to be 78% pure by NMR analysis (using TMB as internal standard) – the impurities have been idenitifed as HOBpin and $(Bpin)_2O$.



^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.92 (ddt, *J* = 17.0, 9.9, 6.7 Hz, 1H, C2-H), 5.32 – 5.21 (dd, *J* = 17.0, 6.7 1H, C1-HB), 5.19 – 5.08 (dd, *J* = 9.9, 6.7 1H, C1-HA), 4.96 – 4.81 (m, 1H, C3-H), 3.40 (ddd, *J* = 10.5, 8.5, 3.8 Hz, 1H, C4-H), 3.03 (ddd, *J* = 10.6, 8.0, 2.3 Hz, 1H, C4-H), 2.64 (d, 7.3 Hz, 1H, C6-H), 2.50 (ddt, *J* = 15.4, 7.6, 1.3 Hz, 1H, C6-H), 1.42 (m, 1H, C7-H), 1.25 – 1.18 (m, 12H, C10-H), 1.02 (d, *J* = 7.5 Hz, 3H, C8-H).

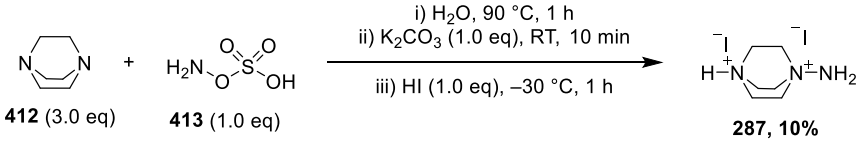
^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.7 (C5), 137.6 (C2), 116.0 (C1), 83.2 (C9), 78.5 (C3), 38.9 (C4), 37.7 (C6), 24.9 (C10), 15.2 (C8). C7 not observed due to quadrupolar coupling.

IR ν_{max}/cm^{-1} (neat) 2976, 2930, 1369, 1317, 851

HRMS (ESI+) calcd. 281.1615 for $[C_{14}H_{24}NO_2BS+H]$, found 281.1618.

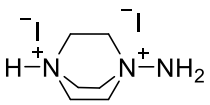
R_f = Unstable to silica

4-Ammonio-1,4-λ^4-diazabicyclo[2.2.2]octan-1-ium iodide (287)



To a solution of DABCO (**412**) (16.8 g, 150 mmol, 3.0 eq) in H_2O (20 mL) was added a solution of H_2NOSO_3H (**413**) (5.65 g, 50 mmol, 1.0 eq) in H_2O (10 mL) over 2 min. The reaction was heated to 90 °C and stirred for 1 h, then cooled to room temperature before the addition of K_2CO_3 (6.90 g, 50 mmol, 1.0 eq). The mixture was then stirred at room temperature for 10 min. The solvent was removed and the crude was washed with THF four times (4 x 100 mL) to remove the excess DABCO. The remaining residue was then redissolved in EtOH, the K_2CO_3 filtered off, the reaction cooled to –30 °C, and HI (57% by weight, 7.0 mL, 50 mmol, 1.0 eq) added dropwise. The reaction was then stirred at this temperature for 1 h before being warmed backup to room temperature. The precipitate

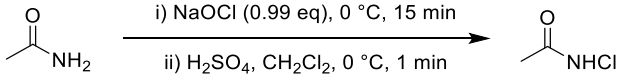
was then filtered and washed with cold EtOH to give the title compound (**287**) as a crystalline white solid (1.87 g, 10%).



^{1}H NMR (400 MHz, Deuterium Oxide) δ 3.6 – 3.5 (m, 6H), 3.3 – 3.2 (m, 6H).

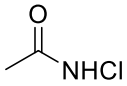
The data matches that reported in the literature.[94]

***N*-Chloroacetamide (347)**



346 **347, 17%**

To acetamide (**346**) (2.36 g, 40 mmol, 1.0 eq) at 0 °C was added aq. NaOCl (0.73 M, 5.7% active chlorine) (54.2 mL, 39.6 mmol, 0.99 eq). The reaction was stirred for 15 min, CH_2Cl_2 (30 mL) was then added, followed by the dropwise (1.0 mLmin^{-1}) addition of 2 M H_2SO_4 (24 mL, 48 mmol, 1.2 eq) with vigorous stirring. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 four times (4 x 30 mL). The organic layers were dried over $MgSO_4$, filtered and concentrated to give the title compound (**347**) as a white solid (620 mg, 17%).

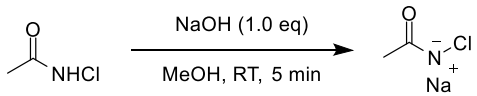


^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.1 (s, 3H).

IR ν_{max}/cm^{-1} (powder) 1677 (C=O)

The data matches that reported in the literature.[119]

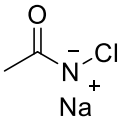
Sodium acetylchloroamide (348)



347 **348, 80%**

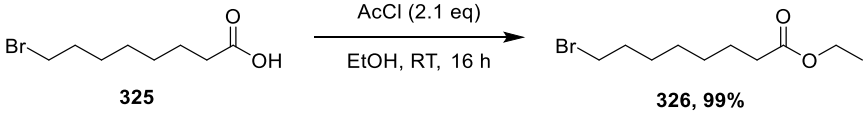
To a solution of NaOH (141 mg, 3.53 mmol, 1.0 eq) in MeOH (6 mL) was added *N*-chloroacetamide **347** (330 mg, 3.53, 1.0 eq) in MeOH (2 mL). The reaction was stirred for 5 min at room temperature, then evaporated to dryness under reduced pressure. The

solid residue was washed with Et_2O (20 mL), and the residue again evaporated to dryness to give the title compound as a white solid (327 mg, 80%).



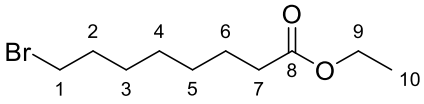
IR ν_{max}/cm^{-1} (powder) 1547 (C=O)

Ethyl 8-bromooctanoate (326)



325 **326, 99%**

To a flame dried flask containing a solution of 8-bromooctanoic acid (**325**) (5.57 g, 25.0 mmol, 1.0 eq) in anhydrous EtOH (35 mL) was added acetyl chloride (3.75 mL, 52.5 mmol, 2.1 eq) dropwise. The mixture was stirred at room temperature for 16 h, or until complete consumption of the starting material (monitored by thin-layer chromatography). The volatiles were removed under reduced pressure to give the title compound (**326**) as a colourless oil (6.19 g, 99%).

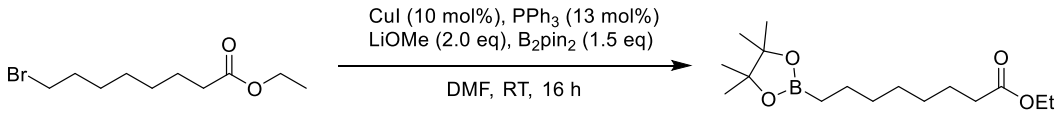


^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.11 (q, *J* = 7.1 Hz, 2H, C9-H), 3.39 (t, *J* = 6.8 Hz, 2H, C1-H), 2.28 (t, *J* = 7.5 Hz, 2H, C7-H), 1.84 (tt, *J* = 6.9, 6.8 Hz, 2H, C2-H), 1.67 – 1.56 (m, 2H, C6-H), 1.48 – 1.38 (m, 2H, C3-H), 1.35 – 1.30 (m, 4H, C4-H, C5-H), 1.24 (t, *J* = 7.1 Hz, 3H, C10-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.9 (C8), 60.3 (C9), 34.4 (C7), 34.0 (C1), 32.8 (C2), 29.0 (C5), 28.5 (C4), 28.1 (C3), 25.0 (C6), 14.4 (C10).

The data matches that reported in the literature.[120]

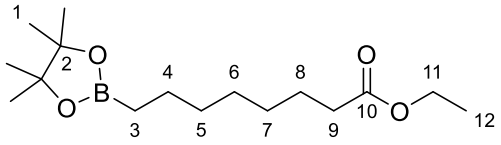
Ethyl 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octanoate (327)



326 **327, 70%**

To a flame dried flask containing CuI (467 mg, 2.45 mmol, 0.1 eq), PPh_3 (837 mg, 3.19 mmol, 0.13 eq), LiOMe (1.86 g, 49.0 mmol, 2.0 eq) and 4,4,4',4',5,5,5',5'-octamethyl-

2,2'-bi(1,3,2-dioxaborolane) (9.34 g, 36.8 mmol, 1.5 eq) was added anhydrous DMF (49 mL), followed by ethyl 8-bromooctanoate (**326**) (6.15 g, 24.5 mmol, 1.0 eq). The reaction was stirred at room temperature for 16 h. The mixture was then diluted with EtOAc (100 mL) and H_2O (100 mL) were added. The layers were separated, and the organic layer was extracted with H_2O five times (100 x 5). The organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crure boronic ester, which was purified using flash column chromatography (3% to 5%, EtOAc in pentane) to give the title compound (**327**) as a pale-yellow oil (5.12 g, 70%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.11 (q, *J* = 7.1 Hz, 2H, C11-H), 2.27 (t, *J* = 7.4 Hz, 2H, C9-H), 1.62 – 1.56 (m, 2H, C8-H), 1.38 (m, 2H, C4-H), 1.32 – 1.26 (m, 6H, C5-H, C6-H, C7-H), 1.25 (t, *J* = 7.1 Hz, 3H, C12-H), 1.23 (s, 12H, C1-H), 0.75 (t, *J* = 7.7 Hz, 2H, C3-H).

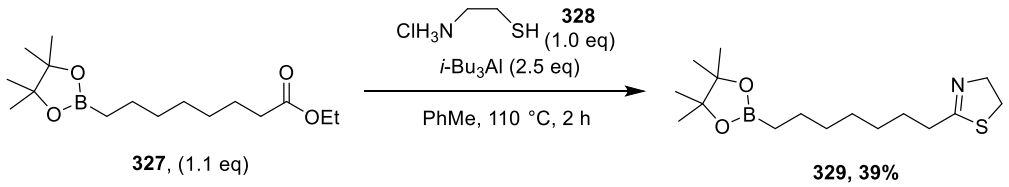
^{13}C NMR (101 MHz, Chloroform-*d*) δ 174.1 (C10), 83.0 (C2), 60.3 (C11), 34.5 (C9), 32.3 (C5), 29.2 (C6), 29.1 (C7), 25.1 (C8), 24.9 (C1), 24.0 (C4), 14.4 (C12). C3 not observed due to quadrupolar relaxation.

IR ν_{max}/cm^{-1} (neat) 1740, 1630, 1443, 909

HRMS (ESI+) calcd. 299.2315 for [$C_{16}H_{31}O_4B$+H], found 299.2319

R_f = 0.30 in 5% EtOAc in pentane

2-(7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)heptyl)-4,5-dihydrothiazole (329)

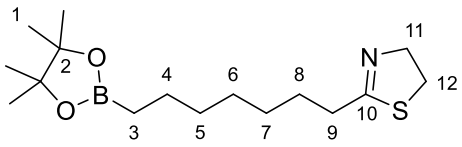


327, (1.1 eq)

329, 39%

To a flask fitted with a condenser under N_2 containing cysteamine·HCl (**328**) (1.09 g, 9.57 mmol, 1.0 eq) and toluene (38 mL) was added triisobutylaluminium (1 M in hexanes) (23.9 mL, 23.9 mmol, 2.5 eq) dropwise at room temperature (0.7 mLmin^{-1}). The mixture

was then refluxed for 30 min, after which ethyl 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octanoate (**327**) (3.14 g, 10.5 mmol, 1.1 eq) was added. The mixture was refluxed for a further 2 h or until complete consumption of starting material (monitored by TLC). Toluene (50 mL) was then added, and the reaction was allowed to cool to room temperature before being quenched via the dropwise addition of MeOH (7.5 mL) and then stirred for 5 min. Saturated aq. potassium sodium tartrate (Rochelle's salt, 40 mL) was then added, followed immediately by the addition of sat. aq. $NaHCO_3$ (40 mL), sat. aq. NaCl (40 mL) and EtOAc (100 mL). This mixture was then vigorously stirred for 10 minutes, after which the phases were separated, and the aqueous layer extracted three times with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude product which was purified using flash column chromatography (5% to 20%, EtOAc in pentane) to give the title compound (**329**) as a yellow oil (1.17 g, 39%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.20 (t, *J* = 8.3 Hz, 2H, C11-H), 3.27 (t, *J* = 8.3 Hz, 2H, C12-H), 2.50 (t, *J* = 7.4 Hz, 2H, C9-H), 1.62 (tt, *J* = 7.8, 4.7 Hz, 2H, C8-H), 1.43 – 1.26 (m, 8H, C4-H, C5-H, C6-H, C7-H), 1.23 (s, 12H, C1-H), 0.75 (t, *J* = 7.7 Hz, 2H, C3-H).

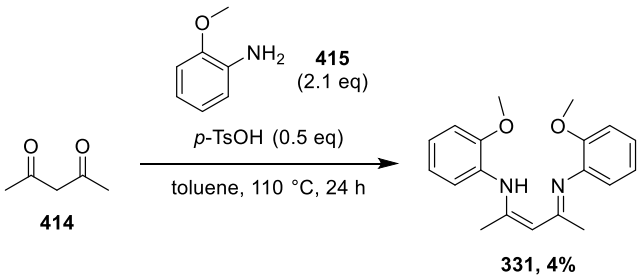
^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.8 (C10, observed by HMBC), 83.0 (C2), 64.2 (C11), 34.4 (C9), 33.8 (C12), 32.4 (C5), 29.2 (C7), 29.2 (C6), 27.7 (C8), 24.9 (C1), 24.1 (C4). C3 not observed due to quadrupolar relaxation.

IR ν_{max}/cm^{-1} (neat) 2957, 1370, 1309, 851, 776

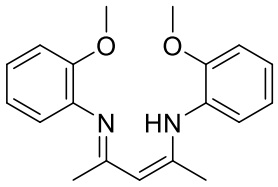
HRMS (ESI+) calcd. 312.2160 for [$C_{16}H_{30}O_2BNS$+H], found 312.2160

R_f = 0.20 in 10% EtOAc in pentane

2-Methoxy-*N*-((2*Z*,4*E*)-4-((2-methoxyphenyl)imino)pent-2-en-2-yl)aniline (331)



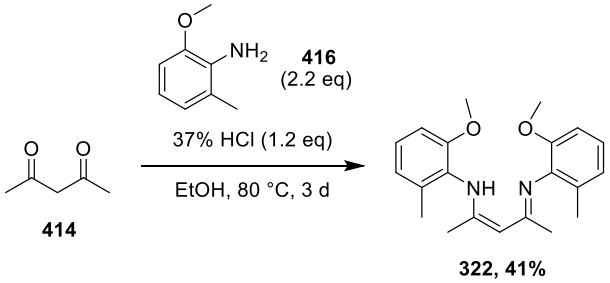
To solution of acetyl acetone (**414**) (3.06 mL, 30.0 mmol, 1.0 eq) and *p*-toluenesulfonic acid monohydate (2.85 g, 15.0 mmol, 0.5 eq) in anhydrous toluene (150 mL) was added *o*-anisidine (**415**) (7.12 mL, 63.0 mmol, 2.1 eq). The mixture was then heated under Dean-Stark conditions for 24 h. After cooling to room temperature, the reaction was diluted with Et_2O (100 mL), washed with sat. aq. NaCl three times (3 × 100 mL), dried over $MgSO_4$, filtered and concentrated. The crude mixture was then recrystalised from hot MeOH to give the title comound (**331**) as a white crystalline solid (400 mg, 4%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.70 (s, 1H), 7.03 – 6.97 (m, 4H), 6.93 – 6.84 (m, 4H), 4.93 (s, 1H), 3.78 (s, 6H), 1.98 (s, 6H).

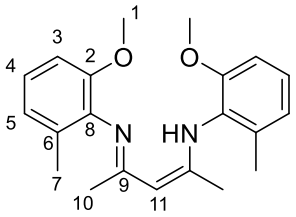
The data matches that reported in the literature.[99]

2-Methoxy-*N*-((2*Z*,4*E*)-4-((2-methoxy-6-methylphenyl)imino)pent-2-en-2-yl)-6-methylaniline (322)



To a flask containing acetyl acetone (**414**) (102 µL, 1.0 mmol, 1.0 eq) and 2-methoxy-6-methylaniline (**416**) (302 mg, 2.2 mmol, 2.2 eq) in ethanol (5.0 mL) was added dropwise 37% HCl (0.1 mL) at room temperature. A reflux condenser was attached, and the mixture was heated at 80 °C for three days. The reaction was allowed to cool to room temperature,

and then the volatiles were removed under reduced pressure to give a solid. Hexane (10 mL) was added, and the suspension was filtered using a Buchner funnel, washing three times with hexane (3 × 5 mL). These hydrochloride salts were dissolved in CH_2Cl_2 (25 mL), and washed with sat. aq. $NaHCO_3$ five times (5 x 10 mL). The aqueous layer was then extracted with CH_2Cl_2 twice (2 x 10 mL) after which the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resultant residue consisted of a mixture of the title compound and 2-methoxy-6-methylaniline; this was heated at 60 °C under reduced pressure to remove the 2-methoxy-6-methylaniline and the remaining solid was transferred to a flask and recrystallised from boiling isopropanol to give the title compound (**322**) as a white crystalline solid (140 mg, 41%).

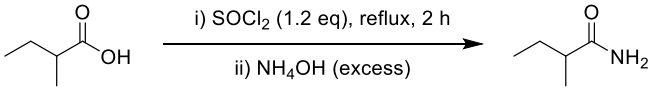


^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.10 (s, 1H, N-H), 6.98 (t, *J* = 7.9 Hz, 2H, C4-H), 6.81 (dd, *J* = 7.9, 1.3 Hz, 2H, C5-H), 6.74 (dd, *J* = 7.9, 1.3 Hz, 2H, C3-H), 4.92 (s, 1H, C11-H), 3.78 (s, 6H, C1-H), 2.19 (s, 6H, C7-H), 1.75 (s, 6H, C10-H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.98 (C9), 153.06 (C2), 134.00 (C8), 133.77 (C6), 124.62 (C4), 122.51 (C5), 109.41 (C3), 94.51 (C11), 55.87 (C1), 20.67 (C10), 18.34 (C7).

The data matches that reported in the literature.[99]

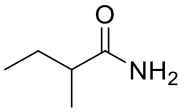
2-Methylbutanamide (330)



417 **330, 98%**

To a round bottom flask equipped with a long reflux condenser containing 2-methylbutanoic acid (**417**) (10.9 mL, 100 mmol, 1.0 eq) $SOCl_2$ (8.7 mL, 120 mmol, 1.2 eq) was added dropwise. The reaction was heated to reflux and left to stir for 2 h. The acyl chloride was then distilled out of the reaction mixture alongside a small amount of $SOCl_2$. This was then added to a second reaction vessel. NH_4OH was then added dropwise at 0 °C and the reaction stirred for 2 min. Et_2O (100 mL) and H_2O (100 mL) were then

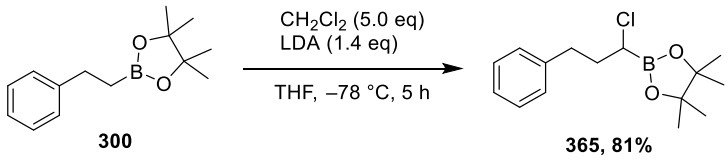
added, the layers separated and the aqueous layer extracted with Et_2O twelve times (12 x 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the title compound (**330**) as a white crystalline solid (9.9 g, 98% yield).



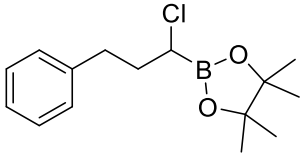
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.51 (d, *J* = 51.0 Hz, 2H), 2.30 – 2.09 (m, 1H), 1.71 – 1.58 (m, 1H), 1.54 – 1.36 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H).

The data matches that reported in the literature.[121]

2-(1-Chloro-3-phenylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (365)



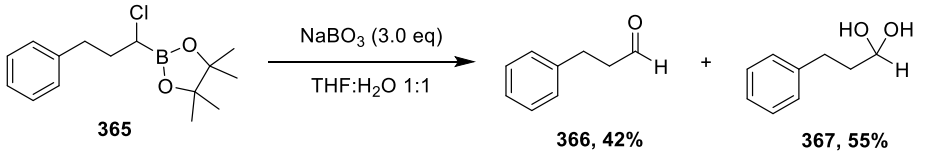
To a flask containing 4,4,5,5-tetramethyl-2-phenethyl-1,3,2-dioxaborolane (**300**) (232 mg, 1.0 mmol, 1.0 eq) and anhydrous CH_2Cl_2 (319 µL, 5.0 mmol, 5.0 eq) in anhydrous THF (8.0 mL) was added freshly prepared lithium diisopropylamine (1 M solution, prepared using 283 µL *i*-Pr_2NH, 1.25 mL *n*-BuLi (1.6 M in hexanes) and 467 µL THF) (1.4 mL, 1.4 mmol, 1.4 eq) dropwise at – 78 °C. The mixture was stirred at this temperature for 5 h, and then allowed to warm to room temperature. Sat. aq. NH_4Cl (20 mL) was added and the layers were separated. The aqueous layer was extracted three times with EtOAc (3 × 20 mL), dried over $MgSO_4$, filtered and concentrated to give the title compound (**365**) as a colourless oil (229 mg, 81%).



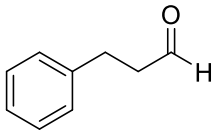
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.25 (m, 3H), 7.22 – 7.18 (m, 2H), 3.41 (t, *J* = 7.4 Hz, 1H), 2.84 (dt, *J* = 14.3, 7.4 Hz, 1H), 2.75 (dt, *J* = 14.3, 7.4 Hz, 1H), 2.15 – 2.08 (m, 2H), 1.28 (s, 12H).

The data matches that reported in the literature.[122]

3-Phenylpropanal (366)



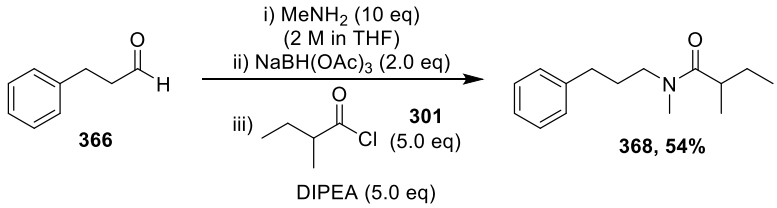
To a solution of 2-(1-Chloro-3-phenylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**365**) (28.1 mg, 0.1 mmol, 1.0 eq) in THF (0.1 mL) and H_2O (0.1 mL) was added $NaBO_3$•$4H_2O$ (46.2 mg, 0.3 mmol, 3.0 eq) at room temperature. The mixture was stirred for 2 h, and then DCE (2 mL) was added. The reaction mixture was filtered through a phase-separating frit and the organic layer was concentrated under reduced pressure to give the product as a 4:5 ratio of the aldehyde and its corresponding hydrate (130 mg, 97%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.83 (s, 1H), 7.34 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.79 (t, *J* = 7.4 Hz, 2H).

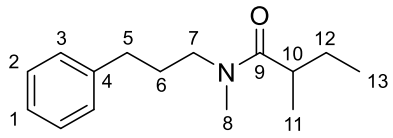
The data matches that reported in the literature.[123]

***N*,2-Dimethyl-*N*-(3-phenylpropyl)butanamide (368)**



To a solution of $MeNH_2$ (2 M in THF) (0.5 mL, 1.0 mmol, 10 eq) was added 3-phenylpropanal (**366**) (13.1 µL, 0.1 mmol, 1.0 eq) at 0 °C. The reaction was warmed to room temperature and stirred for 2 h. $NaBH(OAc)_3$ (42.4 mg, 0.2 mmol, 2.0 eq) in MeOH (0.4 mL) was then added and the reaction was then stirred at room temperature for a further 2 h. The solvent was then removed under reduced pressure under inert atmosphere, and THF (0.5 mL) was then added, followed by the addition of diisopropylethylamine (81.6 µL, 0.5 mmol, 5.0 eq) and 2-methylbutanoyl chloride (**301**) (62.0 µL, 0.5 mmol, 5.0 eq). The reaction was stirred for 1.5 h, filtered through silica, and then concentrated

under reduced pressure to give the crude amide which was purified using flash column chromatography (10% to 40%, EtOAc in pentane) to give the title compound (**368**) as a pale-yellow oil (12.6 mg, 54%).



This compound exists as an approximately 1:1 mixture of rotamers at room temperature – non-integer proton integrations reflect this fact.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.29 (m, 2H, C2-H), 7.27 – 7.17 (m, 3H, C1-H, C3-H), 3.53 (dt, *J* = 13.3, 7.5 Hz, 0.5H, C7-H), 3.44 – 3.36 (m, 0.5H, C7-H), 3.36 – 3.27 (m, 1H, C7-H), 3.03 (s, 1.5H, C8-H), 2.95 (s, 1.5H, C8-H), 2.64 (m, 2.5H, C5-H, C10-H), 2.50 – 2.42 (m, 0.5H, C10-H), 1.94 (p, *J* = 7.8 Hz, 1H, C6-H), 1.87 (p, *J* = 7.8 Hz, 1H, C6-H), 1.78 – 1.63 (m, 1H, C12-H), 1.49 – 1.35 (m, 1H, C12-H), 1.12 (d, *J* = 6.8 Hz, 1.5H, C11-H), 1.08 (d, *J* = 6.8 Hz, 1.5H, C11-H), 0.91 (t, *J* = 7.4 Hz, 1.5H, C13-H), 0.85 (t, *J* = 7.4 Hz, 1H, C13-H).

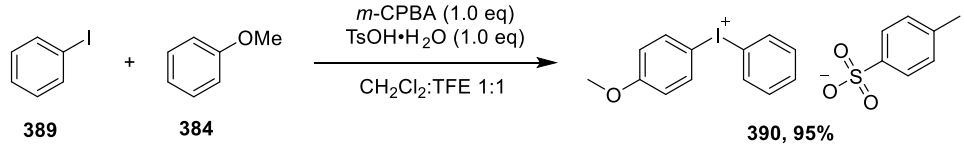
^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.70 (C9), 176.44 (C9), 141.84 (C4), 140.88 (C4), 128.58 (C1), 128.39 (C1), 128.32 (C3), 128.25 (C3), 126.24 (C2), 125.86 (C2), 49.20 (C7), 47.69 (C7), 37.45 (C10), 37.13 (C10), 35.34 (C8), 33.70 (C8), 33.24 (C5), 32.92 (C5), 30.48 (C6), 29.03 (C6), 27.35 (C12), 27.09 (C12), 17.64 (C11), 17.15 (C11), 12.06, 12.04.

IR ν_{max}/cm^{-1} (neat) 2977, 1673, 1443, 788

HRMS (ESI+) calcd. 234.1852 for [$C_{15}H_{23}ON$+Na], found 234.1855

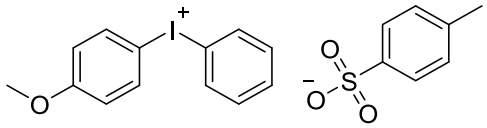
R_f = 0.45 in 30% EtOAc in pentane.

(4-Methoxyphenyl)(phenyl)iodonium 4-methylbenzenesulfonate (390)



To a flask containing iodobenzene (**389**) (5.57 mL, 50 mmol, 1.0 eq), methoxybenzene (**384**) (5.43mL, 50 mmol, 1.0 eq) and *m*-CPBA (66% active oxidant) (13.1 g, 50 mmol, 1.0 eq) in CH_2Cl_2 (100 mL) and 2,2,2-trifluoroethanol (100 mL) was added TsOH•H_2O

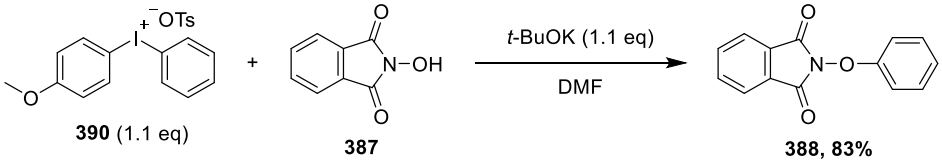
(9.51 g, 50 mmol, 1.0 eq) as a single portion. The reaction was stirred at room temperature for 16 h. The solvent was evaporated under reduced pressure, and Et_2O (200 mL) was added. This mixture was stirred for 10 min to precipitate the product, which was collected by filtration. The solid was then dried under reduced pressure to give the title compound (**390**) as a white solid (22.8 g, 95%).



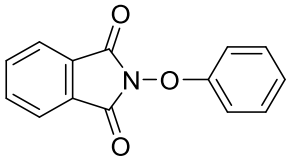
^{1}H NMR (400 MHz, Methanol-*d*$_4$) δ 8.14 – 8.05 (m, 4H), 7.72 – 7.63 (m, 3H), 7.54 – 7.47 (m, 2H), 7.25 – 7.19 (m, 2H), 7.08 – 7.02 (m, 2H), 3.84 (s, 3H), 2.36 (s, 3H).

The data matches that reported in the literature.[124]

2-Phenoxyisoindoline-1,3-dione (388)



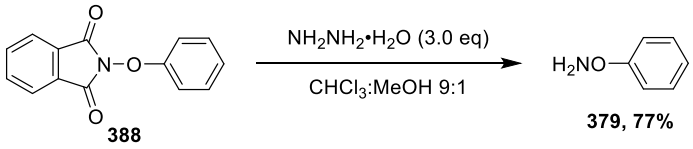
To a solution of *N*-hydroxyphthalamide (**387**) (5.95 g, 36.5 mmol, 1.0 eq) in DMF (146 mL) at room temperature was added *t*-BuOK (4.5 g, 40.1 mmol, 1.1 eq). The mixture was stirred at room temperature for 10 minutes before the addition of (4-methoxyphenyl)(phenyl)iodonium 4-methylbenzenesulfonate (**390**) (19.3 g, 40.1 mmol, 1.1 eq). The mixture was stirred at 60 °C for 1 h, then cooled to room temperature. EtOAc (500 mL) and H_2O (100 mL) were added, and the layers were separated. The orgnanic layer was washed five times with H_2O (5 x 100 mL), then washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crudeproduct which was purified using flash column chromatography (10% to 100%, EtOAc in pentane) to give the title compound (**388**) as an off-white solid (7.21 g, 83%).



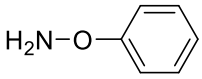
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.86 (m, 2H), 7.86 – 7.76 (m, 2H), 7.38 – 7.29 (m, 2H), 7.19 – 7.09 (m, 3H).

The data matches that reported in the literature.[124]

_O_-Phenylhydroxylamine (379)



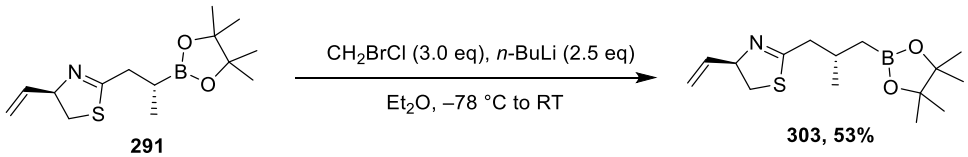
To a solution of 2-phenoxyisoindoline-1,3-dione (**388**) (7.1 g, 29.7 mmol, 1.0 eq) in $CHCl_3$ (266 mL) and MeOH (29.5 mL) was added hydrazine monohydrate (4.35 mL, 89.1 mmol, 3.0 eq) dropwise (0.1 $mLmin^{-1}$). The solution was stirred at room temperature for 16 h and then filtered through celite, and washed with 9:1 $CHCl_3$:MeOH (200 mL). The solution was then concentrated under reduced pressure to give the crude product which was purified using flash column chromatography (10 – 30% EtOAc in pentane) to give the title compound (**379**) as an orange oil (2.66 g, 77% yield). (Note: $PhONH_2$ is unstable to silica so should be columned as quickly as possible.)



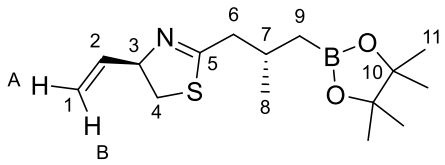
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.25 (m, 2H), 7.19 – 7.11 (m, 2H), 7.01 – 6.92 (m, 1H), 5.83 (br s, 2H).

The data matches that reported in the literature.[125]

(*R*)-2-((*S*)-2-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-4-vinyl-4,5-dihydrothiazole (303)



To a solution of (*R*)-2-((*R*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-4-vinyl-4,5-dihydrothiazole (**291**) (140 mg, 0.50 mmol, 1.0 eq) and CH_2BrCl (0.10 mL, 1.50 mmol, 3.0 eq) in anhydrous Et_2O (2.0 mL) at −78 °C was added *n*-BuLi (1.6 M in hexanes) (0.78 mL, 1.25 mmol, 2.5 eq) dropwise (0.03 $mLmin^{-1}$). The reaction was stirred at −78 °C or 20 min, then warmed to room temperature and stirred for a further 1 h. The reaction was then filtered through a pad of silica and the solvent was removed to give the crude product which was purified by flash column chromatography (10 – 40% EtOAc in pentane) to give the title compound (**303**) as a colourless oil (81 mg, 53%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.94 (ddd, *J* = 17.1, 10.3, 6.8 Hz, 1H, C2-H), 5.28 (dt, *J* = 17.1, 1.3 Hz, 1H, C1-HB), 5.15 (dt, *J* = 10.3, 1.3 Hz, 1H, C1-HA), 4.97 – 4.84 (m, 1H, C3-H), 3.42 (dd, *J* = 10.9, 8.7 Hz, 1H, C4-H), 3.05 (ddd, *J* = 10.9, 8.5, 1.3 Hz, 1H, C4-H), 2.53 (dd, *J* = 14.0, 6.0 Hz, 1H, C6-H), 2.41 (dd, *J* = 14.0, 8.5 Hz, 1H, C6-H), 2.24 – 2.07 (m, 1H, C7-H), 1.24 (s, 12H, C11-H), 0.99 (dd, *J* = 6.6, 1.3 Hz, 3H, C8-H), 0.93 (dd, *J* = 15.6, 5.4 Hz, 1H, C9-H), 0.76 (dd, *J* = 15.6, 8.7 Hz, 1H, C9-H).

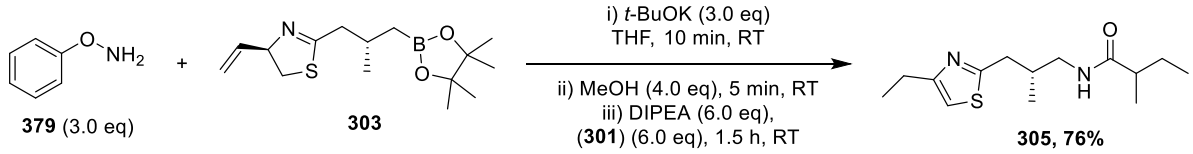
^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.3 (C5), 137.6 (C2), 116.2 (C1), 83.2 (C10), 78.7 (C3), 44.0 (C6), 38.8 (C4), 29.1 (C7), 25.0 (C11), 24.9 (C11), 21.9 (C8). C9 not observed due to quadrupolar coupling.

IR ν_{max}/cm^{-1} (neat) 2973, 2924, 1367, 1320, 917, 877

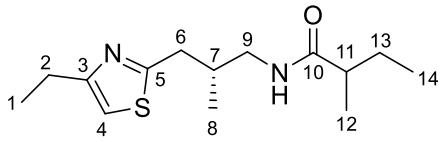
HRMS (ESI+) calcd. 295.1777 for [$C_{15}H_{26}NO_2BS$+H], found 295.1779.

R_f = 0.50 in 20% EtOAc in pentane

***N*-((*R*)-3-(4-Ethylthiazol-2-yl)-2-methylpropyl)-2-methylbutanamide (305)**



To a solution of (*R*)-2-((*S*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)-4-vinyl-4,5-dihydrothiazole (**303**) (14.8 mg, 0.05 mmol, 1.0 eq) and *O*-phenylhydroxylamine (**379**) (16.4 mg, 0.15 mmol, 3.0 eq) in anhydrous THF (0.3 mL) was added *t*-BuOK (1 M in THF) (0.15 mL, 0.15 mmol, 3.0 eq). The reaction was stirred at room temperature for 10 min, after which MeOH (8.1 µL, 0.2 mmol, 4.0 eq) was added. The reaction was then stirred for a further 5 minutes before the addition of diisopropylethylamine (48.9 µL, 0.3 mmol, 6.0 eq) and 2-methylbutanoyl chloride (**301**) (37.2 µL, 0.3 mmol, 6.0 eq). After being stirred at room temperature for 1.5 h, the reaction was filtered through a pad of silica and the solvent was removed to give the crude product. This was purified using flash column chromatography (50 – 100% EtOAc in pentane) to give the title compound (**305**) as a colourless oil (10.2 mg, 76%).



^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.74 (s, 1H, C4-H), 6.22 (s, 1H, N-H), 3.26 (ddd, *J* = 13.5, 5.9, 5.9 Hz, 1H, C9-H), 3.16 (ddd, *J* = 13.5, 7.1, 5.9 Hz, 1H, C9-H), 2.94 (dd, *J* = 6.6, 2.8 Hz, 2H, C6-H), 2.77 (qd, *J* = 7.6, 1.1 Hz, 2H, C2-H), 2.25 – 2.15 (m, 1H, C7-H), 2.07 (dq, *J* = 8.1, 6.8 Hz, 1H, C11-H), 1.71 – 1.58 (m, 1H, C13-H), 1.47 – 1.35 (m, 1H, C13-H), 1.28 (t, *J* = 7.6 Hz, 3H, C1-H), 1.11 (d, *J* = 7.1 Hz, 3H, C12-H), 0.99 (d, *J* = 6.8 Hz, 3H), C8-H, 0.88 (t, *J* = 7.4 Hz, 3H, C14-H).

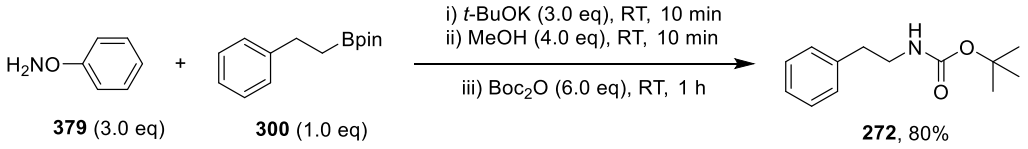
^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.7 (C10), 168.6 (C5), 158.9 (C3), 111.7 (C4), 44.5 (C9), 43.6 (C11), 38.2 (C6), 34.6 (C7), 27.5 (C13), 24.9 (C2), 18.2 (C8), 17.7 (C12), 13.5 (C1), 12.1 (C14).

IR ν_{max}/cm^{-1} (neat) 2973, 2924, 1540, 1367, 917,

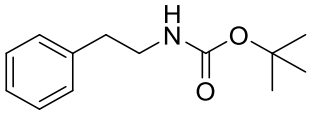
HRMS (ESI+) calcd. 269.1682 for [$C_{14}H_{24}N_2OS$+H], found 269.1679.

R_f = 0.60 in 100% EtOAc

***Tert*-butyl phenethylcarbamate (272)**



This reaction was performed following general procedure **4** using $PhONH_2$ (**379**) (32.7 mg, 0.3 mmol, 3.0 eq), 4,4,5,5-tetramethyl-2-phenethyl-1,3,2-dioxaborolane (**300**) (23.1 mg, 0.1 mmol, 1.0 eq), THF (0.3 mL), *t*-BuOK (0.3 mL), MeOH (16 µL, 0.4 mmol, 0.4 eq) and Boc_2O (138 µL, 0.6 mmol, 6.0 eq). The crude product was purified using flash column chromatography (10% EtOAc in pentane) to give the title compound (**272**) as a colourless oil (17.7 mg, 80%).

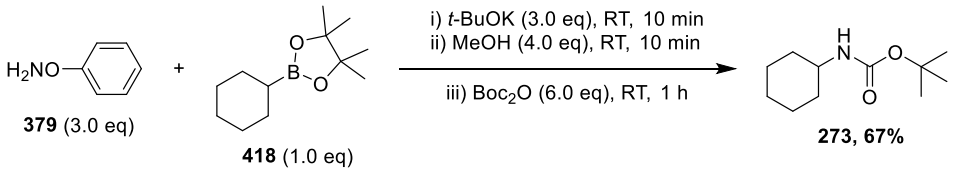


^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (dd, *J* = 8.1, 6.6 Hz, 2H), 7.26 – 7.21 (m, 3H), 4.56 (s, 1H), 3.46 (td, *J* = 7.1, 6.8 Hz, 2H), 2.81 (t, *J* = 7.1 Hz, 2H), 1.47 (s, 9H).

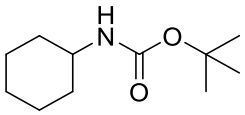
^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.0, 139.1, 128.9, 128.7, 126.5, 79.3, 41.9, 36.3, 28.5.

The data matches that reported in the literature.[126]

***Tert*-butyl cyclohexylcarbamate (273)**



This reaction was performed following general procedure **4** using $PhONH_2$ (**379**) (32.7 mg, 0.3 mmol, 3.0 eq), 2-cyclohexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**418**) (21.0 mg, 0.1 mmol, 1.0 eq), THF (0.3 mL), *t*-BuOK (0.3 mL), MeOH (16 µL, 0.4 mmol, 0.4 eq) and Boc_2O (138 µL, 0.6 mmol, 6.0 eq). The crude product was purified using flash column chromatography (5% EtOAc in pentane) to give the title compound (**273**) as a colourless oil (12.9 mg, 67%).

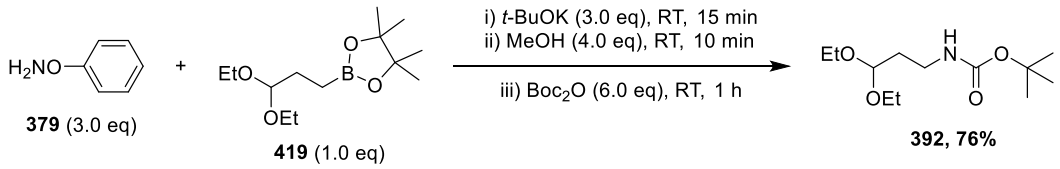


^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.44 (s, 1H), 3.43 (t, *J* = 10.3 Hz, 1H), 1.90 (m, 2H), 1.71 – 1.67 (m, 2H), 1.55 (m, 1H), 1.42 (s, 8H), 1.32 – 1.26 (m, 2H), 1.21 – 1.07 (m, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.3, 79.0, 49.5, 33.6, 28.5, 25.6, 25.0.

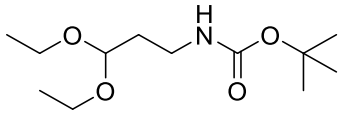
The data matches that reported in the literature.[126]

***Tert*-butyl (3,3-diethoxypropyl)carbamate (392)**



This reaction was performed following general procedure **4** using $PhONH_2$ (**379**) (32.7 mg, 0.3 mmol, 3.0 eq), 2-(3,3-diethoxypropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**419**) (25.8 mg, 0.1 mmol, 1.0 eq), THF (0.3 mL), *t*-BuOK (0.3 mL), MeOH (16 µL, 0.4 mmol, 0.4 eq) and Boc_2O (138 µL, 0.6 mmol, 6.0 eq). The crude product was purified

using flash column chromatography (10% EtOAc in pentane) to give the title compound (**392**) as a colourless oil (18.7 mg, 76%).

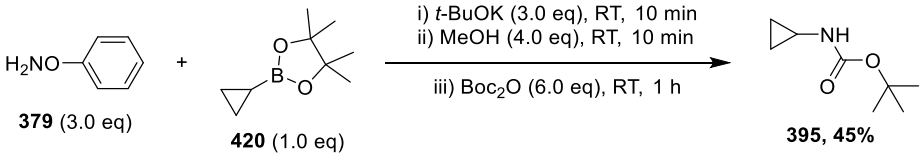


^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.9 (s, 1H), 4.5 (t, *J* = 5.4 Hz, 1H), 3.6 (dq, *J* = 9.3, 7.0 Hz, 2H), 3.5 (dq, *J* = 9.3, 7.0 Hz, 2H), 3.2 (q, *J* = 6.6 Hz, 2H), 1.8 (td, *J* = 6.6, 5.4 Hz, 2H), 1.4 (s, 9H), 1.2 (t, *J* = 7.0 Hz, 6H).

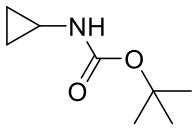
^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.0, 102.1, 79.0, 61.7, 36.8, 33.5, 28.5, 15.4.

The data matches that reported in the literature.[127]

***Tert*-butyl cyclopropylcarbamate (395)**



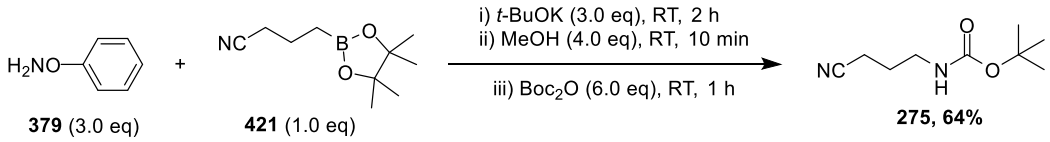
This reaction was performed following general procedure **4** using $PhONH_2$ (**379**) (32.7 mg, 0.3 mmol, 3.0 eq), 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**420**) (16.8 mg, 0.1 mmol, 1.0 eq), THF (0.3 mL), *t*-BuOK (0.3 mL), MeOH (16 µL, 0.4 mmol, 0.4 eq) and Boc_2O (138 µL, 0.6 mmol, 6.0 eq). The crude product was purified using flash column chromatography (10% EtOAc in pentane) to give the title compound (**395**) as a colourless oil (7.0 mg, 45%).



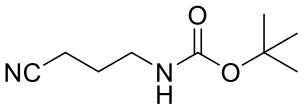
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.71 (s, 1H), 2.58 – 2.45 (m, 1H), 1.44 (s, 10H), 0.71 – 0.66 (m, 3H), 0.52 – 0.42 (m, 2H).

The data matches that reported in the literature.[128]

***Tert*-butyl (3-cyanopropyl)carbamate (275)**



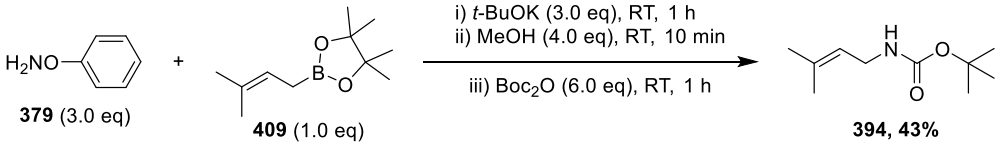
This reaction was performed following general procedure **4** using $PhONH_2$ (**379**) (32.7 mg, 0.3 mmol, 3.0 eq), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanenitrile (**421**) (21.4 mg, 0.1 mmol, 1.0 eq), THF (0.3 mL), *t*-BuOK (0.3 mL), MeOH (16 µL, 0.4 mmol, 0.4 eq) and Boc_2O (138 µL, 0.6 mmol, 6.0 eq). The crude product was purified using flash column chromatography (20% EtOAc in pentane) to give the title compound (**275**) as a colourless oil (11.8 mg, 64%).



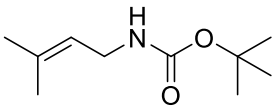
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.69 (s, 1H), 3.24 (dt, *J* = 6.5, 6.3 Hz, 2H), 2.39 (t, *J* = 7.2 Hz, 2H), 1.85 (h, *J* = 6.9 Hz, 2H), 1.44 (s, 9H).

The data matches that reported in the literature.[126]

***Tert*-butyl (3-methylbut-2-en-1-yl)carbamate (394)**



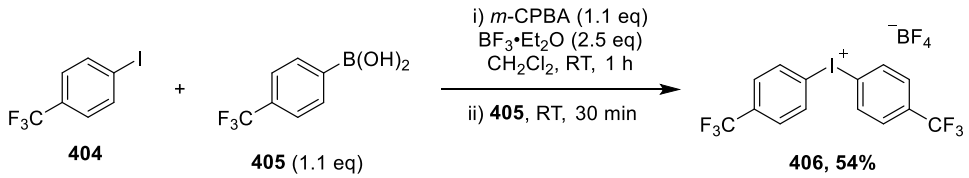
This reaction was performed following general procedure **4** using $PhONH_2$ (**379**) (32.7 mg, 0.3 mmol, 3.0 eq), 4,4,5,5-tetramethyl-2-(3-methylbut-2-en-1-yl)-1,3,2-dioxaborolane (**409**) (19.6 mg, 0.1 mmol, 1.0 eq), THF (0.3 mL), *t*-BuOK (0.3 mL), MeOH (16 µL, 0.4 mmol, 0.4 eq) and Boc_2O (138 µL, 0.6 mmol, 6.0 eq). The crude product was purified using flash column chromatography (20% EtOAc in pentane) to give the title compound (**394**) as a colourless oil (7.9 mg, 43%).



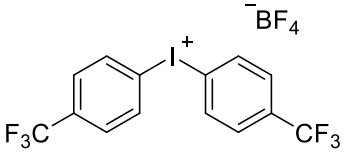
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.18 (thept, *J* = 6.8, 1.5 Hz, 1H), 4.42 (s, 1H), 3.69 (t, *J* = 6.8 Hz, 2H), 1.70 (d, *J* = 1.5 Hz, 3H), 1.65 (d, *J* = 1.5 Hz, 3H), 1.44 (s, 9H).

The data matches that reported in the literature.[129]

***Bis*(4-(trifluoromethyl)phenyl)iodonium tetrafluoroborate (406)**



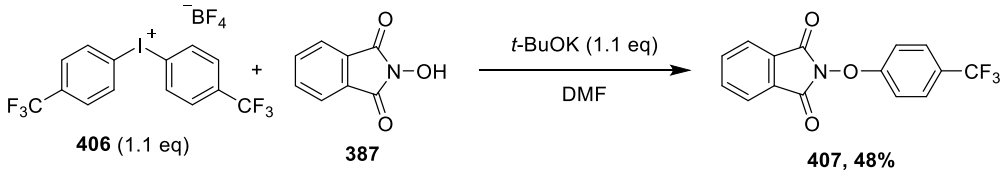
To a solution of *m*-CPBA (66% active oxidant) (4.35 g, 16.7 mmol, 1.1 eq) in CH_2Cl_2 (56 mL) was added 1-iodo-4-(trifluoromethyl)benzene (**404**) (2.20 mL, 15 mmol, 1.0 eq), followed by the dropwise addition of boron trifluoride diethyletherate (4.61 mL, 37.5 mmol, 2.5 eq). The reaction was stirred at room temperature for one hour, then cooled to 0 °C before the addition of (4-(trifluoromethyl)phenyl)boronic acid (**405)** (3.16 g, 16.7 mmol, 1.1 eq). The reaction was stirred at room temperature for 30 min, then filtered through 33 g of silica, washed first with CH_2Cl_2 (300 mL) to remove impurities, then with 5% MeOH in CH_2Cl_2 (600 mL) to elute the product. This latter solution was concentrated under reduced pressure and Et_2O (50 mL) was added to induce precipitation of the product. This solution was stirred for 15 min at room temperature, then Et_2O was decanted and the residue washed two times with Et_2O (2 x 50 mL), and then dried under reduce pressure to give the title compound (**406**) as an off-white solid (4.05 g, 54%).



^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 8.6 Hz, 1H).

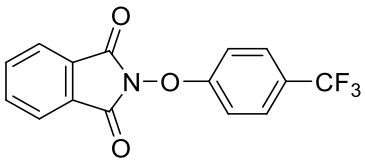
The data matches that reported in the literature.[130]

2-(4-(Trifluoromethyl)phenoxy)isoindoline-1,3-dione (407)



To a solution of *N*-hydroxyphthalamide (**387**) (1.03 g, 6.31 mmol, 1.0 eq) in DMF (25 mL) at room temperature was added *t*-BuOK (780 mg, 6.95 mmol, 1.1 eq). The mixture was stirred at room temperature for 10 minutes before the addition of bis(4-(trifluoromethyl)phenyl)iodonium tetrafluoroborate (**406**) (3.50 g, 6.95 mmol, 1.1 eq). The mixture was stirred at 60 °C for 1 h, then cooled to room temperature. EtOAc (150

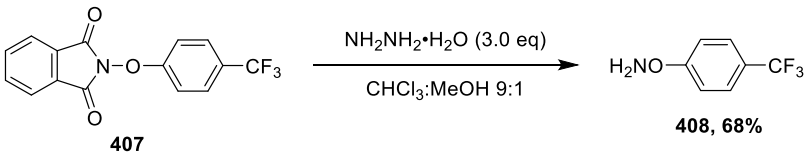
mL) and H_2O (30 mL) were added, and the layers were separated. The organic layer was washed five times with H_2O (5 x 300 mL), then washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product. This was purified using flash column chromatography (10% to 20%, EtOAc in pentane) to give the title compound (**407**) as an off-white solid (1.25 g, 48%).



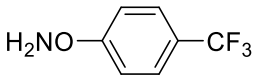
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 7.89 (m, 2H), 7.87 – 7.81 (m, 2H), 7.63 – 7.56 (m, 2H), 7.27 – 7.20 (m, 2H).

The data matches that reported in the literature.[131]

***O*-(4-(Trifluoromethyl)phenyl)hydroxylamine (408)**



To a solution of 2-(4-(trifluoromethyl)phenoxy)isoindoline-1,3-dione (**407**) (1.1 g, 3.58 mmol, 1.0 eq) in $CHCl_3$ (32.2 mL) and MeOH (3.60 mL) was added hydrazine monohydrate (524 µL, 10.7 mmol, 3.0 eq) dropwise (0.1 $mLmin^{-1}$). The solution was stirred at room temperature for 16 h and then filtered through celite, washing with 9:1 $CHCl_3$:MeOH (50 mL). The solution was then concentrated under reduced pressure to give the crude product which was purified using flash column chromatography (10 – 30% EtOAc in pentane) to give the product (**408**) as a colourless oil (432 mg, 68% yield). (Note: **408** is extremely unstable to silica so should be columned as quickly as possible.)



^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.50 (m, 2H), 7.25 – 7.20 (m, 2H), 5.93 (s, 2H).

The data matches that reported in the literature.[132]

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