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Copper-Catalysed Cross-Couplings: Applications in Target Synthesis and Multicomponent Reactions

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Contents

Abstract

Copper-catalysed reactions have proved to be extremely valuable, especially for the formation of C-C bonds in organic chemistry. This has been enhanced by the recent advances in methods that replace less abundant, toxic metals with copper for the efficient construction of useful building blocks for synthesis.

Here we present the use of copper catalysis in two very different projects. The first utilises copper in a 1,4-conjugate addition to a chloroenone, to form an all carbon quaternary centre. This allows access to cascade cyclisation substrates that on exposure to samarium diiodide result in an efficient cascade reaction to form the tricyclic core of pleuromutilin analogues.

The second project details the development of an enantioselective three-component coupling reaction between allenes, diboranes, and imines catalysed by copper. This procedure assembles homoallylic amines with adjacent stereocentres with high enantiocontrol, and exploits a commercially available chiral ligand. The approach has been extended to electrophiles other than imines, with preliminary work on an enantioselective borylcyanation of allenes being reported.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Part of this work has been published in peer reviewed journals:

- "Copper-Catalyzed Double Additions and Radical Cyclization Cascades in the Re-Engineering of the Antibacterial Pleuromutilin"
  Rebecca E. Ruscoe, Neal J. Fazakerley, Huanming Huang, Sabine Flitsch and David J. Procter, *Chem. Eur. J.*, 2016, **22**, 116.

- "Enantioselective Generation of Adjacent Stereocentres in a Copper-Catalyzed Three-Component Coupling of Imines, Allenes, and Diboranes"
  Kay Yeung, Rebecca E. Ruscoe, James Rae, Alexander P. Pulis, and David J. Procter, *Angew. Chem. Int. Ed.*, 2016, **55**, 11912.

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I would like to thank my entire family for your prolonged support and encouragement, I love you all. Finally, Jack, without you I would not be the person I am today and this thesis would not have been possible without your endless support and love.

Thank You!

List of Abbreviations

Ac	acyl
AIBN	2,2′-azo*bis*(2-methylpropionitrile)
Ar	aryl
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br.	broad (NMR)
Bu	butyl
Bz	benzoyl
Comins' Reagent	*N*-(5-chloro-2-pyridyl)*bis*(trifluoromethanesulfonimide)
Cy	cyclohexyl
d	doublet (NMR)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	di*iso*butylaluminium hydride
DIPEA	*N*,*N*-di*iso*propylethylamine
DMAP	*N*,*N*-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dr	diastereoisomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv.	equivalent
ES	electrospray ionisation
Et	ethyl

GGPP	geranylgeranyl diphosphate
h	hours
HMDS	hexamethyldisilazane
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
ICy	1,3-dicyclohexylimidazolium
Im.	imidazole
IMes	1,3-*bis*(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-*bis*(2,6-diisopropylphenyl)imidazolium
*i*Pr	isopropyl
IR	infrared
LDA	lithium di-*iso*-propylamine
m	multiplet (NMR)
m-	*meta*-
m/z	mass/charge ratio (MS)
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
min	minutes
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MS	mass spectrum
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance

nOe	nuclear Overhauser effect
o-	*ortho*-
p-	*para*-
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
pin	pinacol
Piv	pivaloyl
PMP	*para*-methoxyphenyl
ppm	parts per million (NMR)
PTC	peptidyl transfer centre
PTSA	*para*-toluenesulfonic acid
py.	pyridine
q	quartet (NMR)
quin	quintet (NMR)
RCM	ring closing metathesis
*r*RNA	ribosomal ribose nucleic acid
rt	room temperature
s	singlet (NMR)
SIMes	1,3-*bis*(2,4,6-trimethylphenyl)imidazolinium
t	triplet (NMR)
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicat
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
Tf	trifluoromethanesulfonate

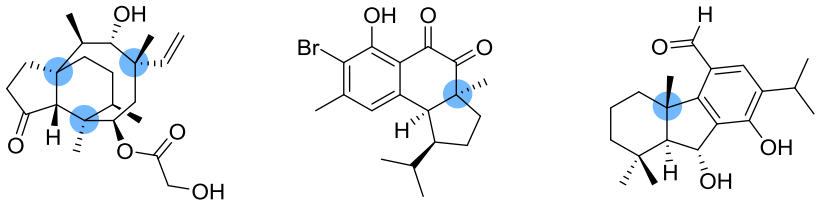
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl
*t*RNA	transfer ribose nucleic acid
Ts	*para*-toluenesulfonyl
WHO	World Health Organisation

Part 1

Copper-Catalysed Double Additions and Radical Cyclisation Cascades in the Re-Engineering of the Antibacterial Pleuromutilin

1.1 Copper-Catalysed Conjugate Additions to Enones

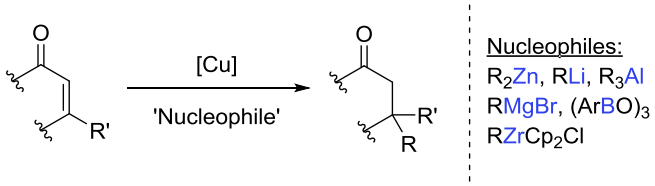
Natural products and their derivatives are an extremely important resource from which potential drug candidates may be discovered and developed. A challenging to build, structural feature that can often be found in such compounds is the all-carbon quaternary centre (Figure 1).[1]



Pleuromutilin (antimicrobial) **Hamigeran B (antiviral)** **Standishinal (anticancer)**

Figure 1 Examples of natural products with all-carbon quaternary centres.

In order to synthesise these complex molecules, it is imperative that methods to install the quaternary centres are developed; a well-known approach is the copper-catalysed 1,4-conjugate addition to enones (Scheme 1). This transformation is a classical and extremely useful approach to forming C-C bonds in organic chemistry which has been investigated extensively, with recent work focusing on asymmetric conjugate additions (ACA).[2]



Scheme 1 General scheme for the copper-catalysed 1,4-addition to enones.

These reactions generally involve the transmetallation of an organometallic species to copper, followed by an oxidative addition to the 4-position of the enone and reductive elimination to form the new C-C bond. There are multiple reagents that can be used for the addition; organolithiums,[2] alkyl aluminiums,[2–6] alkylzirconiums,[1] dialkyl zincs,[2–4,7] Grignards,[2–4,8,9] and more recently organoborons.[10]

1.2 Antibiotics and Resistance

The rapid growth of the population in the Western world during the 19th century and advances in transportation caused an acceleration in the spread of infectious diseases. This necessitated the exploration of compounds for possible treatments. Finally, in 1911 an antimicrobial compound fit for human use emerged from the laboratories of Ehrlich, which was swiftly followed by the accidental discovery of Penicillin by Fleming in 1928.[11]

The initial excitement surrounding the discovery of antibiotics for the treatment of infections that would previously have caused fatalities was soon met with an anti-climax when antibiotic resistance emerged. To understand how bacteria have become resistant to these compounds, the mode of action of antibiotics must be understood. This is key when designing and searching for new antibiotics.

Antibiotics bring about their desired effects in many ways. For example, compounds such as the Penicillins interfere with the cell membrane of the bacteria,[12,13] whereas classes like the Pleuromutilins interact with the bacteria at the ribosomal level.[14–16] Bacteria can develop resistance to antibiotics over time, by gradually evolving mechanisms in which the antibiotic target is modified or they can gain a functional advantage that reduces the effects of the antibiotic.[17]

There are many classes of antibiotics that have been discovered in the last 100 years. Each class contains compounds that are related by their structure, mechanism and usually the bacteria they target. Generally, classes have been created from generations of modifications to the parent compound in order to overcome the resistances that bacteria have evolved. These modifications are usually achieved by the variation of substituents on the core scaffold that the class has in common. This process is iterated to produce new variations in the class.[18]

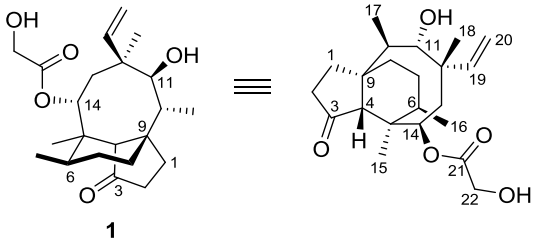
There are many theories on how resistance can be eradicated or controlled. Some people propose that the prescribing of antibiotics needs to be monitored more carefully, but on the other hand, it seems bacteria will always find ways to become resistant and therefore we should stay one step ahead by finding more antibiotics.

Some natural products have antibacterial properties that operate *via* mechanisms that are more difficult for the targets to develop resistance towards. As chemists, it thus seems logical to focus our attention on developing methods to produce antibiotic-like molecules that are inspired by such compounds. Resistance is currently classed as a global concern,[19] as more and more of our current antibiotics

are proving to be obsolete and in some recent cases, no antibiotics showed any activity.[20] It maybe that we are returning towards a society where infections are once again becoming fatal and therefore, research in this field is becoming increasingly invaluable.

1.**3 Discovery of Pleuromutilin**

Pleuromutilin (Figure 2) is a tricyclic diterpene antibiotic produced by the fungus *Clitopilus*.[21] It was first isolated in 1951 by Kavanagh *et al*. from two basiomycetes species called *Pleurotus mutilis* and *Pleurotus passeckeranius.*[22,23] This compound initially showed promising activity against some Gram-positive bacteria and mild activity against some Gram-negative bacteria.[24]



1

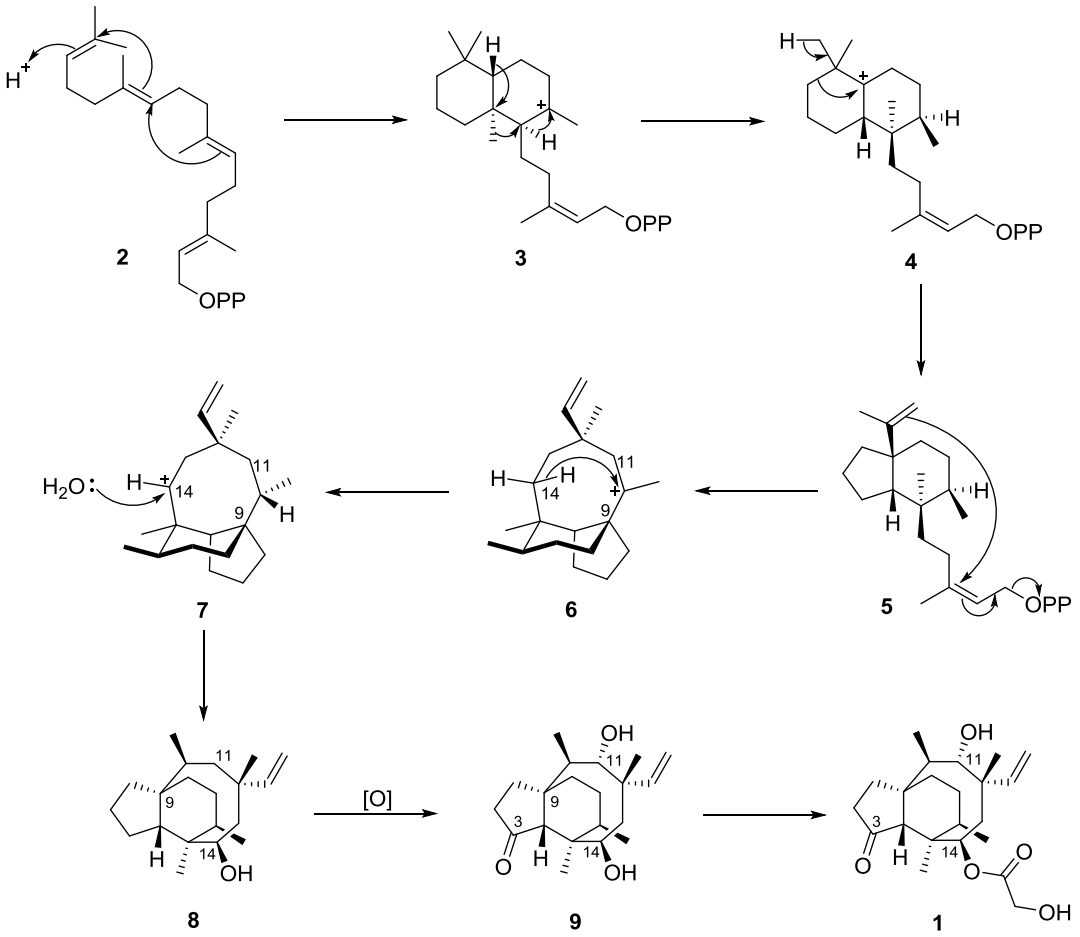
Figure 2 Structure and numbering of Pleuromutilin **1**.

1.2.1 Biosynthesis

Arigoni and Birch determined the structure and stereochemistry of Pleuromutilin. They also investigated its biosynthesis and proposed the pathway shown in Scheme 2.[25–27] As with most diterpene natural products, the key precursor is geranylgeranyl diphosphate (GGPP) **2**, which is derived from acetate carboxyl units and is converted into cyclic terpenes.

The biosynthesis of Pleuromutilin is believed to be catalysed by a diterpene synthase enzyme. The presence of an external proton source is enough to cause the initial cyclisation to form intermediate **3**. The second step is promoted by an initial hydride shift and eventually the migration of one of the four methyl groups, in a Wagner-Meerwein type rearrangement, causing a ring contraction to form the five-membered ring in **5**. The second cyclisation to form the 8-membered ring is driven by the loss of the phosphate group to form **6**.

It has been proposed that the C11 hydroxyl group in **8** is installed by a mono-oxygenase, such as a cytochrome P450 enzyme. [28] Intermediate **8** is then likely to be oxidised at position C3. This produces Mutilin **8**, which is subsequently transformed into the glycolic ester pleuromutilin **1**.



Scheme 2 The biosynthesis of Pleuromutilin.

1.2.2 Bioactivity

Although it was known that pleuromutilin was an active antibiotic due to its ability to prevent protein synthesis,[27] its mechanism of action was only truly investigated using analogues possessing variations at C14.[29–32]

In 1974 Högenauer investigated the cause of protein synthesis inhibition with pleuromutilin and its analogues, and found that the compound interferes with the peptidyl-transferase (PTC) region of a eukaryotic ribosome. The PTC contains two sites located next to each other called the A- and P- sites, where amino acids dock into the ribosome (Figure 3a). This allows the formation of a peptide bond between them to eventually form the desired peptide chain.

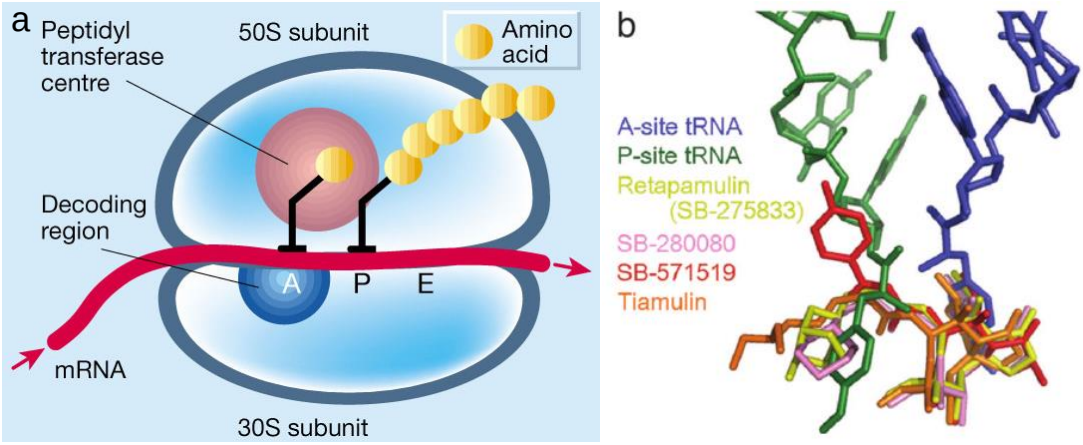


Figure 3 a) A simple representation of the ribosome and how peptides are produced.[33] b) Pleuromutilin derivatives interfering with the A- and P-sites.[34]

In his earlier investigations, he discovered that the compound occupies a position in the P-site, which blocks the attachment of an amino-acyl-tRNA to the A-site. In later studies, he identified that one compound binds to one site per ribosome and this suggested that pleuromutilins bind at a location in the PTC that can interact with both the A- and P- sites. This prevents the whole tRNA molecule from attaching to the ribosome, hence translation does not occur, as shown in Figure 3b.[14,15] The interactions with the A- and P- sites were validated by X-ray crystallographic data with a Pleuromutilin derivative.[29]

Högenauer's work was supported later by Poulsen *et al*, who showed that the pleuromutilins are effective at completely preventing the peptidyl transferase reaction and identified the individual nucleotides involved.[35] They also concluded that these interactions were mediated through hydrophobic interactions and hydrogen bonding with the nucleotides. The keto group at C21 forms two or three hydrogen bonds with a neighbouring nucleotide and the C14 extension undergoes some minor hydrophobic contacts.[21] Upon interaction with these nucleotides, there is a conformational change in the binding pocket that is consistent with an induced fit mechanism.[34]

This mechanism of action is distinct from that of several other classes of antibiotics that are currently in clinical use, making this class of compounds extremely attractive, as it suggests that there is a low likelihood that cross-resistance by target mutation would develop during therapy. This theory has been supported by lab experiments.[31,36]

The pleuromutilins' mechanism of action is clearly quite complex and differs from that seen by current protein-inhibiting antibiotics. This has encouraged research into the pleuromutilin class, as these compounds have the potential to treat susceptible and multidrug resistant pathogens.

1.3.3 Problems with the Pleuromutilin Class

Even though pleuromutilin initially showed potential as an antibiotic over 60 years ago, the class has not been extensively exploited. The main reason is that these compounds show some undesirable pharmacokinetic properties.

The most substantial problem is the fast metabolism of the compounds, which reduces their bioactivity.[21] For example, it has been shown that there are three main metabolites of Tiamulin **10** (see Section 1.4.1), shown in Figure 4.[37] Metabolites **11** and **12** are formed by the hydroxylation of the 5- and 6-membered rings respectively and have less than 1% potency when compared to **10**. The third metabolite isolated is generated by the removal of one of the *N*-ethyl groups to form **13**, which reduces the metabolite's activity when compared to **10**.[38] It is hypothesised that the new hydroxyl groups on the rings prevent some of the favourable hydrophobic interactions in the ribosome, hence reducing activity (Section 1.3.2).

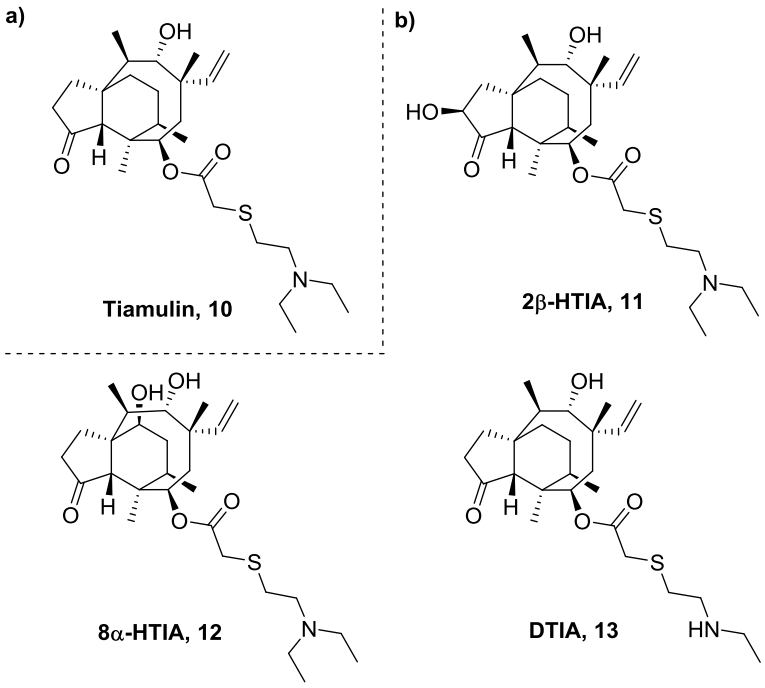


Figure 4 a) Structure of Tiamulin. b) Three metabolites of Tiamulin; 2β-hydroxy-tiamulin (2β-HTIA), 8α-hydroxy-tiamulin (8α-HTIA) and N-ethyl-tiamulin (DTIA).

The undesirable properties associated with the pleuromutilin class and the cost of development have discouraged pharmaceutical companies from taking up the

enormous challenge of synthesising derivatives that are fit for human use. Along with the poor pharmacokinetic properties of these tricyclic core compounds, pleuromutilins can be quite challenging to produce synthetically, especially if the tricyclic ring system is to be constructed.[21]

1.4 Analogues of Pleuromutilin

Due to the unfavourable pharmacokinetic properties of pleuromutilin, research has turned towards the development of analogues. The hope is that a derivative will not only retain the antibacterial activity seen with the natural product, but will also show improved pharmacokinetic properties.

1.4.1 Analogues *via* Semi-Synthesis

Pleuromutilin is easily obtained by fermentation,[24] which affords the opportunity to investigate analogues of the natural product using semi-synthesis.[39] Figure 5 shows the regions of the molecule that have received most attention with regard to modification. Modifications that have been published include variations at C12,[40–42] C13[43] and C14.[44-45] The core is also susceptible to alkyl and hydride shifts under certain conditions, which has allowed access to analogues possessing an altered tricyclic architecture.[39]

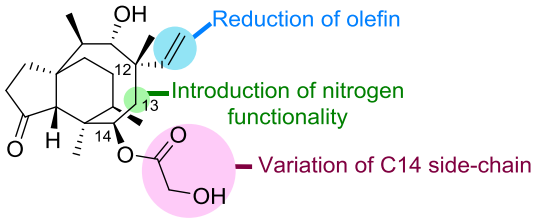


Figure 5 Summary of modifications of pleuromutilin, introduced by semi-synthesis.

The most successful derivatives have emerged from the modification of the side chain at C14. Some analogues have proved to be very promising, as they have equal or improved activity when compared to the natural product.[46] Pleasingly, they also have improved pharmacokinetic properties, with some compounds established in veterinary medicine (**10** and **14**) and one known analogue successfully utilised in human medicine (**15**). Figure 6 shows the most successful analogues made *via* semi-synthesis and some that are in current development.

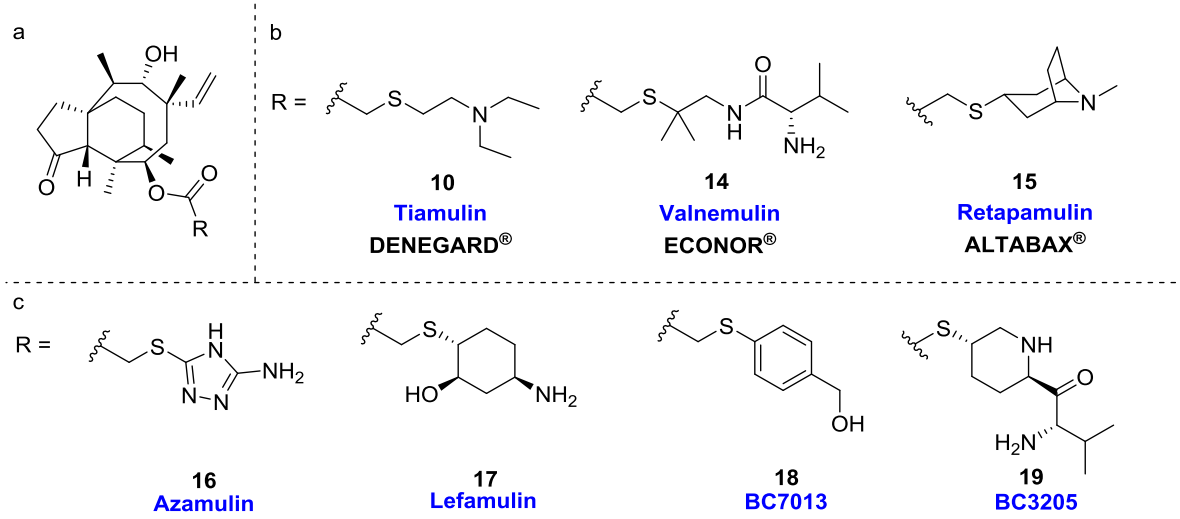


Figure 6 Analogues of pleuromutilin, synthesised by semi-synthesis with modifications of the glycolic side chain. a) General structure of analogues. b) Compounds administered for clinical use. c) Nabriva's analogues.

These analogues only differ in the side chain at C14 of the natural product and all possess a sulfur atom at C22. Tiamulin (**10**) and Valnemulin (**14**) were both synthesised by Novartis and were registered for veterinary use in 1979 and 1999 respectively. Retapamulin, developed by GSK, was registered in 2007 and has encouraging activity. This is the first example of an analogue fit for human use, however it is restricted to use as a topical cream.[21]

Azamulin (**16**) reached phase II clinic trials, however did not progress any further due to water solubility issues. Lefamulin (**17**), synthesised by Nabriva, is currently in clinical trials at phase III for intravenous/oral treatment of community acquired bacterial pneumonia and phase II for various skin infections.[47–50] Nabriva also has another analogue (BC7013, **18**) in their pipeline, which is due to enter phase II clinical trials for topical skin treatment, and work is on-going on analogue BC3205 (**19**) at the time of writing.[51]

The research conducted appears to suggest that modifications by semi-synthesis could potentially result in a pleuromutilin analogue that could be orally administered for use in humans. However, there are no derivatives currently entering clinical trials that have modifications of the natural product at a site other than the C14 side chain. SAR studies have shown that the side chain has a minor role in binding and the activity of the compound (see section 1.2.2), however, with the metabolic issues being associated with the core scaffold, it would be logical to investigate the formation of derivatives with core modifications.

1.4.2 Analogues by *de Novo* Synthesis

Sorensen and co-workers wanted to pursue the use of *de novo* chemical synthesis to develop direct access to pleuromutilin-like scaffolds.[52] This is an approach that was utilised by the Myers laboratory to successfully expand the tetracycline class of antibiotics.[53]

They took note of the SAR studies of the parent compound and its derivatives to decide which features could be eliminated from their compounds to shorten the synthetic route. They designed their synthesis to produce analogues that possessed the tricyclic core, the hydroxyl group at C11 and the carbonyls at C3 and C21. Using their previously developed synthesis they envisaged developing a straight forward route to four different analogues (Figure 7).[54]

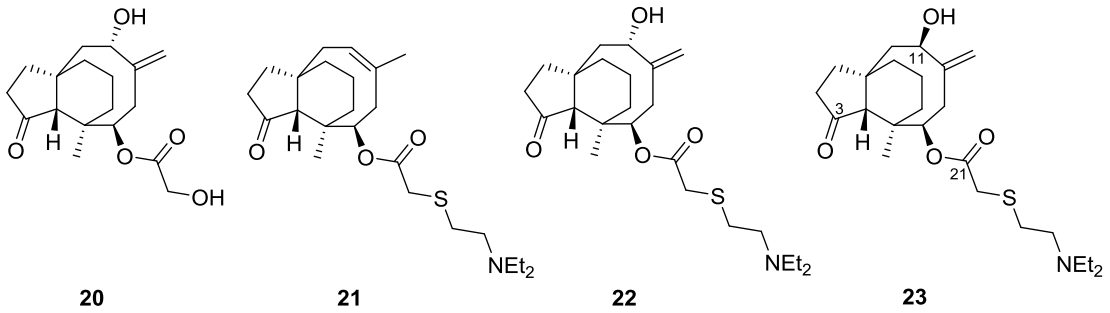


Figure 7 Sorensen's analogues prepared by de novo synthesis.

The group went on to evaluate the compounds' effects on the growth of *M. tuberculosis*, with the natural product and Tiamulin tested for comparison.[55] From their results only compound **23** showed good potency, being as active as Tiamulin. This is an intriguing result as the hydroxyl group at C11 has unnatural stereochemistry and has two-fold greater minimum inhibitory concentration (MIC) when compared to its twin **22**, which possesses the natural stereochemistry at C11. Compound **21** has a similar MIC as that shown for Pleuromutilin, which is interesting as this compound does not bear the hydroxyl group at C11 that was deemed necessary for activity from previous SAR studies (see Section 1.3.2). Compound **20** performed the worst, having an MIC value four times that of the natural product.

1.5 Total Synthesis

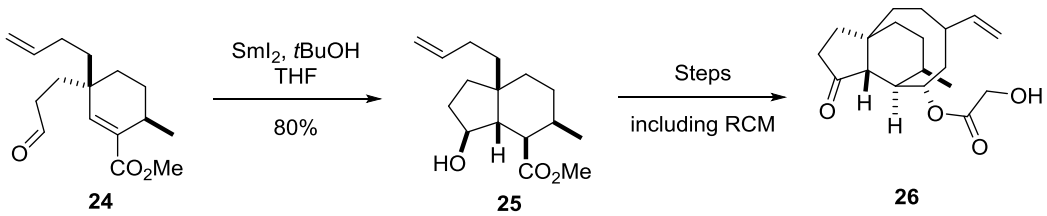
To date, there have been three successful total syntheses of pleuromutilin. Gibbons[56] and Boeckman[57] published their racemic syntheses in 1982 and 1989, respectively. More recently, in 2013, the Procter group published the first non-racemic synthesis of (+)-pleuromutilin.[58]

The next section will focus on the previous work carried out by the Procter group to gain access to this complex natural product.

1.5.1 The Procter Group Approach

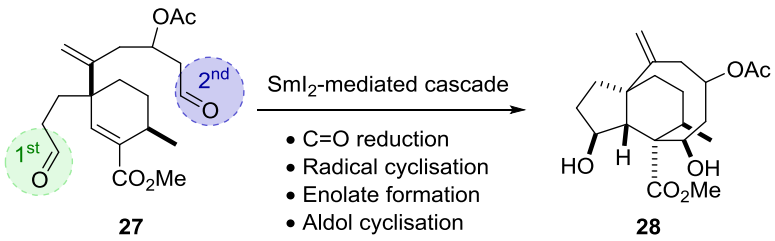
In 2008 the Procter group published a paper detailing a stereoselective approach to the decorated *cis*-hydrindane skeleton. This paper focused on the construction of Faurine, utilising the single electron transfer (SET) reducing agent SmI_2.[59] The first figure in this paper highlights a selection of natural products containing this important hydrindane core, one of which is Pleuromutilin. This work was important as it went on to fuel the group's ambitions to utilise this reagent to complete the total synthesis of Pleuromutilin.

The team applied this strategy to form the skeleton of Pleuromutilin **26** (Scheme 3).[60] The method for the formation of the hydrindane core **25** was the same as that used in previous work and the 8-membered ring was eventually formed by ring-closing metathesis (RCM) using Grubb's second generation catalyst.



Scheme 3 Procter group's approach to the pleuromutilin skeleton.

The group also began investigating SmI_2-mediated cascade cyclisations using dialdehydes, which led to the development of their 'radical then aldol' sequence. They discovered that they could control chemoselectivity in this reaction, by an apparently selective reduction of one aldehyde.[61,62] The combination of a radical cyclisation, followed by an aldol reaction was key to unlocking a rapid assembly of the tricyclic core **28** as shown in Scheme 4.[63]

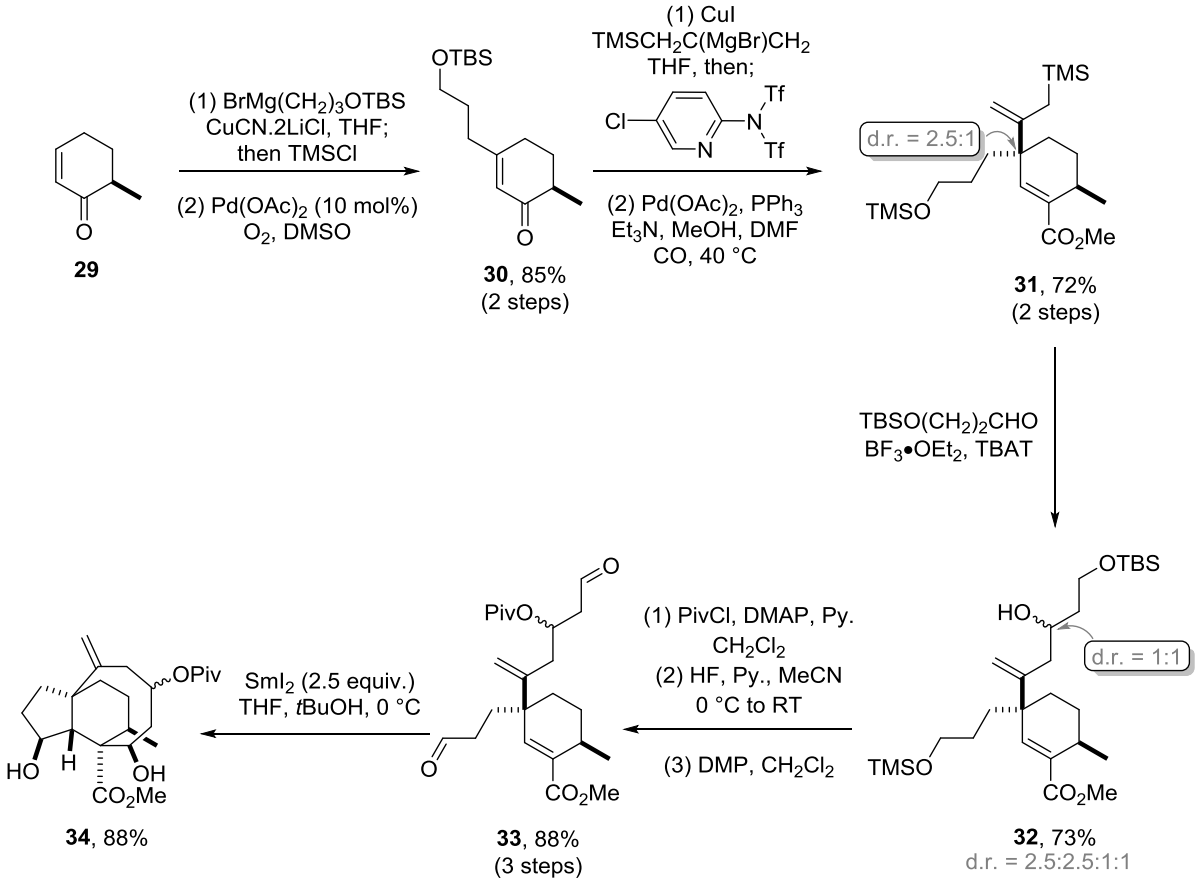


Scheme 4 A SmI_2-mediated cascade approach to the pleuromutilin scaffold.

The group's radical cascade approach to the pleuromutilin ring system represented a unique strategy for the assembly of the natural product.[54,64–68]

1.5.2 Procter's Total Synthesis

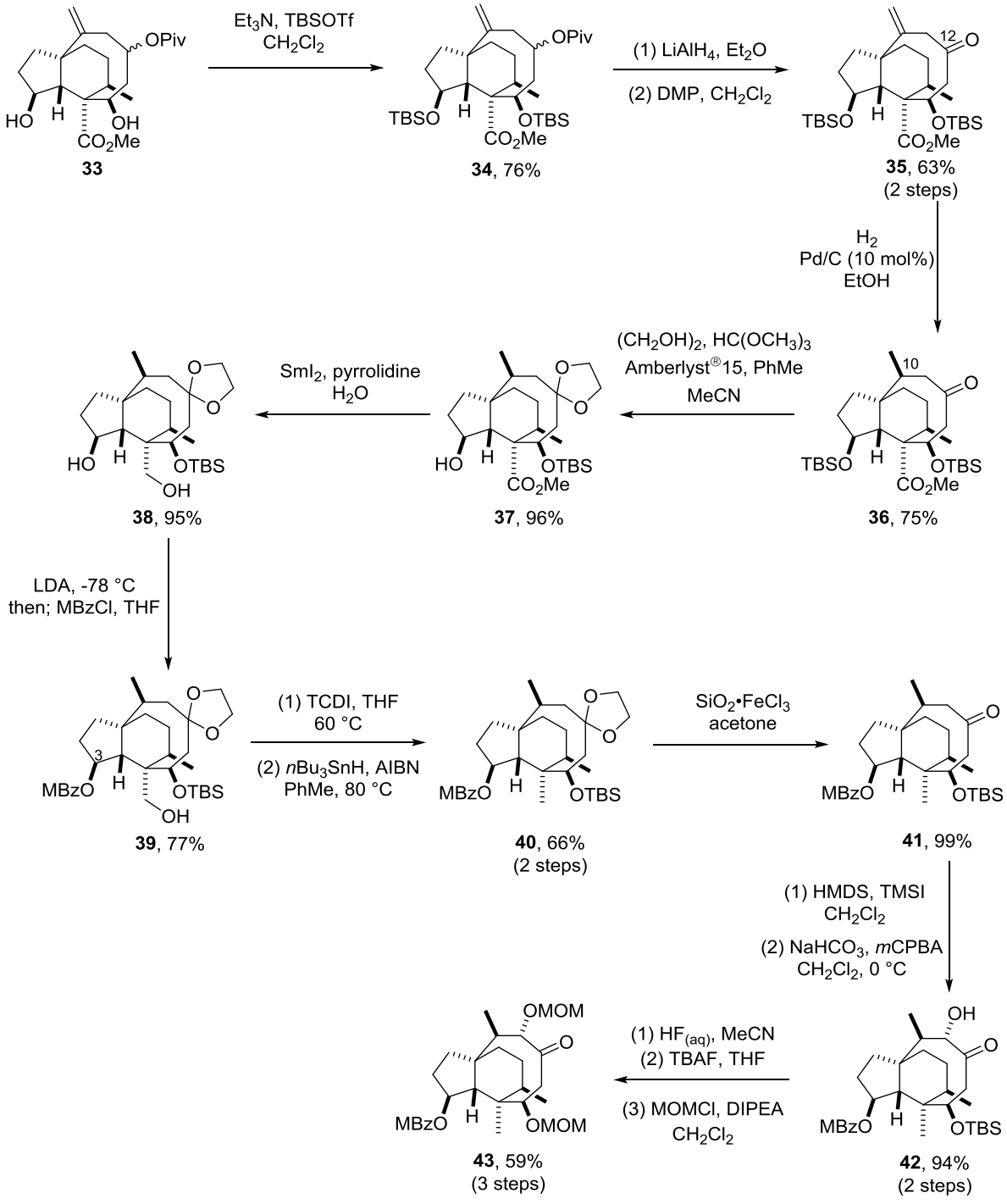
The Procter group completed the first total synthesis of (+)-pleuromutilin in 2013 (Scheme 5).[58] The synthesis begins with a conjugate addition to the enantiomerically pure enone **29**. This intermediate was oxidised using a catalytic Saegusa-Ito oxidation to give **30**. In the next step, an organocopper species was formed from the Grignard shown and CuI, which installs the other side chain. The enolate is then trapped as a vinyl triflate using Comins' reagent, which then allows for the production of the *α,β*-unsaturated ester **31** using a palladium-catalysed methoxycarbonylation reaction. A Hosomi-Sakurai reaction then gives compound **32** and the secondary alcohol is protected as a pivalate group. This is followed by *bis*-desilylation and *bis*-oxidation using the Dess-Martin periodinane then delivers the critical dialdehyde cascade substrate **33**. Compound **33** then underwent a SmI_2-mediated cyclisation cascade, to give core **34**, with complete selectivity achieved at all 4 contiguous stereocentres constructed during the process.



Scheme 5 Synthesis of the tricyclic skeleton by the Procter group.

The cascade reaction was followed by *bis*-silylation, removal of the pivalate and oxidation at C12 to form the ketone **35** (Scheme 6). The alkene was selectively

reduced using a palladium-catalysed hydrogenation to produce the methyl group at C10 in **36**. The methyl ester was then reduced, followed by *p*-methylbenzoate protection of the hydroxyl group at C3 to give **39**.

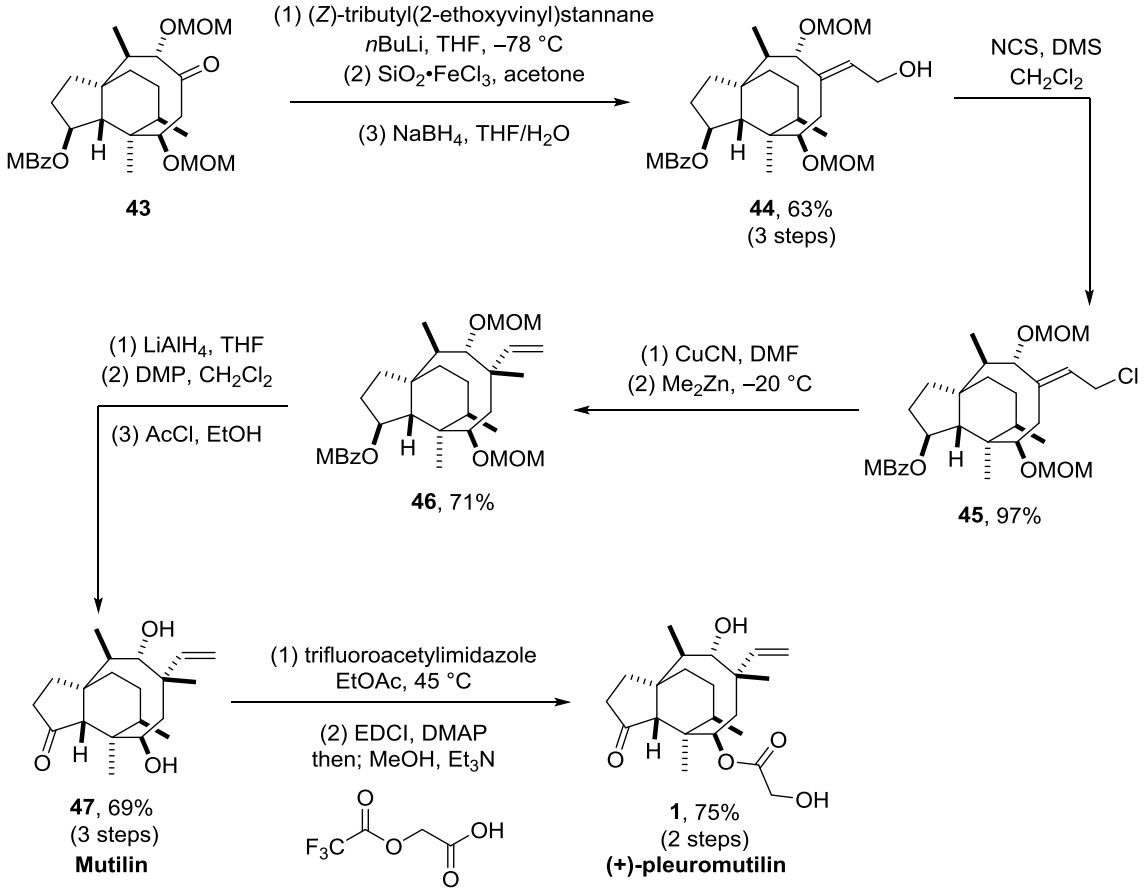


Scheme 6 Further functionalisation of the tricyclic core in Procter's total synthesis.

The next few steps involved deoxygenation, deprotection, followed by ketone oxidation, and delivered the *α*-hydroxy ketone **42** with high regio- and diastereocontrol. Ketone oxidation was achieved by formation and epoxidation of the

silyl enol ether followed by rearrangement and addition of TBAF. The resulting compound **42** was then converted into the *bis*-MOM ketone **43**.

The allylic alcohol **44** was next prepared by the treatment of **43** with a lithiated enol ether, and hydrolysis of the initial adduct to give an enal, which was then reduced. The allylic chloride **45** was then produced using a Corey-Kim chlorination, which was followed by an S_N2' alkylation to form alkene **46**. Removal of the MBz protecting group and oxidation using the Dess-Martin Periodinane, followed by MOM deprotection produced (+)-mutilin **47**. The remaining two steps in Scheme 7 show how the conversion of (+)-mutilin to (+)-pleuromutilin **1** was achieved efficiently. One hydroxyl group was selectively converted to the trifluoroacetate, followed by addition of 2-[2,2,2-trifluoroacetoxy]acetic acid and *bis*-deprotection.



Scheme 7 Final steps towards (+)-pleuromutilin.

This total synthesis was the third to be published, but was the first enantiospecific route. It was also the first approach to involve the formation of two rings of the core in just one synthetic step; the highly selective SmI_2-mediated cyclisation cascade allowed rapid construction of the tricyclic core and represents a unique approach to

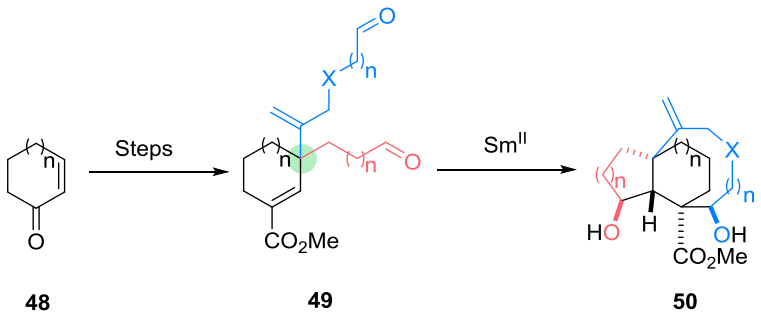
the natural product. The group also developed the first efficient conversion of (+)-mutilin into the natural product.[69]

The group's total synthesis of (+)-pleuromutilin illustrates the application and potential efficiency of SmI_2-mediated cyclisations and the synthetic route developed presents a clear opportunity to adapt the chemistry for the construction of analogues by *de novo* synthesis.

2.0 Project Aims

As mentioned in Section 1.5.2, in 2013 the Procter group published a total synthesis of (+)-pleuromutilin (**1**).[58] Since this publication, we have been investigating the potential of the cascade approach to the mutilin core to deliver analogues of pleuromutilin that cannot be obtained from the natural product by semi-synthesis. In order to access analogues efficiently, the route to dialdehyde cascade substrates **49** needs to be re-assessed in order to reduce the overall number of steps. A route to pleuromutilin analogues should be short, simple, and divergent to be practical for medicinal chemistry studies.

The aim of this project is to develop a concise route to access cascade precursors **49**, where groups introduced early in the synthesis are varied, so that diverse collections of SmI_2-mediated cascade products can be accessed. The scope of the cascade cyclisations of intermediates **49** to give tricyclic cores **50** will be assessed to allow for the synthesis of mutilin analogues (Scheme 8).



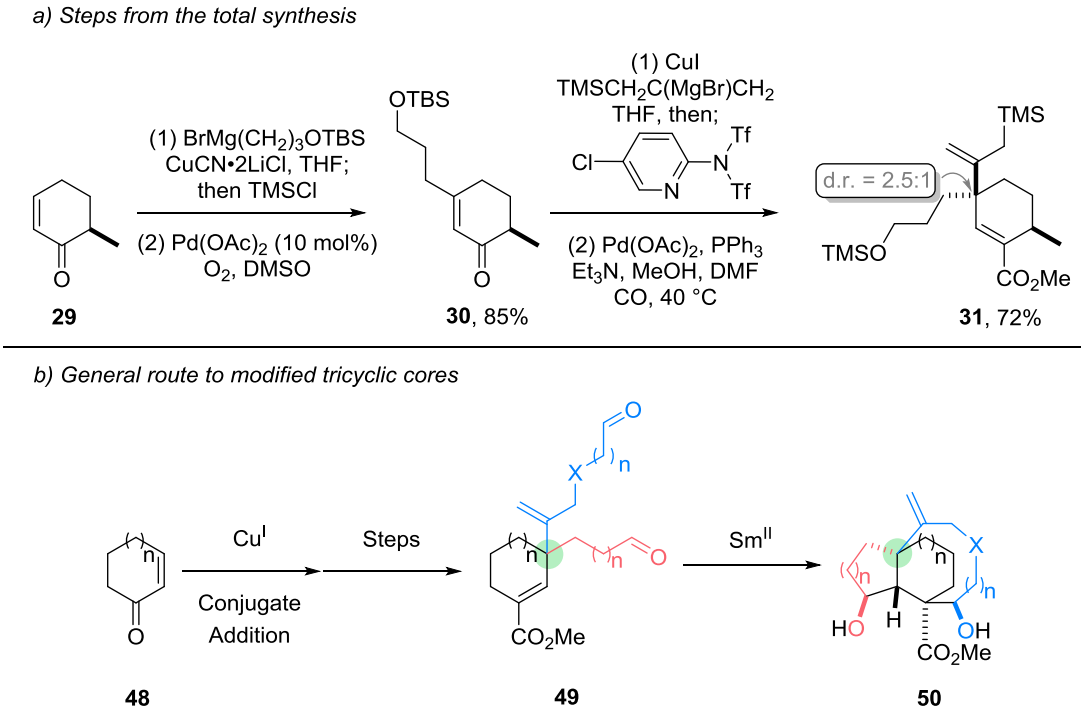
Scheme 8 Rapid construction of tricyclic cores of pleuromutilin analogues.

The newly synthesised cores **50**, will then be manipulated in the hope of delivering analogues that mimic the antibacterial properties of the parent compound. This will provide access to unique pleuromutilin derivatives *via de novo* synthesis that cannot be formed from the natural product, and therefore are inaccessible *via* the current semi-synthetic routes currently used in the pharmaceutical industry and by medicinal chemistry teams in academia.[21,39,70,71]

3.0 Results and Discussion

Working closely with a fellow PhD student, Neal Fazakerley, who had recently completed the total synthesis of (+)-pleuromutilin (see section 1.5.2),[58] the initial goal was to develop a route to simplified analogues of dialdehyde cascade substrates, which could be used to access unique tricyclic molecules inspired by pleuromutilin.

In the Procter synthesis of (+)-pleuromutilin, dialdehyde intermediates were synthesised by an 8-step sequence (see section 1.5.2). Once the side chains (represented as the red and blue substituents in Scheme 9b), are installed, the process to form compounds such as **49** is straight forward, and involves *bis*-deprotection and *bis*-oxidation. Due to this trivial sequence, it seemed that the main issue was the efficient formation of the quaternary centre highlighted. In our original work, the two conjugate additions used were separated by a key oxidation step, that regenerated the enone system (Scheme 9a). Therefore, a direct route to the dialdehydes using a more expedient procedure to install the quaternary centre was desired.



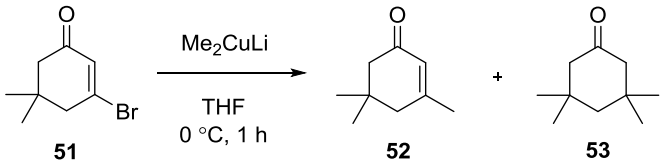
Scheme 9 a) Steps from the total synthesis of (+)-pleuromutilin that were used to install the quaternary centre. b) Proposed modified route to new unnatural tricyclic cores.

We required a sequence that would allow convienient variation of the tricyclic core by modifying the starting materials and our aim was to develop a route to **50** that

was less than 10 steps to make the synthesis more appealing. The presence of a methyl group on enone **29** (Scheme 9a) introduces diastereoisomeric complexity in the synthetic route, and this group was not deemed necessary in SAR studies[21] (see Section 1.3.2) and so could be omitted. Scheme 9b shows the proposed variations on the three-rings of the core and how this could originate from the starting materials used. The conjugate addition seemed to be a good point at which to introduce the proposed diversity.

3.1 The Development of a Double Addition – Preliminary Work

In a method published in 1982, β-bromo α,β-unsaturated ketone **51** was reacted with an organocuprate to produce the corresponding β,β-dialkyl product **53** (Entry 1, Table 1).[72] More importantly, the *α,β*-unsaturated ketone **52** could be obtained by lowering the equivalents of the organocuprate. The researchers showed that the reaction was compatible with a variety of leaving groups and different organocuprates.



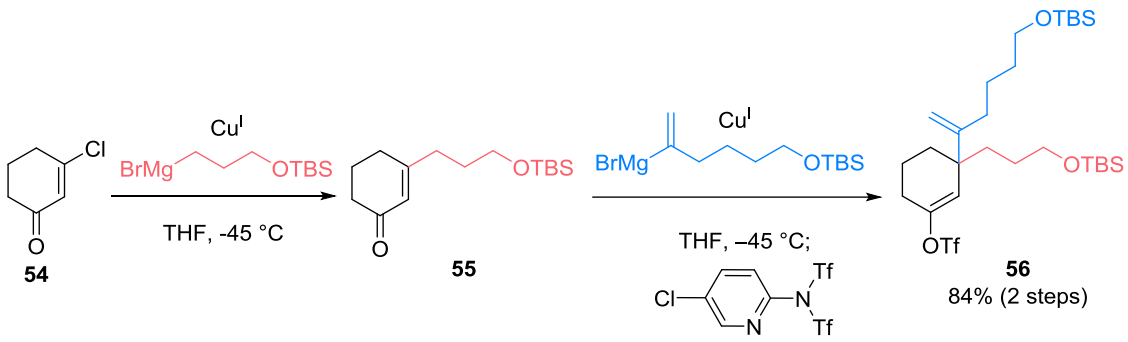
51 **52** **53**

Table 1 Addition of an organocuprate to an enone possessing a leaving group in the β-position.

Entry	Equiv. of Me_2CuLi	Temperature (°C)	Yield (%), (52:53)
1	3	0	86, (0:100)
2	1.1	–78	87, (97:3)

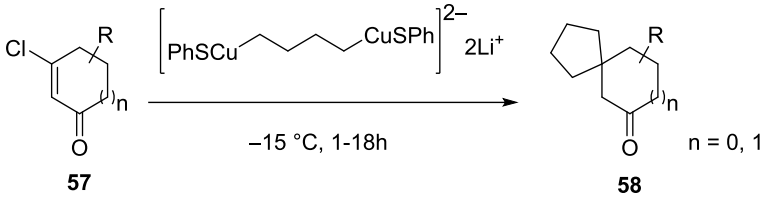
Using this approach in the current synthesis would, for example, allow for the formation of enone **55**, which after another 1,4-conjugate addition and exposure to Comins' reagent, would give triflate **56** (Scheme 10). Thus, by using an enone possessing a leaving group at the β-position the Saegusa-Ito oxidation step used in our original approach to reform the enone is avoided.

Installing the first side-chain *via* a copper-catalysed 1,4-conjugate addition to form the mono-substituted enone **55** was attempted. This was followed by a second independent conjugate addition, and enolate trapping with Comins' reagent to form triflate intermediate **56** (Scheme 10). Pleasingly, this route worked successfully and the triflate **56** was formed in 84% yield.[69]



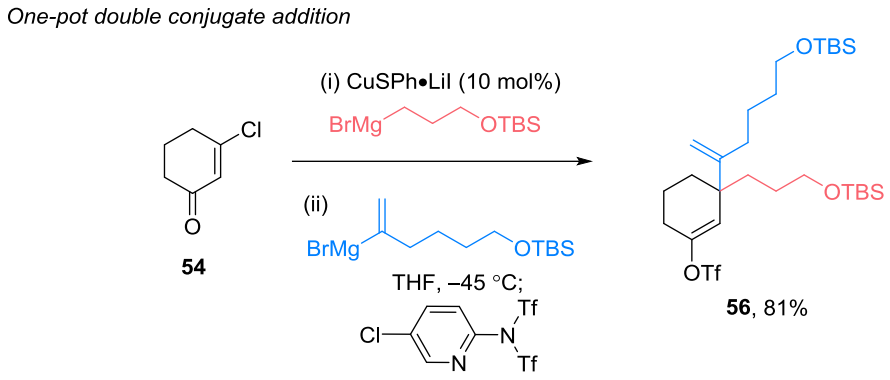
Scheme 10 Organocopper addition to an enone bearing a β-leaving group.

By using strictly one equivalent of Grignard reagent in the formation of **55**, further conjugate addition to form the ketone could be avoided, therefore, the opportunity to carry out the approach in a one-pot fashion emerged. We were further encouraged by the report of a double addition of an organo*bis*-cuprate species to enones **57** to form spirocycles **58** by Wender in 1988 (Scheme 11).[73,74]



Scheme 11 Wender's double additions of an organobis-cuprate to enones bearing a β-leaving group.

Considering this, Neal Fazakerley attempted the copper-catalysed addition of two different Grignards to enone **54,** followed by treatment with Comins' reagent, in one-pot, and obtained **56** in a pleasing 81% yield (Scheme 12).[69] The one-pot addition of two different organometallic species to an enone bearing a β-leaving group has not been previously reported.



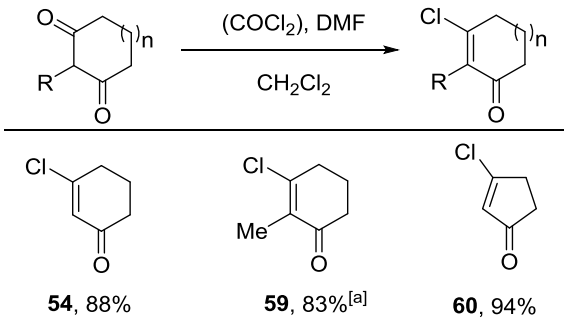
Scheme 12 Preliminary result: one-pot, copper-catalysed double addition to a β-chloro enone.

3.2 Formation of Starting Materials

For the introduction of diversity, three species can be modified: the chloroenone, the first organometallic, and the second organometallic. After SmI_2-mediated cascade, our one-pot double conjugate addition approach would allow access to tricyclic systems that have different sized rings and functionality to that of the natural product pleuromutilin (Scheme 1b). Therefore, the first task was to synthesise the starting materials needed for the copper-catalysed double addition approach.

3.2.1 Synthesis of Chloroenones

The synthesis of three chloroenones was achieved *via* a simple one-step transformation (Scheme 13).[75]



Scheme 13 Chloroenones synthesised. [a] Synthesised by Miles Aukland.

Chloroenones **54**, **59** and **60** were prepared in good yields. These three chloroenones were chosen as there is literature precedent for their formation[75,76] and they would allow us to investigate changing the central ring in the tricyclic system of the natural product (highlighted in Figure 8). The natural skeleton of pleuromutilin possesses a 5,6,8-ring system and compound **54** would be used to prepare analogues containing such a scaffold (Figure 8b). In contrast, compound **60** would allow access to cores where the central ring is 5-membered, that is, 5,5,8-

tricyclic cores (Figure 8c). Finally, chloroenone **59** was synthesised as this possesses a methyl group, which after the cascade cyclisation reaction would be located at a bridge head. Hence, use of this starting chloroenone could furnish 5,6,8-tricyclic cores with an additional quaternary centre (Figure 8d).

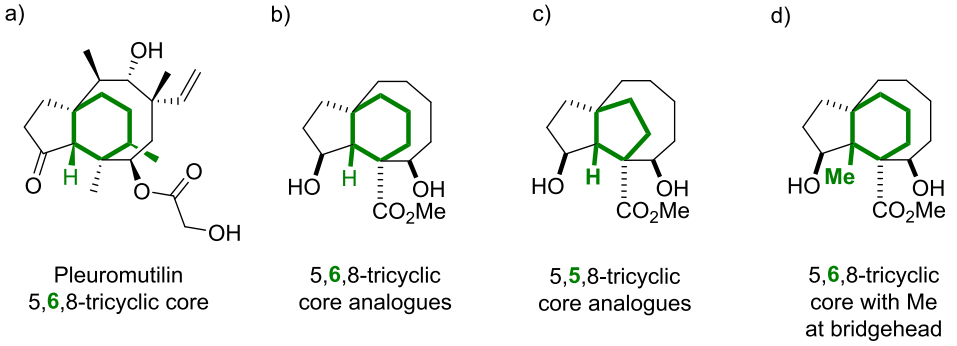
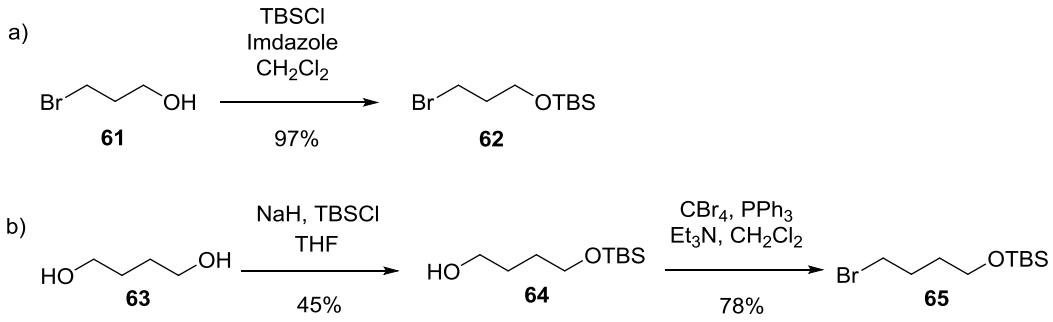


Figure 8 The central ring in the tricyclic system highlighted for: a) pleuromutilin, b) 5,6,8 core analogues from **54**, c) 5,5,8 cores analogues from **59** and d) 5,6,8 core analogues from **60**.

3.2.2 Synthesis of Alkyl Bromides

Two simple bromides were synthesised to vary the first substituent introduced in the copper-catalysed one-pot double addition reaction. TBS-protection of commercially available 3-bromopropan-1-ol **61** gave access to silyl ether **62** in an excellent yield (Scheme 14a). This bromide **62** can be converted to an organometallic that can ultimately lead to analogues bearing a 5-membered left-hand ring (Figure 9a and 9b).[77]



Scheme 14 Synthesis of bromide precursor to the organometallics needed for the first addition.

Mono-protection of 1,4-butanediol **63**, followed by an Appel reaction formed silyl ether **64** (Scheme 14b). This bromide **65** would give access to unnatural 6-membered ring analogues (Figure 9c).[78,79]

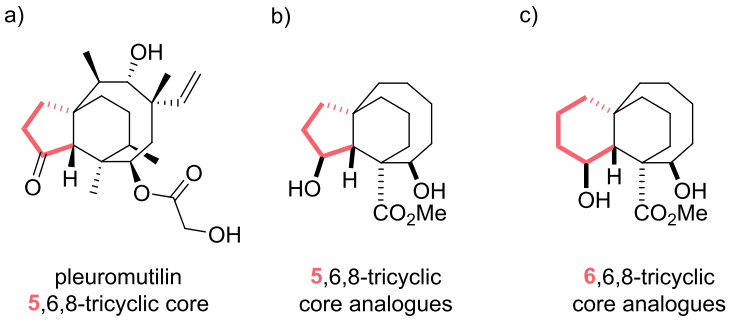


Figure 9 Highlighting the rings formed by modifying the first substituent introduced in the double addition reaction. a) pleuromutilin, b) 5,6,8-tricylic core analogues, and c) 6,6,8-tricyclic core analogues.

3.2.3 Synthesis of Vinyl Bromides

To modify the second organometallic added, vinyl bromides of different length and containing various functionality were synthesised (Scheme 15). Vinyl bromides were chosen as after cyclisation the alkene functionality is located at the same position as the methyl group in pleuromutilin and could also be a means to install the adjacent hydroxyl group *via* an allylic oxidation. The shortest vinylbromide synthesis required only a simple TBS-protection of commerically available 3-bromobut-3-en-1-ol **66** (Scheme 15a). During the cascade reaction this would form a 6-membered right-hand ring (Figure 10b). Vinyl bromides capable of forming 7-membered right-hand rings were synthesised (Figure 10c), with one substrate possessing a *gem*-dimethyl group (Scheme 15b). It was postulated that the *gem*-dimethyl group would lead to a better yield in the SmI_2-mediated cascade reaction due to a pre-deposition towards formation of the ring, as predicted by the Thorpe-Ingold Effect.[80] A *gem*-dimethyl group may also mimic the quaternary all carbon stereocentre present in the natural product.

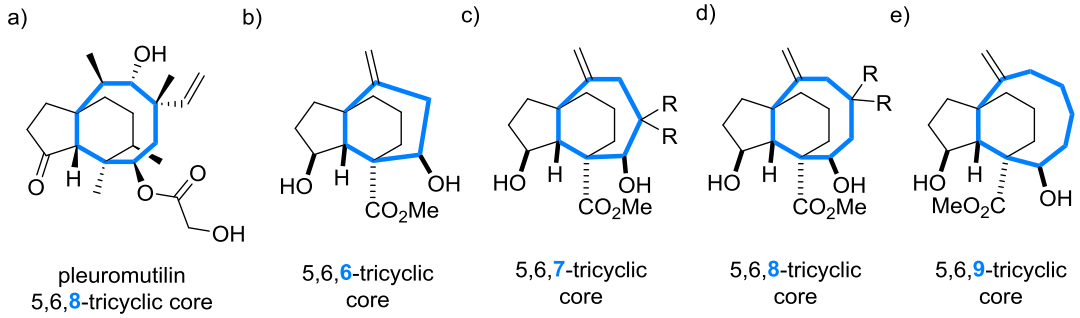
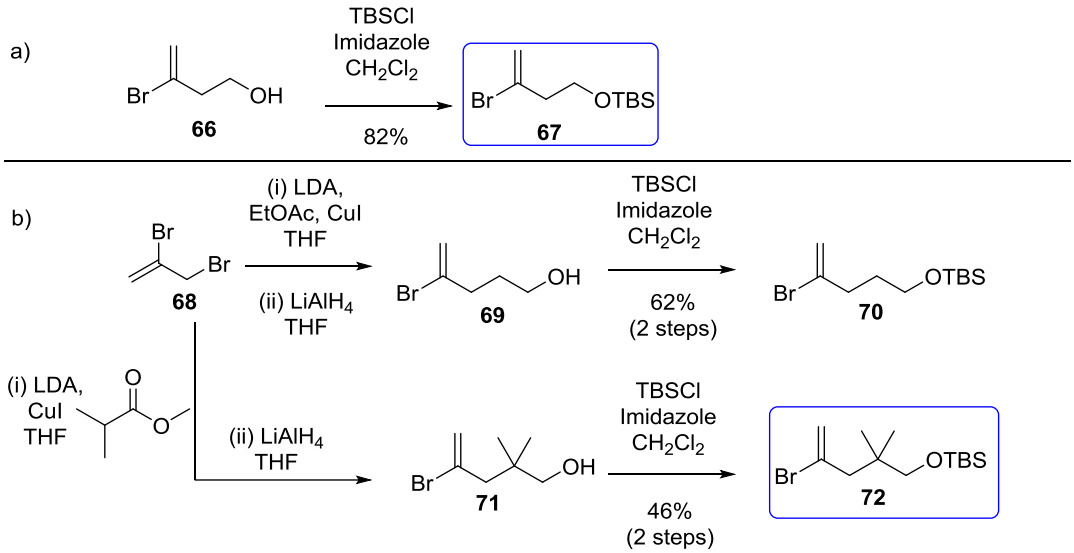


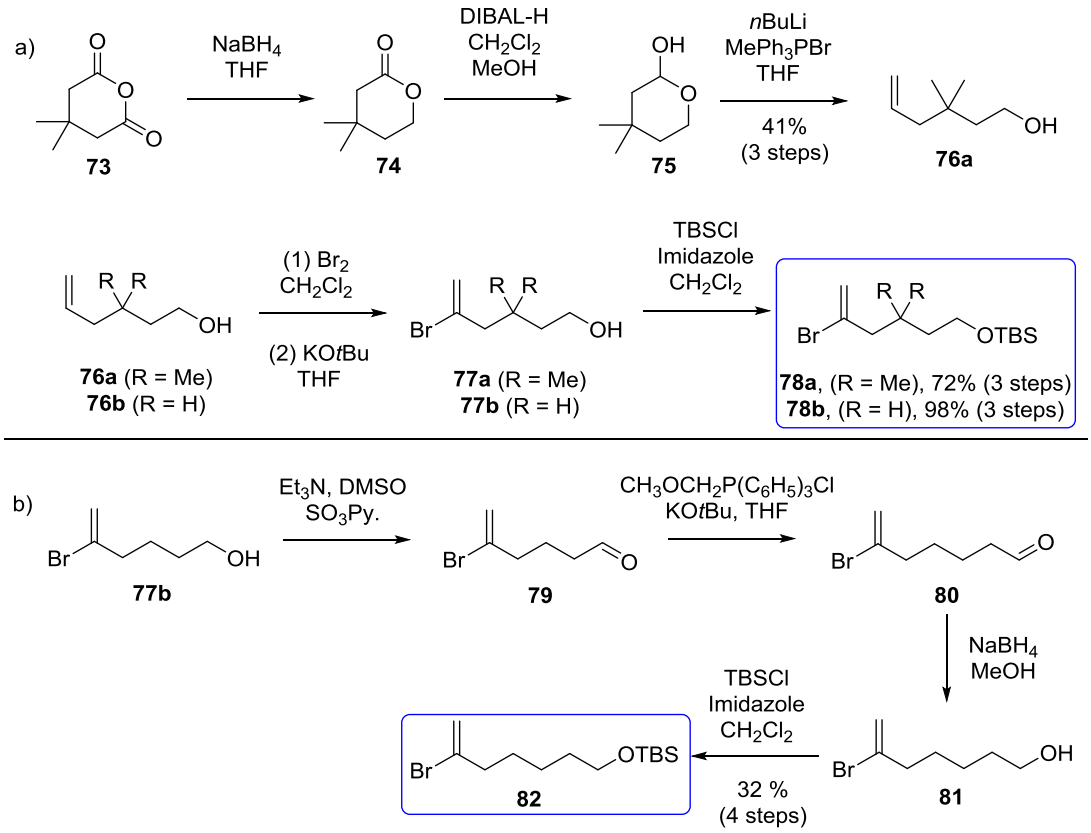
Figure 10 Highlighting the right-hand ring in the system of a) Pleuromutilin, b) 5,6,6 cores, c),5,6,7 cores, d) 5,6,8 cores, and e) 5,6,9 cores.

A literature procedure for the alkylation of ethyl acetate with 2,3-dibromopropene **68**, followed by treatment of the resulting ester with $LiAlH_4$ gave **69**.[81] Employing the same approach, methyl *iso*butyrate was successfully alkylated and reduction then gave vinyl bromide **71**. Finally, TBS-protection gave vinyl bromides **70** and **72**.



Scheme 15 The synthesis of two vinyl bromides.

As disscussed previously, the natural product has a 5,6,8-tricyclic ring system, therefore vinyl bromides that would deliver simplified 8-membered right-hand rings were of particular interest (Figure 10d). Vinyl bromides **78a** and **78b** were synthesised, with one variant containing a *gem*-dimethyl group (Scheme 16). Reduction of anhydride **73** gave access to lactone **74**, which after partial reduction gave lactol **75**.[82] Alkene **76a** could then be produced *via* a Wittig reaction.[83] The last steps to produce target vinyl bromides **78a** and **78b** are the same; treatment of alkene **76a** and commerically available 5-hexen-1-ol **76b** with bromine gave the corresponding dibromides. Upon treatment with potassium *tert*butoxide, selective elimination of the terminal bromide occurred to give alcohols **77a** and **77b**, which were protected with TBSCl to form silyl ethers **78a** and **78b**.[84]

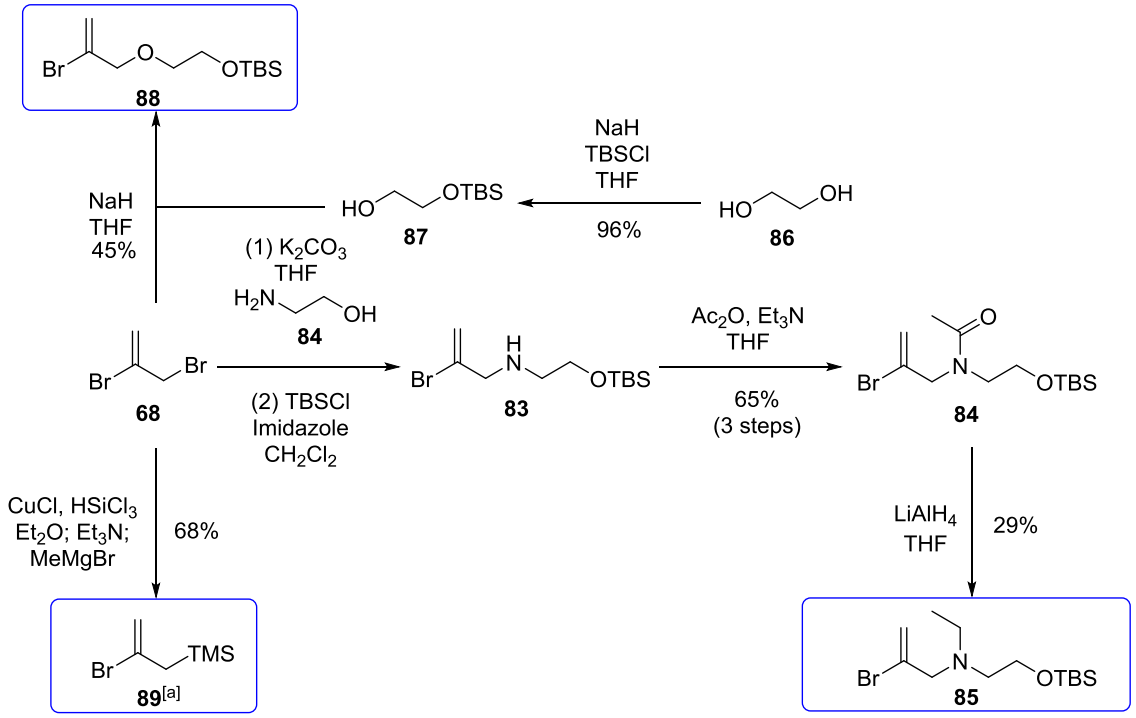


Scheme 16 The synthesis of three, longer chain vinyl bromides.

A vinyl bromide that could potentially form a 9-membered ring in the SmI_2-mediated cascade reaction was next synthesised (Figure 10e). Its synthesis began with the oxidation of primary alcohol **77b** (Scheme 16), to give aldehyde **79**, which was subjected to a one-pot olefination/hydrolysis to provide **80**. Reduction with sodium borohydride followed by TBS-protection furnished the desired vinyl bromide **82**.[85]

By modifying the vinyl bromide component, the opportunitity to introduce heteroatoms presented itself. The incorporation of heteroatoms is very attractive as they can lead to compounds with improved activity and/or ADMET (absoprtion, distribution, metabolism, excretion and toxicity) properties; an approach utilised in drug discovery projects.[86] Therefore, vinyl bromides **85** and **88** containing heteroatoms were synthesised (Scheme 17).

Vinyl bromide **88** was synthesised with the aim of introducing an oxygen atom into the 8-membered ring of the tricyclic system of the final products (Figure 11b). **88** was accessed by TBS-protection of one hydroxyl groups of ethane-1,2-diol to form **87**, followed by deprotonation with sodium hydride and addition of 2,3-dibromopropene **68**.[87–89]



Scheme 17 Synthesis of vinyl bromides containing heteroatom substituents. [a] Synthesised by Neal Fazakerley.

Similarly, bromide **85** was successfully synthesised with the idea that this would eventually form a 5,6,8 tricyclic core with a nitrogen atom at C12 (Figure 11c). Upon treatment with potassium carbonate, 2-aminoethanol **84** successfully reacted with 2,3-dibromopropene **68** to give the corresponding alcohol that was protected as the silyl ether to yield **83**.[90] *N*-acetylation followed by reduction with $LiAlH_4$ gave *N*-ethyl amine **85**.

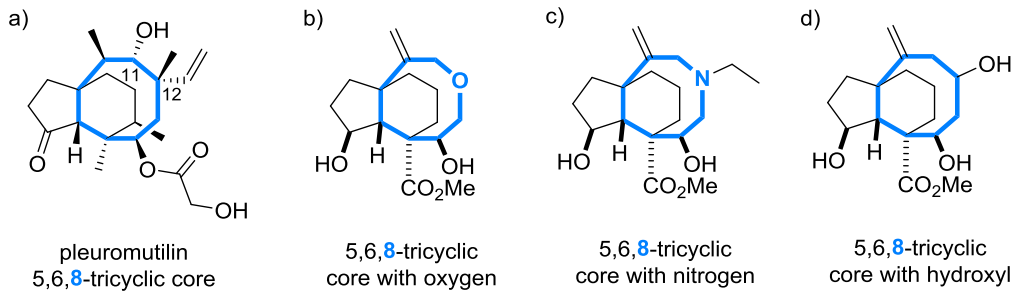


Figure 11 Cores with 5,6,8 scaffolds. a) pleuromutilin, b) heterocycle containing oxygen, c) heterocycle containing N, and c) containing a hydroxyl substituent.

Vinyl bromide **89** was also synthesised from **68**, by reaction with trichlorosilane in the presence of copper chloride, exposure to triethylamine and addition of MeMgBr.[91] Use of substrate **89** in the copper-catalysed one-pot double addition

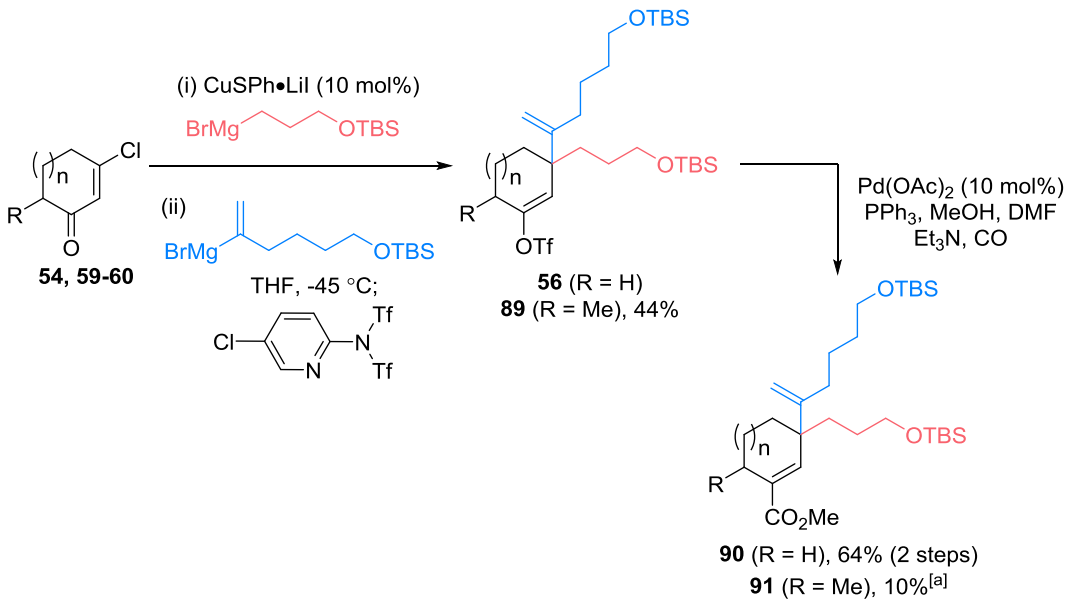
would, after a Sakurai reaction with a suitable aldehyde (see later), give access to tricyclic cores with a hydroxyl group installed at the C12 position (Figure 11d). From SAR studies (Section 1.2.2), it was suggested that a hydroxyl group at C11 may be important when interacting with the ribosome and thus bringing about the favourable antibacterial properties exhibited by the natural product. It was hoped therefore, that a hydroxyl group at C12 in analogues could interact similarly, in order to mimic this effect.

3.3 Scope of the One-Pot, Copper-Catalysed Double Addition to Chloroenones

With the starting materials synthesised in Section 3.2 in hand, the scope of the novel copper-catalysed double addition could be investigated. Using the conditions developed in preliminary work (Section 3.1), variation of each component was explored.

3.3.1 Variation of the Chloroenone Component

The chloroenone component was first varied whilst keeping the two Grignard reagents fixed (Scheme 18). The organometallic reagents used were those found to work well in the preliminary studies into the double-addition reaction and were formed using magnesium turnings (3.0 equiv.) in THF using bromides **62** and **78b** to form the red and blue tethers shown in Scheme 18, respectively.

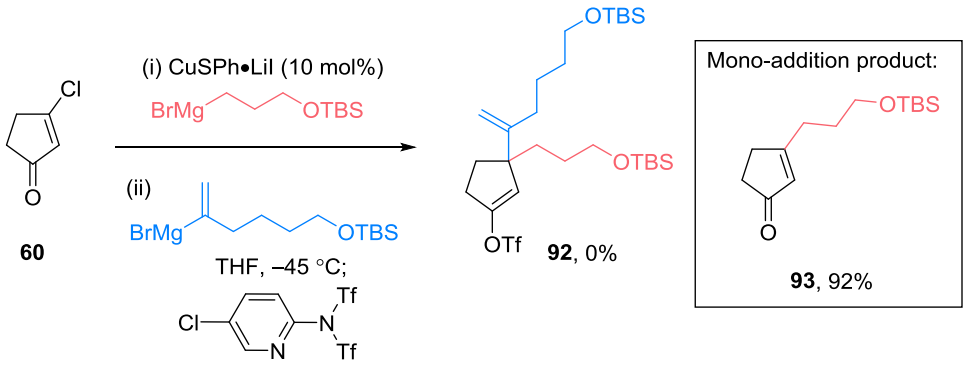


Scheme 18 Attempting the double addition reaction with the three chloroenone variants. [a] ^{1}H NMR yield measured against a nitromethane internal standard.

As discussed in Section 3.2.1, enone **59** would give access to 5,6,8-tricyclic cores with an additional quaternary centre (Figure 8d). Subjection of **59** to the double

addition reaction conditions formed triflate intermediate **89** in 44% yield. Unfortunately, the palladium-catalysed methoxycarbonylation reaction suffered from very low yields (10%) using the conditions shown in Scheme 18 and also suffered from reproducibility issues when forming **91**. Higher loading of palladium (40 mol%) and longer reaction times (up to 72 h) failed to give any product. The triflate starting material was isolated in each instance.

The 5-membered enone **60** performed disappointingly in the one-pot double addition reaction, as the desired product **92** was not observed after multiple attempts (Scheme 19). A literature search suggested that formation of **92** ought to be possible and so these results proved particularly frustrating.[92] In order to form the desired triflate, the reaction was carried out stepwise, with addition of the first Grignard reagent followed by isolation of the enone **93** in 92% yield. Multiple attempts to add the second Grignard in a separate reaction failed. Clearly, something specific about this 5-membered ring substrate negatively impacts the desired reaction, however, the exact reasons for this are currently unknown.



Scheme 19 Attempted one-pot double addition using 5-membered ring chloroenone **63**.

At this point in the project, the idea of changing the chloroenone for use in the double addition reaction was 'put on hold' and we decided to work only with 6-membered chloroenone **54**, which was working well.

3.3.2 Changing the First Addition

In the initial investigation of a one-pot double addition, the first addition was carried out using a Grignard reagent synthesised from 3-carbon-chain bromide **62**, which eventually forms the 5-membered left-hand ring of the tricyclic core (Figure 12a). An increase in the length of the carbon chain by one unit would potentially allow access to cores containing a 6,6,8 scaffold (Figure 12b). Therefore, the use of bromide **65** to form the first organometallic was pursued.

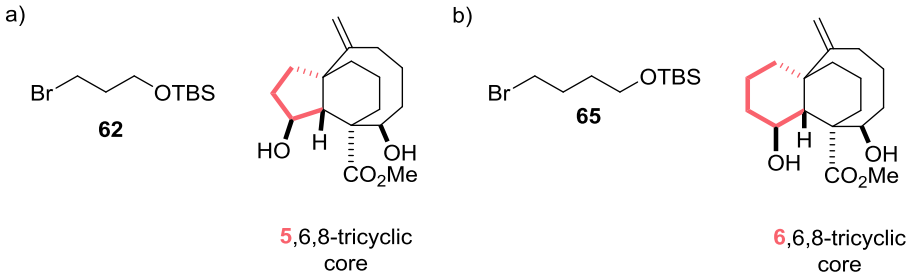


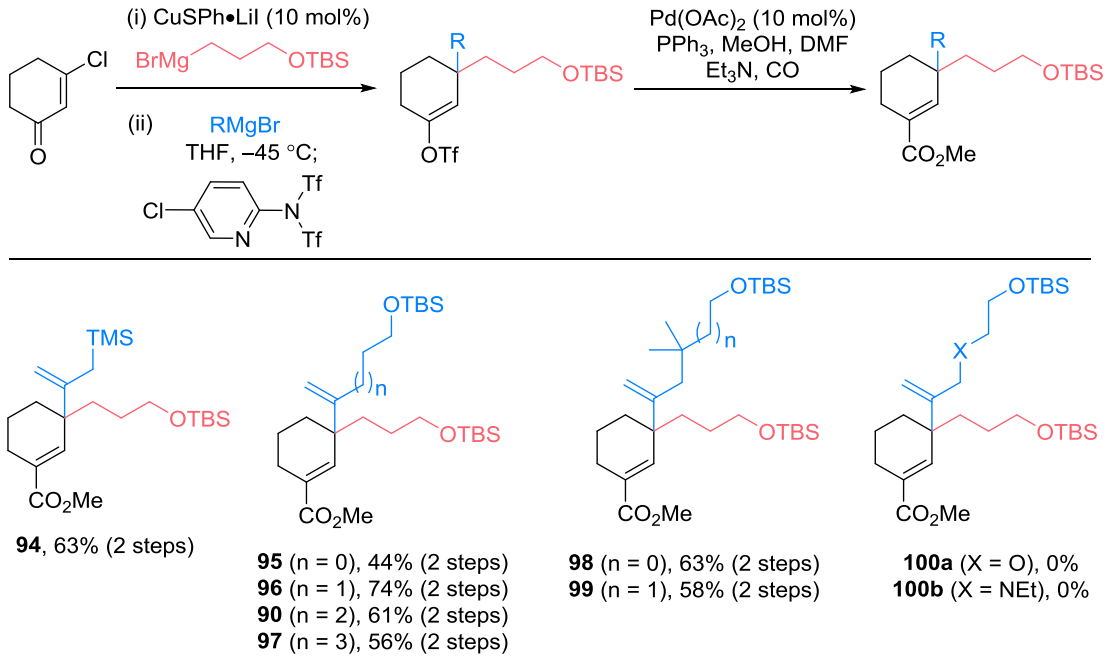
Figure 12 Tricyclic cores originating from variation of the first organometallic. (a) Bromide **62** leads to a 5,6,8 core, and (b) bromide **65** leads to a 6,6,8 core.

Unfortunately, there were issues with the formation of the Grignard reagent from **65**, which could not be resolved; no desired product or starting materials could be obtained from the reactions. A search of the literature revealed that there is no reference to this organometallic being used, presumably due to its instability.

We therefore decided to focus our efforts on the introduction of diversity through variation of the second organomagnesium reagent formed from the vinyl bromides prepared in section 3.2.3.

3.3.3 Changing the Second Addition

Changing the length of the tether introduced in the second addition would translate into rings of varied sizes ranging from 6 to 9 in the analogues (as shown previously in Figure 10 and 11). This tether eventually becomes the right-hand ring in the tricyclic system and so functionality was also introduced at the position where the all carbon quaternary centre is found in the natural product (C11). This would also be a good opportunity to introduce a heteroatom; this was an exciting proposition as it would allow access to the first pleuromutilin analogues containing a heterocyclic ring. Thus, the framework of the cascade substrates could be assembled in one-pot and after partial purification, palladium-catalysed methoxycarbonylation gave unsaturated esters **90** and **94** - **100** in moderate to good yields (44 - 64%) (Scheme 20).

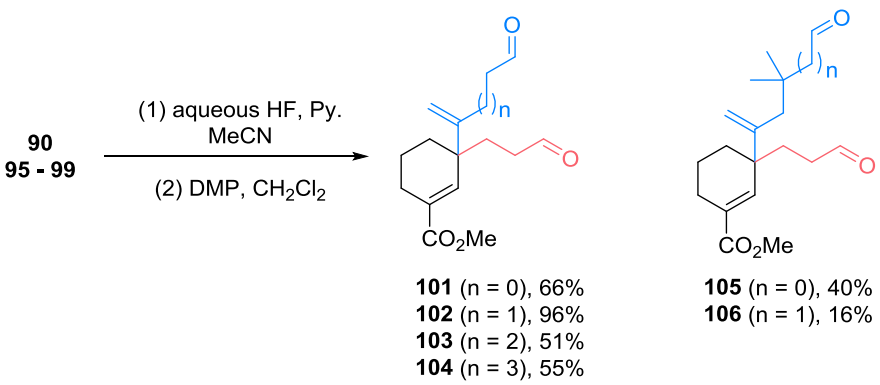


Scheme 20 Methyl esters synthesised in two steps from chloroenone **54**.

Most vinyl bromides (Section 3.2.3) were successfully transformed into the corresponding Grignard reagents required for the second addition, however, Grignard reagents containing heteroatoms in the chain could not be formed successfully under the usual conditions. On investigating the reaction, it was found that only the starting material could be recovered and no other products were observed. Therefore, the proposed methyl ester compounds **100a** and **100b** have yet to be synthesised.

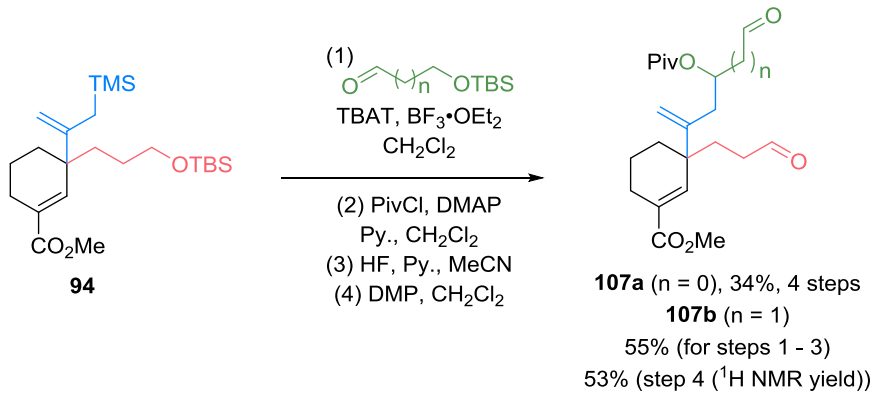
3.4 Formation of Cascade Cyclisation Substrates

Unsaturated esters **90**, and **95** - **99** were then converted into dialdehydes by a *bis*-desilylation and *bis*-oxidation sequence (Scheme 16). Thus, in just four steps the cascade cyclisation substrates **101** - **106** were synthesised from **54** in moderate to good overall yields with unoptimised reaction conditions.



Scheme 21 Formation of dialdehyde cascade cyclisation substrates.

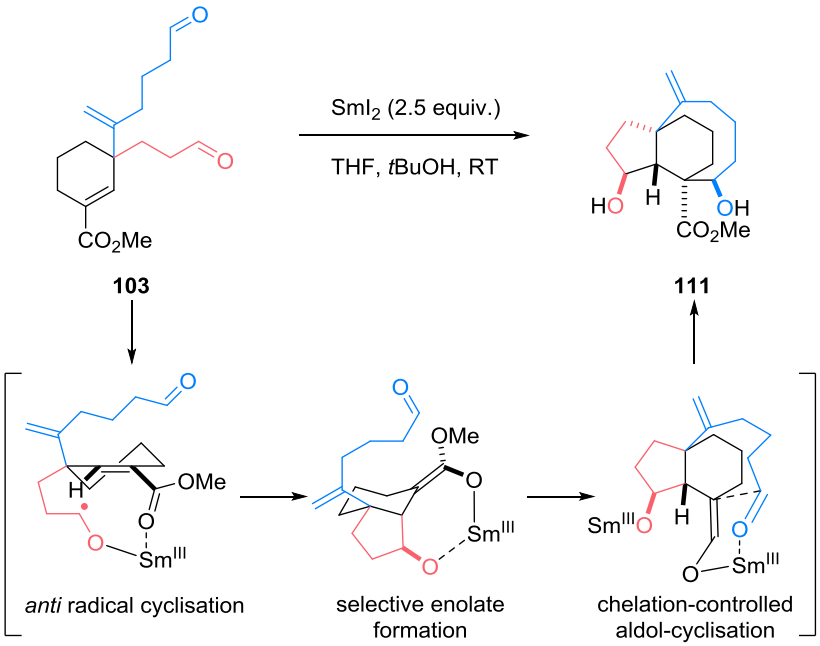
Additional cascade substrates **107a** and **107b**, which bear an oxygenated tether were constructed by Sakurai coupling of ester **94** with different length aldehydes, followed by protection of the resulting secondary alcohol as the pivalate.[93,94] The standard *bis*-desilylation and *bis*-oxidation steps were then employed to give dialdehydes within just 6 steps from chloroenone **54**, in low but unoptimised yields (Scheme 22).



Scheme 22 Formation of dialdehydes **107a** and **107b** bearing oxygenated tethers.

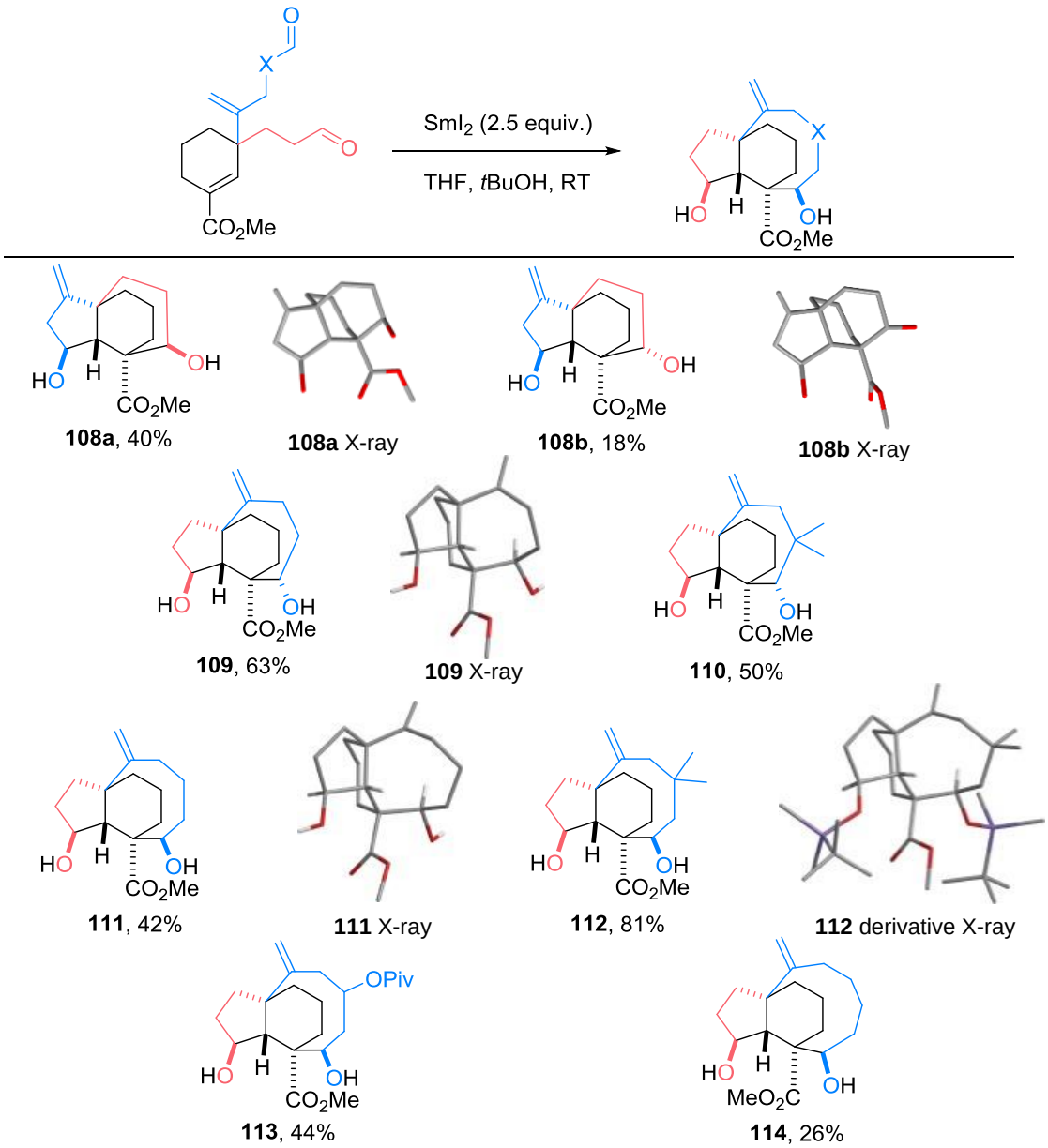
3.5 SmI_2-Mediated Cascade Cyclisation Step

With the dialdehyde intermediates in hand, they could be submitted to the cascade cyclisation conditions. Mutilin-like compounds which have 6, 7 ,8 and 9-membered right-hand rings in the tricyclic system (**108** - **114**) were formed in moderate to good yields (Scheme 24). The shortest aldehyde tether (red) was involved in the radical cyclisation step of the cascade and the longer (blue) tether in the aldol cyclisation (Scheme 23), with the exception being substrate **108** (see later).



Scheme 23 Proposed mechanism for the Sm_2-mediated cyclisation cascade.

The cascade cyclisation of **101** is an intriguing example, as the aldehyde functionality in both tethers is three carbon units away from the quaternary centre. Pleasingly, a simple cascade product **108** was obtained (as a mixture of diastereoisomers), as the tether containing the alkene undergoes the 5-*exo*-*trig*-cyclisation selectively. This can be rationalised by considering the restricted conformation of the tether due to the sp^2-hybridised carbon of the alkene. Thus, a Thorpe-Ingold Effect promotes the selective cyclisation.

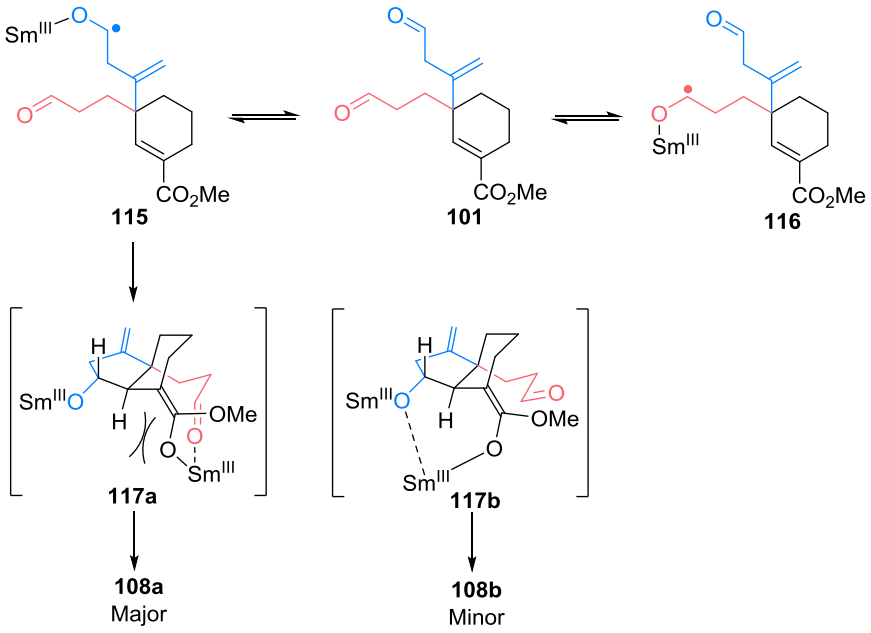


Scheme 24 Tricyclic cores produced by the SmI_2-mediated cascade reaction.

The cyclisation of **108** was the only cascade in which complete diastereoselectivity at the four newly formed stereocentres was not observed. The transition state structure of the aldol cyclisation could explain this lack of stereocontrol at one of the four new stereocentres (Scheme 25).

On exposure of dialdehyde **101** to SmI_2, the cyclisation of radical anion **115** results in the formation of Sm^{III}-enolate **117**, which after a subsequent aldol-cyclisation *via* the closed transition structure **117a** gives rise to the major product **108a**. Due to the presence of the minor product **108b** it is hypothesised that the aldol-cyclisation is also possible through the open transition structure **117b**.[95-96] In the closed transition structure **117a**, the unfavourable 1,3-*trans*-diaxial interactions shown may be the

reason for a lack of diastereocontrol that isn't observed with the other substrates. The relative stereochemistry of **108a** and **108b** were determined by X-ray crystallographic analysis.



Scheme 25 Challenging the sequence integrity of the dialdehyde cascade: cyclisation of **97a** using SmI_2.

Turning our attention to the 5,6,7-tricyclic core **109**, the cascade cyclisation worked well and gave access to the desired product in 63% yield. Compound **110** with the *gem*-dimethyl group alpha to the hydroxyl was also formed, albeit in a lower yield of 50%, which is possibly due to the steric crowding adjacent to the second aldehyde functionality. The substrate possessing a methylene between the *gem*-dimethyl and the second aldehyde group, underwent radical cyclisation cascade to form the 5,6,8 architecture **112** with high efficiency. The high 81% yield obtained illustrates the power of the Thorpe-Ingold Effect for facilitating cyclisations.

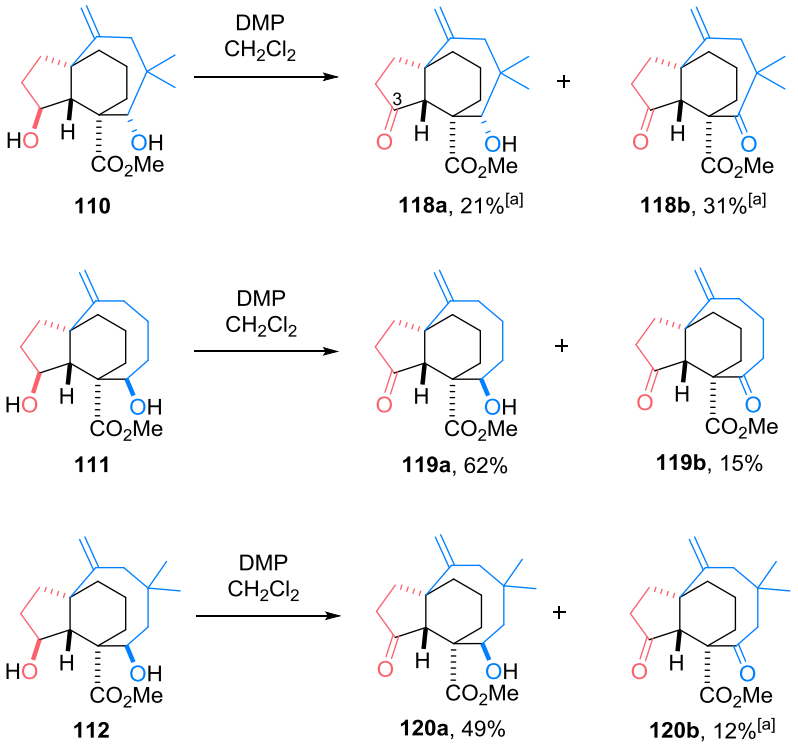
The use of a SmI_2-mediated aldol reaction to form nine-membered rings is unprecedented, so **104** was an exciting dialdehyde substrate to work with.[97–100] Pleasingly, **104** underwent the desired cascade cyclisation to form **114**, possessing a 5,6,9-tricyclic scaffold as a single diastereoisomer in 26% yield. This result highlights that a 9-membered ring represents the likely limit of the cascade's scope with a low yield observed in comparison to the other cores synthesised.

Relative stereochemistry for **109** and **111** were also confirmed by X-ray crystallography. The relative stereochemistry of **114** was confirmed by formation of the *bis*-TBS adduct which gave appropriate crystals for X-ray analysis.

3.6 Formation of an Analogue of Pleuromutilin

To prepare novel analogues of pleuromutilin, reaction of the cascade products to give the C3 ketone group was necessary. To keep the step-count low, we investigated the selective oxidation of the diol products of the cascade reaction.

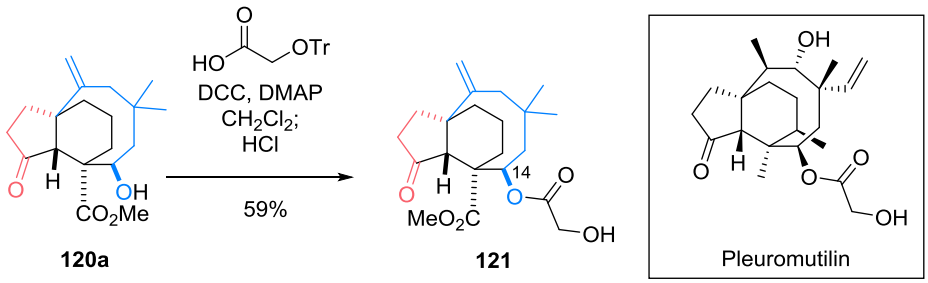
Diols **110** - **112** were treated with one equivalent of Dess-Martin Periodinane and the desired C3 ketones **118a** – **120a** and unwanted diketones **118b** - **120b** were observed (Scheme 26).



Scheme 26 Yields for the oxidation of three cores. [a] ^{1}H NMR yields measured against a nitromethane internal standard.

Diol **111** performed the best in terms of yield and selectivity for the mono-oxidation product. The optimisation of this reaction with respect to selectivity is on-going in the group.

To illustrate the potential of this concise route to pleuromutilin analogues, mono-oxidised product **120a**, possessing a 5,6,8-tricyclic scaffold was taken forward and the C14 glycolate ester was installed using the method developed by the group for their total synthesis of the natural product. Pleuromutilin analogue **121** was obtained in a 59% unoptimised yield. Therefore, a simplified analogue of pleuromutilin was accessed in just seven steps from starting enone **54** (Scheme 27), with a 15% overall yield.

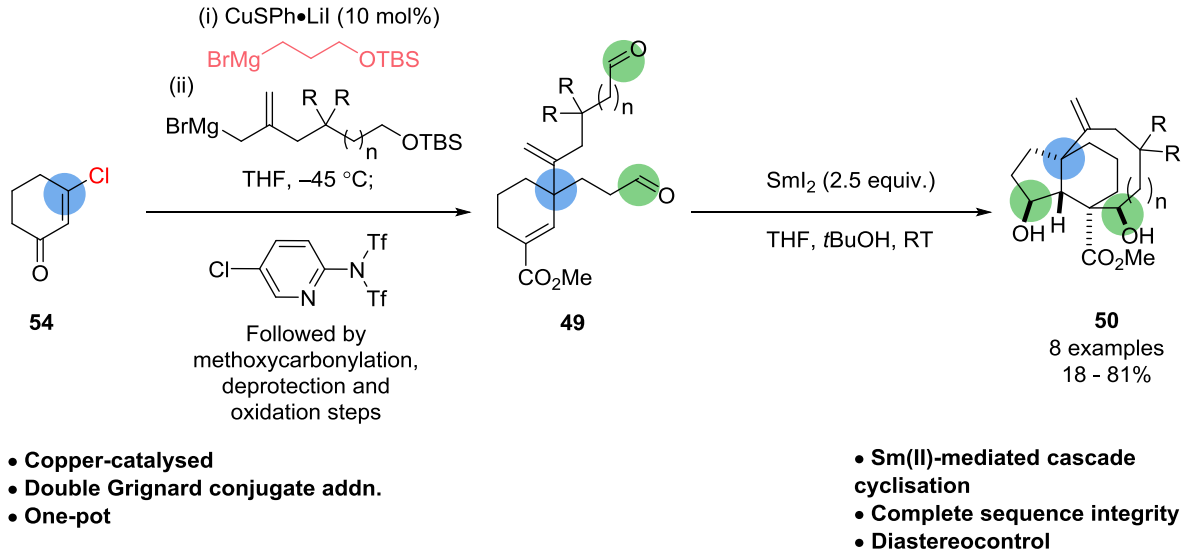


Scheme 27 Concluding a seven-step synthesis of pleuromutilin analogue **121**.

The formation of analogue **121** highlights the potential for combining core-variation illustrated in this project, with the 'classical' side-chain modification approach used in the past, to produce derivatives of pleuromutilin that cannot be accessed by other means.

4.0 Conclusion

This project has resulted in the development of a new one-pot copper-catalysed double 1,4-conjugate addition of two different organomagnesium reagents to β-chlorocyclohexenone **54** to generate a quaternary centre in **49** (Scheme 28). Using chloroenone **54** as the Michael acceptor in the one-pot reaction, variation of the second Grignard reagent gave access to eight dialdehyde cascade substrates. These intermediates were subsequently used to evaluate the scope of the SmI_2-mediated radical cyclisation cascade to produce eight unique tricyclic cores **50**.

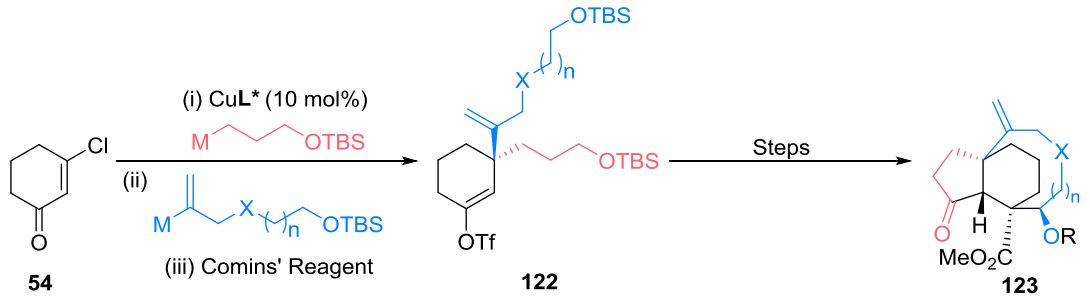


Scheme 28 A short approach to the tricyclic cores of pleuromutilin analogues.

One of these cores was converted into a simplified analogue of pleuromutilin, that cannot be prepared *via* semi-synthesis from the natural product, in a total of seven-steps from chloroenone **54**.

5.0 Future Work

The synthesis of the cores and analogues in Sections 3.5 and 3.6 delivers racemic products. A potentially rewarding extension to the project would investigate whether chiral ligands could be used to form compounds **122** in enantioenriched form. This would be a powerful reaction in general and specifically for this project, it would mean that the pleuromutilin scaffold could be built with enantiocontrol (**123**). As mentioned in Section 1.1, there are many organometallics that can be used and it would be worth investigating multiple methods to construct the quaternary centre asymmetrically (Scheme 29).[2–4,6,8,9] However, there is currently no precedent for an asymmetric 1,4-conjugate addition to install tethers similar to those seen in **122**, which only highlights the potential utility of such a transformation.



Scheme 29 Proposed asymmetric copper-catalysed double 1,4-conjugate addition.

The progression of this project is expected to involve the scale-up of the synthesis and the construction of multiple analogues that utilise the double conjugate addition and SmI_2-mediated cascade methodology investigated in this project. The analogues should then be tested against appropriate bacteria, alongside the natural product, to determine essential bioactivity and in particular, what ring systems and scaffolds are efficacious.[101–104] There are several aspects of the derivatives synthesised in this project that warrant investigation (Figure 13).

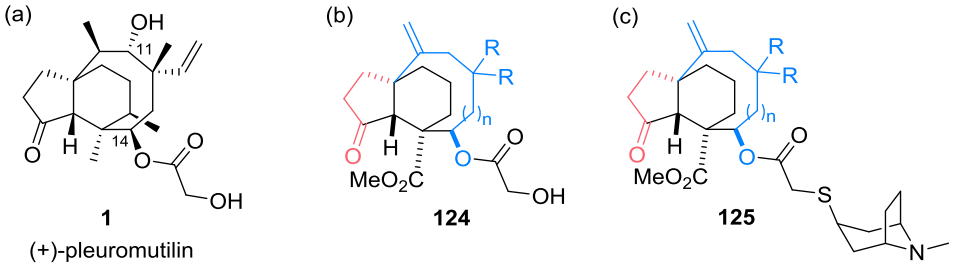
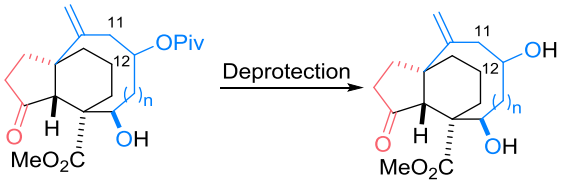


Figure 13 Proposed derivatives; (a) (+)-pleuromutilin, (b) analogues resulting from this project, (c) analogues with Retapamulin side chain.

Firstly, the effect that the change in the ring systems within the tricyclic cores has on the compounds' antibacterial activity needs to be investigated (Figure 13b). The ring system that results in the greatest activity should then be taken forward to make new derivatives that contain the thioether side chain seen in Retapamulin (Figure 13c). As discussed in Section 1.4.1 this derivative has a superior potency when compared to pleuromutilin and has improved pharmacokinetic properties that ensure it is suitable for human use.[21,16] The combination of the new ring system and the Retapamulin C14 side chain may result in a simplified analogue with promising properties.

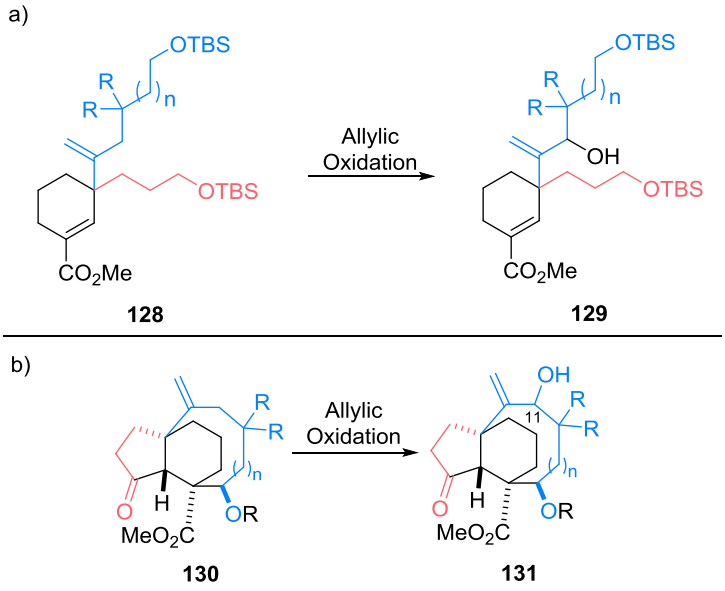
From previous SAR studies[21] (Section 1.4.1) it was suggested that the hydroxyl group at C11 is forming an important interaction within the ribosome, heightening the compounds potency and this key functionality is missing from the cores synthesised in this project. Deprotection of core **126**, will result in the secondary alcohol **127**, which situates the hydroxyl group one-carbon away from the 'natural' location (Scheme 30). Potentially this C12 hydroxyl could mimic the C11 hydroxyl group by interacting with the same nucleotides, especially if the size of this ring is also modified.



126 **127**

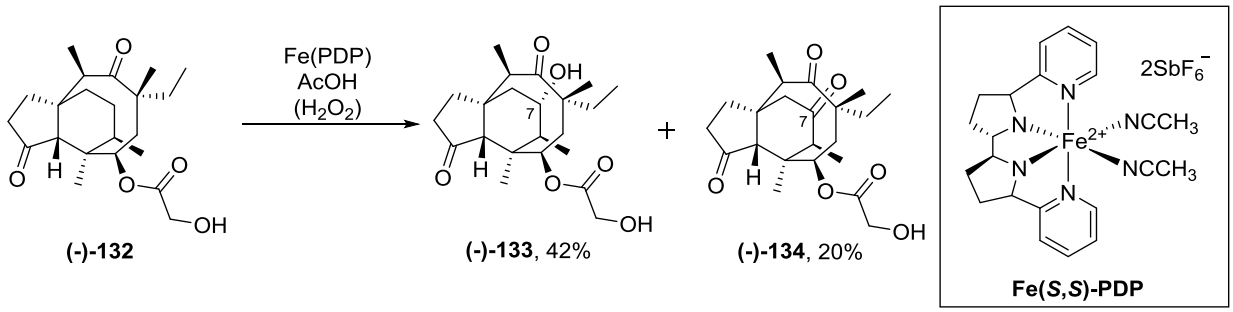
Scheme 30 Deprotection of x to reveal a hydroxyl group at C12.

Simplified analogues that possess a hydroxyl group at C11 (the natural point at which it is seen in pleuromutilin), should also be synthesised and the resulting activity of these compounds assessed. These molecules should be accessible by allylic oxidation either before (Scheme 31a) or after the cascade cyclisation step (Scheme 31b).[105,106]



Scheme 31 Proposed analogues with hydroxyl groups. (a) Allylic oxidation of the methyl ester intermediates prior to cascade cyclisation and (b) allylic oxidation of cores.

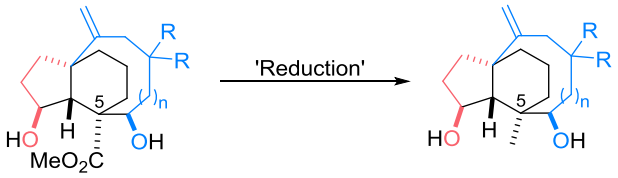
The other possible method for installing this hydroxyl group could be by an aliphatic C-H oxidation using Fe(PDP) as a catalyst. White *et al* showed that this catalyst was effective at performing late stage C-H oxidations and this method has been utilised for the oxidation of a protected pleuromutilin derivative **132**, with oxidations occurring at C7 to give compounds **133** and **134** (Scheme 32).[107] The oxidations that are possible on the unnatural tricyclic cores synthesised in this project using White's procedure are worth exploring. It may lead to the installation of the desired hydroxyl group or introduce this functionality at a position on the rings that proves to be favourable to its activity.



Scheme 32 Whites' oxidation of modified pleuromutilin using Fe(PDP).

The ester attached at C5 of analogues **135** is not present in the natural product, instead there is a methyl group (Figure 13a). This ester functionality may form hydrogen bonds within the ribosome that promotes activity, however it could also

prove to be detrimental. Therefore, it would be useful to investigate the effect of the ester group by synthesising cores **136** *via* a simple reduction protocol (Scheme 33).



135 **136**

Scheme 33 Removal of the C5 ester functionality in analogues.

As a result of this project, there are multiple avenues that can be explored in the future, that will allow expedient access to novel families of pleuromutilin analogues that cannot be prepared from the natural product by semi-synthesis and that, until now, have been inaccessible to medicinal chemists.

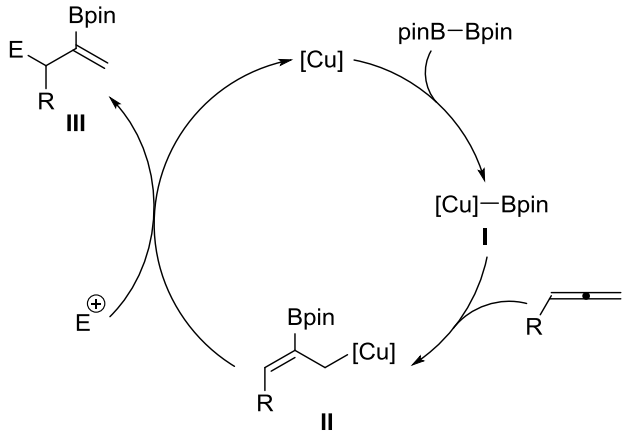
Part 2

Enantioselective Generation of Adjacent Stereocentres in a Copper-Catalysed Three-Component Coupling of Imines, Allenes and Diboranes

6.0 Introduction

Allenes possess two contiguous carbon–carbon double bonds, which results in interesting reactivity.[108,109] This along with developments in their formation, has increased their popularity in organic synthesis.[110–113] The functional group is used in a variety of transformations including propargylations, cyclisations, additions, and cycloisomerisations, to name a few.[114] Therefore, allenes are extremely useful building blocks in the construction of complex molecules, and have been utilised in the synthesis of natural products.[115,116] In addition, the use of these compounds has been enhanced further by advances in their borylation.

The use of copper in place of toxic or precious metal alternatives in catalysis has been increasing in popularity as a more sustainable option.[117–120] This has led to the recent developments of the functionalisation of allenes using copper catalysis. These reactions are generally initiated by the formation of a copper-element complex and for the purpose of this thesis, the borylation of allenes will be the focus. However, it is worth noting that other complexes have been reported. A general mechanism for the boryl-cupration of allenes is shown in Scheme 34.

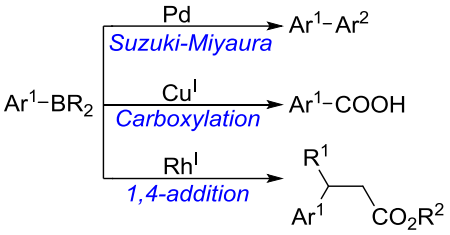


Scheme 34 General mechanism for the boryl-cupration of allenes.

These reactions generally occur by an initial transmetallation of the boryl reagent with the catalyst to form **I**, which is followed by the insertion of an allene into the newly formed Cu-B bond. The resulting allyl copper intermediate **II** can, in principle, be trapped with a variety of electrophiles, to form compounds **III**.[121–124]

Organoboron compounds are also extremely useful building blocks and are utilised for the formation of carbon–carbon bonds through the use of cross–coupling reactions, such as the Suzuki–Miyaura coupling, metal–catalysed 1,2–addition of carbonyl compounds and 1,4–addition to electron deficient alkenes or alkynes

(Scheme 35).[125–129] Their use has increased as the development of diboron reagents and organoboron chemistry have advanced in recent years.[130]

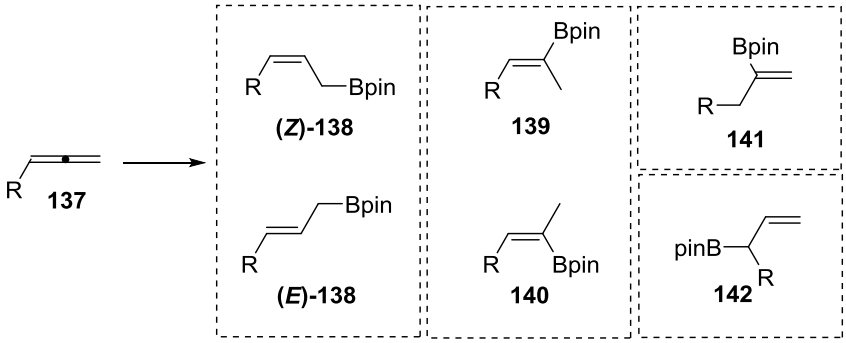


Scheme 35 A selection of reactions that can be carried out using organoboron compounds.

The following sections discuss the recent work that has been reported on the borylation of allenes catalysed by copper.

6.1 Copper-Catalysed Borylcupration of Allenes – Substrate Control

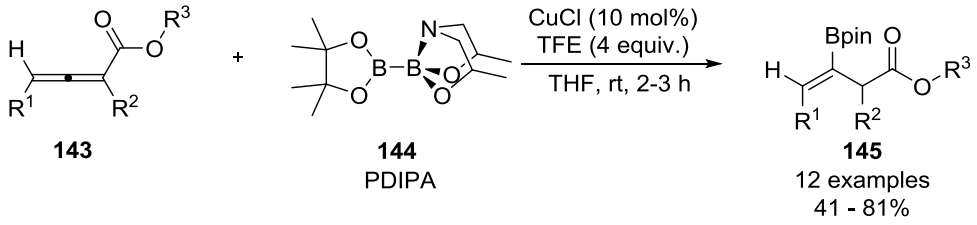
The hydroboration of allenes is a versatile reaction that allows access to many different products. However, this presents a significant regio- and stereoselectivity problem in the formation of organoboranes, as there are six different isomers that can in theory be produced (Scheme 36).



Scheme 36 Potential isomers formed from the hydroboration of monosubstituted allenes.

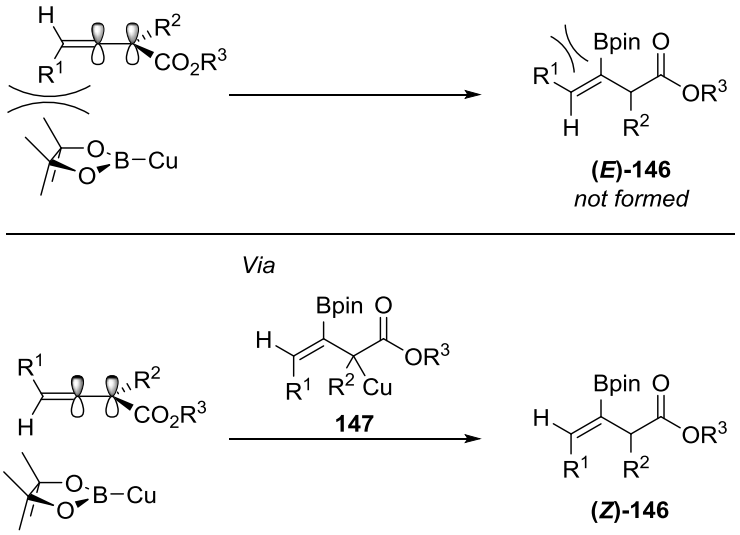
Recent work in this area has illustrated that the product formed in these reactions can be controlled by using allenes possessing an electron-withdrawing group or by changing the ligand used in the reaction.

Santos *et al* reported the first copper-catalysed formal hydroboration of an electron–deficient allene **143** in 2011, in which the allene used controls the selectivity (Scheme 37).[131] An sp^2–sp^3 mixed hybridised preactivated diboron reagent, PDIPA (**144**), was utilised to install a boron moiety at the β–position of the allenoate partner in moderate to good yields.



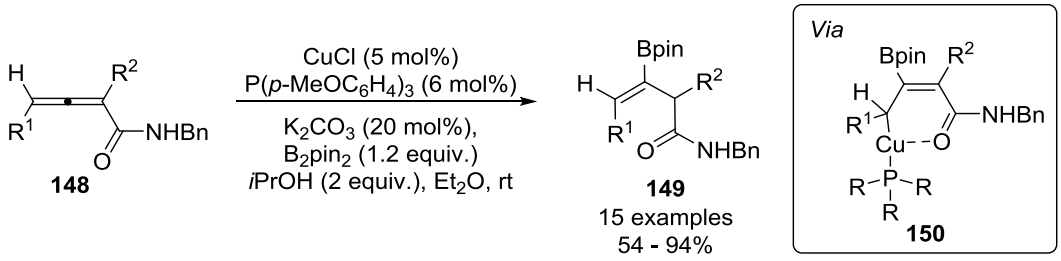
Scheme 37 Santos' copper-catalysed borylation of allenoates.

Due to the steric interactions with the γ-substituent of the allenoate, the boryl addition occurs on the opposite side of R^1, favouring the formation of the (*Z*)-product via intermediate **147**, and avoids the 1,2-allylic strain between R^1 and Bpin that would occur if the (*E*)-isomer was formed (Scheme 38). It is worth noting that Santos developed a procedure for the hydrosilylation of allenes using silylborane, $PhMe_2Si$-Bpin, to access analogous vinylsilane products.[132]



Scheme 38 Selective formation of the (*Z*)-product due to steric interactions of R^1 with the Cu-B complex.

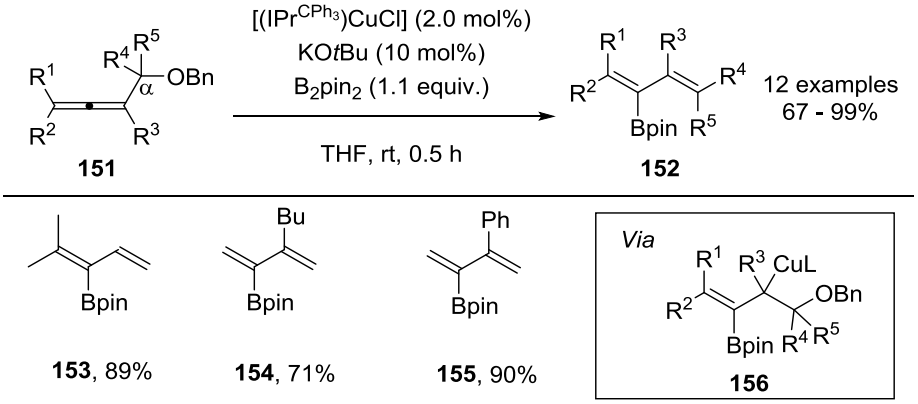
Ma decided to focus his attention on allenamides in order to control which products are formed.[133] As discussed previously, the borylation of monosubstituted allenes can result in complex mixtures of isomers (Scheme 36), however the challenge is much greater with trisubstituted allenes, as there are 8 possible isomers that can be produced. Ma investigated the use of different directing groups to control selectivity and was pleased to discover that the synthetically attractive amide group was effective at promoting the formation of β–borylated β,γ–unsaturated enoamides **148**, with (*Z*)-selectivity arising from intermediate **150** (Scheme 39).



Scheme 39 Cu-catalysed hydroboration of 2,3-allenamides by Ma *et al*.

The efficient selectivity shown in this reaction gave access to functionalised borylated products **149** under mild conditions in moderate to good yields.

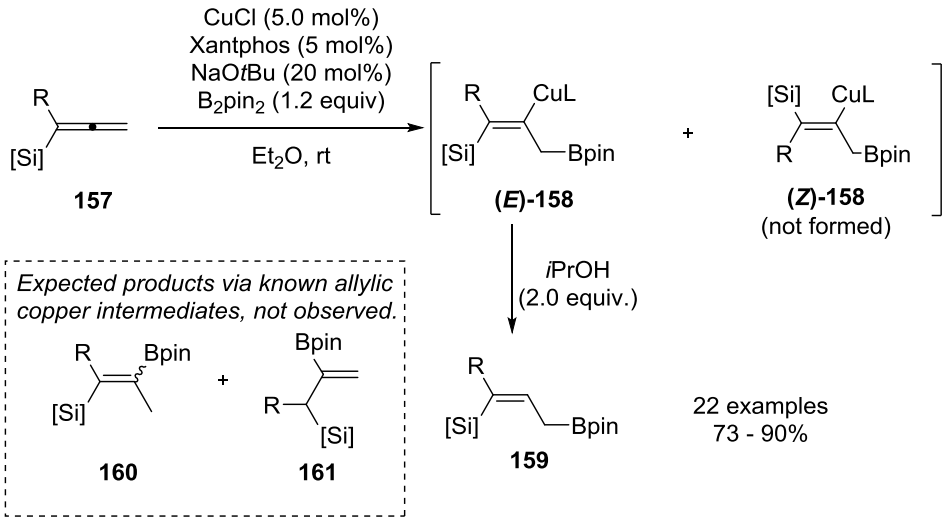
Tsuji and co-workers went on to develop a method for the borylation of allenes, containing a leaving group in the α-position, to selectively form 2-boryl 1,3-butadienes **152** (Scheme 40).[123] Different ligands were screened and the bulky NHC complex, [(IPr^{CPh_3})CuCl] gave the best results. The group swiftly investigated the tolerance of different leaving groups and found that -OBn performed well in the reaction.



Scheme 40 Selected examples for Tsuji *et al*'s copper-catalysed borylation of α-alkoxy allenes.

Under their optimised conditions, the substrate scope was investigated, to give 12 diene examples *via* intermediate **156**, in good to excellent yields.

In 2016 Ma and co-workers published the first example of a copper-catalysed borylcupration of an allene, where the boryl group becomes attached to the terminal carbon atom (Scheme 41).[134] They achieved this by using 1,2-allenylsilanes **157**, which resulted in the selective formation of allyl copper **(*E*)-158**, which results in selective formation of **159** in high yields and with excellent selectivity. Mechanistic studies showed that the expected allylic copper intermediates **160** and **161** were not observed.

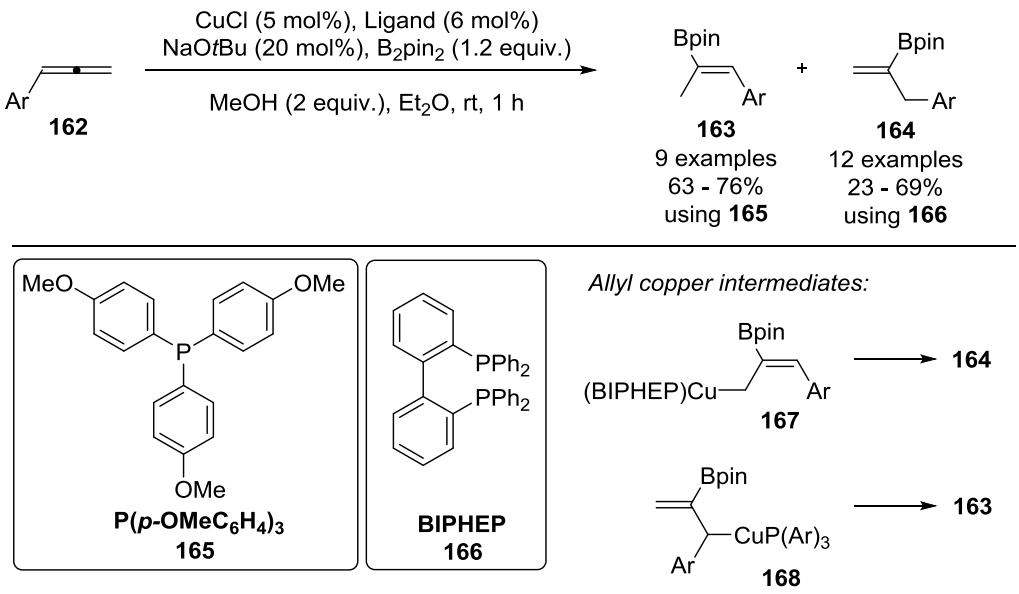


Scheme 41 Ma's copper-catalysed borylcupration of allenylsilanes.

Silyl allenes bearing primary and secondary alkyl groups all worked well, with more bulky substituents resulting in reactions with improved regio- and stereoselectivities. Functional groups such as a protected alcohol and an alkene were also tolerated. In addition, the silyl group could also be varied with good yields and excellent stereoselectivities observed.

6.2 Copper-Catalysed Borylcupration of Allenes – Ligand Controlled

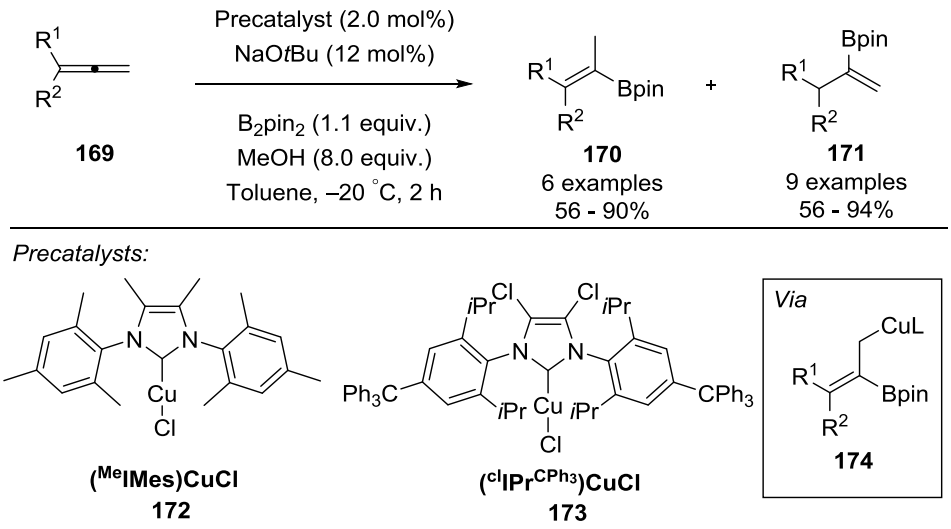
Yuan and Ma *et al* investigated whether the choice of ligand could influence selectivity in the borylcupration of allenes.[135] They subsequently developed a copper–catalysed hydroboration of allenes using B_2pin_2, which produced two different vinylboronates, **163** and **164**, with high regio- and stereoselectivity, depending on the ligand used (Scheme 42).



Scheme 42 Ma's borylcupration of allenes: illustrating the effect the ligand has on the regioselectivity of the reaction.

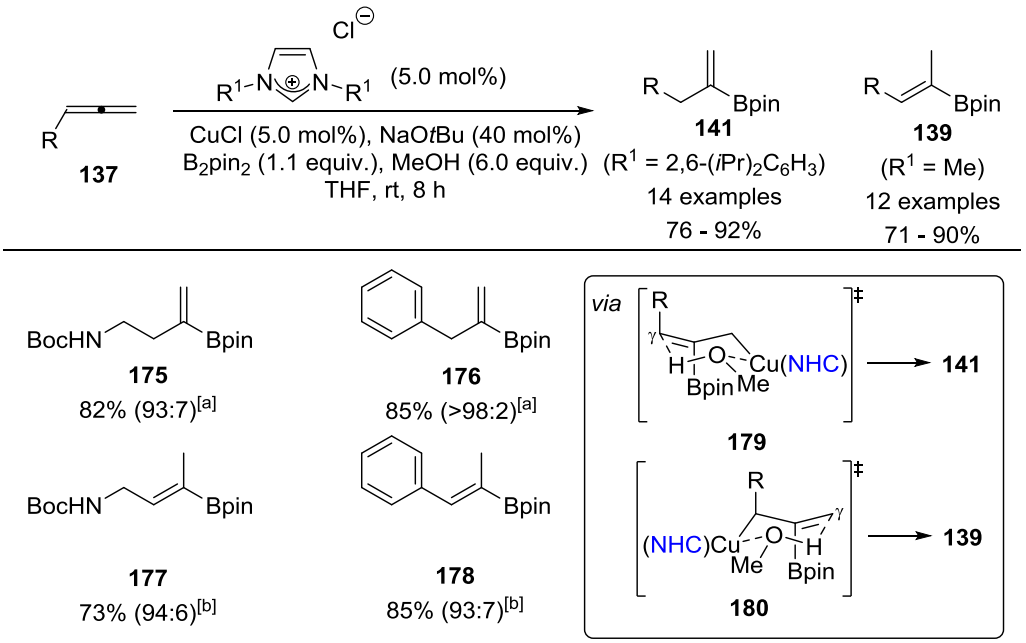
When monodentate phosphine ligand **165** was used in the reaction, 2-alken-2-yl boronates **163** were formed with exclusively (*Z*)-geometry. Upon changing to bidentate phosphine ligand **166** the regioselectivity switched to afford 1-alken-2-yl boronates **164**. This is due to the ligands influencing the allyl copper intermediate formed (Scheme 42). Although the substrate scope of this reaction is limited to arylallenes for the monodentate ligands, the reaction does however tolerate electron-withdrawing and -donating substituents at either the *ortho*-, *meta*- or *para*-position of the aromatic ring with little effect on the reactivity.

Tsuji and co-workers also developed a regioselective copper-catalysed hydroboration of allenes by employing different ligands in the reaction to control selectivity, with ligand **172** forming compounds **170** and ligand **173** forming compounds **171** *via* allyl copper intermediate **174** (Scheme 43).[136] The substrate scope in Yuan and Ma's work with mono-substituted allenes showed limitations, however, here Tsuji developed a system that was tolerant of allenes possessing primary alkyl, secondary alkyl and aromatic substituents and good yields and excellent selectivity was observed.



Scheme 43 Tsuji's Cu-catalysed hydroboration of allenes.

Similarly, in 2013 Hoveyda *et al* developed an NHC-Cu-catalysed protoboration of monosubstituted allenes and found that the size of the NHC ligand could control site selectivity (Scheme 44).[137]

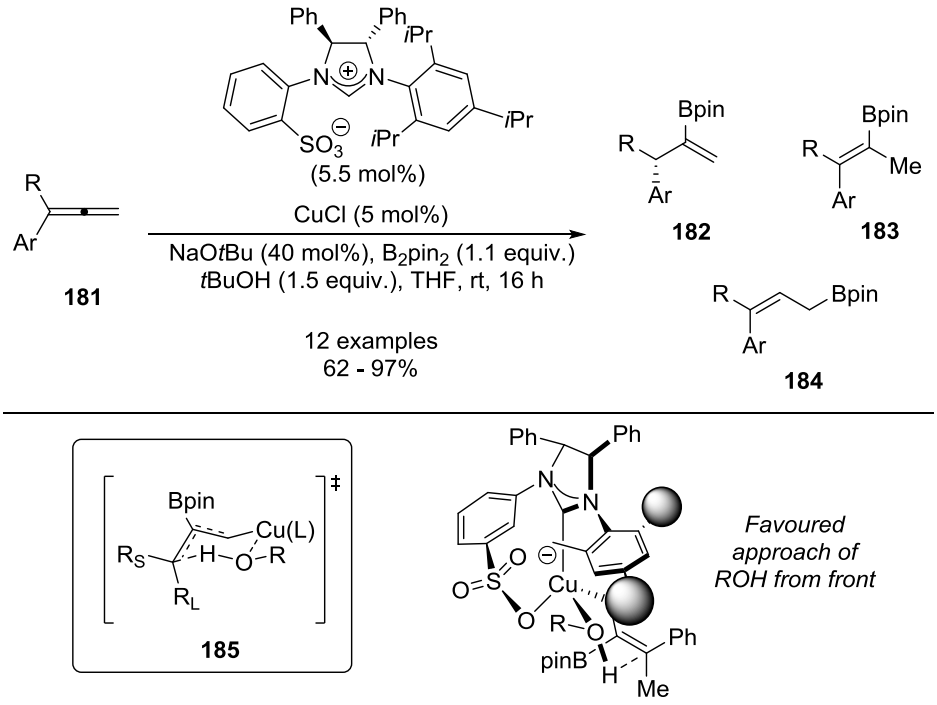


Scheme 44 NHC-Cu-catalysed protoboration of monosubstituted allenes by Hoveyda. [a] R^1 = 2,6-(*i*Pr)$_2$C$_6$H$_3$, [b] R^1 = Me.

The size of the NHC determines which intermediate is formed in the reaction, which subsequently determines the product formed. Larger NHCs promote the formation of 1,1–disubstituted vinylborons *via* transition structure **179** (CuNHC added at the least substituted end of the allene), whereas smaller NHCs form the *Z*–trisubstituted vinylboron compounds by transition state **180** (CuNHC added at most substituted

end of the allene) (Scheme 44). To illustrate the use of this method, they applied this chemistry to the synthesis of a fragment of an antibiotic macrolide, elansolid A.

They also developed a method for the catalytic enantioselective protoboration of disubstituted allenes.[138] They envisaged a reaction in which a 1,1-disubstituted allene **181** would react with a L-Cu-Bpin chiral complex and the resulting copper intermediate would be protonated in the γ-position, to give access to useful enantiomerically enriched alkenylboron products. Aryl-allenes possessing various substitution patterns and functional groups, including heteroaromatic groups, were found to be suitable for the reaction and transformations proceeded with good to excellent yields and selectivity (Scheme 12).



Scheme 45 Hoveyda and co-workers' catalytic, enantioselective protoboration of disubstituted allenes. R_S = Smaller substituent and R_L = Larger substituent.

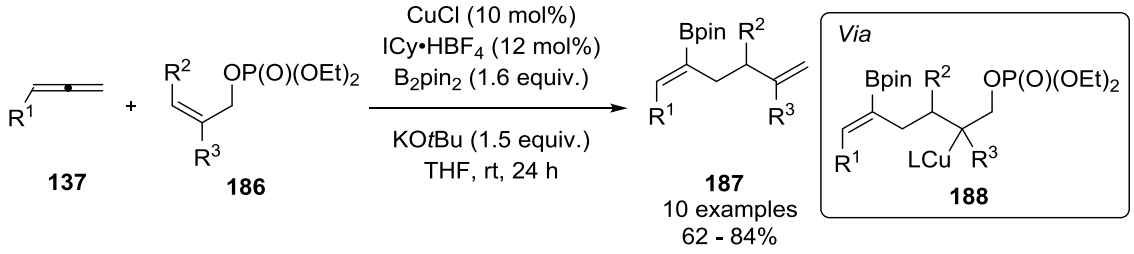
Again, the choice of ligand proved to be extremely important, with the combination of an NHC ligand and a bulky alcohol providing access to products **182** with high enantioselectivity, whereas phosphine ligand [(*S*)-Segphos] resulted in lower enantioselectivity and produced large amounts of undesired isomers **183** and **184**.

The copper-catalysed borylation of allenes initially focused on gaining control of regioselectivity in the reaction, however, once this was better understood, investigations into three-component couplings emerged.

6.3 Copper-Catalysed Borylcupration of Allenes - Multicomponent Reactions

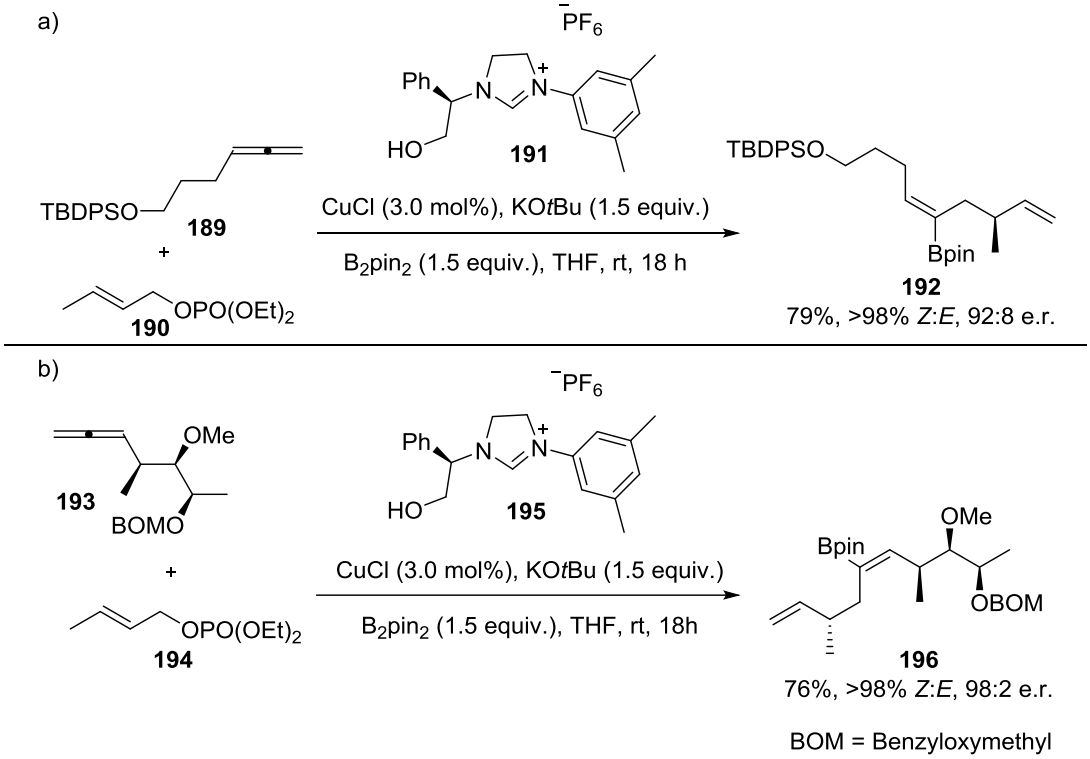
Extensive investigation of transition metal catalysed three-component couplings of allenes has been carried out utilising palladium, nickel and rhodium.[139] In recent years the focus has been switched to using copper catalysis to carry out such couplings, and the following section discusses the relevant advances.

In 2014, Tsuji *et al* reported the first example of a borylative allyl-allyl coupling. This one-pot three-component reaction consisted of monosubstituted allenes, B_2pin_2 and allyl phosphates, and produced a variety of boryl-substituted 1,5-dienes **187** in moderate to high yields, and high stereo- and regioselectivity (Scheme 46).[140] The formation of the 1,5-diene products occurs *via* the copper intermediate **188**, and elimination of the phosphate group. Unfortunately, 1-phenylallenes, 1,1-disubstituted and 1,3-disubstituted allenes were unsuccessful when applied in this reaction.



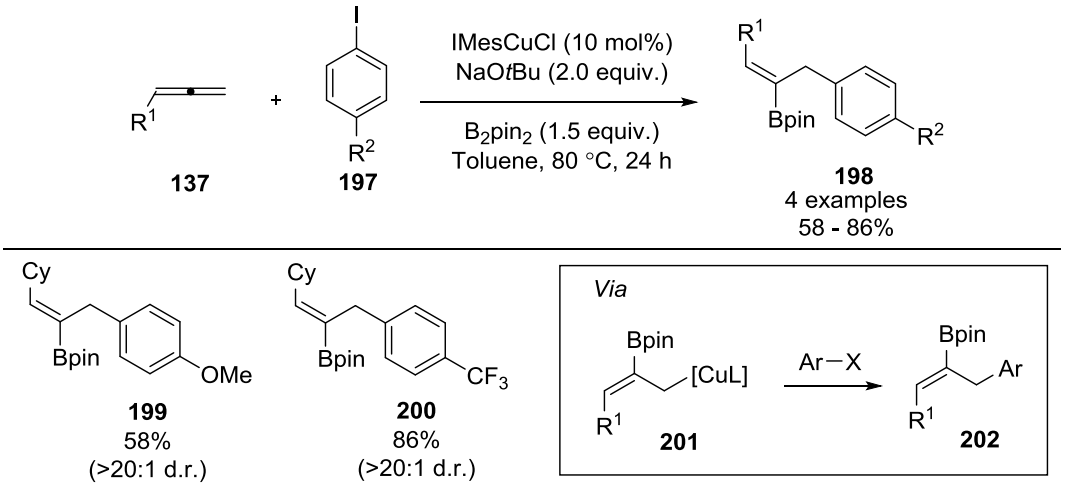
Scheme 46 Tsuji's borylative allyl-allyl coupling. Isomeric purity of all products > 95%.

The Hoveyda group went on to develop an asymmetric version of Tsuji's three-component coupling reaction using an allylic phosphate as the electrophile, which provided access to compounds bearing an alkenyl boron group for later transformations.[141] To illustrate the utility of this approach, the group used their method in the enantioselective synthesis of two natural products on a multi-gram scale (Scheme 47).



Scheme 47 Hoveyda's utilisation of a three-component reaction for natural product synthesis. (a) Fragment for the synthesis of Rottnestol. (b) Fragment for the synthesis of Herboxidiene (GEX1A).

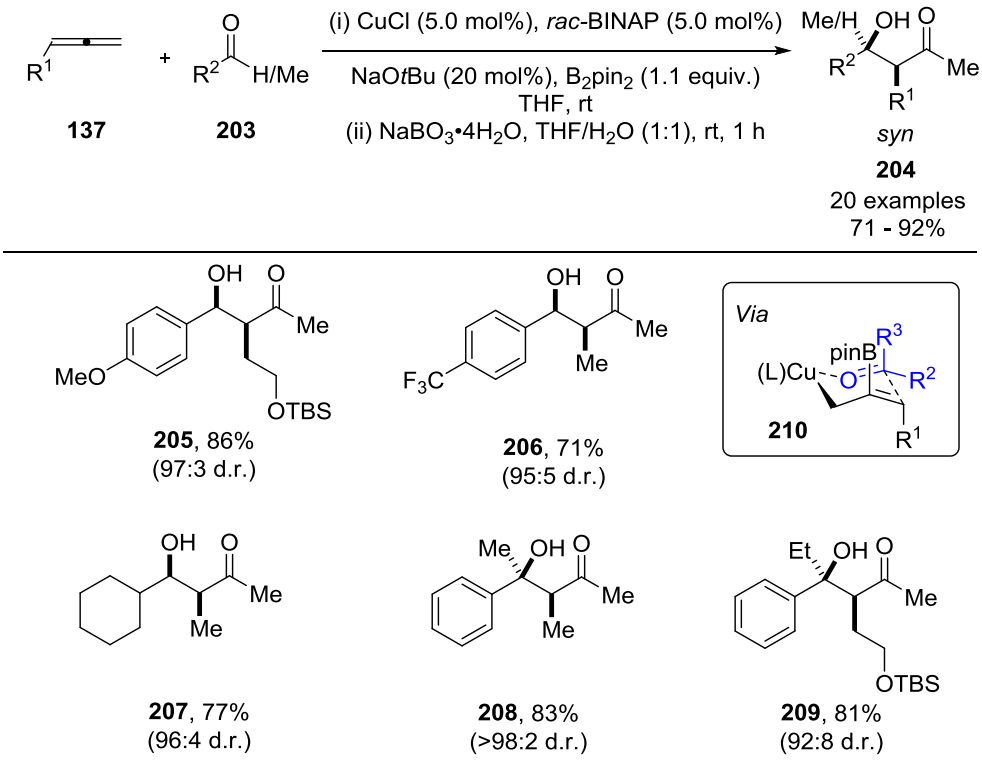
Building on the knowledge that Cu-Bpin borocupration can occur with allenes and that an allylcopper results, Brown *et al* investigated the use of aryl iodides as carbon-based electrophiles to intercept the intermediate **201** (Scheme 48).[142] The group found that the proposed carboboration was possible by utilising IMesCuCl as the precatalyst, and vinyl boronic esters **198** were produced with exclusive Z-alkene geometry.



Scheme 48 Brown's copper-catalysed carboboration of allenes.

From Brown's short substrate scope, the reaction was found to be tolerant of electron-donating and withdrawing substituents on the aryl iodide and in all cases the *Z*-alkene was the sole product. This example represents a promising advancement into the carboboration of allenes.

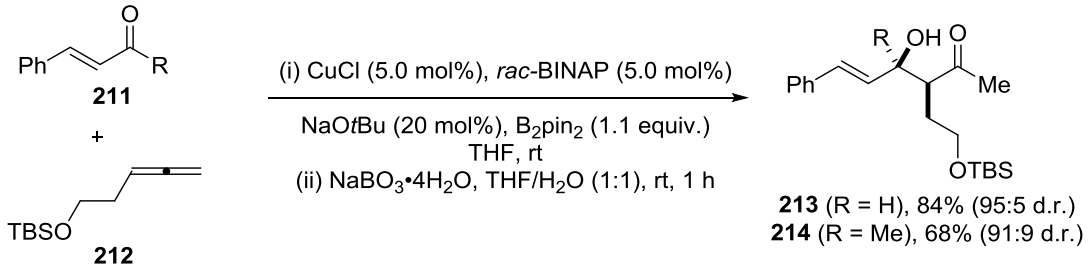
Hoveyda went on to develop a three-component coupling between allenes, B_2pin_2 and aldehydes/ketones, in which *rac*-BINAP was the best performing ligand (Scheme 49).[143]



Scheme 49 Intercepting allylcopper intermediates to form β-hydroxy ketones by Hoveyda.

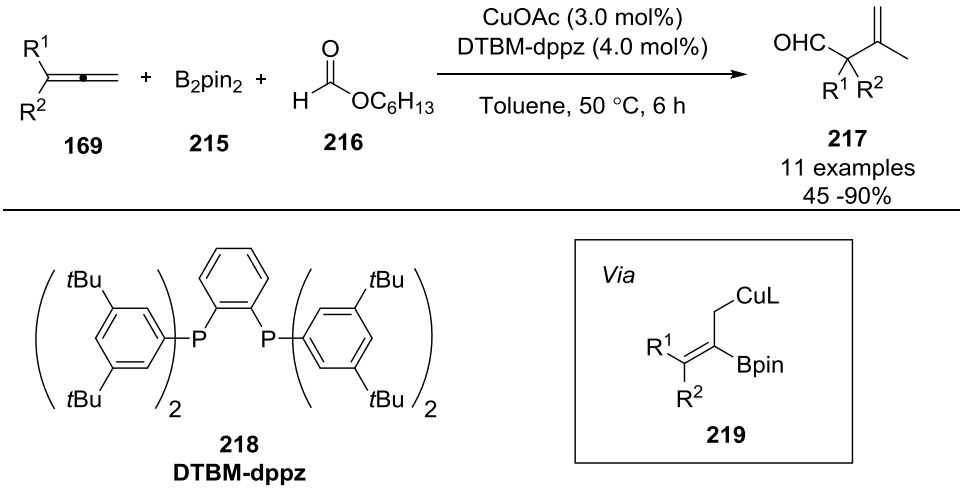
Various aryl-substituted aldehydes are suitable for this reaction, giving rise to methyl ketones containing secondary alcohols **204**, after subsequent oxidation of the C-B bond, with complete γ-selectivity and high diastereoselectivity observed. The reaction is tolerant of steric challenges and diverse electronics implemented on the aryl group of the allene, however, electron withdrawing substituents on the allene necessitate the use of an increased amount of that component. Aryl ketones can also be used to intercept the allyl-copper to form tertiary alcohols **208** and **209** with high yields and excellent diastereoselectivity. It is worth noting that related procedures have been reported by Procter *et al* and Tsuji, to produce vinyl silanes by the copper-catalysed three-component coupling of allenes, a silylborane reagent and aldehydes/ketones.[144,145]

α,β-Unsaturated carbonyls were also compatible with the process and proved to be impressive examples due to the complication of possible competing side reactions, such as an allyl conjugate addition (Scheme 50).



Scheme 50 Catalytic allylcopper additions to unsaturated aldehydes and ketones by Hoveyda.

More recently in 2017, Tsuji and co-workers reported the boraformylation of 1,1-disubstituted allenes, utilising B_2pin_2 as the boron source (Scheme 51).[146] This method was successfully applied to a variety of disubstituted allenes to give the corresponding β-boryl β, γ-unsaturated aldehydes **217** in good to high yields *via* allyl copper intermediate **219**.



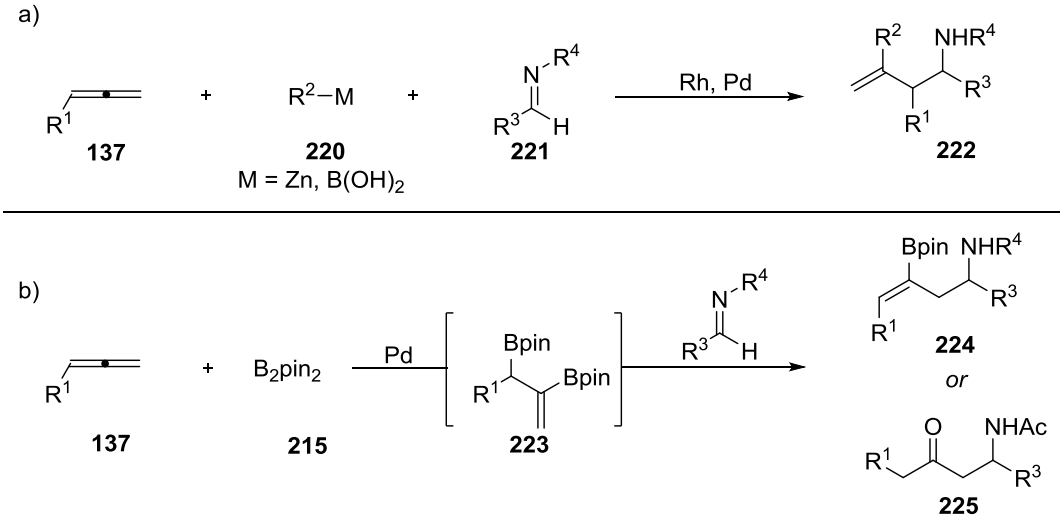
Scheme 51 Tsuji's boraformylation of allenes.

With the use of carbonyl based electrophiles to trap allyl copper intermediates being extensively investigated, the use of imines as electrophiles became of interest.

6.3.1 Copper-Catalysed Borylative Cross-Coupling of Allenes and Imines

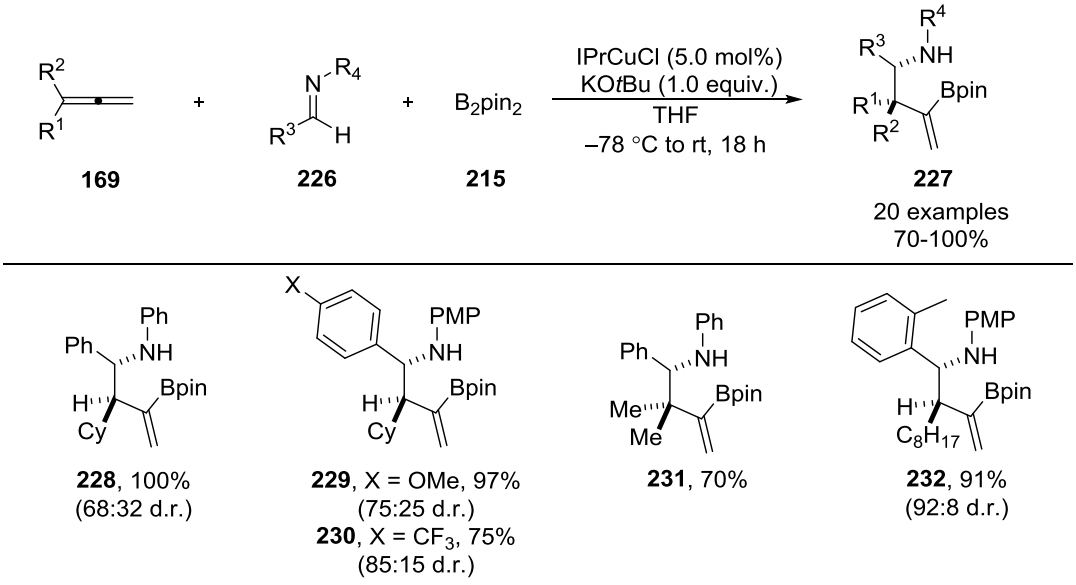
Homoallylic amines are valuable precursors for the formation of biologically active molecules and in 2016 Procter *et al* reported using a copper-catalysed borylative cross-coupling between allenes and imines.[147] Homoallylic amines have been previously synthesised from allenes and imines using Rh and Pd catalysts and organozinc/boronic acid partners (Scheme 52a).[148–150] They have also been

accessed by Morken's group by palladium catalysed asymmetric diboration of allenes to form **223**, followed by its subsequent addition to an imine (Scheme 52b).[151] This produces linear boryl compounds **224** that are converted into Mannich products **225** during the work-up for ease of isolation.



Scheme 52 Previous approaches using allenes and imines in catalytic three-component couplings. (a) With allyl metals produced from organometallic addition to allenes. (b) Using allyl boranes produced by diboration of allenes and in which products are enantioenriched.

This encouraged the Procter group to pursue a copper-catalysed three-component coupling reaction of allenes, B_2pin_2 and imines. Their reaction furnished readily isolable, branched homoallylic amines **227** in high yields and with excellent regioselectivity (Scheme 53). [147]



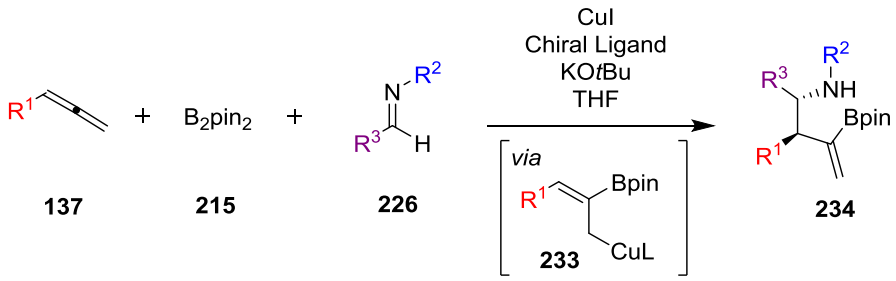
Scheme 53 Selected examples of Procter's copper-catalysed borylative allylation of imines.

This reaction proved to be tolerant of many different allene and imine coupling partners: linear alkyl, aryl, 1,1-dialkyl and 1,1-disubstituted allenes were all effective, and the presence of electron-donating and -withdrawing substituents on the aryl group of the imine coupling partner was tolerated. The majority of borylated homoallylic amines **227** were stable to silica and could be isolated, with no signs of protodeborylation. The products could also be converted to Mannich-type products after an oxidative work-up.

This protocol utilises a cheap and readily available copper catalyst. The procedure is an attractive one-pot reaction in which branched homoallylic amines are formed that possess not only the amine group, but also alkene and vinyl borane functionality.

7.0 Project Aims

Previous work in the group focused on the copper-catalysed three-component coupling reaction between allenes, diboranes and imines to form racemic branched homoallylic amines **234** with high diastereoselective control (Section 6.3.1).[147,152] The next step for this work was to develop an asymmetric version of this reaction, bringing together the components in diastereoselective and enantioselective fashion (Scheme 54).[153]



Scheme 54 Proposed asymmetric three-component coupling reaction.

The reaction proceeds via the formation and trapping of allyl-copper **233** and by employing a chiral ligand it may be possible to achieve facial selectivity in addition to the imine and thus develop an asymmetric version of the reaction. This would provide an attractive route to enantioenriched homoallylic amines possessing adjacent 1,2-stereocentres.

8.0 Preliminary Results

The next step for this work was to develop an enantioselective version of the reaction, by utilising a chiral ligand and a low-cost copper catalyst.[153]

I joined first year PhD student, Kay Yeung on this project at a time when she had carried out screening of different commercially available chiral ligands (Figure 14). A selection of her preliminary results are shown in Table 2, to access homoallylic amine **237**.

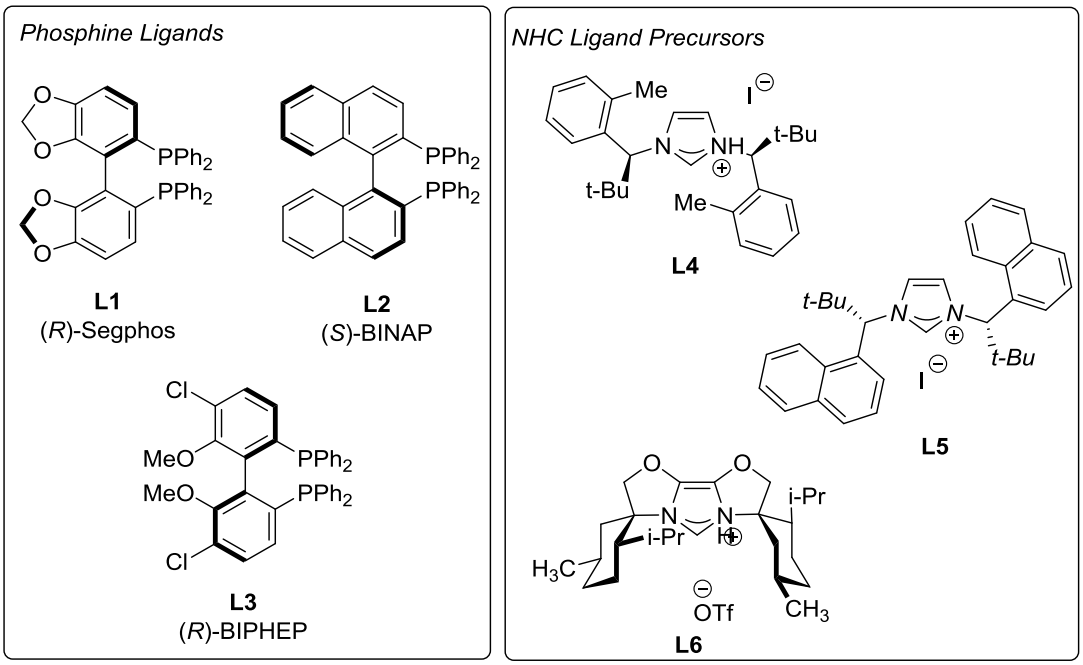


Figure 14 Ligands screened by Kay Yeung.

Kay Yeung began her efforts by screening chiral phosphine ligands **L1**, **L2** and **L3**, however, with these ligands the reaction proceeded with low conversion and poor enantioselectivity (Entries 1 - 3). Considering this, she turned her attention to commercially available imidazolium salts that would generate the desired chiral NHC ligand *in situ*. On employing **L4** (Entry 4) there was a promising increase in the yield, albeit with modest enantioselectivity observed, and no product was observed when using **L6** (Entry 6).[154,155] The best NHC ligand was derived from Kündig's imidazolium salt **L5**.[156] As far as we are aware, this is the first example of NHCs derived from **L4** and **L5** being utilised in asymmetric copper-catalysed reactions. Pleasingly, after an investigation into the effect of temperature on this reaction, room temperature was discovered to be optimum.

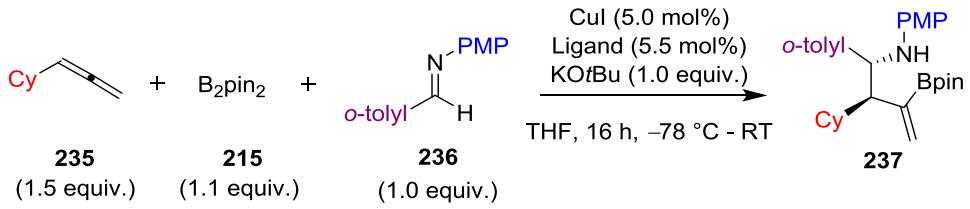
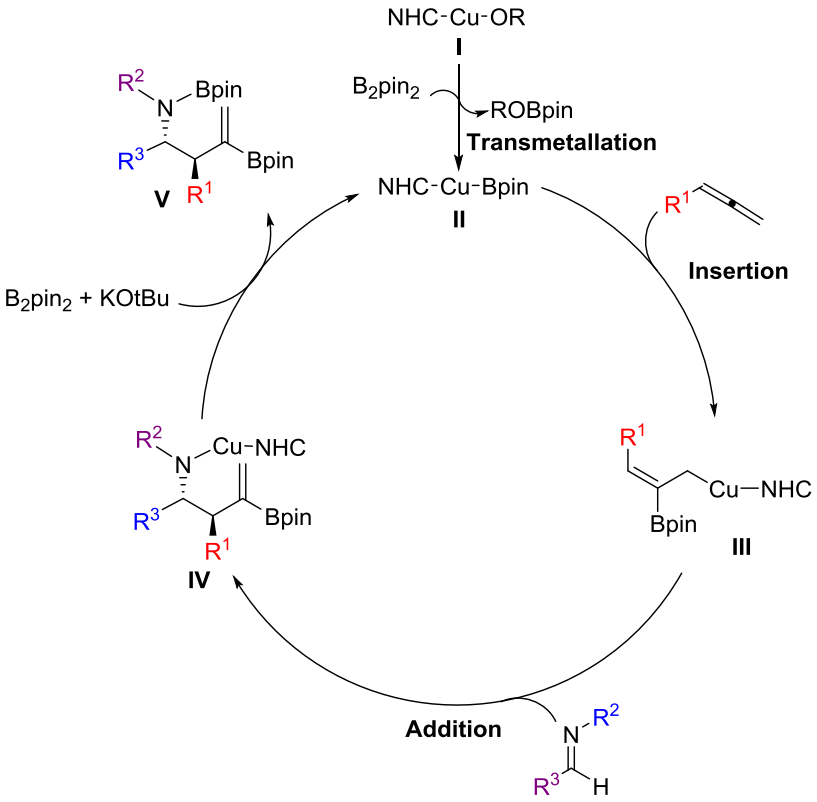


Table 2 Ligand screening by Kay Yeung using the conditions shown in Scheme 1.

Entry	Ligand	Yield of 237 (%)	d.r.	e.r.
1	**L1**	19	> 98:2	55:45
2	**L2**	7	> 98:2	51.5:48.5
3	**L3**	8	> 98:2	50.5:49.5
4	**L4**	26	> 98:2	67:33
5	**L5**	84	> 98:2	98:2
6	**L6**	0	-	-

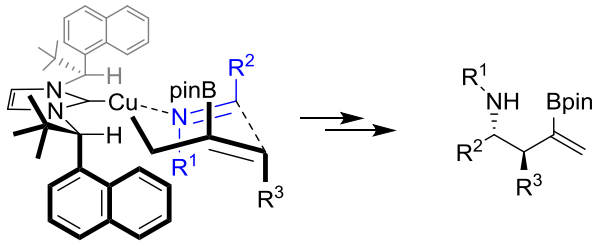
8.1 Mechanism and Origin of Selectivity

A proposed mechanism for the reaction is shown in Scheme 55. The catalytic cycle begins with the formation of copper alkoxide **I** by the addition of KO*t*Bu to a mixture of CuI and the NHC precursor, and this is followed by transmetallation with B_2pin_2 to form **II**. Allylcopper **III** is then formed by the regioselective insertion of the allene into the Cu-B bond. Diastero- and enantioselective addition to the imine then results in the formation of intermediate **IV**. The regeneration of **II** is achieved by base-assisted transmetallation which also forms the desired homoallylic amine after work-up.



Scheme 55 Proposed mechanism for the three-component coupling reaction.

The *anti*-selectivity in these reactions is believed to originate from the six-membered-ring chair transition state shown in Scheme 2. Previous computational studies carried out in the group suggest that this chair transition state is favoured despite several groups adopting pseudoaxial orientations.[147] The absolute stereochemical control observed is proposed to arise from the naphthyl rings of the C_2 symmetrical NHC ligand causing one face of the allyl copper species to be more accessible to the imine.

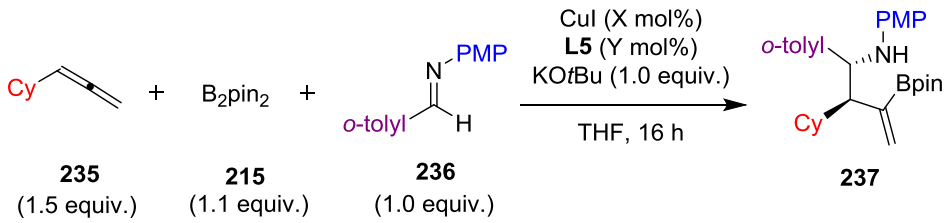


238 **239**

Scheme 56 Proposed transition state to explain the diastereo- and enantioselectivity of the reaction.

8.2 Investigating Catalyst Loading

On beginning work on the project, I investigated the effects of changing the catalyst and ligand loading on the yield of the reaction (Table 3). The loadings used prior to this had been adopted from the racemic version of the reaction and so it was important to investigate the effect the changes had on this new system.



235 (1.5 equiv.) **215** (1.1 equiv.) **236** (1.0 equiv.) **237**

Table 3 Investigating the loading of CuI and **L5**. [a] NMR yields measured against a nitromethane internal standard (see General Experimental Section). [b] Isolated Yield.

Entry	X mol%	Y mol%	Yield of 237 (%)[a]
1	0.5	0.55	48
2	1.0	1.1	51
3	2.5	2.75	57
4	5.0	5.5	79 (86%)[b]

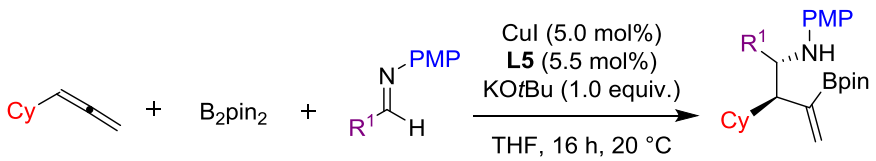
Attempts to lower the catalyst loading used in the reaction resulted in a decrease in the yield (Entries 1 - 3). Therefore, the conditions for exploring the scope of the reaction used 5.0 mol% loading of CuI and 5.5 mol% of **L5**. Combining this outcome with the optimisation investigations of ligand and temperature performed by Kay Yeung, we were obtaining promising results and so the next step was to investigate the scope of the reaction. This work was a collaborative effort and so substrates synthesised by other chemists have been marked accordingly.

8.3 Scope of the Reaction – Variation of the Imine

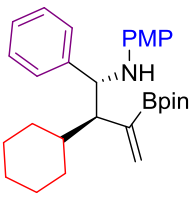
Firstly, the imine component was varied, whilst keeping the allene and diborane reagent constant (Scheme 57). Generally, the reaction proceeded well and tolerated a range of steric and electronic variations in R^1, the substituent on the imine. The reaction was successfully applied to imines containing electronically neutral arenes (to form **242** and **243**), along with those containing electron-donating (**246**) and electron-withdrawing groups (**245**), to form the corresponding products in high yields, with excellent enantioselectivity (Scheme 57). The reaction also responded well to steric challenges, with *ortho*-substituted imines forming the corresponding

products **237** and **246**, in high yields and with excellent enantioselectivites. The *ortho*-SMe imine to form **249** worked well in the reaction, but with lower enantioselectivity than seen with other substrates. This may be due to a disruption in the proposed transition state, possibly due to coordination of the SMe group with the copper catalyst. Use of an aryl imine containing a BOC-protected amine in the *ortho*-position was unsuccessful and product **250** was not formed. This is thought to be due to the coordination of the nitrogen of the imine and the carbonyl from the BOC group with copper, thus preventing further interaction of the copper-catalyst with the allene. Imines containing heterocycles gave access to products **253** and **254**, although in lower yields and with lower diastereoselectivity, however enantioselectivity remained high. We believe that the reduced diastereoselectivity observed with these substrates is due to the smaller size of R^1. Disappointingly, on submitting a ketamine to the reaction, no trace of product **255** was observed, suggesting that increasing the steric bulk around the imine functionality is preventing the reaction or tautomerisation of the imine is occurring.

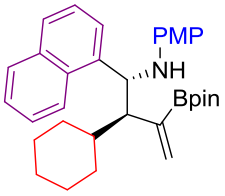
A large-scale reaction was carried out to produce 2.08 g (4.35 mmol) of product **237**, utilising 1.0 mol% of CuI and 1.1 mol% of the ligand precursor **L5**. The product was formed in excellent yield and with exceptional selectivity (98%, > 95:5 d.r. and 98:2 e.r.) with a lower catalyst loading than used previously.



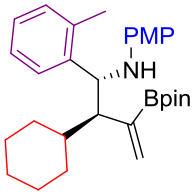
235 (1.5 equiv.) **215** (1.1 equiv.) **240** (1.0 equiv.) **241**



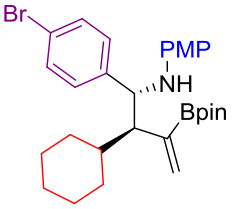
242, 76%
98:2 e.r.
74:26 d.r.



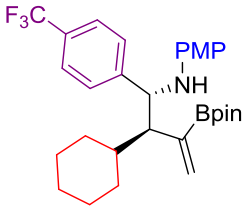
243, 93%[a]
97:3 e.r.
90:10 d.r.



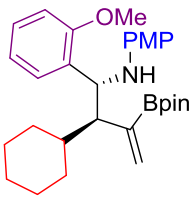
237, 86%[b]
99:1 e.r.
98:2 d.r.



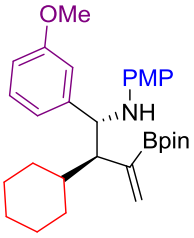
244, 86%[a]
98:2 e.r.
76:24 d.r.



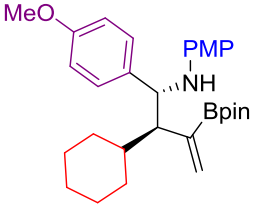
245, 85%
96:4 e.r.
76:24 d.r.



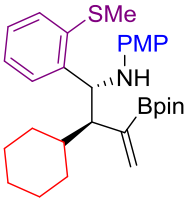
246, 75%[a]
98.5:1.5 e.r.
86:14 d.r.



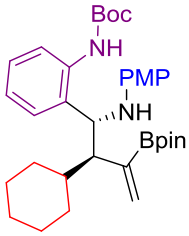
247, 87%
98.5:1.5 e.r.
82:18 d.r.



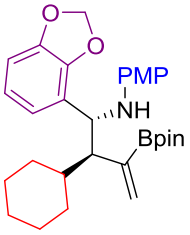
248, 66%[a]
99:1 e.r.
70:30 d.r.



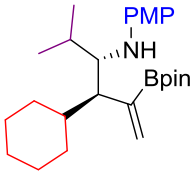
249, 70%
84:16 e.r.
95:5 d.r.



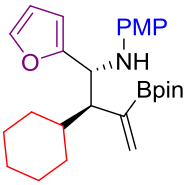
250, 0%



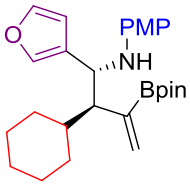
251, 71%
97:3 e.r.
82:18 d.r.



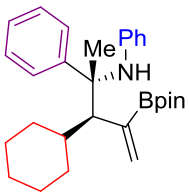
252, 44%[a]
60:40 e.r.
89:11 d.r.



253, 60%
97:3 e.r.
68:32 d.r.



254, 34%
97:3 e.r.
68:32 d.r.

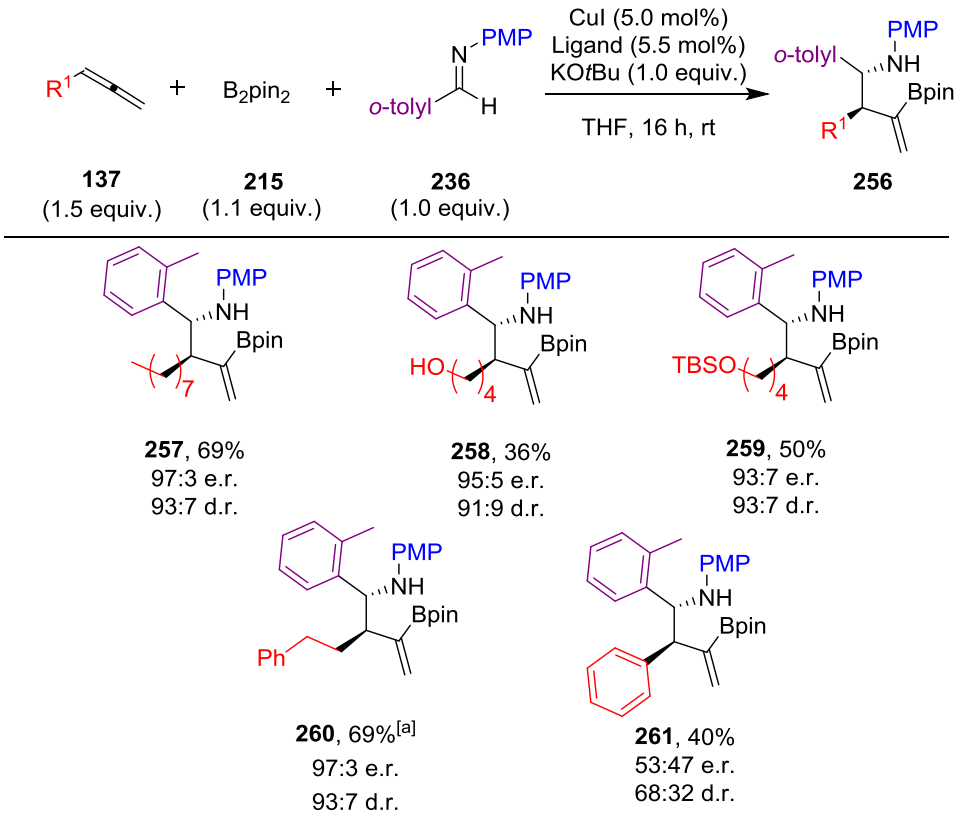


255, 0%

Scheme 57 Scope of the three-component coupling reaction with variation of the imine. [a] In collaboration with Kay Yeung. [b] Large scale reaction was carried out by Kay Yeung.

8.3.1 Variation of the Allene

The next component of the reaction to be investigated was the allene. It was found that monosubstituted allenes possessing primary alkyl groups gave access to the desired coupling products with high enantioselectivity (Scheme 58). The reaction was tolerant of the presence of a silyl ether (**259**) and a free alcohol (**258**), although a lower yield was obtained with a free hydroxyl group, with both products formed with diastereo- and enantiocontrol. Competitive protonation of the allylcopper by the hydroxyl group is not observed, therefore the reduced yield of **258** may be due to the deprotonated alcohol interacting with the copper-catalyst, which could potentially reduce turnover.



Scheme 58 Investigating the reaction with various mono-substituted allenes. [a] In collaboration with Kay Yeung.

On employing 1-phenylallene in the reaction, the coupled product **263** was formed in low yield (40%) under the standard reaction conditions and with essentially no enantioselectivity (53:47 e.r.). Therefore, a change in ligand was investigated, along with temperature and solvent variation (Table 4). Lowering the temperature at which the coupling was carried out (20 to –15 °C) led to a slight improvement in enantioselectivity (Entries 1 and 2). On changing the solvent for the coupling (Entries 3 to 5), no significant improvement in the yield was achieved, and

essentially no change in the enantioselectivity was observed (Entry 5). A series of ligands were screened (Entries 6,11,12 and 13), with the use of ligands **L1**, **L6** and **L7** producing the desired product in disappointing yields and in virtually racemic form. The *o*-tolyl ligand precursor **L4** led to improved enantioselectivity (Entry 6), although the reasons for this are currently unknown. Pleasingly, when lowering the temperature of the reaction to –15 °C, the enantioselectivity of the reaction could be significantly improved further (81:19 e.r.) when using **L4** in the reaction, although this was at the cost of a reduction in the yield (Entry 7).

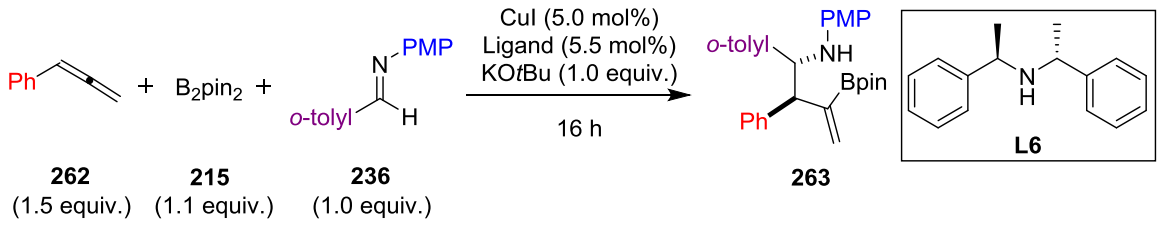


Table 4 Optimisation of the reaction employing 1-phenylallene. [a] 10 mol% CuI and 11 mol% **L4**.

Entry	Ligand	Temperature (°C)	Solvent	Yield of 263 (%)	d.r.	e.r.
1	**L5**	20	THF	40	68:32	53:47
2	**L5**	–15	THF	30	58:42	51:49
3	**L5**	20	Et_2O	42	65:35	53:47
4	**L5**	20	CH_2Cl_2	0	-	-
5	**L5**	20	Toluene	44	64:36	56:44
6	**L4**	20	THF	39	81:19	72:28
7	**L4**	–15	THF	32	83:17	81:19
8	**L4**	–30	THF	35	70:30	68:32
9	**L4**	–45	THF	34	75:25	76:24
10	**L4**[a]	–45	THF	38	62:38	63:37
11	**L1**	20	THF	6	51:49	53:47
12	**L6**	20	THF	12	53:47	51:49
13	**L7**	20	THF	0	-	-

Under the standard conditions, 1,1-disubstituted allenes gave poor yields (37%), but with good enantioselectivity (94:6 e.r.). In an attempt to improve this, the copper salt

and ligand loading, along with the amount of base, B_2pin_2 and allene used were investigated (Table 5).

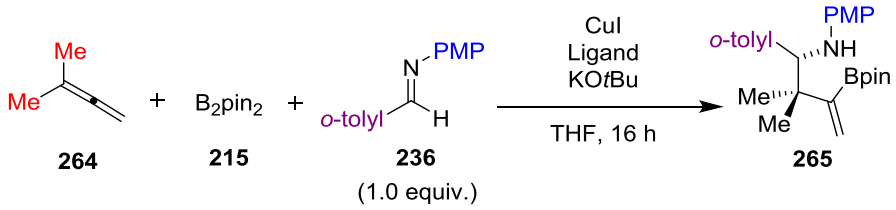


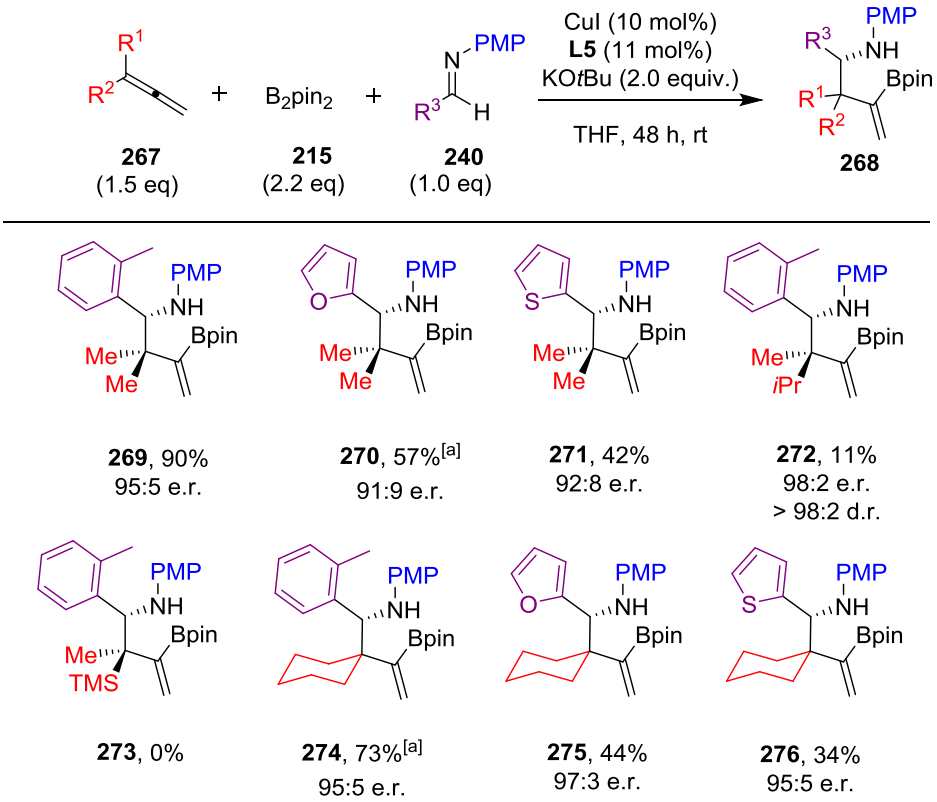
Table 5 Optimisation of the reaction using a 1,1-disubstituted allene. [a] NMR yield measured against a nitromethane internal standard. [b] 2 x 5 mol% CuI, 2 x 5.5 mol% **L5**, 2 x 1.0 eq KOtBu, and 2 x 1.1 eq B_2pin_2 added 16 hours apart. n.d. = not determined.

Entry	CuI (mol%)	L5 (mol%)	KO*t*Bu equiv.	B_2pin_2 equiv.	Allene equiv.	Temp (°C)	Yield (%)	e.r.
1	5	5.5	1.0	1.1	1.5	20	37	94:6
2	5	5.5	1.0	1.1	1.5	–45 to 20	29[a]	n.d.
3	10	11	2.0	2.2	2.25	20	86	95:5
4	10	11	2.0	1.1	1.5	20	62	95:5
5[b]	10	11	2.0	2.2	1.5	20	90	95:5

It was believed that there could be an issue with the turnover of the catalyst or that the catalyst was being rendered inactive due to the presence of both allene and imine in the reaction mixture, therefore more catalyst and ligand was introduced to the reaction mixture after 16 hours. An increase in the yield was noted on adding more CuI, **L5**, base, B_2pin_2 and allene to the reaction (86% of **265**) (Entry 3), however, only a slight increase in yield was observed when the amount of CuI, ligand and base was increased (62% of **265**) (Entry 4). The best results were obtained when more CuI, **L5**, base and B_2pin_2 were added *via* cannula after one day stirring under normal conditions. This led to an improved yield of **265** of 90% (Entry 5). It is worth noting that the cannula addition is essential to obtain higher yields and enantioselectivity. For example, beginning the reaction with 10 mol% of CuI, 11 mol% of **L5** and base (2.0 equiv.) gave the desired product in only 48% yield (75:25 e.r.) as opposed to 90% (95:5 e.r.) using the 'extra addition method'. This suggests that the catalyst is being rendered inactive at a faster rate than the desired reaction is occurring and recharging the catalyst is important.

These optimised conditions were applied to various 1,1-disubstitued allenes to give products bearing a quaternary centre in the β-position (Scheme 59). All products

were obtained with excellent enantioselectivity and product yields varied depending on the imine used in the reaction; for example, heterocyclic imine coupling partners produced the desired products in lower yield (formation of **270**, **271**, **275** and **276**).

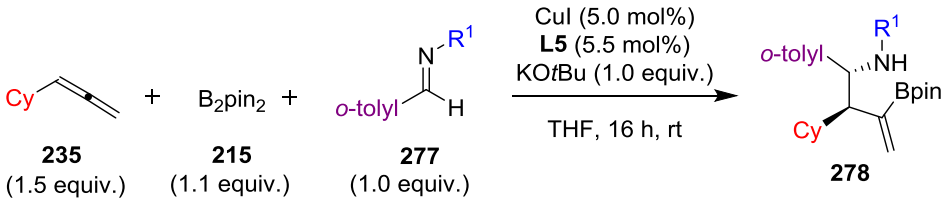


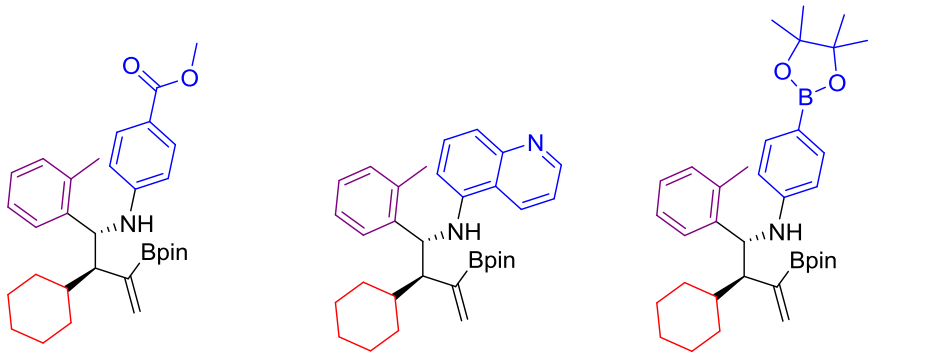
Scheme 59 Couplings to form homoallylic amines bearing quaternary centres in the β-position. [a] In collaboration with Kay Yeung.

The three-component coupling reaction was attempted with unsymmetrical 1,1-disubstitued allenes in order to install an all-carbon quaternary stereocentre in the β-position (Scheme 59). While product **273** was not formed under the reaction conditions, homoallylic amine **272** possessing a chiral centre bearing a methyl and *iso*-propyl group in the β-position was successfully formed, but in poor yield (11% yield of **272**). Despite the poor yield, compound **272** was produced with impressive diastereo- and enantioselectivity (98:2 e.r., > 98:2 d.r.). From NMR experiments, there seemed to be a mass balance issue, with the amount of imine diminishing in the reaction, but not resulting in the formation of the desired product. To rectify this, the amount of imine used in the reaction was increased to 2.0 equivalents and a slow addition of imine was also attempted. Neither change yielded better results. This preliminary result is an exciting one as the enantioselective formation of all-carbon quaternary stereocentres is notoriously difficult.

8.3.2 Variation of the Substituent on Nitrogen

We next explored variation of the substituent on nitrogen of the imine. In particular, we focused on installing versatile, functionalisable, medicinally relevant substituents, such as, a methyl ester (formation of **279**), quinolinyl (formation of **280**), morpholinyl (formation of **283**) and (pinacolato)boryl (**281**), in the substituent on nitrogen. All motifs were tolerated in the three-component coupling reaction and attractive products were formed (Scheme X).

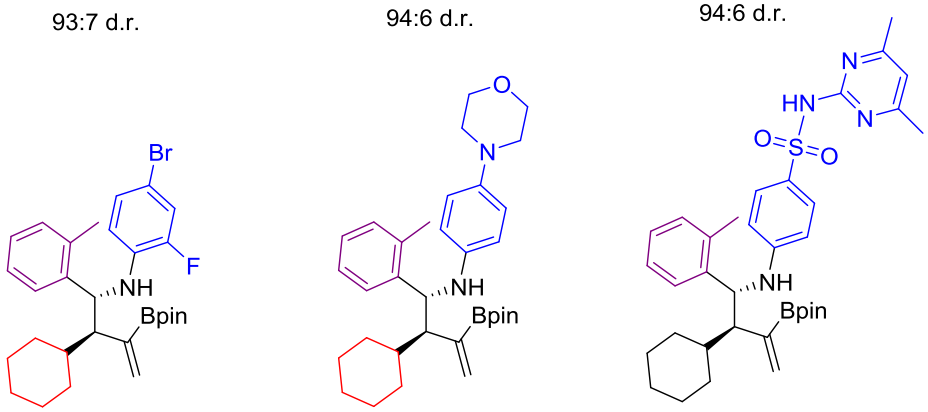




279, 86%[a]
97:3 e.r.
93:7 d.r.

280, 68%
96:4 e.r.
94:6 d.r.

281, 69%
98:2 e.r.
94:6 d.r.



282, 72%[c]
94:6 d.r.

283, 91%
>99:1 e.r.
>95:5 d.r.

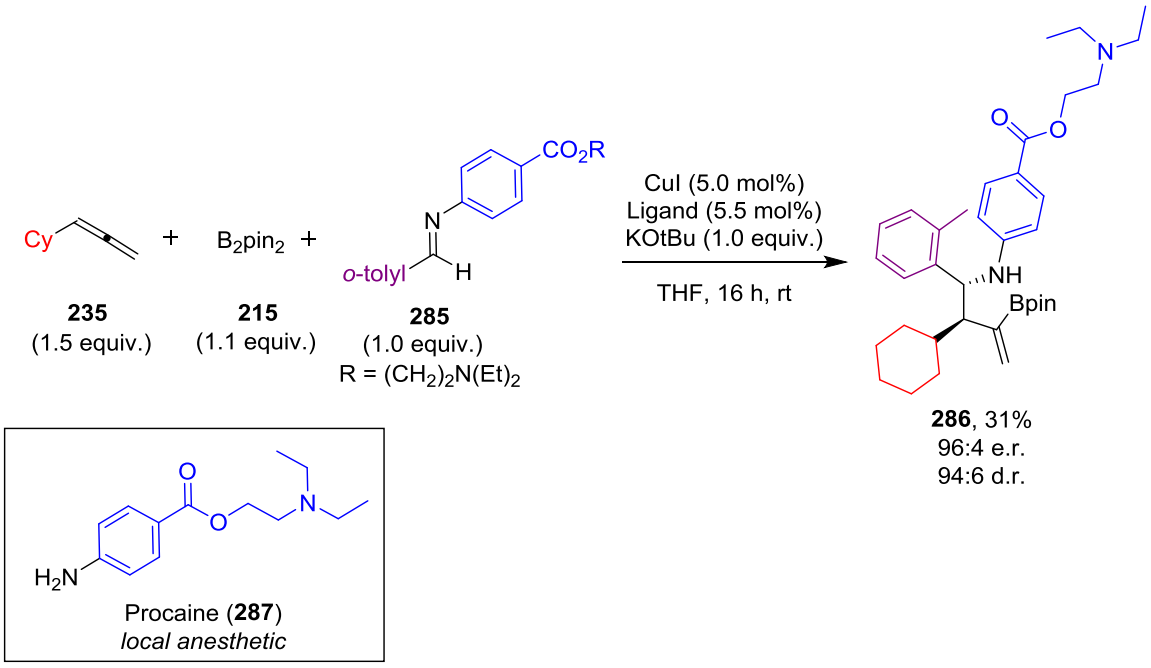
284, 0%[b]

Scheme 60 Variation of the substituent on nitrogen of the imine. [a] In collaboration with Kay Yeung. [b] 2.0 eq of base. [c] Yield measured against NMR standard nitromethane.

Unfortunately, for the formation of homoallylic amine **282**, the non-enantioselective version of the reaction did not proceed to provide a racemic standard and therefore

the enantiomeric ratio of the product could not be determined. On introduction of a sulfonamide to the substituent on the nitrogen, coupling did not proceed and product **284** was not observed. This was unsurprising as the group has had difficulties with an *N*-sulfonyl imine in previous studies on the non-enantioselective version of the reaction. The lack of reactivity is thought to arise from NSO_2 group binding to the copper catalyst.

The imine derived from the local anaesthetic Procaine **287** was submitted to the reaction under standard conditions to produce the three-component coupling product **286** with excellent diastereo- and enantioselectivity (Scheme 61).[157]

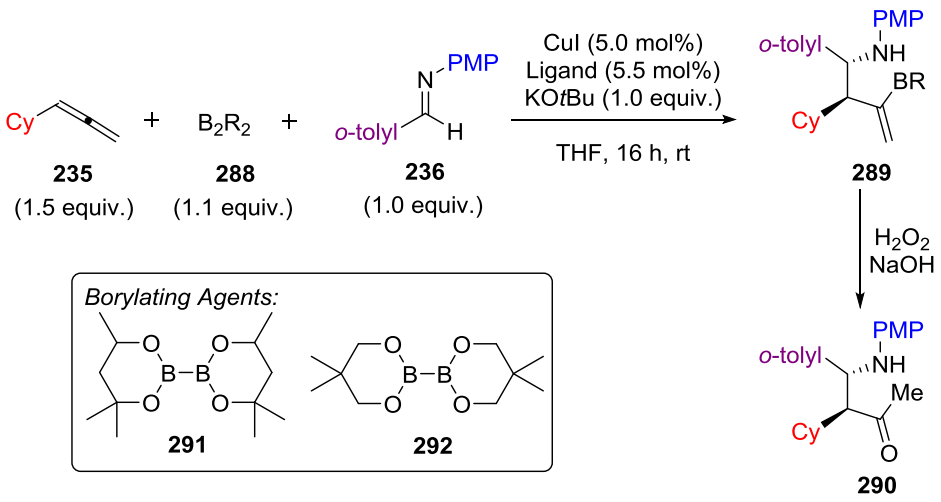


Scheme 61 Three-component coupling reaction using an imine derived from procaine.

Pleasingly, couplings to form **280** (quino), **283** (morpholino) and **286**, highlight that a basic nitrogen is compatible with the reaction.

8.3.3 Variation of the Borylating Reagent

The final component of the reaction that was investigated was the borylating reagent. Unfortunately, attempted used of diboron compounds **291** and **292** in the reaction, resulted in the formation of no homoallylic amine (Scheme 62).



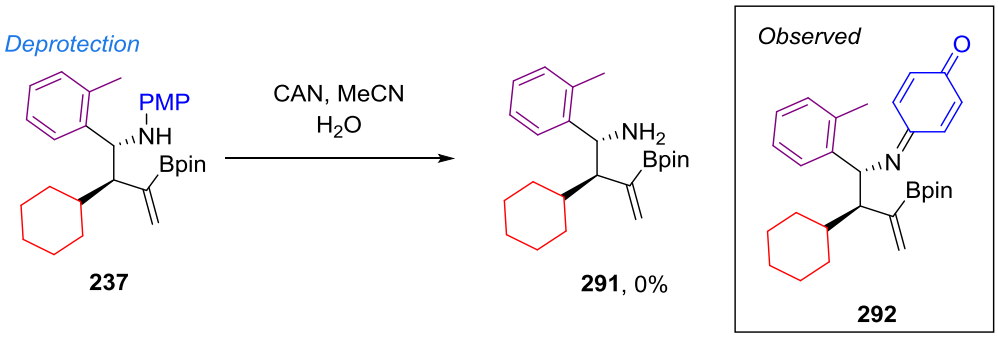
Scheme 62 Attempts to carry out the reaction with other borylating reagents.

The work-up of the reaction involves filtering the crude mixture through a silica plug, and it was postulated that the homoallylic amine products may have been formed but were unstable to the work-up conditions. Therefore, the three-component reaction was carried out as normal, followed by an *in situ* oxidation to the corresponding methyl ketone, but again no coupling product was observed.

8.4 Product Manipulation

To show the value of our enantioselective, copper-catalysed three-component coupling, we investigated the synthetic manipulation of the homoallylic amine products.

A method was desired to remove the PMP-protecting group from nitrogen as this group is present in most of the products formed in the reaction. Following a literature procedure, deprotection was attempted using CAN (Scheme 63).

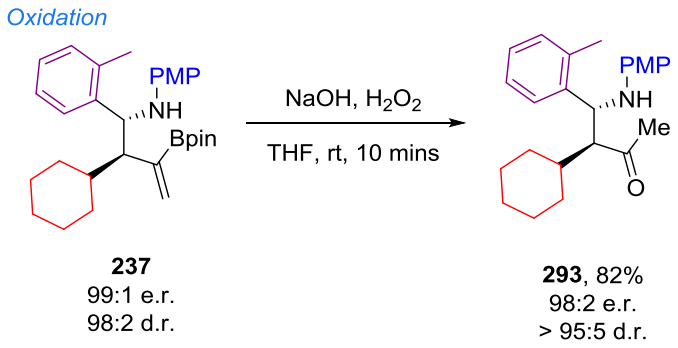


Scheme 63 Attempted removal of the PMP protecting group.

Unfortunately, reaction with CAN did not result in the formation of the desired amine product **291**. Instead, intermediate **292** was observed. Optimisation of this

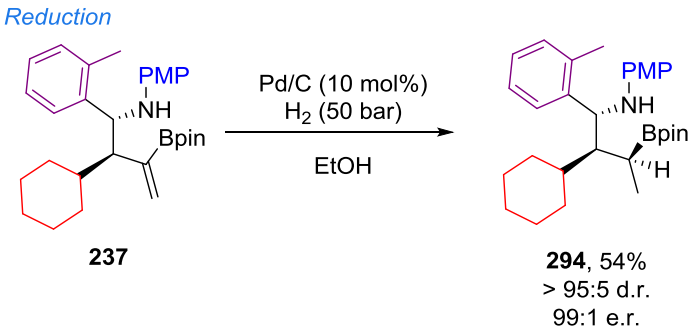
deprotection is currently underway in the group and is likely to produce primary homoallylic amine **291**.

Oxidation of the C-B bond in **242** was successful and methyl ketone **296** was formed in 82% yield and without erosion of the enantiomeric excess of the starting materials (Scheme 64). This step could also be carried out *in situ* directly after the three-component coupling.[147]



Scheme 64 Oxidation of **237** to the corresponding methyl ketone in collaboration with Kay Yeung.

In keeping with modification of the alkene, a hydrogenation of the C-C double bond was attempted (Scheme 65).



Scheme 65 Highly diastereoselective hydrogenation of the alkene in **294**.

After a screen of catalysts (Pd/C, Rh/C and PtO_2) and solvents (ethanol and acetic acid). The reaction was found to only be successful using pressures of 50 bar in a Parr reactor. The best performing catalyst was Pd/C and product **294** was obtained in 54% yield. The resulting product contains three contiguous centres and is formed with high diastereocontrol. The diastereoselectivity of this hydrogenation reaction is controlled by the substrate and a model for the origin of selectivity can be seen in Figure 15a. Interaction between the nitrogen and boron results in the substrate adopting a 5-membered cyclic structure, this results in the hydrogenation occurring on the opposite face of the alkene to the cyclohexyl substituent with high selectivity.

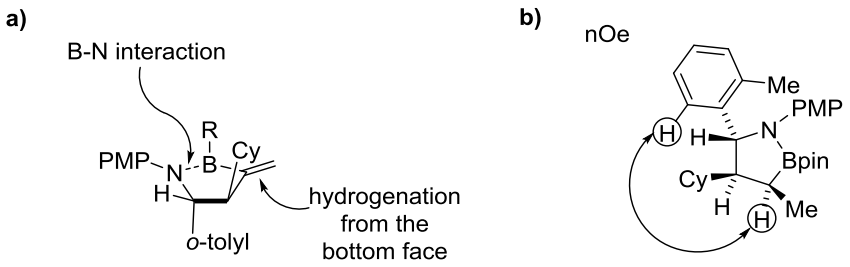
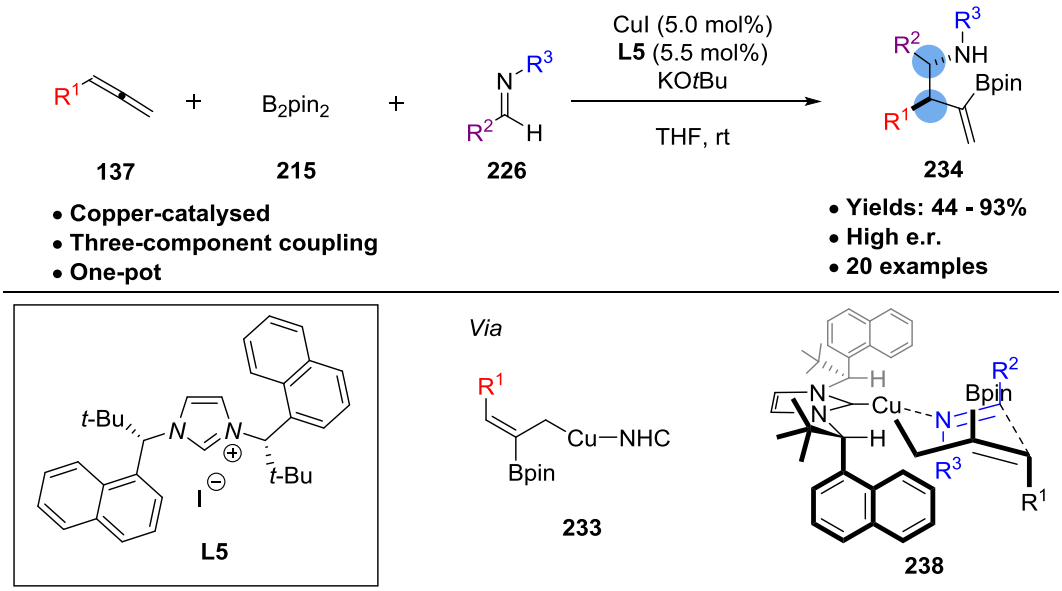


Figure 15 (a) Substrate controlled selectivity seen in the hydrogenation reaction. (b) nOe signals to confirm product **294**.

The structure of hydrogenation product **294** was confirmed by nOe analysis, with diagnostic couplings shown in Figure 15b.

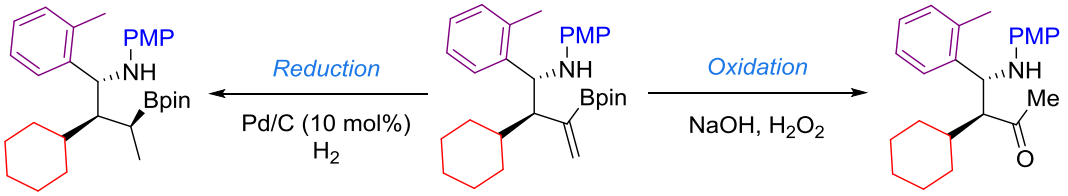
9.0 Conclusion

The multicomponent coupling utilises low cost CuI and a commercially available chiral NHC at room temperature to form functionalised homoallylic amines containing adjacent stereocentres with high diastereo- and enantioselectivity (Scheme 66). Achiral allenes, imines and diboranes are utilised in the reaction, which involves the borocupration of an allene, followed by the addition of an allylic copper intermediate **233** to an imine. The compounds formed bear versatile alkenyl, amino and boryl units, that can be used in further transformations.



Scheme 66 Summary of the enantioselective three-component coupling of allenes, imines and B_2pin_2.

On exploring the substrate scope, it was found that imines possessing a variety of functional groups were tolerated under the reaction conditions. Alkyl allenes gave the desired products with excellent enantioselectivty. Whilst aryl allenes typically gave poor enantioselectivity, upon changing the ligand and lowering the temperature, the desired products were obtained with moderate enantioselectivity. 1,1-disubstituted allenes could be employed in the reaction to give products containing a quaternary centre with excellent enantioselectivity. The substituent on the nitrogen of the imine could also be varied to impose further variation in the products formed and to incorporate medicinally relevant motifs. Elaboration of the products gave rise, for example, to compounds containing three contiguous stereocentres and to β-amino ketones (Scheme 67).



294, 54%
> 95:5 d.r.
99:1 e.r.

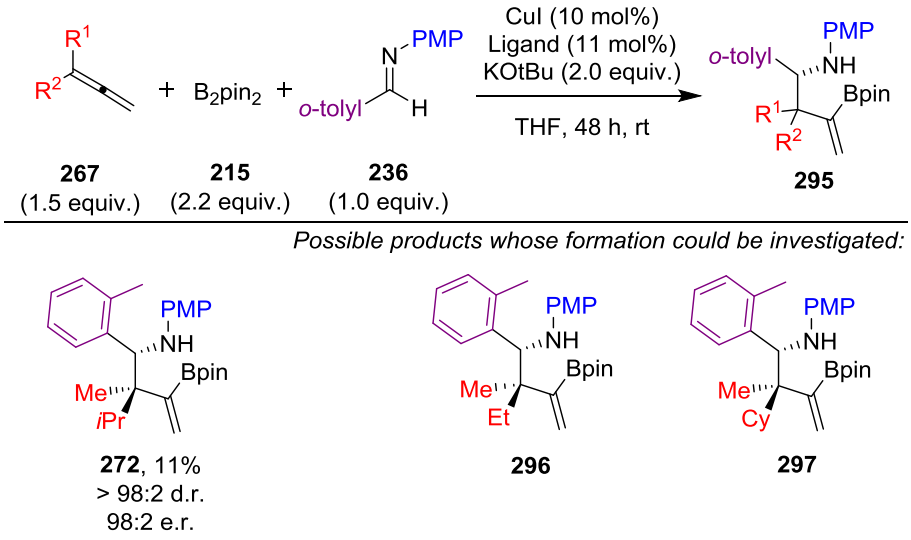
237

293, 82%[a]
> 95:5 d.r.
98:2 e.r.

Scheme 67 Derivatisation of the products of the enantioselective three-component coupling.

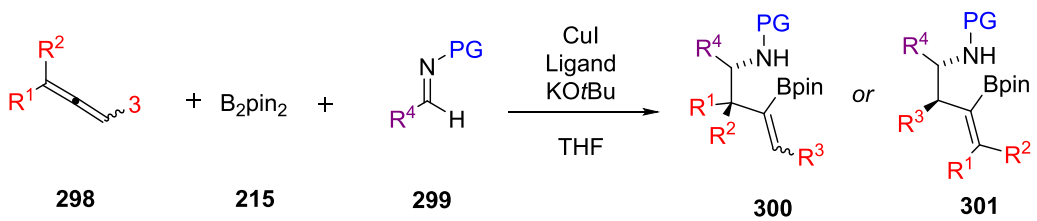
9.1 Future Work

The construction of all-carbon quaternary centres is extremely challenging and therefore has high value in organic synthesis. Encouraged by the formation of **272** with high diastereo- and enantiocontrol, further investigation should be carried out to improve the low yield observed. It was unclear based on experimental evidence whether the low yield was caused by steric challenges or whether the issue was substrate specific. Therefore, it would seem logical to attempt the reaction with 1,1-disubstituted allenes bearing alternative substituents (Scheme 68), alongside a re-examination of the reaction conditions. If the yields can be improved upon, then this would result in an efficient method for the formation of homoallylic amines bearing 1,2-stereocentres, in which one centre is an all-carbon quaternary centre.



Scheme 68 Formation of homoallylic amines bearing all-carbon quaternary centres.

It would be interesting to see how 1,3-substituted allenes **298** perform in the three-component coupling, as this would form homoallylic amines **300** or **301** that possess further substitution on the alkene (Scheme 69).

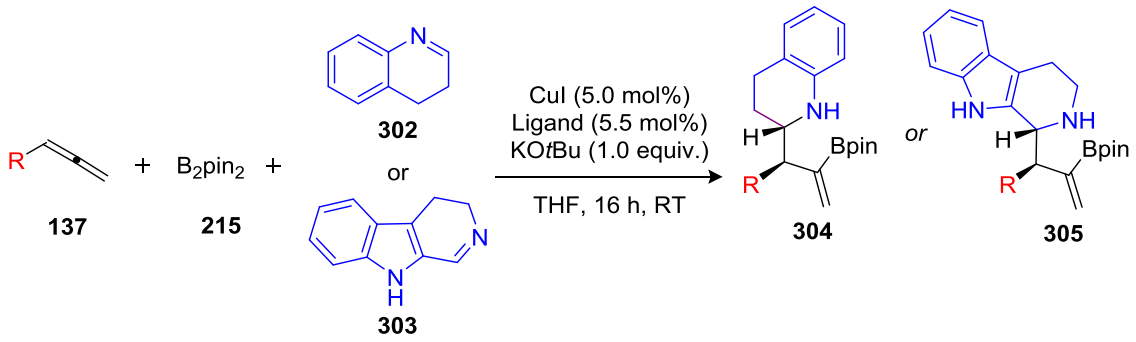


Scheme 69 Using 1,3-substituted allenes in the three-component coupling.

The use of trisubstituted allenes in related borylcupration reactions is unprecedented, with the only related examples involving the use of electronically biased allenamides and allenoates.[131,133] There is the possibility that a mixture of

regioisomeric products could be formed (**300** and **301**), and so it would be interesting to see how such substrates perform under the reaction conditions and whether any selectivity is observed in the reaction.

The use cyclic imines has not been attempted in the reaction and this could produce attractive products (Scheme 70).



Scheme 70 Employing cyclic imines in the reaction three-component coupling.

Utilising imine **302** and **303** in the three-component coupling reaction would give rise to products **304** and **305** possessing tetrahydroquinoline and indole moieties, respectively. Such scaffolds can be found in many drug molecules. For example, Vincanol and Rutacarpine possess structures resemble product **305** (Figure 16). Of course, other cyclic imines are also worth investigating as this will further diversify the compounds formed in this reaction and will extend the substrate scope.

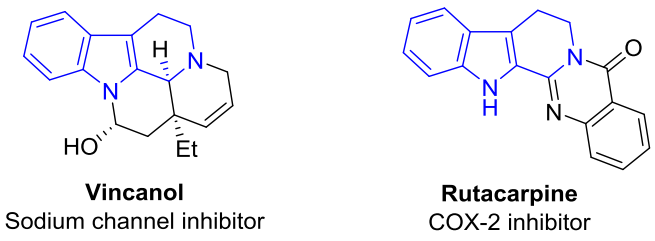
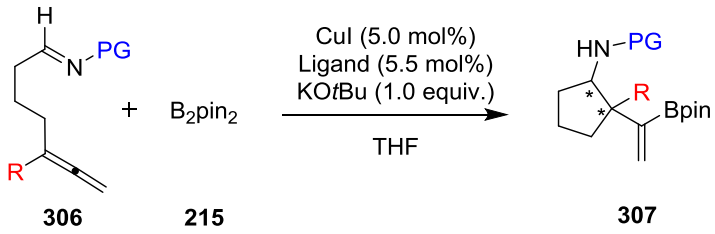


Figure 16 Possible targets accessible through use of cyclic imine **303**.

An avenue that is also worth investigating would be the tethering of the allene and imine component and subsequent intramolecular cyclisation of the allyl copper intermediate. This would result in carbocycles **307** bearing amine functionality and two adjacent stereocentres (Scheme 71).



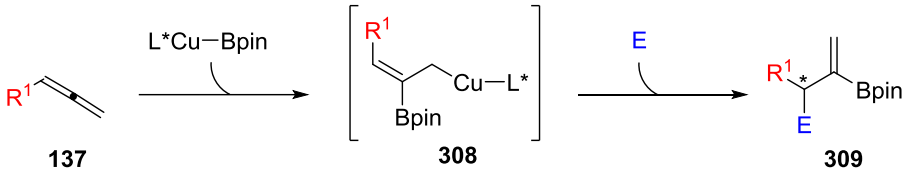
Scheme 71 Tethering the allene and imine component: an intramolecular coupling reaction.

Clearly there are multiple directions that can be taken to further develop this project, with each providing exciting prospects for the future.

The following section is dedicated to the late Thomas Shearer, whose friendship and hard work contributed to this research.

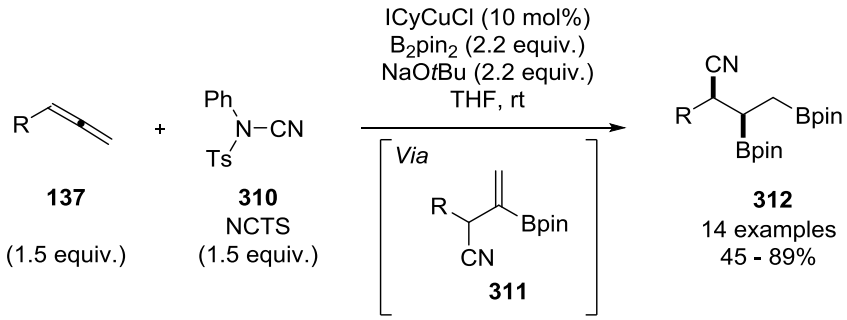
10.0 Further Developments in the Project

The previously described reaction involved the formation of an allyl copper species **310**, which was then intercepted with an imine electrophile. This presents us with the opportunity to vary the electrophile to form highly functionalised products (Scheme 72).



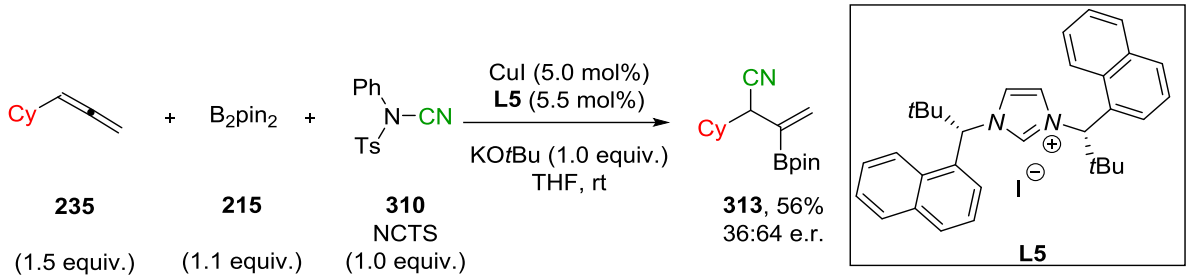
Scheme 72 General formation of an allyl copper followed by quenching with an electrophile.

Alternative electrophiles have been utilised to intercept allylcopper intermediates. For example, aldehydes and ketones have been employed as discussed in section 6.3.[140–143] Recently, Montgomery and co-workers published the formation of **312** by reaction of an allyl copper intermediate with *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) **310** (Scheme 73).[158]



Scheme 73 Cyanation diborylation of allenes performed by Montgomery *et al*.

Montgomerys' method utilises a racemic NHC ligand to form 1,2,3-trifunctionalised products **312** with exceptional chemo-, regio- and diastereoselectivity and highlights the potential for using NCTS as an electrophile to intercept allylcopper species as shown in Scheme 72. To investigate whether this was a viable future direction for our studies, NCTS was coupled with B_2pin_2 and cyclohexylallene **235** using the conditions developed during the previous imine project (Section 8.0). Pleasingly, the reaction worked well with an encouraging 56% yield of the desired product **313**, however, only moderate enantioselectivity was observed (36:64 e.r.) (Scheme 74).



235 (1.5 equiv.) + **215** (1.1 equiv.) + **310** NCTS (1.0 equiv.) → **313**, 56%, 36:64 e.r.

Scheme 74 Preliminary reaction for the cyanoborylation of allenes.

Surprisingly, the monoborylated product **313** was the only product, with Montgomerys' diborylated product **312** not observed. In addition, the absolute stereochemistry of the major enantiomer formed is not yet known. This was an inspiring result and so optimisation of the reaction was carried out to improve the enantioselectivity of the transformation.

10.1 Ligand Screen - Chiral NHCs

In order to improve the enantioselectivity of the cyanoborylation process, different ligands were screened under the reaction conditions and initially commercially available NHC ligands were tested (Figure 17, Table 6).

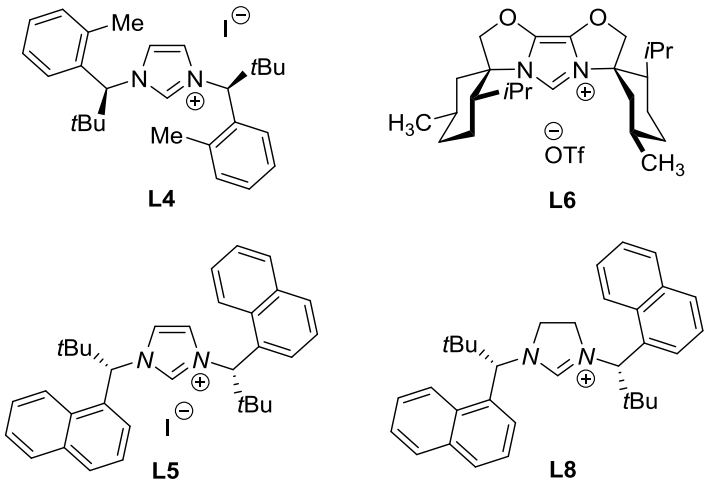


Figure 17 Chiral NHC ligand precursors screened in the reaction.

It can be seen from the results that **L4** also forms the desired product, however, in a notably lower yield compared to the preliminary reaction (Entry 2). Also noted is a lack of enantioselectivity in this reaction (49:51 e.r.). **L6** is incompatible with the reaction and no product formation was observed (Entry 3). Finally, **L8** resulted in a much poorer reaction and slightly lower enantioselectivity (Entry 4). Therefore, **L5** remained the best performing NHC ligand with the highest yield and best enantioselectivity observed so far.

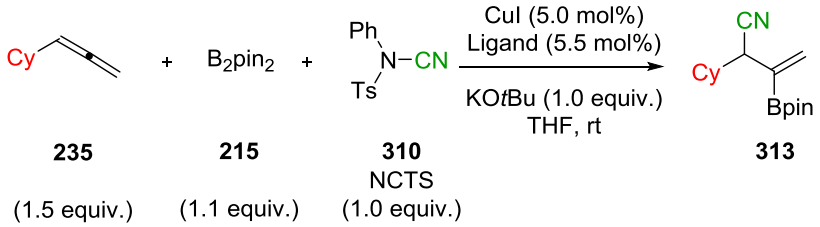


Table 6 Screening NHC ligand precursors.

Entry	Ligand	310 Recovered (%)	315 Yield (%)	e.r.
1	**L4**	39	34	49:51
2	**L5**	32	56	36:64
3	**L6**	40	0	-
4	**L8**	69	14	40:60

With no improvement in enantioselectivity, Thomas Shearer, an undergraduate Masters student working under my supervision on this project, investigated whether a change in reaction conditions could improve the enantioselectivity of the reaction when using **L5**. On exploring this, he attempted the reaction in different solvents (THF, Et_2O, dioxane, CH_2Cl_2, toluene, DMSO and acetonitrile), using a variety of bases (Cs_2CO_3, K_2CO_3 and NaOMe), and he investigated the effect of scale and temperature on the reaction. All changes imposed on the system led to a reduction in yields and no improvement in the enantioselectivity of the process.

10.1.1 Ligand Screen – Chiral Phosphines

With poor enantioselectivity (36:64 e.r.) achieved on applying chiral NHC ligands in the reaction, attention was turned to the use of chiral phosphine ligands (Figure 18).

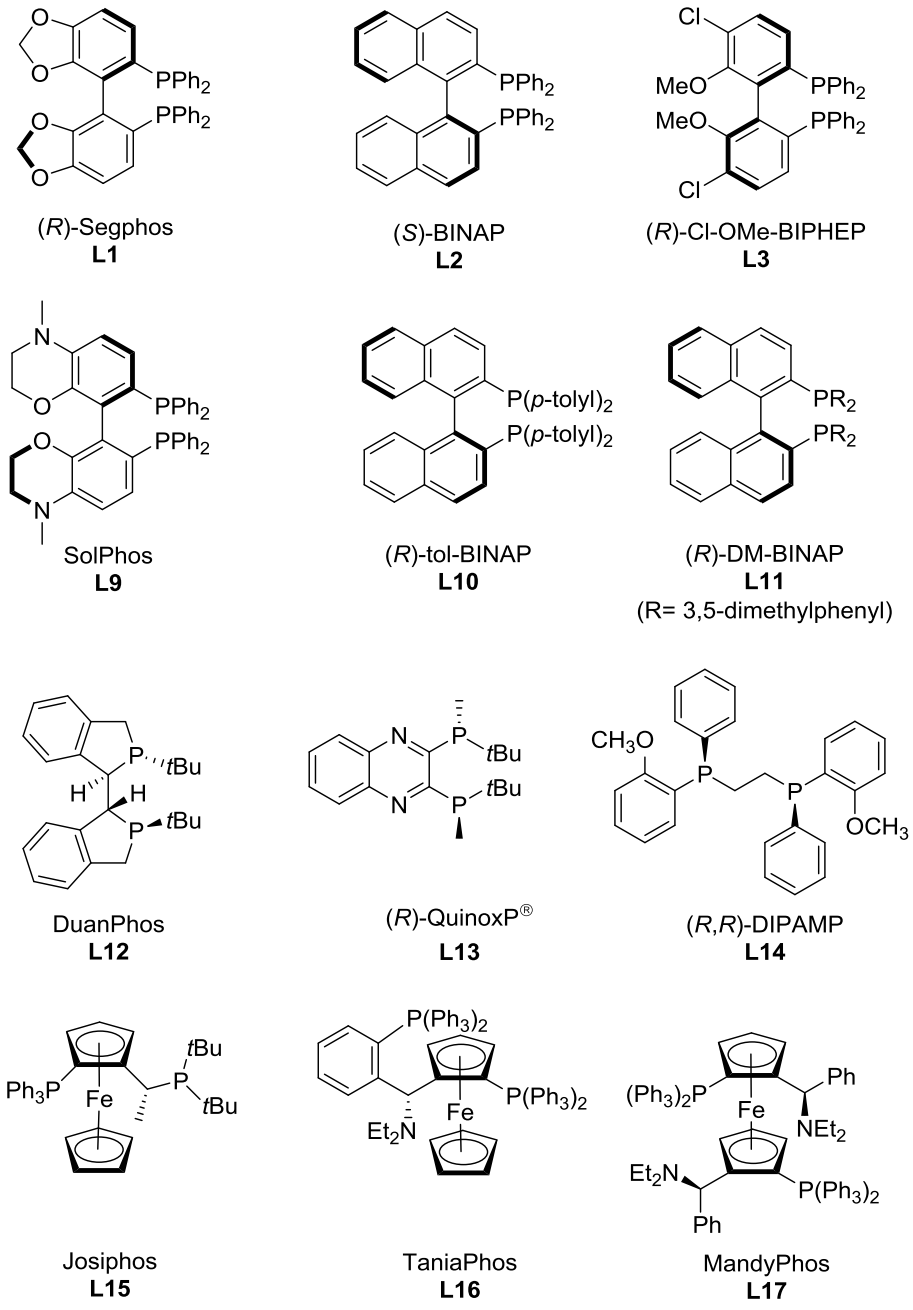


Figure 18 Chiral phosphine ligands screened in the cyanoboration of allenes.

Initial reactions were carried out using chiral phosphines **L1** and **L2** (Entries 1 and 2, Table 7), with both resulting in low yields of **315**, but good enantioselectivity (e.g. 10:90 e.r.), however poor mass balance was observed with the reaction utilising **L1**. Good enantioselectivity was observed when biaryl chiral phosphine ligands **L3** (Entry 3) was screened under the reaction conditions. However, the product was

observed in disappointing yields in all cases (Entries 1 - 6). In addition, the product resulting from the use of **L3** (Entry 3) had a reduced enantiomeric ratio (15:85) when compared to the original result with **L2** (Entry 2).

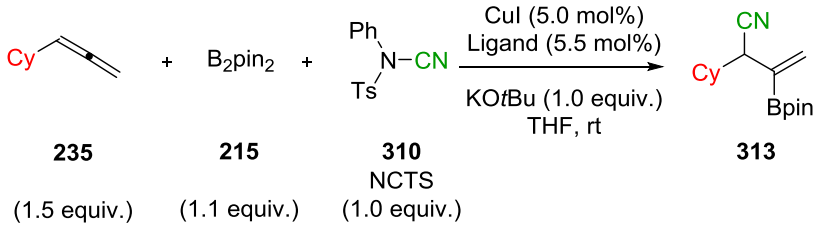


Table 7 Results from screening chiral phosphine ligands. [a] Yield determined by ^{1}H NMR measured against a nitromethane internal standard.

Entry	Ligand	NCTS Remaining (%)	Yield (%)	e.r.
1	**L1**	27	23 (17[a])	10:90
2	**L2**	82	17	90:10
3	**L3**	54	10	15:85
4	**L9**	53	<1[a]	n.d.
5	**L10**	27	10[a]	n.d.
6	**L11**	37	3	n.d.
7	**L12**	n.d.	46	36:64
8	**L13**	37	17	15:85
9	**L14**	47	<1[a]	n.d.
10	**L15**	51	19	8:92
11	**L16**	40	11	48:52
12	**L17**	44	<1[a]	n.d.

In keeping with bidentate chiral phosphine ligands, **L12** and **L13** were submitted to the reaction, both giving access to the desired product (Entries 7 and 8). DuanPhos (**L12**) resulted in the highest yield of product out of all phosphine ligands tested (46%), however only moderate enantioselectivity was observed (36:64 e.r.). In comparison, QuinoxP® (**L13**) gave product with a slightly improved enantiomeric ratio, but with low yields (Entry 8). DIPAMP ligand **L14** formed trace amounts of product (Entry 9), which could be observed in the crude ^{1}H NMR, with no alternative products being formed despite consumption of NCTS. Finally, ferrocene-based chiral phosphines **L15** to **L17** were screened, with Josiphos giving the best enantioselectivity (8:92 e.r.) observed in this reaction so far (Entry 10).

From the ligand screen, there seemed to be an inverse relationship between yield and enantioselectivity. For example, when the yield is good using **L5** (56%), the enantioselectivity achieved is low (36:64 e.r.). Alternatively, when the yield of the reaction is low using **L15** (19%), the reaction proceeds with high enantioselectivity (8:92 e.r.).

10.2 Optimisation of the Reaction Using (*S*)-BINAP

As mentioned previously, Thomas Shearer had attempted to optimise the reaction when using chiral NHC **L5**, however, we were unable to improve on the enantioselectivity of the reaction. Therefore, attention was focused on the optimisation of the cyanoborylation reaction using a phosphine ligand that can deliver high enantioselectivity. Ideally the ligand of choice would have been Josiphos **L15**, as this returned the product in the highest enantiomeric ratio (8:92). However, due to the cost of ligand, (*S*)-BINAP **L2**, which showed comparable enantioselectivty (90:10 e.r.), was used instead.

Firstly, a series of reactions were carried out to investigate the effect of solvent, temperature and catalyst loading (Table 8).

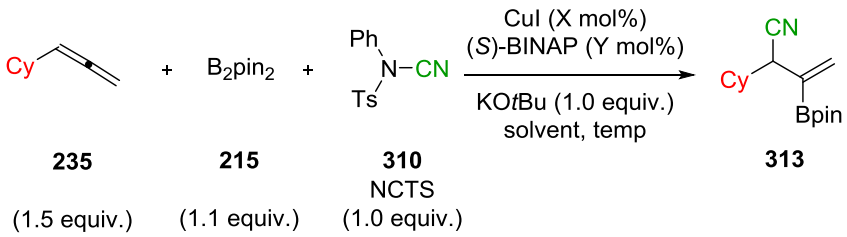


Table 8 Investigating the effect of changing solvent, temperature, catalyst and ligand loading on the cyanoborylation of allenes.

Entry	X (mol%)	Y (mol%)	Solvent	Temp (°C)	Yield 315 (%), (e.r.)
1	5.0	5.5	CH_2Cl_2	19	11, (90:10)
2	5.0	5.5	Toluene	19	4, (84:16)
3	5.0	5.5	THF	–78 to 19	7, (n.d.)
4	10	11	THF	19	14, (89:11)
5	5.0	11	THF	19	6, (n.d.)

Running the reaction in CH_2Cl_2 (Entry 1, Table 8) furnished the desired product in high enantiomeric ratio (90:10 e.r.), however the yield was slightly lower than that observed in THF (17%). A reaction carried out in toluene (Entry 2) proceeded with a

decrease in the yield and enantioselectivity. On investigating the effect of temperature, the reaction was carried out at –78 °C and allowed to warm to room temperature gradually over 16 hours (Entry 3). This also resulted in a reduction in the yield of **313**. A two-fold increase in the amount of catalyst and ligand used in the reaction (Entry 4) gave a slight decrease in the yield and the enantiomeric ratio of **313** was unchanged. Using 2.2 times as much ligand as CuI (Entry 5) proved to be detrimental to the yield of the reaction. From these results, no improvements to the reaction conditions were identified.

The next component of the reaction to be investigated was the base used (Table 9). Either the base was changed completely (Entries 3 - 5) or an additive was also employed (Entries 1 and 2); for the later entries potassium *tert*-butoxide was used to form the copper alkoxide to initiate the reaction. In all cases, no improvement was observed.

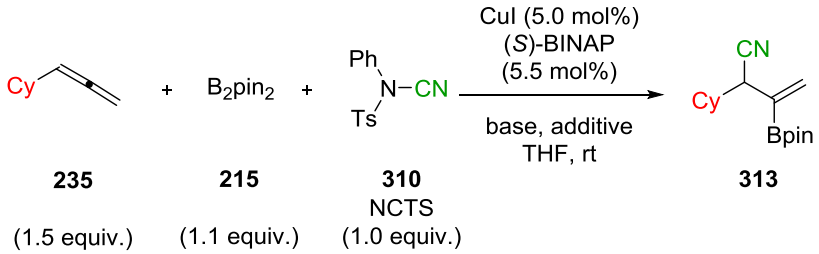


Table 9 Investigating the effect of changing the base in the cyanoborylation reaction.

Entry	Base	Additive (equiv.)	Yield 315 (%)
1	KO*t*Bu (16.5 mol%)	K_3PO_4 (1.0)	7
2	KO*t*Bu (16.5 mol%)	Cs_2CO_3 (1.0)	3
3	NaO*t*Bu (1.0 equiv)	-	3
4	KO*t*Bu (1.5 equiv)	-	6
5	NaOMe (1.0 equiv)	-	2

10.3 Optimisation of the Reaction Using DuanPhos

Returning to the results from the original screen of chiral phosphine ligands, the use of DuanPhos (**L12**) formed the desired product in encouraging yield (46%) and with moderate enantioselectivity (36:64 e.r.). Thus, the optimisation of the reaction was next attempted using **L12**.

A short screen of reaction conditions, including solvent, temperature and base, was carried out (Table 10). Changing the solvent resulted in a slight reduction in the

yield and little change in the enantioselectivity of the reaction (Entries 1 to 4). Carrying out the reaction at –78 °C, and allowing the reaction to warm to room temperature over 16 hours, had no effect on the selectivity of the reaction and the yield was reduced by 12% (Entry 5). On investigating the base/additive used in the reaction, all changes resulted in no improvement in the enantiomeric ratio of the product, with Cs_2CO_3 being the only additive whose use resulted in a promising yield (Entry 6).

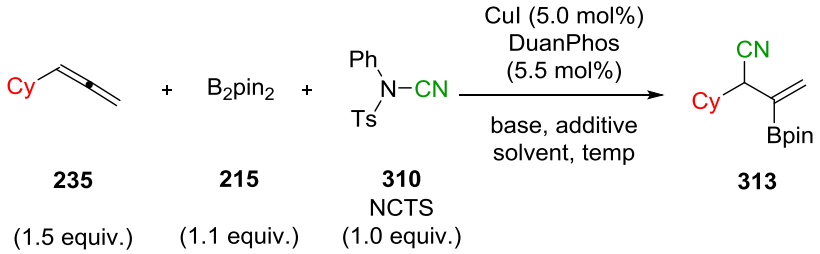
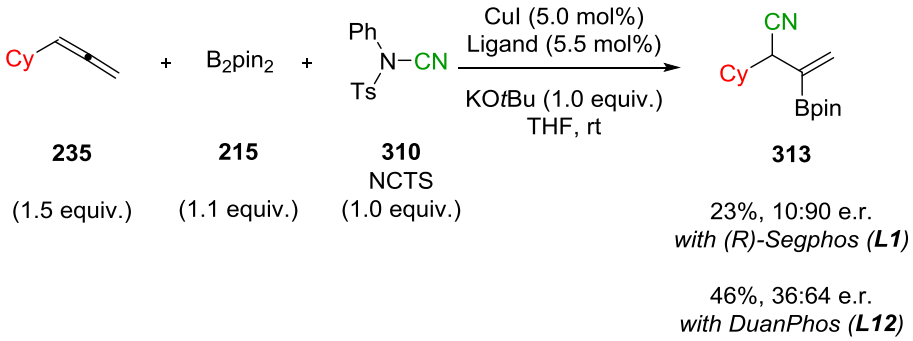


Table 10 Optimisation of the cyanoborylation reaction when employing DuanPhos as the ligand.

Entry	Solvent	Temp (°C)	Base (equiv.)	Additive	Yield 315 (%), (e.r.)
1	THF	19	KO*t*Bu (1.0)	-	46, (36:64)
2	CH_2Cl_2	19	KO*t*Bu (1.0)	-	6, (n.d.)
3	Toluene	19	KO*t*Bu (1.0)	-	37, (38:62)
4	Et_2O	19	KO*t*Bu (1.0)	-	34, (35:65)
5	THF	–78 to 19	KO*t*Bu (1.0)	-	34, (36:64)
6	THF	19	KO*t*Bu (16.5 mol%)	Cs_2CO_3 (1.0)	42, (36:64)
7	THF	19	KO*t*Bu (16.5 mol%)	K_3PO_4 (1.0)	17, (36:64)
8	THF	19	KO*t*Bu (16.5 mol%)	NaOMe (1.0)	11, (36:64)

11.0 Conclusion of the Cyanoborylation of Allenes

This preliminary investigation has resulted in the identification of an asymmetric three-component coupling reaction between cyclohexylallene, B_2pin_2 and an electrophilic cyanating agent (Scheme 75).

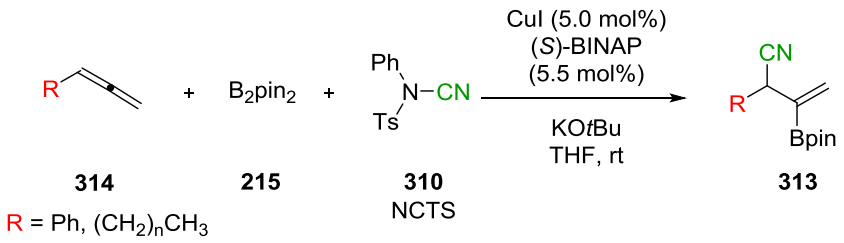


Scheme 75 Best results to date for the asymmetric cyanoborylation of cyclohexylallene using phosphine ligands.

The reaction proceeds to form the desired product **313** with excellent enantioselectivity, albeit in disappointingly low yields with (*R*)-Segphos (**L1**) and with good yields and poor enantioselectivity with DuanPhos (**L12**). Multiple attempts to optimise the reaction were carried out with no improvement observed to date.

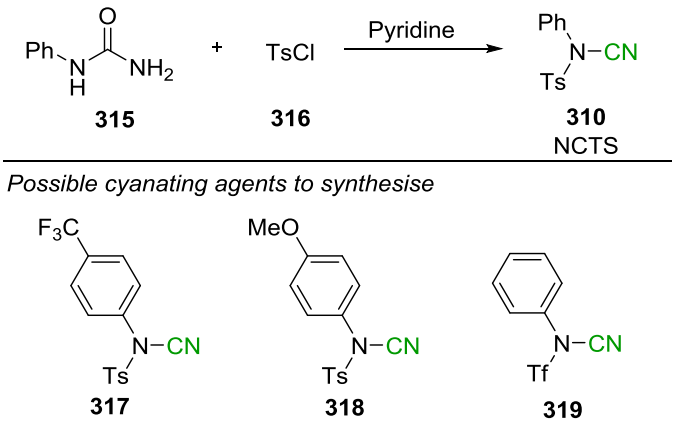
11.1 Future Work

After our initial attempts to optimise the reaction, the best ligandseither gave good yields or good enantioselectivity, but not both, and changing temperature, solvents, scale, length of the reaction, or the base added had not proved helpful. It is possible that the optimisation studies were carried out on a challenging substrate, therefore the next investigations proposed should involve a different allene **314** (Scheme 76).



Scheme 76 Exploring the scope of the reaction using different allene substrates.

There is also the opportunity to vary the cyanating reagent used in these reactions. NCTS **310** is formed from the reaction of phenylurea and tosyl chloride (Scheme 77). Therefore, by carrying out the reaction with functionalised aryl ureas, the reactivity of the electrophile can be modified (e.g. **317** and **318**).



Scheme 77 Proposed cyanating reagents to synthesise and use in the cyanoborylation of allenes.

As seen in the previous project, a tosyl group on the imine proved to be detrimental to the reaction, therefore, by replacing tosyl chloride with triflic anhydride in the reaction, cyanating agent **319** bearing a triflyl group could be prepared. Cyanating reagent **319** may be less coordinating to copper and could therefore help improve turnover.

The development of this project has stemmed from the three-component coupling reaction of allenes, imines and diboranes (Section 8) and has illustrated that

electrophiles other than imines can be used to trap the allyl copper intermediate (Scheme 72). Therefore, it is worth investigating the use of different electrophiles in this reaction (Figure 19). This would aid us in developing a general asymmetric allylation protocol that provides access to highly functionalised products that are difficult or impossible to form by other means. For example, use of electrophilic sources of fluorine (**320**), trifluoromethyl (**321**) and also using enones (**322**), could give rise to enantioenriched products **323**, **324** and **325**, respectively.

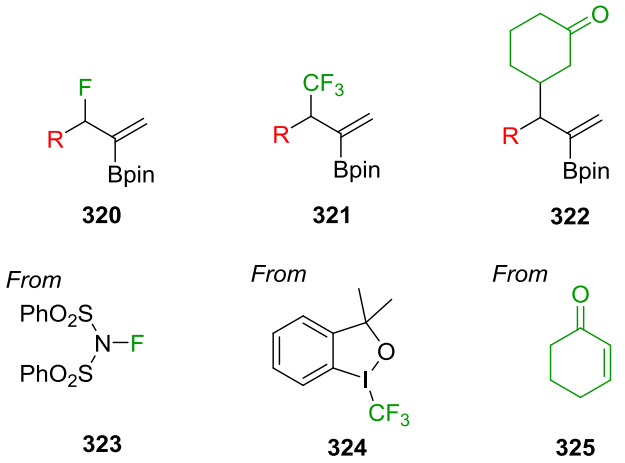


Figure 19 Potential products from three-component couplings using different electrophiles.

While this project is in its early stages, an asymmetric three-component coupling reaction between allenes, B_2pin_2 and NCTS is clearly possible. Further optimisation of the asymmetric, copper-catalysed cyanoborylation of allenes is now underway in the group and the use of different electrophilic quenches is also under investigation.

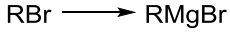
12.0 Experimental Part 1

12.1 General Information

All reactions were carried out under an inert nitrogen atmosphere unless otherwise stated. Glassware for inert atmosphere reactions was oven-dried and cooled under a flow of nitrogen. Tetrahydrofuran (THF) was distilled over sodium wire and benzophenone. Dichloromethane, toluene and triethylamine were distilled over calcium hydride, and dimethyl formamide (DMF) was dried over activated molecular sieves. All other solvents and reagents were purchased from commercial sources and used as supplied unless otherwise stated. ^{1}H NMR spectra were recorded at 400 or 500 MHz; ^{13}C NMR spectra were recorded at 101 or 126 MHz. ^{19}F NMR spectra were recorded at 376 MHz. All chemical shift values are reported in parts per million (ppm) relative to the solvent signal and were determined in $CDCl_3$, with coupling constant (*J*) values reported in Hz. Crude reaction mixtures were dissolved in a solution of chloroform containing a known concentration of nitromethane to calculate ^{1}H NMR yields. The notation of signals is: Proton: δ *chemical shift (number of protons, multiplicity, J value(s), proton assignment)*. Carbon: δ *chemical shift (carbon assignment)*. Fluorine: δ *chemical shift (fluorine assignment)*. For multiplets and overlapping signals a range of shifts is reported. Routine TLC analysis was carried out on aluminum sheets coated with silica gel 60 Å F254, 0.2 mm thickness. Plates were viewed using 254 nm ultraviolet light and dipped in aqueous potassium permanganate or *p*-anisaldehyde. Flash column chromatography was carried out on 40-63 μ, 60 Å silica gel. Low resolution and high resolution mass spectra were obtained using either positive and/or negative electrospray ionisation (ES), electron impact ionisation (EI) or chemical ionisation (CI) techniques. IR spectra were recorded on an ATR FTIR spectrometer as evaporated films (from $CHCl_3$) or neat.

12. 2 General Procedures

General Procedure A: Formation of Grignard Reagents



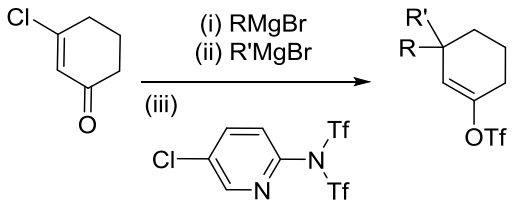
Grignard reagents were synthesised using the Schlenk method. 1,2-Dibromoethane (0.1 equiv.) was added to thermally activated magnesium turnings (3.0 equiv.) in THF (4.0 M) under an atmosphere of argon. The reaction was allowed to return to room temperature. The solution was then placed in a water bath at 40 - 50 °C and a solution of RBr (1.0 equiv.) in THF (1.3 M) was added at a rate of 1 mL/min. After the addition of the bromide the water bath was removed. Once the solution had cooled to room temperature, THF was added until the precipitate was completely

dissolved. The resulting Grignard solution was titrated against a solution of iodine in THF to determine its concentration.

General preparation of PhSLi (0.8 M in THF/hexanes)

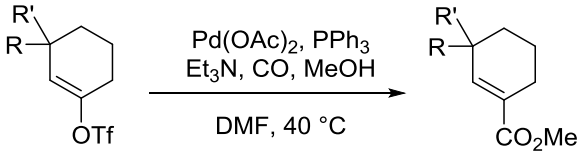
To a stirred solution of PhSH (0.21 mL, 2.00 mmol, 1.0 equiv.) in THF (1.3 mL) at −78 °C (acetone/CO_2) under argon, was added *n*BuLi (1.27 mL, 1.58 M in hexanes, 2.0 mmol, 1.0 equiv.). The resultant solution was stirred for 10 minutes before being allowed to warm to ambient temperature. The deprotonation was assumed to be quantitative and the total volume of the solution was measured. The resultant solution of PhSLi (0.8 M in THF/*n*hexane, 2.5 mL) was used directly.

General Procedure B: **1,4-Double Addition Reactions Followed by Enolate Trapping with Comins' Reagent**



The chloroenone (1.0 equiv.) was added to a solution of PhSLi (0.1 equiv.) and CuI (0.1 equiv.) at –45 °C under an atmosphere of argon. After 10 minutes, the first Grignard reagent, RMgBr (1.0 equiv.), was added dropwise and the reaction mixture was left to stir for 30 minutes. The second Grignard reagent, R'MgBr (1.5 equiv.), was then added dropwise and the reaction was left to stir for 4 hours. The solution was then allowed to warm to –25 °C and a solution of Comins' reagent (1.6 equiv.) in THF was added in one portion and the reaction mixture was allowed to warm to room temperature and stirred for 72 hours. The reaction was quenched with aqueous saturated NH_4Cl and left to stir for 1 hour, followed by extraction into Et_2O. The organic component was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by column chromatography (50:1, hexane:ethyl acetate).

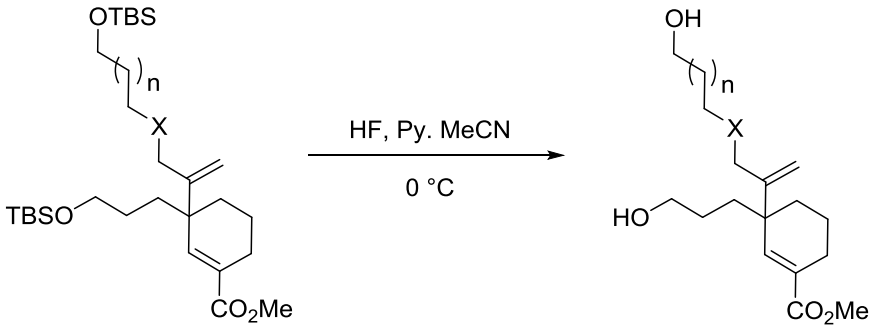
General Procedure C: Palladium-Catalysed Methoxycarbonylation



Carbon monoxide was bubbled through a solution of the triflate (1.0 equiv.), dimethylformamide (0.2 M), anhydrous methanol (40 equiv.), anhydrous Et_3N (2.0

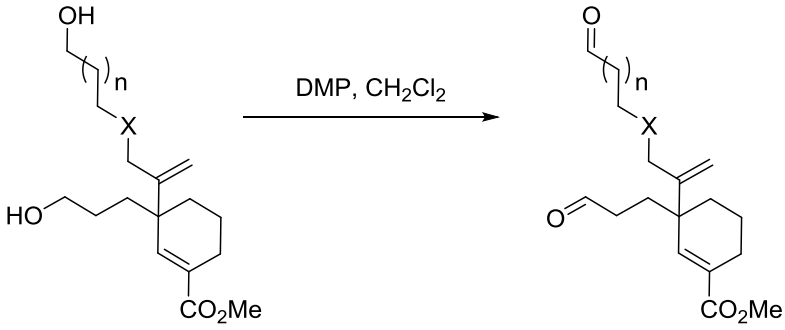
equiv.), $Pd(OAc)_2$ (0.2 equiv.), and PPh_3 (0.4 equiv.) for 30 minutes. The resulting yellow solution was then heated to 40 °C under an atmosphere of carbon monoxide, to give a red solution. After 24 hours, the black solution was quenched with distilled water and extracted into Et_2O. The organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by column chromatography (50:1, hexane:ethyl acetate).

General Procedure D: Double-TBS Deprotection



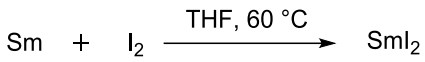
A solution of HF (60% aqueous solution, 20 equiv.) was added to a mixture of the *bis*-silyl ether (1.0 equiv.), pyridine (0.2 M) and acetonitrile (0.1 M) at 0 °C. After 18 hours, the reaction was quenched with aqueous saturated $NaHCO_3$ and extracted into Et_2O. The organic layer was washed successively with aqueous $CuSO_4$ and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. The compound was purified by column chromatography on silica gel (EtOAc) to give the desired diol.

General Procedure E: Double-Oxidation with Dess-Martin Periodinane



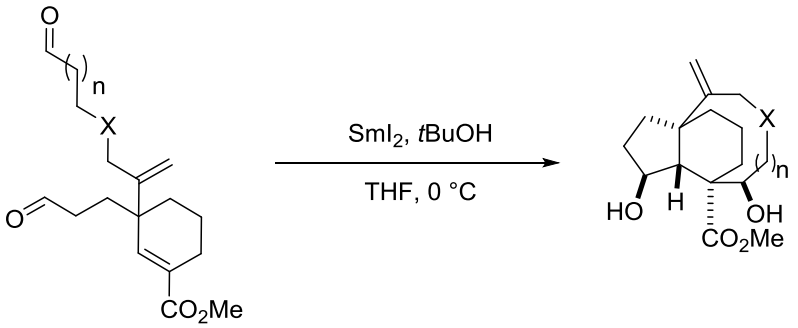
Dess-Martin Periodinane (2.2 equiv.) was added to a solution of the diol (1.0 equiv.) in CH_2Cl_2 (0.1 M) under an atmosphere of nitrogen. After 3 hours, the mixture was concentrated *in vacuo* to give the crude product, which was purified using column chromatography (3% EtOAc/hexane) to give the desired dialdehyde.

General Procedure F: Formation of SmI_2 Solution[159]



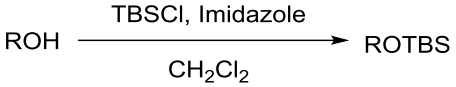
The reaction vessel was flushed with nitrogen for 30 minutes prior to the addition of Sm (1.4 equiv.) and THF (1.0 M). Nitrogen was then bubbled through the solution for a further 10 minutes. Iodine (1.0 equiv.) was added and the resulting mixture was heated to 60 °C for 12 hours to give the desired SmI_2 solution (0.1 M). The concentration was determined using the method developed by Hilmersson.[160]

General Procedure G: SmI_2-Mediated Cascade Reaction



A mixture of degassed *t*BuOH (5.0 equiv.) and SmI_2 (2.5 equiv.) under a nitrogen atmosphere were stirred at room temperature for 15 minutes before being cooled to 0 °C. The dialdehyde (1.0 equiv.) was added dropwise to the solution *via* cannula and the reaction was stirred for 30 minutes before being quenched by exposure to air at 0 °C. After the addition of aqueous saturated NaK tartrate and Et_2O, the reaction mixture was allowed to warm to room temperature. The product was extracted into Et_2O, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by column chromatography (60% EtOAc/hexane).

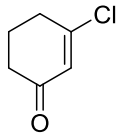
General Procedure H: TBS-Protection



Imidazole (1.6 equiv.) was added to solution of ROH (1.0 equiv.) in CH_2Cl_2 at room temperature. The resulting mixture was left to stir until homogeneous, after which, TBSCl (1.2 equiv.) was added portion-wise. The reaction was then left to stir for 18 - 20 hours in air, before the reaction was quenched with aqueous saturated $NaHCO_3$ and extracted into Et_2O. The combined organic layers were dried ($MgSO_4$) and

concentrated *in vacuo* to give the crude product, which was purified by column chromatography (petroleum ether [40-60]) - 1% Ethyl acetate/petroleum ether [40-60]).

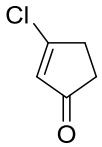
3-Chlorocyclohex-2-en-1-one (54)



54

A mixture of 1,3-cyclohexanedione (5.61 g, 50.0 mmol, 1.0 equiv.), dichloromethane (125 mL) and dimethylformamide (5.00 mL, 65.0 mmol, 1.3 equiv.) were cooled to 0 °C under a nitrogen atmosphere. Oxalyl chloride (5.10 mL, 60.0 mmol, 1.2 equiv.) was added to this solution dropwise. The reaction was allowed to warm to room temperature and left to stir for one hour before being quenched with distilled water (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification by column chromatography (3% EtOAc/petroleum ether [40/60]) gave **54** (5.76 g, 44.1 mmol, 88%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (1H, s, C*H*=CCl), 2.69 (2H, t, *J* = 6.2 Hz, CH_2C=O), 2.41 (2H, t, *J* = 6.7 Hz, CH_2CCl), 2.09 (2H, quin, *J* = 6.4 Hz, CH_2CH$_2$C(O)); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.0 (*C*=O), 158.7 (*C*Cl), 128.5 (*C*H), 36.4 (*C*H$_2$C=O), 33.9 (*C*H$_2$CCl), 22.2 (*C*H$_2$); ν_{max} (thin film/cm^{-1}): 2953, 2887, 1678, 1606, 1426, 1341, 1289, 1187, 991. Data consistent with literature.[161]

3-Chlorocyclopent-2-en-1-one (60)

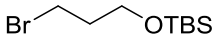


60

A mixture of 1,3-cyclopentanedione (5.00 g, 50.9 mmol, 1.0 equiv.) and dimethylformamide (5.10 mL, 66.2 mmol, 1.3 equiv.) in dichloromethane (127 mL) was cooled to 0 °C. Oxalyl chloride (5.60 mL, 66.2 mmol, 1.2 equiv.) was added dropwise and the reaction mixture was allowed to warm to room temperature and left to stir for one hour. The reaction was quenched with water (50 mL) and extracted into diethyl ether (3 x 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification by

chromatography (20% EtOAc/petroleum ether [40/60]) gave **60** (4.92 g, 42.2 mmol, 83%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (1H, s, C=C*H*), 2.88 (2H, m, CH_2C=O), 2.57 - 2.61 (2H, m, CH_2CCl). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.0 (*C*=O), 171.0 (*C*-Cl), 131.5 (*C*-H), 36.5 (*C*H_2C=O), 34.7 (*C*H_2CCl). Data consistent with literature.[162]

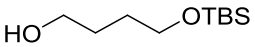
(3-Bromopropoxy)(*tert*-butyl)dimethylsilane (62)



62

General procedure H was followed: 3-bromo-propan-1-ol (25.2 g, 0.18 mol, 1.0 equiv.), imidazole (19.6 g, 0.28 mol, 1.6 equiv.), TBSCl (32.6 g, 0.22 mol, 1.2 equiv.) in CH_2Cl_2 (400 mL) gave the crude product. Purification by chromatography on silica gel (5% EtOAc/petroleum ether [40/60]) gave **62** (41.0 g, 0.17 mol, 97%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (2H, t, *J* = 5.7 Hz, CH_2OTBS), 3.53 (2H, t, *J* = 6.5 Hz, CH_2Br), 2.04 (2H, quin, *J* = 6.1 Hz, CH_2), 0.91 (9H, s, SiC(CH_3)$_3$), 0.08 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 60.4 (*C*H_2OTBS), 35.5 (*C*H_2CH$_2$OTBS), 30.7 (*C*H_2Br), 25.9 (SiC(*C*H_3)$_3$), –18.3 (Si*C*), –5.4 (Si(*C*H_3)$_2$). Data consistent with literature.[163]

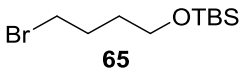
4-((*tert*-Butyldimethylsilyl)oxy)butan-1-ol (64)



64

1,4-Butanediol **63** (8.11 g, 90.0 mmol, 1.0 equiv.) was added dropwise to a suspension of sodium hydride (4.03 g, 101 mmol, 1.1 equiv.) in THF (200 mL) at 0 °C under an atmosphere of nitrogen. The reaction mixture was allowed to stir for 2.5 hours, at which point a solution of TBSCl (15.2 g, 101 mmol, 1.1 equiv.) in THF (20 mL) was added. After stirring for 20 hours the mixture was quenched with aqueous sat. Na_2CO_3 (100 mL) and left to stir for 30 minutes and extracted into Et_2O (3 x 100 mL). The combined organic components were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified on silica gel (10% - 20% EtOAc/petroleum ether [40/60]) to give **64** (8.28 g, 40.5 mmol, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.63 - 3.71 (4H, m, CH_2OTBS and CH_2OH), 2.04 - 2.06 (1H, m, O*H*), 1.61 - 1.71 (4H, m, CH_2CH$_2$OTBS and CH_2CH$_2$CH$_2$OTBS), 0.91 (9H, s, SiC(CH_3)$_3$), 0.08 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 63.2 (*C*H_2), 62.6 (*C*H_2), 30.1 (*C*H_2), 29.8 (*C*H_2), 25.7 (SiC(*C*H_3)$_3$), 18.3 (Si*C*), –5.4 (Si(*C*H_3)$_2$). Data consistent with literature.[164]

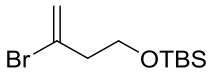
(4-Bromobutoxy)(*tert*-butyl)dimethylsilane (65)



65

Carbon tetrabromide (4.87 g, 14.7 mmol, 3.0 equiv.) and PPh_3 (3.90 g, 14.7 mmol, 3.0 equiv.) were added to a solution of **64**, Et_3N (4.10 mL, 29.4 mmol, 6.0 equiv.) and CH_2Cl_2 (50 mL) at 0 °C under nitrogen. The reaction was allowed to warm to room temperature and stirred for 3 hours. The reaction was quenched with aqueous sat. $NaHCO_3$ (30 mL), extracted into pentane (3 x 20 mL) and concentrated *in vacuo* to give the crude product. Purification by column chromatography (5% EtOAc/petroleum ether [40/60]) gave **65** (1.02 g, 3.82 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (2H, t, *J* = 6.2 Hz, C*H*$_2$OTBS), 3.46 (2H, t, *J* = 6.8 Hz, C*H*$_2$Br), 1.95 (2H, dt, *J* = 14.5, 7.1 Hz, C*H*$_2$CH$_2$OTBS), 1.62 - 1.71 (2H, m, C*H*$_2$CH$_2$Br), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.06 (6H, s, Si(CH$_3$)$_2$); ^{13}C (101 MHz, $CDCl_3$) δ 62.3 (*C*H$_2$), 34.0 (*C*H$_2$), 31.4 (*C*H$_2$), 29.5 (*C*H$_2$), 26.2 (SiC(*C*H$_3$)$_3$), 25.5 (Si*C*), –5.3 (Si(*C*H$_3$)$_2$). Data consistent with literature.[165]

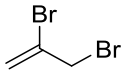
((3-Bromobut-3-en-1-yl)oxy)(*tert*-butyl)dimethyllsilane (67)



67

Prepared according to general procedure H. TBSCl (8.32 g, 55.2 mmol, 1.2 equiv.), 3-bromo-3-buten-1-ol (7.00 g, 46.0 mmol, 1.0 equiv.), imidazole (5.00 g, 73.6 mmol, 1.6 equiv.) in CH_2Cl_2 (92 mL), after quenching with aqueous sat. $NaHCO_3$ (100 mL) and extraction into Et_2O (3 x 100 mL), gave the crude product, which was then purified on silica gel (10% EtOAc/petroleum ether) to give **67** (10.1 g, 38.1 mmol, 82%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (1H, apparent s, 1H from C=C*H*$_2$), 5.47 (1H, d, *J* = 1.2 Hz, 1H from C=C*H*$_2$), 3.79 (2H, t, *J* = 6.4 Hz, C*H*$_2$OTBS), 2.55 (2H, t, *J* = 6.4 Hz, C*H*$_2$CH$_2$OTBS), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.08 (6H, s, Si(C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.9 (*C*=CH$_2$), 118.4 (C=*C*H$_2$), 60.9 (*C*H$_2$OTBS), 44.8 (*C*H$_2$CH$_2$OTBS), 25.9 (Si(*C*H$_3$)$_2$), 14.2 (Si*C*), -5.3 (SiC(*C*H$_3$)$_3$); ν_{max} (thin film/cm^{-1}): 2954, 2928, 2857, 1630, 1471, 1388, 252, 1099, 1006, 925, 886, 833, 774. Data consistent with literature.[166]

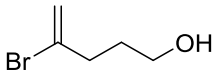
2,3-Dibromoprop-1-ene (68)



68

A solution of 1,2,3-tibromopropane (306 g, 1.10 mol, 1.0 equiv.) and NaOH (52.8 g, 1.32 mol, 1.2 equiv.) was distilled at 100 °C. The temperature was then increased to 180 °C, in intervals of 10 °C. The resulting distilled solution was washed with water. $CaCl_2$ was added to the organic phase, which was then distilled a second time under vacuum to give **68** (165 g, 0.83 mmol, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 - 6.05 (1H, m, 1H from C=CH_2), 5.64 (1H, m, 1H from C=CH_2), 4.20 (2H, d, *J* = 0.6 Hz, CH_2Br); ^{13}C NMR (126 MHz, $CDCl_3$) δ 127.5 (CH_2=*C*), 121.0 (*C*H_2=C), 36.6 (*C*H_2). Data consistent with literature.[167]

4-Bromopent-4-en-1-ol (69)[168]



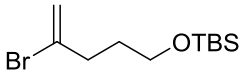
69

*n*BuLi (47.5 mL, 1.58 M in hexanes, 75.0 mmol, 1.0 equiv.) was added to a solution of di*iso*propylamine (10.7 mL, 75.8 mmol, 1.0 equiv.) in THF (25 mL) at ─78 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature over 2 hours. The resulting LDA solution was added to a suspension of EtOAc (7.35 mL, 75.0 mmol, 1.0 equiv.) and CuI (28.6 g, 150 mmol, 2.0 equiv.) in THF (75 mL) at -45 °C. The reaction was allowed to warm to -30 °C, before the addition of a solution of 2,3-dibromopropene **68** (3.88 mL, 37.5 mmol, 0.5 equiv.) in THF (17.5 mL). After stirring for 2.5 hours, the reaction mixture was quenched with aqueous sat. NH_4Cl (100 mL), extracted into Et_2O (3 x 50 mL) and washed with brine (100 mL). The organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude ester product.

A solution of the crude ester in THF (50 mL) was added to a mixture of $LiAlH_4$ (1.89 g, 50.0 mmol, 0.7 equiv.) in THF (150 mL) at 0 °C and stirred for 1 hour. Et_2O (50 mL) was added followed by; distilled water (2 mL), 1 M aqueous NaOH (2 mL), and distilled water (3 x 2 mL). The mixture was allowed to warm to room temperature and Na_2SO_4 was added and left to stir for 15 minutes. Concentration *in vacuo* then

gave the crude product, which was taken onto the next step without further purification.

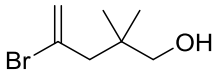
((4-Bromopent-4-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (70)



70

Prepared according to general procedure H. **69** (75.0 mmol, 1.0 equiv.), imidazole (7.62 g, 112 mmol, 1.5 equiv.), TBSCl (11.3 g, 90.0 mmol, 1.2 equiv.) in CH_2Cl_2 (150 mL), after quenching with aqueous sat. $NaHCO_3$ (100 mL), extraction into Et_2O (3 x 100 mL) and purification by column chromatography (5-10% EtOAc/petroleum ether [40/60]) gave **70** (12.9 g, 46.1 mmol, 62% [2 steps]). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (1H, d, *J* = 1.5 Hz, 1H from C=C*H*$_2$), 5.41 (1H, d, *J* = 1.5 Hz, 1H from C=C*H*$_2$), 3.64 (2H, t, *J* = 6.2 Hz, C*H*$_2$OTBS), 2.52 (2H, td, *J* = 7.4, 0.9 Hz, C*H*$_2$C=CH$_2$), 1.78 (2H, tt, *J* = 7.3, 6.2 Hz, C*H*$_2$CH$_2$OTBS), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.06 (6H, s, Si(C*H*$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.4 (*C*=CH$_2$), 116.6 (C=*C*H$_2$), 61.5 (*C*H$_2$OTBS), 37.9 (*C*H$_2$C=CH$_2$), 31.0 (*C*H$_2$CH$_2$OTBS), 25.9 (SiC(*C*H$_3$)$_3$), 18.3 (Si*C*), −5.3 (Si(*C*H$_3$)$_2$); MS (ES$^+$) *m/z* (%): 279 (M+H$^+$, 70), 301 (M+Na$^+$, 50). Data consistent with literature.[162]

4-Bromo-2,2-dimethylpent-4-en-1-ol (71)

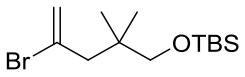


71

*n*BuLi (35.7 mL, 1.40 M in hexanes, 50.0 mmol, 1.0 equiv.) was added dropwise to a solution of di*iso*propylamine (7.00 mL, 50.0 mmol, 1.0 equiv.) in THF (36 mL) at –78 °C under an atmosphere of nitrogen and left to stir for 30 minutes. After warming to room temperature, the solution of LDA was added to a suspension of methyl *iso*butyrate (5.70 mL, 50.0 mmol, 1.0 equiv.), CuI (19.1 g, 100 mmol, 2.0 equiv.) in THF (50 mL) at –40 °C under an atmosphere of nitrogen. After stirring for 30 minutes, 2,3-dibromoprop-1-ene **68** (2.44 mL, 25.0 mmol, 0.5 equiv.) was added to the reaction mixture. After being allowed to stir for 1 hour, the reaction was quenched with aqueous saturated NH_4Cl (100 mL) followed by extraction into Et_2O (3 x 50 mL). The organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude ester was dissolved in THF (25 mL) and was added dropwise to a

suspension of $LiAlH_4$ (1.27 g, 33.5 mmol, 0.7 equiv.) in THF (152 mL) under nitrogen at 0 °C and left to stir for 4 hour. The reaction was quenched at 0 °C by the addition of water (1.27 mL), 1 M aqueous NaOH (1.3 mL) followed by another addition of water (3.8 mL). The mixture was then diluted in Et_2O (10 mL), exposed to the air and allowed to warm to room temperature. $MgSO_4$ was then added and the suspension was left to stir for 15 minutes. The precipitate was removed by filtration, washed with a mixture of Et_2O (40 mL) and EtOAc (40 mL) and was then concentrated *in vacuo* to give the crude product, which was taken onto the next step without further purification.

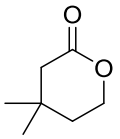
((4-Bromo-2,2-dimethylpent-4-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (72)



72

Prepared according to general procedure H. Imidazole (170 mg, 2.50 mmol, 1.6 equiv.), **71** (775 mg, 4.00 mmol, 1.0 equiv.), TBSCl (723 mg, 4.80 mmol, 1.2 equiv.) in CH_2Cl_2 (8 mL) after quenching with aqueous saturated $NaHCO_3$ (10 mL), extraction into Et_2O (3 x 10 mL) and purification by column chromatography (10% EtOAc/hexane) gave **72** (0.56 g, 1.82 mmol, 46% [2 steps]) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 - 5.57 (2H, m, C=CH_2), 3.31 (2H, s, CH_2OTBS), 2.49 (2H, s, CH_2C$(CH_3)_2$), 0.95 (6H, s, C(C$H_3)_2$), 0.87 (9H, s, SiC(C$H_3)_3$), 0.02 (6H, s, Si(C$H_3)_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 130.4 (*C*=CH_2), 120.1 (C=*C*H_2), 70.7 (*C*H_2OTBS), 48.9 (*C*H_2C$(CH_3)_2$), 36.5 (CH_2*C*$(CH_3)_3$), 25.9 (SiC(*C*$H_3)_3$), 24.3 (CH_2C(*C*$H_3)_2$), 18.3 (Si*C*), –5.50 (Si(*C*$H_3)_2$); ν_{max} (thin film/cm^{-1}): 3002, 2944, 1442, 1375, 1038, 918. MS was uninformative.

4,4-Dimethyltetrahydro-2*H*-pyran-2-one (74)[82]

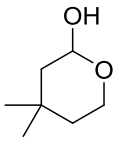


74

A solution of 3,3-dimethylglutaric anhydride **73** (10.0 g, 70.0 mmol, 1.0 equiv.) in THF (30 mL), was added to a suspension of sodium borohydride (2.66 g, 70.3 mmol, 1.0 equiv.) in THF (40 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and was stirred for 20 hours. The reaction was quenched with 6M aqueous HCl (20 mL) and extracted into Et_2O (3 x

50 mL). The organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was taken onto the next step with no further purification.

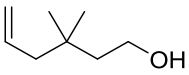
4,4-Dimethyltetrahydro-2*H*-pyran-2-ol (75)[169]



75

A solution of DIBAL-H (84.0 mL, 1 M in hexanes, 1.2 equiv.) was added to a mixture of **74** (70.0 mmol, 1.0 equiv.), pentane (70 mL) and dichloromethane (70 mL) at –78 °C under a nitrogen atmosphere. After 4 hours, methanol (11.7 mL, 70 mmol, 1.0 equiv.) was added, stirred for 15 minutes and allowed to warm to room temperature for 4 hours. The reaction mixture was poured onto aqueous saturated NaK tartrate (50 mL) and extracted into Et_2O (3 x 50 mL). The organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was taken onto the next step with no further purification.

3,3-Dimethylhex-5-en-1-ol (76a)

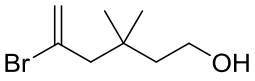


76a

*n*BuLi (87.5 mL, 1.60 M in hexanes, 140 mmol, 2.0 equiv.) was added dropwise to a stirred solution of Me_3PhPBr (55.0 g, 154 mmol, 2.2 equiv.) in THF (350 mL) at –78 °C under an atmosphere of nitrogen. The resulting yellow mixture was allowed to warm to room temperature over 2 hours. At which point a solution of **75** (70.0 mmol, 1.0 equiv.) in THF (70 mL) was added dropwise and the reaction was refluxed for 4 hours. Once cooled the reaction was quenched with aqueous saturated NH_4Cl (200 mL), extracted into Et_2O (3 x 100 mL) and dried ($MgSO_4$). The organic layers were concentrated *in vacuo* to give the crude product. Purification by flash column chromatography (30% EtOAc/hexane) gave **76a** (3.68 g, 28.7 mmol, 41% (3 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (1H, ddt, *J* = 16.8, 10.3, 7.3, 7.3 Hz, C*H*=CH_2), 4.97 - 5.08 (2H, m, CH=CH_2), 3.72 (2H, td, *J* = 7.6, 4.8 Hz, CH_2OH), 1.98 (2H, d, *J* =

7.3 Hz, CH_2CH=CH_2), 1.53 (2H, t, *J* = 7.6 Hz, C$H_2$$CH_2$OH), 0.92 (6H, s, C(C$H_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.0 (CH_2=*C*), 116.8 (*C*H_2=C), 59.5 (*C*H_2OH), 46.6 (*C*H_2C(CH_3)$_2$), 44.0 (*C*$H_2$$CH_2$OH), 32.2 (*C*(C$H_3$)$_2$), 26.9 (2 x *C*$H_3$). Data consistent with the literature.[83]

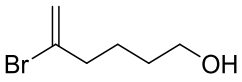
5-Bromo-3,3-dimethylhex-5-en-1-ol (77a)



77a

A solution of bromine (2.40 mL, 460 mmol, 1.0 equiv.) in CH_2Cl_2 (8.3 mL) was added to a solution of **76a** (5.90 g, 460 mmol, 1.0 equiv.) in CH_2Cl_2 (8.3 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 1 hour. The resulting mixture was concentrated *in vacuo* to give the crude dibromide. A solution of KO*t*Bu (4.74 g, 460 mmol, 1.0 equiv.) in dry THF (23 mL) was added to a solution of the dibromide in THF (23 mL) under a nitrogen atmosphere at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 4 hours. The reaction was quenched with water (40 mL), extracted into Et_2O (3 x 30 mL) and dried ($MgSO_4$). The organic component was concentrated *in vacuo* to give crude product as a brown oil, which was used in the next steps without further purification.

5-Bromohex-5-en-1-ol (77b)[170]

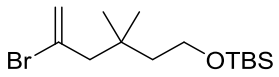


77b

A solution of bromine (1.13 mL, 22.0 mmol, 1.0 equiv.) in CH_2Cl_2 (1.8 mL) was added to a solution of 5-hexen-1-ol **76b** (2.20 g, 22.0 mmol, 1.0 equiv.) in CH_2Cl_2 (1.8 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The resulting mixture was concentrated *in vacuo* to give the crude dibromide. A solution of KO*t*Bu (2.47 g, 22.0 mol, 1.0 equiv.) in dry THF (10.0 mL) was added to a solution of the crude dibromide in THF (10.0 mL) under a nitrogen atmosphere at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 4 hours before being quenched with water (15 mL),

extracted into Et_2O (3 x 10 mL) and dried ($MgSO_4$). The organic component was concentrated *in vacuo* to give crude **78b** as a brown oil, which was taken onto the next step without further purification.

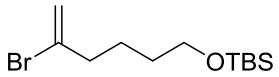
((5-Bromo-3,3-dimethylhex-5-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (78a)



78a

Prepared according to general Procedure H. Crude **77a** (9.16 mmol, 1.0 equiv), imidazole (1.00 g, 14.7 mmol, 1.6 equiv.), TBSCl (1.66 g, 11.0 mmol, 1.2 equiv.) in CH_2Cl_2 (18.3 mL), after purification gave **78a** (2.13 g, 6.63 mmol, 72% [3 steps]). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (1H, s, 1H from C=CH_2), 5.54 (1H, s, 1H from C=CH_2), 3.71 (2H, t, *J* = 7.3 Hz, CH_2OTBS), 2.45 (2H, s, CH_2=CCH_2), 1.58 (2H, t, *J* = 7.1 Hz, C$H_2$$CH_2$OTBS), 1.02 (6H, s, (C$H_3$)$_2$), 0.89 - 0.92 (9H, m, OSiC(CH_3)$_3$), 0.05 - 0.08 (6H, m, OSi(CH_3)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 130.2 (*C*=CH_2), 120.4 (C=*C*H_2), 59.9 (*C*H_2OTBS), 53.1 (*C*H_2C=CH_2), 44.3 (*C*$H_2$$CH_2$OTBS), 33.6 (*C*(C$H_3$)$_2$), 27.4 (C(*C*$H_3$)$_2$), 26.0 (SiC(*C*$H_3$)$_3$), 18.3 (Si*C*), −5.3 (Si(*C*H_3)$_2$); v_{max} (thin film/cm^{-1}): 2955, 2928, 2885, 2856, 1622, 1471, 1463, 1431, 1388, 1367, 1361, 1254, 1171, 1090, 1047, 999, 939, 887, 834, 810. MS was uninformative.

((5-Bromohex-5-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (78b)

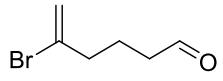


78b

Prepared according to general procedure H. Imidazole (1.84 g, 27.0 mmol, 1.5 equiv.), crude **77b** (22.0 mmol, 1.0 equiv.), TBSCl (3.26 g, 21.6 mmol, 1.2 equiv.) in CH_2Cl_2 (80 mL), after purification by column chromatography (30% EtOAc/petroleum ether [40/60]) gave **78b** (5.28 g, 18.0 mmol, 82%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (1H, d, *J* = 1.5 Hz, 1H from C=CH_2), 5.40 (1H, d, *J* = 1.5 Hz, 1H from C=CH_2), 3.63 (2H, t, *J* = 6.3 Hz, CH_2OTBS), 2.41 - 2.51 (2H, m, *J* = 7.2, 0.8 Hz, CH_2C=CH_2), 1.57 - 1.67 (2H, m, CH_2(CH_2)$_2$OTBS), 1.49 - 1.56 (2H, m, C$H_2$$CH_2$OSi), 0.90 (9H, s, SiC(C$H_3$)$_3$), 0.06 (6H, s, Si(C$H_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.7 (CH_2=*C*), 116.4 (*C*H_2=C), 62.8 (*C*H_2OTBS), 41.2 (*C*H_2(CH_2)$_2$OTBS), 31.5 (*C*H_2(CH_2)$_3$OTBS), 26.0 (SiC(*C*H_3)$_3$), 24.3 (*C*H_2), 18.3 (Si*C*), –5.3 (Si(*C*H_3)$_2$);

v_{max} (thin film/cm^{-1}): 2930, 2885, 2858, 1471, 1387, 1361, 1254, 1146, 1101. MS was uninformative.

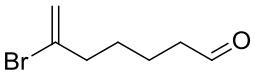
5-Bromohex-5-enal (79)



79

Et_3N (132 mL, 0.95 mol, 7.0 equiv.) and anhydrous DMSO (94.4 mL, 1.33 mol, 9.5 equiv.) were added to a solution of **77b** (24.3 g, 0.14 mol, 1.0 equiv.), which was then cooled to 0 °C, followed by the addition of SO_3Py. (66.8 g, 0.42 mol, 3.0 equiv.). The reaction mixture was allowed to warm to room temperature and left to stir for 16 hours. The reaction was diluted with EtOAc (200 mL), washed with water (200 mL), aqueous saturated $NaHCO_3$ (200 mL) and brine (200 mL). After drying ($MgSO_4$) the organic layers were concentrated *in vacuo* to give the crude product as an oil, which was taken onto the next step without further purification.

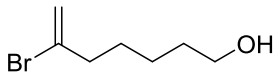
6-Bromohept-6-enal (80)



80

A solution of anhydrous KO*t*Bu (20.0 g, 0.18 mol, 1.3 equiv.) in THF (140 mL) was added to (methoxymethyl)tri-phenylphosphonium chloride (61.7 g, 0.18 mol, 1.3 equiv.) in THF (140 mL) at 0 °C. Crude **79** (0.14 mol, 1.0 equiv.) in THF (47 mL) was added dropwise, after which the reaction mixture was allowed to warm to room temperature over 4 hours. The reaction mixture was quenched with water (140 mL), cooled to 0 °C for the addition of H_2SO_4 (30% aqueous solution, 39 mL) and was allowed to warm to room temperature. After 18 hours, the reaction mixture was cooled to 0 °C, aqueous saturated $NaHCO_3$ (50 mL) was added and the reaction mixture was extracted into pentane (3 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as an oil, which was taken onto the next step without further purification.

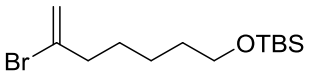
6-Bromohept-6-en-1-ol (81)



81

Sodium borohydride (15.9 g, 0.42 mol, 2.0 equiv.), was added portionwise to crude **80** (0.14 mol, 1.0 equiv.) in MeOH (460 mL) at 0 °C. After 10 minutes the reaction was allowed to warm to room temperature. After 16 hours, the solvent was removed *in vacuo,* extracted into Et_2O (3 x 200 mL), washed with water (300 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The product was taken onto the next step with no further purification.

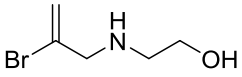
((6-Bromohept-6-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (82)



82

Prepared according to general procedure H. TBSCl (16.3 g, 108 mmol, 1.2 equiv.), imidazole (9.80 g, 144 mmol, 1.6 equiv.), crude **81** (90.0 mmol, 1.0 equiv.) in CH_2Cl_2 (200 mL), after purification (5% EtOAc/petroleum ether [40/60]) gave **82** (13.8 g, 44.8 mmol, 32% [4 steps]) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (1H, d, *J* = 1.5 Hz, 1H from C=C*H*$_2$), 5.33 (1H, d, *J* = 1.5 Hz, 1H from C=C*H*$_2$), 3.56 (2H, t, *J* = 6.4 Hz, C*H*$_2$OTBS), 2.38 (2H, t, *J* = 7.3 Hz, CH_2=CC*H*$_2$), 1.44 - 1.56 (4H, m, 2 x C*H*$_2$), 1.26 - 1.35 (2H, m, C*H*$_2$), 0.82 - 0.86 (9H, m, C(C*H*$_3$)$_3$), -0.03 - 0.03 (6H, m, Si(C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8 (*C*=CH_2), 116.3 (C=*C*H_2), 63.0 (*C*H_2OTBS), 41.4 (CH_2=C*C*H_2), 32.5 (*C*H_2), 27.7 (*C*H_2), 26.0 (C(*C*H_3)$_3$), 24.7 (*C*H_2), 18.4 (*C*(CH$_3$)$_3$), -5.3 (Si(*C*H$_3$)$_2$); ν_{max} (thin film/cm^{-1}): 2929, 2896, 2857, 1629, 1471, 1388, 1388, 1254, 1099, 1021, 938, 883, 833, 813, 773. MS was uninformative.

2-((2-Bromoallyl)amino)ethan-1-ol (327)

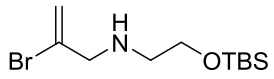


327

2,3-Dibromopropene **68** (4.66 g, 23.3 mmol, 1.0 equiv.) was added to a stirred solution of 2-aminoethanol (4.27 g, 69.9 mmol, 3.0 equiv.) and anhydrous potassium carbonate (3.22 g, 23.3 mmol, 1.0 equiv.) in dry THF (75 mL) under a nitrogen atmosphere. The reaction mixture was left to stir for 18 hours at room temperature. The mixture was quenched with water (75 mL) and extracted into Et_2O (3 x 50 mL). The organic component was dried ($MgSO_4$) and concentrated *in vacuo*

to give the crude product as an oil, which was taken onto the next step with no further purification.

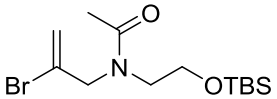
2-Bromo-*N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)prop-2-en-1-amine (83)



83

General procedure H was followed. Imidazole (2.38 g, 35.0 mmol, 1.5 equiv.) alcohol **327** (23.0 mmol, 1.0 equiv.), TBSCl (4.21 g, 28.0 mmol, 1.2 equiv.) in CH_2Cl_2 (50 mL) gave crude product, which was taken onto the next step with no further purification.

***N*-(2-Bromoallyl)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)acetamide (84)**

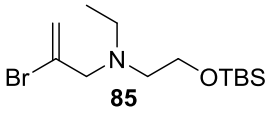


84

Acetic anhydride (15.2 mL, 161 mmol, 7.0 equiv.) was added dropwise to a solution of **83** (5.07 g, 23.0 mmol, 1.0 equiv.) and anhydrous Et_3N (25.6 mL, 184 mmol, 8.0 equiv.) in THF (23 mL) under an atmosphere of nitrogen and the reaction was left to stir at room temperature for 42 hours. The mixture was quenched with aqueous saturated $NaHCO_3$ solution (20 mL) and extracted into Et_2O (3 x 20 mL). The organic component was dried ($MgSO_4$) and concentrated *in vacuo* to give crude product. Purification by chromatography on silica gel (10% EtOAc/hexane) gave **84** (5.04 g, 15.0 mmol, 65% [3 steps]) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (1H, br. s., 1H from C=CH_2 [one rotamer]), 5.73 (1H, br. s., 1H from C=CH_2 [one rotamer]), 5.65 (1H, s, 1H from C=CH_2 [one rotamer]), 5.58 (1H, s, 1H from C=CH_2 [one rotamer], 4.31 - 4.33 (2H, m, CCH_2N [one rotamer]), 4.26 - 4.28 (2H, m, CCH_2N [one rotamer]), 3.79 (2H, m, CH_2OTBS [one rotamer]), 3.75 (2H, m, CH_2OTBS [one rotamer], 3.48 (4H, m, CH_2CH$_2$OTBS [both rotamers]), 2.19 (3H, s, CH_3 [one rotamer]), 2.12 (3H, s, CH_3 [one rotamer]), 0.91 (12H, s, Si(CH_3)$_2$ [both rotamers]), 0.06 (18H, br. s., SiC(CH_3)$_3$ [both rotamers]; ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9

(*C*=O [both rotamers]), 128.8 (*C*=CH_2 [one rotamer]), 117.6 (C=*C*H_2 [one rotamer]), 117.1 (C=*C*H_2 [one rotamer]), 61.8 (*C*H_2OTBS [one rotamer]), 61.0 (*C*H_2OTBS [one rotamer]), 58.0 (*C*H_2N [one rotamer]), 52.8 (*C*H_2N [one rotamer]), 50.1 (*C*$H_2$$CH_2$OTBS [one rotamers]), 48.2 (*C*$H_2$$CH_2$OTBS [one rotamer]), 25.8 (Si(*C*H_3)$_2$ [both rotamers]), 21.2 (*C*H_3 [both rotamers]), 18.1 (Si*C* [both rotamers]), –5.5 (SiC(*C*H_3)$_3$ [both rotamers]); ν_{max} (thin film/cm^{-1}) 2929, 2885, 2857, 1653, 1470, 1411, 1361, 1249, 1101, 1040, 931. MS (ES$^+$) *m/z* (%): 337 (M^+H^+, 100), 358 (M^+Na^+, 50); HRMS (ES$^+$) calcd. for $C_{13}H_{26}BrNO_2Si$ (M^+H^+): 337.0896. Found: 337.0992.

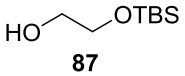
2-Bromo-*N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-*N*-ethylprop-2-en-1-amine (85)



85

To a suspension of $LiAlH_4$ (113 mg, 2.97 mmol, 1.0 equiv.) in THF (60 mL) under an atmosphere of nitrogen, a solution of **84** (1.00 g, 2.97 mmol, 1.0 equiv.) was added and the reaction was left to stir for 48 hours. The reaction was then quenched with water (5 mL) at 0 °C and extracted into Et_2O (3 x 5 ml). The organic component was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification by chromatography on silica gel (10% EtOAc/hexane) gave **85** (282 mg, 0.88 mmol, 29%) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (1H, s, 1H from C=C*H*$_2$), 5.49 - 5.56 (1H, m, 1H from C=C*H*$_2$), 3.70 (2H, t, *J* = 6.6 Hz, C*H*$_2$OTBS), 3.34 (2H, s, C*H*$_2$N(Et)), 2.67 (2H, t, *J* = 6.6 Hz, C*H*$_2$$CH_2$OTBS), 2.63 (2H, m, *J* = 7.1 Hz, NC*H*$_2$$CH_3$), 1.04 (3H, t, *J* = 7.1 Hz, NCH_2C*H*$_3$), 0.87 - 0.92 (9H, m, SiC(C*H*$_3$)$_3$), 0.03 - 0.08 (6H, m, Si(C*H*$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.9 (CH_2=*C*), 117.3 (*C*H_2=C), 62.9 (*C*H_2N), 61.9 (*C*H_2OTBS), 55.3 (*C*$H_2$$CH_2$OTBS), 48.2 ($CH_3$*C*$H_2$), 25.9 (*C*$H_3$$CH_2$), 18.3 (Si*C*), 12.2 (Si(*C*H_3)$_2$), –5.6 (SiC(*C*H_3)$_3$); ν_{max} (thin film/cm^{-1}): 2954, 2928, 2854, 1470, 1413, 1246, 1103, 1040, 933. MS inconclusive.

2-((*tert*-Butyldimethylsilyl)oxy)ethan-1-ol (87)

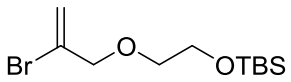


87

Ethylene glycol **86** (3.10 g, 50.0 mmol, 1.0 equiv.) was added neat to a suspension of NaH (2.20 g, 55.0 mmol, 1.1 equiv.) in THF (100 mL) at 0 °C under nitrogen and the reaction mixture allowed to warm to room temperature. After 3 hours, a solution

of TBSCl (8.29 g, 55.0 mmol, 1.1 equiv.) in THF (10 mL) was added. After stirring for 18 hours, the reaction was quenched with aqueous saturated Na_2CO_3 (90 mL), extracted into Et_2O (3 x 50 mL) and washed with brine (50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by chromatography to give **87** (7.89 g, 45.0 mmol, 90%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 - 3.74 (2H, m, C*H*$_2$OTBS), 3.62 - 3.68 (2H, m, C*H*$_2$OH), 0.92 (9H, s, SiC(C*H*$_3$)$_3$), 0.09 (6H, s, Si(C*H*$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 64.0 (*C*H$_2$), 63.6 (*C*H$_2$), 25.8 (Si*C*), 18.3 (Si(*C*H$_3$)$_2$), –5.3 (SiC(*C*H$_3$)$_3$). Data consistent with literature.[171]

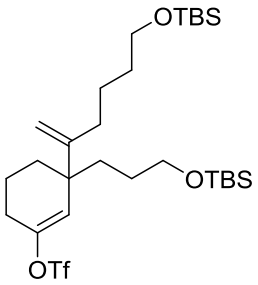
(2-((2-Bromoallyl)oxy)ethoxy)(*tert*-butyl)dimethylsilane (88)



88

Alcohol **87** (3.00 g, 18.2 mmol, 1.0 equiv.) was added to a solution of NaH (0.80 g, 20.0 mmol, 1.1 equiv.) in THF (36 mL) at 0 °C under an atmosphere of nitrogen and the mixture left to stir at this temperature for 30 minutes. 2,3-Dibromoprop-1-ene **68** (5.3 mL, 54.6 mmol, 3.0 equiv.) was then added dropwise. After stirring for a further 15 minutes, the reaction vessel was allowed to warm to room temperature. A white to brown colour change was observed and stirring was continued for 20 hours. The reaction was quenched with distilled water (15 mL), extracted into Et_2O (3 x 15 mL), the organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography (50% EtOAc/petroleum ether [40/60]) to give **88** (2.33 g, 7.89 mmol, 43%) as an oil. ^{1}H NMR (500 MHz,$CDCl_3$) δ 5.97 (1H, s, 1H from C=C*H*$_2$), 5.61 (1H, s, 1H from C=C*H*$_2$), 4.16 (2H, s, C*H*$_2$O), 3.80 (2H, t, *J* = 5.1 Hz, C*H*$_2$OTBS), 3.58 (2H, t, *J* = 5.1 Hz, C*H*$_2$CH$_2$OTBS), 0.91 (9H, s, SiC(C*H*$_3$)$_3$), 0.08 (6H, s, Si(C*H*$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 129.8 (CH$_2$=*C*), 117.3 (*C*H$_2$=C), 75.4 (*C*H$_2$O), 72.1 (*C*H$_2$CH$_2$OTBS), 63.0 (*C*H$_2$OTBS), 26.2 (Si*C*), 18.6 (Si(*C*H$_3$)$_2$), -5.1 (SiC(*C*H$_3$)$_3$); ν_{max} (thin film/cm^{-1}): 2955, 2929, 2857, 1641, 1471, 1388, 1361, 1255, 1098. MS inconclusive.

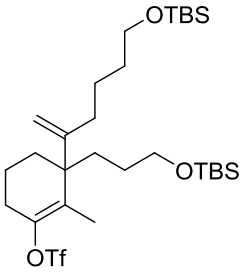
3-(6-((*tert*-Butyldimethylsilyl)oxy)hex-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-en-1-yl-trifluoromethanesulfonate (56)



56

Prepared according to general procedure B. CuI (27.6 mg, 0.15 mmol, 0.1 equiv.), PhSLi (0.18 mL, 0.83 M in THF, 0.20 mmol, 0.1 equiv.), **54** (189 mg, 1.45 mmol, 1.0 equiv.), (3-((*tert*-butyldimethylsilyl)oxy)propyl)magnesium bromide (12.2 mL, 0.12 M in THF, 1.45 mmol, 1.0 equiv.), (6-((*tert*-butyldimethylsilyl)oxy)hex-1-en-2-yl)magnesium bromide (20.0 mL, 0.11 M in THF, 2.18 mmol, 1.5 equiv.), Comins' reagent (94.2 mg, 0.24 mmol, 1.6 equiv.) and partial purification by column chromatography (50:1, hexane:EtOAc) gave **56**, which was taken onto the next step with no further purification.

3-(6-((*tert*-butyldimethylsilyl)oxy)hex-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-2-methylcyclohex-1-en-1-yl trifluoromethanesulfonate (89)

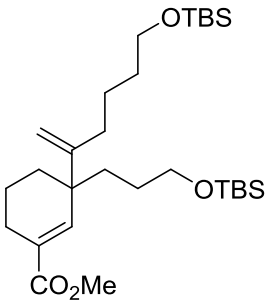


89

A solution of (3-((*tert*-butyldimethylsilyl)oxy)propyl)magnesium bromide (17.2 mL, 0.13 M in THF, 2.24 mmol, 1.0 equiv.) was added to a mixture of lithium 2-thienylcyanocuprate solution (0.88 mL, 0.25 M in THF, 0.22 mmol, 0.1 equiv.) and **59** (324 mg, 2.24 mmol, 1.0 equiv.) at –45 °C. After stirring for 30 minutes, (6-((*tert*-butyldimethylsilyl)oxy)hex-1-en-2-yl)magnesium bromide (42.0 mL, 0.80 M in THF, 3.36 mmol, 1.5 equiv.) was added dropwise and the resulting mixture was left to stir for 4 hours. This was followed by the addition of Comins' reagent (1.41 g, 3.58 mmol, 1.6 equiv.) in THF (1.5 mL) and stirring for 72 hours. Aqueous saturated NH_4Cl (10 mL) was added and the crude product was extracted with Et_2O (3 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The crude

product was purified by chromatography (50:1 hexane:EtOAc) to give **89** (620 mg, 0.99 mmol, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (1H, s, C=CH_2), 4.92 (1H, s, C=CH_2), 3.59 - 3.64 (4H, m, 2 x CH_2OTBS), 2.25 (2H, t, *J* = 7.2 Hz, CH_2C=CH_2), 1.97 - 2.16 (2H, m, CH_2), 1.69 - 1.96 (2H, m, CH_2), 1.41 - 1.65 (10H, m, 5 x CH_2), 1.30 - 1.37 (3H, s, CCH_3), 0.90 (18H, s, 2 x SiC(CH_3)$_3$), 0.05 (12H, s, 2 x Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7 (*C*=CH_2), 147.9 (*C*=CCH_3), 126.5 (C=*C*CH_3), 111.9 (C=*C*H_2), 63.6 (*C*H_2OTBS), 63.4 (*C*H_2OTBS), 49.7 (*C*C=CH_2), 37.9 (*C*H_2), 36.3 (*C*H_2), 34.2 (*C*H_2COTf), 33.2 (*C*H_2), 32.9 (*C*H_2), 31.7 (*C*H_2), 26.3 (2 x SiC(*C*H_3)$_3$), 25.9 (*C*H_2), 25.1 (*C*H_2), 18.7 (2 x Si*C*), –5.0 (2 x Si(*C*H_3)$_2$), (*C*F_3 not observed); ν_{max} (thin film/cm^{-1}): 2951, 2929, 2857, 1473, 1419, 1247, 1208, 1144, 1099, 1004, 906. MS uninformative.

Methyl 3-(6-((*tert*-Butyldimethylsilyl)oxy)hex-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-ene-1-carboxylate (90)

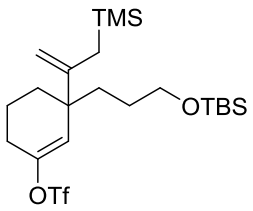


90

Prepared according to general procedure C. Crude **56** (1.45 mmol, 1.0 equiv.), $Pd(OAc)_2$ (65.1 mg, 0.29 mmol, 0.2 equiv.), PPh_3 (152.1 mg, 0.58 mmol, 0.4 equiv.), anhydrous Et_3N (294 mg, 2.90 mmol, 2.0 equiv.), anhydrous MeOH (2.35 mL, 58.0 mmol, 40 equiv.), in DMF (8.1 mL), after purification by column chromatography (50:1, hexane:EtOAc) gave **90** (0.49 g, 0.93 mmol, 64% [2 steps]). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (1H, s, C=C*H*), 4.95 (1H, s, 1H from CH_2=C), 4.72 (1H, m, 1H from CH_2=C), 3.72 - 3.76 (3H, m, CO_2CH_3), 3.59 - 3.65 (4H, m, 2 x CH_2OTBS), 2.11 - 2.22 (2H, m, CH_2CCO_2CH_3), 1.95 - 2.01 (2H, m, CH_2=CCH_2), 1.72 - 1.78 (1H, m, 1H from CH_2), 1.56 - 1.65 (3H, m, CH_2, 1H from CH_2), 1.46 - 1.56 (8H, m, 4 x CH_2), 0.90 (18H, br. s, 2 x SiC(CH_3)$_3$), 0.05 (12H, br. s, 2 x Si(CH_3)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4 (*C*O_2CH_3), 152.6 (CH_2=*C*), 145.5 (*C*H=C), 129.9 (*C*CO_2CH_3), 112.2 (*C*H_2=C), 63.7 (C$CH_2CH_2CH_2$*C*H_2OTBS), 63.4 (*C*H_2OTBS), 51.2 (CO_2*C*H_3), 45.2 (*C*(CH_2)$_3$OTBS), 35.2 (*C*H_2), 32.1 (*C*H_2), 32.2 (*C*H_2), 30.4 (*C*H_2), 27.9 (*C*H_2), 26.2

(SiC(CH_3)$_3$), 25.0 (CH_2), 22.9 (CH_2), 18.8 (CH_2), 18.61 (OSi*C*), –5.02 (Si(CH_3)$_2$; ν_{max} (thin film/cm^{-1}): 2950, 2929, 2856, 1717, 1645, 1471, 1435, 1387, 1251, 1099, 1006. MS (ES$^+$) *m/z* (%): 525 (M^+H^+, 5), 547 (M^+Na^+, 100); HRMS (ES$^+$) calcd. for $C_{29}H_{56}O_4NaSi_2$ (M^+Na^+): 547.3609. Found: 547.3622.

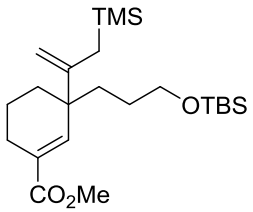
3-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-3-(3-(trimethylsilyl)prop-1-en-2-yl)cyclohex-1-en-1-yl trifluoromethanesulfonete (328)



328

Prepared according to general procedure B. CuI (74 mg, 0.39 mmol, 0.1 equiv.), THF (4 mL), PhSLi (0.47 mL, 0.83 M in THF, 0.39 mmol, 0.1 equiv.), **54** (505 mg, 3.87 mmol, 1.0 equiv.), (3-((*tert*-butyldimethylsilyl)oxy)propyl)magnesium bromide (35 mL, 0.11 M in THF, 3.87 mmol, 1.0 equiv.), (3-(trimethylsilyl)prop-1-en-2-yl)magnesium bromide (37 mL, 0.14 M in THF, 5.81 mmol, 1.5 equiv.), and Comins' reagent (2.43 g, 6.19 mmol, 1.6 equiv.) in THF (3 mL). After partial purification by column chromatography (1:80 [ethyl acetate:hexane]) gave the triflate intermediate, which was taken onto the next step without further purification.

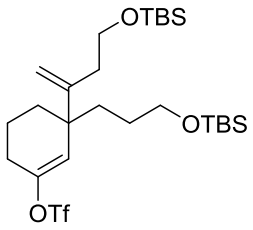
Methyl 3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3-(3-(trimethylsilyl)prop-1-en-2-yl)cyclohex-1-ene-1-carboxylate (94)



94

Prepared according to general procedure C. Triflate intermediate **328** (3.87 mmol), MeOH (6.27 mL, 155 mmol, 40 equiv.), Et_3N (1.08 mL, 7.74 mmol, 2.0 equiv.), $Pd(OAc)_2$ (174 mg, 0.77 mmol, 0.2 equiv.), PPh_3 (406 mg, 1.54 mmol, 0.4 equiv.) in DMF (19.4 mL). After purification by column chromatography (50:1 [hexane/EtOAc]) gave **94** (1.04 g, 2.45 mmol, 63% [2 steps]) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (1H, s, C*H*=C), 4.81 (1H, s, 1H from C=CH_2), 4.63 (1H, s, 1H from C=CH_2), 3.74 (3H, s, CO_2CH_3), 3.50 - 3.61 (2H, m, CH_2OTBS), 2.22 - 2.36 (1H, m, 1H from CH_2CCO$_2$Me), 2.07 - 2.19 (1H, m, 1H from CH_2CCO$_2$Me), 1.59 - 1.76 (4H, m, CH_2CH$_2$CCO$_2$Me and CH_2CH$_2$CH$_2$CCO$_2$Me), 1.25 - 1.52 (6H, m, 3 x CH_2), 0.89 (9H, s, SiC(CH_3)$_3$), 0.09 (6H, s, Si(CH_3)$_2$), 0.05 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8 (*C*=O), 149.6 (*C*=CH$_2$), 145.1 (*C*H=C), 129.3 (*C*=CH), 111.8 (*C*H$_2$=C), 63.1 (*C*H$_2$OTBS), 51.3 (CO_2CH_3), 45.2 (*C*C=CH$_2$), 34.6 (*C*H$_2$TMS), 30.8 (*C*H$_2$), 27.1 (*C*H$_2$), 25.6 (*C*H$_2$), 24.5 (*C*H$_2$), 19.8 (*C*H$_2$), 18.4 (Si*C*(CH$_3$)$_3$), 18.0 (SiC(*C*H$_3$)$_3$), –0.9 (Si(*C*H$_3$)$_3$), –5.7 (Si(*C*H$_3$)$_2$); ν_{max} (thin film/cm^{-1}): 2952, 2858, 1418, 1246, 1209, 1143, 1099, 1000, 908, 835. MS (ES$^+$) *m/z* (%): 425 (M+H$^+$, 50), 447 (M+Na$^+$, 100); HRMS (ES$^+$) calcd for $C_{23}H_{44}O_3NaSi_2$ (M+Na$^+$): 447.2727. Found: 447.2741.

3-(4-((*tert*-Butyldimethylsilyl)oxy)but-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (329)

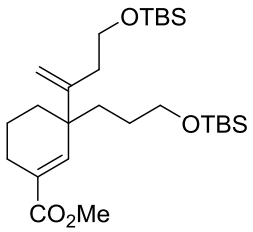


329

Prepared according to general procedure B. PhSLi (0.44 mL, 0.91 M in THF, 0.40 mmol, 0.1 equiv.), CuI (76.0 mg, 0.40 mmol, 0.1 equiv.), **54** (517 mg, 3.96 mmol, 1.0 equiv.), (3-((*tert*-butyldimethylsilyl)oxy)propyl)magnesium bromide (22 mL, 0.18 M in THF, 3.96 mmol, 1.0 equiv.), (4-((*tert*-butyldimethylsilyl)oxy)but-1-en-2-

yl)magnesium bromide (33 mL, 0.18 M in THF, 5.94 mmol, 1.5 equiv.), and Comins' reagent (2.49 g, 6.34 mmol, 1.6 equiv.). Partial purification by column chromatography (50:1, [hexane:EtOAc]) gave the triflate intermediate, which was taken onto the next step.

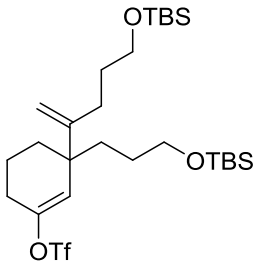
Methyl-3-(4-((*tert*-butyldimethylsilyl)oxy)but-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-ene-1-carboxylate (95)



95

Prepared according to general procedure C. Triflate intermedate **329** (3.66 mmol), $Pd(OAc)_2$ (177 mg, 0.79 mmol, 0.2 equiv.), PPh_3 (414 mg, 1.58 mmol, 0.4 equiv.), Et_3N (1.1 mL, 7.92 mmol, 2.0 equiv.), MeOH (6.41 mL, 158 mmol, 40 equiv.) and DMF (19.8 mL). After purification by column chromatography (50:1, [hexane:EtOAc]) gave **95** (863 mg, 1.74 mmol, 44% [2 steps]) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (1H, s, C=C*H*), 4.87 (1H, s, 1H from C=CH_2), 4.70 (1H, s, 1H from C=CH_2), 3.70 (3H, s, CO_2CH_3), 3.63 - 3.69 (2H, m, CH_2OTBS), 3.50 - 3.58 (2H, m, CH_2OTBS), 2.25 - 2.29 (1H, m, 1H from CH_2), 2.17 - 2.22 (2H, m, CH_2), 2.05 - 2.15 (1H, m, 1H from CH_2), 1.66 - 1.73 (1H, m, 1H from CH_2), 1.55 - 1.63 (1H, m, 1H from CH_2), 1.25 - 1.52 (6H, m, 3 x CH_2) 0.85 (18H, s, 2 x SiC(CH_3)$_3$), –0.04 (12H, s, 2 x Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (*C*O_2CH_3), 149.2 (*C*=CH_2), 144.7 (*C*=CH), 130.0 (*C*H=C), 113.5 (C=*C*H_2), 63.5 (*C*H_2OTBS), 63.1 (*C*H_2OTBS), 51.6 (CO_2*C*H_3), 45.0 (*C*C=CH_2), 34.9 (*C*H_2), 33.8 (*C*H_2), 31.6 (*C*H_2), 27.4 (*C*H_2), 26.0 (2 x Si(*C*H_3)$_2$), 24.8 (*C*H_2), 22.7 (*C*H_2), 18.6 (Si*C*), 18.4 (Si*C*), –5.2 (SiC(*C*H_3)$_3$), –5.3 (SiC(*C*H_3)$_3$); ν_{max} (thin film/cm^{-1}): 2929, 2856, 1719, 1407, 1435, 1097, 835, 775. MS (ES$^+$) *m/z* (%): 519 (M+Na$^+$, 100). HRMS (ES$^+$) cald. for $C_{27}H_{52}O_4NaSi_2$ (M+Na$^+$): 519.3309. Found: 519.3297.

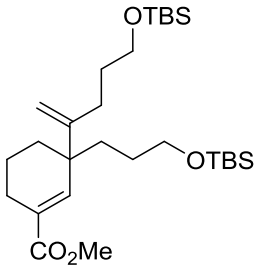
3-(5-((*tert*-Butyldimethylsilyl)oxy)pent-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (330)



330

Prepared according to general procedure B. **54** (435 mg, 1.62 mmol, 1.0 equiv.), CuI (30.5 mg, 0.16 mmol, 0.1 equiv.), THF (1.3 mL), PhSLi (0.22 mL, 0.74 M in THF, 0.10 mmol, 0.1 equiv.), (3-((*tert*-butyldimethylsilyl)oxy)propyl)magnesium bromide (10.8 mL, 0.15 M in THF, 1.62 mmol, 1.0 equiv.), (5-((*tert*-butyldimethylsilyl)oxy)pent-1-en-2-yl)magnesium bromide (9.00 mL, 0.27 M in THF, 1.50 mmol, 1.5 equiv.) and Comins' reagent (1.02 g, 2.59 mmol, 1.6 equiv.) in THF (2.6 mL). Partial purification by column chromatography (50:1 [hexane:EtOAc]) gave the triflate intermediate **330** (940 mg, 1.56 mmol), which was taken onto the next step.

Methyl 3-(5-((*tert*-butyldimethylsilyl)oxy)pent-1-en-2-yl)-3-(3-((*tert*-butyldimethyl silyl)oxy)propyl)cyclohex-1-ene-1-carboxylate (96)

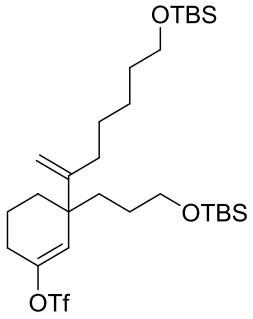


96

Prepared according to general procedure C. Triflate intermediate **330** (940 mg, 1.56 mmol, 1.0 equiv.), $Pd(OAc)_2$ (70 mg, 0.31 mmol, 0.2 equiv.), PPh_3 (163 mg, 0.63 mmol, 0.4 equiv.), anhydrous MeOH (2.5 mL, 62.4 mmol, 40 equiv.) and anhydrous Et_3N (0.44 mL, 3.12 mmol, 2.0 equiv.) in DMF (7.8 mL). Purification by column chromatography (50:1 [hexane:EtOAc]), gave **96** (591 mg, 1.20 mmol, 74% [2 steps]) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (1H, s, C=C*H*), 4.90 (1H, s, 1H from C=CH_2), 4.68 (1H, s, 1H from C=CH_2), 3.70 (3H, s, CO_2CH_3), 3.60

(2H, t, *J* = 6.4 Hz, C*H*$_2$OTBS), 3.52 (2H, td, *J* = 6.1, 1.9 Hz, C*H*$_2$OTBS), 2.19 - 2.31 (1H, m, 1H from C*H*$_2$), 2.06 - 2.16 (1H, m, 1H from C*H*$_2$), 1.91 - 2.05 (2H, m, CH$_2$=CC*H*$_2$), 1.24 - 1.76 (10H, m, 5 x C*H*$_2$), 0.86 (9H, s, SiC(C*H*$_3$)$_3$), 0.85 (9H, s, SiC(C*H*$_3$)$_3$), 0.02 (6H, s, 2 x SiC*H*$_3$), 0.00 (6H, s, 2 x SiC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (*C*=O), 152.1 (*C*=CH$_2$), 145.1 (C=*C*H), 129.6 (*C*=CH), 111.9 (C=*C*H$_2$), 63.5 (*C*H$_2$OTBS), 62.9 (*C*H$_2$OTBS), 51.6 (CO_2CH_3), 45.1 (CH$_2$=C*C*), 35.0 (*C*H$_2$), 31.9 (*C*H$_2$), 31.7 (*C*H$_2$), 27.4 (*C*H$_2$), 26.6 (CH$_2$=C*C*H$_2$), 26.0 (SiC(*C*H$_3$)$_3$), 25.9 (SiC(*C*H$_3$)$_3$), 24.8 (*C*H$_2$), 18.6 (*C*H$_2$), 18.3 (Si*C*), 18.3 (Si*C*), –5.3 (2 x Si(*C*H$_3$)$_2$); ν_{max} (thin film/cm^{-1}): 2950, 2930, 2886, 2857, 1718, 1647, 1633, 1472, 1463, 1435, 1387, 1361, 1250, 1190, 1101, 1006, 972, 939, 836, 813, 775. MS (ES$^+$) *m/z* (%): 533 (M+Na$^+$, 100); HRMS (ES$^+$) calcd. for $C_{28}H_{54}O_4NaSi_2$ (M+Na$^+$): 533.3453. Found: 533.3440.

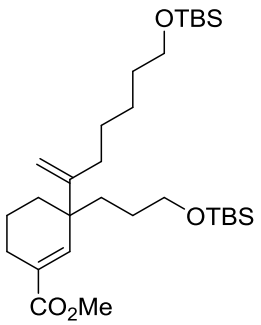
3-(7-((*tert*-Butyldimethylsilyl)oxy)hept-1-en-2-yl)-3-(3-((*tert* butyldimethylsilyl)oxy)propyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (331)



331

Prepared according to general procedure B. CuI (59 mg, 0.31 mmol, 0.1 equiv.), THF (3 mL), PhSLi (0.37 mL, 0.83 M in THF, 0.31 mmol, 0.1 equiv.), **54** (403 mg, 3.09 mmol, 1.0 equiv.), (3-((*tert*-butyldimethylsilyl)oxy)propyl)magnesium bromide (20.6 mL, 0.15 M in THF, 3.09 mmol, 1.0 equiv.), (7-((*tert*-butyldimethylsilyl)oxy)hept-1-en-2-yl)magnesium bromide (29.0 mL, 0.16 M in THF, 4.64 mmol, 1.5 equiv.), and Comins' reagent (1.94 g, 4.94 mmol, 1.6 equiv.). Partial purification by column chromatography [50:1 (hexane:EtOAc]) gave the triflate intermediate **331**, which was taken onto the next step without further purification.

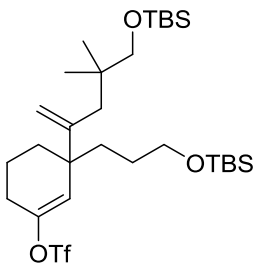
Methyl 3-(6-((*tert*-butyldimethylsilyl)oxy)hexyl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-ene-1-carboxylate (97)



97

Prepared according to general procedure C. Triflate intermediate **331** (3.09 mmol), anhydrous MeOH (4.20 mL, 103.6 mmol, 40 equiv.), anhydrous Et_3N (0.72 mL, 5.18 mmol, 2.0 equiv.), $Pd(OAc)_2$ (117 mg, 0.52 mmol, 0.2 equiv.), and PPh_3 (273 mg, 1.04 mmol, 0.4 equiv.) in DMF (13.0 mL). Purification by column chromatography (50:1 [hexane:EtOAc]) gave **97** (0.78 g, 1.45 mmol, 56% [2 steps]) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (1H, s, C=C*H*), 4.93 (1H, s, 1H from CH_2=C), 4.70 (1H, s, CH_2=C), 3.74 (3H, s, CO_2CH_3) 3.56 - 3.64 (4H, m, 2 x CH_2OTBS) 1.93 - 2.36 (6H, m, 3 x CH_2) 1.23 - 1.58 (12H, m, 6 x CH_2) 0.90 (18H, s, 2 x SiC(CH_3)$_3$), –0.05 (12H, s, 2 x Si(CH_2)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (CO_2Me), 152.4 (CH_2=*C*), 145.3 (*C*H=C), 129.6 (*C*=CH), 111.9 (CH_2=C), 63.5 (CH_2OTBS), 63.2 (CH_2OTBS), 51.6 (CO_2CH_3), 45.0 (*C*CCH$_2$), 35.0 (CH_2), 32.9 (CH_2), 31.6 (CH_2), 30.4 (CH_2), 28.3 (CH_2), 27.4 (CH_2), 26.0 (2 x SiC(CH_3)$_3$), 24.8 (CH_2), 22.7 (CH_2), 18.3 (2 x Si*C*), 14.2 (CH_2), –5.3 (2 x Si(CH_3)$_2$); ν_{max} (thin film/cm^{-1}): 2930, 2895, 2857, 1718, 1471, 1254, 1100, 1005, 908, 835, 774. MS (ES$^+$) *m/z* (%): 539 (M+H$^+$, 75), 561 (M+Na$^+$, 100); HRMS (ES$^+$) cald for $C_{30}H_{58}O_4NaSi_2$ (M+Na$^+$): 561.3771. Found: 561.3762.

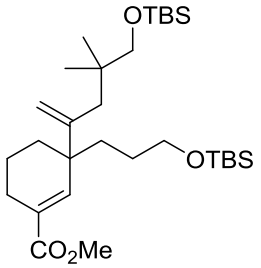
3-(5-((*tert*-Butyldimethylsilyl)oxy)-4,4-dimethylpent-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (332)



332

Prepared according to general procedure B. CuI (57.1 mg, 0.30 mmol, 0.1 equiv.), THF (3 mL), PhSLi (0.83 M, 0.36 mL, 0.30 mmol, 0.1 equiv.), **54** (392 mg, 3.00 mmol, 1.0 equiv.), (3-((*tert*-butyldimethylsilyl)oxy)propyl)magnesium bromide (37.5 mL in THF, 0.08 M, 3.00 mmol, 1.0 equiv.), (5-((*tert*-butyldimethylsilyl)oxy)-4,4-dimethylpent-1-en-2-yl)magnesium bromide (37.5 mL in THF, 0.12 M, 4.50 mmol, 1.5 equiv.), Comins' reagent (1.89 g, 4.80 mmol, 1.6 equiv.). Partial purification by column chromatography (50:1 [hexane:EtOAc]) was carried out to obtain the triflate intermediate **332**, which was taken onto the next step with no further purification.

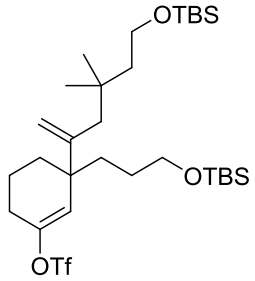
Methyl 3-(5-((*tert*-butyldimethylsilyl)oxy)-4,4-dimethylpent-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-ene-1-carboxylate (98)



98

Prepared according to general procedure C. Triflate intermediate **332** (1.88 g, 3.00 mmol, 1.0 equiv.), $Pd(OAc)_2$ (135 mg, 0.60 mmol, 0.2 equiv.), PPh_3 (315 mg, 1.20 mmol, 0.4 equiv.), anhydrous MeOH (5.00 mL, 120 mmol, 40 equiv.) and anhydrous Et_3N (0.84 mL, 6.0 mmol, 2.0 equiv.) in DMF (15 mL). Purification by column chromatography (50:1 [hexane:EtOAc]) gave **98** (0.99 g, 1.84 mmol, 63% [2 steps]) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (1H, s, C=C*H*), 5.06 (1H, s, 1H from C=CH_2), 4.83 (1H, s, 1H from C=CH_2), 3.70 (3H, s, CO_2CH_3), 3.49 - 3.58 (2H, m, CH_2CH_2OTBS), 3.22 (2H, s, CCH_2OTBS), 2.05 - 2.46 (3H, m, CH_2 and 1H from CH_2), 1.21 - 1.78 (9H, m, 4 x CH_2 and 1H from CH_2), 0.83 - 0.88 (24H, m, 2 x CH_3 and 2 x $SiC(CH_3)_3$), –0.02 - 0.02 (12H, m, 2 x $Si(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (CO_2CH_3), 149.5 (CH_2=*C*), 145.8 (C=*C*H), 129.5 (*C*=CH), 114.6 (C=*C*H_2), 71.9 (*C*H_2OTBS), 63.6 (*C*H_2OTBS), 51.6 (CO_2CH_3), 45.7 (*C*C=CH_2), 37.3 (*C*H_2), 36.4 (*C*$(CH_3)_2$), 35.2 (*C*H_2), 32.9 (*C*H_2), 31.4 (*C*H_2), 27.5 (*C*H_2), 26.0 (2 x $SiC(CH_3)_3$), 25.9 (*C*H_3), 25.6 (*C*H_3), 24.8 (2 x Si*C*), 18.7 (*C*H_2), –5.27 ($Si(CH_3)_2$), –5.46 ($Si(CH_3)_2$); ν_{max} (thin film/cm^{-1}): 2949, 2856, 1716, 1645, 1434, 1246, 1097, 833, 773. MS (ES^+) *m/z* (%): 539 ($M+H^+$, 100); HRMS (ES^+) calcd. for $C_{30}H_{58}O_4Si_2$ ($M+H^+$): 539.3952. Found: 539.3955.

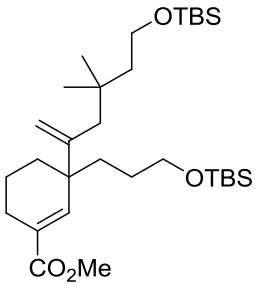
3-(6-((*tert*-Butyldimethylsilyl)oxy)-4,4-dimethylhex-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (333)



333

Prepared according to general procedure B. CuI (26.7 mg, 0.14 mmol, 0.1 equiv.), PhSLi (0.17 mL, 0.83 M in THF, 0.14 mmol, 0.1 equiv.), **54** (187 mg, 1.43 mmol, 1.0 equiv.), (3-((*tert*-butyldimethylsilyl)oxy)propyl)magnesium bromide (14.3 mL, 0.10 M in THF, 1.43 mmol, 1.0 equiv.) and (6-((*tert*-butyldimethylsilyl)oxy)-4,4-dimethylhex-1-en-2-yl)magnesium bromide (16.5 mL, 0.13 M in THF, 2.15 mmol, 1.5 equiv.) and Comins' reagent (899 mg, 2.29 mmol, 1.6 equiv.). Partial purification by column chromatography (50:1 [hexane:EtOAc]) gave the triflate intermediate **333** (0.81 g, 1.26 mmol), which was used in the next step.

Methyl 3-(6-((*tert*-butyldimethylsilyl)oxy)-4,4-dimethylhex-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-ene-1-carboxylate (99)

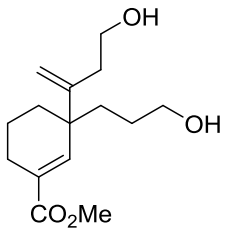


99

Prepared according to general procedure C. Triflate intermediate **333** (0.81 g, 1.26 mmol, 1.0 equiv.), $Pd(OAc)_2$ (58.4 mg, 0.26 mmol, 0.2 equiv.), PPh_3 (136 mg, 0.52 mmol, 0.4 equiv.), anhydrous Et_3N (0.36 mL, 2.6 mmol, 2.0 equiv.), anhydrous MeOH (2.1 mL, 52 mmol, 40 equiv.) in DMF (8.0 mL), after purification by column chromatography (50:1 (hexanes:EtOAc) gave **99** (0.46 g, 0.83 mmol, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (1H, s, C=C*H*), 5.13 (1H, s, 1H from C=CH_2), 4.87 (1H, s, 1H from C=CH_2), 3.73 - 3.77 (3H, s, CO_2CH_3), 3.65 - 3.72 (2H, m, CH_2OTBS), 3.58 -

3.63 (2H, m, CH_2OTBS), 2.24 - 2.48 (2H, m, CH_2), 2.11 - 2.17 (1H, m, 1H from CH_2=CCH_2), 1.93 - 1.97 (1H, m, CH_2=CCH_2), 1.72 - 1.78 (1H, m, 1H from CH_2), 1.59 - 1.64 (2H, m, CH_2), 1.56 - 1.36 (1H, m, 1H from CH_2), 1.50 - 1.55 (4H, m, 2 x CH_2), 1.38 - 1.47 (2H, m, CH_2), 0.96 - 1.00 (6H, m, C(CH_3)$_2$), 0.90 (18H, s, 2 x OSiC(CH_3)$_3$), 0.02 - 0.08 (12H, br. s, 2 x OSi(CH_3)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3 (*C*$O_2$$CH_3$), 149.7 ($CH_2$=*C*), 145.9 (C=*C*H), 129.9 (CH=*C*), 114.5 (*C*H_2=C), 63.7 (*C*H_2OTBS), 60.4 (*C*H_2OTBS), 51.8 (CO_2*C*H_3), 46.0 (*C*C=CH_2), 45.5 (*C*H_2), 41.6 (CH_2=C*C*H_2), 35.5 (*C*H_2), 33.5 (*C*(CH_3)$_2$), 31.9 (*C*H_2), 28.9 (2 x *C*H_3), 27.7 (*C*H_2), 26.3 (2 x SiC(*C*H_3)$_3$), 25.0 (*C*H_2), 18.0 (*C*H_2), 18.6 (2 x Si*C*), –5.0 (2 x Si(*C*H_3)$_2$); ν_{max} (thin film/cm^{-1}): 2952, 2929, 2857, 1716, 1471, 1252, 1094, 1005. MS (ES$^+$) *m/z* (%): 575 (M+Na$^+$, 100); HRMS (ES$^+$) calcd. for $C_{31}H_{60}O_4NaSi_2$ (M+Na$^+$): 575.3922. Found: 575.3920.

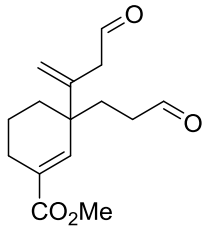
Methyl 3-(4-hydroxybut-1-en-2-yl)-3-(3-hydroxypropyl)cyclohex-1-ene-1-carboxylate (334)



334

Prepared according to general procedure D. Hydrofluoric acid (60%, w/v H_2O) (1.20 mL, 34.6 mmol, 20 equiv.), **95** (863 mg, 1.73 mmol, 1.0 equiv.), pyridine (8.65 mL, 1.73 mmol, 0.2 M), MeCN (17.3 mL), after purification by column chromatography gave the titled diol **334** (360 mg, 1.34 mmol, 78%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (1H, s, C=C*H*), 4.97 (1H, s, 1H from C=CH_2), 4.80 (1H, s, 1H from C=CH_2), 3.76 (2H, t, *J* = 6.3 Hz, CCH_2CH_2OH), 3.73 (3H, s, CO_2CH_3), 3.52 - 3.64 (2H, m, $(CH_2)_2$CH_2OH), 2.53 - 2.67 (2H, m, 2 x OH), 2.24 - 2.35 (3H, m, CH_2 and 1H from CH_2), 2.08 - 2.19 (1H, m, 1H from CH_2), 1.74 (1H, dd, *J* = 12.6, 5.3 Hz, 1H from CH_2), 1.30 - 1.68 (7H, m, 3 x CH_2 and 1H from CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (*C*$O_2$$CH_3$), 148.7 (*C*C=CH), 144.3 (C=*C*H), 130.1 (*C*=CH_2), 113.4 (C=*C*H_2), 62.8 (*C*H_2OH), 61.4 (*C*H_2OH), 51.7 (CO_2*C*H_3), 44.8 (*C*C=CH_2), 34.7 (*C*H_2), 33.3 (*C*H_2), 31.8 (*C*H_2), 27.1 (*C*H_2), 24.7 (*C*H_2), 18.4 (*C*H_2); ν_{max} (thin film/ cm^{-1}): 3349, 2939, 2867, 1714, 1698, 1643, 1435, 1338, 1248, 1190, 1057, 900. MS was uninformative.

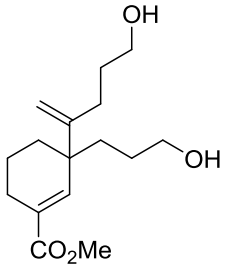
Methyl 3-(4-oxobut-1-en-2-yl)-3-(3-oxopropyl)cyclohex-1-ene-1-carboxylate (101)



101

Prepared according to general procedure E. DMP (292 mg, 0.69 mmol, 2.2 equiv.), **334** (84.2 mg, 0.31 mmol, 1.0 equiv.), in CH_2Cl_2 (3.1 mL), after evaporation of the solvent and purification by column chromatography gave **101** (69 mg, 0.26 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (1H, s, C*H*O), 9.52 (1H, t, *J* = 2.5 Hz, C*H*O), 6.72 (1H, s, C=C*H*), 5.03 (1H, s, 1H from C=CH_2), 5.00 (1H, s, 1H from C=CH_2), 3.69 (3H, s, CO_2CH_3), 3.02 (2H, d, *J* = 2.4 Hz, CH_2CHO), 2.41 - 2.51 (1H, m, 1H from CH_2), 2.23 - 2.37 (2H, m, CH_2), 2.06 - 2.16 (1H, m, 1H from CH_2), 1.69 - 1.84 (2H, m, CH_2), 1.50 - 1.65 (4H, m, 2 x CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3 (*C*HO), 199.5 (*C*HO), 167.5 (CO_2CH_3), 142.9 (C=*C*H), 141.6 (*C*=CH_2), 131.9 (*C*C=CH), 118.8 (C=*C*H_2), 51.9 (*C*H_2CHO), 46.4 (*C*H_2CHO), 44.2 (*C*C=CH_2), 38.9 (CO_2CH_3), 31.1 (*C*H_2), 29.7 (*C*H_2), 24.6 (*C*H_2), 18.2 (*C*H_2); ν_{max} (thin film/cm^{-1}): 2918, 2850, 1727, 1463, 1378, 1262, 1122, 1072, 1018, 908. Complete characterisation was not possible due to instability.

Methyl 3-(5-hydroxypent-1-en-2-yl)-3-(3-hydroxypropyl)cyclohex-1-ene-1-Carboxylate (335)

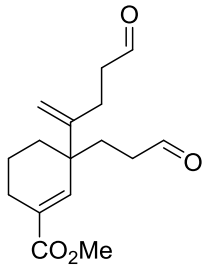


335

Prepared according to general procedure D. **96** (591 mg, 1.20 mmol, 1.0 equiv.), MeCN (12 mL), pyridine (5.8 mL), and HF (60% aqueous solution, 0.77 mL, 23.0 mmol, 20 equiv.). Purification by column chromatography (EtOAc) gave the titled diol **335** (320 mg, 1.10 mmol, 98%) as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (1H, d, *J* = 1.3 Hz, C*H*=C), 4.97 (1H, s, 1H from C=CH_2), 4.78 (1H, d, *J* = 0.6

Hz, 1H from C=CH_2), 3.75 (3H, s, CO_2CH_3), 3.70 (2H, td, *J* = 6.2, 1.4 Hz, CH_2OH), 3.56 - 3.67 (2H, m, CH_2OH), 2.30 (1H, dt, *J* = 18.0, 4.4 Hz, 1H from CH_2), 2.12 - 2.22 (1H, m, 1H from CH_2), 2.10 (2H, td, *J* = 7.7, 3.2 Hz, CH_2), 1.72 -1.83 (3H, m, 1H from CH_2=CCH_2 and CH_2), 1.32 - 1.71 (7H, m, 1H from CH_2=CCH_2 and 3 × CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1 (*C*O_2CH_3), 151.6 (*C*=CH_2), 144.6 (C=*C*H), 130.0 (*C*=CH), 112.2 (C=*C*H_2), 63.2 (*C*H_2OH), 62.4 (*C*H_2OH), 51.6 (CO_2*C*H_3), 45.1 (*C*C=CH_2), 34.9 (*C*H_2), 32.0 (CH_2=C*C*H_2), 31.4 (*C*H_2), 27.3 (*C*H_2), 26.3 (*C*H_2), 24.8 (*C*H_2), 18.5 (*C*H_2); ν_{max} (thin film/cm^{-1}): 3339, 3088, 2941, 2867, 1714, 1699, 1644, 1632, 1435, 1378, 1338, 1249, 1204, 1190, 1164, 1106, 1057, 974, 946, 900. MS (ES$^+$) *m/z* (%): 283 (M+H$^+$, 100), 300 (M+NH_4^+, 25), 305 (M+Na$^+$, 80); HRMS (ES$^+$) calcd. for $C_{16}H_{30}O_4N$ (M+NH_4^+): 300.2169. Found: 300.2168.

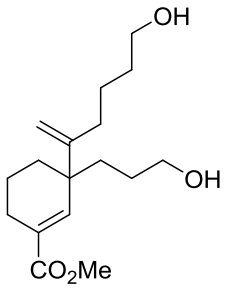
Methyl 3-(5-oxopent-1-en-2-yl)-3-(3-oxopropyl)cyclohex-1-ene-1-carboxylate (102)



102

Prepared according to general procedure E. Dess-Martin periodinane (187 mg, 0.44 mmol, 2.2 equiv.), diol **335** (56.5 mg, 0.20 mmol, 1.0 equiv.), in CH_2Cl_2 (2 mL), after purification by column chromatography (30% EtOAc/hexane) gave **102** (54.3 mg, 0.20 mmol, 98%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (1H, t, *J* = 1.3 Hz, C*H*O), 9.77 (1H, t, *J* = 1.3 Hz, C*H*O), 6.83 (1H, d, *J* = 1.3 Hz, C*H*=C), 4.89 (1H, t, *J* = 1.4 Hz, 1H from C=CH_2), 4.82 (1H, s, 1H from C=CH_2), 3.74 (3H, s, CO_2CH_3), 1.06 - 2.77 (14H, m, 7 × CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.6 (*C*HO), 201.5 (*C*HO), 167.7 (*C*O_2CH_3), 149.9 (*C*=CH_2), 142.9 (*C*H=C), 131.1 (CH=*C*), 113.1 (C=*C*H_2), 51.8 (CO_2*C*H_3), 44.5 (CH_2=C*C*), 42.1 (*C*H_2), 39.1 (*C*H_2), 31.8 (*C*H_2), 30.2 (*C*H_2), 24.6 (*C*H_2), 22.7 (*C*H_2), 18.4 (*C*H_2); ν_{max} (thin film/cm^{-1}): 2945, 2863, 2842, 2725, 2359, 2343, 1842, 1716, 1647, 1634, 1435, 1414, 1389, 1250, 1164, 1107, 1079, 1062, 1017, 906. Complete characterisation was not possible due to instability.

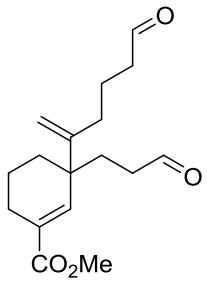
Methyl 3-(6-hydroxyhex-1-en-2-yl)-3-(3-hydroxypropyl)cyclohex-1-ene-1-carboxylate (336)



336

Prepared according to general procedure D. **90** (490 mg, 0.94 mmol, 1.0 equiv.), pyridine (4.70 mL, 0.20 M), HF (60% aqueous solution) (0.64 mL, 18.8 mmol, 20 equiv.) in MeCN (9.4 mL), after purification by column chromatography gave the titled diol **336** (195 mg, 0.66 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) ð 6.94 (1H, d, *J* = 1.0 Hz, C=C*H*), 4.97 (1H, s, 1H from C=CH_2), 4.75 (1H, apparent d, *J* = 0.5 Hz, 1H from C=CH_2), 3.75 (3H, s, CO_2CH_3), 3.66 - 3.71 (2H, m, CH_2OH), 3.63 (2H, d, *J* = 4.8 Hz, CH_2OH), 2.30 (1H, dt, *J* = 18.1, 4.5 Hz, 1H from CH_2CCO_2Me), 2.10 - 2.22 (1H, m, 1H from CH_2CCO_2Me), 2.01 (2H, t, *J* = 8.0 Hz, $CH_2C=CH_2$), 1.76 (1H, dd, *J* = 12.5, 5.3 Hz, 1H from CH_2), 1.30 - 1.70 (11H, m, 1H from CH_2, 5 x CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1 (CO_2CH_3), 152.0 ($C=CH_2$), 144.7 (*C*H=C), 129.9 (*C*=CH), 112.2 (CH_2=C), 63.3 (CH_2OH), 62.7 (CH_2OH), 50.4 (CO_2CH_3), 44.9 (CH_2=C*C*), 35.0 (CH_2), 32.6 (CH_2), 32.0 (CH_2), 30.1 (CH_2), 27.4 (CH_2), 24.8 (CH_2), 21.1 (CH_2), 18.5 (CH_2); ν_{max} (thin film/cm^{-1}): 3349, 2938, 2866, 1713, 1644, 1435, 1252, 1057. MS (ES+) *m/z* (%): 319 (M+Na$^+$, 100). HRMS (ES$^+$) calcd. For $C_{17}H_{28}O_4Na$ (M+Na$^+$): 319.1885. Found: 319.1887.

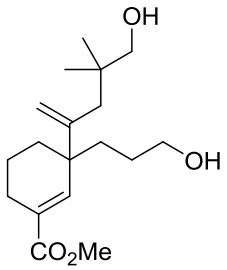
Methyl 3-(6-oxohex-1-en-2-yl)-3-(3-oxopropyl)cyclohex-1-ene-1-carboxylate (103)



103

Prepared according to general procedure E. Diol **336** (195 mg, 0.66 mmol, 1.0 equiv.), DMP (614 mg, 1.45 mmol, 2.2 equiv.) in CH_2Cl_2 (6.6mL), after purification by column chromatography gave **103** (0.14 g, 0.48 mmol, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 - 9.81 (1H, m, C*H*O), 9.77 - 9.78 (1H, m, C*H*O), 6.83 (1H, 1 br. s, C=C*H*), 5.02 (1H, br. s, 1H from CH_2=C), 4.83 (1H, br. s, 1H from CH_2=C), 3.76 (3H, s, CO_2CH_3), 2.27 - 2.55 (6H, m, 3 x CH_2), 1.96 - 2.05 (2H, m, CH_2), 1.62 - 1.92 (8H, m, 4 x CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.1 (*C*HO), 201.8 (*C*HO), 167.8 (CO_2CH_3), 150.8 (*C*=CH_2), 143.2 (C=*C*H), 130.9 (*C*=CH), 113.22 (CH_2=C), 51.8 (CO_2CH_3), 44.5 (CH_2=C*C*), 43.6 (CH_2), 39.1 (CH_2), 31.7 (CH_2), 30.2 (CH_2), 29.6 (CH_2), 24.7 (CH_2), 20.8 (CH_2), 18.5 (CH_2). Complete characterisation was not possible due to instability.

Methyl 3-(5-hydroxy-4,4-dimethylpent-1-en-2-yl)-3-(3-hydroxypropyl)cyclohex-1-ene-1-carboxylate (337)

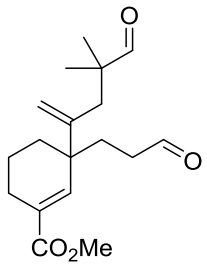


337

Prepared according to general procedure D. **98** (871 mg, 1.62 mmol, 1.0 equiv.), pyridine (8.1 mL, 0.2 M), HF (60% aqueous solution, 1.80 mL, 36.4 mmol, 20 equiv.) in MeCN (16.2 mL). After purification by column chromatography (EtOAc) gave the titled diol **337** (239 mg, 0.77 mmol, 48%) as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 6.95 (1H, d, *J* = 1.3 Hz, C=C*H*), 5.13 (1H, s, 1H from C=CH_2), 4.93 (1H, s, 1H from C=CH_2), 3.75 (3H, s, CO_2CH_3), 3.56 - 3.65 (2H, m, CCH_2OH), 3.33 - 3.40

(2H, m, CH_2CH_2OH), 2.24 - 2.31 (1H, m, 1H from CH_2), 2.14 - 2.21 (1H, m, 1H from CH_2), 2.08 - 2.12 (1H, m, 1H from CH_2), 1.98 - 2.03 (1H, m, 1H from CH_2), 1.75 - 1.83 (1H, m, 1H from CH_2), 1.61 - 1.68 (1H, m, 1H from CH_2), 1.51 - 1.60 (3H, m, 3 x 1H from CH_2), 1.42 - 1.51 (2H, m, 2 x 1H from CH_2), 1.35 (1H, ddd, *J* = 13.6, 11.0, 2.8 Hz, 1H from CH_2), 0.96 (6H, d, *J* = 1.9 Hz, 2 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) 168.2 (CO_2CH_3), 149.2 (C=CH_2), 145.3 (C=CH), 129.9 (C=CH), 114.7 (C=CH_2), 71.8 (CH_2CH_2OH), 63.2 (CCH_2OH), 51.7 (CO_2CH_3), 45.7 (CC=CH_2), 37.5 (CH_2), 36.2 ($C(CH_3)_2$), 35.2 (CH_2), 31.5 (CH_2), 27.3 (CH_2), 25.3 (CH_3), 25.0 (CH_3), 24.8 (CH_2), 18.7 (CH_2); ν_{max} (thin film/cm^{-1}): 3345, 3080, 2939, 2863, 1716, 1701, 1649, 1628, 1374, 1243, 1180, 1164, 1090, 1045, 945. MS (ES+) *m/z* (%): 333 (M+Na$^+$, 75). HRMS (ES$^+$) calcd. for $C_{30}H_{58}O_4Sa$ (M+Na$^+$): 333.2042. Found: 333.2049.

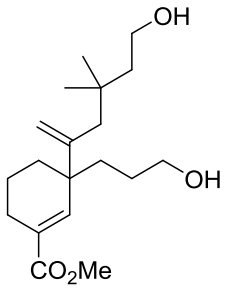
Methyl 3-(4,4-dimethyl-5-oxopent-1-en-2-yl)-3-(3-oxopropyl)cyclohex-1-ene-1-carboxylate (105)



105

Prepared according to general procedure E. Dess-Martin periodinane (250 mg, 0.58 mmol, 2.2 equiv.), diol **337** (80 mg, 0.26 mmol, 1.0 equiv.), CH_2Cl_2 (3 mL), after purification by column chromatography (30% EtOAc/hexane) gave **105** (65.8 mg, 0.22 mmol, 83%), as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (1H, t, *J* = 1.1 Hz, C*H*O), 9.48 (1H, s, C*H*O), 6.72 (1H, d, *J* = 1.3 Hz, C=C*H*), 4.79 (1H, s, 1H from C=CH_2), 4.67 (1H, s, 1H from C=CH_2), 3.68 (3H, s, CO_2CH_3), 2.40 - 2.49 (1H, m, 1H from CH_2), 2.28 - 2.35 (1H, m, 1H from CH_2), 1.67 - 2.12 (6H, m, 3 x CH_2), 1.57 - 1.65 (2H, m, CH_2), 1.37 - 1.48 (2H, m, CH_2), 1.02 - 1.07 (6H, m, 2 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.9 (*C*HO), 201.6 (*C*HO), 167.6 (CO_2CH_3), 147.2 (C=*C*H), 142.8 (C=CH_2), 131.2 (C=CH), 115.2 (C=CH_2), 51.7 (CO_2CH_3), 45.9 (CC=CH_2), 44.6 ($C(CH_3)_2$), 39.0 (CH_2), 38.0 (CH_2), 31.4 (CH_2), 29.9 (CH_2), 24.6 (CH_2), 22.7 ($C(CH_3)_2$), 22.0 ($C(CH_3)_2$), 18.32 (CH_2); ν_{max} (thin film/cm^{-1}): 2931, 2715, 1713, 1646, 1434, 1394, 1248, 1104, 1045, 904, 812, 777. Complete characterisation was not possible due to instability.

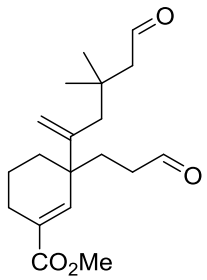
Methyl 3-(6-hydroxy-4,4-dimethylhex-1-en-2-yl)-3-(3-hydroxypropyl)cyclohex-1-ene-1-carboxylate (338)



338

Prepared according to general procedure D. **99** (340 mg, 0.61 mmol, 1.0 equiv.), pyridine (3.1 mL), HF (60% aqueous solution) (0.41 mL, 12.2 mmol, 20.0 equiv.) in MeCN (6.1 mL). After purification gave the titled diol **338** (63.4 mg, 0.20 mmol, 33%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (1H, s, C=C*H*), 5.14 (1H, s, 1H from C=CH_2), 4.92 (1H, s, 1H from C=CH_2), 3.75 (3H, s, CO_2CH_3), 3.70 - 3.73 (2H, m, CCH_2CH_2OH), 3.60 - 3.63 (2H, m, $CH_2CH_2CH_2OH$), 2.24 - 2.28 (1H, m, 1H from CH_2C=CH), 2.16 - 2.20 (1H, m, 1H from CH_2C=CH), 1.92 - 2.05 (2H, m, $CH_2C=CH_2$), 1.75 - 1.81 (1H, m, 1H from CH_2), 1.40 - 1.67 (8H, m, 4 x CH_2), 1.35 (1H, ddd, *J* = 13.5, 11.0, 3.0 Hz, 1H from CH_2), 1.00 (3H, s, CH_3), 0.95 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0 (CO_2Me), 149.3 ($C=CH_2$), 145.2 (C=CH), 129.9 (*C*=CH), 114.5 (C=CH_2), 63.3 (CH_2OH), 59.9 (CH_2OH), 51.6 (CO_2CH_3), 45.7 ($CC=CH_2$), 45.2 (CH_2), 41.5 ($CH_2C=CH_2$), 35.2 (CH_2), 33.3 ($C(CH_3)_2$), 31.7 (CH_2), 28.7 (CH_3), 28.6 (CH_3), 27.4 (CH_2), 24.7 (CH_2), 18.7 (CH_2); ν_{max} (thin film/cm^{-1}): 3339, 2942, 2869, 1714, 1698, 1644, 1435, 1384, 1384, 1365, 1339, 1246, 1190, 1103, 1056, 1025, 976, 903, 814. MS (ES$^+$) *m/z* (%): 325 (M+H$^+$, 10), 347 (M+Na$^+$, 100). HRMS (ES$^+$) calcd. for $C_{19}H_{33}O_4$ (M+H$^+$): 325.2373. Found: 325.2382.

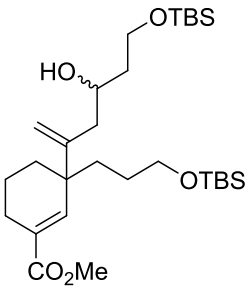
Methyl 3-(4,4-dimethyl-6-oxohex-1-en-2-yl)-3-(3-oxopropyl)cyclohex-1-ene-1-carboxylate (106)



106

Prepared according to general procedure E. Diol **338** (63.4 mg, 0.20 mmol, 1,0 equiv.), DMP (187 mg, 0.44 mmol, 2.2 equiv.) in CH_2Cl_2 (2 mL), after purification by column chromatography gave **106** (32.0 mg, 0.10 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (1H, apparent t, *J* = 2.9 Hz, C*H*O), 9.77 (1H, apparent t, *J* = 1.6 Hz, C*H*O), 6.81 (1H, d, *J* = 1.0 Hz, C=C*H*), 5.17 (1H, s, 1H from C=CH_2), 4.98 (1H, s, 1H from C=CH_2), 3.75 (3H, s, CO_2CH_3), 2.42 - 2.52 (1H, m, 1H from CH_2), 2.39 (2H, d, *J* = 2.8 Hz, CH_2CHO), 2.16 - 2.28 (3H, m, 1H from CH_2, CH_2), 2.08 (2H, s, CH_2), 1.73 - 1.83 (3H, m, 1H from CH_2, CH_2), 1.61 - 1.68 (1H, m, 1H from CH_2), 1.62 - 1.67 (1H, m, 1H from CH_2), 1.47 - 1.56 (1H, m, 1H from CH_2), 1.14 (6H, apparent d, *J* = 3.3 Hz, 2 x CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2 (*C*HO), 201.8 (*C*HO), 167.7 (*C*O_2CH_3), 148.0 (*C*=CH_2), 143.6 (C=*C*H), 130.9 (*C*=CH), 115.6 (C=*C*H_2), 55.2 (*C*H_2), 51.8 (CO_2*C*H_3), 45.1 (*C*C=CH_2), 41.7 (*C*H_2), 39.1 (*C*H_2), 34.3 (*C*(CH_3)$_2$), 31.3 (*C*H_2), 30.4 (*C*H_2), 28.6 (2 x *C*H_3), 24.6 (*C*H_2), 18.5 (*C*H_2). Incomplete data due to instability of compound.

Methyl 3-(6-((*tert*-butyldimethylsilyl)oxy)-4-hydroxyhex-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-ene-1-carboxylate (339)

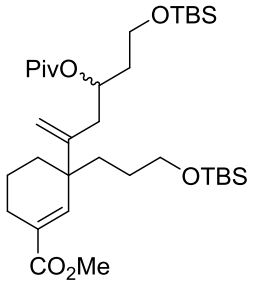


339

A solution of **94** (200 mg, 0.47 mmol, 1.0 equiv.) and 3-((*tert*-butyldimethylsilyl)oxy)propanal[172] (134 mg, 0.71 mmol, 1.5 equiv.) in CH_2Cl_2 (0.6

mL) was added to TBAT (25.4 mg, 0.05 mmol, 0.1 equiv.), activated 4Å MS (200 mg) in CH_2Cl_2 (0.2 mL) at –78 °C under nitrogen. After 1 hour BF_3•OEt_2 (0.09 mL, 0.75 mmol, 1.6 equiv.) was added and the reaction was left to stir at –78 °C. After 18 hours, the reaction was allowed to warm to –35 °C and was then quenched with aqueous saturated NH_4Cl (5 mL), extracted into CH_2Cl_2 (3 x 5 mL) and dried ($MgSO_4$). Partial purification by column chromatography (5% EtOAc/hexane) gave the titled alcohol **339** (222 mg, 0.41 mmol), which was taken onto the next step without further purification.

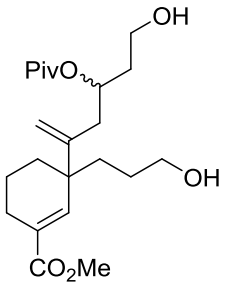
Methyl 3-(6-((*tert*-butyldimethylsilyl)oxy)-4-(pivaloyloxy)hex-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-ene-1-carboxylate (340)



340

PivCl (0.25 mL, 2.05 mmol, 5.0 equiv.) was added to a mixture of **339** (0.41 mmol, 1.0 equiv.), DMAP (5.00 mg, 0.04 mmol, 0.1 equiv.) and pyridine (1.23 mL, 0.41 mmol, 1.0 equiv.) in CH_2Cl_2 (1.2 mL). After 18 hours, the reaction was quenched with aqueous saturated $NaHCO_3$ (4 mL), extracted into Et_2O (3 x 5 mL) and was washed successively with aqueous saturated $CuSO_4$ (3 x 5 mL) and brine (2 x 5 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was taken onto the next step with no further purification.

Methyl 3-(6-((*tert*-butyldimethylsilyl)oxy)-4-(pivaloyloxy)hex-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-ene-1-carboxylate (341)

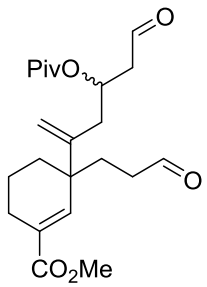


341

Prepared according to general procedure D. HF (60% aqueous solution) (0.27 mL, 8.20 mmol, 20 equiv.), **340** (0.41 mmol, 1.0 equiv.), pyridine (2.05 mL, 0.2 M, 1.0 equiv.), in MeCN (4.1 mL). Purification by column chromatography (20% EtOAc/hexane) gave the titled compound **341** (76.5 mg, 0.19 mmol, 40% (3 steps) [dr:1:1]) as a pale-yellow oil. ^{1}H NMR (500 MHz,$CDCl_3$) δ 6.89 (1H, d, *J* = 9.77 Hz, C=C*H* [both diastereoisomers]), 5.24 - 5.28 (1H, m, C*H*(OPiv) [both diastereoisomers]), 4.96 (1H, d, *J* = 4.41 Hz, 1H from C=CH_2 [both diastereoisomers]), 4.82 (1H, d, *J* = 11.35 Hz, 1H from C=CH_2 [both diastereoisomers]), 3.74 (3H, s, CO_2CH_3 [both diastereoisomers]), 3.57 - 3.67 (3H, m, 1H from CH_2OH, 2H CH_2OH [both diastereoisomers]), 3.45 - 3.52 (1H, m, 1H from CH_2OH [both diastereoisomers]), 2.61 - 2.78 (1H, br. s., O*H*), 2.36 - 2.43 (1H, m, 1H from CH_2 [both diastereoisomers]), 2.11 - 2.32 (2H, m, CH_2 [both diastereoisomers]), 1.87 - 1.97 (1H, m, 1H from CH_2 [both diastereoisomers]) 1.35 - 1.78 (10H, m, 5 x CH_2 [both diastereoisomers]) 1.19 (9H, d, *J* = 3.78 Hz, C(O)C(CH_3)$_3$ [both diastereoisomers]); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.7 (*C*(O)C$(CH_3)_3$ [one diastereoisomer]), 179.6 (*C*(O)C$(CH_3)_3$ [one diastereoisomer]), 167.9 (*C*O_2CH_3 [both diastereoisomers]), 147.5 (*C*=CH [both diastereoisomers]), 144.0 (C=*C*H [both diastereoisomers]), 130.4 (*C*=CH_2 [one diastereoisomer]), 130.3 (*C*=CH_2 [one diastereoisomer]), 114.7 (C=*C*H_2 [one diastereoisomer]), 114.3 (C=*C*H_2 [one diastereoisomer]), 69.2 (*C*H(OPiv) [one diastereoisomer]), 69.1 (*C*H(OPiv) [one diastereoisomer]), 63.1 (*C*H_2OH [one diastereoisomer]), 63.0 (*C*H_2OH [one diastereoisomer]), 58.3 (*C*H_2OH [one diastereoisomer]), 58.2 (*C*H_2OH [one diastereoisomer]), 51.7 (CO_2*C*H_3 [both diastereoisomers]), 44.8 (*C*C=CH_2 [both diastereoisomers]), 38.9 (*C*$(CH_3)_3$ [both diastereoisomers]), 38.0 (*C*H_2 [one diastereoisomer]), 37.8 (*C*H_2 [one diastereoisomer]), 36.1 (*C*H_2 [both diastereoisomers]), 34.9 (*C*H_2 [both diastereoisomers]), 32.1 (*C*H_2 [both diastereoisomers]), 31.7 (*C*H_2 [both diastereoisomers]), 27.2 (C(*C*$H_3)_3$ [both

diastereoisomers]), 24.7 (*C*H_2 [both diastereoisomers]), 18.5 (*C*H_2 [one diastereoisomer]), 18.4 (*C*H_2 [one diastereoisomer]); v_{max} (thin film/cm^{-1}): 3433, 2938, 2870, 1716, 1645, 1480, 1435, 1280, 1160, 1105, 1053, 957, 903. MS (ES^+) *m/z* (%): 397 ($M+H^+$, 5), 419 ($M+Na^+$, 100); HRMS (ES^+) calcd. for $C_{22}H_{36}O_6Na$ ($M+Na^+$): 419.2410. Found: 419.2405.

Methyl 3-(6-oxo-4-(pivaloyloxy)hex-1-en-2-yl)-3-(3-oxopropyl)cyclohex-1-ene-1-carboxylate (107a)

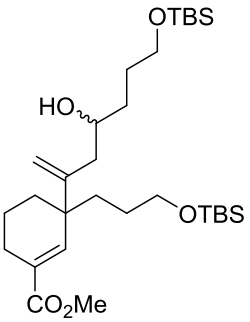


107a

Prepared according the general procedure E. DMP (178 mg, 0.42 mmol, 2.2 equiv.), diol **341** (76.5 mg, 0.19 mmol, 1.0 equiv.), CH_2Cl_2 (1.9 mL), after concentrated *in vacuo* and purification by column chromatography (30% EtOAc/hexane) gave **107a** (54.3 mg, 0.14 mmol, 73% [dr:1:1]) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.8 (1H, s, C*H*O [both diastereoisomers]) 9.71 - 9.74 (1H, s, C*H*O [both diastereoisomers]), 6.79 (1H, d, *J* = 11.0 Hz, C=C*H* [both diastereoisomers]), 5.44 - 5.51 (1H, m, C*H*(OPiv) [both diastereoisomers]), 5.04 (1H, s, 1H from C=CH_2 [both diastereoisomers]), 4.90 (1H, d, *J* = 2.5 Hz, 1H from C=CH_2 [both diastereoisomers]), 3.75 (3H, s, CO_2CH_3 [both diastereoisomers], 2.63 - 2.75 (2H, m, CH_2 [both diastereoisomers]), 2.14 - 2.54 (8H, m, 4 x CH_2 [both diastereoisomers]), 1.71 - 1.92 (4H, m, 2 x CH_2 [both diastereoisomers]), 1.15 (9H, d, *J* = 3.8 Hz, $(CH_3)_3$ [both diastereoisomers]); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.5 (*C*HO [both diastereoisomers]), 199.0 (*C*HO [both diastereoisomers]), 177.8 (O*C*(O)C$(CH_3)_3$ [both diastereoisomers]), 167.6 (*C*O_2CH_3 [both diastereoisomers]), 146.6 (*C*=CH_2 [both diastereoisomers]), 142.5 (C=*C*H [one diastereoisomer]), 142.4 (C=*C*H [one diastereoisomer]), 131.5 (*C*=CH, one diastereoisomer), 131.4 (*C*=CH [one diastereoisomer]), 115.5 (C=*C*H_2 [one diastereoisomer]), 115.4 (C=*C*H_2 [one diastereoisomer]), 67.3 (*C*HOPiv [one diastereoisomer]), 67.2 (*C*HOPiv [one diastereoisomer]), 51.8 (CO_2CH_3 [both diastereoisomers]), 48.2 (*C*C=CH_2 [both diastereoisomers]), 44.4 (*C*H_2 [one diastereoisomer]), 44.3 (*C*H_2 [one diastereoisomer]), 39.0 ((*C*H_2 [both diastereoisomers]), 38.7 (*C*$(CH_3)_3$ [both

diastereoisomers]), 35.5 (*C*H_2 [one diastereoisomer]), 35.2 (*C*H_2 [one diastereoisomer]), 31.6 (*C*H_2 [both diastereoisomers]), 31.1 (*C*H_2 [one diastereoisomer]), 31.0 (*C*H_2 [one diastereoisomer]), 27.0 (C(*C*H_3)$_3$ [both diastereoisomers]), 24.6 (*C*H_2 [both diastereoisomers]), 18.4 (*C*H_2 [both diastereoisomers]); ν_{max} (thin film/cm^{-1}): 2934, 2870, 2849, 2724, 1721, 1648, 1480, 1460, 1436, 1396, 1366, 1279, 1251, 1156, 1108, 1036, 968, 921, 823. Complete characterisation was not possible due to instability.

Methyl 3-(7-((*tert*-butyldimethylsilyl)oxy)-4-hydroxyhept-1-en-2-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)cyclohex-1-ene-1-carboxylate (342)

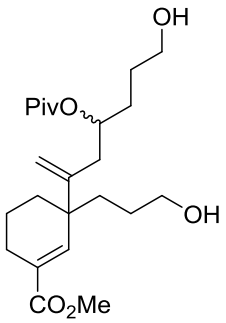


342

A solution of TBAT (65.0 mg, 0.12 mmol, 0.1 equiv.) and molecular sieves (4 Å, 512 mg) in CH_2Cl_2 (0.5 mL) was cooled to –78 °C. A solution of **94** (512 mg, 1.21 mmol, 1.0 equiv.) and 4-((*tert*-butyldimethylsilyl)oxy)butanal[173] (368 mg, 1.82 mmol, 1.5 equiv.) in CH_2Cl_2 (1.6 mL) was added and left to stir for 1 hour, before BF_3•OEt_2 (0.24 mL, 1.94 mmol, 1.6 equiv.) was added dropwise. The resulting orange solution was stirred for 16 hours at –78 °C and then was allowed to warm to –35 °C, before being quenched with aqueous saturated NH_4Cl (15 mL) and extracted into Et_2O (3 x 15 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product, which was purified by column chromatography (5% EtOAc/hexane) to give **342** (63.4 mg, 0.11 mmol, 24%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.89 - 6.94 (1H, m, C=C*H* [both diastereoisomers]), 5.06 (1H, s, 1H from C=C*H*$_2$ [both diastereoisomers]), 4.87 (1H, s, 1H from C=C*H*$_2$ [both diastereoisomers]), 3.79 - 3.88 (1H, m, C*H*OPiv [both diastereoisomers]), 3.74 (3H, s, CO_2CH_3 [both diastereoisomers]), 3.67 (2H, t, *J* = 5.7 Hz, C*H*$_2$OTBS [both diastereoisomers]), 3.53 - 3.60 (2H, m, C*H*$_2$OTBS [both diastereoisomers]), 2.24 - 2.34 (1H, m, 1H from C*H*$_2$ [both diastereoisomers]), 2.16 (3H, d, *J* = 5.0 Hz, 1H from C*H*$_2$ and C*H*$_2$ [both diastereoisomers]), 1.25 - 1.83 (12H, m, 6 x C*H*$_2$ [both diastereoisomer]), 0.88 - 0.91 (18H, m, 2 x SiC(C*H*$_3$)$_3$ [both diastereoisomers]), 0.03 - 0.08 (12H, m, 2 x Si(C*H*$_3$)$_2$ [both diastereoisomers]); ^{13}C NMR (101 MHz, $CDCl_3$) δ

168.0 (*C*O_2CH_3, [both diastereoisomers]), 149.8 (*C*=CH_2 [one diastereoisomer]), 149.7 (*C*=CH_2 [one diastereoisomer]), 144.6 (C=*C*H [one diastereoisomer]), 144.6 (C=*C*H [one diastereoisomer]), 130.1 (*C*=CH [one diastereoisomer]), 130.0 (*C*=CH [one diastereoisomer]), 114.2 (C=*C*H_2 [one diastereoisomers]), 113.7 (C=*C*H_2 [one diastereoisomer]), 69.6 (*C*HOPiv [one diastereoisomer]), 69.6 (*C*HOPiv [one diastereoisomer]), 63.4 (*C*H_2OTBS [both diastereoisomers]), 63.4 (*C*H_2OTBS [both diastereoisomers]), 51.6 (CO_2C*H*$_3$ [both diastereoisomers]), 45.0 (*C*C=CH_2 [one diastereoisomer]), 45.0 (*C*C=CH_2 [one diastereoisomers]), 39.1 (*C*H_2CHOPiv [one diastereoisomer]), 38.9 (*C*H_2CHOPiv [one diastereoisomer]), 35.0 (*C*H_2 [both diastereoisomers]), 34.3 (*C*H_2 [one diastereoisomer]), 34.3 (*C*H_2 [one diastereoisomer]), 32.0 (*C*H_2 [both diastereoisomers]), 31.4 (*C*H_2 [both diastereoisomers]), 29.3 (*C*H_2 [both diastereoisomers]), 27.4 (*C*H_2 [one diastereoisomer]), 27.3 (*C*H_2 [one diastereoisomer]), 26.0 (2 x SiC(*C*H_3)$_3$ [one diastereoisomer]), 26.0 (2 x SiC(*C*H_3)$_3$ [one diastereoisomer]), 24.7 (*C*H_2 [both diastereoisomers]), 18.6 (2 x Si*C* [both diastereoisomers]), 18.4 (Si*C* [one diastereoisomer]), 18.3 (Si*C* [one diastereoisomers]), –5.3 (2 x Si(*C*H_3)$_2$ [one diastereoisomer]), –5.3 (2 x Si(*C*H_3)$_2$ [one diastereoisomer]); ν_{max} (thin film/cm^{-1}): 3452, 2949, 2929, 2956, 1716, 1646, 1472, 1435, 1251, 1096, 1006, 834, 813, 775. MS (ES+) *m/z* (%): 555 ($M+H^+$, 70), 577 ($M+Na^+$, 70); HRMS (ES^+) calcd for $C_{30}H_{58}O_5Si_2$ ($M+H^+$): 555.3823. Found: 555.3768.

Methyl 3-(7-hydroxy-4-(pivaloyloxy)hept-1-en-2-yl)-3-(3-hydroxypropyl)cyclohex-1-ene-1-carboxylate (343)

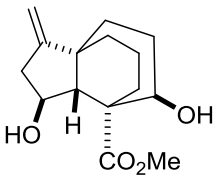


343

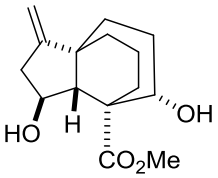
Pivolyl chloride (0.07 mL, 0.55 mmol, 5.0 equiv.) was added to a solution of **342** (63.4 mg, 0.11 mmol, 1.0 equiv.), DMAP (1.22 mg, 0.01 mmol, 0.1 equiv.), pyridine (0.33 mL, 0.33 M), in CH_2Cl_2 (0.3 mL). After 16 hours, the reaction was quenched with aqueous saturated $NaHCO_3$ (5 mL), extracted into Et_2O (3 x 5 mL), dried ($MgSO_4$), concentrated *in vacuo*. The crude protected alcohol product was dissolved

in a mixture of pyridine (0.55 mL, 0.2 M) and MeCN (1.10 mL, 0.1 M). The solution was cooled to 0 °C before the addition of HF (60% aqueous solution) (0.07 mL, 2.20 mmol, 20 equiv.) and allowed to warm to room temperature. After 16 hours, the reaction was quenched with aqueous saturated $NaHCO_3$ (5 mL), extracted into Et_2O, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (EtOAC) gave **343** (27 mg, 0.07 mmol, 60% [d.r.= 1:1]) as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 6.88 - 6.93 (1H, m, C=C*H* [both diastereoisomers]), 5.17 - 5.09 (1H, m, C*H*OPiv [both diastereoisomers]), 4.99 (1H, s, 1H from C=CH_2 [both diastereoisomers]), 4.80 - 4.84 (1H, m, 1H from C=CH_2 [both diastereoisomers]), 3.75 (3H, s, CO_2CH [both diastereoisomers]), 3.59 - 3.70 (4H, m, 2 x CH_2OH [both diastereoisomers]), 2.12 - 2.37 (4H, m, 2 x CH_2 [both diastereoisomers]), 1.35 - 1.83 (12H, m, 6 x CH_2 [both diastereoisomers]), 1.17 - 1.21 (9H, m, C(CH_3)$_3$ [both diastereoisomers]); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5 (CO*C*(O)CCH_3 [both diastereoisomers]), 168.0 (*C*O_2CH_3 [both diastereoisomers]), 147.6 (*C*=CH [both diastereoisomers]), 144.2 (C=*C*H [both diastereoisomers]), 130.4 (*C*=CH_2 [one diastereoisomer]), 130.3 (*C*=CH_2 [one diastereoisomer]), 114.9 (C=*C*H_2 [one diastereoisomer]), 114.8 (C=*C*H_2 [one diastereoisomer]), 72.0 (*C*HOPiv [one diastereoisomer]), 71.9 (*C*HOPiv [one diastereoisomer]), 63.2 (*C*H_2OH [one diastereoisomer]), 63.2 (*C*H_2OH [one diastereoisomer]), 62.4 (*C*H_2OH [one diastereoisomer]), 62.4 (*C*H_2OH [one diastereoisomer]), 51.7 (CO_2*C*H_3 [both diastereoisomers]), 44.9 (*C*C=CH_2 [both diastereoisomers]), 38.9 (C(O)*C*$(CH_3)_3$ [both diastereoisomers]), 35.7 (*C*H_2 [both diastereoisomers]), 34.9 (*C*H_2 [both diastereoisomers]), 32.1 (*C*H_2 [one diastereoisomer]), 31.8 (*C*H_2 [one diastereoisomer]), 30.9 (*C*H_2 [one diastereoisomer]), 30.7 (*C*H_2 [one diastereoisomer]), 28.2 (*C*H_2 [one diastereoisomer]), 28.2 (*C*H_2 [one diastereoisomer]), 27.4 (*C*H_2 [one diastereoisomer]), 27.3 (*C*H_2 [one diastereoisomer]), 27.2 (C(*C*H_3)$_3$ [both diastereoisomers]), 18.5 (*C*H_2 [one diastereoisomer]), 18.5 *C*H_2 [one diastereoisomer]); ν_{max} (thin film/cm^{-1}): 3434, 2936, 1716, 1479, 1433, 1368, 1245, 1158, 1100, 1055, 903. MS (ES$^+$) *m/z* (%): 411 (M+H$^+$, 50), 433 (M+Na$^+$, 100); HRMS (ES$^+$) calcd. for $C_{23}H_{38}O_6Na$ (M+Na$^+$): 433.2566. Found: 433.2587.

Methyl (1*S*,6*S*,7*S*,7a*R*)-1,6-dihydroxy-3-methylenehexahydro-3a,7-propanoindene-7(4*H*)-carboxylate (108a), methyl (1*S*,3a*S*,7*S*,8*S*,8a*R*)-1,7-dihydroxy-3-methyleneoctahydro-8*H*-3a,8-propanoazulene-8-carboxylate (108b)



108a



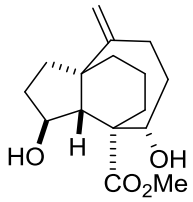
108b

Prepared according to general procedure G. *t*BuOH (0.13 mL, 1.35 mmol, 5.0 equiv.), SmI_2 (6.7 mL, 0.10 M in THF, 0.67 mmol, 2.4 equiv.), **101** (70.7 mg, 0.27 mmol, 1.0 equiv.), after purification by column chromatography (30% ethyl acetate/hexane) gave **108a** (29 mg, 0.10 mmol, 40%) as a white solid and **108b** (13 mg, 0.045 mmol, 18%) as a white solid. Data for **108a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (1H, s, O*H*), 4.59 - 4.65 (2H, m, C=CH_2), 4.48 (1H, td, *J* = 8.7, 5.8 Hz, CHC*H*(OH)), 4.14 (1H, d, *J* = 2.8 Hz, CC*H*(OH)), 3.69 (3H, s, CO_2CH_3), 2.96 - 3.06 (1H, m, 1H from CH_2=CCH_2), 2.18 - 2.33 (2H, m, 1H from CH_2=CCH_2, 1H from CH_2), 2.12 (1H, d, *J* = 9.0 Hz, C*H*CH(OH)), 1.98 (1H, br. s., O*H*), 1.68 - 1.87 (5H, m, 1H from CH_2, 2 x CH_2), 1.47 - 1.65 (2H, m, CH_2), 1.29 - 1.38 (2H, m., CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.1 (CO_2CH_3), 157.1 (*C*=CH_2), 102.7 (C=*C*H_2), 72.6 (C*C*HOH), 69.2 (CH*C*H(OH)), 52.6 (CO_2CH_3), 52.3 (CCO_2CH_3), 49.1 (*C*HCHOH), 45.5 (CH_2=C*C*), 39.2 (*C*H_2), 31.5 (*C*H_2), 31.5 (*C*H_2), 30.8 (*C*H_2), 25.5 (*C*H_2), 20.7 (*C*H_2); v_{max} (thin film/cm^{-1}): 3385, 2983, 2935, 2915, 1709, 1655, 1534, 1435, 1346, 1273, 1210, 1182, 1027, 995, 878. MS (ES$^+$) *m/z* (%): 267 (M+H$^+$, 100), 289 (M+Na$^+$, 75); HRMS (ES$^+$) calcd. for $C_{15}H_{22}O_4Na$ (M+Na$^+$): 289.1416. Found: 298.1410. Melting point = 110 - 112 °C (recrystallised from hexane).

Data for **108b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.64 (1H, t, *J* = 4.0 Hz, 1H from C=CH_2), 4.61 (1H, t, *J* = 2.4 Hz, 1H from C=CH_2), 4.50 (1H, m, CHC*H*(OH)), 4.18 (1H, m, CC*H*(OH)), 3.69 (3H, s, CO_2CH_3), 2.97 - 3.04 (1H, m, 1H from CH_2C=CH_2), 2.48 (1H, d, *J* = 4.0 Hz, 1H from CH_2C=CH_2), 2.24 - 2.30 (2H, m, CH_2CH_2CH(OH)), 1.93 - 2.22 (5H, m, 2 x CH_2, 1H from C*H*CH(OH), 1.83 - 1.89 (2H, m, CH_2), 1.32 - 1.39 (2H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9 (CO_2CH_3), 155.9 (*C*=CH_2), 103.6 (C=*C*H_2), 74.1 (C*C*H(OH)), 69.1 (CH*C*H(OH)), 55.5 (*C*HCH(OH)), 52.5 (CO_2CH_3), 49.5 (CCO_2CH_3), 44.3 (CH_2=C*C*), 40.0 (*C*H_2), 33.9 (*C*H_2), 31.5 (*C*H_2), 31.0 (*C*H_2), 21.4 (*C*H_2), 20.72 (*C*H_2); v_{max} (thin film/cm^{-1}): 3430, 2946, 2870, 1715, 1632, 1451, 1246, 1203, 1057, 924, 890. MS (ES$^+$) *m/z* (%): 267 (M+H$^+$, 50), 289

(M+Na$^+$, 100); HRMS (ES$^+$) calcd for $C_{15}H_{22}O_4Na$ (M+Na): 289.1416. Found: 289.1418; Melting point = 114 - 118 °C (recrystallized from hexane).

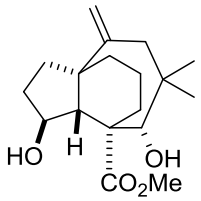
Methyl (1*S*,3a*R*,7*R*,8*S*,8a*R*)-1,7-dihydroxy-4-methyleneoctahydro-8*H*-3a,8-propanoazulene-8-carboxylate (109)



109

Prepared according to general procedure G. SmI_2 (7.25 mL, 0.10 M in THF, 0.73 mmol, 2.5 equiv.), *t*BuOH (0.07 mL, 0.73 mmol, 2.5 equiv.), **102** (74 mg, 0.26 mmol, 1.0 equiv.) in THF (2 mL) and purification by column chromatography (60% EtOAc/hexane) gave **109** (46 mg, 0.16 mmol, 63%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (1H, t, *J* = 1.4 Hz, 1H from C=C*H*$_2$), 4.76 (1H, s, 1H from C=C*H*$_2$), 4.27 (1H, td, *J* = 8.5, 3.5 Hz, CHC*H*(OH)), 3.98 (1H, d, *J* = 3.8 Hz, CH$_2$C*H*(OH)), 3.74 (3H, s, CO$_2$C*H*$_3$), 2.94 (1H, br. s., O*H*), 2.71 (1H, t, *J* = 9.0 Hz, 1H from CH$_2$=CC*H*$_2$), 2.55 (1H, br. s., O*H*), 2.45 (1H, d, *J* = 7.6 Hz, C*H*CH(OH)), 2.15 - 2.33 (3H, m, 1H from CH$_2$=CC*H*$_2$, 1H from C*H*$_2$, 1H from CCH(OH)C*H*$_2$), 1.80 - 1.98 (4H, m, 1H from CCH(OH)C*H*$_2$, 3 × 1H from C*H*$_2$), 1.75 (1H, dd, *J* = 14.2, 2.8 Hz, 1H from C*H*$_2$), 1.48 - 1.68 (4H, m, 2 x 1H from C*H*$_2$, 2 x C*H*$_2$), 1.35 (1H, td, *J* = 13.4, 3.8 Hz, 1H from C*H*$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9 (*C*O$_2$CH$_3$), 154.8 (*C*=CH$_2$), 110.4 (C=*C*H$_2$), 73.9 (CH*C*H(OH)), 72.8 (C*C*H(OH)), 52.3 (*C*CO$_2$CH$_3$), 52.3 (O*C*H$_3$), 52.1 (*C*HCH(OH)), 49.7 (*C*C=CH$_2$), 39.0 (*C*H$_2$), 32.7 (CCH(OH)*C*H$_2$), 32.1 (CHCH(OH)*C*H$_2$), 32.1 (*C*H$_2$) 29.4 (*C*H$_2$C=CH$_2$), 26.3 (*C*H$_2$), 19.2 (*C*H$_2$); ν_{max} (thin film/cm^{-1}): 3420, 3075, 2946, 2871, 1716, 1633, 1452, 1434, 1403, 1339, 1246, 1204, 1159, 1058, 1070, 1025, 1007, 992, 975, 962, 924, 890. MS (ES$^+$) *m/z* (%): 281 (M+H$^+$, 100), 303 (M+Na$^+$, 50); MS (ES$^-$) *m/z* (%): 279 (M−H$^+$, 95); HRMS (ES$^+$) calcd. for $C_{16}H_{25}O_4$ (M+H$^+$): 281.1747. Found: 281.1746; Melting point = 116 - 117 °C (recrystallized from hexane).

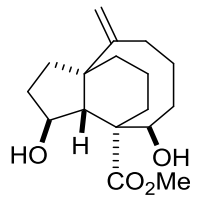
Methyl (1*S*,7*R*,8*S*,8a*R*)-1,7-dihydroxy-6,6-dimethyl-4-methyleneoctahydro-8*H*-3a,8-propanoazulene-8-carboxylate (110)



110

Prepared according to general procedure G. SmI_2 (4.90 mL, 0.10 M in THF, 0.49 mmol, 2.5 equiv.), *t*BuOH (94.0 µL, 0.98 mmol, 5.0 equiv.), **105** (60 mg, 0.20 mmol, 1.0 equiv.) in THF (1.3 mL), and purification by column chromatography (60% EtOAc/hexane) gave **110** (29 mg, 0.09 mmol, 50%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (1H, s, 1H from C=CH_2), 4.80 (1H, s, 1H from C=CH_2), 4.30 (1H, td, *J* = 8.8, 4.0 Hz, CH_2CH(OH)), 3.64 (3H, s, CO_2CH_3), 3.56 (1H, s, CC*H*(OH)), 2.46 (1H, d, *J* = 13.6 Hz, 1H from $CH_2C=CH_2$), 2.40 (1H, d, *J* = 8.3 Hz, CC*H*), 2.04 - 2.28 (5H, m, CH_2, 2 x O*H*, 1H from $CH_2C=CH_2$), 1.14 - 1.86 (8H, m, 4 x CH_2), 1.13 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3 (CO_2CH_3), 148.8 ($CH_2=C$), 110.1 ($CH_2=C$), 77.2 (CCH(OH)), 72.5 (CH_2CH(OH)), 53.3 (CCH), 52.7 (CCO_2CH_3), 51.8 (CO_2CH_3), 48.5 ($CH_2=CC$), 46.5 ($CH_2C=CH_2$), 39.2 ($C(CH_3)_2$), 37.5 (CH_2), 32.3 (CH_2), 31.5 (CH_3), 27.8 (CH_2), 26.4 (CH_2), 23.1 (CH_3), 17.9 (CH_2); ν_{max} (thin film/cm^{-1}) 3466, 2950, 2873, 1711, 1635, 1469, 1256, 1077, 1049, 993, 892, 755. MS (ES$^+$) *m/z* (%) 309 (M+H$^+$, 100), 331 (M+Na$^+$, 100); HRMS (ES$^+$) calcd. for $C_{18}H_{29}O_4$ (M+H$^+$): 309.2066. Found: 309.2071. Melting point = 122 - 127 °C (recrystallized from hexanes).

Methyl (1*S*,3a*R*,8*R*,9*S*,9a*R*)-1,8-dihydroxy-4-methyleneoctahydro-3a,9-propanocyclopenta[8]annulene-9(4*H*)-carboxylate (111)

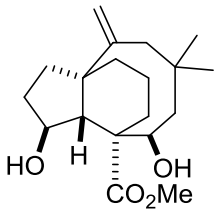


111

Prepared according to general procedure G. SmI_2 (2.50 mL, 0.10 M in THF, 0.25 mmol, 2.5 equiv.), *t*BuOH (24.0 µL, 0.25 mmol, 2.5 equiv.) and **103** (0.67 mL, 0.15 M in THF, 0.10 mmol, 1.0 equiv.). Column chromatography (60% EtOAc/*n*-hexane) gave **111** (12.4 mg, 0.04 mmol, 42%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ

4.92 (1H, s, 1H from C=CH_2), 4.90 (1H, s, 1H from C=CH_2), 4.42 (1H, ddt, *J* = 8.3, 7.8, 4.0 Hz, CHC*H*(OH)), 3.97 (1H, td, *J* = 6.9, 2.5 Hz, CC*H*(OH)), 3.71 (3H, s, CO_2CH_3), 2.71 (1H, dddd, *J* = 15.6, 13.6, 7.9, 2.5 Hz, CCH(OH)CH_2), 2.42 (1H, d, *J* = 7.8 Hz, C*H*CH(OH)), 2.21 - 2.37 (2H, m, 1H from CH_2C=CH_2, 1H from CHCH(OH)CH_2), 1.99 - 2.13 (2H, m, 1H from CH_2C=CH_2, 1H from CH_2), 1.89 - 1.97 (2H, m, CH_2), 1.42 - 1.86 (7H, m, 1H from CCH(OH)CH_2, 1H from CHCH(OH)CH_2, 3 x 1H from CH_2, CH_2), 1.08 - 1.30 (2H, m, 2 x 1H from CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6 (*C*(O)OCH_3), 153.5 (*C*=CH_2), 110.5 (C=*C*H_2), 74.1 (CH*C*H(OH)), 72.7 (C*C*H(OH)), 52.2 (*C*HCH(OH)), 52.2 (*C*CO_2CH_3), 51.8 (CO_2*C*H_3), 48.6 (*C*C=CH_2), 37.9 (*C*H_2), 35.3 (CCH(OH)*C*H_2), 33.2 (*C*H_2), 32.0 (CHCH(OH)*C*H_2), 32.0 (*C*H_2C=CH_2), 27.5 (*C*H_2), 25.8 (*C*H_2), 17.3 (*C*H_2); ν_{max} (thin film/cm^{-1}): 3436, 3082, 2945, 2872, 1710, 1628, 1459, 1434, 1348, 1332, 1289, 1226, 1206, 1163, 1127, 1087, 1068, 1058, 1023, 1005, 976, 952, 932, 914, 894, 864. MS (ES$^+$) *m/z* (%): 317 (M+Na$^+$, 100); HRMS (ES$^+$) calcd. for $C_{17}H_{26}O_4Na$ (M+Na$^+$): 317.1723. Found: 317.1718. Melting point = 101 - 102 °C (recrystallised from hexane).

Methyl (1*S*,3a*R*,8*R*,9*S*,9a*R*)-1,8-dihydroxy-6,6-dimethyl-4-methyleneoctahydro-3a,9-propanocyclopenta[8]annulene-9(4*H*)-carboxylate (112)

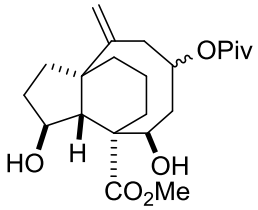


112

Prepared according to general procedure G. SmI_2 (2.5 mL, 0.10 M in THF, 0.25 mmol, 2.5 equiv.), *t*BuOH (50.0 µL, 0.50 mmol, 5.0 equiv.) and **906** (0.67 mL, 0.15 M in THF, 0.10 mmol, 1.0 equiv.). Purification by column chromatography (60% EtOAc/n-hexane) gave **112** (26 mg, 0.08 mmol, 81%) as a colourless foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (1H, s, 1H from C=CH_2), 4.83 (1H, s, 1H from C=CH_2), 4.45 (1H, ddd, *J* = 10.8, 7.5, 3.3 Hz, CHC*H*(OH)), 3.86 - 3.96 (1H, m, CC*H*(OH)), 3.71 (3H, s, CO_2CH_3), 2.65 (1H, dd, *J* = 15.4, 7.2 Hz, 1H from CCH(OH)CH_2), 2.38 (1H, d, *J* = 3.3 Hz, O*H*, 2.32 (1H, d, *J* = 7.5 Hz, C*H*CH(OH)), 2.21 - 2.32 (1H, m, 1H from CHCH(OH)CH_2), 2.14 (1H, d, *J* = 13.6 Hz, 1H from CH_2), 1.74 - 2.03 (6H, m, 2 × CH_2, 2 × 1H from CH_2), 1.55 - 1.73 (3H, m, O*H*, 1H from CHCH(OH)CH_2, and 1H from CH_2), 1.44 - 1.54 (1H, m, 1H from CH_2), 1.22 - 1.31 (1H, m, 1H from CH_2), 1.10 - 1.16 (1H, m, 1H from CH_2), 1.09 (3H, s, CCH_3), 1.03 (3H, s, CCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8 (*C*=O), 148.2 (*C*=CH_2), 112.0 (C=*C*H_2), 73.8 (CH*C*H(OH)),

67.8 (C*C*H(OH)), 52.5 (*C*HCH(OH)), 51.9 (CO_2CH_3), 51.7 (CCO_2CH_3), 49.1 ($CC=CH_2$), 48.2 (CCH(OH)CH_2), 44.5 (CH_2), 38.5 (CH_2), 34.1 ($C(CH_3)_2$), 33.7 (CCH_3), 31.7 (CHCH(OH)CH_2), 27.4 (CH_2), 25.7 (CH_2), 25.5 (CCH_3), 17.3 (CH_2); v_{max} (thin film/cm^{-1}): 3457, 3085, 2949, 2870, 2237, 1710, 1624, 1462, 1434, 1387, 1364, 1346, 1329, 1271, 1229, 1197, 1169, 1095, 1066, 1058, 1033, 1020, 966, 947, 896, 878, 854, 815. MS (ES^+) *m/z* (%): 345 ($M+Na^+$, 100); HRMS (ES^+) calcd. for $C_{19}H_{30}O_4Na$ ($M+Na^+$): 345.2036. Found: 345.2035.

Methyl (1*S*,8*R*,9*S*,9a*R*)-1,8-dihydroxy-4-methylene-6-(pivaloyloxy)octahydro-3a,9-propanocyclopenta[8]annulene-9(4*H*)-carboxylate (113)

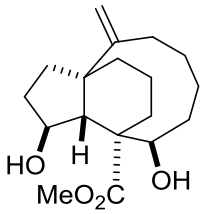


113

Prepared according to general procedure G. **107a** (22.3 mg, 0.06 mmol, 1.0 equiv.), SmI_2 (1.50 mL, 0.1 M in THF, 0.15 mmol, 2.5 equiv.), *t*BuOH (22.0 mg, 0.30 mmol, 5.0 equiv.), in THF (0.5 mL), purification by column chromatography (60 % EtOAc/hexane) gave **113** (10.2 mg, 25.8 µmol, 44% [dr = 1:1]). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 - 5.13 (1H, m, C*H*OPiv [both diastereoisomers]), 5.02 (1H, s, 1H from C=CH_2 [both diastereoisomers]), 4.86 (1H, s, 1H from C=CH_2 [both diastereoisomers]), 4.36 - 4.45 (1H, m, C*H*(OH) [both diastereoisomer]), 4.23 (1H, s, C*H*(OH) [both diastereoisomers]), 3.66 (3H, s, CO_2CH_3 [both diastereoisomers]), 2.85 - 2.94 (1H, m, 1H from CH_2 [both diastereoisomers]), 2.55 - 2.67 (1H, m, C*H*CH(OH) [both diastereoisomers]), 2.21 - 2.30 (2H, m, 2 x 1H from CH_2 [both diastereoisomers]), 2.15 (1H, d, *J* = 7.9 Hz, 1H from CH_2 [both diastereoisomers]), 1.91 - 1.95 (2H, m, 2 x 1H from CH_2 [both diastereoisomers]), 1.81 - 1.86 (1H, m, 1H from CH_2 [both diastereoisomers]), 1.70 - 1.78 (1H, m, 1H from CH_2 [both diastereoisomers]), 1.43 - 1.65 (6H, m, 3 x CH_2 [both diastereoisomers]), 1.18 - 1.21 (9H, m, C(CH_3)$_3$ [both diastereoisomers]); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4 (*C*(O)C$(CH_3)_3$ [both diastereoisomers], 176.3 (CO_2CH_3 [both diastereoisomers]), 151.4 (*C*=CH_2, [both diastereoisomers]), 110.7 (C=*C*H_2 [both diastereoisomers]), 78.5 (*C*H(OPiv) [both diastereoisomers]), 77.3 (*C*H(OH) [both diastereoisomers]), 51.8 (*C*H(OH) [both diastereoisomers]), 50.8 (*C*HCH(OH) [one diastereoisomer], 50.8 (*C*HCH(OH), [one diastereoisomer]), 49.3 (CCO_2CH_3 [both diastereoisomers]), 42.6 (CO_2CH_3, [both diastereoisomers]), 32.4 (*C*C=CH_2, [one diastereoisomer]),

32.4 (*C*C=CH_2, [one diastereoisomer]), 32.2 (*C*H_2 [both diastereoisomers]), 31.8 (*C*H_2 [both diastereoisomers]), 31.6 (*C*H_2 [both diastereoisomers]), 29.4 (*C*H_2 [both diastereoisomers]), 27.2 (*C*$(CH_3)_3$ [both diastereoisomers]), 26.3 (*C*H_2 [both diastereoisomers]), 22.7 (*C*H_2 [both diastereoisomers]), 20.2 ((*C*$H_3)_3$ [both diastereoisomers]), 14.2 (*C*H_2 [both diastereoisomers]); ν_{max} (thin film/cm^{-1}): 3457, 2953, 2933, 2873, 1725, 1632, 1479, 1455, 1435, 1397, 1366, 1283, 1262, 1227, 1163, 1091, 1060, 1028, 974, 933, 905. MS (ES+) *m/z* (%): 417 ($M+Na^+$, 100); HRMS (ES^+) calcd. for $C_{22}H_{34}O_6Na$ ($M+Na^+$): 417.2253. Found: 417.2266.

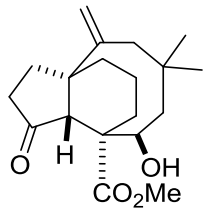
Methyl (1*S*,3a*R*,9*R*,10*S*,10a*R*)-1,9-dihydroxy-4-methylenedecahydro-10*H*-3a,10-propanocyclopenta[9]annulene-10-carboxylate (114)



114

Prepared according to general procedure G. SmI_2 (2.60 mL, 0.10 M in THF, 0.26 mmol, 2.5 equiv.), *t*BuOH (0.05 mL, 0.55 mmol, 5.0 equiv.), **104** (32.2 mg, 0.11 mmol, 1.0 equiv.) in THF (0.75 mL), after purification by column chromatography (60% EtOAc/hexane) gave **114** (8.80 mg, 0.03 mmol, 26%) as a colourless foam. ^{1}H NMR (400 MHz, $CDCl_3$) 4.84 (2H, d, *J* = 8.8 Hz, C=C*H*$_2$), 4.35 (1H, td, *J* = 8.3, 4.0 Hz, CHC*H*(OH)), 3.90 (1H, d, *J* = 7.8 Hz, CC*H*(OH)), 3.62 - 3.65 (3H, m, CO_2CH_3), 2.58 - 2.70 (1H, m, 1H from C*H*$_2$), 2.35 (1H, d, *J* = 7.5 Hz, C*H*CH(OH)), 2.13 - 2.29 (3H, m, C*H*$_2$, 1H from CH_2), 1.93 - 2.03 (2H, m, C*H*$_2$), 1.86 (2H, dd, *J* = 10.2, 3.9 Hz, *C*H_2), 1.50 - 1.78 (5H, m, 1H from C*H*$_2$, 2 x C*H*$_2$), 1.12 - 1.45 (4H, m, 2 x C*H*$_2$), 1.07 (1H, ddd, *J* = 12.9, 9.1, 2.1 Hz, 1H from C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6 (*C*O_2CH_3), 153.5 (*C*=CH_2), 110.6 (C=*C*H_2), 74.1 (CH*C*H(OH)), 72.7 (C*C*H(OH)), 52.2 (*C*HCH(OH)), 52.2 (*C*CO_2CH_3), 51.8 (CO_2CH_3), 48.6 (*C*C=CH_2), 37.9 (*C*H_2), 35.2 (*C*H_2), 33.2 (*C*H_2), 32.0 (*C*H_2), 32.0 (*C*H_2), 27.5 (*C*H_2), 25.8 (*C*H_2), 22.6 (*C*H_2), 17.3 (*C*H_2); ν_{max} (thin film/cm^{-1}): 3434, 2945, 2871, 1714, 1629, 1460, 1434, 1258, 1227, 1086, 1056, 895, 799, 755. MS was inconclusive.

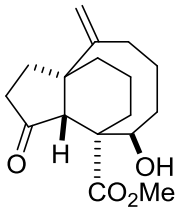
Methyl (8*R*,9*S*,9a*R*)-8-hydroxy-6,6-dimethyl-4-methylene-1-oxooctahydro-3a,9-propanocyclopenta[8]annulene-9(4*H*)-carboxylate (120a)



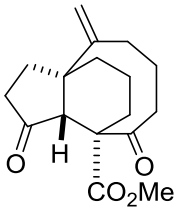
120a

DMP (132 mg, 0.31 mmol, 1.0 equiv.) was added to a solution of **112** (101 mg, 0.31 mmol, 1.0 equiv,) in CH_2Cl_2 (3.0 mL) under nitrogen and after 1 hour the reaction was quenched with 5% NaOH (w/v water) (3 mL). Extraction into Et_2O (3 x 5 mL) and purification by column chromatography (30% ethyl acetate/hexane) gave **120a** (48.3 mg, 0.15 mmol, 49%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (1H, s, 1H from C=C*H*$_2$), 4.87 (1H, s, 1H from C=C*H*$_2$), 3.86 (1H, d, *J* = 7.6 Hz, CH_2CH(OH)), 3.66 (3H, s, CO_2CH_3), 3.01 (1H, s, C*H*C(O)), 2.47 (1H, dd, *J* = 15.6, 7.6 Hz, 1H from C*H*$_2$CH(OH)), 2.08 - 2.33 (4H, m, 2 x C*H*$_2$), 1.78 - 1.96 (4H, m, 2 x C*H*$_2$), 1.34 - 1.62 (4H, m 2 x C*H*$_2$), 1.14 (1H, dd, *J* = 15.8, 1.7 Hz, 1H from C*H*$_2$CH(OH)), 1.03 (3H, s, C*H*$_3$), 0.97 (3H, s, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.9 (CH_2C=O), 174.8 (CO_2CH_3), 147.4 (C=CH_2), 113.3 (C=CH_2), 67.5 (CH_2CH(OH)), 56.5 (C*C*H), 51.7 (CO_2CH_3), 48.8 (CCO_2CH_3), 46.7 (CH_2CH(OH)), 46.5 (CH_2CC), 44.7 (CH_2), 34.0 ($C(CH_3)_2$), 33.9 (($CH_3)_2$), 33.4 (CH_2), 33.4 (CH_2), 27.8 (CH_2), 25.4 (CH_2), 25.6 (CH_2), 17.2 (CH_2); v_{max} (thin film/cm^{-1}): 3473, 3087, 2950, 2873, 1744, 1723, 1626, 1460, 1433, 1388, 1364, 1342, 1295, 1268, 1225, 1205, 1168, 1142, 1105, 1080, 1036, 1011, 985, 897, 859, 813. MS (ES+) *m/z* (%): 321 (M+H$^+$, 50), 338 (M+NH_4^+, 40), 343 (M+Na$^+$, 40); HRMS (ES$^+$) calcd. for $C_{19}H_{32}O_4N$ (M+NH_4^+): 338.2326. Found: 338.2329.

Methyl (3a*R*,8*R*,9*S*,9a*R*)-8-hydroxy-4-methylene-1-oxooctahydro-3a,9-propanocyclopenta[8]annulene-9(4*H*)-carboxylate (119a) and methyl (3a*R*,9*S*,9a*R*)-4-methylene-1,8-dioxooctahydro-3a,9-propanocyclopenta[8]annulene-9(4*H*)-carboxylate (119b)



119a



119b

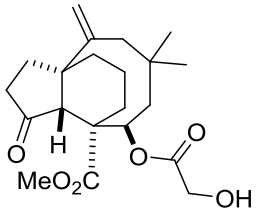
DMP (35.7 mg, 0.08 mmol, 1.0 equiv.) was added to a solution of **111** (24.8 mg, 0.08 mmol, 1.0 equiv,) in CH_2Cl_2 (1.0 mL) under nitrogen and after 1 hour the reaction was quenched with 5% NaOH (w/v water) (1 mL). Extraction into Et_2O (3 x 3 mL) and purification by column chromatography (30% ethyl acetate/hexane) gave **119a** (14.7 mg, 60%) and **119b** (4 mg, 16%).

Data for **119a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (2H, s, C*H*$_2$=C), 3.94 - 4.01 (1H, m, C*H*(OH)), 3.74 (3H, s, CO_2CH_3), 3.17 (1H, m, C*H*C(O)), 2.41 - 2.59 (2H, m 1H from CH_2=CC*H*$_2$ and 1H from C*H*$_2$CH(OH)), 2.21 - 2.39 (2H, m, C*H*$_2$), 2.04 - 2.13 (2H, m, 1H from CH_2=CC*H*$_2$ and 1H from C*H*$_2$), 1.84 - 2.02 (4H, m, 2 x C*H*$_2$), 1.59 - 1.72 (2H, m, 1H from C*H*$_2$CH(OH) and 1H from C*H*$_2$), 1.43 - 1.54 (2H, m, C*H*$_2$), 1.23 - 1.32 (1H, m, 1H from C*H*$_2$), 1.05 - 1.14 (1H, m, 1H from C*H*$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.2 (*C*(O)), 174.9 (*C*O_2CH_3), 152.4 (CH_2=*C*), 111.6 (*C*H_2=C), 72.2 (*C*H(OH)), 56.2 (*C*HC(O)), 51.8 (CO_2*C*H_3), 49.3 (*C*CO_2CH_3), 46.2 (CH_2=C*C*), 33.9 (*C*H_2CH(OH)), 33.4 (*C*H_2), 32.8 (*C*H_2), 32.7 (*C*H_2), 32.3 (*C*H_2), 27.7 (*C*H_2), 25.9 (*C*H_2), 17.2 (*C*H_2); ν_{max} (thin film/cm^{-1}): 2959, 2932, 2874, 1746, 1704, 1456, 1313, 1235, 1195, 1173, 1077, 1026, 908. MS (ES+) *m/z* (%): 293 (M+H$^+$, 35), 315 (M+Na$^+$, 100); HRMS (ES$^+$) calcd. for $C_{17}H_{24}O_4Na$ (M+Na$^+$): 315.1567. Found: 315.1559.

Data for **119b**: ^{1}H NMR (400 MHz,$CDCl_3$) δ 5.00 (1H, s, 1H from C=C*H*$_2$), 4.95 (1H, s, 1H from C=C*H*$_2$), 3.72 (1H, s, C*H*C=O), 3.66 (3H, s, CO_2CH_3), 3.15 - 3.25 (1H, m, 1H from C*H*$_2$), 2.35 - 2.42 (2H, m, C*H*$_2$), 2.30 - 2.35 (1H, m, 1H from C*H*$_2$C=CH_2), 2.20 - 2.28 (1H, m, 1H from C*H*$_2$), 2.04 - 2.19 (3H, m, 1H from C*H*$_2$C=CH_2, and C*H*$_2$), 1.87 - 1.95 (1H, m, 1H from C*H*$_2$), 1.79 - 1.86 (1H, m, 1H from C*H*$_2$), 1.66 - 1.77 (1H, m, 1H from C*H*$_2$), 1.45 (2H, ddd, *J* = 13.2, 9.21, 2.27 Hz, 2 x 1H from C*H*$_2$), 1.29 - 1.40 (2H, m, 2 x 1H from C*H*$_2$), 0.93 - 1.03 (1H, m, 1H from C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.7 (*C*=O), 206.9 (*C*=O), 170.5 (*C*O_2CH_3), 149.7

(*C*=CH_2), 115.1 (*C*H_2=C), 59.6 (*C*CO_2CH_3), 55.3 (*C*HC=O), 52.8 (CO_2*C*H_3), 46.5 (*C*C=CH_2), 38.2 (*C*H_2), 33.1 (2 x *C*H_2), 32.3 (*C*H_2), 31.9 (*C*H_2), 28.0 (*C*H_2), 23.6 (*C*H_2), 17.5 (*C*H_2); ν_{max} (thin film/cm^{-1}): 3086, 2950, 2932, 2874, 1746, 1705, 1631, 1456, 1440, 1343, 1313, 1254, 1235, 1195, 1174, 1160, 1103, 1077, 1026, 1012, 981, 965, 908, 883, 855. MS (ES^+) *m/z* (%): 291 ($M+H^+$, 70), 313 ($M+Na^+$, 60); HRMS (ES^+) calcd. for $C_{17}H_{22}O_4Na$ ($M+Na^+$): 313.1410. Found: 313.1410.

Methyl (8*R*,9*S*,9a*R*)-8-(2-hydroxyacetoxy)-6,6-dimethyl-4-methylene-1-oxooctahydro-3a,9-propanocyclopenta[8]annulene-9(4*H*)-carboxylate (121)



121

DCC (124 mg, 0.60 mmol, 4.0 equiv.) and DMAP (73 mg, 0.60 mmol, 4.0 equiv.) were added to a solution of **120a** (48.3 mg, 0.15 mmol, 1.0 equiv.) and Ph_3COCH_2COOH[174] (191 mg, 0.60 mmol, 4.0 equiv.) in CH_2Cl_2 (14 mL). After 2 hours, the reaction mixture was quenched with water (15 mL), extracted into CH_2Cl_2 (3 x 15 mL) and dried ($MgSO_4$). Concentration *in vacuo* and partial purification by column chromatography (10% EtOAc/hexane) gave the trityl protected product, which was taken onto the next step.

1M aqueous HCl (0.15 mL, 0.15 mmol) was added to a solution of the protected product in MeOH (10 mL). After 18 hours, $NaHCO_3$ (150 mg) was added to the reaction and it was left to stir for 15 minutes before being filtered through a pad of celite. Concentration *in vacuo* and purification by column chromatography (15% EtOAc/hexane) gave **121** (33.3 mg, 88.0 µmol, 59%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (1H, d, *J* = 8.0 Hz, C(*H*)OC(O)CH_2), 5.24 (1H, s, 1H from C=C*H*$_2$), 5.06 (1H, s, 1H from C=C*H*$_2$), 4.08 (AB system, 1H, d, *J* = 2.8 Hz, 1H from C*H*$_2$OH), 4.07 (AB system, 1H, d, *J* = 2.8 Hz, 1H from C*H*$_2$OH), 3.74 (3H, s, CO_2CH_3), 3.13 (1H, br. s., C*H*C=O), 2.68 (1H, dd, *J* = 16.1, 8.0 Hz, 1H from C*H*$_2$CHOC(O)), 2.28 (1H, t, *J* = 5.5 Hz, O*H*), 2.21 - 2.41 (1H, m, 1H from CH_2), 2.21 (1H, d, *J* = 14.6 Hz, 1H from C*H*$_2$C=CH_2), 2.19 - 2.40 (4H, m, 1H from 4 x C*H*$_2$), 1.87 – 2.16 (4H, m, 1H from 4 x CH_2), 1.68 - 1.80 (1H, m, 1H from C*H*$_2$), 1.43 - 1.56 (4H, m, 2 x C*H*$_2$), 1.18 (1H, dd, *J* = 16.1, 1.3 Hz, 1H from C*H*$_2$), 1.14 (3H, s, CC*H*$_3$), 1.05 (3H, s, CC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.4 (*C*(O)), 171.9 (*C*O_2CH_3), 171.9 (CHO*C*(O)CH_2), 146.4 (*C*=CH_2),114.5 (C=*C*H_2), 71.0 (*C*HOC(O)CH_2), 60.6 (*C*H_2OH), 56.2 (*C*HC(O)), 51.8 (CO_2*C*H_3), 47.6 (*C*C(O)OCH_3), 46.5 (*C*C=CH_2), 44.4

($CH_2C=CH_2$), 44.2 ($CH_2CHOC=O$), 34.1 ($C(CH_3)_2$), 33.8 (CCH_3), 33.5 (CH_2), 32.3 (CH_2), 27.8 (CH_2), 26.0 (CCH_3), 25.6 (CH_2), 17.1 (CH_2); ν_{max} (thin film/cm^{-1}): 3468, 2951, 2877, 1742, 1728, 1462, 1433, 1390, 1366, 1314, 1289, 1267, 1225, 1205, 1196, 1169, 1144, 1097, 1055, 1002, 984, 962, 948, 918, 903, 890. MS (ES^+) *m/z* (%): 401 ($M+Na^+$, 80); HRMS (ES^+) calcd. for $C_{21}H_{30}O_6Na$ ($M+Na^+$): 401.1940. Found: 401.1932.

13.0 Experimental Part 2

13.1 General Information

All experiments were performed under an atmosphere of nitrogen, using anhydrous solvents, unless stated otherwise. THF was distilled from sodium/benzophenone, dichloromethane and trimethylamine were distilled from CaH_2. ^1H NMR spectra were recorded at 400 or 500 MHz; ^{13}C NMR spectra were recorded at 101 or 126 MHz. All chemical shift values are reported in ppm relative to residual chloroform as internal standards. All chemical shift values are reported in parts per million (ppm) relative to the solvent signal and were determined in $CDCl_3$, with coupling constant (*J*) values reported in Hz. Crude reaction mixtures were dissolved in a solution of chloroform containing a known concentration of nitromethane to calculate ^1H NMR yields. The notation of signals is: Proton: δ *chemical shift (number of protons, multiplicity, J value(s), proton assignment)*. Carbon: δ *chemical shift (carbon assignment)*. Fluorine: δ *chemical shift (fluorine assignment)*. For multiplets and overlapping signals a range of shifts is reported. Routine TLC analysis was carried out on aluminum sheets coated with silica gel 60 Å F254, 0.2 mm thickness. Plates were viewed using 254 nm ultraviolet light and dipped in aqueous potassium permanganate or *p*-anisaldehyde. Column chromatography was carried out on 40-63 µ, 60 Å silica gel. Infrared spectra were recorded as evaporated films or neat using a FT/IR spectrometer. Mass spectra were obtained using positive and negative ($ES^{\pm}$) or gas chromatography (GC) methodology. Enantiomeric ratios were determined by HPLC analysis (Phenomenex® Lux 5 µm Amylose-1 (4.6 x 250 mm), Chiral Technologies Chiralpak® IA (4.6 x 250 mm), Chiralcel® OD-H [4.6 x 250 mm]) in comparison with authentic racemic materials. Specific rotations were measured on a Rudolph Research Analytical Autopol I Automatic Polarimeter. Melting points were measured on a Stuart Scientific capillary melting point apparatus and are uncorrected. All imines and allenes used in the reactions were either commercially available or obtained from the literature procedures by Kay Yeung or James Rae.[147,152]

13.2 General Procedures

General Procedure 1

To a solution of CuI (2.50 mg, 0.013 mmol, 5.00 mol%) and ligand **L5** (8.40 mg, 0.014 mmol, 5.50 mol%) in THF (0.80 mL), was added *t*BuOK (0.26 mL, 1.00 M THF solution, 0.258 mmol, 1.0 equiv.), and the reaction was stirred for 75 minutes at

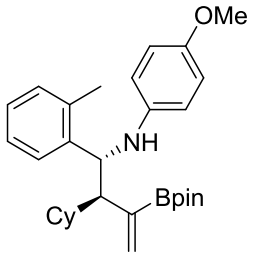
room temperature. B_2pin_2 (72.0 mg, 0.284 mmol, 1.1 equiv.) in THF (0.75 mL) was then added and the resulting mixture was stirred for 30 minutes. A solution of the imine (0.258 mmol, 1.0 equiv.) and allene (0.387 mmol, 1.5 equiv.) in THF (1 mL) was then added dropwise at room temperature and the reaction was left to stir overnight. The mixture was then filtered through a silica plug, concentrated *in vacuo* and the crude mixture was purified by column chromatography on silica gel.

General Procedure 2

To a solution of CuI (2.50 mg, 0.013 mmol, 5.00 mol%) and ligand **L5** (8.40 mg, 0.014 mmol, 5.50 mol%) in THF (0.80 mL), was added *t*BuOK (0.26 mL, 1.00 M THF solution, 0.258 mmol, 1.0 equiv.), and the reaction was stirred for 75 minutes at room temperature. B_2pin_2 (72.0 mg, 0.284 mmol, 1.1 equiv.) in THF (0.75 mL) was then added and the resulting mixture was stirred for 30 minutes. A solution of the imine (0.258 mmol, 1.0 equiv.) and allene (0.387 mmol, 1.5 equiv.) in THF (1 mL) was then added dropwise at room temperature and the reaction was left to stir overnight to give solution A.

To a solution of CuI (2.50 mg, 0.013 mmol, 5.00 mol%) and ligand **L5** (8.40 mg, 0.014 mmol, 5.50 mol%) in THF (0.8 mL), was added *t*BuOK (0.26 mL, 1.00 M THF solution, 0.258 mmol, 1.0 equiv.), and the reaction was stirred for 75 minutes at room temperature. This reaction mixture was then transferred by cannula to solution A at room temperature and left to stir overnight. The mixture was then filtered through a silica plug, concentrated *in vacuo* and the crude mixture was purified by column chromatography on silica gel.

***N*-((1*R*,2*R*)-2-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(*o*-tolyl)but-3-en-1-yl)-4-methoxyaniline (237)**

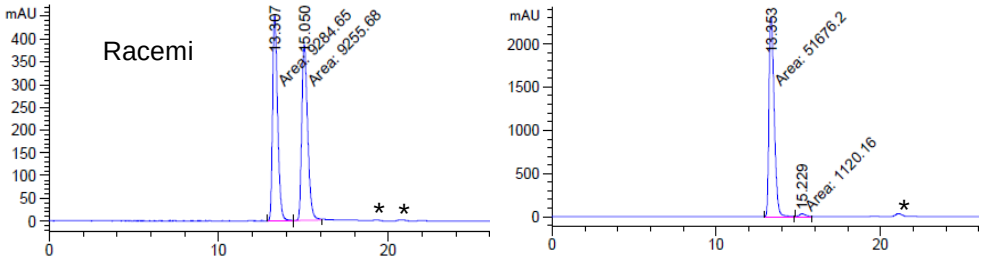


237

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (>95:5 d.r. of crude material), column chromatography (3% EtOAc in Hexanes) afforded the title compound as a white foam (106 mg, 0.223 mmol, 86%, 98:2 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ

6.94 - 7.15 (4H, m, 4 x ArC*H*), 6.66 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 6.30 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 5.70 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 5.56 (1H, br. s, N*H*), 4.88 (2H, d, *J* = 3.5 Hz, C*H*N and 1H from C=CH_2), 3.68 (3H, s, OCH_3), 2.46 (3H, br. s, Ar-CH_3), 2.20 (1H, dd, *J* = 10.1, 4.0 Hz, C*H*C=CH_2), 1.88 - 2.08 (2H, m, 1H from CH_2 and C*H*), 1.55 - 1.79 (4H, m, 2 x CH_2), 1.36 (6H, s, 2 x CH_3), 1.31 (6H, s, 2 x CH_3), 0.71 - 1.23 (5H, m, 1H from CH_2 and 2 x CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ150.8 (Ar*C*), 142.5 (Ar*C*), 140.9 (Ar*C*), 134.8 (C=*C*H_2), 134.2 (Ar*C*), 130.1 (Ar*C*H), 127.8 (Ar*C*H), 125.9 (Ar*C*H), 125.4 (Ar*C*H), 114.8 (Ar*C*H), 112.9 (Ar*C*H), 83.7 (BO*C*), 58.2 (*C*HC=CH_2), 55.8 (O*C*H_3), 54.4 (*C*HN), 36.9 (*C*H), 33.0 (*C*H_2), 31.0 (*C*H_2), 26.6 (*C*H_2), 26.5 (*C*H_2), 26.4 (*C*H_2), 25.0 (*C*H_3), 24.4 (*C*H_3), 19.1 (Ar-*C*H_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, CDCl3) 8.0; ν_{max} (thin film/cm^{-1}): 3408, 2976, 2927, 2850, 1525, 1462, 1447, 1421, 1371, 1300, 1277, 1233, 1180, 1165, 1142, 1041; MS (ES$^+$) *m/z*: 476 (M+H$^+$); HRMS (ES$^+$) calcd. for $C_{30}H_{42}NBO_3$ (M+H$^+$): 476.3341. Found: 476.3357. Specific rotation: $[\alpha]_D^{27}$ –54.2 (c 1.06, $CHCl_3$) for an enantiomerically enriched sample of 98:2 e.r.

Enantiomeric purity of **237** was determined by HPLC analysis in comparison with authentic racemic material (98:2 e.r.; Lux 5 µm Amylose-1 column, 99:1 hexanes:*i*PrOH, 0.3 mL/min, 20 °C, 254 nm).



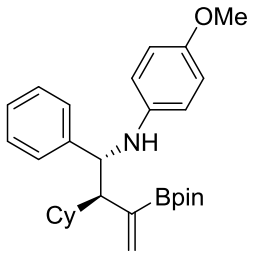
* = minor diastereoisomer

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.307	MF	0.3429	9284.65332	451.34103	50.0781
2	15.050	FM	0.3987	9255.67578	386.94217	49.9219

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.353	MM	0.3724	5.16762e4	2312.75049	97.8783
2	15.229	MM	0.5273	1120.15515	35.40219	2.1217

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	13.307	50.0781	1	13.353	97.8783
2	15.050	49.9219	2	15.229	2.1217

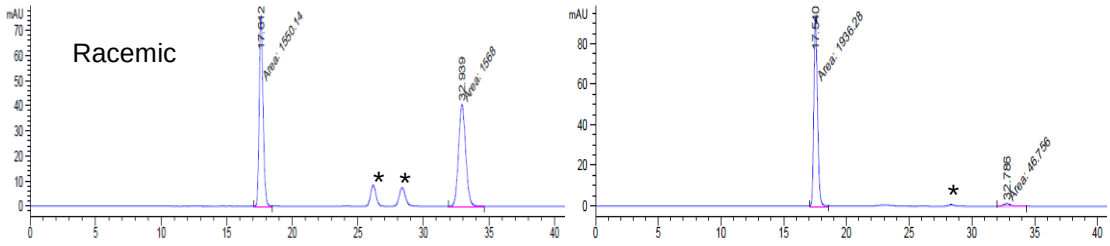
***N*-((1*R*,2*R*)-2-Cyclohexyl-1-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)-4-methoxyaniline (242)**



242

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (74:26 d.r. of crude material), column chromatography (3% EtOAc in Hexanes) afforded the title compound as an orange gum (91.0 mg, 0.197 mmol, 76%, 92:2 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 - 7.26 (2H, m, 2 x ArC*H*), 7.16 - 7.21 (2H, m, 2 x ArC*H*), 7.13 (1H, tt, *J* = 6.9, 1.3 Hz, ArC*H*), 6.66 (2H, d, *J* = 9.0 Hz, 2 x ArC*H*), 6.38 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 5.72 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 5.33 (1H, br. s, N*H*), 5.02 (1H, d, J = 3.5 Hz, 1H from C=CH_2), 4.67 (1H, d, *J* = 5.3 Hz, C*H*N), 3.68 (3H, s, OCH_3), 2.24 (1H, dd, *J* = 9.0, 5.3 Hz, C*H*C=CH_2), 1.75 - 1.89 (2H, m, 1H from CH_2 and 1H from C*H*), 1.60 - 1.75 (4H, m, 2 x CH_2), 1.31 (6H, s, 2 x CH_3), 1.28 (6H, s, 2 x CH_3), 1.09 - 1.23 (3H, m, 1H from CH_2 and CH_2), 1.02 (1H, m, 1H from CH_2), 0.73 - 0.85 (1H, m, 1H from CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9 (Ar*C*), 144.0 (Ar*C*), 142.6 (Ar*C*), 134.6 (C=*C*H_2), 127.9 (Ar*C*H), 127.3 (Ar*C*H), 126.1 (Ar*C*H), 114.8 (Ar*C*H), 113.3 (Ar*C*H), 83.6 (BO*C*), 61.4 (*C*HC=CH_2), 58.1 (O*C*H_3), 55.8 (*C*HN), 36.9 (*C*H), 32.3 (*C*H_2), 31.4 (*C*H_2), 26.6 (*C*H_2), 26.4 (*C*H_2), 26.4 (*C*H_2), 25.0 (*C*H_3), 24.4 (*C*H_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 1.5; ν_{max} (thin film/cm^{-1}): 3407, 2976, 2925, 2850, 1510, 1450, 1421, 1389, 1371, 1300, 1233, 1218, 1140, 1115, 1069, 1040; MS (ES$^+$) *m/z*: 462 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{29}H_{41}NBO_3$ (M+H$^+$): 462.3179. Found: 462.3162; Specific rotation: $[\alpha]_D^{27}$ –31.7 (c 0.90, $CHCl_3$) for an enantiomerically enriched sample of 98:2 e.r.

Enantiomeric purity of **242** was determined by HPLC analysis in comparison with authentic racemic material (98:2 e.r.; Lux 5 µm Amylose-1 column, 99:1 hexanes:*i*PrOH, 0.3 mL/min, 20 °C, 254 nm).



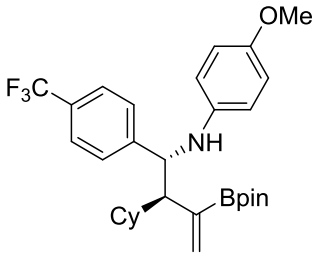
* = minor diastereoisomer

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.612	MM	0.3394	1550.13989	76.11987	49.7136
2	32.939	MM	0.6432	1568.00183	40.63127	50.2864

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.540	MM	0.3433	1936.27563	94.01144	97.6422
2	32.786	MM	0.6662	46.75599	1.16968	2.3578

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	17.612	49.7136	1	17.540	97.6422
2	32.939	50.2864	2	32.786	2.3578

_N_-((1_R_,2_R_)-2-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(trifluoromethyl)phenyl)but-3-en-1-yl)-4-methoxyaniline (245)

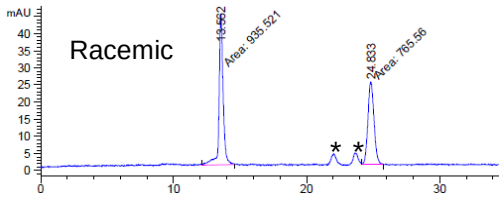


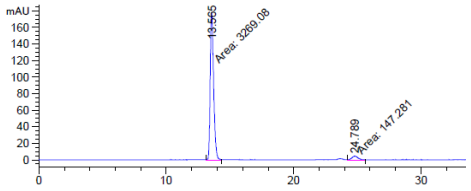
245

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (76:24 d.r. of crude material), column chromatography (4% EtOAc in Hexanes) afforded the title compound as an orange gum (117 mg, 0.220 mmol, 85%, 96:4 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 8.3 Hz, 2 x ArC*H*), 7.29 (2H, d, *J* = 8.3 Hz, 2 x ArC*H*), 6.67 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 6.34 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 5.72 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 5.43 (1H, br. s, N*H*), 4.99 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 4.72 (1H, br. s, C*H*N), 3.69 (3H, s, OCH_3), 2.23 (1H, dd, *J* = 9.4, 4.6 Hz, C*H*C=CH_2), 1.78 - 1.94 (2H, m, CH_2), 1.57 - 1.77 (4H, m, CH_2, 1H from CH_2 and 1H from C*H*), 1.32 (6H, s, 2 x CH_3), 1.29 (6H, s, 2 x CH_3), 1.10 - 1.24 (3H, m, 1H from CH_2 and CH_2), 0.95 - 1.08 (1H, m, CH_2), 0.73 - 0.85 (1H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2 (Ar*C*), 148.5 (Ar*C*), 142.0 (Ar*C*), 135.1 (C=*C*H_2), 128.4 (q, *J* = 31.7 Hz, *C*CF_3), 127.5 (Ar*C*H), 124.9 (Ar*C*H), 124.4 (q, *J* = 272.0 Hz, *C*F_3), 114.8 (Ar*C*H), 113.3

(Ar*C*H), 83.8 (BO*C*), 61.1 (*C*HC=CH_2), 57.9 (OCH_3), 55.8 (*C*HN), 36.8 (*C*H), 32.4 (CH_2), 31.2 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 24.9 (CH_3), 24.4 (CH_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 29.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.2; v_{max} (thin film/cm^{-1}): 3405, 2977, 2927, 2851, 1617, 1511, 1420, 1371, 1334, 1234, 1066, 1040, 1016; MS (ES$^+$) *m/z*: 530 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{30}H_{40}NBO_2F_3$ (M+H$^+$): 530.3062. Found: 530.3059. Specific rotation: $[\alpha]_D^{27}$ –26.2 (c 1.06, $CHCl_3$) for an enantiomerically enriched sample of 96:4 e.r.

Enantiomeric purity of **245** was determined by HPLC analysis in comparison with authentic racemic material (96:4 e.r.; Lux 5 µm Amylose-1 column, 99:1 hexanes:*i*PrOH, 0.3 mL/min, 20 °C, 254 nm).





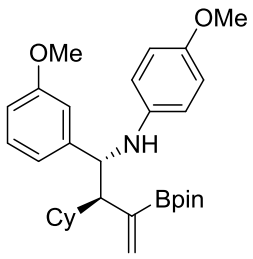
* = minor diastereoisomer

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.944	BB	0.2714	423.63309	23.59918	50.5866
2	26.738	BB	0.5190	413.80804	12.04012	49.4134

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.836	BB	0.2735	2363.40601	130.36607	96.0079
2	26.385	BB	0.5097	98.27366	2.82595	3.9921

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	13.944	50.5866	1	13.836	96.0079
2	26.738	49.4134	2	26.385	3.9921

_N_-((1_R_,2_R_)-2-Cyclohexyl-1-(3-methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)-4-methoxyaniline (247)

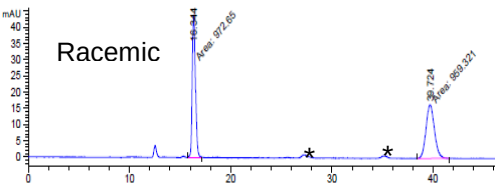


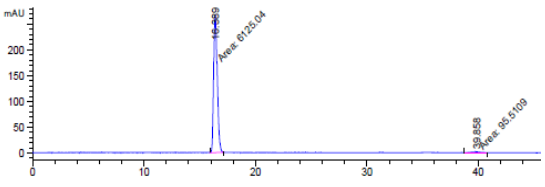
247

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (82:18 d.r. of crude material), column chromatography (4% EtOAc in Hexanes) afforded the title compound as an orange gum (111 mg, 0.225 mmol, 87%, 98:2 e.r.). A pure

sample of the major diastereoisomer was obtained; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (1H, t, *J* = 7.9 Hz, ArC*H*), 6.80 (1H, d, *J* = 7.9 Hz, ArC*H*), 6.75 (1H, s, ArC*H*), 6.63 - 6.71 (3H, m, 3 x ArC*H*), 6.38 (2H, m, 2 x ArC*H*), 5.74 (1H, d, *J* = 3.7 Hz, 1H from C=CH_2), 5.27 (1H, br. s, N*H*), 5.08 (1H, d, *J* = 3.7 Hz, 1H from C=CH_2), 4.63 (1H, d, *J* = 5.2 Hz, C*H*N), 3.76 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 2.23 (1H, dd, *J* = 9.0, 5.2 Hz, C*H*C=CH_2), 1.74 - 1.88 (2H, m, 1H from CH_2 and C*H*), 1.58 - 1.73 (4H, m, 2 x CH_2), 1.30 (6H, s, 2 x CH_3), 1.28 (6H, s, 2 x CH_3), 1.09 - 1.25 (3H, m, 1H from CH_2 and CH_2), 1.01 (1H, qd, *J* = 11.7, 3.0 Hz, CH_2), 0.79 (1H, q, *J* = 10.7 Hz, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (Ar*C*), 150.9 (Ar*C*), 146.0 (Ar*C*), 142.6 (Ar*C*), 134.5 (C=*C*H_2), 128.8 (Ar*C*H), 119.8 (Ar*C*H), 114.7 (Ar*C*H), 113.3 (Ar*C*H), 113.0 (Ar*C*H), 111.4 (Ar*C*H), 83.6 (BO*C*), 61.2 (*C*HC=CH_2), 58.2 (*C*HN), 55.8 (O*C*H_3), 55.1 (O*C*H_3), 36.9 (*C*H), 32.2 (*C*H_2), 31.4 (*C*H_2), 26.6 (*C*H_2), 26.4 (*C*H_2), 26.3 (*C*H_2), 24.9 (*C*H_3), 24.4 (*C*H_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ, 29.3, 22.4; ν_{max} (thin film/cm^{-1}): 3407, 2976, 2925, 2849, 1600, 1511, 1486, 1435, 1371, 1300, 1233, 1168, 1140, 1081, 1042; MS (ES$^+$) *m/z*: 492 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{30}H_{43}NBO_4$ (M+H$^+$): 492.3280. Found: 492.3276; Specific rotation: $[\alpha]_D^{27}$ –28.5 (c 0.82, $CHCl_3$) for an enantiomerically enriched sample of 98:2 e.r.

Enantiomeric purity of **247** was determined by HPLC analysis in comparison with authentic racemic material (98:2 e.r.; Lux 5 µm Amylose-1 column, 99:1 hexanes:*i*PrOH, 0.3 mL/min, 10 °C, 254 nm).





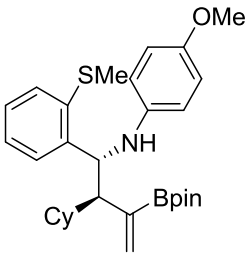
* = minor diastereoisomer

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.344	MM	0.3689	972.65021	43.94279	50.3450
2	39.724	MM	0.9625	959.32123	16.61178	49.6550

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.389	MM	0.3814	6125.04248	267.63364	98.4646
2	39.858	MM	0.9346	95.51088	1.70328	1.5354

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	16.344	50.3450	1	16.389	98.4646
2	39.724	49.6550	2	39.858	1.5354

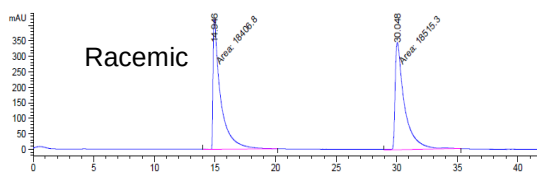
***N*-((1*R*,2*R*)-2-Cyclohexyl-1-(2-(methylthio)phenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)-4-methoxyaniline (249)**

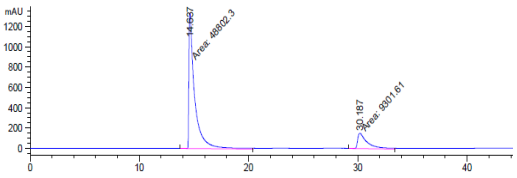


249

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (95:5 d.r. of crude material), column chromatography (3% EtOAc in Hexanes) afforded the title compound as a brown gum (92.0 mg, 0.181 mmol, 70%, 84:16 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 - 7.22 (1H, m, ArC*H*), 7.13 (1H, td, *J* = 7.5, 1.5 Hz, ArC*H*), 7.04 (1H, dd, *J* = 7.5, 1.5 Hz, ArC*H*), 6.93 - 6.98 (1H, m, ArC*H*), 6.67 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 6.32 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 7.72 (1H, br. s, N*H*), 5.66 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 5.10 (1H, d, *J* = 3.8 Hz, C*H*N), 4.88 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 3.68 (3H, s, OCH_3), 2.56 (3H, s, SCH_3), 2.43 (1H, dd, *J* = 10.3, 3.8 Hz, C*H*C=CH_2), 1.90 - 2.08 (2H, m, 1H from CH_2 and C*H*), 1.54 - 1.79 (5H, m, 2 x CH_2 and 1H from CH_2), 1.30 - 1.39 (12H, 2 x s, 2 x (CH_3)$_2$), 1.12 - 1.25 (4H, m, 2 x CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8 (Ar*C*), 142.3 (Ar*C*), 140.9 (Ar*C*), 135.5 (Ar*C*), 135.0 (C=*C*H_2), 128.2 (Ar*C*H), 126.7 (Ar*C*H), 125.0 (Ar*C*H), 124.3 (Ar*C*H), 114.9 (Ar*C*H), 112.9 (Ar*C*H), 83.8 (BO*C*), 57.4 (*C*HC=CH_2), 55.8 (O*C*H_3), 54.7 (*C*HN), 37.1 (*C*H), 33.1 (*C*H_2), 30.5 (*C*H_2), 26.6 (*C*H_2), 26.5 (*C*H_2), 26.4 (*C*H_2), 25.1 (*C*H_3), 24.4 (*C*H_3), 16.1 (S*C*H_3), (*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.5, –4.0; ν_{max} (thin film/cm^{-1}): 3406, 2977, 2922, 2849, 1511, 1439, 1371, 1299, 1278, 1233, 1141, 1039; MS (ES$^+$) *m/z*: 508 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{30}H_{43}NBSO_3$ (M+H$^+$): 508.3051. Found: 508.3057. Specific rotation: $[\alpha]_D^{27}$ –41.1 (c 0.68, $CHCl_3$) for an enantiomerically enriched sample of 84:16 e.r.

Enantiomeric purity of **249** was determined by HPLC analysis in comparison with authentic racemic material (84:16 e.r.; Lux 5 µm Amylose-1 column, 99:1 hexanes:*i*PrOH, 0.3 mL/min, 20 °C, 254 nm).



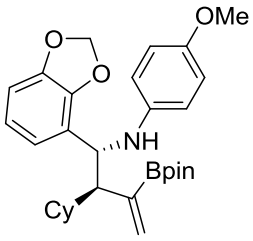


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.946	MM	0.7311	1.84068e4	419.63699	49.8531
2	30.048	MM	0.8911	1.85153e4	346.30432	50.1469

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.637	MM	0.6111	4.88023e4	1331.06421	83.9914
2	30.187	MM	1.0252	9301.60840	151.21303	16.0086

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	14.946	49.8531	1	14.637	83.9914
2	30.048	50.1469	2	30.187	16.0086

_N_-((1_R_,2_R_)-1-(Benzo[d][1,3]dioxol-4-yl)-2-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)-4-methoxyaniline (251)

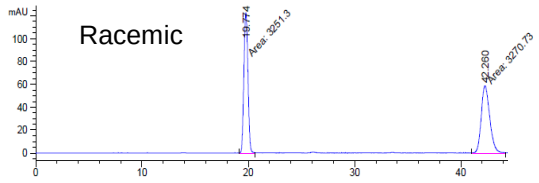


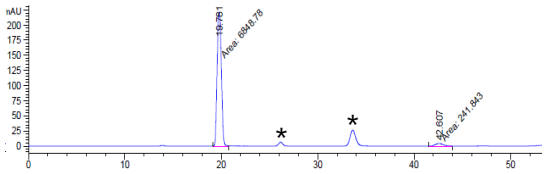
251

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (82:18 d.r. from crude material), column chromatography (10% EtOAc in Hexanes) afforded the title compound as a brown gum (92.0 mg, 0.182 mmol, 71%, 97:3 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 - 6.63 (5H, m, 5 x ArC*H*), 6.31 - 6.37 (2H, m, 2 x ArC*H*), 5.85 (2H, q, *J* = 1.5 Hz, OCH_2O), 5.68 (1H, d, *J* = 3.8 Hz, 1H from C=CH_2), 5.09 - 5.16 (2H, m, 1H from C=CH_2 and 1H from N*H*), 4.78 (1H, d, *J* = 5.5 Hz, C*H*N), 3.61 (3H, s, OCH_3), 2.32 (1H, dd, *J* = 8.8, 5.5 Hz, C*H*C=CH_2), 1.69 - 1.80 (2H, m, 1H from CH_2 and C*H*), 1.50 - 1.64 (4H, m, 2 x CH_2), 1.14 - 1.24 (12H, 2 x s, 2 x (CH_3)$_2$), 0.92 - 1.11 (4H, m, 2 x CH_2), 0.66 - 0.76 (1H, m, 1H from CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0 (Ar*C*), 146.9 (Ar*C*), 144.5 (Ar*C*), 142.4 (Ar*C*), 134.0 (C=*C*H_2), 126.0 (Ar*C*), 121.1 (2 x Ar*C*H), 114.7 (2 x Ar*C*H), 113.3 (2 x Ar*C*H), 106.6 (Ar*C*H), 100.5 (O*C*H_2O), 83.6 (BO*C*), 58.2 (*C*HC=CH_2), 55.8 (O*C*H_3), 53.4 (*C*HN), 36.9 (*C*H), 32.1 (*C*H_2), 31.2 (*C*H_2), 26.6 (*C*H_2), 26.5 (*C*H_2), 26.3 (*C*H_2), 25.0 (*C*H_3), 24.5 (*C*H_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.0, –3.0; ν_{max} (thin film/cm^{-1}): 3406, 2977, 2925, 2650, 1511, 1455, 1371, 1302, 1246, 1141, 1053, 1040; MS

(ES$^+$) *m/z*: 506 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{30}H_{41}NBO_5$ (M+H$^+$): 506.3072. Found: 506.3069. Specific rotation: $[\alpha]_D^{27}$ –17.6 (c 1.11, $CHCl_3$) for an enantiomerically enriched sample of 97:3 e.r.

Enantiomeric purity of **251** was determined by HPLC analysis in comparison with authentic racemic material (97:3 e.r.; Lux 5 µm Amylose-1 column, 99:1 hexanes:*i*PrOH, 0.3 mL/min, 20 °C, 254 nm).



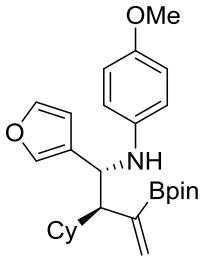


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.774	MM	0.4427	3251.29614	122.41525	49.8510
2	42.260	MM	0.9264	3270.73267	58.84336	50.1490

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.781	MM	0.5149	6848.78125	221.69031	96.5893
2	42.607	MM	0.9592	241.84343	4.20238	3.4107

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	19.774	49.8510	1	19.781	96.5893
2	42.260	50.1490	2	42.607	3.4107

_N_-((1_R_,2_R_)-2-Cyclohexyl-1-(furan-3-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)-4-methoxyaniline (254)

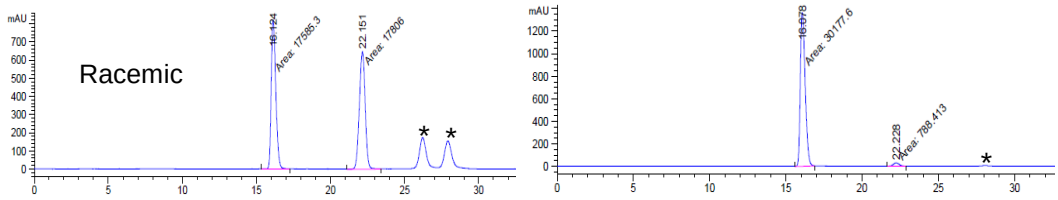


254

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (68:32 d.r. of crude material), column chromatography (3% EtOAc in Hexanes) afforded the title compound as a brown gum (70.0 mg, 0.155 mmol, 60%, 97:3 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (1H, apparent s, ArC*H*), 7.18 (1H, s, ArC*H*), 6.70 (2H, d, *J* = 8.7 Hz, 2 x ArC*H*), 6.47 (2H, d, *J* = 8.7 Hz, 2 x ArC*H*), 6.23 (1H, s, ArC*H*), 5.88 (1H, d, J = 3.5 Hz, 1H from C=CH_2), 5.37 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 4.84 (1H, br. s, N*H*), 4.65 (1H, d, *J* = 6.1 Hz, C*H*N), 3.71 (3H, s, OCH_3), 2.23 (1H, t, *J* = 7.0 Hz, C*H*C=CH_2),

1.60 - 1.77 (6H, m, 2 x CH_2, 1H from CH_2 and CH), 1.26 (6H, s, 2 x CH_3), 1.25 (6H, s, 2 x CH_3), 1.07 - 1.20 (3H, m, CH_2 and 1H from CH_2), 0.99 (1H, qd, J = 12.2, 2.7 Hz, 1H from CH_2), 0.75 - 0.86 (1H, m, 1H from CH_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2 (ArC), 142.6 (ArCH), 142.6 (ArC), 140.1 (ArC), 134.2 (C=CH$_2$), 128.3 (ArCH), 114.7 (ArCH), 113.6 (ArCH), 109.6 (ArCH), 83.5 (BOC), 59.6 (CHC=CH$_2$), 55.8 (OCH$_3$), 50.7 (CHN), 36.9 (CH), 31.7 (CH_2), 31.5 (CH_2), 26.5 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 24.9 (CH_3), 24.4 (CH_3), (BC=CH$_2$ not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.6; ; ν_{max} (thin film/cm^{-1}): 3404, 2976, 2926, 2850, 1516, 1448, 1422, 1371, 1301, 1233, 1142, 1039; MS (ES$^+$) *m/z*: 452 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{27}H_{39}NBO_4$ (M+H$^+$): 452.2972. Found: 452.2976. Specific rotation: $[\alpha]_D^{27}$ –18.7 (c 0.65, $CHCl_3$) for an enantiomerically enriched sample of 97:3 e.r.

Enantiomeric purity of **254** was determined by HPLC analysis in comparison with authentic racemic material (97:3 e.r.; Lux 5 µm Amylose-1 column, 99:1 hexanes:*i*PrOH, 0.3 mL/min, 20 °C, 254 nm).



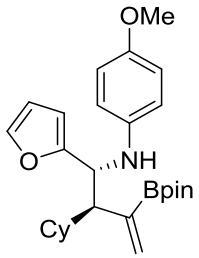
* = minor diastereoisomer

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.124	MM	0.3576	1.75853e4	819.48541	49.6882
2	22.151	MM	0.4587	1.78060e4	646.94922	50.3118

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.078	MM	0.3685	3.01776e4	1364.87659	97.4539
2	22.228	MM	0.4413	788.41272	29.77478	2.5461

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	16.124	49.6882	1	16.078	97.4539
2	22.151	50.3118	2	22.228	2.5461

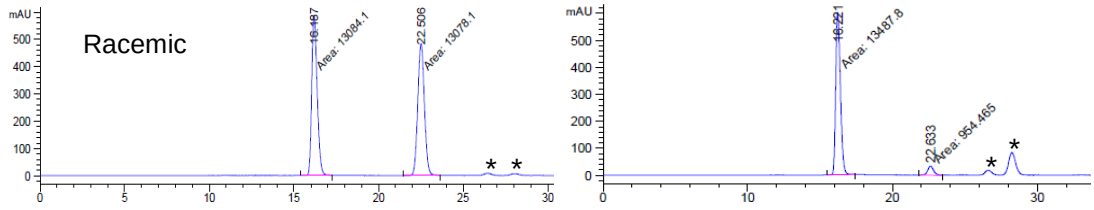
***N*-((1*R*,2*R*)-2-Cyclohexyl-1-(furan-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3- en-1-yl)-4-methoxyaniline (253)**



253

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (68:32 d.r. of crude material), column chromatography (3% EtOAc in Hexanes) afforded the title compound as a mixture of diastereoisomers, as a brown gum (40 mg, 0.0886 mmol, 34%, 93:7 e.r.). Data for the major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (1H, t, *J* = 1.8 Hz, ArC*H*), 7.17 - 7.19 (1H, m, ArC*H*), 6.70 (2H, d, *J* = 9.0 Hz, 2 x ArC*H*), 6.47 (2H, d, *J* = 9.0 Hz, 2 x ArC*H*), 6.23 (1H, dd, *J* = 1.8, 0.8 Hz, ArC*H*), 5.88 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 5.37 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 4.65 (1H, d, *J* = 6.3 Hz, C*H*N), 3.71 (3H, s, OCH_3), 2.23 (1H, dd, *J* = 7.8, 6.3 Hz, C*H*C=CH_2), 1.58 - 1.78 (6H, m, 2 x CH_2, 1H from CH_2 and 1H from C*H*), 1.26 (6H, s, 2 x CH_3), 1.25 (6H, s, 2 x CH_3), 1.08 - 1.18 (3H, m, CH_2 and 1H from CH_2), 0.95 - 1.06 (1H, m, 1H from CH_2), 0.74 - 0.87 (1H, m, 1H from CH_2), (N*H* not observed); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2 (Ar*C*), 142.6 (Ar*C*), 142.6 (Ar*C*H), 140.1 (Ar*C*H), 134.2 (C=*C*H_2), 128.3 (Ar*C*), 114.7 (Ar*C*H), 113.6 (Ar*C*H), 109.6 (Ar*C*H), 83.5 (BO*C*), 59.6 (*C*HC=CH_2), 55.8 (O*C*H_3), 50.7 (*C*HN), 36.9 (*C*H), 31.7 (*C*H_2), 31.5 (*C*H_2), 26.5 (*C*H_2), 26.5 (*C*H_2), 26.4 (*C*H_2), 24.9 (*C*H_3), 24.4 (*C*H_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.3, –4.3; v_{max} (thin film/cm^{-1}): 3404, 2978, 2926, 2851, 1617, 1603, 1511, 1465, 1447, 1422, 1390, 1379, 1371, 1363, 1339, 1301, 1274, 1233, 1214, 1165, 1141, 1113, 1079, 1063, 1039; MS (ES^+) *m/z*: 452 ($M+H^+$). HRMS (ES^+) calcd. for $C_{27}H_{39}NBO_4$ ($M+H^+$): 452.2967. Found: 452.2965. Specific rotation: $[\alpha]_D^{27}$ –9.41 (c 0.18, $CHCl_3$) for an enantiomerically enriched sample of 93:7 e.r.

Enantiomeric purity of **253** was determined by HPLC analysis in comparison with authentic racemic material (93:7 e.r.; Lux 5 µm Amylose-1 column, 99:1 hexanes:*i*PrOH, 0.3 mL/min, 20 °C, 254 nm).



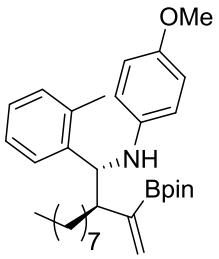
* minor diastereoisomer

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.187	MM	0.3726	1.30841e4	585.24603	50.0114
2	22.506	MM	0.4524	1.30781e4	481.83466	49.9886

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.221	MM	0.3751	1.34878e4	599.31647	93.3912
2	22.633	MM	0.4695	954.46497	33.88182	6.6088

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	16.187	50.0114	1	16.221	93.3912
2	22.506	49.9886	2	22.633	6.6088

4-Methoxy-*N*-((1*R*,2*R*)-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1-(*o*-tolyl) decyl)aniline (257)

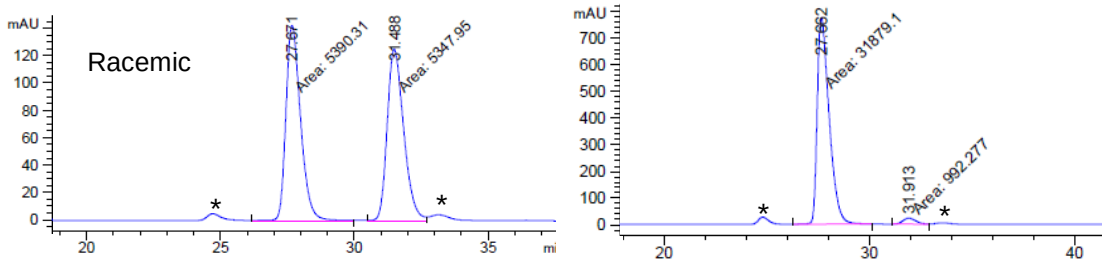


257

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (93:7 d.r. of crude material), column chromatography (5% EtOAc in Hexanes) afforded the title compound as an orange gum (89.0 mg, 0.177 mmol, 69%, 97:3 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 - 7.27 (1H, m, ArC*H*), 7.04 - 7.15 (3H, m, 3 x ArC*H*), 6.62 (2H, d, *J* = 8.4 Hz, 2 x ArC*H*), 6.32 (2H, d, *J* = 8.4 Hz, 2 x ArC*H*), 5.90 (1H, d, *J* = 2.9 Hz, 1H from C=CH_2), 5.44 (1H, d, *J* = 2.9 Hz, 1H from C=CH_2), 4.63 (1H, d, *J* = 7.2 Hz, C*H*N), 4.54 (1H, br. s, N*H*), 3.66 (3H, s, OCH_3), 2.49 (3H, s, Ar-CH_3), 2.33 - 2.44 (1H, m, C*H*C=CH_2), 1.65 - 1.76 (1H, m, 1H from CH_2), 1.26 - 1.37 (3H, m, CH_2 and 1H from CH_2), 1.24 (6H, s, 2 x CH_3), 1.23 (6H, s, 2 x CH_3), 1.01 - 1.21 (10H, m, 5 x CH_2), 0.87 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3 (Ar*C*), 142.6 (Ar*C*), 141.8 (Ar*C*), 135.4 (Ar*C*), 132.8 (C=*C*H_2), 130.0 (Ar*C*H), 126.8 (Ar*C*H), 126.1 (Ar*C*H), 126.0 (Ar*C*H), 114.6 (Ar*C*H), 113.8 (Ar*C*H), 83.4 (BO*C*), 58.1 (*C*HC=CH_2),

55.8 (OCH_3), 54.1 (*C*HN), 31.8 (CH_2), 30.4 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 27.9 (CH_2), 24.8 (CH_3), 24.7 (CH_3), 22.6 (CH_2), 19.6 (Ar-CH_3), 14.1 (CH_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 10.2; ν_{max} (thin film/cm^{-1}): 3406, 2924, 2854, 1606, 1510, 1463, 1417, 1365, 1307, 1237, 1167, 1141, 1110, 1041; MS (ES$^+$) *m/z*: 505 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{32}H_{49}NBO_3Na$ (M+H$^+$): 506.3806. Found: 506.3802. Specific rotation: $[\alpha]_D^{27}$ –35.5 (c 0.91, $CHCl_3$) for an enantiomerically enriched sample of 97:3 e.r.

Enantiomeric purity of **257** was determined by HPLC analysis in comparison with authentic racemic material (97:3 e.r.; Chiralcel OD-H column, 99.5:0.5 hexanes:*i*PrOH, 0.2 mL/min, 20 °C, 254 nm).

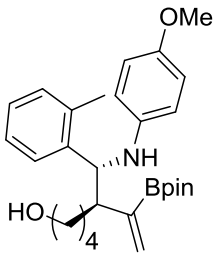


* = minor diastereoisomer

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %	Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.671	MM	0.6318	5390.31396	142.20291	50.1973	1	27.662	MM	0.6747	3.18791e4	787.50946	96.9813
2	31.488	MF	0.7143	5347.94873	124.78006	49.8027	2	31.913	MM	0.7222	992.27704	22.89993	3.0187

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	27.671	50.1973	1	27.662	96.9813
2	31.488	49.8027	2	31.913	3.0187

(*R*)-5-((*R*)-((4-Methoxyphenyl)amino)(*o*-tolyl)methyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-en-1-ol (258)

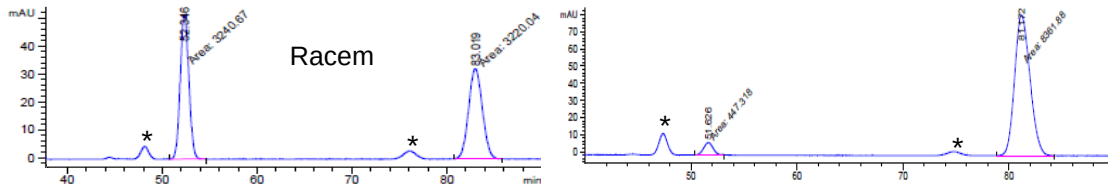


258

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (91:9 d.r. of crude material), column chromatography (2-50% EtOAc in Hexanes) afforded

the title compound as a yellow gum (43.0 mg, 0.093 mmol, 36%, 95:5 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 - 7.15 (4H, m, 4 x ArC*H*), 6.62 (2H, d, *J* = 9.0 Hz, 2 x ArC*H*), 6.33 (2H, d, *J* = 9.0 Hz, 2 x ArC*H*), 5.91 (1H, d, *J* = 3.3 Hz, 1H from C=CH_2), 5.47 (1H, d, *J* = 3.3 Hz, 1H from C=CH_2), 4.63 (1H, d, *J* = 7.5 Hz, C*H*N), 3.66 (3H, s, OCH_3), 3.54 (2H, t, *J* = 6.7 Hz, CH_2OH), 2.48 (3H, s, Ar-CH_3), 2.36 - 2.44 (1H, m, C*H*C=CH_2), 1.69 - 1.78 (1H, m, 1H from CH_2), 1.38 - 1.54 (2H, m, CH_2), 1.28 - 1.32 (1H, m, 1H from CH_2), 1.21 - 1.24 (12H, 2 x s, 2 x (CH_3)$_2$), 1.07 - 1.16 (2H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5 (Ar*C*), 142.5 (Ar*C*), 141.7 (Ar*C*), 135.4 (C=*C*H_2), 132.9 (Ar*C*), 130.2 (Ar*C*H), 126.8 (Ar*C*H), 126.3 (Ar*C*H), 126.1 (Ar*C*H), 114.7 (Ar*C*H), 114.0 (Ar*C*H), 83.6 (BO*C*), 62.8 (*C*H_2OH), 58.1 (O*C*H_3), 55.8 (*C*HN), 54.3 (*C*H), 32.5 (*C*H_2), 30.1 (*C*H_2), 24.8 (*C*H_3), 24.7 (*C*H_3), 24.0 (*C*H_2), 19.6 (Ar-*C*H_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 29.0, –15.0; ν_{max} (thin film/cm^{-1}): 3404, 2976, 2933, 1607, 1501, 1370, 1307, 1237, 1140, 1039; MS (ES$^+$) *m/z*: 466 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{28}H_{41}NBO_4$ (M+H$^+$): 466.3123. Found: 466.3125. Specific rotation: $[\alpha]_D^{27}$ –32.6 (c 0.72, $CHCl_3$) for an enantiomerically enriched sample of 95:5 e.r.

Enantiomeric purity of **258** was determined by HPLC analysis in comparison with authentic racemic material (95:5 e.r.; Lux 5 µm Amylose-1 column, 98:2 hexanes:*i*PrOH, 0.5 mL/min, 20 °C, 254 nm).



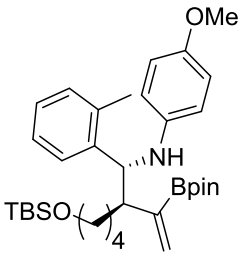
* = minor diastereoisomer

Peak #	RetTime Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	52.346 MM	1.0538	3240.67383	51.25257	50.1597
2	83.019 MM	1.6808	3220.03540	31.92910	49.8403

Peak #	RetTime Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.626 MM	1.0331	447.31760	7.21677	5.0778
2	81.172 MM	1.6938	8361.87988	82.28037	94.9222

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	52.346	50.1597	1	51.626	5.0778
2	83.019	49.8403	2	81.172	94.9222

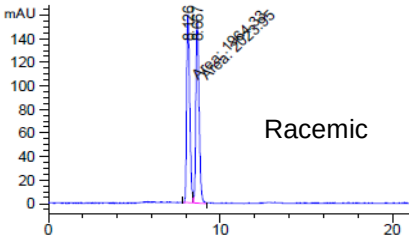
***N*-((1*R*,2*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1-(*o*-tolyl)hexyl)-4-methoxyaniline (259)**

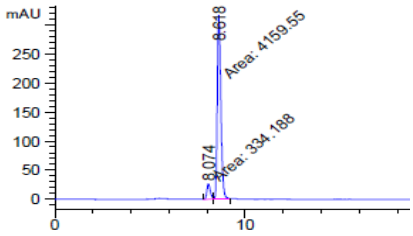


259

Prepared according to General Procedure 1, on a 0.129 mmol scale (93:7 d.r. of crude material), column chromatography (3% EtOAc in Hexanes) afforded the title compound as an orange gum (39.0 mg, 0.0645 mmol, 50%, 93:7 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 - 7.27 (1H, m, ArC*H*), 7.03 - 7.19 (3H, m, 3 x ArC*H*), 6.62 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 6.32 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 5.91 (1H, d, *J* = 3.3 Hz, 1H from C=CH_2), 5.46 (1H, d, *J* = 3.3 Hz, 1H from C=CH_2), 4.64 (1H, d, *J* = 7.3 Hz, C*H*N), 4.51 (1H, br. s, N*H*), 3.66 (3H, s, OCH_3), 3.49 (2H, t, *J* = 6.5 Hz, OCH_2), 2.49 (3H, s, Ar-CH_3), 2.35 - 2.44 (1H, m, C*H*C=CH_2), 1.65 - 1.79 (1H, m, 1H from CH_2), 1.28 - 1.46 (4H, m, 2 x CH_2), 1.23 (6H, s, 2 x CH_3), 1.22 (6H, s, 2 x CH_3), 1.03 - 1.15 (1H, m, 1H from CH_2), 0.88 (9H, s, SiC(CH_3)$_3$), 0.00 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (Ar*C*), 142.5 (Ar*C*), 141.7 (Ar*C*), 135.4 (Ar*C*), 132.8 (C=*C*H_2), 130.1 (Ar*C*H), 126.8 (Ar*C*H), 126.2 (Ar*C*H), 126.1 (Ar*C*H), 114.6 (Ar*C*H), 113.9 (Ar*C*H), 83.4 (BO*C*), 63.1 (O*C*H_2), 58.0 (*C*HN), 55.8 (O*C*H_3), 54.2 (*C*HC=CH_2), 32.6 (*C*H_2), 30.1 (*C*H_2), 26.0 (SiC(*C*H_3)$_3$), 24.8 (*C*H_3), 24.7 (*C*H_3), 24.1 (*C*H_2), 19.6 (Ar-*C*H_3), 18.3 (Si*C*(CH$_3$)$_3$), -5.3 (Si(*C*H_3)$_2$), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 31.0, –3.3; ν_{max} (thin film/cm^{-1}): 3407, 2929, 2857, 1606, 1511, 1463, 1441, 1417, 1379, 1363, 1308, 1237, 1179, 1167, 1141, 1105, 1041, 1005; MS (ES$^+$) *m/z*: 580 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{34}H_{55}NBO_4Si$: 580.3988 (M+H$^+$). Found: 580.3975. Specific rotation: $[\alpha]_D^{27}$ –15.5 (c 0.43, $CHCl_3$) for an enantiomerically enriched sample of 93:7 e.r.

Enantiomeric purity of **259** was determined by HPLC analysis in comparison with authentic racemic material (93:7 e.r.; Lux 5 µm Amylose-1 column, 99.5:0.5 hexanes:*i*PrOH, 0.2 mL/min, 30 °C, 254 nm).



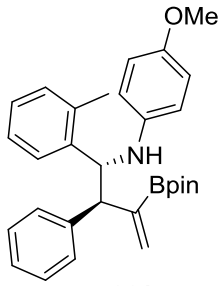


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.126	MF	0.2054	1964.33484	159.41408	49.2527
2	8.667	FM	0.2176	2023.94519	155.00246	50.7473

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.074	MF	0.2111	334.18808	26.39030	7.4367
2	8.618	FM	0.2187	4159.55078	316.92255	92.5633

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	8.126	49.2527	1	8.074	7.4367
2	8.667	50.7473	2	8.618	92.5633

4-Methoxy-*N*-((1*R*,2*S*)-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(*o*-tolyl)but-3-en-1-yl)aniline (261)

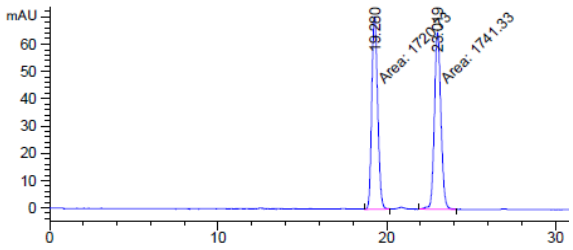


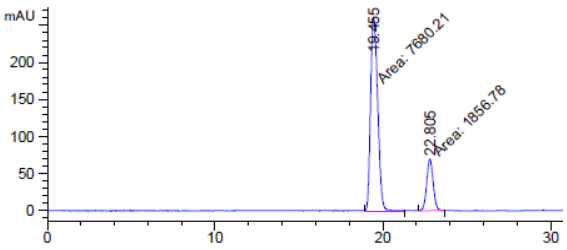
261

To a solution of CuI (2.50 mg, 0.013 mmol, 5.00 mol%) and ligand **L4** (7.30 mg, 0.014 mmol, 5.50 mol%, 81:19 e.r.) in THF (0.80 mL), was added *t*BuOK (0.26 mL, 1.00 M THF solution, 0.258 mmol, 1.0 equiv.), and the reaction was stirred for 85 minutes at room temperature. B_2pin_2 (72.0 mg, 0.284 mmol, 1.1 equiv) in THF (0.75 mL) was then added and the resulting mixture stirred for 50 minutes. The reaction mixture was cooled to –15 °C. A solution of propa-1,2-dien-1-ylbenzene (45.0 mg, 0.387 mmol, 1.5 equiv) and (*E*)-*N*-(4-methoxyphenyl)-1-(*o*-tolyl)methanimine (58.0 mg, 0.258 mmol, 1 equiv.) in THF (1.00 mL) was then added dropwise at –15 °C with stirring overnight. The mixture was then filtered through a silica plug, concentrated *in vacuo* and the crude product mixture (83:17 d.r. of crude material) was purified by column chromatography (3% EtOAc in hexanes) to afford the title compound as a yellow gum (38.0 mg, 0.081 mmol, 32%). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 - 7.27 (3H, m, 3 x ArC*H*), 7.14 (1H, d, *J* = 7.3 Hz, ArC*H*), 7.07 - 7.12 (3H, m, 3 x ArC*H*), 6.98 -

7.07 (2H, m, 2 x ArC*H*), 6.62 (2H, d, *J* = 8.7 Hz, 2 x ArC*H*), 6.30 (2H, d, *J* = 8.7 Hz, 2 x ArC*H*), 5.89 (1H, apparent s, 1H from C=CH_2), 5.72 (1H, apparent s, 1H from C=CH_2), 5.12 (1H, d, *J* = 6.1 Hz, C*H*N), 3.98 (1H, d, *J* = 6.1 Hz, C*H*C=CH_2), 3.83 (1H, br. s, N*H*), 3.67 (3H, s, OCH_3), 2.50 (3H, s, Ar-CH_3), 1.09 (6H, s, 2 x CH_3), 1.02 (6H, s, 2 x CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7 (Ar*C*), 141.6 (Ar*C*), 140.8 (Ar*C*), 139.6 (Ar*C*), 135.3 (Ar*C*), 130.3 (Ar*C*H), 130.1 (C=*C*H_2), 129.8 (Ar*C*H), 127.9 (Ar*C*H), 127.6 (Ar*C*H), 126.6 (Ar*C*H), 126.4 (Ar*C*H), 125.7 (Ar*C*H), 114.6 (Ar*C*H), 114.4 (Ar*C*H), 83.4 (BO*C*), 56.5 (*C*HN), 55.7 (O*C*H_3), 55.3 (*C*HC=CH_2), 24.6 (*C*H_3), 24.4 (*C*H_3), 19.7 (Ar-*C*H_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 29.5, 22.5; ν_{max} (thin film/cm^{-1}): 3061, 3030, 2978, 2907, 1619, 1511, 1452, 1360, 1311, 1239, 1141, 1037; MS (ES$^+$) *m/z*: 470 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{30}H_{37}NBO_3$ (M+H$^+$): 470.2861. Found: 470.2860. Specific rotation: $[\alpha]_D^{27}$ –19.7 (c 0.70, $CHCl_3$) for an enantiomerically enriched sample of 81:19 e.r.

Enantiomeric purity of **261** was determined by HPLC analysis in comparison with authentic racemic material (81:19 e.r.; Lux 5 µm Amylose-1 column, 99:1 hexanes:*i*PrOH, 0.3 mL/min, 20 °C, 254 nm).



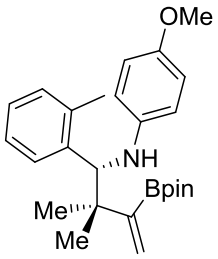


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.280	MM	0.4067	1720.72644	70.50817	49.7025
2	23.019	MM	0.4488	1741.32886	64.66728	50.2975

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.455	MM	0.4907	7680.20605	260.84500	80.5307
2	22.805	MM	0.4455	1856.78381	69.46232	19.4693

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	19.280	49.7025	1	19.455	80.5307
2	23.019	50.2975	2	22.805	19.4693

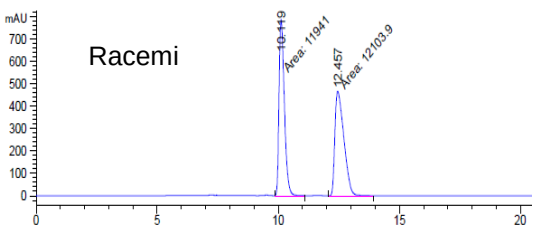
(*R*)-*N*-(2,2-Dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(*o*-tolyl)but-3-en-1-yl)-4-methoxyaniline (269)



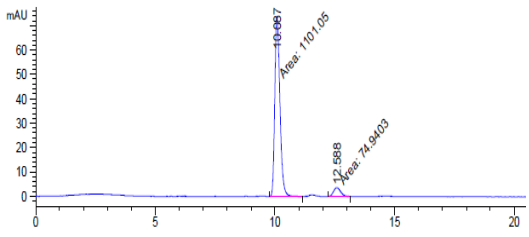
269

Prepared according to General Procedure 2, on a 0.258 mmol scale of imine, column chromatography (3% EtOAc in Hexanes) afforded the title compound as a brown gum (98.0 mg, 0.232 mmol, 90%, 94:6 e.r.). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 - 7.42 (1H, m, ArC*H*), 7.14 - 7.18 (1H, m, ArC*H*), 7.10 - 7.14 (2H, m, 2 x ArC*H*), 6.59 (2H, d, *J* = 8.9 Hz, 2 x ArC*H*), 6.30 (2H, d, *J* = 8.9 Hz, 2 x ArC*H*), 5.97 (1H, d, *J* = 2.6 Hz, 1H from C=CH_2), 5.75 (1H, d, *J* = 2.6 Hz, 1H from C=CH_2), 4.92 (1H, s, C*H*N), 3.97 (1H, br. s, N*H*), 3.65 (3H, s, OCH_3), 2.57 (3H, s, Ar-CH_3), 1.16 (12H, s, 2 x (CH_3)$_2$), 1.09 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.7 (Ar*C*), 142.8 (Ar*C*), 139.3 (Ar*C*), 137.0 (Ar*C*), 130.2 (Ar*C*H), 129.1 (Ar*C*H), 127.7 (C=*C*H$_2$), 126.3 (Ar*C*H), 125.3 (Ar*C*H), 114.5 (Ar*C*H), 114.3 (Ar*C*H), 83.3 (BO*C*), 60.3 (*C*HN), 55.8 (O*C*H$_3$), 44.8 (*C*C=CH$_2$), 26.2 (*C*H$_3$), 24.7 (*C*H$_3$), 24.7 (*C*H$_3$), 20.6 (*C*H$_3$), 20.4 (Ar-*C*H$_3$), (B*C*=CH$_2$ not observed); ^{11}B NMR (160 MHz, $CDCl_3$) δ –2.63; ν_{max} (thin film/cm^{-1}): 2976, 1510, 1464, 1411, 1353, 1302, 1235, 1218, 1145, 1124, 1101, 1039; MS (ES$^+$) *m/z*: 422 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{26}H_{37}NBO_3$ (M+H$^+$): 422.2861. Found: 422.2850. Specific rotation: $[\alpha]_D^{27}$ –55.3 (c 1.06, $CHCl_3$) for an enantiomerically enriched sample of 94:6 e.r.

Enantiomeric purity of **269** was determined by HPLC analysis in comparison with authentic racemic material (94:6 e.r.; Chiralcel OD-H column, 99.5:0.5 hexanes:*i*PrOH, 0.5 mL/min, 20 °C, 254 nm).



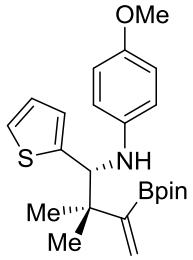
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.119	MM	0.2539	1.19410e4	783.94434	49.6613
2	12.457	MM	0.4331	1.21039e4	465.74948	50.3387



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.087	MM	0.2485	1101.04968	73.84858	93.6275
2	12.588	MM	0.3420	74.94032	3.65226	6.3725

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	10.119	49.6613	1	10.087	93.6275
2	12.457	50.3387	2	12.588	6.3725

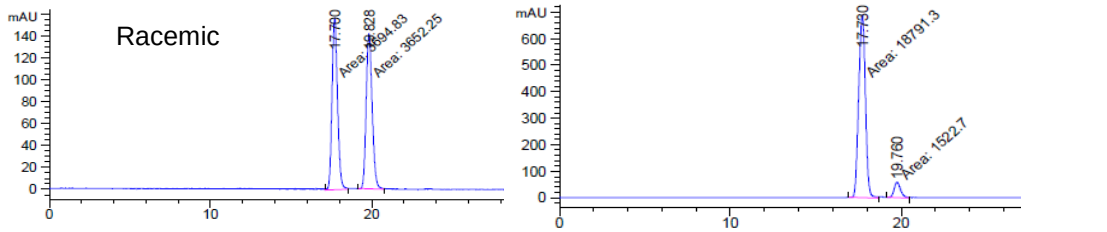
(*R*)-*N*-(2,2-Dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(thiophen-2-yl)but-3-en-1-yl)-4-methoxyaniline (271)



271

Prepared according to General Procedure 2, on a 0.258 mmol scale of imine, column chromatography (5% EtOAc in Hexanes) afforded the title compound as a brown gum (45.0 mg, 0.109 mmol, 42%, 93:7 e.r.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, dd, *J* = 4.8, 1.5 Hz, ArC*H*), 6.86 - 6.92 (2H, m, 2 x ArC*H*), 6.57 (2H, d, *J* = 9.0 Hz, 2 x ArC*H*), 6.38 (2H, d, *J* = 9.0 Hz, 2 x ArC*H*), 5.87 (1H, d, *J* = 2.5 Hz, 1H from C=CH_2), 5.64 (1H, d, *J* = 2.5 Hz, 1H from C=CH_2), 4.75 (1H, d, *J* = 3.3 Hz, C*H*N), 4.01 (1H, d, *J* = 3.3 Hz, N*H*), 3.60 (3H, s, OCH_3), 1.14 (3H, s, CH_3), 1.08 (6H, s, 2 x CH_3), 1.05 (6H, s, 2 x CH_3), 1.03 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (Ar*C*), 147.4 (Ar*C*), 142.3 (Ar*C*), 128.3 (C=*C*H_2), 126.2 (Ar*C*H), 125.1 (Ar*C*H), 123.8 (Ar*C*H), 114.6 (Ar*C*H), 114.5 (Ar*C*H), 83.4 (BO*C*), 62.2 (*C*HN), 55.7 (O*C*H_3), 43.4 (C*C*=CH_2), 26.3 (*C*H_3), 24.7 (*C*H_3), 24.6 (*C*H_3), 21.7 (*C*H_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.3; ν_{max} (thin film/cm^{-1}): 3389, 2976, 2359, 1602, 1503, 1465, 1411, 1372, 1353, 1300, 1235, 1144, 1105, 1039; MS (ES^+) *m/z*: 414 ($M+H^+$). HRMS (ES^+) calcd. for $C_{23}H_{33}NBO_3S$ ($M+H^+$): 414.2269. Found: 414.2259. Specific rotation: $[\alpha]_D^{27}$ –37.4 (c 0.60, $CHCl_3$) for an enantiomerically enriched sample of 93:7 e.r.

Enantiomeric purity of **271** was determined by HPLC analysis in comparison with authentic racemic material (93:7 e.r.; Chiralcel OD-H column, 99:1 hexanes:*i*PrOH, 0.3 mL/min, 20 °C, 254 nm).

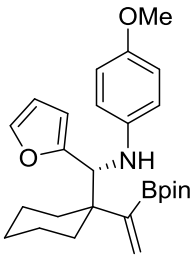


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.700	MM	0.3939	3694.83301	156.32742	50.2898
2	19.828	MM	0.4298	3652.25024	141.62860	49.7102

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.730	MM	0.4536	1.87913e4	690.40002	92.5042
2	19.760	MM	0.4383	1522.70288	57.89712	7.4958

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	17.700	50.2898	1	17.730	92.5042
2	19.828	49.7102	2	19.760	7.4958

(*R*)-*N*-(Furan-2-yl(1-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)cyclohexyl)methyl)-4-methoxyaniline (275)

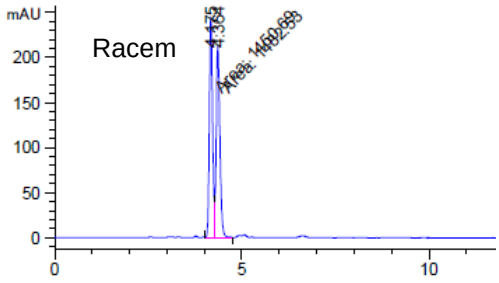


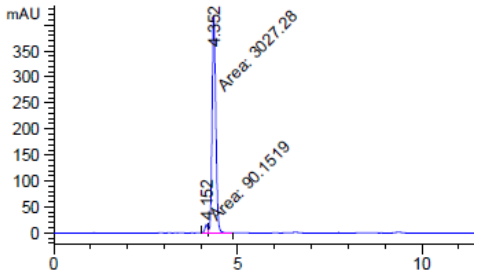
275

Prepared according to General Procedure 2, on a 0.258 mmol scale of imine, column chromatography (5% EtOAc in Hexanes) afforded the title compound as a brown gum (50.0 mg, 0.114 mmol, 44%, 97:3 e.r.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (1H, t, *J* = 1.6 Hz, ArC*H*), 7.22 - 7.24 (1H, m, ArC*H*), 6.65 - 6.70 (2H, m, 2 x ArC*H*), 6.40 - 6.46 (2H, m, 2 x ArC*H*), 6.28 - 6.31 (1H, m, ArC*H*), 6.08 (1H, d, *J* = 2.3 Hz, 1H from C=CH_2), 5.50 (1H, d, *J* = 2.3 Hz, 1H from C=CH_2), 4.87 (1H, br. s, N*H*), 4.06 (1H, s, C*H*N), 3.69 (3H, s, OCH_3), 2.20 - 2.31 (1H, m, CH_2), 2.06 - 2.13 (1H, m, CH_2), 1.32 - 1.56 (7H, m, 3 x CH_2 and 1H from CH_2), 1.30 (12H, s, 2 x (CH_3)$_2$), 1.10 - 1.22 (1H, m, 1H from CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2 (Ar*C*), 141.7 (Ar*C*), 141.0 (Ar*C*), 132.2 (Ar*C*H), 125.6 (C=*C*H_2), 122.0 (Ar*C*H), 114.7 (Ar*C*H), 113.7 (Ar*C*H), 111.6 (Ar*C*H), 83.7 (BO*C*), 61.2 (*C*HN), 55.8 (O*C*H_3), 46.4 (*C*C=CH_2), 34.2 (*C*H_2), 32.0 (*C*H_2), 26.6 (*C*H_2), 24.7 (*C*H_3), 24.7 (*C*H_3), 22.5 (*C*H_2), 22.0 (*C*H_2), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ –2.94; ν_{max} (thin film/cm^{-1}): 3410, 2975, 2931, 2855, 1631, 1511, 1453, 1371, 1244, 1142, 1119, 1036; MS (ES$^+$) *m/z*: 438 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{26}H_{37}NBO_4$ (M+H$^+$):

438.2816. Found: 438.2824. Specific rotation: $[\alpha]_D^{27}$ –11.2 (c 0.45, $CHCl_3$) for an enantiomerically enriched sample of 97:3 e.r.

Enantiomeric purity of **275** was determined by HPLC analysis in comparison with authentic racemic material (97:3 e.r.; Lux 5 µm Amylose-1 column, 99:1 hexanes:*i*PrOH, 1.2 mL/min, 40 °C, 254 nm).



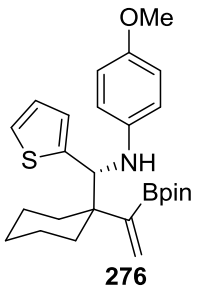


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.175	MF	0.0985	1450.68689	245.41954	49.4572
2	4.364	FM	0.1160	1482.52991	213.09689	50.5428

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.152	MF	0.0966	90.15189	15.55558	2.8919
2	4.352	FM	0.1208	3027.27515	417.54025	97.1081

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	4.175	49.4572	1	4.152	2.8919
2	4.364	50.5428	2	4.352	97.1081

(*R*)-4-Methoxy-*N*-((1-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)cyclohexyl)(thiophen-2-yl)methyl)aniline (276)

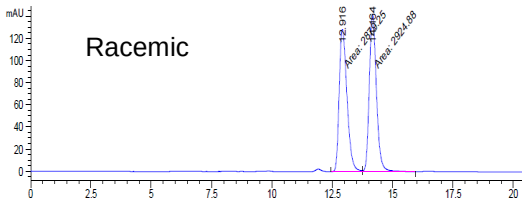


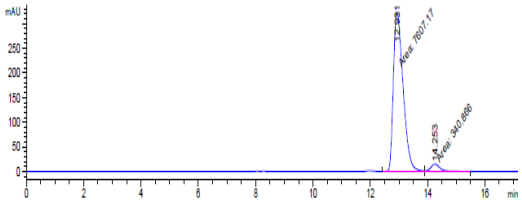
276

Prepared according to general Procedure 2, on a 0.258 mmol scale of imine, column chromatography (3% EtOAc in Hexanes) afforded the title compound as a brown gum (40.0 mg, 0.0882 mmol, 34%, 96:4 e.r.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (1H, dd, *J* = 4.8, 1.5 Hz, ArC*H*), 6.91 - 6.96 (2H, m, 2 x ArC*H*), 6.63 - 6.70 (2H, m, 2 x ArC*H*), 6.40 - 6.47 (2H, m, 2 x ArC*H*), 6.11 (1H, d, *J* = 2.3 Hz, 1H from C=CH_2), 5.52 (1H, d, *J* = 2.3 Hz, 1H from C=CH_2), 5.22 (1H, d, *J* = 4.3 Hz, N*H*),

4.35 (1H, d, *J* = 4.3 Hz, C*H*N), 3.68 (3H, s, OCH_3), 2.24 - 2.33 (1H, m, 1H from CH_2), 2.13 - 2.22 (1H, m, 1H from CH_2), 1.35 - 1.58 (7H, m, 3 x CH_2 and 1H from CH_2), 1.31 (6H, s, 2 x CH_3), 1.31 (6H, s, 2 x CH_3), 1.08 - 1.22 (1H, m, 1H from CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (Ar*C*), 147.3 (Ar*C*), 142.7 (Ar*C*), 132.8 (Ar*C*H), 126.0 (C=*C*H_2), 125.3 (Ar*C*H), 123.7 (Ar*C*H), 114.6 (Ar*C*H), 113.7 (Ar*C*H), 83.8 (BO*C*), 65.4 (*C*HN), 55.7 (O*C*H_3), 46.7 (*C*C=CH_2), 34.4 (*C*H_2), 31.7 (*C*H_2), 26.5 (*C*H_2), 24.7 (*C*H_3), 24.7 (*C*H_3), 22.5 (*C*H_2), 22.1 (*C*H_2), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 6.4; ν_{max} (thin film/cm^{-1}): 3405, 2975, 2930, 2855, 1616, 1510, 1451, 1371, 1296, 1275, 1246, 1194, 1141, 1118, 1036; MS (ES$^+$) *m/z*: 454 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{26}H_{37}NBO_3S$ (M+H$^+$): 454.2587. Found: 454.2568. Specific rotation: $[\alpha]_D^{27}$ –1.69 (c 0.71, $CHCl_3$) for an enantiomerically enriched sample of 96:4 e.r.

Enantiomeric purity of **276** was determined by HPLC analysis in comparison with authentic racemic material (96:4 e.r.; Chiralcel OD-H column, 99.5:0.5 hexanes:***i***PrOH, 0.5 mL/min, 20 °C, 254 nm).



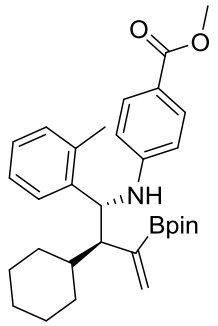


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.916	MF	0.3736	2879.25024	128.42960	49.6069
2	14.164	FM	0.3436	2924.88232	141.87025	50.3931

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.931	MF	0.3940	7607.16553	321.78543	95.7113
2	14.253	FM	0.3801	340.86597	14.94472	4.2887

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	12.916	49.6069	1	12.931	95.7113
2	14.164	50.3931	2	14.253	4.2887

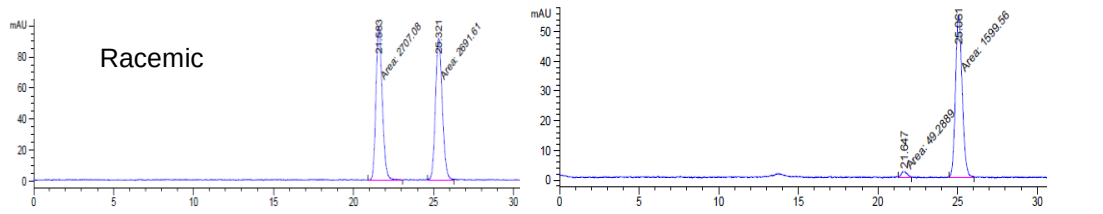
Methyl 4-(((1*R*,2*R*)-2-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(*o*-tolyl)but-3-en-1-yl)amino)benzoate (279)



279

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (93:7 d.r. from crude material), column chromatography (5-10% EtOAc in Hexanes) afforded the title compound as a yellow gum (112 mg, 0.223 mmol, 86%, 97:3 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 7.11 - 7.16 (1H, m, ArC*H*), 7.06 (1H, td, *J* = 7.3, 1.5 Hz, ArC*H*), 6.99 (1H, td, *J* = 7.3, 1.4 Hz, ArC*H*), 6.90 - 6.95 (1H, m, ArC*H*), 6.62 (1H, br. s, N*H*), 6.33 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 5.72 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 5.02 (1H, d, *J* = 4.1 Hz, C*H*N), 4.89 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 3.81 (3H, s, CO_2CH_3), 2.48 (3H, s, Ar-CH_3), 2.25 (1H, dd, *J* = 10.2, 4.1 Hz, C*H*C=CH_2), 1.89 - 2.02 (2H, m, CH_2), 1.64 - 1.78 (4H, m, 2 x CH_2), 1.38 (6H, s, 2 x CH_3), 1.34 (6H, s, 2 x CH_3), 1.13 - 1.24 (3H, m, CH_2 and C*H*), 0.98 - 1.10 (1H, m, 1H from CH_2), 0.79 - 0.84 (1H, m, 1H from CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4 (*C*=O), 151.8 (Ar*C*), 139.8 (Ar*C*), 135.9 (C=*C*H_2), 134.2 (Ar*C*), 131.4 (Ar*C*H), 130.3 (Ar*C*H), 127.5 (Ar*C*H), 126.3 (Ar*C*H), 125.5 (Ar*C*H), 117.0 (Ar*C*), 111.2 (Ar*C*H), 84.1 (BO*C*), 58.0 (*C*HC=CH_2), 53.7 (*C*HN), 51.4 (CO_2CH_3), 37.0 (*C*H), 33.1 (*C*H_2), 30.9 (*C*H_2), 26.5 (*C*H_2), 26.4 (*C*H_2), 26.3 (*C*H_2), 25.1 (*C*H_3), 24.4 (*C*H_3), 19.1 (Ar-*C*H_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.0; ν_{max} (thin film/cm^{-1}): 3397, 2977, 2927, 2851, 1602, 1531, 1358, 1311, 1276, 1216, 1141, 1090; MS (ES$^+$) *m/z*: 504 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{31}H_{43}NBO_4$ (M+H$^+$): 504.3280. Found: 504.3271. Specific rotation: $[\alpha]_D^{27}$ –27.2 (c 1.64, $CHCl_3$) for an enantiomerically enriched sample of 97:3 e.r.

Enantiomeric purity of **279** was determined by HPLC analysis in comparison with authentic racemic material (97:3 e.r.; Chiralpak IA column, 99:1 hexanes:*i*PrOH, 0.3 mL/min, 20 °C, 254 nm).

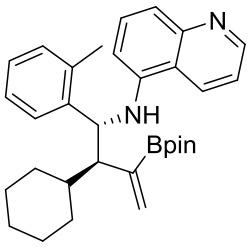


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.583	MM	0.4572	2707.08179	98.67846	50.1433
2	25.321	MM	0.4942	2691.61182	90.77528	49.8567

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.647	MM	0.4278	49.28886	1.92009	2.9893
2	25.061	MM	0.4884	1599.55957	54.58958	97.0107

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	21.583	50.1433	1	21.647	2.9893
2	25.321	49.8567	2	25.061	97.0107

_N_-((1_R_,2_R_)-2-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(_o_-tolyl)but-3-en-1-yl)quinolin-5-amine (280)

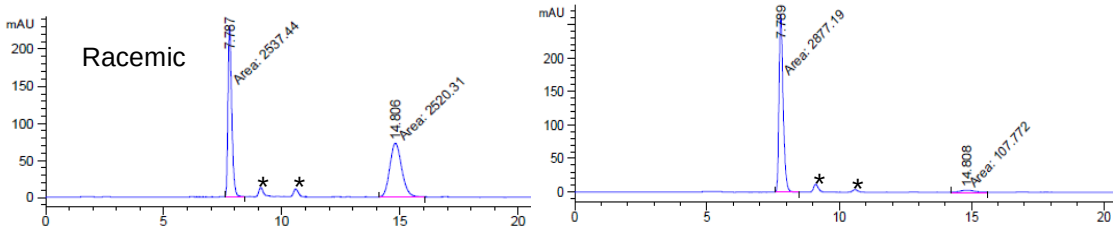


280

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (94:6 d.r. of crude material), column chromatography (10% EtOAc in Hexanes) afforded the title compound as a brown gum (87.0 mg, 0.175 mmol, 68%, 96:4 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (1H, dd, *J* = 4.3, 1.5 Hz, ArC*H*), 8.64 (1H, dd, *J* = 8.5, 1.5 Hz, ArC*H*), 7.30 - 7.36 (3H, m, 3 x ArC*H*), 7.16 (1H, d, *J* = 7.5 Hz, ArC*H*), 7.06 (1H, m, ArC*H*), 6.93 - 7.01 (2H, m, 2 x ArC*H*), 6.50 (1H, d, *J* = 5.1 Hz, N*H*), 6.08 (1H, dd, *J* = 5.7, 3.1 Hz, ArC*H*), 5.73 (1H, d, *J* = 3.3 Hz, 1H from C=CH_2), 5.10 (1H, t, *J* = 5.1 Hz, C*H*N), 4.89 (1H, d, *J* = 3.3 Hz, 1H from C=CH_2), 2.53 (3H, s, Ar-CH_3), 2.37 (1H, dd, *J* = 10.5, 5.1 Hz, C*H*C=CH_2), 1.93 - 2.08 (2H, m, 1H from CH_2 and C*H*), 1.60 - 1.77 (5H, m, 2 x CH_2 and 1H from CH_2), 1.41 (6H, s, 2 x CH_3), 1.38 (6H, s, 2 x CH_3), 1.16 - 1.29 (3H, m, 1H from CH_2 and CH_2), 0.80 - 0.92 (1H, m, 1H from CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7 (Ar*C*-N), 149.3 (Ar*C*H), 143.6 (Ar*C*), 134.0 (Ar*C*), 136.2 (C=*C*H_2), 134.2 (Ar*C*), 130.8 (Ar*C*H), 130.4 (Ar*C*H), 129.8 (Ar*C*H), 127.3 (Ar*C*H), 126.3 (Ar*C*H), 125.5 (Ar*C*H), 118.6 (Ar*C*), 118.4 (Ar*C*H), 116.8 (Ar*C*H), 104.6 (Ar*C*H), 84.2

(BO*C*), 57.7 (*C*HC=CH_2), 54.8 (*C*HN), 37.3 (*C*H), 33.3 (CH_2), 30.7 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 26.4 (CH_2), 25.1 (CH_3), 24.3 (CH_3), 19.1 (Ar-CH_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.0, –6.0; ν_{max} (thin film/cm^{-1}): 3421, 2976, 2925, 2850, 2244, 1587, 1535, 1415, 1371, 1330, 1140; MS (ES^+) *m/z*: 497 ($M+H^+$). HRMS (ES^+) calcd. for $C_{32}H_{42}N_2BO_2$ ($M+H^+$): 497.3334. Found: 497.3346. Specific rotation: $[\alpha]_D^{27}$ –129 (c 0.33, $CHCl_3$) for an enantiomerically enriched sample of 96:4 e.r.

Enantiomeric purity of **280** was determined by HPLC analysis in comparison with authentic racemic material (96:4 e.r.; Lux 5 µm Amylose-1 column, 95:5 hexanes:*i*PrOH (+1% diethylamine), 0.5 mL/min, 20 °C, 254 nm).



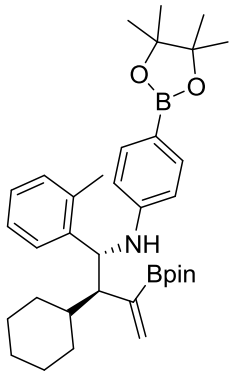
* = minor diastereoisomer

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.787	MM	0.1834	2537.44141	230.55040	50.1693
2	14.806	MM	0.5804	2520.31274	72.37698	49.8307

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.789	MM	0.1805	2877.18848	265.65210	96.3895
2	14.808	MM	0.5766	107.77163	3.11503	3.6105

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	7.787	50.1693	1	7.789	96.3895
2	14.806	49.8307	2	14.808	3.6105

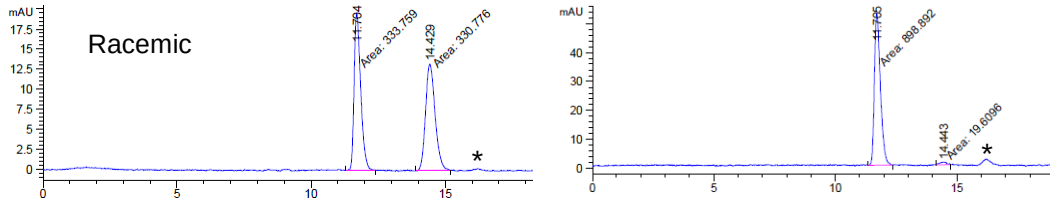
***N*-((1*R*,2*R*)-2-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(*o*-tolyl)but-3-en-1-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (281)**



281

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (94:6 d.r. of crude material), column chromatography (3% EtOAc in Hexanes) afforded the title compound as a yellow foam (102 mg, 0.179 mmol, 69%, 98:2 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (2H, d, *J* = 8.5 Hz, 2 x ArC*H*), 7.07 - 7.12 (1H, m, ArCH), 7.01 (1H, m, ArCH), 6.95 (2H, d, *J* = 3.8 Hz, 2 x ArCH), 6.33 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 6.24 - 6.28 (1H, apparent m, N*H*), 5.68 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 4.95 - 5.01 (1H, m, C*H*N), 4.88 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 2.45 (3H, s, Ar-CH_3), 2.23 (1H, dd, *J* = 10.3, 4.0 Hz, C*H*C=CH_2), 1.87 - 2.03 (2H, m, CH_2), 1.60 - 1.73 (4H, m, 2 x CH_2), 1.23 - 1.39 (24H, m, 8 x CH_3), 1.09 - 1.23 (3H, m, CH_2 and C*H*), 0.94 - 1.05 (1H, m, 1H from CH_2), 0.73 - 0.84 (1H, m, 1H from CH_2), ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5 (Ar*C*), 140.3 (Ar*C*), 136.2 (Ar*C*H), 135.4 (C=*C*H_2), 134.2 (Ar*C*), 130.1 (Ar*C*H), 127.6 (Ar*C*H), 126.0 (Ar*C*H), 125.5 (Ar*C*H), 111.5 (Ar*C*H), 83.9 (BO*C*), 83.0 (BO*C*), 58.0 (*C*HC=CH_2), 53.5 (*C*HN), 36.9 (*C*H), 33.1 (*C*H_2), 30.9 (*C*H_2), 26.6 (*C*H_2), 26.5 (*C*H_2), 26.4 (*C*H_2), 25.0 (*C*H_3), 24.8 (*C*H_3), 24.8 (*C*H_3), 24.4 (*C*H_3), 19.1 (Ar-*C*H_3), (B*C*=CH_2 and Ar*C*-Bpin not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 30.0, –17.0; ν_{max} (thin film/cm^{-1}): 3397, 2977, 2927, 2851, 1602, 1358, 1311, 1275, 1216, 1141, 1090; MS (ES^+) m/z: 572 ($M+H^+$). HRMS (ES^+) calcd. for $C_{35}H_{52}NB_2O_4$ ($M+H^+$): 572.4077. Found: 572.4079. Specific rotation: $[\alpha]_D^{27}$ –23.3 (c 1.45, $CHCl_3$) for an enantiomerically enriched sample of 98:2 e.r.

Enantiomeric purity of **281** was determined by HPLC analysis in comparison with authentic racemic material (98:2 e.r.; Lux 5 µm Amylose-1 column, 99:1 hexanes:*i*PrOH, 0.3 mL/min, 20 °C, 254 nm).



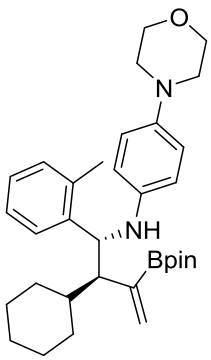
* = minor diastereoisomer

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.704	MM	0.2838	333.75864	19.60228	50.2244
2	14.429	MM	0.4140	330.77625	13.31750	49.7756

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.705	MM	0.2857	898.89154	52.43394	97.8650
2	14.443	MM	0.3340	19.60959	9.78414e-1	2.1350

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	11.704	50.2244	1	11.705	97.8650
2	14.429	49.7756	2	14.443	2.1350

_N_-((1_R_,2_R_)-2-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(_o_-tolyl)but-3-en-1-yl)-4-morpholinoaniline (283)

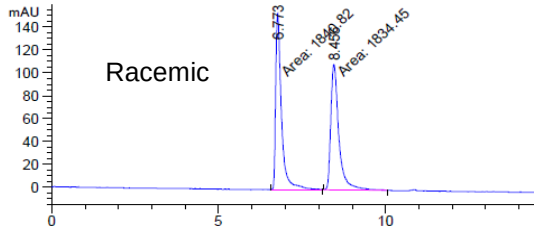


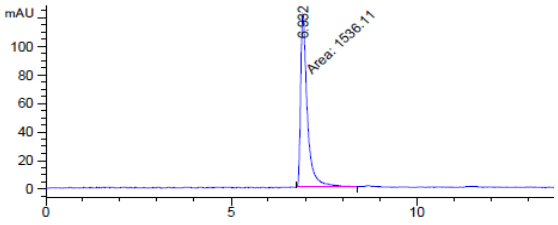
283

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (>95:5 d.r. of crude material), column chromatography (10-20% EtOAc in Hexanes) afforded the title compound as a yellow/green gum (125 mg, 0.235 mmol, 91%, 99:1 e.r.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 - 7.14 (1H, m, ArC*H*), 6.97 - 7.07 (3H, m, 3 x ArC*H*), 6.72 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 6.33 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 5.71 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 5.58 (1H, br. s, N*H*), 4.87 - 4.93 (2H, m, 1H from C=CH_2 and C*H*N), 3.80 - 3.85 (4H, m, 2 x CH_2), 2.88 - 2.98 (4H, m, 2 x CH_2), 2.47 (3H, s, Ar-CH_3), 2.21 (1H, dd, *J* = 10.0, 3.8 Hz, C*H*C=CH_2), 1.92 - 2.07 (2H, m, 1H from CH_2 and C*H*), 1.58 - 1.74 (5H, m, 2 x CH_2 and 1H from CH_2), 1.30 - 1.38 (12H, 2 x s, 2 x (CH_3)$_2$), 1.13 - 1.24 (2H, m, CH_2), 0.97 - 1.08 (1H, m, 1H from CH_2), 0.73 - 0.85 (1H, m, 1H from CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0 (Ar*C*), 142.1 (Ar*C*), 141.0 (Ar*C*), 134.9 (C=*C*H_2), 134.2 (Ar*C*), 130.1 (Ar*C*H), 127.9 (Ar*C*H), 125.9

(Ar*C*H), 125.4 (Ar*C*H), 118.5 (Ar*C*H), 112.9 (Ar*C*H), 83.7 (BO*C*), 67.2 (*C*HC=CH_2), 58.2 (CH_2), 51.5 (CH_2), 37.0 (*C*H), 33.1 (CH_2), 31.0 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 25.1 (CH_3), 24.4 (CH_3), 19.1 (Ar-*C*H_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.0, –1.0; ν_{max} (thin film/cm^{-1}): 3408, 2924, 2851, 1514, 1421, 1371, 1299, 1218, 1140, 1069; MS (ES^+) m/z: 531 ($M+H^+$). HRMS (ES^+) calcd. for $C_{33}H_{48}N_2BO_3$ ($M+H^+$): 531.3753. Found: 531.3756. Specific rotation: $[\alpha]_D^{27}$ –31.1 (c 1.19, $CHCl_3$) for an enantiomerically enriched sample of >99:1 e.r.

Enantiomeric purity of **283** was determined by HPLC analysis in comparison with authentic racemic material (>99:1 e.r.; Lux 5 µm Amylose-1 column, 98:2 hexanes:*i*PrOH, 0.7 mL/min, 20 °C, 254 nm).



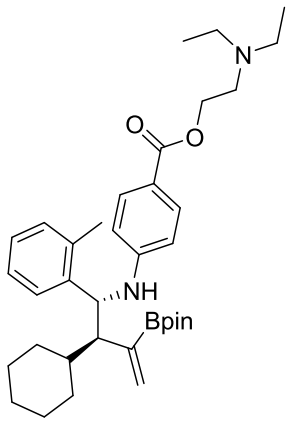


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.773	MM	0.1998	1840.81885	153.54163	50.0867
2	8.456	MM	0.2794	1834.44800	109.41995	49.9133

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.932	MM	0.2117	1536.11475	120.93266	100.0000

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	6.773	50.0867	1	6.932	100.0000
2	8.456	49.9133	2	-	-

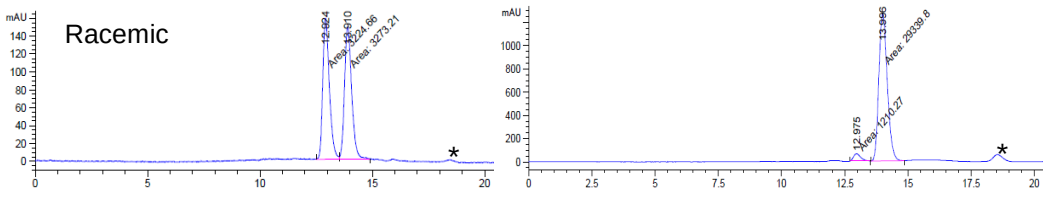
2-(Diethylamino)ethyl 4-(((1*R*,2*R*)-2-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(*o*-tolyl)but-3-en-1-yl)amino)benzoate (286)



286

Prepared according to General Procedure 1, on a 0.258 mmol scale of imine (94:6 d.r. of crude material), column chromatography (10-100% EtOAc in Hexanes) afforded the title compound as a yellow gum (48.0 mg, 0.081 mmol, 31%, 96:4 e.r.). A pure sample of the major diastereoisomer was obtained; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 7.10 - 7.14 (1H, m, ArC*H*), 7.05 (1H, td, *J* = 7.4, 1.5 Hz, ArC*H*), 6.95 - 7.01 (1H, m, ArC*H*), 6.87 - 6.94 (1H, m, ArC*H*), 6.66 (1H, d, *J* = 5.7 Hz, N*H*), 6.31 (2H, d, *J* = 8.8 Hz, 2 x ArC*H*), 5.69 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 5.00 (1H, dd, *J* = 5.7, 4.4 Hz, C*H*N), 4.86 (1H, d, *J* = 3.5 Hz, 1H from C=CH_2), 4.30 (2H, t, *J* = 6.3 Hz, OCH_2), 2.81 (2H, t, *J* = 6.3 Hz, OCH_2CH_2), 2.62 (4H, q, *J* = 7.2 Hz, 2 x CH_2CH_3), 2.46 (3H, s, Ar-CH_3), 2.22 (1H, dd, *J* = 10.3, 4.4 Hz, C*H*C=CH_2), 1.56 - 2.00 (9H, m, 4 x CH_2 and C*H*), 1.32 - 1.41 (12H, 2 x s, 4 x CH_3), 1.13 - 1.26 (2H, m, CH_2), 1.06 (6H, t, *J* = 7.2 Hz, 2 x CH_2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (*C*=O), 151.8 (Ar*C*), 139.7 (Ar*C*), 136.0 (C=*C*H_2), 134.2 (Ar*C*), 131.5 (Ar*C*H), 130.3 (Ar*C*H), 127.5 (Ar*C*H), 126.3 (Ar*C*H), 125.5 (Ar*C*H), 117.0 (Ar*C*), 111.2 (Ar*C*H), 84.1 (BO*C*), 62.3 (O*C*H_2), 58.0 (*C*HC=CH_2), 53.7 (*C*HN), 51.0 (OCH_2CH_2), 47.7 (CH_2CH_3), 36.9 (*C*H), 33.1 (*C*H_2), 30.8 (*C*H_2), 26.5 (*C*H_2), 26.4 (*C*H_2), 26.3 (*C*H_2), 25.1 (*C*H_3), 24.4 (*C*H_3), 19.1 (Ar-*C*H_3), 12.0 (CH_2CH_3), (B*C*=CH_2 not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ –6.0, 30.0; ν_{max} (thin film/cm^{-1}): 3384, 2972, 2927, 2850, 1702, 1601, 1527, 1447, 1371, 1301, 1269, 1171, 1140, 1106, 1075; MS (ES$^+$) *m/z*: 589 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{36}H_{54}N_2BO_4$ (M+H$^+$): 589.4171. Found: 589.4177. Specific rotation: $[\alpha]_D^{27}$ –36.5 (c 0.49, $CHCl_3$) for an enantiomerically enriched sample of 96:4 e.r.

Enantiomeric purity of **286** was determined by HPLC analysis in comparison with authentic racemic material (96:4 e.r.; Lux 5 µm Amylose-1 column, 94:6 hexanes:*i*PrOH (+0.1% diethylamine), 0.3 mL/min, 10 °C, 220 nm).



* = minor diastereoisomer

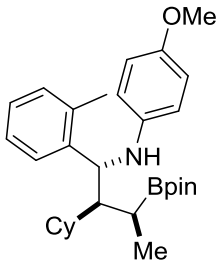
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.924	MF	0.3406	3224.65918	157.80739	49.6264
2	13.910	FM	0.3682	3273.21338	148.15764	50.3736

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.975	MM	0.3265	1210.26660	61.78379	3.9616
2	13.996	MM	0.3865	2.93398e4	1265.30859	96.0384

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	12.924	49.6264	1	12.975	3.9616

2	13.910	50.3736	2	13.996	96.0384

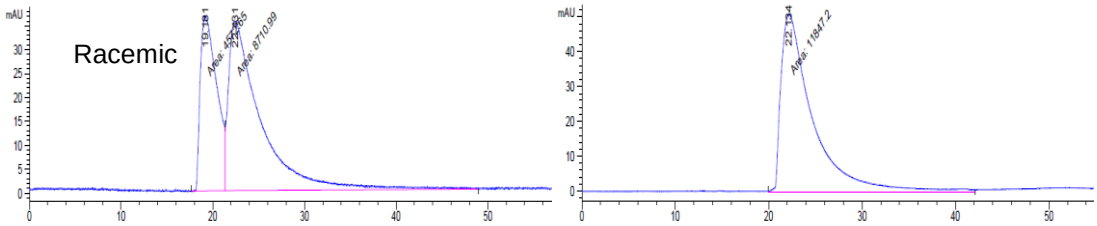
***N*-((1*R*,2*S*,3*S*)-2-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(*o*-tolyl)butyl)-4-methoxyaniline (294)**



294

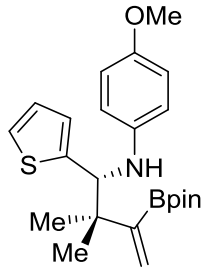
A suspension of *N*-((1*R*,2*R*)-2-cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(*o*-tolyl)but-3-en-1-yl)-4-methoxyaniline (**237**) (30.0 mg, 0.063 mmol, 1.0 equiv, 98:2 e.r., >95:5 d.r.) and palladium (6.70 mg, 10 wt.% loading on carbon) in ethanol (1.00 mL) was stirred for 16 hours at 20 °C in a Parr reactor at 49 bar of H_2. The reaction mixture was filtered through a pad of Celite® and concentrated in vacuo. The crude product mixture (>95:5 d.r.) was purified by column chromatography on silica gel (5% EtOAc in hexanes) to afford the title compound as a colourless gum (16.0 mg, 0.034 mmol, 54%, >99:1 e.r.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.39 (1H, m, ArC*H*), 7.06 - 7.15 (3H, m, 3 x ArC*H*), 6.66 (2H, d, *J* = 9.0 Hz, 2 x ArC*H*), 6.29 (2H, d, *J* = 9.0 Hz, 2 x ArC*H*), 5.45 (1H, br. s, N*H*), 4.73 (1H, apparent s, C*H*N), 3.68 (3H, s, OCH_3), 2.41 (3H, s, 3 x Ar-CH_3), 1.95 (1H, d, *J* = 12.5 Hz, 1H from CH_2), 1.61 - 1.86 (5H, m, 2 x CH_2 and C*H*), 1.50 (1H, dd, *J* = 9.3, 3.8 Hz, C*H*CH(CH_3)), 1.35 - 1.42 (1H, m, C*H*(CH_3)), 1.33 (12H, s, 4 x CH_3), 1.10 - 1.21 (3H, m, CH_2 and 1H from CH_2), 0.96 - 1.09 (2H, m, CH_2), 0.75 (3H, d, *J* = 7.8 Hz, CH(CH_3)); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9 (Ar*C*), 142.3 (Ar*C*), 141.2 (Ar*C*), 134.8 (Ar*C*), 130.6 (Ar*C*H), 127.4 (Ar*C*H), 126.1 (Ar*C*H), 125.7 (Ar*C*H), 114.8 (Ar*C*H), 113.3 (Ar*C*H), 83.4 (BO*C*), 55.8 (OCH_3), 55.3 (*C*HN), 53.0 (*C*HCH(CH_3)), 39.5 (*C*H), 32.9 (*C*H_2), 31.5 (*C*H_2), 26.7 (*C*H_2), 26.7 (*C*H_2), 26.5 (*C*H_2), 25.1 (*C*H_3), 25.0 (*C*H_3), 19.3 (Ar-*C*H_3), 18.5 (CH(*C*H_3)) (B*C*H(CH_3) not observed); ^{11}B NMR (128 MHz, CDCl3) δ 34.3, –5.5; ν_{max} (thin film/cm^{-1}): 3405, 2924, 2851, 1511, 1461, 1371, 1306, 1233, 1142, 1110, 1041; MS (ES$^+$) *m/z*: 478 (M+H$^+$). HRMS (ES$^+$) calcd. for $C_{30}H_{45}NBO_3$ (M+H$^+$): 478.3487. Found: 478.3469; Specific rotation: $[\alpha]_D^{28}$ –14.9 (c 0.78, $CHCl_3$) for an enantiomerically enriched sample of >99:1 e.r.

Enantiomeric purity of **294** was determined by HPLC analysis in comparison with authentic racemic material (>99:1 e.r.; Lux 5 µm Amylose-1 column, 100% hexanes, 0.5 mL/min, 20 °C, 254 nm).

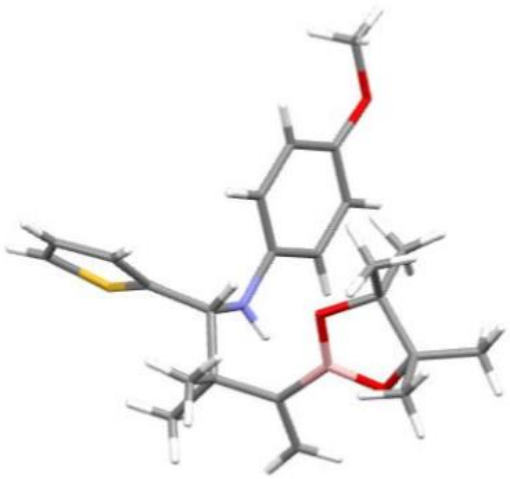


X-ray structure:

(*R*)-*N*-(2,2-Dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(thiophen-2-yl)but-3-en-1-yl)-4-methoxyaniline (**271**)



CCDC 1489264

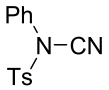


13.3 Cyanoborylation of Allenes

General Procedure 3

To a solution of CuI (2.50 mg, 0.013 mmol, 5.00 mol%) and ligand (0.014 mmol, 5.50 mol%) in THF (0.80 mL), was added *t*BuOK (0.26 mL, 1.00 M THF solution, 0.26 mmol, 1.0 equiv.), and the reaction was stirred for 75 minutes at room temperature. B_2pin_2 (72.1 mg, 0.284 mmol, 1.1 equiv.) in THF (0.75 mL) was then added and the resulting mixture was stirred for 30 minutes. A solution of NCTS (70.0 mg, 0.258 mmol, 1.0 equiv.) and cyclohexylallene (47.3 mg, 0.387 mmol, 1.5 equiv.) in THF (1.00 mL) was then added dropwise at room temperature and the reaction was left to stir overnight. The mixture was then filtered through a silica plug, concentrated *in vacuo* and the crude mixture was purified by column chromatography on silica gel (CH_2Cl_2).

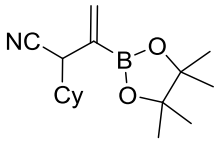
***N*-Cyano-4-methyl-*N*-phenylbenzenesulfonamide (310)**



310

p-Toluenesulfonyl chloride (7.55 g, 39.5 mmol, 3.5 equiv.) was added portionwise to a solution of phenylurea (1.54 g, 11.3 mmol, 1.0 equiv.) in pyridine (7.5 mL) and left to stir for 30 minutes. The reaction mixture was poured onto ice-water. After stirring for 15 minutes, a precipitate formed, which was collected by filtration and washed with water (3 x 5 mL) and ethanol (3 x 5 mL). The crude product was purified by column chromatography (10% EtOAc/hexane) to give **310** (1.72 g, 6.32 mmol, 60%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (2H, d, *J* = 8.0 Hz, 2 x ArC*H*), 7.33 - 7.45 (5H, m, 5 x ArC*H*), 7.20 (2H, d, *J* = 8.0 Hz, 2 x ArC*H*), 2.48 (3H, s, Ar-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7 (Ar*C*), 134.5 (Ar*C*), 132.3 (Ar*C*), 130.2 (2 x ArC*H*), 130.0 (ArC*H*), 129.8 (2 x ArC*H*), 128.4 (2 x ArC*H*), 126.5 (2 x ArC*H*), 108.6 (*C*N), 21.8 (Ar-CH_3). Data consistent with literature.[175]

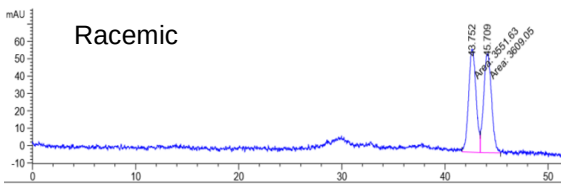
2-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enenitrile (313)



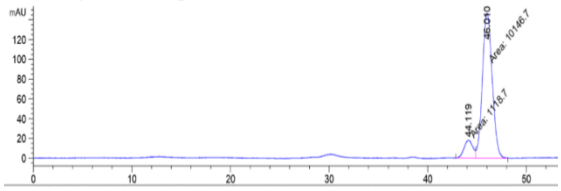
313

Prepared according to general procedure 3, on a 0.58 mmol scale of **310** using Segphos **L1**, Column chromatography (CH_2Cl_2) afforded the title compound (16.0 mg, 0.06 mmol, 23%, 10:90 e.r.) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (1H, d, *J* = 1.8 Hz, 1H from C=C*H*$_2$), 6.01 (1H, br. S, 1H from C=C*H*$_2$), 3.39 (1H, d, *J* = 5.5 Hz, C*H*(CN)), 1.62 - 1.83 (7H, m, 3 x C*H*$_2$ and CH), 1.27 (12H, 2 x s, 2 x C(C*H*$_3$)$_2$), 1.14 - 1.22 (3H, m, CH_2 and 1H from CH_2), 1.00 - 1.09 (1H, m, 1H from CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.6 (C=*C*H$_2$), 119.6 (*C*N), 83.8 (BO*C*), 42.3 (*C*H(CN)), 39.6 (*C*H), 31.21 (*C*H$_2$), 28.6 (*C*H$_2$), 25.9 (*C*H$_2$), 25.6 (2 x *C*H$_2$), 24.6 (C(*C*H$_3$)$_2$), 24.1 (C(*C*H$_3$)$_2$), (B*C*=CH$_2$ not observed); MS (ES$^+$) m/z (%): 276 (M+H+, 100), 298 (M+Na$^+$, 90); HRMS (ES$^+$) calcd. for $C_{16}H_{26}O_2NBNa$ (M$^+$Na$^+$): 298.1949. Found: 298.1956. Data consistent with literature.[158]

Enantiomeric purity of **313** was determined by HPLC analysis in comparison with authentic racemic material (10:90 e.r.; Lux 5 µm Amylose-1 column, 99:1 hexanes:*i*PrOH, 0.1 mL/min, 20 °C, 254 nm).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	43.752	MF	1.0886	3551.62744	54.37561	49.5990
2	45.709	FM	1.1527	3609.05347	52.18287	50.4010



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	44.119	MF	1.0295	1118.70251	18.11027	9.9305
2	46.010	FM	1.1529	1.01467e4	146.68414	90.0695

Peak #	Time (min)	Area (%)	Peak #	Time (min)	Area (%)
1	43.752	49.5990	1	44.119	9.9305
2	45.709	50.4010	2	46.010	90.0695

14.0 References

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