SYNTHESIS OF 4- AND 5-MEMBERED NITROGEN-CONTAINING HETEROCYCLES FROM HOMOALLYL AMINES

By

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Abstract

Nitrogen-containing heterocycles are important structural motifs for the pharmaceutical industry with a least one nitrogen-containing heterocycle found in 640 out of 1086 FDA approved drugs.[1] Our group have previously reported the synthesis of *cis*-azetidine and *cis*-pyrrolidine derivatives *via* the iodine mediated cyclisation of homoallyl amines with thermally controlled regioselectivity.[2] More recently the group has developed the electrochemical mediated cyclisation of γ-aminoalkenes into phenylselanyl pyrrolidines with selectivity controlled by the addition or omission of sodium methoxide.[3]

Herein is reported the exploration of new methodologies towards the synthesis of azetidine and pyrrolidine compounds from homoallylic amine starting materials. Three approaches are discussed: palladium-catalysed carboamination, hypervalent iodine mediated cyclisation and electrochemical mediated cyclisation. Although no azetidines were isolated from these methodologies, pyrrolidine products were obtained from hypervalent iodine and electrochemical mediated cyclisations. Despite achieving regioselective synthesis of pyrrolidine product with hypervalent iodine reaction conditions, the method is limited by poor yields at its current state. The electrochemical method had the greatest success with excellent yield of 96% obtained for one compound. However, synthesis of 3-iodopyrrolidines with the electrochemical reaction conditions were low yielding and therefore the previously reported iodine mediated synthesis of iodopyrrolidines remains superior.

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Abbreviations

°C	degrees Celsius
Δ	Heat
Å	Angstrom
ABB	Azabicyclo[1.1.0]butane
Ar	Aromatic
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase
Calc'd	Calculated
Cbz	Benzyl chloroformate
COSY	Correlated Spectroscopy
CPhos	2-Dicyclohexylphosphino-2',6'-bis(*N,N*-dimethylamino)biphenyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide

DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
Dpe-phos	Bis(2-diphenylphosphinophenyl)ether
dr	Diastereomeric ratio
e^-	Electron
ee	Enantiomeric excess
eq.	Equivalents
et al.	*et alia*
Et	Ethyl
EU	European Union
EWG	Electron Withdrawing Group
FDA	Federal Drugs Agency
F/mol	Faradays per mole
g	Grams
GC	Gas Chromatography
h	Hours
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HMBC	Heteronuclear Multiple Bond Correlation spectroscopy

HMDS	Hexamethyldisilazane
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence spectroscopy
Hz	Hertz
IC_{50}	Half maximal inhibitory concentration
ICU	Intensive Care Unit
IPA	Isopropanol
i-Pr	*iso*-Propyl
IR	Infrared
Jmod	J-modulated spin-echo spectroscopy
kcal	Kilocalorie
L-Aze	L-Azetidine-2-carboxylic acid
LDA	Lithium diisopropylamide
LED	Light Emitting Diode
M	Molar
mA	Milliampere
*m*CPBA	*meta*-Chloroperoxybenzoic acid
MEK	MAPK/extracellular signal regulated kinase

MDR	Multi-Drug Resistant
Me	Methyl
MIC_{99}	Minimum Inhibitory Concentration 99%
min	Minutes
mol	Moles
m.p.	Melting point
MS	Mass Spectrometry
Mts	2,4,6-Trimethylphenylsufonyl
NBS	*N*-Bromosuccinimide
*n*Bu	*normal*-Butyl
NIS	*N*-Iodosuccinimide
Nixantphos	4,6-Bis(diphenylphosphino)phenoxazine
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
PG	Protecting group
Ph	Phenyl
PIDA	(Diacetoxyiodo)benzene
PIFA	(Bis(trifluoroacetoxy)iodo)benzene

Pf	9-Phenyl-fluoren-9-yl
ppm	Parts per million
RNA	Ribonucleic acid
(*R*)-Siphos-PE	*N*-Di[(*R*)-1-phenylethyl]-[(*R*)-1,1'-spirobiindane-7,7'-diyl]-phosphoramidite
RT	Room temperature
RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
RVC	Reticulated Vitreous Carbon
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
SM	Starting material
S_N2	Second order nucleophilic substitution
TB	Tuberculosis
*t*Bu	*tertiary*-Butyl
TDS	Thexyldimethylsilyl
Tf	Triflate
TFAA	Trifluoroacetic anhydride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

TMS	Trimethylsilyl
Ts	Tosyl, *para*-toluenesulfonamide
UV	Ultraviolet
WHO	World Health Organisation
XMDR	Extremely Multi-Drug Resistant

Contents

1 Introduction

This introduction will predominantly discuss 4- and 5-membered nitrogen-containing heterocycles, azetidines and pyrrolidines. The main discussion will focus on the synthesis of azetidines as they are less frequently reported in literature compared to pyrrolidine and therefore represent a greater gap in the existing knowledge. The synthesis of pyrrolidines will focus on the ring expansion of azetidine rings and synthesis from aminoalkene starting materials as they are the relevant syntheses for the work reported in this thesis.

1.1 Nitrogen-Containing Heterocycles

Nitrogen-containing heterocycles, also referred to as aza-heterocycles, are a broad class of compounds that consist of at least one nitrogen atom within a carbon ring. They are an important class of compounds with many industrial applications including dyes, imaging and diagnostics, colour changing compounds, fire retardancy materials, photographic materials, and cosmetics.[4]

There is a vast source of nitrogen-containing natural products from a variety of biological sources. A selection of natural product aza-heterocycles obtained between 1990 and 2015 were reviewed by John A. Joule.[5] The human body relies on several aza-heterocyclic compounds to function correctly. Of the twenty amino acids encoded by the human body, three of them, proline, tryptophan, and histidine contain an aza-heterocycle. The nucleobases in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are comprised of a mixture of purines (adenine and guanine) and pyrimidines (cytosine, thymine, and uracil). There are thirteen currently recognised vitamins, of which seven incorporate an aza-heterocycle. These

seven vitamins are vitamins B1, B2, B3, B6, B7, B9 and B12. Vitamin B5 is the only vitamin B that does not possess an aza-heterocycle in its structure (Figure 1).

With aza-heterocyclic containing natural products found throughout the human body, it is no surprise that aza-heterocycles are important structural motifs used in the pharmaceutical industry. A study published in 2014 by E. Vitaku, D. T. Smith and J. T. Njardarson looked at the frequency of aza-heterocycles in FDA approved drugs. Starting from a database of 1994 FDA approved drugs, the authors reduced this down to 1086 unique small molecule drugs. It was found that 910 drugs contained at least one nitrogen atom and 640 of these (59% of the 1086 drugs and 70% of the 910 nitrogen-containing drugs) contained at least one nitrogen-containing heterocycle.[1]

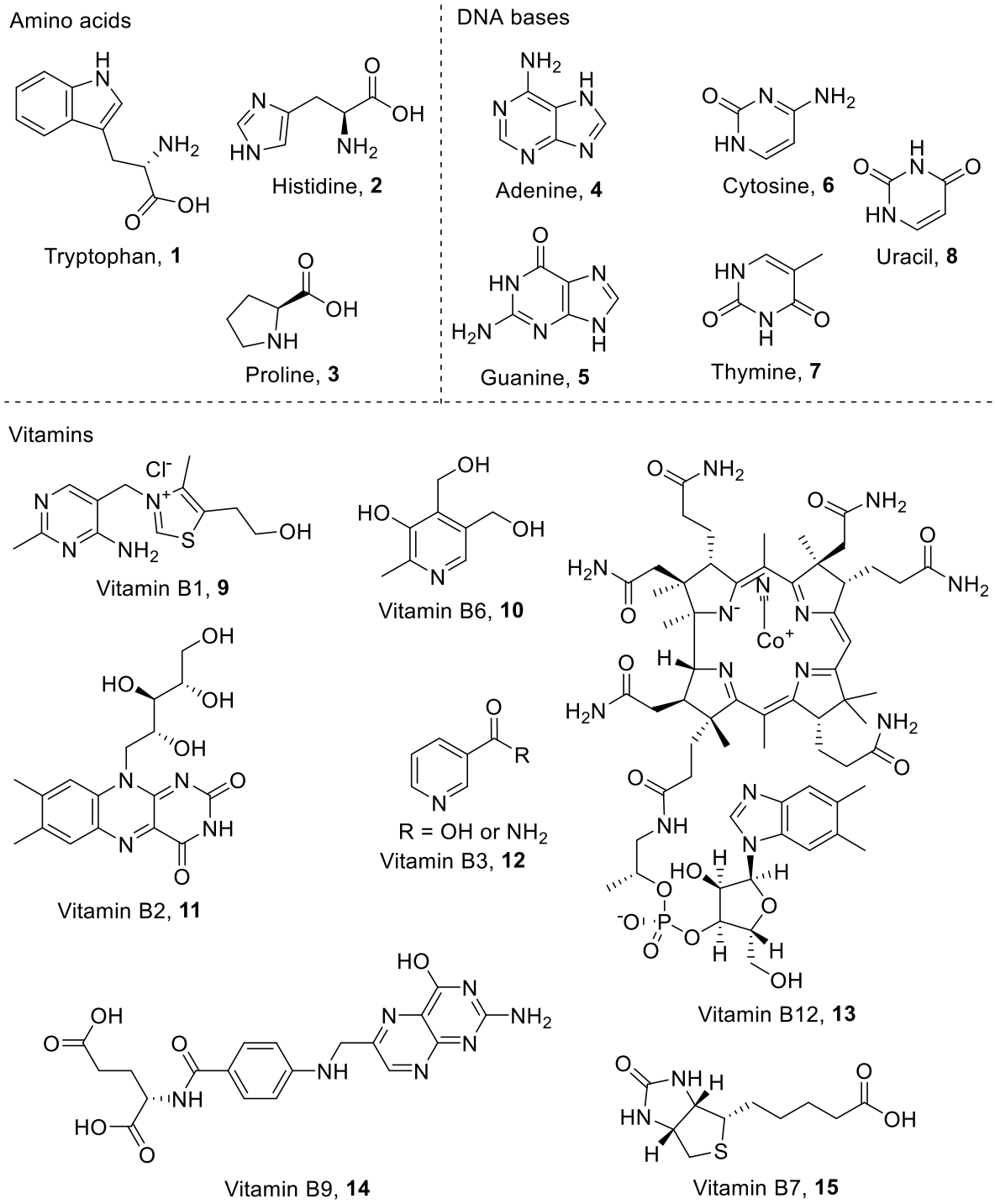
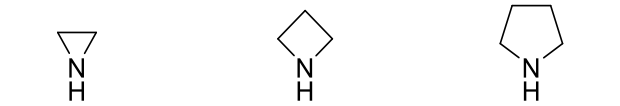


Figure 1: Examples of aza-heterocycles in amino acids, nucleobases and vitamins.

1.2 Azetidines

Azetidine is a four membered saturated ring consisting of one nitrogen atom and three carbon atoms and its physical properties share some similarities with its three membered and five

membered counterparts, aziridine and pyrrolidine (Figure 2). The ring strain energy of azetidine is almost as high as aziridine, 25.2 kcal/mol and 26.7 kcal/mol respectively, unlike pyrrolidine which has a ring strain energy of 5.8 kcal/mol. However, in terms of basicity, azetidine resembles pyrrolidine rather than aziridine with pK_a of azetidine (11.29), very close to the pK_a of pyrrolidine (11.31) compared to the pK_a of aziridine (7.98).[6]



aziridine, **16** azetidine, **17** pyrrolidine, **18**

Figure 2: Nitrogen-containing heterocycles aziridine, azetidine and pyrrolidine.

1.2.1 Naturally Occurring Azetidines

As with many aza-heterocycles mentioned in section 1.1, the azetidine structure can be found in natural products. L-Azetidine-2-carboxylic acid also known as L-Aze was first isolated by Fowden from the *liliaceae Convallaria Majalis* and was the first known example of an azetidine natural product. It is believed to be an antagonist of proline by not taking part in protein synthesis.[7] Since its discovery, L-Aze has been found as a structural motif in other natural products including nicotianamine,[8] mugineic acid,[8] 2'-deoxymugineic acid,[8] isomugineic acid[7] and medicanine[7] (Figure 3). Further details on L-Aze pertaining to its biosynthesis, synthetic synthesis and applications have been covered in a review by Couty and Evano.[7]

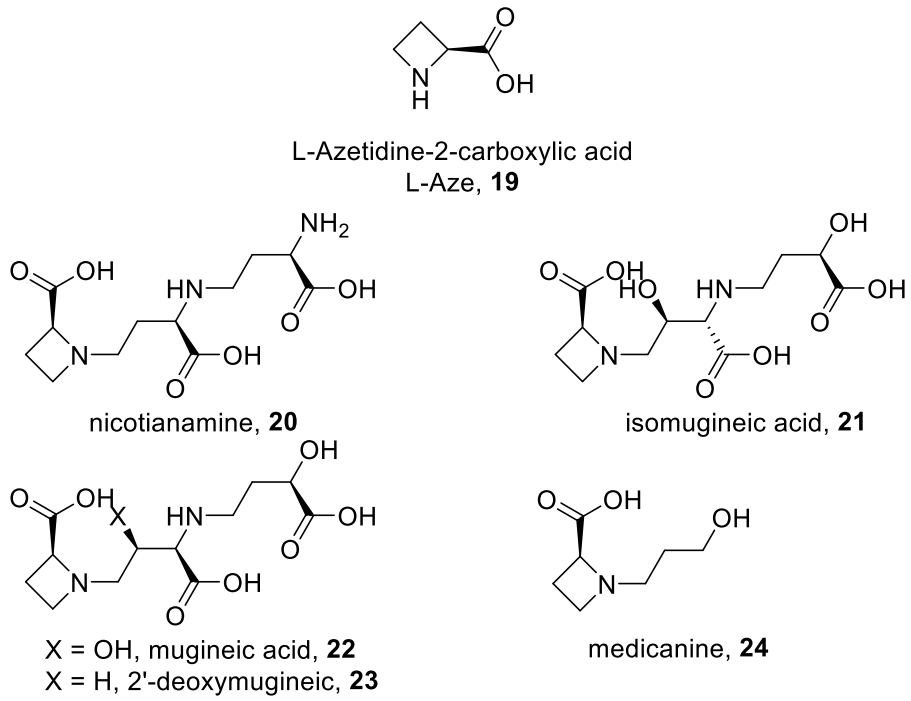


Figure 3: Examples of natural products that contain L-Aze as a structural motif.

Penarisidins A and B were the first isolation of sphingosine derived azetidine alkaloids from a marine source. They were first isolated from *Penares sp.* in 1991 by Kobayashi and co-workers and show biological activity against actomyosin ATPase.[9] Obtained from the same genus *Penares,* penazetidine A is related to penarisidins A and B (Figure 4). It was isolated by Alvi *et al.* in 1994 from *Penares sollasi* and has demonstrated activity against protein kinase C with an IC_{50} = 1 μM.[10]

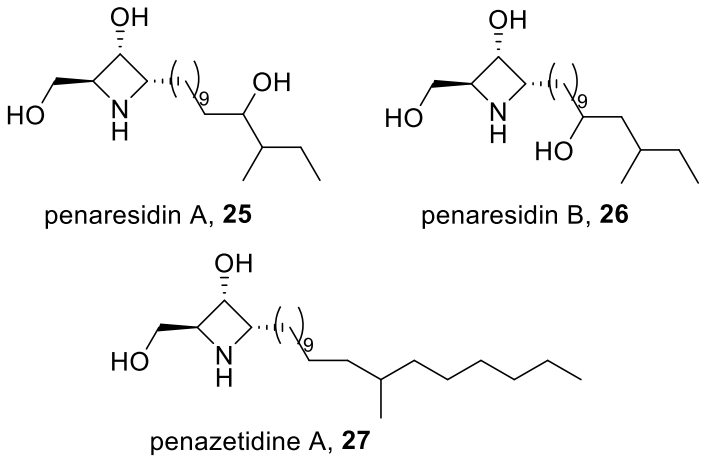


Figure 4: The related natural products penaresidin A and B and penazetidine A.

Polyoxin are a class of peptide nucleoside antibiotics that were discovered from *Streptomyces cacaoi var. asoenisis* and are used as agricultural fungicides. The azetidine motif is found in the structures of Polyoxins A, F, H and K which were elucidated by Isono and co-workers (Figure 5).[11] Probably the most complex of the azetidine containing natural products is calydaphninone, a *Daphniphyllum* alkaloid isolated from the leaves and twigs of *Daphniphyllum calycillum* Benth (Daphniphyllaceae) (Figure 5). Its isolation and structural confirmation were reported by Di *et al.* in 2007.[12]

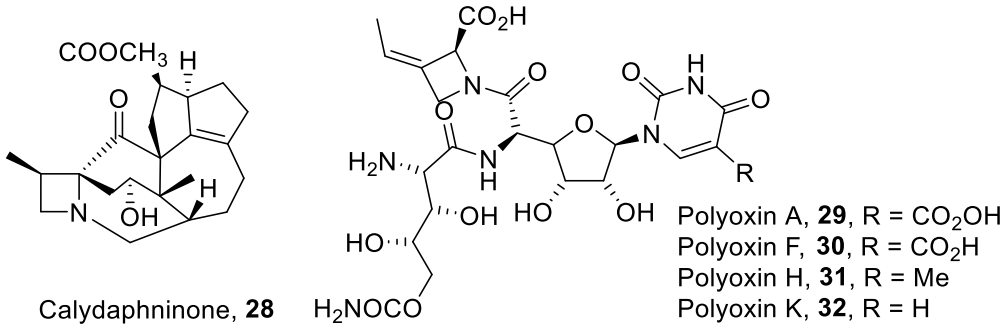


Figure 5: Calydaphninone (left) and azetidine containing polyoxins (right).

1.2.2 Azetidines in Drug Discovery

The azetidine ring is an interesting structural motif in pharmaceutical research, that has a wide range of biological activity including antibacterial,[13] antimicrobial,[14] antischizophrenic,[15] antimalarial,[16] antiobesity,[17] dopamine antagonists,[18] analgesic,[19] antioxidant,[20] CSF1R inhibitors,[21] and anticancer.[22] Several successfully marketed drugs contain the azetidine moiety as shown in Figure 6. Interestingly, none of the marketed drugs have a substituent on the 2-position of the azetidine moiety. This could be a potentially underexplored chemical space in which the synthesis of azetidines bearing substitution at the 2-position could address.

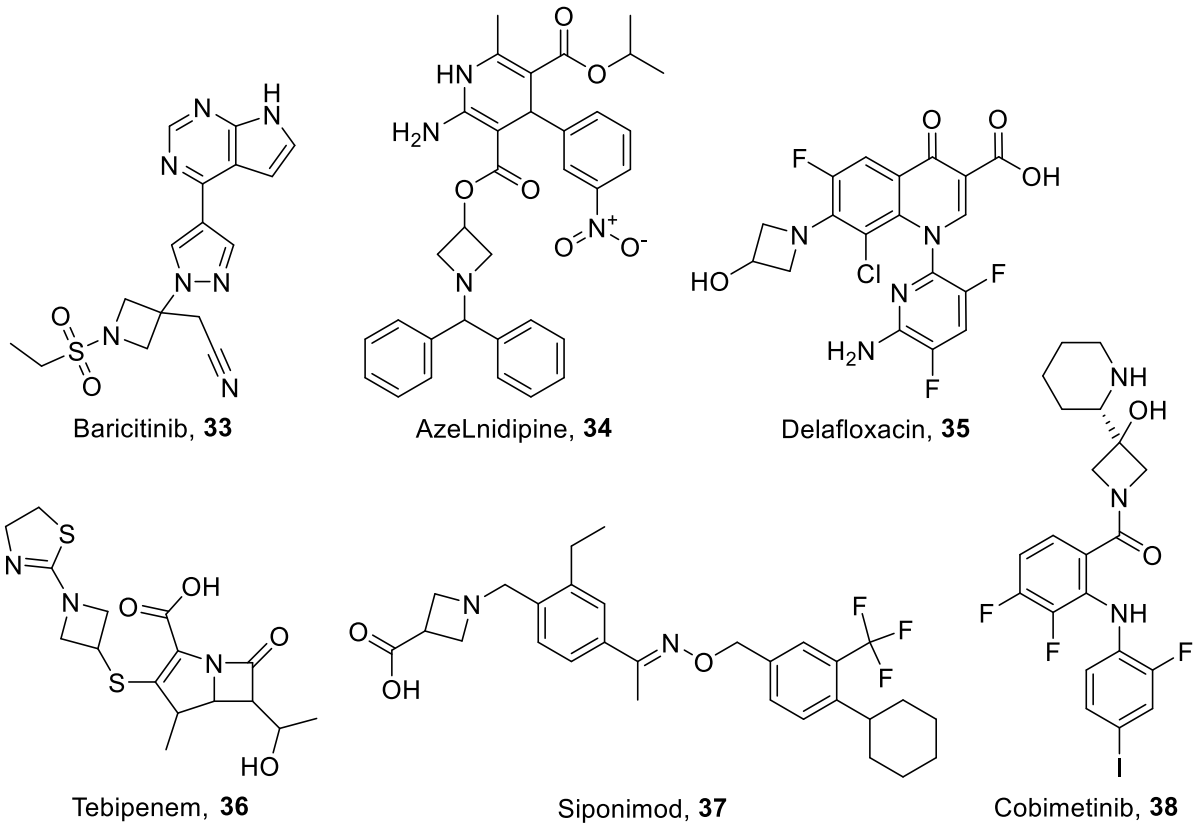


Figure 6: Marketed drugs that contain azetidine as a structural motif.

Baricitinib was approved by the EU in 2017 and the FDA in 2018 for the treatment of rheumatoid arthritis. It targets a type of tyrosine kinases used in cell signalling called Janus

kinases.[23] It has garnered more interest during the Covid-19 pandemic as a potential therapeutic for patients with Covid-19. Kalil *et al.* found that patients receiving a combination of barticitinib and remdesivir had a 30% improvement in clinical status at day 15 than with patients receiving just remdesivir.[24] Hasan and co-workers concluded that increasing the daily dose of barticitinib from 4 mg to 8 mg for 14 days in cases of severe Covid-19 pneumonia led to early normalisation of respiratory function, reduced need for ICU, minimized the 60-day rehospitalisation rate and declined the 30-day mortality rate.[25]

AzeLnidipine is a racemic drug that acts as a reversible calcium channel antagonist.[26] It has been used to treat Japanese and Chinese patients with hypertension since 2003 and is selective for L-type calcium channels.[27]

Delafloxacin is part of the fluoroquinolone family and was approved by the FDA in 2017 for the treatment of acute bacterial skin and skin structure infections.[28] Compared to other fluoroquinolones, delafloxacin has a lower pK_a of 5.4 as the position that normally contains a strongly basic group in the fluoroquinolone family is replaced by a 2-hydroxyazetidine moiety. As a result of this, delafloxacin is not zwitterionic and exists mostly as an uncharged molecule in acidic pH, which leads to greater potency of delafloxacin in acidic environments compared to the other fluoroquinolones.[29] In 2020, Millar *et al.* reported the potential of delafloxacin to be used as a treatment for cystic fibrosis as delafloxacin had greater *in vitro* activity than ciprofloxacin against *P aeruginosa*. As *P aeruginosa* has shown resistance to ciprofloxacin, the potential of delafloxacin as an alternative treatment could solve this issue for cystic fibrosis patients with ciprofloxacin-resistant *P aeruginosa* strains.[30]

Cobimetinib, first approved by Swissmedic in August 2015 and then by the FDA in November 2015, is the second MAPK/extracellular signal regulated kinase (MEK) inhibitor following two years after trametinib.[31,32] MEK inhibitors were designed to treat metastatic melanoma by overcoming tumour resistance to B-Raf Proto-Oncogene, Serine/Threonine Kinase (BRAF) inhibition. Cobimetinib is used in combination with the BRAF inhibitor vemurafenib.[31,32]

Tebipenem is a beta lactam drug under the carbapenem family and was approved in Japan as treatment for paediatric otitis media, sinusitis, and pneumonia in 2009 but is not marketed for adults. The marketed drug tebipenem pivoxil is a prodrug, with tebipenem being the active drug, and is the only orally administered carbapenem as the prodrug pivoxil ester greatly improves the oral bioavailability.[33] The carbapenem family have the greatest beta-lactamase stability amongst the beta lactam drugs and Hazra and co-workers found that tebipenem is an extremely poor substrate that hydrolyses very slowly from the beta-lactamase in Mycobacterium tuberculosis. Based on this study and combination therapy of meropenem and clavulanate (a beta-lactamase inhibitor) in the treatment of Multi-Drug Resistant TB (MDR-TB), Hazra and co-workers suggest that tebipenem has potential advantages in the treatment of MDR-TB and Extremely Multi-Drug Resistant TB (XMDR-TB).[34]

Siponimod is used for the treatment of secondary progressive multiple sclerosis reducing clinical and MRI defined outcomes of disease activity and disability progression. It was approved by the FDA in 2019 and beneficial effects of siponimod were maintained for up to five years. Fingolimod was the first oral drug for relapsing-remitting multiple sclerosis that acted as a S1P agonist for four of the five S1P receptors, $S1P_1$, $S1P_3$, $S1P_4$ and $S1P_5$.[35] Unwanted side effects were thought to come from $S1P_3$ agonism, leading Novartis to develop fingolimod

analogues which had greater rigidity and arrived at siponimod as their clinical candidate, an $S1P_3$ sparing $S1P_1$ agonist.[36]

1.2.3 Synthesis of Azetidines

Although the syntheses of azetidines is not as extensive as other aza-heterocycles, there are still many methods for synthesising azetidines reported in the literature. These methods can be broadly grouped into three main approaches: transformations of other aza-heterocycles, cycloadditions or cyclisation by nucleophilic substitution.

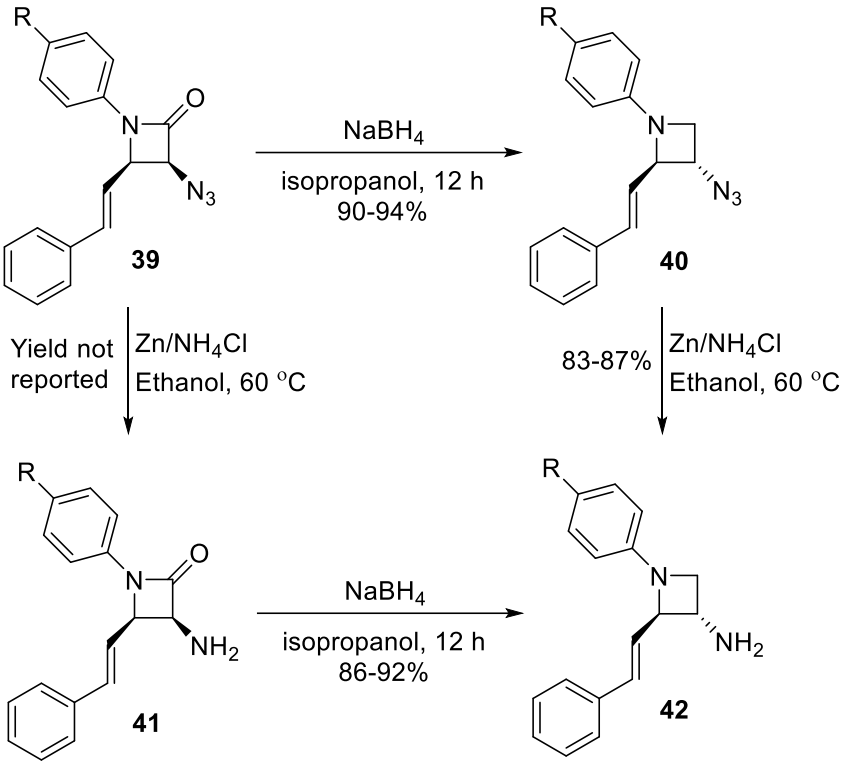
1.2.3.1 Transformations of Other Aza-heterocycles

There are several aza-heterocycles that can be transformed into azetidine rings such as the ring expansion of the three membered aziridines,[37,38,39] reduction of the four membered rings; 1-azetines,[40] 2-azetines,[41] and azetidin-2-ones[42,43,44] as well as ring contraction of larger rings such as the five membered pyrrolidin-2-ones[45] and the six membered triazines.[46]

The most common of these transformations employed is the reduction of azetidin-2-ones, more commonly referred to as β-lactams. Azetidin-2-one is an important structural motif to the pharmaceutical industry, especially for antibiotics where the β-lactam is a broad class of antibiotics that have been used for many years and still relied on today to treat a wide range of infections. The β-lactam antibiotics can be split into several classes with the most well-known being penicillin, cephalosporins and carbapenems. As a result of this, azetidin-2-ones are reasonably accessible materials making them a popular choice of starting material to access azetidines.

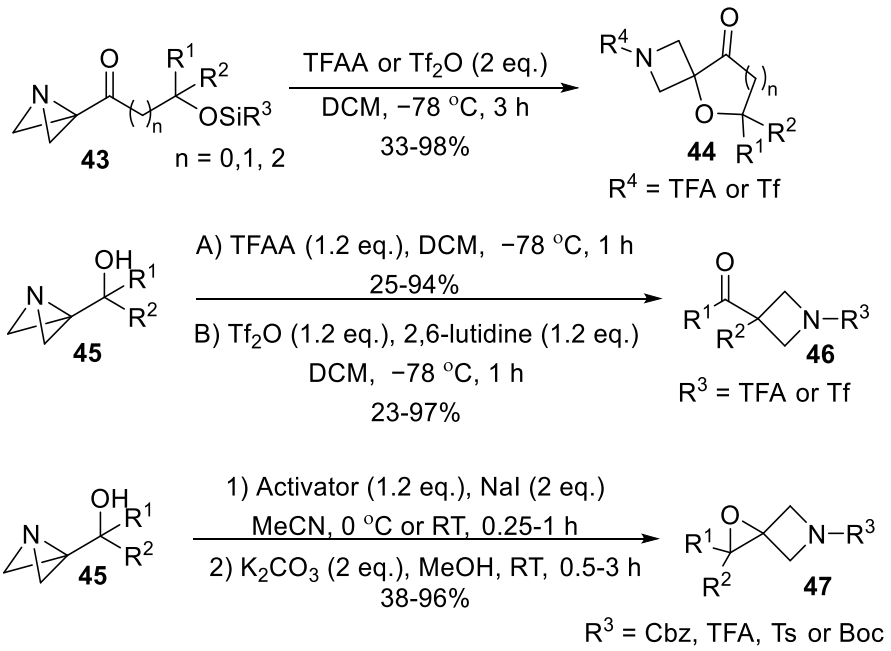
Azetidin-2-ones can be reduced to azetidines by using chloroalanes, prepared *in situ* from lithium aluminium chloride and aluminium chloride. Ojima *et al.* were the first to use

chloroalanes for the reduction of azetidin-2-ones in 1983 and found it to be a superior reducing method compared to lithium aluminium hydride, diborane and Raney nickel.[42] With trifluoromethyl substituent known to add favourable properties to druglike molecules, Dao Thi and co-workers used the chloroalane method to reduce 4-(trifluoromethyl)azetidin-2-ones with monochloroalane to access trifluoromethylated azetidines.[43] Mehra *et al.* used sodium borohydride to selectively reduce azetidin-2-one **39** to azetidine **40** in the presence of an azide substituent on the ring. The 3-azido-azetidine **40** could then be reduced to 3-amino-azetidine **42** using a zinc and ammonium chloride reduction which they also found could be performed in the presence of azetidin-2-one **41**. Mehra *et al.* proposed that the reduction of *cis*-azetidine-2-one **39** and **40** leads to the formation of a dihydroazete intermediate. Addition of a hydride ion to the dihydroazete intermediate followed by [1,5] H-shift affords the thermodynamically stable *trans*-azetidine **40** and **42** products. The advantage of this method is that the substituents can be independently reduced in either order, adding greater flexibility for synthetic routes and further derivatisation of products (Scheme 1).[44]



Scheme 1: Amino-azetidine **42** accessible regardless of the order of the reductions.

More recently the Aggarwal group has used azabicyclo[1.1.0]butane (ABB) compounds to obtain azetidines. The ABB system is a highly strained compound and releasing this strain affords the azetidine ring. In one approach, the Aggarwal group prepared ABB ketones **43** that have a silyl protected alcohol, that reacted with trifluoroacetic anhydride or triflic anhydride to afford azetidine spirocycles **44**. Ring sizes from 4-membered to 6-membered were tolerated as well as aromatic fused ring systems (Scheme 2).[47] The Aggarwal group have also prepared ABB carbinols that can afford either spiroepoxy azetidines **47** through spirocyclisations or keto azetidines **46** through semipinacol rearrangements depending on the electrophilicity of the activating agent. Less electrophilic activating agents afforded the spiroepoxy azetidines **47** and the more electrophilic activating agents gave access to the keto azetidines **46** (Scheme 2).[48]



Scheme 2: Strain release of ABB derivatives **43** and **45** affords azetidine spirocyclics **44** and **47** and ketones **46**.

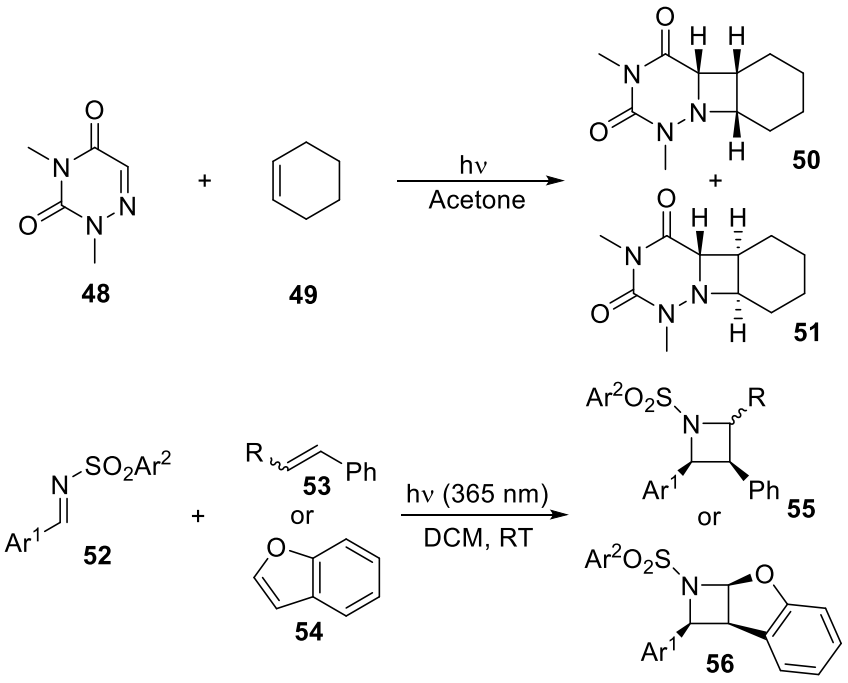
1.2.3.2 Cycloaddition Reactions

Imines are the main choice of starting material for synthesising azetidines *via* cycloaddition methods. They can undergo [2 + 2] cycloadditions with a variety of starting materials including aldehydes,[49] isocyanides,[50] allenoates[51] and (alkoxymethylene)cyclopropanes.[52] Ketimines have also been used in [2 + 2] cycloadditions with allenamides.[53]

The [2 + 2] cycloaddition can also be performed photochemically, often affording fused ring systems. Fraga-Timiraos *et al.* made tricyclic azetidine products **50** and **51** through photochemical reaction between 6-aza-1,3-dimethyluracil **48** and cyclohexane **49** during their investigation relating to photo-driven DNA damage and repair (Scheme 3).[54] Sakamoto and co-workers were able to perform cycloadditions between arylsulfonylimines **52** and either styrene **53** or benzofurans **54**. However, they found that photocycloaddition would not occur unless the imine had a sulfonyl protecting group and an absorption band at about 365 nm, which may limit the scope and application of this method (Scheme 3).[55] Intramolecular [2 + 2]

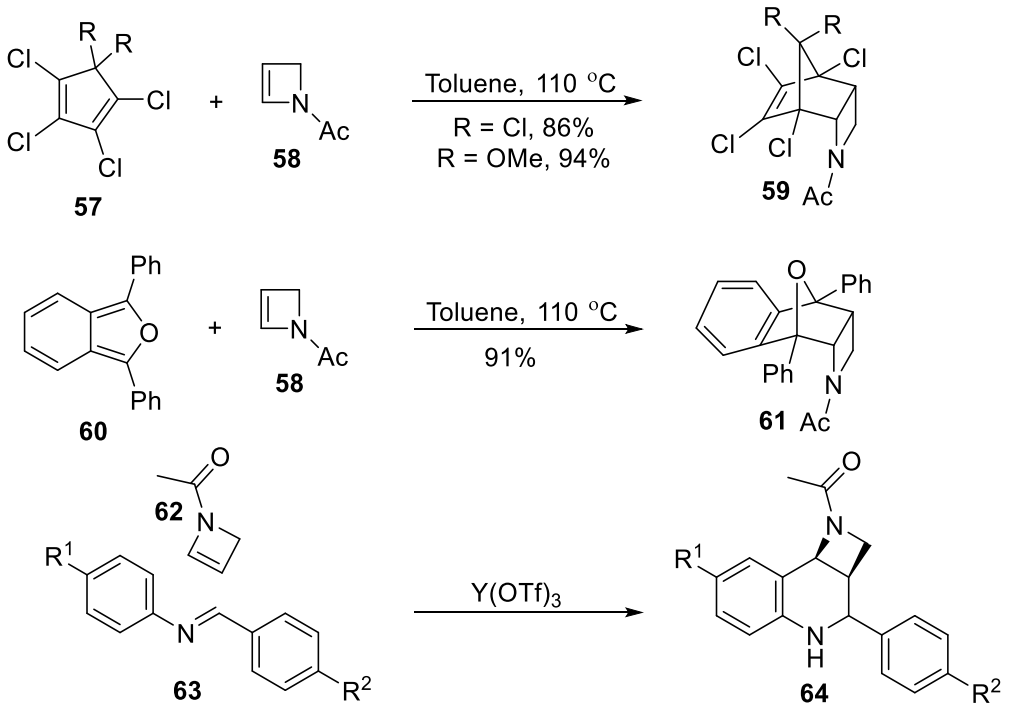
photocycloaddition to synthesise an azetidine ring has also been demonstrated by Fischer *et al.*[56]

Three component reaction using imines, azides and alkynes have been used by Gouthaman and co-workers and Shang *et al.* to access azetidinimines.[57,58] It is thought that the azide and alkyne react together first to provide an intermediate that then undergoes [2 + 2] cycloaddition with the imine to afford the azetidinimine product.[57,58]



Scheme 3: Photochemical induced cycloadditions towards fused azetidine derivatives.

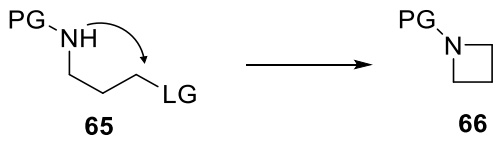
While it is more common to use imines as starting materials for cycloadditions, 2-azetines can also be used to make fused azetidine ring systems through dimerization. The Diels-Alder reactions between 2-azetine **58** and cyclic dienes **57** and diphenylisobenzofuran **60** and [4 + 2] cycloaddition between 2-azetine **62** and imine **63** have been reported for the synthesis of fused azetidine ring products (Scheme 4).[59,60]



Scheme 4: Fused azetidine products from cycloaddition reactions with 2-azetines **58** and **62**.

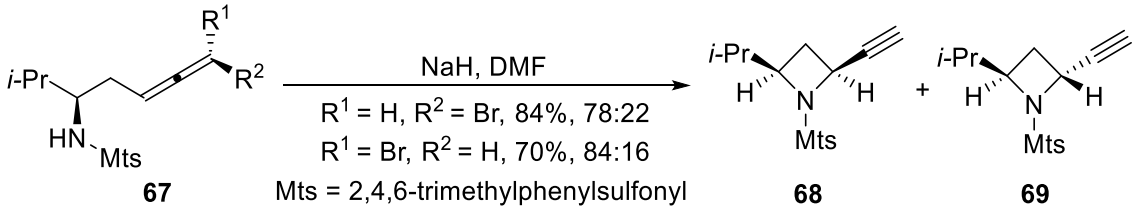
1.2.3.3 Cyclisation *via* Nucleophilic Substitution

The most common method for cyclising azetidine rings *via* nucleophilic substitution is to use 1,3-aminocompounds, where the substituent at the 3-position acts as the leaving group (Scheme 5). It is commonly used as there are several different types of substituents that can act as the leaving group leading to a wide choice of starting materials. Substituents that can act as leaving groups include halides,[61,62] the phenylselenonyl group[63] and sulfates.[64] 1,3-aminoalcohols can be cyclised into azetidines by either the Mitsunobu reaction[65] or by first converting the hydroxy substituent into a better leaving group such as a mesylate,[66] tosylate[67] or triflate.[68]



Scheme 5: 1,3-Aminocompound cyclised into azetidine by displacement of a leaving group.

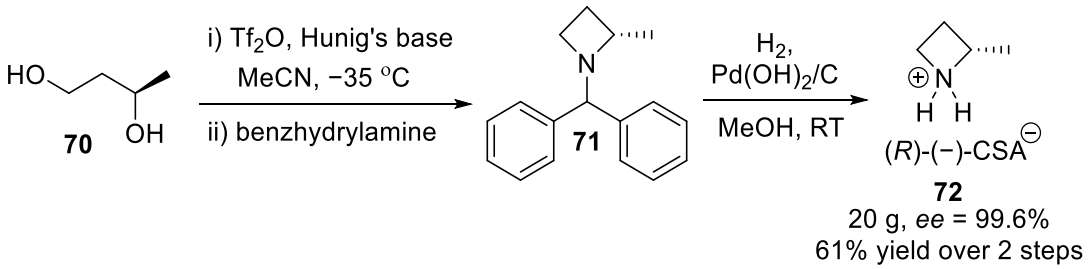
Ohno *et al.* used 1,3-aminoallenes **67** to afford *cis*-favoured 2-ethynylazetidines **68** and **69** using NaH as a base (Scheme 6). The reaction works in a similar way to the other 1,3-aminocompounds mentioned in the paragraph above. The deprotonated nitrogen attacks the allene to form the azetidine ring. The double bond displaced by the formation of the N-C bond moves to make the alkyne substituent with a bromine substituent, that was at the end of allene group, acting as the leaving group.[69] Alternatively, the Gao group,[70] Ibuka group,[71] Rutjes *et al.*[72] and Kang and co-workers[73] have used 1,3-aminoallenes in palladium-catalysed intramolecular amination chemistry as a way to access 2-alkenylazetidines.



Scheme 6: Synthesis of 2-ethynylazetidines **68** and **69** from 1,3-aminoallenes **67**.

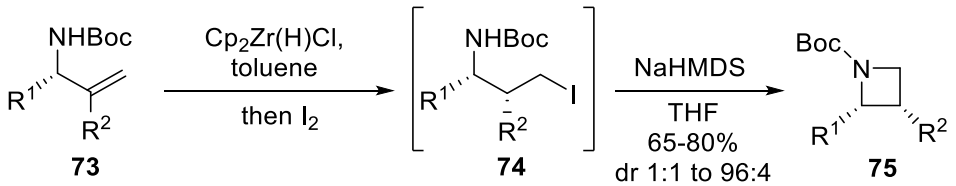
An alternative intermolecular substitution approach to using 1,3-aminocompounds, is to perform bis-alkylation with primary amines using 1,3-bis-electrophiles as starting materials. For example, Dowling *et al.* were able to obtain (*S*)-2-methylazetidine salt **72** with >99% *ee* over two steps from commercially available (*R*)-(−)-1,3-butanediol **70**. Through addition of triflic anhydride and Hünig's base to (*R*)-(−)-1,3-butanediol **70**, the diol is converted to triflates that are better leaving groups, which are subsequently substituted by benzhydrylamine to obtain the azetidine ring. Hydrogenolysis of the azetidine with palladium hydroxide over

carbon gives access to (*S*)-2-methylazetidine salt **72** in 61% yield over the two steps (Scheme 7). The advantage of this method is that it does not need to be purified by column chromatography. Dowling *et al.* had used the method to make over 200 g of (*S*)-2-methylazetidine salt **72** when they published their work.[74]



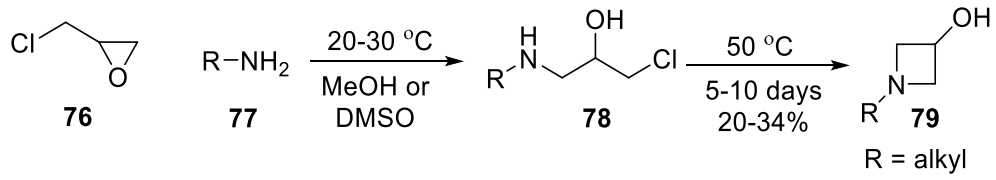
Scheme 7: Synthesis of azetidine salt **72** from **70** in high *ee* on large scale of 20 g.

Activation of the C=C double bond on allyl amine substrates followed by intramolecular attack from nitrogen can lead to the formation of azetidine rings. Robin and Rousseau activated tosyl protected allyl amines with bis(collidine)bromonium (I) hexafluorophosphate which formed the azetidine ring and installed bromine at the 3-position.[75] During an investigation into glycoside mimics, Eniade and Martin unexpectedly synthesised an azetidine ring with NIS promoted iodo-cyclisation of an allyl amine moiety within a heptenitol derivative instead of the expected 6-membered C-glycosyl compound.[76] Pradhan *et al.* described diastereoselective hydrozirconation reaction conditions to access enantiomerically enriched *cis*-2,3-disubstituted azetidine derivatives **75** from Boc protected chiral allyl amines **73**. The allyl amine is activated by hydrozirconation and affords a hydrozirconated intermediate that reacts with iodine to obtain an iodocarbamate **74**. Subsequent addition of sodium bis(trimethylsilyl)amide promotes cyclisation of the iodocarbamate **74** into the corresponding *cis*-azetidine **75** with dr ranging from 50:50 to 96:4 (Scheme 8).[77]



Scheme 8: Allyl amine **73** activated by hydrozirconation followed by I_2 to induce cyclisation to azetidine ring **75**.

Epoxides can be ring opened and then cyclised by amines to access 3-hydroxazetidine derivatives. Gaertner was the first to report the synthesis of azetidine derivatives from epoxides in 1967 in a two-step synthesis.[78] The azetidine was discovered as a side product when converting stored 1-alkylamino-3-chloro-2-propanols **78** into *N*-alkyl-2,3-epoxypropylamines. It was found that the 1-alkylamino-3-chloro-2-propanols **78** would spontaneously cyclise into the 3-hydroxyazetidine derivatives **79** even at 0 °C, albeit slowly at low temperature. To synthesise the azetidine compounds directly, primary amines **77** were condensed with the epoxide, epichlorohydrin **76**, to afford the aminochloropropanols **78** that were subsequently heated at 50 °C for 5-10 days to afford the 3-hydroxyazetidines **79** in 20-34% yields (Scheme 9).[78] Constantieux *et al.* was able to synthesise 3-hydroxazetidine derivatives in 70-83% yield with α-C-silylated amines in a synthetic approach based on Gaertner's work.[79] Instead of ring opening the epoxide to install the amine followed by cyclisation to the azetidine products, Tam and co-workers reported the synthesis of a 3-hydroxyazetidine derivative from β-amino epoxide in which ring opening of the epoxide lead directly to the formation of the azetidine ring.[80]

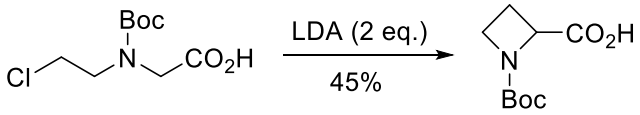


Scheme 9: Synthesis of azetidines **79** from epoxides **76** reported by Gaertner.

1.2.3.4 Cyclisation *via* C-C Bond Formation

The cyclisations discussed so far have occurred through the formation of a C-N bond. However, C-C bond formation is also a viable route.

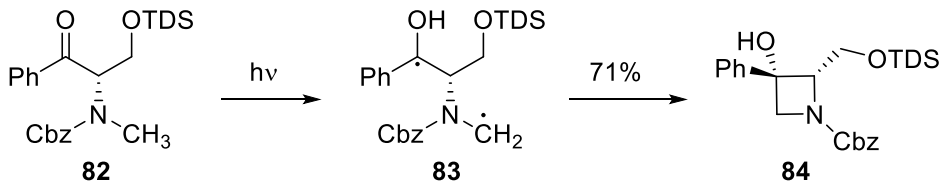
One approach is a nucleophilic displacement of the halide in 1,2-haloamine substrates. The 1,2-haloamine requires a tertiary amine with an additional substituent bearing a beta electron withdrawing group. Strong, non-nucleophilic base, such as LiHMDS or LDA, deprotonates the carbon atom between the nitrogen atom and electron withdrawing group, which allows for cyclisation. De Nicola *et al.* synthesised the Boc protected azetidine-2-carboxylic acid **81** from a Boc protected 1,2-chloroamine substrate **80** that contained a carboxylic acid as the electron withdrawing group with LDA at room temperature in 45% yield (Scheme 10).[81]



80 **81**

Scheme 10: LDA induced cyclisation of **80** into azetidine **81**.

1,2-Aminoketones **82** which contain a tertiary nitrogen cyclise into azetidine rings **84** by photochemical activation (Scheme 11). This cyclisation was first reported by Yang and Yang in the formation of cyclobutene.[82] The excited carbonyl group following irradiation abstracts a hydrogen from the CH_2 adjacent to nitrogen on a different alkyl chain to afford biradical species **83** which undergoes cyclisation to give the azetidine product **84**. A Norrish-Type-II cleavage side reaction can also occur from the biradical species to give an imine and enol, which can then react further in an aldol like reaction as reported by Wessig and Schwarz, limiting the potential applications of this method.[83]



Scheme 11: Wessig and Schwarz synthesis of azetidine **84** *via* photochemically induced cyclisation of 1,2-aminoketone **82**.

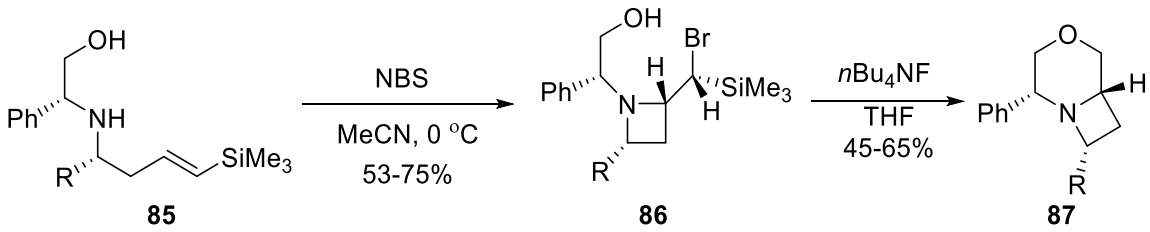
Kise *et al.* have described the synthesis of azetidine derivatives from the electroreductive intramolecular coupling of aromatic iminoesters. To the surprise of Kise *et al*., cyclisation of an aromatic iminoester prepared from (*S*)-glutamic acid gave azetidine derivatives stereospecifically, as no piperidine derivatives were observed.[84]

1.2.3.5 Homoallylic Amine Substrates

Homoallylic amine substrates can be cyclised into azetidine products through activation of the C=C double bond of the allyl group followed by intramolecular nitrogen attack. Homoallyl amines are good starting material for addressing the potential underexplored 2-substituted azetidine moiety in the pharmaceutical industry, mentioned in section 1.2.2, as the azetidine products synthesised from homoallyl amines bear substitution at the 2-position.

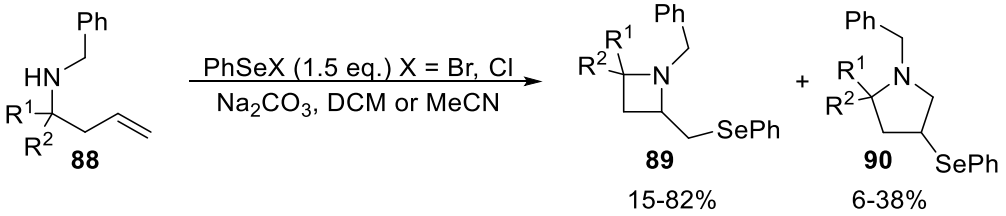
The Kadouri-Puchot group have reported the transformation of homoallyl amines **85** with terminal (*E*)-vinylsilane and a β-aminoalcohol substituents into azetidine products **86** regioselectively in the presence of *N*-bromosuccinimide *via* a bromonium intermediate in 53-75% yield. Cyclisation occurs regioselectively during intramolecular nitrogen attack of the bromonium ion due to the β effect of the silicium. Desilylation of the azetidine products **86** with *tetra*-butylammonium fluoride was subsequently followed by intramolecular attack from the β-aminoalcohol to afford bicyclic azetidine derivatives **87** in 45-65% yield (Scheme 12).

The hydroxy group was critical for formation of the bicyclic product as no product occurred when the hydroxy functional group was protected with a methyl group.[85,86]



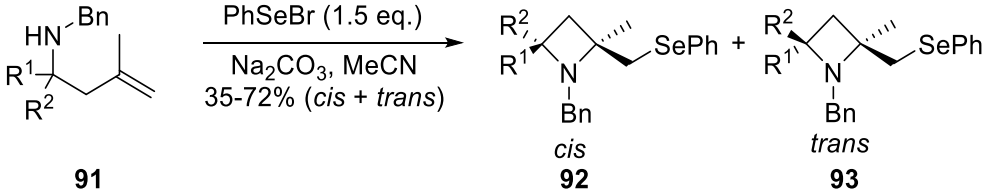
Scheme 12: NBS activated cyclisation of homoallyl amine **85**. Fused azetidine **87** afforded during desilylation of **86**.

Outurquin and co-workers have activated homoallyl amines **88** with phenylselenium bromide and chloride in the presence of sodium carbonate to afford azetidines **89** and pyrrolidines **90** in 15-82% isolated yield for the azetidine products **89** (Scheme 13). With acetonitrile as the solvent, azetidines **89** were the major product in all but one example. The presence of two substituents adjacent to the nitrogen gave the highest ratio of the azetidine isomer with only azetidine formation in 2 examples.[87]



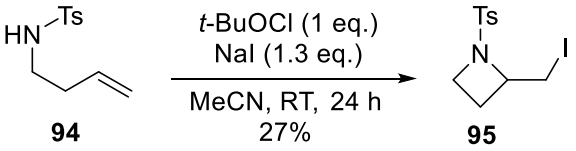
Scheme 13: Mixture of azetidine and pyrrolidine products **89** and **90** from homoallyl amine **88**.

The absence of sodium carbonate leads to the formation of azetidinium and pyrrolidinium halides.[88] Regioselectivity could be controlled to give exclusively azetidine derivatives **92** and **93** with a methyl substituent at the 3-position in 35-72% yield (Scheme 14).[89]



Scheme 14: Homoallyl amines **91** afford mixture of *cis*- and *trans*-azetidines **92** and **93**.

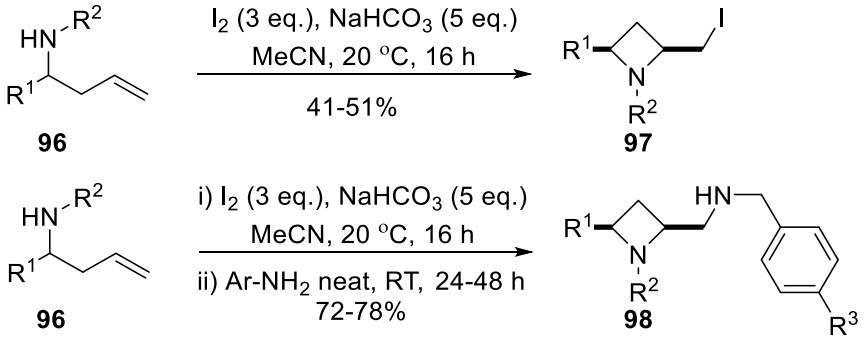
Several aminoalkenes substrates including homoallyl amine **94** were cyclised into nitrogen-containing heterocycles with *tert*-butyl hypoiodite generated *in situ* from *tert*-butyl hypochlorite and sodium iodide in a procedure described by Minakata *et al* (Scheme 15). Compared to previous examples of homoallyl amine cyclisation whereby the activating reagent interacts with the allyl group to activate the C=C double bond, the *tert*-butyl hypoiodite iodinates the nitrogen. Subsequent intramolecular transfer of the iodonium atom to the allyl group affords the three membered iodonium intermediate. Intramolecular attack of the iodonium intermediate by the nitrogen affords the azetidine product **95** in 27% yield.[90]



Scheme 15: Iodoazetidine **95** prepared from homoallyl amine **94** by protocol described by Minakata *et al*.

Previous group member Antonio Feula reported cyclisation of homoallylic amine substrates **96** with molecular iodine in the presence of sodium hydrogen carbonate to afford *cis*-iodoazetidine derivatives **97** as the major product in 41-51% yield (Scheme 16). Selectivity of the reaction was controlled thermally as iodoazetidine products **97** would ring expand to 3-iodopyrrolidine products at reaction temperatures greater than 20 °C. However, Feula *et al.* discovered that the iodoazetidine products **97** would isomerise into the 3-iodopyrrolidine products over time, even when stored at 4 °C. As a result of this, iodoazetidine products **97**

were reacted with neat amine immediately to afford *cis*-aminoazetidines **98**, in 72-78% yield over two steps, that were stable with respect to thermal ring expansion (Scheme 16). Sodium azide was also reported to displace iodide and subsequently transformed into a 1,2,3-triazole to isolate triazole appended *cis*-azetidine product in 46% yield over three steps.[91]

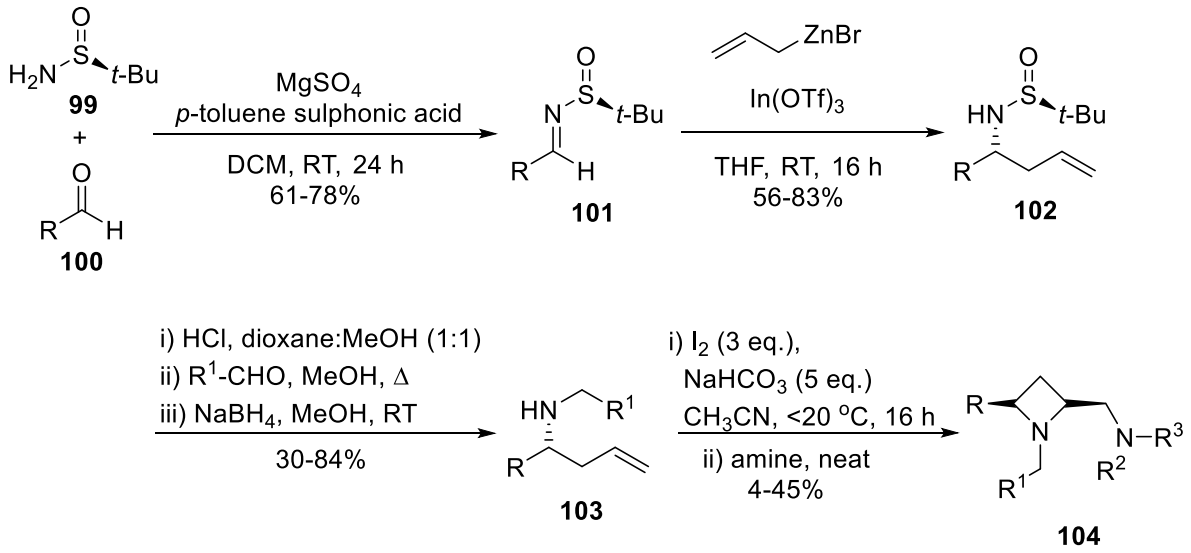


Scheme 16: Synthesis of iodo- and amino-azetidines **97** and **98** from homoallyl amine **96**.

Feula *et al.* found that the aminoazetidine derivatives synthesised with this protocol were biologically active. A sample of 6 racemic *cis*-aminoazetidine derivatives were screened in a zebrafish embryo development morphology assay. Three of the compounds had at least a moderate effect (25-50%) on three of the morphological defect indicators with one compound that had a very severe effect (75-100%) on 8 of the 9 indicators and a severe effect (50-75%) on the remaining indicator.[92] The Fossey group have created a series of *cis*-aminoazetidine derivatives that have minimum inhibitory concentration 99 (MIC_{99}) values <10 μM against drug sensitive and multi-drug-resistant *Mycobacterium tuberculosis* with no detectable drug resistance.[93] Yoshizawa *et al.* have synthesised palladium and platinum 2,4-*cis*-aminoazetidine complexes with azetidines synthesised with the protocol described by Feula *et al*.[94]

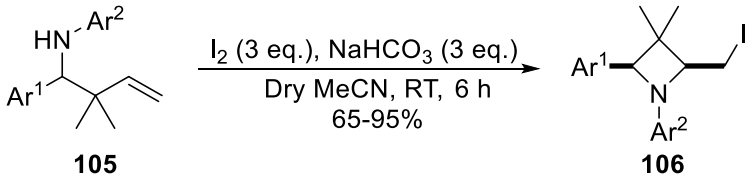
Copper-catalysed Henry reactions were performed under asymmetric conditions with single enantiomer azetidine ligands. Fifteen single enantiomer *cis*-aminoazetidines **104** were

synthesised by Yoshizawa *et al.* using an Ellman auxiliary approach. Ellman auxiliary (*S*)-*tert*-butanesulfinamide **99** was used to obtain single enantiomer homoallyl amines **103** in five steps. Cyclisation was achieved with the protocol described by Feula *et al.* to afford single enantiomer *cis*-aminoazetidines **104** in 4-45% yield (Scheme 17).[95]



Scheme 17: Synthetic route to single enantiomer azetidines **104**, with Feula *et al.* reported cyclisation as the key step to azetidine formation from single enantiomer homoallyl amines **103**.

Jin and co-workers have also reported iodine mediated cyclisation of homoallyl amines to synthesise azetidine products. Molecular iodine in the presence of sodium hydrogen carbonate cyclised 20 *cis*-3,3-dimethylazetidines **106** with a methyliodo substituent at the 2-position in 65-95% yield (Scheme 18).[96] The key differences between this protocol and the protocol described by Feula *et al.* were the equivalents of sodium hydrogen carbonate (3 compared to 5 respectively), the acetonitrile solvent (dried for Jin *et al.*) and the reaction time (6 compared to 16 h respectively). The thermal ring expansion of the azetidines **106** due to the 2-methyliodo substituent was not reported by Jin and co-workers.



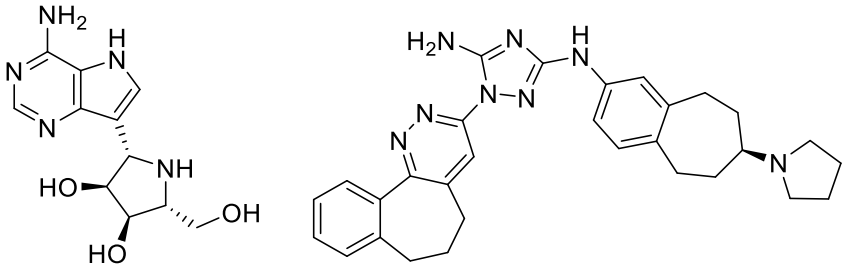
105 **106**

Scheme 18: Regioselective synthesis of azetidines **106** from homoallyl amines **105** that bear a dimethyl substituent.

1.3 Pyrrolidine

Pyrrolidine is a five-membered fully saturated ring consisting of one nitrogen atom and four carbon atoms. As pyrrolidine is fully saturated, it can have up to four stereogenic centres giving rise to derivatives with sixteen possible stereoisomers.

As previously mentioned in section 1.1, a study published in 2014 found that 59% of unique FDA approved small molecule drugs contained an aza-heterocycle within its structure. Pyrrolidine was the fifth most common nitrogen-containing heterocycle to be used as a structural motif within the FDA approved drugs.[1] More recently galidesivir and bemcentinib gained interest in the research community due to their potential use as treatments in the Covid-19 pandemic that impacted the global community.



Galidesivir, **107** Bemcentinib, **108**

Figure 7: Pyrrolidine containing marketed drugs, galidesivir and bemcentinib.

Arouche *et al.* conducted docking studies with AutoDock Vina 4.4.2 between galidesivir and Covid-19 protease which had a relative binding affinity of -7.0 kcal/mol. However, further investigation in the study was performed with different molecules suggesting that galidesivir

is not the most suitable drug against Covid-19.[97] Kovacs and co-workers screened 29 FDA approved repurposed antiviral compounds for the treatment of Covid-19 using wildtype isolates of SARS-CoV-2 isolated from UK patients. Galidesivir had *in vitro* activity against GLA1 and PHE2 isolates and was able to increase the survival of VeroE6-ACE2 and A549-NPro-ACE2 cells. Across the two cell lines and viral isolates, galidesivir had an IC_{50} between 60.5 and 106.5 µM at a multiplicity of infection of 0.5.[98]

Bemcentinib was studied in the ACcelerating Covid-19 Research and Development (ACCORD) trial. The recovery of hospitalised patients was improved when bemcentinib was used in combination with standard care treatments. On an average of seven days, 90% of patients receiving bemcentinib improved by two out of nine points on the WHO clinical scale system or were discharged from hospital, whereas only 69% of patients without receiving bemcentinib achieved the same level of recovery and took an average of nine days to reach that point. As the study only contained a total of 61 patients, bemcentinib will progress to a larger study as part of the EU-SolidAct trial.[99]

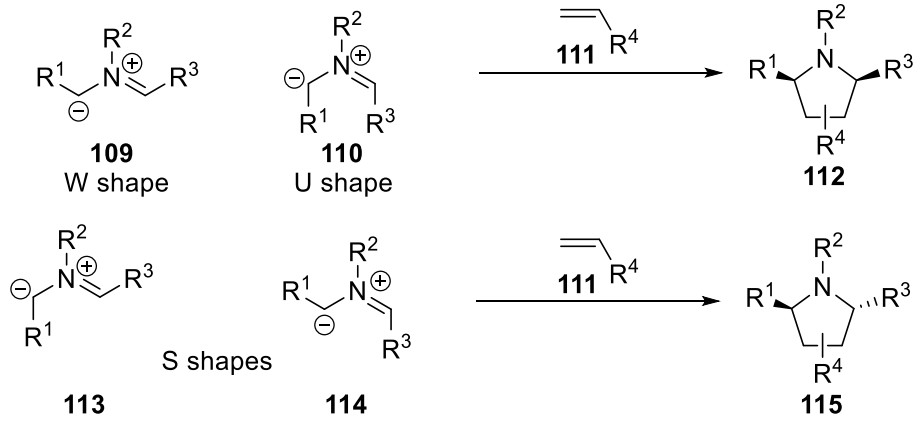
1.3.1 Pyrrolidine Synthesis

The simplest pyrrolidine can be prepared by heating either tetrahydrofuran or tetrahydrothiophene with ammonia at 300 °C in the presence of alumina.[100] Proline is an attractive starting material for synthesising pyrrolidine derivatives as it is commercially available and a chiral compound.[101] The carboxylic acid is a good handle for further derivatisation and as proline is a natural product, it has favourable biological properties for medicinal projects.

1.3.1.1 Cycloaddition Reactions

The two main cycloaddition methods for making pyrrolidines are 1,3-dipolar cycloaddition and formal [3 + 2] annulations.[102,103,104,105] Several natural product syntheses have used these two approaches for constructing the pyrrolidine ring motif.[102,104]

1,3-Dipolar cycloaddition typically uses an azomethine ylide as a starting material with the first reaction reported in 1976. The azomethine ylide can be prepared from aldehydes, imines, and heterocycles such as aziridines.[103] These ylides have four different geometries: W-, U- and two S-shapes and the ylides can isomerise between the shapes. *Cis*-products are obtained from the W- and U- shaped ylides whilst *trans*-products are obtained from the two S-shaped ylides (Scheme 19).[106]



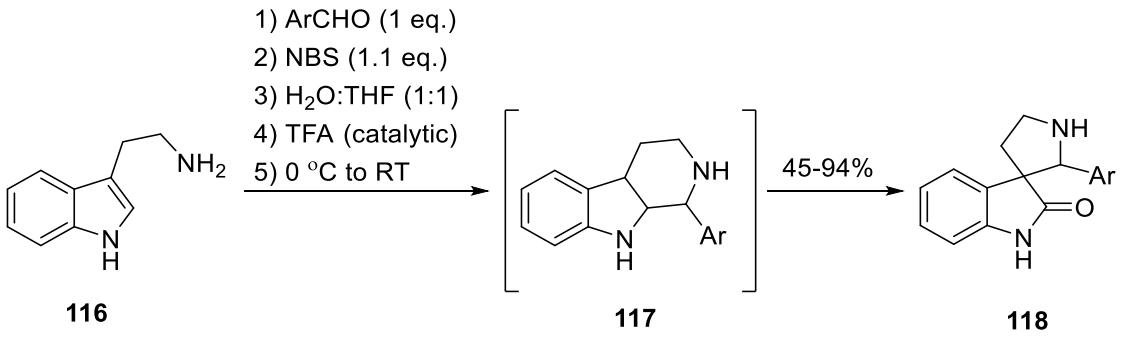
Scheme 19: Stereochemistry of the product influenced from the geometry of the ylide.

As fully substituted pyrrolidines have sixteen possible stereoisomers (and then only if the substituents at the 1 and 4 position and 2 and 3 position differ), catalytic asymmetric 1,3-dipolar cycloaddition reactions have been developed to access pyrrolidine products with high stereospecificity. Adrio and Carretero published a review on the diversity of pyrrolidine

products that can be obtained *via* catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides which included stereodivergent protocols.[105]

1.3.1.2 Transformation of Aza-heterocycles

Transformation of aza-heterocycles into pyrrolidines include ring expansion of aziridines[107] and azetidines,[91,108,109,110,111,2] and reduction of pyrroles,[112] pyrrolidinones[113] and pyrroline.[114] Hati *et al.* synthesised a series of spiro pyrrolidine products **118** using a one pot Pictet Spengler-Oxidative ring contraction from tryptamine **116**. Tryptamine **116** and an appropriate aldehyde would form a tetrahydro-β-carboline intermediate **117** *via* the Pictet Spengler reaction and then in the presence of water, *N*-bromosuccinimide and trifluoroacetic acid, the intermediate would undergo oxidative ring contraction to afford the desired spiro pyrrolidine **118** (Scheme 20).[115]

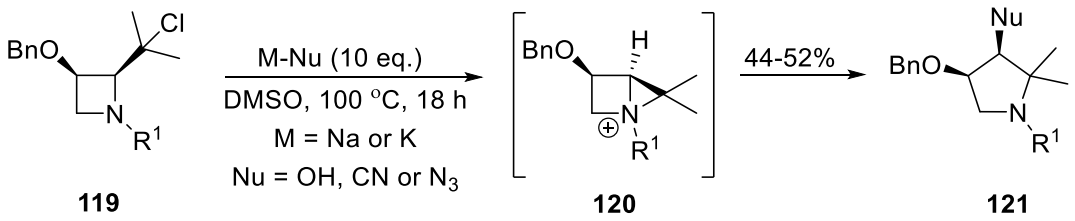


Scheme 20: One pot Pictet Spengler-Oxidative ring contraction from tryptamine **116**.

1.3.1.2.1 Ring Expansion of Azetidines

Bradandt *et al.* reported the thermal ring expansion of 2,3-substituted azetidine **119** with a 1-chloroalkyl substituent at the 2-position to 2,3,4-substituted pyrrolidine **121** *via* a bicyclic azetidinium intermediate **120**. The chloride could be substituted for hydroxy, cyano and azido

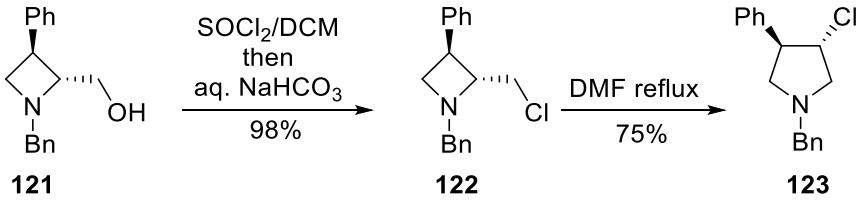
substituents in 44-52% yield by heating 2-(1-chloroalkyl)azetidine at 100 °C in DMSO with 10 equivalents of either sodium hydroxide, potassium cyanide or sodium azide (Scheme 21).[108]



119 **120** **121**

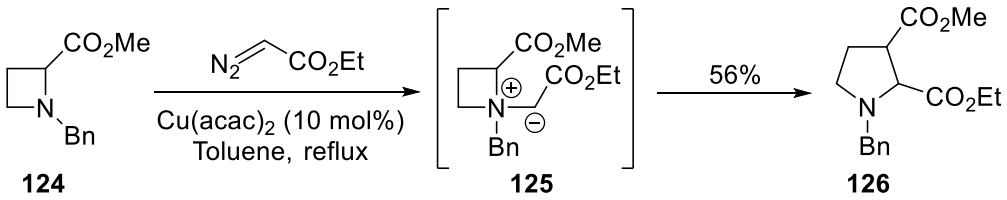
Scheme 21: Ring expansion of azetidine **119** into pyrrolidine **121** *via* bicyclic azetidinium **120**.

Starting from stereodefined primary or secondary 2-hydroxyalkyl azetidines, 3-chloro and 3-mesyloxy pyrrolidines were reported *via* ring expansion of azetidines by Couty and co-workers. The hydroxy substituent was converted into either the chloride or mesyloxy substituents as they act as better leaving groups. The chlorinated azetidines from the primary alcohols were ring expanded into 3-chloropyrrolidines by heating at 120 °C in DMF whereas the 3-mesyloxy pyrrolidines were obtained by heating in chloroform at reflux in 39-80% yield (Scheme 22). Mesylation of secondary alcohols afforded the ring expanded 3-chloropyrrolidine with no detectable amount of the mesylate intermediate. The *anti*-isomer of the chloro azetidines readily expanded to the pyrrolidine products in 94% and 95% yield by heating in chloroform at reflux whereas the *syn*-isomer required heating in DMF at reflux for ring expansion to initiate.[109] The mechanism for ring expansion was proposed to involve a bicyclic azetidinium intermediate in agreement with Bradandt *et al*.[110,108] Taking inspiration from Bradandt *et al*. several pyrrolidine derivatives were synthesised by Couty and co-workers *via* the ring expansion of 2-(chloro or mesyloxy)azetidines in the presence of a nucleophile.[110]



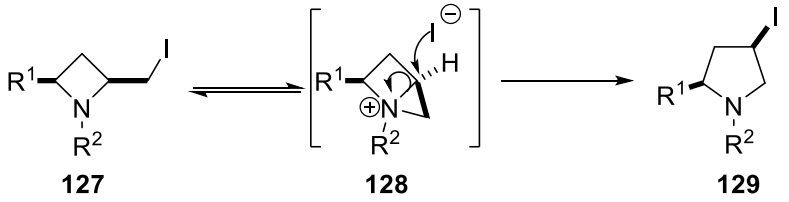
Scheme 22: Ring expansion of chloroazetidine **122**, derived from primary alcohol **121**, into pyrrolidine **123**.

Bott *et al.* reported the ring expansion of *N*-substituted azetidines into pyrrolidine products through the formation of an azetidinium ylide intermediate. Heating azetidine **124** with diazocarbonyl compounds in the presence of catalytic copper(II) acetylacetone gave the azetidinium ylide **125** which ring expanded into the pyrrolidine **126** *via* the Stevens [1,2]-shift (Scheme 23). Thermal and microwave assisted heating conditions were used to synthesise 12 pyrrolidine products in 20-81% yield.[111]



Scheme 23: Ring expansion *via* Stevens [1,2]-shift of azetidinium ylide **125**.

As previously mentioned in the synthesis of azetidines (section 1.2.3.5), Feula *et al*. discovered that the *cis*-iodoazetidine products would ring expand into 3-iodopyrrolidine products even when stored at 4 °C (Scheme 24). Heating *cis*-iodoazetidine compounds in acetonitrile at reflux afforded the 3-iodopyrrolidine compounds in 95-98% yield.[91] The 3-iodopyrrolidine could be accessed selectively during cyclisation of the homoallylic amine substrate by heating the reaction at 50 °C.[2]

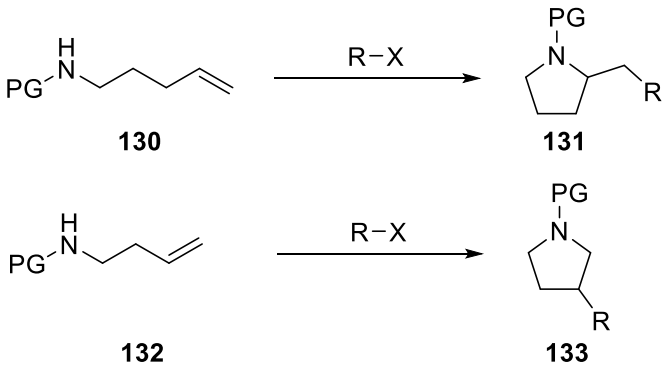


Scheme 24: Proposed ring expansion mechanism from *cis*-azetidine **127** into *cis*-pyrrolidine **129**.

1.3.1.3 Nucleophilic Substitution

Pyrrolidines can be synthesised *via* nucleophilic substitution from starting materials such as epoxides[107], nitrogen-containing acetals and ketals[116] or reductive amination of diketones[117,118] to name a few. However, this section will only focus on those that use aminoalkenes for constructing the pyrrolidine ring.

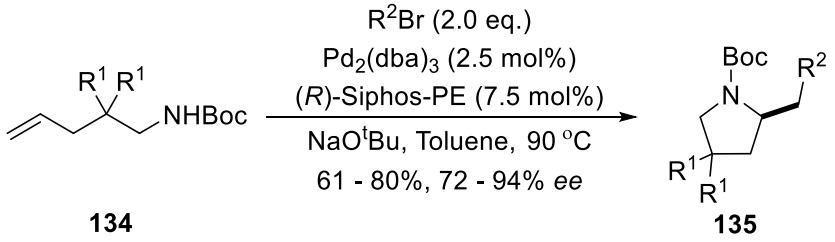
Two types of aminoalkenes can be used to make pyrrolidine rings, γ-aminoalkenes and homoallyl amines. γ-Aminoalkenes **130** afford pyrrolidines **131** with branched substitution at the 2-position whereas homoallyl amines **132** afford pyrrolidines **133** with direct substitution at the 3-position of the pyrrolidine ring (Scheme 25). Cyclisation of these starting materials can occur by a variety of methods to afford a broad scope of pyrrolidine derivatives.



Scheme 25: γ-Aminoalkenes **130** afford pyrrolidines **131** and homoallyl amines **132** afford pyrrolidines **133**.

The Wolfe group used palladium-catalysed carboamination as a method to cyclise γ-aminoalkenes along with aryl bromides into 2-(arylmethyl)pyrrolidine derivatives *via syn*-

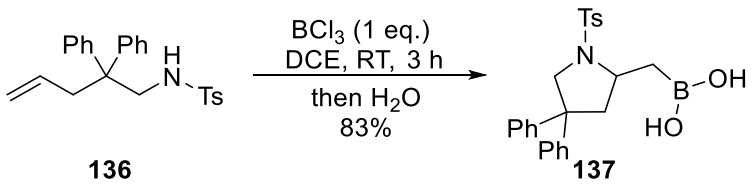
aminopalladaition of intermediate palladium(aryl)(amido)complexes.[119] By selecting a chiral ligand, the Wolfe group demonstrated that the method could be used to synthesise enantiomerically enriched 2-(arylmethyl)- and 2-(alkenylmethyl)pyrrolidine derivatives **135** with *ee* ranging from 72 – 94% (Scheme 26).[120]



134 **135**

Scheme 26: Asymmetric conditions to afford pyrrolidines **135** from γ-aminoalkene **134** in 72-94% *ee*.

Yang and co-workers reported an intramolecular aminoboration method, in which boron trichloride is used as a reagent along with a γ-aminoalkene sulfonamide derivative. After loss of hydrogen chloride, a N-BCl_2 intermediate is formed which activates the double bond and then undergoes intramolecular aminoboration to construct the pyrrolidine ring. The pyrrolidine product is then hydrolysed during the work up to afford 2-methylpyrrolidine boronic acid **137** (Scheme 27).[121]

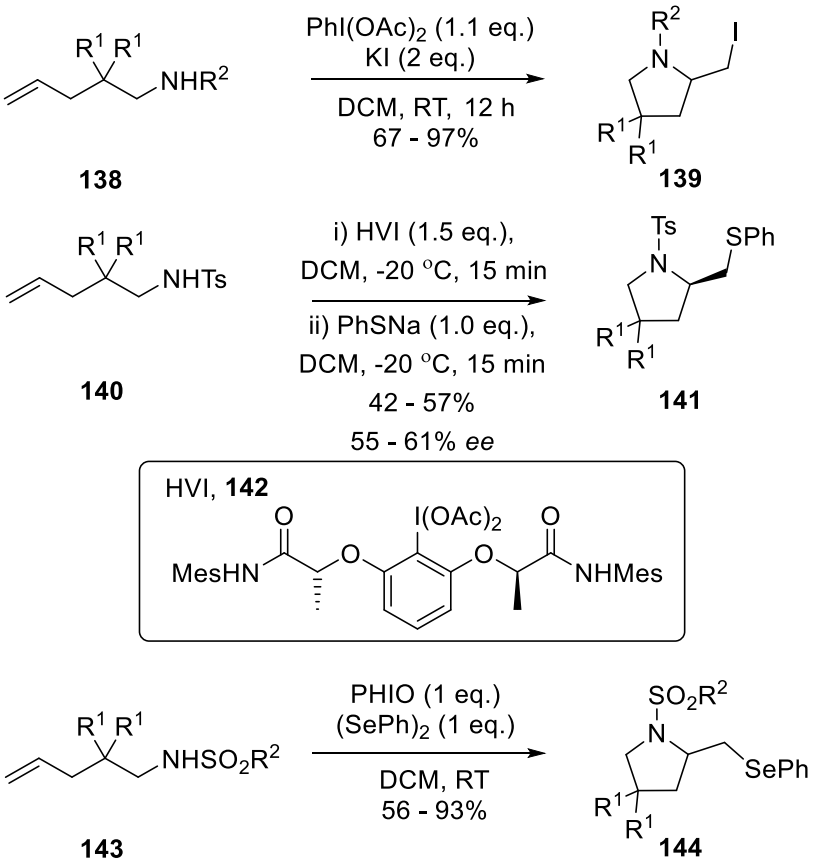


136 **137**

Scheme 27: Boronic acid pyrrolidine **137** from γ-aminoalkene **136**.

Lui and Li used the hypervalent iodine reagent (diacetoxyiodo)benzene (PIDA) to activate the C=C double bond of the γ-aminoalkene **138**, which then cyclised *via* intramolecular nucleophilic attack from nitrogen to construct the pyrrolidine ring **139**. Iodide from potassium iodide displaced PIDA to afford the 2-(iodomethyl)pyrrolidine derivatives (Scheme 28).[122]

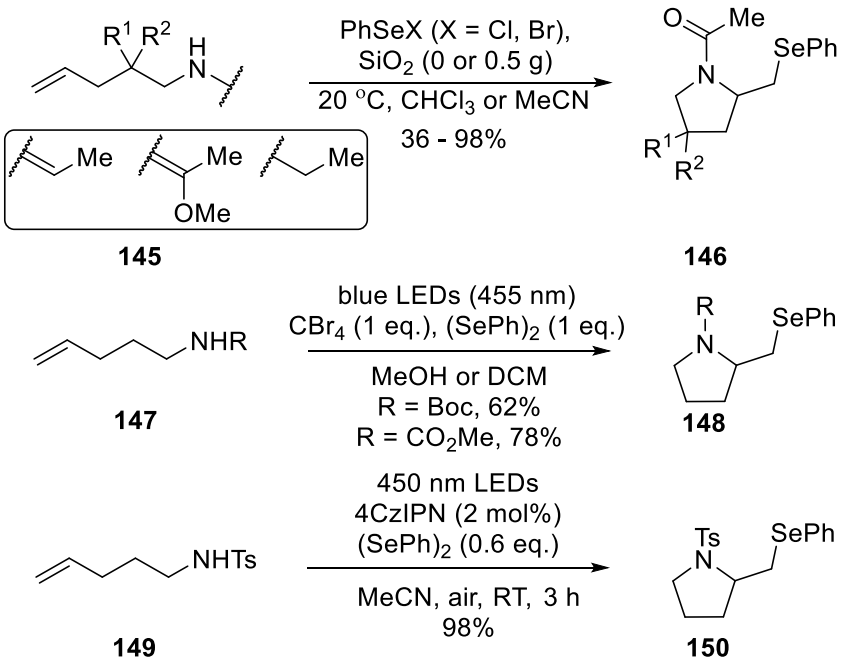
Using a similar method, Mizar *et al.* demonstrated that using chiral hypervalent iodine reagent **142** could afford enantioenriched pyrrolidine products **141** (Scheme 28).[123] More recently Wang and co-workers used the hypervalent iodine reagent iodosobenzene as a promoter along with diphenyl diselenide to afford 2-((phenylselanyl)methyl)pyrrolidines **144** from γ-aminoalkenes **143** (Scheme 28). The advantage of using diphenyl diselenide is that only 0.5 equivalents of diphenyl diselenide is required to make 1 equivalent of the product.[124]



Scheme 28: Cyclisation of γ-aminoalkenes into pyrrolidines from hypervalent iodine induced methodologies.

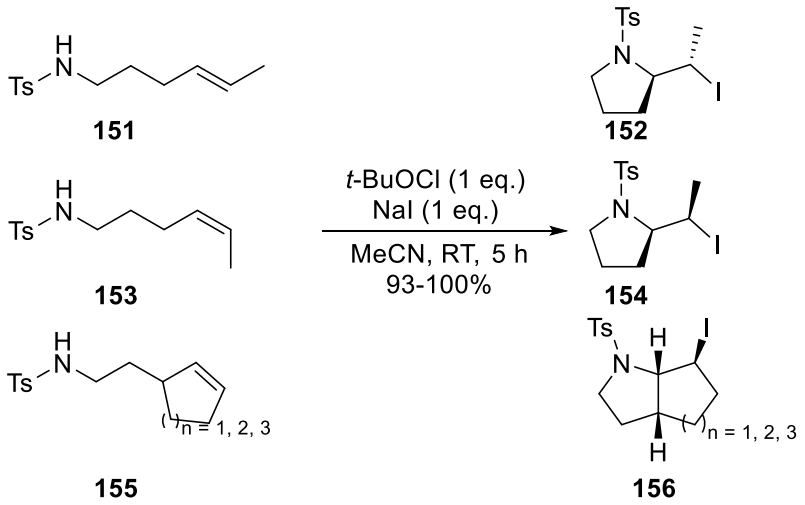
The Uemura group has used phenylselenenyl halide reagents to induce intramolecular amidoseleniation of γ-aminoalkenes **145** to afford 2-((phenylselanyl)methyl)pyrrolidine derivatives **146** (Scheme 29).[125,126] Conner and co-workers and Zhang *et al.* have both used

visible light approaches in the presence of diphenyl diselenide and γ-aminoalkenes **147** and **149** to obtain 2-((phenylselanyl)methyl)pyrrolidine derivatives **148** and **150** (Scheme 29).[127,128]



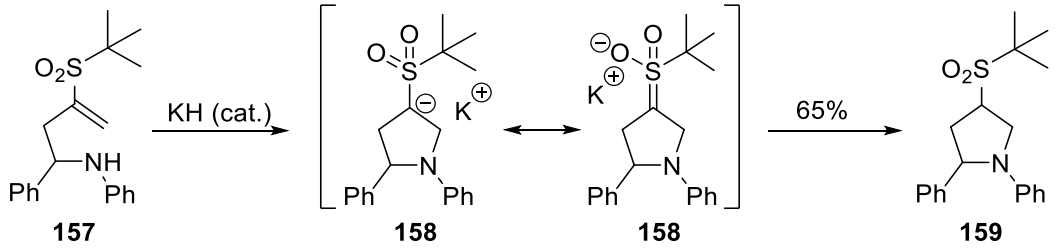
Scheme 29: Strategies employing selenium reagents to synthesise pyrrolidine derivatives from γ-aminoalkenes.

As previously mentioned in the synthesis of azetidines (section 1.2.3.5), Minakata *et al.* cyclised several nitrogen-containing heterocycles from aminoalkenes *via* activation with *tert*-butyl hypoiodite. 2-Methyliodopyrrolidine was isolated from γ-aminoalkene in 98% yield. Terminal methyl **151** and **153** on the allyl group in the (*E*)- and (*Z*)-configuration were tolerated with pyrrolidine products **152** and **154** obtained in 93% and 100% yield respectively. Pyrrolidine fused bicyclic products **156** with five, six and seven membered cycloalkanes were achieved in 94-97% yield (Scheme 30).[90]



Scheme 30: Pyrrolidine products **152**, **154** and **156** obtained from γ-aminoalkenes **151**, **153** and **155** respectively.

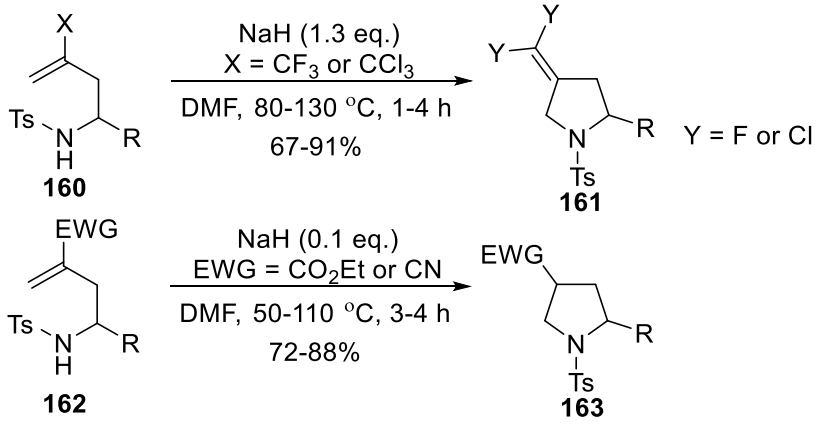
The cyclisation of homoallylic amine substrate **157**, that has a sulfone substituent on the allyl group, with catalytic amount of potassium hydride affords pyrrolidine **159** in 65% yield was reported by Auvray *et al.* (Scheme 31). In the proposed mechanism, deprotonation leads to the formation of pyrrolidine ring **158** with a carbanion stabilised by the sulfone group. This carbanion then deprotonates homoallyl amine **157** to afford pyrrolidine **159** and restart the catalytic cycle.[129]



Scheme 31: Potassium hydride catalysed cyclisation of homoallyl amine **157** to afford pyrrolidine **159**.

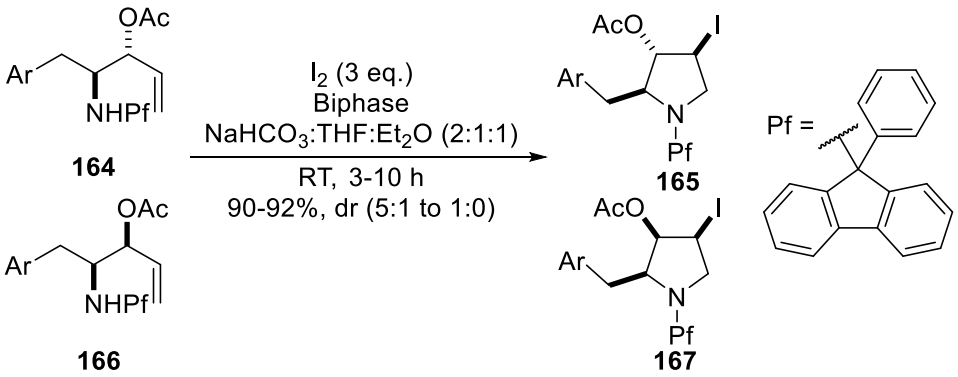
Ichikawa *et al.* used sodium hydride to cyclise homoallylic sulfonamide substrates into pyrrolidine substrates with an electron withdrawing substituent on the allyl group. With 1.3 equivalents of sodium hydride, sulfonamides **160** with either trifluoromethyl or trichloromethyl substituents were cyclised to afford either difluoromethylene or

dichloromethylene substituted pyrrolidines **161** in 67-91% yield. Reducing the equivalents of sodium hydride to 0.1 gave cyano and ethyl ester substituted pyrrolidines **163** in 72-88% yield (Scheme 32).[130]



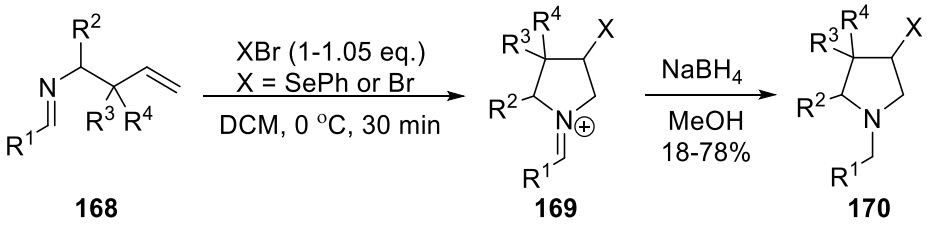
Scheme 32: Sodium hydride induced cyclisation of homoallyl amines **160** and **162** to afford pyrrolidines **161** and **162**.

The transformation of acetyloxyhomoallyl amines **164** and **166** with the 9-phenyl-fluoren-9-yl nitrogen protecting group into pyrrolidine products through diasteroselective iodoamidation was described by Lee *et al.* Biphasic conditions (Sodium bicarbonate: tetrahydrofuran: diethyl ether, 2:1:1) were used in four examples to afford pyrrolidines **165** and **167** in 90-92% yield and diastereomeric ratio ranging from 5:1 to 1:0 with pyrrolidine **165** as the major product for **164** and pyrrolidine **167** as the major product for **166** (Scheme 33).[131]



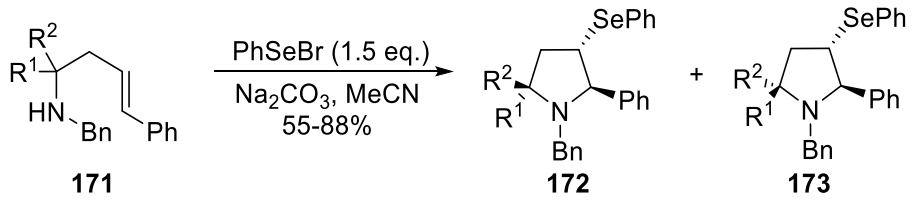
Scheme 33: Iodine induced cyclisation of **164** and **166** in biphasic conditions to afford pyrrolidines **165** and **167**.

Smaele and Kimpe reported the addition of bromine and phenylselenium bromide to homoallyl imines **168** at 0 °C that gave iminium salts **169**. Reduction of **169** with sodium borohydride afforded 3-bromo- and 3-phenylselanyl-pyrrolidines **170** in 18-78% yield (Scheme 34).[132]



Scheme 34: Transformation of homoallyl imines **168** into pyrrolidines **170** *via* iminium salt **169**.

As previously mentioned in the synthesis of azetidines (section 1.2.3.5), Outurquin and co-workers described a protocol for the cyclisation of homoallyl amines with either phenylselenium bromide or chloride that afforded azetidine products as the major isomer. However, homoallylic amine substrates **171** that had a terminal phenyl group afford *cis*- and *trans*-pyrrolidines **172** and **173** regioselectively in 55-88% yield (Scheme 35).[89]



Scheme 35: Regioselective synthesis of pyrrolidines **172** and **173** from homoallyl amine **171**.

Outurquin and co-workers discovered when an excess of either phenylselenium bromide or chloride (2.5 equivalents) were used, the corresponding 3-halopyrrolidine was isolated in 72-85% yield when R^2 = H. Further investigation found that 3-halopyrrolidine products could be isolated in 41-81% yield when $R^2 \neq$ H in the absence of sodium carbonate. Heating the reaction in acetonitrile at reflux in the absence of sodium carbonate formed the 3-halopyrrolidinium

intermediate, which then afforded the 3-halopyrrolidine products through alkaline hydrolysis with sodium carbonate in water.[133]

The cyclisation of homoallylic sulfonamides with a terminal substituent on the allyl group activated by phenylselenium chloride was reported by Jones *et al.* to afford 10 phenylselanylpyrrolidine products in 77-84% yield. No azetidine products were observed during the reactions which corroborates with Outurquin and co-workers' observation with the terminal phenyl **171** that regioselectively afforded pyrrolidine products.[126]

1.4 Aims and Objectives

The aim of the project was to develop a method for synthesising azetidine or pyrrolidine products from homoallylic amine substrates with high regio- and stereo-selectivity, that either complements the molecular iodine mediated cyclisation described by previous group member Antonio Feula or provides access to asymmetric reaction conditions.[2]

As previously discussed in sections 1.2.3.5 and 1.3.1.3, *cis*-iodoazetidines **97** and 3-iodopyrrolidine derivatives were obtained from the protocol described by Feula *et al.* with thermally controlled regioselectivity. The azetidines **97** were discovered to be unstable and ring expanded to pyrrolidines when stored. As a result of this, azetidines **97** were reacted with amines immediately to afford stable *cis*-aminoazetidines **98**.[91] Complementary methodologies include protocols that would give access to a different series of derivatives from the aminoazetidines **98**, access to *trans*-azetidine derivatives or allow the use of more readily removed nitrogen protecting groups than were achieved by Feula.[2] An asymmetric methodology would be favourable as the cyclisation protocol described by Feula *et al.* does not have asymmetric reaction conditions. Protocols that are more efficient with respect to the

reagents required for the reaction to proceed would be desirable: The iodine mediated reaction requires three equivalents of molecular iodine and five equivalents of sodium bicarbonate.[91]

As mentioned in section 1.2.3.5, homoallyl amines afford azetidine products that bear substitution at the 2-position. Methodologies that selectively synthesise azetidine products would be preferable, as these derivatives could address the potentially underexplored 2-subsituted azetidine moiety in the pharmaceutical industry (section 1.2.2). However, selective synthesis of pyrrolidine products would still be a good result, considering the many pharmaceutical applications of the pyrrolidine motif (section 1.3).

To achieve these aims, inspiration was taken from the synthesis of pyrrolidine derivatives from γ-aminoalkenes, with three methodologies chosen for investigation: palladium-catalysed carboamination, hypervalent iodine induced cyclisation and electrochemical induced cyclisation. Control reactions with γ-aminoalkenes, that are analogous to the homoallylic amine model substrates, will be performed to gain insight into the selected method before subjecting the homoallylic amine substrates to the reaction conditions. Achiral homoallyl amines will be used as model substrates in initial optimisation of the reaction conditions towards homoallylic amine substrates. This will limit the number of possible products expected from the reaction to regioisomers, as stereoisomers would not be obtained from achiral substrates which will simplify the analysis of the reaction outcome. Racemic homoallyl amines will then be used to assess the stereoselectivity of the method and investigate asymmetric reaction conditions.

2 Palladium

2.1 Inspiration for Palladium-Catalysed Cyclisation

It was hypothesised that literature procedures for palladium-catalysed cyclisation of γ-aminoalkenes into pyrrolidine derivatives, could be adapted for the cyclisation of homoallylic amine substrates into aza-heterocycles (Figure 8). The testing of this hypothesis is outlined in this chapter.

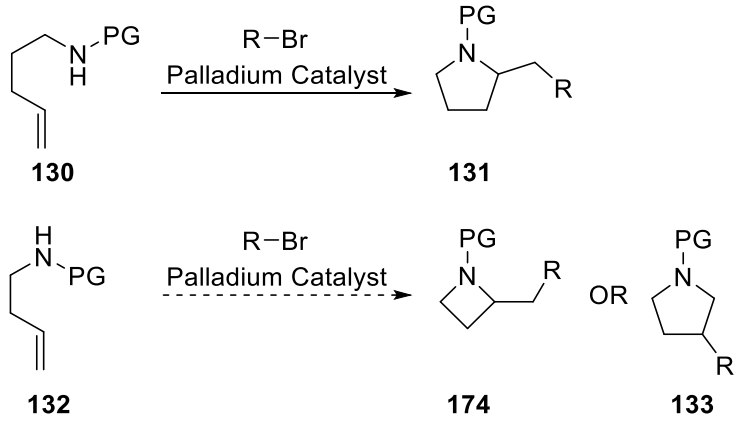
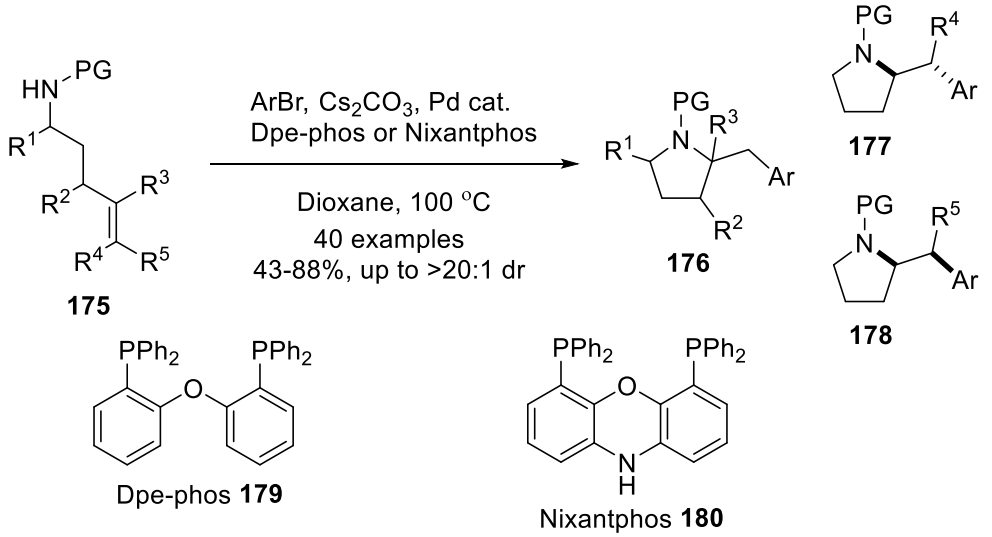


Figure 8: Hypothesis that aza-hetercycles **174** and **133** can be synthesised from homoallyl amines **132** with procedures used for cyclisation of γ-aminoalkenes **130** into pyrrolidines **131**.

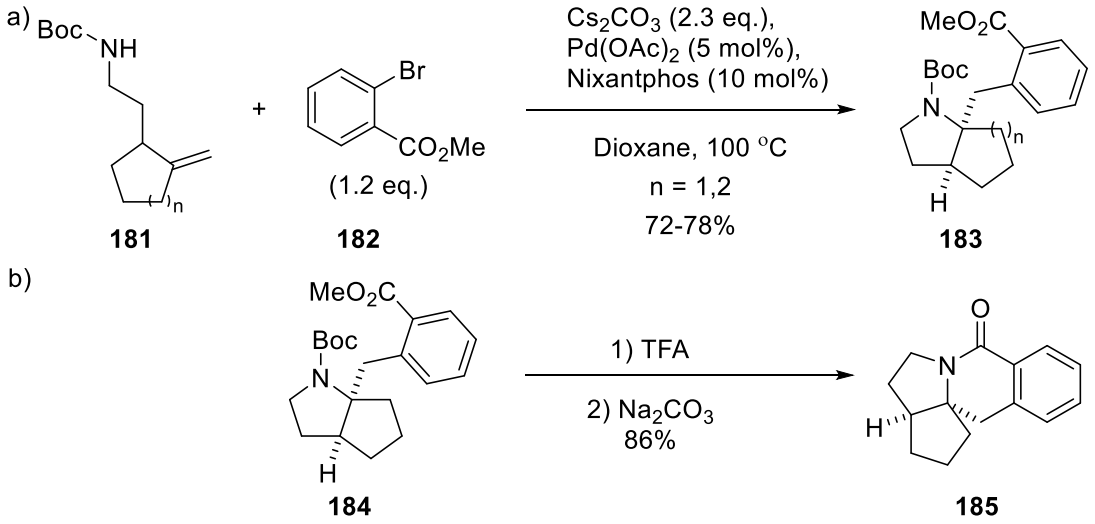
As briefly described in section 1.3.1.3, the Wolfe group have developed methods for synthesising pyrrolidine products from γ-aminoalkenes *via* palladium-catalysed carboamination. In the presence of caesium carbonate, forty 2-(arylmethyl)pyrrolidine derivatives were synthesised from aryl bromides and γ-aminoalkenes **175** with various substitution at positions; 1, 3, 4 and 5, demonstrating the capability of the method to tolerate a broad scope of γ-aminoalkene starting materials (Scheme 36). Isolated yields of 43-88% and >20:1 diastereoselectivity was achieved for most products with more than one substituent on the pyrrolidine ring. Bis(2-diphenylphosphinophenyl)ether **179** (Dpe-phos) was used as the ligand for most of the transformations, however, 4,6-bis(diphenylphosphino)phenoxazine **180**

(Nixantphos) was used when substituents were present on the 4- or 5-position of the γ-aminoalkene chain. Substrates with substituents at the 4- and 5-position were low yielding when Dpe-phos was used as the ligand, whereas Nixantphos was found to afford pyrrolidine derivatives **177** and **178** in moderate to good yield.[119]



Scheme 36: Pyrrolidine derivatives synthesised from γ-aminoalkenes **175** using Dpe-phos or nixantphos as ligands.

Pyrrolidine derivatives **183** fused to either cyclopentane or cyclohexane were obtained when cyclopentane or cyclohexane were present at the 3- and 4-positions of the γ-aminoalkene **181** in 72-78% yield. In addition to this Bertrand, Neukom and Wolfe have taken Boc-protected pyrrolidine **184** that contained an *ortho*-methyl ester on the aryl substituent and converted it into tetrahydropyrroloisoquinolin-5-one **185** in two steps using trifluoracetic acid and sodium carbonate (Scheme 37).[119] The ability to make multicyclic ring systems shows the utility of this method for scaffold synthesis, useful in the generation of compound libraries in the pharmaceutical industry.



Scheme 37: a) Bicyclic ring formation from γ-aminoalkenes **181**. b) Using bicyclic pyrrolidine **184** to synthesise tetrahydropyrroloisoquinolin-5-one **185** in 2 steps.

The proposed mechanism for this reaction starts with *in situ* generation of palladium(0) species from palladium(II) acetate and the ligand, followed by oxidative addition of the aryl bromide. In the presence of caesium carbonate base, ligand exchange takes place to convert the palladium(aryl)(bromide) intermediate **186** into the palladium(aryl)(amido) complex **187**. Intramolecular *syn*-aminopalladation constructs the pyrrolidine ring **188** which is then converted to product **189** through reductive elimination (Figure 9).[119]

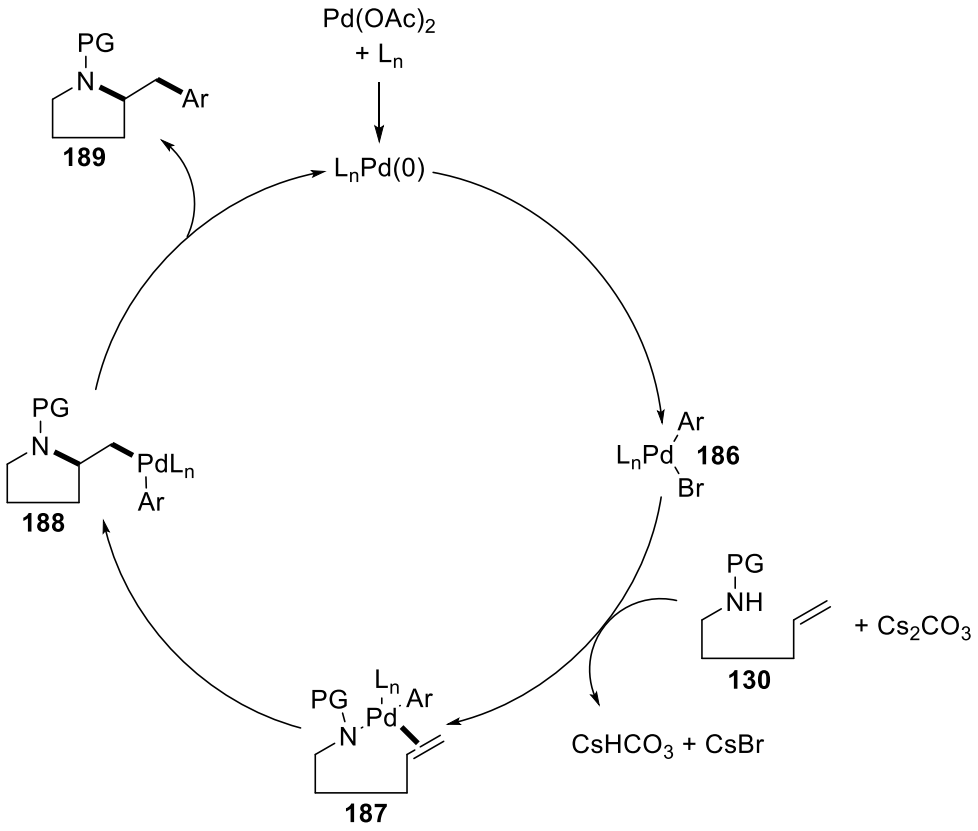
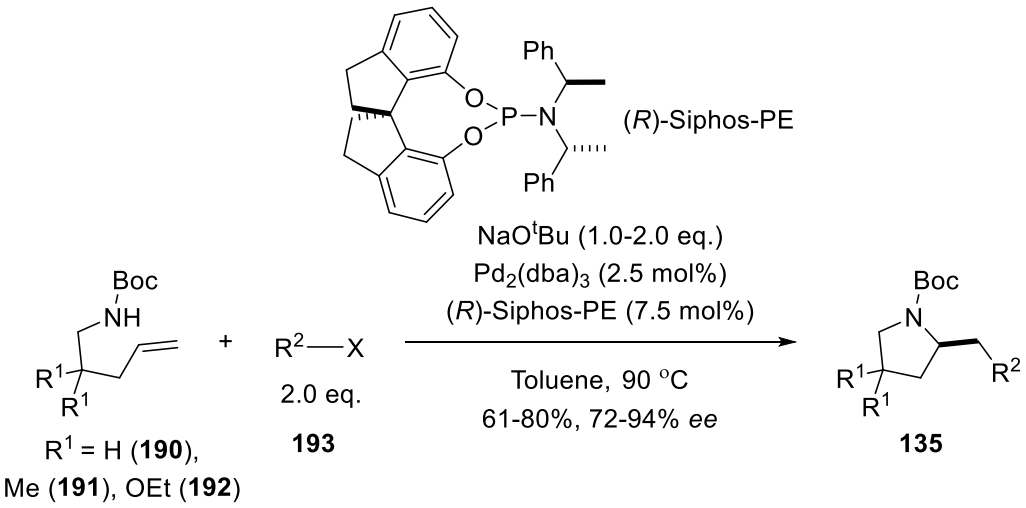


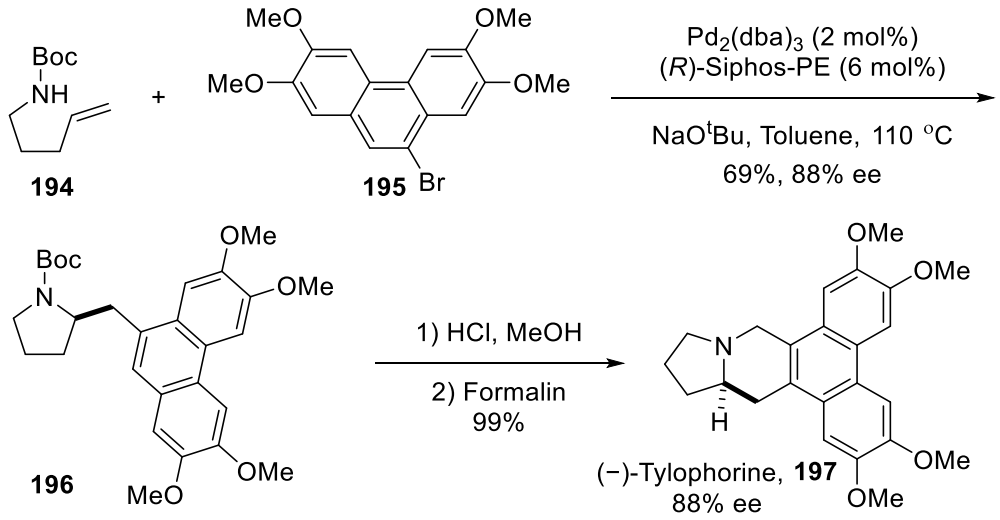
Figure 9: Simplified palladium mechanism for *syn*-aminopalladation products proposed by Wolfe group.

Mai and Wolfe have reported conditions for asymmetric synthesis for this reaction to obtain enantiomerically enriched 2-(arylmethyl) and 2-(alkenylmethyl)pyrrolidine derivatives **135** using *N*-di[(*R*)-1-phenylethyl]-[(*R*)-1,1'-spirobiindane-7,7'-diyl]-phosphoramidite ((*R*)-Siphos-PE) as the chiral ligand. Utilising these optimised conditions, nineteen enantiomerically enriched pyrrolidine derivatives were synthesised with 61-80% yield and 72-94% enantiomeric excess (*ee*) (Scheme 38). Only three γ-aminoalkenes were used with most products derived from either γ-aminoalkene **190** or γ-aminoalkene **191** with one example using γ-aminoalkene **192**.[120]



Scheme 38: Asymmetric conditions for the cyclisation of γ-aminoalkenes **190**, **191** and **192** into pyrrolidines **135**.

This asymmetric method was applied to the synthesis of (−)-tylophorine by Mai and Wolfe affording the desired intermediate **196** in 69% yield and 88% *ee*. The intermediate was transformed into (−)-tylophorine in two steps in 99% yield while retaining an *ee* of 88% (Scheme 39).[120]



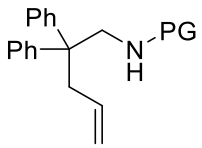
Scheme 39: Synthesis of (−)-tylophorine using Wolfe group asymmetric cyclisation reaction to afford key intermediate **196** in good yield and high *ee*.

The methods described above from the Wolfe group were a great source of inspiration for several reasons. Firstly, the racemic method reported had good tolerance of starting materials and was capable of using γ-aminoalkenes with substituents at various positions along the

carbon chain. This means the likelihood of the method accepting homoallyl amines as starting materials was higher than a method that only used a very rigid type of starting material. Secondly, the method would complement the iodine mediated method described by Feula *et al.* as it gives access to 2-(arylmethyl) and 2-(alkenylmethyl) derivatives which cannot be easily accessed with the procedure reported by Feula *et al.* Thirdly, the Wolfe group have shown that the nitrogen can be deprotected successfully after performing the cyclisation reaction. This opens the potential for the synthesis of azetidine products that can undergo nitrogen deprotection which has not yet been achieved using the method described by Feula *et al.* Lastly, enantiomerically enriched products were obtained from achiral starting materials with a chiral ligand in high yield and *ee*. Using the asymmetric conditions reported by the Wolfe group on homoallyl amines would potentially address the limitations of the method described by Yoshizawa *et al.* for asymmetric synthesis of azetidines while retaining good *ee* of products.

2.2 Control System with γ-Aminoalkene

The substrate chosen as the control for this reaction was the diphenyl substituted γ-aminoalkene **198** (Figure 10). As the substrate was used to investigate the hypervalent iodine method (section 3.1), it was also used in this study.

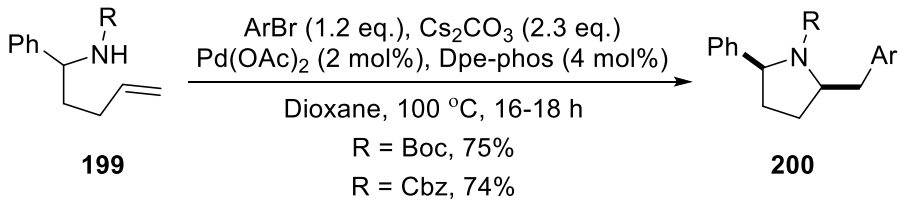


198

Figure 10: Model γ-aminoalkene substrate **198**.

While the Wolfe group had not used this substrate, they had shown that two substituents were tolerated at the 2-position in the asymmetric method (Scheme 38) and the phenyl

substituent was tolerated in the racemic method (Scheme 40) so the risk of the substrate not reacting as expected was low.[119,120]



Scheme 40: Bertrand *et al.* reported the synthesis of pyrrolidines **200** from γ-aminoalkene **199** under racemic conditions.

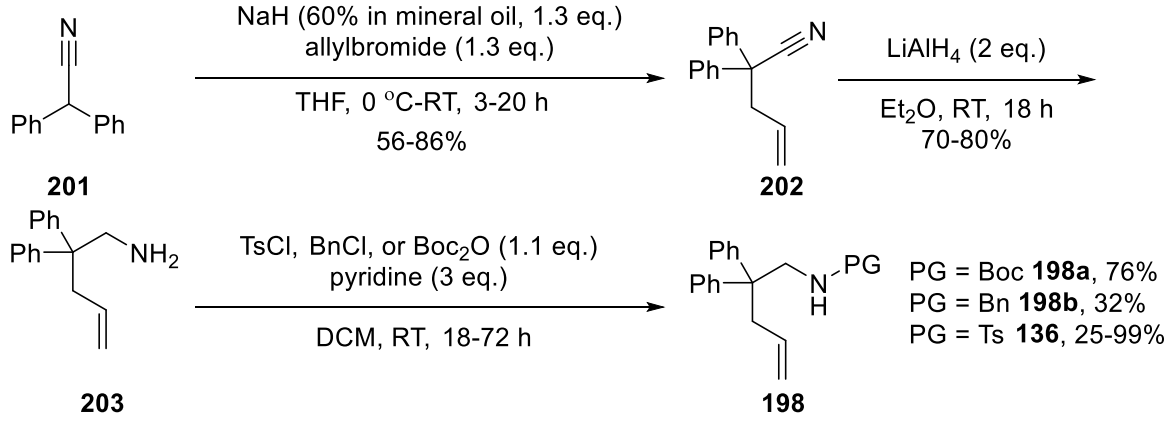
To explore how the electronic character of the nitrogen protecting group affected the intramolecular *syn*-aminopalladation to afford intermediate **188** (Figure 9), three protecting groups were chosen: *tert*-butoxycarbonyl (Boc), benzyl (Bn) and tosyl (Ts).

The Boc group was chosen as it was the most popular nitrogen protecting group used by the Wolfe group in the racemic method and was used in the asymmetric method described in section 2.1. The relative ease of deprotection of the Boc group is desirable as it would allow access to the free amine which could then be further derivatised as demonstrated by the Wolfe group with products **185** (Scheme 37) and **197** (Scheme 39).[119,120]

The benzyl group was chosen as it was used by Feula *et al.* and Yoshizawa *et al.* in the iodine mediated cyclisation method for homoallylic amine substrates.[134,95] Although it could not be removed, the compounds synthesised were still of interest with biological activity observed and applications of single enantiomer derivatives used in catalysis as discussed in more detail in section 1.2.3.5.[92,95] Therefore, using the benzyl group in the palladium-catalysed carboamination reaction, could afford products that could be directly compared to the compounds synthesised by Feula *et al*. and Yoshizawa *et al.*

The tosyl group was chosen as it was the protecting group used for the hypervalent iodine mediated reaction (section 3.2) and would therefore offer direct comparison of the scope and limitations between these methodologies.

The nitrogen-protected γ-aminoalkenes **198** were synthesised in three steps from cheap commercially available diphenylacetonitrile **201** using literature procedures described by Mizar *et al*.[123] In the first step **201** was deprotonated with sodium hydride and then subsequently alkylated with dropwise addition of allyl bromide to give **202** in 56-86% yield. Reduction of **202** with lithium aluminium hydride gave **203** in 70-80% yield. Finally, nitrogen protection of **198** was achieved in 25-99% yield using either Boc anhydride, benzyl chloride or *p*-toluenesulfonyl chloride with pyridine acting as a base (Scheme 41). Although yield of the reaction varied, particularly for **136**, sufficient material was obtained to probe the cyclisation reactions and therefore optimisation of the reaction was not pursued.

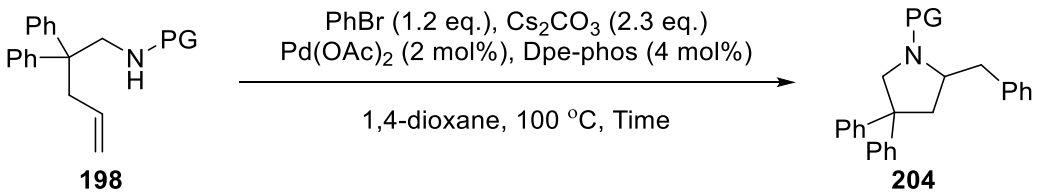


Scheme 41: Three step synthesis of γ-aminoalkenes **198** from commercially available **201**.

The three synthesised γ-aminoalkenes **198** were then subjected to the palladium-catalysed carboamination conditions reported by Bertrand, Neukom and Wolfe.[119] As there were no substituents at the 4- or 5-position of the γ-aminoalkene chain, the conditions using Dpe-phos

as the ligand were selected and reaction completion was determined by thin layer chromatography (TLC) (Table 1).

Table 1: Comparison of nitrogen protecting groups when used in palladium-catalysed carboamination reaction. Reaction completion was determined by TLC.



198 **204**

Nitrogen Protecting Group	Time (h)	Isolated Yield (%)
Boc (**198a**)	22	62
Bn (**198b**)	90	-
Ts (**136**)	20	42

(Reactions performed with 100 mg of γ-aminoalkene **198**)

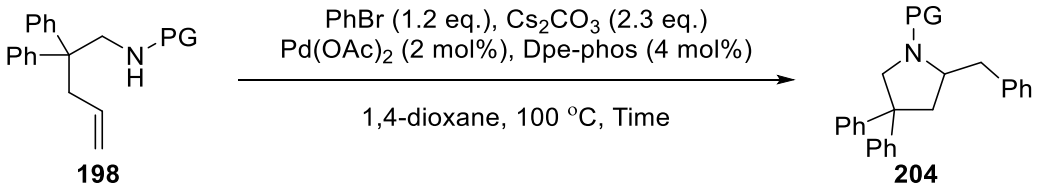
The γ-aminoalkene **198** was tolerated by the reaction conditions even though it was not a reported substrate used by the Wolfe group. The Boc protecting group had the highest isolated yield, and indeed was the most frequently used by the Wolfe group in both the racemic and asymmetric methods. Pleasingly, the tosyl protected substrate was successfully cyclised into desired product with a moderate yield. No benzyl protected product was observed despite the increased reaction time compared to the other protecting groups. As benzyl amines are not compatible with these reaction conditions, then the generation of a series of compounds with one-point changes to the compounds synthesised by Feula *et al.* and Yoshizawa *et al.* would not be feasible. As a result of this, direct comparisons between compounds synthesised from the palladium-catalysed carboamination method and the iodine mediated method would not be possible.

As a possible way to reduce reaction times and improve the yield of the reaction, microwave assisted conditions were explored. Microwave technology was implemented in organic

chemistry from the mid-1980s; the main advantage of using microwave assisted organic synthesis was the shorter reaction times compared to traditional heating using oil baths, sand baths and heating jackets.[135] The reduction of reaction times is not fully understood, while some believe that it is the result of a microwave specific effect, it was thought that the rapid and uniform heating achieved from microwave heating was responsible.[136] Unlike traditional heating that relies on heat transfer through the reaction that can lead to a temperature gradient and local overheating, which can result in decomposition, microwave radiation passes through the vessel to heat only the solvent and reagents, resulting in a uniform heating of the sample.[135] Uniform heating throughout the sample, which can lead to fewer by-products and/or decomposition products, might also be a contributing factor to the shorter reaction times of microwave assisted organic synthesis.

In keeping with the thermal conditions, reaction completion of the microwave assisted conditions were determined by TLC (Table 2).

Table 2: Microwave assisted conditions for palladium-catalysed carboamination reaction with thermal conditions included for comparison.



198 **204**

Nitrogen protecting group	Microwave assisted conditions		Thermal Conditions	
	Time (h)	Isolated Yield (%)	Time (h)	Isolated Yield
Boc (**198a**)	2	61	22	62
Bn (**198b**)	1	-	90	-
Ts (**136**)	2	49	20	42

(Reactions performed with 100 mg of γ-aminoalkene **198**)

The microwave assisted conditions did not have a significant affect on yield but did reduce the reaction time to a tenth of the literature conditions for both the Boc and the tosyl group. Despite the potential for fewer by-products and/or decomposition products with the microwave assisted conditions, no benzyl protected product was observed. This gave further evidence that benzyl amine substrates are not compatible with palladium-catalysed carboamination and therefore benzyl protected homoallylic amine substrates would not be pursued with this method.

2.3 Palladium-Catalysed Cyclisation with Homoallylic Amines

In the case of γ-aminoalkene **198**, there are two comparable homoallylic amine substrates depending on which side of the diphenyl substituted carbon is 'deleted' (Figure 11).

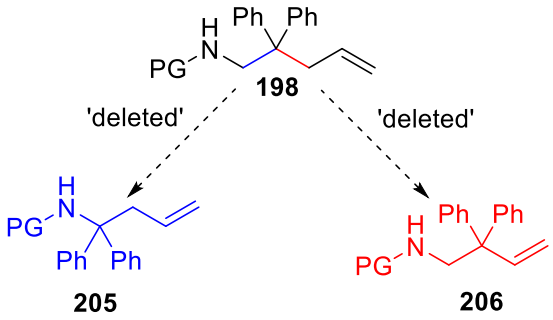
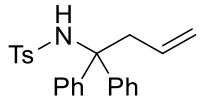


Figure 11: Two equivalent homoallyl amines **205** and **206** from **198** depending on which carbon atom is 'deleted' from **198**.

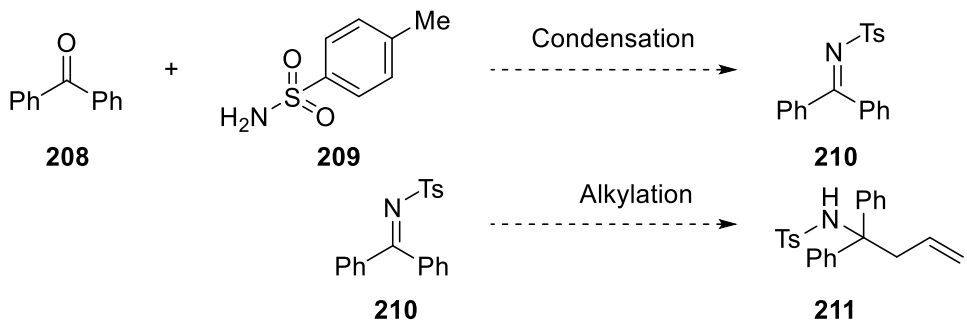
Homoallyl amine **207** was chosen as the model substrate as it had substitution adjacent to the amine in keeping with compounds synthesised by Feula *et al.*[134] Despite the higher yields obtained with Boc protected **198**, tosyl protected **207** was chosen as the model substrate as it could also be used for the hypervalent iodine mediated method (Figure 12).



207

Figure 12: Model substrate, tosyl protected homoallyl amine **207**.

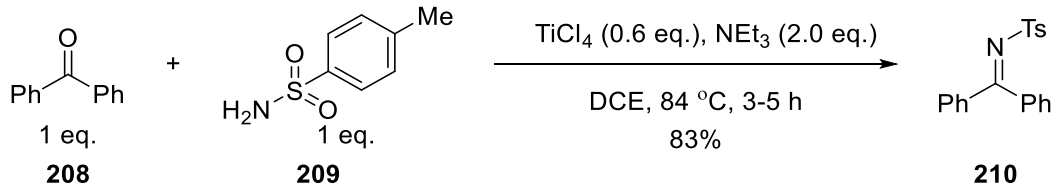
The proposed synthetic route for homoallyl amine **211** was based on Feula *et al.*'s work and consisted of two steps, imine formation, followed by alkylation using a Grignard reagent.[134] The key differences of the proposed route were in the imine formation step in which a ketone would be used in place of an aldehyde and a sulfonamide would be used in place of a benzylic amine (Scheme 42).



Scheme 42: Proposed synthetic route to homoallyl amine **211** from ketone **208**.

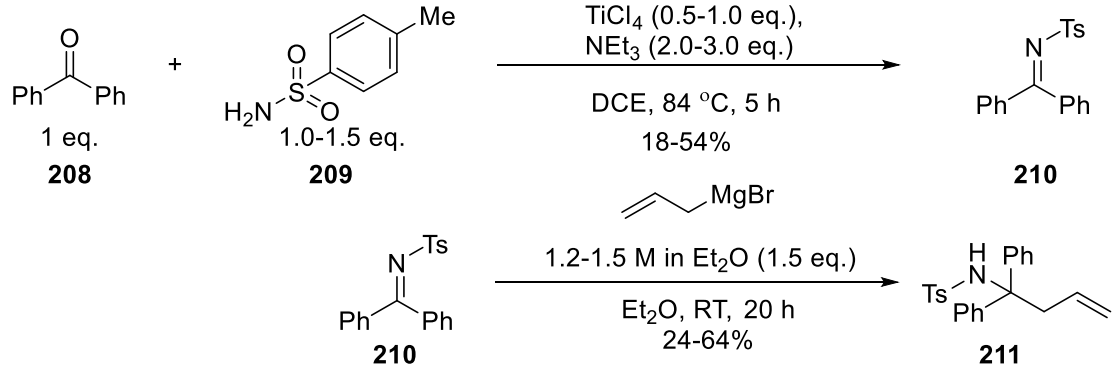
Under the imine formation procedure described by Feula *et al.*,[2] in which an aldehyde is stirred with an amine at 60 °C in ethanol for 4 hours, no product was observed so the reaction was modified to use Dean-Stark apparatus to remove water from the reaction and drive the equilibrium towards the product. However, no product formation was observed when using the Dean-Stark apparatus.

Ram and Khan published a method for condensing *p*-toluenesulfonamide **209** with benzophenone **208** in 83% yield by using titanium tetrachloride as a Lewis acid and triethylamine as a base (Scheme 43).[137]



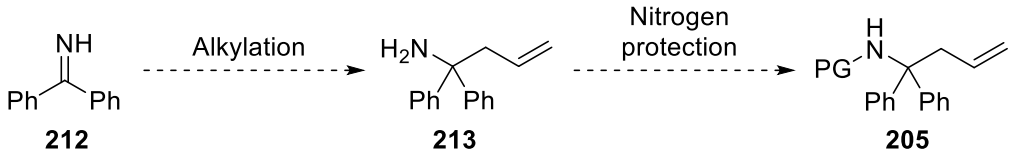
Scheme 43: Ram and Khan synthesis of imine **210**.

Using the method published by Ram and Khan imine **210** was obtained, although the reaction was unreliable and often low yielding (≈ 20%), with the exception of one attempt that had a yield of 54%. Homoallyl amine **211** was successfully obtained by alkylating imine **210** using allylmagnesium bromide with yields between 24 and 64% (Scheme 44).



Scheme 44: Synthetic route to homoallyl amine **211** from ketone **208** with poor to moderate yields.

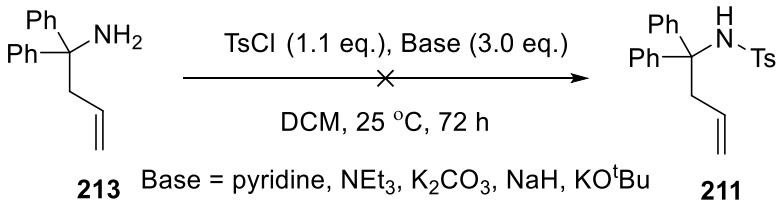
While the desired homoallyl amine was successfully obtained, the poor reproducibility of the imine formation step made it difficult to quickly prepare suitable amount of material for probing the cyclisation methods. To address this issue, a new synthetic route was designed starting from the commercially available benzophenone imine **212** to bypass the imine formation issues experienced in the previous route. The route was still two steps starting with alkylation of imine **212** using Grignard reagent to afford homoallyl amine **213**, followed by a nitrogen protecting step, which also allowed different nitrogen protecting groups to be accessed faster from a building block compared to the previous route (Scheme 45).



212 213 205

Scheme 45: New proposed synthetic route to homoallyl amine **205** from commercially available imine **212**.

Allylmagnesium bromide as a solution in diethyl ether, used in the previous route and by Feula *et al.* to alkylate imines, did not react with benzophenone imine **212**; only decomposed starting material was obtained after reaction work up. However, switching to allylmagnesium chloride as a solution in THF afforded the homoallyl amine **212** with yields around 70%. No tosyl or Boc protected homoallyl amine **205** was isolated using conditions described by Mizar *et al.* with pyridine as the base.[123] Using stronger or inorganic base did not improve the reaction, as no protected homoallyl amine **211** was observed with triethylamine, potassium carbonate, sodium hydride or potassium *tert*-butoxide (Scheme 46). This synthetic route was abandoned at this point as no progress towards the desired model substrate was made.

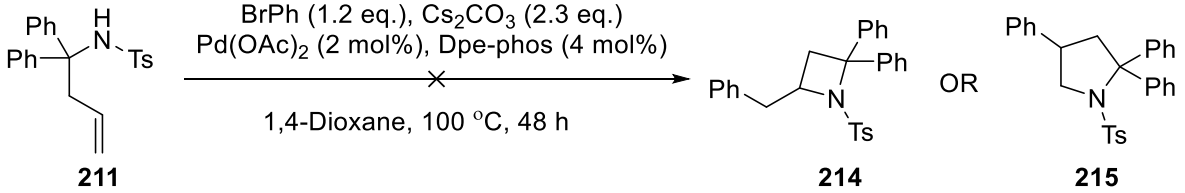


213 211

Scheme 46: Nitrogen protection of **213** was unsuccessful with pyridine, NEt_3, K_2CO_3, NaH or KO^tBu acting as a base.

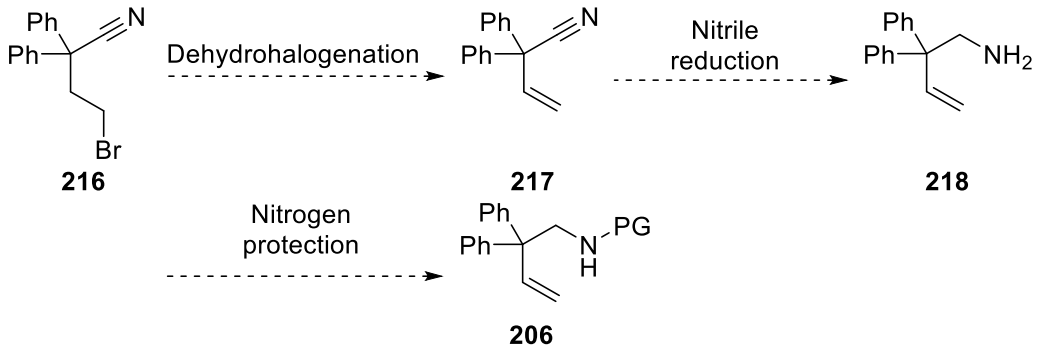
As the nitrogen protection step did not afford homoallyl amine **211**, the preparation of homoallyl amine **211** was limited due to the unreliability of the first synthetic route as discussed above, which would make it difficult to probe the palladium-catalysed carboamination reaction conditions. However, there was sufficient amount to perform initial tests. The thermal opposed to the microwave assisted conditions were employed to minimise

differences with the work reported by the Wolfe group. No reaction occurred as only starting material was observed by TLC (Scheme 47).



Scheme 47: Unsuccessful reaction under thermal conditions, only starting material **211** observed by TLC.

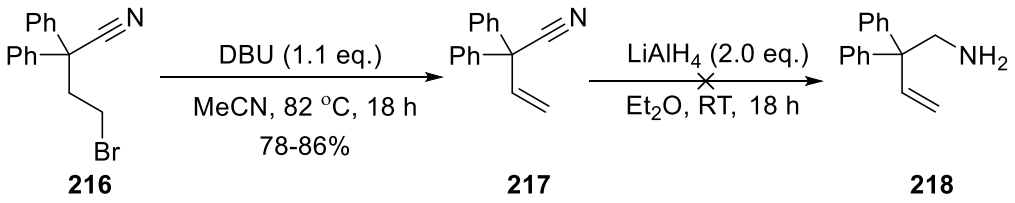
A possible explanation for no reaction to occur is the steric hinderance of the diphenyl substituents adjacent to the nitrogen atom of homoallyl amine **211**. With this in mind, efforts were focussed on the less sterically hindered homoallyl amine **206**. Inspiration for the synthetic route was taken from Mizar *et al.* with only the first step changed as unlike allyl bromide, S_N2 substitution of the bromide in vinyl bromide is not feasible.[123] Instead, the proposed route installed the alkene group *via* elimination of bromide from commercially available 4-bromo-2,2'-diphenylbutyronitrile **216**, using a strong base (Scheme 48).



Scheme 48: Proposed synthetic route to less sterically hindered homoallyl amine **206** from commercially available **216**.

Using a modified procedure by Arumugam and Verkade the dehydrohalogenation reaction afforded product **217** in around 80% yields.[138] However, the subsequent reduction step using lithium aluminium hydride observed no desired product, which was surprising given that the

same conditions reduced the one carbon longer nitrile compound **202** in high yield (section 2.2) (Scheme 49).



Scheme 49: Dehydrohalogenation afforded **217** in high yields 78-86%. Nitrile reduction of **217** was unsuccessful.

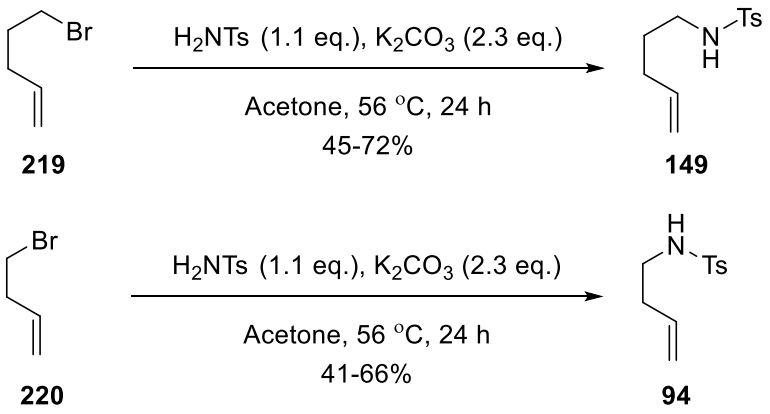
Considering the aim of the project was to investigate methods for cyclising homoallyl amines into heterocycles, as opposed to the synthesis of homoallyl amines, optimisation of the nitrile reduction step was not pursued. Therefore, the diphenyl homoallyl amines **205** and **206** were unsuitable as model reaction substrates.

2.3.1 New Model Substrates

Efforts then turned to aminoalkenes **94** and **149** as the respective homoallylic amine model substrate and γ-aminoalkene control to remove potential steric hinderance adjacent to the nitrogen atom.

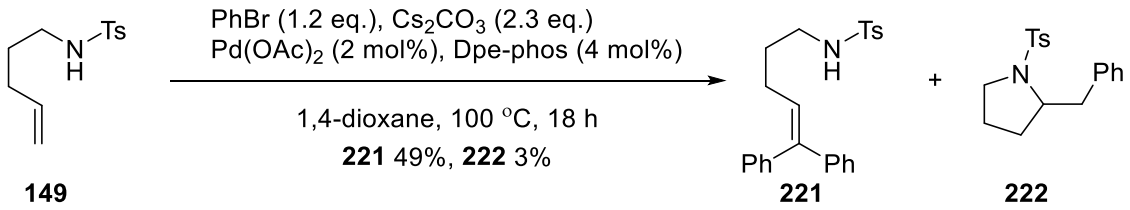
γ-Aminoalkene **149** was synthesised in one step from commercially available 5-bromo-1-pentene **219** with *p*-toluenesulfonamide, by heating at reflux in acetone in the presence of potassium carbonate with moderate to high yields (45 – 72%). Pleasingly, the equivalent homoallyl amine **94** could be synthesised using the same conditions from commercially available 4-bromo-1-butene **220** in moderate yields (41 – 66%) (Scheme 50). Although the yield of the reactions were inconsistent, it was deemed unnecessary to optimise as the reaction was only step to cyclisation starting material and the reaction always afforded

product unlike the condensation reaction used in the synthesis of diphenyl homoallyl amine **211** (section 2.3).



Scheme 50: γ-Aminoalkene **149** and homoallyl amine **94** obtained in moderate to good yields from respective commercially available bromoalkenes **219** and **220**.

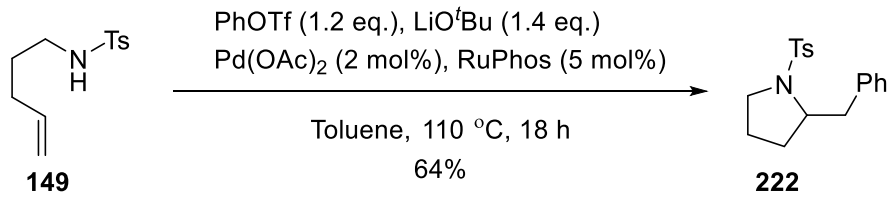
Despite tosyl protected diphenyl γ-aminoalkene **136** affording tosyl protected pyrrolidine **204c** when subjected to the thermal palladium-catalysed carboamination conditions (section 2.2), γ-aminoalkene **149** did not afford heterocycles as the major product, with pyrrolidine **222** isolated as the minor product in 3% yield. Analysis of the proton NMR spectrum suggested that the major product **221** was formed from a double Heck reaction which installed two benzene rings on the terminal alkene bond (Scheme 51).



Scheme 51: Pyrrolidine **222** afforded as minor product when γ-aminoalkene **149** was subjected to thermal palladium-catalysed carboamination reaction conditions reported by Bertrand *et al*.

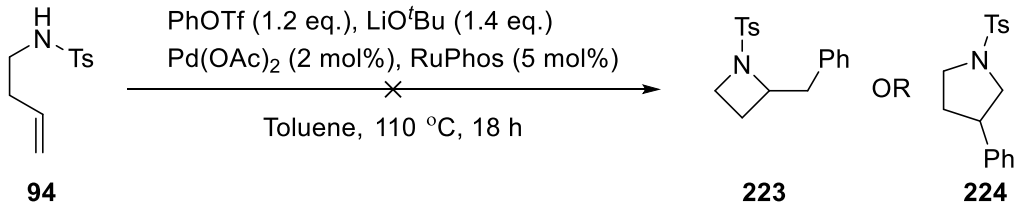
Re-examination of the literature found that the Wolfe group had isolated a Heck product as the major product when using γ-aminoalkene **149** and reported alternative conditions that gave pyrrolidine **222** as the major product.[139] Subjecting γ-aminoalkene **149** to the alternative

reaction conditions reported by Peterson and Wolfe afforded pyrrolidine **222** in 64% yield (Scheme 52).



Scheme 52: Pyrrolidine **222** obtained from γ-aminoalkene **149** with reaction conditions described by Peterson and Wolfe.

These conditions were then used on homoallyl amine **94** but yielded inconclusive results. Conflicting data was obtained for the product mixture. The mass spectra for the mixture had peaks that were consistent with starting material **94** and either Heck or cyclised products **223** and **224**. However, the proton NMR spectrum of the mixture did not have enough protons in the aromatic region which suggested that the aromatic group was not installed. The aromatic region was less clear in the carbon NMR spectrum due to overlapping peaks from starting material **94**. No CH peaks were observed in the aliphatic region in the ^{13}C Jmod NMR spectrum that would be expected for cyclised products **223** and **224**, leading to the conclusion that cyclisation did not occur in the reaction (Scheme 53).



Scheme 53: Unsuccessful reaction with homoallyl amine **94** using reaction conditions described by Peterson and Wolfe.

With no evidence of heterocyclic products from homoallylic amine substrates, work on the palladium-catalysed carboamination method was halted. At this point in the project the other two methods under investigation (hypervalent iodine mediated cyclisation and

electrochemically mediated cyclisation, sections 3 and 4 respectively) had more promising results with cyclisation of homoallylic amine substrates observed.

2.4 Conclusions and Future Work

To summarise, Boc protected γ-aminoalkene **198a** and tosyl protected γ-aminoalkene **136** were compatible with the procedure described by Bertrand *et al.* No product was observed with benzyl protected γ-aminoalkene **198b**. Microwave assisted conditions did not affect the yield of the reaction but were found to significantly reduce the reaction time. The synthesis of diphenyl homoallyl amines **211** and **206** were challenging as the synthesis for less sterically hindered diphenyl homoallyl amines **206** was not completed and the synthesis of diphenyl homoallyl amine **211** was unreliable. No cyclised products were observed when diphenyl homoallyl amine **211** was subjected to the palladium-catalysed reaction conditions described by Bertrand *et al*. Steric hinderance was suspected to be preventing cyclisation from occurring, but this was not confirmed. Synthesis of γ-aminoalkene **149** and homoallyl amine **94** were reliably obtained in one step from commercially available starting materials. Although pyrrolidine **222** was isolated from γ-aminoalkene **149** as the minor product under Bertrand *et al.* conditions, it was obtained as the major product with conditions described by Peterson and Wolfe. The cyclisation of homoallyl amine **94** using reaction conditions reported by Peterson and Wolfe was unsuccessful as no cyclised products were isolated from the reaction.

In conclusion the palladium-catalysed carboamination method has not achieved the aim of developing a regio- and stereo-selective synthesis of azetidine and/or pyrrolidine derivatives from homoallylic amine starting materials, as no azetidine or pyrrolidine products have been isolated from homoallyl amines. Although the aim of the project has not been achieved,

synthetic challenges in preparing substrates and time constraints in the laboratory have prevented a full investigation of the method with avenues still to be explored that could achieve the goals of the project.

Future work needs to confirm if it is possible for heterocyclic products to be obtained from homoallyl amines with this method as that is the first key objective of the project. Although the reaction was unsuccessful with homoallyl amine **94**, the reaction could still be optimised towards heterocyclic products. Screening ligands such as CPhos and SPhos, that were also used by Peterson and Wolfe, against homoallyl amine **94** may afford cyclised product as the RuPhos ligand might not be optimal for homoallylic amine substrates.[139] The synthesis of the Boc protected analogue of homoallyl amine **94** would be worth pursuing as it should be amenable to the reaction conditions described by Bertrand *et al*. and Mai and Wolfe given the reported success of Boc protected γ-aminoalkene **190**.[119,120]

3 Hypervalent Iodine

3.1 Inspiration for Hypervalent Iodine Mediated Cyclisation

It was hypothesised that subjecting a homoallylic amine substrate to literature protocols, for cyclisation of γ-aminoalkenes into pyrrolidines with hypervalent iodine reagents, would afford an azetidine product and this chapter outlines the testing of this hypothesis (Figure 13).

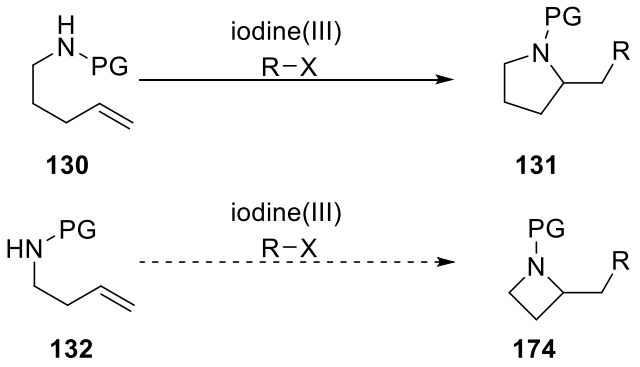
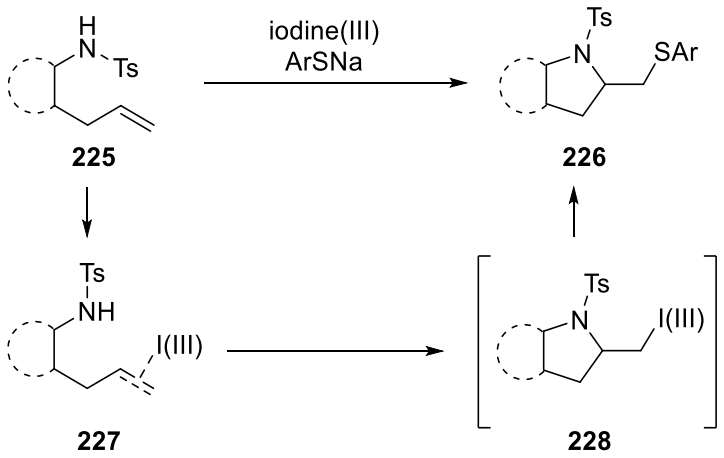


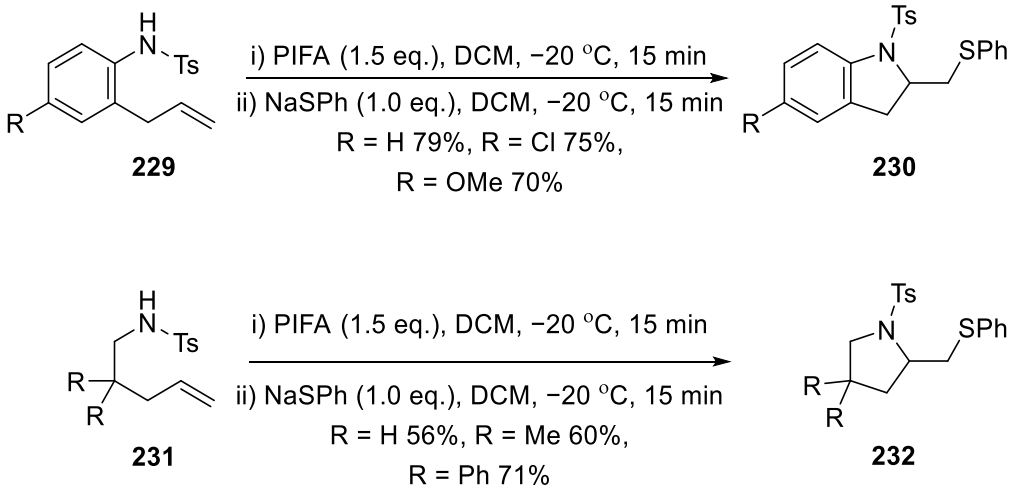
Figure 13: Hypothesis that azetidine products **174** could be synthesised from homoallyl amines **132** with hypervalent iodine from literature procedures for synthesising pyrrolidines **131** from γ-aminoalkenes **130**.

Mizar *et al.* have reported the use of hypervalent iodine(III) reagents to construct nitrogen-containing heterocycles **226** through oxidative thioamination of alkenes **225**. The hypervalent iodine activates the double bond which is followed by intramolecular cyclisation from the sulfonamide nucleophile affording the 5-membered intermediate **228**, with the hypervalent iodine attached to the methyl group adjacent to the nitrogen atom. Subsequent reaction *via* a thiolate nucleophile transforms intermediate **228** into a thiomethyl substituted nitrogen-containing heterocycle **226** (Scheme 54).[123]



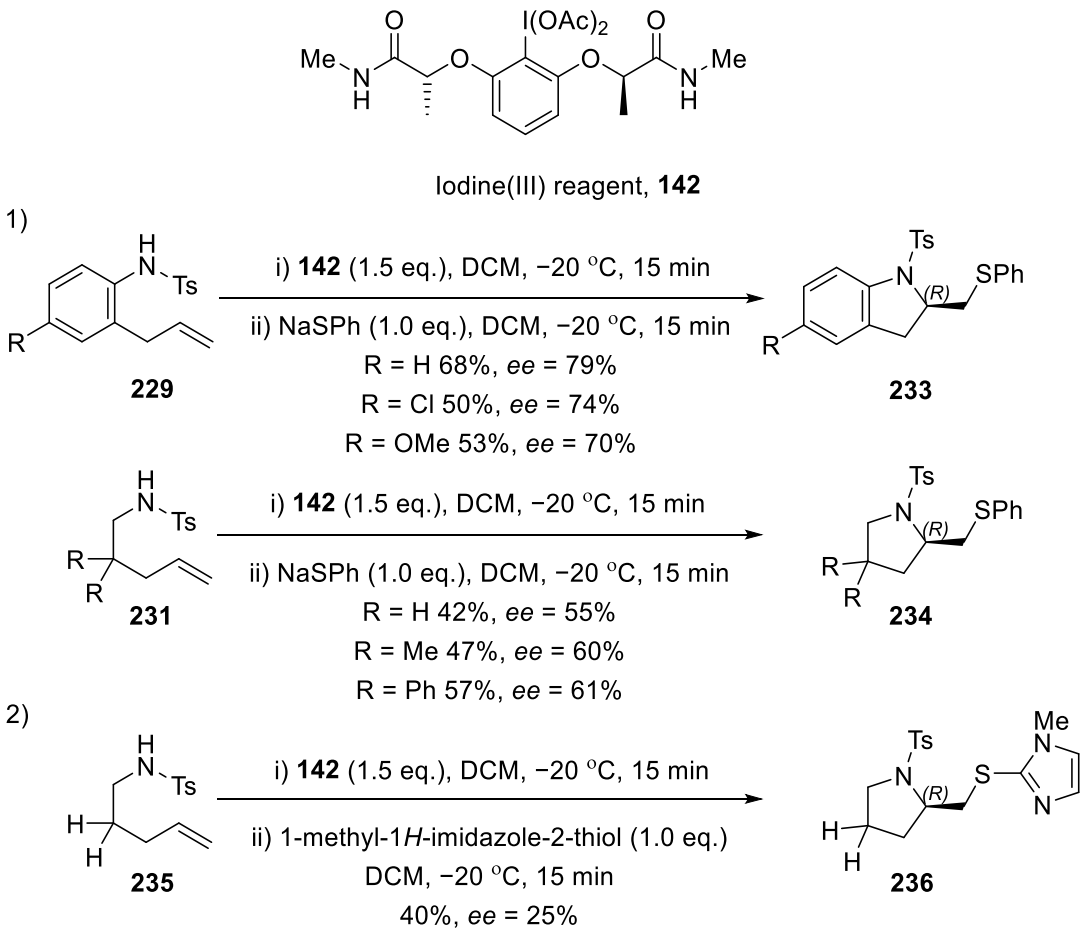
Scheme 54: General reaction scheme of work reported by Mizar *et al*. in which thiomethyl nitrogen-containing heterocycles **226** were synthesised from alkenes **225** activated by a hypervalent iodine(III) reagent.

Using achiral (bis(trifluoroacetoxy)iodo)benzene (PIFA) and sodium thiophenolate at −20 °C for 30 minutes, Mizar *et al.* reported three indoline products **230** from aniline **229** in high yields of 70-79% and three pyrrolidines **232** from γ-aminoalkenes **231** in moderate to high yields of 56-71% (Scheme 55).[123] Interestingly, the yield obtained increased with the size of the substituents at the 4-position of γ-aminoalkene **231**. This suggests that the Thorpe-Ingold effect, in which *gem*-disubstituents promote ring closure, is aiding the cyclisation step of the oxidative thioamination method by promoting ring closure of the pyrrolidine ring, leading to greater yield of product **231**.



Scheme 55: Racemic indoline and pyrrolidine products **230** and **232** afforded in moderate yields of 56-71% from **229** and **231** respectively.

Stereoselective synthesis was achieved using chiral hypervalent iodine(III) reagents. The C2-symmetric lactate-based iodine(III) reagent **142**, was the most effective stereoselective hypervalent iodine reagent. As with the achiral conditions, higher yield and *ee* was observed for (*R*)-indolines **233** (50-68% yield, 70-79% *ee*) compared to (*R*)-pyrrolidines **234** (42-57% yield, 55-61% *ee*). While yield was maintained, using 1-methyl-1H-imidazole-2-thiol in place of sodium thiophenolate resulted in a significant reduction in *ee* (25% compared to 55% respectively) (Scheme 56).[123]



Scheme 56: Asymmetric conditions described by Mizar *et al*. with the chiral iodine(III) reagent shown at the top. 1) Reaction with NaSPh as the nucleophile afforded (*R*)-products **233** and **234**. 2) Reaction with 1-methyl-1H-imidazole-2-thiol as the nucleophile afforded (*R*)-**236**.

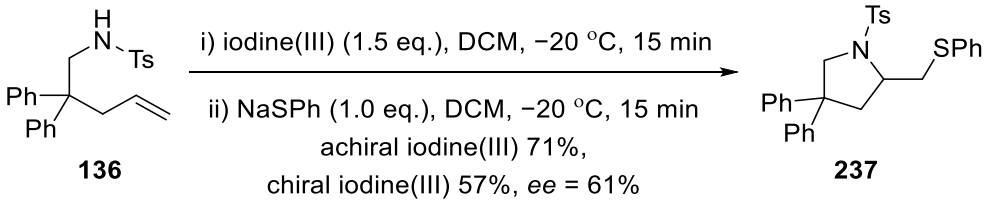
The oxidative thioamination procedure described by Mizar *et al.* was an attractive method for cyclising homoallyl amines for several reasons. The methodology presents similarities to that of Feula *et al.* whereby the iodine species activates the double bond to induce cyclisation, which could be followed by displacement of the iodide with a nucleophile.[91] However, Mizar's method has three main advantages over Feula's method: less waste, lower toxicity and shorter reaction times. The reaction has less waste in the hypervalent iodine method as only 1.5 equivalents of the iodine(III) reagent is used to induce cyclisation compared to 3 equivalents of iodine and 5 equivalents of sodium bicarbonate. The main hazards associated with PIFA are irritation whereas iodine is harmful, can damage the thyroid and is toxic to aquatic life in

addition to being an irritant. The Feula *et al.* method requires an 18 hour reaction time for cyclisation, followed by up to an additional 24 hour reaction for nucleophilic substitution to afford the substituted azetidine product, whereas Mizar *et al.* were able to obtain substituted pyrrolidine products in 30 minutes.

The Feula *et al.* method does not have asymmetric conditions. The single enantiomer azetidines reported by Yoshizawa *et al.*, that used the iodine mediated procedure described by Feula *et al.*, required single enantiomer homoallylic amine substrates.[95] In comparison, the asymmetric conditions described by Mizar *et al.* access stereospecific products from racemic substrates.[123] Therefore, successful application of the asymmetric conditions described by Mizar *et al.* to homoallyl amines, could access stereospecific azetidines without the requirement to synthesise single enantiomer homoallylic amine substrates.

3.2 Challenges with the γ-Aminoalkene Control System

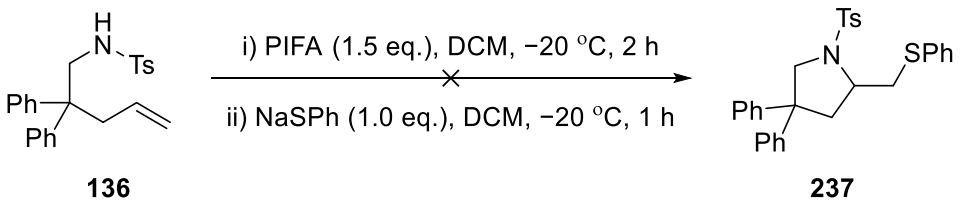
The γ-aminoalkene **136** was chosen as the control substrate because this substrate afforded pyrrolidine **237** in the highest yield from the examples reported by Mizar *et al.*, with 71% yield under achiral conditions and 57% yield and 61% *ee* for the asymmetric conditions (Scheme 57).[123]



Scheme 57: γ-Aminoalkene **136** results reported by Mizar *et al.* for both the racemic and asymmetric reaction conditions.

Subjecting γ-aminoalkene **136** to the literature procedure described by Mizar *et al.* did not afford pyrrolidine **237** as the reaction mixture consisted predominantly of starting material

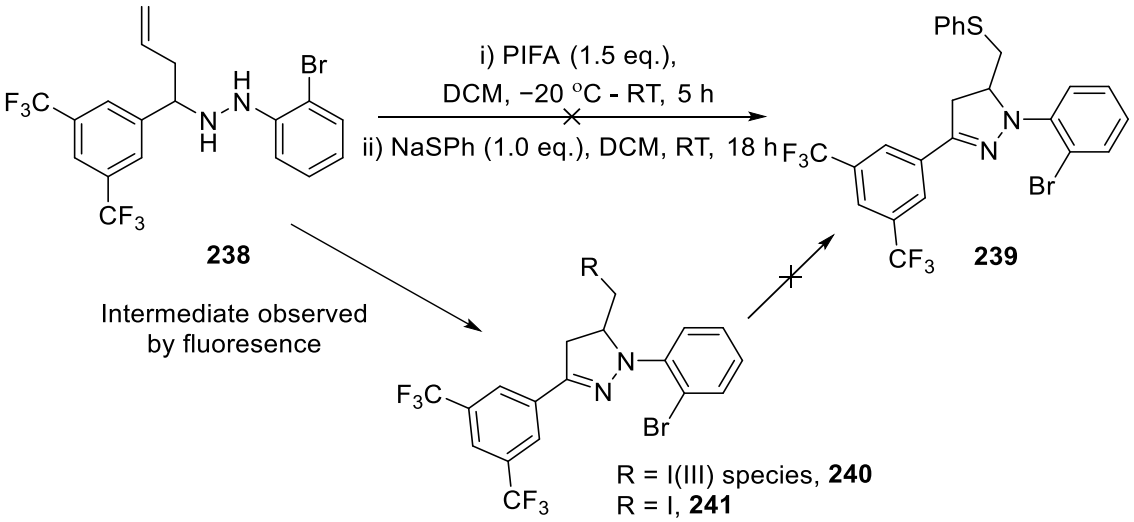
136. To encourage cyclisation the reaction time was increased. However, as with previous attempts, starting material **136** was obtained from the reaction (Scheme 58).



136 **237**

Scheme 58: Predominately starting material **136** obtained when reaction time was increased.

To probe the reaction further, hydrazine **238** was selected as the starting material. It was known in our group that hydrazine **238** could be cyclised with the iodine mediated method described by Feula *et al*. into dihydropyrazole derivatives that were fluorescent. This meant that ring formation could be observed by fluorescence of the reaction mixture with a UV torch. After 5 hours at room temperature a colour change was observed that gave a fluorescent response with a UV torch indicating ring formation in the reaction. However, no phenylthiol product **239** was isolated from the reaction. A peak matching iodo product **241** was observed in the mass spectrum. As only trace amounts of product was obtained after purification, full characterisation was not possible (Scheme 59).

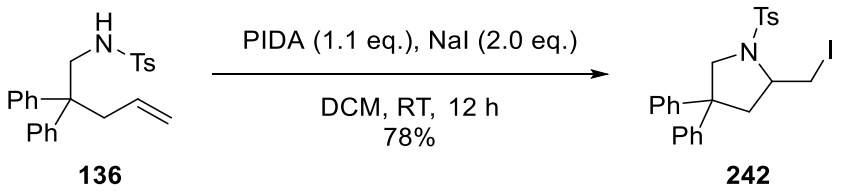


Scheme 59: Synthesis of **239** from **238** was unsuccessful. However, peak matching iodo product **241** was observed by mass spectrometry.

Although product **239** had not been obtained, it was concluded that PIFA was not the cause for the unsuccessful reactions as starting material **238** was consumed and an intermediate had been observed by fluorescence and mass spectrometry. The result also prompted follow up investigation by Yixin Cui on the synthesis of dihydropyrazole derivatives using hypervalent iodine. As I could not reproduce the results of Mizar *et al.*, alternative inspiration for hypervalent iodine mediated cyclisation was pursued.

3.3 New Strategy to Hypervalent Iodine Mediated Cyclisation

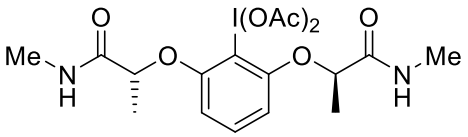
Synthesis of iodopyrrolidine derivatives from γ-aminoalkenes *via* hypervalent iodine activation was reported by Liu and Li. The γ-aminoalkene **136** was transformed into iodopyrrolidine **242** with 1.1 equivalents of (diacetoxyiodo)benzene (PIDA) and 2 equivalents of sodium iodide at room temperature in 78% yield (Scheme 60).[122]



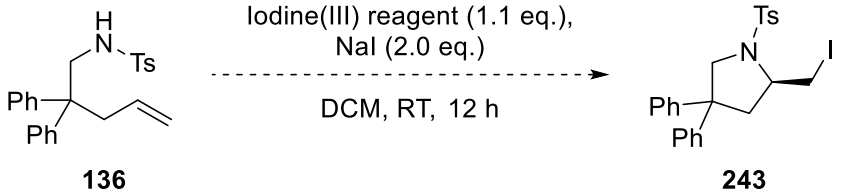
136 **242**

Scheme 60: Procedure reported by Liu and Li for the cyclisation of γ-aminoalkene **136** into iodopyrrolidine **242**.

This procedure described by Liu and Li was of interest as it had potential to improve upon the method described by Feula *et al.* with homoallylic amine substrates used in place of the reported γ-aminoalkenes. The same iodo products synthesised by Feula *et al.* could be obtained with greater reaction efficiency as only 1.1 equivalents of hypervalent iodine and 2 equivalents of an iodine source are required to effect cyclisation, compared to the 3 equivalents of molecular iodine and 5 equivalents of base.[134] In addition, the hypervalent iodine reagents are significantly less hazardous than molecular iodine. Although Liu and Li did not report asymmetric conditions, the procedure described by them still had potential for asymmetric synthesis through the use of the chiral hypervalent iodine reagent that was shown to be feasible from the results reported by Mizar *et al.* (Scheme 61).[123]



Iodine(III) reagent, **142**

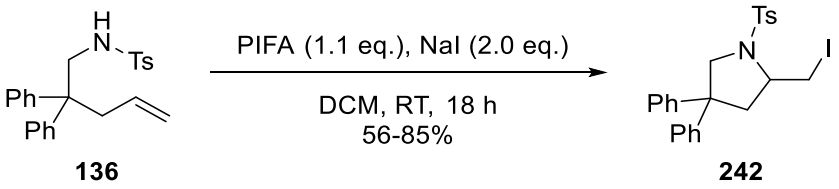


136 **243**

Scheme 61: Potential for asymmetric reaction conditions for procedure described by Liu and Li with chiral hypervalent iodine(III) reagent **142**.

3.3.1 Control System with γ-Aminoalkene

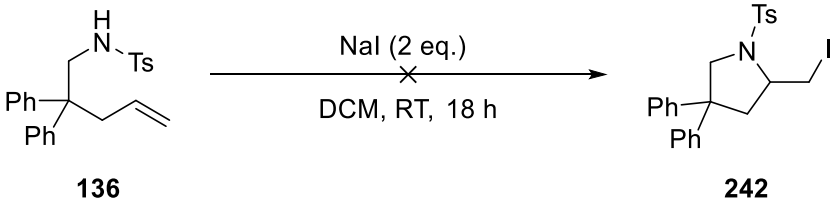
The desired iodopyrrolidine **242** was successfully obtained from γ-aminoalkene **136** with PIFA and sodium iodide in 56% yield. In subsequent reactions, iodopyrrolidine **242** was obtained in yields between 56% and 85% (Scheme 62).



136 **242**

Scheme 62: Pyrrolidine **242** obtained in 56-85% yield from γ-aminoalkene with PIFA and sodium iodide.

As product was successfully obtained with γ-aminoalkene **136** and PIFA as the hypervalent iodine source, it gave greater confidence that they were not the reason for the problems encountered while attempting to replicate Mizar *et al.*'s work (section 3.2). No reaction was observed in the absence of PIFA which confirmed that cyclisation was promoted by the hypervalent iodine reagent (Scheme 63).



136 **242**

Scheme 63: Only starting material **136** obtained with control reaction omitting hypervalent iodine reagent.

The data for the iodo product **242** reported by Liu and Li was not enough to distinguish between two possible structural isomers, pyrrolidine **242** and piperidine **244** (Figure 14).[122]

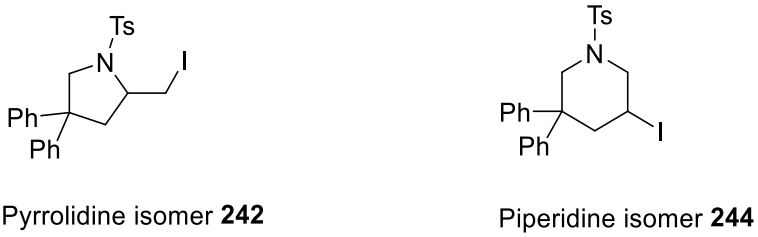


Figure 14: Two possible structural isomers from the cyclisation reaction, pyrrolidine **242** and piperidine **244**.

The ring size was determined by the HMBC interactions of the carbon with the single hydrogen labelled b within the heterocyclic ring. Analysis of the HMBC coupling interactions of the product, observed an interaction between the carbon of H_b and all three CH_2 protons (H_a, H_c and H_d) which identified the product as the pyrrolidine isomer **242**, in keeping with the isomer reported by Liu and Li. This rules out piperidine **244** as only coupling interactions between the carbon of H_b and the CH_2 protons H_c and H_d would be observed (Figure 15).

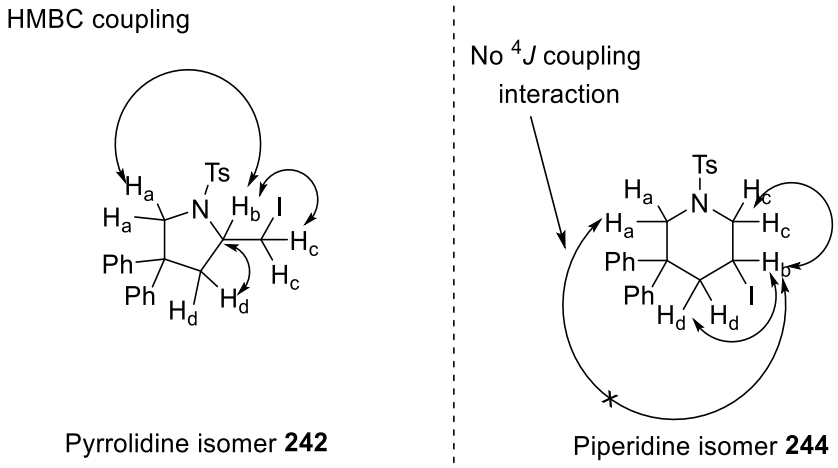
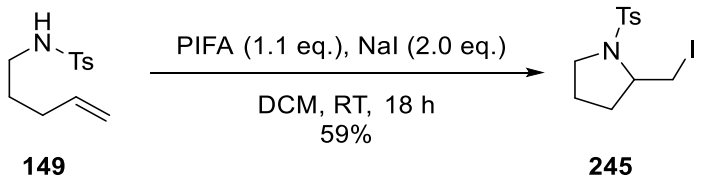


Figure 15: HMBC coupling interactions of the two possible isomers with the relevant hydrogen atoms displayed.

With the ring size of the product confirmed, γ-aminoalkene **149** was subjected to the reaction conditions to test whether substitution on the carbon chain was required for cyclisation. Pyrrolidine **245** was obtained in moderate yield of 59% (Scheme 64).



149 245

Scheme 64: Iodopyrrolidine **245** obtained in moderate yield of 59% from γ-aminoalkene **149** with PIFA and sodium iodide.

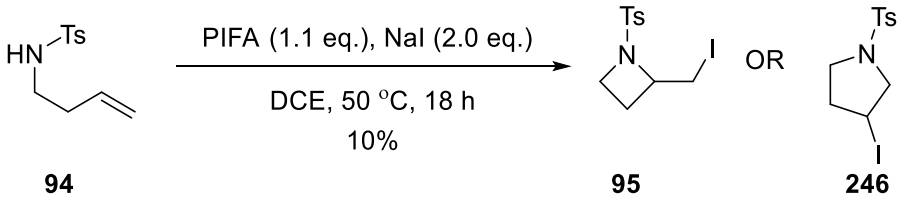
3.3.2 Cyclisation with Homoallylic Amine Substrate

Attention moved towards application of the procedure to homoallylic amine substrates to afford aza-heterocyclic products. Due to the synthetic challenges to obtain homoallyl amine **207**, as discussed in section 2.3, homoallyl amine **94** was selected as the model substrate (Figure 16).

207 94

Figure 16: Homoallyl amine substrates **207** and **94** with **94** chosen as the model substrate.

No cyclised product was observed when the homoallyl amine **94** was stirred in dichloromethane with PIFA and sodium iodide at room temperature. However, switching the solvent to dichloroethane and heating at 50 °C afforded a cyclised product, albeit in low yield of 10% (Scheme 65).



94 95 246

Scheme 65: Cyclised product obtained in poor yield at 50 °C in DCE. Identity of the product isomer was either **95** or **246**.

It was expected that pyrrolidine **246** had been isolated as Feula *et al.* had reported the thermal ring expansion of azetidine compounds into pyrrolidine compounds at 50 °C as discussed in

section 1.3.1.2.1.[134] The structure of the product was confirmed as pyrrolidine **246** with HMBC which observed coupling interactions between the carbon with protons labelled H_a and the two CH_2 protons (H_c and H_d) in addition to an interaction with H_b. This ruled out azetidine **95** as an interaction between the carbon with protons labelled H_a and CH_2 protons H_c would not be observed by HMBC, as that is a ^4J coupling interaction (Figure 17).

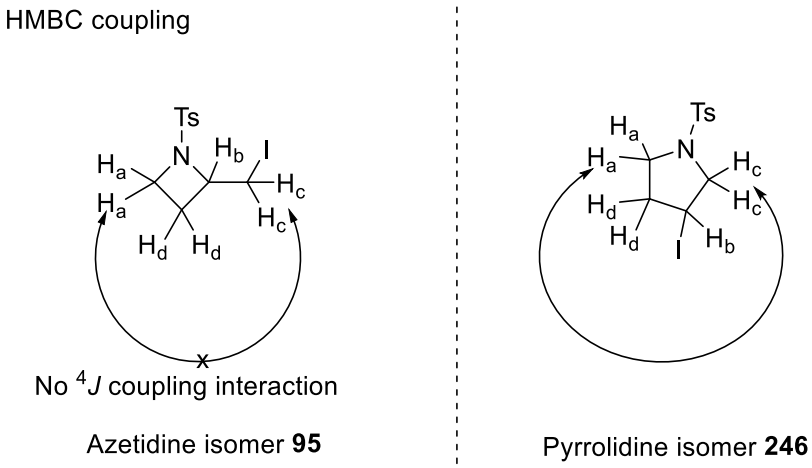
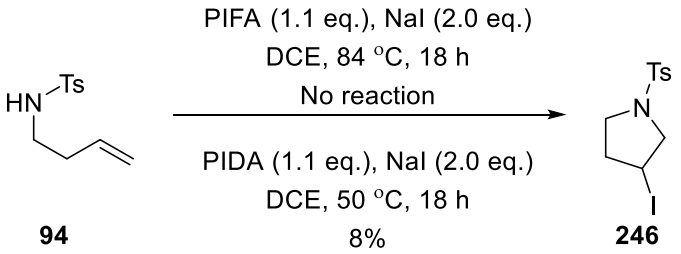


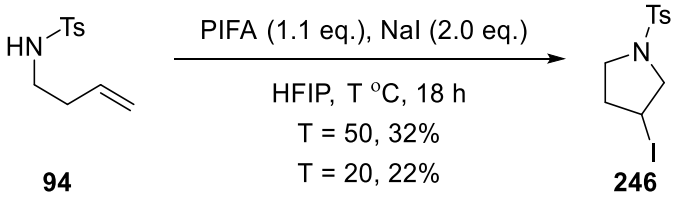
Figure 17: Key coupling interaction from HMBC analysis that would not be observed by azetidine **95**.

With the product identified, the priority was to optimise the reaction to enable exploration of scope or asymmetric conditions. It was proposed that heating the reaction at higher temperature would increase yield as product formation was not observed at room temperature but was obtained at 50 °C. However, no product was isolated when the reaction was heated at reflux in dichloroethane. Whilst PIFA had demonstrated good yield for γ-aminoalkenes **136** and **149**, the procedure reported by Liu and Li used PIDA. No significant change in yield was observed when PIDA was used as the hypervalent iodine reagent with pyrrolidine **246** isolated in 8% yield (Scheme 66).



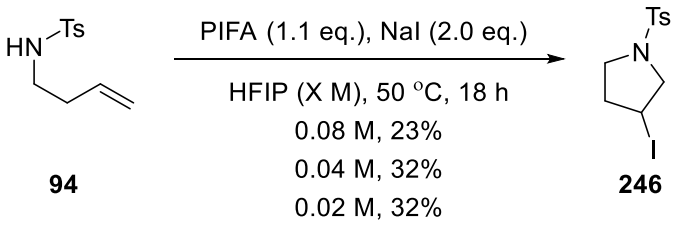
Scheme 66: (Top) Reaction at reflux in DCE was unsuccessful. (Bottom) Pyrrolidine **246** obtained in poor yield of 8% with PIDA.

A review of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) published by Colomer *et al.* highlighted that HFIP was an optimal solvent to use with hypervalent iodine reagents, as it could access products not obtained when other solvents are used.[140,141] HFIP had proven to be a critical solvent for electrochemical cyclisation of aminoalkenes as discussed in section 4. Homoallyl amine **94** was stirred in HFIP at 50 °C and pyrrolidine **246** was obtained in significantly improved yield of 32%. In the same solvent the reaction was stirred at 20 °C as it was hypothesised that azetidine **95** could be obtained at lower reaction temperatures based on the results reported by Feula *et al.*[134] However, only pyrrolidine **246** was obtained in slightly lower yield of 22% (Scheme 67).



Scheme 67: Reaction performed with HFIP at 50 °C and 20 °C to afford pyrrolidine **246**. Azetidine **95** was not observed.

To test the effect of concentration on the reaction outcome, the reaction was performed at 0.08 M and 0.02 M compared to the previous 0.04 M. Increasing the concentration to 0.08 M observed a slight decrease of yield (23%), whereas reducing the concentration to 0.02 M had no change with pyrrolidine **246** isolated in 32% yield (Scheme 68).



Scheme 68: Reaction performed at concentrations 0.08 M, 0.04 M and 0.02 M afforded **246** in low yield.

Whilst the yield had been improved from the initial 10%, it was not at an acceptable level to consider exploring the scope of the reaction or to start investigating asymmetric reaction conditions. A more thorough optimisation study was required to improve the yield of the reaction. In the interest of time, hypervalent iodine induced cyclisation was deprioritised to focus on the electrochemical cyclisation of homoallyl amines that had more promising results.

3.4 Conclusions and Future Work

Replication of the thioamination method described by Mizar *et al.* was unsuccessful in my hands. However, construction of a dihydropyrazole ring with the method described by Mizar *et al.* was observed by fluorescence which prompted further investigation by Yixin Cui, who worked on synthesis of dihydropyrazoles project. Replication of the halocyclisation method reported by Liu and Li was successful with PIFA. Cyclisation of homoallyl amine **94** was successful in dichloroethane at 50 °C with pyrrolidine **246** obtained in 10% yield.

The yield was improved to 32% by switching the solvent to HFIP. A possible explanation for the improvement with HFIP as the solvent, is that HFIP is able to form hydrogen bonds with PIFA which encourages the activation of the alkene bond. Colomer *et al.* reported the formation of a H-bonded adduct between PIDA and HFIP which was responsible for hypervalent iodine-mediated [2+2] cycloaddition of styrenes. Although significantly weaker than PIDA, interaction between PIFA and HFIP was also reported.[142]

It is speculated that pyrrolidine **246** is formed directly in the reaction instead of proceeding *via* the ring expansion of azetidine **95**, as no evidence of azetidine **95** has been observed including the reaction at 20 °C. With the electron-withdrawing tosyl protecting group, the nitrogen of azetidine **95** is less nucleophilic than the benzyl protected nitrogen in the azetidine derivatives reported by Feula *et al.* and therefore less likely to undergo ring expansion. Considering that Feula *et al.* obtained azetidine derivatives as the major product at 20 °C with benzyl protected homoallyl amines, it would be expected that azetidine **95** would be isolated if pyrrolidine **246** was obtained *via* ring expansion.

In conclusion, this method in its current state does not satisfy the aims of the project. Although regioselective synthesis of pyrrolidine **246** from achiral homoallyl amine **94** has been achieved, a key objective of the project, the yield is poor. Therefore, the method does not satisfy the aims of the project as it is neither complementary nor an improvement on the protocol described by Feula *et al.* Due to the reaction being low yielding, the stereoselectivity of the reaction with racemic homoallyl amines and asymmetric reaction conditions have not been explored.

Future work needs to start with optimisation of the reaction conditions to obtain at least moderate yields. If this cannot be achieved, then the method should be abandoned as it would not be able to satisfy the aims of the project. Assuming that the improvement of yield with use of HFIP was a result of H-bonding between HFIP and PIFA then screening hypervalent iodine reagents could be suitable starting point for optimisation. Considering the strong H-bonded adduct reported by Colomer *et al.*, PIDA used with HFIP could resolve the issue with the yield of the reaction.[142]

4 Electrochemical Mediated Cyclisation

This chapter will first discuss efforts to progress the work started by previous student in the group, Joe Milton in which pyrrolidine products were synthesised from γ-aminoalkenes.[3] It was hypothesised that the methodology developed by Milton could be adapted for the synthesis of aza-heterocycles from homoallyl amines that would complement the work reported by Feula *et al.*[2] The testing of this hypothesis is outlined in section 4.3.

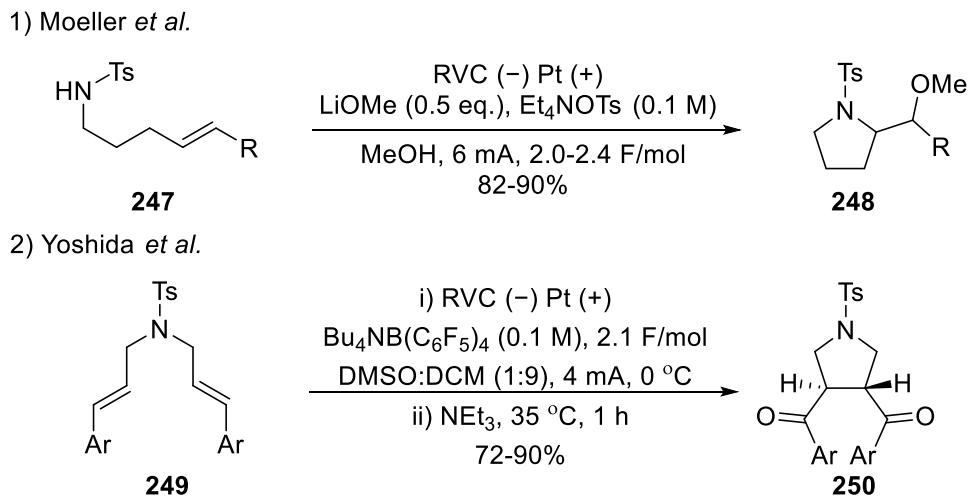
4.1 Background

Electrochemistry is considered a powerful tool for synthesis that has many benefits over more traditional forms of organic synthesis including reduction of waste, replacement of toxic or hazardous materials, generally mild conditions and scalability through continuous flow conditions, discussed in more detail by reviews written by Horn *et al.*,[143] Frontana-Uribe *et al.*[144] and Mohle and co-workers.[145] While these attractive qualities of electrochemistry make it a greener and more sustainable method of synthesis, it is worth noting that not all electrochemical reactions can be considered green as cautioned by Yuan and Lei.[146]

Despite the benefits of electrochemistry, adoption into synthetic strategies has been slow due to specialised equipment required, which can lead to reproducibility issues between research groups.[143,147] To address this issue, a collaboration between IKA and Professor Phil S. Baran to create a new instrument for electrochemistry in organic synthesis was undertaken to give the ElectraSyn 2.0 (Figure 18).[148]

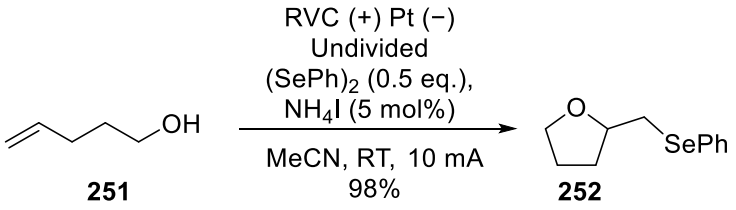
Figure 18: The ElectraSyn 2.0

The Moeller group and Yoshida group are the only authors to report the electrochemical synthesis of pyrrolidine derivatives since the start of this century (Scheme 69).[149,150] Moeller *et al.* added the methoxy group across the double bond of γ-aminoalkenes **247** during electrochemical cyclisation, to construct the pyrrolidine ring by using methanol as part of the solvent system. Anodic oxidation was achieved using reticulated vitreous carbon as an anode and platinum as a cathode along with a proton scavenger.[149] Yoshida *et al.* used anodic oxidation to cyclise homoallyl amine derivatives **249** with DMSO at 0 °C to form the pyrrolidine ring. With the addition of triethylamine at 35 °C, pyrrolidines **250** bearing a ketone at the 3- and 4-position are formed.[150]



Scheme 69: 1) Electrochemical synthesis of pyrrolidines **248** reported by Moeller *et al.* 2) Electrochemical synthesis of pyrrolidines **250** reported by Yoshida *et al.*

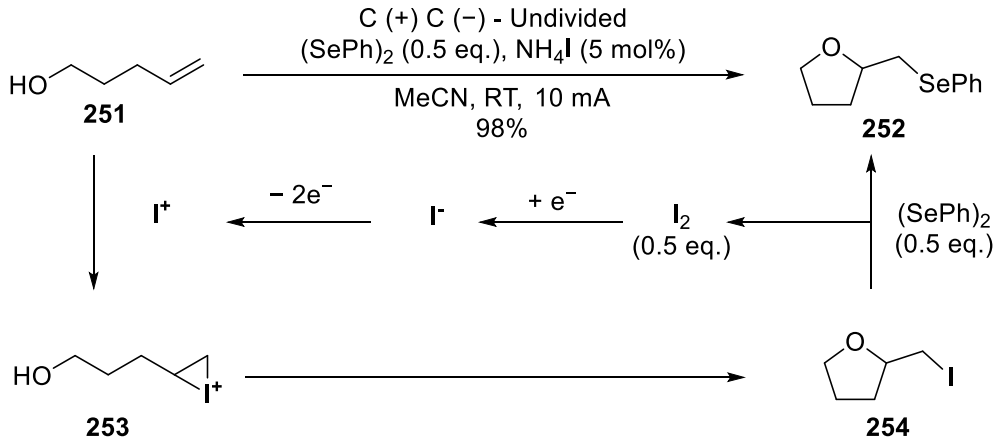
Milton investigated the electrochemical synthesis of pyrrolidines with the aid of an IKA ElectraSyn 2.0 (section 4.1.1) taking inspiration from Meng *et al.*[3] The electrochemically mediated synthesis of cyclic ethers with diphenyl diselenide in the presence of electrolyte, ammonium iodide, was reported by Meng *et al.* Tetrahydrofuran **252** was obtained in 98% yield using sub-stoichiometric amounts of reagents (Scheme 70).[151]



Scheme 70: Meng *et al.* electrochemically mediated cyclisation of hydroxyalkene **251** to afford tetrahydrofuran **252**.

In the mechanism proposed by Meng *et al.*, iodide from ammonium iodide acts as an electrolyte and is oxidised electrochemically to an iodonium cation which subsequently reacts with the alkene of the olefinic alcohol **251** to afford a 3-membered iodonium ring intermediate **253**. Intramolecular cyclisation of intermediate **253** results in formation of cyclic ether **254** followed by substitution with diphenyl diselenide to afford product **252** and half an equivalent

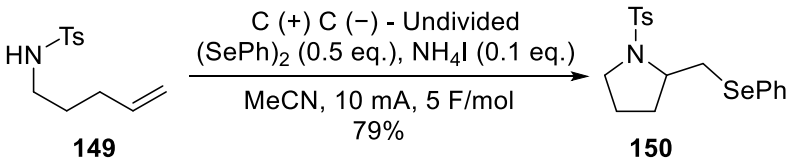
of molecular iodine. As the electrolyte was used catalytically, the molecular iodine was reduced electrochemically back to iodide to start the process again (Scheme 71).[151]



Scheme 71: Proposed mechanism by Meng *et al.* with iodonium cation involved in cyclisation step.

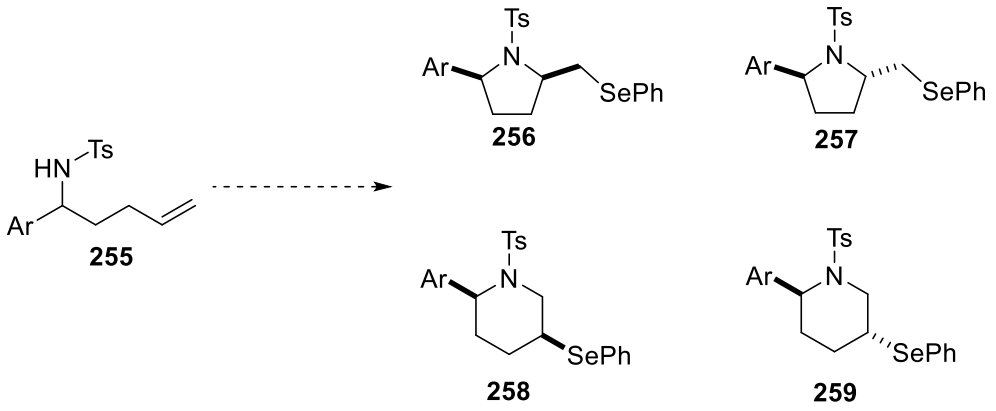
4.1.1 Previous Work in the Group

Pyrrolidine **150** was isolated in 79% yield from achiral γ-aminoalkene **149** (Scheme 72). Alternating the polarity of the electrodes prevented build-up of diphenyl diselenide on the surface of the anode. Pyrrolidine **150** was isolated in 70% yield when the polarity of the electrodes was not alternated.[3]



Scheme 72: Pyrrolidine **150** isolated from γ-aminoalkene **149** with conditions inspired from Meng *et al.*

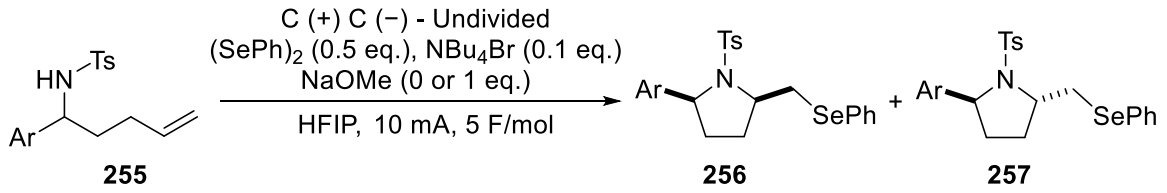
When racemic γ-aminoalkene **255** were subjected to these conditions two products were obtained that were difficult to separate from each other. As ring formation on either carbon of the alkene bond is possible, there are four possible aza-heterocyclic products expected: *cis*- and *trans*-pyrrolidine **256** and **257** and *cis*- and *trans*-piperidine **258** and **259** (Scheme 73).[3]



Scheme 73: Four possible aza-heterocycles: **256**, **257**, **258** and **259** expected from cyclisation of racemic **255**.

With the aid of X-ray crystallography, the two cyclised products were confirmed to be racemic mixtures of *cis*- and *trans*-pyrrolidine **256** and **257**. After conducting an optimisation study, reaction conditions that controlled stereoselectivity through the addition (*trans*-selective) or omission (*cis*-selective) of sodium methoxide were obtained. It was noted during optimisation that a 9:1 solvent mixture of HFIP:water without sodium methoxide also gave *trans*-selective results. Seven racemic substrates have been subjected to the stereoselective conditions with 12 pyrrolidine products isolated as no reaction was observed with 4-pyridinyl substrate **255g** (Table 3).[3]

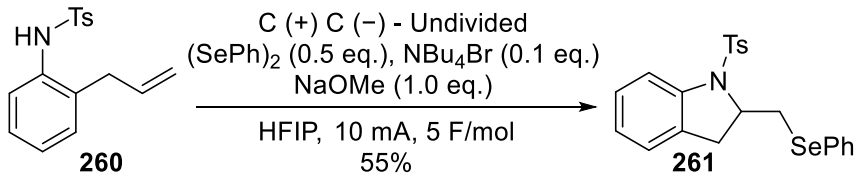
Table 3: Racemic substrates **255** subjected to *cis*- and *trans*-selective conditions.



255 **256** **257**

Substrate	Ar	Equivalents of NaOMe	*cis*:*trans*	Isolated yield of Major Isomer (%)
255a	4-$(CF_3)C_6H_4$	0	4:1	40
		1	1:6	56
255b	3,5-$(CF_3)_2C_6H_3$	0	3:1	48
		1	1:7	65
255c	4-BrC_6H_4	0	12:1	65
		1	1:7	57
255d	C_6H_5	0	4:1	50
		1	1:4	46
255e	4-MeC_6H_4	0	2:1	42
		1	1:4	45
255f	4-$OMeC_6H_4$	0	11:1	79
		1	1:4	55
255g	4-pyridinyl	0	No reaction	
		1		

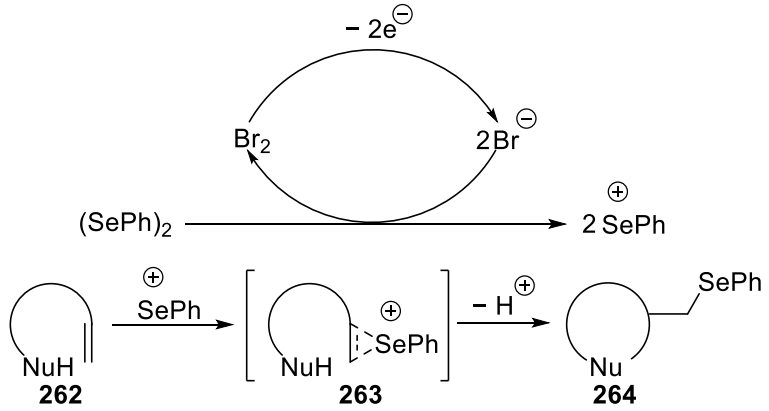
The substrate scope was widened with the inclusion of achiral **260** that afforded indoline **261** in 55% yield with sodium methoxide and 15% yield without sodium methoxide (Scheme 74).[3]



Scheme 74: Electrochemical synthesis of indoline **261** in the presence of sodium methoxide.

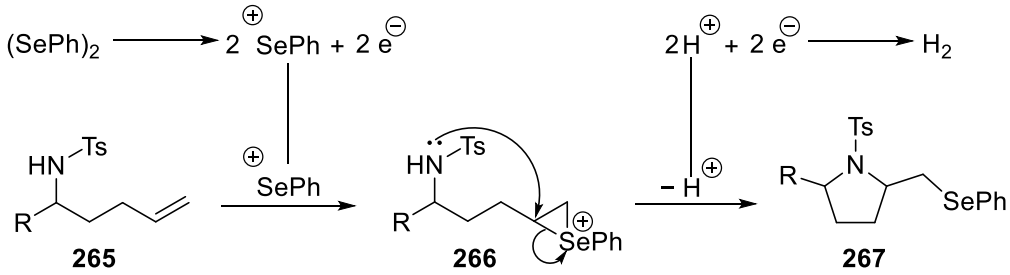
The proposed mechanism by Meng *et al.* discussed in section 4.1 is not plausible for the protocol described by Milton as the proposed mechanism emphasises the requirement of an iodide electrolyte to form the intermediate **253**.[151] However, the reaction described by Milton successfully proceeds with *tert*-butylammonium bromide, lithium tetrafluoroborate and potassium hexafluorophosphate as electrolytes. While it is possible that the bromide could form a three-membered ring intermediate analogous to intermediate **253**, lithium tetrafluoroborate and potassium hexafluorophosphate would be unable to form three-membered intermediates.[3]

An alternative theory that three-membered intermediate **263** is generated with a phenylselenium cation was suggested by Vukićević *et al.*[152] The phenylselenium cation is formed at the anode through indirect oxidation mediated by a halide anion electrolyte (Scheme 75).[152] The formation of intermediate **263** from a phenylselenium cation is plausible but the theory does not adequately explain the reaction proceeding with electrolytes lithium tetrafluoroborate and potassium hexafluorophosphate. It is unlikely that tetrafluoroborate or hexafluorophosphate would be able to mediate the indirect oxidation to generate the phenylselenium cation performed by the bromide, as they are not reactive.[3]



Scheme 75: Vukićević *et al.* proposed mechanism of electrochemical cyclisation with diphenyl diselenide.

The mechanism proposed by Milton is that phenylselenium cations are generated by a two-electron oxidation from diphenyl diselenide and activate the alkene of **265** to form intermediate **266**. Intramolecular attack from nitrogen affords pyrrolidine **267** as the product (Scheme 76). The mechanism for the stereoselective control through the addition or omission of sodium methoxide was still not understood.[3]



Scheme 76: Milton proposed mechanism for electrochemical mediated cyclisation of γ-aminoalkene **265**.

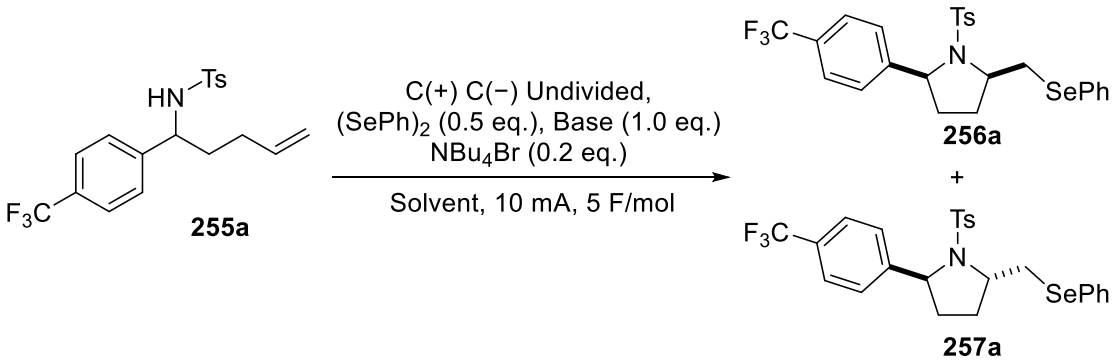
4.2 Cyclisation with γ-Aminoalkene Substrates

4.2.1 Investigation of Stereoselective Reaction Conditions

To build upon the work completed by Milton, a series of experiments were conducted to gain insight into the mechanism of selectivity. As addition of water to the solvent mixture shifts selectivity towards the *trans*-isomer, it was proposed that the selectivity control observed with sodium methoxide was a result of water present in the base. It was also proposed that

increasing the ratio of water in the solvent mixture would result in greater *trans*-selectivity. In order to test whether water present in the base was the cause of the *trans*-selectivity, the reaction needed to be performed under anhydrous conditions. γ-Aminoalkene **255a** was chosen to provide a direct comparison with the study by Milton.

Table 4: Investigation into role of base and water on selectivity.



Entry	HFIP	Base	Molecular sieve powder (3 Å, 50 mg)	HFIP:H_2O	Before purification *cis*:*trans*[a]	After purification *cis*:*trans*[a] (Isolated yield)
1	Supplied	NaOMe Supplied	✗	1:0	1:6.0	1:6.2 (69%)
2	Dried	NaOMe Supplied	✓	1:0	1:6.0	1:6.8 (69%)
3	Dried	NaOMe Dried	✓	1:0	1:6.2	1:6.0 (65%)
4	Supplied	$NaHCO_3$ Supplied	✗	1:0	2.7:1	2.6:1 (72%)
5	Supplied	✗	✗	95:5	1:5.2	0:1 (72%)
6	Supplied	✗	✗	9:1	1:4.0	1:3.5 (52%)
7	Supplied	✗	✗	8:2	1:2.9	1:3.0 (54%)
8	Supplied	✗	✗	4:6	No reaction	
9	Supplied	✗	✗	2:8	No reaction	

(0.1 mmol of **255a**, solvent (0.04 M) at room temperature. [a]*cis*:*trans* ratio determined by GC analysis.)

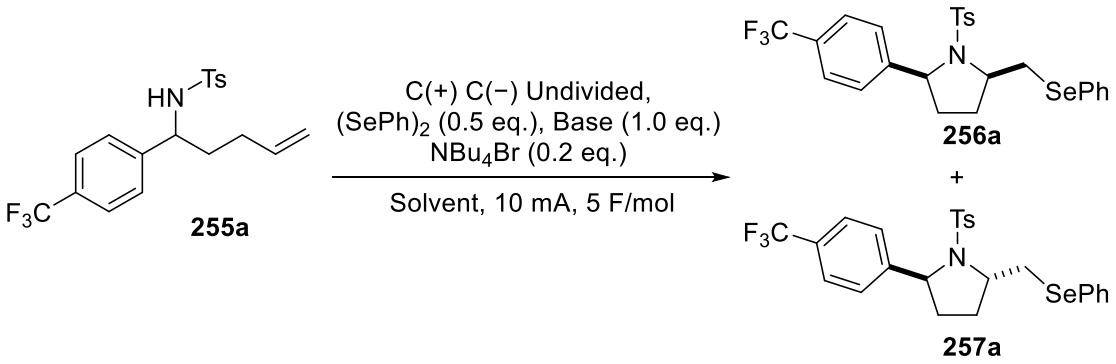
A dry control reaction was performed using commercial sodium methoxide as supplied under anhydrous conditions to test whether the zeolite in the molecular sieve powder was inert under electrochemical reaction conditions. Pleasingly, there was no observed change in selectivity (entry 2 vs 1). With the control reactions in place, the reaction was performed using dried sodium methoxide (entry 3). As there was no significant change in yield or *cis*:*trans* ratio between the three reaction conditions (entries 1, 2 and 3) it was concluded that the *trans*-selectivity observed was a result of the sodium methoxide and not water present within the base.

In the optimisation performed by Milton, reaction with sodium bicarbonate was *cis*-selective whereas all the other bases tested (sodium methoxide, sodium *tert*-butoxide, DIPEA and DBU) led to *trans*-selective reactions.[3] This result was reproducible in my hands (entry 4). A possible explanation could be that the *trans*-selectivity is from the deprotonation of HFIP. The pK_a of HFIP was reported as 9.3[153] and the pK_a's of the conjugate acids for sodium bicarbonate, sodium methoxide, sodium *tert*-butoxide, DIPEA and DBU were reported as 6.0, 15.1, 19.2, 12.5 and 10.8 respectively.[154] Sodium bicarbonate is the only base with pK_a lower than HFIP and therefore not strong enough to deprotonate HFIP. HFIP therefore may have a key role in the selectivity of the reaction.

With sodium methoxide concluded to be responsible for the *trans*-selectivity, the effect of water in the solvent mixture was probed. Increasing the amount of water from 95:5 HFIP:water to 9:1 HFIP:water reduced *trans*-selectivity with significantly lower yield of 52% (entry 6 vs 5). Doubling the amount of water in the solvent mixture to 8:2 HFIP:water observed a reduction of *trans*-selectivity with no loss of yield (entry 7 vs 6). No reaction was observed

when the amount of water was greater than HFIP (entry 8 and 9). From these results, it was concluded that addition of water has a detrimental effect on product formation as observed when above 95:5 HFIP:water ratio. In a review on HFIP by Colomer *et al.*, the properties of HFIP that make it an ideal solvent for electrochemical reactions and stabilising cations were highlighted. In particular, the first order decay of cations increased with addition of water.[140] A possible explanation for the effect on yield with addition of water is that the proposed phenylselenium cation and/or three-membered intermediate **266** are not stabilised long enough for the reaction to procced when the amount of water is greater than HFIP.

Table 5: Investigation into the nature of HFIP on reaction selectivity.



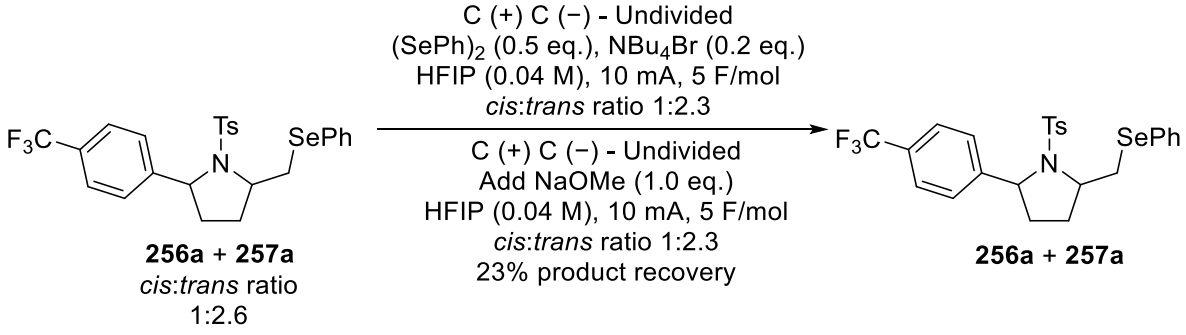
Entry	HFIP	Base	Molecular sieve powder (3 Å, 50 mg)	HFIP:H_2O	Before purification *cis*:*trans*[a]	After purification *cis*:*trans*[a] (Isolated yield)
1	Supplied	✗	✗	1:0	2.1:1	2.0:1 (81%)
2	Dry	✗	✓	1:0	1:2.2	1:2.0 (72%)
3	Dry	✗	✗	1:0	1:3.0	1:2.9 (65%)
4	Supplied degassed with argon	✗	✗	1:0	3.0:1	3.4:1 (56%)
5	Distilled	✗	✗	1:0	7.4:1	6.7:1 (65%)
6	Distilled	NaOMe Supplied	✗	1:0	2.6:1	2.5:1 (70%)
7	Distilled	✗	✗	95:5	1:4.4	1:4.9 (69%)

(0.1 mmol of **255a**, solvent (0.04 M) at room temperature. [a]*cis*:*trans* ratio determined by GC analysis.)

To probe the nature of the selectivity further the *cis*-selective conditions (omission of sodium methoxide) were investigated. It was proposed that the absence of water from the reaction would give a more *cis*-selective result. However, *trans*-selective results were observed (entry 2 vs 1). Using dried HFIP without molecular sieve powder also gave *trans*-selective results (entry 3), which suggests that the molecular sieve powder was not affecting the selectivity of the reaction. It follows that the HFIP drying process must be responsible for the observed change. However, the removal of water cannot be the cause of the shift in selectivity in this case. If removal of water shifted selectivity towards *trans*-products, then it would be expected that the addition of water would be *cis*-selective. The opposite was observed as addition of water from 95:5 HFIP:water to 8:2 HFIP:water gave *trans*-selective results (Table 4, entries 5, 6 and 7). It was proposed that removing oxygen when drying HFIP may have influenced the selectivity. Although a drop in yield was observed compared to the control, the reaction was still *cis*-selective (entry 4 vs 1).

Given the proceeding results it was hypothesised that an impurity present in the supplied HFIP could be responsible for the *cis*-selectivity. However, using distilled HFIP gave the most *cis*-selective results reported for this reaction with a *cis*:*trans* ratio of 7.4:1 (entry 5). Furthermore, using distilled HFIP with sodium methoxide gave the *cis*-isomer as the major product (entry 6) as opposed to the expected *trans*-isomer observed with undistilled HFIP (Table 4, entries 1, 2 and 3). A 95:5 distilled HFIP:water solvent mixture still gave *trans*-selectivity (entry 7) as expected from results with water added to HFIP as supplied (Table 4, entries 5, 6 and 7). This suggests that the sodium methoxide base may not have had as great of an effect on selectivity as previously thought.

To confirm that the *cis*- and *trans*-isomers did not interconvert after the product was isolated, a mixture of the *cis*- and *trans*-product was subjected to the reaction conditions with the *cis*:*trans* ratio monitored by gas chromatography. The *cis*:*trans* ratio before subjecting the product to the reaction conditions was 1:2.6. As the major product was the *trans*-isomer, the mixture was first subjected to the *cis*-selective conditions. After 5 F/mol of electricity had passed an aliquot of the reaction mixture was taken and the *cis*:*trans* ratio was determined to be 1:2.3. Sodium methoxide was added to the reaction mixture and the reaction was continued under the *trans*-selective conditions until another 5 F/mol of electricity had passed. An aliquot of the reaction mixture was taken and the *cis*:*trans* ratio was determined to be 1:2.3 (Scheme 77).



Scheme 77: Subjecting mixture of *cis*- and *trans*-isomer into *cis*-selective followed by *trans*-selective conditions monitoring the ratio of the isomers by GC.

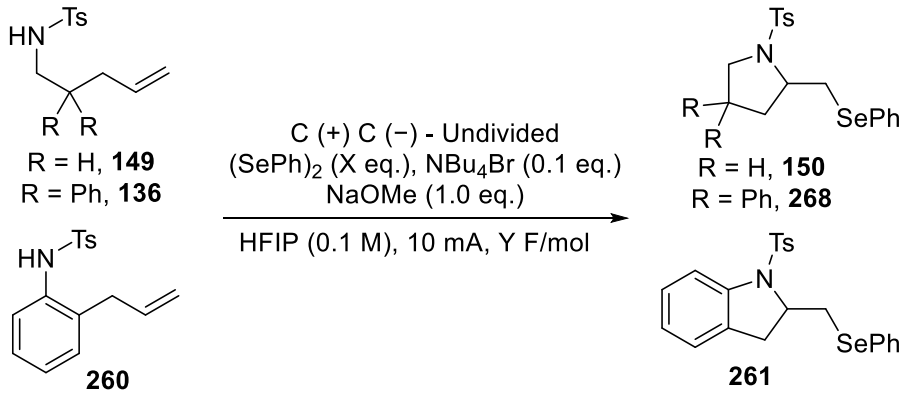
Whilst no significant change was observed in the *cis*:*trans* ratio after subjecting the product mixture to each of the conditions, the recovery of the product mixture was poor with just 23% recovered after purification. This suggested that either long reaction time or high equivalents of electrons lead to decomposition of the desired products.

4.2.2 Optimisation and Scope with Achiral Substrates

Alongside the investigation into the mechanism of selectivity, better understanding of the scope and limitations of the reaction was probed using achiral starting materials.

To optimise the yield of the reaction, equivalents of diphenyl diselenide and electrons (F/mol) were varied with addition of sodium methoxide (Table 6) as these reaction conditions gave indoline **261** in higher yield (section 4.1.1).[3] γ-Aminoalkene **149** and substrate **260** were chosen as both substrates were known and had previously been cyclised into products **150** and **261** with this method.[3] γ-Aminoalkene **136** was chosen as it had been successfully cyclised into pyrrolidine products under palladium-catalysed and hypervalent iodine conditions discussed in sections 2 and 3 respectively.

Table 6: Optimisation of yield by varying equivalents of $(SePh)_2$ and e^- on 3 achiral substrates.



Entry	Substrate	Equivalents of $(SePh)_2$	Equivalents of e^- (F/mol)	Isolated Yield[a] (%)
1	**149**	0.5	5	60
2	**136**			80
3	**260**			50
4	**149**	0.5	20	46
5	**136**			14
6	**260**			26
7	**149**	1.5	5	63
8	**136**			80
9	**260**			96
10	**149**	1.5	20	81
11	**136**			86
12	**260**			93

(100 mg of starting material, at room temperature. [a]Isolated after purification by flash column chromatography.)

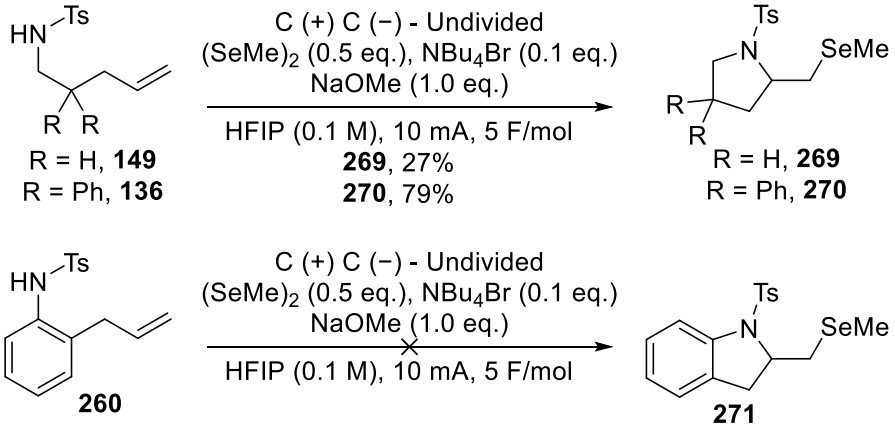
Increasing the equivalents of electrons from 5 to 20 F/mol (entries 4, 5 and 6) not only made the reactions four times longer as the current was kept constant (10 mA) but had a detrimental effect on yield. Significant reduction of yield was observed for all three substrates, with >50% reduction in yield observed for pyrrolidine **268** (entry 5 vs 2). The results were consistent with the earlier observation where only 23% of a pyrrolidine mixture of **256a** and **257a** was

recovered after purification when resubjected to the cyclisation reaction conditions (Scheme 77).

For the γ-aminoalkenes **136** and **149**, no significant increase in yield was observed when increasing the equivalents of diphenyl diselenide to 1.5 (entries 7 and 8 vs 1 and 2 respectively). However, the yield nearly doubled for substrate **260** from moderate yield of 50% to excellent yield of 96% (entry 3 vs 9).

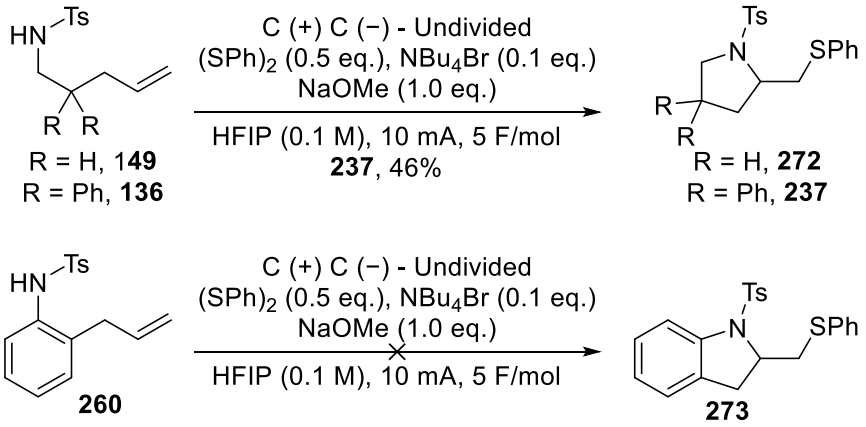
Increasing both the equivalents of diphenyl diselenide to 1.5 and the equivalents of electrons to 20 F/mol greatly improved the yield of γ-aminoalkene **149** (entry 10 vs 1). Reaction with γ-aminoalkene **136** and substrate **260** observed no significant change in yield for these conditions (entries 11 and 10 vs 2 and 3 respectively). This conflicted with previous observations where the total equivalents of electrons were greater than 5 F/mol afforded poor yields of product which was considered to be the result of product decomposition.

At this point only diphenyl diselenide had been used in the cyclisation reaction. To ascertain if the reaction scope could be expanded beyond 2-((phenylselanyl)methyl) derivatives, the alkyl equivalent dimethyl diselenide and the diphenyl disulfide were tested in the reaction.



Scheme 78: Reaction with $(SeMe)_2$ was successful for γ-aminoalkenes **149** and **136** but unsuccessful for **260**.

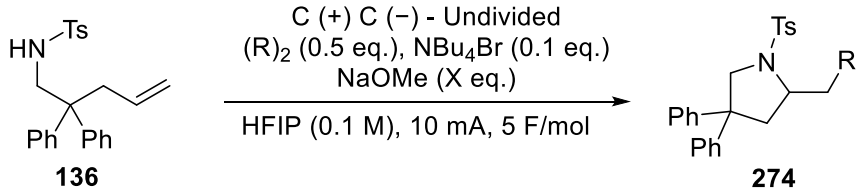
For the reactions with dimethyl diselenide, pyrrolidines **269** and **270** were isolated from γ-aminoalkenes **149** and **136** in low yield of 27% for pyrrolidine **269** and high yield of 79% for pyrrolidine **270.** The reaction was unsuccessful for aniline derivative **260** as there was no indication of the methylselanyl group in either the proton or carbon NMR spectra. In addition to this, there was no peak observed in the selenium NMR spectrum (Scheme 78).



Scheme 79: Reaction with $(SPh)_2$ was successful **136** but unsuccessful for **149** and **260**.

For reactions with diphenyl disulfide, pyrrolidine **237** was obtained in moderate yield of 46% from γ-aminoalkene **136**. Pyrrolidine **272** was observed in the mass spectrum and the proton NMR spectrum was consistent with literature, although impurities were present and so the product was not isolated. For indoline **273**, mass peak consistent with **273** was observed in the mass spectrum. However, aliphatic protons were not consistent with literature and the reaction was determined to be unsuccessful with diphenyl disulfide (Scheme 79).

Table 7: Comparison of isolated yields from γ-aminoalkene **136** with different reagents.



136 **274**

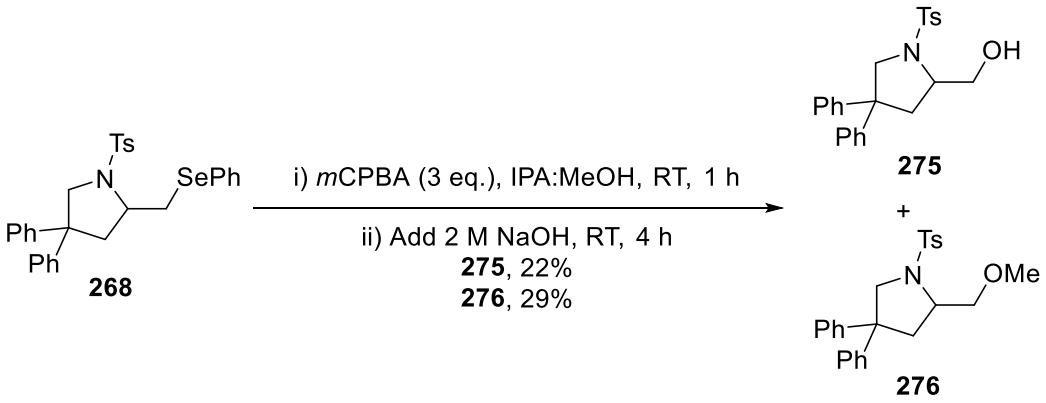
Entry	R	Equivalents of NaOMe	Isolated yield[a] (%)
1	SePh	1	80
2	SeMe	1	79
3[b]	SPh	1	46
4	SPh	0	81
5	SePh	0	80

(100 mg of **136**, at room temperature. [a]Isolated after purification by flash column chromatography. [b]63 mg of **136** used.)

The best results obtained when diphenyl diselenide was replaced with either dimethyl diselenide or diphenyl disulfide was with the γ-aminoalkene **136**. Whilst no significant change in yield was observed between the two diselenide reagents (entry 1 vs 2), lower yield of 46% was obtained with diphenyl disulfide (entry 3). However, when diphenyl disulfide was used in the absence of sodium methoxide, a comparable yield of 81% was obtained (entry 4 vs 1 and 2). With the increase in yield observed with diphenyl disulfide, diphenyl diselenide was used in the absence of sodium methoxide. No change in yield was observed with the omission or addition of sodium methoxide (entry 5 vs 1) which suggested that there was a side reaction not identified between the base and disulfide which reduced the yield of pyrrolidine **237**.

Further utility of this method was considered by substituting the phenylselenium group. Cooper and Ward developed a substitution method in which they oxidised the phenylselenium group into a selenone using *m*-chloroperoxybenzoic acid. The resultant selenone acts as a leaving group and was displaced by nucleophiles such as hydroxide.[155] When this method was

applied to pyrrolidine **268**, it was observed that the starting pyrrolidine did not dissolve in isopropanol, so methanol was added to the reaction mixture. As a result, two products were isolated from this reaction, the expected hydroxy product **275** and the methoxy side product **276** in 22% and 29% yield respectively (Scheme 80).



Scheme 80: Hydroxy and methoxy pyrrolidines **275** and **276** from oxidation and displacement of SePh.

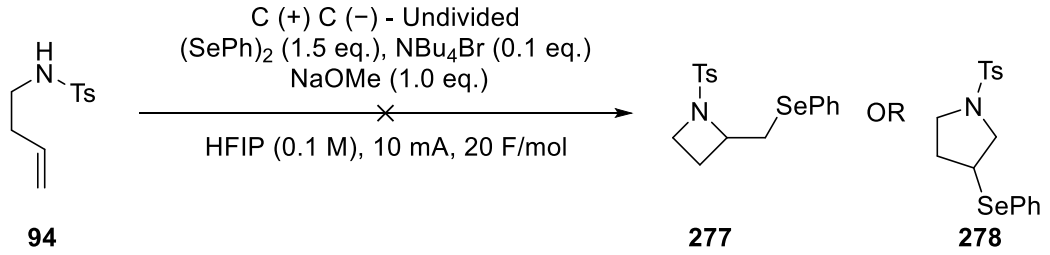
For pyrrolidine **150**, product was observed but a pure sample was not successfully isolated. The proton NMR spectrum, mass spectrometry and IR data collected suggested formation of the desired product despite the unsuccessful purification.

4.3 Cyclisation with Homoallylic Amine Substrates

As it was established that pyrrolidine derivatives could be synthesised from γ-aminoalkenes using the electrochemical protocol developed by Milton, it was hypothesised that the method could be applied to homoallylic amine substrates to obtain azetidine derivatives.

The homoallyl amine **94** was chosen as the model substrate as it is the equivalent starting material to γ-aminoalkene **149**. The reaction was performed using 1.5 equivalents of diphenyl diselenide and 20 equivalents of electrons (20 F/mol) as it gave the highest yield for γ-

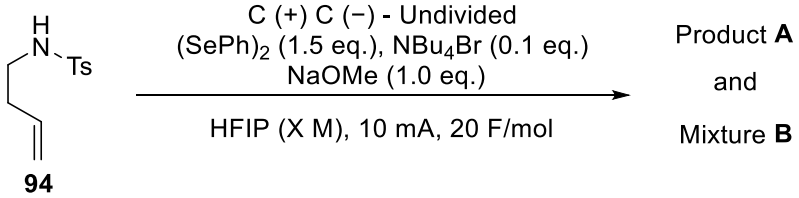
aminoalkene **149** (section 4.2.2). However, no aza-heterocycles were observed when homoallyl amine **94** was subjected to the reaction conditions (Scheme 81).



Scheme 81: The reaction was unsuccessful when homoallyl amine **95** was subjected to electrochemical conditions.

It was proposed that reducing the concentration of homoallyl amine **94** in the reaction would favour intramolecular reactions over intermolecular reactions, leading to the formation of aza-heterocyclic products. After purification when the reaction was performed at lower concentrations (Table 8) a cyclised product (either azetidine or pyrrolidine) termed product **A**, and a mixture of two other products termed mixture **B** were obtained. Attempts to separate the two products in mixture **B** were not successful which meant that the identities were not elucidated.

Table 8: Amounts of product **A** and mixture **B** obtained at different reaction concentrations.

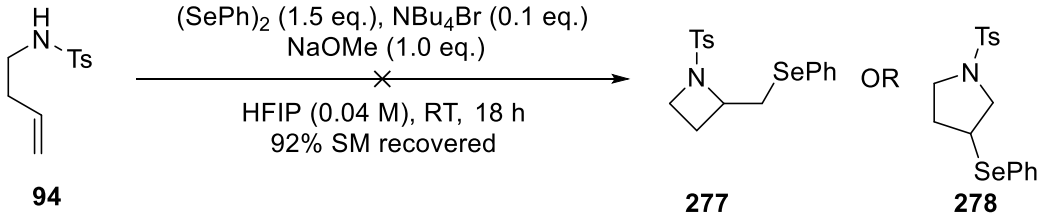


Entry	Concentration (M)	Homoallyl amine (mmol)	HFIP (mL)	Product **A** (mg)	Mixture **B** (mg)
1	0.04	0.22	5.5	9	33
2	0.02	0.18	9	11	19
3	0.01	0.09	9	36	

(For concentrations 0.02 M and 0.01 M, the maximum amount of homoallyl amine **94** was used. For concentration 0.04 M, 0.22 mmol of homoallyl amine **94** was used as this equated to 50 mg of **94** for convenience.)

The reactions were performed at different scale and concentration, due to maximum solvent levels. The largest available reaction vessel for the ElectraSyn 2.0 was 10 mL but the maximum amount of solvent was limited to 9 mL to allow for the electrodes to be added to the reaction mixture. It was decided that a concentration of 0.04 M (entry 1) was used moving forward due to the limitations on the scale of the reaction.

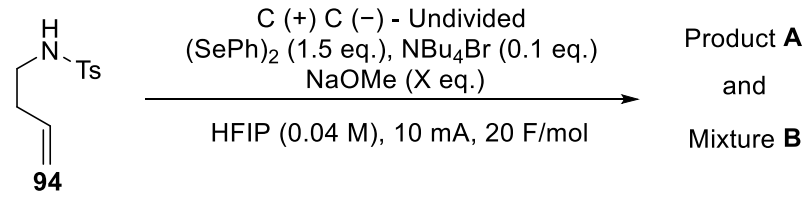
After observing cyclised product, a control reaction was performed to confirm that the reaction was electrochemically driven. The reaction conditions from Table 8, entry 1 were used in the absence of electricity passing through the reaction mixture. After 18 hours, no reaction was observed and 92% of the starting material was recovered (Scheme 82).



Scheme 82: Control reaction without electricity. 92% of the starting material **94** was recovered.

Whilst cyclised product was obtained by reducing the concentration of the reaction, it was still the minor product. To investigate if the reaction could be optimised, the equivalents of sodium methoxide were varied (Table 9).

Table 9: Isolated yield of product **A** against equivalents of sodium methoxide.

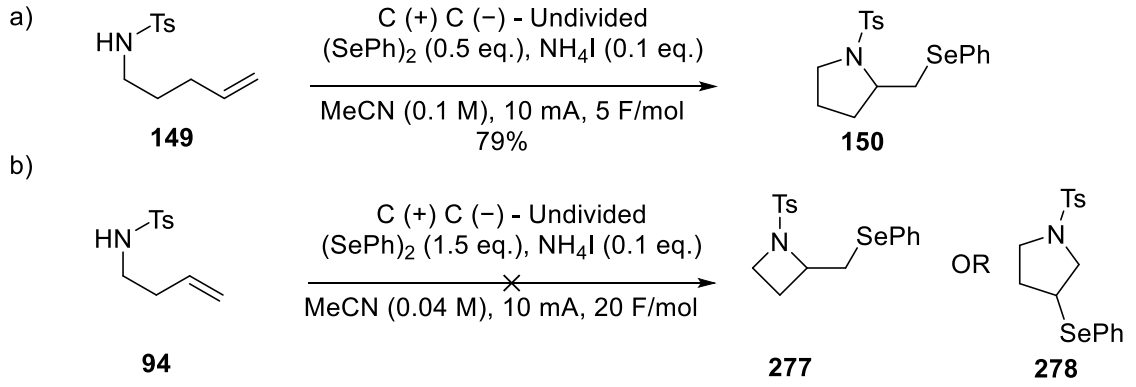


Entry	Equivalents of NaOMe	Product **A** (mg)	Mixture **B** (mg)	Isolated yield of **A** (%)
1	4	8	46	10
2	2	3	26	4
3	1	9	33	11
4	0	54	9	64

(0.22 mmol scale of homoallyl amine **94** at room temperature. Isolated yield after purification by column chromatography.)

Despite varying the equivalents of sodium methoxide, both product **A** and mixture **B** were isolated in each reaction. Increasing the equivalents of sodium methoxide decreased the yield of product **A** (entry 3 vs 1 and 2). However, in the absence of sodium methoxide, product **A** was isolated as the major product in 64% yield (entry 4).

Before optimising conditions for selectivity, Milton had used acetonitrile as a solvent and ammonium iodide as an electrolyte in the absence of base to afford pyrrolidine **150** in 79% yield from γ-aminoalkene **149** (Scheme 83a).[3] In an attempt to improve the yield of product **A**, these conditions were used at the reduced concentration of 0.04 M but no cyclised product was observed (Scheme 83b).



Scheme 83: a) **150** was afforded from **149** with MeCN and NH_4I in 79% yield as reported by Milton. b) Unsuccessful reaction when conditions applied to homoallyl amine **94**.

With conditions in hand that afforded product **A** as the major product in moderate yield, its identity was investigated. Analysis of the HMBC coupling for the product observed an interaction between the carbon of H_a and the diastereotopic protons H_c and an interaction between proton H_b and the aromatic quaternary carbon adjacent to selenium which identified the product as pyrrolidine **278**. For azetidine **277**, interaction between carbon of H_a and diastereotopic protons H_c would not be observed by HMBC coupling and coupling interaction between the aromatic quaternary carbon adjacent to selenium and the diastereotopic protons H_c would be expected (Figure 19).

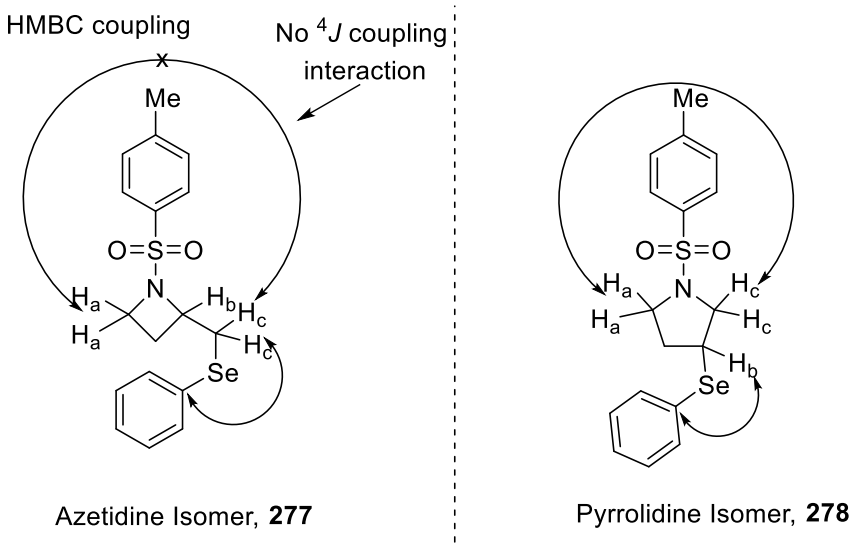


Figure 19: HMBC coupling interactions between key carbon and protons for azetidine **277** and pyrrolidine **278**.

Additional evidence for the pyrrolidine isomer was obtained from satellites present in the carbon NMR spectrum that were a result of selenium-77 splitting, the only NMR active isotope of selenium with a natural abundance of 7.63%.[156] The selenium splitting was observed on 3 aliphatic carbons and one aromatic carbon.

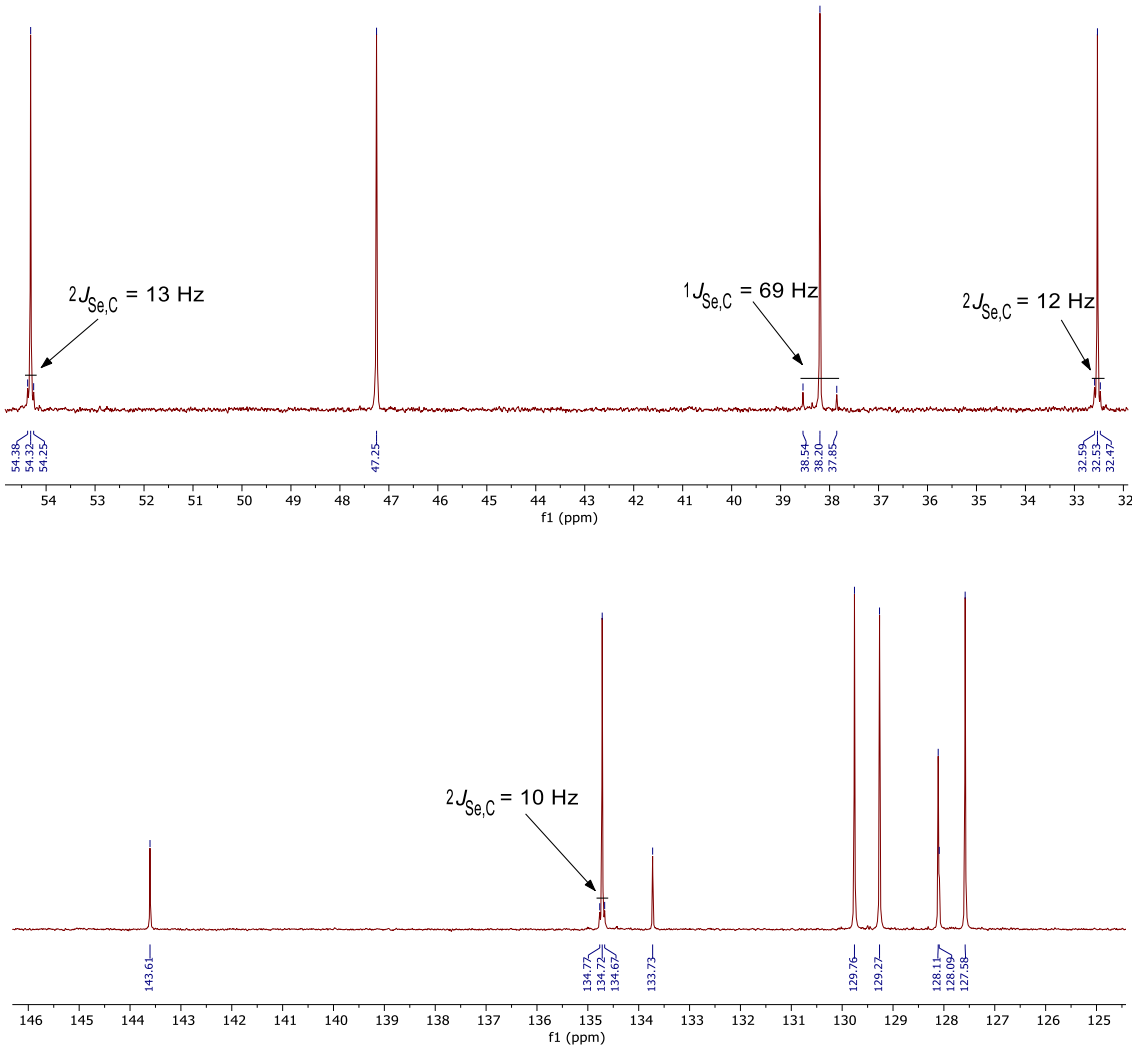


Figure 20: Four peaks in carbon NMR spectrum with selenium splitting observed. *J* coupling values labelled on each peak.

Three of the couplings observed (2 aliphatic carbons and the aromatic carbon) had similar values of 12, 13 and 10 Hz. It was determined that these three carbons were the same number of bonds away from the selenium atom. Whereas the remaining aliphatic carbon had a

significantly larger value of 69 Hz which indicated that it was a smaller number of bonds away from the selenium atom compared to the previous carbon atoms (Figure 20).

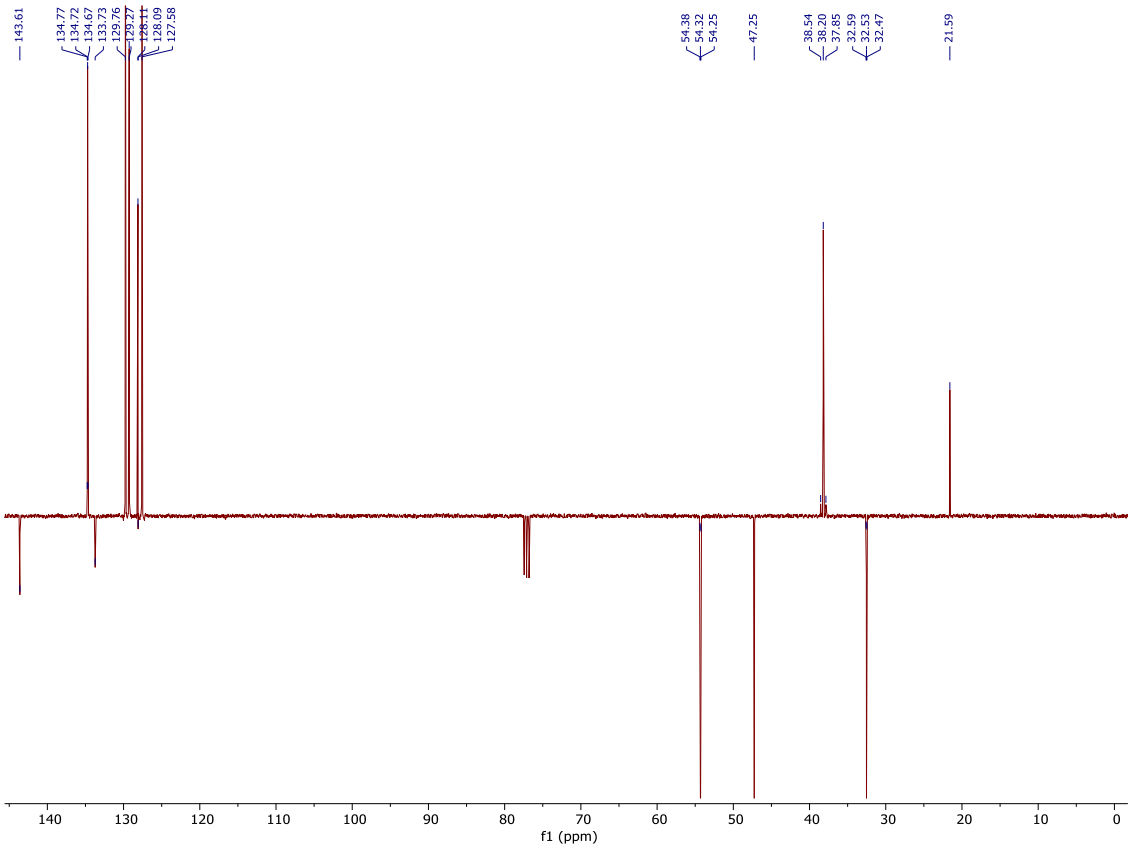


Figure 21: The ^{13}C Jmod spectrum. Primary and tertiary carbons are above the baseline and secondary and quaternary carbons are below the baseline.

The ^{13}C Jmod NMR spectrum was used to determine the nature of the carbon atoms split by selenium. The aromatic carbon was primary and therefore the coupling was determined to be ^{2}J coupling between the selenium atom and the three carbon atoms with coupling values of 12, 13 and 10 Hz. The two aliphatic carbons with ^{2}J coupling were secondary. The remaining aliphatic carbon was determined to be primary with ^{1}J coupling. An aromatic quaternary carbon with selenium splitting was not observed. Satellite peaks were not observed and were assumed to be hidden within the baseline as the quaternary carbons had much weaker resonance in comparison to the other carbons (Figure 21).

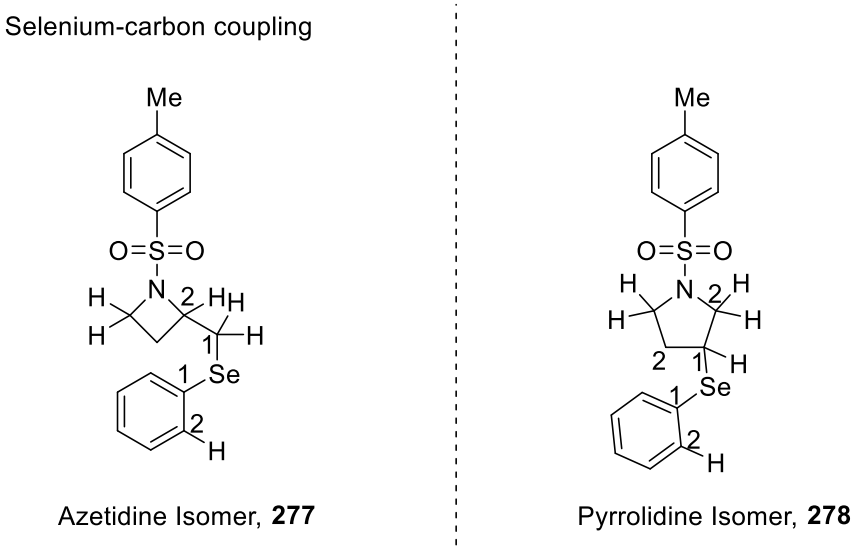
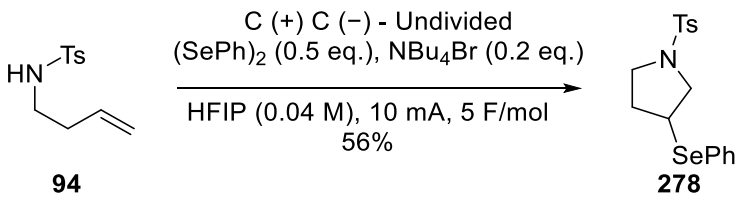


Figure 22: The two possible isomers, azetidine **277** and pyrrolidine **278**, and potential sites for Se splitting in ^{13}C NMR.

With the NMR showing selenium splitting at a primary and two secondary aliphatic carbon atoms, the product was assigned as pyrrolidine **278**. The azetidine isomer would not show this pattern, instead selenium splitting at a secondary and a primary aliphatic carbon atom would be expected (Figure 22).

4.3.1 Optimisation for Homoallylic Amine Substrates

A review of the optimisation by Milton in which the reactions were performed at 0.04 M, found that the electrolyte had been doubled from 0.1 to 0.2 equivalents. The reason for this increase was to ensure that a sufficient current was able to pass through the reaction mixture in the diluted conditions.[3] The base free conditions with increased electrolyte were applied to homoallyl amine **94** which afforded pyrrolidine **278** in moderate yield of 56% (Scheme 84).

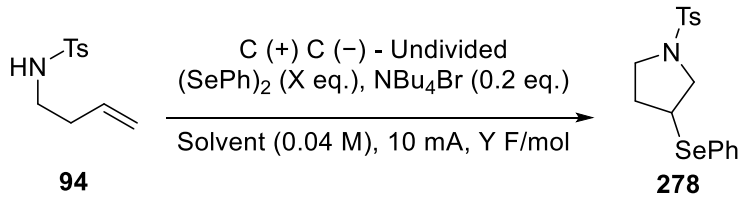


94 **278**

Scheme 84: Synthesis of **278** from **94** with 0.2 equivalents of electrolyte and 0.5 equivalents of $(SePh)_2$.

Despite using significantly less diphenyl diselenide (0.5 compared to 1.5 equivalents) only a slightly lower yield of 56%, compared to previous 64%, was obtained with 0.2 equivalents of *tert*-butylammonium bromide. Based on these results, a short optimisation of the reaction conditions was carried out using 0.2 equivalents of *tert*-butylammonium bromide (Table 10).

Table 10: Optimisation of the reaction with 0.2 equivalents of electrolyte.



94 **278**

Entry	Solvent	Equivalents of $(SePh)_2$	Equivalents of e^- (F/mol)	Yield (%)
1	HFIP	0.5	5	57
2	HFIP	1.5	5	96
3	HFIP	1.5	20	96
4	HFIP	1.0	5	83
5	MeCN	1.5	20	-

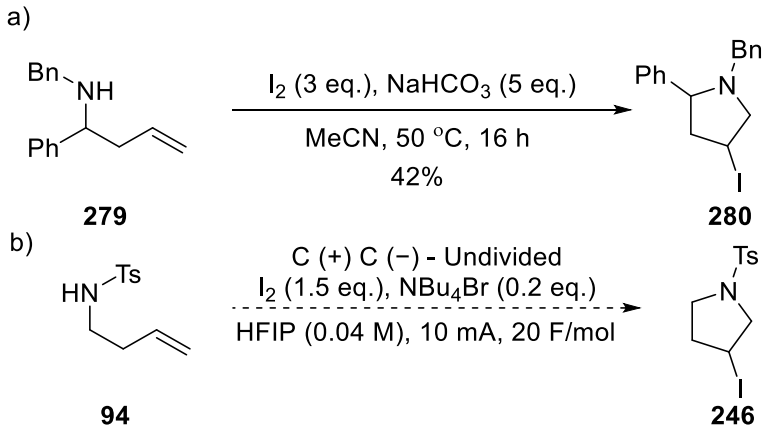
(Reactions performed with 0.22 mmol of **94** at room temperature.)

Increasing the equivalents of diphenyl diselenide from 0.5 to 1.5 (entry 1 vs 2) significantly improved the yield of pyrrolidine **278**. No improvement of yield was observed when the equivalents of electrons were increased from 5 to 20 F/mol (entry 3 vs 2). It was clear that increasing the equivalents of *tert*-butylammonium bromide significantly improved the reaction yield, as only 64% yield was obtained previously when using 1.5 equivalents of diphenyl diselenide at 20 F/mol compared to the 96% yield achieved in entry 3. Using just 1.0 equivalent of diphenyl diselenide gave pyrrolidine **278** in 83% yield (entry 4), which made for an excellent compromise between yield of product and establishing reagent efficient reaction conditions. The reaction was attempted using acetonitrile as the solvent and 0.2 equivalents of *tert*-butylammonium bromide, however, no pyrrolidine product was observed in the

reaction (entry 5) which suggests that HFIP has an important role during cyclisation of the homoallylic amine substrates.

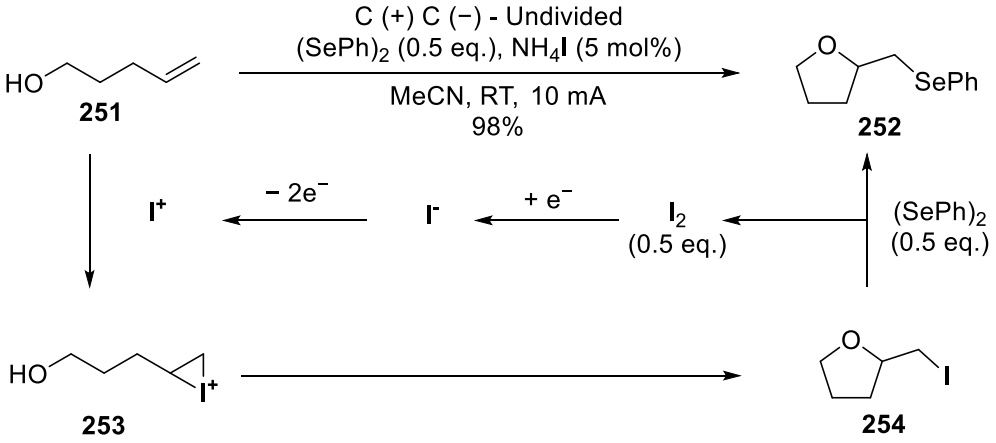
4.3.2 Electrochemical Mediated Cyclisation with Iodine

As stated previously in section 1.4, the aim of the project was to develop a method for cyclising homoallyl amines into 4- or 5-membered rings that either complemented or improved upon the iodine mediated method reported by Feula *et al.*[91,92] Whilst synthesis of azetidine products had remained elusive, this electrochemically driven method had demonstrated the synthesis of pyrrolidine **278** from homoallyl amine **94** in excellent yield using diphenyl diselenide under mild conditions. It was hypothesised that substituting diphenyl diselenide for molecular iodine in this protocol would result in a more reagent efficient reaction for obtaining 3-iodopyrrolidine derivatives compared to the method reported by Feula *et al.*, that required 3 equivalents of molecular iodine and 5 equivalents of sodium bicarbonate heated at 50 °C. Based on the results with diphenyl diselenide it was proposed that high yield of 3-iodopyrrolidine products could be realised using 1.5 equivalents of molecular iodine in the absence of base at room temperature with the ElectraSyn 2.0 (Scheme 85).



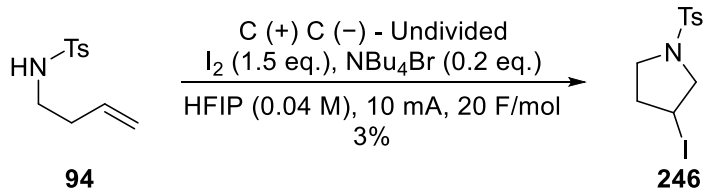
Scheme 85: a) Feula *et al.* reaction conditions to synthesise 3-iodopyrrolidine **280**. b) Proposed synthesis of pyrrolidine **246** with electrochemical reaction conditions.

The replacement of diphenyl diselenide with molecular iodine was reasonable, as the synthesis of cyclic ethers described by Meng *et al.* was thought to be achieved *via* an iodonium intermediate in the proposed mechanism discussed in section 4.1 (Scheme 71).[151] Molecular iodine was chosen as the reagent as 0.5 equivalents could in theory produce 1 equivalent of the iodonium cation.



Scheme 71: Proposed mechanism by Meng *et al.* with iodonium cation involved in cyclisation step.

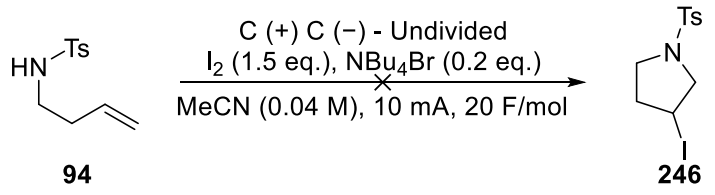
The reaction was attempted with homoallyl amine **94** and 1.5 equivalents of molecular iodine as that gave the best yields with diphenyl diselenide. Cyclised product was obtained in very poor yield of 3% and identified as pyrrolidine **246** as the proton NMR spectrum was identical to the confirmed pyrrolidine **246** obtained with hypervalent iodine mediated synthesis (section 3.3.2). It was observed that the electrodes used in the reaction were coated in molecular iodine (Scheme 86). It was proposed that the accumulation of iodine on the electrodes during the reaction prevented the reaction from proceeding which resulted in the poor yield of product.



94 **246**

Scheme 86: Pyrrolidine **246** obtained from **94** in very poor yield. Accumulation of iodine on the electrodes observed.

To prevent molecular iodine from accumulating on the electrodes, the solvent was changed to acetonitrile as iodine is very soluble in acetonitrile. Whilst no molecular iodine was present on the electrodes at the end of the reaction, no desired product was observed (Scheme 87). This gave further evidence that HFIP plays an important role during the cyclisation of homoallylic amine substrates for this electrochemical method.

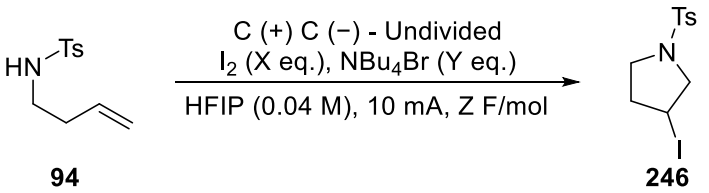


94 **246**

Scheme 87: Unsuccessful reaction for homoallyl amine **94** with MeCN as the solvent.

A brief optimisation was conducted with HFIP as the solvent to find reaction conditions that would prevent the accumulation of molecular iodine on the electrodes and thus improve the yield of the reaction (Table 11).

Table 11: Brief optimisation of the reaction focused on equivalents of I_2.



94 **246**

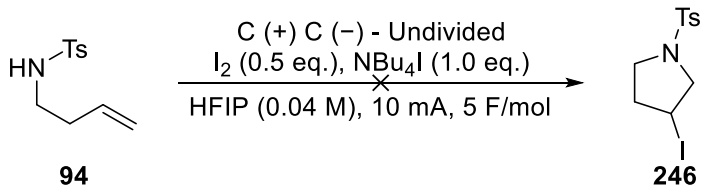
Entry	Equivalent of I_2	Equivalent of e^- (F/mol)	Equivalent of NBu_4Br	Yield (%)
1	1.5	20	0.2	3
2	0.5	5	0.2	28
3	1.0	5	0.2	10
4	1.5	5	0.2	11
5	0.5	5	1.0	-

(Reaction performed with 0.22 mmol of **94** at room temperature.)

Homoallyl amine **94** was observed at the end of the reaction in all cases. Excess molecular iodine in the reaction appeared to have a detrimental effect, as yields for 1.0 and 1.5 equivalents were significantly lower compared to 0.5 equivalents of molecular iodine (entry 2 vs 3 and 4). Surprisingly, no coating of molecular iodine was observed for entries 2, 3 and 4 unlike entry 1, which suggests that the accumulation of molecular iodine was a result of high F/mol of electricity instead of the previously assumed high equivalents of molecular iodine. No desired product was observed when *tert*-butylammonium bromide was increased to 1.0 equivalent (entry 5). Although best results were obtained with entry 2, yield of pyrrolidine **246** was still poor.

To test whether bromide of *tert*-butylammonium bromide was competing against iodine, the reaction was performed with *tert*-butylammonium iodide as the electrolyte (Scheme 88). However, pyrrolidine **246** was not observed in the reaction, which means that *tert*-

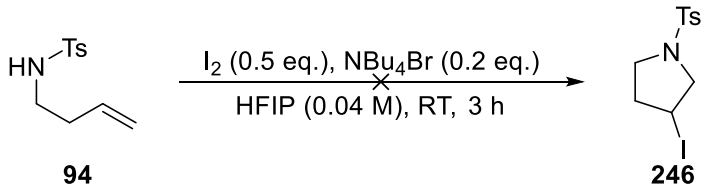
butylammonium bromide was not responsible for the poor yields obtained when using molecular iodine.



94 **246**

Scheme 88: Reaction was unsuccessful with *tert*-butylammonium iodide as the electrolyte.

Given the consistently poor yields of the reaction, the possibility that the reaction was not electrochemically driven and was in fact proceeding *via* an iodine mediated cyclisation as described by Feula *et al.* was considered. To test this possibility, a control reaction was performed by stirring 0.5 equivalents of molecular iodine and 0.2 equivalents of *tert*-butylammonium bromide at room temperature for 3 hours. Pyrrolidine **246** was not observed from the control reaction which concluded that the reaction was electrochemically driven, albeit with poor conversion to desired product (Scheme 89).



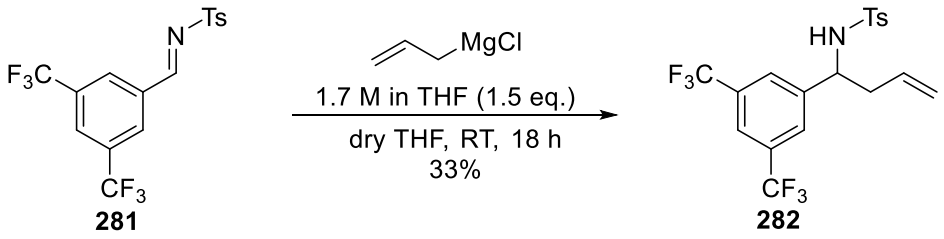
94 **246**

Scheme 89: No reaction observed in control reaction without electricity.

4.3.3 Cyclisation of Racemic Homoallyl Amine

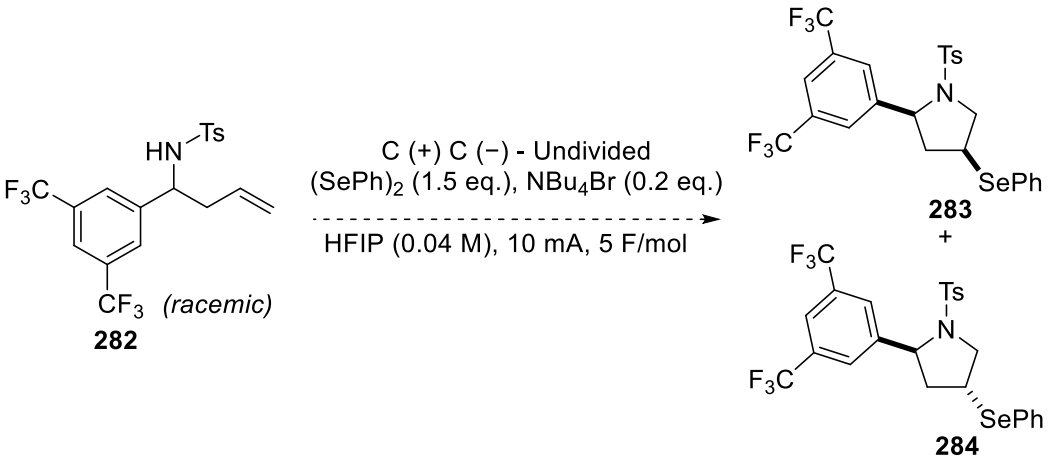
Pyrrolidine **278** could be obtained regiospecifically in excellent yield with diphenyl diselenide for achiral homoallyl amine **94**. To expand the reaction scope, racemic homoallyl amine **282** was subjected to the reaction conditions. Racemic **282** had a 3,5-bis(trifluoromethyl)phenyl group at the 2-position, which has two distinctive singlets with a 2:1 integral ratio in the

aromatic region of proton NMR spectra. Homoallyl amine **282** was obtained *via* alkylation of imine **281** with allylmagnesium chloride (Scheme 90).



Scheme 90: Racemic **282** synthesised from alkylation of imine **281** with allylmagnesium chloride.

Two products were expected from the cyclisation reaction, *cis*- and *trans*-pyrrolidine **283** and **284**, so the highest yielding reaction conditions were used to maximise the chances of success of the reaction (Scheme 91).



Scheme 91: Proposed reaction conditions with 1.5 equivalents of $(SePh)_2$ to obtain pyrrolidines **283** and **284**.

Two products, **A** and **B**, thought to be the *cis*- and *trans*-isomers **283** and **284** were isolated from the reaction but contained impurities in their proton NMR spectra.

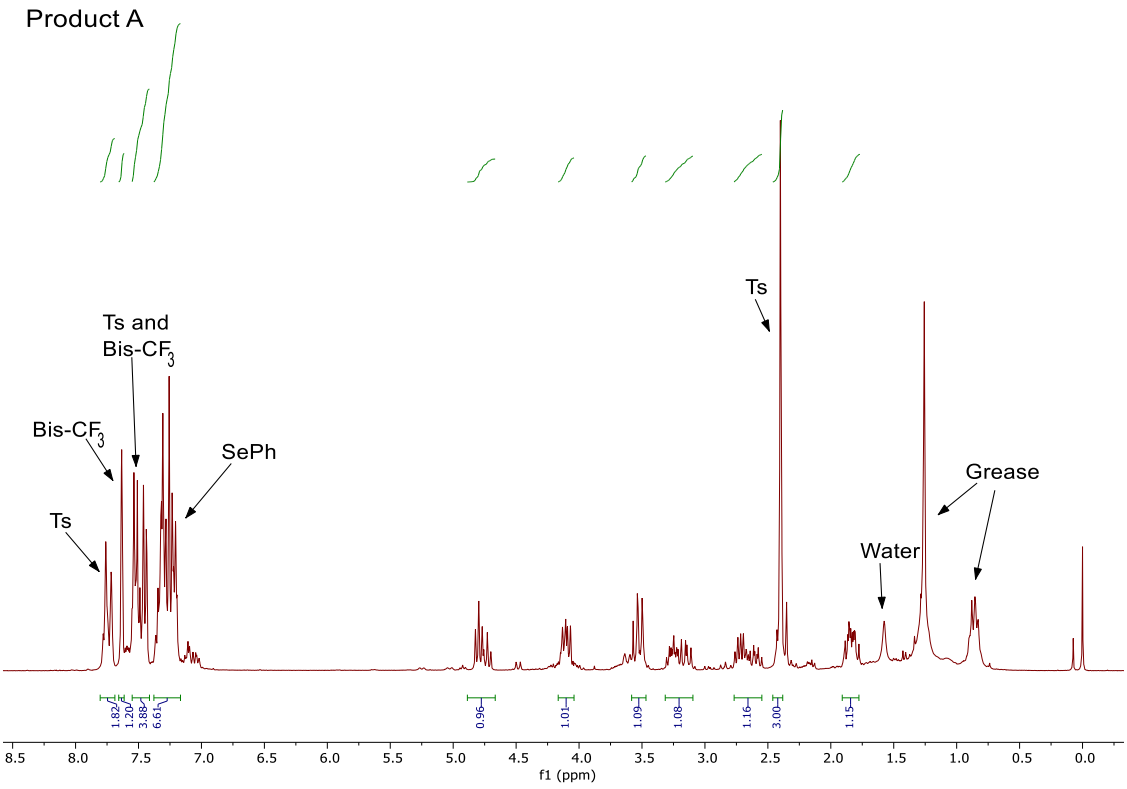


Figure 23: Proton NMR spectrum of product **A** that contained impurities.

Integration of the proton NMR spectrum of product **A**, suggests that product **A** was predominantly one product with 9 protons in the aliphatic region and with no alkene protons observed, which was consistent with ring formation (Figure 23). The aromatic region of the proton NMR spectrum and the mass spectrum of the product was also in agreement with formation of cyclised product.

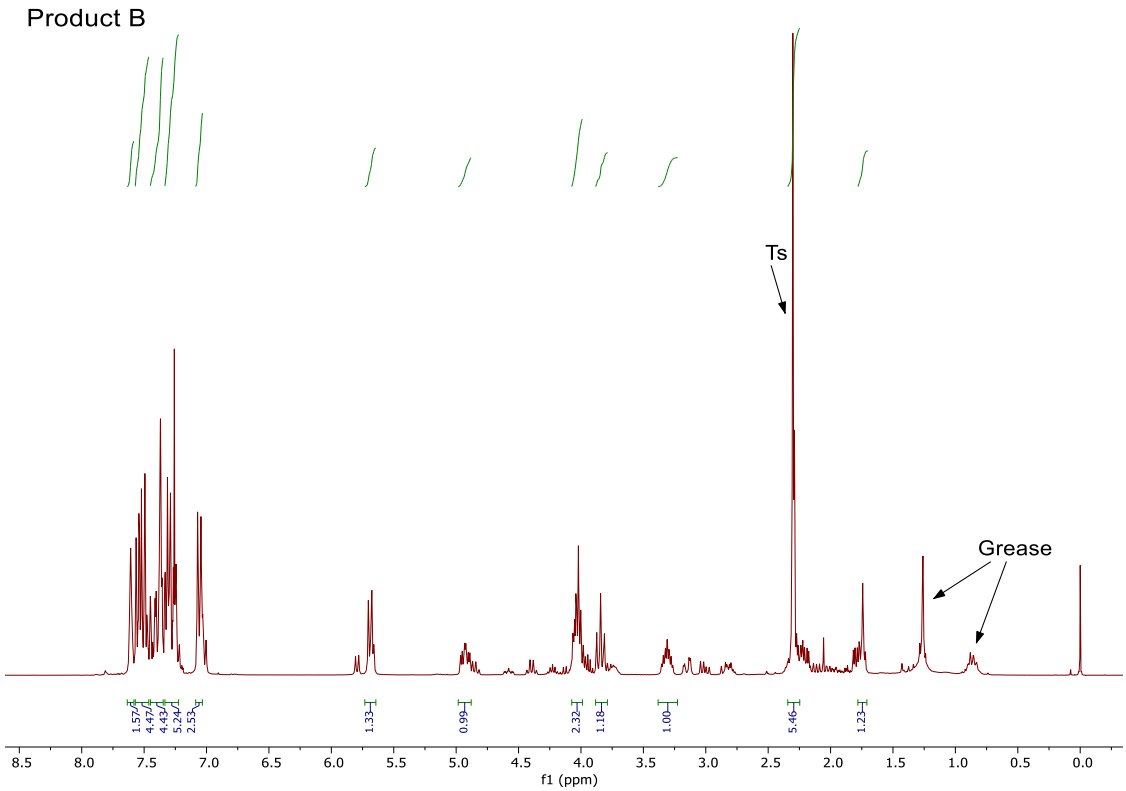


Figure 24: Proton NMR spectrum of product **B** that contained impurities.

The impurity to product ratio was much higher in product **B**, which made it difficult to distinguish if the other expected pyrrolidine isomer was present (Figure 24). However, the mass spectrum of product **B** showed desired product peak which suggested that cyclised product was present in the sample.

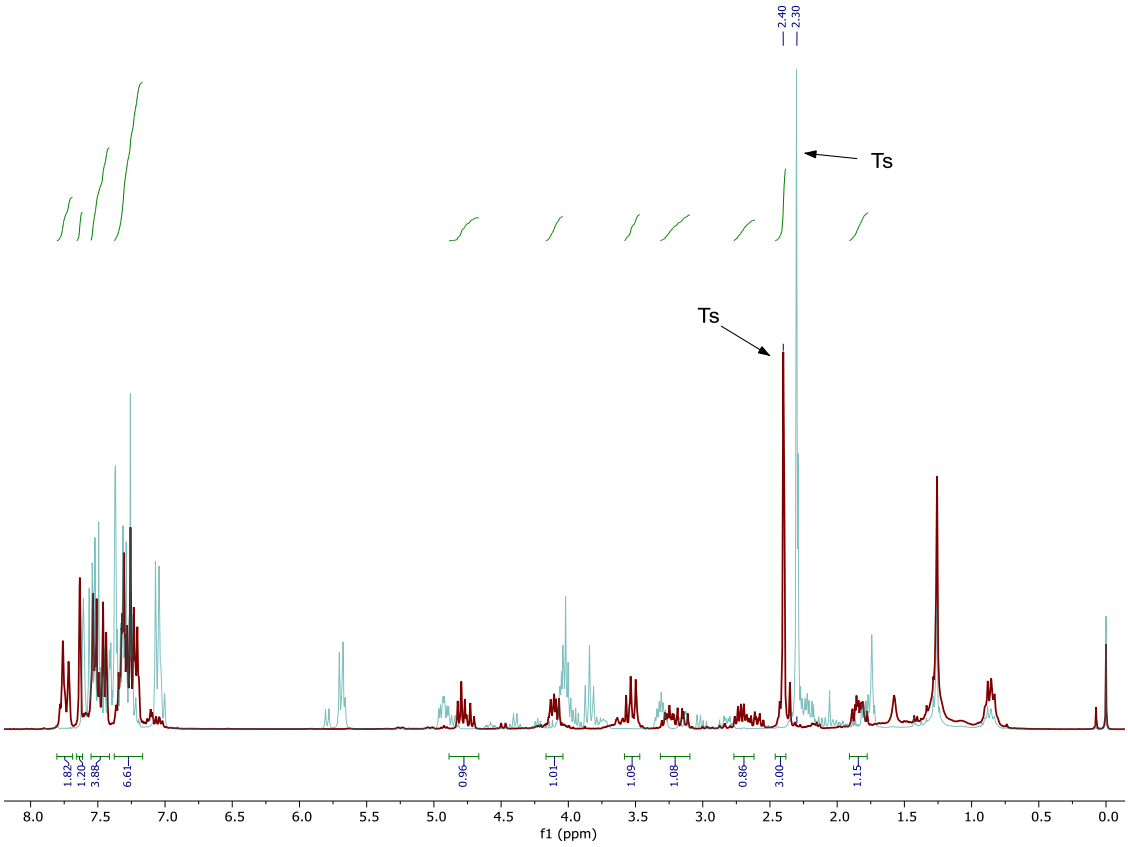


Figure 25: Product **A** (red) superimposed over product **B** (blue).

The two peaks in the aliphatic region assigned to the tosyl group were 2.40 ppm and 2.30 ppm for products **A** and **B** respectively (Figure 25). This is consistent with the equivalent pyrrolidines **256b** and **257b** synthesised by Milton, where the assigned tosyl methyl singlets were 2.40 ppm for **256b** and 2.28 ppm for **257b** (Figure 26).[3]

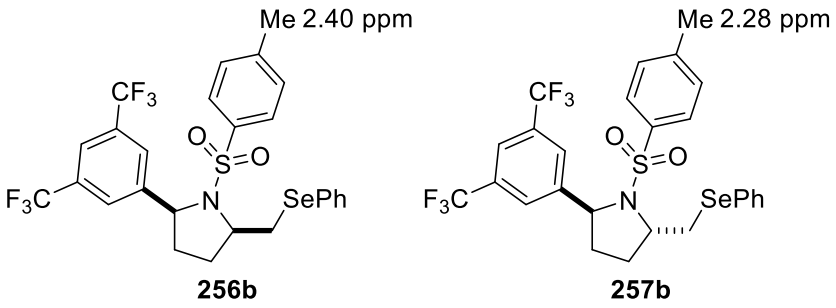


Figure 26: Pyrrolidines **256b** and **257b** synthesised by Milton with tosyl methyl peak labelled from proton NMR spectra.

Although consistent with the expected products, more work is required to confirm that both products were synthesised in the reaction and to identify the isomer of each product.

4.4 Conclusions and Future Work

4.4.1 γ-Aminoalkene Substrates

To summarise, the nature of HFIP influences the selectivity of the reaction towards *cis*- and *trans*-pyrrolidines. When HFIP was dried over molecular sieves or mixed with water, *trans*-selectivity was observed whereas if HFIP was distilled or used as supplied, *cis*-selectivity was observed. Whilst the *trans*-selectivity of the reaction with addition of sodium methoxide was verified when HFIP was used as supplied, it was not observed when the HFIP was distilled. Preliminary test found that *cis*- and *trans*-pyrrolidine products were stable with respect to interconversion of stereoisomers. However, issues of product stability has been observed when high equivalents are electrons are used with 0.5 equivalents of diphenyl diselenide.

Optimisation found that greater yields could be obtained at the cost of longer reaction times and excess of reagent with 1.5 equivalents of diphenyl diselenide and 20 equivalents of electrons. However, reasonable yields could still be obtained for γ-aminoalkenes with the more attractive sub-stoichiometric conditions of 0.5 equivalents of diphenyl diselenide and 5 equivalents of electrons. Initial expansion of reaction scope with dimethyl diselenide and diphenyl disulfide had shown promise with high yield obtained of pyrrolidines **270** and **237**. The reactions were less successful with γ-aminoalkene **149**. Preliminary results for converting the phenylselanyl pyrrolidine products into hydroxy or alkoxy pyrrolidine derivatives were promising. For pyrrolidine **268**, both hydroxy and methoxy pyrrolidines **275** and **276** were isolated, albeit in low yield.

Excellent yield of indoline **261** was obtained when diphenyl diselenide was increased to 1.5 equivalents. No indoline products were isolated with either dimethyl diselenide or diphenyl disulfide.

Based on these findings it can be concluded that sodium methoxide had a less significant role in the selectivity of the reaction than previously thought and that HFIP had the greatest influence on selectivity. Water had a greater *trans*-selectivity than sodium methoxide as *trans*-selective results were still achieved when water was mixed with distilled HFIP. However, the amount of water used in the solvent mixture was critical as no reaction occurred when the amount of water was greater than HFIP. While progress has been made, the mechanism of the reaction is still not understood. Further utility can be found for this method as the reaction is not limited to just phenylselanyl pyrrolidine derivatives, but further investigation into scope and optimisation is required to maximise this potential.

Future work would benefit from computational studies looking at HFIP interacting with the reaction site as this may offer some explanations for the influence HFIP has on selectivity and improve understanding of the reaction mechanism. To improve reaction yields and prevent isolation of both pyrrolidines **275** and **276** in the same reaction, the conversion of pyrrolidine **268** into hydroxypyrrolidine **275** needs to be repeated in the absence of methanol and sodium methoxide could be used in methanol to obtain methoxypyrrolidine **276**. Efforts on racemic γ-aminoalkene substrates for further expansion of scope would ascertain if switching to dimethyl diselenide or diphenyl disulfide effects the selectivity of the reaction and if there is any stereoconversion when converting *cis*- and *trans*-pyrrolidine products into hydroxy and alkoxy derivatives. Finally, the removal of the tosyl protecting group warrants investigation as

access to the free amine would open further derivatisation possibilities and greatly enhance the desirability of this method for use in industry.

4.4.2 Homoallylic Amine Substrates

In summary, pyrrolidine **278** was obtained in excellent yield of 96% from homoallyl amine **94** with 1.5 equivalents of diphenyl diselenide. Whilst sub-stoichiometric equivalents of diphenyl diselenide afforded product in moderate yield, a good compromise between quantities of reagent and product yield was found with 1.0 equivalent of diphenyl diselenide. Preliminary reaction with racemic homoallyl amine **282** appeared to have obtained at least one of the expected *cis*- or *trans*-pyrrolidine products **283** and **284**, although pure sample had not been successfully isolated. When molecular iodine was used in place of diphenyl diselenide, iodopyrrolidine **246** was obtained in poor yield. Optimisation did not improve the yield of iodopyrrolidine **246** enough to make the reaction feasible. Reactions of homoallyl amine **94** were unsuccessful with acetonitrile as the solvent, which was surprising given that analogous γ-aminoalkene **149** afforded pyrrolidine **150** in acetonitrile. Selenium splitting in the carbon NMR spectrum could be used to identify the ring size of the product from two possible regioisomers.

In conclusion, although no azetidine products have been observed, the aim to develop a highly regioselective method has been achieved as regioselective synthesis of pyrrolidines from homoallyl amines were achieved under mild conditions. While the synthesis of iodopyrrolidine **246** from molecular iodine demonstrates milder reaction conditions compared to the protocol described by Feula *et al.*, its usability is limited by the poor yield of product. Therefore, the protocol described by Feula *et al.* should still be used for the synthesis of iodopyrrolidine

products instead of this method. In its current state the stereoselectivity of this method cannot be evaluated as no *cis*- or *trans*-products have been successfully isolated and therefore the development of a highly stereoselective method has not been achieved with the work reported in this chapter. The removal of the tosyl protecting group has yet to be attempted. This method shows great potential for the regioselective synthesis of pyrrolidine derivatives, but more work is required for it to be adopted by the wider scientific community.

Future work should focus on the reaction of racemic homoallyl amines with diphenyl diselenide to isolate *cis*- and *trans*-products. This will allow optimisation of stereoselective reaction conditions to be completed and then the method can be evaluated to see if it meets the full aim of the project that delivers pyrrolidine products in both high regio- and stereo-selectivity. Successful removal of the tosyl protecting group would show that this method further complements the protocol described by Feula *et al.* Continued expansion of scope with dimethyl diselenide and diphenyl disulfide for instance, would also highlight the potential of this method.

5 Experimental

5.1 General Information

Commercially available solvents and reagents were purchased and used from suppliers without further purification, unless otherwise stated. Dry tetrahydrofuran was obtained from a PureSolv Solvent Purification System. Microwave heated reactions were conducted with a CEM Discover S microwave reaction heating system. Electrochemical reactions were conducted with an ElectraSyn 2.0. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60 F254 plates. TLC plates were visualised with UV light and/or by staining with an appropriate dip. Column chromatography for purification was carried out using a Combiflash R*f* 200i and commercially available prepacked silica stationary phase columns. Column traces were recorded at two wavelengths (254 nm and 280 nm) alongside evaporative light scattering (ELS) detection when required. Gas chromatography was carried out with a Shimadzu GC-2010 with FID using a Phenomenex ZB-5 column (95% dimethylpolysiloxane/5% diphenylpolysiloxane) of dimensions 30 mm × 0.25 mm (ID) × 0.25 µm (film thickness). All NMR spectra were recorded using chloroform-*d* as solvent at room temperature. Proton and carbon NMR spectra were recorded with either a Bruker AVIII400 or a Bruker AVANCE NEO NMR spectrometer at room temperature at 400 and 101 MHz respectively. Carbon NMR spectra are proton decoupled. ^{19}F and ^{77}Se spectra were recorded with a Bruker AVANCE NEO at room temperature at 377 MHz and 76 MHz respectively. Proton NMR chemical shifts (δ) are reported in ppm relative residual chloroform-*H* (δ 7.26 in chloroform-*d*) or TMS (δ 0.00). Carbon NMR spectra are reported relative to the signal for chloroform-*d* (δ 77.16). Fluorine NMR spectra are reported relative to indirectly referenced $CFCl_3$ (δ 0.00 in chloroform-*d*) and selenium NMR spectra are indirectly referenced

to diphenyldiselenide (δ 463.00 in chloroform-*d*). Coupling constants (*J*) are reported in Hertz (Hz). Multiplicities of the signals are abbreviated as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p) and multiplet (m). The abbreviations app and br denote apparent and broad respectively. Stack is used to label overlapping peaks. Infrared spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrometer using an ATR attachment; selected frequencies (ν_{max}) are reported in wavenumbers (cm^{-1}). Mass spectra were recorded with electrospray MS Waters LCT Time of Flight Mass Spectrometer (TOF-MS) and with EI (GC/MS) Waters GCT Premier TOF-MS. All mass spectrometry data was processed with MassLynx version 4.1, in which the calculated and observed m/z are reported as neutral. Melting points were measured using a Stuart Scientific Melting Point SMP1 with a 300 °C thermometer and are uncorrected.

General procedure A: Procedure described by Mizar *et al.*[157] To a solution of 2,2-diphenyl-4-penten-1-amine **203** (1 eq.) in dichloromethane (10 mL) were added either tosyl chloride, benzyl chloride or di-*tert*-butyl dicarbonate (1.1 eq.) and pyridine (3 eq.). The resultant solution was stirred at room temperature for 36 – 72 h. The reaction mixture was diluted with water and extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and then concentrated *in vacuo* to afford a crude product. Purification by flash column chromatography afforded the desired product.

General procedure B: Modified procedure described by Feltenberger *et al.*[158] To a solution of bromoalkene (1.0 eq.) in acetone (15 mL) were added *p*-toluenesulfonamide (1.1 eq.) and potassium carbonate (2.0 eq.). The resultant suspension was fitted with a reflux condenser and stirred at 56 °C for 18 h. The reaction mixture was cooled to room temperature, filtered

through celite, solids washed with ethyl acetate, and then the combined washings were concentrated *in vacuo* to afford a crude product. Purification by flash chromatography afforded the desired product.

General procedure C: Procedure described by Bertrand *et al.*[119] An oven dried flask cooled under a stream of argon was charged with bromobenzene (1.2 eq.), caesium carbonate (2.3 eq.), palladium acetate (2 mol%) and bis((2-diphenylphosphino)phenyl)ether (4 mol%) was added amine (1 eq.) as a solution in 1,4-dioxane (5 mL/mmol substrate). The resultant suspension was fitted with a reflux condenser and stirred at 100 °C for 18-24 h. The reaction was cooled to room temperature, quenched with aqueous saturated ammonium chloride and extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and then concentrated *in vacuo*. Purification by flash column chromatography afforded the desired product.

General procedure D: Modified procedure described by Liu and Li.[122] To a solution of sulfonamide (1 eq.) in dichloromethane (10 mL) were added (bis(trifluoroacetoxy)iodo)benzene (1.1 eq.) and sodium iodide (2 eq.). The resultant suspension was stirred at room temperature for 18 h. The reaction was quenched with aqueous saturated sodium thiosulfate and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and then concentrated *in vacuo*. Purification by flash column chromatography afforded the desired product.

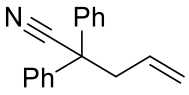
General procedure E: Procedure described by Joe Milton.[3] Sulfonamide (1 eq.), diphenyl diselenide or dimethyl diselenide (0.5 eq.), tetra-butylammonium bromide (0.1 eq.), sodium

methoxide (1 eq.) and 1,1,1,3,3,3-hexafluoroisopropanol (0.1 M) were added to an ElectraSyn vial equipped with a graphite anode and cathode. The suspension was subjected to constant current electrolysis at 10 mA with the polarity of the electrodes alternating every 10 minutes until 5 F/mol of electricity had passed. The mixture was transferred to a round bottom flask and all components rinsed with acetonitrile followed by concentration of the reaction mixture *in vacuo* to afford a crude product. Purification by flash column chromatography afforded the desired product.

General procedure F: Modified procedure described by Joe Milton.[3] Sulfonamide (1 eq.), diphenyl diselenide or molecular iodine (1.5 eq.), tetra-butylammonium bromide (0.2 eq.) and 1,1,1,3,3,3-hexafluoroisopropanol (0.04 M) were added to an ElectraSyn vial equipped with a graphite anode and cathode. The suspension was subjected to constant current electrolysis at 10 mA with the polarity of the electrodes alternating every 10 minutes until 5 F/mol of electricity had passed. The mixture was transferred to a round bottom flask and all components rinsed with acetonitrile followed by concentration of the reaction mixture *in vacuo* to afford a crude product. Purification by flash column chromatography afforded the desired product.

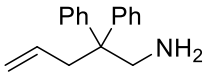
5.2 Characterisation Data of Compounds

2,2-Diphenylpent-4-enenitrile, 202



Modified procedure described by Mizar *et al.*[157] To a suspension of sodium hydride (60% in mineral oil, 520 mg, 13.0 mmol) in tetrahydrofuran (4 mL) cooled with an ice bath was added diphenylacetonitrile **201** (1.93 g, 10.0 mmol) dropwise in tetrahydrofuran (6 mL) over 10 minutes. The resultant yellow suspension was stirred at room temperature for 1.25 h. The suspension was cooled with an ice bath and then allyl bromide (1.1 mL, 13.0 mmol) was added dropwise over 5 minutes. The resultant suspension was stirred at room temperature for 3 h, quenched with saturated aqueous ammonium chloride (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 98:2) afforded the title compound as a colourless oil in 79% yield (1.84 g, 7.89 mmol). R_f 0.61 (hexane:ethyl acetate 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.30 (10 H, stack, Ph*H*), 5.74 (1 H, ddt, *J* = 17.2, 10.2, 7.0 Hz, C*H*=CH_2), 5.27 – 5.18 (2 H, stack, CH=C*H*$_2$), 3.17 (2 H, app dt, *J* = 7.0, 1.2 Hz, C*H*$_2$CH=CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8 (2 × C), 131.8 (CH), 128.9 (4 × CH), 128.0 (2 × CH), 127.1 (4 × CH), 122.0 (C), 120.4 (CH_2), 51.7 (C), 44.0 (CH_2); IR: 3063, 3029, 2983, 2923, 2238, 1955, 1807, 1643, 1598, 1494, 1449, 924, 695 cm^{-1}; TOF MS: (EI$^+$) 234.16 [M + H]. Data in agreement with literature.[159]

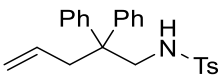
2,2-Diphenyl-4-penten-1-amine, 203



Modified procedure described by Mizar *et al.*[157] To a suspension of lithium aluminium hydride (553 mg, 14.60 mmol) in diethyl ether (18 mL) cooled with an ice bath was added 2,2-diphenylpent-4-enenitrile **202** (1.70 g, 7.29 mmol) dropwise in diethyl ether (6 mL) over 10

minutes. The resultant suspension was stirred at room temperature for 18 h. The reaction was quenched with sequential dropwise addition of water (0.6 mL), aqueous sodium hydroxide (2 M, 0.6 mL) and water (1.7 mL). The suspension was stirred at room temperature for 30 minutes, the solid by-products filtered off, washing with diethyl ether (10 mL) and the filtrate dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford the title compound as a colourless oil in 80% yield (1.38 g, 5.81 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (4 H, stack, Ph*H*), 7.23 – 7.16 (6 H, stack, Ph*H*), 5.40 (1 H, ddt, *J* = 17.1, 10.1, 7.1 Hz, C*H*=CH_2), 5.05 (1 H, ddt, *J* = 17.1, 2.2, 1.4 Hz, CH=C*H*$_a$H$_b$), 4.98 (1 H, ddt, *J* = 10.1, 2.1, 1.0 Hz, CH=CH_a*H*$_b$), 3.33 (2 H, s, C*H*$_2$NH$_2$), 2.93 (2 H, app dt, *J* = 7.1, 1.2 Hz, C*H*$_2$CH=CH_2), 0.85 (2 H, br s, N*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3 (2 × C), 134.7 (CH), 128.2 (4 × CH), 128.1 (4 × CH), 126.1 (2 × CH), 117.7 (CH_2), 51.4 (C), 48.6 (CH_2), 41.2 (CH_2); IR: 3388, 3058, 3026, 2976, 2927, 2860, 1951, 1809, 1638, 1598, 1494, 1444, 914, 754, 696 cm^{-1}, TOF MS: (ES$^+$) 238.16 [M + H]. Data in agreement with literature.[159]

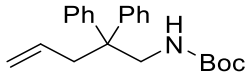
_N_-(2,2-Diphenylpent-4-en-1-yl)-4-methylbenzene sulfonamide, 136



Prepared from 2,2-diphenyl-4-penten-1-amine **203** and tosyl chloride following general procedure A, on a 2.64 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 90:10) afforded the title compound as a white solid in 79% yield (820 mg, 2.09 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.3, $J_{A\text{-}X}$ = 1.7 Hz, Ar*H*), 7.31 – 7.19 (8 H, stack, Ar*H*), 7.09 – 7.03 (4 H, stack, Ar*H*), 5.28 (1 H, ddt, *J* = 16.5, 10.8, 7.1 Hz, C*H*=CH_2), 4.98 – 4.95 (1 H, m, CH=C*H*$_a$H$_b$), 4.94 – 4.91 (1 H, m, CH=CH_a*H*$_b$), 3.83 (1

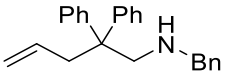
H, br t, *J* = 6.5 Hz, N*H*), 3.53 (2 H, d, *J* = 6.5 Hz, C*H*$_2$NH), 2.91 (2 H, app d, *J* = 7.1 Hz, C*H*$_2$CH=CH$_2$), 2.44 (3 H, s, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6 (2 × C), 143.5 (C), 136.2 (C), 133.1 (CH), 129.7 (2 × CH), 128.5 (4 × CH), 127.8 (4 × CH), 127.2 (2 × CH), 126.8 (2 × CH), 119.1 (CH_2), 49.4 (C), 49.3 (CH_2), 41.3 (CH_2), 21.6 (CH_3); IR: 3256, 3056, 3023, 2978, 2932, 2861, 1925, 1813, 1639, 1597, 1497, 1459, 1445, 1417, 1330, 1163, 922, 755, 694 cm^{-1}; TOF MS: (ES$^+$) 414.15 [M + Na]; m.p. 138-143 °C. Data in agreement with literature.[160]

tert-Butyl (2,2-diphenylpent-4-en-1-yl)carbamate, 198a



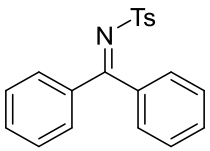
Prepared from 2,2-diphenyl-4-penten-1-amine **203** and di-*tert*-butyl dicarbonate following general procedure A, on a 5.81 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 95:5) afforded the title compound as a colourless oil in 71% yield (1.39 g, 4.15 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (4 H, stack, Ph*H*), 7.24 – 7.12 (6 H, stack, Ph*H*), 5.42 (1 H, ddt, *J* = 13.9, 10.4, 7.2 Hz, C*H*=CH$_2$), 5.04 – 4.93 (2 H, stack, CH=C*H*$_2$), 4.14 (1 H, app br s, N*H*), 3.85 (2 H, d, *J* = 6.0 Hz, C*H*$_2$NH), 2.86 (2 H, app d, *J* = 7.1 Hz, C*H*$_2$CH=CH$_2$), 1.38 (9 H, s, 3 × C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 (C), 145.5 (2 × C), 133.9 (CH), 128.3 (4 × CH), 128.1 (4 × CH), 126.4 (2 × CH), 118.5 (CH_2), 79.3 (C), 50.3 (C), 47.2 (CH_2), 41.8 (CH_2), 28.4 (3 × CH_3); IR: 3286, 3135, 3089, 3015, 2984, 2932, 2888, 1946, 1690, 1640, 1597, 1496, 1445, 1389, 1167, 1071, 696 cm^{-1}; TOF MS: (ES$^+$) 360.19 [M + Na]; TOF HRMS: (ES$^+$) Calc'd for $C_{22}H_{27}NO_2Na$: 360.1939; found: 360.1948. Data in agreement with literature.[161]

_N_-Benzyl-2,2-diphenylpent-4-en-1-amine, 198b



Prepared from 2,2-diphenyl-4-penten-1-amine **203** and benzyl chloride following general procedure A, on a 3.00 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 80:20) afforded the title compound as a colourless oil in 29% yield (289 mg, 0.88 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.14 (15 H, stack, Ph*H*), 5.34 (1 H, ddt, *J* = 17.2, 10.1, 7.1 Hz, C*H*=CH_2), 4.98 (1 H, ddt, *J* = 17.0, 2.5, 1.3 Hz, CH=C*H*$_a$H$_b$), 4.89 (1 H, ddt, *J* = 10.1, 2.2, 1.0 Hz, CH=CH$_a$*H*$_b$), 3.71 (2 H, s, C*H*$_2$), 3.20 (2 H, s, C*H*$_2$), 3.03 (2 H, app dt, *J* = 7.1, 1.2 Hz, C*H*$_2$CH=CH_2), 0.84 (1 H, br s, N*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9 (2 × C), 140.8 (C), 134.9 (CH), 128.6 (CH), 128.3 (2 × CH), 128.1 (4 × CH), 128.0 (4 × CH), 126.6 (2 × CH), 126.0 (2 × CH), 117.7 (CH_2), 55.3 (CH_2), 54.2 (CH_2), 50.2 (C), 41.7 (CH_2); IR: 3060, 3026, 2908, 2836, 1950, 1638, 1599, 1494, 1445, 755, 695 cm^{-1}; TOF MS: (ES$^+$) 328.21 [M + H]; TOF HRMS: (ES$^+$) Calc'd for $C_{24}H_{26}N$: 328.2065; found 328.2065. Data in agreement with literature.[162]

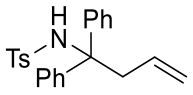
_N_-(Diphenylmethylene)-4-methylbenzenesulfonamide, 210



Modified procedure described by Ram and Khan.[137] To a solution of benzophenone **208** (456 mg, 2.50 mmol) in dichloroethane (10 mL) were added *p*-toluenesulfonamide (642 mg, 3.75 mmol) and titanium tetrachloride (1 M, 2.5 mL, 2.50 mmol) followed by dropwise addition of triethylamine (1.0 mL, 7.50 mmol) over 5 minutes. The solution was fitted with a reflux condenser and stirred at 110 °C for 5 h. The reaction was cooled to room temperature,

washed with aqueous hydrochloric acid (1 M, 10 mL), aqueous saturated sodium bicarbonate (10 mL) and water (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (hexane:ethyl acetate:triethylamine 80:18:2) afforded the title compound as an off white powder in 54% yield (457 mg, 1.36 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.3, $J_{A\text{-}X}$ = 1.7 Hz, Ar*H*), 7.60 – 7.36 (10 H, m, Ph*H*), 7.29 (2 H, app d, *J* = 8.2 Hz, Ar*H*), 2.44 (3 H, s, CH_3); IR: 3062, 2917, 1600, 1586, 1558, 1314, 1152, 818, 678 cm^{-1}; TOF MS: (EI$^+$) 336.15 [M+H]. Data in agreement with literature.[137]

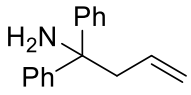
_N_-(1,1-Diphenylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 211



To a solution of *N*-(diphenylmethylene)-4-methylbenzenesulfonamide **210** (150 mg, 0.45 mmol) in dry diethyl ether (9 mL) was added allylmagnesium bromide in diethyl ether (1.2 M, 600 µL, 0.67 mmol) dropwise over 1 minute. The solution was stirred at room temperature for 20 h. The reaction was quenched with aqueous saturated sodium bicarbonate (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 90:10) afforded the title compound as a white solid in 64% yield (109 mg, 0.29 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.08 (12 H, stack, Ar*H*), 6.95 (2 H, B of ABX, $J_{B\text{-}A}$ = 8.4, $J_{B\text{-}X}$ = 0.6 Hz, Ar*H*), 5.38 (1 H, ddt, *J* = 16.8, 9.8, 6.9 Hz, C*H*=CH_2), 5.32 (1 H, br s, N*H*), 5.29 – 5.22 (1 H, m, CH=C$H_a$$H_b$), 5.18 – 5.13 (1 H, m, CH=C$H_a$$H_b$), 3.31 (2 H, app dt, *J* = 7.0, 1.0 Hz, CH_2CH=CH_2),

2.32 (3 H, s, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5 (2 × C), 142.3 (C), 139.0 (C), 132.8 (CH), 128.9 (2 × CH), 128.0 (4 × CH), 127.8 (4 × CH), 127.1 (2 × CH), 126.9 (2 × CH), 121.1 (CH_2), 66.3 (C), 45.1 (CH_2), 21.4 (CH_3); IR: 3280, 3069, 3026, 2921, 1638, 1599, 1495, 1445, 1399, 1329, 1161, 664 cm^{-1}; TOF MS: (ES$^+$) 400.14 [M + Na]; TOF HRMS: (ES$^+$) Calc'd for $C_{23}H_{23}NO_2SNa$: 400.1347; found 400.1350; m.p. 121-125 °C. Data in agreement with literature.[163]

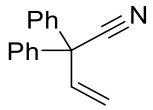
1,1-Diphenylbut-3-en-1-amine, 213



To a solution of benzophenone imine **212** (1.9 mL, 11.00 mmol) in dry tetrahydrofuran (4 mL) cooled with an ice bath was added allylmagnesium chloride in tetrahydrofuran (1.7 M, 19 mL, 33.00 mmol) dropwise over twenty minutes. The solution was stirred at room temperature for 18 h. The reaction was cooled with an ice bath, quenched with dropwise addition of ammonium chloride over ten minutes and then extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered, and then concentrated *in vacuo*. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 90:10) afforded the title compound as a colourless oil in 75% yield (1.84 g, 8.06 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (4 H, m, Ph*H*), 7.32 – 7.26 (4 H, m, Ph*H*), 7.23 – 7.17 (2 H, m, Ph*H*), 5.52 (1 H, ddt, *J* = 17.2, 10.1, 7.1 Hz, C*H*=CH_2), 5.15 (1 H, ddt, *J* = 17.1, 2.2, 1.4 Hz, CH=C*H*$_a$H$_b$), 5.09 (1 H, ddt, *J* = 10.1, 2.1, 1.0 Hz, CH=CH$_a$*H*$_b$), 3.02 (2 H, app dt, *J* = 7.1, 1.2 Hz, C*H*$_2$CH=CH_2), 1.79 (2 H, br s, N*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2 (2 × C), 134.2 (CH), 128.2 (4 × CH), 126.6 (4 × CH), 126.4 (2 × CH), 119.2 (CH_2), 60.3 (C), 47.6 (CH_2); IR: 3060, 3023, 2977, 2928, 1638, 1598, 1492, 1445, 915, 754, 696 cm^{-1}; TOF MS: (ES$^+$) 207.12

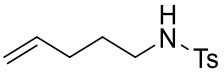
[M – NH_2]; TOF HRMS: (ES^+) Calc'd for $C_{16}H_{15}$ 207.1174; found 207.1167. Data in agreement with literature.[164]

2,2-Diphenylbut-3-enenitrile, 217



To a solution of 4-bromo-2,2-diphenylbutyronitrile **216** (1.50 g, 5.00 mmol) in acetonitrile (20 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (800 µL, 5.50 mmol). The solution was fitted with a reflux condenser and stirred at 82 °C for 24 h. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (10 mL), washed with water (3 × 10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford the title compound as a pale-yellow oil in 86% yield (950 mg, 4.33 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (10 H, stack, Ph*H*), 6.29 (1 H, dd, *J* = 16.9, 10.1 Hz, C*H*=CH_aH_b), 5.54 (1 H, d, *J* = 16.9 Hz, CH=C*H*$_a$$H_b$), 5.49 (1 H, d, *J* = 10.1 Hz, CH=CH_a*H*$_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.1 (CH), 128.9 (4 × CH), 128.4 (2 × CH), 127.7 (4 × CH), 120.6 (CN), 117.7 (CH_2), 54.8 (C), Quaternary aromatic carbons not observed; IR: 3061, 2240, 1637, 1598, 1490, 1448, 753, 695 cm^{-1}; GC MS: 218.10 [M – H]. Data in agreement with literature.[165]

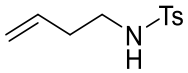
4-Methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide, 149



Prepared from 5-bromopentene **219** following general procedure B, on a 4.12 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 80:20) afforded

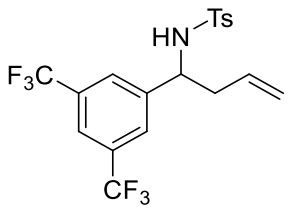
the title compound as a colourless oil in 72% yield (720 mg, 3.01 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.72 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.3, $J_{A\text{-}X}$ = 2.0 Hz, Ar*H*), 7.34 – 7.29 (2 H, B of ABX, $J_{B\text{-}A}$ = 8.3, $J_{B\text{-}X}$ = 0.7 Hz, Ar*H*), 5.70 (1 H, ddt, *J* = 17.0, 10.2, 6.7 Hz, C*H*=CH_2), 5.00 – 4.92 (2 H, stack, CH=CH_2), 4.59 (1 H, br t, *J* = 6.2 Hz, N*H*), 2.95 (2 H, app q, *J* = 6.4 Hz, CH_2), 2.43 (3 H, s, CH_3), 2.08 – 2.00 (2 H, m, CH_2), 1.56 (2 H, app p, *J* 7.2 Hz, NCH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (C), 137.3 (CH), 137.0 (C), 129.7 (2 × CH), 127.1 (2 × CH), 115.6 (CH_2), 42.7 (CH_2), 30.7 (CH_2), 28.7 (CH_2), 21.5 (CH_3); IR: 3282, 3074, 2930, 1641, 1599, 1424, 1321, 1155, 1093, 813, 660 cm^{-1}; TOF MS: (ES$^+$) 240.11 [M + H]; TOF HRMS: (ES$^+$) Calc'd for $C_{12}H_{18}NO_2S$: 240.1058; found: 240.1064. Data in agreement with literature.[166]

_N_-(But-3-en-1-yl)-4-methylbenzenesulfonamide, 94



Prepared from 4-bromo-1-butene **220** following general procedure B, on a 4.44 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 85:15) afforded the title compound as a colourless oil in 53% yield (532 mg, 2.36 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.4, $J_{A\text{-}X}$ = 2.1 Hz, Ar*H*), 7.31 (2 H, B of ABX, $J_{B\text{-}A}$ = 8.4, $J_{B\text{-}X}$ = 0.6 Hz, Ar*H*), 5.63 (1 H, ddt, *J* = 17.1, 10.3, 6.8 Hz, C*H*=CH_2), 5.10 – 4.99 (2 H, stack, CH=CH_2), 4.55 (1 H, br t, *J* = 6.2 Hz, N*H*), 3.02 (2 H, app q, *J* = 6.5 Hz, CH_2), 2.43 (3 H, s, CH_3), 2.20 (2 H, app qt, *J* = 6.8, 1.3 Hz, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (C), 137.0 (C), 134.2 (CH), 129.7 (2 × CH), 127.2 (2 × CH), 118.2 (CH_2), 42.1 (CH_2), 33.6 (CH_2), 21.5 (CH_3); IR: 3281, 3088, 2926, 1642, 1599, 1425, 1321, 1155, 1093, 813, 659 cm^{-1}; TOF MS: (ES$^+$) 248.07 [M + Na]. Data in agreement with literature.[166]

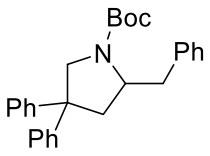
***N*-(1-(3,5-Bis(trifluoromethyl)phenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide, 282**



To a solution of *N*-(3,5-bis(trifluoromethyl)benzylidene)-4-methylbenzenesulfonamide **281** (synthesised by Milton,[3] 1.00 g, 2.53 mmol) in dry tetrahydrofuran (10 mL) was added allylmagnesium chloride in tetrahydrofuran (1.7 M, 2.3 mL, 3.79 mmol) dropwise over 10 minutes. The solution was stirred at room temperature for 18 h. The reaction was quenched with aqueous saturated sodium bicarbonate (10 mL), filtered, and then extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 90:10) afforded the title compound as a white solid in 33% yield (362 mg, 0.83 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (1 H, s, $(CF_3)CCHC(CF_3)$), 7.51 (2 H, s, $(CF_3)CCHCCH$), 7.47 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.3, $J_{A\text{-}X}$ = 1.7 Hz, ArH), 7.10 (2 H, B of ABX, $J_{B\text{-}A}$ = 8.3, $J_{B\text{-}X}$ = 0.6 Hz, ArH), 5.53 (1 H, dddd, *J* = 16.9, 10.2, 7.6, 6.6, $CH{=}CH_2$), 5.20 – 5.11 (2 H, stack, $CH{=}CH_2$), 5.09 (1 H, d, *J* = 5.3 Hz, NH), 4.55 (1 H, app dt, *J* = 7.8, 5.7 Hz, CHNH), 2.53 – 2.36 (2 H, m, $CH_2CH{=}CH_2$), 2.34 (3 H, s, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.96; ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 143.1 (C), 136.8 (C), 131.7 (CH), 131.5 (q, $^{2}J_{C\text{-}F}$ = 33.4 Hz, 2 × C), 129.5 (2 × CH), 127.1 (2 × CH), 127.0 (2 × CH), 123.0 (q, $^{1}J_{C\text{-}F}$ = 272.3 Hz, 2 × C), 121.4 (q, $^{3}J_{C\text{-}F}$ = 3.6 Hz, CH), 120.9 (CH_2), 56.3 (CH), 41.7 (CH_2), 21.3 (CH_3); IR: 3251, 3069, 2932, 1804, 1645, 1598, 1446, 1421, 1376, 1318, 1275, 1134, 708, 679 cm^{-1}; TOF MS:

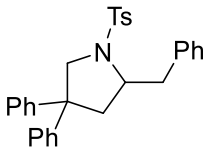
(ES$^+$) 460.08 [M + Na]; TOF HRMS: (ES$^+$) Calc'd for $C_{19}H_{17}F_6NO_2SNa$: 460.0782; found 460.0789; m.p. 114-116 °C.

tert-Butyl 2-benzyl-4,4-diphenylpyrrolidine-1-carboxylate, 204a



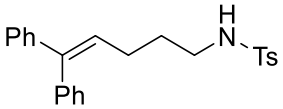
Prepared from *tert*-butyl (2,2-diphenylpent-4-en-1-yl)carbamate **198a** following general procedure C, on a 0.30 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 98:2) afforded the title compound as a colourless oil in 62% yield (77 mg, 0.19 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) Signals appear doubled in approximately 3:2 ratio due to restricted rotation, chemical shift reported at middle point of the 2 signals. δ 7.29 – 7.09 (15 H, stack, Ph*H*), 4.56 (1 H, 2 × dd, *J* = 11.7, 2.2 Hz, NC*H*$_a$H$_b$C(Ph)$_2$), 3.85 (1 H, 2 × app tdd, *J* = 9.4, 6.6, 3.5 Hz, C*H*), 3.50 (1 H, 2 × d, *J* = 11.7 Hz, NCH$_a$*H*$_b$C(Ph)$_2$), 3.32 (1 H, 2 × dd, *J* = 13.0, 3.6 Hz, CHC*H*$_a$H$_b$Ph), 2.64 – 2.51 (2 H, stack, CHCH$_a$*H*$_b$Ph & CHC*H*$_a$H$_b$C(Ph)$_2$), 2.35 (1 H, 2 × dd, *J* = 12.5, 9.1 Hz, CHCH$_a$*H*$_b$C(Ph)$_2$), 1.51 (9 H, 2 × s, 3 × C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) Signals appear doubled in approximately 3:2 ratio due to restricted rotation, chemical shift reported at middle point of the 2 signals. δ 154.7 (C), 145.8 (C), 145.3 (C), 138.6 (C), 129.6 (2 × CH), 128.6 (2 × CH), 128.5 (2 × CH), 126.9 (2 × CH), 126.6 (2 × CH), 126.4 (CH), 126.2 (CH), 79.8 (C), 58.0 (CH), 56.0 (CH_2), 52.8 (C), 43.4 (CH_2), 40.6 (CH_2), 28.6 (3 × CH_3), 3 aromatic carbons not observed; IR: 3061, 3026, 2974, 2930, 1686, 1601, 1495, 1480, 1448, 1392, 1365, 1162, 749, 696 cm^{-1}; TOF MS: (ES$^+$) 436.23 [M + Na]; TOF HRMS: (ES$^+$) Calc'd for $C_{28}H_{31}NO_2Na$: 436.2253; found 436.2256.

2-Benzyl-4,4-diphenyl-1-tosylpyrrolidine, 204c



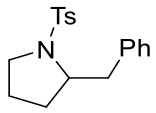
Prepared from *N*-(2,2-diphenylpent-4-en-1-yl)-4-methylbenzene sulfonamide **136** following general procedure C, on a 0.26 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 98:2) afforded the title compound as a white solid in 42% yield (51 mg, 0.11 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (2 H, app d, *J* = 8.2 Hz, Ar*H*), 7.33 – 7.16 (10 H, stack, Ar*H*), 7.14 – 7.00 (7 H, stack, Ar*H*), 4.39 (1 H, d, *J* = 10.2 Hz, NC*H*$_a$H$_b$C(Ph)$_2$), 3.89 (1 H, app ddt, *J* = 11.7, 8.3, 4.4 Hz, C*H*), 3.67 (1 H, d, *J* = 10.2 Hz, NCH$_a$*H*$_b$C(Ph)$_2$), 3.41 (1 H, dd, *J* = 13.2, 3.7 Hz, CHC*H*$_a$H$_b$Ph), 2.45 – 2.36 (4 H, stack, C*H*$_3$ & CHC*H*$_a$H$_b$C(Ph)$_2$), 2.33 (1 H, dd, *J* = 12.7, 4.7 Hz, CHCH$_a$*H*$_b$C(PH)$_2$), 2.19 (1 H, dd, *J* = 13.2, 11.0 Hz, CHCH$_a$*H*$_b$Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4 (C), 145.0 (C), 143.4 (C), 138.6 (C), 134.5 (C), 129.7 (2 × CH), 129.4 (2 × CH), 128.6 (4 × CH (128.62 2 × CH, 128.57 2 × CH)), 127.5 (2 × CH), 127.0 (2 × CH), 126.7 (CH), 126.5 (2 × CH), 126.4 (2 × CH (126.43 CH, 126.42 CH)), 61.4 (CH), 58.4 (CH_2), 52.4 (C), 41.9 (CH_2), 41.8 (CH_2), 21.6 (CH_3), 2 aromatic carbons not observed; IR: 3025, 2904, 2865, 1598, 1493, 1482, 1453, 1447, 1348, 1167, 1088, 1014, 703, 667 cm^{-1}; TOF MS: (ES$^+$) 490.18 [M + Na]; TOF HRMS: (ES$^+$) Calc'd for $C_{30}H_{29}NO_2SNa$: 490.1817; found 490.1827; m.p. 160-164 °C. Data in agreement with literature.[121]

***N*-(5,5-Diphenylpent-4-en-1-yl)-4-methylbenzenesulfonamide, 221**



Prepared from 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **149** following general procedure C, on a 0.42 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 95:5) afforded the title compound as a colourless oil in 49% yield (80 mg, 0.20 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (2 H, app d, *J* = 8.3 Hz, Ar*H*), 7.37 – 7.19 (8 H, stack, Ar*H*), 7.17 – 7.13 (2 H, m, Ar*H*), 7.11 – 7.06 (2 H, m, Ar*H*), 5.93 (1 H, t, *J* = 7.4 Hz, C*H*), 4.72 (1 H, br t, *J* = 6.2 Hz, N*H*), 2.89 (2 H, app q, *J* = 6.8 Hz, NHCH_2CH_2), 2.39 (3 H, s, CH_3), 2.06 (2 H, app q, *J* = 7.4 Hz, CHCH_2CH_2), 1.57 (2 H, app p, *J* = 7.3 Hz, CH_2CH_2CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (C), 142.7 (C), 142.4 (C), 139.9 (C), 137.0 (C), 129.8 (4 × CH (129.80 2 × CH, 129.75 2 × CH)), 128.4 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 127.2 (3 × CH (127.22 2 × CH, 127.17 CH)), 127.1 (3 × CH (127.14 2 × CH, 127.10 CH)), 42.7 (CH_2), 29.8 (CH_2), 26.7 (CH_2), 21.6 (CH_3); IR: 3275, 3024, 2926, 1598, 1495, 1443, 1322, 1154, 1093, 814, 761, 731, 698, 660 cm^{-1}; TOF MS: (ES$^+$) 392.17 [M + H]; TOF HRMS: (ES$^+$) Calc'd for $C_{24}H_{26}NO_2S$: 392.1684; found 392.1681.

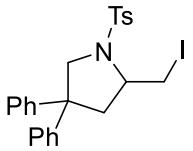
2-Benzyl-1-tosylpyrrolidine, 222



Modified procedure described by Peterson and Wolfe.[139] An oven dried flask cooled under a stream of argon was charged with lithium *tert*-butoxide (47 mg, 0.59 mmol), palladium acetate (1.9 mg, 8.40 µmol) and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (9.8 mg, 21.00 µmol) and phenyl trifluoromethanesulfonate (100 µL, 0.50 mmol) was added in dry toluene (1 mL). The suspension was stirred at room temperature for 5 minutes and then 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **149** (100 mg, 0.42 mmol) was added in dry

toluene (1.5 mL). The suspension was fitted with a reflux condenser and stirred at 110 °C for 18 h. The reaction mixture was cooled to room temperature, quenched with aqueous saturated ammonium chloride (10 mL) and extracted with dichloromethane (6 × 5 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 90:10) afforded the title compound as a colourless oil in 64% yield (84 mg, 0.27 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (2 H, app d, *J* = 8.2 Hz, Ar*H*), 7.37 – 7.12 (7 H, stack, Ar*H*), 3.87 – 3.75 (1 H, m, C*H*), 3.39 (1 H, ddd, *J* = 10.1, 7.3, 4.2 Hz, NCH_aH$_b$CH$_2$), 3.24 (1 H, dd, *J* = 13.3, 3.5 Hz, CHCH_aH$_b$Ph), 3.12 (1 H, app dt, *J* = 10.1, 6.9 Hz, NCH$_a$$H_bCH_2$), 2.76 (1 H, dd, *J* = 13.3, 9.6 Hz, CHCH$_a$$H_b$Ph), 2.41 (3 H, s, C$H_3$), 1.69 – 1.55 (2 H, stack, NCH$_2$CH_aH$_b$ & CHCH_aH$_b$), 1.50 – 1.34 (2 H, stack, NCH$_2$CH$_a$$H_b$ & CHCH$_a$$H_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4 (C), 138.5 (C), 134.7 (C), 129.7 (4 × CH (129.74 2 × CH, 129.67 2 × CH)), 128.5 (2 × CH), 127.5 (2 × CH), 126.5 (CH), 61.6 (CH), 49.3 (CH_2), 42.8 (CH_2), 29.9 (CH_2), 23.8 (CH_2), 21.6 (CH_3); IR: 3028, 2977, 2927, 2870, 1598, 1493, 1453, 1331, 1153, 1091, 1029, 700, 660 cm^{-1}; TOF MS: (ES$^+$) 316.14 [M + H]; TOF HRMS: (ES$^+$) Calc'd for $C_{18}H_{22}NO_2S$: 316.1371; found 316.1373. Data in agreement with literature.[167]

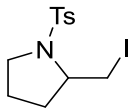
2-(Iodomethyl)-4,4-diphenyl-1-tosylpyrrolidine, 242



Prepared from *N*-(2,2-diphenylpent-4-en-1-yl)-4-methylbenzene sulfonamide **136** following general procedure D, on a 0.26 mmol scale. Purification by flash column chromatography

(hexane:ethyl acetate 100:0 → 95:5) afforded the title compound as a white solid in 85% yield (115 mg, 0.22 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.3, $J_{A\text{-}X}$ = 1.6 Hz, Ar*H*), 7.31 – 7.24 (4 H, stack, Ar*H*), 7.22 – 7.10 (6 H, stack, Ar*H*), 7.07 (2 H, A of ABX, $J_{A\text{-}B}$ = 6.3, $J_{A\text{-}X}$ = 1.7 Hz, Ar*H*), 4.44 (1 H, d, *J* = 10.3 Hz, NC*H*$_a$H$_b$C(Ph)$_2$), 3.86 (1 H, dddd, *J* = 10.8, 8.1, 5.2, 3.1 Hz, C*H*), 3.75 (1 H, d, *J* = 10.3 Hz, NCH$_a$*H*$_b$C(Ph)$_2$), 3.67 (1 H, dd, *J* = 9.5, 3.1 Hz, CHC*H*$_a$H$_b$I), 2.88 – 2.76 (2 H, stack, CHCH$_a$*H*$_b$I & CHC*H*$_a$H$_b$C(Ph)$_2$), 2.66 (1 H, dd, *J* = 13.0, 5.3 Hz, CHCH$_a$*H*$_b$C(Ph)$_2$), 2.39 (3 H, s, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7 (C), 144.4 (C), 143.7 (C), 134.0 (C), 129.8 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 127.4 (2 × CH), 126.8 (CH), 126.6 (2 × CH), 126.5 (CH), 126.3 (2 × CH), 60.4 (CH), 59.2 (CH_2), 52.2 (C), 43.8 (CH_2), 21.6 (CH_3), 11.4 (CH_2); IR: 3027, 2904, 2867, 1787, 1597, 1482, 1449, 1348, 1167, 1012, 702, 665 cm^{-1}; TOF MS: (ES$^+$) 518.07 [M + H]; TOF HRMS: (ES$^+$) Calc'd for $C_{24}H_{25}INO_2S$: 518.0651; found 518.0660; m.p. 163-168 °C. Data in agreement with literature.[122]

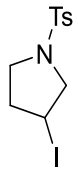
2-(Iodomethyl)-1-tosylpyrrolidine, 245



Prepared from 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **149** following general procedure D, on a 0.42 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 95:5) afforded the title compound as a white solid in 59% yield (90 mg, 0.25 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.2, $J_{A\text{-}X}$ = 1.7 Hz, Ar*H*), 7.34 (2 H, B of ABX, $J_{B\text{-}A}$ = 8.2, $J_{B\text{-}X}$ = 0.6 Hz, Ar*H*), 3.74 (1 H, dddd, *J* = 11.4, 7.3, 4.0, 3.1 Hz, C*H*), 3.62 (1 H, ddd, *J* = 9.7, 3.1, 0.6 Hz, CHC*H*$_a$H$_b$I), 3.54 – 3.43 (1 H, m, NC*H*$_a$H$_b$CH$_2$), 3.27 – 3.14 (2 H, stack, CHCH$_a$*H*$_b$I & NCH$_a$*H*$_b$CH$_2$), 2.44 (3 H, s, C*H*$_3$), 1.94 – 1.74 (3 H, stack, C*H*$_2$), 1.59

– 1.46 (1 H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8 (C), 134.2 (C), 129.9 (2 × CH), 127.6 (2 × CH), 60.7 (CH), 50.1 (CH_2), 32.0 (CH_2), 23.9 (CH_2), 21.6 (CH_3), 11.6 (CH_2); IR: 2983, 1596, 1492, 1432, 1331, 1158, 1090, 813, 660 cm^{-1}; TOF MS: (ES^+) 366.00 [M + H]; TOF HRMS: (ES^+) Calc'd for $C_{12}H_{17}INO_2S$: 366.0025; found 366.0032; m.p. 93-97 °C. Data in agreement with literature.[122]

3-Iodo-1-tosylpyrrolidine, 246



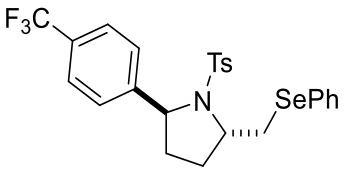
Prepared from *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **94** on 0.44 mmol scale, following a modified version of general procedure D with 1,1,1,3,3,3-hexafluoroisopropanol (20 mL) at 50 °C in place of dichloromethane (10 mL) at room temperature. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 90:10) afforded the title compound as a white solid in 27% yield (42 mg, 0.12 mmol). Prepared from *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide **94** and molecular iodine following general procedure F, on a 0.22 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 90:10) afforded the title compound as a white solid in 11% yield (9.0 mg, 0.03 mmol) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.3, $J_{A\text{-}X}$ = 1.8 Hz, 2 × CHCSO_2N), 7.34 (2 H, B of ABX, $J_{B\text{-}A}$ = 8.3, $J_{B\text{-}X}$ = 0.5 Hz, 2 × CHCCH_3), 4.17 (1 H, app p, J = 5.4 Hz, CH), 3.91 (1 H, dd, J = 11.7, 5.9 Hz, NCH_aH$_b$CH), 3.56 (1 H, dd, J = 11.7, 4.8 Hz, NCH$_a$$H_b$CH), 3.44 (2 H, dd, J = 7.5, 6.0 Hz, NCH_2CH$_2$), 2.44 (3 H, s, CH_3), 2.26 (1 H, dtd, J = 13.3, 7.5, 5.8 Hz, CHCH_aH$_b$CH$_2$), 2.18 – 2.08 (1 H, m, CHCH$_a$$H_bCH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8 (C), 133.8 (C), 129.8 (2 × CH), 127.6

(2 × CH), 58.6 (CH_2), 47.0 (CH_2), 38.1 (CH_2), 21.6 (CH_3), 17.3 (CH); IR: 2921, 2886, 2849, 1925, 1596, 1337, 1157, 1107, 1031, 811, 661 cm^{-1}; TOF MS: (ES^+) 351.99 [M + H]; TOF HRMS: (ES^+) Calc'd for $C_{11}H_{15}INO_2S$: 351.9868; found 351.9873; m.p. 113-119 °C. Data in agreement with literature.[168]

2-((Phenylselanyl)methyl)-1-tosyl-5-(4-(trifluoromethyl)phenyl)pyrrolidine

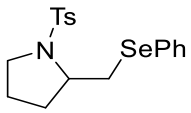
4-Methyl-*N*-(1-(4-(trifluoromethyl)phenyl)pent-4-en-1-yl)benzenesulfonamide **255a** (synthesised by Milton,[3] 1 eq.), diphenyl diselenide (0.5 eq.), tetra-butylammonium bromide (0.2 eq.), base (0 or 1 eq.), molecular sieve powder (3 Å, 0 or 50 mg) and solvent (0.04 M) were added to an ElectraSyn vial equipped with a graphite anode and cathode. The suspension was subjected to constant current electrolysis at 10 mA with the polarity of the electrodes alternating every 10 minutes until 5 F/mol had passed. The mixture was transferred to a round bottom flask and all components rinsed with acetonitrile followed by concentration of the reaction mixture *in vacuo*. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 80:20) afforded a mixture of *cis*- and *trans*-2-((phenylselanyl)methyl)-1-tosyl-5-(4-(trifluoromethyl)phenyl)pyrrolidine **256a** and **257a**. Several 2-((phenylselanyl)methyl)-1-tosyl-5-(4-(trifluoromethyl)phenyl)pyrrolidine product mixtures were combined and purified by flash column chromatography (hexane:ethyl acetate 100:0 → 95:5) to afford *trans*-2-((phenylselanyl)methyl)-1-tosyl-5-(4-(trifluoromethyl)phenyl)pyrrolidine **257a**. The isolated products stereochemistry was assigned as the *trans*-isomer by comparing the data with the data obtained for the *cis*- and *trans*-isomers **256a** and **257a** reported by Milton.[3]

***trans*-2-((Phenylselanyl)methyl)-1-tosyl-5-(4-(trifluoromethyl)phenyl)pyrrolidine, 257a**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.3, $J_{A\text{-}X}$ = 1.6 Hz, Ar*H*), 7.39 – 7.24 (5 H, stack, Ph*H*), 7.09 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.3, $J_{A\text{-}X}$ = 1.7 Hz, Ar*H*), 6.98 (2 H, app d, *J* = 8.1 Hz, Ar*H*), 6.93 (2 H, B of ABX, $J_{B\text{-}A}$ = 8.3, $J_{B\text{-}X}$ = 0.6 Hz, Ar*H*), 5.05 (1 H, app d, *J* = 8.5 Hz, CHC*H*$_a$H$_b$Se), 4.34 – 4.20 (1 H, m, NC*H*(Ar)CH_2), 3.94 (1 H, ddd, *J* = 12.7, 2.9, 1.7 Hz, NC*H*CH_2Se), 2.87 (1 H, dd, *J* = 12.5, 11.3 Hz, $CHCH_aH_b$Se), 2.50 (1 H, app tt, *J* = 12.9, 8.3 Hz, C*H*$_2$), 2.30 (3 H, s, C*H*$_3$), 2.27 – 2.11 (2 H, stack, C*H*$_2$), 1.72 (1 H, dd, *J* = 12.8, 6.7 Hz, C*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5 (2 × C (145.46 C, 145.45 C)), 143.0 (C), 138.0 (C), 132.3 (2 × CH), 129.4 (2 × CH), 129.3 (q, $^{2}J_{C\text{-}F}$ = 34.2 Hz, C), 129.0 (2 × CH), 127.1 (3 × CH (127.09 2 × CH, 127.07 CH)), 126.8 (2 × CH), 125.0 (q, $^{3}J_{C\text{-}F}$ = 3.7 Hz, 2 × CH), 63.8 (CH), 61.6 (CH), 32.5 (CH_2), 31.4 (CH_2), 28.9 (CH_2), 21.3 (CH_3), $^{1}J_{C\text{-}F}$ CF_3 carbon not observed, Se splitting not observed; ^{77}Se NMR (76 MHz, $CDCl_3$) δ 277.51 (app d, *J* = 23.0 Hz); IR: 3064, 2952, 2928, 1942, 1619, 1596, 1579, 1482, 1324, 1151, 1104, 1068, 732, 669 cm^{-1}; TOF MS: (ES$^+$) 562.05 [M + Na]; TOF HRMS: (ES$^+$) Calc'd for $C_{25}H_{24}F_3NO_2SSeNa$: 562.0544; found 562.0545. Data in agreement with literature.[3]

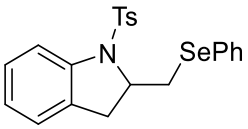
2-((Phenylselanyl)methyl)-1-tosylpyrrolidine, 150



Prepared from 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **149** and diphenyl diseleinde following general procedure E, on a 0.42 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 90:10) afforded the title compound as a

white solid in 60% yield (99 mg, 0.25 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.56 (2 H, m, Ph*H*), 7.50 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.2, $J_{A\text{-}X}$ = 1.8 Hz, Ar*H*), 7.35 – 7.26 (3 H, stack, Ph*H*), 7.21 (2 H, B of ABX, $J_{B\text{-}A}$ = 8.2, $J_{B\text{-}X}$ = 0.7 Hz, Ar*H*), 3.67 – 3.57 (2 H, stack, C*H* & CHCH_aH$_b$Se), 3.51 – 3.44 (1 H, m, NCH_aH$_b$CH$_2$), 3.12 (1 H, app dt, *J* = 9.9, 7.2 Hz, NCH$_a$$H_bCH_2$), 2.90 – 2.77 (1 H, m, CHCH$_a$$H_b$Se), 2.39 (3 H, s, C$H_3$), 1.86 – 1.73 (2 H, stack, CH_2), 1.72 – 1.61 (1 H, m, CH_2), 1.53 – 1.41 (1 H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (C), 133.9 (C), 132.5 (d, $^{2}J_{C\text{-}Se}$ = 10.8 Hz, 2 × CH), 129.7 (2 × CH), 129.4 (C), 129.3 (2 × CH), 127.5 (2 × CH), 127.0 (CH), 59.9 (CH), 49.9 (CH$_2$), 33.0 (d, $^{1}J_{C\text{-}Se}$ = 66.2 Hz, CH$_2$), 31.1 (CH$_2$), 23.9 (CH$_2$), 21.5 (CH$_3$); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 270.01 (app dt, *J* = 23.6, 4.7 Hz); IR: 2946, 2873, 1596, 1578, 1479, 1422, 1332, 1156, 818, 739, 668 cm^{-1}; TOF MS (ES$^+$): 395.06 [M + H]; TOF HRMS: (ES$^+$) Calc'd for $C_{18}H_{22}NO_2SSe$: 395.0575; found 395.0563; m.p. 96-99 °C. Data in agreement with literature.[169]

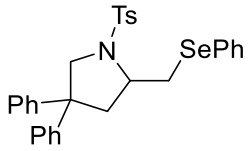
2-((Phenylselanyl)methyl)-1-tosylindoline, 261



Prepared from *N*-(2-allylphenyl)-4-methylbenzenesulfonamide **260** (synthesised by Milton[3]) and diphenyl diselenide following general procedure E, on a 0.35 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 80:20) afforded the title compound as a colourless oil in 50% yield (77 mg, 0.17 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (1 H, app d, *J* = 8.0 Hz, Ar*H*), 7.59 – 7.54 (2 H, m, Ar*H*), 7.36 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.3, $J_{A\text{-}X}$ = 1.7 Hz, Ar*H*), 7.33 – 7.25 (3 H, stack, Ar*H*), 7.22 – 7.15 (1 H, m, Ar*H*), 7.06 (2 H, B of ABX, $J_{B\text{-}A}$ = 8.3, $J_{B\text{-}X}$ = 0.6 Hz, Ar*H*), 7.02 – 6.97 (2 H, m, Ar*H*), 4.24 (1 H, dddd, *J* = 10.6, 8.4, 4.3, 3.5 Hz, C*H*), 3.63 (1 H, dd, *J* = 12.5, 3.5 Hz, CHCH_aH$_b$Se), 2.91 (1 H, dd, *J* = 12.5, 10.7 Hz, CHCH$_a$$H_b$Se), 2.86 –

2.78 (2 H, stack, CHCH_2C), 2.29 (3 H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (d, $^1J_{C\text{-}Se}$ = 56.8 Hz, C), 141.4 (C), 134.6 (C), 132.5 (d, $^2J_{C\text{-}Se}$ = 10.9 Hz, 2 × CH), 131.0 (C), 129.7 (2 × CH), 129.4 (2 × CH), 128.9 (C), 127.9 (CH), 127.2 (CH), 127.0 (2 × CH), 125.3 (CH), 124.8 (CH), 117.0 (CH), 61.7 (CH), 34.1 (CH_2), 33.1 (d, $^1J_{C\text{-}Se}$ = 67.3 Hz, CH_2), 21.6 (CH_3); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 258.78 (app dt, *J* = 23.3, 4.7 Hz); IR: 3049, 2921, 2853, 1597, 1578, 1478, 1460, 1352, 1165, 1089, 736, 659 cm^{-1}; TOF MS (ES$^+$): 443.06 [M + H]; TOF HRMS: (ES$^+$) Calc'd for $C_{22}H_{22}NO_2SSe$: 443.0576; found 443.0556. Data in agreement with literature.[169]

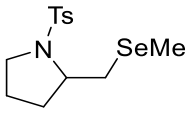
4,4-Diphenyl-2-((phenylselanyl)methyl)-1-tosylpyrrolidine, 268



Prepared from *N*-(2,2-diphenylpent-4-en-1-yl)-4-methylbenzene sulfonamide **136** and diphenyl diselenide following general procedure E, on a 0.26 mmol scale. Purification by flash column chromatography (toluene:hexane:ethyl acetate 20:80:0 → 16:64:20) afforded the title compound as a white solid in 80% yield (113 mg, 0.21 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.49 (2 H, m, Ar*H*), 7.35 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.2, $J_{A\text{-}X}$ = 1.8 Hz, Ar*H*), 7.32 – 7.20 (7 H, stack, Ar*H*), 7.18 – 6.99 (8 H, stack, Ar*H*), 4.48 (1 H, d, *J* = 10.2 Hz, NCH_aH$_b$C(Ph)$_2$), 3.70 (1 H, dddd, *J* = 11.0, 7.8, 4.6, 3.0 Hz, C*H*), 3.63 (1 H, dd, *J* = 12.5, 3.0 Hz, CHCH_aH$_b$Se), 3.51 (1 H, d, *J* = 10.2 Hz, NCH$_a$$H_b$C(Ph)$_2$), 2.73 – 2.59 (2 H, stack, CHCH_2C(Ph)$_2$), 2.37 – 2.26 (4 H, stack, CH_3 & CHCH$_a$$H_b$Se); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (C), 144.9 (C), 143.4 (C), 133.3 (C), 133.1 (d, $^2J_{C\text{-}Se}$ = 10.2 Hz, 2 × CH), 129.7 (2 × CH), 129.3 (2 × CH), 129.0 (C), 128.7 (2 × CH), 128.6 (2 × CH), 127.5 (2 × CH), 127.2 (CH), 126.9 (2 × CH), 126.7 (CH), 126.5 (CH), 126.4 (2 × CH), 59.6 (CH), 58.9 (CH_2), 52.1 (C), 42.6 (CH_2), 32.6 (d, $^1J_{C\text{-}Se}$ = 65.5 Hz, CH_2), 21.5 (CH_3); ^{77}Se NMR (76 MHz,

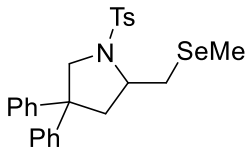
$CDCl_3$) δ 273.60 (app d, *J* = 25.4 Hz); IR: 3020, 2934, 2868, 2001, 1945, 1599, 1579, 1488, 1448, 1337, 1166, 694, 662 cm^{-1}; TOF MS (ES^+): 548.12 [M + H]; TOF HRMS: (ES^+) Calc'd for $C_{30}H_{30}NO_2SSe$: 548.1164; found 548.1161; m.p. 129-132 °C. Data in agreement with literature.[170]

2-((Methylselanyl)methyl)-1-tosylpyrrolidine, 269



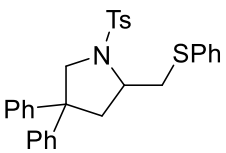
Prepared from 4-methyl-*N*-(pent-4-en-1-yl)benzenesulfonamide **149** and dimethyl diselenide following general procedure E, on a 0.42 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 80:20) afforded the title compound as a yellow oil in 27% yield (38 mg, 0.11 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (2 H, app d, *J* = 8.2 Hz, Ar*H*), 7.32 (2 H, app d, *J* = 8.0 Hz, Ar*H*), 3.79 (1 H, app ddt, *J* = 10.6, 7.0, 3.4 Hz, C*H*), 3.50 – 3.42 (1 H, m, $NCH_aCH_bCH_2$), 3.17 (1 H, app dt, *J* = 10.2, 7.0 Hz, $NCH_aH_bCH_2$), 3.02 (1 H, dd, *J* = 12.4, 3.1 Hz, $CHCH_aH_bSe$), 2.70 (1 H, dd, *J* = 12.4, 10.0 Hz, $CHCH_aH_bSe$), 2.44 (3 H, s, CCH_3), 2.10 (3 H, s, $SeCH_3$), 1.91 – 1.74 (2 H, m, CH_2), 1.77 – 1.65 (1 H, m, CH_2), 1.58 – 1.45 (1 H, m, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (C), 134.5 (C), 129.8 (2 × CH), 127.5 (2 × CH), 60.4 (CH), 49.6 (CH_2), 31.9 (CH_2), 31.2 (CH_2), 24.0 (CH_2), 21.6 (CH_3), 5.1 (d, $^1J_{C\text{-}Se}$ = 61.5 Hz, CH_3); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 51.29 (carbon splitting not observed); IR: 2977, 2931, 2855, 1713, 1598, 1445, 1417, 1335, 1153, 813, 668 cm^{-1}; TOF MS: (ES^+) 334.04 [M + H]; TOF HRMS: (ES^+) Calc'd for $C_{13}H_{20}NO_2SeS$: 334.0380; found 334.0379.

2-((Methylselanyl)methyl)-4,4-diphenyl-1-tosylpyrrolidine, 270



Prepared from *N*-(2,2-diphenylpent-4-en-1-yl)-4-methylbenzene sulfonamide **136** and dimethyl diselenide following general procedure E, on a 0.26 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 80:20) afforded the title compound as a yellow oil in 79% yield (100 mg, 0.21 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.1, $J_{A\text{-}X}$ = 1.7 Hz, Ar*H*), 7.24 (4 H, app d, *J* = 4.1 Hz, Ph*H*), 7.19 – 7.06 (8 H, stack, Ar*H*), 4.39 (1 H, d, *J* = 10.1 Hz, NC*H*$_a$H$_b$C(Ph)$_2$), 3.89 (1 H, dddd, *J* = 10.8, 8.2, 5.3, 3.0 Hz, C*H*), 3.73 (1 H, d, *J* = 10.1 Hz, NCH$_a$*H*$_b$C(Ph)$_2$), 3.11 (1 H, dd, *J* = 12.3, 3.0 Hz, CHC*H*$_a$H$_b$Se), 2.81 (1 H, dd, *J* = 12.9, 7.9 Hz, CHC*H*$_a$H$_b$C(Ph)$_2$), 2.56 (1 H, dd, *J* = 12.8, 5.2 Hz, CHCH$_a$*H*$_b$C(Ph)$_2$), 2.37 (3 H, s, C*H*$_3$CCH), 2.27 (1 H, dd, *J* = 12.4, 10.6 Hz, CHCH$_a$*H*$_b$Se), 1.99 (3 H, s, C*H*$_3$Se); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (C), 144.7 (C), 143.4 (C), 134.3 (C), 129.8 (2 × CH), 128.6 (2 × CH), 127.4 (2 × CH), 126.8 (2 × CH), 126.7 (CH), 126.5 (2 × CH), 126.4 (CH), 60.1 (CH), 58.8 (CH_2), 52.4 (C), 43.1 (CH_2), 31.4 (d, $^{1}J_{C\text{-}Se}$ = 64.1 Hz, CH_2), 21.6 (CH_3), 5.1 (d, $^{1}J_{C\text{-}Se}$ = 61.9 Hz, CH_3); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 50.16 (app ddt, *J* = 16.6, 10.6, 5.3 Hz), 2 aromatic carbons not observed; IR: 3055, 3028, 2917, 2898, 2863, 1740, 1599, 1483, 1448, 1339, 1163, 1012, 699, 662 cm^{-1}; TOF MS: (ES$^+$) 486.10 [M + H], 390.15 [M – $SeCH_3$]; TOF HRMS: (ES$^+$) Calc'd for $C_{25}H_{28}NO_2SSe$: 486.1007; found 486.1004. Data in agreement with literature.[170]

4,4-Diphenyl-2-((phenylthio)methyl)-1-tosylpyrrolidine, 237

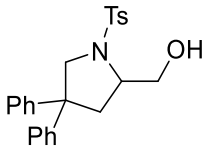


Prepared from *N*-(2,2-diphenylpent-4-en-1-yl)-4-methylbenzene sulfonamide **136** on a 0.16 mmol scale, following a modified version of general procedure E with diphenyl disulfide in place of either diphenyl diselenide or dimethyl diselenide. Purification by flash column chromatography (toluene:hexane:ethyl acetate 70:30:0 → 70:29:1) afforded the title compound as a white solid in 46% yield (37 mg, 0.07 mmol). Prepared from *N*-(2,2-diphenylpent-4-en-1-yl)-4-methylbenzene sulfonamide **136** on a 0.26 mmol scale, following a modified version of general procedure E with diphenyl disulfide in place of either diphenyl diselenide or dimethyl diselenide and in the absence of sodium methoxide. Purification by flash column chromatography (toluene:hexane:ethyl acetate 70:30:0 → 70:29:1) afforded the title compound as a white in 81% yield (105 mg, 0.21 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (4 H, m, Ar*H*), 7.36 – 7.20 (7 H, stack, Ar*H*), 7.18 – 7.06 (6 H, stack, Ar*H*), 7.05 – 7.01 (2 H, m, Ar*H*), 4.52 (1 H, d, *J* = 10.1 Hz, $NCH_aH_bC(Ph)_2$), 3.73 – 3.59 (2 H, stack, C*H* & $CHCH_aH_bS$), 3.42 (1 H, d, *J* = 10.1 Hz, $NCH_aH_bC(Ph)_2$), 2.70 (1 H, dd, *J* = 13.0, 3.0 Hz, $CHCH_aH_bC(PH)_2$), 2.61 (1 H, dd, *J* = 13.0, 8.3 Hz, $CHCH_aH_bC(PH)_2$), 2.33 (3 H, s, CH_3), 2.22 (1 H, dd, *J* = 14.3, 11.6 Hz, $CHCH_aH_bS$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0 (C), 144.9 (C), 143.6 (C), 135.0 (C), 133.0 (C), 129.7 (2 × CH), 129.2 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 127.6 (2 × CH), 126.9 (2 × CH), 126.7 (CH), 126.5 (CH), 126.4 (3 × CH (126.40 2 × CH, 126.37 CH)), 58.6 (CH & CH_2 (3 protons in HSQC and signal not present on Jmod)), 52.2 (C), 41.8 (CH_2), 37.9 (CH_2), 21.6 (CH_3), 2 aromatic carbons not observed; IR: 3056, 3020, 2924, 2864, 1888, 1809, 1727, 1599, 1488, 1449, 1438, 1337, 1167, 1089, 1011, 74, 694 cm^{-1}; TOF MS: (ES^+) 500.17 [M + H]; TOF HRMS: (ES^+) Calc'd for $C_{30}H_{30}NO_2S_2$: 500.1718; found 500.1712, m.p. 143-148 °C. Data in agreement with literature.[171,123]

Substitution of phenylselanyl group

Modified procedure described by Cooper and Ward.[155] To a suspension of 4,4-diphenyl-2-((phenylselanyl)methyl)-1-tosylpyrrolidine **268** (120 mg, 0.22 mmol) in propan-2-ol:methanol (5:2, 7 mL) was added *meta*-chloroperoxybenzoic acid (≤77% with benzoic acid, 114 mg, 0.66 mmol). The resultant suspension was stirred at room temperature for 1 h and then aqueous sodium hydroxide (2 M, 5 mL) was added. The resulting solution was stirred at room temperature for 4 h and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (10 mL), washed with aqueous sodium bicarbonate (2 × 10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 0:100) afforded two products (4,4-diphenyl-1-tosylpyrrolidin-2-yl)methanol **275** and 2-(methoxymethyl)-4,4-diphenyl-1-tosylpyrrolidine **276**.

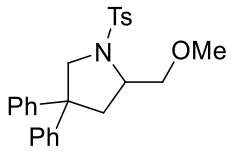
(4,4-Diphenyl-1-tosylpyrrolidin-2-yl)methanol, 275



Product eluted at (hexane:ethyl acetate 0:100) to afford the title compound as a colourless oil in 22% yield (20 mg, 0.05 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.3, $J_{B\text{-}X}$ = 1.7 Hz, Ar*H*), 7.28 – 7.22 (2 H, m, Ar*H*), 7.20 – 7.11 (5 H, stack, Ar*H*), 7.10 – 7.00 (5 H, stack, Ar*H*), 4.28 (1 H, d, *J* = 10.6 Hz, NC*H*$_a$H$_b$C(Ph)$_2$), 4.00 (1 H, dd, *J* = 10.6, 1.3 Hz, NCH$_a$*H*$_b$C(Ph)$_2$), 3.72 (1 H, app tt, *J* = 7.5, 4.4 Hz, C*H*), 3.62 (2 H, app t, *J* = 5.0 Hz, C*H*$_2$OH), 2.98 (1 H, br t, *J* = 6.5 Hz, O*H*), 2.77 (1 H, ddd, *J* = 13.0, 7.5, 1.3, CHC*H*$_a$H$_b$C(Ph)$_2$), 2.46 (1 H, dd, *J* = 13.0, 7.5, CHCH$_a$*H*$_b$C(Ph)$_2$), 2.39 (3 H, s, C*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (C), 144.3 (C), 143.6 (C), 134.1 (C), 129.7 (2 × CH), 128.7 (2 × CH), 128.6 (2 × CH), 127.3 (2 × CH), 126.7 (CH), 126.6 (2 ×

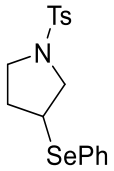
CH), 126.4 (3 × CH, (126.43 2 × CH, 126.35 CH)), 65.5 (CH_2), 61.8 (CH), 59.8 (CH_2), 52.2 (C), 40.9 (CH_2), 21.5 (CH_3); IR: 3485, 3027, 2925, 1598, 1495, 1448, 1331, 1154, 1090, 1030, 748, 698, 662 cm^{-1}; TOF MS: (ES^+) 430.15 [M + Na]; HRMS: Calc'd for $C_{24}H_{25}NO_3SNa$: 430.1453; found: 430.1454. Data in agreement with literature.[121]

2-(Methoxymethyl)-4,4-diphenyl-1-tosylpyrrolidine, 276



Product eluted at (hexane:ethyl acetate 90:10) to afford the title compound as a colourless oil in 29% yield (27 mg, 0.06 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.4, $J_{A\text{-}X}$ = 1.7 Hz, Ar*H*), 7.26 (4 H, app d, *J* = 4.3 Hz, Ar*H*), 7.20 – 7.07 (8 H, stack, Ar*H*), 4.30 (1 H, d, *J* = 10.2 Hz, NC*H*$_a$H$_b$C(Ph)$_2$), 3.84 – 3.73 (2 H, stack, C*H* & NCH$_a$*H*$_b$C(Ph)$_2$), 3.68 (1 H, dd, *J* = 9.2, 3.7 Hz, C*H*$_a$H$_b$OMe), 3.19 (3 H, s, OCH_3), 2.96 (1 H, app t, *J* = 8.9 Hz, CH$_a$*H*$_b$OMe), 2.72 – 2.60 (2 H, m, CHC*H*$_2$C(Ph)$_2$), 2.38 (3 H, s, CC*H*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3 (C), 144.9 (C), 143.3 (C), 134.4 (C), 129.6 (2 × CH), 128.6 (4 × CH (128.58 2 × CH, 128.55 2 × CH)), 127.4 (2 × CH), 126.7 (2 × CH), 126.5 (3 × CH (126.54 CH, 126.46 2 × CH)), 126.4 (CH), 74.3 (CH_2), 58.9 (CH_3), 58.4 (CH & CH_2 (58.41 CH_2 & 58.37 CH)), 52.5 (C), 40.7 (CH_2), 21.5 (CH_3); IR: 3028, 2924, 2255, 1599, 1495, 1448, 1344, 1158, 1090, 698 cm^{-1}; TOF MS: (ES^+) 444.16 [M + Na]; HRMS: Calc'd for $C_{25}H_{27}NO_3SNa$: 444.1609; found: 444.1613.

3-(Phenylselanyl)-1-tosylpyrrolidine, 278



Prepared from *N*-(But-3-en-1-yl)-4-methylbenzenesulfonamide **94** and diphenyl diselenide following general procedure F, on a 0.22 mmol scale. Purification by flash column chromatography (hexane:ethyl acetate 100:0 → 85:15) afforded the title compound as a colourless oil in 96% yield (81 mg, 0.21 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (2 H, A of ABX, $J_{A\text{-}B}$ = 8.3, $J_{A\text{-}X}$ = 1.7 Hz, Ar*H*), 7.45 – 7.41 (2 H, m, Ph*H*), 7.33 – 7.22 (5 H, stack, Ar*H*), 3.71 (1 H, dd, *J* = 10.7, 6.8 Hz, NC$H_a$$H_b$CH), 3.55 (1 H, app p, *J* = 6.7 Hz, C*H*), 3.41 – 3.27 (2 H, m, NC$H_2$$CH_2$), 3.20 (1 H, dd, *J* = 10.8, 6.4, NC$H_a$$H_b$CH), 2.43 (3 H, s, C$H_3$), 2.19 (1 H, app dq, *J* = 13.2, 6.6 Hz, CH_2C$H_a$$H_b$CH), 1.79 (1 H, app dq, *J* = 13.8, 7.1 Hz, CH_2C$H_a$$H_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6 (C), 134.7 (d, $^{2}J_{C\text{-}Se}$ = 9.7 Hz, 2 × CH), 133.7 (C), 129.8 (2 × CH), 129.3 (2 × CH), 128.1 (CH & C), 127.6 (2 × CH), 54.3 (d, $^{2}J_{C\text{-}Se}$ = 12.4 Hz, CH_2), 47.3 (CH_2), 38.2 (d, $^{1}J_{C\text{-}Se}$ = 69.3 Hz, CH), 32.5 (d, $^{2}J_{C\text{-}Se}$ = 11.7 Hz, CH_2), 21.6 (CH_3); ^{77}Se NMR (76 MHz, $CDCl_3$) δ 366.54 (m); IR: 3056, 2951, 2873, 1597, 1578, 1477, 1438, 1342, 1155, 1096, 1022, 739, 658 cm^{-1}; TOF MS: (ES$^+$) 382.04 [M + H]; TOF HRMS: (ES$^+$) Calc'd for $C_{17}H_{20}NO_2SSe$: 382.0380; found 382.0375. Data in agreement with literature.[172]

5.3 2D NMR Analysis of Compounds 242, 246 and 278

Compound **242**

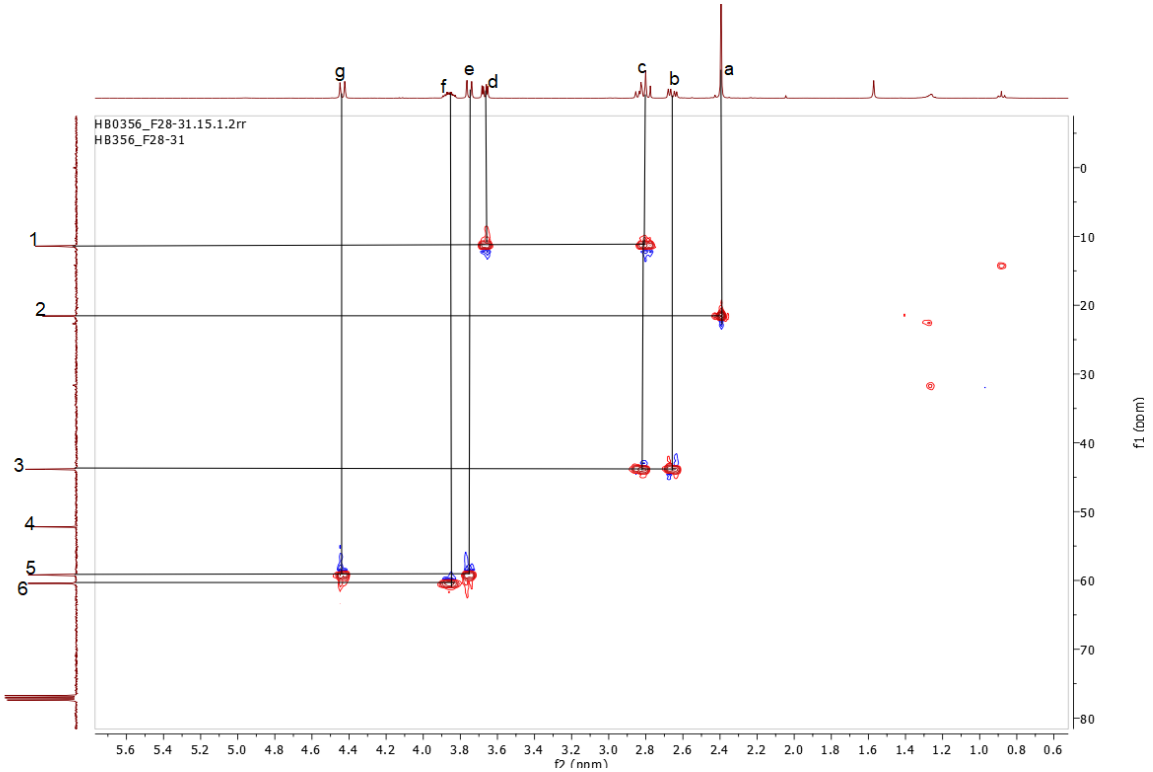


Figure 27: Aliphatic region of HSQC NMR for compound **242**.

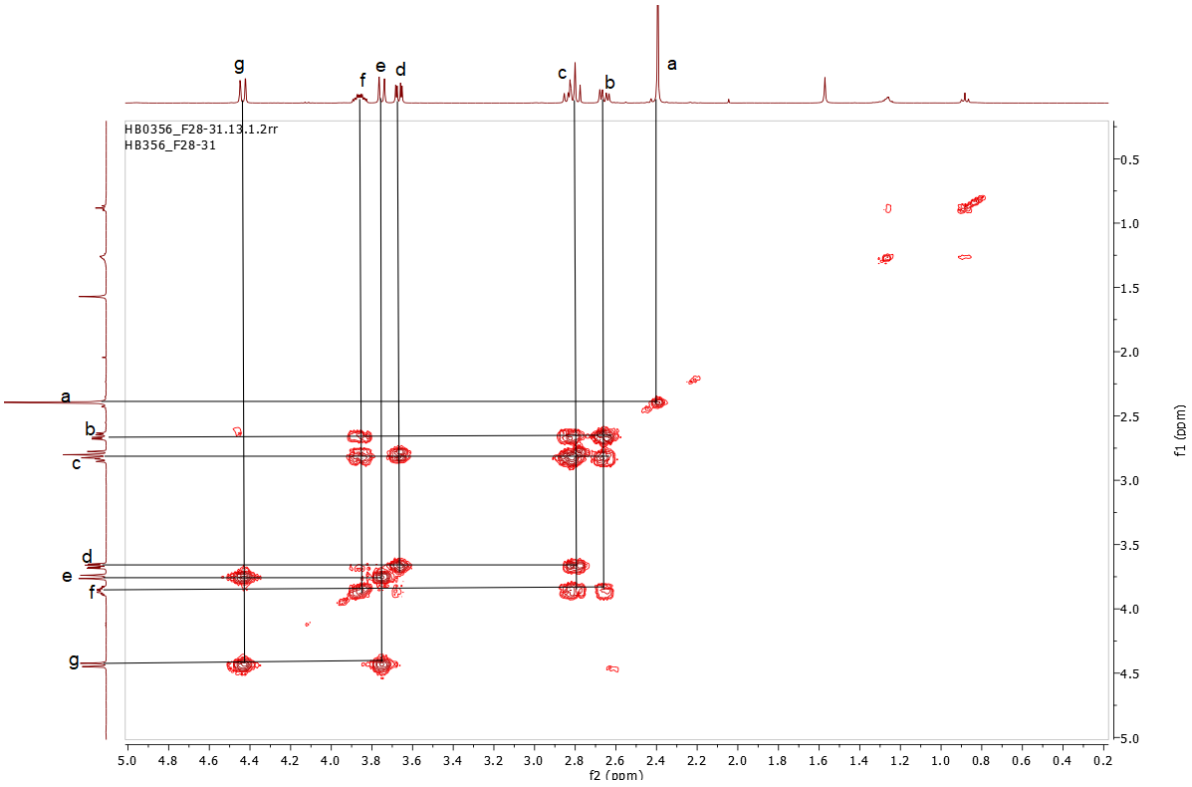


Figure 28: Aliphatic region of COSY NMR for compound **242**.

Interpretation of the aliphatic region of the HSQC (Figure 27) and COSY (Figure 28) NMR data for compound **242** labels the carbon and hydrogen atoms on the heterocyclic rings for isomers **242** and **244** except for the two CH_2 adjacent to the CH (Figure 29).

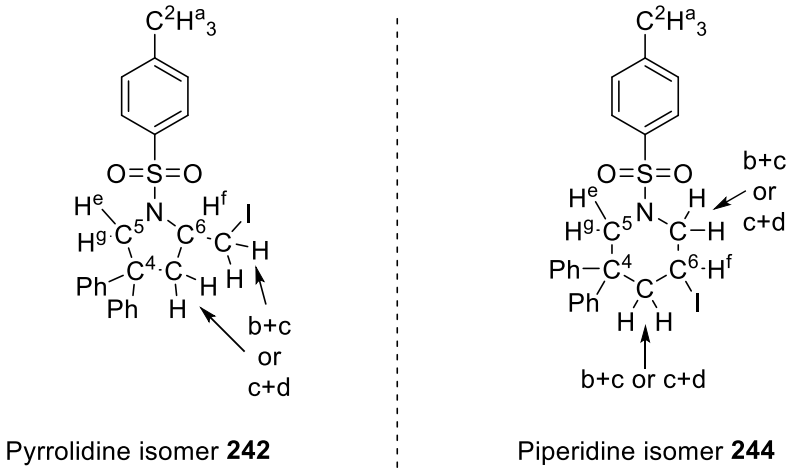


Figure 29: Aliphatic carbon and hydrogens labelled from analysis of HSQC and COSY data for compound **242**.

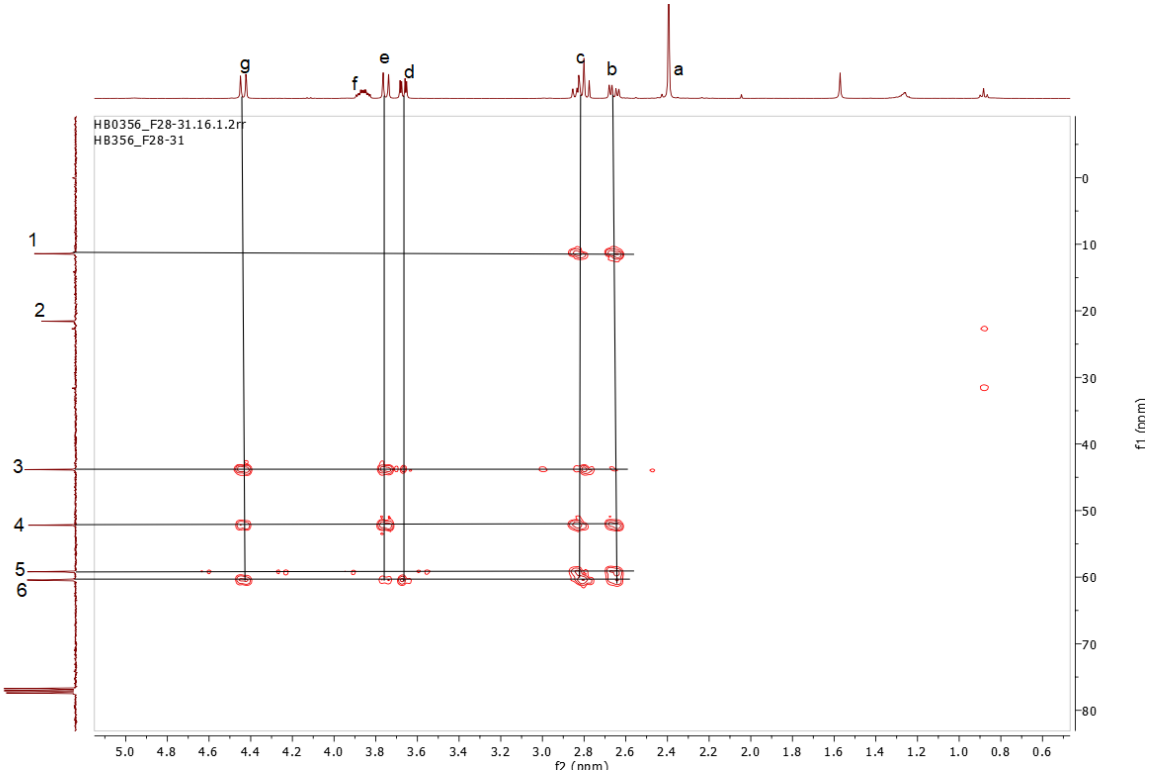


Figure 30: Aliphatic region of HMBC NMR for compound **242**.

Interpretation of the HMBC data for compound **242** observes an interaction between C^4 and protons H^b and H^c which means that C^3 with protons H^b and H^c is the CH_2 between C^4 and C^6 and the remaining unlabelled CH_2 is C^1 with protons H^b and H^c. With the aliphatic carbon and hydrogens fully assigned to the isomers, the ring size is determined to be isomer **242** as there is an interaction between C^6 and protons H^e and H^g which would only be observed for the pyrrolidine isomer (Figure 30). An interaction between C^1 and protons H^e and H^g or between C^5 and protons H^c and H^d was not observed which would be expected for the piperidine isomer.

Compound **246**

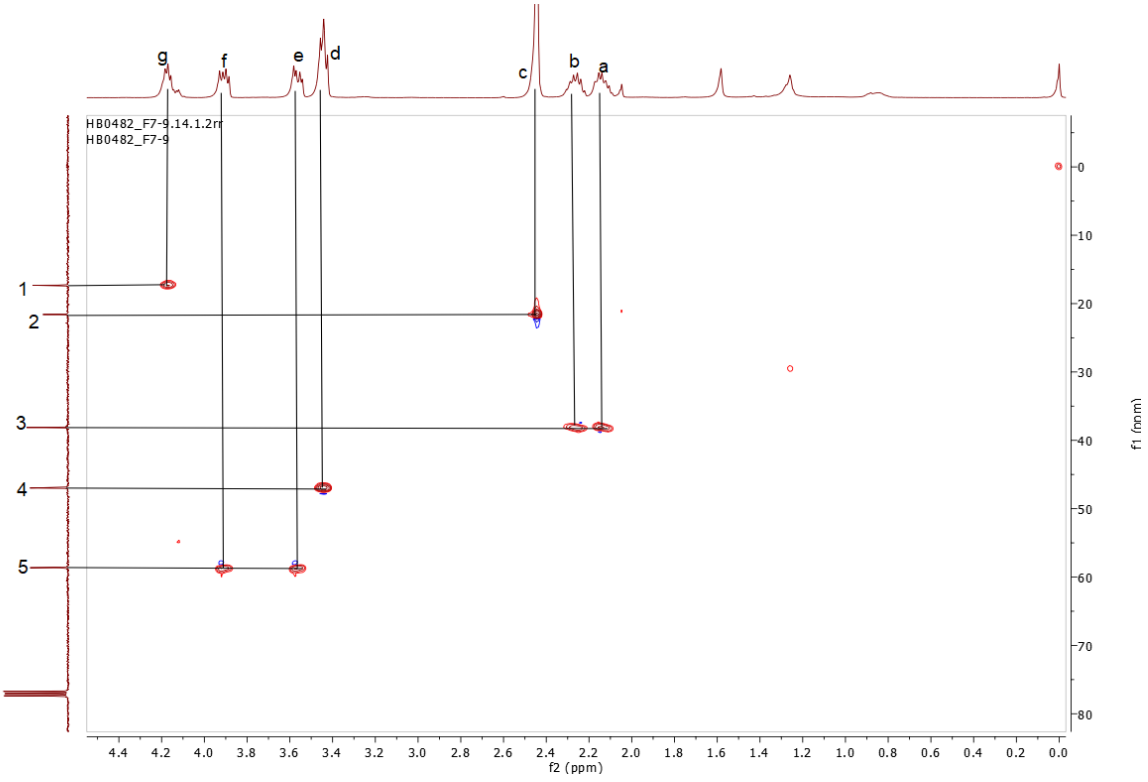


Figure 31: Aliphatic region of HSQC NMR for compound **246**.

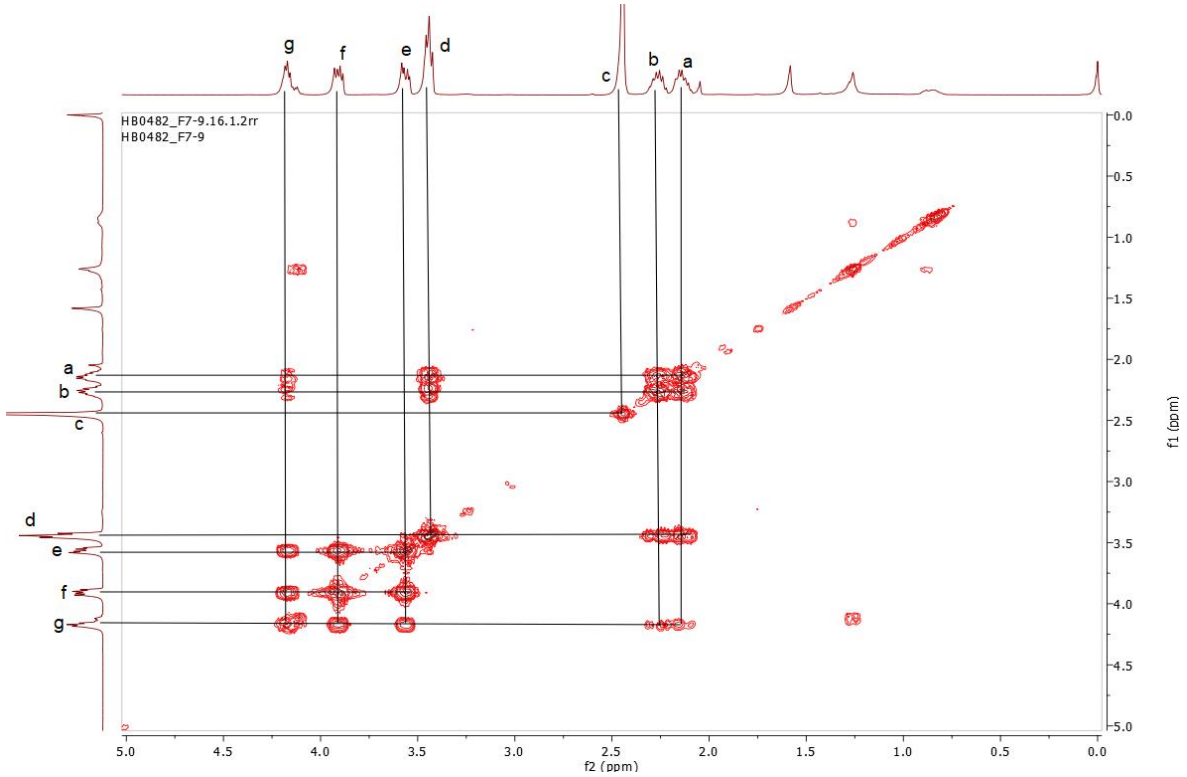


Figure 32: Aliphatic region of COSY NMR for compound **246**.

Interpretation of the aliphatic region of the HSQC (Figure 31) and COSY (Figure 32) NMR data for compound **246** labels the carbon and hydrogen atoms on the heterocyclic rings for isomers **95** and **246** (Figure 33).

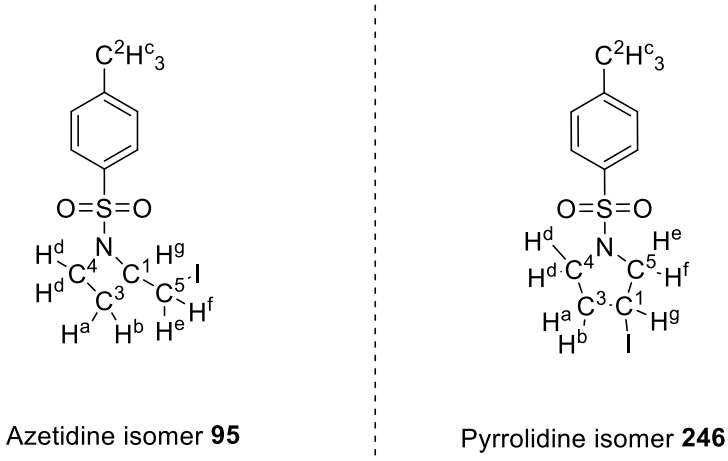


Figure 33: Aliphatic carbon and hydrogens labelled from analysis of HSQC and COSY data for compound **246**.

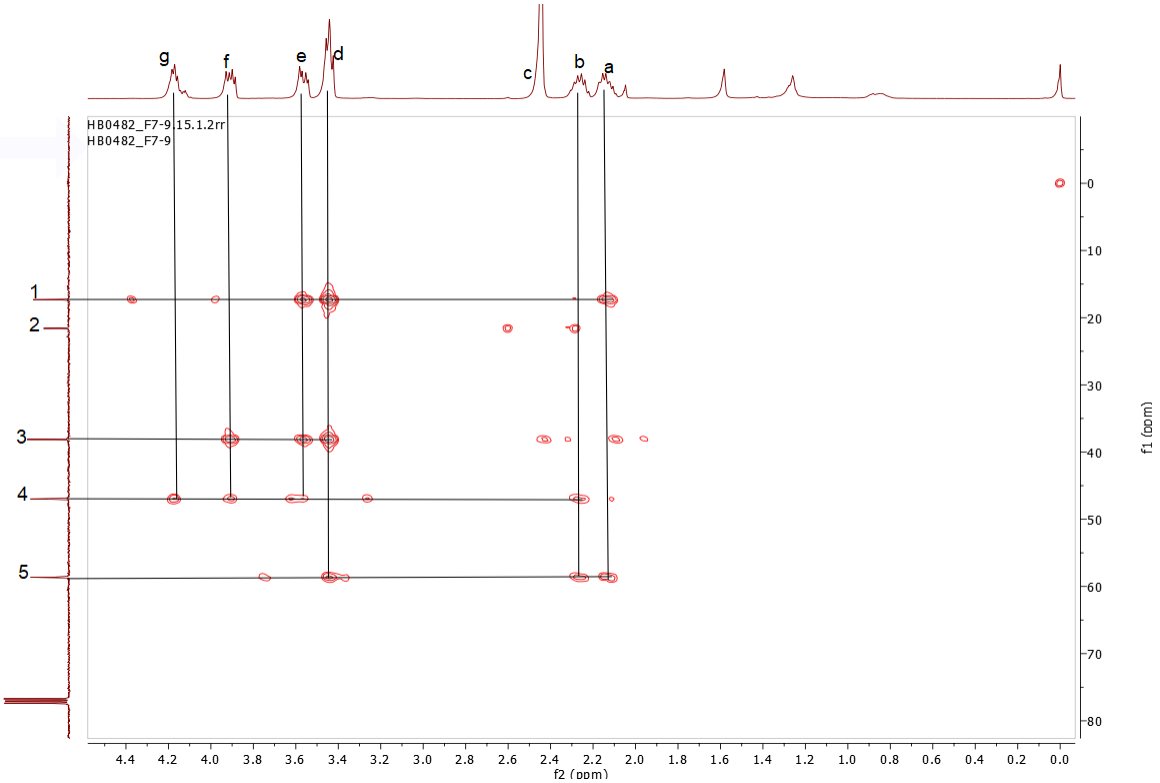


Figure 34: Aliphatic region of HMBC NMR for compound **246**.

Analysis of the HMBC data for compound **246** observes an interaction between C^4 and protons H^e and H^f and an interaction between C^5 and H^d which identified the compound as pyrrolidine **246** (Figure 34).

Compound **278**

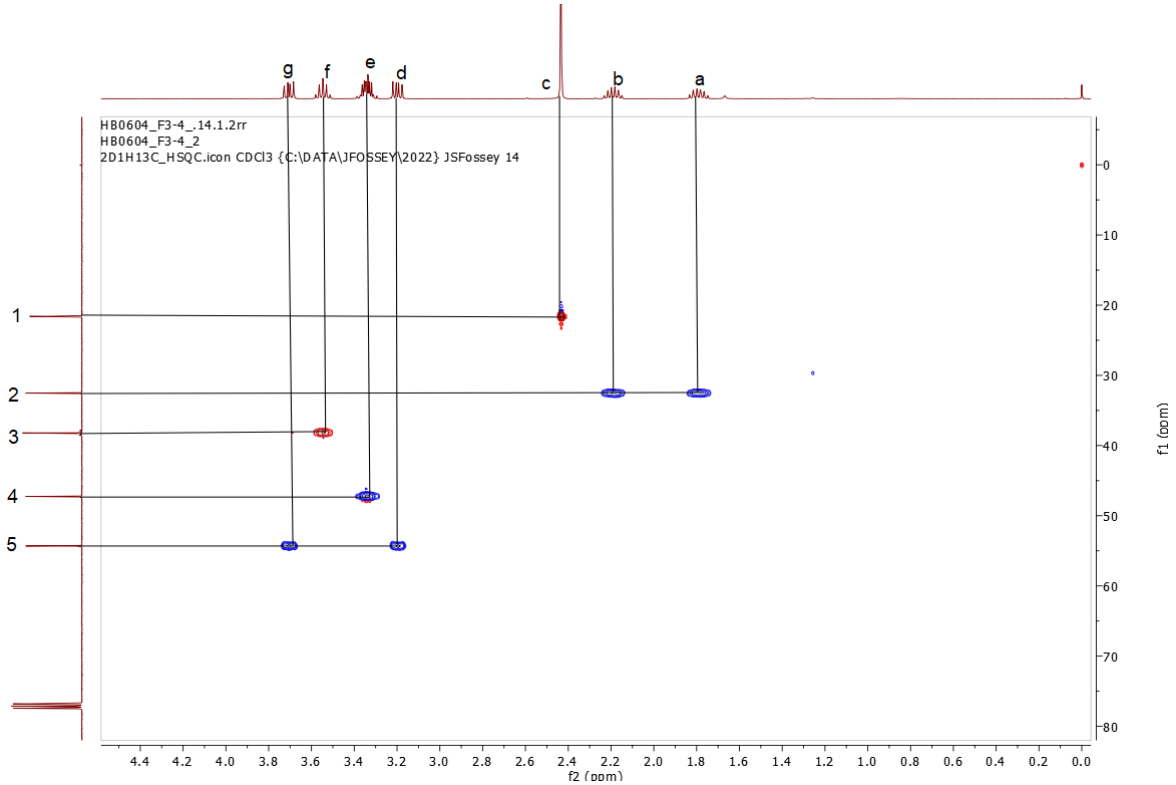


Figure 35: Aliphatic region of HSQC NMR for compound **278**.

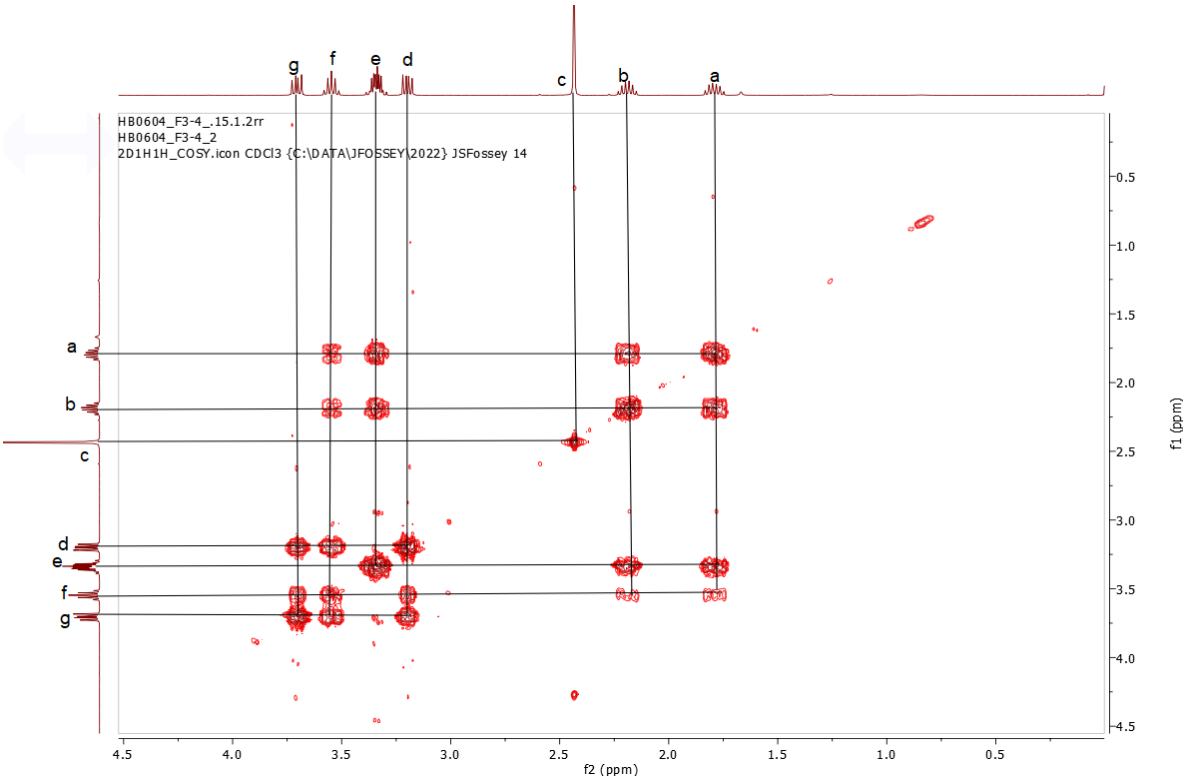


Figure 36: Aliphatic region of COSY NMR for compound **278**.

Interpretation of the aliphatic region of the HSQC (Figure 35) and COSY (Figure 36) NMR data for compound **278** labels the carbon and hydrogen atoms on the heterocyclic rings for isomers **277** and **278** (Figure 37).

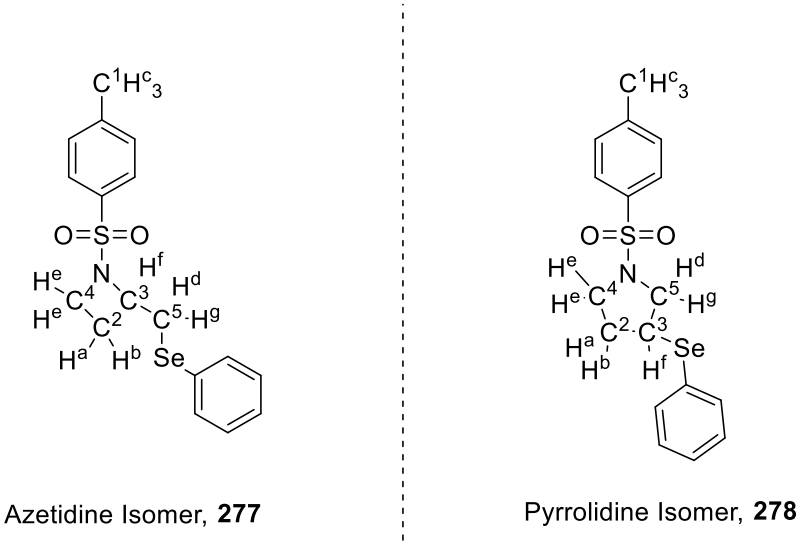


Figure 37: Aliphatic carbon and hydrogens labelled from analysis of HSQC and COSY data for compound **278**.

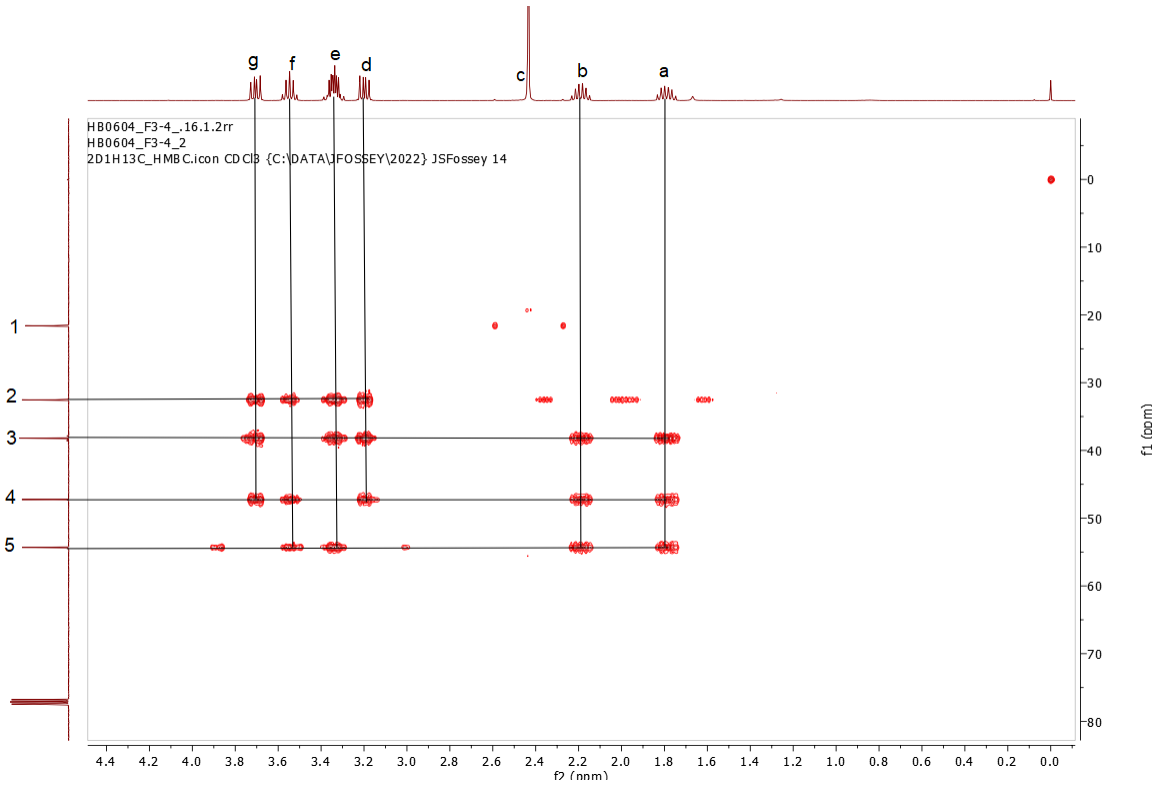


Figure 38: Aliphatic region of HMBC NMR for compound **278**.

Analysis of the HMBC data for compound **278** observes an interaction between C^4 and protons H^d and H^g and an interaction between C^5 and H^e which identified the compound as pyrrolidine **278** (Figure 38).

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