Synthesis of Substituted Azetidines and Spirocyclic Diazetidines

by

Alpa Kishor Pancholi

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry

Department of Chemistry, University of Warwick

September 2017

Table of Contents

Acknowledgements

First and foremost, I would like to thank my supervisor Professor Mike Shipman for not only the project, but for all of the help, guidance and support over the years. It has been very much appreciated and this thesis would not have been possible without it. I would also like to thank the University of Warwick and EPSRC for the financial support.

Thank you to Guy Clarkson for his expertise on X-ray crystallography. Many thanks to Ivan Prokes, Robert Perry, Lijiang Song and Phil Aston at the University of Warwick for all of their analytical expertise over the years. Thank you to members of the Wills group for all of their help and advice regarding chiral GC.

Thank you to all of the members of the Shipman and Chan groups both past and present for the fun, laughter and unforgettable memories over the years: Conor, Dave, Eduardo, George, Greg, Ina, Jo, Jon, Lauren, Martin, Nastja, Nat, Nicola, Paul, Raj, Ricky, Sam, Stefan and Stuart. Also a thank you to the members of the Chaplin group for the added laughter.

Most importantly, I would like to thank my parents for all of their unconditional love and support over the years. You always had faith and believed in me, and this would not have been possible without you. Thank you to my family and friends for their support.

Declaration

Except where clearly indicated, the work reported in this thesis is an account of my own independent research at the University of Warwick, carried out between October 2013 and April 2017.

The research reported in this thesis has not been submitted, either wholly or in part, for a degree at another institution.

At the time of submission, part of this work has appeared in the scientific literature:

Asymmetric Synthesis of 2-Substituted Azetidin-3-ones via Metalated SAMP/RAMP Hydrazones. Pancholi, A. K.; Geden, J. V.; Clarkson, G. J.; Shipman, M. *J. Org. Chem*. **2016**, *81*, 7984-7992.

Synthesis of 4,5-Diazaspiro[2.3]hexanes and 1,2-Diazaspiro[3.3]heptanes as Hexahydropyridazine Analogues. Pancholi, A. K.; Iacobini, G. P.; Clarkson, G. J.; Porter, D. W.; Shipman, M. *J. Org. Chem*. **2018**, *83*, 491-498.

Abstract

This thesis describes work focused on the asymmetric synthesis of substituted azetidin-3-ones and spirocyclic 1,2-diazetidines, as potential building blocks for the incorporation into drug-like scaffolds.

Chapter 1 begins with an introduction to azetidines, including a discussion of the methodologies for their synthesis, their applications, relevance in natural products and as building blocks in medicinal chemistry. It then describes the development of a new asymmetric route to 2-substituted azetidin-3-ones using Enders' SAMP/RAMP auxiliary. A one-pot process was developed involving the metalation of SAMP hydrazones of *N*-Boc-azetidin-3-one, alkylation and subsequent *in situ* hydrolysis to give the substituted products. Various bases and reaction conditions were explored to find optimal conditions for maximal yield and enantioselectivity. A representative range of electrophiles were screened including alkyl, allyl and benzyl halides and carbonyl compounds, producing enantioselectivities of up to 85% *ee*. Multiple substitution on the azetidin-3-one ring was briefly explored by repetition of the alkylation/hydrolysis sequence. Derivitisation by way of Pictet-Spengler reactions was used to confirm the absolute configuration at the newly created stereocentre.

Chapter 2 begins with an introduction to 1,2-diazetidines outlining methods for their synthesis, before introducing the relevance of these nitrogen spirocycles. This chapter then describes two routes for the synthesis of these novel spirocyclic 1,2-diazetidines by (i) formation of the diazetidine ring and (ii) functionalisation of a range of 3-methylene-1,2-diazetidines including differentially protected variants. The diazetidines were subjected to dichloro- and difluorocyclopropanation with the latter achieved in high yields. Additionally, reactions with tetracyanoethylene by way of highly asynchronous [2π+2π] cycloadditions proceeded in near quantitative yield. In this way, a range of novel 4,5-diazaspiro[2.3]hexane and 1,2-diazaspiro[3.3]heptane spirocycles were produced.

Chapter 3 details the experimental procedure and characterisation for all the novel compounds synthesised.

Abbreviations

Ac_2O	Acetic anhydride
Aq	Aqueous
Boc	*tert*-Butyloxycarbonyl
br	Broad
Calcd.	Calculated
Cbz	Carboxybenzyl
$CHCl_3$	Chloroform
CH_2Cl_2	Dichloromethane
COSY	Correlated Spectroscopy
δ	Chemical shift
d	Day(s) or doublet
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCC	*N,N'*-Dicyclohexylcarbodiimide
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DFT	Density Functional Theory
DIBAL	Diisobutyl aluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMDO	Dimethyldioxirane
DMEDA	*N,N'*-Dimethylethylenediamine

DMF	*N,N'*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
eq or equiv	Equivalents
ESI	Electrospray ionisation
Et_2O	Diethyl ether
Et_3N	Triethylamine
EWG	Electron withdrawing group
Fmoc	Fluorenylmethyloxycarbonyl
FT-IR	Fourier Transform-Infrared
GC	Gas Chromatography
GC-MS	Gas Chromatography-Mass Spectrometry
h	Hour(s)
HMBC	Heteronuclear Multiple Bond Correlation
HOMO	Highest Occupied Molecular Orbital
HSQC	Heteronuclear Single Quantum Coherence
HPLC	High-Performance Liquid Chromatography
HSAB	Hard-Soft Acids and Bases
^{i}Pr	Isopropyl
IR	Infrared Radiation
J	Coupling constant
LC-MS	Liquid Chromatography-Mass Spectrometry
LDA	Lithium diisopropylamide

LUMO	Lowest Unoccupied Molecular Orbital
m.p.	Melting point
M	Molarity concentration
m	Multiplet
Me	Methyl
*m*CPBA	*meta*-Chloroperoxybenzoic acid
MeCN	Acetonitrile
MeOH	Methanol
mg	Milligrams
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mmol	Millimolar
MS	Mass Spectrometry
μW	Microwave
m/z	Mass/charge ratio
NHC	N-Heterocyclic carbene
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
Nosyl	Nitrobenzenesulfonyl
P	Pressure
p-	*para*-
PCC	Pyridinium Chlorochromate

PE	Photoelectron
pg	Protecting group
pKa	Acid dissociation constant
PPh_3	Triphenylphosphine
ppm	Parts per million
PTC	Phase Transfer Catalyst
q	Quartet
quint	Quintet
RAMP	(*R*)-1-Amino-2-methoxymethylpyrrolidine
R_f	Retention factor
rt	Room temperature
s	Singlet
SAMP	(*S*)-1-Amino-2-methoxymethylpyrrolidine
T	Temperature
t	Triplet
TBS	*tert*-Butyldimethylsilyl
TDS	Thexyldimethylsilyl
TCNE	Tetracyanoethylene
TEBAC	Benzyltriethylammonium chloride
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin Layer Chromatography

TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
t_R	Retention time
Ts	Tosyl
TSA	Toluene sulfonic acid
wt	Weight
UV	Ultraviolet

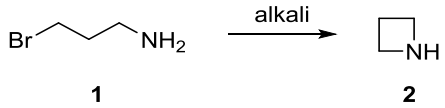
Chapter 1: Asymmetric Synthesis of 2-Substituted Azetidin-3-ones

1.1 Introduction to Azetidines

This thesis describes the development of new methods for the synthesis of two related four-membered nitrogen heterocycles: chiral 2-substituted azetidin-3-ones (Chapter 1) and spirocyclic 1,2-diazetidines (Chapter 2). By way of introduction, this chapter provides a brief introduction to azetidines and azetidin-3-ones before detailing our efforts for the synthesis of chiral 2-substituted azetidin-3-ones. Several comprehensive reviews have been published on azetidines, hence, only pertinent literature is described herein.[1,2]

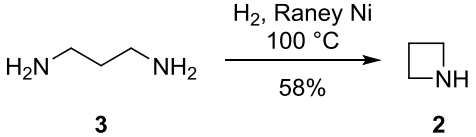
1.1.1 Structure and Properties of Azetidines

Azetidines are an important class of azaheterocycles, with one nitrogen atom contained in a strained four-membered ring. Azetidine **2** was first synthesised by Gabriel and Weiner in 1888, by cyclisation of γ-bromopropylamine under basic conditions (Scheme 1.1).[3]



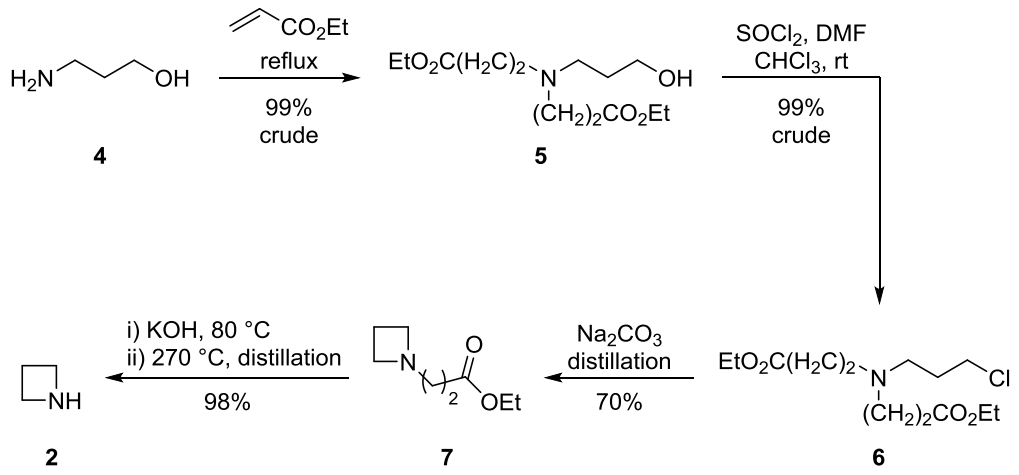
Scheme 1.1. Gabriel's synthesis of azetidine **2**.[3]

Today, more convenient methods for azetidine formation are available. Yasamura *et al* demonstrated the efficient formation of azetidine **2** from 1,3-diamine **3** under catalytic hydrogenation conditions employing Raney nickel as the catalyst (Scheme 1.2).[4]



Scheme 1.2. Catalytic hydrogenation for the synthesis of **2** by Yasamura *et al*.[4]

Another efficient and convenient synthesis of azetidine **2** was reported by Wadsworth, whereby 3-amino-1-propanol **4** is converted to azetidine **2** in four high yielding steps.[5] Conversion of the alcohol to 3-aminopropyl chloride **6** proceeded in high yields under straightforward conditions. Cyclisation of **6** in the presence of sodium carbonate formed **7**, and subsequent cleavage of the *N*-protecting group gave azetidine **2** with potassium hydroxide at elevated temperatures in near quantitative yield (Scheme 1.3).



Scheme 1.3. Synthesis of **2** by Wadsworth.[5]

The structure and geometry of the azetidine ring was first elucidated by electron diffraction and spectroscopic methods in the 1970s. Studies have found it to be highly puckered, with a dihedral angle (ϕ) of 33.1° (Figure 1.1). Compared to cyclobutane, the dihedral angles are comparable (ϕ = ~35° for cyclobutane), but with a higher barrier to ring inversion of 1.26 kcal mol^{-1}.[6] The geometry of the azetidine ring can adopt both an equatorial and axial conformation with respect to the hydrogen on the nitrogen atom. However, the equatorial position for the hydrogen was found to be more stable.[6–8]

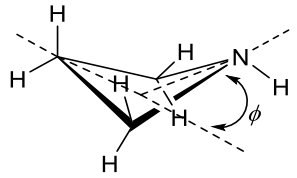
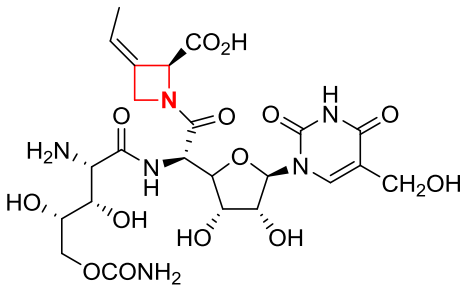


Figure 1.1. Ring-puckering of azetidine.[6]

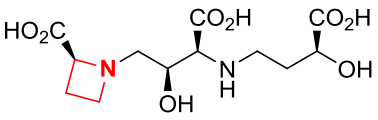
1.2 Application of Azetidines

1.2.1 Azetidines in Natural Products

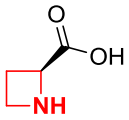
The azetidine core is found in very few natural products, the most common of which are shown in Figure 1.2. The discovery of the naturally occurring *L*-azetidine-2-carboxylic acid in 1956 sparked interest in the field of azetidines, as an analogue of *L*-proline, and is found as a significant constituent in many plants.[9] The polyoxins including polyoxin A comprise a group of peptide nucleoside antibiotics which are potent inhibitors of chitin biosynthesis in the cell wall and possess antifungal properties.[10] Mugineic acid is a phytosiderophore extracted from the roots of barley that is known to promote the uptake and transport of iron for the biosynthesis of chlorophyll in higher plants.[11] The azetidine subunit is a key structural requirement for the uptake of iron from the soil. More recently, the alkaloid Calydaphninone has been isolated from the Daphniphyllum plant species, and bears an azetidine moiety amidst its complex polycyclic skeleton.[12]



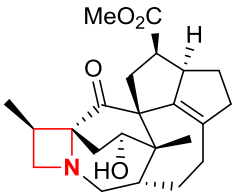
Polyoxin A



Mugineic Acid



L-Azetidine-2-carboxylic acid



Calydaphninone

Figure 1.2. Natural products containing an azetidine core.[9–12]

1.2.2 Azetidines in Drug Discovery

For many decades, the azetidine subunit has been used to make pharmaceutically relevant compounds, and interest in this area is continually growing. Several representative examples are shown in Figure 1.3. The DDP-4 inhibitor **7** was identified as a lead compound against diabetes after testing it in acute and chronic disease models of obesity.[13] Azetidinecarboxamide **8** has been patented for the treatment of central nervous system disorders, in light of similar substrates displaying anti-convulsant and anti-epileptic activity.[14] Medicinal chemists at Pfizer have identified CE-178,253 **9** as a CB_1 antagonist, which is currently in clinical development for the treatment of metabolic disorders including obesity.[15] Current development of broad spectrum antidepressants led to the identification of 3-substituted azetidine **10**. This substrate displayed inhibitory activity against a range of neurotransmitters, with further studies underway to establish its use as a potential treatment for depression.[16] Novel benzodioxane **11** is patented for the inhibition of leukotriene hydrolase, with application in the treatment of cardiovascular diseases.[17]

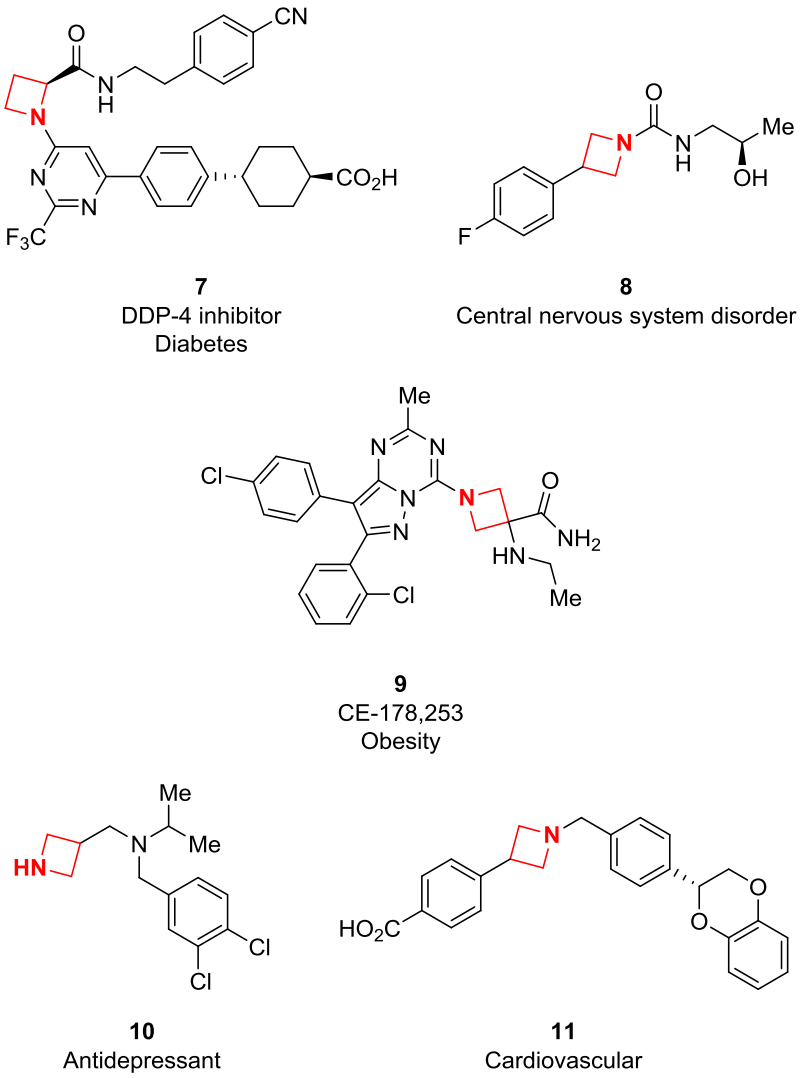


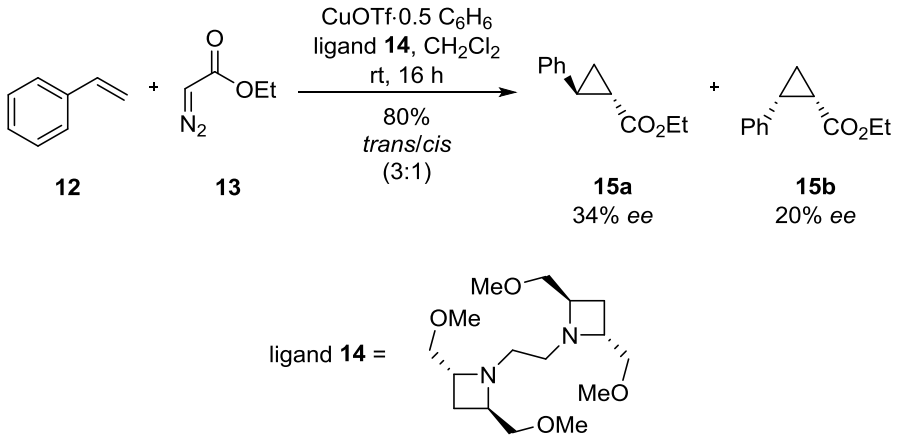
Figure 1.3. Biologically active azetidines.[13–17]

More recently, Lowe *et al* carried out the synthesis of a collection of azetidine-based scaffolds for application in central nervous system disorders, using diversity-orientated synthesis. Analysis of these compounds revealed interesting physiochemical properties of both substituted and fused azetidine compounds.[18]

1.2.3 Azetidines as Chiral Ligands

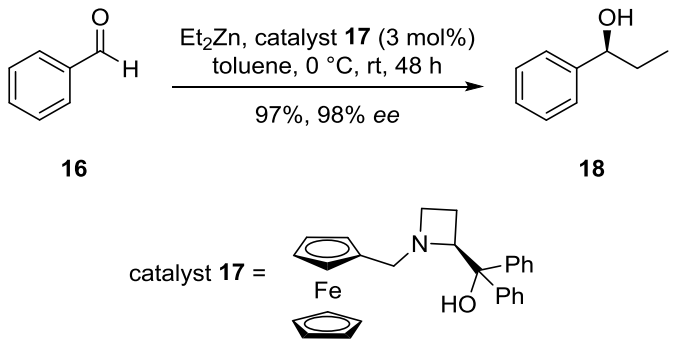
Optically pure azetidines have long been the topic of interest as ligands for metal-catalysed reactions or as chiral auxiliaries. This work has been dominated by Yamamoto's and Guanti's research groups, focussing on the synthesis of C2-symmetric azetidine diols for asymmetric amide alkylations.[19,20] In other work, Shi

et al demonstrated the use of bidentate ligand **14** for the asymmetric cyclopropanation of styrene using a copper (I) triflate catalyst.[21] Good yields were obtained for the transformation, however, only poor to moderate enantioselectivities of **15a** and **15b** were obtained using **14** as the ligand (Scheme 1.4). Marinetti *et al* have also published a series of 2,4-disubstituted azetidines with potential application as chiral ligands.[22]



Scheme 1.4. Asymmetric cyclopropanation using azetidine chiral bidentate ligand **14**.[21]

More recently, advances in this field have enabled the formation of materials with excellent enantioselectivities. Wang and co-workers have demonstrated the asymmetric addition of ketones using a novel *N*-ferrocenylmethyl azetidin-2-yl(diphenyl)methanol catalyst **17**.[23] This catalyst was prepared in a facile one-pot process, and successfully enabled the enantioselective ethylation and arylation of ketones in up to 98% *ee* (Scheme 1.5).



Scheme 1.5. Asymmetric addition to aryl ketones using catalyst **17**.[23]

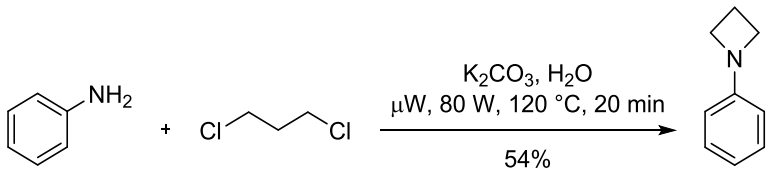
1.3 Synthetic Routes to Azetidines

In view of their growing importance, it is somewhat surprising that there has been relatively little interest in the syntheses of azetidines. This can be attributed in part to their intrinsic ring strain and difficulty of formation. The most common methods for their preparation are discussed below.

1.3.1 Cyclisation by Nucleophilic Substitution

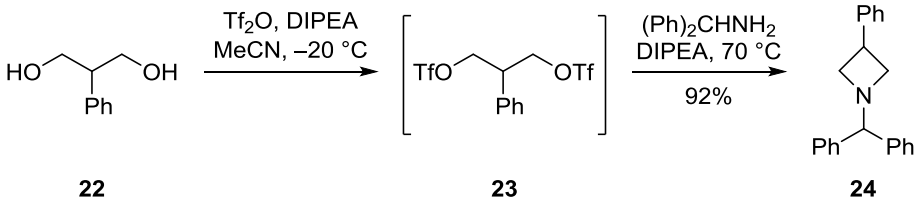
Cyclisation of amines has long since been the preferred method for azetidine formation. Most commonly, nucleophilic displacement of a leaving group by a nitrogen nucleophile efficiently forms the cyclic product, with halides being most commonly employed as the leaving group.

Ju *et al* have demonstrated this to form mono-substituted azetidines from simple reagents in a microwave assisted process.[24] The cyclisation of dihalides and primary amines occurred in aqueous media in a condensation reaction to give *N*-arylated azetidine **21** in moderate yield (Scheme 1.6).



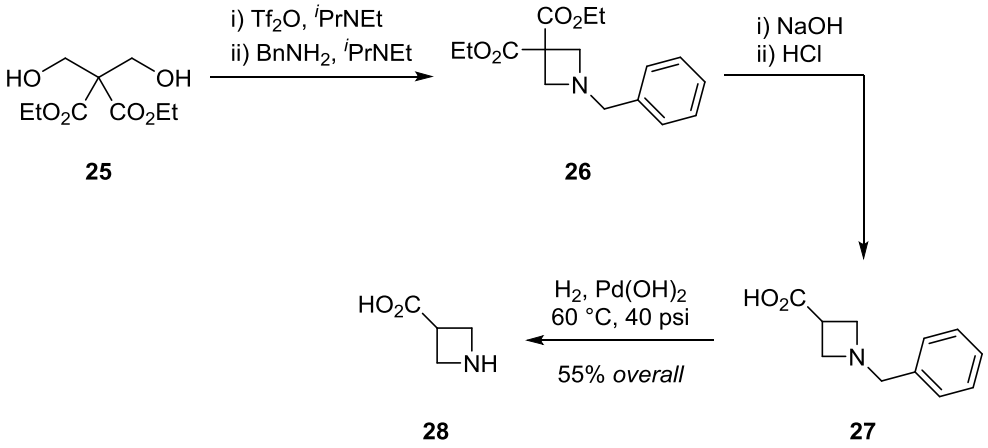
Scheme 1.6. Nucleophilic substitution reaction to form arylated azetidine **21**.[24]

Alongside halides, triflate or sulfonate esters are known to undergo base-mediated cyclisation. The Hillier group reported the efficient formation of a variety of 1,3-disubstituted azetidines from 1,3-propanediols in a one step process, which was further adapted to form spirocyclic azetidines.[25] For example, alkylation of primary amines by bistriflate **23** formed 1,3-disubstituted azetidine **24** in 92% yield (Scheme 1.7).



Scheme 1.7. One-pot formation of 1,3-disubstituted azetidine **24** by Hillier *et al*.[25]

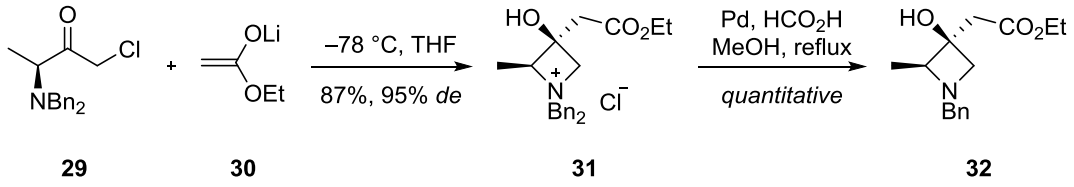
An application of this methodology was in the synthesis of azetidine-3-carboxylic acid **28** by Miller *et al*. This novel *β*-amino acid was incorporated into a variety of pharmaceutically active compounds, including CCR5 receptor modulators and protein inhibitors.[26] Malonate **25** was converted to the corresponding triflate, which underwent cyclisation with benzylamine to give azetidine **26**. Subsequent hydrolysis, decarboxylation and removal of the benzyl group under catalytic hydrogenation conditions then yielded azetidine-3-carboxylic acid **28** in good overall yield (Scheme 1.8).



Scheme 1.8. Synthesis of azetidine-3-carboxylic acid **28** by Miller *et al*.[26]

Concellón and co-workers have developed enantiopure azetidinium salts through a samarium mediated iodomethylation procedure in high diastereoselectivities of up to 90% *de*.[27] This group subsequently published the formation of azetidinium esters from ketone derivatives.[28] The addition of ester enolate **30** to *N*-dibenzylaminoketone **29** afforded enantiomerically pure ester **31** in 87% yield with excellent diastereoselectivity. Bulkier substituents on the ester substrate were shown to favour epoxidation over the

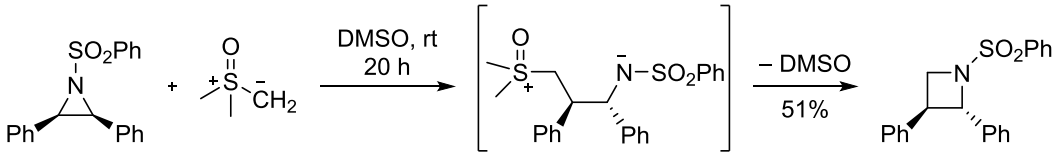
azetidinium salt formation. Hydrogenolysis of **31** yielded **32** in quantitative yield by way of debenzylation in the presence of a palladium catalyst (Scheme 1.9).



29 **30** **31** **32**

Scheme 1.9. Enantiopure azetidines from ketones by Concellón and co-workers.[28]

The ring-opening of epoxides and aziridines has been well documented as a convenient methodology to access four-membered azaheterocycles. Indeed, the intramolecular cyclisation of substituted amino oxiranes is known to efficiently yield *N*-alkyl-3-azetidinols through a based mediated process, starting from epichlorohydrin.[29,30] Switching to the nitrogen counterpart, the Nadir group has demonstrated the application of aziridines to undergo ring-opening by dimethylsulfoxonium methylide **34**, forming azetidines such as **35** *via* a 4-*exo*-*tet* ring-closure of the intermediate (Scheme 1.10).[31] Although yields were moderate in most cases, the group confirmed the reaction to be highly stereospecific, with the *cis*-aziridine forming the *trans*-azetidine exclusively, and *vice versa*. Further optimisation provided a procedure to synthesise **35** under microwave irradiation under solvent-free conditions.[32]

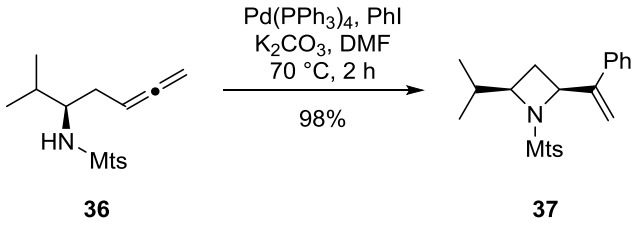


33 **34** **35**

Scheme 1.10. Ring-opening of aziridine **33** to form 2-substituted azetidine **35**.[31]

Other methods for the synthesis of azetidines have been developed, including the metal-catalysed cyclisation reactions published by Ohno and co-workers.[33] These authors utilised palladium chemistry for the efficient cyclisation of *β*-amino allene **36** into alkenylazetidine **37** in high yields. By variation of the reaction conditions, exclusively *cis*-substituted vinyl azetidines could be obtained in excellent

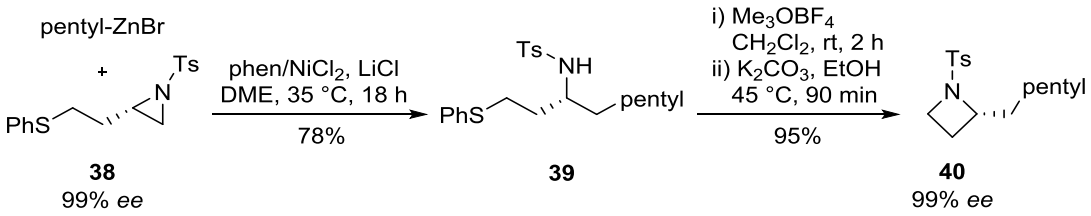
diastereoselectivities (Scheme 1.11). A similar strategy was reported by the Chen group to form azetidines through intramolecular amination.[34]



36 **37**

Scheme 1.11. Palladium-catalysed cyclisation of allene **36** to *cis*-azetidine **37**.[33]

More recently, Jamison and co-workers used Nickel catalysis for the synthesis of enantiomerically pure azetidines starting from aziridines.[35] Initial cross coupling with $NiCl_2$ and an organozinc reagent formed sulfonamide **39**. Subsequent selective methylation of the sulphide paved the way for facile 4-*exo*-*tet* cyclisation forming azetidine **40** with no evidence of racemisation (Scheme 1.12).

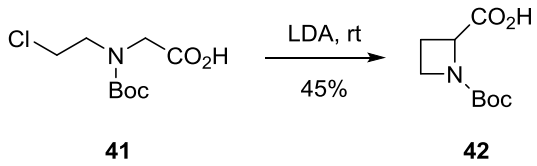


38 99% *ee* **39** **40** 99% *ee*

Scheme 1.12. Nickel-catalysed cross coupling to form azetidine **40**.[35]

1.3.2 Cyclisation by C–C Bond Formation

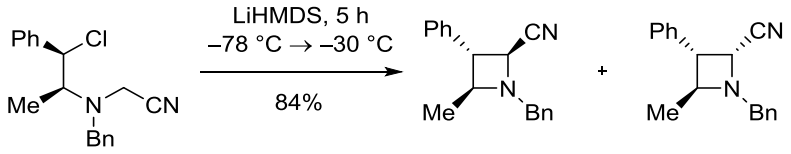
Although less widely used, several syntheses have applied the nucleophilic displacement of halides in a cyclisation to form azetidines through C–C bond formation. In 1994, de Nicola *et al* demonstrated the facile formation of 2-substituted azetidine **42** from the intramolecular cyclisation of carboxylic acid **41** in the presence of LDA.[36] The reaction proceeded in moderate yield at ambient temperatures to give **42** in 45% yield (Scheme 1.13).



41 **42**

Scheme 1.13. Carbanion-mediated cyclisation to form **42**.[36]

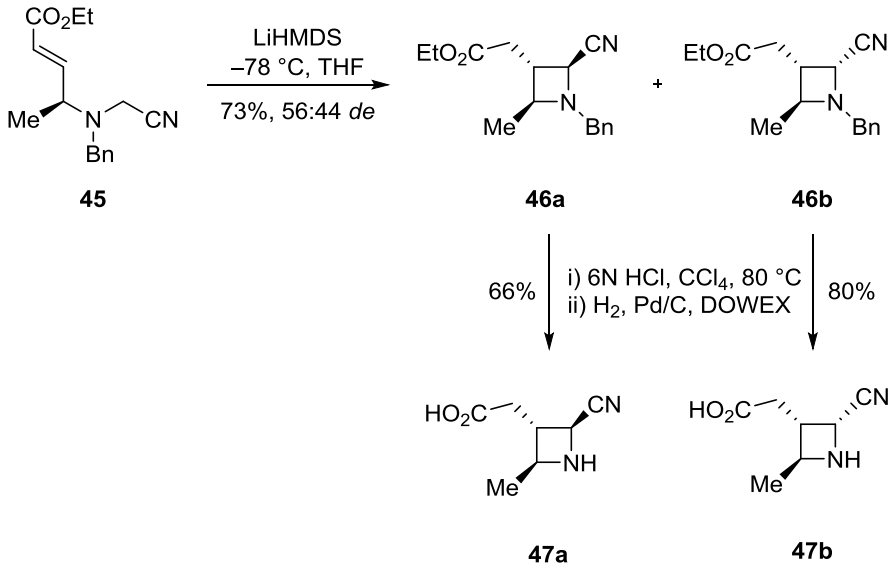
This carbanion chemistry was further developed by the Couty group, who effectively synthesised enantiopure derivatives of azetidines using LiHMDS.[37] The group discovered that by varying the equivalents of base and reaction time, the stereoselectivity of the reaction could be controlled. Keeping the reaction at –30 °C for 2 h led to a 70:30 ratio of isomers **44a**:**44b**, whilst increasing the reaction time to 5 h increased the stereoselectivity towards diastereomer **44a** to a 92:8 ratio (Scheme 1.14).



43 **44a** **44b**

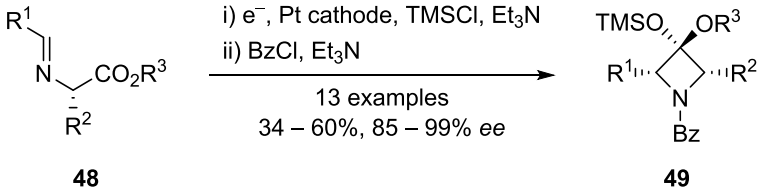
Scheme 1.14. Synthesis of azetidines by Couty *et al*.[37]

Further work by the group extended this chemistry by variation of the electrophilic partner. Ester **45** was subjected to 4-*exo*-*trig* ring-closure of the lithiated intermediate through an intramolecular Michael addition to give azetidines **46a**/**46b**.[38] Moderate yields and diastereoselectivities were obtained with a 56:44 ratio of **46a**/**46b** respectively, which the authors attributed to thermodynamic control in the Michael addition step. Subsequent hydrolysis and deprotection of the benzyl group provided azetidines **47a**/**47b** (Scheme 1.15).



Scheme 1.15. Intramolecular Michael addition to form azetidines **47a**/**47b**.[38]

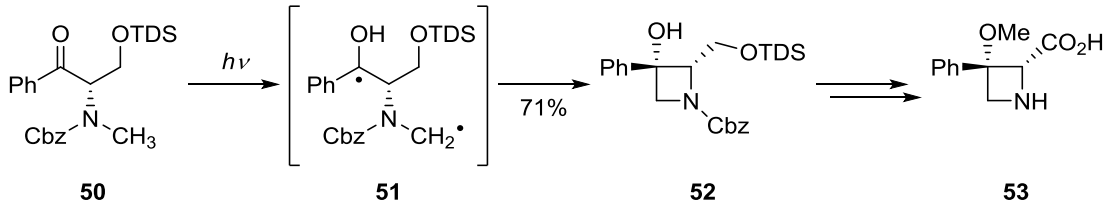
An alternative route was proposed by Kise and co-workers as shown in Scheme 1.16.[39] Initial formation of chiral *α*-imino ester **48** derived from amino acids was followed by electroreductive intramolecular cross coupling to give enantiomerically pure azetidine **49**. The presence of chlorotrimethylsilane (TMSCl) was found to be crucial for the electroreduction, with ^{1}H NMR analysis indicating the formation of an imine-TMSCl complex under the reaction conditions. A series of single electron transfer steps enabled formation of **49** in moderate to good yields.



Scheme 1.16. Formation of enantiomerically pure azetidines by electroreductive cross coupling.[39]

A radical-promoted cyclisation was also adopted by Wessig *et al* in the photochemical activation of aminoketone **50** to form azetidinol **52** (Scheme 1.17).[40] Thus, irradiation of **50** led to the intramolecular photochemical alkylation of the aminoketone, with abstraction of a hydrogen from the *N*-methyl group by the carbonyl to form biradical intermediate **51**. Diastereoselective ring cyclisation

afforded the azetidine scaffold in 71% yield. Subsequent steps lead to the formation of azetidine-2-carboxylic acid **53**.

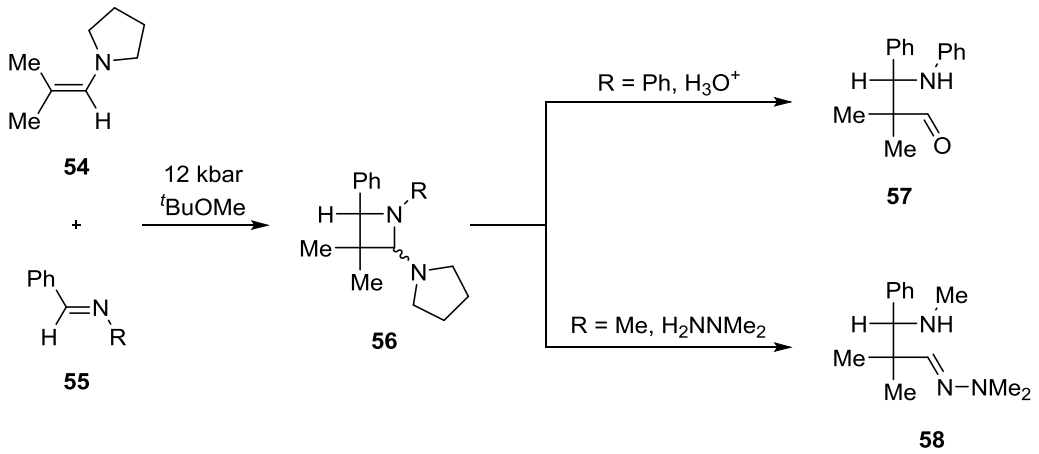


50 **51** **52** **53**

Scheme 1.17. Photochemical activation of aminoketone **50** to form azetidine-2-carboxylic acid **53**.[40]

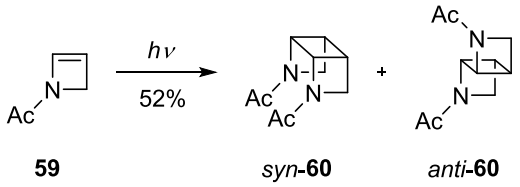
1.3.3 Synthesis *via* Cycloaddition Reactions

Very few syntheses are known employing cycloaddition reactions to directly form the azetidine ring. Formally, the most straightforward route to azetidines would be the [2+2] cycloaddition of imines with electron rich alkenes, although there is little precedence for this transformation. Smit and co-workers have shown that under high pressure conditions of 12 kbar, alkene **54** and imine **55** can be converted into azetidine **56**.[41] Although the stability of **56** was found to be poor at ambient conditions, azetidine **56** can be transformed to *β*-amino carbonyl **57** by hydrolysis, or into hydrazone **58** (Scheme 1.18). Although successful, the applicability of this methodology was limited.



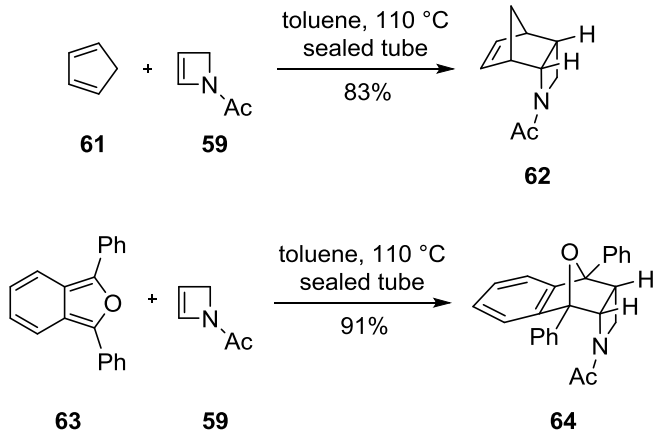
Scheme 1.18. Cycloaddition to synthesise azetidine **56**.[41]

Prinzbach and co-workers have extensively studied the intramolecular [2+2] photochemical cycloaddition reactions of imines and alkenes to form polycyclic systems.[42] These cage-like structures were found to be thermally stable and could be accessed in up to 85% yield. At a similar time, Dave *et al* demonstrated the photodimerisation of *N*-acetyl-2-azetine **59** into diazatricyclooctanes **60** by exclusive head-to-head dimerisation. Both *syn*-**60** and *anti*-**60** were formed in a 1:1 mixture in moderate yields (Scheme 1.19).[43]



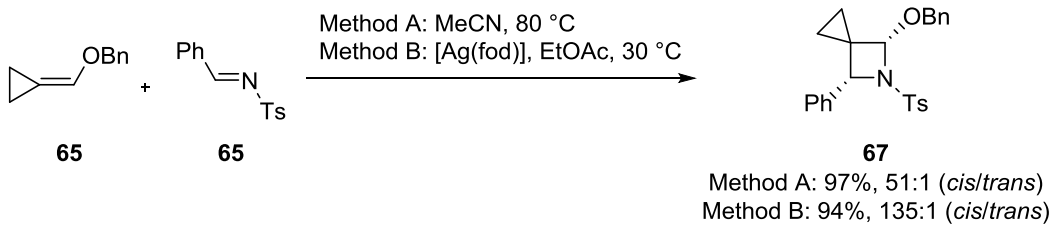
Scheme 1.19. Photodimerisation of *N*-acetyl-2-azetine **59**.[43]

The group further applied these strained substrates in Diels-Alder reactions, as shown in Scheme 1.20. The [4+2] cycloaddition of **59** with both cyclopentadiene **61** and diphenylisobenzofuran **63** gave the corresponding cyclic products in good to excellent yields.[44] Spectroscopic evidence confirmed the *endo* stereochemistry.



Scheme 1.20. Diels-Alder reaction of **59** with reactive dienes.[44]

Owing to the ring strain associated with small rings, cycloaddition reactions proceed smoothly in such cases. For example, thermally induced [2+2] cycloaddition of **65** with imine **66** afforded spirocyclopropane azetidine **67** in excellent yield with high levels of diastereocontrol favouring the *cis* isomer. In comparison to the thermal conditions, the use of a silver catalyst [Ag(fod)] allowed the reaction to proceed at lower temperatures with higher *cis* selectivity (Scheme 1.21).[45]

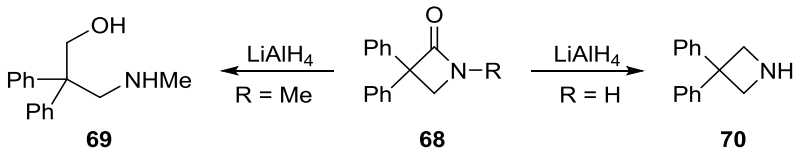


Scheme 1.21. Cycloaddition to form spirocyclopropane azetidine **67** by Nakamura *et al*.[45]

1.3.4 Reduction of Azetidin-2-ones

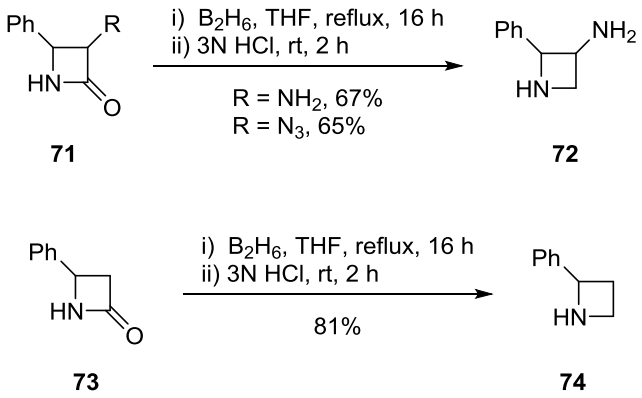
With many procedures to azetidin-2-ones available, it is not surprising that these compounds provide another useful route to azetidines. A number of recent reviews have highlighted the reagents available for *β*-lactam reduction, which include $LiAlH_4$, diborane, Raney nickel and alanes.[46,47]

Testa and co-workers developed the initial reduction of azetidin-2-ones using $LiAlH_4$, and observed that this chemistry was only applicable for *N*-unsubstituted azetidin-2-ones.[48] Substituents on the nitrogen atom typically led to C–C bond cleavage forming substituted 3-aminopropanol **69** (Scheme 1.22).



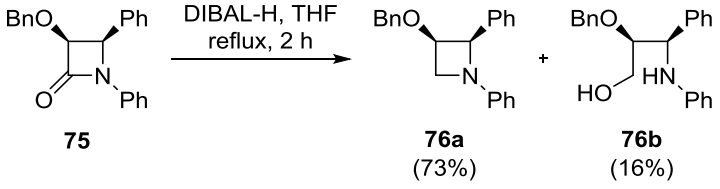
Scheme 1.22. Reduction of azetidin-2-ones using $LiAlH_4$.[48]

Azetidin-2-one reduction by diborane was first introduced by Wells *et al* in the early 1970s.[49] When 3,4-substituted azetidin-2-ones were treated with excess diborane in THF followed by hydrolysis with HCl, the azetidines were obtained in moderate yields. Starting from **71**, both the azido and carbonyl groups were reduced simultaneously to give **72**. When 4-phenyl-2-azetidinone **73** was subjected to the reaction conditions, the reduction occurred in 81% yield to form **74** (Scheme 1.23).



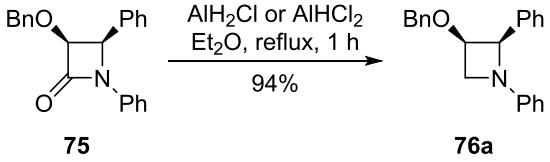
Scheme 1.23. Reduction of azetidin-2-ones using diborane in THF.[49]

Ojima and co-workers have pioneered the use of DIBAL-H and chloroalanes (AlH_2Cl and $AlHCl_2$) for this reduction, the latter of which is highly selective for a wide variety of substrates.[50,51] Azetidin-2-one **75** underwent reduction with DIBAL-H successfully to form the corresponding azetidine **76a** in 73% yield, alongside 3-(phenylamino)-3-phenyl-2-(benzyloxy)propanol **76b** in 16% yield (Scheme 1.24).[50] Addition of electron donating groups on the phenyl ring at the 4-position almost exclusively led to the formation of the azetidine, with only traces amounts of the ring cleavage product detected.



Scheme 1.24. Reduction of azetidin-2-one **75** using DIBAL-H.[50]

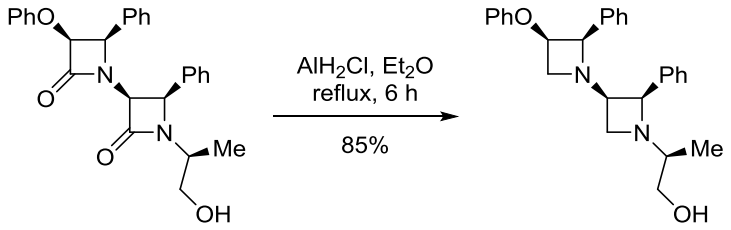
Switching to the chloroalanes led solely to compound **76a** in 94% yield, when either monochloroalane or dichloroalane were used (Scheme 1.25).[50]



75 **76a**

Scheme 1.25. Chloroalanes as reducing agents for azetidin-2-one reduction.[50]

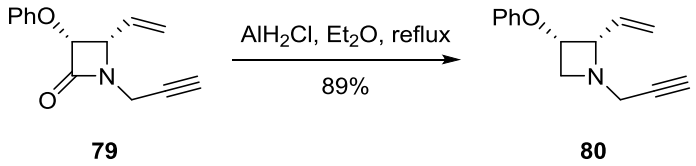
The generality and efficiency of this process was later demonstrated through direct reduction of bis-*β*-lactam **77** with chlorohydroalane, forming bisazetidine **78** in 85% yield (Scheme 1.26).[51]



77 **78**

Scheme 1.26. Bis-*β*-lactam reduction of **77** using chlorohydroalane.[51]

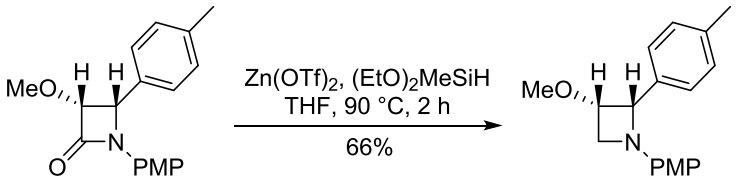
Shortly after the introduction of chloroalanes, several asymmetric syntheses employed this methodology. Alcaide and co-workers adopted this method for the formation of fused tricyclic azetidines.[52] Precursor **79** underwent selective reduction of the amide bond forming **80** in a highly chemoselective manner (Scheme 1.27). The stereochemistry of the monolactam was retained in the reaction, with no reduction of the double or triple bond observed.



79 80

Scheme 1.27. Chemoselective reduction of *β*-lactam **79**.[52]

More recently, the same group developed a metal-catalysed chemoselective approach using hydrosilanes as the reducing agent.[53] In the presence of zinc catalyst, *β*-lactam **81** was successfully reduced to give enantiopure azetidine **82** with no erosion of stereoselectivity (Scheme 1.28). This method tolerates the presence of other reducible functional groups such as azides and cyanohydrins.



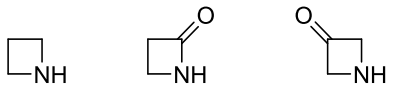
81 82

Scheme 1.28. Chemoselective reduction of **81** using hydrosilanes.[53]

1.4 Introduction to Azetidin-3-ones

In this chapter, new methodology for the synthesis of 2-substituted azetidin-3-ones is described. Before outlining our own work, we highlight the importance of these molecules in medicinal chemistry, and describe existing methods for their synthesis.

Whilst there is considerable interest in the synthesis and application of azetidines, both azetidin-2-ones (*β*-lactams) **83** and azetidin-3-ones **84** have received much attention as well (Figure 1.4).



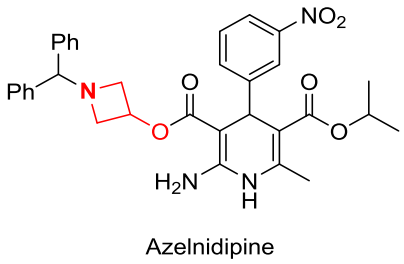
2 83 84

Figure 1.4. Structure of azetidine **2**, azetidin-2-one **83** and azetidin-3-one **84**.

Azetidin-3-ones are isosteres of *β*-lactams, with the carbonyl group one carbon removed from the nitrogen atom. Although this class of compounds have not yet been found in nature, they have been proposed as an alternative route to access substituted azetidines.[54]

1.4.1 Medicinal Relevance of Azetidin-3-ones

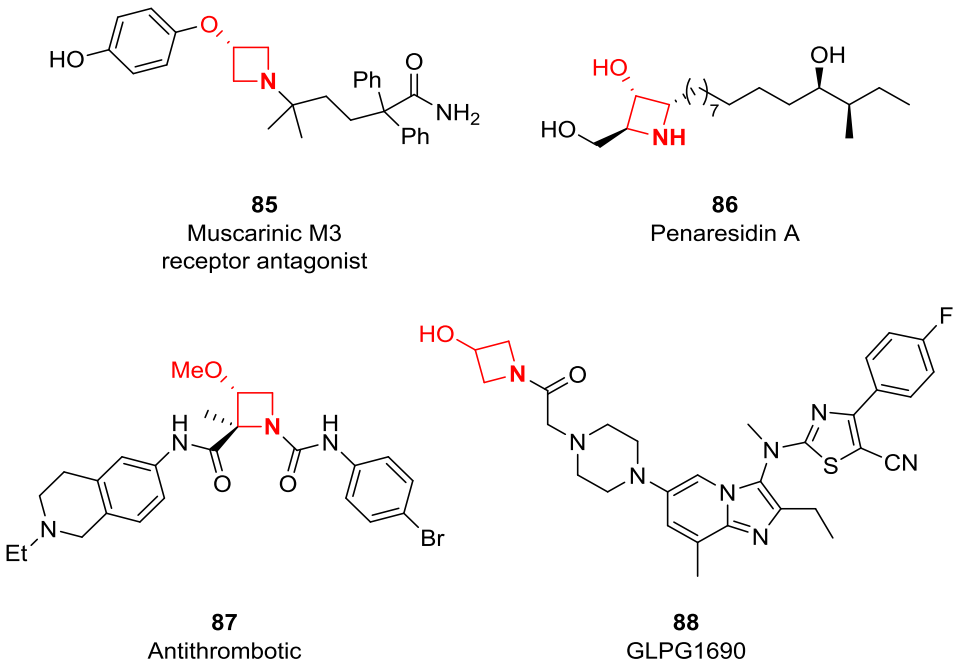
Azetidines and their 3-oxygenated derivatives are found in a number of natural products and medicinal agents. For example, Azelnidipine is a compound patented for pharmaceutical application as a dihydropyridine calcium channel blocker (Figure 1.5). The introduction of the diphenylmethylazetidine substituent was said to initiate a gradual onset of lowering the blood pressure due to its hydrophobic character, enabling the molecules to travel slowly through the cell membrane and induce a long-lasting hypotensive effect.[55]



Azelnidipine

Figure 1.5. Structure of Azelnidipine.[55]

Further examples are shown in Figure 1.6. Penaresidin A was isolated in 1991 from the Okinawan marine sponge, and its structure confirmed to contain an azetidine core. Penaresidin A behaves as a potent actomysin ATPase activator for muscle contraction.[56,57] Novel muscalinic M3 receptor antagonist **85** has been identified as a potential long-acting bronchodilator, with the four-membered heterocyclic core displaying excellent binding affinities.[58] Recently, patented compound **87** was shown to exhibit antithrombotic properties,[59] whilst GLPG1690 **88** is the first autotaxin inhibitor in clinical trials for the treatment of idiopathic pulmonary fibrosis.[60]



85
Muscarinic M3 receptor antagonist

86
Penaresidin A

87
Antithrombotic

88
GLPG1690

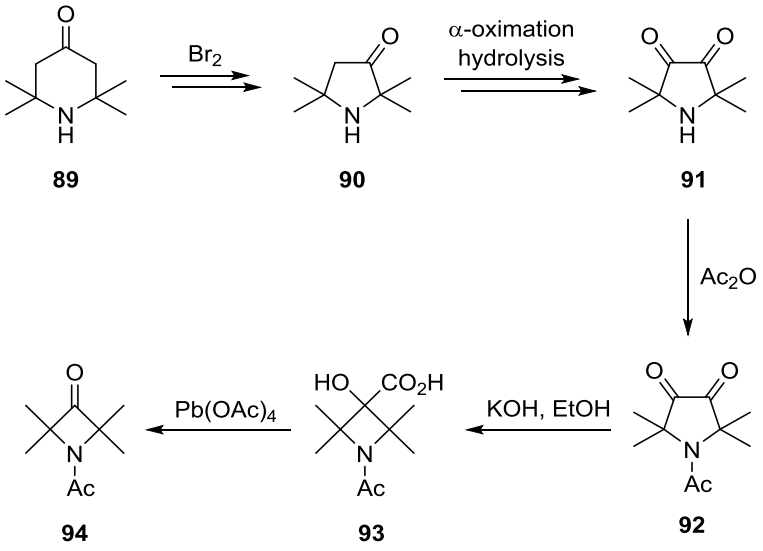
Figure 1.6. Examples of biologically active 3-oxygenated azetidines.[56–60]

1.5 Synthesis of Azetidin-3-ones

The formation of azetidin-3-ones are largely grouped into two methodologies: carbonyl group generation on the azetidine ring and intramolecular cyclisation of carbonyl containing substrates. The latter comprises the cyclisation of aminohaloketones and α-diazoketones, which generally enable the synthesis of 2-substituted derivatives.[54]

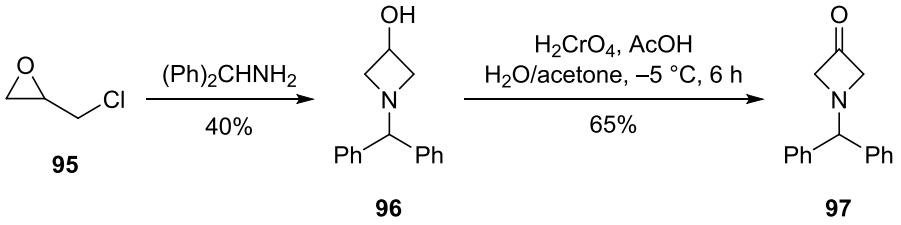
1.5.1 Synthesis by Carbonyl Group Generation

The first reported synthesis of azetidin-3-ones was by oxidative ring contraction, starting from piperidin-4-one **89**.[61] Bromination and Hofmann rearrangement formed **90** with subsequent installation of the adjacent carbonyl to give pyrrolidine-3,4-dione **91**. Acetylation, rearrangement under basic conditions followed by oxidation with lead (IV) acetate then provided azetidin-3-one **94** (Scheme 1.29). However, this approach required many steps and was limited in terms of substrate scope, providing only tetrasubstituted azetidin-3-ones.



Scheme 1.29. Oxidative ring contraction to tetrasubstituted azetidin-3-one **94**.[61]

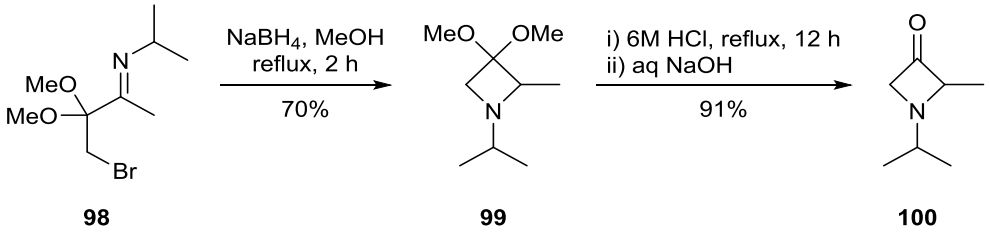
One of the most common approaches to generate azetidin-3-ones is through the oxidation of the corresponding azetidin-3-ol. Various routes have been employed for this transformation, with initial synthesis of **96** stemming from reaction of primary amines with epichlorohydrin **95**.[29] The Jones reagent generated ketone **97** in 40% yield, with poor stability of the compound at low temperatures (Scheme 1.30).[62]



Scheme 1.30. Oxidation of azetidin-3-ols to form ketone **97**.[62]

The use of alternative chromium reagents has also been documented, including PCC, pyridinium dichromate and chromium trioxide in acetic acid.[54] Alternatively, sulfur reagents work well for these oxidations, using the Parikh-Doering conditions.[63]

A convenient method was reported by the De Kimpe group, starting from imine **98**, synthesised from butane-2,3-dione in several steps.[64] This imine was converted to aminoacetal **99** using excess sodium borohydride, by way of reduction of the imino functionality and subsequent cyclisation. Finally, acidic hydrolysis provided azetidin-3-one **100** in high yield (Scheme 1.31).

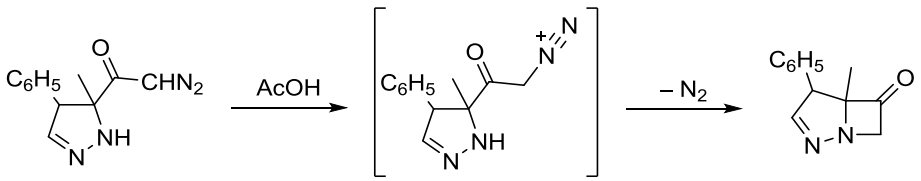


98 **99** **100**

Scheme 1.31. Synthesis of 2-substituted azetidin-3-one **100**.[64]

1.5.2 Synthesis by Ring Closure

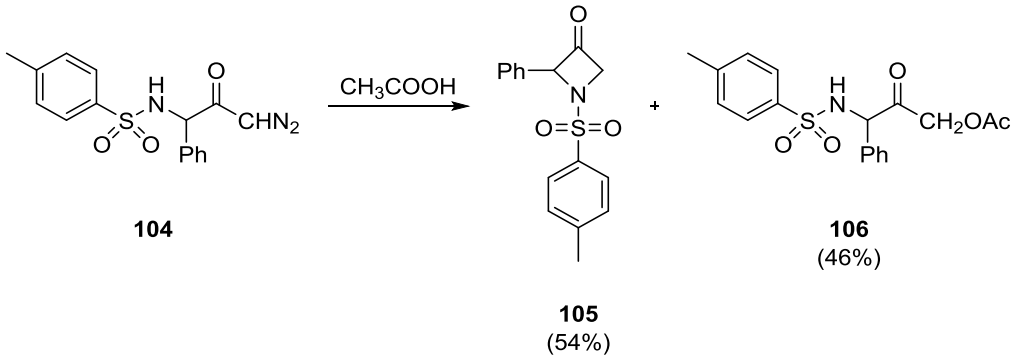
The cyclisation of α-diazoketones to form azetidin-3-ones was first reported in 1959, whereby bicyclic **103** was formed from diazoketone **101** under acidic conditions.[65] The reaction is presumed to proceed by loss of molecular nitrogen from intermediate cation **102** (Scheme 1.32).



101 **102** **103**

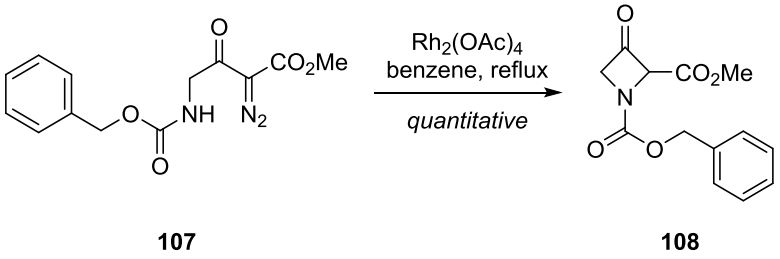
Scheme 1.32. Cyclisation of α-diazoketone **101** in the presence of acetic acid.[65]

The extent of cyclisation for monocyclic azetidin-3-ones is dependent on the nucleophilicity of the acid employed, as reported by Pusino *et al*.[66] For example, when **104** was heated with acetic acid, a mixture of the cyclised product **105** and the linear α-acetoxymethyl ketone **106** were obtained. The presence of alkyl or benzyl substituents on the α-position of the diazoketone increased the ratio towards the cyclised ketone (Scheme 1.33).



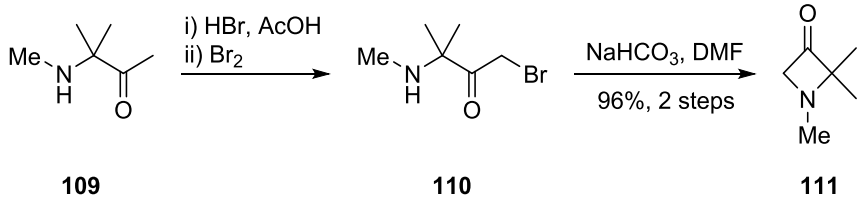
Scheme 1.33. Cyclisation of α-diazoketone **104** to give azetidin-3-one **105** and linear ketone **106**.[66]

Metal-catalysed carbon–carbon bond formation reactions for the synthesis of carbocycles have been extensively studied. Rapoport and co-workers reported the first intramolecular carbene insertion involving diazo precursors to form azetidin-3-one **108** using rhodium acetate (Scheme 1.34).[67] Since then, Wang and co-workers have used $Cu(acac)_2$ for the metal catalysed N-H insertion of α-diazocarbonyls.[68]



Scheme 1.34. Rhodium catalysed N-H insertion by Rapoport *et al*.[67]

Several examples of cyclisations of α-amino-α-haloketones to substituted azetidin-3-ones exist. These procedures commonly employ mild reaction conditions and proceed in high yields. Hargrove *et al* have extensively explored this topic, demonstrating the formation of 2,2-dimethylazetidin-3-one **111** from *N*-substituted bromo-butan-2-one **110**, using basic conditions (Scheme 1.35).[54]

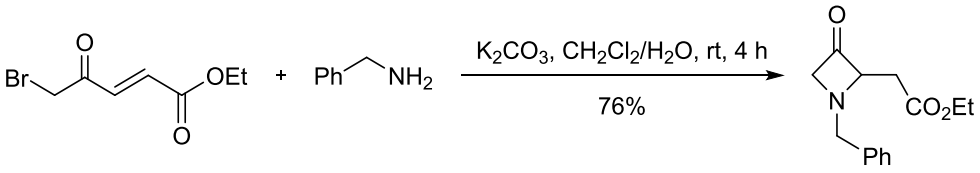


109 **110** **111**

Scheme 1.35. Cyclisation to form 2,2-disubstituted azetidin-3-one **111** using basic conditions.[54]

1.5.3 Direct Synthesis of 2-Substituted Azetidin-3-ones

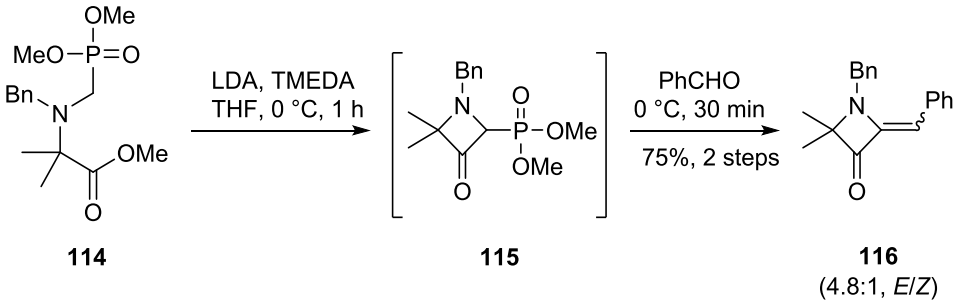
A convenient one-pot process to access *N*-alkylated-2-substituted azetidin-3-ones was demonstrated by Gérard *et al*, starting from primary amines and alkyl enoates.[69] The enoate was synthesised in three steps, then reacted with benzylamine in a biphasic system in the presence of potassium carbonate to yield **113** in 76% yield (Scheme 1.36). The reaction proceeded through conjugate addition and subsequent 4-*exo*-*trig* cyclisation to afford ketone **113**. Efforts to extend this work to asymmetric variants using chiral amines proved difficult, with moderate yields and low diastereoselectivities obtained.



112 **113**

Scheme 1.36. One-pot synthesis of **113** from alkyl enoates.[69]

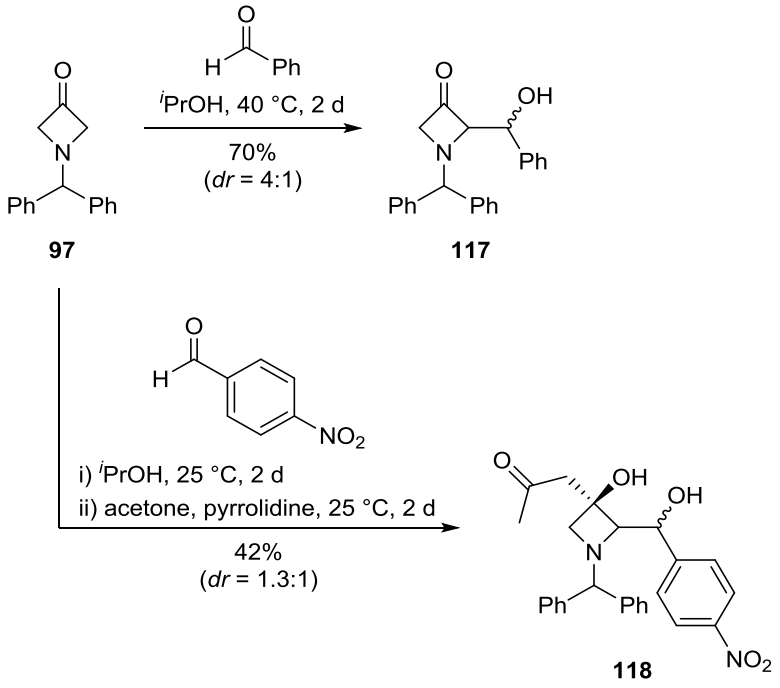
Whilst this approach offers a convenient route to 2-substituted azetidin-3-ones, an alternative method for the synthesis of 2,4-disubstituted derivatives was proposed by Maegawa *et al*.[70] Starting from the phosphonate ester **114**, base-induced cyclisation of the *N*,*P*-acetal formed ketone **115**. Sequential addition of benzaldehyde enabled **115** to undergo a Horner-Wadsworth-Emmons reaction, forming alkene **116** in 75% yield over two steps, and with moderate *E*/*Z* selectivity (Scheme 1.37).



114 **115** **116** (4.8:1, *E*/*Z*)

Scheme 1.37. Synthesis of **116** under Horner-Wadsworth-Emmons conditions.[70]

Several of these methods involve introduction of substituents prior to the heterocycle formation to synthesise substituted azetidin-3-ones. A very limited number of methods exist for the direct introduction of substituents onto pre-existing azetidine rings. Recently, Dobi *et al* developed an organocatalytic direct cross-aldol reaction to access such compounds, avoiding the need for preformed enol or "enolate-like" intermediates.[71] Starting from the ketone, **97** reacted with benzaldehyde in isopropanol to provide the 2-substituted product **117** in 70% yield and 4:1 diastereomeric ratio. Interestingly, ketone **97** could undergo an iterative cross-aldol and ketol sequence in one-pot to generate **118** in modest yields. Two diastereomers were formed and isolated from the reaction, albeit with poor diastereocontrol (Scheme 1.38).

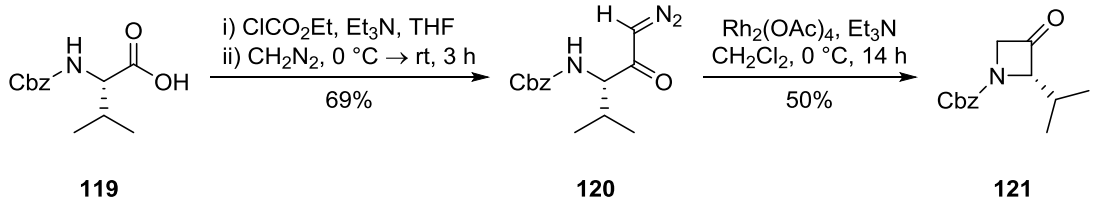


Scheme 1.38. Cross-aldol and ketol sequences of **97** to form 2-substituted azetidines.[71]

These examples are all based on 3-substituted azetidine scaffolds which are formed as racemates. In the context of drug discovery, where control of chirality is usually essential, access to enantiomerically pure 2-substituted azetidines is highly desirable. Currently, there are only a very limited number of methods for accessing such materials, and these are discussed below.

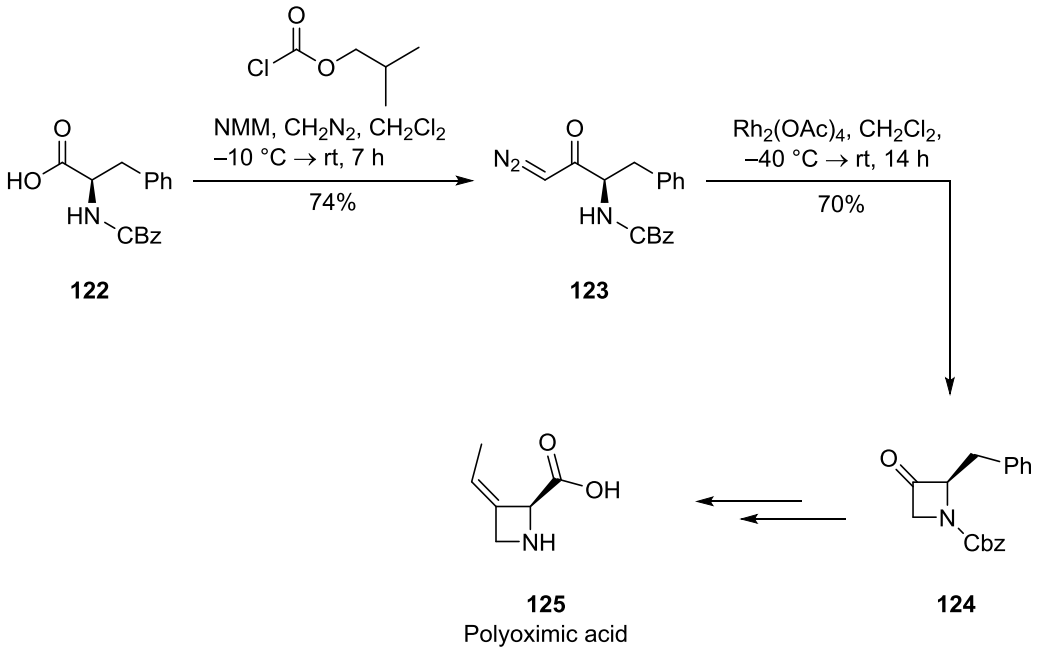
1.5.4 Asymmetric Synthesis of 2-Substituted Azetidin-3-ones

The stereocontrolled synthesis of chiral azetidin-3-one **121** from N-H insertion was first introduced by Seebach and co-workers, starting from diazoketone **120** derived from α-amino acid **119** (Scheme 1.39).[72] Moderate yields were obtained for the reactions, and further functionalisation of the keto group was demonstrated.



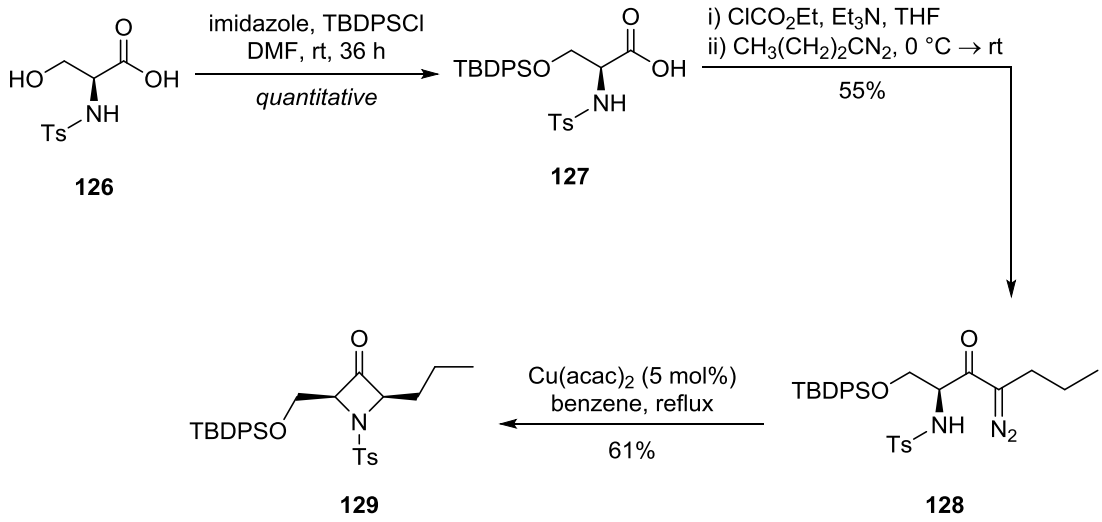
Scheme 1.39. Stereocontrolled synthesis of **121** using N-H insertion by Seebach and co-workers.[72]

Furthermore, Hanessian *et al* demonstrated the application of this methodology in the synthesis of polyoximic acid from enantiomerically pure amino acids. The synthesis of the four-membered nitrogen heterocycle from **123** was the key transformation in the synthesis of **125** (Scheme 1.40).[73]



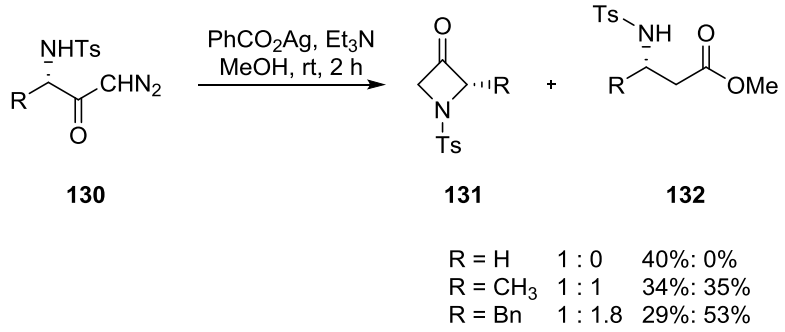
Scheme 1.40. Synthesis of polyoximic acid **125** using chiral diazoketones.[73]

Correia *et al* extended this methodology to the asymmetric formation of *cis*-2,4-dialkylsubstituted azetidin-3-one **129** using copper catalysis, as shown in Scheme 1.41.[74,75]



Scheme 1.41. Formation of *cis*-2,4-disubstituted azetidin-3-one **129**.[74]

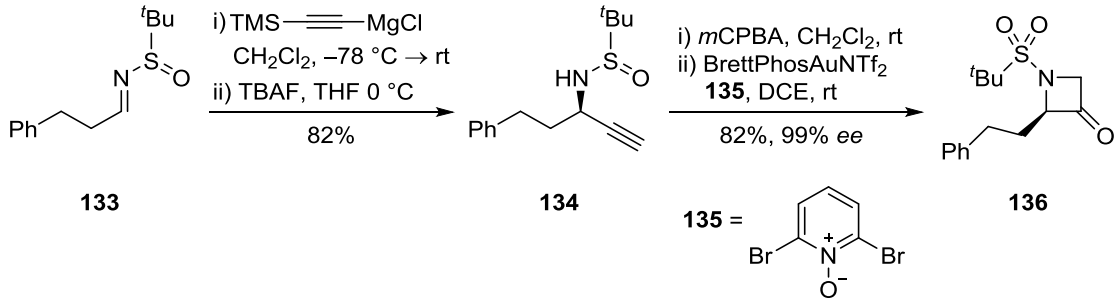
Silver catalysts have also been employed under Wolff rearrangement conditions to form the corresponding 2-substituted azetidin-3-ones (Scheme 1.42).[76] Using silver benzoate and triethylamine in methanol, the cyclisation proceeded with retention of configuration through nucleophilic attack on the intermediate ketene. The degree of steric bulk of the amino acid side chain in **130** impacted the ratio of the expected Wolff rearrangement product **132** to cyclised product **131** formed through direct N-H insertion.



Scheme 1.42. Silver-catalysed synthesis of **131** using Wolff rearrangement conditions.[76]

Whilst the approach using diazoketones is widely applicable, the yields are variable, and involve the use of toxic and potentially explosive diazo compounds. Moreover, substituents that can be introduced are largely those found in natural α-amino acids.

In 2010, Zhang and co-workers pioneered the introduction of gold-catalysed carbenes accessible by the oxidation of alkynes.[77] The group extended this work to form enantiomerically enriched azetidin-3-ones by gold-catalysed oxidative cyclisation of chiral *N*-propagylsulfonamides.[78] Using Ellman's method, enantiomerically enriched *tert*-butylsulfinamide **134** was readily formed by stereocontrolled ethynylation. Oxidation with *m*CPBA to the sulfonamide, followed by gold-catalysed cyclisation in the presence of *N*-oxide **135** formed ketone **136** with high enantioselectivity and good yields over the two steps (Scheme 1.43).

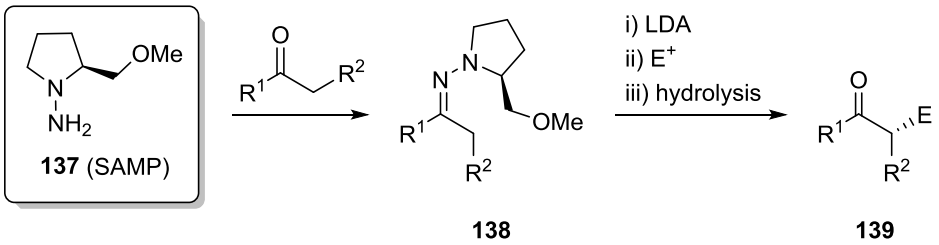


Scheme 1.43. Gold-catalysed oxidative cyclisation to form **136**.[78]

1.6 Research Aims

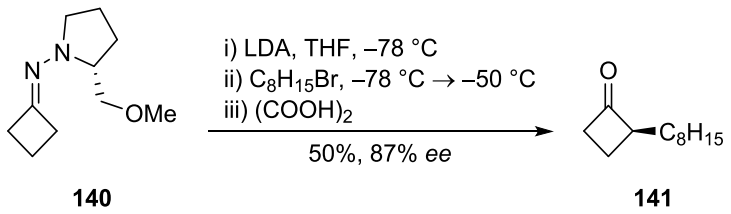
Whilst examples of azetidin-3-one syntheses are known, most of these scaffolds are inherently achiral, or require the installation of the chirality prior to their formation, as illustrated above. These approaches either have limited scope or involve multiple steps, neither of which provides a general method for their synthesis. With the limited access to 2-substituted azetidin-3-ones, we sought to develop a more flexible and direct approach to enantioenriched variants using Enders' SAMP/RAMP methodology. A brief introduction to this methodology precedes our own studies.

In 1976, Enders and co-workers pioneered the use of (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) and (*R*)-1-amino-2-methoxymethylpyrrolidine (RAMP) for the asymmetric synthesis of alkylated derivatives and α-substituted ketones **139** (Scheme 1.44).[79] A number of reviews have been published outlining the broad utility of this chemistry.[80]



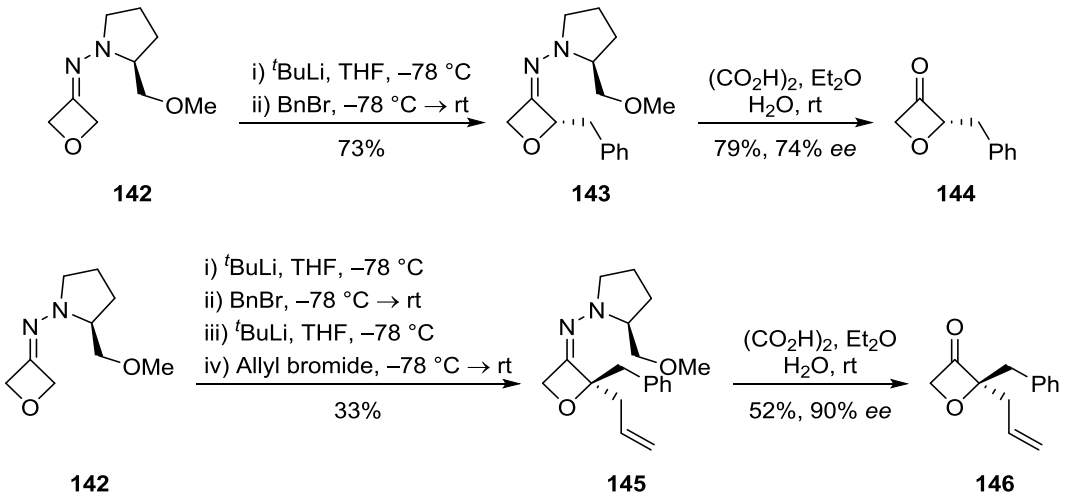
Scheme 1.44. Generalised use of SAMP hydrazone **137**.[80]

The application of this methodology to strained cyclic systems has been well documented. Hazelard and co-workers have demonstrated the synthesis of chiral cyclobutanones using RAMP auxiliary, to give **141** in moderate yields and good enantioselectivities (Scheme 1.45).[81]



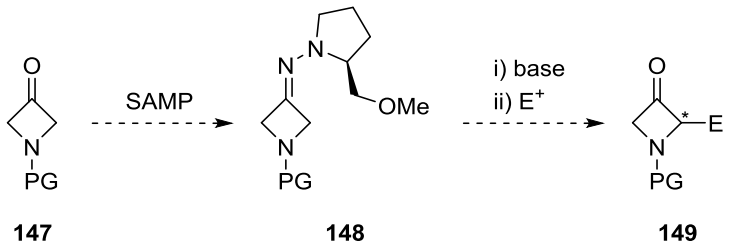
Scheme 1.45. Asymmetric synthesis of 2-substituted cyclobutanone **141**.[81]

This work was recently extended to include 2-substituted oxetan-3-ones in our group.[82] Using a two-step process, a range of 2-substituted derivatives were synthesised in good yields and enantioselectivities. This chemistry could also be used to make 2,2- and 2,4-disubstituted derivatives by repetition of the lithiation/alkylation sequence, demonstrating the power of this methodology to introduce quaternary centres (Scheme 1.46). The presence of the hydrazone protects the highly reactive carbonyl from nucleophilic attack and facilitates alkylation at the 2-position.



Scheme 1.46. Asymmetric synthesis of substituted oxetan-3-ones **144** and **146**.[82]

Based on this precedent, we were encouraged to apply this methodology to the synthesis of 2-substituted azetidin-3-ones (Scheme 1.47). The α-lithiation and alkylation of *N*-protected azetidines is well documented, providing further encouragement for this study.[83,84] We envisaged that access to compounds such as **149** could be achieved from the parent azetidin-3-one **147**, thereby offering a flexible enantioselective route to a wide range of derivatives, limited only by the availability of suitable electrophiles.



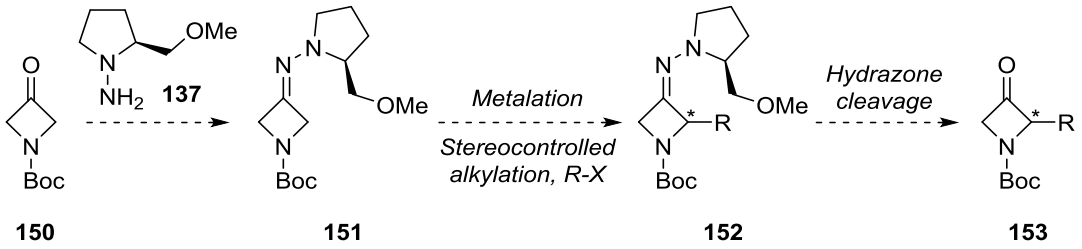
Scheme 1.47. Proposed route using Enders' SAMP auxiliary.

1.7 Results and Discussion

There are several key challenges to be addressed in the proposed methodology. A suitable nitrogen protecting group is required to direct lithiation to the α-position of the hydrazone, facilitate effective introduction of substituents and be readily removed. High levels of diastereocontrol are hoped to be achieved in the alkylation

step for a range of electrophiles, and mild hydrazone cleavage conditions are required to ensure no racemisation occurs and there is no concomitant cleavage of the protecting group. By addressing these factors, it is hoped that a general and efficient methodology can be achieved to form chiral 2-substituted azetidin-3-ones.

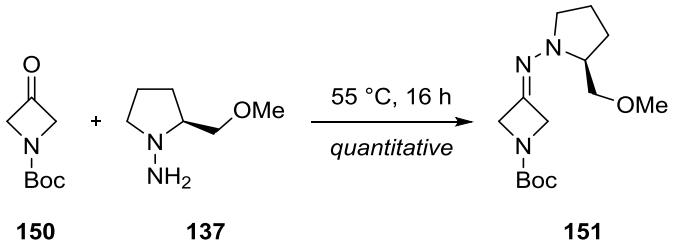
Our proposed route is outlined in Scheme 1.48. Starting from commercially available *N*-Boc azetidin-3-one **150** (£10/g),[85] condensation with Enders' SAMP auxiliary would provide hydrazone **151**. Subsequent metalation and stereocontrolled alkylation would provide the 2-substituted hydrazone **152**, which could then undergo cleavage of the auxiliary to reveal the asymmetric 2-substituted azetidin-3-one **153**.



Scheme 1.48. Proposed synthetic route to form **153**.

1.7.1 Formation of Hydrazone from Azetidin-3-one

Our initial studies centred on the use of *N*-Boc azetidin-3-one. Previously, it was demonstrated that the SAMP hydrazone of oxetan-3-one could be formed from the ketone: hydrazine in a 2:1 ratio in the absence of solvent.[82] Using these conditions, formation of the hydrazone proceeded smoothly with gentle heating to give **151** in quantitative yield. It was found that reducing the amount of ketone to 1.2 equivalents provided the product in the same yield with easier purification by column chromatography (Scheme 1.49).



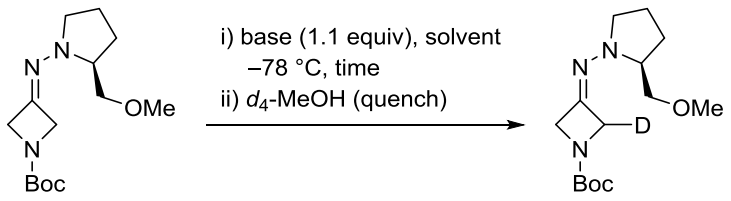
Scheme 1.49. Synthesis of hydrazone (*S*)-**151**.

Spectroscopic evidence confirmed the formation of hydrazone (*S*)-**151**. The ^{1}H NMR of **151** displayed a multiplet at 4.76−4.68 ppm for one ring hydrogen, with the remaining three hydrogens at 4.64−4.52 ppm, signifying the chemical inequivalence of the protons. The ^{13}C NMR indicated the presence of signals for the carbamate group (156.2 ppm) and C=N bond (135.9 ppm) respectively. Mass spectrometry confirmed the correct molecular weight of **151** (*m/z* = 284, $[M+H]^+$), with an optical rotation, $[\alpha]_D^{26}$ +23.4 (*c* 0.12, $CHCl_3$), indicating that the compound was enantiomerically enriched.

1.7.2 Metalation and Alkylation of Azetidine SAMP Hydrazone

With hydrazone **151** in hand, we next turned our attention to the metalation step to find the optimal conditions for this reaction. A variety of bases, solvents, metalation times and concentrations were screened. The lithiated intermediate was quenched with d_4-MeOH, and the percentage conversion of **151** to **154** assessed by mass spectrometry after purification by column chromatography (Table 1.1).

Initial efforts began with ^{t}BuLi as the base, as this was optimal for the synthesis of 2-substituted oxetan-3-ones. Using 1.1 equivalents of ^{t}BuLi in THF for a 2 h lithiation time gave 55% of **151**/**154**, with 84% conversion to **154** as determined by mass spectrometry (entry 1). Little evidence for the di-deuterated product was observed by mass spectrometry. Switching to LDA as the base proved less effective, with both lower recovery and conversion (entry 2). Using ^{t}BuLi, an increase in the metalation time to 3 h proved detrimental to the yield (entry 3), whilst a decrease to 1 h led to an increase to 73% yield (entry 4). These results suggested that the lithiated intermediate had moderate stability under the reaction conditions. Lowering the concentration to 0.1 M and reverting to 2 h lithiation time resulted in a further improvement to 77% yield, whilst maintaining the conversion (entry 6). A mixture of THF:pentane as solvent led to no improvement (entry 7), whilst switching to ^{n}BuLi as the base gave a satisfying 81% yield and a cheaper and safer alternative to ^{t}BuLi for the reaction (entry 8). These latter conditions with ^{n}BuLi proved optimal conditions for the lithiation step.



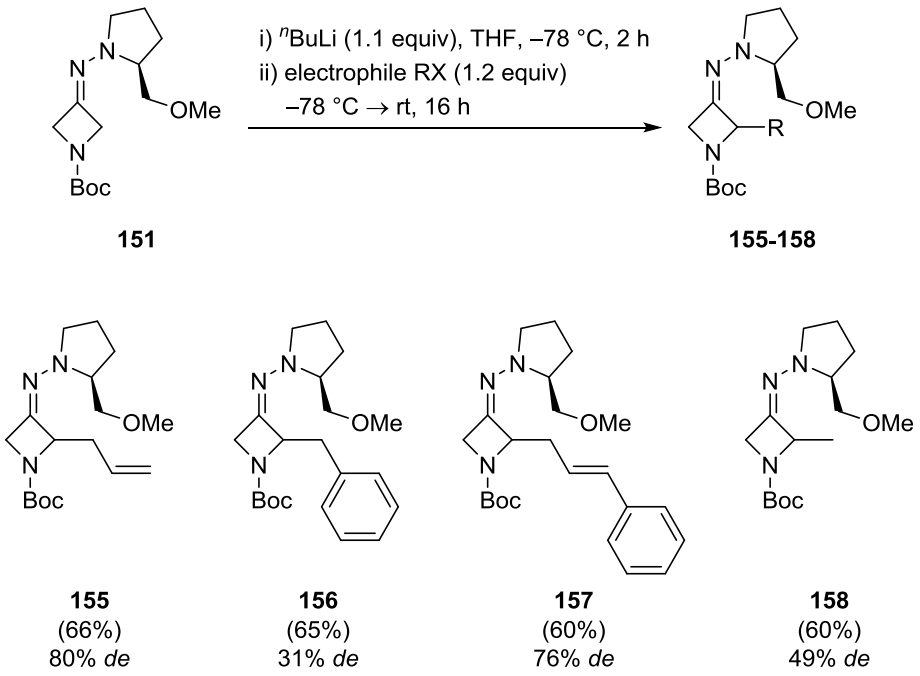
151 **154**

Entry	Base	Solvent	Time (h)	Concentration (M)	Yield (%)[a]	Conversion (%)[b]
1	^{t}BuLi	THF	2	0.3	55	84
2	LDA	THF	2	0.3	49	72
3	^{t}BuLi	THF	3	0.3	45	83
4	^{t}BuLi	THF	1	0.3	73	83
5	^{t}BuLi	THF	1	0.1	69	85
6	^{t}BuLi	THF	2	0.1	77	86
7	^{t}BuLi	THF: pentane (1:1)	2	0.1	67	86
8	^{n}BuLi	THF	2	0.1	81	84

Table 1.1. Optimisation of conditions for lithiation of **151**. [a]Isolated yield of **151** and **154** after column chromatography. [b]Determined by mass spectrometry.

With optimised lithiation conditions, alkylation of (*S*)-**151** was attempted with various electrophiles, quenching at –78 °C, and warming slowly to room temperature over 16 h. Using 1.2 equivalents of allyl bromide, the alkylated hydrazone **155** was obtained in an encouraging 66% yield after purification by column chromatography. Although **155** was isolated as a single spot by TLC during purification, an inseparable mixture of diastereomers was seen by ^{1}H NMR. The spectra revealed a 9:1 mixture of stereoisomers. At this point, it was unclear if the diastereomers arose from incomplete facial selectivity in the C–2 alkylation step, or from *E*/*Z* isomers about the C=N bond. The alkylation conditions were repeated using benzyl bromide, 3-bromo-1-phenyl-1-propene and iodomethane to give alkylated hydrazones **156**–**158** respectively in comparable yields (Scheme 1.50). Lower

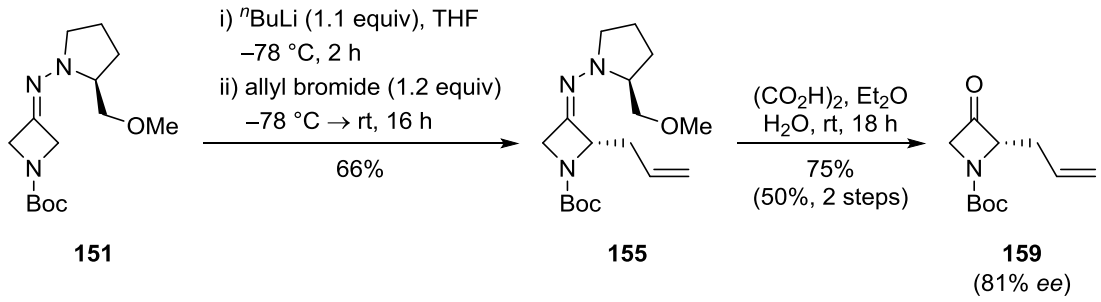
diastereoselectivities were observed for benzyl and methyl substituted derivatives **156** and **158**.



Scheme 1.50. Initial scope of the alkylation of (*S*)-**151**.

1.7.3 Hydrazone Cleavage

A variety of methods exist for the cleavage of the auxiliary.[80,86,87] Geden *et al* demonstrated the facile cleavage of the SAMP auxiliary from oxetan-3-ones using mild hydrolysis conditions (Scheme 1.46).[82] Thus, subjection of **155** to aqueous oxalic acid with vigorous stirring at room temperature for 18 h provided ketone **159** in 75% yield. The enantioselectivity of **159** was determined by chiral GC analysis, which revealed an 81% *ee* (Scheme 1.51). At this point, the stereochemistry of **159** was arbitrarily assigned based upon established models developed by Enders.[80]

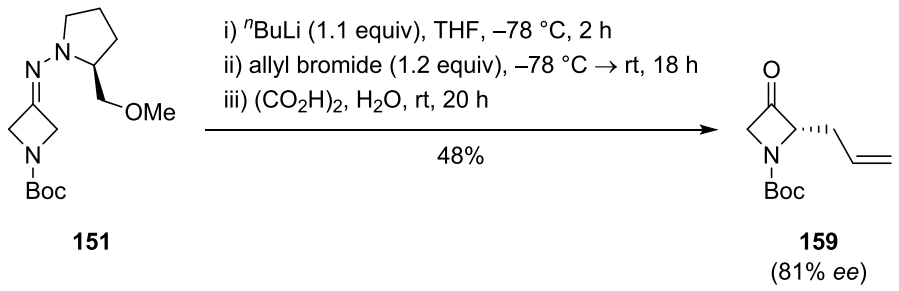


Scheme 1.51. Alkylation and subsequent hydrolysis of **151** to give ketone **159**.

The assignment of **159** was based upon spectroscopic analysis. ^{1}H NMR analysis revealed a multiplet at 5.01–4.87 ppm for the azetidine CH proton. The COSY showed coupling of this proton to the adjacent allylic CH_2 protons. The ^{13}C NMR displayed a downfield quaternary peak at 199.9 ppm for the carbonyl of **159**. A diagnostic IR band at 1822 cm^{-1} for the four-membered ring ketone was observed and is in agreement with previous reports of azetidin-3-one carbonyl stretches.[54]

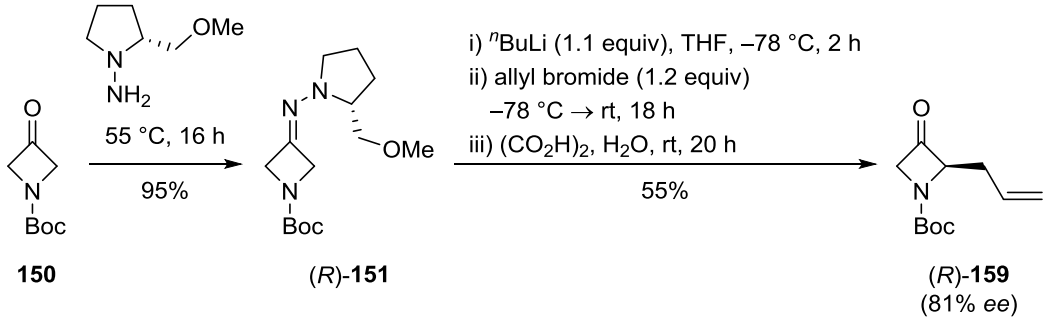
1.7.4 One-pot Synthesis of 2-Substituted Azetidin-3-ones

At this point, it was important to establish if all diastereomers from the stereoselective alkylation had been isolated during the purification of **155**, and then subsequently hydrolysed to give ketone **159**. Confirmation of this would establish that an accurate enantioselectivity for the alkylation process had been determined. Consequently, the alkylation reaction was repeated with direct hydrolysis of the crude material to give **159** in 48% overall yield over two steps, and 81% *ee* as confirmed by chiral GC. Since the minor diastereomer could not be removed by column chromatography, there was no benefit in isolating the intermediate hydrazone. It was therefore most convenient to conduct the one-pot process depicted in Scheme 1.52.



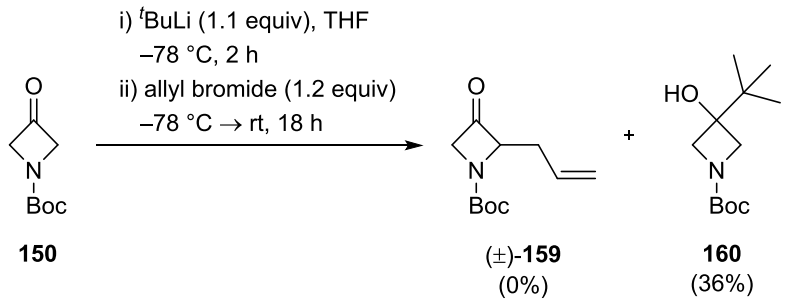
Scheme 1.52. One pot synthesis of (*S*)-**159**.

The opposite enantiomer (*R*)-**159** was prepared using RAMP derived hydrazone (*R*)-**151** in a similar fashion. This hydrazone was formed in 95% yield, with a slightly improved yield for the ketone (*R*)-**159** isolated in 55% yield *via* the one-pot process. Using previously established chiral GC conditions, the enantiomeric excess of (*R*)-**159** was confirmed to be 81% (Scheme 1.53).



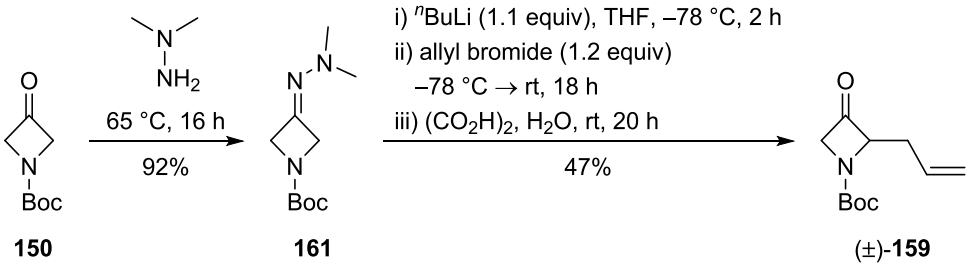
Scheme 1.53. One pot synthesis of (*R*)-**159** from hydrazone (*R*)-**151**.

For comparative purposes, an authentic racemic sample of **159** needed to be prepared. Direct formation of the racemic ketone was attempted by treating **150** with ^{t}BuLi at –78 °C, and subsequently trapping with allyl bromide. Upon work-up and purification, only carbinol **160** was isolated, resulting from direct addition of the organolithium to the ketone. No evidence for (±)-**159** was detected (Scheme 1.54). This result clearly illustrates the role the hydrazone plays in protecting the carbonyl C=O bond from nucleophilic addition in these reactions.



Scheme 1.54. Formation of carbinol **160** from the direct alkylation of **150**.

The use of *N*,*N*-dimethyl hydrazones to form azaenolates has been well documented.[86] Following this approach, we condensed *N*,*N*-dimethyl hydrazine with *N*-Boc azetidin-3-one **150** to form the achiral hydrazone **161** in high yield. Subsequent metalation, alkylation and hydrolysis using the same one-pot approach formed racemic **159** in 47% yield (Scheme 1.55). This material was used to establish the enantiomeric excess by chiral GC analysis (see Appendix I).

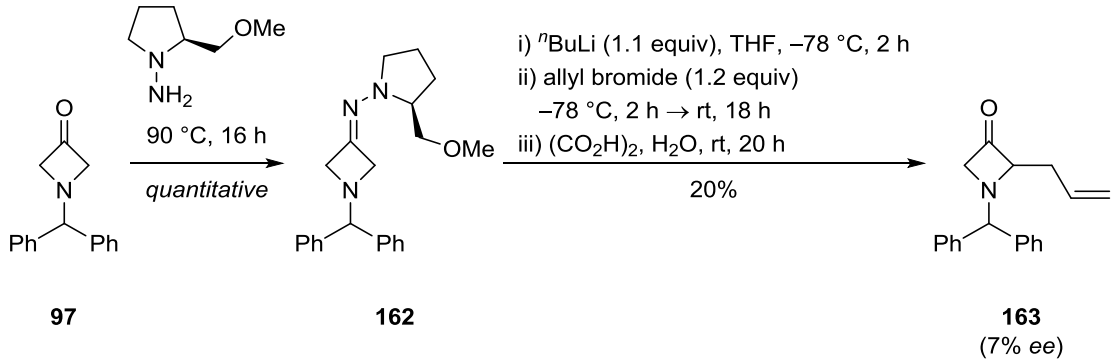


Scheme 1.55. Synthesis of achiral hydrazone **161** and racemic **159**.

1.7.5 Variation of the *N*-Protecting Group

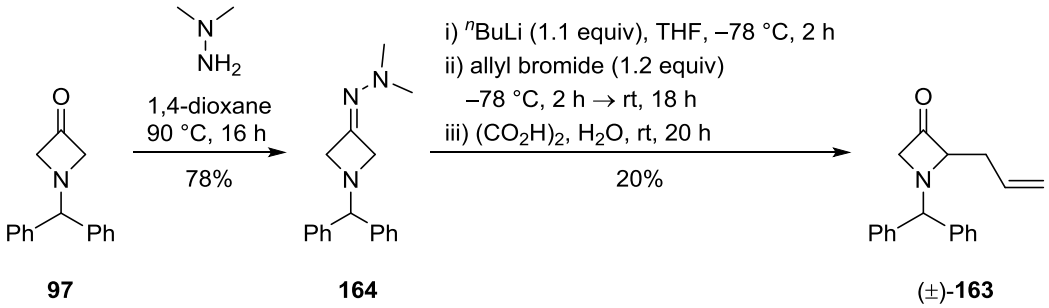
Although we had success with the Boc protecting group, we wanted to explore the use of alternative nitrogen protecting groups to potentially improve the levels of diastereoselectivity achieved. Such studies would also help to determine if the Boc group was playing a facilitating role in the lithiation reaction. With only a limited number of commercially available azetidin-3-ones, we next explored the benzhydryl protecting group as a possible alternative.

Hydrazone **162** was formed in quantitative yield from ketone **97** (£15/g)[88] by heating it at 90 °C for 16 h. Hydrazone **162** was then subjected to the one-pot alkylation hydrolysis sequence to give allylated ketone **163** in 20% yield (Scheme 1.56). No evidence of alkylation at the benzhydryl position was observed. The enantiomeric excess of **163** was determined to be just 7% *ee* by chiral HPLC. In this case, the sense of asymmetric induction was not established.



Scheme 1.56. Synthesis of **163** from the corresponding SAMP hydrazone **162**.

The corresponding racemic variant (±)-**163** was prepared from achiral hydrazone **164**, formed from *N*,*N*-dimethyl hydrazine (Scheme 1.57).

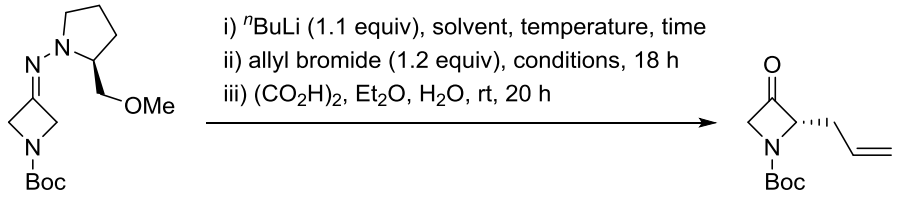


Scheme 1.57. Synthesis of racemic **163** from the corresponding hydrazone **164**.

With the lack of enantiocontrol and low yields for this reaction, it was clear that the Boc group is a better *N*-protecting group for this chemistry. In light of this result, no further experiments were performed using benzhydryl hydrazone **162**.

1.7.6 Optimising Enantioselectivity

With optimised lithiation conditions in hand and a method for determining the levels of enantiocontrol by chiral GC, we next turned our attention to optimising the enantioselectivity of the alkylation using Boc protecting group. A range of solvents, temperatures and conditions were screened, as shown in Table 1.2. Switching to diethyl ether as the solvent was detrimental to the yield (entry 2), whilst introduction of the additive TMEDA led to a drop in the *ee* (entry 3). A change in the solvent system to 1:1 THF:pentane promoted an increase in enantioselectivity to 85% *ee*, however, a slightly lower yield was obtained, suggesting slower lithiation (entry 4). Reverting back to THF as the solvent and performing the lithiation at higher temperatures gave no desired product (entries 5 and 6), indicating instability of the azaenolate at these temperatures. Maintaining the temperature at –78 °C for 2 h after electrophile addition led to a much improved yield of 67%, whilst retaining the same enantioselectivity as initially reported (entry 7). Yet, prolonging the time to 3 h led to a lower yield, indicating that a 2 h time seemed optimal (entry 8). As a mixture of solvents had previously shown an increase in enantioselectivity, maintaining the temperature at –78 °C for 2 h in a THF:pentane solvent mixture was tested. Although an increase in *ee* was observed for a lithiation time of 1 h, a significant drop in yield occurred (entry 9). A similar yield was obtained for a 3 h lithiation time, although a loss of *ee* was observed (entry 10). Performing the lithiation and alkylation at –90 °C in THF led to no improvement (entry 11). Based on these observations, using THF as the solvent and performing the lithiation at –78 °C for 2 h, followed by a 2 h hold at –78 °C after electrophile addition (entry 7) seemed optimal, offering good yields and levels of enantiocontrol.



151 **159**

Entry	Solvent	Lithiation Temperature (°C)	Time (h)	Alkylation Temperature (°C)	Yield (%)[a,b]	*ee* (%)[c]
1	THF	–78	2	–78 °C to rt	48	81
2	Et_2O	–78	2	–78 °C to rt	26	79
3	THF, TMEDA[d]	–78	2	–78 °C to rt	44	74
4	THF: pentane (1:1)	–78	2	–78 °C to rt	42	85
5	THF	–78 to –40	2	–78 °C to rt	0	-
6	THF	–40 to –78	2	–78 °C to rt	0	-
7	THF	–78	2	–78 °C, 2 h then rt	67	81
8	THF	–78	2	–78 °C, 3 h then rt	46	81
9	THF: pentane (1:1)	–78	1	–78 °C, 2 h then rt	25	89
10	THF: pentane (1:1)	–78	3	–78 °C, 2 h then rt	26	77
11	THF	–90	2	EA, –90 °C to rt	30	71

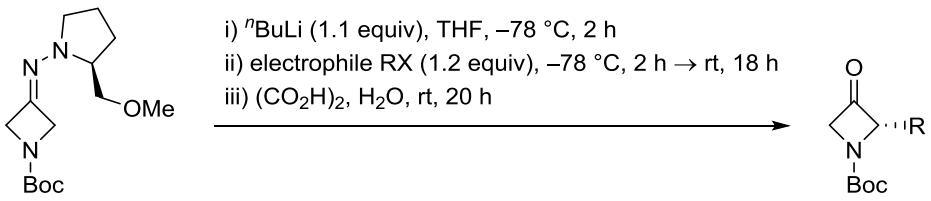
Table 1.2. Optimisation of yield and enantioselectivity for (*S*)-**159**. [a]Each reaction was repeated twice and the highest yield reported. [b]Remainder of the mass balance revealed unknown products. [c]Enantioselectivity determined by chiral GC analysis. Each chiral GC was repeated twice and the highest enantioselectivity reported. [d]1.1equiv. of TMEDA added.

1.7.7 Establishing Scope of the Reaction

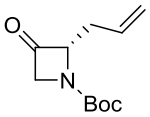
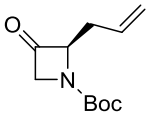
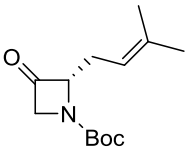
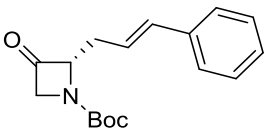
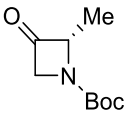
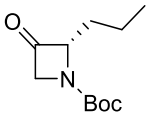
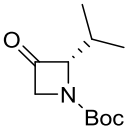
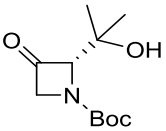
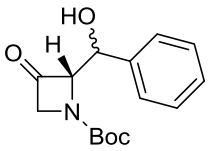
Having established suitable conditions for the one-pot synthesis of **159** from (*S*)-**151** in good yield and high enantioselectivity, we sought to establish the scope of the

alkylation step and subsequent *in situ* hydrolysis. The enantiomeric excess of **165**–**173** was determined using either chiral GC or HPLC analysis. In each case, the racemic analogue was made for comparison purposes from achiral hydrazone **161**. However, these alkylations were less efficient than with SAMP/RAMP hydrazones, owing to the lack of directing group (see Section 1.7.10). A representative range of electrophiles was screened, and the results are presented in Table 1.3.

Additional allyl bromides were found to react in good yields and high selectivities of up to 81% *ee* (entries 3 and 4). Both primary and secondary alkyl iodides reacted well, with the observed enantioselectivity reflecting the steric demand of the electrophile. Using the smaller iodomethane, a moderate 41% yield and 51% *ee* was obtained (entry 5). Further experiments and purification of the electrophile by passing it through a column of activated alumina prior to addition led to no improvement. Comparable yields were obtained for the propyl and isopropyl variants (entries 6 and 7), with 85% *ee* obtained for the more sterically demanding electrophile. Carbonyl electrophiles worked well under these conditions, achieving good yields and levels of enantiocontrol as seen with acetone as electrophile (entry 8). However, low selectivity was observed with benzaldehyde (entry 9). An inseparable 1.5:1 mixture of diastereomers was obtained in this case, with the enantiomeric excess of the diastereomers determined to be 31% and 17% respectively. The lower selectivity of **171** may be attributed to the lone pair of the carbonyl *anti* to the aryl group coordinating to the lithium of the azaenolate, displacing the methoxy group of the SAMP auxiliary and resulting in a loss of stereochemical influence. However, with acetone the lone pairs are less sterically accessible due to the methyl groups either side, therefore restricting the ability for it to bind. A similar observation was made with oxetan-3-ones.[82] Low enantioselectivity was observed with benzyl bromide (entry 10), and the more reactive *para*-methoxybenzyl chloride (entry 11). This suggested a different mechanism may be operating for these benzylic halides, perhaps *via* electron transfer.



151

Entry	Electrophile	Product	X	Yield (%)	*ee* (%)
1	CH_2=$CHCH_2Br$		**159**	67	81[a]
2	CH_2=$CHCH_2Br$[b]		**159**	55	81[a]
3	$(CH_3)_2C$=$CHCH_2Br$		**165**	53	81[a]
4	PhCH=$CHCH_2Br$		**166**	74	77[c]
5	CH_3I		**167**	41	51[a]
6	$CH_3CH_2CH_2I$		**168**	50	79[a]
7	$(CH_3)_2CHI$		**169**	52	85[a]
8	$(CH_3)_2CO$		**170**	59	78[c]
9	PhCHO		**171**	71	31, 17[c,d]

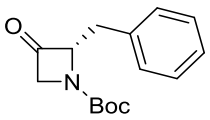
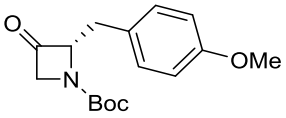
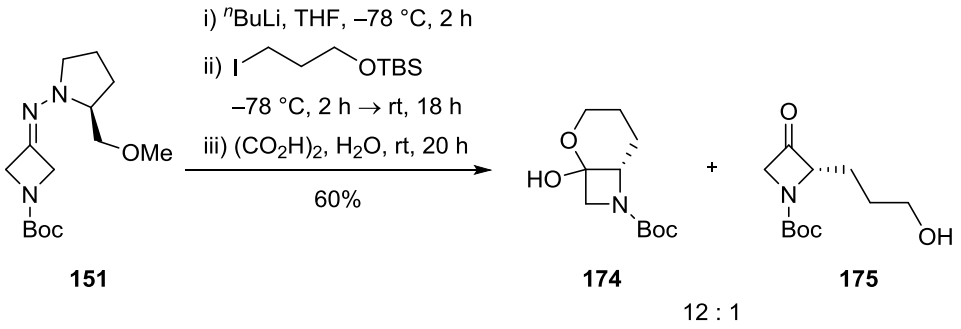
10	$PhCH_2Br$		**172**	57	33[c]
11	$CH_3OC_6H_4CH_2Cl$		**173**	9	33[c]

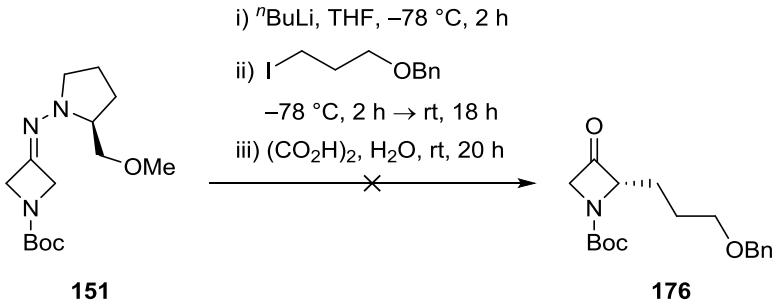
Table 1.3. Stereoselective synthesis of azetidin-3-ones. [a]Enantioselectivity determined by chiral GC analysis. [b](*R*)-**151** was used. [c]Enantioselectivity determined by chiral HPLC analysis. [d]Isolated as an inseparable 1.5:1 mixture of diastereomers.

When hydrazone (*S*)-**151** was subjected to the one-pot reaction conditions with TBS protected iodide, a mixture of cyclic acetal **174** and alkylated **175** was isolated in a 12:1 ratio respectively (Scheme 1.58). Product **174** arose from alkylation, hydrolysis, removal of the TBS protecting group and cyclisation. The products were inseparable by column chromatography, and a complex mixture was observed by chiral HPLC analysis. Further derivatisation by treating the mixture with Ac_2O/Et_3N failed to enable separation of the peaks.



Scheme 1.58. Formation of cyclic acetal **174** and alkylated **175**.

In order to prevent the complications arising from deprotection and cyclisation, the electrophile was switched to ((3-iodopropoxy)methyl)benzene. Unfortunately, when **151** was subjected to the reaction conditions a complex mixture was observed with no evidence for product formation or **151**. (Scheme 1.59). Failure was also witnessed using *tert*-butyl bromoacetate, 1-bromo-2-butyne or trimethylacetaldehyde as the electrophile, with unidentifiable decomposed mixtures obtained.



151 **176**

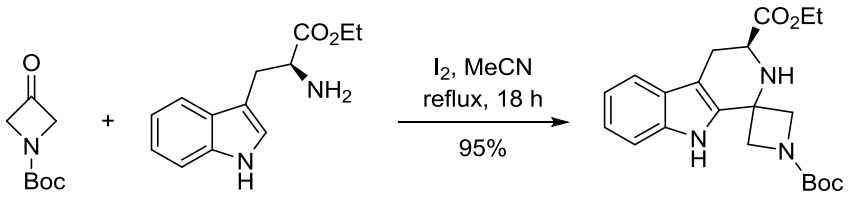
Scheme 1.59. Attempted synthesis of **176**.

Having established the scope of this chemistry, we next turned our attention to establishing the absolute configuration of these 2-substituted azetidin-3-ones.

1.7.8 Determination of Sense of Asymmetric Induction

The Pictet-Spengler reaction has recently been used to form tetrahydro-*β*-carbolines using iodine as a catalyst, forming spirocyclic compounds with four-membered ring ketones.[82,89] By using a chiral tryptophan derivative of known absolute configuration, we hoped to use this method to establish the configuration at C–2 of the new 2-substituted azetidin-3-ones.

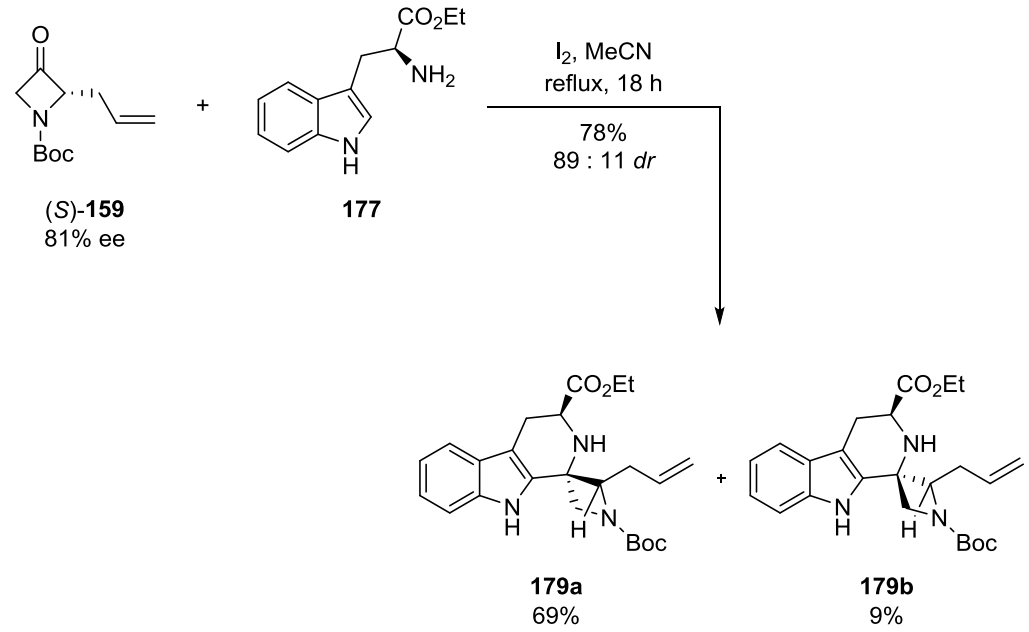
We initially reacted *N*-Boc-azetidin-3-one **150** with *L*-tryptophan ethyl ester **177** to test the suitability of this reaction for our substrates. Indeed, the reaction proceeded well to give spirocycle **178** in high yield (Scheme 1.60).



150 **177** **178**

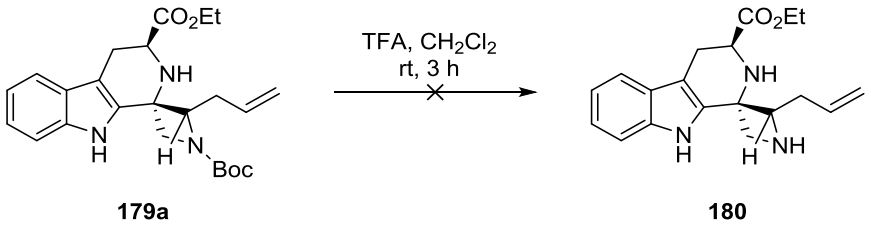
Scheme 1.60. Pictet-Spengler reaction of **150**.

In light of this success, we decided to subject our 2-substituted azetidin-3-ones to these reaction conditions. Compound (*S*)-**159** was subjected to the reaction conditions to give a diastereomeric mixture of two products in 89:11 ratio as determined by ^{1}H NMR analysis, broadly reflecting the enantioselectivity of (*S*)-**159** (81% *ee*). Purification by column chromatography afforded a separable mixture of the diastereomers **179a**/**179b** in 69% and 9% yields respectively (Scheme 1.61). Both products were isolated as solids, however, all attempts to grow single crystals suitable for X-ray crystallography from a variety of solvent systems failed.



Scheme 1.61. Pictet-Spengler reaction of (*S*)-**159** to give diastereomers **179a**/**179b**.

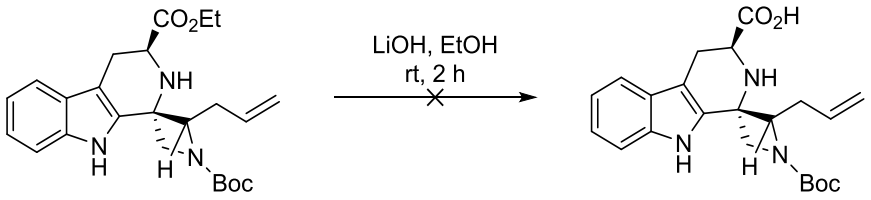
With the lack of success for crystal formation, deprotection of the Boc group of **179a** was attempted using standard conditions with TFA. Evidence of a more polar compound was observed by TLC, and no starting material detected by mass spectrometry. However, a complex mixture of products was isolated, with no signs of product **180** formation upon analysis by ^{1}H NMR (Scheme 1.62).



179a **180**

Scheme 1.62. Attempted deprotection of the Boc group in **179a**.

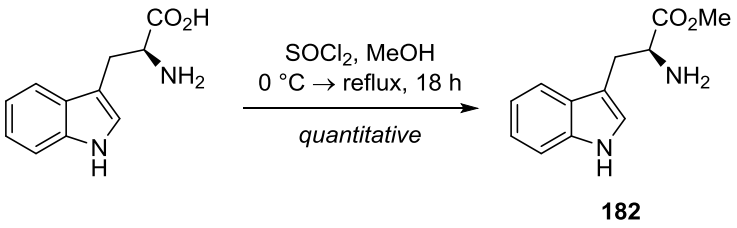
Hydrolysis of the ester group to acid **181** was performed using LiOH and monitored by TLC. Once again, a complex mixture of products was isolated upon work-up, with no evidence for **181** (Scheme 1.63).



179a **181**

Scheme 1.63. Attempted ester hydrolysis of **179a**.

At this point, it seemed substrate **159** was not suitable for determining the absolute configuration for this new class of compounds. It was believed that the ethyl substituent was encouraging disorder through rotation about the C–C bond, hampering crystallisation. We next decided to switch to the methyl ester to limit such rotations. From *L*-tryptophan, the corresponding methyl ester **182** was formed in quantitative yield by reaction of the acid in thionyl chloride for 18 h (Scheme 1.64).[90]

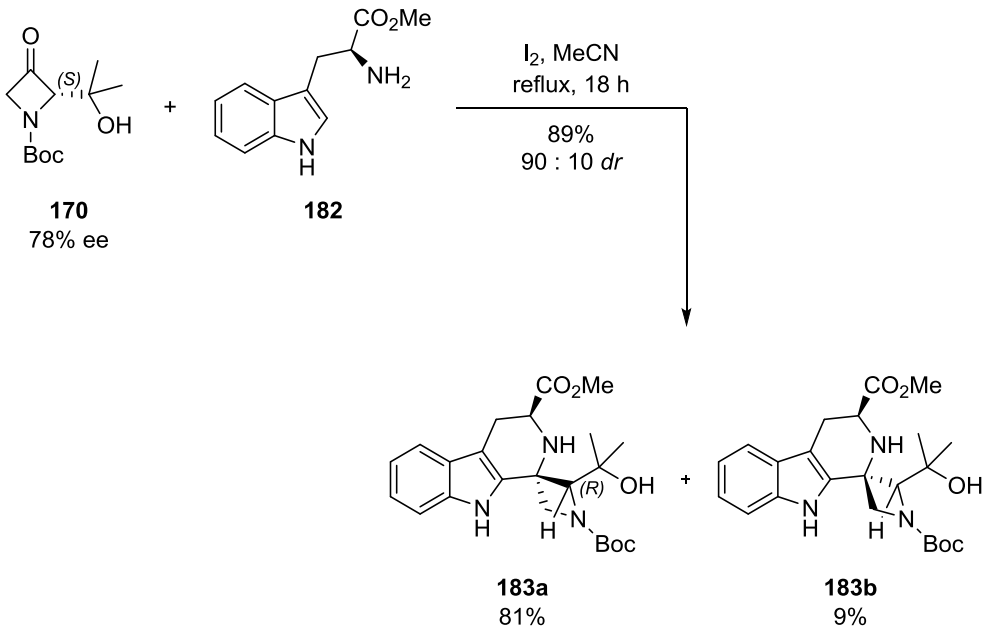


182

Scheme 1.64. Synthesis of *L*-tryptophan methyl ester **182**.[90]

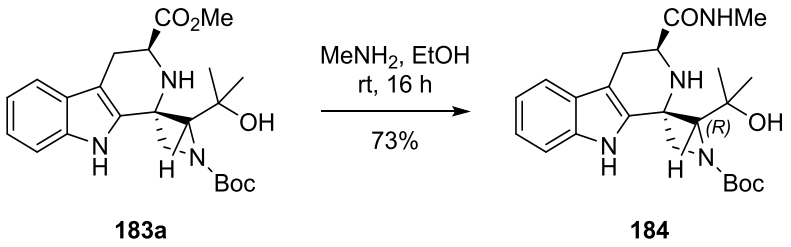
Furthermore, we switched from the allyl substituent to the alcohol for further reactions. The introduction of a hydrogen bonding group may further help to implant more order in the solid state, enabling crystal formation.

A Pictet-Spengler reaction was performed on alcohol **170** using *L*-tryptophan methyl ester **182** under the same reaction conditions as reported above. Satisfyingly, two diastereomers were isolated following purification in 81% and 9% yield respectively. The product ratio (90:10) reflected the enantiomeric ratio determined by chiral GC analysis of ketone **170** (89:11 *er*), and was in agreement with the crude diastereomeric ratio (90:10 *dr*) of the reaction as determined by ^{1}H NMR. This provided evidence that no racemisation is occurring during the Pictet-Spengler cyclisation (Scheme 1.65).



Scheme 1.65. Pictet Spengler reaction of **170** to give diastereomers **183a**/**183b**.

Various techniques were employed to encourage crystal growth formation but with no success. Working with co-worker Dr Joanna Geden, the major diastereomer **183a** was treated with a 33% solution of methylamine in ethanol, and converted to give secondary amide **184** as a crystalline solid (Scheme 1.66).



183a **184**

Scheme 1.66. Formation of amide **184**.

Gratifyingly, suitable crystals were grown of **184** from methanol, and an X-ray crystal structure obtained (Figure 1.7). Analysis of **184** revealed the relative orientation of the substituents, and hence unambiguously determined the (*S*)-configuration of the azetidine C–2 stereocentre of **170**. The hindered alcohol tertiary centre was shown to be positioned on the opposite face to the indole unit, and away from the amide substituent. Hydrogen bonding was observed between the hydrogen of the alcohol moiety and the oxygen of the carbamate protecting group, locking the orientation of **184** into its preferred configuration. The sense of asymmetric induction in the other alkylations reported herein was made by analogy to this example.

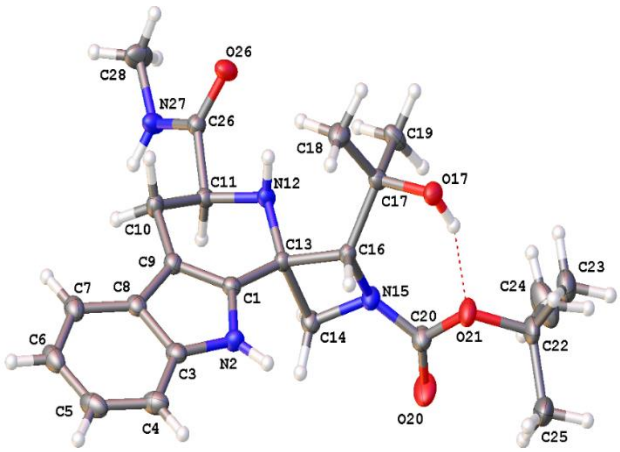
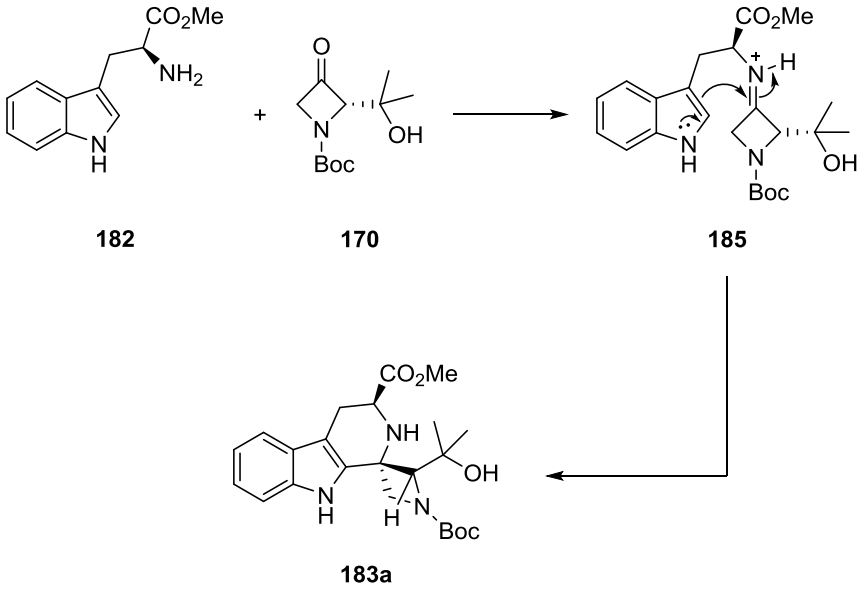


Figure 1.7. X-ray crystal structure of **184**.

During the Pictet-Spengler cyclisation, two new stereocentres are generated, which could result in the formation of four diastereomers. Initial condensation of tryptophan **182** and azetidin-3-one **170** forms imine **185**, with both diastereomer products **183a** and **183b** arising from the new C–C bond being formed *anti* to the

C–2 substituent on the azetidine ring. This in turn, results in the formation of only two diastereomers from the cyclisation, with the major diastereomer depicted in Scheme 1.67. The configuration of the minor diastereomer depicted is based upon this analogy. In the case of oxetan-3-ones, similar observations were made.[89]

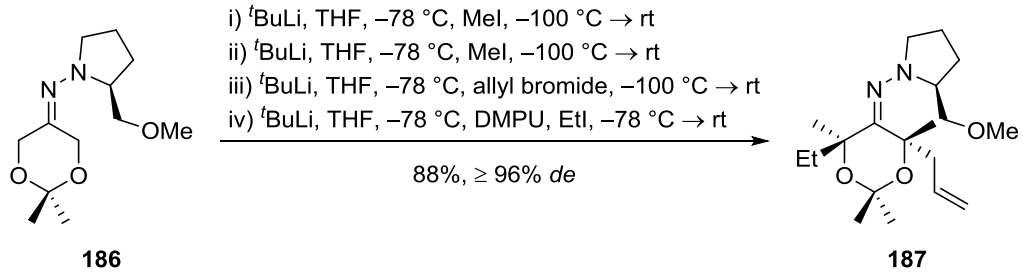


Scheme 1.67. Pictet-Spengler cyclisation to form major diastereomer **183a**.

Having achieved stereoselective monoalkylation of azetidin-3-ones with a good range of electrophiles and established the absolute configuration of the newly formed stereocentre, we next turned our attention to the possibility of making disubstituted derivatives.

1.7.9 Attempted Synthesis of Disubstituted Derivatives

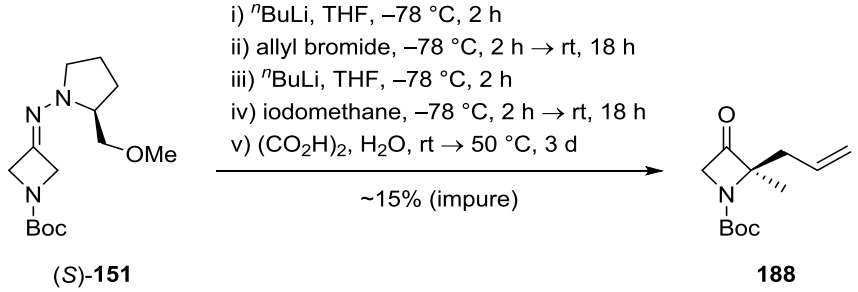
When Enders' established the work using SAMP as an auxiliary, many alkylation reactions were investigated. Enders and co-workers demonstrated that this process can be repeated multiple times on all possible sites, until full substitution is achieved (Scheme 1.68).[91]



Scheme 1.68. Synthesis of tetrasubstituted **187** by Enders *et al*.[91]

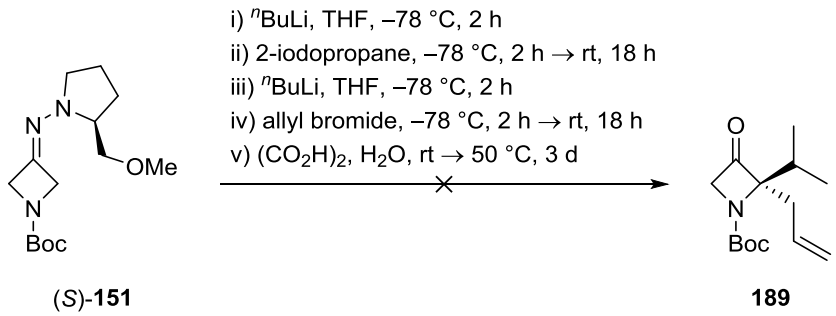
This concept was adapted by Geden *et al* to synthesise 2,2-disubstituted oxetan-3-ones with high enantiocontrol following cleavage of the auxiliary (Scheme 1.46). This was the first example of a tetrasubstituted centre generated from an α-CH_2 unit where no prior monoalkylation of an alternate site was needed.[82]

Following on from this, we explored the possibility of multiple alkylations of the azetidin-3-one core by repetition of the deprotonation/alkylation sequence. Hydrazone (*S*)-**151** was treated with ^{n}BuLi and quenched with allyl bromide, then further subjected to ^{n}BuLi and iodomethane before hydrolysis with aqueous oxalic acid (Scheme 1.69). A complex mixture of products was obtained, with **188** isolated in an impure state in *ca*. 15% yield. Evidence for **188** was indicated by the presence of an AB pattern for the ring protons by ^{1}H NMR, and an additional quaternary centre in the ^{13}C NMR spectra. Mass spectrometry confirmed the correct molecular weight of **188** (*m/z* = 226, $[M+H]^+$). No evidence for alkylation at C–4 was detected. Attempts to isolate the alkylated hydrazone prior to hydrolysis proved unproductive.



Scheme 1.69. Repetition of deprotonation/alkylation to synthesise 2,2-disubstituted **188**.

Switching the first electrophile to 2-iodopropane was expected to improve the yield, since it was known to be a good electrophile in this chemistry (Table 1.3, entry 7, pg. 56). However, these efforts were not successful either (Scheme 1.70).

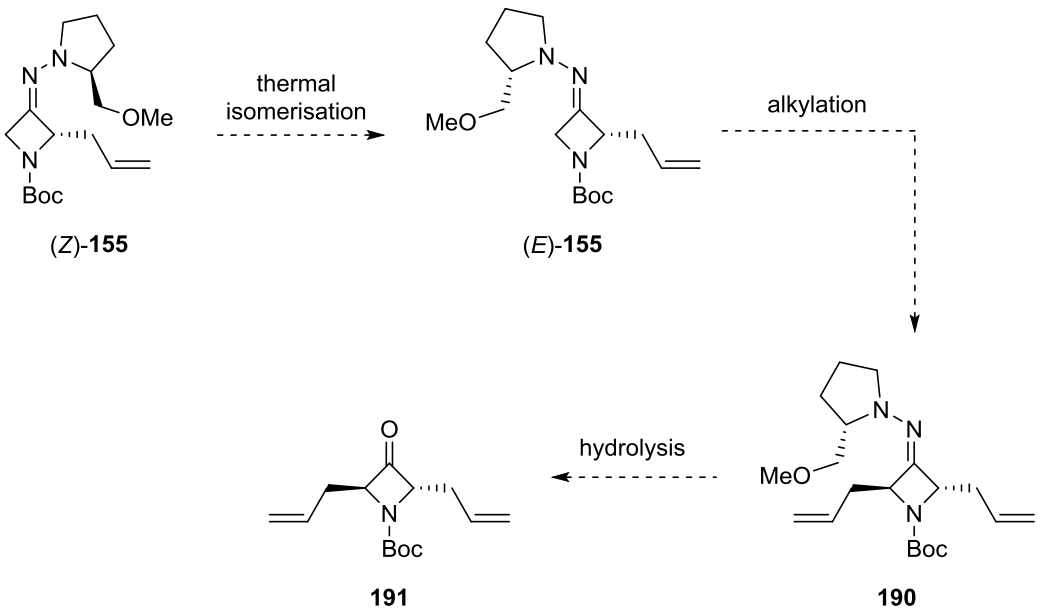


(*S*)-**151** **189**

Scheme 1.70. Attempted synthesis of **189** using 2-iodopropane.

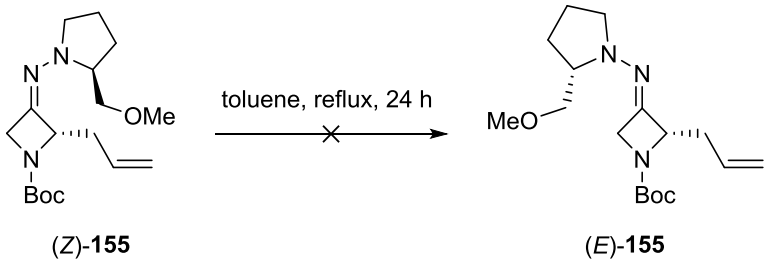
In comparison to the oxetane series (Scheme 1.46), we were disappointed to find that these reactions proved less fruitful for azetidin-3-ones. A possible explanation is that the steric bulk of the Boc group inhibits the second lithiation. Thus, the organometallic may be attacking the Boc group resulting in side reactions. In hindsight, it perhaps would have been fruitful to try the second lithiation with a more powerful base such as ^{t}BuLi.

We next turned our attention to the formation of 2,4-disubstituted compounds, based on the work with oxetanes. It was envisaged that alkylated hydrazone (*Z*)-**155** could undergo thermal isomerisation to provide (*E*)-**155**. Under the optimised alkylation conditions, it was hoped that **190** would be formed, which would lead to C_2-symmetric ketone **191** after hydrolysis (Scheme 1.71).



Scheme 1.71. Proposed route to chiral C_2-symmetric 2,4-disubstituted **191**.

The first step began with the thermal isomerisation of the allylated hydrazone (*Z*)-**155**, by heating it in toluene under reflux. The reaction was monitored by TLC and ^{1}H NMR, however, a complex mixture was formed, with no evidence of isomerisation of the C=N bond (Scheme 1.72). It is possible that the Boc group is thermally unstable under these reaction conditions resulting in decomposition of the material. The level of pyramidalization of the nitrogen atom in the X-ray structure of **184** (Figure 1.7) was calculated to be 9.34°, indicating imperfect trigonal geometry of the nitrogen atom. This suggests there is little overlap between the lone pair on the nitrogen and the carbonyl, which might lead to poorer stability of the Boc group.



Scheme 1.72. Attempted thermal isomerisation of (*Z*)-**155**.

With no success obtained for this isomerisation, this work was abandoned.

1.7.10 Mechanistic Insights

Since the discovery of the SAMP auxiliary by Enders in 1976, extensive research has been undertaken to determine the mechanistic details of the transformation, and to understand the stereochemical outcome of the reaction.[92] Deprotonation of the hydrazone by lithium bases results in the formation of azaenolates, of which four geometric isomers are theoretically possible. Spectroscopic analysis revealed that the lithium anion coordinates to both the nitrogen of the auxiliary, and the oxygen of the methoxy substituent, with two possible sites for electrophilic attack to give diastereomerically enriched compounds (Figure 1.8).[93–95]

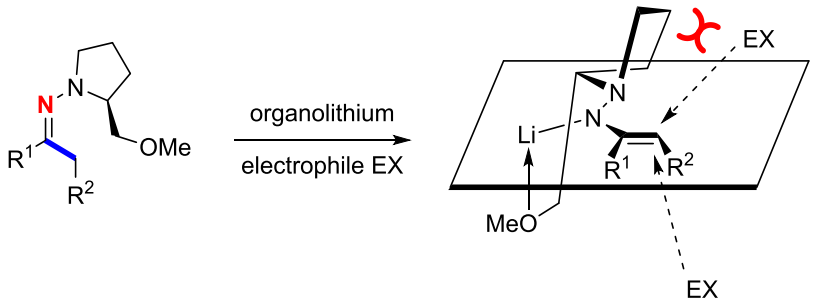


Figure 1.8. Proposed lithium coordination of hydrazone alkylation.[94]

Two sites for lithium chelation are possible. The lithium atom can either be antiperiplanar to the C=C bond forming the $Z_{C\text{-}N}$ conformer (A/B), or the lithium and the C=C are orientated to the same side, adopting the $E_{C\text{-}N}$ conformer (C/D) (Figure 1.9). Alongside the *E*/*Z* geometry of the C–N bond, two further geometric isomers exist about the C=C bond, where the *N*-chelating auxiliary can be on the same side or opposite side of the R^2 group. Of course, for cyclic systems, B and D are not relevant as one has to constrain it within a ring whereby R^1 and R^2 groups are *cis* to one another. Conformational studies and X-ray analysis have indicated that the $E_{C=C}Z_{C\text{-}N}$ conformation (A) is preferred out of the isomers, due to steric restrictions disfavouring the other configurations.[93,94]

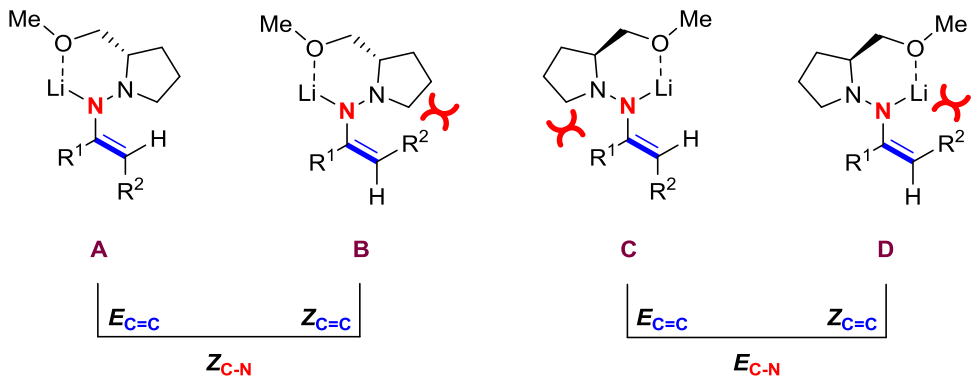
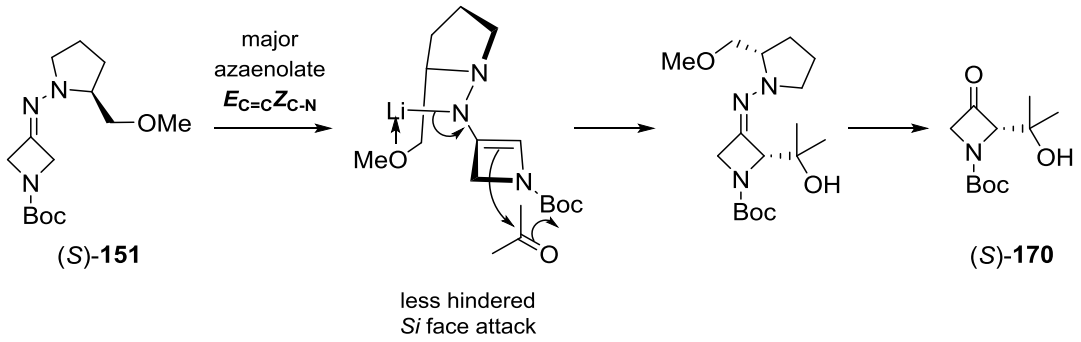


Figure 1.9. Four possible isomers from lithium chelation.

The stereochemical outcome of the reactions to form 2-substituted azetidin-3-ones was based by analogy to the studies conducted by Enders and co-workers. The major azaenolate should arise from the $E_{C=C}Z_{C-N}$ conformation (A), whereby the lithium atom is intramolecularly coordinated to the methoxy group of the auxiliary, forming a conformationally rigid structure. This should allow for preferential attack of the electrophile from the less sterically hindered *Si* face to give the stereochemistry observed stereoisomer (Scheme 1.73).

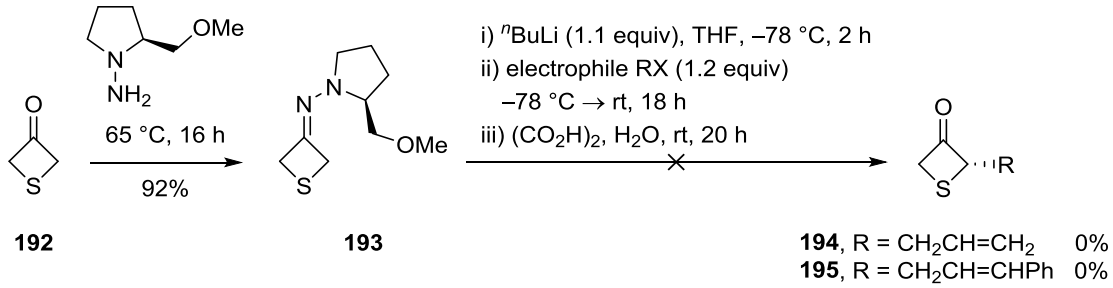


Scheme 1.73. Proposed mechanism for formation of the major enantiomer of (*S*)-**170**.

The role of the Boc group could be assisting to make deprotonation easier by directing the lithiation, and subsequently allowing the effective introduction of substituents. This is consistent with our observation of lower yields and enantioselectivities with the benzhydryl protecting group (Scheme 1.56).

1.7.11 Attempted Synthesis of 2-Substituted Thietan-3-ones

With the success achieved functionalising oxetan-3-ones and azetidin-3-ones using SAMP hydrazone, we briefly sought to examine if sulphur based thietan-3-ones could also be functionalised in this way. Using the established method, the corresponding hydrazone **193** was formed in high yield. When **193** was deprotonated with ^{n}BuLi at –78°C in THF then quenched with allyl bromide, no evidence for product formation was observed after hydrolysis. Due to the potential volatility of **194**, we switched to the heavier electrophile to form **195**. However, again no signs of product formation were seen by crude ^{1}H NMR or mass spectrometry (Scheme 1.74).



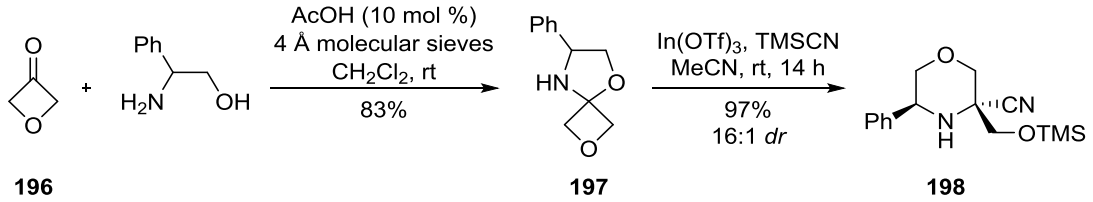
Scheme 1.74. Attempted synthesis of alkylated derivatives from SAMP thietane-3-one **192**.

A possible explanation for the results could be the difficulty for the organolithium to deprotonate at the carbon centre, or the thietan-3-one is relatively unstable to acid under the hydrolysis conditions. Alternatively, since the C–S bond is presumably weaker, complications from ring cleavage by attack of the base may be arising. In hindsight, the reaction should also have been attempted using ^{t}BuLi, however, no further experiments were carried out exploring alternative bases and reaction conditions.

1.8 Application to Fused Heterocyclic Systems

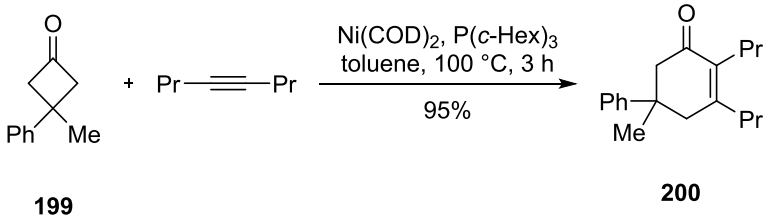
Four-membered rings have been shown to undergo metal catalysed transformations to form ring expanded products owing to their intrinsic ring strain. Recently, Carreira and co-workers outlined the diversity of heterocycles that can be formed from the oxetan-3-one derivatives.[96] Reaction of ketone **196** with amino compounds afforded

spirocycles, whose exposure to an indium catalyst and a nucleophile enabled ring expansion to morpholines with high diastereoselectivity (Scheme 1.75).



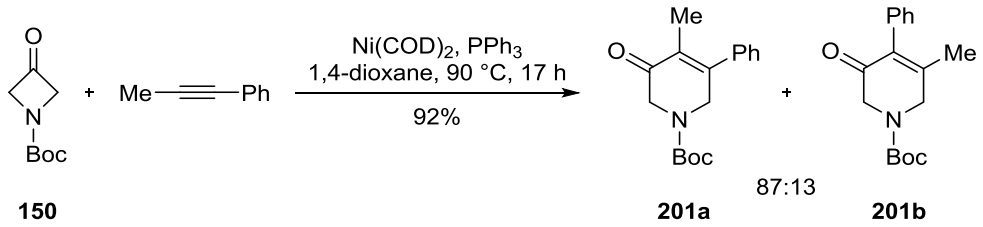
Scheme 1.75. Ring expansion of spirocyclic oxetan-3-one **197** to form morpholine **198**.[96]

In 2005, Murakami and co-workers reported that 3,3-disubstituted cyclobutanones can undergo alkyne insertion in the presence of a nickel catalyst to give six-membered rings in excellent yields (Scheme 1.76).[97]



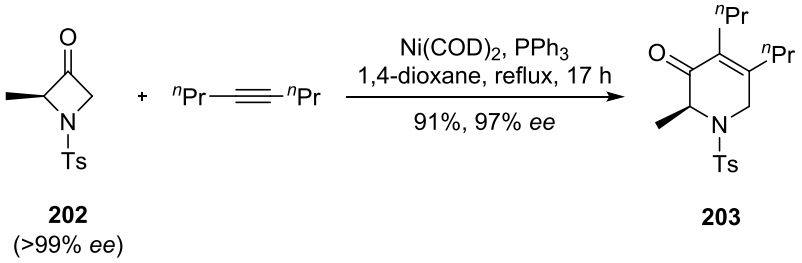
Scheme 1.76. Nickel-catalysed ring expansion of cyclobutanone **199** to give 2-cyclohexenone **200**.[97]

Since this discovery, Aïssa and co-workers have extended Murakami's work on cyclobutanones by demonstrating this transformation on strained heterocycles.[98] Their studies showed the first example of azetidin-3-ones to undergo regioselective cycloaddition with unsymmetrical alkynes to form six-membered rings (Scheme 1.77). High levels of regioselectivity were observed in these reactions.



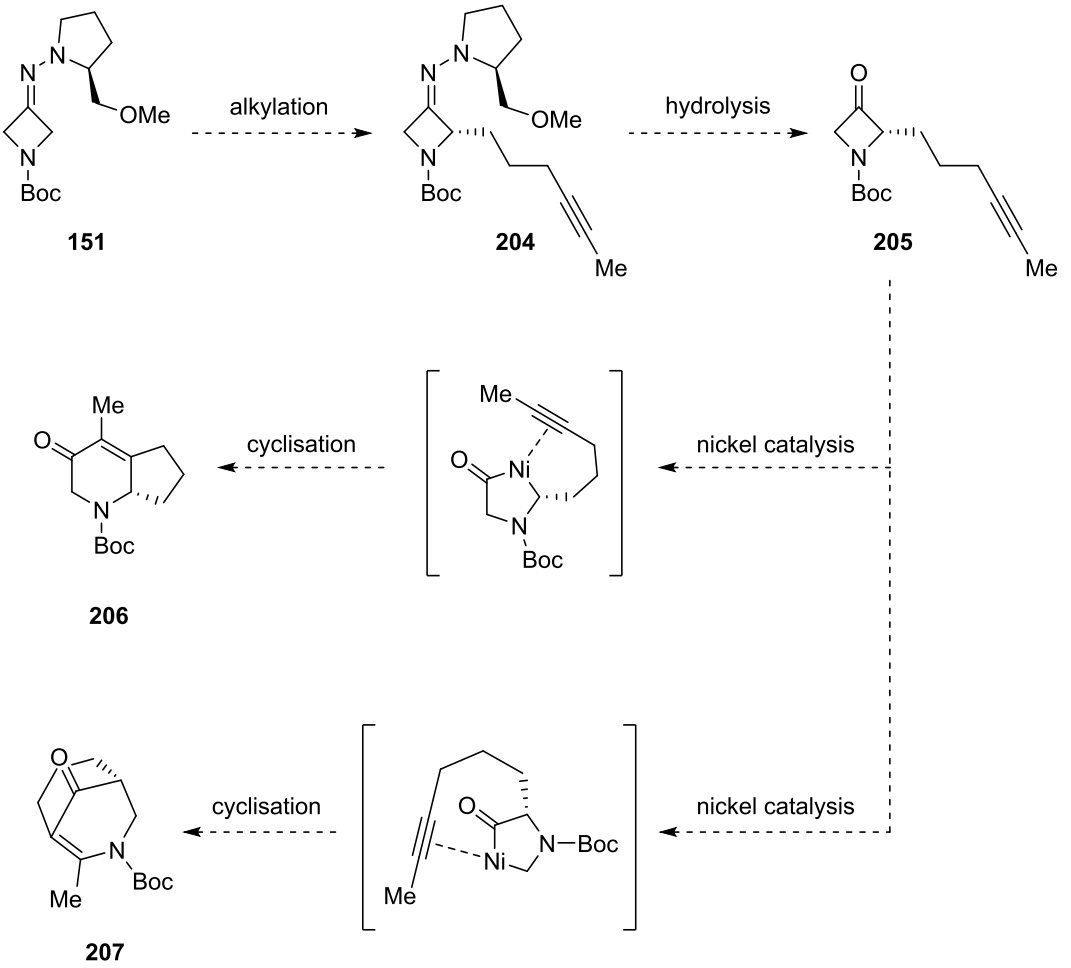
Scheme 1.77. Nickel-catalysed ring expansion of azetidin-3-one by Aïssa and co-workers.[98]

Additional studies by the Aïssa group demonstrated the application of this approach to α-substituted azetidin-3-ones and symmetrical alkynes, giving **203** exclusively in high yield. The chiral centre was retained during the cycloaddition process (Scheme 1.78).[98] Simultaneously, Ishida *et al* reported the synthesis of enantiopure dehydropiperidinones from α-amino acids in a similar fashion.[99]



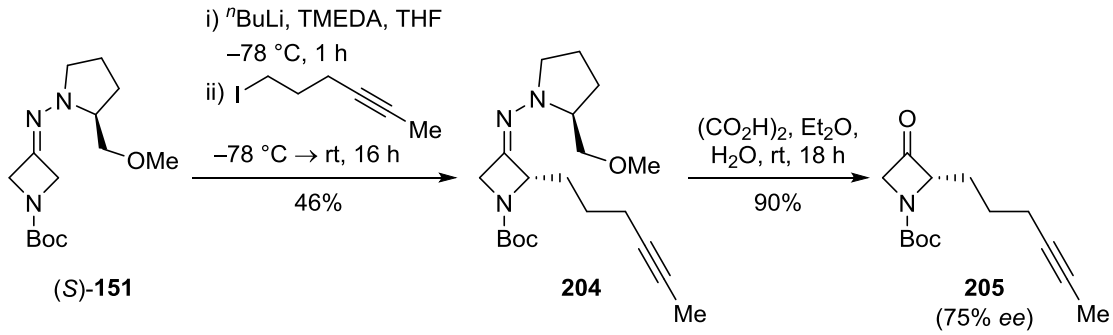
Scheme 1.78. Regioselective ring-opening of α-substituted azetidin-3-one **202**.[98]

In collaboration with the Aïssa group, we set out to explore if the cycloaddition process mentioned above can be performed intramolecularly. We envisaged that our 2-substituted azetidin-3-ones made using our methodology could be subjected to the nickel-catalysed conditions developed by Aïssa, as an alkyne at the 2-position of the azetidin-3-one could provide a tether for the reaction to proceed. Our strategy is outlined in Scheme 1.79. Starting from hydrazone **151**, stereoselective alkylation with 6-iodo-2-hexyne would provide alkylated hydrazone **204**, followed by subjection to the hydrolysis conditions to cleave the auxiliary and provide ketone **205**. Subsequent nickel catalysis might then provide cyclised product **206** through insertion into the more substituted C–C bond, or bridged product **207** by nickel insertion into the less substituted C–C bond.



Scheme 1.79. Proposed route for the synthesis of **206** or **207**.

Our studies began with the synthesis of ketone **205** in a stepwise process. Alkylation of (*S*)-**151** with 6-iodo-2-hexyne proceeded in moderate yield to give **204** using ^{n}BuLi as the base with the additive TMEDA at low temperatures. Mild hydrolysis conditions using aqueous oxalic acid then provided ketone **205** in 90% yield. The enantiomeric excess of **205** was determined by chiral GC to be 75% *ee* (Scheme 1.80). The sense of asymmetric induction was made by analogy to our previous assignment.



Scheme 1.80. Stereoselective synthetic route to **205**.

This chemistry was scaled up and a significant quantity (> 1g) of **205** was formed and delivered to the Aïssa group. At the time of writing, the outcome of the nickel catalysed cyclisation is still pending.

1.9 Conclusions

We have developed a convenient one-pot asymmetric route to 2-substituted azetidin-3-ones in good yields and enantioselectivities using Enders' SAMP/RAMP methodology.[100] Initial hydrazone synthesis and screening of conditions identified optimised metalation conditions for the SAMP hydrazone of *N*-Boc-azetidin-3-one, using ^{n}BuLi as the base (Table 1.1). Subsequent alkylation with a range of electrophiles formed 2-substituted azetidin-3-ones **159**,**166**-**173** in generally good yields and good enantioselectivities after *in situ* hydrolysis. A range of electrophiles, including alkyl, allyl and benzyl halides and carbonyl compounds were effective, with best enantioselectivities seen with more hindered electrophiles such as isopropyl iodide (Table 1.3).

Direct alkylation of ketone **150** using ^{t}BuLi led to formation of carbinol **160**, indicating the role the SAMP hydrazone plays in both encouraging deprotonation and protecting the π-bond from nucleophilic addition (Scheme 1.54). The importance of the Boc protecting group in this chemistry was demonstrated through comparison studies using the benzhydryl protecting group (Scheme 1.56). In contrast to work with oxetan-3-ones, the extension of this work to 2,2- and 2,4-disubstituted

derivatives was not fruitful, perhaps due to the greater steric bulk of the substrates (Schemes 1.69 and 1.70). The sense of asymmetric induction of the newly formed stereocentre was unambiguously determined in one case by a Pictet-Spengler reaction, with other examples inferred by extrapolation (Scheme 1.65). The sense of induction is in line with stereochemical models developed by Enders.[79,80,92]

In collaboration with the Aïssa group, an initial application of our methodology has been initiated. Ketone **205** was formed in moderate yield in a step-wise process, and submitted to the Aïssa group for them to conduct the nickel-catalysed cyclisations (Scheme 1.79).

Overall, we have developed an efficient methodology to synthesise chiral 2-substituted azetidin-3-ones in good yields and good levels of enantiocontrol.[100] These products are expected to be useful in the preparation of a variety of chiral 2,3-disubstituted azetidine-containing scaffolds.

1.10 Future Work

Having established routes to 2-substituted azetidin-3-ones, it would be of interest to further optimise the enantioselectivity of the reaction. As well as SAMP/RAMP auxiliaries which are commercially available, there are other alternatives such as SADP and SAPP (Figure 1.10).[80] Whilst these are more difficult to source, these might have led to improved levels of selectivity for the reactions due to the increased steric hindrance of the auxiliary providing preferential attack from the less hindered face of the azaenolate.

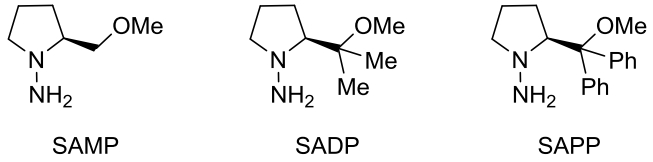
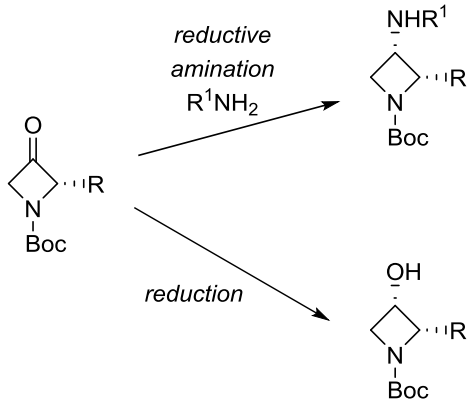


Figure 1.10. Variants of Ender's auxiliary.

Another alternative would be to explore alkylations using Ellman's auxiliary on azetidines to improve the selectivity.[101] Coordination of the lithium atom to the *N*-sulfinyl imine may have led to improved enantioselectivities in these cases.

An extension of this chemistry would be to introduce aryl substituents at the 2-position of azetidin-3-ones. For example, Negishi couplings by transmetallation of the lithium azaenolate to zinc could be explored.

Screening of methods for the deprotection and functionalisation of these systems such as reductive amination and reduction could further expand the applicability of these substrates to medicinal and drug discovery programmes (Scheme 1.81).

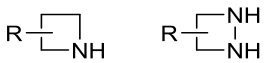


Scheme 1.81. Functionalisation of asymmetric 2-substituted azetidin-3-ones.

Chapter 2: Synthesis of Spirocyclic 1,2-Diazetidines

2.1 Introduction to 1,2-Diazetidines

In recent years, the diazetidine moiety is beginning to gather interest. These four-membered heterocyclic rings **209** contain two adjacent nitrogen atoms and have been less widely explored compared to their azetidine analogues **208** (Figure 2.1). With increasing interest, new methodologies are needed to access these compounds. We sought to develop a route to synthesise spirocyclic 1,2-diazetidines, thereby branching into a new field with access to larger regions of chemical space and potentially attractive compounds for medicinal chemistry.



208 **209**

Figure 2.1. Structure of azetidine **208** and 1,2-diazetidine **209**.

In particular, the pyridazine nucleus containing two adjacent nitrogen atoms within a six-membered ring is a privileged substructure in medicinal chemistry.[102] An important member of this group is the saturated hexahydropyridazine nucleus, with a number of molecules including actinoramide A,[103] cilazapril,[104] and 1-azafagomine[105] possessing prominent bioactivity (Figure 2.2).

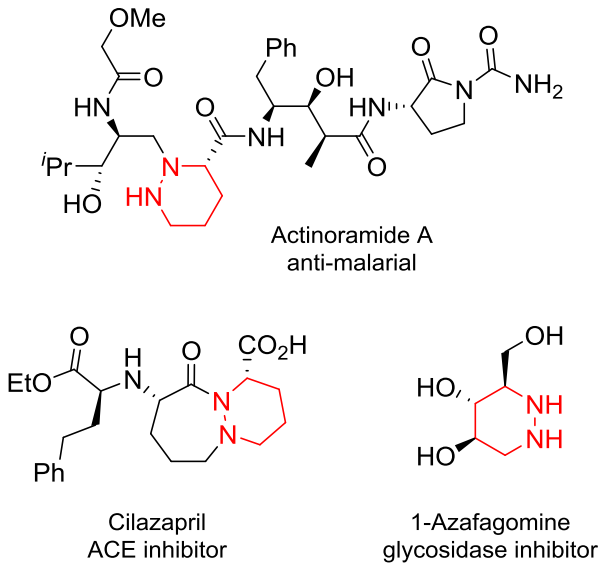


Figure 2.2. Bioactive compounds containing the hexahydropyridazine nucleus.[103–105]

Since introduction of a spirocenter into other saturated nitrogen heterocycles has proved valuable,[106–108] we reasoned that rigidification of the hexahydropyridazine nucleus might have considerable merit to access spirocyclic 1,2-diazetidines (Figure 2.3).

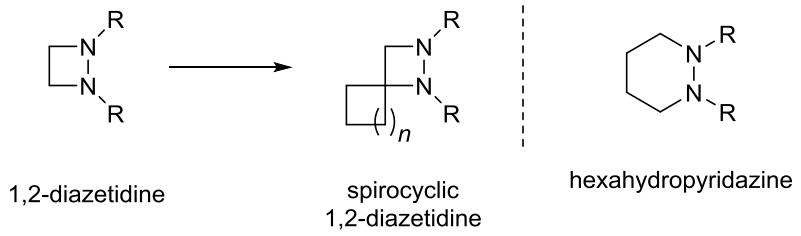


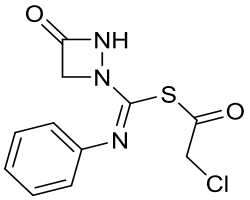
Figure 2.3. Structures of 1,2-diazetidine, spirocyclic 1,2-diazetidine and hexahydropyridazine.

This chapter begins by introducing previous work on 1,2-diazetidine formation and the value of spirocyclic compounds, before detailing our work towards spirocyclic 1,2-diazetidines.

2.1.1 Background & Application of 1,2-Diazetidines

Horvitz and co-workers initially developed a procedure to form simple 1,2-dialkyl-1,2-diazetidine derivatives from dialkyl substituted hydrazines.[109] These compounds were shown to be effective as rocket fuels or rocket fuel additives, with their high energy stemming in part from the strained nature of the four-membered ring.

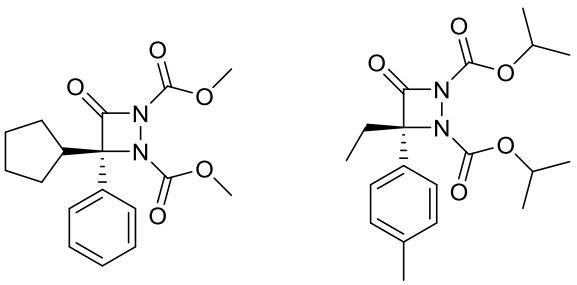
1,2-Diazetidines have been known to exhibit biological and pharmacological activity, due to their structural similarity to *β*-lactams. In 1986, Morioka *et al* demonstrated that aza-*β*-lactam **210** was able to induce the differentiation of three types of Friend leukaemia cells and initiate haemoglobin synthesis.[110] The lactam ring structure was necessary for the differentiation-inducing activity, and presence of a phenyl substituent further enhanced the bioactivity (Figure 2.4).



210

Figure 2.4. Structure of **210** for the differentiation of Friend leukaemia cells.[110]

More recently, the Cravatt group have discovered a class of aza-*β*-lactam inhibitors through a series of high-throughput assays.[111,112] Compounds **211** and **212** were identified as potential targets for selective inhibition of serine hydrolase protein phosphatase methylesterase-1 (PME-1), which is involved in cancer and neurodegeneration pathways (Figure 2.5).



211 **212**

Figure 2.5. Compounds for the selective inhibition of PME-1.[112]

2.1.2 Structure and Properties of 1,2-Diazetidines

Hall and Bigard studied a series of simple 1,2-dialkyl-1,2-diazetidines to determine their stability and properties. Compounds **213a**-**213d** were found to be highly stable, with no effect observed when **213c** was subjected to butyllithium, or strong acidic conditions of concentrated hydrochloric acid or 98% sulphuric acid. Catalytic hydrogenation using platinum on charcoal failed to cleave the N–N bond of **213c**, and **213d** could be distilled at elevated temperatures. No changes were detected when **213b** was subjected to sodium amide for prolonged periods of time.

The same authors performed conformational studies on compounds **213a**-**213d**. ^{1}H NMR studies of **213a** indicated an AABB coupling pattern for the methylene hydrogens, with a large coupling constant difference for proton J_{14} and J_{23}, indicating a highly-puckered structure (Figure 2.6). Using modifications of the Karplus equation, it was estimated that the dihedral angle between H_1 and H_4 is 166, 161, 152 and 159° for **213a**-**213d** respectively. Only a small difference in the rates of *N*-inversion for **213a**-**213c** were seen, but restricted rotation and slower inversion was observed for the bulkier *tert*-butyl groups on **213d**. Moreover, the ring tended to flatten as the size of the alkyl substituent increases.

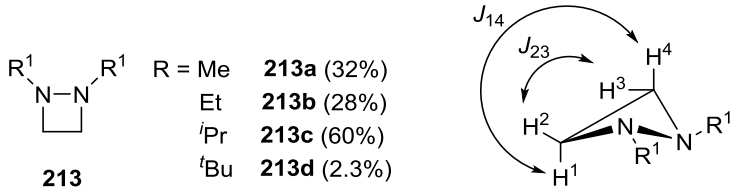


Figure 2.6. Structural orientation of the simplest 1,2-dialkyl-1,2-diazetidines **213a**-**213d**.[113]

Independently, Rademacher and Nelson used photoelectron spectroscopy (PE) to probe conformations of **213a**.[114,115] These studies by Rademacher revealed a dihedral angle (φ) for **213a**, which was estimated to be 145 ± 10° between the nitrogen lone pairs (Figure 2.7). Later, Gebhardt confirmed these findings using calculations and estimated the ring puckering angle to be ϕ = 24.3° when the methyl substituents in **213a** are in an equatorial position.[116]

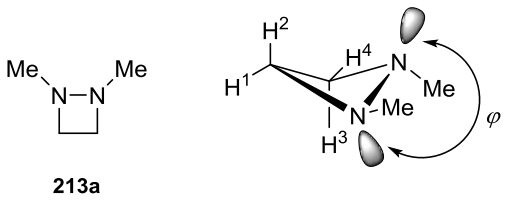


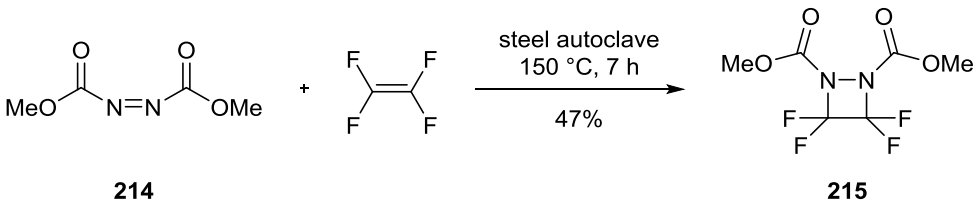
Figure 2.7. Dihedral angle of **213a** estimated by Rademacher.[114]

These calculations further supported the proposed puckered structure of 1,2-diazetidines, and are in agreement with reports on barriers for the inversion of substituted 1,2-diazetidines, and the conformational orientation of the R substituents.[115,117]

2.2 Synthetic Routes to 1,2-Diazetidines

2.2.1 Synthesis by [2+2] Cycloaddition Reactions

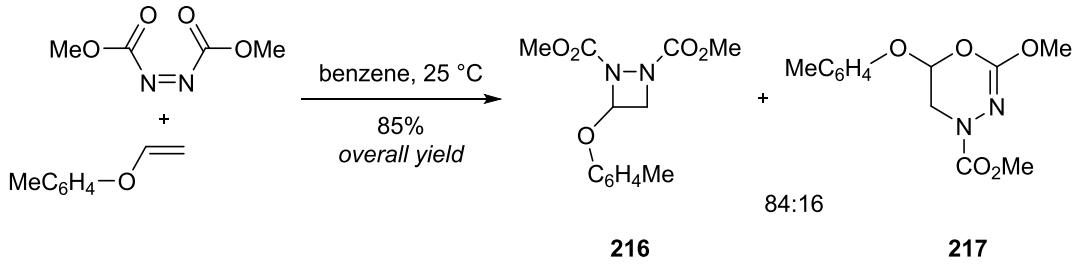
Thermal [2+2] cycloadditions are strictly forbidden according to the Woodward-Hoffman rules,[118] but have been widely used as a route to access 1,2-diazetidines. The first synthesis of 1,2-diazetidines was reported in 1948 by Cramer,[119] and later adapted by Kauer and Schneider.[120] Thus, the thermal [2+2] cycloaddition of dimethylazodicarboxylate **214** with tetrafluoroethylene in a steel autoclave at elevated temperatures provided 1,2-diazetidine **215** (Scheme 2.1).



214 **215**

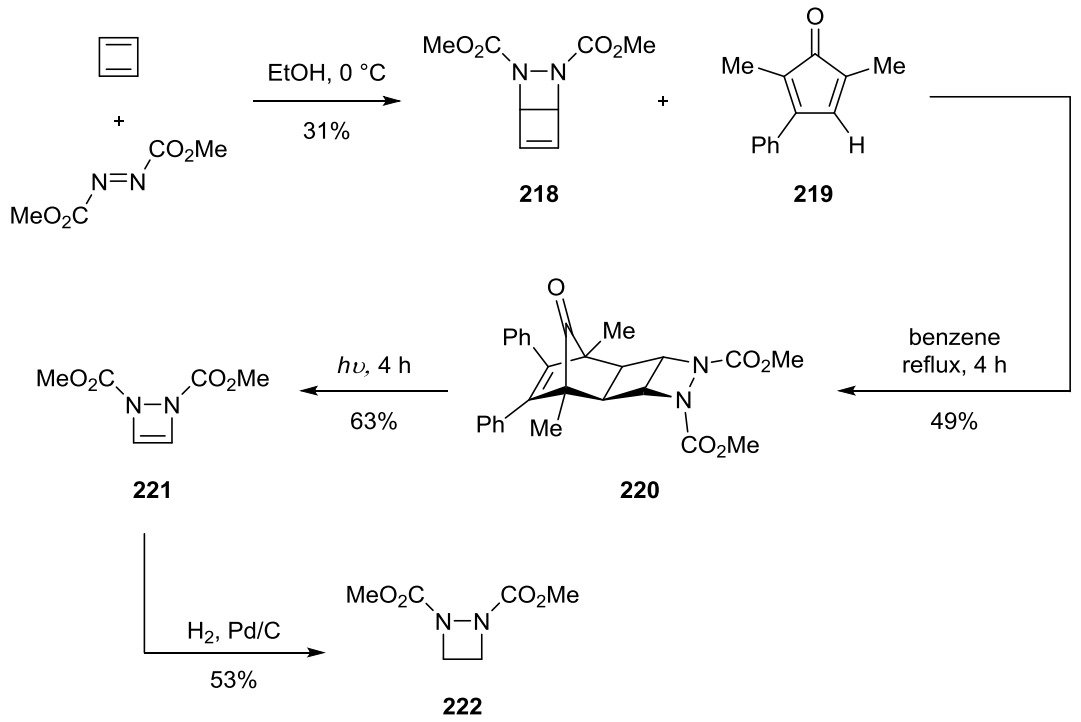
Scheme 2.1. Thermal [2+2] cycloaddition to form 1,2-diazetidine **215**.[120]

Hoffman and Hauser reported the thermal reaction of azodicarbonyl compounds with olefins, leading to 1,2-diazetidines through a [2+2] cycloaddition reaction.[121] They discounted dihydrooxadiazine formation resulting from a [2+4] cycloaddition product, which was further supported by spectroscopic analysis conducted by Gustorf.[122,123] In 1969, Firl and Sommer using dimethyl azodicarboxylate, provided evidence that with aryl vinyl ethers a mixture of **216** and **217** in an 84:16 ratio is produced in favour of the 1,2-diazetidine (Scheme 2.2).[124] It is thought that the reaction involves a stepwise cycloaddition process, whereby the inherent polarity of the substrates is a determining factor in the outcome of the reaction.[125]



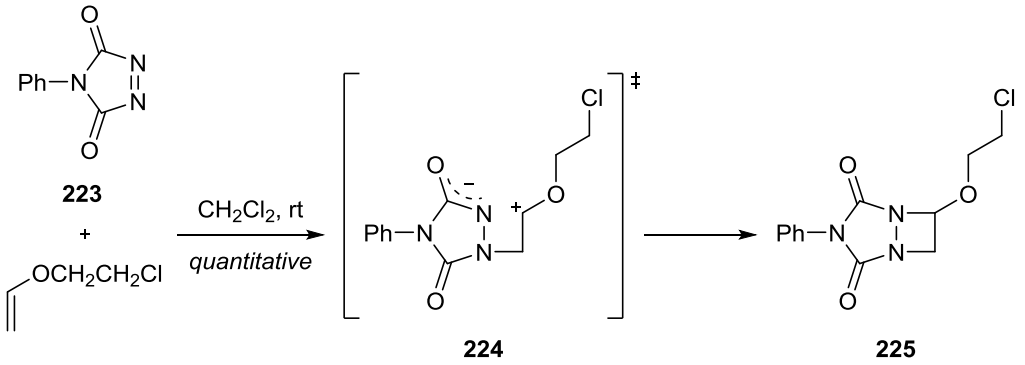
Scheme 2.2. [2+2] Cycloaddition of dimethyl azodicarboxylate with aryl vinyl ethers.[124]

Warrener and Nunn demonstrated an alternative route to access dimethyl 1,2-diazetine-1,2-dicarboxylate **222**, as shown in Scheme 2.3.[126] Reaction of cyclobutadiene and dimethyl azodicarboxylate furnished diazobicyclo[2.2.0]hexane **218** in moderate yield. A further thermal [4+2] cycloaddition of **218** with dienone **219** provided **220** in a 49% yield. Irradiation of this cycloadduct at low temperatures eliminated CO to form the unstable diazetine **221**, which after catalytic hydrogenation using Pd/C gave **222** in moderate yield.



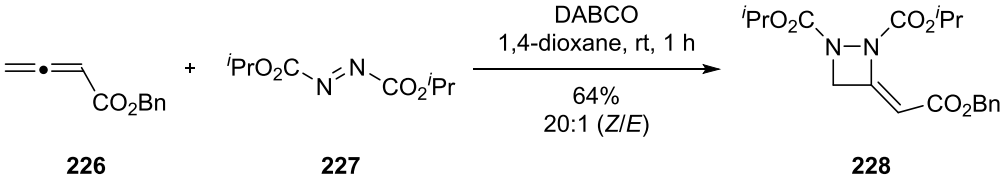
Scheme 2.3. Thermal cycloadditions to form diazetidine **222**.[126]

Hall and co-workers demonstrated the reaction between 4-substituted-1,2,4-triazoline-3,5-dione (R-TAD) **223** and 2-chloroethyl vinyl ether to form 1,2-diazetidine **225** through dipolar intermediate **224** (Scheme 2.4).[127]



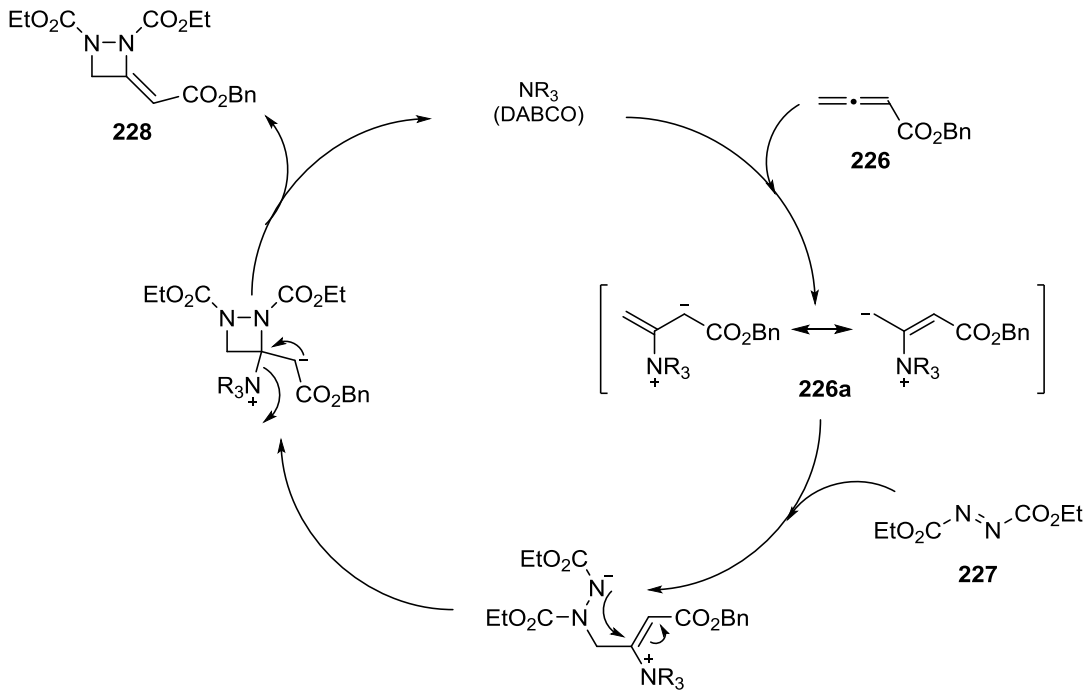
Scheme 2.4. Thermal [2+2] cycloaddition to form bicyclic 1,2-diazetidine **225**.[127]

Xu and co-workers have since reported an effective divergent amine-catalysed [2+2] annulation of allenoates **226** with azodicarboxylate **227** as a route to access 3-alkylidene-1,2-diazetidines **228** (Scheme 2.5).[128] Using DABCO as the catalyst, the reaction proceeds in a few hours for a range of substrates, generally leading to excellent *Z*-selectivity (20:1, *Z*/*E*).



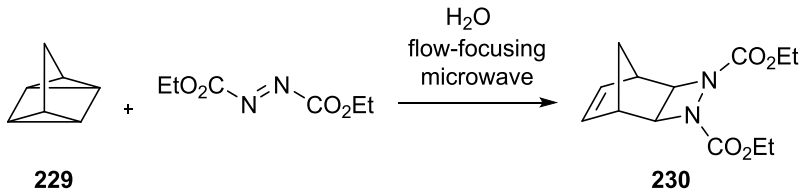
Scheme 2.5. [2+2] Annulation to generate 3-alkylidene-1,2-diazetidines **228**.[128]

The proposed mechanism involves nucleophilic attack of the amine catalyst on the *β*-carbon of allenoate **226**, generating zwitterionic intermediate **226a**. Attack of this intermediate on azodicarboxylate **227**, subsequent 4-*exo*-*trig* cyclisation and 1,2-elimination of the DABCO catalyst generates 1,2-diazetidine **228** (Scheme 2.6).



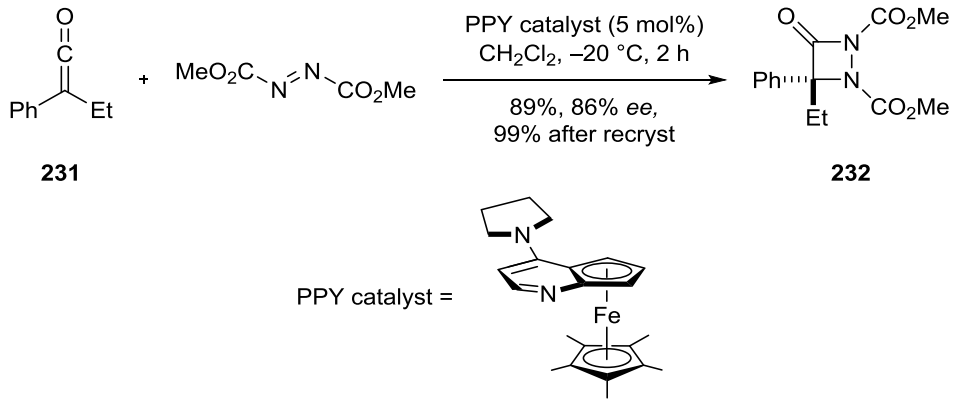
Scheme 2.6. Proposed mechanism for the generation of **228** using DABCO.[128]

Guo and co-workers have reported the cycloaddition of diethyl azodicarboxylate to quadricyclane **229**, generating tricyclic 1,2-diazetidine **230** conducted in a flow-focusing microwave (Scheme 2.7).[129]



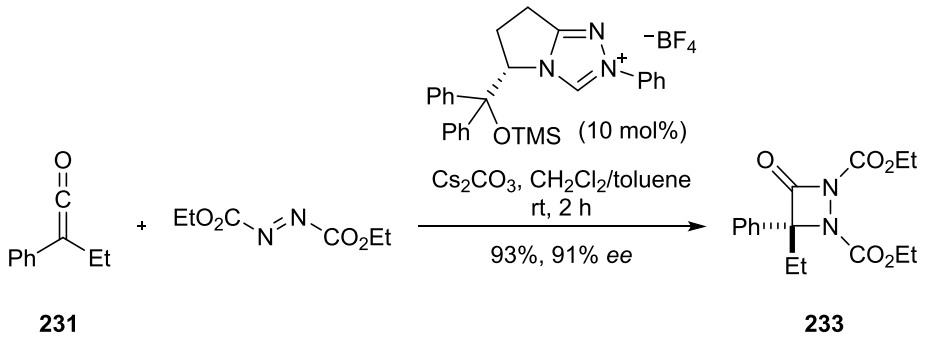
Scheme 2.7. Synthesis of tricyclic 1,2-diazetidine **230** from quadricycle **229**.[129]

In 2008, Fu and co-workers stereoselectively synthesised a variety of aza-*β*-lactams through a [2+2] cycloaddition of ketene **231** with azodicarboxylates.[130] The nucleophile-catalysed procedure provided product **232** using the chiral catalyst PPY in excellent yields and high enantioselectivities (Scheme 2.8).



Scheme 2.8. Enantioselective [2+2] cycloaddition of ketene **231** to synthesise **232**.[130]

Huang *et al* applied a similar approach to enantioselectively synthesise aza-*β*-lactams using *N*-heterocyclic carbene (NHC) catalysts. The cycloaddition of diethyl azodicarboxylate with ketene **231** generated **233** in high yield and enantioselectivity (Scheme 2.9).[131]

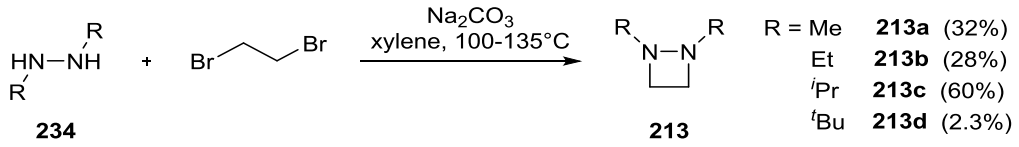


Scheme 2.9. Enantioselective synthesis of aza-*β*-lactam **233** from NHC-catalysed [2+2] cycloaddition.[131]

Whilst these examples demonstrated the [2+2] cycloaddition reaction of azodicarboxylates with electron rich alkenes, competitive formation of the six-membered [4+2] cycloaddition by-product can be limiting in some instances.

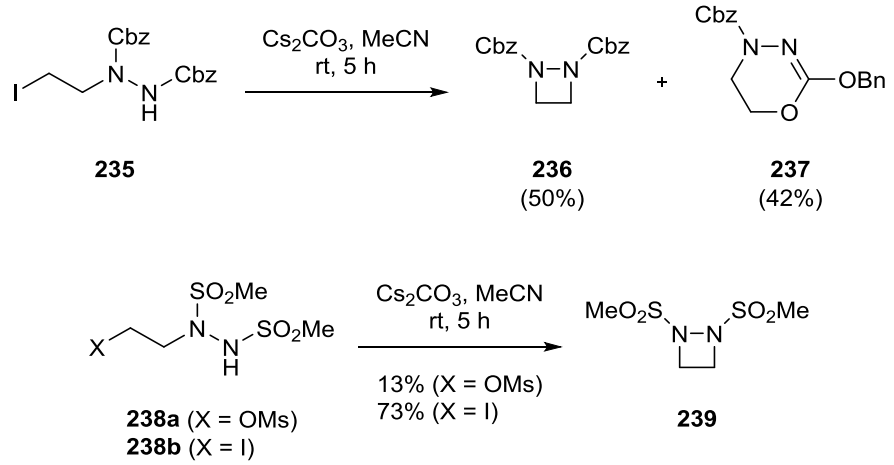
2.2.2 Intramolecular Ring Closure of Hydrazine Derivatives

Hall and Bigard developed a procedure to synthesise a series of simple non-functionalised 1,2-dialkyl-1,2-diazetidine derivatives from 1,2-dialkylhydrazines **234** and 1,2-dibromoethane in hot xylene (Scheme 2.10).[113]



Scheme 2.10. Synthesis of simple 1,2-dialkyl-1,2-diazetidines **213a**-**213d**.[113]

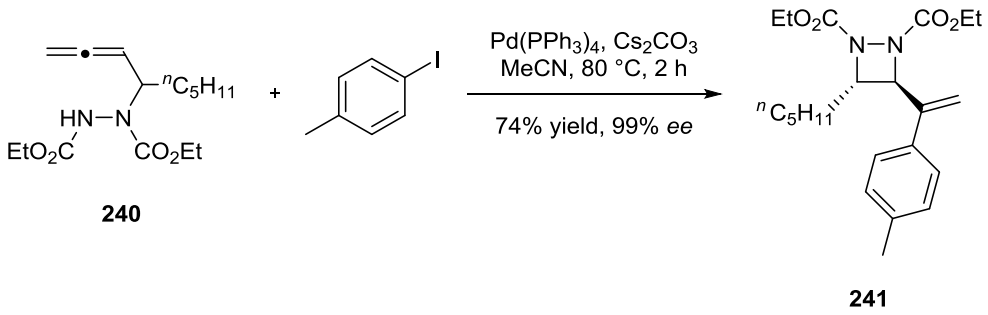
Brown *et al* reported the synthesis of simple 1,2-diazetidines by nucleophilic ring closure.[132] Competing reactions were observed leading to formation of both diazetidine **236** and oxadiazine **237**, as the ambidentate carbamate nucleophile facilitates ring closure through either the nitrogen or the oxygen atom in **235** (Scheme 2.11). These reactions were shown to be sensitive to the nature of the leaving group, rationalised through the HSAB principle introduced by Pearson.[133] When substrate **235** containing a 'hard' electrophile (e.g. methanesulfonate) was subjected to the cyclisation conditions, the oxadiazine was the only product formed. Switching to a 'soft' electrophile such as iodide resulted in a more polarisable C–I bond, and encouraged formation of the four-membered ring. Sulfonamide **239** was the sole product from the reaction with **238a**, as cyclisation could only proceed through the nitrogen atom, whilst converting to the iodide substrate **238b** led to a large improvement in reaction yield. These observations corrected earlier findings made by Miao.[134]



Scheme 2.11. Nucleophilic ring closure to provide 1,2-diazetidines using the HSAB principle.[132]

2.2.3 Metal Catalysed Synthesis of Substituted 1,2-Diazetidines

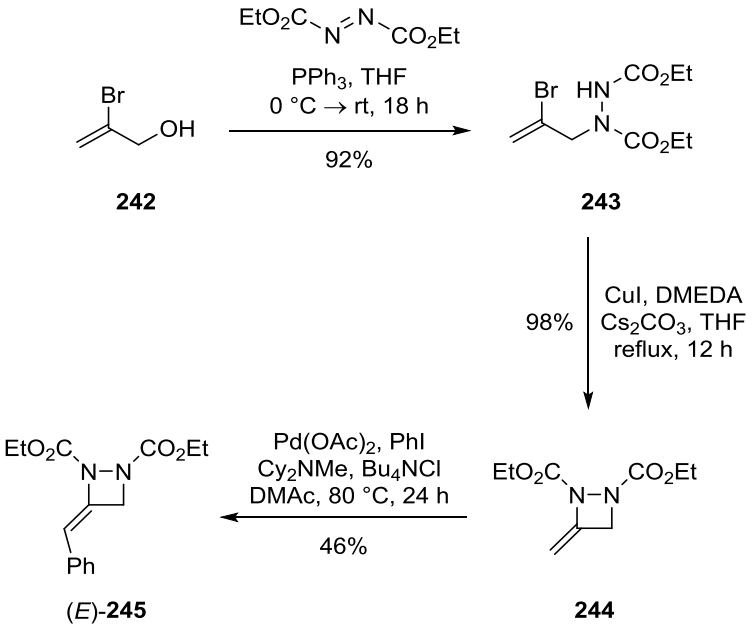
In 2008, Ma and co-workers reported the Pd-catalysed cyclisation of 2,3-allenyl hydrazines **240** with aryl halides for the synthesis of *trans*-1,2-diazetidines **241** in up to 77% yield (Scheme 2.12).[135] This work was extended to include optically active substrates with excellent enantiocontrol, thereby providing a mild stereocontrolled methodology for the synthesis of 1,2-diazetidines.



Scheme 2.12. Diastereoselective synthesis of **241** from allenoate **240**.[135]

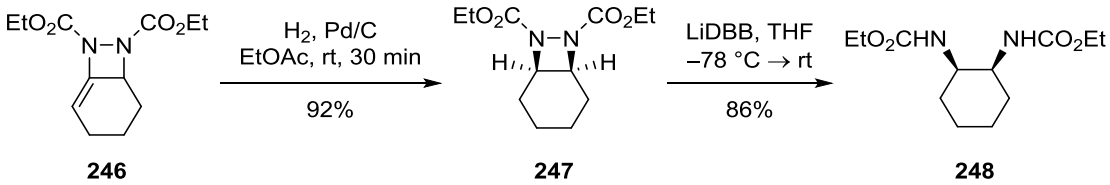
Brown *et al* demonstrated the efficient two step synthesis of 3-methylene-1,2-diazetidine **244** using Cu(I)-catalysed 4-*exo*-*trig* ring cyclisation from 2-halo-2-propenyl hydrazine **243**, as illustrated in Scheme 2.13.[136] The hydrazine precursor **243** was accessed through a variation on the Mitsunobu reaction in yields of up to 92%, with the subsequent cyclisation producing diazetidine **244** in near quantitative

yield. The exocyclic double bond of **244** was further functionalised by Pd-catalysed Heck reaction to provide (*E*)-**245** in high diastereoselectivity.



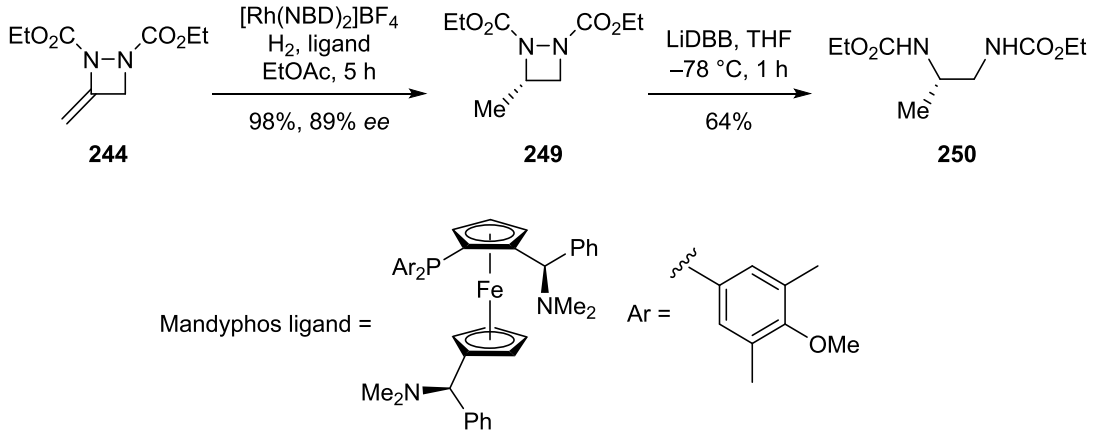
Scheme 2.13. Synthesis and functionalisation of **244**.[136]

Further transformation allowed access to saturated 1,2-diazetidines and vicinal diamines through chemoselective reduction of **246**. Catalytic hydrogenation formed **247** exclusively as the *cis*-stereoisomer, with no evidence of N–N bond cleavage. Treatment of **247** with LiDBB provided enamide **248** through chemoselective reduction of the N–N bond in excellent yield (Scheme 2.14).



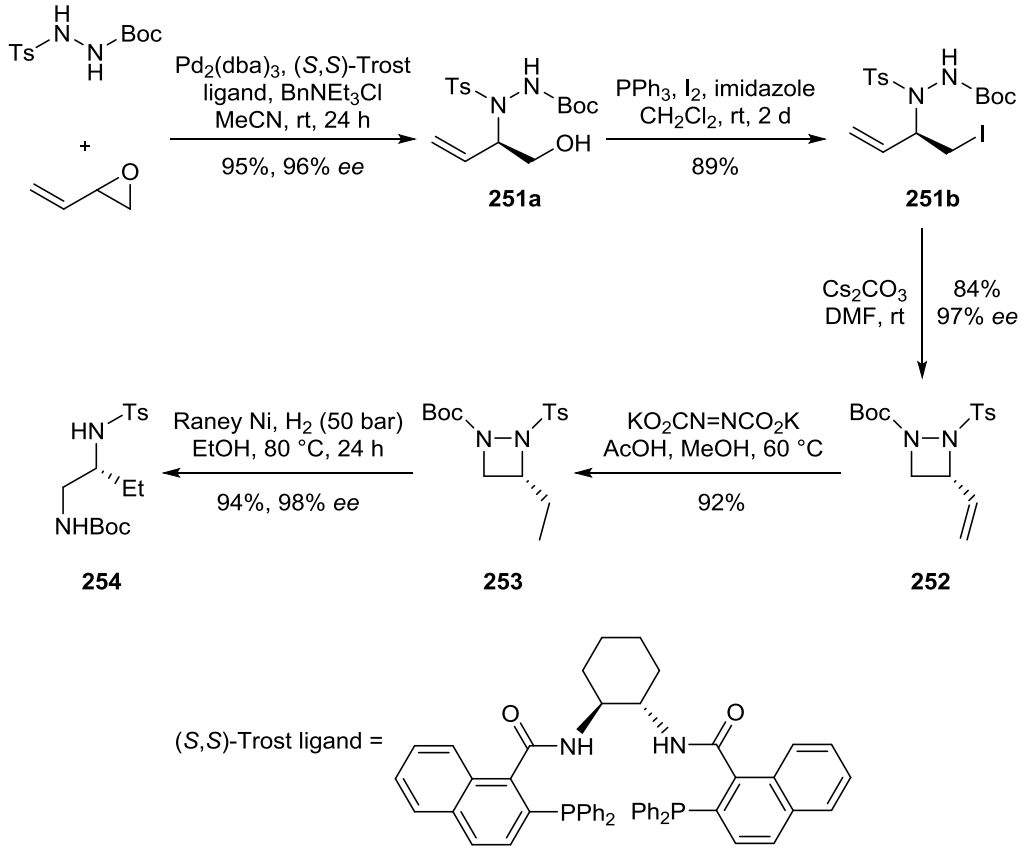
Scheme 2.14. Chemoselective reduction of **246**.[136]

Iacobini *et al* demonstrated highly chemo- and enantioselective hydrogenation of the exocyclic double bond in **244** using rhodium catalysis (Scheme 2.15).[137] Asymmetric hydrogenation with Mandyphos ligand proceeded in excellent yield and enantioselectivity to give monosubstituted 1,2-diazetidine **249**. Cleavage of the N–N bond with LiDBB gave the vicinal 1,2-diamine **250** in 64% yield.



Scheme 2.15. Asymmetric hydrogenation and N-N bond cleavage of **244**.[137]

In 2017, Shipman and co-workers developed a Pd-catalysed asymmetric allylic amination of a racemic vinyl epoxide, to provide differentially protected 3-vinyl-1,2-diazetidines **252** in excellent yield.[138] High regio- and enantiocontrol was observed during the formation of **251a** by kinetic resolution, using (*S*,*S*)-Trost ligand for the allylic amination step. Conversion of the alcohol to iodide **251b** and subsequent cyclisation gave 1,2-diazetidine **252** in good yield and with no loss of enantiopurity. Further manipulations of the double bond were achieved as demonstrated by the reduction of the alkene to give **253**, and subsequent cleavage of the N–N bond using RaNi to reveal differentially protected 1,2-diamine **254** with high yield and enantioselectivity. Cross-metathesis reactions using Grubbs catalyst, ozonolysis and reductive amination were also performed on the 3-vinyl-1,2-diazetidines in this study (Scheme 2.16).



Scheme 2.16. Synthetic route to 3-substituted 1,2-diazetidines **252** and further functionalisation.[138]

2.3 Spirocyclic 1,2-Diazetidines

2.3.1 Introduction to Spirocyclic Rings

Spirocyclic compounds or spiranes are ring systems where two or more rings are fused by a single atom, known as the spiroatom (Figure 2.8). The introduction of this structural features provides three-dimensionality to the compound, allowing access to compounds which deviate away from planarity.[139,140]

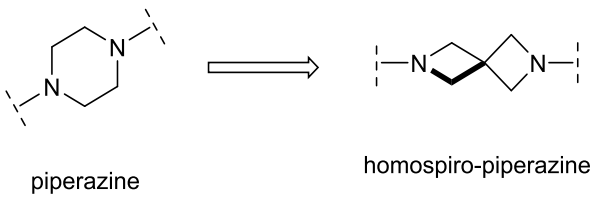


Figure 2.8. Structure of piperazine and homospiro-piperazine.[140]

Spirocycles have been employed as both core structures and substructures of molecules for medicinal programmes, with spirocyclic drug molecules dating back over 50 years.[141] In general, spirocycles have a number of beneficial properties including their inherent rigidity, structural novelty and reduced lipophilicity. The 'twisted' confirmations adopted by these compounds provide access to extended regions of chemical space, and project functionality in precise three dimensional space.[107] Structural rigidity arising from spirocycles is attractive in drug design, as this further reduces the conformational entropy penalty associated with binding a protein target.[106]

Carreira and co-workers demonstrated the effect of implementing an azaspirocycle in place of the piperazinyl group in the antibacterial agent Ciprofloxacin. The compound displayed comparable activity and high stabilities, suggesting the potential of azetidine frameworks in drug-like structures (Figure 2.9).[142]

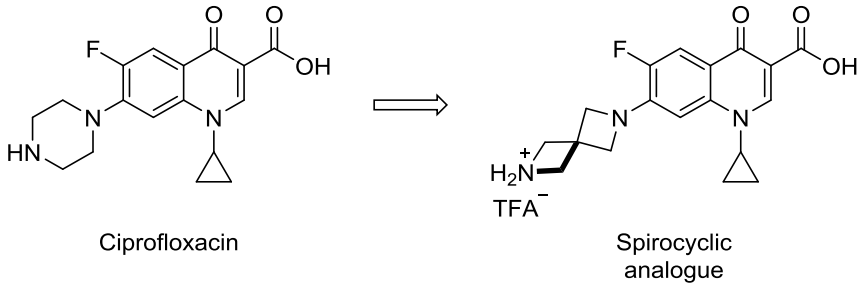
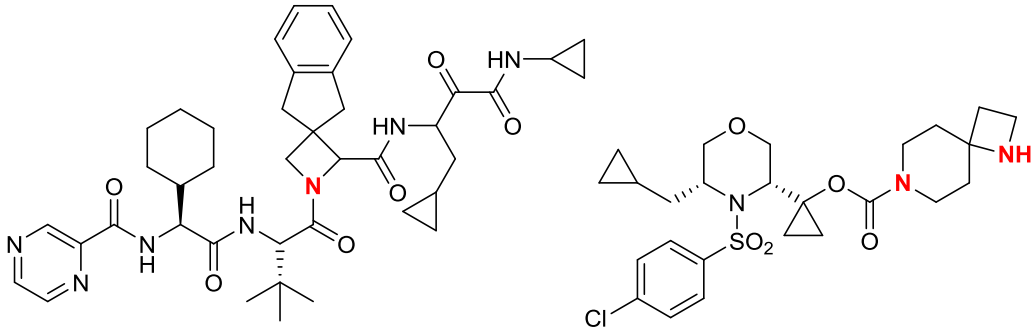


Figure 2.9. Ciprofloxacin and azaspirocycle analogue .[142]

As previously stated, spirocyclic heterocycles are emerging as valuable tools in medicinal chemistry,[106–108] with those containing a four-membered ring being of prominent interest.[140,142] Recent advances in the synthesis of these compounds have provided a platform for these scaffolds to be incorporated into pharmaceutically active compounds. Several drug candidates **255-257** containing a strained four-membered heterocyclic component are known (Figure 2.10).[106,107,143]

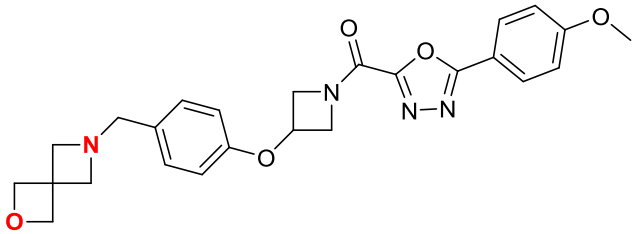


255

Hepatitis C treatment

256

Alzheimer's treatment



257

Weight management

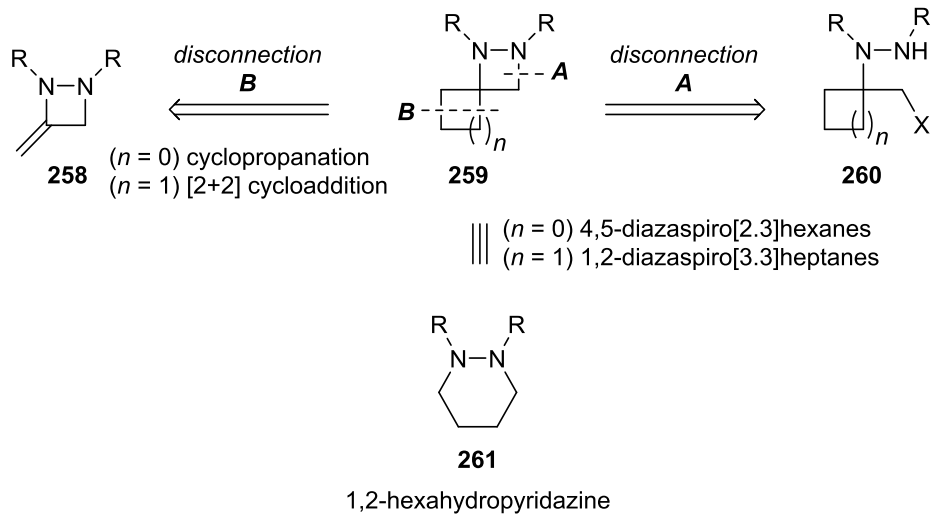
Figure 2.10. Examples of spirocyclic four-membered ring compounds.[106,107,143]

Methodologies developed to synthesise spirocyclic heterocycles include alkylation reactions, transition-metal based reactions, cycloadditions, rearrangements and ring closure reactions.[108] A recent review by Carreira and co-workers highlighted the synthetic procedures available for accessing four-membered ring containing spirocycles.[140]

2.4 Research Aims

Hexahydropyridazines display significant bioactivity in several medicinal compounds, as previously discussed (Figure 2.2). With the introduction of a spirocenter to nitrogen heterocycles proving beneficial, we reasoned that a spirocyclic variant of hexahydropyridazine nucleus may be of interest.

With this in mind, we targeted the synthesis of novel 4,5-diazaspiro[2.3]hexanes and 1,2-diazaspiro[3.3]heptanes as analogues of hexahydropyridazine **261**. Our proposed route is outlined in Scheme 2.17 and follows two separate approaches through disconnection of bonds A or B. Disconnection A involves ring closure of **260** by S_N2 displacement to provide spirocycle **259**, whilst disconnection B proceeds through manipulations of readily accessible 3-methylene-1,2-diazetidines **258**. Various spirocycle ring sizes could potentially be accessed through cyclopropanation or cycloaddition on the exocyclic double bond of **258**.



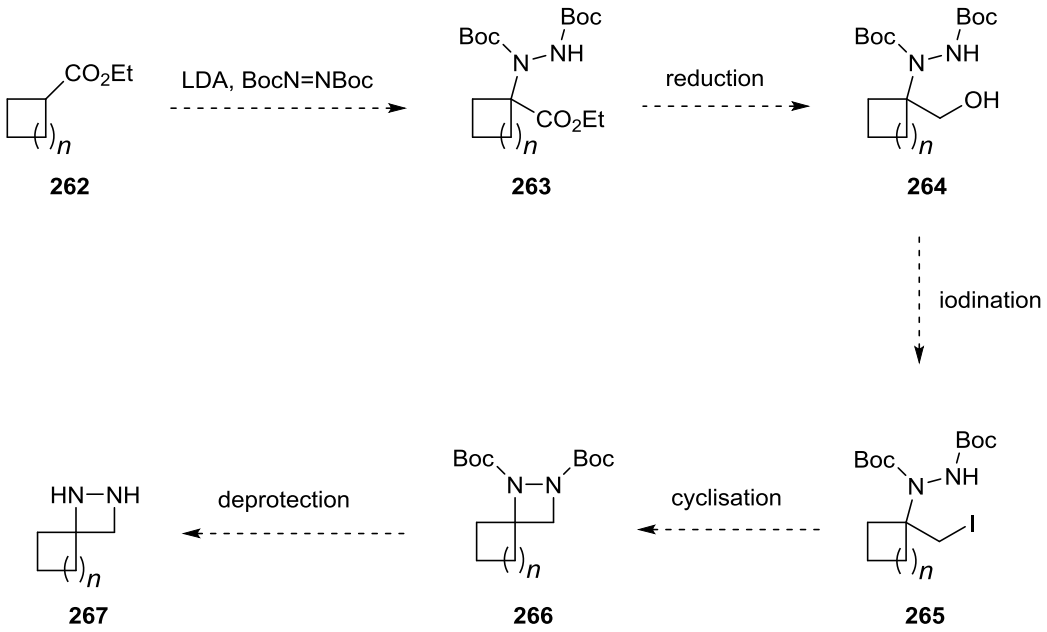
Scheme 2.17. Synthetic approaches to form 1,2-diazetidine spirocycles.

We began our efforts focussing on disconnection A through ring closure to form **259**, and our efforts to synthesise these substrates are discussed below.

2.5 Synthesis of Spirocyclic 1,2-Diazetidines by Ring Closure

Our proposed synthetic route based on ring closure is outlined in Scheme 2.18. This strategy was inspired by the work of Mike Brown, who synthesised 1,2-diazetidines by nucleophilic cyclisation (Scheme 2.11).[136] Starting from **262**, deprotonation and trapping with di-*tert*-butyl azodicarboxylate was expected to provide **263**. Reduction of the ester to alcohol **264** followed by iodination would give **265** ready for

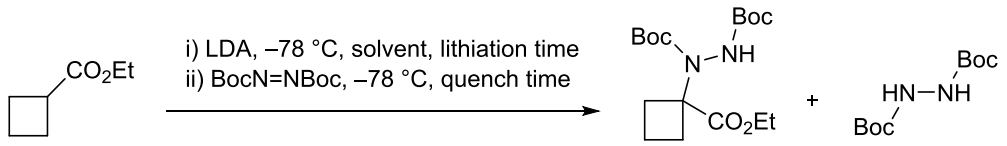
cyclisation to spirocycle **266**. Further diversification on nitrogen could be achieved by deprotection and *N*-alkylation.



Scheme 2.18. Proposed route by ring closure for the synthesis of spirocyclic 1,2-diazetidine **266**.

2.5.1 Synthesis of Hydrazine Substrates

We began our synthesis with commercially available ethyl cyclobutanecarboxylate **268**, and di-*tert*-butyl azodicarboxylate to access the four-membered ring spirocycle. At first, we began with screening of conditions for the deprotonation and amination step, with LDA chosen as base for the reaction (Table 2.1). Initially, metalation was carried out in diethyl ether at –78 °C for 40 min, followed by addition of di-*tert*-butyl azodicarboxylate and warming to ambient temperature over 1 h (entry 1). Satisfyingly, **269** was obtained in a 51% yield, alongside by-product **269a** identified by ^{1}H NMR and mass spectrometry. Switching to the more polar solvent THF increased formation of **269** (entry 2). Longer metalation times were detrimental to the yield (entry 3), whilst maintaining the temperature for 2 h after electrophile addition led to a much improved yield of 83% (entry 4). Leaving the reaction to warm to room temperature for a longer time led to no improvement (entry 5). From these results, entry 4 was chosen as the optimised reaction conditions, providing **269** in good yield.

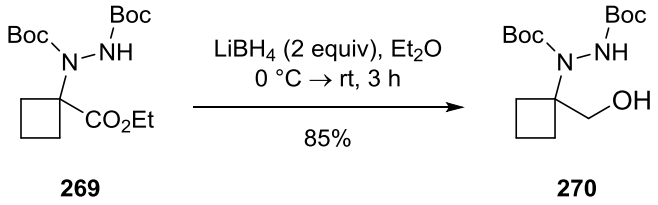


268 **269** **269a**

Entry	Solvent	Lithiation time (h)	Quench time[a]	269 (%)	269a (%)
1	Et_2O	1	40 min then 1 h to rt	51	20
2	THF	1	40 min then 1 h to rt	67	9
3	THF	2	1 h then 1 h to rt	15	7
4	THF	1	2 h then 1 h to rt	83	3
5	THF	1	2 h then 18 h to rt[b]	66	7

Table 2.1. Optimisation of formation of **269**. [a]Reaction quenched with BocN=NBoc, held at –78 °C for set time then warmed to room temperature for 1 hour by removal of dry ice/acetone bath. [b]Dry ice/acetone bath was not removed and the reaction warmed slowly to room temperature for 18 hours.

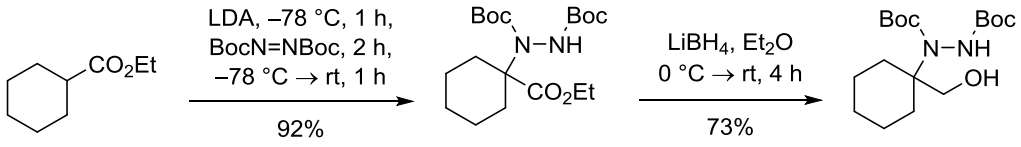
The next step involved reduction of ester **269** to alcohol **270** (Scheme 2.19). Kumar *et al* reported the reduction of an ester in the presence of a hydrazine moiety using 2 equivalents of $LiBH_4$ in THF.[144] Encouraged by this, **269** was subjected to these reaction conditions, with an additional 2 equivalents of $LiBH_4$ added after 18 h. No reaction was observed and only starting material **269** was re-isolated after work-up. However, switching the solvent from THF to Et_2O resulted in an 85% yield of the required product, indicating a strong solvent dependency of the reaction. When a mixture of Et_2O-MeOH was used, this reduced the rate of the reaction, with only 18% of **270** isolated, suggesting the instability of $LiBH_4$ in MeOH. With this in mind, diethyl ether was chosen as the solvent for the reduction step.



269 **270**

Scheme 2.19. Reduction of ester **269** to alcohol **270**.

Similarly, starting form ethyl cyclohexanecarboxylate **271**, deprotonation and amination using the optimised conditions gave **272** in excellent yield. Subsequent reduction of the ester provided alcohol **273** in 72% yield (Scheme 2.20).

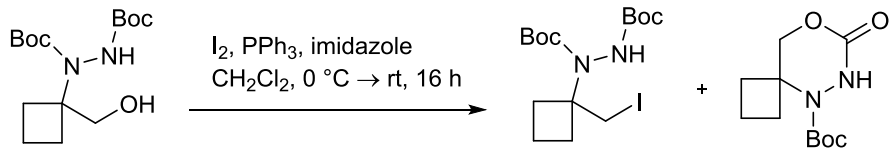


271 **272** **273**

Scheme 2.20. Synthesis to form alcohol **273**.

2.5.2 Attempted Iodination of the Alcohol

Conversion of alcohol **270** to iodide **274** was encouraged by findings by Brown *et al*, who demonstrated that the leaving group was critical for ring closure to 1,2-diazetidines.[132] Based on the HSAB principle, softer electrophiles such as iodide favour ring closure through the softer nitrogen site to form the four-membered ring. However, reaction of **270** under Appel conditions led to the formation of spirocycle **275** (Scheme 2.21). This was confirmed by ^{13}C NMR, revealing a single Boc carbonyl peak. Mass spectrometry indicted the correct mass for **275** (*m/z* = 265, $[M+Na]^+$), with no evidence for the formation of **274**.

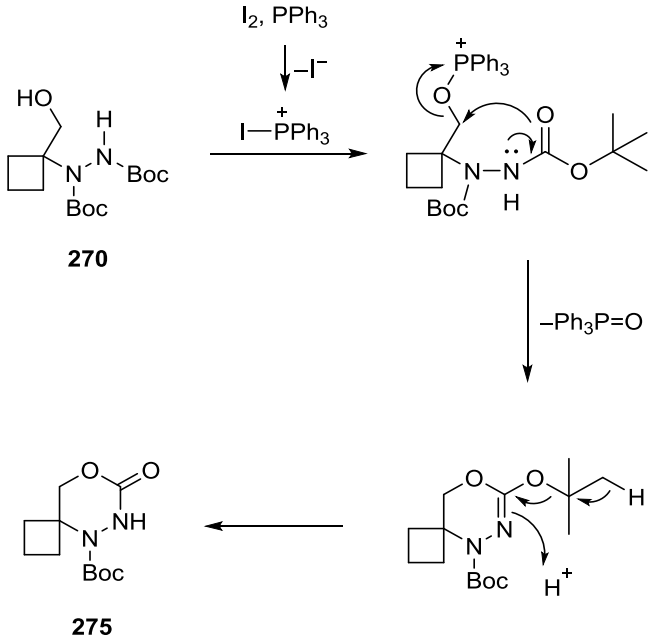


270 **274** **275**

0% 79%

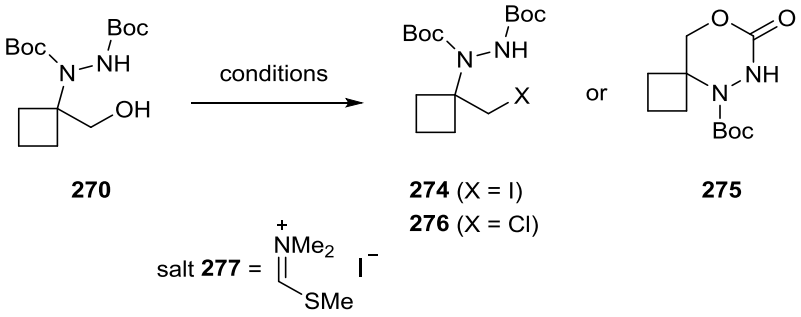
Scheme 2.21. Attempted iodination of alcohol **270**.

A proposed mechanism for the formation of **275** is outlined below (Scheme 2.22). Reaction of alcohol **270** with the phosphonium species results in the phosphonium intermediate. Cyclisation through the carbamate oxygen of the Boc group leads to the six-membered ring, with loss of triphenylphosphine oxide. Further loss of the *tert*-butyl group then provides the observed product **275**.



Scheme 2.22. Proposed mechanism for the formation of **275**.

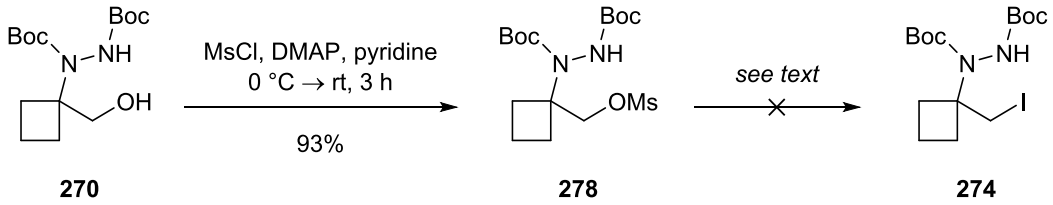
Attempts to iodinate **273** under Appel conditions were also not fruitful. As the Appel reaction on **270** led to the formation of cyclised product **275**, a different approach needed to be adopted. A variety of chlorination and iodination conditions were tested, as summarised in Table 2.2. Results using iodine and triphenylphosphine (entry 1) gave **275** in 79% yield. In absence of iodine, only starting material was recovered (entry 2). Thionyl chloride in chloroform under reflux led to exclusive formation of **275** (entry 3). Switching to caesium iodide in the presence of a Lewis acid led to poor recovery of the starting material and a complex mixture of products (entry 4). Use of the iodide salt, formed by the reaction of *N*,*N*-dimethylthioformamide and iodomethane, resulted in no reaction (entry 5). When the latter reaction was subjected to microwave irradiation, no evidence of product formation was observed (entry 6).



Entry	Reaction Conditions	Product
1	I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C → rt, 18 h	**275**, 79%
2	PPh_3, imidazole, CH_2Cl_2, 0 °C → rt, 18 h	**270**, 94%
3	$SOCl_2$, $CHCl_3$, 0 °C → reflux, 18 h[145]	**275**, 58%
4	CsI, $BF_3{\cdot}Et_2O$, MeCN, rt, 20 h[146]	**270**, 16%
5	salt **277**, imidazole, toluene, 80 °C[147]	**270**, 92%
6	salt **277**, imidazole, toluene, 100 °C, 1 h, µW	**274**, 0%

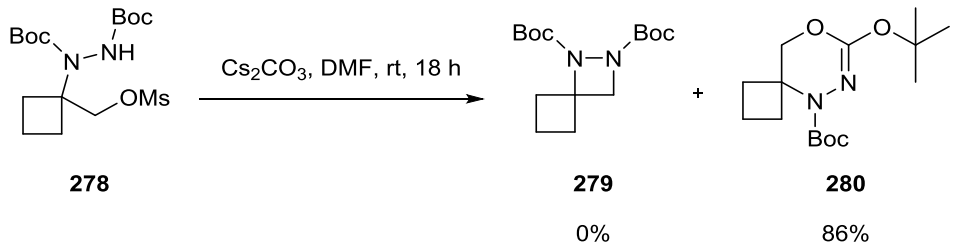
Table 2.2. Investigation into the conversion of **270** into halide **274** or **276**.

As direct halogenation was proving difficult, the alcohol was converted into the corresponding mesylate **278**, which could then undergo S_N2 displacement to afford the corresponding iodide **274** (Scheme 2.23). Conversion of **278** using Finkelstein reaction conditions (NaI (2 equiv), acetone, rt to reflux, 18 h) only resulted in recovered mesylate **278**. Switching to a large excess of LiI (10 equiv) in THF at reflux for 16 h recovered **278** alongside uncharacterised products. Performing this reaction under microwave irradiation for 1 h at 100 °C yielded no product.



Scheme 2.23. Investigation into the conversion of mesylate **278** into iodide **274**.

Direct cyclisation from mesylate **278** was attempted using caesium carbonate, however, only **280** was isolated, with no evidence of formation of **279** (Scheme 2.24). These results were consistent with previous reports of ring closure through the carbamate oxygen.[148]

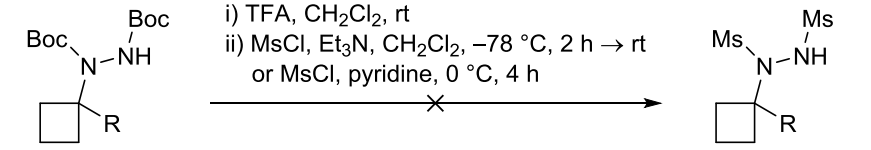


278 **279** **280**

0% 86%

Scheme 2.24. Direct cyclisation from mesylate **278**.

As competing cyclisation through the carbamate oxygen of the terminal Boc group was problematic, switching the protecting group might prevent these unwanted reactions. The most direct approach would involve using $ArO_2SN{=}NSO_2Ar$ in the amination reaction. However, such materials appear to be unknown. As an alternative, deprotection of the Boc group from **269** and **270**, followed by *bis*-mesylation under a variety of conditions was examined. Unfortunately, these all proved unsuccessful, with complex mixtures produced (Scheme 2.25).

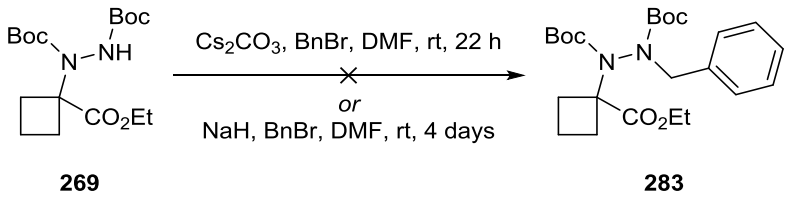


269 (R = CO_2Et)
270 (R = CH_2OH)

281 (R = CO_2Et)
282 (R = CH_2OH)

Scheme 2.25. Attempted synthesis of **281**/**282**.

Additionally, attempts to benzylate the free NH using caesium carbonate[149] or sodium hydride[150] as base were unsuccessful (Scheme 2.26).



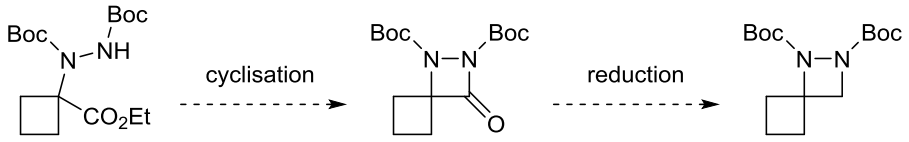
269 **283**

Scheme 2.26. Attempted benzylation of **269**.

It seemed that substitution at the neopentylic position was difficult, and subsequent activation of the alcohol under a variety of conditions resulted in intramolecular cyclisation outcompeting formation of the desired spirocycle.

2.5.3 Attempted Cyclisation to Spirocyclic 1,2-Diazetidin-3-ones

Next, we turned our attention to the synthesis of spirocycle **279** *via* a modified approach, in which the cyclisation and reduction steps were reversed. Direct cyclisation from ester **269** would provide a route to spirocyclic 1,2-diazetidin-3-one **284**, which could then potentially be reduced, as illustrated in Scheme 2.27.

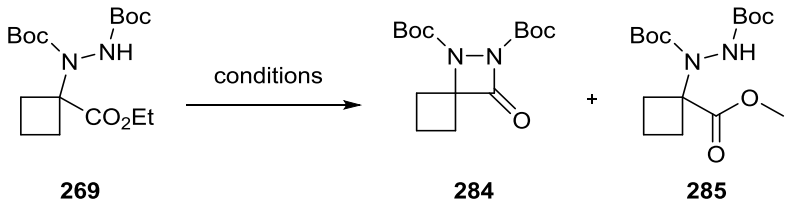


269 **284** **279**

Scheme 2.27. Revised synthetic route to **279**.

Our initial attempts for the cyclisation followed reported conditions using caesium carbonate for diazetidine formation,[132] where only starting material **269** was recovered even with prolonged stirring for 2 days (Table 2.3, entry 1). Similar observations were made using LiOH (entry 2) and MeMgBr (entry 3). Use of NaOMe/MeOH resulted in transesterification, forming methyl ester **285** as the sole

product (entry 4). Using potassium carbonate a mixture of **269** and **285** was obtained (entry 5). Similar ratios were obtained performing the reaction under microwave irradiation (entry 6).

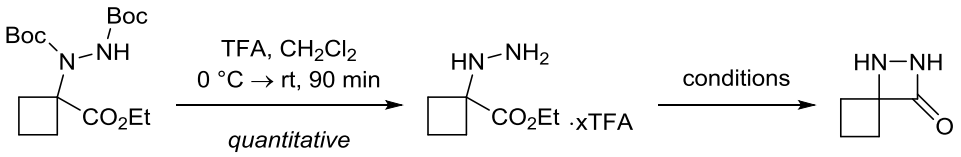


269 **284** **285**

Entry	Reaction Conditions	Product
1	Cs_2CO_3 (4 eq), MeCN, rt, 2 d[132]	**269**
2	LiOH, THF/H_2O, rt, 2 d[151]	**269**
3	MeMgBr, Et_2O, 0 °C → rt, 2 d[152]	**269**
4	NaOMe, MeOH, reflux, 2 d[153]	**285**, 60%
5	K_2CO_3, MeOH/H_2O, rt 2 d	**269**:**285**, 3.57:1
6	K_2CO_3, MeOH/H_2O, 70 °C, 1 h, µW	**269**:**285**, 3.45:1

Table 2.3. Investigation into the direct cyclisation of **269**.

We felt that removal of the protecting groups may allow more facile ring closure. Thus, **286** was formed in quantitative yield using TFA, and a variety of conditions screened for cyclisation (Table 2.4). Unfortunately, none of these led to the formation of **287**.

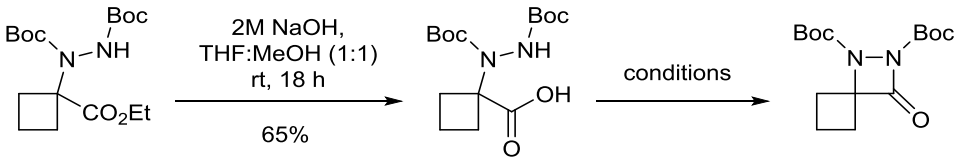


269 **286** **287**

Entry	Cyclisation Conditions	Product
1	pyridine, 100 °C, 18 h[154]	0%[a]
2	Et_3N, toluene, rt → 50 °C, 2 d	**286**, 92%
3	Et_3N, toluene, 50 °C, 1 h, μW	**286** and unknown[b]
4	NaH, DMF, rt, 18 h[155]	0%[a]
5	DBU, DMF, rt, 18 h[156]	0%[a]
6	K_2CO_3, toluene, rt, 20 h[157]	**286**, 94%

Table 2.4. Investigation of the direct cyclisation of **286**. [a]Unknown products formed with good mass balance recovery. [b]Evidence of **286** by crude ^{1}H NMR alongside unknown products in good mass balance recovery.

Next, an alternative approach was examined involving converting ester **269** into the acid, and then subjecting it to lactamisation conditions. A diverse array of conditions are known for *β*-lactam synthesis using this strategy.[158–161] Facile hydrolysis of ester **269** to **288** was achieved using sodium hydroxide in moderate yield.[162] A range of coupling reagents were explored, as outlined in Table 2.5. Phosphorus based reagents led to a complex mixture of products at both ambient temperature and with heating (entries 1, 2 and 6). Use of the more conventional coupling reagent DCC recovered largely starting material **288** after 2 days (entry 3). Carbon tetrachloride and *N*-bromosuccinimide led to unidentified by-product formation (entries 4 and 5), whilst the Mukaiyama reagent led to no reaction even after 3 days of stirring (entry 6).



269 **288** **284**

Entry	Reaction Conditions	Product
1	Ph_2POCl, Et_3N, MeCN, rt, 2 d[158]	0%[a]
2	Ph_2POCl, Et_3N, MeCN, reflux, 20 h[158]	0%[a]
3	DCC, CH_2Cl_2, rt, 2 d	**288**, 79%
4	CCl_4, PPh_3, Et_3N, MeCN, reflux, 20 h[159]	0%[a]
5	NBS, PPh_3, Et_3N, MeCN, rt, 20 h[159]	0%[a]
6	$POCl_3$, Et_3N, CH_2Cl_2, 0 °C → rt, 20 h[160]	0%[a]
7	Mukaiyama reagent, Et_3N, CH_2Cl_2, rt, 3 d[161]	**288**, 89%

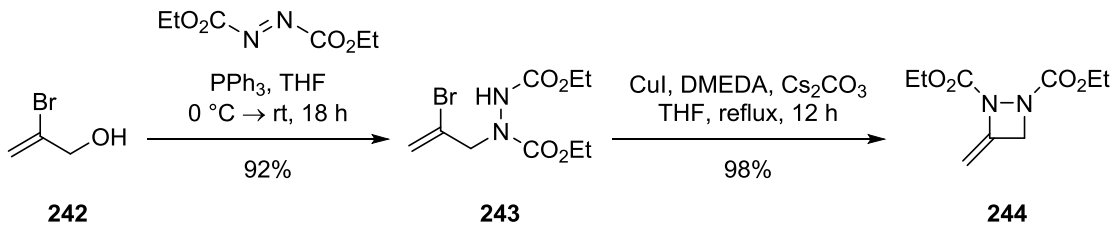
Table 2.5. Lactamisation studies of **288**. [a]Unknown products formed with good mass balance recovery.

Discouraged by these results, we elected to explore alternate disconnections to these spirocycles by alkene addition, depicted as disconnection B in Scheme 2.17.

2.6 Synthesis of Spirocyclic 1,2-Diazetidines by Alkene Addition

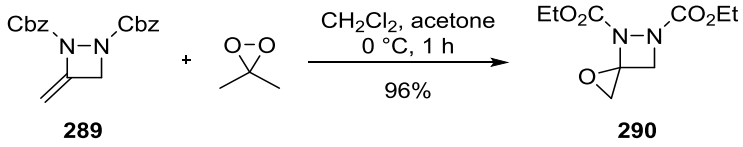
2.6.1 Background to 3-Methylene-1,2-Diazetidines

Shipman and co-workers have reported the two-step synthesis of 3-methylene-1,2-diazetidines from 2-haloallyl alcohols by Mitsunobu reaction with azodicarboxylate. Subsequent copper-catalysed cyclisation afforded the 1,2-diazetidines in high yields (Scheme 2.28).[136]



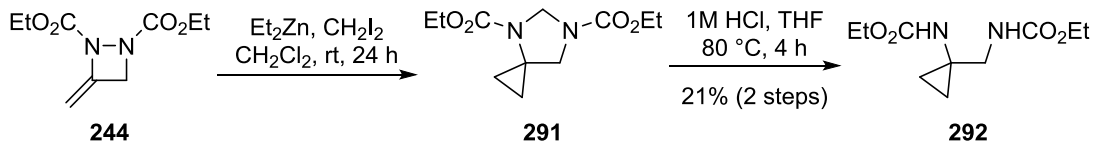
Scheme 2.28. Copper-catalysed synthesis of **244**.[136]

At the outset of my investigations, the reactivity of the double bond of this ring system, was largely unexplored. Asymmetric hydrogenations had been reported (Scheme 2.15),[136] as had Pd-catalysed Heck couplings (Scheme 2.13).[137] In unpublished work, the successful epoxidation of **289** using DMDO provided spirocycle **290** in excellent yield (Scheme 2.29).[163] This product was rather unstable, decomposing rapidly even when stored under nitrogen.



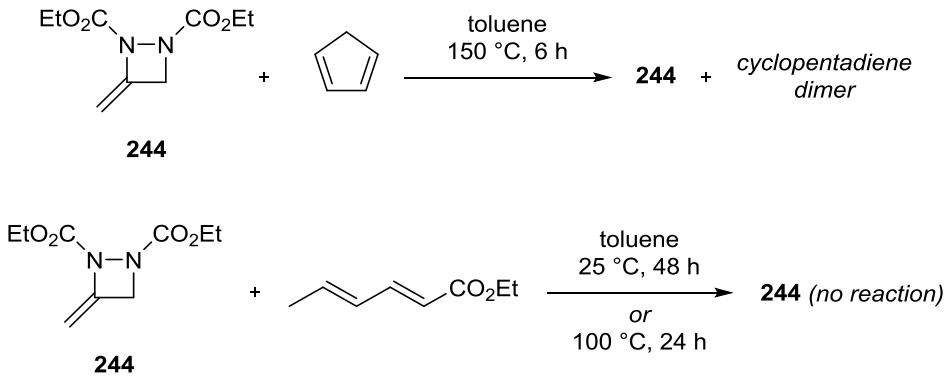
Scheme 2.29. Epoxidation of **289** using DMDO.[163]

Greg Iacobini and Mike Brown had attempted the cyclopropanation of 3-methylene-1,2-diazetidines.[148,163] Cyclopropanation of **244** under Simmons-Smith conditions provided ring expanded product **291** by way of addition of 2 equivalents of the carbene (Scheme 2.30). Due to the instability of **291**, it was directly hydrolysed to **292** in 21% yield over the two steps.



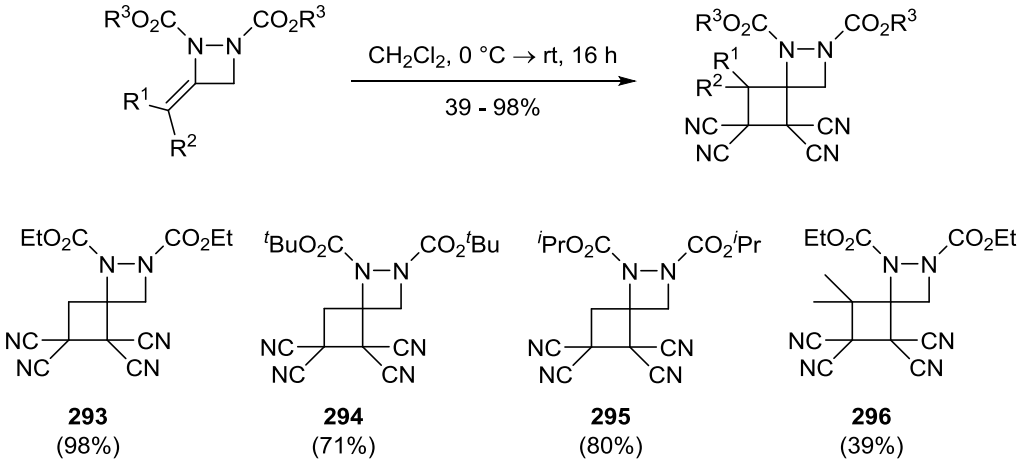
Scheme 2.30. Cyclopropanation of **244** and subsequent hydrolysis to give 1,2-diamine **292**.[163]

Diels-Alder reactions of **244** using both highly reactive and electron deficient dienes have been previously explored. No reaction was observed, indicating a lack of reactivity of the double bond (Scheme 2.31).[163]



Scheme 2.31. Attempted Diels-Alder reactions with **244**.[163]

Greg Iacobini had previously demonstrated the reaction of tetracyanoethylene with 3-methylene-1,2-diazetidines in a [2+2] cycloaddition reaction to generate several spirocyclic 1,2-diazetidines (Scheme 2.32).[163]



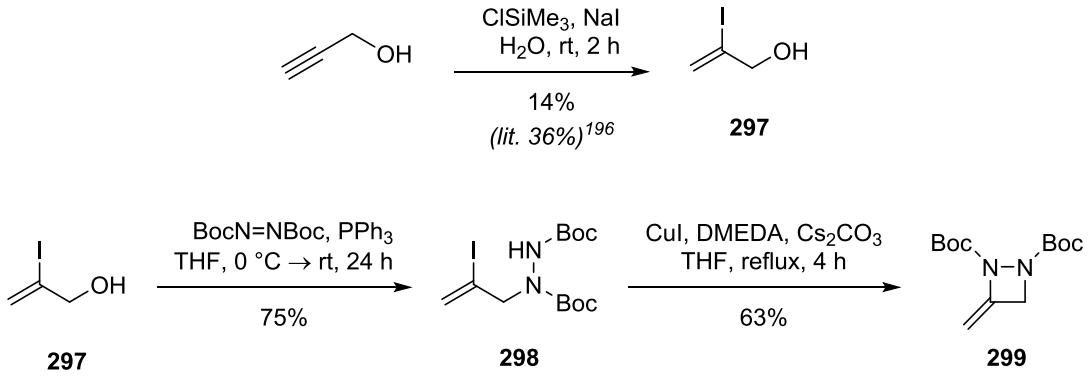
Scheme 2.32. Formation of spirocyclic diazetidines **293-296** using TCNE.[163]

2.6.2 Synthesis of 3-Methylene-1,2-Diazetidines

2.6.2.1 Synthesis of Hydrazodicarboxylates

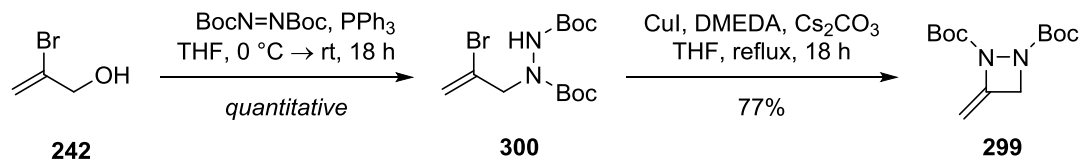
These findings suggested that the exocyclic double bond of 3-methylene-1,2-diazetidines is quite inert, but with appropriately reactive partners will undergo addition reactions. Encouraged by these preliminary results, we wanted to determine if general practical routes to 4,5-diazaspiro[2.3]hexanes and 1,2-diazaspiro[3.3]heptanes could be developed.

Following the chemistry developed in the group,[136] methylene diazetidine **299** was synthesised from iodo alcohol **297** according to the reported method (Scheme 2.33).



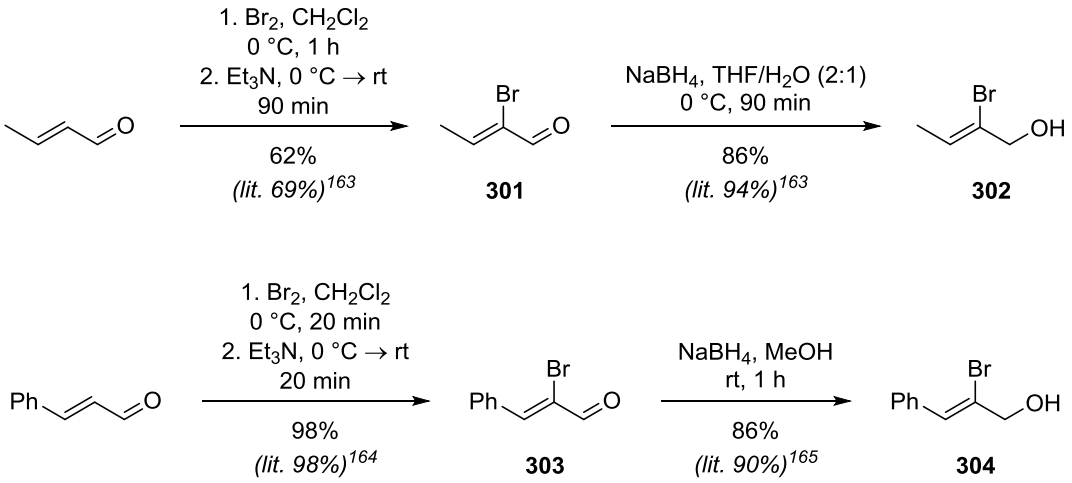
Scheme 2.33. Formation of methylene diazetidine **299** from alcohol **297**.

As the formation of iodo alcohol **297** was poor yielding, we switched to the commercially available 2-bromoallyl alcohol. This gave an improved yield for both the Mitsunobu reaction and the subsequent cyclisation to **299** (Scheme 2.34).



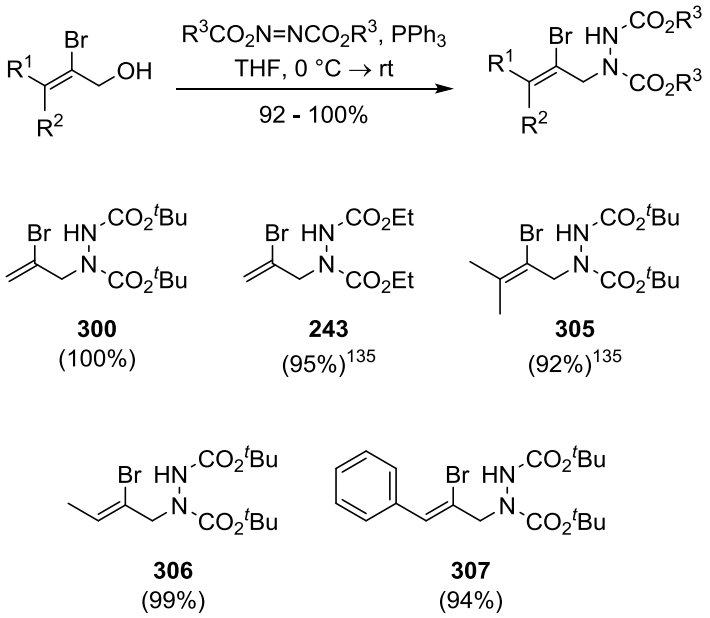
Scheme 2.34. Formation of 3-methylene-1,2-diazetidine **299** from 2-bromoallyl alcohol **242**.

To make other 3-methylene-1,2-diazetidines, we first had to synthesise the allylic alcohol starting materials. These were synthesised according to modified literature procedures from the unsaturated aldehydes.[164–166] Selective bromination of the double bond and subsequent reduction of the aldehyde provided the alcohols in good yields (Scheme 2.35). Compound **302** was isolated as a single geometric isomer consistent with literature precedence.[165]



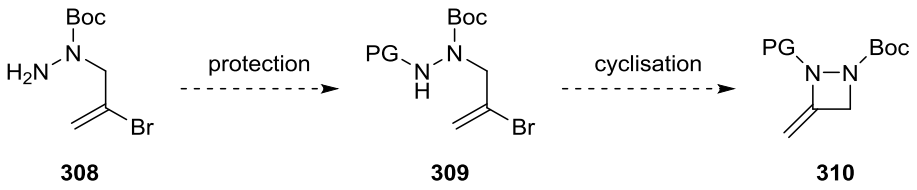
Scheme 2.35. Bromination and subsequent reduction to form alcohols **302** and **304**.[164–166]

Next, a range of hydrazodicarboxylates were synthesised in excellent yields using the Mitsunobu reaction conditions, starting from corresponding 2-bromoallyl alcohols (Scheme 2.36). Compounds **243** and **305** were made according to known literature procedures.[136]



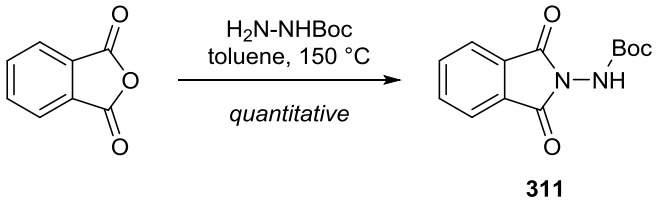
Scheme 2.36. Formation of hydrazodicarboxylates using Mitsunobu conditions.

Access to differentially protected 3-methylene-1,2-diazetidines posed a challenge, and their preparation has not previously been reported. Our approach is outlined in Scheme 2.37. In essence, it required selective protection of 1,1-disubstituted hydrazine **308** and further copper catalysed ring closure to give the desired product **310**.



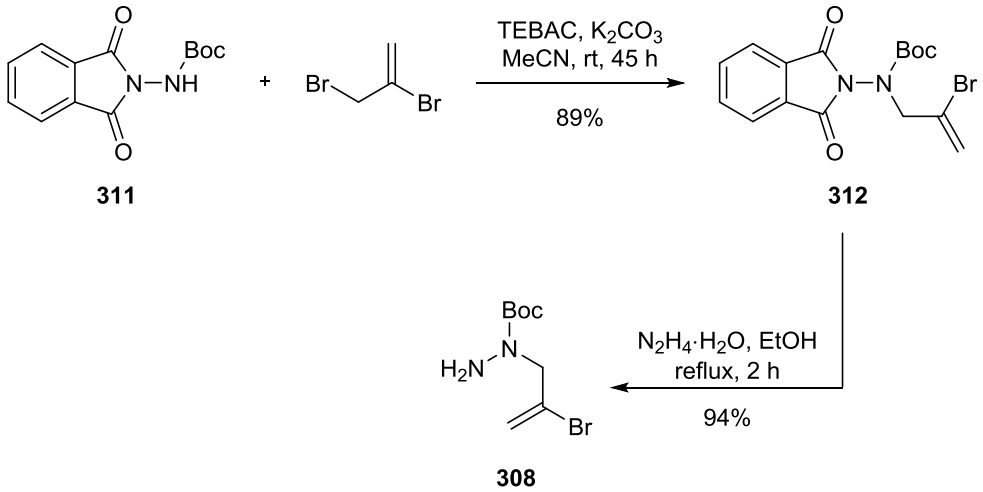
Scheme 2.37. Proposed route to differentially protected spirocyclic diazetidines **310**.

To this end, we repeated the known synthesis of **308** in three steps from phthalic anhydride. The first step involved synthesis of **311** from phthalic anhydride and *tert*-butyl carbazate. This reaction was performed according to a modified literature procedure using a Dean-Stark apparatus, producing **311** in quantitative yield (Scheme 2.38).[167,168]



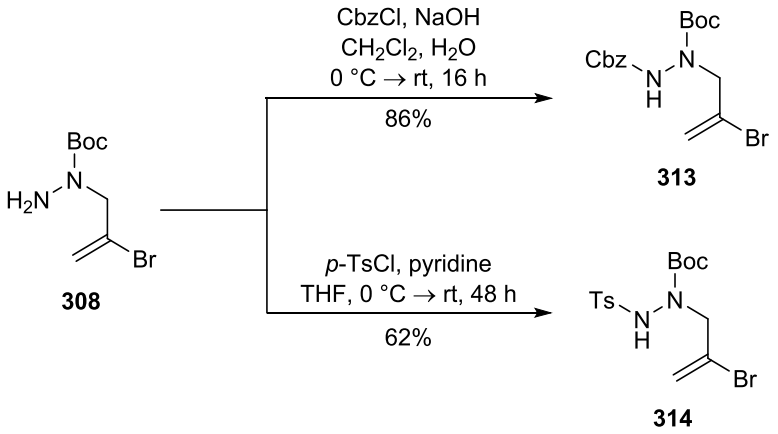
Scheme 2.38. Formation of **311** using Dean-Stark apparatus.[167,168]

Formation of *N*-allylhydrazine was performed according to the procedure of Mundal *et al*.[169] Alkylation of **311** occurred in good yields albeit slowly to provide **312**. Deprotection of the phthalimide group is known to occur using methylhydrazine hydrate.[169] However, due to the toxicity and limited availability of this material, we decided to switch to the use of hydrazine hydrate.[170] The reaction proceeded smoothly to give **308** without the need for further purification (Scheme 2.39).



Scheme 2.39. Alkylation followed by phthalimide cleavage to synthesise *N*-allylhydrazine **308**.

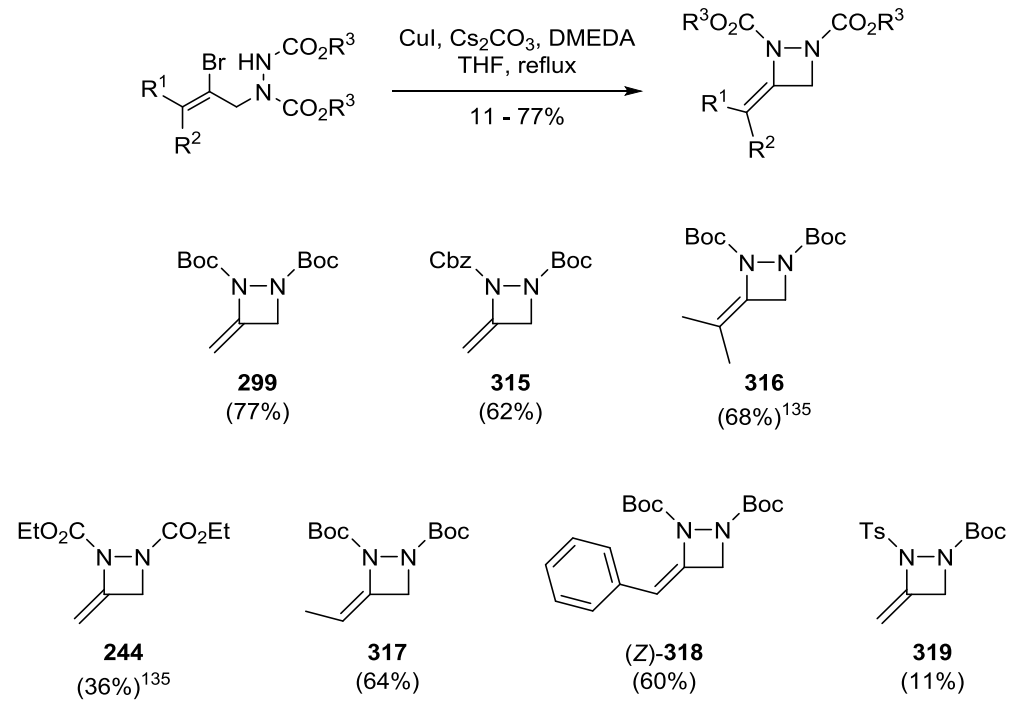
The primary amine of **308** could be protected with a variety of protecting groups to lay the foundation for the cyclisation reaction. Both carboxybenzyl (Cbz) and tosyl (Ts) protecting groups were introduced to allow selective cleavage in the presence of the Boc protecting group. Protection of **308** proceeded in good yields to give **313** and **314** respectively after purification (Scheme 2.40).



Scheme 2.40. Differential protection of *N*-allylhydrazine **308**.

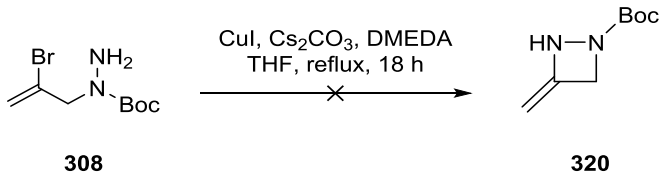
2.6.2.2 Cyclisation to 3-Methylene-1,2-Diazetidines

With the differentially protected hydrazodicarboxylates in hand, copper-catalysed cyclisation gave 3-methylene-1,2-diazetidines in moderate to good yields, as shown in Scheme 2.41. Low yield was observed with **319**, bearing a differentially protected sulphonamide. Compounds **244** and **316** were synthesised according to literature procedures.[136]



Scheme 2.41. Cyclisation to form 3-methylene-1,2-diazetidines.

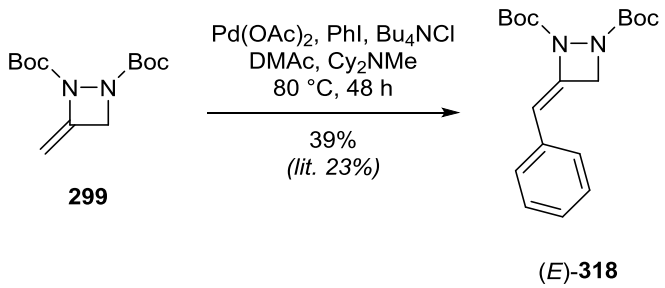
Direct cyclisation of **308** under the copper-catalysed conditions was attempted, but resulted in a complex mixture of products, with no evidence for **320** by ^{1}H NMR or mass spectrometry analysis (Scheme 2.42).



308 **320**

Scheme 2.42. Attempted cyclisation to form mono-protected 1,2-diazetidine **320**.

1,2-Diazetidine (*E*)-**318** was synthesised to observe if any changes occurred in the outcome/yield of the addition reaction to the double bond. Compound (*E*)-**318** was prepared following a reported Heck reaction procedure (Scheme 2.43).[148]



299 (*E*)-**318**

Scheme 2.43. Heck reaction of **299** to form (*E*)-**318**.

NOE studies were carried out on both (*E*)-**318** and (*Z*)-**318** to confirm the olefin geometries (Figure 2.11). Irradiation of H-1 on (*E*)-**318** caused an enhancement of phenyl H-3, which is indicative for the formation of the (*E*)-geometry. This enhancement was not observed for (*Z*)-**318**.

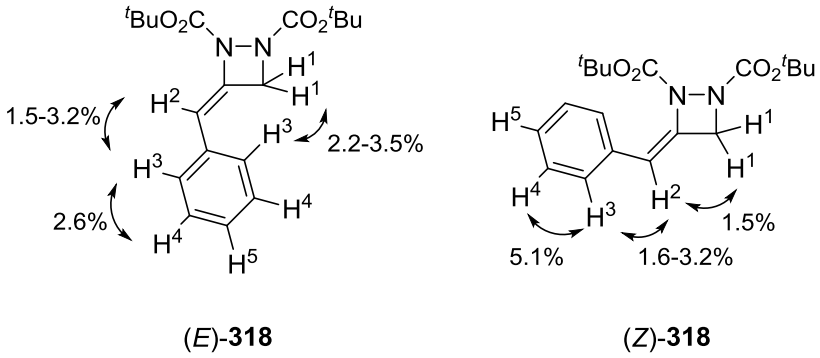


Figure 2.11. NOE enhancements of (*E*)-**318** and (*Z*)-**318**.

NOE studies were then conducted on the methyl series **317** (Figure 2.12). Enhancements were seen between H-1 and H-2 upon irradiation of H-1, however no enhancement was observed between H-1 and H-3, supporting the proposition of the (Z)-stereochemistry of **317**.

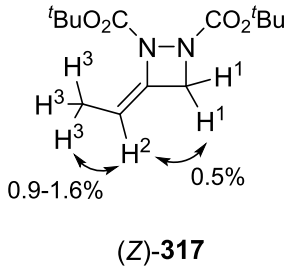
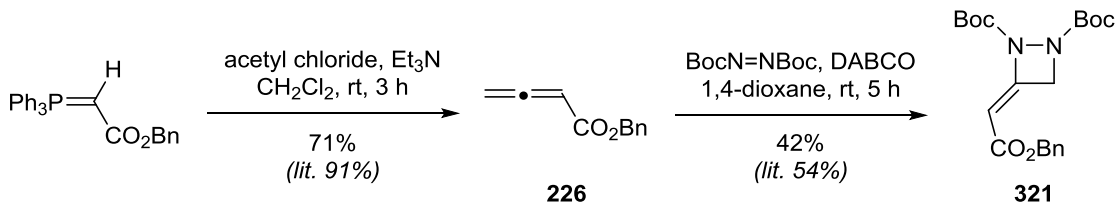


Figure 2.12. NOE enhancements of (*Z*)-**317**.

Xu *et al* have demonstrated the facile formation of 1,2-diazetidines from allenoates.[128] We used this approach to access 3-substituted methylene 1,2-diazetidines, bearing an electron withdrawing group on the exocyclic double bond. Allene **226** was synthesised according to literature procedures,[171] with subsequent formation of diazetidine **321** occurring in moderate yield (Scheme 2.44).



Scheme 2.44. Substituted methylene diazetidine **321** from allenonate **226**.[128,171]

With a variety of 1,2-diazetidines in hand, the next step involved testing these substrates under cyclopropanation conditions. Carbene chemistry is well explored for cyclopropanation reactions.[172] Since low yields and double addition was observed with carbene itself (Scheme 2.30), we chose to examine less reactive carbenes. Our studies began with exploring difluorocarbene chemistry.

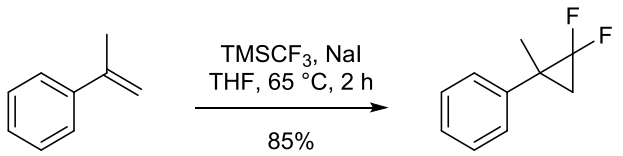
2.7 Synthesis of 4,5-Diazaspiro[2.3]hexanes

2.7.1 Cyclopropanation by Difluorocarbenes

Organofluorine compounds have gathered much attention in recent decades, in particular due to their biological properties. The introduction of fluorine into drug structures to block sites of metabolism and improve physiochemical properties is well understood.[173] A recent review on fluorinated carbenes highlights the extensive use of these reactive species for a wide range of reactions, including cyclopropanation reactions.[174] Due to stabilisation from π-donation of the fluorine atoms to the carbon, coupled with the negative inductive effect, the resulting difluorocarbene is highly reactive towards electron rich substrates.[175]

Several methods have been developed for synthesising difluorocarbenes, with the simplest route from chlorodifluoromethane developed by Buddrus and co-workers.[176] Difluorocarbene has been reported to be generated through a phase transfer catalysed (PTC) method, albeit in poor yields using an arsenium catalyst, although most methods have indicated rapid hydrolysis at the phase boundary, which prevents cycloaddition reactions with alkenes.[177]

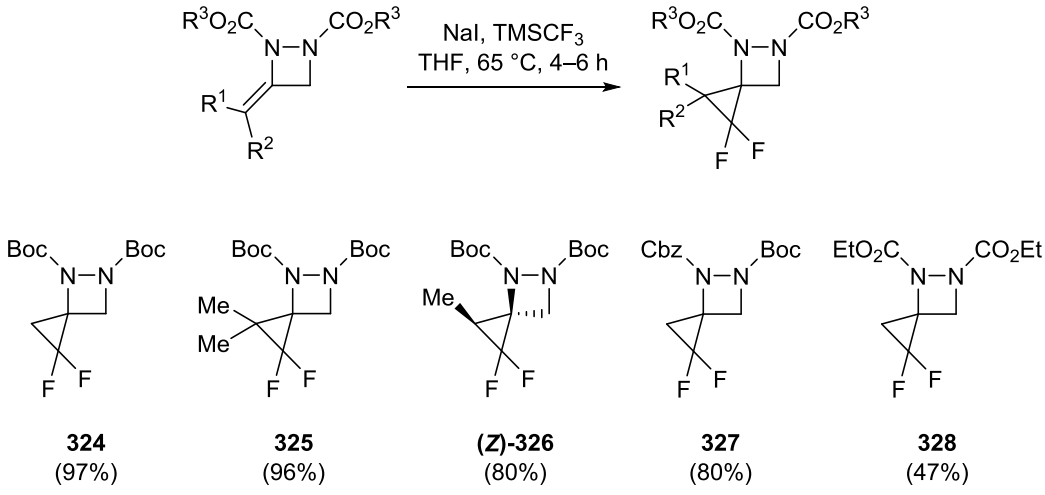
Alternative routes have been developed, most commonly involving trifluoromethyl reagents.[178,179] Waldman and co-workers generated difluorocarbene from trimethyl(trifluoromethy1)tin at elevated temperatures, which subsequently reacted with alkenes to form difluorocyclopropanes in high yields.[180] More recently, Wang *et al* have used the Ruppert-Prakash reagent $TMSCF_3$ as a difluorocarbene source under sodium iodide activation for the synthesis of *gem*-difluorocyclopropanes in high yields (Scheme 2.45).[181]



322 **323**

Scheme 2.45. Difluorocyclopropanation of **322** using the Ruppert-Prakash reagent.[181]

Attracted by this mild method, we examined these conditions for the difluorocyclopropanation of 3-methylene-1,2-diazetidines. We were pleased to observe efficient cyclopropanation with a range of substrates by way of difluorocarbene addition to the exocyclic double bond, achieving near quantitative yields for **324** and **325** (Scheme 2.46). The scope of this chemistry revealed that it works well for di-, tri- and tetrasubstituted alkenes, and tolerates variation of the nitrogen protecting group.



324 (97%) **325** (96%) **(*Z*)-326** (80%) **327** (80%) **328** (47%)

Scheme 2.46. Difluorocyclopropanation of 3-methylene-1,2-diazetidines.

Suitable crystals were grown of **324** for X-ray crystallography, unambiguously establishing the structure and revealing the spirocyclic scaffold (Figure 2.13). In the solid-state, the two nitrogen atoms display tetrahedral character with the Boc groups projecting on opposite faces of the four-membered ring. The fluorine atoms also appear to play a role in controlling the *N*-stereochemistry with the difluoromethylene and the adjacent Boc group orientating themselves away from one another.

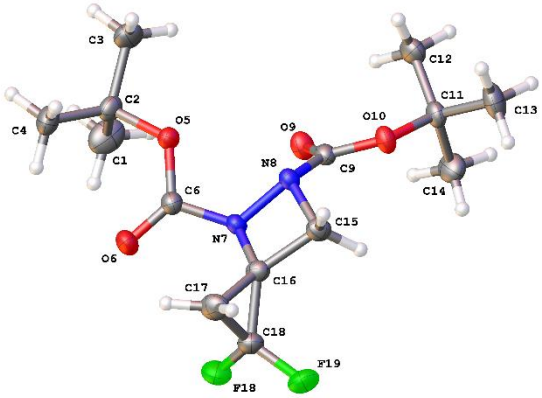
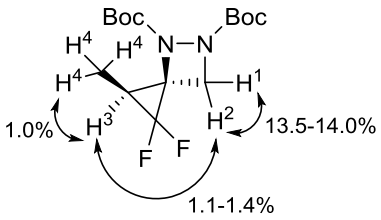


Figure 2.13. X-ray crystal structure of **324**.

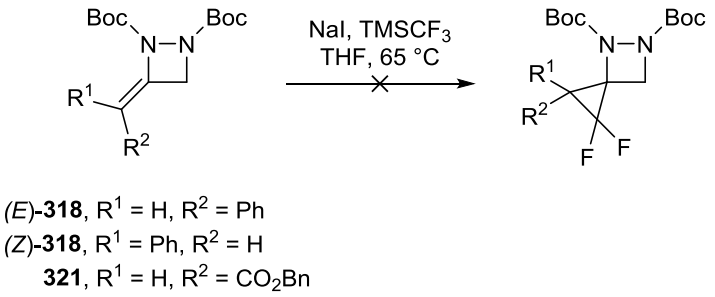
In the difluorocarbene addition to (*Z*)-**317**, only a single diastereoisomer of **326** was produced, whose stereochemistry was determined on the basis of NOE experiments (Figure 2.14). Irradiation of H-2 revealed an enhancement to H-3, whilst no enhancements were observed between H-1/H-2 and H-4, consistent with stereospecific addition across (*Z*)-**317** with net retention of the olefin geometry.



(*Z*)-**326**

Figure 2.14. NOE enhancements of (*Z*)-**326**.

When electron deficient substituents were present on the double bond no reaction was observed for diazetidines **318** and **321**. Only starting material was recovered from these reactions even with prolonged reaction times and increased reaction temperatures (Scheme 2.47).



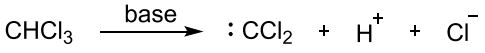
(*E*)-**318**, R^1 = H, R^2 = Ph
(*Z*)-**318**, R^1 = Ph, R^2 = H
321, R^1 = H, R^2 = CO_2Bn

Scheme 2.47. Attempted difluorocyclopropanation of methylene diazetidines **318** and **321**.

With the success obtained with difluorocarbenes, we next turned our attention to dichlorocarbenes.

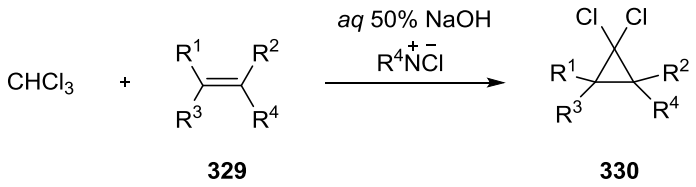
2.7.2 Cyclopropanation by Dichlorocarbenes

In the 1950s, Doering and Hoffman used dihalocarbenes for the synthesis of *gem*-dihalocyclopropanes.[182] These carbenes are typically generated from chloroform in an α-elimination process, with loss of hydrogen chloride (Scheme 2.48).[177]



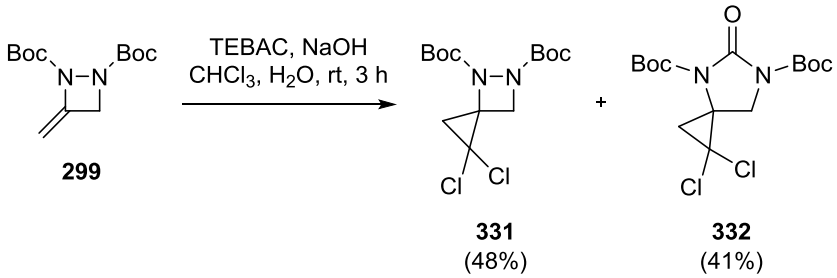
Scheme 2.48. Formation of dichlorocarbene from chloroform.[177]

Due to the rapid hydrolysis of the intermediate anion, early reports indicated the requirement for these reactions to be conducted under anhydrous conditions.[183] In 1969, Mąkosza demonstrated the reaction can be performed in aqueous media in a two-phase system with the presence of a quaternary salt acting as a phase-transfer catalyst (Scheme 2.49).[184] Many examples including enantioselective variants have since been reported.[177,185]



Scheme 2.49. General formation of dichlororcyclopropane **330**.[177]

3-Methylene-1,2-diazetidine **299** was subjected to such cyclopropanation conditions using a 50% solution of NaOH and TEBAC as the phase transfer catalyst (Scheme 2.50). The reaction was complete within 3 hours giving spirocycle **331** in 48% yield, alongside ring expanded by-product **332** in near equal quantity. Scaling up the reaction (2 mmol) led to no significant change in the yield of **331** (49%).



Scheme 2.50. Cyclopropanation to give desired spirocycle **331** and ring expanded compound **332**.

Spectroscopic evidence revealed the major isolated product to be **331**. The ^{1}H NMR spectrum displayed four sets of doublets, corresponding to the ring hydrogens. The diastereotopic protons at 2.79 ppm and 1.57 ppm were assigned to the cyclopropane ring protons, with the large shift difference attributed to the closeness of one of the hydrogens to the Boc protecting group on the adjacent nitrogen atom. Carbon NMR analysis revealed two carbonyl peaks, alongside two quaternary signals for the spiroatom and CCl_2 carbon atom at 57.4 ppm and 56.0 ppm. Mass spectrometry revealed the chlorine isotopic distribution (9:6:1) for the presence of two chlorine atoms.

As the product was isolated as a white crystalline solid, an X-ray crystal structure was also obtained, confirming its identity as the four-membered ring (Figure 2.15). In the solid-state, the nitrogen atoms adopt a pyramidal geometry, with the two Boc protecting groups projected away from one another. The two chlorine atoms are also seen to orientate away from the nitrogen adjacent to the spirocentre.

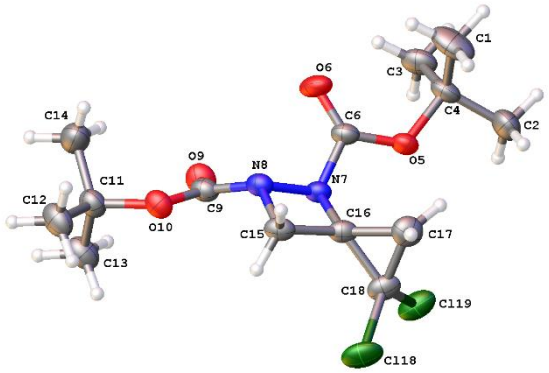


Figure 2.15. X-ray crystal structure of **331**.

Compound **332** possessed an additional carbonyl peak in the ^{13}C NMR spectrum, alongside an additional band for a carbonyl stretch in the IR spectrum. X-ray crystallography confirmed its identity to be that of the five-membered ring, arising from over-insertion into the N-N bond (Figure 2.16).

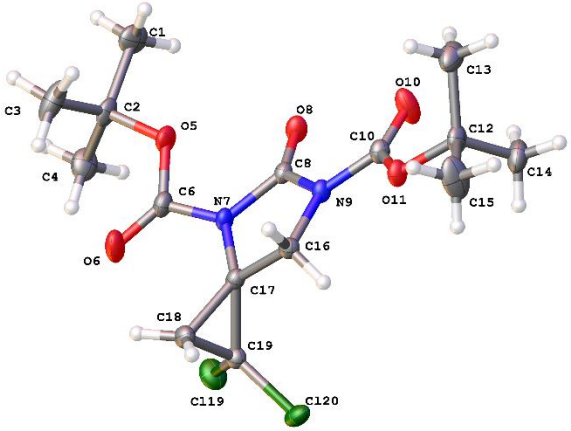
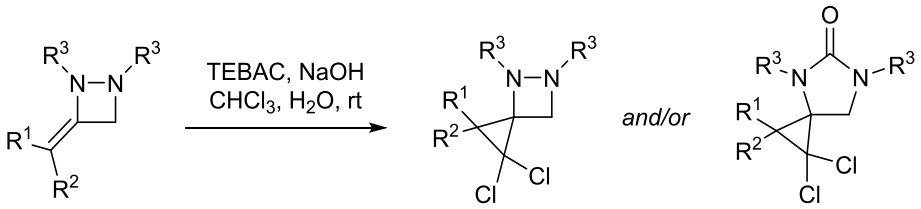
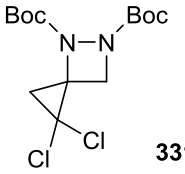
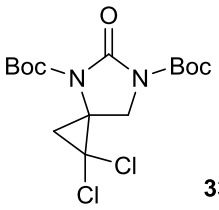
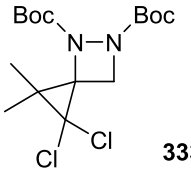
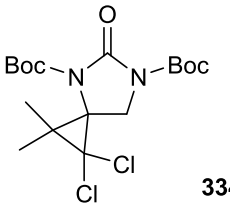
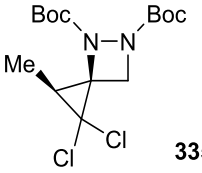
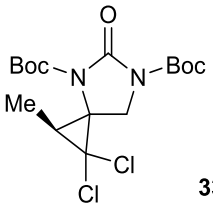
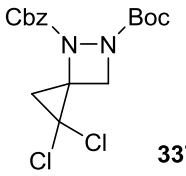
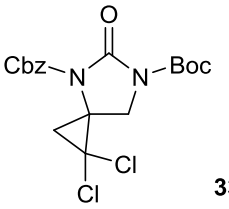
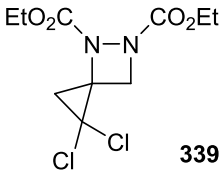
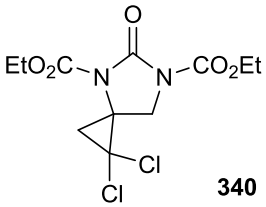
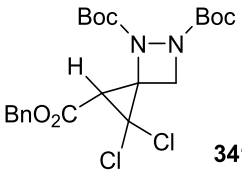
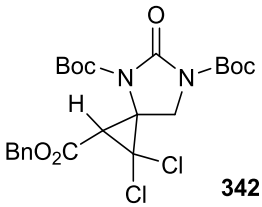


Figure 2.16. X-ray crystal structure of **332**.

2.7.2.1 Scope of Dichlorocyclopropanation

Methylene 1,2-diazetidines were subjected to the chlorination conditions to test the scope of this reaction. In most cases, a mixture of four and five membered rings (4MR:5MR) was obtained, with the results outlined in Table 2.6. Optimisation of the reaction time with careful monitoring of product formation by TLC was necessary to obtain satisfactory yields in these dichlorocarbene additions. Higher yields of 57% were observed with tetrasubstituted product **333** for the 4MR (entry 2). A single diastereomer was isolated for **335** in a 42% yield (entry 3). Differentially protected diazetidine **315** revealed formation of only the 5MR **338**, with no evidence for 4MR formation (entry 4). Surprisingly, only the 4MR **339** was isolated after purification with the less bulky ethyl carboxylate protecting group, with no evidence of the ring expanded product detected by mass spectrometry (entry 5). The addition of an electron withdrawing group on the exocyclic double bond led to no improvement in yield, with only traces of **342** isolated for the benzyl ester and no evidence of the desired addition product (entry 6). Most likely steric hindrance of this bulky substituent alongside the bulky Boc groups account for the poor yield of this reaction. Diazetidine (*E*)-**318** gave only 11% of **343** isolated as a single diastereomer (entry 7), whilst no evidence for **345** was observed with (*Z*)-**318** (entry 8).



Entry	Diazetidine	Time (min)	Product(s) of 4MR and 5MR	Yield (%) 4MR: 5MR[a]
1	**299**	180	 **331**  **332**	48 : 41
2	**316**	75	 **333**  **334**	57 : 9
3	**317**	15	 **335**  **336**	42 : 9
4	**315**	120	 **337**  **338**	0 : 42
5	**244**	360	 **339**  **340**	64 : 0
6	**321**	360	 **341**  **342**	0: 12

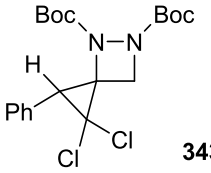
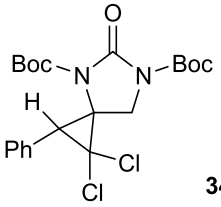
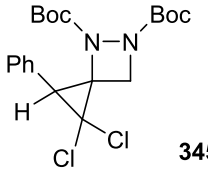
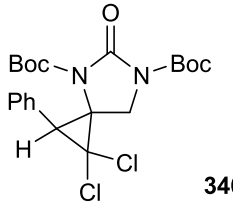
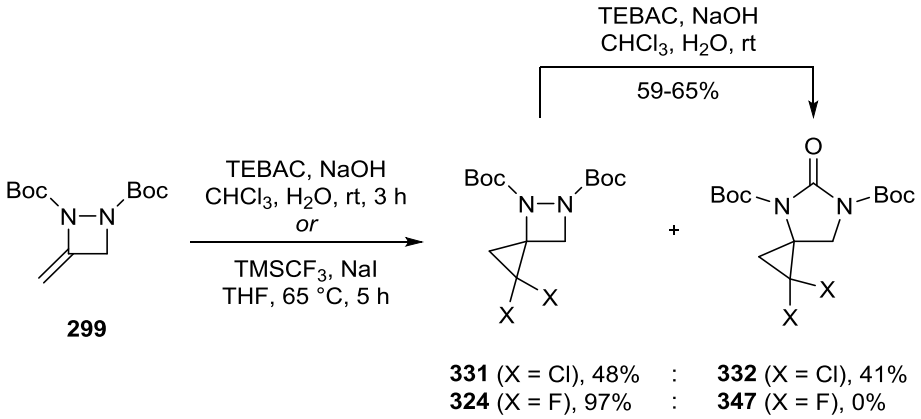
7	(*E*)-**318**	300	 **343**	 **344**	11 : 58
8	(*Z*)-**318**	300	 **345**	 **346**	0 : 0

Table 2.6. Dichlorocyclopropanations of 3-methylene-1,2-diazetidines. [a]Isolated yields of four membered-ring (4MR) and five-membered ring (5MR) products following column chromatography.

In an attempt to improve the yields of 4,5-diazaspiro[2.3]hexanes, the reactions of **316** and **317** with dichlorocarbene were repeated with careful monitoring of the reaction by TLC and mass spectrometry. Performing the reaction of **316** for a longer period of time of 3 h gave a higher quantity of the urea by-product (**333**, 42%: **334**, 21%). However, quenching the reaction after 75 min enabled isolation of **333** in an improved 57% yield. A similar observation was seen with **317**, with largely only 5MR **336** isolated after reacting **317** for 4 h. Thus, by altering the reaction time, more of the desired product could be isolated.

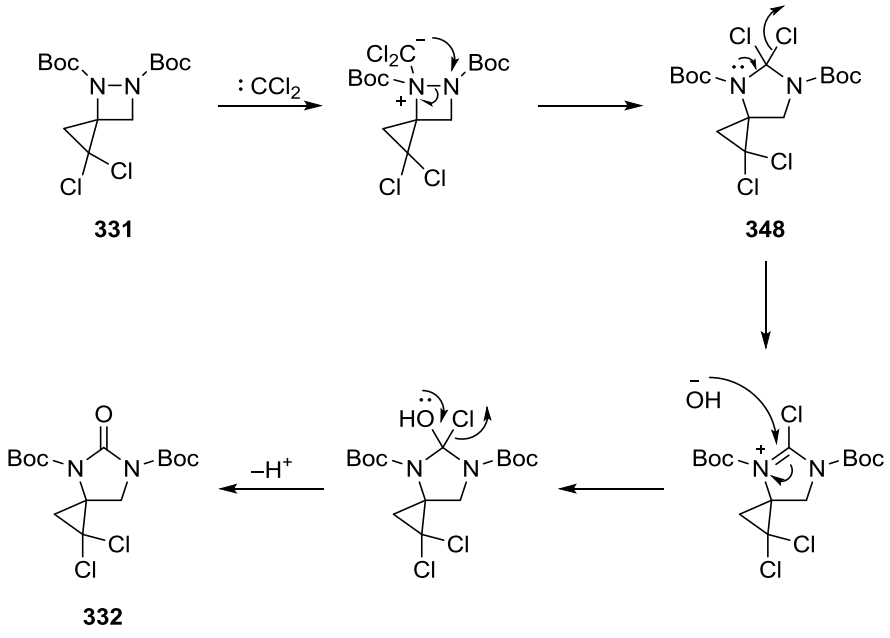
The observation that increasing quantities of **334** were seen over longer reaction times suggested that the ring expanded product is arising from **333**. To test this theory, **331** was re-subjected to the chlorination conditions. Clean conversion to **332** was observed in 65% yield, providing evidence that initial cyclopropanation is the faster process, with further ring expansion of the diazetidine ring occurring in the presence of excess dichlorocarbene (Scheme 2.51). Although this process is essentially unprecedented, Taylor and Davies have reported evidence for intramolecular insertion of a rhodium carbenoid into the N–N bond of a 1,2-diazetidin-3-one.[186] Whilst ring expansion was not observed in reactions involving difluorocarbene, indirect access to these products is possible by treatment of **324** with dichlorocarbene to form **347** in 59% yield.



Scheme 2.51. Subjecting **324** and **331** to dichlorocyclopropanation conditions.

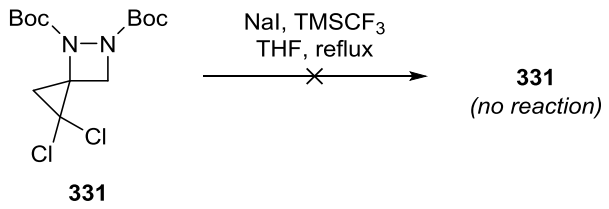
2.7.2.2 Mechanistic Proposal for Formation of Ring Expanded Product

It is proposed that initial dichlorocarbene insertion into the N–N bond forms intermediate **348**, which upon hydrolysis of the two labile C–Cl bonds under the phase transfer catalysed conditions leads to **332** with presence of the urea carbonyl bond (Scheme 2.52).



Scheme 2.52. Proposed mechanism for the formation of **332**.

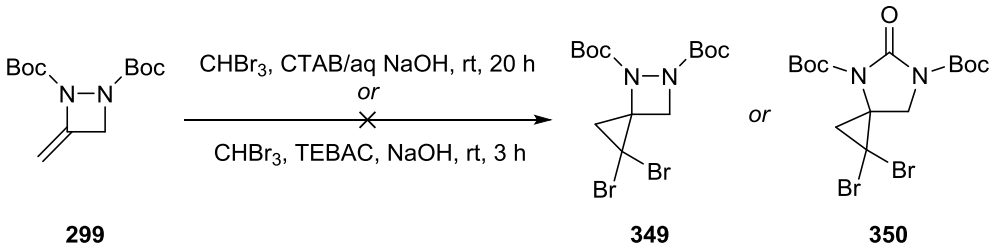
For a direct comparative study, **331** was subjected to the difluorination conditions, and no evidence of the five-membered ring was observed, with only starting material isolated from the reaction (Scheme 2.53).



Scheme 2.53. Subjecting spirocycle **331** to difluorocyclopropanation conditions.

2.7.3 Attempted Cyclopropanation by Dibromocarbenes

Attempts to use dibromocarbene in this chemistry was not productive. When **299** was reacted with conditions reported by Yu *et al*,[187] using cetyltrimethylammonium bromide as the phase transfer catalyst in aqueous NaOH, formation of **349** was not observed even after prolonged reaction times. A complex mixture of products was obtained following work-up. The same observation was made using TEBAC as catalyst, although the starting material **299** was consumed at a much faster rate (Scheme 2.54).

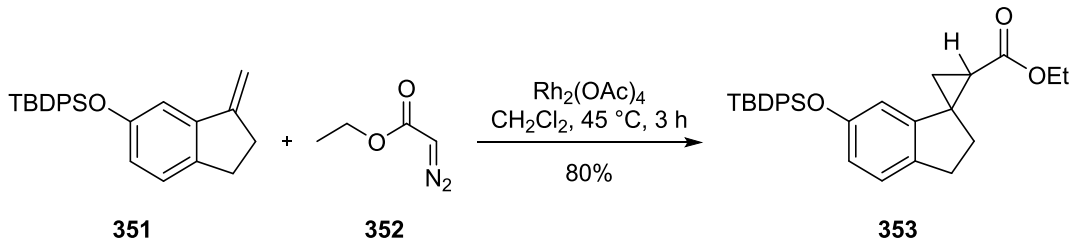


Scheme 2.54. Attempted dibromocyclopropanation of diazetidine **299**.

Earlier studies have suggested that hydrolysis occurs rapidly with dibromocarbenes under PTC conditions.[177] Nagarajan *et al* reported the use of potassium fluoride and alkali can be more effective in these reactions.[188] Due to time constraints, further investigations using these conditions was not explored.

2.7.4 Asymmetric Cyclopropanations of 1,2-Diazetidines

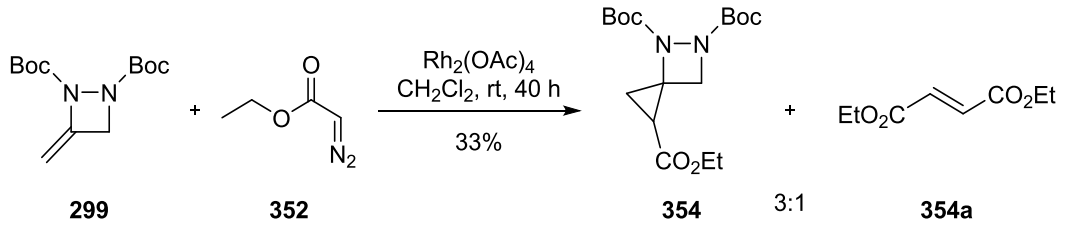
This chemistry also offers the potential to effect enantioselective additions.[189] Our work on Rh(I) catalysed asymmetric hydrogenations[137] further encouraged this line of investigation. Metal-catalysed carbene chemistry has long been known as a convenient method for cyclopropanation reactions. Most commonly, carbenes generated from the decomposition of diazo compounds have widely been applied for stereoselective cyclopropanation reactions.[189] For example, Wang and co-workers synthesised **353** using rhodium(II) acetate dimer catalysed addition of ethyl diazoacetate **352** to **351** in 70% yield. This compound was used for the synthesis of GPR40, a target pursued for type II diabetes (Scheme 2.55).[190,191]



351 **352** **353**

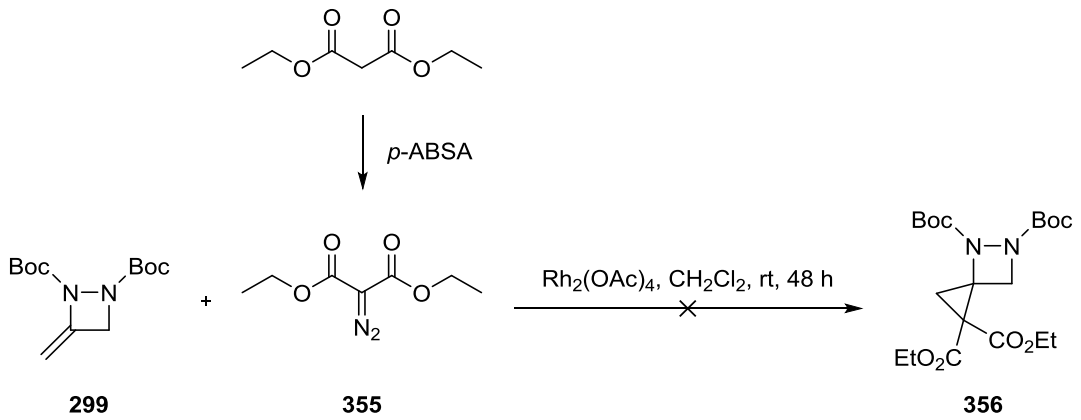
Scheme 2.55. Synthesis of **353** using rhodium carbene chemistry.[191]

Thus, we sought to explore the application of this methodology to 3-methylene-1,2-diazetidine substrates. Diazo substrates with electron-withdrawing groups are known to be most effective for these reactions.[189] Using ethyl diazoacetate **352**, 1,2-diazetidine **299** was subjected to the reaction conditions at ambient temperature. Further equivalents of **352** were added over two days until full consumption of starting material **299**. Purification afforded the desired product **354** as a mixture of diastereomers by ^{1}H NMR co-eluting with dimerised carbene **354a** in a 3:1 ratio respectively (Scheme 2.56). However, attempts at removing by-product **354a** were unsuccessful.



Scheme 2.56. Rhodium catalysed cyclopropanation of **299**.

As the yield of the reaction was poor, the carbene source was switched to disubstituted carbene **355**, with the aim to help prevent dimerization, and eliminate the complications arising from diastereoisomers. Diazo compound **355** was prepared from diethyl malonate in quantitative yield using a modified procedure.[192] Subjecting **299** to the reaction conditions indicated slow consumption of the starting material, and formation of the desired product **356** (*m/z* = 451, $[M+Na]^+$) by mass spectrometry. Additional equivalents of **355** were added over two days until the reaction was complete. Unfortunately, attempts to isolate **356** were again unsuccessful (Scheme 2.57).



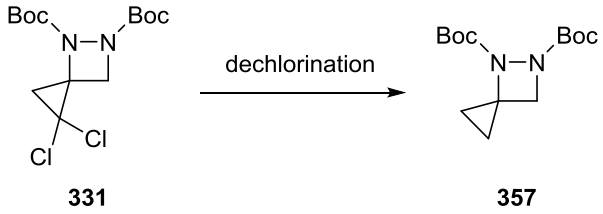
Scheme 2.57. Attempted cyclopropanation of **299** using diazo **355**.

Due to time constraints, this chemistry was not further explored. However, it was anticipated that through further optimisation a suitable set of conditions could be obtained, with a view to applying this to the asymmetric synthesis of spirocyclic diazetidines.

2.7.5 Manipulations of 4,5-Diazaspiro[2.3]hexanes

2.7.5.1 Attempted Dechlorination

Dehalogenation of *gem*-dichlorocyclopropanes is an efficient method for the preparation of cyclopropane derivatives, as an alternative to the direct synthesis by the Simmons-Smith cyclopropanation. A variety of methods are known for the removal of one or both of the halogen atoms,[177] most often following a radical based approach. Using alkali metals in a mixture of alcohol and diethyl ether solvents has been shown to be effective.[193,194] However, when **331** was subjected to these conditions, a complex mixture of compounds was obtained with no evidence of the monohalogenated compound or the desired product **357**. Catalytic hydrogenation of **331** gave only recovered starting material even with additional catalyst added (10 mol%). These latter conditions can result in ring opening of the cyclopropane ring, however, this was not seen for **331** (Table 2.7).[177]



331 **357**

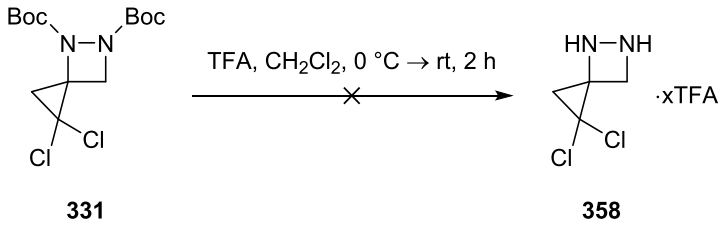
Entry	Reaction Conditions	Product
1	Na, MeOH, Et_2O, 0 °C → rt, 18 h[193]	0%[a]
2	Li, ^{t}BuOH, Et_2O, rt → 70 °C, 18 h[194]	0%[a]
3	H_2, Pd/C, MeOH, rt, 16 h	**331**, 92%

Table 2.7. Dechlorination studies on **331**. [a]Complex mixture produced.

2.7.5.2 Deprotection of Spirocyclic 1,2-Diazetidines

Going forward, we next examined the deprotection of the spirocyclic compounds. Initially, we began with substrate **331**, as deprotection of both Boc groups would allow for diversification on both free NH's. Deprotection was attempted using conventional methods with trifluoroacetic acid. Full consumption of **331** was

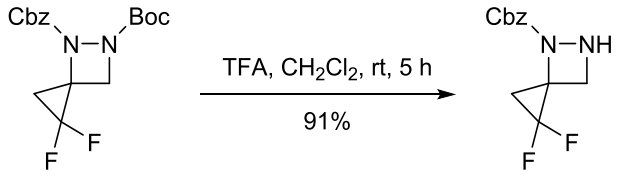
achieved in two hours with evidence of a polar compound by TLC. However, ^{1}H NMR analysis of the crude reaction revealed no evidence of **358** formation, and rapid decomposition of the material was observed (Scheme 2.58).



331 **358**

Scheme 2.58. Attempted deprotection of the Boc protecting groups of **331**.

With the differentially protected spirocyclic compounds in hand, we explored deprotection of the respective protecting groups individually to provide a single free NH, which could undergo further selective transformations. Facile deprotection of the Boc group was achieved using TFA, with subsequent removal of the TFA by washing with sodium bicarbonate to form **359** in a 91% yield (Scheme 2.59).

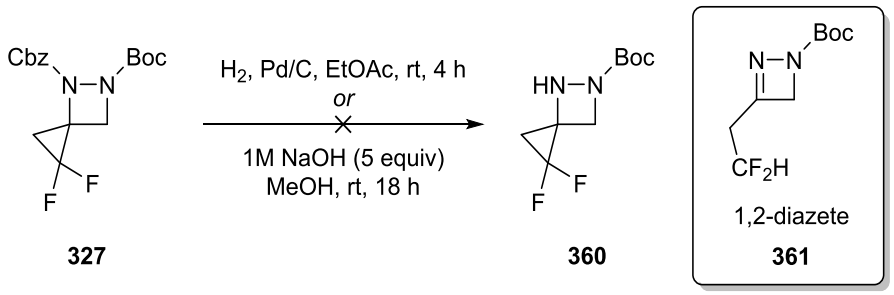


327 **359**

Scheme 2.59. Deprotection of the *tert*-butyloxycarbonyl group in **327**.

Deprotection of the Cbz group was attempted using catalytic hydrogenation, with **327** consumed by mass spectrometry analysis and presence of a polar compound by TLC. Analysis of the crude material revealed unknown products, despite mass spectrometry evidence suggesting that the product **360** (*m/z* = 242, $[M+Na]^{+}$) had been successfully formed (Scheme 2.60). Half of the crude material was treated with 2.0 M HCl in Et_2O in an attempt to isolate it as the HCl salt, and the remainder subjected to column chromatography in an attempt to isolate the free amine. Neither approach was fruitful. NMR analysis of the crude material suggested possible

formation of 1,2-diazete **361** through involvement of the free NH following deprotection, but spectroscopic analysis was inconclusive. Possible evidence for this arose from lack of a Cbz COO group, and increased splitting of the difluoro substituent from ring opening of the spirocycle. Due to the nature of the Cbz protecting group on the diazetidine NH, it was thought that its behaviour may resemble an ester more than a carbamate group. Thus, **327** was subjected to hydrolysis conditions using NaOH. However, this reaction also failed to yield **360**.



Scheme 2.60. Attempted removal of Cbz group from **327**.

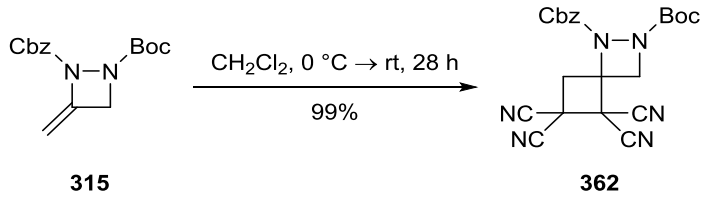
This chemistry was also unsuccessful on larger ring systems (Scheme 2.64).

Having explored cyclopropanation reactions on the exocyclic double bond of methylene-1,2-diazetidines, our efforts moved onto other spirocyclic ring sizes. We next turned our attention to the formation of 1,2-diazaspiro[3.3]heptanes as discussed below.

2.8 Synthesis of 1,2-Diazaspiro Compounds

2.8.1 Synthesis of 1,2-Diazaspiro[3.3]heptanes

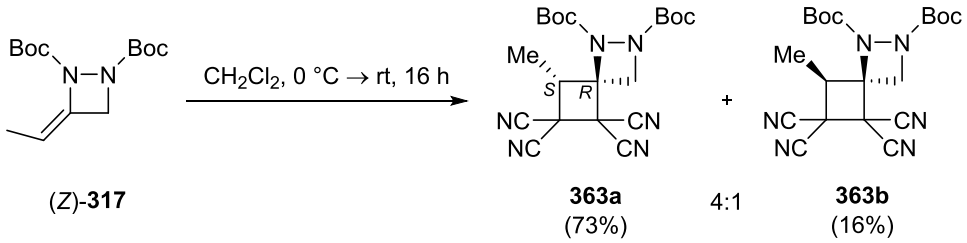
Here, we wished to expand the scope of [2+2] cycloadditions as previously reported (Scheme 2.32). Specifically, to explore the use of differentially protected 3-methylene-1,2-diazetidine and those bearing a single substituent on the alkene. Thus, reaction of **315** with TCNE (1 equiv) efficiently provided **362** in near quantitative yield. A further 0.5 equiv of TCNE were added at 0 °C after 20 h to ensure complete consumption of **315** (Scheme 2.61).



315 **362**

Scheme 2.61. [2+2] cycloaddition of differentially protected diazetidine **362** using TCNE.

Using (*Z*)-**317**, reaction with TCNE proceeded in good yield to give a 4:1 mixture of diastereomers as determined by ^{1}H NMR, with the major diastereomer **363a** isolated in 73% yield (Scheme 2.62). Unfortunately, during purification the minor diastereomer proved unstable to column chromatography.



(*Z*)-**317** **363a** (73%) 4:1 **363b** (16%)

Scheme 2.62. Synthesis of **363** from [2+2] cycloaddition using TCNE.

Surprisingly, the major diastereomer **363a** from this reaction possesses the (*R*,*S*)-stereochemistry, which was confirmed by NOE experiments (Figure 2.17). Irradiation of H-2 saw an enhancement of H-4, whilst an irradiation of H-3 only saw an enhancement of H-4. This was further seen in the NOESY spectrum, which showed a correlation between H-2 and H-4 (see Appendix III). These results indicated that the methyl group is located on the same face as the methylene group of the diazetidine ring.

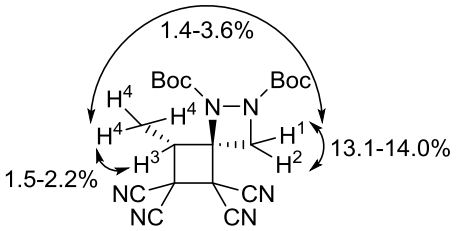
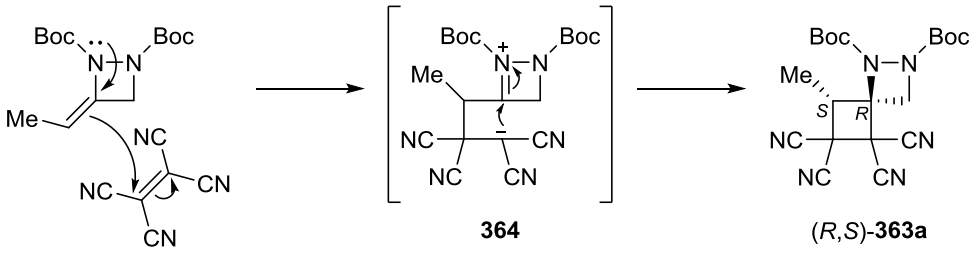


Figure 2.17. NOE enhancements of **363a**.

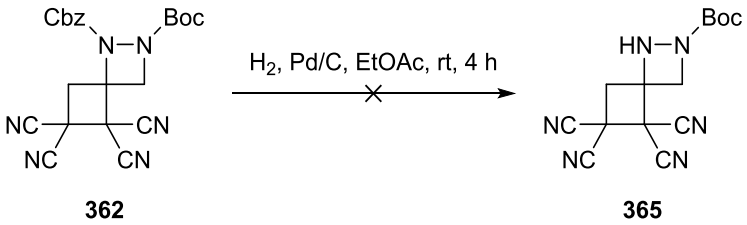
Unlike the carbene additions to (*Z*)-**317** which proceed stereospecifically with retention of the olefin geometry, (*R*,*S*)-**363a** arises from inversion of configuration with respect to the starting alkene. This outcome suggests that the reaction proceeds in a stepwise manner via zwitterionic intermediate **364**, with subsequent ring closure to (*R*,*S*)-**363a** (Scheme 2.63). Studies on the [2+2] cycloaddition reactions with TCNE with electron-rich alkenes have established the mechanism to commonly proceed through a non-concerted ionic process, involving a zwitterionic intermediate.[195,196] In earlier accounts, the reaction has been reported to favour retention of the olefin stereochemistry in non-polar solvents such as dichloromethane.[196] Analysis of molecular models indicates that (*R*,*S*)-**363a** diastereoisomer is less sterically crowded than the (*R*,*R*)-diastereomer, which presumably explains why it is favoured in ring closure of **364**.



Scheme 2.63. Proposed stepwise mechanism for synthesis of (*R*,*S*)-**363a**.

The scope of this reaction was further explored. Unfortunately, no reaction was observed for both the phenyl (*E*)-**318** and the benzyl ester derivative (*E*)-**321**. Only starting material was recovered for both reactions, even after prolonged reaction times and/or heating.

Next, deprotection of the Cbz group of spirocycle **362** was attempted using hydrogenation conditions as previously examined for 4,5-diazaspiro[2.3]hexanes (Scheme 2.60). However, no evidence of **365** was detected (Scheme 2.64).

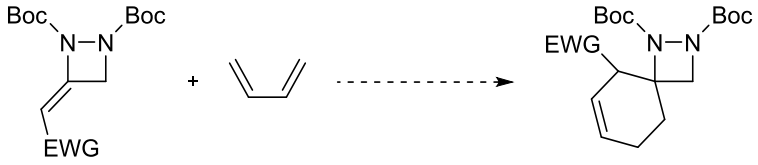


362 **365**

Scheme 2.64. Attempted removal of Cbz group of **362**.

2.8.2 Attempted Synthesis of 1,2-Diazaspiro[3.5]nonanes

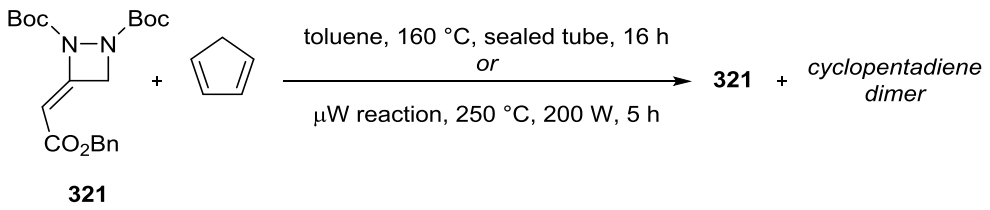
With previous attempts at Diels Alder reactions on 3-methylene-1,2-diazetidines unsuccessful, it was envisaged that adding an electron withdrawing group onto the end of the double bond may increase its reactivity. Thus, by lowering the LUMO of the dienophile, it might enable [4+2] cycloadditions to proceed (Scheme 2.65).



366 **367**

Scheme 2.65. Proposed synthetic route to accessing variants of **367** using Diels-Alder cycloaddition.

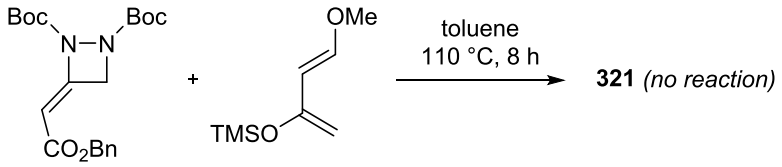
Diazetidine **321** was subjected to freshly cracked cyclopentadiene, and the reaction heated to 160 °C in a sealed tube. Unfortunately, only **321** and cyclopentadiene dimer were isolated. No evidence of product was observed by performing the reaction in a microwave reactor, with only starting material recovered (Scheme 2.66).



321

Scheme 2.66. Attempted cycloaddition of **321** using conventional and microwave methods.

Next, the Diels-Alder reaction was attempted with the electron-rich Danishefsky's diene **368**. However, again no reaction was observed, even with heating to reflux for an extended period of time (Scheme 2.67).



321 **368**

Scheme 2.67. Attempted Diels-Alder reaction of **321** using Danishefsky's diene.

With no initial success achieved with the Diels-Alder reactions, no further work was carried out on this topic. It seemed that activation of the double bond for a [4+2] cycloaddition reaction was proving difficult. An alternative solution would be to have two electron withdrawing groups attached to the exocyclic double bond of 3-methylene-1,2-diazetidines to further encourage the cycloaddition.

2.9 Conclusions

We have successfully developed the first synthesis of spirocyclic 1,2-diazetidines by way of carbene addition across the double bond of 3-methylene-1,2-diazetidines.[197] The success of this chemistry was demonstrated to be dependent upon the reactivity of the carbene. Unreactive carbenes such as difluorocarbene gave clean reactions to generate 1,1-difluoro-4,5-diazaspiro[2.3]hexanes from di-, tri- and tetrasubstituted alkenes in up to 97% yield and tolerated variations in the *N*-protecting group

(Scheme 2.46). When electron withdrawing groups were present on the double bond, no reaction was observed. When reactions were performed with a stereochemically defined double bond, stereospecific addition across the double bond provided the spirocycles with net retention of the olefin geometry.

With the more reactive dichlorocarbene, acceptable yields of the 1,1-chloro-4,5-diazaspiro[2.3]hexanes were achieved by controlling the reaction conditions under phase transfer catalysed conditions (Table 2.6). Alongside the desired spirocycle, a novel ring expansion of the four-membered ring to give a urea by-product was seen, arising from N–N bond insertion in the presence of excess dichlorocarbene. Competitive experiments provided insight into the order of events, suggesting that carbene addition across the double bond is the faster process (Scheme 2.51).

Preliminary reactions on asymmetric Rh-catalysed cyclopropanations gave encouraging results, forming a mixture of diastereoisomers alongside a dimerised by-product (Scheme 2.56).

Successful deprotection of the Boc protecting group from differentially protected spirocycle was high yielding, revealing a free NH for functionalisation. Unfortunately, attempted removal of the Cbz protecting group resulted in the formation of a complex mixture (Scheme 2.60).

Facile [2+2] cycloaddition reactions of methylene diazetidines with tetracyanoethylene formed 1,2-diazaspiro[3.3]heptane in near quantitative yield for differentially protected substrates. This chemistry was extended to trisubstituted double bonds with mono-methylated **317** providing a mixture of diastereomers (Scheme 2.62). Based on NOE experiments, it was established that the major diastereomer resulted from an asynchronous [2+2] cycloaddition with inversion of configuration with respect to the starting alkene. This key insight revealed the mechanism of the reaction to proceed *via* a non-concerted process. Extension of this work to [4+2] Diels-Alder cycloadditions was unsuccessful, isolating only starting material from the reactions (Scheme 2.68 and 2.69).

2.10 Future Work

Due to time constraints, the asymmetric cyclopropanation using rhodium catalysis could not be further developed. Optimisation of the reaction conditions and testing of chiral catalysts would allow for investigations of diastereoselective and enantioselective variants, which would be of considerable interest. This would allow access to asymmetric spirocyclic 1,2-diazetidines, which are currently not known.

With the differentially protected 4,5-diazaspiro[2.3]hexanes, switching the Boc and Cbz protecting groups may allow for efficient removal of the Cbz group. This would reveal if the complications lie with the location of the group being next to the spirocentre, or if the protecting group is not suitable for this chemistry. In the latter case, switching to alternate groups such as fluorenylmethyloxycarbonyl (Fmoc) or 4-nitrobenzenesulfonyl (Nosyl) may be appropriate.

With an established route available to access spirocyclic 1,2-diazetidines, further diversification could be achieved with removal of the protecting groups and additional functionalisation of the free NH to expand the application of these compounds. Further extension of this work to include exploring [3+2] dipolar cycloadditions may be of interest.

It would be of interest to undertake DFT calculations of the 3-methylene-1,2-diazetidines to determine where the HOMO and LUMO of the double bond lies. This in turn would provide insight into the reactivity of the double bond from a theoretical perspective to support our experimental observations.

Finally, work to integrate these spirocyclic structures into drug scaffolds to establish if they possess useful properties would be of interest. In particular, to ascertain if they serve as useful hexahydropyridazine surrogates.

Chapter 3: Experimental

3.1 General Information

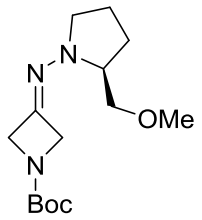
All reactions were performed under an atmosphere of anhydrous nitrogen in oven-dried glassware unless otherwise stated. Anhydrous solvents were purchased from Sigma-Aldrich in Sure/Seal^{TM} bottles and used as reaction solvents. All other solvents were reagent grade and used as received. Commercially available starting materials were used without purification unless otherwise stated. Thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck Silicagel 60 F_{254}), visualised by UV 254, then stained with phosphomolybdic acid or ceric ammonium molybdate solution followed by heating. Flash column chromatography was performed using Fluorochem LC60A 40-63 micron silica, or Sigma-Aldrich 60 Å pore size, 40 – 64 μm particle size silica. Petrol refers to the petroleum ether fraction which boils in the range 40 – 60 °C.

Melting points were recorded on a Gallenkamp MPD350 apparatus and are reported as observed. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer or a Bruker Alpha Platinum ATR spectrometer with internal calibaration, and are given in cm^{-1}. Enantiomeric excess (*ee*) were determined by chiral HPLC using an Agilent 1260 Infinity system, or by chiral GC using a Hewlett Packard HP5890 series, Perkin Elmer 8500 Gas Chromatograph system, or on a Perkin Elmer Autosystem XL Gas Chromatograph. Single crystal X-ray diffraction data were obtained using an Oxford Diffraction Gemini XRD system.

Low resolution mass spectra were recorded on an Agilent Technologies 6130 Quadrupole LC-MS instrument with electrospray ionisation. High resolution mass spectra were recorded on a Bruker Maxis ESI-TOF instrument. GC-MS spectra were recorded on a Varian 4000 GC-MS spectrometer using a Factorfour Capillary Column VF-5MS 30MX0.25mm, ID DF = 0.25 with helium as the delivery gas. Optical rotations were measured on an AA-1000 Polarimeter from Optical Activity Ltd. Warwick Analytical Service carried out all elemental analysis.

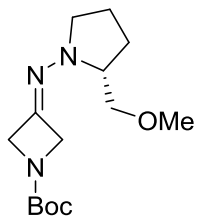
Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Spectrospin DPX300 or HD300 (^{1}H at 300 MHz and ^{13}C at 75 MHz); Bruker Spectrospin DPX400 or HD400 (^{1}H at 400 MHz and ^{13}C at 100 MHz); Bruker Spectrospin HD500 (^{1}H at 500 MHz and ^{13}C at 125 MHz); Bruker Spectrospin AV600 (^{13}C at 150 MHz) or on a Bruker Spectrospin AV700 (^{13}C at 176 MHz). Chemical shifts are reported in parts per million (ppm) using TMS as an internal standard. Structures were assigned using 2D NMR of COSY, HSQC and HMBC experiments. The peak multiplicities were specified as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m). Coupling constants (*J*) are reported in Hertz.

(*S*)-3-(2-(Methoxymethyl)-*N*-(azetidine-3-ylidene)pyrrolidin-1-amine)-1-*tert*-butylcarboxylate ((*S*)-151)



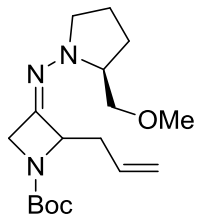
(*S*)-(–)-1-Amino-2-(methoxymethyl)pyrrolidine (537 µL, 4.00 mmol) was added dropwise to *N*-Boc-azetidin-3-one (822 mg, 4.80 mmol). The mixture was heated to 55 °C for 16 h, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 3:1, hexane: EtOAc) provided (*S*)-**151** (1.13 g, 100%) as a pale yellow oil. R_f = 0.31 (3:1, hexane: EtOAc); $[\alpha]_D^{26}$ +23.4 (*c* 0.12, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 2929, 2867, 1703, 1457, 1365, 1087, 940, 859, 767; δ_H (400 MHz, $CDCl_3$) 4.76−4.68 (1H, m, NC*H*H), 4.64−4.52 (3H, m, NCH*H*, NCH_2), 3.50 (1H, dd, *J* = 8.0, 4.0 Hz, C*H*HOCH_3), 3.44−3.39 (2H, m, CH*H*OCH_3, NCH), 3.38 (3H, s, CH_2OCH_3), 3.33−3.26 (1H, m, NC*H*H), 2.79 (1H, q, *J* = 8.0 Hz, NCH*H*), 1.98−1.84 (3H, m, C*H*H, CH_2), 1.78−1.69 (1H, m, CH*H*), 1.46 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 156.2 (COO), 135.9 (C=N), 80.1 ($C(CH_3)_3$), 74.9 (CH_2OCH_3), 65.2 (NCH), 61.4 (NCH_2), 60.4 (NCH_2), 59.3 (CH_2OCH_3), 52.5 (NCH_2), 28.4 ($C(CH_3)_3$), 25.9 (CH_2), 22.7 (CH_2); MS (ESI$^+$) *m/z* 284 (MH^+); HRMS calcd. for $C_{14}H_{26}N_3O_3$ $[M+H]^+$ 284.1969, found 284.1972.

(*R*)-3-(2-(Methoxymethyl)-*N*-(azetidine-3-ylidene)pyrrolidin-1-amine)-1-*tert*-butylcarboxylate ((*R*)-151)



(*R*)-(+)-1-Amino-2-(methoxymethyl)pyrrolidine (269 μL, 2.00 mmol) was added dropwise to *N*-Boc-azetidin-3-one (411 mg, 2.40 mmol). The mixture was heated to 55 °C for 16 h, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 3:1, hexane: EtOAc) provided (*R*)-**151** (540 mg, 95%) as a pale yellow oil. R_f = 0.24 (3:1, hexane: EtOAc); $[\alpha]_D^{29}$ −21.2 (*c* 0.11, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 2979, 2930, 2888, 2835, 1687, 1460, 1364, 1146, 1105, 941, 858, 767; δ_H (400 MHz, $CDCl_3$) 4.77−4.68 (1H, m, NC*H*H), 4.65−4.53 (3H, m, NCH*H*, NCH_2), 3.54−3.46 (1H, m, C*H*HOCH_3), 3.45−3.35 (2H, m, CH*H*OCH_3, NCH), 3.38 (3H, s, CH_2OCH_3), 3.34−3.26 (1H, m, NC*H*H), 2.79 (1H, q, *J* = 8.1 Hz, NCH*H*), 1.98−1.83 (3H, m, C*H*H, CH_2), 1.79−1.69 (1H, m, CH*H*), 1.46 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 156.2 (COO), 135.9 (C=N), 80.1 (*C*$(CH_3)_3$), 74.9 (*C*H_2OCH_3), 65.1 (NCH), 61.4 (2 x NCH_2), 59.3 (CH_2OCH_3), 52.5 (NCH_2), 28.3 ($C(CH_3)_3$), 25.9 (CH_2), 22.7 (CH_2); MS (ESI^+) *m/z* 284 (MH^+); HRMS calcd. for $C_{14}H_{26}N_3O_3$ $[M+H]^+$ 284.1969, found 284.1964.

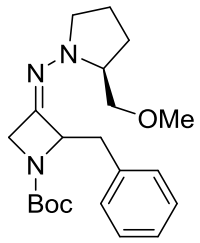
(*S*)-3-(2-(Methoxymethyl)-*N*-(2-allylazetidine-3-ylidene)pyrrolidin-1-amine)-1-*tert*-butylcarboxylate (155)



To a stirred solution of (*S*)-**151** (113 mg, 0.40 mmol) in anhydrous THF (4 mL) at –78 °C under an atmosphere of nitrogen, was added *n*butyllithium (2.43 M solution in hexanes, 180 μL, 0.44 mmol) dropwise. After 2 h at –78 °C, allyl bromide (42 μL, 0.48 mmol) was added, and the solution allowed to warm slowly to room temperature over 16 h. The reaction mixture was diluted with diethyl ether (40 mL), and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 3:1, hexane: EtOAc) provided **155** as an inseparable mixture of diastereomers in the ratio 9:1 (85 mg, 66%) as a pale yellow oil. R_f = 0.34 (3:1, hexane: EtOAc); IR υ_{max} (film)/cm^{-1} 2925, 2870, 1703, 1477, 1457, 1390, 1365, 1129, 1030, 913, 768;

δ_H (400 MHz, $CDCl_3$) major isomer, 5.73−5.86 (1H, m, CH_2CH=CH_2), 5.19−5.07 (2H, m, CH_2CH=CH_2), 5.01−4.91 (1H, m, NC*H*CH_2CH=CH_2), 4.48−4.40 (1H, m, NC*H*H), 4.37 (1H, dd, *J* = 13.6, 3.4 Hz, NCH*H*), 3.52 (1H, dd, *J* = 9.1, 4.1 Hz, C*H*HOCH_3), 3.46−3.25 (3H, m, CH*H*OCH_3, NC*H*CH_2, NC*H*HCH_2), 3.37 (3H, s, CH_2OCH_3), 2.81−2.60 (1H, m, NCH*H*CH_2), 2.66 (1H, q, *J* = 8.3 Hz, C*H*HCH=CH_2), 2.55−2.46 (1H, m, CH*H*CH=CH_2), 2.06−1.83 (3H, m, NC*H*H, NCH_2), 1.71−1.63 (1H, m, NCH*H*), 1.47 (9H, s, $C(CH_3)_3$); δ_C (176 MHz, $CDCl_3$) 155.2 (COO), 141.8 (C=N), 132.2 (CH_2CH=CH_2), 118.0 (CH_2CH=CH_2), 79.2 ($C(CH_3)_3$), 75.1 (CH_2OCH_3), 72.4 (N*C*HCH_2CH=CH_2), 65.3 (N*C*HCH_2OCH_3), 58.5 (CH_2OCH_3), 53.0 (NCH_2CH_2), 33.0 (CH_2CH=CH_2), 27.7 ($C(CH_3)_3$), 26.0 (CH_2), 22.3 (CH_2), azetidine CH_2 not observed; MS (ESI^+) *m/z* 346 (MNa^+); HRMS calcd. for $C_{17}H_{29}N_3NaO_3$ $[M+Na]^+$ 346.2101, found 346.2101.

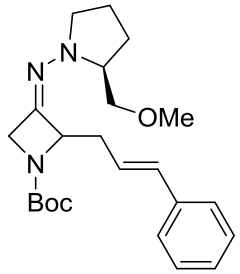
(*S*)-3-(2-(Methoxymethyl)-*N*-(2-benzylazetidine-3-ylidene)pyrrolidin-1-amine)-1-*tert*-butylcarboxylate (156)



To a stirred solution of (*S*)-**151** (113 mg, 0.40 mmol) in anhydrous THF (4 mL) was added TMEDA (66.0 μL, 0.44 mmol) at –78 °C under an atmosphere of nitrogen. ^{n}Butyllithium (2.43 M solution in hexanes, 181 μL, 0.44 mmol) was added dropwise. After 1 h at –78 °C, benzyl bromide (57 μL, 0.48 mmol) was added, and the solution allowed to warm slowly to room temperature over 16 h. The reaction mixture was diluted with diethyl ether (40 mL), and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 3:1, hexane: EtOAc) provided **156** as an inseparable mixture of diastereomers in the ratio 1.9:1 (97 mg, 65%) as a pale yellow oil. R_f = 0.40 (3:1, hexane: EtOAc); IR υ_{max} (film)/cm^{-1} 2925, 2871, 1703, 1477, 1403, 1366, 1128, 1023, 972,766, 703; δ_H (400 MHz, $CDCl_3$) major isomer, 7.56−7.18 (5H, m, Ar H), 5.20−5.02 (1H, m, NC*H*CH_2Ar), 4.29−4.17 (1H, m, NC*H*H), 3.76−3.63 (1H, m, NCH*H*), 3.50 (1H, dd, *J* = 8.5, 3.6 Hz, C*H*HOCH_3), 3.46−3.40 (2H, m, C*H*HOCH_3, NCH), 3.43 (3H, s, CH_2OCH_3), 3.34−3.31 (1H, m, NC*H*H), 3.23−3.14 (1H, m, C*H*HAr), 3.03 (1H, dd, *J* = 14.0, 3.2

Hz, CH*H*Ar), 2.73 (1H, q, *J* = 8.3 Hz, NCH*H*), 1.97−1.87 (2H, m, CH_2), 1.78−1.68 (2H, m, CH_2), 1.46 (9H, s, C(C*H*$_3$)$_3$); δ_C (150 MHz, $CDCl_3$) 155.2 (COO), 139.3 (C=N), 136.1 (C, Ar), 130.0 (CH, Ar), 127.9 (CH, Ar), 126.3 (CH, Ar), 79.9 (*C*(CH$_3$)$_3$), 75.4 (NCH$_2$), 74.9 (N*C*HCH$_2$Ar), 74.2 (*C*H$_2$OCH$_3$), 66.2 (NCH), 59.2 (CH$_2$O*C*H$_3$), 52.6 (CH_2), 36.5 (*C*H$_2$Ar), 29.5 (C(*C*H$_3$)$_3$), 26.6 (CH_2), 23.2 (CH_2); MS (ESI^+) *m/z* 374 (MH^+); HRMS calcd. for $C_{21}H_{32}N_3O_3$ $[M+H]^+$ 374.2438, found 374.2434.

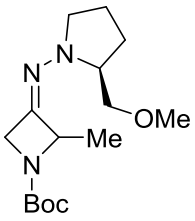
(*S*)-3-(2-(Methoxymethyl)-*N*-(2-phenylallylazetidine-3-ylidene)pyrrolidin-1-amine)-1-*tert*-butylcarboxylate (157)



To a stirred solution of (*S*)-**151** (113 mg, 0.40 mmol) in anhydrous THF (4 mL) at –78 °C under an atmosphere of nitrogen, was added ^{n}butyllithium (2.45 M solution in hexanes, 180 μL, 0.44 mmol) dropwise. After 2 h at –78 °C, 3-bromo-1-phenyl-1-propene (95 mg, 0.48 mmol) was added, and the solution allowed to warm slowly to room temperature over 16 h. The reaction mixture was diluted with diethyl ether (40 mL), and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 3:1, hexane: EtOAc) provided **157** as an inseparable mixture of diastereomers in the ratio 7.3:1 (96 mg, 60%) as a pale yellow oil. R_f = 0.27 (3:1, hexane: EtOAc); IR υ_{max} (film)/cm^{-1} 2926, 2874, 1701, 1477, 1450, 1390, 1365, 1127, 1016, 966, 745, 694; δ_H (400 MHz, $CDCl_3$) major isomer, 7.38−7.15 (5H, m, Ar H), 6.48 (1H, d, *J* = 15.7 Hz, CH=C*H*Ar), 6.25−6.14 (1H, m, C*H*=CHAr), 5.08−4.97 (1H, m, NC*H*CH$_2$), 4.60−4.33 (2H, m, NCH$_2$), 3.56−3.49 (1H, m, C*H*HOCH$_3$), 3.47−3.31 (2H, m, CH*H*OCH$_3$, NC*H*CH$_2$OCH$_3$), 3.37 (3H, s, CH$_2$OC*H*$_3$), 3.29−3.21 (1H, m, NC*H*HCH$_2$), 2.89−2.73 (1H, m, NCH*H*CH$_2$), 2.73−2.61 (2H, m, C*H*$_2$CH=CHAr), 2.06−1.96 (1H, m, C*H*H), 1.95−1.81 (2H, m, CH_2), 1.77−1.61 (1H, m, CH*H*), 1.46 (9H, s, C(CH$_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 155.8 (COO), 142.7 (C=N), 137.6 (C, Ar), 133.7 (CH=*C*HAr), 128.5 (CH, Ar), 127.2 (CH, Ar), 126.2 (CH, Ar), 124.5 (*C*H=CHAr), 80.0 (*C*(CH$_3$)$_3$), 74.8 (*C*H$_2$OCH$_3$), 72.8 (N*C*HCH$_2$CH=CH), 65.1

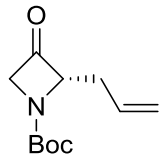
(N*C*HCH$_2$OCH$_3$), 60.4 (NCH$_2$), 59.2 (CH$_2$O*C*H$_3$), 52.7 (N*C*H$_2$CH$_2$), 36.1 (*C*H$_2$CH=CHAr), 28.4 (C(*C*H$_3$)$_3$), 25.9 (CH$_2$), 23.1 (CH$_2$); MS (ESI$^+$) *m/z* 422 (MNa$^+$); HRMS calcd. for $C_{23}H_{33}N_3NaO_3$ [M+Na]$^+$ 422.2414, found 422.2417.

(*S*)-3-(2-(Methoxymethyl)-*N*-(2-methylazetidine-3-ylidene)pyrrolidin-1-amine)-1-*tert*-butylcarboxylate (158)



To a stirred solution of (*S*)-**151** (113 mg, 0.40 mmol) in anhydrous THF (4 mL) at –78 °C under an atmosphere of nitrogen, was added ^{n}butyllithium (2.45 M solution in hexanes, 180 μL, 0.44 mmol) dropwise. After 2 h at –78 °C, iodomethane (30 μL, 0.48 mmol) was added, and the solution allowed to warm slowly to room temperature over 16 h. The reaction mixture was diluted with diethyl ether (40 mL), and washed with H$_2$O (10 mL) and brine (10 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO$_2$, 3:1, hexane: EtOAc) provided **158** as an inseparable mixture of diastereomers in the ratio 2.9:1 (71 mg, 60%) as a pale yellow oil. R_f = 0.23 (3:1, hexane: EtOAc); IR υ_{max} (film)/cm^{-1} 2929, 2876, 1703, 1479, 1455, 1387, 1364, 1111, 1020, 746; δ_H (400 MHz, CDCl$_3$) major isomer, 4.88−4.78 (1H, m, NC*H*CH$_3$), 4.68−4.53 (2H, m, NCH$_2$), 3.50−3.43 (1H, m, C*H*HOCH$_3$), 3.41−3.33 (2H, m, CH*H*OCH$_3$, NC*H*CH$_2$), 3.36 (3H, s, CH$_2$OC*H*$_3$), 3.30−3.23 (1H, m, NC*H*H), 2.75 (1H, q, *J* = 8.0 Hz, NCH*H*), 1.93−1.83 (3H, m, C*H*H, CH$_2$), 1.77−1.67 (1H, m, CH*H*), 1.44 (9H, s, C(CH$_3$)$_3$), 1.44−1.41 (3H, m, NCHC*H*$_3$); δ_C (100 MHz, CDCl$_3$) 156.0 (COO), 79.8 (*C*(CH$_3$)$_3$), 74.9 (*C*H$_2$OCH$_3$), 69.3 (N*C*HCH$_3$), 64.9 (NCH), 59.3 (CH$_2$O*C*H$_3$), 52.6 (NCH$_2$), 28.4 (C(*C*H$_3$)$_3$), 26.0 (CH$_2$), 22.8 (CH$_2$), 18.9 (NCH*C*H$_3$), C=N not observed, azetidine NCH$_2$ not observed; MS (ESI$^+$) *m/z* 298 (MH$^+$), 320 (MNa$^+$); HRMS calcd. for $C_{15}H_{27}N_3NaO_3$ [M+Na]$^+$ 320.1945, found 320.1943.

(*S*)-2-(Allyl-3-oxoazetidine)-1-*tert*-butylcarboxylate ((*S*)-159)



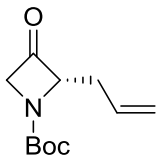
To **155** (61 mg, 0.19 mmol) was added saturated aqueous oxalic acid (1.5 mL) and diethyl ether (2.5 mL), and the reaction stirred vigorously at room temperature for 18 h. The reaction mixture was diluted with diethyl ether (50 mL), and the layers separated. The organic layer was washed with brine (25 mL), saturated aqueous $NaHCO_3$ solution (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 7:1, hexane: EtOAc) provided (*S*)-**159** (30 mg, 75%) as a pale yellow oil. R_f = 0.32 (7:1, hexane: EtOAc); $[\alpha]_D^{25}$ +55.4 (*c* 0.11, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 3082, 2979, 2928, 1822, 1704, 1479, 1458, 1392, 1365, 1177, 1124, 923, 772; δ_H (400 MHz, $CDCl_3$) 5.91−5.73 (1H, m, CH_2CH=CH_2), 5.24−5.12 (2H, m, CH_2CH=CH_2), 5.01−4.87 (1H, m, NC*H*CH_2), 4.67 (1H, d, *J* = 16.6 Hz, NC*H*H), 4.47 (1H, dd, *J* = 16.6, 2.2 Hz, NCH*H*), 2.72−2.61 (1H, m, NCHC*H*H), 2.61−2.51 (1H, m, NCHCH*H*), 1.49 (9H, s, C(CH_3)$_3$), broadening of peaks observed; δ_C (125 MHz, $CDCl_3$) 199.9 (C=O), 155.9 (COO), 131.6 (CH_2CH=CH_2), 119.3 (CH_2CH=CH_2), 82.2 (N*C*HCH_2), 80.8 (*C*(CH_3)$_3$), 69.1 (NCH_2), 34.1 (NCH*C*H_2), 28.3 (C(*C*H_3)$_3$); MS (ESI^+) *m/z* 234 (MNa^+); HRMS calcd. for $C_{11}H_{17}NNaO_3$ $[M+Na]^+$ 234.1101, found 234.1093; 81% *ee* (determined by chiral GC analysis on a Chrompac cyclodextrin-β-236M-19 50m x 0.25mm x 0.25μm column, T = 110 °C, P = 15 psi, H_2 carrier gas, t_R 63.35 min and t_R 64.55 min).

General Method A: One Pot Synthesis of 2-Substituted Azetidin-3-ones

*n*Butyllithium (2.5 M solution in hexanes, 1.1 eq) was added dropwise to a stirred solution of **151** (0.40 mmol) in anhydrous THF (4 mL) at –78 °C under an atmosphere of nitrogen. After 2 h at –78 °C, the electrophile (1.2 eq) was added, and the solution was stirred at –78 °C for 2 h before warming slowly to room temperature over 18 h. Saturated aqueous oxalic acid solution (4 mL) was added and the solution stirred vigorously at room temperature for 20 h. The reaction mixture was diluted with diethyl ether (50 mL), and the layers separated. The organic layer was washed with brine (25 mL), saturated aqueous $NaHCO_3$ solution (25 mL), dried

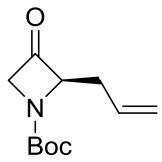
over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography provided the product.

(*S*)-2-(Allyl-3-oxoazetidine)-1-*tert*-butylcarboxylate ((*S*)-159)



(*S*)-**151** (113 mg, 0.40 mmol), ^{n}butyllithium (2.45 M solution in hexanes, 180 µL, 0.44 mmol), anhydrous THF (4 mL) and allyl bromide (42 µL, 0.48 mmol) were reacted according to General Method A. Work-up, followed by purification by column chromatography (SiO_2, 7:1, hexane: EtOAc) provided (*S*)-**159** (57 mg, 67%) as a pale yellow oil. R_f = 0.32 (7:1, hexane: EtOAc); $[\alpha]_D^{25}$ +52.7 (*c* 0.11, $CHCl_3$). Analytical data as previously reported. 81% *ee* (determined by chiral GC analysis on a Chrompac cyclodextrin-β-236M-19 50m x 0.25mm x 0.25µm column, T = 110 °C, P = 15 psi, H_2 carrier gas, t_R 63.35 min and t_R 64.55 min).

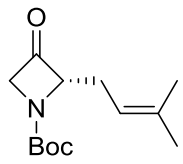
(*R*)-2-(Allyl-3-oxoazetidine)-1-*tert*-butylcarboxylate ((*R*)-159)



(*R*)-**151** (113 mg, 0.40 mmol), ^{n}butyllithium (2.35 M solution in hexanes, 187 µL, 0.44 mmol), anhydrous THF (4 mL) and allyl bromide (42 µL, 0.48 mmol) were reacted according to General Method A. Work-up, followed by purification by column chromatography (SiO_2, 7:1, hexane: EtOAc) provided (*R*)-**159** (46 mg, 55%) as a pale yellow oil. R_f = 0.32 (7:1, hexane: EtOAc); $[\alpha]_D^{30}$ −47.4 (*c* 0.12, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 3079, 2976, 2925, 1821, 1700, 1456, 1432, 1391, 1365, 1175, 1119, 921, 769; δ_H (400 MHz, $CDCl_3$) 5.88−5.75 (1H, m, CH_2CH=CH_2), 5.22−5.14 (2H, m, CH_2CH=CH_2), 4.98−4.91 (1H, m, NC*H*CH_2), 4.66 (1H, d, *J* = 16.6 Hz, NC*H*H), 4.48 (1H, dd, *J* = 16.6, 4.3 Hz, NCH*H*), 2.71−2.61 (1H, m, NCHC*H*H), 2.61−2.51 (1H, m, NCHCH*H*), 1.49 (9H, s, $C(CH_3)_3$), broadening of peaks observed; δ_C (125 MHz, $CDCl_3$) 199.9 (C=O), 155.9 (COO), 131.6 (CH_2CH=CH_2), 119.4 (CH_2CH=CH_2), 82.2 (N*C*HCH_2), 80.8 ($C(CH_3)_3$), 69.1 (NCH_2), 34.1 (NCHCH_2), 28.3 ($C(CH_3)_3$); MS (ESI^+) *m/z* 234 (MNa^+); HRMS calcd. for $C_{11}H_{17}NNaO_3$ $[M+Na]^+$ 234.1101, found 234.1102; 81% *ee* (determined by chiral GC analysis on a

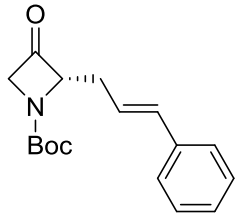
Chrompac cyclodextrin-β-236M-19 50m x 0.25mm x 0.25µm column, T = 110 °C, P = 15 psi, H_2 carrier gas, t_R 41.37 min and t_R 42.52 min).

(*S*)-2-((3-Methylbut-2-en-1-yl)-3-oxoazetidine)-1-*tert*-butylcarboxylate (165)



(*S*)-**151** (113 mg, 0.40 mmol), ^{n}butyllithium (2.35 M solution in hexanes, 187 µL, 0.44 mmol), anhydrous THF (4 mL) and 3,3-dimethylallyl bromide (56 µL, 0.48 mmol) were reacted according to General Method A. Work-up, followed by purification by column chromatography (SiO_2, 7:1, hexane: EtOAc) provided **165** (51 mg, 53%) as a pale yellow oil. R_f = 0.39 (7:1, hexane: EtOAc); $[\alpha]_D^{25}$ +30.3 (*c* 0.13, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 2977, 2927, 1821, 1701, 1365, 1176, 1129, 856, 772; δ_H (400 MHz, $CDCl_3$) 5.18 (1H, t, *J* = 7.2 Hz, CH_2CH=$C(CH_3)_2$), 4.94−4.86 (1H, m, $NCHCH_2$), 4.64 (1H, d, *J* = 16.5 Hz, $NCHH$), 4.45 (1H, dd, *J* = 16.6, 4.1 Hz, $NCHH$), 2.61−2.51 (2H, m, $NCHCH_2$), 1.72 (3H, s, $C(CH_3)(CH_3)$), 1.63 (3H, s, $C(CH_3)(CH_3)$), 1.49 (9H, s, $C(CH_3)_3$), broadening of peaks observed; δ_C (125 MHz, $CDCl_3$) 200.6 (C=O), 155.9 (COO), 136.3 ($CH=C(CH_3)_2$), 116.9 ($CH=C(CH_3)_2$), 82.8 ($NCHCH_2$), 80.6 ($C(CH_3)_3$), 68.9 (NCH_2), 28.6 ($NCHCH_2$), 28.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)(CH_3)$), 17.9 ($C(CH_3)(CH_3)$); MS (ESI^+) *m/z* 262 (MNa^+); HRMS calcd. for $C_{13}H_{21}NNaO_3$ $[M+Na]^+$ 262.1414, found 262.1415; 81% *ee* (determined by chiral GC analysis on a Chrompac cyclodextrin-β-236M-19 50m x 0.25mm x 0.25µm column, T = 140 °C, P = 15 psi, He carrier gas, t_R 68.27 min and t_R 69.17 min).

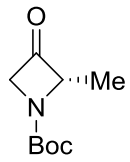
(*S*)-2-(Phenylallyl-3-oxoazetidine)-1-*tert*-butylcarboxylate (166)



(*S*)-**151** (113 mg, 0.40 mmol), ^{n}butyllithium (2.45 M solution in hexanes, 180 µL, 0.44 mmol), anhydrous THF (4 mL) and 3-bromo-1-phenyl-1-propene (95 mg, 0.48 mmol) were reacted according to General Method A. Work-up, followed by purification by column chromatography (SiO_2, 7:1, hexane: EtOAc) provided **166** (85 mg, 74%) as a pale yellow oil. R_f = 0.36 (7:1, hexane: EtOAc); $[\alpha]_D^{19}$ +71.3 (*c* 0.12, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 2976, 2929, 1822, 1699,

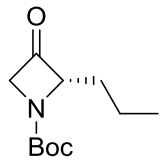
1494, 1391, 1365, 1129, 966, 743, 693; δ_H (400 MHz, $CDCl_3$) 7.40−7.19 (5H, m, Ar H), 6.51 (1H, d, *J* = 15.8 Hz, CH=C*H*Ar), 6.24−6.13 (1H, m, C*H*=CHAr), 5.05−4.97 (1H, m, NC*H*CH_2), 4.67 (1H, d, *J* = 16.6 Hz, NC*H*H), 4.48 (1H, dd, *J* = 16.6, 4.3 Hz, NCH*H*), 2.88−2.66 (2H, m, NCHC*H*$_2$), 1.48 (9H, s, C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 199.9 (C=O), 155.9 (COO), 136.9 (C, Ar), 134.4 (CH_2CH=*C*H), 128.6 (CH, Ar), 127.5 (CH, Ar), 126.3 (CH, Ar), 122.8 (CH_2*C*H=CH), 82.4 (N*C*HCH_2), 80.9 (*C*(CH_3)$_3$), 69.2 (NCH_2), 33.4 (NCH*C*H_2), 28.3 (C(*C*H_3)$_3$); MS (ESI^+) *m/z* 310 (MNa^+); HRMS calcd. for $C_{17}H_{21}NNaO_3$ $[M+Na]^+$ 310.1414, found 310.1412; 77% *ee* (determined by chiral HPLC (25 °C) on a Chiralcel OJ column (0.46 cm ø x 25 cm), 97-3 hexane-propan-2-ol, 0.5 mL/min, detection wavelength = 254 nm, t_R 34.35 min and t_R 41.68 min).

(*S*)-2-(Methyl-3-oxoazetidine)-1-*tert*-butylcarboxylate (167)



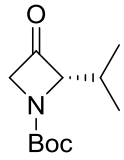
(*S*)-**151** (113 mg, 0.40 mmol), ^{n}butyllithium (2.35 M solution in hexanes, 187 µL, 0.44 mmol), anhydrous THF (4 mL) and iodomethane (30 µL, 0.48 mmol) were reacted according to General Method A. Work-up, followed by purification by column chromatography (SiO_2, 7:1, hexane: EtOAc) provided **167** (30 mg, 41%) as a colourless oil. R_f = 0.25 (7:1, hexane: EtOAc); $[\alpha]_D^{26}$ +15.4 (*c* 0.23, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 2959, 2925, 2856, 1828, 1709, 1458, 1389, 1367, 1180, 1144, 1126, 772; δ_H (400 MHz, $CDCl_3$) 4.98−4.88 (1H, m, NC*H*CH_3), 4.70 (1H, d, *J* = 16.6 Hz, NC*H*H), 4.57 (1H, dd, *J* = 16.6, 4.3 Hz, NCH*H*), 1.49 (9H, s, C(CH_3)$_3$), 1.45 (3H, d, *J* = 7.0 Hz, NCHC*H*$_3$), broadening of peaks observed; δ_C (125 MHz, $CDCl_3$) 199.8 (C=O), 155.0 (COO), 79.7 (*C*(CH_3)$_3$), 77.6 (N*C*HCH_3), 67.4 (NCH_2), 27.3 (C(*C*H_3)$_3$), 14.4 (NCH*C*H_3); GCMS $(EI)^+$ *m/z* 185 ($M^{+\bullet}$)**;** 51% *ee* (determined by chiral GC analysis on a CP-ChiraSil-DEX CB 25m x 0.25mm x 0.25µm column, T = 130 °C, P = 18 psi, He carrier gas, t_R 5.25 min and t_R 5.53 min).

(*S*)-2-(Propyl-3-oxoazetidine)-1-*tert*-butylcarboxylate (168)



(*S*)-**151** (113 mg, 0.40 mmol), ^{n}butyllithium (2.45 M solution in hexanes, 180 µL, 0.44 mmol), anhydrous THF (4 mL) and 1-iodopropane (47 µL, 0.48 mmol) were reacted according to General Method A. Work-up, followed by purification by column chromatography (SiO_2, 7:1, hexane: EtOAc) provided **168** (43 mg, 50%) as a pale yellow oil. R_f = 0.41 (7:1, hexane: EtOAc); $[\alpha]_D^{19}$ +54.8 (*c* 0.10, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 2964, 2934, 2875, 1819, 1701, 1478, 1458, 1389, 1365, 1138, 1119, 774; δ_H (400 MHz, $CDCl_3$) 4.93−4.86 (1H, m, NC*H*CH_2), 4.68 (1H, d, *J* = 16.7 Hz, NC*H*H), 4.51 (1H, dd, *J* = 16.7, 4.3 Hz, NCH*H*), 1.87−1.77 (2H, m, NCHC*H*$_2$), 1.60−1.37 (2H, m, $CH_2CH_2CH_3$), 1.49 (9H, s, $C(CH_3)_3$), 0.95 (3H, t, *J* = 7.3 Hz, $CH_2CH_2CH_3$); δ_C (125 MHz, $CDCl_3$) 201.1 (C=O), 156.3 (COO), 82.9 (N*C*HCH_2), 80.7 (*C*$(CH_3)_3$), 68.9 (NCH_2), 32.4 (NCH*C*H_2), 28.3 (C(*C*$H_3)_3$), 18.1 ($CH_2CH_2CH_3$), 13.9 ($CH_2CH_2CH_3$); MS (ESI$^+$) *m/z* 236 (MNa^+); HRMS calcd. for $C_{11}H_{19}NNaO_3$ $[M+Na]^+$ 236.1257, found 236.1254; 79% *ee* (determined by chiral GC analysis on a CP-ChiraSil-DEX CB 25m x 0.25mm x 0.25µm column, T = 130 °C, P = 18 psi, He carrier gas, t_R 9.64 min and t_R 10.00 min).

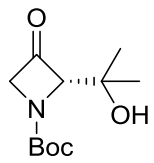
(*S*)-2-(Isopropyl-3-oxoazetidine)-1-*tert*-butylcarboxylate (169)



(*S*)-**151** (113 mg, 0.40 mmol), ^{n}butyllithium (2.45 M solution in hexanes, 180 µL, 0.44 mmol), anhydrous THF (4 mL) and 2-iodopropane (48 µL, 0.48 mmol) were reacted according to General Method A. Work-up, followed by purification by column chromatography (SiO_2, 7:1, hexane: EtOAc) provided **169** (44 mg, 52%) as a colourless oil. R_f = 0.40 (7:1, hexane: EtOAc); $[\alpha]_D^{28}$ +85.2 (*c* 0.26, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 2966, 2931, 2875, 1818, 1704, 1460, 1387, 1366, 1174, 1120, 776; δ_H (500 MHz, $CDCl_3$) 4.76−4.71 (1H, m, NC*H*$CH(CH_3)_2$), 4.65 (1H, d, *J* = 16.7 Hz, NC*H*H), 4.44 (1H, dd, *J* = 16.7, 4.3 Hz, NCH*H*), 2.17 (1H, octet, *J* = 6.7 Hz, NCHC*H*$(CH_3)_2$), 1.49 (9H, s, $C(CH_3)_3$), 1.04 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3$)(CH_3)), 1.03 (3H, d, *J* = 6.7 Hz, CH(CH_3)(C*H*$_3$)); δ_C (125 MHz, $CDCl_3$) 201.0 (C=O), 156.7 (COO), 88.4 (N*C*H$CH(CH_3)_2$), 80.8 (*C*$(CH_3)_3$), 69.4 (NCH_2), 30.0 (*C*H$(CH_3)_2$), 28.3 (C(*C*$H_3)_3$), 18.2 (CH(*C*H_3)(CH_3)),

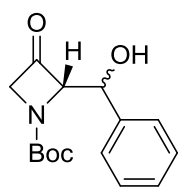
17.7 ($CH(CH_3)(CH_3)$); MS (ESI^+) *m/z* 236 (MNa^+); HRMS calcd. for $C_{11}H_{19}NNaO_3$ $[M+Na]^+$ 236.1257, found 236.1255; 85% *ee* (determined by chiral GC analysis on a CP-ChiraSil-DEX CB 25m x 0.25mm x 0.25µm column, T = 130 °C, P = 18 psi, He carrier gas, t_R 8.05 min and t_R 8.96 min).

(*S*)-2-((2-Hydroxypropan-2-yl)-3-oxoazetidine)-1-*tert*-butylcarboxylate (170)



(*S*)-**151** (113 mg, 0.40 mmol), ^{n}butyllithium (2.35 M solution in hexanes, 187 µL, 0.44 mmol), anhydrous THF (4 mL) and acetone (36 µL, 0.48 mmol) were reacted according to General Method A. Work-up, followed by purification by column chromatography (SiO_2, 3:1, hexane: EtOAc) provided **180** (54 mg, 59%) as a colourless oil. R_f = 0.34 (3:1, hexane: EtOAc); $[\alpha]_D^{27}$ +38.2 (*c* 0.11, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 3459, 2955, 2912, 2872, 2850, 1826, 1472, 1391, 1371, 1114, 1095, 717; δ_H (400 MHz, $CDCl_3$) 4.90−4.84 (1H, m, NCH), 4.70 (1H, d, *J* = 16.6 Hz, NC*H*H), 4.51 (1H, dd, *J* = 16.6, 3.9 Hz, NCH*H*), 1.51 (9H, s, $C(CH_3)_3$), 1.33 (3H, s, $C(CH_3)(CH_3)OH$), 1.30 (3H, s, $C(CH_3)(CH_3)OH$); δ_C (125 MHz, $CDCl_3$) 197.1 (C=O), 156.9 (COO), 91.2 (NCH), 82.0 ($C(CH_3)_3$), 71.2 ($C(CH_3)_2OH$), 70.0 (NCH_2), 28.2 ($C(CH_3)_3$), 26.1 ($C(CH_3)(CH_3)OH$), 24.3 ($C(CH_3)(CH_3)OH$); MS (ESI^+) *m/z* 252 (MNa^+); HRMS calcd. for $C_{11}H_{19}NNaO_4$ $[M+Na]^+$ 252.1206, found 252.1204; 78% *ee* (determined by chiral HPLC (25 °C) on a Chiralcel OJ column (0.46 cm ø x 25 cm), 9-1 hexane-propan-2-ol, 0.5 mL/min, detection wavelength = 254 nm, t_R 9.49 min and t_R 10.91 min).

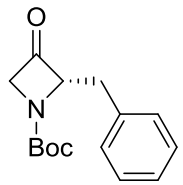
(*S, R*)- and (*S,S*)-2-(Hydroxy(phenyl)methyl-3-oxoazetidine)-1-*tert*-butylcarboxylate (171)



(*S*)-**151** (113 mg, 0.40 mmol), ^{n}butyllithium (2.45 M solution in hexanes, 180 µL, 0.44 mmol), anhydrous THF (4 mL) and benzaldehyde (49 µL, 0.48 mmol) were reacted according to General Method A. Work-up, followed by purification by column chromatography (SiO_2, 4:1, hexane: EtOAc) provided **171** (79 mg, 71%) as a yellow

oil and inseparable 1.5:1 mixture of diastereromers. R_f = 0.29 (4:1, hexane: EtOAc); IR υ_{max} (film)/cm^{-1} 3414, 2978, 2927, 1824, 1678, 1455, 1393, 1367, 1171, 1145, 1119, 768, 733; δ_H (500 MHz, $CDCl_3$) 7.38−7.29 (12.5H, m, Ar H,), 5.27−5.18 (1H, m, NC*H*CH), 5.17−5.12 (1.5H, m, NCHC*H*), 5.10−5.03 (2.5H, m, NC*H*CH, NCHC*H*), 4.65 (2H, d, *J* = 16.5 Hz, NC*H*H, NC*H*H), 4.52 (1H, br s, COH), 4.47 (3H, dd, *J* = 16.5, 3.5 Hz, NCH*H*, NCH*H*), 1.50 (9H, s, $C(CH_3)_3$), 1.44 (13.5H, s, $C(CH_3)_3$), OH not observed; δ_C (125 MHz, $CDCl_3$) 195.8 (C=O), 195.6 (C=O), 156.9 (COO), 156.3 (COO), 138.8 (C, Ar), 138.6 (C, Ar), 128.5 (CH, Ar), 128.42 (CH, Ar), 128.40 (CH, Ar), 128.1 (CH, Ar), 126.8 (CH, Ar), 126.5 (CH, Ar), 87.8 (N*C*HCH), 87.7 (N*C*HCH), 82.0 (*C*$(CH_3)_3$), 81.8 (*C*$(CH_3)_3$), 73.4 (NCH*C*H), 72.6 (NCH*C*H), 70.0 (NCH_2), 69.8 (NCH_2), 28.3 (C(*C*$H_3)_3$), 28.1 (C(*C*$H_3)_3$); MS (ESI$^+$) *m/z* 300 (MNa$^+$); HRMS calcd. for $C_{15}H_{19}NNaO_4$ $[M+Na]^+$ 300.1206, found 300.1204; 33% (major diastereomer), 17% (minor diastereomer) *ee* (determined by chiral HPLC (25 °C) on a Chiralpak IA column (0.46 cm ø x 25 cm), 95-5 hexane-propan-2-ol, 0.5 mL/min, detection wavelength = 254 nm; t_R 24.96 min, t_R 27.94 min, t_R 41.38 min and t_R 44.16 min).

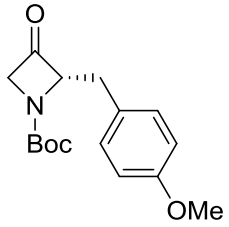
(*S*)-2-(Benzyl-3-oxoazetidine)-1-*tert*-butylcarboxylate (172)



(*S*)-**151** (113 mg, 0.40 mmol), ^{n}butyllithium (2.45 M solution in hexanes, 180 µL, 0.44 mmol), anhydrous THF (4 mL) and benzyl bromide (57 µL, 0.48 mmol) were reacted according to General Method A. Work-up, followed by purification by column chromatography (SiO_2, 7:1, hexane: EtOAc) provided **172** (60 mg, 57%) as a pale yellow oil. R_f = 0.31 (7:1, hexane: EtOAc); $[\alpha]_D^{19}$ +65.5 (*c* 0.10, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 2955, 2915, 2850, 1820, 1695, 1498, 1392, 1367, 1176, 1125, 776, 717, 703; δ_H (400 MHz, $CDCl_3$) 7.33−7.17 (5H, m, Ar H), 5.15−5.09 (1H, m, NC*H*CH_2), 4.54 (1H, d, *J* = 16.6 Hz, NC*H*H), 4.05 (1H, dd, *J* = 16.6, 4.3 Hz, NCH*H*), 3.20 (1H, dd, *J* = 14.2, 6.4 Hz, NCHC*H*H), 3.11 (1H, dd, *J* = 14.2, 4.1 Hz, NCHCH*H*), 1.48 (9H, s, $C(CH_3)_3$), broadening of peaks observed; δ_C (125 MHz, $CDCl_3$) 199.8 (C=O), 155.6 (COO), 135.5 (C, Ar), 129.8 (CH, Ar), 128.5 (CH, Ar), 127.0 (CH, Ar), 83.2 (N*C*HCH_2), 80.8 (*C*$(CH_3)_3$), 69.0 (NCH_2), 35.8 (NCH*C*H_2), 28.3 (C(*C*$H_3)_3$); MS (ESI$^+$) *m/z* 284 (MNa$^+$); HRMS calcd. for $C_{15}H_{19}NNaO_3$ $[M+Na]^+$ 284.1257, found

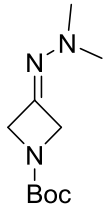
284.1266; 33% *ee* (determined by chiral HPLC (23 °C) on a Chiralcel OD column (0.46 cm ø x 25 cm), 99-1 hexane-propan-2-ol, 0.5 mL/min, detection wavelength = 254 nm; t_R 20.62 min and t_R 22.24 min).

(*S*)-2-((4-Methoxybenzyl)-3-oxoazetidine)-1-*tert*-butylcarboxylate (173)



(*S*)-**151** (113 mg, 0.40 mmol), ^{n}butyllithium (2.45 M solution in hexanes, 180 µL, 0.44 mmol), anhydrous THF (4 mL) and 4-methoxybenzyl chloride (66 µL, 0.48 mmol) were reacted according to General Method A. Work-up, followed by purification by column chromatography (SiO_2, 2:1, hexane: EtOAc) provided **173** (11 mg, 9%) as a yellow oil. R_f = 0.67 (2:1, hexane: EtOAc); $[\alpha]_D^{25}$ +93.9 (*c* 0.14, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 2976, 2924, 1822, 1613, 1587, 1514, 1457, 1391, 1365, 1176, 1126, 834; δ_H (400 MHz, $CDCl_3$) 7.11 (2H, d, *J* = 8.5 Hz, Ar H), 6.82 (2H, d, *J* = 8.5 Hz, Ar H), 5.12−5.04 (1H, m, NC*H*CH_2), 4.52 (1H, d, *J* = 16.6 Hz, NC*H*H), 4.03 (1H, dd, *J* = 16.5, 4.3 Hz, NCH*H*), 3.79 (3H, s, OCH_3), 3.15 (1H, dd, *J* = 14.4, 6.3 Hz, NCHC*H*H), 3.05 (1H, dd, *J* = 14.4, 3.8 Hz, NCHCH*H*), 1.49 (9H, s, $C(CH_3)_3$), broadening of peaks observed; δ_C (125 MHz, $CDCl_3$) 200.0 (C=O), 158.6 (C, Ar), 155.6 (COO), 130.9 (CH, Ar), 127.4 (C, Ar), 113.9 (CH, Ar), 83.4 (N*C*HCH_2), 80.7 (*C*$(CH_3)_3$), 69.0 (NCH_2), 55.2 (OCH_3), 34.8 (NCH*C*H_2), 28.4 (C(*C*$H_3)_3$); MS (ESI$^+$) *m/z* 314 (MNa^+); HRMS calcd. for $C_{16}H_{21}NNaO_4$ $[M+Na]^+$ 314.1363, found 314.1362; 33% *ee*. (determined by chiral HPLC (23 °C) on a Chiralcel OD column (0.46 cm ø x 25 cm), 99-1 hexane-propan-2-ol, 0.3 mL/min, detection wavelength = 254 nm, t_R 51.28 min and t_R 54.61 min).

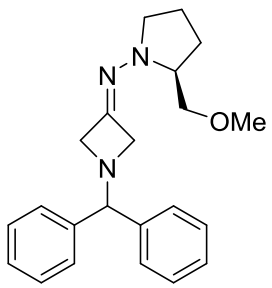
***N*,*N*-Dimethyl-*N*'-azetidine-3-ylidinehydrazine-1-*tert*-butylcarboxylate (161)**



N,*N*-Dimethyl hydrazine (304 µL, 4.00 mmol) was added dropwise to *N*-Boc-azetidin-3-one (822 mg, 4.80 mmol). The mixture was heated to 65 °C for 16 h and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 1:1, hexane: EtOAc) provided **161** (784 mg, 92%) as a pale yellow oil. R_f = 0.53 (1:1, hexane: EtOAc); IR υ_{max} (film)/cm^{-1} 2974, 2864,

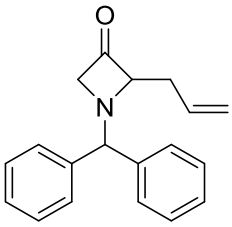
1700, 1452, 1388, 1365, 1124, 1016, 940, 859, 765; δ_H (400 MHz, $CDCl_3$) 4.71 (2H, t, *J* = 2.7 Hz, NCH_2), 4.57 (2H, t, *J* = 2.7 Hz, NCH_2), 2.70 (6H, s, $N(CH_3)_2$), 1.46 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 156.1 (COO), 138.4 (C=N), 80.2 ($C(CH_3)_3$), 61.6 (NCH_2), 61.0 (NCH_2), 45.8 ($N(CH_3)_2$), 28.3 ($C(CH_3)_3$); MS (ESI^+) *m/z* 236 (MNa^+); HRMS calcd. for $C_{10}H_{19}N_3NaO_2$ $[M+Na]^+$ 236.1369, found 236.1365.

(*S*)-3-(2-(Methoxymethyl)-*N*-(azetidine-3-ylidene)pyrrolidin-1-amine)-1-benzhydryl (162)



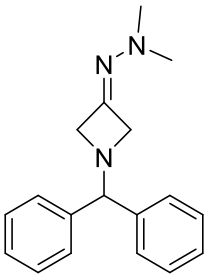
(*S*)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine (671 µL, 5.00 mmol) was added dropwise to 1-benzhydrylazetidin-3-one (1.42 g, 6.00 mmol). The mixture was stirred at 90 °C for 16 h, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 3:1, hexane: EtOAc) provided **162** (1.76 g, 100%) as an orange oil. R_f = 0.37 (3:1, hexane: EtOAc); $[\alpha]_D^{25}$ +33.5 (*c* 0.11, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 2926, 2875, 2825, 1686, 1599, 1451, 1115, 1091, 950, 742, 700; δ_H (400 MHz, $CDCl_3$) 7.44 (4H, d, *J* = 7.6 Hz, Ar H), 7.31−7.24 (4H, m, Ar H), 7.23−7.16 (2H, m, Ar H), 4.53 (1H, s, NCH), 4.00 (2H, s, NCH_2), 3.92 (2H, s, NCH_2), 3.54−3.48 (1H, m, C*H*$HOCH_3$), 3.41−3.28 (2H, m, CH*H*OCH_3, NC*H*CH_2), 3.36 (3H, s, CH_2OCH_3), 3.23−3.15 (1H, m, NC*H*HCH_2), 2.68 (1H, q, *J* = 8.3 Hz, NCH*H*CH_2), 1.96−1.85 (1H, m, C*H*H), 1.85−1.75 (2H, m, CH_2), 1.73−1.62 (1H, m, CH*H*); δ_C (125 MHz, $CDCl_3$) 142.53 (C=N), 142.51 (C, Ar), 128.6 (2 x CH, Ar), 127.4 (2 x CH, Ar), 127.32 (2 x CH, Ar), 127.28 (2 x CH, Ar), 127.25 (2 x CH, Ar), 77.4 (NCH), 75.1 (CH_2OCH_3), 65.3 (N*C*HCH_2), 64.9 (NCH_2), 64.5 (NCH_2), 59.3 (CH_2OCH_3), 53.0 (NCH_2CH_2), 26.0 (CH_2), 22.6 (CH_2); MS (ESI^+) *m/z* 350 (MH^+); HRMS calcd. for $C_{22}H_{28}N_3O$ $[M+H]^+$ 350.2227, found 350.2221.

2-Allyl-1-benzhydrylazetidin-3-one (163)



To a stirred solution of **162** (140 mg, 0.40 mmol) in anhydrous THF (4 mL) at –78 °C under at atmosphere of nitrogen, was added *n*butyllithium (2.35 M solution in hexanes, 187 μL, 0.44 mmol) dropwise. After 2 h at –78 °C, allyl bromide (42 μL, 0.48 mmol) was added, and the solution stirred at –78 °C for 2 h before warming slowly to room temperature over 18 h. Saturated aqueous oxalic acid solution (4 mL) was added, and the solution stirred vigorously at room temperature for 20 h. The reaction mixture was diluted with diethyl ether (50 mL), and the layers were separated. The organic layer was washed with brine (25 mL), saturated aqueous $NaHCO_3$ solution (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 7:1, hexane: EtOAc) provided **163** (22 mg, 20%) as a pale yellow oil. R_f = 0.53 (7:1, hexane: EtOAc); $[\alpha]_D^{24}$ +6.50 (*c* 0.10, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 3063, 2932, 2819, 1804, 1599, 1453, 1429, 920, 743, 698; δ_H (400 MHz, $CDCl_3$) 7.90−6.95 (10H, m, Ar H), 5.74−5.52 (1H, m, CH_2CH=CH_2), 5.01−4.75 (2H, m, CH_2CH=CH_2), 4.53 (1H, s, NCH), 4.18−3.90 (2H, m, NC*H*H, NC*H*CH_2), 3.61 (1H, d, *J* = 16.2 Hz, NCH*H*), 1.96−1.80 (2H, m, NCHCH_2); δ_C (125 MHz, $CDCl_3$) 204.4 (C=O), 142.5 (C, Ar), 142.3 (C, Ar), 133.3 (CH_2CH=CH_2), 128.7 (CH, Ar), 128.5 (CH, Ar), 128.3 (CH, Ar), 127.8 (CH, Ar), 127.4 (CH, Ar), 127.3 (CH, Ar), 117.5 (CH_2CH=CH_2), 84.7 (N*C*HCH_2), 77.9 (NCH), 72.9 (NCH_2), 35.0 (NCH*C*H_2); MS (ESI^+) *m/z* 278 (MH^+); HRMS calcd. for $C_{19}H_{20}NO$ $[M+H]^+$ 278.1539, found 278.1541; 7% *ee* (determined by chiral HPLC (25 °C) on a Chiralpak AD-H column (0.46 cm ø x 25 cm), 99-1 hexane-propan-2-ol, 0.5 mL/min, detection wavelength = 254 nm, t_R 10.44 min and t_R 11.01 min).

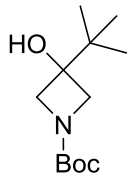
***N*,*N*-Dimethyl-*N*'-azetidine-3-ylidinehydrazine-1-benzyhydryl (164)**



N,*N*-dimethyl hydrazine (153 μL, 2.00 mmol) was added dropwise to 1-benzhydrylazetidin-3-one (570 mg, 2.40 mmol) in anhydrous 1,4-dioxane (2 mL). The mixture was stirred at 90 °C for 16 h, and the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, 2:1, hexane: EtOAc) provided **164** (524

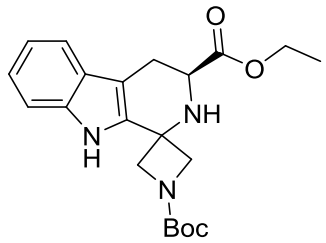
mg, 78%) as a yellow solid. M. p. 114–116 °C; R_f = 0.37 (2:1, hexane: EtOAc); IR υ_{max} (neat)/cm^{-1} 3025, 2850, 2820, 2782, 1688, 1596, 1450, 947, 743, 702; δ_H (400 MHz, $CDCl_3$) 7.44 (4H, d, *J* = 7.5 Hz, Ar H), 7.32−7.24 (4H, m, Ar H), 7.23−7.16 (2H, m, Ar H), 4.53 (1H, s, NCH), 4.03 (2H, s, NCH_2), 3.91 (2H, s, NCH_2), 2.61 (6H, s, $N(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 145.9 (C=N), 142.4 (2 x C, Ar), 128.6 (2 x CH, Ar), 127.34 (2 x CH, Ar), 127.32 (2 x CH, Ar), 77.4 (NCH), 64.7 (NCH_2), 64.4 (NCH_2), 46.3 ($N(CH_3)_2$); MS (ESI^+) *m/z* 280 (MH^+); HRMS calcd. for $C_{18}H_{22}N_3$ $[M+H]^+$ 280.1808, found 280.1808.

3-(*tert*-Butyl)-3-(hydroxyazetidine-1-*tert*-butylcarboxylate (160)



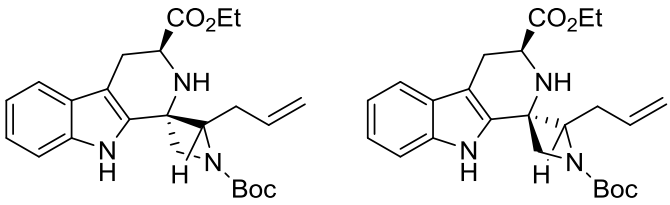
To a stirred solution of *N*-Boc-azetidin-3-one (69 mg, 0.40 mmol) in anhydrous THF (4 mL) at –78 °C under an atmosphere of nitrogen, was added *tert*-butyllithium (1.70 M solution in pentanes, 259 μL, 0.44 mmol) dropwise. After 2 h at –78 °C, allyl bromide (42 μL, 0.48 mmol) was added, and the solution was stirred at –78 °C for 2 h before warming slowly to room temperature over 18 h. The reaction mixture was diluted with diethyl ether (40 mL), and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 1:1, hexane: EtOAc) provided **160** (33 mg, 36%) as a white solid. M. p. 107–111 °C; R_f = 0.73 (1:1, hexane: EtOAc); IR υ_{max} (neat)/cm^{-1} 3326, 2961, 1651, 1422, 1389, 1365, 1164, 1136, 1064, 938, 768; δ_H (400 MHz, $CDCl_3$) 4.02 (2H, d, *J* = 9.5 Hz, NCH_2), 3.66 (2H, d, *J* = 9.5 Hz, NCH_2), 2.54 (1H, br s, OH), 1.44 (9H, s, $OC(CH_3)_3$), 0.96 (9H, s, $CC(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 156.4 (COO), 79.6 ($OC(CH_3)_3$), 76.0 (COH), 58.9 (NCH_2), 58.0 (NCH_2), 34.9 ($CC(CH_3)_3$), 28.4 ($OC(CH_3)_3$), 23.8 ($CC(CH_3)_3$); MS (ESI^+) *m/z* 252 (MNa^+); HRMS calcd. for $C_{12}H_{23}NNaO_3$ $[M+Na]^+$ 252.1570, found 252.1573.

(*S*)-2′,3′,4′,9′-Tetrahydrospiro-[azetidine-3,1′-pyrido[3,4-*b*]indole]-1-*tert*-butyl-3′-ethyl dicarboxylate (178)



To a stirred solution of *N*-Boc-azetidin-3-one (86 mg, 0.50 mmol) in anhydrous CH_3CN (5 mL) was added L-tryptophan ethyl ester (140 mg, 0.60 mmol) and I_2 (6.50 mg, 25 μmol, 5 mol-%), and the mixture stirred under reflux for 18 h. After cooling to room temperature the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (20 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic layers were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, 6:4, petrol: EtOAc) provided **178** (184 mg, 95%) as a light pink crystalline solid. M. p. 83–85 °C; R_f = 0.29 (6:4, petrol: EtOAc); $[\alpha]_D^{19}$ –25.7 (*c* 0.10, $CHCl_3$); IR υ_{max} (neat)/cm^{-1} 3298, 2978, 2934, 2878, 1733, 1684, 1394, 1367, 1125, 1112, 741; δ_H (400 MHz, $CDCl_3$) 8.85−8.55 (1H, br s, NH_{indole}), 7.49 (1H, d, *J* = 7.8 Hz, Ar H), 7.39 (1H, d, *J* = 8.1 Hz, Ar H), 7.21 (1H, t, *J* = 7.5 Hz, Ar H), 7.13 (1H, t, *J* = 7.4 Hz, Ar H), 4.37−4.31 (1H, br d, *J* = 9.2 Hz, NC*H*H), 4.26 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.16 (1H, d, *J* = 9.5 Hz, NCH*H*), 4.07 (2H, s, NCH_2), 3.77 (1H, dd, *J* = 9.8, 4.5 Hz, NHC*H*), 3.13 (1H, dd, *J* = 15.3, 4.6 Hz, NHCHC*H*H), 2.88 (1H, dd, *J* = 15.3, 9.9 Hz, NHCHCH*H*), 2.75−2.42 (1H, br s, NH_{pip}), 1.50 (9H, s, $C(CH_3)_3$), 1.33 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); δ_C (125 MHz, $CDCl_3$) 172.9 (COO), 156.8 (NCOO), 136.3 (C, Ar), 134.4 (C, Ar), 126.5 (C, Ar), 122.5 (CH, Ar), 119.9 (CH, Ar), 118.3 (CH, Ar), 111.2 (CH, Ar), 108.6 (C, Ar), 80.3 ($C(CH_3)_3$), 64.6 (NCH_2), 61.4 ($CO_2CH_2CH_3$), 60.4 (NCH_2), 54.0 ($NCHCH_2$), 51.3 (NHC), 28.4 ($C(CH_3)_3$), 25.4 ($NCHCH_2$), 14.2 ($CO_2CH_2CH_3$); MS (ESI^+) *m/z* 386 (MH^+), 406 (MNa^+); HRMS calcd. for $C_{21}H_{28}N_3O_4$ $[M+H]^+$ 386.2074, found 386.2078.

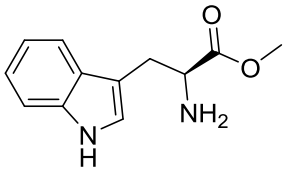
(*2R,3S,3′S*)- and (*2R,3R,3′S*)-2-(2-Allyl)-2′,3′,4′,9′-tetrahydrospiro-[azetidine-3,1′-pyrido[3,4-*b*]indole]-1-*tert*-butyl-3′-ethyl dicarboxylate (179a and 179b)



To a stirred solution of (*S*)-**159** (106 mg, 0.50 mmol) in anhydrous CH_3CN (5 mL) was added L-tryptophan ethyl ester (140 mg, 0.60 mmol) and I_2 (6.50 mg, 25 μmol, 5 mol-%), and the mixture stirred under reflux for 18 h. After cooling to room temperature the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (20 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic layers were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the title compounds as a 7.9:1 mixture of diastereomers as determined by ^{1}H NMR spectroscopy. Purification by flash column chromatography (SiO_2, 8:2, petrol: EtOAc) provided the separable diasteromers, to afford less polar, major diastereomer (*2R,3S,3′S*)-**179a** (147 mg, 69%) as an off-white solid. M. p. 80–83 °C; R_f = 0.38 (8:2, petrol: EtOAc); $[\alpha]_D^{29}$ –78.5 (*c* 0.11 $CHCl_3$); IR υ_{max} (neat)/cm^{-1} 3321, 3301, 2976, 2931, 1735, 1680, 1475, 1452, 1393, 1367, 1173, 1136, 916, 766, 741; δ_H (500 MHz, $CDCl_3$) 9.20−8.15 (1H, br s, NH_{indole}), 7.48 (1H, d, *J* = 7.9 Hz, Ar H), 7.38 (1H, d, *J* = 8.1 Hz, Ar H), 7.21 (1H, td, *J* = 7.6, 1.1 Hz, Ar H), 7.12 (1H, td, *J* = 7.5, 0.8 Hz, Ar H), 5.85−5.75 (1H, m, CH_2CH=CH_2), 5.11 (1H, dd, *J* = 17.3, 1.4 Hz, CH_2CH=C*H*H), 5.05 (1H, dd, *J* = 10.4, 0.9 Hz, CH_2CH=C*H*H), 4.76−4.68 (1H, m, NC*H*CH_2), 4.28 (2H, q, *J* = 7.2 Hz, $CO_2CH_2CH_3$), 4.02 (1H, d, *J* = 8.6 Hz, NC*H*H), 3.96 (1H, d, *J* = 8.6 Hz, NCH*H*), 3.73−3.66 (1H, m, NHC*H*CH_2), 3.09 (1H, dd, *J* = 15.2, 4.3 Hz, NHCHC*H*H), 2.90−2.84 (2H, m, C*H*$_2$CH=CH_2), 2.75 (1H, dd, *J* = 11.2, 4.1 Hz, NHCHCH*H*), 2.64 (1H, br d, *J* = 6.7 Hz, NH_{pip}), 1.51 (9H, s, $C(CH_3)_3$), 1.35 (3H, t, *J* = 7.2 Hz, $CO_2CH_2CH_3$); δ_C (125 MHz, $CDCl_3$) 172.8 (COO), 156.5 (NCOO), 136.4 (C, Ar), 134.7 (C, Ar), 134.2 (CH_2CH=CH_2), 126.7 (C, Ar), 122.4 (CH, Ar), 119.8 (CH, Ar), 118.3 (CH, Ar), 117.9 (CH_2CH=CH_2), 111.2 (CH, Ar), 108.9 (C, Ar), 80.3 ($C(CH_3)_3$), 68.7 (N*C*HCH_2), 62.4 (NCH_2), 61.3 (O*C*H_2CH_3), 54.1 (NHC), 53.7 (NH*C*HCH_2), 33.0 (*C*H_2CH=CH_2), 28.5 ($C(CH_3)_3$), 25.7 (NHCH*C*H_2), 14.2 (OCH_2CH_3); MS (ESI$^+$) *m/z* 426 (MH^+); HRMS calcd. for $C_{24}H_{32}N_3O_4$ $[M+H]^+$

426.2387, found 426.2386. Further elution provided more polar, minor diastereomer (*2R,3R,3'S*)-**179b** (19 mg, 9%) as an off-white solid. M. p. 137–142 °C; R_f = 0.25 (8:2, petrol: EtOAc); $[\alpha]_D^{29}$ +5.37 (*c* 0.12, $CHCl_3$); IR υ_{max} (neat)/cm^{-1} 3367, 2966, 2928, 1721, 1695, 1475, 1447, 1390, 1368, 1168, 1128, 910, 777, 747; δ_H (400 MHz, $CDCl_3$) 8.91−8.84 (1H, br s, NH_{indole}), 7.49 (1H, d, *J* = 7.8 Hz, Ar H), 7.39 (1H, d, *J* = 8.0 Hz, Ar H), 7.20 (1H, t, *J* = 7.5 Hz, Ar H), 7.12 (1H, t, *J* = 7.4 Hz, Ar H), 5.89−5.74 (1H, m, CH_2CH=CH_2), 5.07 (1H, d, *J* = 17.3 Hz, CH_2CH=C*H*H), 5.07 (1H, d, *J* = 10.2 Hz, CH_2CH=CH*H*), 4.45−4.37 (1H, m, NC*H*CH_2), 4.31−4.20 (3H, m, $CO_2CH_2CH_3$, NC*H*H), 3.99 (1H, d, *J* = 9.3 Hz, NCH*H*), 3.80 (1H, dd, *J* = 10.3, 4.1 Hz, NHC*H*CH_2), 3.09 (1H, dd, *J* = 15.1, 4.1 Hz, NHCHC*H*H), 2.85−2.72 (3H, m, NHCHCH*H*, CH_2CH=CH_2), 1.53 (9H, s, $C(CH_3)_3$), 1.33 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), NH_{pip} not observed; δ_C (125 MHz, $CDCl_3$) 172.8 (COO), 156.0 (NCOO), 136.5 (C, Ar), 135.1 (C, Ar), 134.5 (CH_2CH=CH_2), 126.5 (C, Ar), 122.3 (CH, Ar), 119.7 (CH, Ar), 118.3 (CH, Ar), 117.6 (CH_2CH=CH_2), 111.3 (CH, Ar), 108.6 (C, Ar), 80.5 ($C(CH_3)_3$), 72.2 (N*C*HCH_2), 61.3 (OCH_2CH_3), 60.7 (NCH_2), 54.5 (NH*C*HCH_2), 54.4 (NHC), 32.9 (CH_2CH=CH_2), 28.6 ($C(CH_3)_3$), 25.3 (NHCHCH_2), 14.3 (OCH_2CH_3); MS (ESI^+) *m/z* 426 (MH^+); HRMS calcd. for $C_{24}H_{32}N_3O_4$ $[M+H]^+$ 426.2387, found 426.2388.

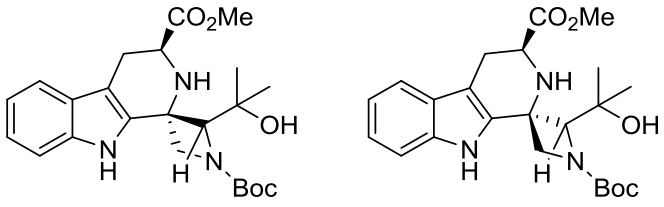
L-Tryptophan methyl ester (182)[90]



To a solution of anhydrous MeOH (14 mL) cooled to 0 °C was added thionyl chloride (445 μL, 6.13 mmol) dropwise, and left stirring. After 30 min, L-tryptophan (500 mg, 2.45 mmol) was added, and the solution heated under reflux for 18 h. After cooling to rt, the solvent was removed *in vacuo*. The reaction was neutralised with aqueous $NaHCO_3$ solution (25 mL), and extracted with EtOAc (3 x 25 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give **182** (534 mg, 100%) as an off-white solid. δ_H (500 MHz, $CDCl_3$) 8.14 (1H, br s, NH_{indole}), 7.62 (1H, d, *J* = 7.9 Hz, Ar H), 7.36 (1H, d, *J* = 8.1 Hz, Ar H), 7.22−7.18 (1H, m, Ar H), 7.15−7.10 (1H, m, Ar H), 7.07 (1H, d, *J* = 1.7 Hz, NHC*H*), 3.84 (1H, dd, *J* = 7.7, 4.9 Hz, NH_2CHCH_2), 3.72 (3H, s, CO_2CH_3), 3.29 (1H, dd, *J* = 14.4, 4.8 Hz, NH_2CHCHH), 3.06 (1H, dd, *J* = 14.4, 7.7

Hz, $NH_2CHCH\mathit{H}$), 1.61 (2H, br s, NH_2); δ_C (125 MHz, $CDCl_3$) 175.8 (COO), 136.3 (C, Ar), 127.5 (C, Ar), 122.9 (NHCH), 122.2 (CH, Ar), 119.6 (CH, Ar), 118.8 (CH, Ar), 111.3 (C, Ar), 111.2 (CH, Ar), 55.0 ($NH_2\mathit{C}HCH_2$), 52.0 ($CO_2\mathit{C}H_3$), 30.8 ($NHCH\mathit{C}H_2$); MS (ESI^+) *m/z* 219 (MH^+), 241 (MNa^+); HRMS calcd. for $C_{12}H_{15}N_2O_2$ $[M+H]^+$ 219.1128, found 219.1131. Analytical data in agreement with literature values.

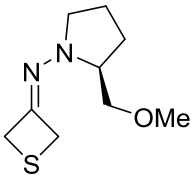
(*2R,3S,3′S*)- and (*2R,3R,3′S*)-2-(2-Hydroxypropan-2-yl)-2′,3′,4′,9′-tetrahydrospiro-[azetidine-3,1′-pyrido[3,4-*b*]indole]-1-*tert*-butyl-3′-methyl dicarboxylate (183a and 183b)



To a stirred solution of (*S*)-**170** (123 mg, 0.54 mmol) in anhydrous CH_3CN (6 mL) was added L-tryptophan methyl ester (142 mg, 0.65 mmol) and I_2 (6.80 mg, 27 μmol, 5 mol-%), and the mixture stirred under reflux for 18 h. After cooling to room temperature the solvent was removed *in vacuo*. The residue was dissolved in EtOAc (20 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic layers were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the title compounds as a 7.4:1 mixture of diastereomers as determined by ^1H NMR spectroscopy. Purification by flash column chromatography (SiO_2, 7:3, petrol: EtOAc) provided the separable diasteromers, to afford less polar, major diastereomer (*2R,3S,3′S*)-**183a** (188 mg, 81%) as an off-white solid. M. p. 118–120 °C; R_f = 0.46 (7:3, petrol: EtOAc); $[\alpha]_D^{26}$ –44.0 (*c* 0.10, $CHCl_3$); IR υ_{max} (neat)/cm^{-1} 3347, 2975, 2939, 2848, 1734, 1677, 1500, 1456, 1380, 1366, 1144, 1133, 747, 736; δ_H (300 MHz, $CDCl_3$) 8.40−8.25 (1H, br s, NH_{indole}), 7.49 (1H, d, *J* = 7.7 Hz, Ar H), 7.36 (1H, d, *J* = 8.0 Hz, Ar H), 7.21 (1H, td, *J* = 7.6, 1.2 Hz, Ar H), 7.15−7.10 (1H, m, Ar H), 4.56 (1H, s, $NC\mathit{H}C(CH_3)_2OH$), 4.09 (1H, d, *J* = 8.6 Hz, $NC\mathit{H}H$), 3.98 (1H, d, *J* = 8.7 Hz, $NCH\mathit{H}$), 3.84 (3H, s, CO_2CH_3), 3.70 (1H, dd, *J* = 11.2, 4.1 Hz, $NHC\mathit{H}CH_2$), 3.11 (1H, dd, *J* = 15.2, 4.1 Hz, $NHCHC\mathit{H}H$), 2.82 (1H, dd, *J* = 15.2, 11.2 Hz, $NHCHCH\mathit{H}$), 1.52 (9H, s, $C(CH_3)_3$), 1.49 (3H, s, $C(C\mathit{H}_3)(CH_3)OH$), 1.25 (3H, s,

C(CH_3)(C*H*$_3$)OH), piperidine NH not observed, OH not observed; δ_C (125 MHz, $CDCl_3$) 172.9 (COO), 158.0 (NCOO), 136.4 (C, Ar), 134.2 (C, Ar), 126.7 (C, Ar), 122.6 (CH, Ar), 120.1 (CH, Ar), 118.4 (CH, Ar), 111.2 (CH, Ar), 109.3 (C, Ar), 81.2 (*C*(CH_3)$_3$), 77.6 (N*C*HC(CH_3)$_2$OH), 72.1 (*C*(CH_3)$_2$OH), 63.9 (NCH_2), 56.4 (NHC), 53.6 (CO_2*C*H_3), 52.4 (NH*C*HCH_2), 28.4 (C(*C*H_3)$_3$), 26.4 (C(*C*H_3)(CH_3)OH), 26.3 (C(CH_3)(*C*H_3)OH), 25.2 (NHCH*C*H_2); MS (ESI$^+$) *m/z* 430 (MH^+); HRMS calcd. for $C_{23}H_{32}N_3O_5$ $[M+H]^+$ 430.2336, found 430.2333. Further elution provided more polar, minor diastereomer (*2R,3R,3'S*)-**183b** (19 mg, 8%) as a yellow oil. R_f = 0.26 (7:3, petrol: EtOAc); $[\alpha]_D^{30}$ +14.8 (*c* 0.25, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 3313, 2929, 2854, 1737, 1674, 1393, 1367, 1219, 1170, 735; δ_H (500 MHz, $CDCl_3$) 8.01 (0.82H, br s, NH*$_{indole}$*, major rotamer), 7.97 (0.18H, br s, NH*$_{indole}$*, minor rotamer), 7.49 (1H, d, *J* = 7.8 Hz, Ar H), 7.33 (1H, d, *J* = 8.1 Hz, Ar H), 7.21 (1H, t, *J* = 7.5 Hz, Ar H), 7.14 (1H, t, *J* = 7.5 Hz, Ar H), 4.25 (1H, d, *J* = 9.4 Hz, NC*H*H), 4.23−4.18 (2H, m, NCH*H*, NC*H*C(CH_3)$_2$OH), 3.93 (1H, dd, *J* = 8.2, 4.6 Hz, NHC*H*CH_2), 3.75 (3H, s, CO_2CH_3), 3.14 (1H, dd, *J* = 15.2, 4.6 Hz, NHCHC*H*H), 2.89 (1H, dd, *J* = 15.2, 8.3 Hz, NHCHCH*H*), 1.55 (9H, s, C(CH_3)$_3$), 1.37 (3H, s, C(C*H*$_3$)(CH_3)OH), 1.30 (3H, s, C(CH_3)(C*H*$_3$)OH), piperidine NH not observed, OH not observed; δ_C (125 MHz, $CDCl_3$) 173.6 (COO), 157.3 (NCOO), 136.5 (C, Ar), 134.9 (C, Ar), 126.3 (C, Ar), 122.7 (CH, Ar), 120.1 (CH, Ar), 118.4 (CH, Ar), 111.2 (CH, Ar), 108.6 (C, Ar), 81.0 (*C*(CH_3)$_3$), 79.6 (N*C*HC(CH_3)$_2$OH), 73.1 (NCH*C*(CH_3)$_2$OH), 64.2 (NCH_2), 55.6 (NHC), 54.2 (NH*C*HCH_2), 52.4 (CO_2*C*H_3), 28.4 (C(*C*H_3)$_3$, rotamer), 28.3 (C(*C*H_3)$_3$, rotamer), 27.4 (C(*C*H_3)(CH_3)OH), 26.7 (C(CH_3)(*C*H_3)OH), 25.1 (NHCH*C*H_2); MS (ESI$^+$) *m/z* 430 [MH^+], 452 [MNa^+]; HRMS calcd. for $C_{23}H_{31}N_3NaO_5$ $[M+Na]^+$ 452.2156, found 452.2159.

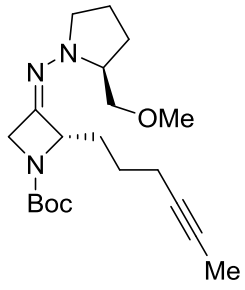
(S)-*N*-(2-(Methoxymethyl)pyrrolidin-1-yl)thietan-3-imine (193)



(*S*)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine (805 µL, 6.00 mmol) was added dropwise to thietan-3-one (634 mg, 7.20 mmol). The mixture was stirred at 65 °C for 16 h, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 3:1, petrol: EtOAc) provided **193** (1.10 g, 92%) as a yellow oil. R_f = 0.35 (3:1, petrol: EtOAc);

$[\alpha]_D^{23}$ +105 (*c* 0.01, $CHCl_3$); IR υ_{max} (film)/cm^{-1} 2968, 2921, 2826, 1638, 1447, 1359, 1097, 745; δ_H (500 MHz, $CDCl_3$) 4.28 (1H, dt, *J* = 14.4, 2.7 Hz, SC*H*H), 4.18 (1H, dt, *J* = 13.6, 2.8 Hz, SCH*H*), 4.07 (1H, dd, *J* = 14.4, 2.7 Hz, SC*H*H), 4.02 (1H, dd, *J* = 13.7, 2.6 Hz, SCH*H*), 3.48 (1H, dd, *J* = 8.7, 3.4 Hz, C*H*HOCH_3), 3.37 (3H, s, CH_2OCH_3), 3.34−3.30 (3H, m, CH*H*OCH_3, NC*H*CH_2, NC*H*H), 2.67 (1H q, *J* = 8.4 Hz, NCH*H*), 1.98−1.90 (3H, m, CH_2, C*H*H), 1.90−1.82 (1H, m, CH*H*); δ_C (125 MHz, $CDCl_3$) 144.8 (C=N), 75.1 (CH_2OCH_3), 65.9 (N*C*HCH_2), 59.3 (CH_2OCH_3), 53.9 (NCH_2), 41.4 (SCH_2), 41.0 (SCH_2), 26.0 (CH_2), 22.9 (CH_2); MS (ESI^+) *m/z* 201 (MH^+), 223 (MNa^+); HRMS calcd. for $C_9H_{16}N_2NaOS$ $[M+Na]^+$ 223.0876, found 223.0878.

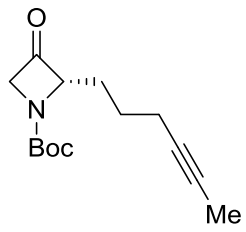
(*S*)-3-(2-(Methoxymethyl)-*N*-(2-*S*-(hex-4-yne)azetidine-3-ylidene)pyrrolidin-1-amine)-1-*tert*-butylcarboxylate (204)



To a stirred solution of (*S*)-**151** (142 mg, 0.50 mmol) in anhydrous THF (5 mL) at –78 °C under at atmosphere of nitrogen, was added TMEDA (83 μL, 0.55 mmol), followed by ^{n}butyllithium (2.43 M solution in hexanes, 226 μL, 0.55 mmol) dropwise. After 1 h at –78 °C, 6-iodo-2-hexyne (125 mg, 0.60 mmol) was added, and the solution allowed to warm slowly to room temperature over 16 h. The reaction mixture was diluted with diethyl ether (40 mL), and washed with H_2O (5 mL) and brine (5 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 3:1, hexane: EtOAc) provided **204** as an inseparable mixture of diastereomers in the ratio 1.56:1 (83 mg, 46%) as a pale yellow oil. R_f = 0.32 (3:1, hexane: EtOAc); IR υ_{max} (film)/cm^{-1} 2922, 2871, 1703, 1451, 1365, 1129, 1024, 860, 770; δ_H (400 MHz, $CDCl_3$) major isomer, 4.94−4.87 (1H, m, NC*H*CH_2), 4.41 (1H, d, *J* = 14.0 Hz, NC*H*H), 4.35 (1H, dd, *J* = 14.0, 3.3 Hz, NCH*H*), 3.46 (1H, dd, *J* = 9.2, 4.1 Hz, C*H*HOCH_3), 3.34−3.31 (2H, m, CH*H*OCH_3, NC*H*$CHOCH_3$), 3.30 (3H, s, CH_2OCH_3), 3.24−3.17 (1H, m, NC*H*HCH_2), 2.41 (1H, q, *J* = 8.3 Hz, NCH*H*CH_2), 2.15−2.06 (2H, m, $CH_2C{\equiv}CCH_3$), 2.02−1.87 (2H, m, CH_2) 1.85−1.73 (4H, m, NCHCH_2, CH_2), 1.70 (3H, t, *J* = 2.2 Hz, $C{\equiv}CCH_3$), 1.61−1.52 (2H, m,

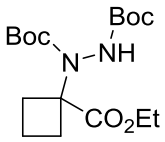
C*H*$_2$CH$_2$C≡CCH$_3$), 1.40 (9H, s, C(CH$_3$)$_3$); δ_C (100 MHz, CDCl$_3$) 156.3 (COO), 143.2 (C=N), 80.0 (*C*(CH$_3$)$_3$), 78.8 (*C*≡C), 75.8 (C≡*C*), 74.9 (*C*H$_2$OCH$_3$), 73.3 (N*C*HCH$_2$), 65.9 (N*C*HCHOCH$_3$), 60.1 (NCH$_2$), 59.2 (CH$_2$O*C*H$_3$), 53.6 (N*C*H$_2$CH$_2$), 29.3 (NCH*C*H$_2$), 28.2 (C(*C*H$_3$)$_3$), 26.7 (CH$_2$), 23.0 (*C*H$_2$CH$_2$C≡CCH$_3$), 22.7 (CH$_2$), 18.5 (*C*H$_2$C≡CCH$_3$), 3.4 (C≡C*C*H$_3$); MS (ESI$^+$) *m/z* 364 (MH$^+$), 386 (MNa$^+$); HRMS calcd. for $C_{20}H_{34}N_3O_3$ [M+H]$^+$ 364.2595, found 364.2593.

(*S*)-2-((Hex-4-yne)-3-oxoazetidine)-1-*tert*-butylcarboxylate (205)



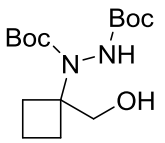
To **204** (40 mg, 0.11 mmol) was added saturated aqueous oxalic acid (1.0 mL) and diethyl ether (1.5 mL), and the reaction stirred vigorously at room temperature for 18 h. The reaction mixture was diluted with diethyl ether (30 mL), and the layers separated. The organic layer was washed with brine (10 mL) and saturated aqueous NaHCO$_3$ solution (10 mL), dried over MgSO$_4$, filtered, and concentrated *in vacuo* to give **205** (25 mg, 90%) as a pale yellow oil, which did not require further purification. R_f = 0.57 (7:1, hexane: EtOAc); $[\alpha]_D^{25}$ +93.6 (*c* 0.09, CHCl$_3$); IR υ_{max} (film)/cm^{-1} 2923, 2860, 1820, 1701, 1433, 1364, 1127, 1060, 774; δ_H (400 MHz, CDCl$_3$) 4.93−4.87 (1H, m, NC*H*CH$_2$), 4.69 (1H, d, *J* = 16.7 Hz, NC*H*H), 4.52 (1H, dd, *J* = 16.7, 4.3 Hz, NCH*H*), 2.21−2.17 (2H, m, C*H*$_2$C≡CCH$_3$), 1.93 (2H, q, *J* = 7.0 Hz, NCHC*H*$_2$), 1.77 (3 H, t, *J* = 2.4 Hz, C≡CCH$_3$), 1.73−1.64 (2H, m, C*H*$_2$CH$_2$C≡CCH$_3$), 1.49 (9H, s, C(CH$_3$)$_3$); δ_C (176 MHz, CDCl$_3$) 200.7 (C=O), 156.3 (COO), 82.7 (N*C*HCH$_2$), 80.9 (*C*(CH$_3$)$_3$), 78.2 (*C*≡C), 76.2 (C≡*C*), 69.0 (NCH$_2$), 29.6 (NCH*C*H$_2$), 28.3 (C(*C*H$_3$)$_3$), 24.3 (*C*H$_2$CH$_2$C≡CCH$_3$), 18.5 (*C*H$_2$C≡CCH$_3$), 3.5 (C≡C*C*H$_3$); MS (ESI$^+$) *m/z* 274 (MNa$^+$); HRMS calcd. for $C_{14}H_{21}NNaO_3$ [M+Na]$^+$ 274.1414, found 274.1406; 75% *ee* (determined by chiral GC analysis on a Chrompac cyclodextrin-β-236M-19 50m x 0.25mm x 0.25µm column, T = 160 °C, P = 15 psi, H$_2$ carrier gas, t_R 46.27 min and t_R 46.71 min).

Di-*tert*-butyl 1-(1-(ethoxycarbonyl)cyclobutyl)hydrazine-1,2-dicarboxylate (269)



To an oven-dried flask purged with nitrogen was added diisopropylamine (108 μL, 0.77 mmol) in anhydrous THF (7 mL) and cooled to 0 °C. ^{n}Butyllithium (2.3 M in hexanes, 335 μL, 0.77 mmol) was added dropwise, and the reaction stirred for 20 min before cooling to –78 °C. Ethyl cyclobutanecarboxylate (97 μL, 0.70 mmol) was added dropwise, and the solution stirred for 1 h before the addition of di-*tert*-butyl azodicarboxylate (194 mg, 0.84 mmol) in anhydrous THF (1 mL). The solution was stirred at –78 °C for 2 h before warming to room temperature over 1 h and quenching with saturated aqueous K_2CO_3 solution (20 mL). The layers were separated, and the aqueous layer extracted with EtOAc (20 mL), organic extracts combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 4:1, petrol: EtOAc) provided **269** (207 mg, 83%) as a pale yellow oil. R_f = 0.44 (4:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 3318, 2978, 1714, 1477, 1392, 1366, 1243, 1152, 755; δ_H (500 MHz, $CDCl_3$) 6.31 (0.75H, br s, NH, major rotamer), 6.01 (0.25H, br s, NH, minor rotamer), 4.32−4.18 (2H, br m, $CO_2CH_2CH_3$), 2.87−2.62 (1H, m, C*H*HCCOO), 2.62−2.36 (2H, m, CH*H*CCOO, C*H*HCCOO), 2.19−2.00 (2H, m, CH*H*CCOO, CH_2CHHCH_2), 1.98−1.83 (1H, m, CH_2CHHCH_2), 1.48 (9H, s, $C(CH_3)_3$), 1.41 (9H, br s, $C(CH_3)_3$), 1.29 (3H, t, J = 7.0 Hz, $CO_2CH_2CH_3$); δ_C (125 MHz, $CDCl_3$) 174.4 (COO), 156.2 (NCOO), 155.5 (NCOO), 82.1 ($C(CH_3)_3$), 81.1 ($C(CH_3)_3$), 65.9 (CH_2CCO_2), 61.3 ($CO_2CH_2CH_3$), 32.7 (CH_2CCO_2), 28.8 (CH_2CCO_2), 28.2 ($C(CH_3)_3$), 28.1 ($C(CH_3)_3$), 14.4 ($CH_2CH_2CH_2$), 14.3 ($CO_2CH_2CH_3$); MS (ESI$^+$) *m/z* 381 [MNa$^+$]; HRMS calcd. for $C_{17}H_{30}N_2NaO_6$ [M+Na]$^+$ 381.1996, found 381.1996.

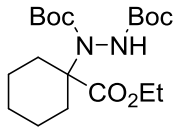
Di-*tert*-butyl 1-(1-(hydroxymethyl)cyclobutyl)hydrazine-1,2-dicarboxylate (270)



To a solution of **269** (36 mg, 0.10 mmol) in anhydrous diethyl ether (2 mL) at 0 °C was added $LiBH_4$ (4.30 mg, 0.20 mmol), and stirred for 3 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL), and extracted with EtOAc (3 x 10 mL). The organic extracts were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered, and

concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2:1, petrol: EtOAc) provided **270** (27 mg, 85%) as a white solid. M. p. 121–123 °C; R_f = 0.44 (4:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 3328, 3208, 2955, 2935, 2874, 1702, 1455, 1394, 1359, 1258, 1161, 761; δ_H (500 MHz, $CDCl_3$) 6.42 (1H, br s, NH), 4.25−3.87 (0.85H, br s, OH, major rotamer), 4.03 (1H, d, *J* = 10.1 Hz, C*H*HOH), 3.79 (0.15H, br s, OH, minor rotamer), 3.55 (1H, t, *J* = 10.8 Hz, CH*H*OH), 2.20−2.07 (3H, m, C*H*HCCH$_2$OH, C*H*$_2$CCH$_2$OH), 2.07−1.96 (1H, m, CH*H*CCH$_2$OH), 1.79−1.68 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.46 (9H, s, C(CH$_3$)$_3$), 1.44 (9H, s, C(CH$_3$)$_3$); δ_C (125 MHz, $CDCl_3$) 158.0 (2 x COO), 82.3 (*C*(CH$_3$)$_3$), 81.6 (*C*(CH$_3$)$_3$), 65.2 (*C*CH$_2$OH), 64.8 (C*C*H$_2$OH), 29.7 (*C*H$_2$CCH$_2$OH), 28.3 (C(*C*H$_3$)$_3$), 28.2 (C(*C*H$_3$)$_3$), 26.8 (*C*H$_2$CCH$_2$OH), 14.0 (CH$_2$*C*H$_2$CH$_2$); MS (ESI$^+$) *m/z* 339 [MNa$^+$]; HRMS calcd. for $C_{15}H_{28}N_2NaO_5$ [M+Na]$^+$ 339.1890, found 339.1895.

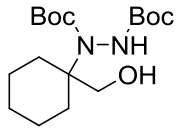
Di-*tert*-butyl 1-(1-(ethoxycarbonyl)cyclohexyl)hydrazine-1,2-dicarboxylate (272)



To an oven-dried flask was added diisopropylamine (771 μL, 5.50 mmol) in anhydrous THF (50 mL) and cooled to 0 °C under an atmosphere of nitrogen. ^{n}Butyllithium (3.48 mL, 1.58 M in hexanes, 5.50 mmol) was added dropwise and the reaction stirred for 20 min before cooling to –78 °C. Ethyl cyclohexanecarboxylate (835 μL, 5.00 mmol) was added dropwise, and the solution stirred for 1 h before the addition of di-*tert*-butyl azodicarboxylate (1.38 g, 6.00 mmol) in anhydrous THF (5 mL). The mixture was stirred for 2 h before warming to room temperature over 1 h. The reaction was quenched with saturated K_2CO_3 solution (50 mL) and the organic layer separated. The aqueous layer was washed with EtOAc (50 mL), the organic extracts combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 6:1, hexane: EtOAc) provided **272** (1.79 g, 92%) as a yellow oil. R_f = 0.31 (6:1, hexane: EtOAc); IR υ_{max} (film)/cm^{-1} 3322, 2977, 2932, 1705, 1391, 1366, 1239, 1154, 760; δ_H (500 MHz, $CDCl_3$) 6.26 (0.75H, br s, NH, major rotamer), 5.98 (0.25H, br s, NH, minor rotamer), 4.19−4.10 (2H, m, CO$_2$C*H*$_2$CH$_3$), 2.34−2.08 (2H, m, CH$_2$), 1.95−1.82 (1H, m C*H*H), 1.80−1.65 (3H, m, CH$_2$, CH*H*), 1.65−1.55 (3H, m, CH$_2$, C*H*H), 1.49 (9H, s, C(CH$_3$)$_3$), 1.43 (10H, s, C(CH$_3$)$_3$, CH*H*), 1.27−1.22 (3H, m, CO$_2$CH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 174.5 (COO), 155.8 (COO),

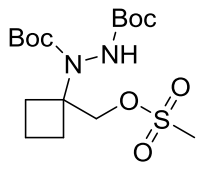
155.4 (COO), 81.9 (*C*(CH_3)$_3$), 80.9 (*C*(CH_3)$_3$), 67.0 (*C*$CO_2CH_2CH_3$), 60.9 (*C*H_2CH_3), 33.7 (CH_2), 32.0 (CH_2), 28.2 (C(*C*H_3)$_3$), 28.1 (C(*C*H_3)$_3$), 25.4 (CH_2), 21.8 (CH_2), 21.7 (CH_2), 14.3 (CH_2*C*H_3); MS (ESI^+) *m/z* 409 [MNa^+]; HRMS calcd. for $C_{19}H_{34}N_2NaO_6$ $[M+Na]^+$ 409.2309, found 409.2310.

Di-*tert*-butyl 1-(1-(hydroxymethyl)cyclohexyl)hydrazine-1,2-dicarboxylate (273)



To an oven-dried flask was added **272** (402 mg, 1.04 mmol) and anhydrous diethyl ether (10 mL), and cooled to 0 °C under an atmosphere of nitrogen. $LiBH_4$ (45 mg, 2.08 mmol) was added, and the reaction stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with EtOAc (3 x 30 mL). The organic extracts were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 4:1, petrol: EtOAc) provided **273** (260 mg, 73%) as a colourless oil. R_f = 0.30 (4:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 3317, 3196, 2977, 2939, 1709, 1392, 1366, 1255, 1165, 763; δ_H (500 MHz, $CDCl_3$) 6.33 (1H, s, NH), 4.26 (1H, d, *J* = 10.2 Hz, OH), 4.14 (1H, d, *J* = 12.1 Hz, C*H*HOH), 3.40−3.33 (1H, m, CH*H*OH), 2.31−2.21 (1H, m, C*H*HCCH_2OH), 1.95−1.88 (1H, m, CH*H*CCH_2OH), 1.49−1.47 (9H, m, C(CH_3)$_3$), 1.46−1.43 (9H, m, C(CH_3)$_3$), 1.44−1.22 (8H, m, 4 x CH_2); δ_C (125 MHz, $CDCl_3$) 158.1 (2 x COO), 82.1 (*C*(CH_3)$_3$), 81.4 (*C*(CH_3)$_3$), 66.4 (*C*CH_2OH), 65.9 (C*C*H_2OH), 31.9 (CH_2), 29.7 (CH_2), 25.9 (CH_2), 22.8 (CH_2), 22.1 (CH_2); MS (ESI^+) *m/z* 367 [MNa^+]; HRMS calcd. for $C_{17}H_{32}N_2NaO_5$ $[M+Na]^+$ 367.2203, found 367.2205.

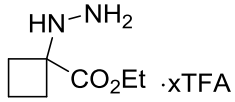
Di-*tert*-butyl 1-(1-(((methylsulfonyl)oxy)methyl)cyclobutyl)hydrazine-1,2-dicarboxylate (278)



To a solution of **270** (145 mg, 0.46 mmol) in pyridine (3 mL) was added DMAP (11 mg, 0.09 mmol) and cooled to 0 °C. Methanesulfonyl chloride (54 µL, 0.69 mmol) was added dropwise, and the reaction stirred at 0 °C for 30 min before warming to room

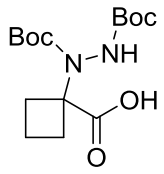
temperature for 3 h. The reaction was quenched with 1 M HCl solution (20 mL), and extracted with EtOAc (3 x 40 mL). The organic extracts were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2:1, petrol: EtOAc) provided **278** (168 mg, 93%) as a colourless oil. R_f = 0.45 (2:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 3331, 2977, 2934, 1704, 1355, 1244, 1152, 733; δ_H (500 MHz, $CDCl_3$) 6.33 (0.80H, br s, NH, major rotamer), 6.10 (0.20H, br s, NH, minor rotamer), 4.84−4.62 (1H, m, C*H*HOSO$_2$CH$_3$), 4.38−4.19 (1H, m, CH*H*OSO$_2$CH$_3$), 3.04 (3H, s, SO$_2$CH$_3$), 2.61−2.26 (2H, m, C*H*$_2$CCH$_2$O), 2.15−2.00 (2H, m, C*H*$_2$CCH$_2$O), 1.92−1.79 (1H, m, CH$_2$C*H*HCH$_2$), 1.76−1.68 (1H, m, CH$_2$CH*H*CH$_2$), 1.54−1.41 (18H, m, C(CH$_3$)$_3$); δ_C (125 MHz, $CDCl_3$) 81.1 (2 x *C*(CH$_3$)$_3$), 71.7 (*C*H$_2$OSO$_2$CH$_3$), 62.3 (*C*CH$_2$O), 37.4 (SO$_2$CH$_3$), 29.9 (*C*H$_2$CCH$_2$O), 28.2 (2 x C(CH$_3$)$_3$), 26.9 (*C*H$_2$CCH$_2$O), 13.9 (CH$_2$*C*H$_2$CH$_2$), COO not observed; MS (ESI$^+$) *m/z* 417 [MNa$^+$]; HRMS calcd. for $C_{16}H_{30}N_2NaO_7S$ [M+Na]$^+$ 417.1666, found 417.1666.

2-(1-(Ethoxycarbonyl)cyclobutyl)hydrazin-1-ium 2,2,2-trifluoroacetate (286)



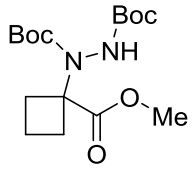
To a solution of **269** (120 mg, 0.33 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was added TFA (2.5 mL) dropwise at 0 °C under an atmosphere of nitrogen. The reaction was stirred for 20 min and then at room temperature for 2 h before being concentrated by purging with nitrogen to give **286** (52 mg, 100%) as an orange oil. IR υ_{max} (film)/cm^{-1} 3250, 2962, 1671, 1428, 1372, 1260, 1138, 723; δ_H (500 MHz, $CDCl_3$) 7.08 (3H, br s, NH, NH$_2$), 4.30 (2H, q, *J* = 7.1 Hz, CO$_2$C*H*$_2$CH$_3$), 2.57−2.49 (2H, m, C*H*$_2$CNH), 2.44−2.35 (2H, m, C*H*$_2$CNH), 2.20−2.10 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.34 (3H, t, *J* = 7.1 Hz, CO$_2$CH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 172.7 (COO), 64.1 (*C*CO$_2$CH$_2$), 62.7 (CO$_2$*C*H$_2$CH$_3$), 28.0 (2 x *C*H$_2$CNH), 14.6 (CH$_2$*C*H$_2$CH$_2$), 13.9 (CO$_2$CH$_2$*C*H$_3$); MS (ESI$^+$) *m/z* 159 [MH$^+$]; HRMS calcd. for $C_7H_{15}N_2O_2$ [M+H]$^+$ 159.1128, found 159.1128.

1-(1,2-Bis(*tert*-butoxycarbonyl)hydrazineyl)cyclobutane-1-carboxylic acid (288)



This compound was prepared according to a modified literature procedure.[162] To a solution of **269** (401 mg, 1.12 mmol) in 1:1 THF: MeOH (8 mL) was added 2 M NaOH (1.12 mL, 2.24 mmol), and the reaction stirred at room temperature for 18 h before the addition of additional 2 M NaOH (1.12 mL, 2.24 mmol). After 5 h, the solvent was removed and H_2O (10 mL) added. The solution was acidified to pH 5 using 1 M HCl solution. The aqueous phase was extracted with EtOAc (3 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 95:5, CH_2Cl_2: MeOH) provided **288** (240 mg, 65%) as a white solid. M. p. 151–153 °C; R_f = 0.26 (95:5, CH_2Cl_2: MeOH); IR υ_{max} (neat)/cm^{-1} 3308, 3005, 2980, 2949, 1741, 1394, 1367, 1246, 1152, 714; δ_H (500 MHz, $CDCl_3$) 6.84 (0.75H, br s, NH, major rotamer), 6.69 (0.25H, br s, NH, minor rotamer), 3.00−2.76 (1H, m, C*H*HCCO$_2$H), 2.63−2.47 (1H, m, CH*H*CCO$_2$H), 2.29−2.15 (1H, m, C*H*HCCO$_2$H), 2.13−1.98 (2H, m, CH$_2$C*H*HCH$_2$, CH*H*CCO$_2$H), 1.91−1.74 (1H, m, CH$_2$CH*H*CH$_2$), 1.50 (9H, s, C(CH$_3$)$_3$), 1.44 (9H, s, C(CH$_3$)$_3$), COOH not observed; δ_C (125 MHz, $CDCl_3$) 174.2 (COO), 159.5 (COO), 153.4 (COO), 84.3 (*C*(CH$_3$)$_3$), 84.0 (*C*(CH$_3$)$_3$), 66.3 (*C*CO$_2$H), 32.5 (*C*H$_2$CCO$_2$H), 28.8 (*C*H$_2$CCO$_2$H), 28.04 (C(*C*H$_3$)$_3$), 28.01 (C(*C*H$_3$)$_3$), 14.0 (CH$_2$*C*H$_2$CH$_2$); MS (ESI$^+$) *m/z* 353 [MNa$^+$]; HRMS calcd. for $C_{15}H_{26}N_2NaO_6$ [M+Na]$^+$ 353.1683, found 353.1681.

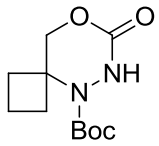
Di-*tert*-butyl 1-(1-(methoxycarbonyl)cyclobutyl)hydrazine-1,2-dicarboxylate (285)



This compound was prepared according to a modified literature procedure.[153] To an oven-dried flask with **269** (51 mg, 0.14 mmol) in anhydrous MeOH (3 mL) under an atmosphere of nitrogen was added NaOMe (15 mg, 0.28 mmol). The solution was heated under reflux for 24 h and the solvent removed *in vacuo*. The residue was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 4:1, petrol: EtOAc) provided **285** (29

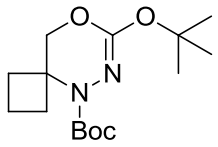
mg, 58%) as a white solid. M. p. 95–96 °C; R_f = 0.37 (4:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 3294, 2978, 2932, 1720, 1365, 1242, 1158, 727; δ_H (500 MHz, $CDCl_3$) 6.34 (0.75H, br s, NH, major rotamer), 6.05 (0.25H, br s, NH, minor rotamer), 3.76 (3H, s, CO_2CH_3), 2.86−2.36 (3H, m, C*H*$_2$CCO$_2$CH$_3$, C*H*HCCO$_2$CH$_3$), 2.20−1.99 (2H, m, CH*H*CCO$_2$CH$_3$, CH$_2$C*H*HCH$_2$), 1.99−1.84 (1H, m, CH$_2$CH*H*CH$_2$), 1.49 (9H, s, C(CH$_3$)$_3$), 1.42 (9H, s, C(CH$_3$)$_3$); δ_C (125 MHz, $CDCl_3$) 174.9 (COO), 156.3 (COO), 155.6 (COO), 82.1 (*C*(CH$_3$)$_3$), 81.1 (*C*(CH$_3$)$_3$), 66.0 (*C*CO$_2$CH$_3$), 52.4 (CO$_2$*C*H$_3$), 32.8 (*C*H$_2$CCO$_2$), 28.6 (*C*H$_2$CCO$_2$), 28.2 (C(*C*H$_3$)$_3$), 28.1 (C(*C*H$_3$)$_3$), 14.4 (CH$_2$*C*H$_2$CH$_2$); MS (ESI$^+$) *m/z* 367 [MNa$^+$]; HRMS calcd. for $C_{16}H_{28}N_2NaO_6$ [M+Na]$^+$ 367.1840, found 367.1840.

tert-Butyl 7-oxo-8-oxa-5,6-diazaspiro[3.5]nonane-5-carboxylate (275)



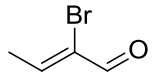
To an oven-dried flask was added **270** (32 mg, 0.10 mmol) in anhydrous $CHCl_3$ (3 mL) and cooled to 0 °C under an atmosphere of nitrogen. Thionyl chloride (9 μL, 0.12 mmol) was added dropwise and the solution warmed to room temperature before heating to 55 °C for 16 h. The reaction was cooled to room temperature and quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (2 x 20 mL). The organic extracts were combined, washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2:1, petrol: EtOAc) provided **275** (14 mg, 58%) as a colourless oil. R_f = 0.24 (2:1 petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 3296, 2910, 2856, 1626, 1443, 1397, 1228, 1143, 742; δ_H (500 MHz, $CDCl_3$) 6.38 (1H, br s, NH), 4.45 (2H, s, CH$_2$O), 2.55−2.44 (2H, m, C*H*$_2$CCH$_2$O), 2.03 (2H, br t, *J* = 8.8 Hz, C*H*$_2$CCH$_2$O), 1.77−1.61 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.50 (9H, s, C(CH$_3$)$_3$); δ_C (125 MHz, $CDCl_3$) 155.0 (COO), 82.4 (*C*(CH$_3$)$_3$), 74.4 (C*C*H$_2$O), 62.3 (*C*CH$_2$O), 31.9 (2 x *C*H$_2$CCH$_2$O), 28.1 (C(*C*H$_3$)$_3$), 13.1 (CH$_2$*C*H$_2$CH$_2$), CONH not observed; MS (ESI$^+$) *m/z* 265 [MNa$^+$]; HRMS calcd. for $C_{11}H_{18}N_2NaO_4$ [M+Na]$^+$ 265.1159, found 265.1159.

tert-Butyl 7-(tert-butoxy)-8-oxa-5,6-diazaspiro[3.5]non-6-ene-5-carboxylate (280)



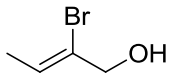
To a solution of **278** (59 mg, 0.15 mmol) in anhydrous DMF (5 mL) was added Cs_2CO_3 (391 mg, 1.20 mmol) at room temperature. The reaction was stirred for 16 h, filtered through Celite® and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2:1, petrol: EtOAc) provided **280** (38 mg, 86%) as a colourless oil. R_f = 0.69 (2:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2977, 2935, 1737, 1699, 1391, 1366, 1254, 1156, 715; δ_H (500 MHz, $CDCl_3$) 4.07 (2H, s, CH_2O), 2.77 (2H, ddd, *J* = 9.9, 9.9, 2.8 Hz, C*H*$_2$CCH$_2$O), 2.16−2.09 (2H, m, C*H*$_2$CCH$_2$O), 1.85−1.74 (1H, m, CH$_2$C*H*HCH$_2$), 1.64−1.54 (1H, m, CH$_2$CH*H*CH$_2$), 1.51 (9H, s, C(CH$_3$)$_3$), 1.46 (9H, s, C(CH$_3$)$_3$); δ_C (125 MHz, $CDCl_3$) 159.8 (COO), 157.4 (C=N), 81.8 (*C*(CH$_3$)$_3$), 81.7 (*C*(CH$_3$)$_3$), 67.6 (*C*CH$_2$O), 61.9 (C*C*H$_2$O), 33.5 (2 x *C*H$_2$CCH$_2$O), 28.3 (C(*C*H$_3$)$_3$), 28.1 (C(*C*H$_3$)$_3$), 12.9 (CH$_2$*C*H$_2$CH$_2$); MS (ESI$^+$) *m/z* 321 [MNa$^+$]; HRMS calcd. for $C_{15}H_{26}N_2NaO_4$ [M+Na]$^+$ 321.1785, found 321.1783.

(*Z*)-2-Bromobut-2-enal (301)



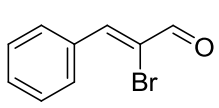
This known compound was prepared according to a modified literature procedure.[164] To a solution of crotonaldehyde (4.14 mL, 50.0 mmol) in anhydrous CH_2Cl_2 (70 mL) at 0 °C was added bromine (2.56 mL, 50.0 mmol) in CH_2Cl_2 (1 mL) dropwise over 10 min. The reaction mixture was stirred at 0 °C for 1 h before the dropwise addition of Et_3N (8.36 mL, 60.0 mmol), stirred at rt over 90 min, then quenched with saturated aqueous $Na_2S_2O_3$ solution (30 mL). The organic layer was separated and washed with 1M HCl (20 mL), brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by Kugelrohr distillation (50 °C, 1 torr) provided **301** (4.62 g, 62%) as a pale yellow oil. IR υ_{max} (film)/cm^{-1} 2831, 1698, 1652, 641; δ_H (500 MHz, $CDCl_3$) 9.22 (1H, s, COH), 7.25 (1H, q, *J* = 6.8 Hz, CH$_3$C*H*=CBr), 2.16 (3H, d, *J* = 6.8 Hz, C*H*$_3$CH=CBr); δ_C (125 MHz, $CDCl_3$) 186.0 (COH), 150.8 (CH$_3$*C*H=CBr), 130.2 (C-Br), 18.0 (*C*H$_3$CH=CBr); MS (ESI$^+$) *m/z* 171 [M(^{79}Br)Na$^+$], 173 [M(^{81}Br)Na$^+$]; HRMS calcd. for $C_4H_5{}^{79}BrONa$ [M+Na]$^+$ 170.9416, found 170.9414. Analytical data in agreement with literature values.

(*Z*)-2-Bromobut-2-en-1-ol (302)



This known compound was prepared according to a modified literature procedure.[164] To a solution of **301** (2.23 g, 15.0 mmol) in THF (10 mL) and H_2O (5 mL) at 0 °C was added $NaBH_4$ (1.13 g, 30.0 mmol) portionwise. The reaction mixture was stirred for 90 min before EtOAc (10 mL) and 10% NaOH solution (5 mL) were added, and the solution was stirred for a further 5 min. The organic phase was separated and washed with 10% NaOH solution (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give **302** (1.95 g, 86%) as a pale yellow oil, which was used without further purification. R_f = 0.41 (4:1 petrol: EtOAc); IR υ_{max} (film/cm^{-1}) 3362, 2918, 2857, 1662, 1083, 809, 671; δ_H (500 MHz, $CDCl_3$) 6.08 (1H, q, *J* = 6.5 Hz, CH_3CH=CBr), 4.25 (2H, d, *J* = 5.2 Hz, CH_2OH), 1.92 (1H, t, *J* = 6.3 Hz, CH_2OH), 1.78 (3H, d, *J* = 6.5 Hz, CH_3CH=CBr); δ_C (125 MHz, $CDCl_3$) 127.8 (CBr), 125.4 (CH_3CH=CBr), 68.5 (CH_2OH), 16.4 (CH_3CH=CBr); MS (ESI$^+$) *m/z* 173 [M(^{79}Br)Na$^+$], 175 [M(^{81}Br)Na$^+$]; HRMS calcd. for $C_4H_7{}^{79}BrONa$ [M+Na]$^+$ 172.9572, found 172.9571. Analytical data in agreement with literature values.

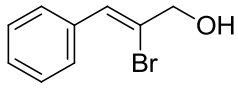
(*Z*)-2-Bromo-3-phenylacrylaldehyde (303)[165]



This known compound was prepared according to a literature procedure.[165] To a solution of *trans*-cinnamaldehyde (1.00 g, 7.95 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added bromine (489 μL, 9.54 mmol) dropwise. The reaction was stirred for 20 min, after which triethylamine (1.88 mL, 13.5 mmol) was added, and stirred for a further 20 min. The solution was diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous $NaHSO_3$ solution (10%, 15 mL), H_2O (15 mL) and brine (15 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give **303** (1.65 g, 98%) as a yellow oil, which was used without further purification. R_f = 0.39 (8:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2850, 1693, 1602, 1115, 758, 690; δ_H (500 MHz, $CDCl_3$) 9.36 (1H, s, COH), 8.04−7.97 (2H, m, Ar H), 7.91 (1H, s, CH=CBr), 7.54−7.47 (3H, m, Ar H); δ_C (125 MHz, $CDCl_3$) 187.1 (COH), 149.1 (*C*H=CBr), 132.9 (C, Ar), 131.6 (CH, Ar), 131.0 (CH, Ar), 128.8 (CH, Ar), 124.3 (CH=*C*Br);

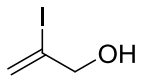
MS (ESI$^+$) *m/z* 233 [M(^{79}Br)Na$^+$], 235 [M(^{81}Br)Na$^+$]; HRMS calcd. for $C_9H_7{}^{79}BrONa$ [M+Na]$^+$ 232.9572, found 232.9570. Analytical data in agreement with literature values.

(*Z*)-2-Bromo-3-phenylprop-2-en-1-ol (304)[166]



This known compound was prepared according to a literature procedure.[166] To a solution of **303** (1.63 g, 7.71 mmol) in anhydrous MeOH (39 mL) was added $NaBH_4$ (292 mg, 7.71 mmol) portionwise, and stirred at rt for 1 h. The reaction was quenched with H_2O (25 mL), and extracted with diethyl ether (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 7:1, hexane: EtOAc) provided **304** (1.25 g, 86%) as a yellow oil. R_f = 0.14 (7:1, hexane: EtOAc); IR υ_{max} (film)/cm^{-1} 3337, 3025, 2920, 2870, 1492, 860, 752, 694; δ_H (500 MHz, $CDCl_3$) 7.62 (2H, d, *J* = 7.6 Hz, Ar H), 7.37 (2H, t, *J* = 7.4 Hz, Ar H), 7.34−7.29 (1H, m, Ar H), 7.09 (1H, s, CH=CBr), 4.43 (2H, d, *J* = 6.2 Hz, C*H*$_2$OH), 2.09 (1H, t, *J* = 6.6 Hz, CH$_2$O*H*); δ_C (125 MHz, $CDCl_3$) 135.0 (C, Ar), 129.0 (CH, Ar), 128.2 (2 x CH, Ar), 127.9 (*C*H=CBr), 125.3 (CH=*C*Br), 69.5 (CH_2OH); MS (ESI$^+$) *m/z* 212 [M(^{79}Br)Na$^+$], 214 [M(^{81}Br)Na$^+$]; HRMS calcd. for $C_9H_9{}^{79}BrONa$ [M+Na]$^+$ 234.9729, found 234.9729. Analytical data in agreement with literature values.

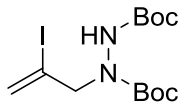
2-Iodoprop-2-en-1-ol (297)[198]



This known compound was prepared according to a modified literature procedure.[198] To a solution of sodium iodide (3.60 g, 24.0 mmol) in acetonitrile (30 mL) was slowly added chlorotrimethylsilane (3.05 mL, 24.0 mmol), water (216 mg, 12.0 mmol) and propargyl alcohol (1.16 mL, 20.0 mmol). The solution was stirred for 2 h, quenched with H_2O (20 mL), and extracted with diethyl ether (3 x 35 mL). The organic layers were combined, washed with 10% aqueous $Na_2S_2O_3$ solution (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 7:1, petrol: EtOAc) provided **297**

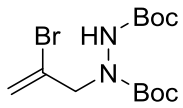
(530 mg, 14%) as a colourless oil. R_f = 0.30 (7:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 3296, 2910, 2856, 1626, 1443, 1026, 896, 552; δ_H (500 MHz, $CDCl_3$) 6.40−6.38 (1H, m, C*H*H=CI), 5.88−5.85 (1H, m, CH*H*=CI), 4.18 (2H, s, CH_2OH), 1.97 (1H, br s, CH_2O*H*); δ_C (125 MHz, $CDCl_3$) 124.5 (*C*H_2=CI), 110.5 (CH_2=*C*I), 71.1 (CH_2OH); GCMS $(EI)^+$ *m/z* 184 ($M^{+\bullet}$). Analytical data in agreement with literature values.

Di-*tert*-butyl 1-(2-iodoallyl)hydrazine-1,2-dicarboxylate (298)



To a solution of **297** (405 mg, 2.20 mmol) and triphenylphosphine (1.15 g, 4.40 mmol) in anhydrous THF (11 mL) at 0 °C was added di-*tert*-butyl azodicarboxylate (1.01 g, 4.40 mmol) portionwise. The reaction was allowed to warm to room temperture over 24 h and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 9:1, petrol: EtOAc) provided **298** (660 mg, 75 %) as a white solid. M. p. 94–96 °C; R_f = 0.30 (9:1 petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 3349, 2981, 2935, 1709, 1627, 1385, 1366, 1255, 1152, 913, 752, 554; δ_H (500 MHz, $CDCl_3$) 6.41 (1H, br m, NH, major rotamer), 6.26 (1H, br m, C*H*H=CI), 6.10 (1H, br s, NH, minor rotamer), 5.88 (1H, s, CH*H*=CI), 4.26 (2H, br s, NCH_2CI), 1.50−1.45 (18H, m, ($C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 154.9 (COO), 154.6 (COO), 128.0 (*C*H_2=CI, rotamer), 127.6 (*C*H_2=CI, rotamer), 106.2 (CH_2=*C*I), 81.8 (*C*$(CH_3)_3$), 81.4 (*C*$(CH_3)_3$), 61.5 (N*C*H_2CI, rotamer), 60.4 (N*C*H_2CI, rotamer), 28.2 (2 x C(*C*$H_3)_3$); MS (ESI^+) *m/z* 421 [MNa^+]; HRMS calcd. for $C_{13}H_{23}IN_2NaO_4$ $[M+Na]^+$ 421.0595, found 421.0594.

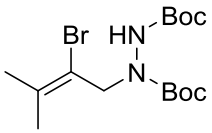
Di-*tert*-butyl 1-(2-bromoallyl)hydrazine-1,2-dicarboxylate (300)



To a solution of 2-bromoallyl alcohol (414 μL, 5.00 mmol) and triphenylphosphine (2.62 g, 10.0 mmol) in anhydrous THF (30 mL) at 0 °C was added di-*tert*-butyl azodicarboxylate (2.30 g, 10.0 mmol) portionwise. The reaction was allowed to warm to room temperature over 18 h and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 6:1, petrol: EtOAc) provided **300** (1.75 g, 100%) as a white solid. M. p. 87–90°C; R_f = 0.41 (6:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 3349, 2982, 2935, 1714, 1642, 1385, 1366,

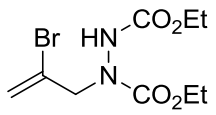
1256, 1135, 906, 753, 571; δ_H (500 MHz, $CDCl_3$) 6.42 (1H, br m, NH, major rotamer), 6.11 (1H, br s, NH, minor rotamer), 5.80 (1H, br m, C*H*H=CBr), 5.59 (1H, s, CH*H*=CBr), 4.55−4.05 (2H, m, NCH_2CBr), 1.47 (18H, m, (C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 154.7 (2 x COO), 128.84 (CH_2=*C*Br, rotamer), 128.78 (CH_2=*C*Br, rotamer), 119.5 (*C*H_2=CBr, rotamer), 119.1 (*C*H_2=CBr, rotamer), 81.9 (*C*(CH_3)$_3$), 81.6 (*C*(CH_3)$_3$), 58.3 (N*C*H_2CBr, rotamer), 57.1 (N*C*H_2CBr, rotamer), 28.19 (C(*C*H_3)$_3$), 28.15 (C(*C*H_3)$_3$); MS (ESI^+) *m/z* 373 [M(^{79}Br)Na^+], 375 [M(^{81}Br)Na^+]; HRMS calcd. for $C_{13}H_{23}{}^{79}BrN_2NaO_4$ $[M+Na]^+$ 373.0733, found 373.0735.

Di-*tert*-butyl 1-(2-bromo-3-methylbut-2-enyl)hydrazine-1,2-dicarboxylate (305)



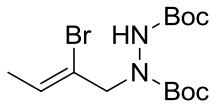
This compound was prepared according to a literature procedure.[136] To a solution of 2-bromo-3-methylbut-2-en-1-ol[199] (540 mg, 3.27 mmol) and triphenylphosphine (1.72 g, 6.54 mmol) in anhydrous THF (12 mL) at 0 °C was added di-*tert*-butylazodicarboxylate (1.51 g, 6.54 mmol) portionwise. The reaction was allowed to warm to room temperature over 24 h and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5:1, petrol: EtOAc) provided **305** (1.14 g, 92%) as a yellow oil. R_f = 0.50 (5:1, petrol: EtOAc); IR υ_{max} (film/cm^{-1}) 3301, 2976, 2932, 1724, 1685, 1384, 1365, 1252, 1146, 754; δ_H (400 MHz, $CDCl_3$) 6.37 (1H, br s, NH, major rotamer), 6.04 (1H, br s, NH, minor rotamer), 4.47 (2H, br s, NCH_2CBr), 1.91 (3H, s, C(C*H*$_3$)(CH_3)), 1.83 (3H, s, C(CH_3)(C*H*$_3$)), 1.50−1.44 (18H, m, C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 155.3 (COO), 155.0 (COO), 136.5 (*C*(CH_3)$_2$, rotamer), 136.1 (*C*(CH_3)$_2$, rotamer), 116.3 (NCH_2*C*Br, rotamer), 116.1 (NCH_2*C*Br, rotamer), 81.3 (*C*(CH_3)$_3$, rotamer), 81.1 (*C*(CH_3)$_3$, rotamer), 53.7 (N*C*H_2CBr, rotamer), 53.0 (N*C*H_2CBr, rotamer), 28.2 (2 x C(*C*H_3)$_3$), 25.6 (C(*C*H_3)(CH_3)), 20.5 (C(CH_3)(*C*H_3)); MS (ESI^+) *m/z* 401 [M(^{79}Br)Na^+], 403 [M(^{81}Br)Na^+]; HRMS calcd. for $C_{15}H_{27}{}^{79}BrN_2NaO_4$ $[M+Na]^+$ 401.1046, found 401.1044.

Diethyl 1-(2-bromoallyl)hydrazine-1,2-dicarboxylate (243)



This compound was prepared according to a literature procedure.[136] To a solution of 2-bromoallyl alcohol (414 μL, 5.00 mmol) and triphenylphosphine (2.62 g, 10.0 mmol) in anhydrous THF (30 mL) at 0 °C was added diethylazodicarboxylate (1.58 mL, 10.0 mmol) portionwise. The reaction was allowed to warm to room temperature over 18 h and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 6:1, petrol: EtOAc) provided **243** (1.40 g, 95%) as a yellow oil. R_f = 0.13 (6:1 petrol: EtOAc); IR υ_{max} (film/cm^{-1}) 3291, 2981, 2934, 1707, 1632, 1381, 1264, 1135, 763; δ_H (400 MHz, $CDCl_3$) 6.62 (1H, br m, NH, major rotamer), 6.37 (1H, br s, NH, minor rotamer), 5.82 (1H, s, C*H*H=CBr), 5.62 (1H, s, CH*H*=CBr), 4.45−4.30 (2H, m, NC*H*$_2$CBr), 4.26−4.16 (4H, m, 2 x C*H*$_2$CH$_3$), 1.28 (6H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 155.8 (COO), 150.6 (COO), 128.0 (CH$_2$=*C*Br), 120.4 (C*H*$_2$=CBr, rotamer), 119.8 (C*H*$_2$=CBr, rotamer), 64.3 (C*H*$_2$CH$_3$, rotamer), 63.1 (C*H*$_2$CH$_3$, rotamer), 62.9 (C*H*$_2$CH$_3$, rotamer), 62.2 (C*H*$_2$CH$_3$, rotamer), 58.0 (N*C*H$_2$CBr, rotamer), 57.2 (N*C*H$_2$CBr, rotamer), 14.5 (CH$_2$C*H*$_3$), 14.1 (CH$_2$C*H*$_3$); MS (ESI^+) *m/z* 317 [M(^{79}Br)Na^+], 319 [M(^{81}Br)Na^+]; HRMS calcd. for $C_9H_{15}{}^{79}BrN_2NaO_4$ $[M+Na]^+$ 317.0107, found 317.0108.

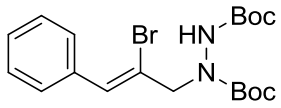
Di-*tert*-butyl (*Z*)-1-(2-bromobut-2-enyl)hydrazine-1,2-dicarboxylate (306)



To a solution of **302** (1.92 g, 12.7 mmol) and triphenylphosphine (6.66 g, 25.4 mmol) in anhydrous THF (60 mL) at 0 °C was added di-*tert*-butylazodicarboxylate (5.85 g, 25.4 mmol) portionwise. The reaction was allowed to warm to room temperature over 16 h and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 6:1, petrol: EtOAc) provided **302** (4.63 g, 99%) as a white solid. M. p. 54–58 °C; R_f = 0.42 (6:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 3318, 2931, 1712, 1393, 1368, 1255, 1158, 758; δ_H (500 MHz, $CDCl_3$) 6.34 (1H, br s, NH), 6.01−5.87 (1H, m, C*H*CH$_3$), 4.31 (2H, br s, NCH$_2$CBr), 1.77 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$), 1.46 (18H, s, C(CH$_3$)$_3$); δ_C (125 MHz, $CDCl_3$) 154.9 (COO), 154.7 (COO), 126.9 (*C*HCH$_3$, rotamer), 127.6 (*C*HCH$_3$, rotamer), 123.6 (NCH$_2$*C*Br), 81.5 (*C*(CH$_3$)$_3$), 81.3 (*C*(CH$_3$)$_3$), 58.5 (N*C*H$_2$CBr,

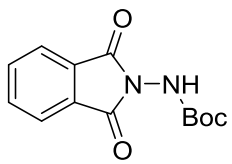
rotamer), 57.4 (N*C*H_2CBr, rotamer), 28.2 (2 x C(*C*H_3)$_3$), 16.7 (CH*C*H_3); MS (ESI$^+$) *m/z* 387 [M(^{79}Br)Na$^+$], 389 [M(^{81}Br)Na$^+$]; HRMS calcd. for $C_{14}H_{25}{}^{79}BrN_2NaO_4$ [M+Na]$^+$ 387.0890, found 387.0889.

(*Z*)-Di-*tert*-butyl-1-(2-bromo-3-phenylallyl)hydrazine-1,2-dicarboxylate (307)



To a solution of **304** (950 mg, 4.46 mmol) and triphenylphosphine (2.34 g, 8.92 mmol) in anhydrous THF (26 mL) at 0 °C was added di-*tert*-butylazodicarboxylate (2.05 g, 8.92 mmol) portionwise. The reaction was allowed to warm to room temperature over 18 h and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 6:1, petrol: EtOAc) provided **304** (1.79 g, 94%) as a yellow oil. R_f = 0.37 (6:1 petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 3322, 2978, 2932, 1707, 1478, 1392, 1366, 1250, 1151, 753, 694; δ_H (400 MHz, $CDCl_3$) 7.62 (2H, d, *J* = 6.9 Hz, Ar H), 7.40−7.29 (3H, m, Ar H), 6.94 (0.45H, br s, CH=CBr, rotamer), 6.90 (0.55H, br s, CH=CBr, rotamer), 6.45 (1H, br s, NH), 4.50 (2H, br s, NC*H*$_2$CBr), 1.48 (18H, s, C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 155.7 (COO), 154.8 (COO), 135.1 (C, Ar, rotamer), 135.0 (C, Ar, rotamer), 130.8 (*C*H=CBr, rotamer), 130.4 (*C*H=CBr, rotamer), 129.0 (CH, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 121.4 (NCH$_2$*C*Br), 81.7 (*C*(CH$_3$)$_3$), 81.5 (*C*(CH$_3$)$_3$), 60.1 (N*C*H$_2$CBr, rotamer), 58.8 (N*C*H$_2$CBr, rotamer), 28.21 (C(*C*H$_3$)$_3$), 28.16 (C(*C*H$_3$)$_3$); MS (ESI$^+$) *m/z* 449 [M(^{79}Br)Na$^+$], 451 [M(^{81}Br)Na$^+$]; HRMS calcd. for $C_{19}H_{27}{}^{79}BrN_2NaO_4$ [M+Na]$^+$ 449.1046, found 449.1045.

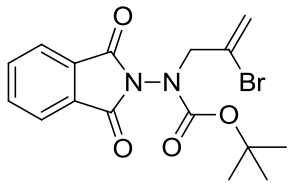
***tert*-Butyl (1,3-dioxoisoindolin-2-yl)carbamate (311)**



This compound was prepared according to a modified literature procedure.[168] A solution of phthalic anhydride (1.55 g, 10.5 mmol) and *tert*-butyl carbazate (1.39 g, 10.5 mmol) in toluene (20 mL) was heated to 150 °C in a Dean-Stark apparatus for 16 h. The solution was cooled to room temperature and the precipitate removed by filtration, washed with hexane and dried under vacuum to give **311** (2.75 g, 100%) as a white solid, which was used without further purification. M. p. 189–192 °C; R_f =

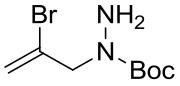
0.32 (3:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 3317, 2978, 2876, 1732, 1492, 1250, 1152, 708; δ_H (400 MHz, $CDCl_3$) 7.91 (2H, dd, *J* = 5.4, 3.1 Hz, Ar H), 7.79 (2H, dd, *J* = 5.3, 3.1 Hz, Ar H), 6.57 (1H, br s, NH), 1.51 (9H, s, C(CH_3)$_3$); δ_C (125 MHz, $CDCl_3$) 165.5 (C=O), 163.5 (C=O), 153.4 (COO), 134.7 (2 x CH, Ar), 130.0 (2 x C, Ar), 124.0 (2 x CH, Ar), 83.2 (*C*(CH_3)$_3$), 28.1 C(*C*H_3)$_3$); MS (ESI$^+$) *m/z* 285 [MNa$^+$]; HRMS calcd. for $C_{13}H_{14}N_2NaO_4$ [M+Na]$^+$ 285.0846, found 285.0849. Analytical data in agreement with literature values.

tert-Butyl (2-bromoallyl)(1,3-dioxoisoindolin-2-yl)carbamate (312)



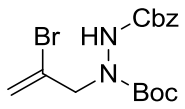
This compound was prepared according to a literature procedure.[169] To a solution of **311** (6.61 g, 25.2 mmol), TEBAC (1.15 g, 5.04 mmol) and potassium carbonate (13.9 g, 101 mmol) in acetonitrile (100 mL) was added 2,3-dibromopropene (4.93 mL, 50.4 mmol) and the reaction stirred for 45 h at room temperature. The solution was diluted with H_2O (50 mL) and brine (50 mL), and extracted with EtOAc (3 x 80 mL). The organic layers were combined, diluted with hexane (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 4:1 petrol: EtOAc) provided **312** (8.59 g, 89%) as a white solid. M. p. 80–84 °C; R_f = 0.40 (4:1 petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 2973, 2928, 1798, 1721, 1629, 1594, 1355, 1254, 1149, 918, 712; δ_H (500 MHz, $CDCl_3$) 7.94−7.85 (2H, m, Ar H), 7.81 (1H, dd, *J* = 5.3, 3.1 Hz, Ar H), 7.77 (1H, dd, *J* = 5.3, 3.1 Hz, Ar H), 6.20 (1H, d, *J* = 10.8 Hz, C*H*H=CBr), 5.62 (1H, d, *J* = 4.3 Hz, CH*H*=CBr), 4.52 (1H, s, NC*H*H), 4.47 (1H, s, NCH*H*), 1.52 (4H, s, C(CH_3)$_3$, minor rotamer), 1.34 (5H, s, C(CH_3)$_3$, major rotamer); δ_C (125 MHz, $CDCl_3$) 165.3 (C=O), 165.0 (C=O), 152.8 (COO, rotamer), 152.6 (COO, rotamer), 134.8 (CH, Ar), 134.7 (CH, Ar), 129.9 (C, Ar), 129.8 (C, Ar), 126.7 (CBr, rotamer), 126.4 (CBr, rotamer), 123.99 (CH, Ar), 123.95 (CH, Ar), 119.7 (*C*H_2=CBr, rotamer), 119.3 (*C*H_2=CBr, rotamer), 83.9 (*C*(CH_3)$_3$, rotamer), 83.1 (*C*(CH_3)$_3$, rotamer), 58.3 (N*C*H_2, rotamer), 56.8 (N*C*H_2, rotamer), 28.1 (C(*C*H_3)$_3$, rotamer), 27.8 (C(*C*H_3)$_3$, rotamer); MS (ESI$^+$) *m/z* 403 [M(^{79}Br)Na$^+$], 405 [M(^{81}Br)Na$^+$]; HRMS calcd. for $C_{16}H_{17}{}^{79}BrN_2NaO_4$ [M+Na]$^+$ 403.0264, found 403.0263. Analytical data in agreement with literature values.

tert-Butyl 1-(2-bromoallyl)hydrazine-1-carboxylate (308)



To a solution of **312** (8.58 g, 22.5 mmol) in EtOH (150 mL) was added hydrazine monohydrate (2.00 g, 7.96 mmol) and the reaction heated under reflux for 2 h. The reaction was cooled to room temperature and concentrated. The crude solid was diluted with cold diethyl ether (30 mL) and filtered, washing with cold diethyl ether (30 mL), then concentrated *in vacuo* to give **308** (5.31 g, 94%) as a yellow oil, which was used without further purification. R_f = 0.29 (4:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 3336, 3218, 2977, 2931, 1694, 1630, 1390, 1366, 1244, 1153, 893, 731; δ_H (500 MHz, $CDCl_3$) 5.72 (1H, s, C*H*H=CBr), 5.58 (1H, s, CH*H*=CBr), 4.22 (2H, s, NCH_2), 4.06 (2H, br s, NH_2), 1.48 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 156.7 (COO), 129.8 (CH_2=*C*Br), 117.8 (*C*H_2=CBr), 81.3 (*C*$(CH_3)_3$), 58.5 (NCH_2), 28.2 ($C(CH_3)_3$); MS (ESI$^+$) *m/z* 273 [M(^{79}Br)Na$^+$], 275 [M(^{81}Br)Na$^+$]; HRMS calcd. for $C_8H_{15}{}^{79}BrN_2NaO_2$ [M+Na]$^+$ 273.0209, found 273.0210. Analytical data in agreement with literature values.[169]

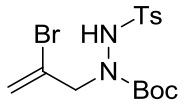
2-Benzyl 1-(*tert*-butyl) 1-(2-bromoallyl)hydrazine-1,2-dicarboxylate (313)



To a solution of sodium hydroxide (318 mg, 7.96 mmol) in H_2O (40 mL) and CH_2Cl_2 (40 mL) at 0 °C was added **308** (2.00 g, 7.96 mmol) followed by dropwise addition of benzyl chloroformate (1.14 mL, 7.96 mmol). The reaction was allowed to warm to room temperature over 16 h. The solution was diluted with H_2O (40 mL) and the organic layer extracted with CH_2Cl_2 (3 x 50 mL), washed with 20% citric acid solution (60 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 4:1, petrol: EtOAc) provided **313** (2.65 g, 86%) as a colourless oil. R_f = 0.47 (4:1, petrol: EtOAc); IR υ_{max} (film/cm^{-1}) 3297, 2934, 1715, 1632, 1499, 1393, 1368, 1260, 1154, 742; δ_H (500 MHz, $CDCl_3$) 7.39−7.31 (5H, m, Ar H), 6.67 (1H, br d, NH), 5.79 (1H, br m, C*H*H=CBr), 5.58 (1H, s, CH*H*=CBr), 5.17 (2H, s, CH_2Ar), 4.45−4.16 (2H, m, NCH_2CBr), 1.49 (5H, br s, $C(CH_3)_3$, major rotamer), 1.39 (4H, br s, $C(CH_3)_3$, minor rotamer); δ_C (125 MHz, $CDCl_3$) 155.9 (COO), 154.6 (COO), 135.6 (C, Ar), 128.6 (CH, Ar), 128.5 (CH, Ar), 128.4 (CH, Ar), 128.3 (CH_2=*C*Br), 120.0 (*C*H_2=CBr, rotamer), 119.5 (*C*H_2=CBr, rotamer), 82.7 (*C*$(CH_3)_3$, rotamer),

82.1 ($C(CH_3)_3$, rotamer), 67.8 (CH_2Ar), 58.3 (NCH_2, rotamer), 56.9 (NCH_2, rotamer), 28.2 ($C(CH_3)_3$, rotamer), 28.0 ($C(CH_3)_3$, rotamer); MS (ESI^+) *m/z* 407 [M(^{79}Br)Na^+], 409 [M(^{81}Br)Na^+]; HRMS calcd. for $C_{16}H_{21}{}^{79}BrN_2NaO_4$ $[M+Na]^+$ 407.0577, found 407.0571.

tert-butyl 1-(2-bromoallyl)-2-tosylhydrazine-1-carboxylate (314)



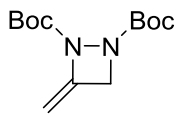
To a solution of **308** (50 mg, 0.20 mmol) and *para*-toluenesulfonyl chloride (42 mg, 0.22 mmol) in anhydrous THF (2 mL) at 0 °C was added pyridine (97 μL, 1.20 mmol) dropwise. The reaction was stirred for 20 min then at room temperature for 16 h. Additional *para*-toluenesulfonyl chloride (42 mg, 0.22 mmol) was added after 16 h until the reaction showed complete conversion after 2 d. The solution was diluted with CH_2Cl_2 (5 mL) and washed with 2 M HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL), the organic layers combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 4:1, petrol: EtOAc) provided **314** (50 mg, 62%) as a white solid. M. p. 120–122 °C; R_f = 0.41 (4:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 3232, 2980, 2930, 1718, 1493, 1368, 1250, 1158, 737; δ_H (500 MHz, $CDCl_3$) 7.77 (2H, d, *J* = 8.2 Hz, Ar H), 7.33−7.27 (2H, m, Ar H), 6.96 (0.75H, br s, NH, major rotamer), 6.74 (0.25H, br s, NH, minor rotamer), 5.76 (1H, s, C*H*H=CBr), 5.62 (1H, s, CH*H*=CBr), 4.70−4.22 (1.8H, m, NCH_2, major rotamer), 3.98−3.72 (0.2H, m, NCH_2, minor rotamer), 2.41 (3H, s, $ArCH_3$), 1.21 (9H, m, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 144.6 (C, Ar) 133.6 (C, Ar), 129.5 (CH, Ar), 128.7 (CH, Ar), 127.6 (CH_2=CBr), 120.2 (CH_2=*C*Br), 83.1 ($C(CH_3)_3$), 58.1 (NCH_2), 27.6 ($C(CH_3)_3$), 21.6 ($ArCH_3$), COO not observed; MS (ESI^+) *m/z* 427 [M(^{79}Br)Na^+], 429 [M(^{81}Br)Na^+]; HRMS calcd. for $C_{15}H_{21}{}^{79}BrN_2NaO_4S$ $[M+Na]^+$ 427.0298, found 427.0305.

General Method B: Cyclisation to Form 3-Methylene-1,2-Diazetidines

To a solution of the hydrazodicarboxylate (1.0 molar equiv) in anhydrous THF was added copper (I) iodide (0.2 molar equiv), Cs_2CO_3 (2 molar equiv) and DMEDA (0.4

molar equiv), and the mixture was heated under reflux until full consumption of the starting material. The reaction was cooled to room temperature and filtered through Celite®, washing with EtOAc. The solution was concentrated, passed through a column of silica, eluting with EtOAc, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography provided the product.

Di-*tert*-butyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (299)

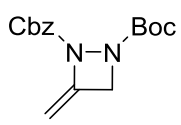


Hydrazodicarboxylate **300** (1.80 g, 5.14 mmol), CuI (196 mg, 1.03 mmol), Cs_2CO_3 (3.36 g, 10.3 mmol) and DMEDA (225 μL, 2.06 mmol) in anhydrous THF (30 mL) were reacted according to General Method B for 18 h. Work-up, followed by purification by column chromatography (SiO_2, 9:1, petrol: EtOAc) provided **299** (1.07 g, 77%) as a pale yellow oil. R_f = 0.34 (9:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2978, 2934, 1716, 1393, 1368, 1256, 1152, 841, 766; δ_H (500 MHz, $CDCl_3$) 4.91−4.86 (1H, m, C=C*H*H), 4.59 (1H, d, *J* = 2.3 Hz, NC*H*H), 4.58 (1H, d, *J* = 2.2 Hz, NCH*H*), 4.36−4.34 (1H, m, C=CH*H*), 1.54 (9H, s, $C(CH_3)_3$), 1.49 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 159.5 (COO), 154.1 (COO), 142.7 (*C*=CH_2), 89.6 (C=*C*H_2), 83.0 (*C*$(CH_3)_3$), 82.7 (*C*$(CH_3)_3$), 57.2 (NCH_2), 28.1 (C(*C*$H_3)_3$), 28.0 (C(*C*$H_3)_3$); MS (ESI^+) *m/z* 293 [MNa^+]; HRMS calcd. for $C_{13}H_{22}N_2NaO_4$ $[M+Na]^+$ 293.1472, found 293.1473.

Di-*tert*-butyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (299)

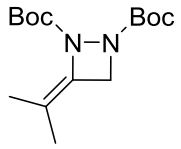
Hydrazodicarboxylate **298** (300 mg, 0.75 mmol), CuI (29 mg, 0.15 mmol), Cs_2CO_3 (489 mg, 1.50 mmol) and DMEDA (33 μL, 0.30 mmol) in anhydrous THF (5 mL) were reacted according to General Method B for 4 h. Work-up, followed by purification by column chromatography (SiO_2, 9:1, petrol: EtOAc) provided **299** (128 mg, 63%) as a pale yellow oil. R_f = 0.33 (9:1, petrol: EtOAc). Analytical data as previously reported.

2-Benzyl 1-(*tert*-butyl) 3-methylene-1,2-diazetidine-1,2-dicarboxylate (315)



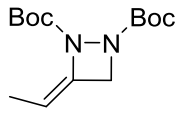
Hydrazodicarboxylate **313** (108 mg, 0.28 mmol), CuI (11 mg, 58 μmol), Cs_2CO_3 (182 mg, 0.56 mmol) and DMEDA (12 μL, 0.11 mmol) in anhydrous THF (8 mL) were reacted according to General Method B for 3 d. Work-up, followed by purification by column chromatography (SiO_2, 6:1, petrol: EtOAc) provided **315** (53 mg, 62%) as a colourless oil. R_f = 0.32 (6:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2933, 1736, 1718, 1498, 1389, 1369, 1259, 1150, 753; δ_H (500 MHz, $CDCl_3$) 7.41−7.32 (5H, m, Ar H), 5.26 (2H, s, CH_2Ar), 4.99−4.94 (1H, m, C=C*H*H), 4.62 (1H, d, *J* = 2.2 Hz, NC*H*H), 4.61 (1H, d, *J* = 2.2 Hz, NCH*H*), 4.43−4.40 (1H, m, C=CH*H*), 1.45 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 159.4 ($CO_2C(CH_3)_3$), 155.2 (CO_2CH_2Ar), 142.3 (C=CH_2), 135.3 (C, Ar), 128.6 (CH, Ar), 128.4 (CH, Ar), 128.1 (CH, Ar), 90.6 (C=CH_2), 83.0 ($C(CH_3)_3$), 68.3 (CH_2Ar), 57.5 (NCH_2), 27.9 ($C(CH_3)_3$); MS (ESI^+) *m/z* 327 [MNa^+]; HRMS calcd. for $C_{16}H_{20}N_2NaO_4$ $[M+Na]^+$ 327.1315, found 327.1315.

Di-*tert*-butyl 3-(propan-2-ylidene)-1,2-diazetidine-1,2-dicarboxylate (316)



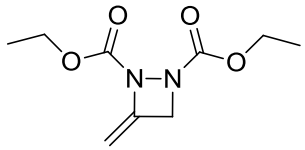
This compound was prepared according to a literature procedure.[136] Hydrazodicarboxylate **305** (1.12 g, 2.95 mmol), CuI (112 mg, 0.59 mmol), Cs_2CO_3 (1.92 g, 5.88 mmol) and DMEDA (129 μL, 1.18 mmol) in anhydrous THF (20 mL) were reacted according to General Method B for 5 d. Work-up, followed by purification by column chromatography (SiO_2, 9:1 petrol: EtOAc) provided **316** (602 mg, 68%) as a white solid. M. p. 81–85 °C; R_f = 0.38 (9:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 2978, 2933, 1708, 1392, 1368, 1255, 1144, 767; δ_H (500 MHz, $CDCl_3$) 4.61 (2H, s, NCH_2), 1.81 (3H, s, $C(CH_3)(CH_3)$), 1.52 (9H, s, $C(CH_3)_3$), 1.50 (12H, s, $C(CH_3)_3$, $C(CH_3)(CH_3)$); δ_C (125 MHz, $CDCl_3$) 159.4 (COO), 156.5 (COO), 129.6 (CCH_2 or $C(CH_3)_2$), 112.5 (CCH_2 or $C(CH_3)_2$), 82.5 ($C(CH_3)_3$), 82.1 ($C(CH_3)_3$), 57.8 (NCH_2), 28.13 ($C(CH_3)_3$), 28.09 ($C(CH_3)_3$), 18.9 ($C(CH_3)(CH_3)$), 18.6 ($C(CH_3)(CH_3)$); MS (ESI^+) *m/z* 321 [MNa^+]; HRMS calcd. for $C_{15}H_{26}N_2NaO_4$ $[M+Na]^+$ 321.1785, found 321.1787.

Di-*tert*-butyl (*Z*)-3-(ethylidene)-1,2-diazetidine-1,2-dicarboxylate (317)



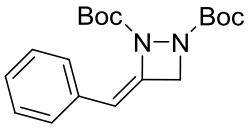
Hydrazodicarboxylate **306** (2.00 g, 5.50 mmol), CuI (209 mg, 1.10 mmol), Cs_2CO_3 (3.58 g, 11.0 mmol) and DMEDA (240 μL, 2.20 mmol) in anhydrous THF (34 mL) were reacted according to General Method B for 5 d. Work-up, followed by purification by column chromatography (SiO_2, 10:1, petrol: EtOAc) provided **317** (990 mg, 64%) as a white solid. M. p. 80–83 °C; R_f = 0.30 (10:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 2981, 2937, 1740, 1392, 1368, 1254, 1148, 763; δ_H (500 MHz, $CDCl_3$) 4.70 (1H, q, *J* = 7.2 Hz, C*H*CH_3), 4.58 (2H, s, NCH_2), 1.80 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 1.53 (9H, s, $C(CH_3)_3$), 1.50 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 159.5 (COO), 155.6 (COO), 135.6 (*C*CH_2), 103.5 (*C*HCH_3), 82.8 (*C*$(CH_3)_3$), 82.3 (*C*$(CH_3)_3$), 58.0 (CH_2), 28.14 (C(*C*$H_3)_3$), 28.07 (C(*C*$H_3)_3$), 12.8 (CH*C*H_3); MS (ESI^+) *m/z* 307 [MNa^+]; HRMS calcd. for $C_{14}H_{24}N_2NaO_4$ $[M+Na]^+$ 307.1628, found 307.1630.

Diethyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate (244)



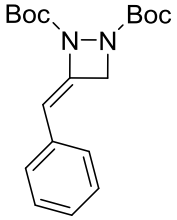
This compound was prepared according to a literature procedure.[136] Hydrazodicarboxylate **243** (1.40 g, 4.76 mmol), CuI (181 mg, 0.95 mmol), Cs_2CO_3 (3.10 g, 9.52 mmol) and DMEDA (208 μL, 1.90 mmol) in anhydrous THF (28 mL) were reacted according to General Method B for 18 h. Work-up, followed by purification by column chromatography (SiO_2, 4:1, petrol: EtOAc) provided **244** (369 mg, 36%) as a pale yellow oil. R_f = 0.38 (4:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2982, 2937, 1721, 1467, 1372, 1228, 1099, 748; δ_H (400 MHz, $CDCl_3$) 4.95 (1H, q, *J* = 2.8 Hz, C=C*H*H), 4.69 (1H, d, *J* = 2.2 Hz, NC*H*H), 4.68 (1H, d, *J* = 2.4 Hz, NCH*H*), 4.43−4.39 (1H, m, C=CH*H*), 4.29 (2H, q, *J* = 7.2 Hz, C*H*$_2$$CH_3$), 4.24 (2H, q, *J* = 7.3 Hz, C*H*$_2$$CH_3$), 1.32 (3H, t, *J* = 7.0 Hz, CH_2C*H*$_3$), 1.29 (3H, t, *J* = 7.0 Hz, CH_2C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 160.6 (COO), 155.4 (COO), 142.3 (*C*=CH_2), 90.6 (C=*C*H_2), 63.2 (*C*H_2CH_3), 63.0 (*C*H_2CH_3), 57.7 (NCH_2), 14.40 (CH_2*C*H_3), 14.36 (CH_2*C*H_3); MS (ESI^+) *m/z* 237 [MNa^+]; HRMS calcd. for $C_9H_{14}N_2NaO_4$ $[M+Na]^+$ 237.0846, found 237.0848.

(*Z*)-Di-*tert*-butyl 3-(benzylidene)-1,2-diazetidine-1,2-dicarboxylate (318)



Hydrazodicarboxylate **307** (1.67 g, 3.91 mmol), CuI (149 mg, 0.78 mmol), Cs_2CO_3 (2.55 g, 7.82 mmol) and DMEDA (170 μL, 1.56 mmol) in anhydrous THF (25 mL) were reacted according to General Procedure B for 3 d. Work-up, followed by purification by column chromatography (SiO_2, 6:1, petrol: EtOAc) and recrystallisation from hexane/$CHCl_3$ provided (*Z*)-**318** (813 mg, 60%) as a white solid. M. p. 154–157 °C; R_f = 0.39 (6:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 2979, 2934, 1713, 1495, 1369, 1254, 1144, 844, 767; δ_H (500 MHz, $CDCl_3$) 7.33 (2H, d, *J* = 7.6 Hz, Ar H), 7.28−7.23 (2H, m, Ar H), 7.16 (1H, t, *J* = 7.3 Hz, Ar H), 5.65 (1H, s, CHAr), 4.82 (2H, m, NCH_2), 1.54 (9H, s, $C(CH_3)_3$), 1.19 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 159.2 (COO), 155.1 (COO), 136.2 (*C*=CHAr), 134.9 (C, Ar), 128.9 (CH, Ar), 127.7 (CH, Ar), 126.7 (CH, Ar), 108.2 (C=*C*HAr), 83.2 ($C(CH_3)_3$), 82.6 ($C(CH_3)_3$), 59.1 (NCH_2), 28.1 ($C(CH_3)_3$), 27.5 ($C(CH_3)_3$); MS (ESI^+) *m/z* 369 [MNa^+]; HRMS calcd. for $C_{19}H_{26}N_2NaO_4$ $[M+Na]^+$ 369.1785, found 369.1789.

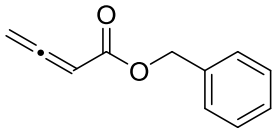
(*E*)-Di-*tert*-butyl 3-(benzylidene)-1,2-diazetidine-1,2-dicarboxylate (318)



To a mixture of **299** (200 mg, 0.74 mmol), iodobenzene (126 μL, 1.13 mmol), tetrabutylammonium chloride (206 mg, 0.74 mmol) and palladium (II) acetate (9 mg, 40 μmol) in anhydrous dimethylacetamide (4 mL) was added *N*,*N*-dicyclohexylmethylamine (242 μL, 1.13 mmol). The reaction was stirred at 80 °C for 48 h, cooled to room temperature and diluted with diethyl ether (10 mL) and H_2O (15 mL). The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The organic extracts were combined, washed with H_2O (5 x 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 9:1, petrol: EtOAc) provided (*E*)-**318** (100 mg, 39%) as a white solid. M. p. 100–103 °C; R_f = 0.34 (9:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 2979, 2934, 1717, 1601, 1392, 1369, 1256, 1151, 847, 752; δ_H (500 MHz, $CDCl_3$) 7.30 (2H, t, *J* = 7.7 Hz, Ar H), 7.17 (1H, t, *J* = 7.4 Hz, Ar H), 7.02 (2H, d, *J* = 7.6 Hz, Ar H), 6.40 (1H, s, CHAr), 4.93 (2H, d, *J* = 2.4 Hz, NCH_2), 1.58 (9H, s,

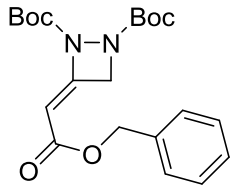
$C(CH_3)_3$), 1.53 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 159.3 (COO), 154.1 (COO), 137.8 (*C*=CHAr), 135.1 (C, Ar), 128.8 (CH, Ar), 126.6 (CH, Ar), 126.3 (CH, Ar), 107.2 (C=*C*HAr), 83.3 ($C(CH_3)_3$), 82.9 ($C(CH_3)_3$), 58.1 (NCH_2), 28.2 ($C(CH_3)_3$), 28.1 ($C(CH_3)_3$); MS (ESI^+) *m/z* 369 [MNa^+]; HRMS calcd. for $C_{19}H_{26}N_2NaO_4$ $[M+Na]^+$ 369.1785, found 369.1788.

Benzyl buta-2,3-dienoate (226)



This compound was prepared according to a literature procedure.[171] To a solution of benzyl (triphenylphosphoranylidene)acetate (8.21 g, 20.0 mmol) in anhydrous CH_2Cl_2 (80 mL) was added triethylamine (2.79 mL, 20.0 mmol) at rt. After 10 min, a solution of acetyl chloride (1.42 mL, 20.0 mmol) in anhydrous CH_2Cl_2 (24 mL) was added slowly, such that the temperature of the reaction remained constant. The reaction was stirred for 18 h and concentrated *in vacuo*. Petroleum ether (80 mL) was added, stirred well and the solution was allowed to sit for 2 h, filtered and the filtrate concentrated. Purification by column chromatography (SiO_2, 15:1, petrol: EtOAc) provided **226** (2.05 g, 71%) as a yellow oil. R_f = 0.33 (15:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 3034, 2991, 2955, 1969, 1940, 1710, 1498, 1244, 1150, 735; δ_H (500 MHz, $CDCl_3$) 7.39−7.30 (5H, m, Ar H), 5.69 (1H, t, *J* = 6.5 Hz, C=CHCOO), 5.24 (2H, d, *J* = 6.6 Hz, CH_2=C=C), 5.20 (2H, s, NCH_2Ar); δ_C (125 MHz, $CDCl_3$) 216.0 (CH_2=*C*=CH), 165.6 (COO), 135.9 (C, Ar), 128.6 (CH, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 87.9 (C=*C*HCOO), 79.5 (*C*H_2=C=CH), 66.7 (CH_2Ar). Analytical data in agreement with literature values.

(*E*)-Di-*tert*-butyl-3-(2-(benzyloxy)-2-oxoethylidene)-1,2-diazetidine-1,2-dicarboxylate (321)



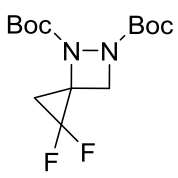
This compound was prepared according to a literature procedure.[128] To a mixture of di-*tert*-butyl azodicarboxylate (115 mg, 0.50 mmol) and DABCO (6 mg, 50 μmol) in anhydrous 1,4-dioxane (2 mL) at room temperature was added slowly a

solution of **226** (87 mg, 0.50 mmol) in anhydrous 1,4-dioxane (1 mL). The reaction was stirred at room temperature for 5 h and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 7:1, petrol: EtOAc) provided **321** (85 mg, 42%) as a yellow oil. R_f = 0.36 (7:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2979, 2934, 1720, 1668, 1498, 1369, 1248, 1130, 839, 742; δ_H (500 MHz, $CDCl_3$) 7.39−7.31 (5H, m, Ar H), 5.72 (1H, br s, C=CH), 5.15 (2H, s, CH_2Ar), 4.88 (2H, d, *J* = 2.2 Hz, NCH_2), 1.55 (9H, s, $C(CH_3)_3$), 1.50 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 166.6 (COO), 158.8 (COO), 154.9 (COO), 151.2 (*C*=CH), 136.1 (C, Ar), 128.6 (CH, Ar), 128.3 (CH, Ar), 128.2 (CH, Ar), 95.2 (C=*C*H), 84.6 ($C(CH_3)_3$), 83.4 ($C(CH_3)_3$), 66.0 (CH_2Ar), 59.3 (NCH_2), 28.04 ($C(CH_3)_3$), 27.97 ($C(CH_3)_3$); MS (ESI^+) *m/z* 427 [MNa^+]; HRMS calcd. for $C_{21}H_{28}N_2NaO_6$ $[M+Na]^+$ 427.1840, found 427.1840. Analytical data in agreement with literature values.

General Method C: Difluorocyclopropanation of 3-Methylene-1,2-Diazetidines

To a sealed tube was added 3-methylene-1,2-diazetidine (1.0 molar equiv) and sodium iodide (0.2 molar equiv) in anhydrous THF. Trimethyl(trifluoromethyl)silane ($TMSCF_3$) (2.5 molar equiv) was added, and the reacted heated at 65 °C until full consumption of the starting material. The reaction was cooled to room temperature and concentrated *in vacuo*. The residue was diluted with diethyl ether (20 mL) and washed with H_2O (15 mL), saturated Na_2SO_3 solution (15 mL), saturated aqueous sodium bicarbonate solution (15 mL) and H_2O (15 mL). The organic extract was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography provided the product.

Di-*tert*-butyl 1,1-difluoro-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate (324)

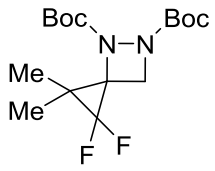


3-Methylene-1,2-diazetidine **299** (90 mg, 0.33 mmol), sodium iodide (10 mg, 67 μmol) and $TMSCF_3$ (123 μL, 0.83 mmol) in anhydrous THF (3 mL) were reacted according to General Method C for 5 h. Work-up, followed by purification by column chromatography (SiO_2, 5:1, petrol: EtOAc) provided **324** (103 mg, 97%) as a white solid. M. p. 96–99 °C; R_f

= 0.43 (5:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 2974, 2933, 1737, 1368, 1242, 1153, 1027, 769; δ_H (500 MHz, $CDCl_3$) 4.34 (1H, d, *J* = 8.4 Hz, NC*H*H), 4.22 (1H, dd, *J* = 8.4, 4.6 Hz, NCH*H*), 2.65 (1H, ddd, *J* = 15.0, 10.1, 4.9 Hz, C*H*HCF$_2$), 1.51 (9H, s, C(CH$_3$)$_3$), 1.49 (9H, s, C(CH$_3$)$_3$), 1.43 (1H, ddd, *J* = 15.3, 10.1, 5.2 Hz, CH*H*CF$_2$); δ_C (125 MHz, $CDCl_3$) 159.5 (COO), 156.8 (COO), 106.9 (dd, J_{CF} = 293.4, 289.9 Hz, CF_2), 83.2 (*C*(CH$_3$)$_3$), 82.8 (*C*(CH$_3$)$_3$), 52.5 (NCH$_2$), 50.0 (dd, J_{CF} = 15.8, 9.8 Hz, *C*CH$_2$), 28.1 (2 x C(*C*H$_3$)$_3$), 16.7 (t, J_{CF} = 10.6 Hz, C*C*H$_2$); δ_F (376 MHz, $CDCl_3$) –136.7 (d, J_{FF} = 170 Hz), –142.8 (d, J_{FF} = 169 Hz); MS (ESI$^+$) *m/z* 343 [MNa$^+$]; HRMS calcd. for $C_{14}H_{22}F_2N_2NaO_4$ [M+Na]$^+$ 343.1440, found 343.1435. A crystal for X-ray analysis was grown from CH_2Cl_2/petrol.

Crystal Data for $C_{14}H_{22}F_2N_2O_4$ (*M* =320.33 g/mol): monoclinic, space group P2$_1$/c (no. 14), *a* = 14.02756(10) Å, *b* = 5.73781(4) Å, *c* = 21.00103(12) Å, *β* = 102.1203(7)°, *V* = 1652.64(2) Å^3, *Z* = 4, *T* = 150(2) K, μ(Cu Kα) = 0.927 mm^{-1}, *Dcalc* = 1.287 g/cm^3, 45210 reflections measured (8.612° ≤ 2Θ ≤ 147.208°), 3327 unique (R_{int} = 0.0250, R_{sigma} = 0.0084) which were used in all calculations. The final R_1 was 0.0378 (I > 2σ(I)) and wR_2 was 0.0968 (all data).

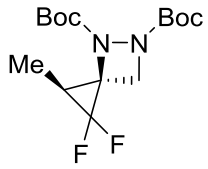
Di-*tert*-butyl 1,1-difluoro-(2,2-dimethyl)-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate (325)



3-Methylene-1,2-diazetidine **316** (90 mg, 0.30 mmol), sodium iodide (9 mg, 60 μmol) and $TMSCF_3$ (111 μL, 0.75 mmol) in anhydrous THF (3 mL) were reacted according to General Method C for 5 h. Work-up, followed by purification by column chromatography (SiO_2, 9:1, petrol: EtOAc) provided **325** (100 mg, 96%) as a white solid. M. p. 85–87 °C; R_f = 0.29 (9:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 2980, 2935, 1727, 1394, 1367, 1254, 1153, 744; δ_H (500 MHz, $CDCl_3$) 4.18 (1H, dd, *J* = 8.3, 1.9 Hz, NC*H*H), 3.95 (1H, dd, *J* = 8.3, 5.4 Hz, NCH*H*), 1.50 (9H, s, C(CH$_3$)$_3$), 1.48 (9H, s, C(CH$_3$)$_3$), 1.38 (3H, s, C(C*H*$_3$)(CH$_3$)), 1.08 (3H, s, C(CH$_3$)(C*H*$_3$)); δ_C (125 MHz, $CDCl_3$) 159.3 (COO), 156.5 (COO), 111.2 (dd, J_{CF} = 309.6, 299.8 Hz, CF_2), 83.0 (*C*(CH$_3$)$_3$), 82.5 (*C*(CH$_3$)$_3$), 55.6 (dd, J_{CF} = 13.1, 8.9 Hz, *C*CH$_2$), 49.4 (d, J_{CF} = 5.9 Hz, C*C*H$_2$), 28.1 (C(*C*H$_3$)$_3$), 27.8 (C(*C*H$_3$)$_3$), 26.2 (t, J_{CF} = 9.9 Hz,

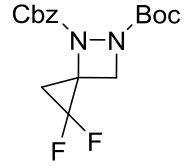
C$(CH_3)_2$), 14.7 (d, *J* = 7.6 Hz, C(*C*H_3)(CH_3)), 13.2 (d, *J* = 5.8 Hz, C(CH_3)(*C*H_3)); δ_F (376 MHz, $CDCl_3$) –136.4 (d, J_{FF} = 164 Hz), –144.9 (d, J_{FF} = 164 Hz); MS (ESI^+) *m/z* 371 [MNa^+]; HRMS calcd. for $C_{16}H_{26}F_2N_2NaO_4$ $[M+Na]^+$ 371.1753, found 371.1751.

(2*S*, 3*S*)-Di-*tert*-butyl 1,1-difluoro-2-methyl-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate (326)



3-Methylene-1,2-diazetidine **317** (85 mg, 0.30 mmol), sodium iodide (9 mg, 60 μmol) and $TMSCF_3$ (111 μL, 0.75 mmol) in anhydrous THF (3 mL) were reacted according to General Method C for 6 h. Work-up, followed by purification by column chromatography (SiO_2, 9:1, petrol: EtOAc) provided (2*S*, 3*S*)-**326** (80 mg, 80%) as a colourless oil. R_f = 0.25 (9:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2980, 2936, 1714, 1393, 1368, 1255, 1146, 1088, 732; δ_H (400 MHz, $CDCl_3$) 4.31 (1H, d, *J* = 8.2 Hz, NC*H*H), 3.97 (1H, dd, *J* = 8.1, 2.7 Hz, NCH*H*), 1.60−1.51 (1H, m, C*H*CH_3), 1.47 (9H, s, C(CH_3)$_3$), 1.46 (9H, s, C(CH_3)$_3$), 1.32 (3H, d, *J* = 6.7 Hz, CHC*H*$_3$); δ_C (125 MHz, $CDCl_3$) 159.3 (COO), 156.2 (COO), 109.8 (dd, J_{CF} = 304.5, 296.1 Hz, CF_2), 83.0 (*C*(CH_3)$_3$), 82.5 (*C*(CH_3)$_3$), 53.1 (dd, J_{CF} = 14.1, 8.1 Hz, *C*CH_2), 52.6 (d, J_{CF} = 6.0 Hz, C*C*H_2), 28.1 (C(*C*H_3)$_3$), 27.7 (C(*C*H_3)$_3$), 24.8 (t, J_{CF} = 9.9 Hz, *C*HCH_3), 5.3 (d, J_{CF} = 4.3 Hz, CH*C*H_3); δ_F (376 MHz, $CDCl_3$) –125.8 (d, J_{FF} = 167 Hz), –147.9 (d, J_{FF} = 167 Hz); MS (ESI^+) *m/z* 357 [MNa^+]; HRMS calcd. for $C_{15}H_{24}F_2N_2NaO_4$ $[M+Na]^+$ 357.1596, found 357.1598.

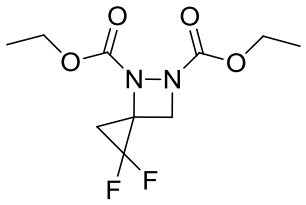
4-Benzyl 5-(*tert*-butyl) 1,1-difluoro-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate (327)



3-Methylene-1,2-diazetidine **315** (371 mg, 1.22 mmol), sodium iodide (36 mg, 0.24 mmol), $TMSCF_3$ (451 μL, 3.05 mmol) in anhydrous THF (15 mL) were reacted according to General Method C for 4 h. Work-up, followed by purification by column chromatography (SiO_2, 5:1, petrol: EtOAc) provided **327** (347 mg, 80%) as a

colourless oil. R_f = 0.23 (5:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2931, 1714, 1496, 1391, 1248, 1152, 737; δ_H (500 MHz, $CDCl_3$) 7.41−7.29 (5H, m, Ar H), 5.27 (1H, d, *J* = 12.3 Hz, C*H*HAr), 5.15 (1H, d, *J* = 12.3 Hz, CH*H*Ar), 4.37 (1H, d, *J* = 8.5 Hz, NC*H*H), 4.27 (1H, dd, *J* = 8.5, 4.6 Hz, NCH*H*), 2.69 (1H, ddd, *J* = 15.1, 10.3, 4.8 Hz, C*H*HCF$_2$), 1.45 (9H, s, C(CH$_3$)$_3$), 1.44−1.39 (1H, m, CH*H*CF$_2$); δ_C (125 MHz, $CDCl_3$) 159.3 (*C*O$_2$C(CH$_3$)$_3$), 158.2 (*C*O$_2$CH$_2$Ar), 135.1 (C, Ar), 128.6 (CH, Ar), 128.4 (CH, Ar), 128.1 (CH, Ar), 106.6 (dd, J_{CF} = 292.3, 290.3 Hz, CF$_2$), 83.2 (*C*(CH$_3$)$_3$), 68.3 (CH$_2$Ar), 52.8 (NCH$_2$), 50.8 (dd, J_{CF} = 16.0, 10.0 Hz, *C*CF$_2$), 28.0 (C(*C*H$_3$)$_3$), 16.6 (t, J_{CF} = 11.0 Hz, *C*H$_2$CF$_2$); δ_F (376 MHz, $CDCl_3$) –137.4 (d, J_{FF} = 170 Hz), –142.8 (d, J_{FF} = 170 Hz); MS (ESI$^+$) *m/z* 377 [MNa$^+$]; HRMS calcd. for $C_{17}H_{20}F_2N_2NaO_4$ [M+Na]$^+$ 377.1283, found 377.1287.

Diethyl 1,1-difluoro-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate (328)

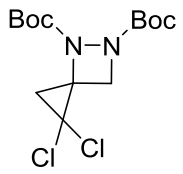


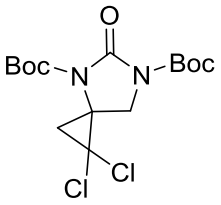
3-Methylene-1,2-diazetidine 244 (56 mg, 0.26 mmol), sodium iodide (8 mg, 50 μmol), $TMSCF_3$ (96 μL, 0.65 mmol) in anhydrous THF (3 mL) were reacted according to General Method C for 6 h. Work-up, followed by purification by column chromatography (SiO_2, 4:1, petrol: EtOAc) provided **328** (32 mg, 47%) as a colourless oil. R_f = 0.21 (4:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2984, 2937, 1713, 1372, 1275, 1095, 987, 727; δ_H (500 MHz, $CDCl_3$) 4.42 (1H, d, *J* = 8.4 Hz, NC*H*H), 4.35 (1H, dd, *J* = 8.5, 4.6 Hz, NCH*H*), 4.32−4.17 (4H, m, C*H*$_2$CH$_3$), 2.72 (1H, ddd, *J* = 15.2, 10.6, 5.2 Hz, C*H*HCF$_2$), 1.48 (1H, ddd, *J* = 15.5, 10.6, 5.8 Hz, CH*H*CF$_2$), 1.33−1.27 (6H, m, CH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 160.6 (COO), 158.2 (COO), 106.6 (dd, J_{CF} = 292.2, 290.3 Hz, CF$_2$), 63.2 (*C*H$_2$CH$_3$), 63.1 (*C*H$_2$CH$_3$), 53.0 (NCH$_2$), 51.0 (dd, J_{CF} = 15.9, 10.1 Hz, *C*CH$_2$), 16.6 (t, J_{CF} = 11.0 Hz, *C*H$_2$CF$_2$), 14.33 (CH$_2$*C*H$_3$), 14.28 (CH$_2$*C*H$_3$); δ_F (376 MHz, $CDCl_3$) –137.5 (d, J_{FF} = 170 Hz), –143.1 (d, J_{FF} = 170 Hz); MS (ESI$^+$) *m/z* 287 [MNa$^+$]; HRMS calcd. for $C_{10}H_{14}F_2N_2NaO_4$ [M+Na]$^+$ 287.0814, found 287.0821.

General Method D: Dichlorocyclopropanation of 3-Methylene-1,2-Diazetidines

To a solution of 3-methylene1,2-diazetidine (1.0 molar equiv) in chloroform was added TEBAC (10 mol %) and aqueous NaOH solution (50 wt %) dropwise. The reaction was stirred vigorously at room temperature until full consumption of the starting material. The solution was neutralised by addition of saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with EtOAc (3 x 30 mL) and the combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography provided the product.

Di-*tert*-butyl 1,1-dichloro-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate (331) and Di-*tert*-butyl 1,1-dichloro-5-oxo-4,6-diazaspiro[2.4]heptane-4,6-dicarboxylate (332)





3-Methylene-1,2-diazetidine **299** (103 mg, 0.38 mmol), TEBAC (9 mg, 39 μmol, 10 mol-%), aqueous NaOH solution (5 mL, 50 wt-%) in chloroform (10 mL) were reacted according to General Method D for 3 h. Work-up, followed by purification by column chromatography (SiO_2, 9:1, petrol: EtOAc) provided less polar **331** (64 mg, 48%) as a white solid. M. p. 122–125 °C; R_f = 0.27 (9:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 3088, 2980, 2934, 1725, 1368, 1252, 1146, 767; δ_H (500 MHz, $CDCl_3$) 4.41 (1H, d, *J* = 8.9 Hz, NC*H*H), 4.29 (1H, d, *J* = 8.9 Hz, NCH*H*), 2.79 (1H, d, *J* = 9.5 Hz, C*H*HCCl_2), 1.57−1.51 (10H, m, CH*H*CCl_2, $C(CH_3)_3$), 1.49 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 159.4 (COO), 156.9 (COO), 83.2 (*C*$(CH_3)_3$), 82.7 (*C*$(CH_3)_3$), 57.4 (CCl_2 or *C*CH_2), 56.0 (CCl_2 or *C*CH_2), 54.1 (NCH_2), 28.1 (2 x C(*C*$H_3)_3$), 25.6 (CH_2Cl_2); MS (ESI^+) *m/z* 375 [M(^{35}Cl)Na^+], 377 [M(^{37}Cl)Na^+]; HRMS calcd. for $C_{14}H_{22}{}^{35}Cl_2N_2NaO_4$ $[M+Na]^+$ 375.0849, found 375.0849. A crystal for X-ray analysis was grown from CH_2Cl_2/petrol.

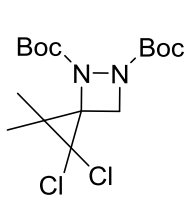
Crystal Data for $C_{14}H_{22}Cl_2N_2O_4$ (*M* =353.23 g/mol): monoclinic, space group C2/c (no. 15), *a* = 27.8891(4) Å, *b* = 11.56007(17) Å, *c* = 11.29536(18) Å, *β* = 96.1043(13)°, *V* = 3620.98(9) $Å^3$, *Z* = 8, *T* = 150(2) K, μ(CuKα) = 3.384 mm^{-1}, *Dcalc* = 1.296 g/cm^3, 37029 reflections measured (8.286° ≤ 2Θ ≤ 148.008°), 3648

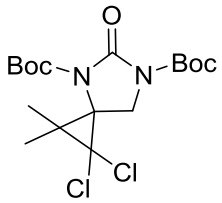
unique (R_{int} = 0.0734, R_{sigma} = 0.0237) which were used in all calculations. The final R_1 was 0.0414 (I > 2σ(I)) and wR_2 was 0.1200 (all data).

Further elution provided more polar **332** (60 mg, 41%) as a white solid. M. p. 124–127 °C; R_f = 0.13 (9:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 3110, 2981, 2929, 1782, 1729, 1366, 1267, 1138, 769; δ_H (500 MHz, $CDCl_3$) 4.10 (1H, d, *J* = 11.4 Hz, NC*H*H), 3.81 (1H, d, *J* = 11.3 Hz, NCH*H*), 3.36 (1H, d, *J* = 9.7 Hz, C*H*HCCl$_2$), 1.67 (1H, d, *J* = 9.7 Hz, CH*H*CCl$_2$), 1.55 (9H, s, C(CH$_3$)$_3$), 1.50 (9H, s, C(CH$_3$)$_3$); δ_C (125 MHz, $CDCl_3$) 149.7 (C=O), 149.6 (COO), 148.6 (COO), 84.4 (*C*(CH$_3$)$_3$), 84.1 (*C*(CH$_3$)$_3$), 61.6 (CCl$_2$ or *C*CH$_2$), 46.9 (CCl$_2$ or *C*CH$_2$), 46.0 (NCH$_2$), 28.1 (*C*H$_2$CCl$_2$), 28.0 (C(*C*H$_3$)$_3$), 27.9 (C(*C*H$_3$)$_3$); MS (ESI$^+$) *m/z* 403 [M(^{35}Cl)Na$^+$], 405 [M(^{37}Cl)Na$^+$]; HRMS calcd. for $C_{15}H_{22}{}^{35}Cl_2N_2NaO_5$ [M+Na]$^+$ 403.0798, found 403.0800. A crystal for X-ray analysis was grown from CH_2Cl_2/petrol.

Crystal Data for $C_{15}H_{22}Cl_2N_2O_5$ (*M* =381.24 g/mol): monoclinic, space group P2$_1$/c (no. 14), *a* = 12.60521(6) Å, *b* = 10.85069(4) Å, *c* = 13.53848(7) Å, *β* = 102.1911(5)°, *V* = 1809.971(15) Å^3, *Z* = 4, *T* = 150(2) K, μ(Cu Kα) = 3.472 mm^{-1}, *Dcalc* = 1.399 g/cm^3, 34089 reflections measured (10.544° ≤ 2Θ ≤ 173.528°), 3613 unique (R_{int} = 0.0266, R_{sigma} = 0.0108) which were used in all calculations. The final R_1 was 0.0296 (I > 2σ(I)) and wR_2 was 0.0824 (all data).

Di-*tert*-butyl-1,1-dichloro-(2,2-dimethyl)-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate (333) and Di-*tert*-butyl 1,1-dichloro-(2,2-dimethyl)-5-oxo-4,6-diazaspiro[2.4]heptane-4,6-dicarboxylate (334)

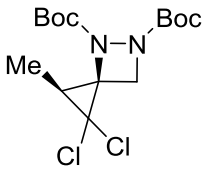


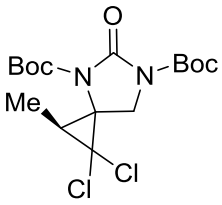


3-Methylene-1,2-diazetidine **316** (90 mg, 0.30 mmol), TEBAC (7 mg, 31 μmol, 10 mol-%) and aqueous NaOH solution (5 mL, 50-wt %) in chloroform (10 mL) were reacted according to General Method D for 75 min. Work-up, followed by purification by column chromatography (SiO_2, 9:1, petrol: EtOAc) provided less polar **333** (65 mg, 57%) as a white solid. M. p. 103–106 °C; R_f = 0.35 (9:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 2978, 2932, 1715, 1368, 1255, 1144, 858, 763; δ_H (400 MHz, $CDCl_3$) 4.12 (1H, q, *J* = 8.4 Hz, NCH$_2$), 1.59 (3H, s,

C(C*H*$_3$)(CH$_3$)), 1.50 (9H, C(CH$_3$)$_3$), 1.48 (9H, s, C(CH$_3$)$_3$), 1.16 (3H, s, C(CH$_3$)(C*H*$_3$)); δ_C (125 MHz, CDCl$_3$) 159.4 (COO), 155.4 (COO), 82.8 (*C*(CH$_3$)$_3$), 82.5 (*C*(CH$_3$)$_3$), 68.7 (CCl$_2$ or *C*CH$_2$), 62.0 (CCl$_2$ or *C*CH$_2$), 52.3 (CH$_2$), 32.4 (*C*(CH$_3$)$_2$), 28.1 (C(*C*H$_3$)$_3$), 27.9 (C(*C*H$_3$)$_3$), 20.9 (C(*C*H$_3$)(CH$_3$)), 19.3 (C(CH$_3$)(*C*H$_3$)); MS (ESI$^+$) *m/z* 403 [M(^{35}Cl)Na$^+$], 405 [M(^{37}Cl)Na$^+$]; HRMS calcd. for $C_{16}H_{26}{}^{35}Cl_2N_2NaO_4$ [M+Na]$^+$ 403.1162, found 403.1161. Further elution provided more polar **334** (11 mg, 9%) as a white solid. M. p. 122–125 °C; R_f = 0.17 (9:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 2980, 2931, 1803, 1742, 1368, 1275, 1132, 771; δ_H (400 MHz, CDCl$_3$) 4.00 (1H, d, *J* = 11.1 Hz, NC*H*H), 3.83 (1H, d, *J* = 11.2 Hz, NCH*H*), 1.54 (9H, C(CH$_3$)$_3$), 1.50 (9H, s, C(CH$_3$)$_3$), 1.46 (3H, s, C(C*H*$_3$)(CH$_3$)), 1.31 (3H, s, C(CH$_3$)(C*H*$_3$)); δ_C (125 MHz, CDCl$_3$) 150.6 (C=O), 150.2 (COO), 149.7 (COO), 84.4 (*C*(CH$_3$)$_3$), 84.0 (*C*(CH$_3$)$_3$), 71.7 (CCl$_2$ or *C*CH$_2$), 50.9 (CCl$_2$ or *C*CH$_2$), 46.9 (CH$_2$), 33.2 (*C*(CH$_3$)$_2$), 28.1 (C(*C*H$_3$)$_3$), 27.6 (C(*C*H$_3$)$_3$), 20.9 (C(*C*H$_3$)(CH$_3$)), 20.7 (C(CH$_3$)(*C*H$_3$)); MS (ESI$^+$) *m/z* 431 [M(^{35}Cl)Na$^+$], 433 [M(^{37}Cl)Na$^+$]; HRMS calcd. for $C_{17}H_{26}{}^{35}Cl_2N_2NaO_5$ [M+Na]$^+$ 431.1111, found 431.1114.

Di-*tert*-butyl 1,1-dichloro-2-methyl-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate 335) and Di-*tert*-butyl-1,1-dichloro-2-methyl-5-oxo-4,6-diazaspiro[2.4]heptane-4,6-dicarboxylate 336)

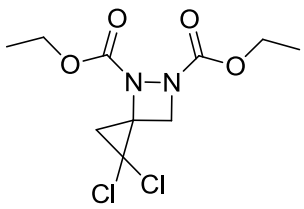




3-Methylene-1,2-diazetidine **317** (85 mg, 0.30 mmol), TEBAC (7 mg, 31 μmol, 10 mol-%) and aqueous NaOH solution (5 mL, 50 wt-%) in chloroform (10 mL) were reacted according to General Method D for 15 min. Work-up, followed by purification by column chromatography (SiO_2, 9:1, petrol: EtOAc) provided less polar (2*S*, 3*S*)-**335** (46 mg, 42%) as a colourless oil. R_f = 0.31 (9:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2979, 2934, 1713, 1368, 1150, 840, 764; δ_H (500 MHz, CDCl$_3$) 4.32 (1H, d, *J* = 8.6 Hz, NC*H*H), 4.13 (1H, d, *J* = 8.6 Hz, NCH*H*), 1.63 (1H, q, *J* = 6.8 Hz, C*H*CH$_3$), 1.53 (3H, d, *J* = 6.7 Hz, CHC*H*$_3$), 1.49 (9H, s, C(CH$_3$)$_3$), 1.46 (9H, s, C(CH$_3$)$_3$); δ_C (125 MHz, CDCl$_3$) 159.4 (COO), 155.6 (COO), 82.9 (*C*(CH$_3$)$_3$), 82.5 (*C*(CH$_3$)$_3$), 63.2 (CCl$_2$ or *C*CH$_2$), 59.0 (CCl$_2$ or *C*CH$_2$), 55.0 (CH$_2$), 34.9 (*C*HCH$_3$), 28.1 (C(*C*H$_3$)$_3$), 27.9 (C(*C*H$_3$)$_3$), 10.7 (CH*C*H$_3$); MS

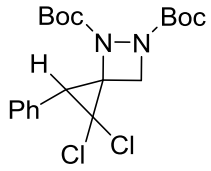
(ESI$^+$) *m/z* 389 [M(^{35}Cl)Na$^+$], 391 [M(^{37}Cl)Na$^+$]; HRMS calcd. for $C_{15}H_{24}{}^{35}Cl_2N_2NaO_4$ [M+Na]$^+$ 389.1005, found 389.1004. Further elution provided more polar **336** (11 mg, 9%) as a colourless oil. R_f = 0.17 (7:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2982, 2933, 1801, 1747, 1369, 1256, 1147, 809, 736; δ_H (400 MHz, $CDCl_3$) 4.06 (1H, d, *J* = 11.2 Hz, NC*H*H), 3.83 (1H, d, *J* = 11.2 Hz, NCH*H*), 1.79 (1H, q, *J* = 6.7 Hz, C*H*CH$_3$), 1.57−1.52 (12H, m, CHC*H*$_3$, C(CH$_3$)$_3$), 1.51 (9H, s, C(CH$_3$)$_3$); δ_C (125 MHz, $CDCl_3$) 149.8 (C=O), 149.6 (COO), 149.5 (COO), 84.2 (*C*(CH$_3$)$_3$), 83.9 (*C*(CH$_3$)$_3$), 67.6 (CCl_2 or *C*CH$_2$), 49.9 (CCl_2 or *C*CH$_2$), 48.7 (CH$_2$), 35.3 (*C*HCH$_3$), 28.1 (C(*C*H$_3$)$_3$), 27.7 (C(*C*H$_3$)$_3$), 10.3 (CH*C*H$_3$); MS (ESI$^+$) *m/z* 417 [M(^{35}Cl)Na$^+$], 419 [M(^{37}Cl)Na$^+$]; HRMS calcd. for $C_{16}H_{24}{}^{35}Cl_2N_2NaO_5$ [M+Na]$^+$ 417.0954, found 417.0951.

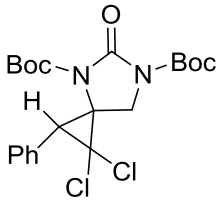
Diethyl 1,1-dichloro-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate (339)



3-Methylene-1,2-diazetidine **244** (75 mg, 35 μmol, 0.35 mmol), TEBAC (8 mg, 10 mol-%) and aqueous NaOH solution (5 mL, 50 wt-%) in chloroform (10 mL) were reacted according to General Method D for 6 h. Work-up, followed by purification by column chromatography (SiO_2, 4:1, petrol: EtOAc) provided **339** (67 mg, 64%) as a colourless oil. R_f = 0.30 (4:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 3087, 2985, 2924, 1724, 1467, 1375, 1270, 1132, 769; δ_H (500 MHz, $CDCl_3$) 4.47 (1H, d, *J* = 9.0 Hz, NC*H*H), 4.38 (1H, d, *J* = 9.0 Hz, NCH*H*), 4.33−4.15 (4H, m, C*H*$_2$CH$_3$), 2.84 (1H, d, *J* = 9.7 Hz, C*H*HCCl$_2$), 1.57 (1H, d, *J* = 9.8 Hz, CH*H*CCl$_2$), 1.33−1.25 (6H, m, CH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$) 160.5 (COO), 158.3 (COO), 63.2 (*C*H$_2$CH$_3$), 63.1 (*C*H$_2$CH$_3$), 57.2 (CCl_2 or *C*CH$_2$), 56.5 (CCl_2 or *C*CH$_2$), 54.5 (NCH$_2$), 25.6 (*C*H$_2$CCl$_2$), 14.4 (CH$_2$*C*H$_3$), 14.3 (CH$_2$*C*H$_3$); MS (ESI$^+$) *m/z* 319 [M(^{35}Cl)Na$^+$], 321 [M(^{37}Cl)Na$^+$]; HRMS calcd. for $C_{10}H_{14}{}^{35}Cl_2N_2NaO_4$ [M+Na]$^+$ 391.0223, found 391.0221.

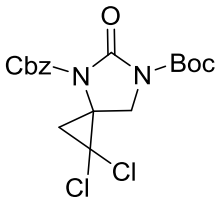
Di-*tert*-butyl 1,1-dichloro-2-phenyl-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate (343) and Di-*tert*-butyl 1,1-dichloro-5-oxo-2-phenyl-4,6-diazaspiro[2.4]heptane-4,6-dicarboxylate (344)





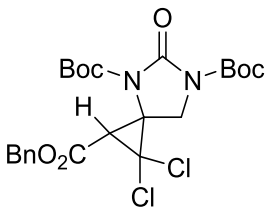
3-Methylene-1,2-diazetidine (*E*)-**318** (45 mg, 0.13 mmol), TEBAC (3 mg, 13 μmol, 10 mol-%) and aqueous NaOH solution (2.5 mL, 50 wt-%) in chloroform (5 mL) were reacted according to General Method D for 5 h. Work-up, followed by purification by column chromatography (SiO_2, 8:1, petrol: EtOAc) provided less polar **343** (6 mg, 11%) as a colourless oil. R_f = 0.39 (8:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2978, 2930, 1712, 1498, 1393, 1369, 1255, 1153, 743; δ_H (500 MHz, $CDCl_3$) 7.40−7.33 (3H, m, Ar H), 7.21 (2H, d, *J* = 7.4 Hz, Ar H), 4.38 (1H, d, *J* = 9.2 Hz, NC*H*H), 4.25 (1H, d, *J* = 9.2 Hz, NCH*H*), 4.06 (1H, s, CHAr), 1.53 (9H, s, $C(CH_3)_3$), 1.52 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 159.3 (COO), 157.0 (COO), 131.2 (C, Ar), 129.3 (CH, Ar), 128.8 (CH, Ar), 128.0 (CH, Ar), 83.4 ($C(CH_3)_3$), 82.8 ($C(CH_3)_3$), 62.3 (CCl_2 or CCH_2), 60.0 (CCl_2 or CCH_2), 51.7 (NCH_2), 35.3 (CHAr), 28.2 ($C(CH_3)_3$), 28.1 ($C(CH_3)_3$); MS (ESI^+) *m/z* 451 [M(^{35}Cl)Na^+], 453 [M(^{37}Cl)Na^+]; HRMS calcd. for $C_{21}H_{26}{}^{35}Cl_2N_2NaO_4$ $[M+Na]^+$ 451.1162, found 451.1166. Further elution provided more polar **344** (35 mg, 58%) as a white solid. M. p. 149–151 °C; R_f = 0.25 (8:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 2981, 2933, 1795, 1723, 1498, 1394, 1369, 1255, 1140, 737; δ_H (500 MHz, $CDCl_3$) 7.41−7.27 (5H, m, Ar H), 4.69 (1H, s, CHAr), 3.81 (1H, d, *J* = 11.8 Hz, NC*H*H), 3.77 (1H, d, *J* = 11.8 Hz, NCH*H*), 1.55 (9H, s, $C(CH_3)_3$), 1.53 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 150.0 (C=O), 149.8 (COO), 148.6 (COO), 130.5 (C, Ar), 129.2 (CH, Ar), 128.8 (CH, Ar), 128.0 (CH, Ar), 84.6 ($C(CH_3)_3$), 84.2 ($C(CH_3)_3$), 66.0 (CCl_2 or CCH_2), 50.4 (CCl_2 or CCH_2), 44.2 (NCH_2), 38.1 ($CHCCl_2$), 28.0 ($C(CH_3)_3$), 27.9 ($C(CH_3)_3$); MS (ESI^+) *m/z* 479 [M(^{35}Cl)Na^+], 481 [M(^{37}Cl)Na^+]; HRMS calcd. for $C_{21}H_{26}{}^{35}Cl_2N_2NaO_5$ $[M+Na]^+$ 479.1111, found 479.1114.

4-Benzyl 6-(*tert*-butyl) 1,1-dichloro-5-oxo-4,6-diazaspiro[2.4]heptane-4,6-dicarboxylate (338)



3-Methylene-1,2-diazetidine **315** (120 mg, 0.394 mmol), TEBAC (9 mg, 39 μmol, 10 mol-%) and aqueous NaOH solution (6 mL, 50-wt%) in chloroform (12 mL) were reacted according to General Method D for 2 h. Work-up, followed by purification by column chromatography (SiO_2, 5:1 petrol: EtOAc) provided **338** (68 mg, 42%) as a colourless oil. R_f = 0.19 (5:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2980, 2934, 1795, 1720, 1370, 1252, 1141, 773, 735, 698; δ_H (400 MHz, $CDCl_3$) 7.42 (2H, d, *J* = 6.7 Hz, Ar H), 7.37−7.30 (3H, m, Ar H), 5.27 (2H, s, CH_2Ar), 4.13 (1H, d, *J* = 11.4 Hz, NC*H*H), 3.84 (1H, d, *J* = 11.4 Hz, NCH*H*), 3.41 (1H, d, *J* = 9.8 Hz, C*H*HCCl_2), 1.67 (1H, d, *J* = 9.8 Hz, CH*H*CCl_2), 1.56 (9H, s, C$(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 151.4 (C=O), 149.4 (COO), 148.3 (COO), 134.8 (C, Ar), 128.6 (CH, Ar), 128.5 (CH, Ar), 128.1 (CH, Ar), 84.4 (*C*$(CH_3)_3$), 68.8 (CH_2Ar), 61.3 (CCl_2 or *C*CH_2), 47.1 (CCl_2 or *C*CH_2), 46.1 (NCH_2), 28.0 (C(*C*$H_3)_3$), 27.7 (*C*H_2CCl_2); MS (ESI^+) *m/z* 437 [M(^{35}Cl)Na^+], 439 [M(^{37}Cl)Na^+]; HRMS calcd. for $C_{18}H_{20}{}^{35}Cl_2N_2NaO_5$ $[M+Na]^+$ 437.0641, found 437.0645.

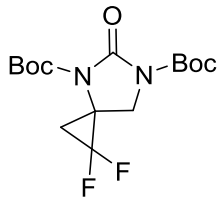
1-Benzyl 4,5-di-*tert*-butyl 2,2-dichloro-4,5-diazaspiro[2.3]hexane-1,4,5-tricarboxylate (342)



3-Methylene-1,2-diazetidine **321** (101 mg, 0.25 mmol), TEBAC (6 mg, 26 μmol, 10 mol-%) and aqueous NaOH solution (5 mL, 50 wt-%) in chloroform (10 mL) were reacted according to General Method D for 6 h. Work-up, followed by purification by column chromatography (SiO_2, 5:1, petrol: EtOAc) provided **342** (15 mg, 12%) as a yellow oil. R_f = 0.35 (5:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2980, 2933, 1822, 1727, 1498, 1370, 1253, 1137, 772; δ_H (400 MHz, $CDCl_3$) 7.38−7.30 (5H, m, Ar H), 5.15 (2H, s, CH_2Ar), 3.98 (1H, s, $CHCCl_2$), 3.74 (1H, d, *J* = 17.3 Hz, NC*H*H), 2.92 (1H, d, *J* = 17.3 Hz, NCH*H*), 1.55 (9H, C$(CH_3)_3$), 1.52 (9H, s, C$(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 168.7 (COO), 149.1 (COO), 147.9 (COO), 135.0 (C, Ar), 128.8 (CH, Ar), 128.6 (CH, Ar), 128.4 (CH, Ar), 85.1

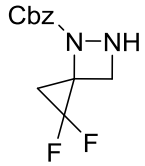
(*C*(CH_3)$_3$), 84.8 (*C*(CH_3)$_3$), 67.4 (CH_2Ar), 61.2 (CCl_2 or *C*CH_2), 47.2 (CCl_2 or *C*CH_2), 44.7 (*C*HCCl_2), 33.0 (NCH_2), 27.9 (C(*C*H_3)$_3$), 27.8 (C(*C*H_3)$_3$); MS (ESI^+) *m/z* 537 [M(^{35}Cl)Na^+], 539 [M(^{37}Cl)Na^+]; HRMS calcd. for $C_{23}H_{28}{}^{35}Cl_2N_2NaO_7$ $[M+Na]^+$ 537.1166, found 537.1169.

Di-*tert*-butyl 1,1-difluoro-5-oxo-4,6-diazaspiro[2.4]heptane-4,6-dicarboxylate (347)



To **324** (28 mg, 0.09 mmol) and TEBAC (2 mg, 9 μmol, 10 mol-%) in chloroform (3 mL) was added aqueous sodium hydroxide (1.5 mL, 50 wt-%) dropwise. The reaction was stirred vigorously at room temperature for 6 h, then quenched with saturated aqueous NH_4Cl solution (10 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 4:1, petrol: EtOAc) provided **347** (18 mg, 59%) as a white solid. M. p. 118–121 °C; R_f = 0.39 (4:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 3111, 2973, 2934, 1789, 1718, 1368, 1234, 1137, 772, 741; δ_H (400 MHz, $CDCl_3$) 3.87 (1H, d, *J* = 10.7 Hz, NC*H*H), 3.69 (1H, dd, *J* = 10.8, 6.4 Hz, NCH*H*), 3.21 (1H, ddd, *J* = 13.4, 9.9, 5.5 Hz, C*H*HCF_2), 1.54 (9H, s, C(CH_3)$_3$), 1.52 (9H, s, C(CH_3)$_3$), 1.48−1.44 (1H, m CH*H*CF_2); δ_C (125 MHz, $CDCl_3$) 149.6 (C=O), 149.1 (COO), 148.6 (COO), 108.8 (t, J_{CF} = 294.8 Hz, CF_2), 84.5 (*C*(CH_3)$_3$), 84.0 (*C*(CH_3)$_3$), 43.7 (d, J_{CF} = 6.5 Hz, NCH_2), 41.9 (dd, J_{CF} = 10.9, 9.3 Hz, *C*CF_2), 28.0 (C(*C*H_3)$_3$), 27.9 (C(*C*H_3)$_3$), 18.5 (t, J_{CF} = 10.3 Hz, *C*H_2CF_2); δ_F (376 MHz, $CDCl_3$) –125.8 (d, J_{FF} = 167 Hz), –147.9 (d, J_{FF} = 167 Hz); MS (ESI^+) *m/z* 371 [MNa^+]; HRMS calcd. for $C_{15}H_{22}F_2N_2NaO_5$ $[M+Na]^+$ 371.1389, found 371.1389.

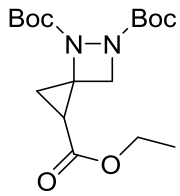
Benzyl 1,1-difluoro-4,5-diazaspiro[2.3]hexane-4-carboxylate (359)

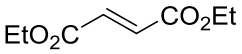


To **327** (82 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (5 mL) under an atmosphere of nitrogen was added dropwise trifluoroacetic acid (176 μL, 2.30 mmol). The reaction was stirred at room temperature for 5 h then concentrated. The residue was diluted with CH_2Cl_2 (10 mL), and

washed with a saturated solution of aqueous sodium bicarbonate (10 mL) and H_2O (10 mL). The aqueous layer was washed with CH_2Cl_2 (10 mL), the organic extracts combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide **359** (53 mg, 91%) as a yellow oil. IR υ_{max} (film)/cm^{-1} 3259, 3030, 2962, 2899, 1709, 1492, 1244, 1077, 699; δ_H (400 MHz, $CDCl_3$) 7.38−7.29 (5H, m, Ar H), 5.60 (1H, br s, NH), 5.22 (1H, d, *J* = 12.2 Hz, C*H*HAr), 5.11 (1H, d *J* = 12.2 Hz, CH*H*Ar), 4.07 (1H, br m, CC*H*H), 3.87 (1H, br m, CCH*H*), 2.67 (1H, br m, C*H*HCF$_2$), 1.38 (1H, ddd, *J* = 15.5, 10.1, 5.2 Hz, CH*H*CF$_2$); δ_C (125 MHz, $CDCl_3$) 157.9 (COO), 135.5 (C, Ar), 128.6 (CH, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 107.4 (t, J_{CF} = 291.9 Hz, CF_2), 67.7 (CH_2Ar), 53.5 (dd, J_{CF} = 16.2, 9.8 Hz, *C*CH$_2$), 46.2 (C*C*H$_2$), 17.2 (t, J_{CF} = 9.4 Hz, *C*H$_2$CF$_2$); δ_F (376 MHz, $CDCl_3$) –137.7 (d, J_{FF} = 169 Hz), –142.7 (d, J_{FF} = 169 Hz); MS (ESI$^+$) *m/z* 255 [MH$^+$], 277 [MNa$^+$]; HRMS calcd. for $C_{12}H_{12}F_2N_2NaO_2$ [M+Na]$^+$ 277.0759, found 277.0763.

4,5-Di-tert-butyl 1-ethyl-4,5-diazaspiro[2.3]hexane-1,4,5-tricarboxylate (354) and diethyl fumarate (354a)

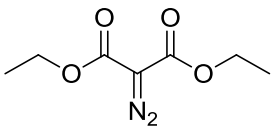




To an oven-dried flask purged with N_2 was added **299** (149 mg, 0.55 mmol) and rhodium (II) acetate dimer (24 mg, 55 μmol) in anhydrous CH_2Cl_2 (5 mL). Ethyl diazoacetate (64 μL, 0.61 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise *via* a dropping funnel, and the reaction stirred at room temperature for 5 h. Additional ethyl diazoacetate (64 μL, 0.61 mmol) was added, and the mixture stirred for 2 d until the reaction was complete, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 9:1, petrol: EtOAc) provided an inseparable mixture of **354: 354a** in a 3: 1 ratio (64 mg, 33%) as a yellow oil. R_f = 0.20 (9:1, petrol: EtOAc); IR υ_{max} (film)/cm^{-1} 2979, 2934, 1708, 1369, 1257, 1161, 767; δ_H (500 MHz, $CDCl_3$) 6.23 (0.66H, s, *H*C=C*H* minor product), 4.30 (1H, d, *J* = 9.0 Hz, NC*H*H), 4.27−4.22 (2.32H, m, NCH*H*, C*H*$_2$CH$_3$ minor product), 4.14 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 2.40 (1H, dd, *J* = 9.8, 6.8 Hz, NCCH), 2.00 (1H, dd, *J* = 9.7, 6.7 Hz, NCC*H*H), 1.50 (9H, s, C(CH$_3$)$_3$), 1.48 (9H, s, C(CH$_3$)$_3$), 1.33−1.25 (4.98H, m, CH$_2$C*H*$_3$, CH$_2$C*H*$_3$ minor product), 1.22 (1H, t, *J* = 6.4 Hz, NCCH*H*); δ_C (125 MHz, $CDCl_3$) 171.0 (COO),

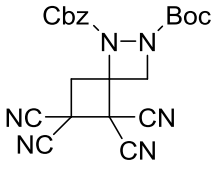
165.3 (2 x COO, minor product), 159.7 (COO), 156.8 (COO), 129.8 (H*C*=*C*H, minor product), 82.7 (*C*(CH_3)$_3$), 82.4 (*C*(CH_3)$_3$), 61.3 (*C*$H_2$$CH_3$, minor product), 61.0 (*C*$H_2$$CH_3$), 54.9 (N$CH_2$), 52.8 (N*C*CH), 28.2 (C(*C*H_3)$_3$), 28.1 (C(*C*H_3)$_3$), 21.1 (NC*C*H), 14.5 (NC*C*H_2), 14.3 (CH_2*C*H_3), 14.0 (CH_2*C*H_3, minor product); MS (ESI^+) *m/z* 379 [MNa^+]; HRMS calcd. for $C_{17}H_{28}N_2NaO_6$ $[M+Na]^+$ 379.1840, found 379.1850.

Diethyl 2-diazomalonate (355)



This compound was preprared according to a modified literature procedure.[192] To an oven-dried flask was added 4-acetamidobenzenesulfonyl azide (360 mg, 1.50 mmol) under an atmosphere of nitrogen. Anhydrous acetonitrile (5 mL) was added, followed by diethyl malonate (152 μL, 1.00 mmol) and triethylamine (335 μL, 2.40 mmol) dropwise at room temperature. The reaction was stirred for 23 h and concentrated *in vacuo*. The crude material was filtered, washed with acetonitrile (20 mL), concentrated, washed with CH_2Cl_2 (20 mL) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 1:1, petrol: Et_2O) provided **355** (186 mg, 100%) as a yellow oil. R_f = 0.50 (1:1, petrol: Et_2O); IR υ_{max} (film)/cm^{-1} 2982, 2930, 2138, 1752, 1087, 739; δ_H (500 MHz, $CDCl_3$) 4.30 (4H, q, *J* = 7.1 Hz, C*H*$_2$$CH_3$), 1.31 (6H, t, *J* = 7.1 Hz); δ_C (125 MHz, $CDCl_3$) 161.1 (COO), 61.6 (*C*$H_2$$CH_3$), 14.4 ($CH_2$*C*$H_3$), C=$N_2$ signal not observed; MS (ESI^+) *m/z* 209 [MNa^+]; HRMS calcd. for $C_7H_{10}N_2NaO_4$ $[M+Na]^+$ 209.0533, found 209.0534.

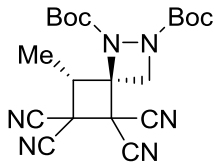
1-Benzyl 2-(*tert*-butyl) 5,5,6,6-tetracyano-1,2-diazaspiro[3.3]heptane-1,2-dicarboxylate (362)



To **315** (50 mg, 0.17 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C was added tetracyanoethylene (21 mg, 0.17 mmol), and the solution was allowed to warm to room temperature. Additional tetracyanoethylene (10 mg, 0.08 mmol) was added after 20 h at 0 °C, and the reaction warmed to room temperature and stirred for 6 h until

completion, then concentrated *in vacuo*. Purification by column chromatography (SiO_2, 2:1, petrol: EtOAc) provided **362** (71 mg, 99%) as a white solid. M. p. 149–151 °C; R_f = 0.55 (2:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 2988, 1714, 1502, 1397, 1148, 723; δ_H (500 MHz, acetone-d_6) 7.48 (2H, d, *J* = 7.3 Hz, Ar H), 7.43−7.31 (3H, m, Ar H), 5.38 (1H, d, *J* = 12.5 Hz, C*H*HAr), 5.25 (1H, d, *J* = 12.5 Hz, CH*H*Ar), 4.91 (1H, d, *J* = 10.4 Hz, NC*H*H), 4.68 (1H, d, *J* = 10.4 Hz, NCH*H*), 4.52 (1H, d, *J* = 15.4 Hz, C*H*HC$(CN)_2$), 4.03 (1H, d, *J* = 15.4 Hz, CH*H*C$(CN)_2$), 1.44 (9H, s, C$(CH_3)_3$); δ_C (125 MHz, acetone-d_6) 158.8 (COO), 155.5 (COO), 135.5 (C, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 128.1 (CH, Ar), 111.8 (CN), 111.2 (CN), 109.3 (CN), 108.3 (CN), 82.8 (*C*$(CH_3)_3$), 69.7 (*C*$(CN)_2$), 68.2 (CH_2Ar), 58.8 (NCH_2), 50.2 (*C*CH_2), 40.9 (*C*H_2C$(CN)_2$), 31.7 (CH_2*C*$(CN)_2$), 27.2 (C(*C*$H_3)_3$); MS (ESI^+) *m/z* 455 [MNa^+]; Anal. calcd. for $C_{22}H_{20}N_6O_4$: C, 61.10; H, 4.66; N, 19.43%. Found: C, 61.17; H, 4.71; N, 19.05%.

(3*R*, 7*S*)-Di-*tert*-butyl 5,5,6,6-tetracyano-7-methyl-1,2-diazaspiro[3.3]heptane-1,2-dicarboxylate (363a)



To **317** (51 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C was added tetracyanoethylene (23 mg, 0.18 mmol). The solution was allowed to warm to room temperature and stirred for 16 h, then concentrated *in vacuo* to give a 4:1 mixture of diastereomers. Purification by column chromatography (SiO_2, 5:1, petrol: EtOAc) provided the major diastereomer (3*R*, 7*S*)-**363a** (54 mg, 73%) as a white solid. M. p. 65–68 °C; R_f = 0.35 (5:1, petrol: EtOAc); IR υ_{max} (neat)/cm^{-1} 2981, 2937, 1717, 1370, 1136, 836, 763; δ_H (500 MHz, acetone-d_6) 4.94 (1H, d, *J* = 10.9 Hz, NC*H*H), 4.80 (1H, q, *J* = 7.0 Hz, C*H*CH_3), 4.43 (1H, d, *J* = 10.8 Hz, NCH*H*), 1.70 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 1.55 (9H, s, C$(CH_3)_3$), 1.51 (9H, s, C$(CH_3)_3$); δ_C (125 MHz, acetone-d_6) 158.6 (COO), 153.8 (COO), 110.5 (CN), 109.1 (CN), 109.0 (CN), 108.6 (CN), 84.4 (*C*$(CH_3)_3$), 82.9 (*C*$(CH_3)_3$), 73.2 (*C*$(CN)_2$), 53.4 (N*C*H_2), 48.4 (*C*CH_2), 45.5 (*C*HCH_3), 37.3 (CH*C*$(CN)_2$), 27.21 (C(*C*$H_3)_3$), 27.19 (C(*C*$H_3)_3$), 11.4 (CH*C*H_3); MS (ESI^+) *m/z* 435 [MNa^+]; Anal. calcd. for $C_{20}H_{24}N_6O_4$: C, 58.24; H, 5.87; N, 20.38%. Found: C, 58.21; H, 5.91; N, 20.24%.

References

(1) Cromwell, N. H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331–358.

(2) Antermite, D.; Degennaro, L.; Luisi, R. *Org. Biomol. Chem.* **2017**, *15*, 34–50.

(3) Gabriel, S.; Weiner, J. *Ber.* **1888**, *21*, 2669–2679.

(4) Yasumura, J. *Chem. Abstr.* **1963**, *59*, 2313d.

(5) Wadsworth, D. H. *J. Org. Chem.* **1967**, *32*, 1184–1187.

(6) Catalán, J.; Mo, O.; Yáñez, M. *J. Mol. Struct.* **1978**, *43*, 251–257.

(7) Mastryukov, V. S.; Dorofeeva, O. V.; Vilkov, L. V. *J. Mol. Struct.* **1976**, *34*, 99–112.

(8) Egawa, T.; Kuchitsu, K. *J. Mol. Spectrosc.* **1988**, *128*, 469–477.

(9) Fowden, L. *Biochem. J.* **1956**, *64*, 323–332.

(10) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490–7505.

(11) Hamada, Y.; Shioiri, T. *J. Org. Chem.* **1986**, *51*, 5490–5492.

(12) Di, Y. T.; He, H. P.; Wang, Y. S.; Bo, L.; Lu, Y.; Gong, J. B.; Fang, X.; Kong, N. C.; Li, S. L.; Zhu, H. J.; Hao, X. J. *Org. Lett.* **2007**, *9*, 1355–1358.

(13) Phillips, D. P.; Gao, W.; Yang, Y.; Zhang, G.; Lerario, I. K.; Lau, T. L.; Jiang, J.; Wang, X.; Nguyen, D. G.; Bhat, B. G.; Trotter, C.; Sullivan, H.; Welzel, G.; Landry, J.; Chen, Y.; Joseph, S. B.; Li, C.; Gordon, W. P.; Richmond, W.; Johnson, K.; Bretz, A.; Bursulaya, B.; Pan, S.; McNamara, P.; Seidel, H. M. *J. Med. Chem.* **2014**, *57*, 3263–3282.

(14) Adams, D. R.; Bentley, J.; Bodkin, C. D.; Cliffe, I. A.; Edward, J.; Davidson, P.; Mansell, H. L.; Monck, N. J.; Shepherd, R. G.; Shepherd, J. M. Azetidinecarboxamide derivatives for treating CNS disorders. US Patent 6,831,078 B1, Dec 14, 2004.

(15) Brandt, T. A.; Caron, S.; Damon, D. B.; DiBrino, J.; Ghosh, A.; Griffith, D. A.; Kedia, S.; Ragan, J. A.; Rose, P. R.; Vanderplas, B. C.; Wei, L. *Tetrahedron* **2009**, *65*, 3292–3304.

(16) Han, M.; Song, C.; Jeong, N.; Hahn, H.-G. *ACS Med. Chem. Lett.* **2014**, *5*, 999–1004.

(17) Brunette, S. R.; Abeywardane, A.; Burke, M. J.; Kapadia, S. R.; Kirrane, T. M.; Netherton, M. R.; Razavi, H.; Rodriguez, S.; Saha, A.; Sibley, R.; Keenan, L. L. S.; Takahashi, H.; Turner, M. R.; Wu, J. P.; Young, E. R. R.; Zhang, Q.; Zhang, Q.; Zindell, R. M. Benzodioxanes for inhibiting leukotriene production. International Patent 2013134226 A1, Sep 12, 2013.

(18) Lowe, J. T.; Lee, M. D.; Akella, L. B.; Davoine, E.; Donckele, E. J.; Durak, L.; Duvall, J. R.; Gerard, B.; Holson, E. B.; Joliton, A.; Kesavan, S.; Lemercier, B. C.; Liu, H.; Marié, J.-C.; Mulrooney, C. A.; Muncipinto, G.; Welzel-O'Shea, M.; Panko, L. M.; Rowley, A.; Suh, B.-C.; Thomas, M.; Wagner, F. F.; Wei, J.; Foley, M. A.; Marcaurelle, L. A. *J. Org. Chem.* **2012**, *77*, 7187–7211.

(19) Hoshino, J.; Hiraoka, J.; Hata, Y.; Sawada, S.; Yamamoto, Y. *J. Chem. Soc., Perkin. Trans. 1* **1995**, 693–697.

(20) Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **2001**, *12*, 605–618.

(21) Shi, M.; Jiang, J.-K.; Shen, Y.-M.; Feng, Y.-S. *J. Chem. Res. Synop.* **2001**, 375–377.

(22) Marinetti, A.; Hubert, P.; Genêt, J.-P. *Eur. J. Org. Chem.* **2000**, 1815–1820.

(23) Wang, M.-C.; Zhang, Q.-J.; Zhao, W.-X.; Wang, X.-D.; Ding, X.; Jing, T.-T.; Song, M.-P. *J. Org. Chem.* **2008**, *73*, 168–176.

(24) Ju, Y.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135–141.

(25) Hillier, M. C.; Chen, C. *J. Org. Chem.* **2006**, *71*, 7885–7887.

(26) Miller, R. A.; Lang, F.; Marcune, B.; Zewge, D.; Song, Z. J.; Karady, S. *Synth. Commun.* **2003**, *33*, 3347–3353.

(27) Concellón, J. M.; Bernad, P. L.; Pérez-Andrés, J. A. *J. Org. Chem.* **1997**, *62*, 8902–8906.

(28) Concellón, J. M.; Riego, E.; Bernad, P. L. *Org. Lett.* **2002**, *4*, 1299–1301.

(29) Gaertner, V. R. *J. Org. Chem.* **1967**, *32*, 2972–2976.

(30) Constantieux, T.; Grelier, S.; Picard, J.-P. *Synlett* **1998**, 510–512.

(31) Nadir, U. K.; Sharma, R. L.; Koul, V. K. *J. Chem. Soc., Perkin. Trans. 1* **1991**, 2015–2019.

(32) Malik, S.; Nadir, U. K. *Synlett* **2008**, 108–110.

(33) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tanaka, T.; Takemoto, Y.; Ibuka, T. *J. Org. Chem.* **2001**, *66*, 4904–4914.

(34) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3–6.

(35) Jensen, K. L.; Nielsen, D. U.; Jamison, T. F. *Chem. Eur. J.* **2015**, *21*, 7379–7383.

(36) Nicola, A. De; Einhorn, C.; Luche, J. L. *J. Chem. Soc., Chem. Commun.* **1994**, 879–880.

(37) Couty, F.; Evano, G.; Rabasso, N. *Tetrahedron: Asymmetry.* **2003**, *14*, 2407–2412.

(38) Carlin-Sinclair, A.; Couty, F.; Rabasso, N. *Synlett* **2003**, 726–728.

(39) Kise, N.; Ozaki, H.; Moriyama, N.; Kitagishi, Y.; Ueda, N. *J. Am. Chem. Soc.* **2003**, *125*, 11591–11596.

(40) Wessig, P.; Schwarz, J. *Helv. Chim. Acta.* **1998**, *81*, 1803–1814.

(41) Aben, R. W. M.; Smit, R.; Scheeren, J. W. *J. Org. Chem.* **1987**, *52*, 365–370.

(42) Fischer, G.; Fritz, H.; Rihs, G.; Hunkler, D.; Exner, K.; Knothe, L.; Prinzbach, H. *Eur. J. Org. Chem.* **2000**, 743–762.

(43) Dave, P. R.; Duddu, R.; Li, J.; Surapaneni, R.; Gilardi, R. *Tetrahedron Lett.* **1998**, *39*, 5481–5484.

(44) Dave, P. R.; Duddu, R.; Surapaneni, R.; Gilardi, R. *Tetrahedron Lett.* **1999**, *40*, 443–446.

(45) Nakamura, I.; Nemoto, T.; Yamamoto, Y.; Meijere, A. de. *Angew. Chem. Int.*

Ed. **2006**, *45*, 5176–5179.

(46) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988–4035.

(47) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437–4492.

(48) Testa, E.; Fontanella, L.; Cristiani, G. F.; Mariani, L. *Helv. Chim. Acta.* **1959**, *42*, 2370–2379.

(49) Wells, J. N.; Tarwater, O. R. *J. Pharm. Sci.* **1971**, *60*, 156–157.

(50) Yamashita, M.; Ojima, I. *J. Am. Chem. Soc.* **1983**, *105*, 6339–6342.

(51) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263–5277.

(52) Alcaide, B.; Polanco, C.; Sierra, M. A. *J. Org. Chem.* **1998**, *63*, 6786–6796.

(53) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Gómez-Campillos, G. *Adv. Synth. Catal.* **2013**, *355*, 2089–2094.

(54) Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29–60.

(55) Oizumi, K.; Nishino, H.; Koike, H.; Sada, T.; Miyamoto, M.; Kimura, T. *Jpn. J. Pharmacol.* **1989**, *51*, 57–64.

(56) Kobayashi, J.; Cheng, J.; Ishibashi, M.; Wälchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin. Trans. 1* **1991**, 1135–1137.

(57) Reddy, B. V. S.; Kishore, C.; Reddy, A. S. *Tetrahedron Lett.* **2014**, *55*, 49–51.

(58) Glossop, P. A.; Watson, C. A. L.; Price, D. A.; Bunnage, M. E.; Middleton, D. S.; Wood, A.; James, K.; Roberts, D.; Strang, R. S.; Yeadon, M.; Perros-Huguet, C.; Clarke, N. P.; Trevethick, M. A.; Machin, I.; Stuart, E. F.; Evans, S. M.; Harrison, A. C.; Fairman, D. A.; Agoram, B.; Burrows, J. L.; Feeder, N.; Fulton, C. K.; Dillon, B. R.; Entwistle, D. A.; Spence, F. J. *J. Med. Chem.* **2011**, *54*, 6888–6904.

(59) Gerlach, K.; Priepke, H.; Wienen, W.; Schuler-Metz, A.; Nar, H. Substituted

azetidines, manufacturing and use thereof as medicaments. International Patent 2008135525 A2, Nov 13, 2008.

(60) Desroy, N.; Joncour, A.; Bock, X.; Housseman, C.; Peixoto, C.; Bienvenu, N.; Labeguere, V.; Cherel, L.; Annoot, D.; Christophe, T. In *Abstract of Papers, 251st ACS National Meeting; San Diego, CA, March 13-17*; 2016.

(61) Sandris, C.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1958**, 345.

(62) Chatterjee, S. S.; Shoeb, A. *Synthesis* **1973**, 153–154.

(63) Morimoto, A.; Okutani, T.; Masuda, K. *Chem. Pharm. Bull.* **1973**, *21*, 228.

(64) Salgado, A.; Dejaegher, Y.; Verniest, G.; Boeykens, M.; Gauthier, C.; Lopin, C.; Tehrani, K. A.; De Kimpe, N. *Tetrahedron* **2003**, *59*, 2231–2239.

(65) Moore, J. A.; Medeiros, R. W. *J. Am. Chem. Soc.* **1959**, *81*, 6026–6028.

(66) Pusino, A.; Saba, A.; Desole, G.; Rosnati, V. *Gazz. Chim. Ital.* **1985**, *115*, 33.

(67) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223–5230.

(68) Wang, J.; Hou, Y.; Wu, P. *J. Chem. Soc., Perkin. Trans. 1* **1999**, 2277–2280.

(69) Gérard, S.; Raoul, M.; Sapi, J. *Eur. J. Org. Chem.* **2006**, 2440–2445.

(70) Maegawa, T.; Otake, K.; Hirosawa, K.; Goto, A.; Fujioka, H. *Org. Lett.* **2012**, *14*, 4798–4801.

(71) Dobi, Z.; Holczbauer, T.; Soós, T. *Org. Lett.* **2015**, *17*, 2634–2637.

(72) Podlech, J.; Seebach, D. *Helv. Chim. Acta.* **1995**, *78*, 1238–1246.

(73) Hanessian, S.; Fu, J. *Can. J. Chem.* **2001**, *79*, 1812–1826.

(74) Burtoloso, A. C. B.; Correia, C. R. D. *Tetrahedron Lett.* **2004**, *45*, 3355–3358.

(75) Burtoloso, A. C. B.; Correia, C. R. D. *J. Organomet. Chem.* **2005**, *690*, 5636–5646.

(76) Wang, J.; Hou, Y. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 1919–1923.

(77) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258–

3259.

(78) Ye, L.; He, W.; Zhang, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 3236–3239.

(79) Enders, D.; Eichenauer, H. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 549–551.

(80) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253–2329.

(81) Hazelard, D.; Fadel, A. *Tetrahedron: Asymmetry* **2005**, *16*, 2067–2070.

(82) Geden, J. V.; Beasley, B. O.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2013**, *78*, 12243–12250.

(83) Hodgson, D. M.; Kloesges, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 2900–2903.

(84) Parisi, G.; Capitanelli, E.; Pierro, A.; Romanazzi, G.; Clarkson, G. J.; Degennaro, L.; Luisi, R. *Chem. Commun.* **2015**, *51*, 15588–15591.

(85) Fluorochem Home Page http://www.fluorochem.co.uk (accessed Aug 10, 2017).

(86) Lazny, R.; Nodzewska, A. *Chem. Rev.* **2010**, *110*, 1386–1434.

(87) Enders, D.; Wortmann, L.; Peters, R. *Acc. Chem. Res.* **2000**, *33*, 157–169.

(88) Fluorochem Home Page http://www.fluorochem.co.uk (accessed Aug 12, 2017).

(89) Beasley, B. O.; Alli-Balogun, A.; Clarkson, G. J.; Shipman, M. *Tetrahedron Lett.* **2014**, *55*, 541–543.

(90) Alqahtani, N.; Porwal, S. K.; James, E. D.; Bis, D. M.; Karty, J. A.; Lane, A. L.; Viswanathan, R. *Org. Biomol. Chem.* **2015**, *13*, 7177–7192.

(91) Enders, D.; Breuer, I.; Raabe, G. *Synthesis* **2005**, 3517–3530.

(92) Koch, R. *Org. Biomol. Chem.* **2011**, *9*, 2885–2891.

(93) Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bergbreiter, D. E. *J. Am. Chem. Soc.* **1979**, *101*, 5654–5659.

(94) Enders, D.; Bachstädter, G.; Kremer, K. A. M.; Marsch, M.; Harms, K.;

Boche, G. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1522–1524.

(95) Krenske, E. H.; Houk, K. N.; Lim, D.; Wengryniuk, S. E.; Coltart, D. M. *J. Org. Chem.* **2010**, *75*, 8578–8584.

(96) Ruider, S. A.; Müller, S.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 11908–11911.

(97) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932–6933.

(98) Ho, K. Y. T.; Aïssa, C. *Chem. Eur. J.* **2012**, *18*, 3486–3489.

(99) Ishida, N.; Yuhki, T.; Murakami, M. *Org. Lett.* **2012**, *14*, 3898–3901.

(100) Pancholi, A. K.; Geden, J. V.; Clarkson, G. J.; Shipman, M. *J. Org. Chem.* **2016**, *81*, 7984–7992.

(101) Jung, H. H.; Buesking, A. W.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 3912–3915.

(102) Wermuth, C. G. *Med. Chem. Commun.* **2011**, *2*, 935–941.

(103) Cheng, K. C. C.; Cao, S.; Raveh, A.; MacArthur, R.; Dranchak, P.; Chlipala, G.; Okoneski, M. T.; Guha, R.; Eastman, R. T.; Yuan, J.; Schultz, P. J.; Su, X.-Z.; Tamayo-Castillo, G.; Matainaho, T.; Clardy, J.; Sherman, D. H.; Inglese, J. *J. Nat. Prod.* **2015**, *78*, 2411–2422.

(104) Szucs, T. *Drugs* **1991**, *41*, 18.

(105) Bols, M.; Hazell, R. G.; Thomsen, I. B. *Chem. Eur. J.* **1997**, *3*, 940–947.

(106) Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673–3682.

(107) Zheng, Y.; Tice, C. M. *Exp. Op. Drug Disc.* **2016**, *11*, 831–834.

(108) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060–1074.

(109) Horvitz, D. Certain 1,2-diazetidines and their preparation. US Patent 3,129,215, Apr 14, 1964.

(110) Morioka, H.; Takezawa, M.; Shibai, H.; Okawara, T.; Furukawa, M. *Agric. Biol. Chem.* **1986**, *50*, 1757–1764.

(111) Bachovchin, D. A.; Mohr, J. T.; Speers, A. E.; Wang, C.; Berlin, J. M.; Spicer, T. P.; Fernandez-Vega, V.; Chase, P.; Hodder, P. S.; Schürer, S. C.; Nomura, D. K.; Rosen, H.; Fu, G. C.; Cravatt, B. F. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6811–6816.

(112) Zuhl, A. M.; Mohr, J. T.; Bachovchin, D. A.; Niessen, S.; Hsu, K. L.; Berlin, J. M.; Dochnahl, M.; López-Alberca, M. P.; Fu, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2012**, *134*, 5068–5071.

(113) Hall, J. H.; Bigard, W. S. *J. Org. Chem.* **1978**, *43*, 2785–2788.

(114) Rademacher, P. *Tetrahedron Lett.* **1974**, *15*, 83–86.

(115) Nelsen, S. F.; Peacock, V. E.; Weisman, G. R.; Landis, M. E.; Spencer, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 2806–2810.

(116) Gebhardt, K. F.; Oberhammer, H.; Zeil, W. *J. Chem. Soc., Faraday II.* **1980**, *76*, 1293–1303.

(117) Carlson, E. H.; Schaap, A. P.; Raban, M. *J. Org. Chem.* **1973**, *38*, 1605–1607.

(118) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395–397.

(119) Cramer, R. D. Monomeric addition products of azobisformates and polyfluoroethylenes. US Patent 2,456,178, Dec 14, 1948.

(120) Kauer, J. C.; Schneider, A. K. *J. Am. Chem.* **1960**, *82*, 852–853.

(121) Hoffmann, R. W.; Häuser, H. *Angew. Chem.* **1964**, *76*, 346.

(122) von Gustorf, E. K.; White, D. V.; Leitich, J. *Tetrahedron Lett.* **1969**, *10*, 3109–3112.

(123) Gustorf, E. K. von; White, D. V; Kim, B.; Hess, D.; Leitich, J. *J. Org. Chem.* **1970**, *35*, 1135–1165.

(124) Firl, J.; Sommer, S. *Tetrahedron Lett.* **1970**, *11*, 1929–1932.

(125) Firl, J.; Sommer, S. *Tetrahedron Lett.* **1972**, *13*, 4713–4716.

(126) Warrener, R. N.; Nunn, E. E.; Paddon-Row, M. N. *Aust. J. Chem.* **1979**, *32*, 2659–2674.

(127) Hall, J. H.; Jones, M. L. *J. Org. Chem.* **1983**, *48*, 822–826.

(128) Xu, S.; Chen, J.; Shang, J.; Qing, Z.; Zhang, J.; Tang, Y. *Tetrahedron Lett.* **2015**, *56*, 6456–6459.

(129) Guo, D.; Zhu, D.; Zhou, X.; Zheng, B. *Langmuir* **2015**, *31*, 13759–13763.

(130) Berlin, J. M.; Fu, G. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 7048–7050.

(131) Huang, X.-L.; Chen, X.-Y.; Ye, S. *J. Org. Chem.* **2009**, *74*, 7585–7587.

(132) Brown, M. J.; Clarkson, G. J.; Fox, D. J.; Inglis, G. G.; Shipman, M. *Tetrahedron Lett.* **2010**, *51*, 382–384.

(133) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533–3539.

(134) Miao, W.; Xu, W.; Zhang, Z.; Ma, R.; Chen, S. H.; Li, G. *Tetrahedron Lett.* **2006**, *47*, 6835–6837.

(135) Cheng, X.; Ma, S. *Angew. Chem.* **2008**, *47*, 4581–4583.

(136) Brown, M. J.; Clarkson, G. J.; Inglis, G. G.; Shipman, M. *Org. Lett.* **2011**, *13*, 1686–1689.

(137) Iacobini, G. P.; Porter, D. W.; Shipman, M. *Chem. Commun.* **2012**, *48*, 9852–9854.

(138) Rajkumar, S.; Clarkson, G. J.; Shipman, M. *Org. Lett.* **2017**, *19*, 2058–2061.

(139) Müller, G.; Berkenbosch, T.; Benningshof, J. C. J.; Stumpfe, D.; Bajorath, J. *Chem. Eur. J.* **2017**, *23*, 703–710.

(140) Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257–8322.

(141) Taylor, F. F.; Faloon, W. W. *J. Clin. Endocrinol. Metab.* **1959**, *19*, 1683–1687.

(142) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3524–3527.

(143) Marson, C. M. *Chem. Soc. Rev.* **2011**, *40*, 5514–5533.

(144) Jha, V.; Kauloorkar, S. V.; Kumar, P. *Eur. J. Org. Chem.* **2014**, *2014* (22),

4897–4902.

(145) Daughenbaugh, P. J.; Allison, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 3665–3667.

(146) Hayat, S.; Rahman, A. ur; Khan, K. M.; Choudhary, I.; Maharvi, G. M.; Ullah, Z.; Bayer, E. *Synth. Commun.* **2003**, *33*, 2531–2540.

(147) Ellwood, A. R.; Porter, M. J. *J. Org. Chem.* **2009**, *74*, 7982–7985.

(148) Brown, M. J. PhD Thesis, University of Warwick, 2011.

(149) Rasmussen, L. K. *J. Org. Chem.* **2006**, *71*, 3627–3629.

(150) Wang, E. Y.; Gao, H.; Salter-cid, L.; Zhang, J.; Huang, L.; Podar, E. M.; Miller, A.; Zhao, J.; Rourke, A. O.; Linnik, M. D. *J. Med. Chem.* **2006**, *49*, 2166–2173.

(151) Koo, K. A.; Kim, N. D.; Chon, Y. S.; Jung, M. S.; Lee, B. J.; Kim, J. H.; Song, W. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2324–2328.

(152) Schantl, J. G.; Decristoforo, M. *Tetrahedron Lett.* **1987**, *28*, 6577–6580.

(153) Melgar-Fernández, R.; González-Olvera, R.; Vargas-Caporali, J.; Pérez-Isidoro, R.; Juaristi, E. *Arkivoc* **2010**, 55–75.

(154) Kamata, M.; Yamashita, T.; Kina, A.; Tawada, M.; Endo, S.; Mizukami, A.; Sasaki, M.; Tani, A.; Nakano, Y.; Watanabe, Y.; Furuyama, N.; Funami, M.; Amano, N.; Fukatsu, K. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4769–4772.

(155) Guillemont, J. E. G.; Lançois, D. F. A.; Motte, M. M. S.; Balemans, W. M. A.; Weidner, S. F. W.; McGowan, D. C.; Koul, A. New antibacterial compounds. International Patent 2014023814 A1, Feb 13, 2014.

(156) Li, L.; Wu, T.; Feng, J.; Ren, P.; Liu, Y. Inhibitors of Erk and methods of use. International Patent 2015051341 A1, Apr 9, 2015.

(157) Watanabe, K.; Uehara, F.; Hiki, S.; Yokoshima, S.; Usui, Y.; Okuyama, M.; Shoda, A.; Aritomo, K.; Kohara, T.; Fukunaga, K. 2, 3, 6-Trisubstituted-4-pyrimidone derivatives. International Patent 2004085408 A1, Oct 7, 2004.

(158) Kunieda, T.; Nagamatsu, T.; Higuchi, T.; Hirobe, M. *Tetrahedron Lett.* **1988**,

29, 2203–2206.

(159) Kim, S.; Lee, P. H.; Lee, T. A. *Synth. Commun.* **1988**, *18*, 247–252.

(160) Sharma, S. D.; Anand, R. D.; Kaur, G. *Synth. Commun.* **2004**, *34*, 1855–1862.

(161) Berrien, J.-F.; Billion, M.-A.; Husson, H.-P.; Royer, J. *J. Org. Chem.* **1995**, *60*, 2922–2924.

(162) Keita, M.; Kaffy, J.; Troufflard, C.; Morvan, E.; Crousse, B.; Ongeri, S. *Org. Biomol. Chem.* **2014**, *12*, 4576–4581.

(163) Iacobini, G. PhD Thesis, University of Warwick, 2012.

(164) Shiers, J. PhD Thesis, University of Warwick, 2005.

(165) Liu, Y.; Chen, J.; Zhang, Z.; Qin, J.; Zhao, M.; Zhang, W. *Org. Biomol. Chem.* **2016**, *14*, 7099–7102.

(166) Luo, F.; Wang, P.; Gong, Y. *Tetrahedron Lett.* **2010**, *51*, 1693–1695.

(167) Abbas, C.; Pickaert, G.; Didierjean, C.; Grégoire, B. J.; Vanderesse, R. *Tetrahedron Lett.* **2009**, *50*, 4158–4160.

(168) Matheson, C. J.; Venkataraman, S.; Amani, V.; Harris, P. S.; Backos, D. S.; Donson, A. M.; Wempe, M. F.; Foreman, N. K.; Vibhakar, R.; Reigan, P. *ACS Chem. Biol.* **2016**, *11*, 921–930.

(169) Mundal, D. A.; Lutz, K. E.; Thomson, R. J. *Org. Lett.* **2009**, *11*, 465–468.

(170) Nara, S.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *Synth. Commun.* **2003**, *33*, 87–98.

(171) Li, R.; Leng, P.; Liu, B.; Wang, X.; Ge, Z.; Li, R. *Tetrahedron* **2016**, *72*, 5707–5712.

(172) de Frémont, P.; Marion, N.; Nolan, S. P. *Coord. Chem. Rev.* **2009**, *253*, 862–892.

(173) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315–8359.

(174) Brahms, D. L. S.; Dailey, W. P. *Chem. Rev.* **1996**, *96*, 1585–1632.

(175) Ni, C.; Hu, J. *Synthesis* **2014**, *46*, 842–863.

(176) Kamel, M.; Kimpenhaus, W.; Buddrus, J. *Chem. Ber.* **1976**, *1090*, 2351–2369.

(177) Fedorynski, M. *Chem. Rev.* **2003**, *103*, 1099–1132.

(178) Zhang, C. *Adv. Synth. Catal.* **2017**, *359*, 372–383.

(179) Bos, M.; Poisson, T.; Pannecoucke, X.; Charette, A. B.; Jubault, P. *Chem. Eur. J.* **2017**, *23*, 4950–4961.

(180) Cullen, W. R.; Waldman, M. C. *Can. J. Chem.* **1969**, *47*, 3093–3098.

(181) Wang, F.; Luo, T.; Hu, J.; Wang, Y.; Krishnan, H. S.; Jog, P. V.; Ganesh, S. K.; Prakash, G. K. S.; Olah, G. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 7153–7157.

(182) Doering, W. v. E.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162–6165.

(183) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195–199.

(184) Makosza, M.; Wawrzyniewicz, M. *Tetrahedron Lett.* **1969**, *10*, 4659–4662.

(185) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222–4266.

(186) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 113–116.

(187) Yu, Z.; Lin, Q. *J. Am. Chem. Soc.* **2014**, *136*, 4153–4156.

(188) Ramana, C. V; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694–7703.

(189) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.

(190) Wang, H.; Guptill, D. M.; Varela-Alvarez, A.; Musaev, D. G.; Davies, H. M. L. *Chem. Sci.* **2013**, *4*, 2844–2850.

(191) Wang, Y.; Liu, J.; Dransfield, P. J.; Zhu, L.; Wang, Z.; Du, X.; Jiao, X.; Su, Y.; Li, A. R.; Brown, S. P.; Kasparian, A.; Vimolratana, M.; Yu, M.; Pattaropong, V.; Houze, J. B.; Swaminath, G.; Tran, T.; Nguyen, K.; Guo, Q.; Zhang, J.; Zhuang, R.; Li, F.; Miao, L.; Bartberger, M. D.; Correll, T. L.; Chow, D.; Wong, S.; Luo, J.; Lin, D. C. H.; Medina, J. C. *ACS Med. Chem.*

Lett. **2013**, *4*, 551–555.

(192) Racine, S.; Hegedüs, B.; Scopelliti, R.; Waser, J. *Chem. Eur. J.* **2016**, *22*, 11997–12001.

(193) Ziyat, H.; Itto, Y.; Ali, M.; Riahi, A.; Karim, A.; Daran, J.-C. *Arkivoc* **2006**, 152–160.

(194) Averina, E. B.; Sedenkova, K. N.; Bakhtin, S. G.; Grishin, Y. K.; Kutateladze, A. G.; Roznyatovsky, V. A.; Rybakov, V. B.; Butov, G. M.; Kuznetsova, T. S.; Zefirov, N. S. *J. Org. Chem.* **2014**, *79*, 8163–8170.

(195) Pizem, H.; Sharon, O.; Frimer, A. A. *Tetrahedron* **2002**, *58*, 3199–3205.

(196) Fatiadi, A. J. *Synthesis* **1987**, 749–789.

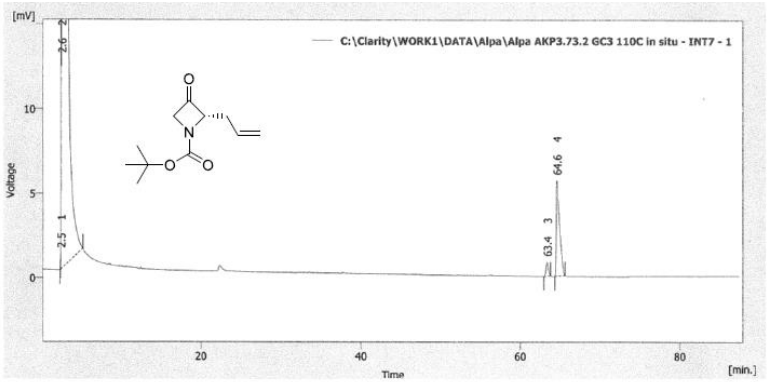
(197) Pancholi, A. K.; Iacobini, G. P.; Clarkson, G. J.; Porter, D. W.; Shipman, M. *J. Org. Chem.* **2018**, *83*, 491–498.

(198) Irifune, S.; Kibayashi, T.; Ishii, Y.; Ogawa, M. *Synthesis* **1988**, 366–369.

(199) Martin, D. B. C.; Nguyen, L. Q.; Vanderwal, C. D. *J. Org. Chem.* **2012**, *77*, 17–46.

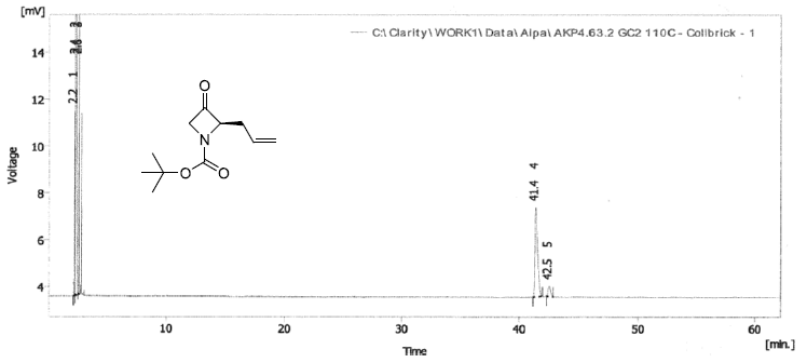
Appendix I – Chiral GC analysis of (*S*)-159, (*R*)-159 and Racemic 159

(Chrompac cyclodextrin-β-236M-19 column, T = 110°C, P = 15 psi, H_2 carrier gas)



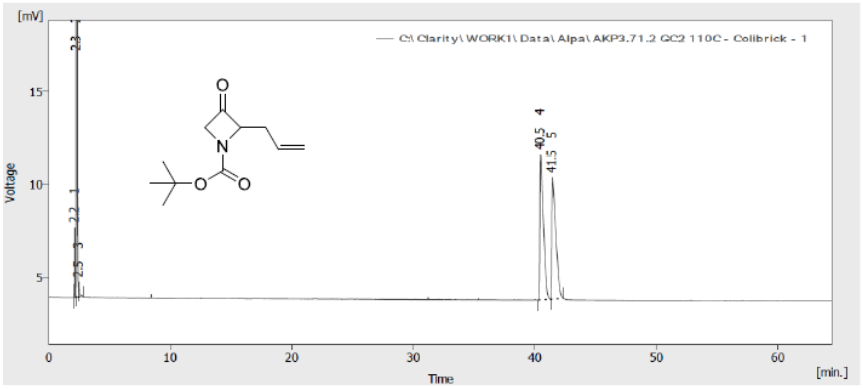
Result Table (Uncal - C:\Clarity\WORK1\DATA\Alpa\Alpa AKP3.73.2 GC3 110C in situ - INT7 - 1)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	2.460	4.400	0.959	0.0	0.1	0.09	
2	2.593	31199.835	1249.448	99.4	99.4	0.39	
3	63.353	17.239	0.853	0.1	0.1	0.32	
4	64.553	166.146	5.661	0.5	0.5	0.47	
	Total	31387.619	1256.922	100.0	100.0		



Result Table (Uncal - C:\Clarity\WORK1\Data\Alpa\AKP4.63.2 GC2 110C - Colibrick - 1)

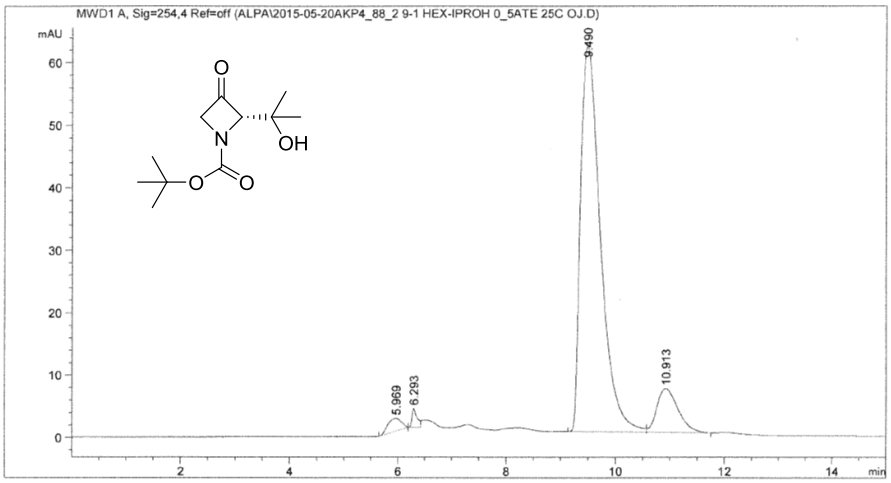
	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]	Compound Name
1	2.228	15.945	7.904	0.3	0.8	0.02	
2	2.368	4935.699	979.956	97.8	97.3	0.09	
3	2.600	27.271	14.861	0.5	1.5	0.02	
4	41.372	63.504	3.810	1.3	0.4	0.26	
5	42.524	6.572	0.433	0.1	0.0	0.24	
	Total	5048.990	1006.964	100.0	100.0		

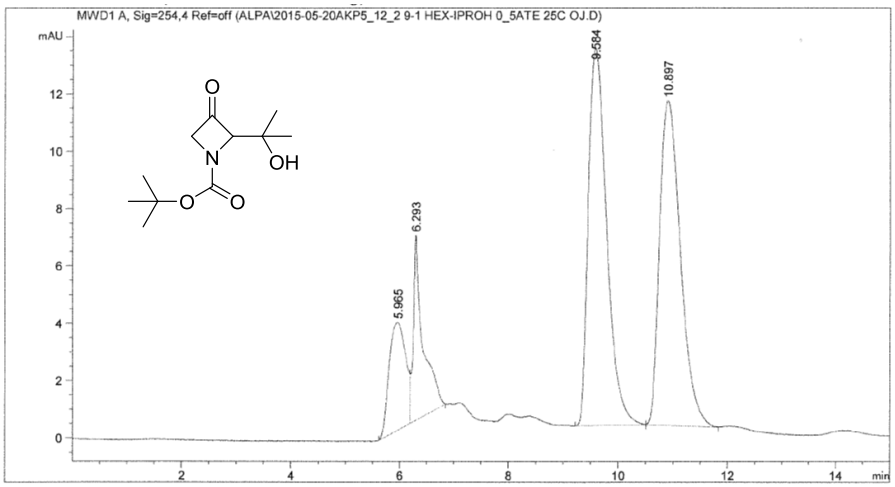


Chiral GC traces of 2-allylated azetidin-3-one **159**.

Appendix II – Chiral HPLC analysis of (*S*)-170

(Chiralcel OJ column (0.46cm ø x 25 cm), 9:1 hexane: propan-2-ol, T = 25°C, flow rate = 0.5 mL/min, λ = 254 nm)





Chiral HPLC traces of 2-alkylated azetidin-3-one **170**.

Appendix III – NOESY spectra of (*R*,S)-363a